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The Merck Manual Of Diagnosis and Therapy, Nineteenth Edition

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Other Merck Books
Preface

At the beginning of the 2nd decade of the 21st century, the amount of information available to health care practitioners is immense. Medical websites and journals send daily messages announcing results of the latest studies. Within minutes, subspecialty data heretofore found only in university libraries can be unearthed, along with a vast array of information from academics, commercial organizations, advocacy groups, the government, and seemingly anyone with a computer and an internet connection.

What is the role of a general reference work such as The Merck Manual when seemingly the entire body of medical knowledge is at one's fingertips electronically? With such a vast body of knowledge available,
finding a good starting place can be difficult. *The Manual* has always been intended as the first stop on the road to understanding for readers encountering a topic for the first time or for the first time in a long time. After digesting a *Merck Manual* topic, readers will be well prepared to understand and evaluate the wealth of more detailed information available elsewhere.

As it has for over 110 years, *The Merck Manual* focuses on discussions of specific disorders, organized by organ system or medical specialty. In its structured introductions to medical disorders, *The Manual* provides health care practitioners and students with straightforward, practical explanations of "what to do" to diagnose and treat those conditions. We discuss when to suspect a disease, the proper sequence of evaluation, and the first-line options for treatment along with selected alternatives. In addition, we provide enough background information on etiology and pathophysiology to ensure comprehension of the management recommendations.

*The Manual* continues to enhance its accessibility. In addition to having introductory "nut-shells" at the beginning of each disease discussion, we have included bulleted lists in the text whenever possible, including at the beginning of diagnosis and treatment discussions.

In the interest of brevity, *The Merck Manual* has never cited references to the medical literature. Nonetheless, readers can be assured that our hundreds of contributors and dozens of peer reviewers are presenting the best current recommendations, soundly based on available evidence.

Although the printed *Merck Manual* has long since grown too big to be carried in a lab coat, it has returned to the pocket as content on many different handheld electronic devices. In addition, *The Merck Manual* continues to be available to all readers free of charge at www.merckmanuals.com. Although our electronic versions have a currency that a printed product cannot, the book still provides a better in-depth reading experience along with a tactile satisfaction and ease of perusal not possessed by electronic devices. Undoubtedly this will change as technology advances, but whatever the platform, we will continue to strive to keep *The Merck Manual* as useful as ever.

We thank the numerous contributors who have worked diligently with us to craft this edition, and we hope you will find it worthy of continued and frequent use. As always, suggestions for improvements will be warmly welcomed and carefully considered.

Robert S. Porter, MD
**Editor-in-Chief**

**Committed to Providing Medical Information: Merck and The Merck Manuals**

In 1899, the American drug manufacturer Merck & Co. first published a small book titled *Merck's Manual of the Materia Medica*. It was meant as an aid to physicians and pharmacists, reminding doctors that "Memory is treacherous." Compact in size, easy to use, and comprehensive, *The Merck Manual* (as it was later known) became a favorite of those involved in medical care and others in need of a medical reference. Even Albert Schweitzer carried a copy to Africa in 1913, and Admiral Byrd carried a copy to the South Pole in 1929.

By the 1980s, the book had become the world's largest selling medical text and was translated into more than a dozen languages. While the name of the parent company has changed somewhat over the years, the book's name has remained constant, known officially as *The Merck Manual of Diagnosis and Therapy* but usually referred to as *The Merck Manual* and sometimes "The Merck."

In 1990, the editors of *The Merck Manual* introduced *The Merck Manual of Geriatrics*. This new book quickly became the best-selling textbook of geriatric medicine, providing specific and comprehensive information on the care of older people. The 3rd edition was published in five languages.

In 1997, *The Merck Manual of Medical Information-Home Edition* was published. In this revolutionary book, the editors translated the complex medical information in *The Merck Manual* into plain language, producing a book meant for all those people interested in medical care who did not have a medical


In 2008, *The Merck Manual of Patient Symptoms* was introduced to complement *The Merck Manual* and was intended to help newcomers to clinical diagnosis approach patients who present with certain common symptoms.

As part of its commitment to ensuring that all who need and want medical information can get it, Merck provides the content of these Merck Manuals on the web for free (www.merckmanuals.com). Registration is not required, and use is unlimited. The web publications are continuously updated to ensure that the information is as up-to-date as possible.

Merck also supports the community of chemists and others with the need to know about chemical compounds with *The Merck Index*. First published in 1889, this publication actually predates *The Merck Manual* and is the most widely used text of its kind. *The Merck Veterinary Manual* was first published in 1955. It provides information on the health care of animals and is the preeminent text in its field.

Merck & Co., Inc., is one of the world's largest pharmaceutical companies. Merck is committed to providing excellent medical information and, as part of that effort, continues to proudly provide all of The Merck Manuals as a service to the community.

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Each Section begins with its own table of contents, listing chapters and topics in that section. Chapters are numbered serially from the beginning to the end of the book.

The Index is highly detailed and contains many cross-entries. In addition, readers will find many cross-references throughout the text to specific pages where additional or related information can be found.

Running heads carry the section number and title on left-hand pages and the chapter number and title on right-hand pages.

Abbreviations and symbols, used throughout the text as essential space savers, are listed on pages ix and x. Other abbreviations in the text are expanded at first mention in the chapter or topic.

Tables and figures are referenced in the index but are not listed in a separate table of contents. An insert of color plates contains photographs of many eye, ear, endocrine, skin, and gynecologic disorders as well as infectious diseases.

Laboratory values in the book are given in conventional units. In most cases, SI units follow in parentheses. Appendix II contains several tables listing normal laboratory values for many tests conducted on blood, plasma, serum, urine, CSF, and stool.
Drugs are designated in the text by generic (nonproprietary) names. In Appendix III, many of the drugs mentioned in the book are listed alphabetically, with each generic name followed by one or more trade names.

Section 23, Special Subjects, has discussions on clinical decision making, radiologic imaging, complementary and alternative medicine, dietary supplements, genetics, smoking cessation, rehabilitation, care of the surgical patient, financial issues in health care, and care of the dying patient, among others.

Important: The authors, reviewers, and editors of this book have made extensive efforts to ensure that treatments, drugs, and dosage regimens are accurate and conform to the standards accepted at the time of publication. However, constant changes in information resulting from continuing research and clinical experience, reasonable differences in opinions among authorities, unique aspects of individual clinical situations, and the possibility of human error in preparing such an extensive text require that the reader exercise individual judgment when making a clinical decision and, if necessary, consult and compare information from other sources. In particular, the reader is advised to check the product information provided by the manufacturer of a drug product before prescribing or administering it, especially if the drug is unfamiliar or is used infrequently.

Note: Readers can find up-to-date information, additional tables and figures, as well as multimedia enhancements at www.merckmanuals.com. Visit the web site frequently for new enhancements and the latest information on clinical developments.

Abbreviations

The following abbreviations are used throughout the text; other abbreviations are expanded at first mention in the chapter or subchapter.

- ABG: arterial blood gas
- ACE: angiotensin converting enzyme
- ACTH: adrenocorticotropic hormone
- ADH: antidiuretic hormone
- AIDS: acquired immunodeficiency syndrome
- ALT: alanine transaminase (formerly SGPT)
- AST: aspartate transaminase (formerly SGOT)
- ATP: adenosine triphosphate
- BCG: bacille Calmette-Guerin
- bid: 2 times a day (only in dosages)
- BMR: basal metabolic rate
- BP: blood pressure
- BSA: body surface area
- BUN: blood urea nitrogen
- C: Celsius; centigrade
- Ca: calcium
- cAMP: cyclic adenosine monophosphate
- CBC: complete blood count
- cGy: centigray
- Ci: curie
- CK: creatine kinase
- CK-MB: creatine kinase of muscle band
- Cl: chloride; chlorine
- cm: centimeter
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<td>central nervous system</td>
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<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>cu</td>
<td>cubic</td>
</tr>
<tr>
<td>D &amp; C</td>
<td>dilation and curettage</td>
</tr>
<tr>
<td>dL</td>
<td>deciliter (= 100 mL)</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DTP</td>
<td>diphtheria-tetanus-pertussis (toxoids/vaccine)</td>
</tr>
<tr>
<td>D/W or D</td>
<td>dextrose</td>
</tr>
<tr>
<td>ECF</td>
<td>extracellular fluid</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram, electrocardiography</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram, electroencephalography</td>
</tr>
<tr>
<td>ENT</td>
<td>ear, nose, and throat</td>
</tr>
<tr>
<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>F</td>
<td>Fahrenheit</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>ft</td>
<td>foot; feet (measure)</td>
</tr>
<tr>
<td>FUO</td>
<td>fever of unknown origin</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>GU</td>
<td>genitourinary</td>
</tr>
<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid; hydrochloride</td>
</tr>
<tr>
<td>HCO₃</td>
<td>bicarbonate</td>
</tr>
<tr>
<td>Hct</td>
<td>hematocrit</td>
</tr>
<tr>
<td>Hg</td>
<td>mercury</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>hydroxymethyl glutaryl coenzyme A</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz (cycles/second)</td>
</tr>
<tr>
<td>ICF</td>
<td>intracellular fluid</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IgA, etc</td>
<td>immunoglobulin A, etc</td>
</tr>
<tr>
<td>IL-1, etc</td>
<td>interleukin-1, etc</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular(ly)</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IU</td>
<td>international unit</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous(ly)</td>
</tr>
<tr>
<td>IVU</td>
<td>intravenous urography</td>
</tr>
<tr>
<td>K</td>
<td>potassium</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalorie (food calorie)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PO2</td>
<td>oxygen partial pressure (or tension)</td>
</tr>
<tr>
<td>PPD</td>
<td>purified protein derivative (tuberculin)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>prn</td>
<td>as needed</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>q</td>
<td>every (only in dosages)</td>
</tr>
<tr>
<td>qid</td>
<td>4 times a day (only in dosages)</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>SaO2</td>
<td>arterial oxygen saturation</td>
</tr>
<tr>
<td>sc</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>sec</td>
<td>second</td>
</tr>
<tr>
<td>SI</td>
<td>International System of Units</td>
</tr>
<tr>
<td>SIDS</td>
<td>sudden infant death syndrome</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>sp</td>
<td>species (when referring to the singular) [eg, <em>Clostridium</em> sp]</td>
</tr>
<tr>
<td>spp</td>
<td>species (when referring to the plural) [eg, <em>Nocardia</em> and <em>Myocardia</em> spp]</td>
</tr>
<tr>
<td>sp gr</td>
<td>specific gravity</td>
</tr>
<tr>
<td>sq</td>
<td>square</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>tid</td>
<td>3 times a day (only in dosages)</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TPN</td>
<td>total parenteral nutrition</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid-stimulating hormone</td>
</tr>
<tr>
<td>URI</td>
<td>upper respiratory infection</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>wk</td>
<td>week</td>
</tr>
<tr>
<td>wt</td>
<td>weight</td>
</tr>
<tr>
<td>yr</td>
<td>year</td>
</tr>
<tr>
<td>μ</td>
<td>micro-; micron</td>
</tr>
<tr>
<td>μCi</td>
<td>microcurie</td>
</tr>
<tr>
<td>μg</td>
<td>microgram</td>
</tr>
<tr>
<td>μL</td>
<td>microliter</td>
</tr>
<tr>
<td>μm</td>
<td>micrometer (= micron)</td>
</tr>
<tr>
<td>μmol</td>
<td>micromole</td>
</tr>
<tr>
<td>μOsm</td>
<td>micro-osmole</td>
</tr>
<tr>
<td>mμ</td>
<td>millimicron</td>
</tr>
</tbody>
</table>

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Sweating Disorders; Benign Tumors; Pressure Ulcers

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Approach to the Care of Normal Infants and Children; Perinatal Physiology; Caring for Sick Children and Their Families

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**Electrical and Lightning Injuries**

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**Mood Disorders**

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**Neurotransmission**

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*Medical Examination of the Rape Victim*

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Tumor Immunology

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Approach to the Patient With Upper GI Complaints; Diagnostic and Therapeutic GI Procedures

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*General Principles of Medical Genetics*

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Menopause

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Approach to the Patient With Liver Disease; Drugs and the Liver; Liver Masses and Granulomas

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Suicidal Behavior

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Pericarditis

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Tumors of the Lungs

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Concepts in Pharmacotherapy

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*Principles of Radiologic Imaging*

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*Vitamin Deficiency, Dependency, and Toxicity; Mineral Deficiency and Toxicity*

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Tumors of Bones and Joints

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Viruses; Herpesviruses; Arboviridae,
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1 - Nutritional Disorders

Chapter 1. Nutrition: General Considerations

Introduction

Nutrition is the science of food and its relationship to health. Nutrients are chemicals in foods that are used by the body for growth, maintenance, and energy. Nutrients that cannot be synthesized by the body and thus must be derived from the diet are considered essential. They include vitamins, minerals, some amino acids, and some fatty acids. Nutrients that the body can synthesize from other compounds, although they may also be derived from the diet, are considered nonessential. Macronutrients are required by the body in relatively large amounts; micronutrients are needed in minute amounts.

Lack of nutrients can result in deficiency syndromes (eg, kwashiorkor, pellagra) or other disorders (see p. 9). Excess intake of macronutrients can lead to obesity (see p. 56) and related disorders; excess intake of micro-nutrients can be toxic. Also, the balance of various types of nutrients, such as how much unsaturated vs saturated fat is consumed, can influence the development of disorders.

Macronutrients

Macronutrients constitute the bulk of the diet and supply energy and many essential nutrients. Carbohydrates, proteins (including essential amino acids), fats (including essential fatty acids), macrominerals, and water are macronutrients. Carbohydrates, fats, and proteins are interchangeable as sources of energy; fats yield 9 kcal/g (37.8 kJ/g); proteins and carbohydrates yield 4 kcal/g (16.8 kJ/g).

Carbohydrates: Dietary carbohydrates are broken down into glucose and other monosaccharides. Carbohydrates increase blood glucose levels, supplying energy. Simple carbohydrates are composed of small molecules, generally monosaccharides or disaccharides, which increase blood glucose levels rapidly. Complex carbohydrates are composed of larger molecules, which are broken down into monosaccharides. Complex carbohydrates increase blood glucose levels more slowly but for a longer time. Glucose and sucrose are simple carbohydrates; starches and fiber are complex carbohydrates.

The glycemic index measures how rapidly consumption of a carbohydrate increases plasma glucose levels. Values range from 1 (the slowest increase) to 100 (the fastest increase, equivalent to pure glucose—see Table 1-1). However, the actual rate of increase also depends on what foods are consumed with the carbohydrate.

Carbohydrates with a high glycemic index may increase plasma glucose to high levels rapidly. It is hypothesized that, as a result, insulin levels increase, inducing hypoglycemia and hunger, which tends to lead to consumption of excess calories and weight gain. Carbohydrates with a low glycemic index increase plasma glucose levels slowly, resulting in lower postprandial insulin levels and less hunger, which probably makes consumption of excess calories less likely. These effects are predicted to result in a more favorable lipid profile and a decreased risk of obesity, diabetes mellitus, and complications of diabetes if present.

Proteins: Dietary proteins are broken down into peptides and amino acids. Proteins are required for tissue maintenance, replacement, function, and growth. However, if the body is not getting enough calories from dietary sources or tissue stores (particularly of fat), protein may be used for energy.

As the body uses dietary protein for tissue production, there is a net gain of protein (positive nitrogen balance). During catabolic states (eg, starvation, infections, burns), more protein may be used (because body tissues are broken down) than is absorbed, resulting in a net loss of protein (negative nitrogen balance). Nitrogen balance is best determined by subtracting the amount of nitrogen excreted in urine and feces from the amount of
nitrogen consumed.

Of the 20 amino acids, 9 are essential amino acids (EAAs); they cannot be synthesized and must be obtained from the diet. All people require 8 EAAs; infants also require histidine.

The weight-adjusted requirement for dietary protein correlates with growth rate, which decreases from infancy until adulthood. The daily dietary protein requirement decreases from 2.2 g/kg in 3-mo-old infants to 1.2 g/kg in 5-yr-old children and to 0.8 g/kg in adults. Protein requirements correspond to EAA requirements (see Table 1-2). Adults trying to increase muscle mass need very little extra protein beyond the requirements in the table.

The amino acid composition of protein varies widely. Biological value (BV) reflects the similarity in amino acid composition of protein to that of animal tissues; thus, BV indicates what percentage of a dietary protein provides EAAs for the body. A perfect match is egg protein, with a value of 100. Animal proteins in milk and meat have a high BV (~90); proteins in cereal and vegetables have a lower BV (~40), and some derived proteins (eg, gelatin) have a BV of 0. The extent to which dietary proteins supply each other's missing amino acids (complementarity) determines the overall BV of the diet. The recommended daily allowances (RDA) for protein assumes that the average mixed diet has a BV of 70.

**Fats:** Fats are broken down into fatty acids and glycerol. Fats are required for tissue growth and hormone production. Saturated fatty acids, common in animal fats, tend to be solid at room temperature. Except for palm and coconut oils, fats derived from plants tend to be liquid at room temperature; these fats contain high levels of monounsaturated fatty acids or polyunsaturated fatty acids (PUFAs).

Partial hydrogenation of unsaturated fatty acids (as occurs during food manufacturing) produces trans fatty acids, which are solid or semisolid at room temperature. In the US, the main dietary source of trans fatty acids is partially hydrogenated vegetable oils, used in manufacturing certain foods (eg, cookies, crackers, chips) to prolong shelf-life. Trans fatty acids may elevate LDL cholesterol and lower HDL; they may also independently increase the risk of coronary artery disease.

Essential fatty acids (EFAs) are linoleic acid, an \( \omega-6 \) (n-6) fatty acid, and linolenic acid, an \( \omega-3 \) (n-3) fatty acid. Other \( \omega-6 \) acids (eg, arachidonic acid) and other \( \omega-3 \) fatty acids (eg, eicosapentaenoic acid, docosahexaenoic acid) are required by the body but can be synthesized from EFAs.

EFAs (see also p. 19) are needed for the formation of various eicosanoids (biologically active lipids), including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. Consumption of \( \omega-3 \) fatty acids may decrease the risk of coronary artery disease.

**Macrominerals:** Na, Cl, K, Ca, P, and Mg are required in relatively large amounts per day (see Tables 1-3, 1-4, and 5-2).

**Water:** Water is considered a macronutrient because it is required in amounts of 1 mL/kcal (0.24 mL/kJ) of energy expended, or about 2500 mL/day. Needs vary with fever, physical activity, and changes in climate and humidity.
Micronutrients

Vitamins and minerals required in minute amounts (trace minerals) are micronutrients (see Chs. 4 and 5).

**Water-soluble vitamins** are vitamin C (ascorbic acid) and 8 members of the vitamin B complex: biotin, folate, niacin, pantothentic acid, riboflavin (vitamin B2), thiamin (vitamin B1), vitamin B6 (pyridoxine), and vitamin B12 (cobalamin).

**Fat-soluble vitamins** are vitamins A (retinol), D (cholecalciferol and ergocalciferol), E (α-tocopherol), and K (phyloquinone and menaquinone).

Only vitamins A, E, and B12 are stored to any significant extent in the body; the other vitamins must be consumed regularly to maintain tissue health.

**Essential trace minerals** include chromium, copper, iodine, iron, manganese, molybdenum, selenium, and zinc. Except for chromium, each of these is incorporated into enzymes or hormones required in metabolism. Except for deficiencies of iron and zinc, micromineral deficiencies are uncommon in developed countries (see Ch. 5).

Other minerals (eg, aluminum, arsenic, boron, cobalt, fluoride, nickel, silicon, vanadium) have not been proved essential for people. Fluoride, although not essential, helps prevent tooth decay by forming a compound with Ca (CaF2), which stabilizes the mineral matrix in teeth.

All trace minerals are toxic at high levels, and some (arsenic, nickel, and chromium) may cause cancer.

**Other Dietary Substances**

The daily human diet typically contains as many as 100,000 chemicals (eg, coffee contains 1000). Of these, only 300 are nutrients, only some of which are essential. However, many nonnutrients in foods are useful. For example, food additives (eg, preservatives, emulsifiers, antioxidants, stabilizers) improve the production and stability of foods. Trace components (eg, spices, flavors, odors, colors, phytochemicals, many other natural products) improve appearance and taste.

**Fiber:** Fiber occurs in various forms (eg, cellulose, hemicellulose, pectin, gums). It increases GI motility, prevents constipation, and helps control diverticular disease. Fiber is thought to accelerate the elimination of cancer-causing substances produced by bacteria in the large intestine. Epidemiologic evidence suggests an association between colon cancer and low fiber intake and a beneficial effect of fiber in patients with functional bowel disorders, Crohn's disease, obesity, and hemorrhoids. Soluble fiber (present in fruits, vegetables, oats, barley, and legumes) reduces the postprandial increase in blood glucose and insulin and can reduce cholesterol levels.

The typical Western diet is low in fiber (about 12 g/day) because of a high intake of highly refined wheat flour and a low intake of fruits and vegetables. Increasing fiber intake to about 30 g/day by consuming more vegetables, fruits, and high-fiber cereals and grains is generally recommended. However, very high fiber intake may reduce absorption of certain minerals.

**Nutritional Requirements**

Good nutrition aims to achieve and maintain a desirable body composition and high potential for physical and mental work. Balancing energy intake with energy expenditure is necessary for a desirable body weight. Energy expenditure depends on age, sex, weight (see Table 1-4), and metabolic and physical activity. If energy intake exceeds expenditure, weight is gained. Taking in about 100 calories/day more than needed results in a weight gain of about 4 to 5 kg in a year. If energy intake is less than expenditure, weight is lost.
Daily dietary requirements for essential nutrients also depend on age, sex, weight, and metabolic and physical activity. Every 5 yr, the Food and Nutrition Board of the National Academy of Sciences/National Research Council and the US Department of Agriculture (USDA) issues the dietary reference intakes (DRIs) for protein, energy, and some vitamins and minerals (see Tables 1-4, 4-1, and 5-2). For vitamins and minerals about which less is known, safe and adequate daily dietary intakes are estimated.

Pregnant women (see p. 2608) and infants (see p. 2703) have special nutritional needs.

The USDA publishes the Food Guide Pyramid, which specifies the number of recommended daily servings of various food groups. The recommendations are individualized based on age, sex, and physical activity (see Table 1-5). Generally, the recommended intake decreases with aging because physical activity tends to decrease, resulting in less energy expended. The new Food Guide Pyramid emphasizes the following:

• Increasing consumption of whole grains
• Increasing consumption of vegetables and fruits
• Substituting fat-free or low-fat milk products (or equivalents) for whole-fat milk products
• Reducing consumption of saturated fats and trans fatty acids
• Exercising regularly

Adequate fluid intake is also important.

Fats should constitute ≤ 30% of total calories, and saturated and trans fatty acids should constitute < 10%. Excess intake of saturated fats contributes to atherosclerosis. Substituting polyunsaturated fatty acids for saturated fats can decrease the risk of atherosclerosis. Routine use of nutritional supplements is not necessary or beneficial; some supplements can be harmful. For example, excess vitamin A can lead to hypervitaminosis A, with headaches, osteoporosis, and rash.

Nutrition in Clinical Medicine

Nutritional deficiencies can often worsen health outcomes (whether a disorder is present or not), and some disorders (eg, malabsorption) can cause nutritional deficiencies. Also, many patients (eg, elderly patients during acute hospitalization) have unsuspected nutritional deficiencies that require treatment. Many medical centers have multi-disciplinary nutrition support teams of physicians, nurses, dietitians, and pharmacists to help the clinician prevent, diagnose, and treat occult nutritional deficiencies.

Overnutrition may contribute to chronic disorders, such as cancer, hypertension, obesity, diabetes mellitus, and coronary artery disease. Dietary restrictions are necessary in many hereditary metabolic disorders (eg, galactosemia, phenylketonuria).

Evaluation of Nutritional Status

Indications for nutritional evaluation include undesirable body weight or body composition, suspicion of specific deficiencies or toxicities

[Table 1-5, Recommended Dietary Intake for 40-yr-Olds with Moderate Physical Activity*]

of essential nutrients, and, in infants and children, insufficient growth or development. Nutritional status should be evaluated routinely as part of the clinical examination for infants and children, the elderly, people taking several drugs, people with psychiatric disorders, and people with systemic disorders that last longer than several days.
Evaluating general nutritional status includes history, physical examination, and sometimes tests. If undernutrition is suspected, laboratory tests (eg, albumin levels) and skin tests for delayed hypersensitivity may be done (see p. 13). Body composition analysis (eg, skinfold measurements, bioelectrical impedance analysis) is used to estimate percentage of body fat and to evaluate obesity (see p. 58).

History includes questions about dietary intake, weight change, and risk factors for nutritional deficiencies and a focused review of systems (see Table 2-1 on p. 11). A dietitian can obtain a more detailed dietary history. It usually includes a list of foods eaten within the previous 24 h and a food questionnaire. A food diary may be used to record all foods eaten. The weighed ad libitum diet, in which the patient weighs and writes down all foods consumed, is the most accurate record.

A complete physical examination, including measurement of height and weight and distribution of body fat, should be done. Body mass index (BMI)—weight(kg)/height(m)^2, which adjusts weight for height (see Table 6-2 on p. 59), is more accurate than height and weight tables. There are standards for growth and weight gain in infants, children, and adolescents (see p. 2756).

Distribution of body fat is important. Disproportionate truncal obesity (ie, waist/hip ratio > 0.8) is associated with cardiovascular and cerebrovascular disorders, hypertension, and diabetes mellitus more often than fat located elsewhere. Measuring waist circumference in patients with a BMI of < 35 helps determine whether they have truncal obesity and helps predict risk of diabetes, hypertension, hypercholesterolemia, and cardiovascular disorders. Risk is increased if waist circumference is > 102 cm (> 40 in) in men or > 88 cm (> 35 in) in women.

**Nutrient-Drug Interactions**

Nutrition can affect the body's response to drugs; conversely, drugs can affect the body's nutrition.

Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs. Some foods affect the body's response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

Nutritional deficiencies can affect drug absorption and metabolism. Severe energy and protein deficiencies reduce enzyme tissue concentrations and may impair the response to drugs by reducing absorption or protein binding and causing liver dysfunction. Changes in the GI tract can impair absorption and affect the response to a drug. Deficiency of Ca, Mg, or zinc may impair drug metabolism. Vitamin C deficiency decreases activity of drug-metabolizing enzymes, especially in the elderly.

Many drugs affect appetite, food absorption, and tissue metabolism (see Table 1-6). Some drugs (eg, metoclopramide) increase GI motility, decreasing food absorption. Other drugs (eg, opioids, anticholinergics) decrease GI motility. Some drugs are better tolerated if taken with food.

Certain drugs affect mineral metabolism. For example, diuretics, especially thiazides, and corticosteroids can deplete body K, increasing susceptibility to digoxin-induced cardiac arrhythmias. Repeated use of laxatives may deplete K. Cortisol, desoxycorticosterone, and aldosterone cause marked Na and water retention, at least temporarily; retention is much less with prednisone, prednisolone, and some other corticosteroid analogs. Sulfonylureas and lithium can impair the uptake or release of iodine by the thyroid. Oral contraceptives can lower blood zinc levels and increase copper levels. Certain antibiotics (eg, tetracyclines) reduce iron absorption, as can certain foods (eg, vegetables, tea, bran).

Certain drugs affect vitamin absorption or metabolism. Ethanol impairs thiamin utilization, and isoniazid interferes with niacin and pyridoxine metabolism. Ethanol and oral contraceptives inhibit folate (folic acid)
absorption. Most patients receiving phenytoin, phenobarbital, primidone, or phenothiazines develop folate deficiency, probably because hepatic microsomal drug-metabolizing enzymes are affected. Folate supplements may

[Table 1-6, Effects of Some Drugs on Nutrition]

make phenytoin less effective. Anticonvulsants can cause vitamin D deficiency. Malabsorption of vitamin B₁₂ can occur with use of aminosalicylic acid, slow-release K iodide, colchicine, trifluoperazine, ethanol, and oral contraceptives. Oral contraceptives with a high progestin dose can cause depression, probably because of metabolically induced tryptophan deficiency.

**Food Additives and Contaminants**

**Additives:** Chemicals are often combined with foods to facilitate their processing and preservation or to enhance their desirability. Only amounts of additives shown to be safe by laboratory tests are permitted in commercially prepared foods.

Weighing the benefits of additives (eg, reduced waste, increased variety of available foods, protection against food-borne illness) against the risks is often complex. For example, nitrite, which is used in cured meats, inhibits the growth of *Clostridium botulinum* and improves flavor. However, nitrite converts to nitrosamines, which are carcinogens in animals. On the other hand, the amount of nitrite added to cured meat is small compared with the amount from naturally occurring food nitrates converted to nitrite by the salivary glands. Dietary vitamin C can reduce nitrite formation in the GI tract. Rarely, some additives (eg, sulfites) cause food hypersensitivity (allergy) reactions. Most of these reactions are caused by ordinary foods (see p. 1118).

**Contaminants:** Sometimes limited amounts of contaminants are allowed in foods because the contaminants cannot be completely eliminated without damaging the foods. Common contaminants are pesticides, heavy metals (lead, cadmium, mercury), nitrates (in green leafy vegetables), aflatoxins (in nuts and milk), growth-promoting hormones (in dairy products and meat), animal hairs and feces, and insect parts.

FDA-estimated safe levels are levels that have not caused illness or adverse effects in people. However, demonstrating a causal relationship between extremely low level exposures and adverse effects is difficult; long-term adverse effects, although unlikely, are still possible. Safe levels are often determined by consensus rather than by hard evidence.
Chapter 2. Undernutrition

Introduction

Undernutrition is a form of malnutrition. (Malnutrition also includes overnutrition—see Ch. 6). Undernutrition can result from inadequate ingestion of nutrients, malabsorption, impaired metabolism, loss of nutrients due to diarrhea, or increased nutritional requirements (as occurs in cancer or infection). Undernutrition progresses in stages; each stage usually takes considerable time to develop. First, nutrient levels in blood and tissues change, followed by intracellular changes in biochemical functions and structure. Ultimately, symptoms and signs appear.

Risk Factors

Undernutrition is associated with many disorders and circumstances, including poverty and social deprivation. Risk is also greater at certain times (ie, during infancy, early childhood, adolescence, pregnancy, breastfeeding, and old age).

Infancy and childhood: Infants and children are particularly susceptible to undernutrition because of their high demand for energy and essential nutrients. Because vitamin K does not readily cross the placenta, neonates may be deficient, so all are given a single injection of vitamin K within 1 h of birth to prevent hemorrhagic disease of the newborn, a life-threatening disorder (see pp. 46 and 2783). Infants fed only breast milk, which is typically low in vitamin D, are given supplemental vitamin D; they can develop vitamin B\textsubscript{12} deficiency if the mother is a vegan. Inadequately fed infants and children are at risk of protein-energy undernutrition (PEU—previously called protein-energy malnutrition) and deficiencies of iron, folate (folic acid), vitamins A and C, copper, and zinc. During adolescence, nutritional requirements increase because the growth rate accelerates. Anorexia nervosa (see p. 1535) may affect adolescent girls in particular.

Pregnancy and breastfeeding: Requirements for nutrients increase during pregnancy and breastfeeding. Aberrations of diet, including pica (consumption of nonnutritive substances, such as clay and charcoal), may occur during pregnancy. Anemia due to iron deficiency is common, as is anemia due to folate deficiency, especially among women who have taken oral contraceptives. Vitamin D deficiency is common during late pregnancy, predisposing the child to decreased bone mass.

Old age: Aging—even when disease or dietary deficiency is absent—leads to sarcopenia (progressive loss of lean body mass), starting after age 40 and eventually amounting to a muscle loss of about 10 kg (22 lb) in men and 5 kg (11 lb) in women. Undernutrition contributes to sarcopenia, and sarcopenia accounts for many of the complications of undernutrition (eg, decreased nitrogen balance, increased susceptibility to infections). Causes of sarcopenia include the following:

- Decreased physical activity
- Decreased food intake
- Increased levels of cytokines (particularly interleukin-6)
- Decreased levels of growth hormone and mechano growth factor (insulin-like growth factor-3)
- In men, decreasing androgen levels

Aging decreases basal metabolic rate (due mainly to decreased fat-free mass), total body weight, height, and skeletal mass; aging increases mean body fat (as a percentage of body weight) to about 30\% (from 20\%) in men and to 40\% (from 27\%) in women.

From age 20 to 80, food intake decreases, especially in men. Anorexia due to aging itself has many causes, including reduced adaptive relaxation of the stomach's fundus, increased release and activity of
cholecystokinin (which produces satiation), and increased leptin (an anorectic hormone produced by fat cells). Diminished taste and smell can decrease eating pleasure but usually decrease food intake only slightly. Anorexia may have other causes (eg, loneliness, inability to shop or prepare meals, dementia, some chronic disorders, use of certain drugs). Depression is a common cause. Occasionally, anorexia nervosa (sometimes called anorexia tardive in the elderly), paranoia, or mania interferes with eating. Dental problems limit the ability to chew and subsequently to digest foods. Swallowing difficulties (eg, due to strokes, other neurologic disorders, esophageal candidiasis, or xerostomia) are common. Poverty or functional impairment limits access to nutrients.

The institutionalized elderly are at particular risk of PEU. They are often confused and may be unable to express hunger or preferences for foods. They may be physically unable to feed themselves. Chewing or swallowing may be very slow, making it tedious for another person to feed them enough food.

In the elderly, particularly the institutionalized elderly, inadequate intake and often decreased absorption or synthesis of vitamin D, increased demand for vitamin D, and inadequate exposure to sunshine contribute to osteomalacia (see p. 41).

**Disorders and medical procedures:** Diabetes, some chronic disorders that affect the GI tract, intestinal resection, and certain other GI surgical procedures tend to impair absorption of fat-soluble vitamins, vitamin B\(_{12}\), Ca, and iron. Gluten enteropathy, pancreatic insufficiency, or other disorders can result in malabsorption. Decreased absorption possibly contributes to iron deficiency and osteoporosis. Liver disorders impair storage of vitamins A and B\(_{12}\) and interfere with metabolism of protein and energy sources. Renal insufficiency predisposes to protein, iron, and vitamin D deficiencies. Anorexia causes some patients with cancer or depression and many with AIDS to consume inadequate amounts of food. Infections, trauma, hyperthyroidism, extensive burns, and prolonged fever increase metabolic demands. Any condition that increases cytokines may be accompanied by muscle loss, lipolysis, low albumin levels, and anorexia.

**Vegetarian diets:** Iron deficiency can occur in ovo-lacto vegetarians (although such a diet can be compatible with good health). Vegans may develop vitamin B\(_{12}\) deficiency unless they consume yeast extracts or Asian-style fermented foods. Their intake of Ca, iron, and zinc also tends to be low. A fruit-only diet is not recommended because it is deficient in protein, Na, and many micronutrients.

**Fad diets:** Some fad diets result in vitamin, mineral, and protein deficiencies; cardiac, renal, and metabolic disorders; and sometimes death. Very low calorie diets (< 400 kcal/day) cannot sustain health for long.

**Drugs and nutritional supplements:** Many drugs (eg, appetite suppressants, digoxin) decrease appetite; others impair nutrient absorption or metabolism. Some drugs (eg, stimulants) have catabolic effects. Certain drugs can impair absorption of many nutrients; eg, anticonvulsants can impair absorption of vitamins.

**Alcohol or drug dependency:** Patients with alcohol or drug dependency may neglect their nutritional needs. Absorption and metabolism of nutrients may also be impaired. IV drug addicts typically become undernourished, as do

[Table 2-1. Symptoms and Signs of Nutritional Deficiency]

alcoholics who consume ≥ 1 quart of hard liquor/day. Alcoholism can cause deficiencies of Mg, zinc, and certain vitamins, including thiamin.

**Symptoms and Signs**

Symptoms vary depending on the cause and type of undernutrition (see p. 15 and Chs. 4 and 5).

**Evaluation**
Diagnosis is based on results of medical and diet histories, physical examination, body composition analysis (see p. 58), and selected laboratory tests.

**History:** History should include questions about dietary intake (see Fig. 2-1), recent changes in weight, and risk factors for undernutrition, including drug and alcohol use. Unintentional loss of ≥ 10% of usual body weight during a 3-mo period indicates a high probability of undernutrition. Social history should include questions about whether money is available for food and whether the patient can shop and cook.

Review of systems should focus on symptoms of nutritional deficiencies (see Table 2-1). For example, impaired night vision may indicate vitamin A deficiency.

**Physical examination:** Physical examination should include measurement of height and weight, inspection of body fat distribution, and anthropometric measurements of lean body mass. Body mass index (BMI = weight(kg)/height(m)^2) adjusts weight for height (see Table 6-2 on p. 59). If weight is < 80% of what is predicted for the patient's height or if BMI is ≤ 18, undernutrition should be suspected. Although these findings are useful in diagnosing undernutrition and are acceptably sensitive, they lack specificity.

![Fig. 2-1. Mini nutritional assessment.]

The mid upper arm muscle area estimates lean body mass. This area is derived from the triceps skinfold thickness (TSF) and mid upper arm circumference. Both are measured at the same site, with the patient's right arm in a relaxed position. The average mid upper arm circumference is about 32 ± 5 cm for men and 28 ± 6 cm for women. The formula for calculating the mid upper arm muscle area in cm^2 is as follows:

\[ \frac{\text{midarm circumference (cm)} - (3.14 \times \text{TSF \text{cm}})}{4 \pi} - 10 \text{ (males)} + 6.5 \text{ (females)} \]

This formula corrects the upper arm area for fat and bone. Average values for the mid upper arm muscle area are 54 ± 11 cm^2 for men and 30 ± 7 cm^2 for women. A value < 75% of this standard (depending on age) indicates depletion of lean body mass (see Table 2-2). This measurement may be affected by physical activity, genetic factors, and age-related muscle loss.

Physical examination should focus on signs of specific nutritional deficiencies. Signs of PEU (eg, edema, muscle wasting, skin changes) should be sought. Examination should also focus on signs of conditions that could predispose to nutritional deficiencies, such as dental problems. Mental status should be assessed, because depression and cognitive impairment can lead to weight loss.

The widely used Subjective Global Assessment (SGA) uses information from the patient history (eg, weight loss, change in intake, GI symptoms), physical examination findings (eg, loss of muscle and subcutaneous fat, edema, ascites), and the clinician's judgment of the patient's nutritional status. The Mini Nutritional Assessment (MNA) has been validated and is widely used, especially for elderly patients (see Fig. 2-1). The Simplified Nutrition Assessment Questionnaire (SNAQ), a simple, validated method of predicting future weight loss, may be used (see Fig. 2-2).

**Testing:** The extent of laboratory testing needed is unclear and may depend on the patient's circumstances. If the cause is obvious and correctable (eg, a wilderness survival situation), testing is probably of little benefit. Other patients may require more detailed evaluation.

Serum albumin measurement is the laboratory test most often used. Decreases in albumin and other proteins (eg, prealbumin [transthyretin], transferrin, retinol-binding protein) may indicate protein deficiency or PEU. As undernutrition progresses, albumin decreases slowly; prealbumin, transferrin, and retinol-binding protein decrease rapidly. Albumin measurement is inexpensive and predicts morbidity and
mortality better than measurement of the other proteins. However, the correlation of albumin with morbidity and mortality may be related to nonnutritional as well as nutritional factors. Inflammation produces cytokines that cause albumin and other nutritional protein markers to extravasate, decreasing serum levels. Because prealbumin, transferrin, and retinol-binding protein decrease more rapidly during starvation than does albumin, their measurements are sometimes used to diagnose or assess the severity of acute starvation. However, whether they are more sensitive or specific than albumin is unclear.

Total lymphocyte count, which often decreases as undernutrition progresses, may be determined. Undernutrition causes a marked decline in CD4+ T lymphocytes, so this count may not be useful in patients who have AIDS.

Skin tests using antigens can detect impaired cell-mediated immunity in PEU and in some other disorders of undernutrition (see p. 1098).

Other laboratory tests, such as measuring vitamin and mineral levels, are used selectively to diagnose specific deficiencies.

[Table 2-2. Mid Upper Arm Muscle Area in Adults]

[Figure 2-2. Simplified Nutrition Assessment Questionnaire (SNAQ).]

Protein-Energy Undernutrition

Protein-energy undernutrition (PEU), previously called protein-energy malnutrition, is an energy deficit due to chronic deficiency of all macronutrients. It commonly includes deficiencies of many micronutrients. PEU can be sudden and total (starvation) or gradual. Severity ranges from subclinical deficiencies to obvious wasting (with edema, hair loss, and skin atrophy) to starvation. Multiple organ systems are often impaired. Diagnosis usually involves laboratory testing, including serum albumin. Treatment consists of correcting fluid and electrolyte deficits with IV solutions, then gradually replenishing nutrients, orally if possible.

In developed countries, PEU is common among the institutionalized elderly (although often not suspected) and among patients with disorders that decrease appetite or impair nutrient digestion, absorption, or metabolism. In developing countries, PEU affects children who do not consume enough calories or protein.

Classification and Etiology

PEU is graded as mild, moderate, or severe. Grade is determined by calculating weight as a percentage of expected weight for length or height using international standards (normal, 90 to 110%; mild PEU, 85 to 90%; moderate, 75 to 85%; severe, <75%).

PEU may be primary or secondary. Primary PEU is caused by inadequate nutrient intake. Secondary PEU results from disorders or drugs that interfere with nutrient use.

Primary PEU: Worldwide, primary PEU occurs mostly in children and the elderly who lack access to nutrients, although a common cause in the elderly is depression. PEU can also result from fasting or anorexia nervosa. Child or elder abuse may be a cause.

In children, chronic primary PEU has 2 common forms: marasmus and kwashiorkor. The form depends on the balance of nonprotein and protein sources of energy. Starvation is an acute severe form of primary PEU.

Marasmus (also called the dry form of PEU) causes weight loss and depletion of fat and muscle. In developing countries, marasmus is the most common form of PEU in children.

Kwashiorkor (also called the wet, swollen, or edematous form) is associated with premature abandonment
of breastfeeding, which typically occurs when a younger sibling is born, displacing the older child from the breast. So children with kwashiorkor tend to be older than those with marasmus. Kwashiorkor may also result from an acute illness, often gastroenteritis or another infection (probably secondary to cytokine release), in a child who already has PEU. A diet that is more deficient in protein than energy may be more likely to cause kwashiorkor than marasmus. Less common than marasmus, kwashiorkor tends to be confined to specific parts of the world, such as rural Africa, the Caribbean, and the Pacific islands. In these areas, staple foods (eg, yams, cassavas, sweet potatoes, green bananas) are low in protein and high in carbohydrates. In kwashiorkor, cell membranes leak, causing extravasation of intravascular fluid and protein, resulting in peripheral edema.

Starvation is a complete lack of nutrients. It occasionally occurs when food is available (as in fasting or anorexia nervosa) but usually occurs because food is unavailable (eg, during famine or wilderness exposure).

Secondary PEU: This type most commonly results from the following:

• Disorders that affect GI function: These disorders can interfere with digestion (eg, pancreatic insufficiency), absorption (eg, enteritis, enteropathy), or lymphatic transport of nutrients (eg, retroperitoneal fibrosis, Milroy's disease).

• Wasting disorders: In wasting disorders (eg, AIDS, cancer) and renal failure, catabolism causes cytokine excess, resulting in undernutrition via anorexia and cachexia (wasting of muscle and fat). End-stage heart failure can cause cardiac cachexia, a severe form of undernutrition; mortality rate is particularly high. Factors contributing to cardiac cachexia may include passive hepatic congestion (causing anorexia), edema of the intestinal tract (impairing absorption), and, in advanced disease, increased O2 requirement due to anaerobic metabolism. Wasting disorders can decrease appetite or impair metabolism of nutrients.

• Conditions that increase metabolic demands: These conditions include infections, hyperthyroidism, pheochromocytoma, other endocrine disorders, burns, trauma, surgery, and other critical illnesses.

Pathophysiology

The initial metabolic response is decreased metabolic rate. To supply energy, the body first breaks down adipose tissue. However, later when these tissues are depleted, the body may use protein for energy, resulting in a negative nitrogen balance. Visceral organs and muscle are broken down and decrease in weight. Loss of organ weight is greatest in the liver and intestine, intermediate in the heart and kidneys, and least in the nervous system.

Symptoms and Signs

Symptoms of moderate PEU can be constitutional or involve specific organ systems. Apathy and irritability are common. The patient is weak, and work capacity decreases. Cognition and sometimes consciousness are impaired. Temporary lactose deficiency and achlorhydria develop. Diarrhea is common and can be aggravated by deficiency of intestinal disaccharidases, especially lactase (see p. 157). Gonadal tissues atrophy. PEU can cause amenorrhea in women and loss of libido in men and women.

Wasting of fat and muscle is common in all forms of PEU. In adult volunteers who fasted for 30 to 40 days, weight loss was marked (25% of initial weight). If starvation is more prolonged, weight loss may reach 50% in adults and possibly more in children.

In adults, cachexia is most obvious in areas where prominent fat depots normally exist. Muscles shrink and bones protrude. The skin becomes thin, dry, inelastic, pale, and cold. The hair is dry and falls out easily, becoming sparse. Wound healing is impaired. In elderly patients, risk of hip fractures and pressure (decubitus) ulcers increases.

With acute or chronic severe PEU, heart size and cardiac output decrease; pulse slows
and BP falls. Respiratory rate and vital capacity decrease. Body temperature falls, sometimes contributing to death. Edema, anemia, jaundice, and petechiae can develop. Liver, kidney, or heart failure may occur.

Cell-mediated immunity is impaired, increasing susceptibility to infections. Bacterial infections (eg, pneumonia, gastroenteritis, otitis media, UTIs, sepsis) are common in both forms of PEU. Infections result in release of cytokines, which cause anorexia, worsen muscle wasting, and cause a marked decrease in serum albumin levels.

Marasmus in infants causes hunger, weight loss, growth retardation, and wasting of subcutaneous fat and muscle. Ribs and facial bones appear prominent. Loose, thin skin hangs in folds.

Kwashiorkor is characterized by peripheral and periorbital edema. The abdomen protrudes because abdominal muscles are weakened, the intestine is distended, the liver enlarges, and ascites is present. The skin is dry, thin, and wrinkled; it can become hyperpigmented and fissured and later hypopigmented, friable, and atrophic. Skin in different areas of the body may be affected at different times. The hair can become thin, reddish brown, or gray. Scalp hair falls out easily, eventually becoming sparse, but eyelash hair may grow excessively. Alternating episodes of undernutrition and adequate nutrition may cause the hair to have a dramatic "striped flag" appearance. Affected children may be apathetic but become irritable when held.

Total starvation is fatal in 8 to 12 wk. Thus, certain symptoms of PEU do not have time to develop.

Diagnosis

• Diagnosis usually based on history

• To determine severity: BMI, serum albumin, total lymphocyte count, CD4+ count, serum transferrin

• To diagnose complications and consequences: CBC, electrolytes, BUN, glucose, Ca, Mg, phosphate

Diagnosis can be based on history when dietary intake is markedly inadequate. The cause of inadequate intake, particularly in children, needs to be identified. In children and adolescents, child abuse and anorexia nervosa should be considered.

Physical examination findings can usually confirm the diagnosis. Laboratory tests are required if dietary history does not clearly indicate inadequate caloric intake. Measurement of serum albumin, total lymphocyte count, CD4+ T lymphocytes, transferrin, and response to skin antigens may help determine the severity of PEU (see Table 2-3) or confirm the diagnosis in borderline cases. Many other test results may be abnormal: eg, decreased levels of hormones, vitamins, lipids, cholesterol, prealbumin, insulin growth factor-1, fibronectin, and retinol-binding protein. Urinary creatine and methylhistidine levels can be used to gauge the degree of muscle wasting. Because protein catabolism slows, urinary urea level also decreases. These findings rarely affect treatment.

Laboratory tests are required to identify causes of suspected secondary PEU. C-reactive protein or soluble interleukin-2 receptor should be measured when the cause of undernutrition is unclear; these measurements can help determine whether there is cytokine excess. Thyroid function tests may also be done.

Other laboratory tests can detect associated abnormalities that may require treatment. Serum electrolytes, BUN, glucose, and possibly levels of Ca, Mg, and phosphate should be measured. Levels of serum glucose, electrolytes (especially K, occasionally Na), phosphate, Ca, and Mg are usually low. BUN is often low unless renal failure is present. Metabolic acidosis may be present. CBC is usually obtained; normocytic anemia (usually due to protein deficiency) or microcytic anemia (due to simultaneous iron deficiency) is usually present.
Stool cultures should be obtained and checked for ova and parasites if diarrhea is severe or does not resolve with treatment. Sometimes urinalysis, urine culture, blood cultures, tuberculin testing, and a chest x-ray are used to diagnose occult infections because people with PEU may have a muted response to infections.

**Prognosis**

**Children:** In children, mortality varies from 5 to 40%. Mortality rates are lower in children with mild PEU and those given intensive care. Death in the first days of treatment is usually due to electrolyte deficits, sepsis, hypothermia, or heart failure. Impaired consciousness, jaundice, petechiae, hyponatremia, and persistent diarrhea are ominous signs. Resolution of apathy, edema, and anorexia is a favorable sign. Recovery is more rapid in kwashiorkor than in marasmus.

Long-term effects of PEU in children are not fully documented. Some children develop chronic malabsorption and pancreatic insufficiency. In very young children, mild intellectual disability may develop and persist until at least school age. Permanent cognitive impairment may occur, depending on the duration, severity, and age at onset of PEU.

**Adults:** In adults, PEU can result in morbidity and mortality (eg, progressive weight loss increases mortality rate for elderly patients in nursing homes). In elderly patients, PEU increases the risk of morbidity and mortality due to surgery, infections, or other disorders. Except when organ failure occurs, treatment is uniformly successful.

**Treatment**

- Usually, oral feeding
- Possibly avoidance of lactose (eg, if persistent diarrhea suggests lactose intolerance)
- Supportive care (eg, environmental changes, assistance with feeding, orexigenic drugs)
- For children, feeding delayed 24 to 48 h

Worldwide, the most important preventive strategy is to reduce poverty and improve nutritional education and public health measures.

Mild or moderate PEU, including brief starvation, can be treated by providing a balanced diet, preferably orally. Liquid oral food supplements (usually lactose-free) can be used when solid food cannot be adequately ingested. Diarrhea often complicates oral feeding because starvation makes the GI tract more likely to move bacteria into Peyer's patches, facilitating infectious diarrhea. If diarrhea persists (suggesting lactose intolerance), yogurt-based rather than milk-based formulas are given because people with lactose intolerance can tolerate yogurt. Patients should also be given a multivitamin supplement.

Severe PEU or prolonged starvation requires treatment in a hospital with a controlled diet. The first priority is to correct fluid and electrolyte abnormalities (see Ch. 97) and treat infections. Next is to supply macronutrients orally or, if necessary (eg, when swallowing is difficult), through a feeding tube, a nasogastric tube (usually), or a gastrostomy tube. Parenteral nutrition is indicated if malabsorption is severe (see p. 23).

Other treatments may be needed to correct specific deficiencies, which may become evident as weight increases. To avoid deficiencies, patients should take micronutrients at about twice the recommended daily allowance (RDA) until recovery is complete.

**Children:** Underlying disorders should be treated. For children with diarrhea, feeding may be delayed 24 to 48 h to avoid making the diarrhea worse; during this interval, children require oral or IV rehydration. Feedings are given often (6 to 12 times/day) but, to avoid overwhelming the limited intestinal absorptive capacity, are limited to small amounts (< 100 mL). During the first week, milk-based formulas with supplements added are usually given in progressively increasing amounts; after a week, the full amounts
of 175 kcal/kg and 4 g of protein/kg can be given. Twice the RDA of micronutrients should be given, using commercial multivitamin supplements. After 4 wk, the formula can be replaced with whole milk plus cod liver oil and solid foods, including eggs, fruit, meats, and yeast.

Energy distribution among macronutrients should be about 16% protein, 50% fat, and 34% carbohydrate. An example is a combination of powdered cow's skimmed milk (110 g), sucrose (100 g), vegetable oil (70 g), and water (900 mL). Many other formulas (eg, whole [full-fat] fresh milk plus corn oil and maltodextrin) can be used. Milk powders used in formulas are diluted with water.

Usually, supplements should be added to formulas:

- Mg 0.4 mEq/kg/day IM is given for 7 days.
- B-complex vitamins at twice the RDA are given parenterally for the first 3 days, usually with vitamin A, phosphorus, zinc, manganese, copper, iodine, fluoride, molybdenum, and selenium.
- Because absorption of oral iron is poor in children with PEU, oral or IM iron supplementation may be necessary.

Parents are taught about nutritional requirements.

**Adults:** Underlying disorders should be treated. For example, if AIDS or cancer results in excess cytokine production, megestrol acetate or medroxyprogesterone may improve food intake. However, because these drugs dramatically decrease testosterone in men (possibly causing muscle loss), testosterone should be replaced. Because these drugs can cause adrenal insufficiency, they should be used only short-term (< 3 mo).

In patients with functional limitations, home delivery of meals and feeding assistance are key.

An orexigenic drug, such as the cannabis extract dronabinol, should be given to patients with anorexia when no cause is obvious or to patients at the end of life when anorexia impairs quality of life. An anabolic steroid (eg, enanthate, nandrolone, testosterone) or growth hormone can benefit patients with cachexia due to renal failure and possibly elderly patients (eg, by increasing lean body mass or possibly by improving function).

Correction of PEU in adults generally resembles that in children; feedings are often limited to small amounts. However, for most adults, feeding does not need to be delayed. A commercial formula for oral feeding can be used. Daily nutrient supply should be given at a rate of 60 kcal/kg and 1.2 to 2 g of protein/kg. If liquid oral supplements are used with solid food, they should be given at least 1 h before meals so that the amount of food eaten at the meal is not reduced.

Treatment of institutionalized elderly patients with PEU requires multiple interventions:

- Environmental measures (eg, making the dining area more attractive)
- Feeding assistance
- Changes in diet (eg, use of food enhancers and caloric supplements between meals)
- Treatment of depression and other underlying disorders
- Use of orexigenics, anabolic steroids, or both

The long-term use of gastrostomy tube feeding is essential for patients with severe dysphagia; its use in patients with dementia is controversial. Increasing evidence supports the avoidance of unpalatable therapeutic diets (eg, low salt, diabetic, low cholesterol) in institutionalized patients because these diets decrease food intake and may cause severe PEU.
Complications of treatment: Treatment of PEU can cause complications (refeeding syndrome), including fluid overload, electrolyte deficits, hyperglycemia, cardiac arrhythmias, and diarrhea. Diarrhea is usually mild and resolves; however, diarrhea in patients with severe PEU occasionally causes severe dehydration or death. Causes of diarrhea (eg, sorbitol used in elixir tube feedings, *Clostridium difficile* if the patient has received an antibiotic) may be correctable. Osmotic diarrhea due to excess calories is rare in adults and should be considered only when other causes have been excluded.

Because PEU can impair cardiac and renal function, hydration can cause intravascular volume overload. Treatment decreases extra-cellular K and Mg. Depletion of K or Mg may cause arrhythmias. Carbohydrate metabolism that occurs during treatment stimulates insulin release, which drives phosphate into cells. Hypophosphatemia that occurs during treatment stimulates insulin release, which drives phosphate into cells. Hypophosphatemia can cause muscle weakness, paresthesias, seizures, coma, and arrhythmias. Because phosphate levels can change rapidly during parenteral feeding, levels should be measured regularly.

During treatment, endogenous insulin may become ineffective, leading to hyperglycemia. Dehydration and hyperosmolarity can result. Fatal ventricular arrhythmias can develop, possibly caused by a prolonged QT interval.

Carnitine Deficiency

Carnitine deficiency results from inadequate intake of or inability to metabolize the amino acid carnitine. It can cause a heterogeneous group of disorders. Muscle metabolism is impaired, causing myopathy, hypoglycemia, or cardiomyopathy. Infants typically present with hypoglycemic, hypoketotic encephalopathy. Most often, treatment consists of dietary L-carnitine.

The amino acid carnitine is required for the transport of long-chain fatty acyl coenzyme A (CoA) esters into myocyte mitochondria, where they are oxidized for energy. Carnitine is obtained from foods, particularly animal-based foods, and via endogenous synthesis.

Causes of carnitine deficiency include the following:

• Inadequate intake (eg, due to fad diets, lack of access, or long-term TPN)

• Inability to metabolize carnitine due to enzyme deficiencies (eg, carnitine palmitoyltransferase deficiency, methylmalonic aciduria, propionic acidemia, isovaleric acidemia)

• Decreased endogenous synthesis of carnitine due to a severe liver disorder

• Excess loss of carnitine due to diarrhea, diuresis, or hemodialysis

• A hereditary disorder in which carnitine leaks from renal tubules

• Increased requirements for carnitine when ketosis is present or demand for fat oxidation is high (eg, during a critical illness such as sepsis or major burns; after major surgery of the GI tract)

• Decreased muscle carnitine levels due to mitochondrial impairment (eg, due to use of zidovudine)

• Use of valproate

The deficiency may be generalized (systemic) or may affect mainly muscle (myopathic).

Symptoms and Signs

Symptoms and the age at which symptoms appear depend on the cause. Carnitine deficiency may cause muscle necrosis, myoglobinuria, lipid-storage myopathy, hypoglycemia, fatty liver, and hyperammonemia with muscle aches, fatigue, confusion, and cardiomyopathy.
Diagnosis

In neonates, carnitine palmitoyltransferase deficiency is diagnosed using mass spectrometry to screen blood. Prenatal diagnosis may be possible using amniotic villous cells. In adults, the definitive diagnosis is based on acylcarnitine levels in serum, urine, and tissues (muscle and liver for systemic deficiency; muscle only for myopathic deficiency).

Treatment

• Avoidance of fasting and strenuous exercise

• Dietary interventions, based on cause

Carnitine deficiency due to inadequate dietary intake, increased requirements, excess losses, decreased synthesis, or (sometimes) enzyme deficiencies can be treated by giving L-carnitine 25 mg/kg po q 6 h.

All patients must avoid fasting and strenuous exercise. Consuming uncooked cornstarch at bedtime prevents early morning hypoglycemia. Some patients require supplementation with medium-chain triglycerides and essential fatty acids (eg, linoleic acid, linolenic acid). Patients with a fatty acid oxidation disorder require a high-carbohydrate, low-fat diet.

Essential Fatty Acid Deficiency

Essential fatty acid (EFA) deficiency is rare, occurring most often in infants fed diets deficient in EFAs. Signs include scaly dermatitis, alopecia, thrombocytopenia, and, in children, growth retardation. Diagnosis is clinical. Dietary replenishment of EFAs reverses the deficiency.

The EFAs linoleic and linolenic acid are substrates for the endogenous synthesis of other fatty acids that are needed for many physiologic processes, including maintaining the integrity of skin and cell membranes and synthesizing prostaglandins and leukotrienes. For example, eicosapentaenoic acid and docosahexaenoic acid, synthesized from EFAs, are important components of the brain and retina.

For EFA deficiency to develop, dietary intake must be very low. Even small amounts of EFAs can prevent EFA deficiency. Cow's milk has only about 25% of the linoleic acid in human milk, but when ingested in normal amounts, it has enough linoleic acid to prevent EFA deficiency. Total fat intake of people in many developing countries may be very low, but the fat is often vegetable based, with large amounts of linoleic acid and enough linolenic acid to prevent EFA deficiency.

Babies fed a formula low in linoleic acid, such as a skim-milk formula, can develop EFA deficiency. EFA deficiency used to result from long-term TPN if fat was not included. But now, most TPN solutions include fat emulsions to prevent EFA deficiency. In patients with fat malabsorption or increased metabolic needs (eg, because of surgery, multiple trauma, or burns), laboratory evidence of EFA deficiency may be present without clinical signs.

Dermatitis due to EFA deficiency is generalized and scaly; in infants, it can resemble congenital ichthyosis. The dermatitis increases water loss from the skin.

Diagnosis is usually clinical; however, laboratory assays are now available in large research centers.

Treatment consists of dietary EFAs, reversing the deficiency.
Chapter 3. Nutritional Support

Introduction

Many undernourished patients need nutritional support, which aims to increase lean body mass. Oral feeding can be difficult for some patients with anorexia or with eating or absorption problems. Behavioral measures that sometimes enhance oral intake include the following:

- Encouraging patients to eat
- Heating or seasoning foods
- Providing favorite or strongly flavored foods
- Encouraging patients to eat small portions
- Scheduling around meals
- Assisting patients with feeding

If behavioral measures are ineffective, nutritional support—oral, enteral tube, or parenteral nutrition—is indicated, except sometimes for dying or severely demented patients (see p. 25).

Predicting Nutritional Requirements

Nutritional requirements are predicted so that interventions can be planned. Requirements can be estimated by formulas or measured by indirect calorimetry. Indirect calorimetry requires use of a metabolic cart (a closed rebreathing system that determines energy expenditure based on total CO2 production), which requires special expertise and is not always available. Thus, total energy expenditure (TEE) and protein requirements usually are estimated.

Energy expenditure: TEE varies based on the patient's weight, activity level, and degree of metabolic stress (metabolic demands); TEE ranges from 25 kcal/kg/day for people who are sedentary and not under stress to about 40 kcal/kg/day for people who are critically ill. TEE equals the sum of

- Resting metabolic rate (RMR, or resting energy expenditure rate), which is normally about 70% of TEE
- Energy dissipated by metabolism of food (10% of TEE)
- Energy expended during physical activity (20% of TEE)

Undernutrition can decrease RMR up to 20%. Conditions that increase metabolic stress (eg, critical illness, infection, inflammation, trauma, surgery) can increase RMR but rarely by > 50%.

The Mifflin-St. Jeor equation estimates RMR more precisely and with fewer errors than the commonly used Harris-Benedict equation, usually providing results that are within 20% of those measured by indirect calorimetry. The Mifflin-St. Jeor equation estimates RMR as follows:

Men: kcal / day = 66 + (13.7 × wt[kg]) + (5 × height[cm]) - (6.8 × age)
Women: kcal / day = 665 + (9.6 × wt[kg]) + (1.8 × height[cm]) - (4.7 × age)

TEE can be estimated by adding about 10% (for sedentary people) to about 40% (for people who are critically ill) to RMR.

Protein requirements: For healthy people, protein requirements are estimated at 0.8 g/kg/day. However, for patients with metabolic stress or kidney failure and for elderly patients, requirements may be higher (see...
Assessing Response to Nutritional Support

There is no gold standard to assess response. Clinicians commonly use indicators of lean body mass such as the following:

- Body mass index (BMI)
- Body composition analysis
- Body fat distribution (see pp. 11 and 58)

Nitrogen balance, response to skin antigens, muscle strength measurement, and indirect calorimetry can also be used.

**Table 3-1. Estimated Adult Daily Protein Requirement**

**Nitrogen balance**, which reflects the balance between protein needs and supplies, is the difference between amount of nitrogen ingested and amount lost. A positive balance (ie, more ingested than lost) implies adequate intake. Precise measurement is impractical, but estimates help assess response to nutritional support. Nitrogen intake is estimated from protein intake: nitrogen (g) equals protein (g)/6.25. Estimated nitrogen losses consist of urinary nitrogen losses (estimated by measuring urea nitrogen content of an accurately obtained 24-h urine collection) plus stool losses (estimated at 1 g/day if stool is produced; negligible if stool is not produced) plus insensible and other unmeasured losses (estimated at 3 g).

**Response to skin antigens**, a measure of delayed hypersensitivity, often increases to normal as undernourished patients respond to nutritional support. However, other factors can affect response to skin antigens.

**Muscle strength** indirectly reflects increases in lean body mass. It can be measured quantitatively, by hand-grip dynamometry, or electrophysiologically (typically by stimulating the ulnar nerve with an electrode).

**Levels of acute-phase reactant** serum proteins (particularly short-lived proteins such as prealbumin [transthyretin], retinol-binding protein, and transferrin) sometimes correlate with improved nutritional status, but these levels correlate better with inflammatory conditions.

**Enteral Tube Nutrition**

Enteral tube nutrition is indicated for patients who have a functioning GI tract but cannot ingest enough nutrients orally because they are unable or unwilling to take oral feedings. Compared with parenteral nutrition, enteral nutrition has the following advantages:

- Better preservation of the structure and function of the GI tract
- Lower cost
- Probably fewer complications, particularly infections

**Specific indications** for enteral nutrition include the following:

- Prolonged anorexia
- Severe protein-energy undernutrition
• Coma or depressed sensorium
• Liver failure
• Inability to take oral feedings due to head or neck trauma or neurologic disorders
• Critical illnesses (eg, burns) causing metabolic stress

Other indications may include bowel preparation for surgery in seriously ill or undernourished patients, closure of enterocutaneous fistulas, and small-bowel adaptation after massive intestinal resection or in disorders that may cause malabsorption (eg, Crohn's disease).

**Procedure:** If tube feeding is needed for ≤ 4 to 6 wk, a small-caliber, soft nasogastric or nasoenteric (eg, nasoduodenal) tube made of silicone or polyurethane is usually used. If a nasal injury or deformity makes nasal placement difficult, an orogastric or other oroenteric tube can be placed.

Tube feeding for > 4 to 6 wk usually requires a gastrostomy or jejunostomy tube, placed endoscopically, surgically, or radiologically. Choice depends on physician capabilities and patient preference.

Jejunostomy tubes are useful for patients with contraindications to gastrostomy (eg, gastrectomy, bowel obstruction proximal to the jejunum). However, these tubes do not pose less risk of tracheobronchial aspiration than gastrostomy tubes, as is often thought. Jejunostomy tubes are easily dislodged and are usually used only for inpatients.

Feeding tubes are surgically placed if endoscopic and radiologic placement is unavailable, technically impossible, or unsafe (eg, because of overlying bowel). Open or laparoscopic techniques can be used.

**Formulas:** Liquid formulas commonly used include feeding modules and polymeric or other specialized formulas.

**Feeding modules** are commercially available products that contain a single nutrient, such as proteins, fats, or carbohydrates. Feeding modules may be used individually to treat a specific deficiency or combined with other formulas to completely satisfy nutritional requirements.

**Polymeric formulas** (including blenderized food and milk-based or lactose-free commercial formulas) are commercially available and generally provide a complete, balanced diet. For oral or tube feedings, they are usually preferred to feeding modules. In hospitalized patients, lactose-free formulas are the most commonly used polymeric formulas. However, milk-based formulas tend to taste better than lactose-free formulas. Patients with lactose intolerance may be able to tolerate milk-based formulas given slowly by continuous infusion.

**Specialized formulas** include hydrolyzed protein or sometimes amino acid formulas, which are used for patients who have difficulty digesting complex proteins. However, these formulas are expensive and usually unnecessary. Most patients with pancreatic insufficiency, if given enzymes, and most patients with malabsorption can digest complex proteins. Other specialized formulas (eg, calorie- and protein-dense formulas for patients whose fluids are restricted, fiber-enriched formulas for constipated patients) may be helpful.

**Administration:** Patients should be sitting upright at 30 to 45° during tube feeding and for 1 to 2 h afterward to minimize incidence of nosocomial aspiration pneumonia and to allow gravity to help propel the food. Tube feedings are given in boluses several times a day or by continuous infusion. Bolus feeding is more physiologic and may be preferred for patients with diabetes. Continuous infusion is necessary if boluses cause nausea.

[Table 3-2, Complications of Enteral Tube Nutrition]

For bolus feeding, total daily volume is divided into 4 to 6 separate feedings, which are injected through
the tube with a syringe or infused by gravity from an elevated bag. After feedings, the tube is flushed with water to prevent clogging.

**Nasogastric or nasoduodenal tube feeding** often causes diarrhea initially; thus, feedings are usually started with small amounts of dilute preparations and increased as tolerated. Most formulas contain 0.5, 1, or 2 kcal/mL. Formulas with higher caloric concentration (less water per calorie) may cause decreased gastric emptying and thus higher gastric residuals than when more dilute formulas with the same number of calories are used. Initially, a 1-kcal/mL commercially prepared solution may be given undiluted at 50 mL/h or, if patients have not been fed for a while, at 25 mL/h. Usually, these solutions do not supply enough water, particularly if vomiting, diarrhea, sweating, or fever has increased water loss. Extra water is supplied as boluses via the feeding tube or IV. After a few days, the rate or concentration can be increased as needed to meet caloric and water needs.

**Jejunostomy tube feeding** requires greater dilution and smaller volumes. Feeding usually begins at a concentration of ≤ 0.5 kcal/mL and a rate of 25 mL/h. After a few days, concentrations and volumes can be increased to eventually meet caloric and water needs. Usually, the maximum that can be tolerated is 0.8 kcal/mL at 125 mL/h, providing 2400 kcal/day.

**Complications:** Complications are common and can be serious (see Table 3-2).

**Total Parenteral Nutrition**

Parenteral nutrition is by definition given IV.

Partial parenteral nutrition supplies only part of daily nutritional requirements, supplementing oral intake. Many hospitalized patients are given dextrose or amino acid solutions by this method.

**Total parenteral nutrition** (TPN) supplies all daily nutritional requirements. TPN can be used in the hospital or at home. Because TPN solutions are concentrated and can cause thrombosis of peripheral veins, a central venous catheter is usually required.

Parenteral nutrition should not be used routinely in patients with an intact GI tract. Compared with enteral nutrition, it causes more complications, does not preserve GI tract structure and function as well, and is more expensive.

**Indications:** TPN may be the only feasible option for patients who do not have a functioning GI tract or who have disorders requiring complete bowel rest, such as the following:

- Some stages of Crohn's disease or ulcerative colitis
- Bowel obstruction
- Certain pediatric GI disorders (eg, congenital GI anomalies, prolonged diarrhea regardless of its cause)
- Short bowel syndrome due to surgery

**Nutritional content:** TPN requires water (30 to 40 mL/kg/day), energy (30 to 60 kcal/kg/day, depending on energy expenditure), amino acids (1 to 2.0 g/kg/day, depending on the degree of catabolism), essential fatty acids, vitamins, and minerals (see Table 3-3). Children who need TPN may have different fluid requirements and need more energy (up to 120 kcal/kg/day) and amino acids (up to 2.5 or 3.5 g/kg/day).

Basic TPN solutions are prepared using sterile techniques, usually in liter batches according to standard formulas. Normally, 2 L/day of the standard solution is needed. Solutions may be modified based on laboratory results, underlying disorders, hypermetabolism, or other factors.

Most calories are supplied as carbohydrate. Typically, about 4 to 5 mg/kg/day of dextrose is given. Standard solutions contain up to about 25% dextrose, but the amount and concentration depend on other
factors, such as metabolic needs and the proportion of caloric needs that are supplied by lipids. Commercially available lipid emulsions are often added to supply essential fatty acids and triglycerides; 20 to 30% of total calories are usually supplied as lipids. However, withholding lipids and their calories may help obese patients mobilize endogenous fat stores, increasing insulin sensitivity.

**Solutions:** Many solutions are commonly used. Electrolytes can be added to meet the patient's needs. Solutions vary depending on other disorders present and patient age, as for the following:

- For renal insufficiency not being treated with dialysis or for liver failure: Reduced protein content and a high percentage of essential amino acids
- For heart or kidney failure: Limited volume (liquid) intake
- For respiratory failure: A lipid emulsion that provides most of nonprotein calories to minimize CO₂ production by carbohydrate metabolism
- For neonates: Lower dextrose concentrations (17 to 18%)

**Beginning TPN administration:** Because the central venous catheter needs to remain in place for a long time, strict sterile technique must be used during insertion and maintenance. The TPN line should not be used for any other purpose. External tubing should be changed every 24 h with the first bag of the day. In-line filters have not been shown to decrease complications. Dressings should be kept sterile and are usually changed every 48 h using strict sterile techniques. If TPN is given outside the hospital, patients must be taught to recognize symptoms of infection, and qualified home nursing must be arranged.

The solution is started slowly at 50% of the calculated requirements, using 5% dextrose to make up the balance of fluid requirements. Energy and nitrogen should be given simultaneously. The amount of regular insulin given (added directly to the TPN solution) depends on the plasma glucose level; if the level is normal and the final solution contains 25% dextrose, the usual starting dose is 5 to 10 units of regular insulin/L of TPN fluid.

**Monitoring:** Progress should be followed on a flowchart. An interdisciplinary nutrition team, if available, should monitor patients. Weight, CBC, electrolytes, and BUN should be monitored often (eg, daily for inpatients). Plasma glucose should be monitored every 6 h until patients and glucose levels become stable. Fluid intake and output should be monitored continuously. When patients become stable, blood tests can be done much less often.

Liver function tests should be done. Plasma proteins (eg, serum albumin, possibly transthyretin or retinol-binding protein), PT, plasma and urine osmolality, and Ca, Mg, and phosphate should be measured twice/wk. Changes in transthyretin and retinol-binding protein reflect overall clinical status rather than nutritional status alone. If possible, blood tests should not be done during glucose infusion. Full nutritional assessment (including BMI calculation and anthropometric measurements—see pp. 11 and 58) should be repeated at 2-wk intervals.

**Complications:** About 5 to 10% of patients have complications related to central venous access.

**Table 3-3. Basic Adult Daily Requirements for Total Parenteral Nutrition**

Catheter-related sepsis occurs in about ≥ 50% of patients. Glucose abnormalities (hyperglycemia or hypoglycemia) or liver dysfunction occurs in > 90% of patients.

**Glucose abnormalities** are common. Hyperglycemia can be avoided by monitoring plasma glucose often, adjusting the insulin dose in the TPN solution and giving subcutaneous insulin as needed. Hypoglycemia can be precipitated by suddenly stopping constant concentrated dextrose infusions. Treatment depends on the degree of hypoglycemia. Short-term hypoglycemia may be reversed with 50% dextrose IV; more prolonged hypoglycemia may require infusion of 5 or 10% dextrose for 24 h before
resuming TPN via the central venous catheter.

**Hepatic complications** include liver dysfunction, painful hepatomegaly, and hyperammonemia. They can develop at any age but are most common among infants, particularly premature ones (whose liver is immature).

• Liver dysfunction may be transient, evidenced by increased transaminases, bilirubin, and alkaline phosphatase; it commonly occurs when TPN is started. Delayed or persistent elevations may result from excess amino acids. Pathogenesis is unknown, but cholestasis and inflammation may contribute. Progressive fibrosis occasionally develops. Reducing protein delivery may help.

• Painful hepatomegaly suggests fat accumulation; carbohydrate delivery should be reduced.

• Hyperammonemia can develop in infants, causing lethargy, twitching, and generalized seizures. Arginine supplementation at 0.5 to 1.0 mmol/kg/day can correct it.

If infants develop any hepatic complication, limiting amino acids to 1.0 g/kg/day may be necessary.

**Abnormalities of serum electrolytes and minerals** should be corrected by modifying subsequent infusions or, if correction is urgently required, by beginning appropriate peripheral vein infusions. Vitamin and mineral deficiencies are rare when solutions are given correctly. Elevated BUN may reflect dehydration, which can be corrected by giving free water as 5% dextrose via a peripheral vein.

**Volume overload** (suggested by > 1 kg/day weight gain) may occur when patients have high daily energy requirements and thus require large fluid volumes.

**Metabolic bone disease**, or bone demineralization (osteoporosis or osteomalacia), develops in some patients given TPN for > 3 mo. The mechanism is unknown. Advanced disease can cause severe periarticular, lower-extremity, and back pain. Temporarily or permanently stopping TPN is the only known treatment.

**Adverse reactions to lipid emulsions** (eg, dyspnea, cutaneous allergic reactions, nausea, headache, back pain, sweating, dizziness) are uncommon but may occur early, particularly if lipids are given at > 1.0 kcal/kg/h. Temporary hyperlipidemia may occur, particularly in patients with kidney or liver failure; treatment is usually not required. Delayed adverse reactions to lipid emulsions include hepatomegaly, mild elevation of liver enzymes, splenomegaly, thrombocytopenia, leukopenia, and, especially in premature infants with respiratory distress syndrome, pulmonary function abnormalities. Temporarily or permanently slowing or stopping lipid emulsion infusion may prevent or minimize these adverse reactions.

**Gallbladder complications** include cholelithiasis, gallbladder sludge, and cholecystitis. These complications can be caused or worsened by prolonged gallbladder stasis. Stimulating contraction by providing about 20 to 30% of calories as fat and stopping glucose infusion several hours a day is helpful. Oral or enteral intake also helps. Treatment with metronidazole, ursodeoxycholic acid, phenobarbital, or cholecystokinin helps some patients with cholestasis.

**Nutritional Support for Dying or Severely Demented Patients**

Anorexia or loss of appetite is common among dying patients (see p. 3485). Behavioral measures (eg, using flexible feeding schedules, feeding slowly, giving small portions or favorite or strongly flavored foods) can often increase oral intake. A small amount of a favorite alcoholic drink, given 30 min before meals, may also help. Certain antidepressants, megestrol acetate, and dronabinol may stimulate appetite. Metoclopramide enhances gastric emptying, but it may take 1 to 2 wk to reach peak effectiveness.

Advanced dementia eventually leads to inability to eat; sometimes affected patients are given tube feedings. However, there is no convincing evidence that tube feedings prolong life, provide comfort, improve function, or prevent complications (eg, aspiration, pressure ulcers).

Tube feedings and parenteral nutrition cause discomfort and are usually not indicated for patients who
are dying or too demented to eat. Forgoing nutritional support may be difficult for family members to accept, but they should understand that patients are usually more comfortable eating and drinking as they choose. Sips of water and easy-to-swallow foods may be useful. Supportive care, including good oral hygiene (eg, brushing the teeth, moistening the oral cavity with swabs and ice chips as needed, applying lip salve), can physically and psychologically comfort the patients and the family members who provide the care.

Counseling may help family members who are dealing with anxieties about whether to use invasive nutritional support.
Chapter 4. Vitamin Deficiency, Dependency, and Toxicity

Introduction

Vitamins may be fat soluble (vitamins A, D, E, and K) or water soluble (B vitamins and vitamin C). The B vitamins include biotin, folate, niacin, pantothenic acid, riboflavin (B<sub>2</sub>), thiamin (B<sub>1</sub>), B<sub>6</sub> (eg, pyridoxine), and B<sub>12</sub> (cobalamins). For dietary requirements, sources, functions, effects of deficiencies and toxicities, blood levels, and usual therapeutic dosages for vitamins, see Tables 4-1 and 4-2.

Dietary requirements for vitamins (and other nutrients) are expressed as daily recommended intake (DRI). There are 3 types of DRI:

• **Recommended daily allowance (RDA):** RDAs are set to meet the needs of 97 to 98% of healthy people.

• **Adequate intake (AI):** When data to calculate an RDA are insufficient, AIs are based on observed or experimentally determined estimates of nutrient intake by healthy people.

• **Tolerable upper intake level (UL):** ULs are the largest amount of a nutrient that most adults can ingest daily without risk of adverse health effects.

In developed countries, vitamin deficiencies result mainly from poverty, food faddism, drugs (see p. 7 and Table 4-3), alcoholism, or prolonged and inadequately supplemented parenteral feeding. Mild vitamin deficiency is common among frail and institutionalized elderly people who have protein-energy undernutrition. In developing countries, deficiencies can result from lack of access to nutrients.

Deficiencies of water-soluble vitamins (except vitamin B<sub>12</sub>) may develop after weeks to months of undernutrition. Deficiencies of fat-soluble vitamins and vitamin B<sub>12</sub> take > 1 yr to develop because the body stores them in relatively large amounts. Intake of vitamins sufficient to prevent classic vitamin deficiencies (like scurvy or beriberi) may not be adequate for optimum health. This area remains one of controversy and active research.

Vitamin dependency results from a genetic defect involving metabolism of a vitamin. In some cases, vitamin doses as high as 1000 times the DRI improve function of the altered metabolic pathway. Vitamin toxicity (hypervitaminosis) usually results from taking megadoses of vitamin A, D, C, B<sub>6</sub>, or niacin.

Because many people eat irregularly, foods alone may provide suboptimal amounts of some vitamins. In these cases, the risk of certain cancers or other disorders may be increased. Because of this risk, routine daily multivitamin supplements are sometimes recommended.

**Biotin and Pantothenic Acid**

Biotin acts as a coenzyme for carboxylation reactions essential to fat and carbohydrate metabolism. Adequate intake for adults is 30 μg/day. Pantothenic acid is widely distributed in foods; it is an essential component of coenzyme A. Adults probably require about 5 mg/day. A beneficial role for pantothenic acid supplementation in lipid metabolism, RA, or athletic performance remains unproved. Isolated deficiency of biotin or pantothenic acid virtually never occurs.

**Folate**

Folate (folic acid) is now added to enriched grain foods in the US. Folate is also plentiful in various plant foods and meats, but its bioavailability is greater when it is in supplements

[Table 4-1. Recommended Daily Intakes for Vitamins] or enriched foods than when it occurs naturally in food.
Folates are involved in RBC maturation and synthesis of purines and pyrimidines. They are required for development of the fetal nervous system. Absorption occurs in the duodenum and upper jejunum. Enterohepatic circulation of folate occurs. Folate supplements do not protect against coronary artery disease or stroke (by lowering homocysteine levels); their role in reducing the risk of various cancers is unclear. The upper limit for folate intake is 1000 μg; higher doses (up to 5 mg) are recommended for women who have had a baby with a neural tube defect. Folate is essentially nontoxic.

**Folate Deficiency**

Folate deficiency is common. It may result from inadequate intake, malabsorption, or use of various drugs. Deficiency causes megaloblastic anemia (indistinguishable from that due to vitamin B₁₂ deficiency). Maternal deficiency increases the risk of neural tube birth defects. Diagnosis requires laboratory testing to confirm. Measurement of neutrophil hypersegmentation is sensitive and readily available. Treatment with oral folate is usually successful.

**Etiology and Pathophysiology**

The most common causes are inadequate intake (usually in patients with undernutrition or alcoholism), increased demand (eg, due to pregnancy or breastfeeding), and impaired absorption (eg, in tropical sprue, due to certain drugs). Deficiency can also result from inadequate bioavailability and increased excretion (see Table 4-4).

Prolonged cooking destroys folate, predisposing to inadequate intake. Intake is sometimes barely adequate (eg, in alcoholics). Liver stores provide only a several-month supply.

Alcohol interferes with folate absorption, metabolism, renal excretion, and enterohepatic reabsorption, as well as intake. 5-Fluorouracil, metformin, methotrexate, phenobarbital, phenytoin, sulfasalazine, triamterene, and trimethoprim impair folate metabolism.

In the US, many dietary staples (eg, cereals, grain products) are routinely enriched with folate, tending to reduce risk of deficiency.

**Symptoms and Signs**

Folate deficiency may cause glossitis, diarrhea, depression, and confusion. Anemia may develop insidiously and, because of compensatory mechanisms, be more severe than symptoms suggest.

Folate deficiency during pregnancy increases the risk of fetal neural tube defects and perhaps other brain defects (see p. 2992).

**Diagnosis**

- CBC and serum vitamin B₁₂ and folate levels

CBC may indicate megaloblastic anemia indistinguishable from that of vitamin B₁₂ deficiency. If serum folate is < 3 μg/L or ng/mL (< 7 nmol/L), deficiency is likely. Serum folate reflects folate status unless intake has recently increased or decreased. If intake has changed, erythrocyte (RBC) folate level better reflects tissue stores. A level of < 140 μg/L or ng/mL (< 305 nmol/L) indicates inadequate status. Also, an increase in the homocysteine level suggests tissue folate deficiency (but the level is also affected by...
vitamin B\textsubscript{12} and vitamin B\textsubscript{6} levels, renal insufficiency, and genetic factors). A normal methylmalonic acid (MMA) level may differentiate folate deficiency from vitamin B\textsubscript{12} deficiency because MMA levels rise in vitamin B\textsubscript{12} deficiency but not in folate deficiency.

**Treatment**

- **Supplemental oral folate**

  Folate 400 to 1000 \(\mu g\) po once/day replenishes tissues and is usually successful even if deficiency has resulted from malabsorption. The normal requirement is 400 \(\mu g\)/day.

  **Table 4-4. Causes of Folate Deficiency**

  (CAUTION: *In patients with megaloblastic anemia, vitamin B\textsubscript{12} deficiency must be ruled out before treating with folate. If vitamin B\textsubscript{12} deficiency is present, folate supplementation can alleviate the anemia but does not reverse and may even worsen neurologic deficits.*) For pregnant women, the recommended daily allowance (RDA) is 600 \(\mu g\)/day. For women who have had a fetus or infant with a neural tube defect, the recommended dose is 1000 to 5000 \(\mu g\)/day.

**Niacin**

Niacin (nicotinic acid, nicotinamide) derivatives include nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are coenzymes in oxidation-reduction reactions. They are vital in cell metabolism. Because dietary tryptophan can be metabolized to niacin, foods rich in tryptophan (eg, dairy products) can compensate for inadequate dietary niacin.

**Niacin Deficiency**

**Dietary niacin deficiency (causing pellagra) is uncommon in developed countries. Clinical manifestations include the "three Ds": localized pigmented rash (dermatitis); gastroenteritis (diarrhea); and widespread neurologic deficits, including cognitive decline (dementia). Diagnosis is usually clinical, and dietary supplementation (oral or, if needed, IM) is usually successful.**

**Etiology**

Primary deficiency results from extremely inadequate intake of both niacin and tryptophan, which usually occurs in areas where maize (Indian corn) constitutes a substantial part of the diet. Bound niacin, found in maize, is not assimilated in the GI tract unless it has been previously treated with alkali, as when tortillas are prepared. Corn protein is also deficient in tryptophan. The high incidence of pellagra in India among people who eat millet with a high leucine content has led to the hypothesis that amino acid imbalance may contribute to deficiency. Deficiencies of protein and many B vitamins commonly accompany primary niacin deficiency.

Secondary deficiency may be due to diarrhea, cirrhosis, or alcoholism. Pellagra also may occur in carcinoid syndrome (tryptophan is diverted to form 5-hydroxytryptophan and serotonin) and in Hartnup disease (absorption of tryptophan by the intestine and kidneys is defective).

**Symptoms and Signs**

Pellagra is characterized by skin, mucous membrane, CNS, and GI symptoms. Advanced pellagra can cause a symmetric photosensitive rash, stomatitis, glossitis, diarrhea, and mental aberrations. Symptoms may appear alone or in combination.

**Skin symptoms** include several types of lesions, which are usually bilaterally symmetric. The distribution of lesions—at pressure points or sun-exposed skin—is more pathognomonic than the form of the lesions. Lesions can develop in a glovelike distribution on the hands (pellagrous glove) or in a boot-shaped
distribution on the feet and legs (pellagrous boot). Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

**Mucous membrane symptoms** affect primarily the mouth but may also affect the vagina and urethra. Glossitis and stomatitis characterize acute deficiency. As the deficiency progresses, the tongue and oral mucous membranes become reddened, followed by pain in the mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth.

**GI symptoms** early in the deficiency include burning in the pharynx and esophagus and abdominal discomfort and distention. Constipation is common. Later, nausea, vomiting, and diarrhea may occur. Diarrhea is often bloody because of bowel hyperemia and ulceration.

**CNS symptoms** include psychosis, encephalopathy (characterized by impaired consciousness), and cognitive decline (dementia). Psychosis is characterized by memory impairment, disorientation, confusion, and confabulation; the predominant symptom may be excitement, depression, mania, delirium, or paranoia.

**Diagnosis**

- **Clinical evaluation**

Diagnosis is clinical and may be straightforward when skin and mouth lesions, diarrhea, delirium, and dementia occur simultaneously. More often, the presentation is not so specific. Differentiating the CNS changes from those in thiamin deficiency is difficult. A history of a diet lacking niacin and tryptophan may help establish the diagnosis. A favorable response to treatment with niacin can usually confirm it. If available, laboratory testing can help confirm the diagnosis, particularly when the diagnosis is otherwise unclear. Urinary excretion of N1-methylnicotinamide (NMN) is decreased; < 0.8 mg/day (< 5.8 μmol/day) suggests a niacin deficiency.

**Treatment**

- **Nicotinamide and other nutrients**

Because multiple deficiencies are common, a balanced diet, including other B vitamins (particularly riboflavin and pyridoxine), is needed. Nicotinamide is usually used to treat deficiency, because nicotinamide, unlike nicotinic acid (the most common form of niacin), does not cause flushing, itching, burning, or tingling sensations. Nicotinamide is given in doses ranging from 40 to 250 mg/day po in divided doses 3 to 4 times a day.

**Niacin Toxicity**

Niacin (nicotinic acid) in large amounts is sometimes used to lower low-density lipoprotein (LDL) cholesterol and triglyceride levels and to increase high-density lipoprotein (HDL) cholesterol levels. Symptoms may include flushing and, rarely, hepatotoxicity.

Immediate- and sustained-release preparations of niacin (but not nicotinamide) may improve lipid levels. Flushing, which is prostaglandin-mediated, is more common with immediate-release preparations. It may be more intense after alcohol ingestion, aerobic activity, sun exposure, and consumption of spicy foods. Flushing is minimized if niacin is taken after meals or if aspirin (325 mg) is taken 30 to 45 min before niacin. The chance of severe flushing can be reduced by starting immediate-release niacin at a low dose (eg, 50 mg tid) and increasing it very slowly. At intermediate doses (1000 mg/day), triglyceride levels decrease 15 to 20%, and HDL cholesterol levels increase 15 to 30%. Reductions in LDL cholesterol are modest (< 10%). Higher doses of niacin (3000 mg/day) reduce LDL cholesterol 15 to 20% but may cause jaundice, abdominal discomfort, blurred vision, worsening of hyperglycemia, and precipitation of preexisting gout. People with a liver disorder probably should not take high-dose niacin.

Hepatotoxicity may be more common with some sustained-release preparations. Some authorities
recommend checking levels of uric acid, serum glucose, and plasma transaminases every 6 to 8 wk until the dose of niacin has been stabilized.

**Riboflavin**

Riboflavin (vitamin B2) is involved in carbohydrate metabolism as an essential coenzyme in many oxidation-reduction reactions. Riboflavin is essentially nontoxic.

**Riboflavin Deficiency**

Riboflavin deficiency usually occurs with other B-vitamin deficiencies. Symptoms and signs include sore throat, lesions of the lips and mucosa of the mouth, glossitis, conjunctivitis, seborrheic dermatitis, and normochromic normocytic anemia. Diagnosis is usually clinical. Treatment consists of oral or, if needed, IM riboflavin.

Primary riboflavin deficiency results from inadequate intake of fortified cereals, milk, and other animal products. The most common causes of secondary deficiency are chronic diarrhea, malabsorption syndromes, liver disorders, hemodialysis, peritoneal dialysis, long-term use of barbiturates, and chronic alcoholism.

**Symptoms and Signs**

The most common signs are pallor and maceration of the mucosa at the angles of the mouth (angular stomatitis) and vermillion surfaces of the lips (cheilosis), eventually replaced by superficial linear fissures. The fissures can become infected with *Candida albicans*, causing grayish white lesions (perleche). The tongue may appear magenta. Seborrheic dermatitis develops, usually affecting the nasolabial folds, ears, eyelids, and scrotum or labia majora. These areas become red, scaly, and greasy.

Rarely, neovascularization and keratitis of the cornea occur, causing lacrimation and photophobia.

**Diagnosis**

The lesions characteristic of riboflavin deficiency are nonspecific. Riboflavin deficiency should be suspected if characteristic signs develop in a patient with other B vitamin deficiencies. Diagnosis can be confirmed by a therapeutic trial or laboratory testing, usually by measuring urinary excretion of riboflavin.

**Treatment**

Riboflavin 5 to 10 mg/day po is given until recovery. Other water-soluble vitamins should also be given.

**Thiamin**

Thiamin (vitamin B1) is widely available in the diet. Thiamin is involved in carbohydrate, fat, amino acid, glucose, and alcohol metabolism. Thiamin is essentially nontoxic.

**Thiamin Deficiency**

Thiamin deficiency (causing beriberi) is most common among people subsisting on white rice or highly refined carbohydrates in developing countries and among alcoholics. Symptoms include diffuse polyneuropathy, high-output heart failure, and Wernicke-Korsakoff syndrome. Thiamin is given to help diagnose and treat the deficiency.

**Etiology**

Primary thiamin deficiency is caused by inadequate intake of thiamin. It is commonly due to a diet of highly refined carbohydrates (eg, polished rice, white flour, white sugar). It also develops when intake of other nutrients is inadequate; it often occurs with other B vitamin deficiencies.
Secondary thiamin deficiency is caused by increased demand (eg, due to hyperthyroidism, pregnancy, breastfeeding, strenuous exercise, or fever), impaired absorption (eg, due to prolonged diarrhea), or impaired metabolism (eg, due to hepatic insufficiency). In alcoholics, many mechanisms contribute to thiamin deficiency; they include decreased intake, impaired absorption and use, increased demand, and possibly an apoenzyme defect.

**Pathophysiology**

Deficiency causes degeneration of peripheral nerves, thalamus, mammillary bodies, and cerebellum. Cerebral blood flow is markedly reduced, and vascular resistance is increased.

The heart may become dilated; muscle fibers become swollen, fragmented, and vacuolized, with interstitial spaces dilated by fluid. Vasodilation occurs and can result in edema in the feet and legs. Arteriovenous shunting of blood increases. Eventually, high-output heart failure may occur.

**Symptoms and Signs**

Early symptoms are nonspecific: fatigue, irritability, poor memory, sleep disturbances, precordial pain, anorexia, and abdominal discomfort.

Dry beriberi refers to peripheral neurologic deficits due to thiamin deficiency. These deficits are bilateral and roughly symmetric, occurring in a stocking-glove distribution. They affect predominantly the lower extremities, beginning with paresthesias in the toes, burning in the feet (particularly severe at night), muscle cramps in the calves, pains in the legs, and plantar dysesthesias. Calf muscle tenderness, difficulty rising from a squatting position, and decreased vibratory sensation in the toes are early signs. Muscle wasting occurs. Continued deficiency worsens polyneuropathy, which can eventually affect the arms.

Wernicke-Korsakoff syndrome, which combines Wernicke's encephalopathy (see p. 1522) and Korsakoff's psychosis (see p. 1523), occurs in some alcoholics who do not consume foods fortified with thiamin. Wernicke's encephalopathy consists of psychomotor slowing or apathy, nystagmus, ataxia, ophthalmoplegia, impaired consciousness, and, if untreated, coma and death. It probably results from severe acute deficiency superimposed on chronic deficiency. Korsakoff's psychosis consists of mental confusion, dysphonia, and confabulation with impaired memory of recent events. It probably results from chronic deficiency and may develop after repeated episodes of Wernicke's encephalopathy.

Cardiovascular (wet) beriberi is myocardial disease due to thiamin deficiency. The first effects are vasodilation, tachycardia, a wide pulse pressure, sweating, warm skin, and lactic acidosis. Later, heart failure develops, causing orthopnea and pulmonary and peripheral edema. Vasodilation can continue, sometimes resulting in shock.

Infantile beriberi occurs in infants (usually by age 3 to 4 wk) who are breastfed by thiamin-deficient mothers. Heart failure (which may occur suddenly), aphonia, and absent deep tendon reflexes are characteristic.

Because thiamin is necessary for glucose metabolism, glucose infusions may precipitate or worsen symptoms of deficiency in thiamin-deficient people.

**Diagnosis**

- Favorable response to thiamin

Diagnosis is usually based on a favorable response to treatment with thiamin in a patient with symptoms or signs of deficiency. Similar bilateral lower-extremity polyneuropathies due to other disorders (eg, diabetes, alcoholism, vitamin B₁₂ deficiency, heavy metal poisoning) do not respond to thiamin. Single-nerve neuritides (mononeuropathies—eg, sciatica) and multiple mononeuropathies (mononeuritis multiplex) are unlikely to result from thiamin deficiency.
Electrolytes, including Mg, should be measured to exclude other causes. For confirmation in equivocal cases, erythrocyte transketolase activity and 24-h urinary thiamin excretion may be measured.

Diagnosis of cardiovascular beriberi can be difficult if other disorders that cause heart failure are present. A therapeutic trial of thiamin can help.

**Treatment**

- Supplemental thiamin, with dose based on clinical manifestations

Ensuring that dietary supplies of thiamin are adequate is important regardless of symptoms. Because IV glucose can worsen thiamin deficiency, alcoholics and others at risk of thiamin deficiency should receive IV thiamin 100 mg before receiving IV glucose solutions.

For mild polyneuropathy, thiamin 10 to 20 mg po once/day is given for 2 wk. For moderate or advanced neuropathy, the dose is 20 to 30 mg/day; it should be continued for several weeks after symptoms disappear. For edema and congestion due to cardiovascular beriberi, thiamin 100 mg IV once/day is given for several days. Heart failure is also treated.

For Wernicke-Korsakoff syndrome, thiamin 50 to 100 mg IM or IV bid must usually be given for several days, followed by 10 to 20 mg once/day until a therapeutic response is obtained. Anaphylactic reactions to IV thiamin are rare. Symptoms of ophthalmoplegia may resolve in a day; improvement in patients with Korsakoff psychosis may take 1 to 3 mo. Recovery from neurologic deficits is often incomplete in Wernicke-Korsakoff syndrome and in other forms of thiamin deficiency.

Because thiamin deficiency often occurs with other B vitamin deficiencies, multiple water-soluble vitamins are usually given for several weeks. Patients should continue to consume a nutritious diet, supplying 1 to 2 times the daily recommended intake of vitamins; all alcohol intake should stop.

**Vitamin A**

Vitamin A (retinol) is required for the formation of rhodopsin, a photoreceptor pigment in the retina. Vitamin A helps maintain epithelial tissues. Normally, the liver stores 80 to 90% of the body's vitamin A. To use vitamin A, the body releases it into the circulation bound to prealbumin (transthyretin) and retinol-binding protein. β-Carotene and other provitamin carotenoids, contained in green leafy and yellow vegetables and deep- or bright-colored fruits, are converted to vitamin A. Carotenoids are absorbed better from vegetables when they are cooked or homogenized and served with some fats or oils.

Retinol activity equivalents (RAE) were developed because provitamin A carotenoids have less vitamin A activity than preformed vitamin A; 1 μg retinol = 3.33 IU.

Synthetic vitamin analogs (retinoids) are being used increasingly in dermatology. The possible protective role of β-carotene, retinol, and retinoids against some epithelial cancers is under study. However, risk of certain cancers may be increased after β-carotene supplementation.

**Vitamin A Deficiency**

Vitamin A deficiency can result from inadequate intake, fat malabsorption, or liver disorders. Deficiency impairs immunity and hematopoiesis and causes rashes and typical ocular effects (eg, xerophthalmia, night blindness). Diagnosis is based on typical ocular findings and low vitamin A levels. Treatment consists of vitamin A given orally or, if symptoms are severe or malabsorption is the cause, parenterally.

**Etiology**

Primary vitamin A deficiency is usually caused by prolonged dietary deprivation. It is endemic in areas such as southern and eastern Asia, where rice, devoid of β-carotene, is the staple food. Xerophthalmia due to primary deficiency is a common cause of blindness among young children in developing countries.
Secondary vitamin A deficiency may be due to decreased bioavailability of provitamin A carotenoids or to interference with absorption, storage, or transport of vitamin A. Interference with absorption or storage is likely in sprue, cystic fibrosis, pancreatic insufficiency, duodenal bypass, chronic diarrhea, bile duct obstruction, giardiasis, and cirrhosis. Vitamin A deficiency is common in prolonged protein-energy undernutrition not only because the diet is deficient but also because vitamin A storage and transport is defective. In children with complicated measles, vitamin A can shorten the duration of the disorder and reduce the severity of symptoms and risk of death.

Symptoms and Signs

Impaired dark adaptation of the eyes, which can lead to night blindness, is an early symptom. Xerophthalmia (which is nearly pathognomonic) results from keratinization of the eyes. It involves drying (xerosis) and thickening of the conjunctivae and corneas. Superficial foamy patches composed of epithelial debris and secretions on the exposed bulbar conjunctiva (Bitot's spots) develop. In advanced deficiency, the cornea becomes hazy and can develop erosions, which can lead to its destruction (keratomalacia).

Keratinization of the skin and of the mucous membranes in the respiratory, GI, and urinary tracts can occur. Drying, scaling, and follicular thickening of the skin and respiratory infections can result. Immunity is generally impaired.

The younger the patient, the more severe are the effects of vitamin A deficiency. Growth retardation and infections are common among children. Mortality rate can exceed 50% in children with severe vitamin A deficiency.

Diagnosis

• Serum retinol levels, clinical evaluation, and response to vitamin A

Ocular findings suggest the diagnosis. Dark adaptation can be impaired in other disorders (eg, zinc deficiency, retinitis pigmentosa, severe refractive errors, cataracts, diabetic retinopathy). If dark adaptation is impaired, rod scotometry and electroretinography are done to determine whether vitamin A deficiency is the cause.

Serum levels of retinol are measured. Normal range is 28 to 86 μg/dL (1 to 3 μmol/L). However, levels decrease only after the deficiency is advanced because the liver contains large stores of vitamin A. Also, decreased levels may result from acute infection, which causes retinol-binding protein and transthyretin (also called prealbumin) levels to decrease transiently. A therapeutic trial of vitamin A may help confirm the diagnosis.

Prevention

The diet should include dark green leafy vegetables, deep- or bright-colored fruits (eg, papayas, oranges), carrots, and yellow vegetables (eg, squash, pumpkin). Vitamin A-fortified milk and cereals, liver, egg yolks, and fish liver oils are helpful. Carotenoids are absorbed better when consumed with some dietary fat. If milk allergy is suspected in infants, they should be given adequate vitamin A in formula feedings. In developing countries, prophylactic supplements of vitamin A palmitate in oil 60,000 RAE (200,000 IU) po every 6 mo are advised for all children between 1 and 5 yr of age; infants < 6 mo can be given a one-time dose of 15,000 RAE (50,000 IU), and those aged 6 to 12 mo can be given a one-time dose of 30,000 RAE (100,000 IU).

Treatment

• Vitamin A palmitate

Dietary deficiency is traditionally treated with vitamin A palmitate in oil 60,000 IU po once/day for 2 days, followed by 4500 IU po once/day. If vomiting or malabsorption is present or xerophthalmia is probable, a
A dose of 50,000 IU for infants < 6 mo, 100,000 IU for infants 6 to 12 mo, or 200,000 IU for children > 12 mo and adults should be given for 2 days, with a third dose at least 2 wk later. The same doses are recommended for infants and children with complicated measles. Infants born of HIV-positive mothers should receive 50,000 IU (15,000 RAE) within 48 h of birth. Prolonged daily administration of large doses, especially to infants, must be avoided because toxicity may result.

For pregnant or breastfeeding women, prophylactic or therapeutic doses should not exceed 10,000 IU (3000 RAE)/day to avoid possible damage to the fetus or infant.

**Vitamin A Toxicity**

Vitamin A toxicity can be acute (usually due to accidental ingestion by children) or chronic. Both types usually cause headache and increased intracranial pressure. Acute toxicity also causes nausea and vomiting. Chronic toxicity also causes changes in skin, hair, and nails; abnormal liver test results; and, in a fetus, birth defects. Diagnosis is usually clinical. Unless birth defects are present, adjusting the dose almost always leads to complete recovery.

Acute vitamin A toxicity in children may result from taking large doses (> 100,000 RAE [> 300,000 IU]), usually accidentally. In adults, acute toxicity has occurred when arctic explorers ingested polar bear or seal livers, which contain several million units of vitamin A.

Chronic toxicity in older children and adults usually develops after doses of > 30,000 RAE (> 100,000 IU)/day have been taken for months. Megavitamin therapy is a possible cause, as are massive daily doses (50,000 to 120,000 RAE [150,000 to 350,000 IU]) of vitamin A or its metabolites, which are sometimes given for nodular acne or other skin disorders. Adults who consume > 1500 RAE (> 4500 IU)/day of vitamin A may develop osteoporosis. Infants who are given excessive doses (6,000 to 20,000 RAE [18,000 to 60,000 IU]/day) of water-miscible vitamin A may develop toxicity within a few weeks. Birth defects occur in children of women receiving isotretinoin (which is related to vitamin A) for acne treatment during pregnancy.

Although carotene is converted to vitamin A in the body, excessive ingestion of carotene causes carotenemia, not vitamin A toxicity. Carotenemia is usually asymptomatic but may lead to carotenodermia, in which the skin becomes yellow. When taken as a supplement, β-carotene has been associated with increased cancer risk; risk does not seem to increase when carotenoids are consumed in fruits and vegetables.

**Symptoms and Signs**

Although symptoms may vary, headache and rash usually develop during acute or chronic toxicity. Acute toxicity causes increased intracranial pressure. Drowsiness, irritability, abdominal pain, nausea, and vomiting are common. Sometimes the skin subsequently peels.

Early symptoms of chronic toxicity are sparsely distributed, coarse hair; alopecia of the eyebrows; dry, rough skin; dry eyes; and cracked lips. Later, severe headache, pseudotumor cerebri, and generalized weakness develop. Cortical hyperostosis of bone and arthralgia may occur, especially in children. Fractures may occur easily, especially in the elderly. In children, toxicity can cause pruritus, anorexia, and failure to thrive. Hepatomegaly and splenomegaly may occur.

In carotenodermia, the skin (but not the sclera) becomes deep yellow, especially on the palms and soles.

**Diagnosis**

- Clinical evaluation

Diagnosis is clinical. Blood vitamin levels correlate poorly with toxicity. However, if clinical diagnosis is equivocal, laboratory testing may help. In vitamin A toxicity, fasting serum retinol levels may increase from normal (28 to 86 μg/dL [1 to 3 μmol/L]) to > 100 μg/dL (> 3.49 μmol/L), sometimes to > 2000 μg/dL (> 69.8 μmol/L). Hypercalcemia is common.
Differentiating vitamin A toxicity from other disorders may be difficult. Carotenodermia may also occur in severe hypothyroidism and anorexia nervosa, possibly because carotene is converted to vitamin A more slowly.

**Prognosis**

Complete recovery usually occurs if vitamin A ingestion stops. Symptoms and signs of chronic toxicity usually disappear within 1 to 4 wk. However, birth defects in the fetus of a mother who has taken megadoses of vitamin A are not reversible.

**Treatment**

Vitamin A is stopped.

**Vitamin B\(_6\)**

Vitamin B\(_6\) includes a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine. They are metabolized in the body to pyridoxal phosphate, which acts as a coenzyme in many important reactions in blood, CNS, and skin metabolism. Vitamin B\(_6\) is important in heme and nucleic acid biosynthesis and in lipid, carbohydrate, and amino acid metabolism.

**Vitamin B\(_6\) Deficiency and Dependency**

Because vitamin B\(_6\) is present in most foods, dietary deficiency is rare. Secondary deficiency may result from various conditions. Symptoms can include peripheral neuropathy, a pellagra-like syndrome, anemia, and seizures, which, particularly in infants, may not resolve when treated with anticonvulsants. Impaired metabolism (dependency) is rare; it causes various symptoms, including seizures, intellectual disability, and anemia. Diagnosis is usually clinical; no laboratory test readily assesses vitamin B\(_6\) status. Treatment consists of giving oral vitamin B\(_6\) and, when possible, treating the cause.

Dietary deficiency, though rare, can develop because extensive processing can deplete foods of vitamin B\(_6\). Secondary deficiency most often results from protein-energy undernutrition, malabsorption, alcoholism, use of pyridoxine-inactivating drugs (eg, anticonvulsants, isoniazid, cycloserine, hydralazine, corticosteroids, penicillamine), or excessive loss. Rarely, it results from increased metabolic demand (eg, in hyperthyroidism).

Rare inborn errors of metabolism can affect pyridoxine metabolism.

The role of vitamin B\(_6\) deficiency in increasing plasma homocysteine levels and in contributing to vascular disorders is under study.

**Symptoms and Signs**

Deficiency causes a pellagra-like syndrome, with seborrheic dermatitis, glossitis, and cheilosis, and, in adults, can cause depression, confusion, EEG abnormalities, and seizures. Rarely, deficiency or dependency causes seizures in infants. Seizures, particularly in infants, may be refractory to treatment with anticonvulsants. Normocytic, microcytic, or sideroblastic anemia can also develop.

**Diagnosis**

- Clinical evaluation

Vitamin B\(_6\) deficiency should be considered in any infant who has seizures, any patient who has seizures refractory to treatment with anticonvulsants, and any patient with deficiencies of other B vitamins.
particularly in patients with alcoholism or protein-energy undernutrition. Diagnosis is usually clinical. There is no single accepted laboratory test of vitamin B₆ status; measurement of serum pyridoxal phosphate is most common.

**Treatment**

- Pyridoxine

- Elimination of risk factors when possible

For secondary deficiency, causes (eg, use of pyridoxine-inactivating drugs, malabsorption) should be corrected if possible. Usually, pyridoxine 50 to 100 mg po once/day corrects the deficiency in adults. Most people taking isoniazid should also be given pyridoxine 30 to 50 mg/day. For deficiency due to increased metabolic demand, amounts larger than the daily recommended intake may be required. For most cases of inborn errors of metabolism, high doses of pyridoxine may be effective.

**Vitamin B₆ Toxicity**

The ingestion of megadoses (> 500 mg/day) of pyridoxine (eg, taken to treat carpal tunnel syndrome or premenstrual syndrome although efficacy is unproved) may cause peripheral neuropathy with deficits in a stocking-glove distribution, including progressive sensory ataxia and severe impairment of position and vibration senses. Senses of touch, temperature, and pain are less affected. Motor and central nervous systems are usually intact.

Diagnosis is clinical. Treatment is to stop taking vitamin B₆. Recovery is slow and, for some patients, incomplete.

**Vitamin B₁₂**

Cobalamin is a general term for compounds with biologic vitamin B₁₂ activity. These compounds are involved in nucleic acid metabolism, methyl transfer, and myelin synthesis and repair. They are necessary for the formation of normal RBCs.

Food-bound vitamin B₁₂ is released in the stomach's acid environment and is bound to R protein (haptocorrin). Pancreatic enzymes cleave this B₁₂ complex (B₁₂-R protein) in the small intestine. After cleavage, intrinsic factor, secreted by parietal cells in the gastric mucosa, binds with vitamin B₁₂. Intrinsic factor is required for absorption of vitamin B₁₂, which takes place in the terminal ileum.

Vitamin B₁₂ in plasma is bound to transcobalamins I and II. Transcobalamin II is responsible for delivering vitamin B₁₂ to tissues. The liver stores large amounts of vitamin B₁₂. Enterohepatic reabsorption helps retain vitamin B₁₂. Liver vitamin B₁₂ stores can normally sustain physiologic needs for 3 to 5 yr if B₁₂ intake stops (eg, in people who become vegans) and for months to 1 yr if enterohepatic reabsorption capacity is absent.

Large amounts of vitamin B₁₂ seem to be nontoxic but are not recommended for regular use (ie, as a general tonic).

**Vitamin B₁₂ Deficiency**

Dietary vitamin B₁₂ deficiency usually results from inadequate absorption, but deficiency can develop in vegans who do not take vitamin supplements. Deficiency causes megaloblastic anemia, damage to the white matter of the spinal cord and brain, and peripheral neuropathy. Diagnosis is usually made by measuring serum vitamin B₁₂ levels. The Schilling test helps determine etiology. Treatment consists of oral or parenteral vitamin B₁₂. Folate (folic acid) should not be used instead of vitamin B₁₂ because folate may alleviate the anemia but allow...
neurologic deficits to progress.

Etiology

Inadequate vitamin B$_{12}$ intake is possible in vegans but is otherwise unlikely. Breastfed babies of vegan mothers may develop vitamin B$_{12}$ deficiency by age 4 to 6 mo because their liver stores (which are normally extensive) are limited and their rapid growth rate results in high demand.

Vitamin B$_{12}$ deficiency usually results from inadequate absorption (see Table 4-5 and p. 153), which, in the elderly, most commonly results from decreased acid secretion. In such cases, crystalline vitamin B$_{12}$ (such as that available in vitamin supplements) can be absorbed, but food-bound vitamin B$_{12}$ is not liberated and absorbed normally. Inadequate absorption may occur in blind loop syndrome (with overgrowth of bacteria) or fish tapeworm infestation; in these cases, bacteria or parasites use ingested vitamin B$_{12}$ so that less is available for absorption. Vitamin B$_{12}$ absorption may be inadequate if ileal absorptive sites are destroyed by inflammatory bowel disease or are surgically removed. Less common causes of inadequate vitamin B$_{12}$ absorption include chronic pancreatitis, gastric surgery, malabsorption syndromes, AIDS, use of certain drugs (eg, antacids, metformin), repeated exposure to nitrous oxide, and a genetic disorder causing malabsorption in the ileum (Imerslund-Graesbeck syndrome).

Pernicious anemia is often used synonymously with vitamin B$_{12}$ deficiency. However, pernicious anemia specifically refers to anemia resulting from vitamin B$_{12}$ deficiency caused by an autoimmune metaplastic atrophic gastritis with loss of intrinsic factor (see p. 133). Patients with classic pernicious anemia, most commonly younger adults, are at increased risk of stomach and other GI cancers.

Subacute combined degeneration refers to degenerative changes in the nervous system due to vitamin B$_{12}$ deficiency; they affect mostly brain and spinal cord white matter. Demyelinating or axonal peripheral neuropathies can occur.

Symptoms and Signs

Anemia usually develops insidiously. It is often more severe than its symptoms indicate because its slow evolution allows physiologic adaptation. Occasionally, splenomegaly and hepatomegaly occur. Various GI symptoms, including weight loss and poorly localized abdominal pain, may occur. Glossitis, usually described as burning of the tongue, is uncommon.

Neurologic symptoms develop independently from and often without hematologic abnormalities. In early stages, decreased position and vibratory sensation in the extremities is accompanied by mild to moderate weakness and hyporeflexia. In later stages, spasticity, extensor plantar responses, greater loss of position and vibratory sensation in the lower extremities, and ataxia emerge. These deficits may develop in a stocking-glove distribution. Tactile, pain, and temperature sensations are usually spared but may be difficult to assess in the elderly.

Some patients are also irritable and mildly depressed. Paranoia (megaloblastic madness), delirium, confusion, spastic ataxia, and, at times, postural hypotension may occur in advanced cases. The confusion may be difficult to differentiate from age-related dementias, such as Alzheimer's disease.

Diagnosis

- CBC and vitamin B$_{12}$ and folate levels
- Sometimes methylmalonic acid levels or Schilling test
Diagnosis is based on CBC and vitamin B₁₂ and folate levels. It is important to remember that severe neurologic disease may occur without anemia or macrocytosis.

CBC detects megaloblastic anemia. Tissue deficiency and macrocytic indexes may precede the development of anemia. A vitamin B₁₂ level < 200 pg/mL (< 145 pmol/L) indicates vitamin B₁₂ deficiency. The folate level is measured because vitamin B₁₂ deficiency must be differentiated from folate deficiency as a cause of megaloblastic anemia; folate supplementation can mask vitamin B₁₂ deficiency and may alleviate megaloblastic anemia but allow the neurologic deficits to progress or even accelerate.

When clinical judgment suggests vitamin B₁₂ deficiency but the vitamin B₁₂ level is low-normal (200 to 350 pg/mL [145 to 260 pmol/L]) or hematologic indexes are normal, other tests can be done. Measuring serum methylmalonic acid (MMA) levels may be useful. An elevated MMA level supports vitamin B₁₂ deficiency but may be due to renal failure. MMA levels can also be used to monitor the response to treatment. MMA levels remain normal in folate deficiency; homocysteine levels may be elevated with either vitamin B₁₂ or folate deficiency. Less commonly, holotranscobalamin II (transcobalamin II-B₁₂ complex) content is measured; when holotranscobalamin II is < 40 pg/mL (< 30 pmol/L), vitamin B₁₂ is deficient.

If malabsorption is identified, the Schilling test can be repeated after a 2-wk trial of an oral antibiotic. If antibiotic therapy corrects malabsorption, the likely cause is intestinal overgrowth of bacteria (eg, blind-loop syndrome).

Treatment

* Supplemental vitamin B₁₂

Vitamin B₁₂ 1000 to 2000 μg po can be given once/day to patients who do not have severe deficiency or neurologic symptoms or signs. A nasal gel preparation of vitamin B₁₂ is available at a higher price. Large oral doses can be absorbed by mass action, even when intrinsic factor is absent. If the MMA level (sometimes used to monitor treatment) does not decrease, patients may not be taking vitamin B₁₂. For more severe deficiency, vitamin B₁₂ 1 mg IM is usually given 1 to 4 times/wk for several weeks until hematologic abnormalities are corrected; then it is given once/mo.

Although hematologic abnormalities are usually corrected within 6 wk (reticulocyte count should improve within 1 wk), resolution of neurologic symptoms may take much longer. Neurologic symptoms that persist
for months or years become irreversible. In most elderly people with vitamin B\textsubscript{12} deficiency and dementia, cognition does not improve after treatment. Vitamin B\textsubscript{12} treatment must be continued for life unless the pathophysiologic mechanism for the deficiency is corrected.

Infants of vegan mothers should receive supplemental vitamin B\textsubscript{12} from birth.

**Vitamin C**

Vitamin C (ascorbic acid) plays a role in collagen, carnitine, hormone, and amino acid formation. It is essential for wound healing and facilitates recovery from burns. Vitamin C is also an antioxidant, supports immune function, and facilitates the absorption of iron.

**Vitamin C Deficiency**

In developed countries, vitamin C deficiency can occur as part of general undernutrition, but severe deficiency (causing scurvy) is uncommon. Symptoms include fatigue, depression, and connective tissue defects (eg, gingivitis, petechiae, rash, internal bleeding, impaired wound healing). In infants and children, bone growth may be impaired. Diagnosis is usually clinical. Treatment consists of oral vitamin C.

Severe deficiency results in scurvy, a disorder characterized by hemorrhagic manifestations and abnormal osteoid and dentin formation.

**Etiology**

In adults, primary deficiency is usually due to inadequate diet. The need for dietary vitamin C is increased by febrile illnesses, inflammatory disorders (particularly diarrheal disorders), achlorhydria, smoking, thyrotoxicosis, iron deficiency, cold or heat stress, surgery, burns, and protein deficiency. Heat (eg, sterilization of formulas, cooking) can destroy some of the vitamin C in food.

**Pathophysiology**

Formation of intercellular cement substances in connective tissues, bones, and dentin is defective, resulting in weakened capillaries with subsequent hemorrhage and defects in bone and related structures.

Bone tissue formation becomes impaired, which, in children, causes bone lesions and poor bone growth. Fibrous tissue forms between the diaphysis and the epiphysis, and costochondral junctions enlarge. Densely calcified fragments of cartilage are embedded in the fibrous tissue. Subperiosteal hemorrhages, sometimes due to small fractures, may occur in children or adults.

**Symptoms and Signs**

In adults, symptoms develop after weeks to months of vitamin C depletion. Lassitude, weakness, irritability, weight loss, and vague myalgias and arthralgias may develop early.

Later, symptoms related to defects in connective tissues develop. Follicular hyperkeratosis, coiled hair, and perifollicular hemorrhages may develop. Gums may become swollen, purple, spongy, and friable; they bleed easily in severe deficiency. Eventually, teeth become loose and avulsed. Secondary infections may develop. Wounds heal poorly and tear easily, and spontaneous hemorrhages may occur, especially as ecchymoses in the skin of the lower limbs or as bulbar conjunctival hemorrhage.

Other symptoms and signs include femoral neuropathy due to hemorrhage into femoral sheaths (which may mimic deep venous thrombosis), lower-extremity edema, and painful bleeding or effusions within joints.

**Diagnosis**
• Usually, skin or gingival findings and risk factors

Diagnosis is usually made clinically in a patient who has skin or gingival signs and is at risk of vitamin C deficiency. Laboratory confirmation may be available. Anemia is common. Bleeding, coagulation, and PT are normal.

Skeletal x-rays can help diagnose childhood (but not adult) scurvy. Changes are most evident at the ends of long bones, particularly at the knee. Early changes resemble atrophy. Loss of trabeculae results in a ground-glass appearance. The cortex thins. A line of calcified, irregular cartilage (white line of Fraenkel) may be visible at the metaphysis. A zone of rarefaction or a linear fracture proximal and parallel to the white line may be visible as only a triangular defect at the bone's lateral margin but is specific. The epiphysis may be compressed. Healing subperiosteal hemorrhages may elevate and calcify the periosteum.

Laboratory diagnosis, which requires measuring blood ascorbic acid, is sometimes done at academic centers. Levels of < 0.6 mg/dL (< 34 μmol/L) are considered marginal; levels of < 0.2 mg/dL (< 11 μmol/L) indicate vitamin C deficiency. Measurement of ascorbic acid levels in the WBC-platelet layer of centrifuged blood is not widely available or standardized.

In adults, scurvy must be differentiated from arthritis, hemorrhagic disorders, gingivitis, and protein-energy undernutrition. Hyperkeratotic hair follicles with surrounding hyperemia or hemorrhage are almost pathognomonic. Bleeding gums, conjunctival hemorrhages, most petechiae, and ecchymoses are nonspecific.

Treatment

• Nutritious diet with supplemental ascorbic acid

For scurvy in adults, ascorbic acid 100 to 500 mg po tid is given for 1 to 2 wk, until signs disappear, and followed by a nutritious diet supplying 1 to 2 times the daily recommended intake. In scurvy, therapeutic doses of ascorbic acid restore the functions of vitamin C in a few days. The symptoms and signs usually disappear over 1 to 2 wk. Chronic gingivitis with extensive subcutaneous hemorrhage persists longer.

Prevention

Vitamin C 75 mg po once/day for women and 90 mg po once/day for men prevents deficiency. Smokers should consume an additional 35 mg/day. Five servings of most fruits and vegetables (recommended daily) provide > 200 mg of vitamin C.

Vitamin C Toxicity

The upper limit for vitamin C intake is 2000 mg/day. Up to 10 g/day of vitamin C are sometimes taken for unproven health benefits, such as preventing or shortening the duration of viral infections or slowing or reversing the progression of cancer or atherosclerosis. Such doses may acidify the urine, cause nausea and diarrhea, interfere with the healthy antioxidant-prooxidant balance in the body, and, in patients with thalassemia or hemochromatosis, promote iron overload. Intake below the upper limit does not have toxic effects in healthy adults.

Vitamin D

Vitamin D has 2 main forms: D2 (ergocalciferol) and D3 (cholecalciferol); the latter is the naturally occurring form and the form used for low-dose supplementation. Vitamin D3 is synthesized in skin by exposure to direct sunlight (ultraviolet B radiation) and obtained in the diet chiefly in fish liver oils and salt water fish. In some developed countries, milk and other foods are fortified with vitamin D. Human breast milk is low in vitamin D, containing an average of only 10% of the amount in fortified cow's milk. Requirements for vitamin D increase with age because skin synthesis declines. Sunscreen use and dark skin pigmentation also reduce skin synthesis of vitamin D.
Vitamin D is a prohormone with several active metabolites that act as hormones. Vitamin D is metabolized by the liver to 25(OH)D, which is then converted by the kidneys to 1,25(OH)₂D (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D hormone). 25(OH)D, the major circulating form, has some metabolic activity, but 1,25(OH)₂D is the most metabolically active. The conversion to 1,25(OH)₂D is regulated by its own concentration, parathyroid hormone (PTH), and serum concentrations of Ca and phosphate.

Table 4-6. Actions of Vitamin D and its Metabolites

Vitamin D affects many organ systems (see Table 4-6), but mainly it increases Ca and phosphate absorption from the intestine and promotes normal bone formation and mineralization. Vitamin D and related analogs may be used to treat psoriasis, hypoparathyroidism, renal osteodystrophy, and possibly leukemia and breast, prostate, and colon cancers; they may also be used for immunosuppression.

Vitamin D Deficiency and Dependency

Inadequate exposure to sunlight predisposes to vitamin D deficiency. Deficiency impairs bone mineralization, causing rickets in children and osteomalacia in adults and possibly contributing to osteoporosis. Treatment usually consists of oral vitamin D; Ca and phosphate are supplemented as needed. Prevention is often possible. Rarely, hereditary disorders cause impaired metabolism of vitamin D (dependency).

Vitamin D deficiency is a common cause of rickets and osteomalacia, but these disorders may also result from other conditions, such as various renal tubular disorders, familial hypophosphatemic (vitamin D-resistant) rickets (see p. 2991), chronic metabolic acidosis, hypoparathyroidism (which reduces vitamin D absorption), inadequate dietary Ca, and disorders or drugs that impair the mineralization of bone matrix.

Vitamin D deficiency causes hypocalcemia, which stimulates production of PTH, causing hyperparathyroidism. Hyperparathyroidism increases absorption, bone mobilization, and renal conservation of Ca but increases excretion of phosphate. As a result, the serum level of Ca may be normal, but because of hypophosphatemia, bone mineralization is impaired.

Etiology

Vitamin D deficiency may result from the following.

Inadequate exposure or intake: Inadequate direct sunlight exposure (or sunscreen use) and inadequate intake usually occur simultaneously to result in clinical deficiency. Susceptible people include the elderly (who are often undernourished and are not exposed to enough sunlight), and certain communities (eg, women and children who are confined to the home or who wear clothing that covers the entire body and face). Inadequate vitamin D stores are common among the elderly, particularly those who are house-bound, institutionalized, or hospitalized or who have had a hip fracture. Recommended direct sunlight exposure is 5 to 15 min (suberythemal dose) to arms and legs, or face, arms and hands, at least 3 times a week.

Reduced absorption: Malabsorption can deprive the body of dietary vitamin D; only a small amount of 25(OH)D is recirculated enterohepatically.

Abnormal metabolism: Vitamin D deficiency may result from defects in the production of 25(OH)D or 1,25(OH)₂D. People with a chronic renal disorder commonly develop rickets or osteomalacia because renal production of 1,25(OH)₂D is decreased and phosphate levels are elevated. Hepatic dysfunction can also interfere with production of active vitamin D metabolites.

Type I hereditary vitamin D-dependent rickets is an autosomal recessive disorder characterized by absent or defective conversion of 25(OH)D to 1,25(OH)₂D in the kidneys. X-linked familial hypophosphatemia
reduces vitamin D synthesis in the kidneys. Many anticonvulsants and glucocorticoid use increase the need for vitamin D supplementation.

**Resistance to effects of vitamin D:** Type II hereditary vitamin D-dependent rickets has several forms and is due to mutations in the 1,25(OH)\(_2\)D receptor. This receptor affects the metabolism of gut, kidney, bone, and other cells. In this disorder, 1,25(OH)\(_2\)D is abundant but ineffective because the receptor is not functional.

**Symptoms and Signs**

Vitamin D deficiency can cause muscle aches, muscle weakness, and bone pain at any age.

Vitamin D deficiency in a pregnant woman causes deficiency in the fetus. Occasionally, deficiency severe enough to cause maternal osteomalacia results in rickets with metaphyseal lesions in neonates. In young infants, rickets causes softening of the entire skull (craniotabes). When palpated, the occiput and posterior parietal bones feel like a ping pong ball. In older infants, in rickets, sitting and crawling are delayed, as is fontanelle closure; there is bossing of the skull and costochondral thickening. Costochondral thickening can look like beadlike prominences along the lateral chest wall (rachitic rosary). In children 1 to 4 yr, epiphyseal cartilage at the lower ends of the radius, ulna, tibia, and fibula enlarges; kyphoscoliosis develops, and walking is delayed. In older children and adolescents, walking is painful; in extreme cases, deformities such as bowlegs and knock-knees develop.

Tetany is caused by hypocalcemia and may accompany infantile or adult vitamin D deficiency. Tetany may cause paresthesias of the lips, tongue, and fingers; carpopedal and facial spasm; and, if very severe, seizures. Maternal deficiency can cause tetany in neonates.

Osteomalacia predisposes to fractures. In the elderly, hip fractures may result from only minimal trauma.

**Diagnosis**

- Levels of 25(OH)D (D\(_2\)+D\(_3\))

Diagnosis may be suspected based on any of the following:

- A history of inadequate sunlight exposure or dietary intake
- Symptoms and signs of rickets, osteomalacia, or neonatal tetany
- Characteristic bone changes seen on x-ray

X-rays of the radius and ulna plus serum levels of Ca, phosphate, alkaline phosphatase, PTH, and 25(OH)D are needed to differentiate vitamin D deficiency from other causes of bone demineralization.

Assessment of vitamin D status and serologic tests for syphilis can be considered for infants with craniotabes based on the history and physical, but most cases of craniotabes resolve spontaneously. Rickets can be distinguished from chondrodystrophy because the latter is characterized by a large head, short extremities, thick bones, and normal serum Ca, phosphate, and alkaline phosphatase levels.

Tetany due to infantile rickets may be clinically indistinguishable from seizures due to other causes. Blood tests and clinical history may help distinguish them.

Bone changes, seen on x-rays, precede clinical signs. In rickets, changes are most evident at the lower ends of the radius and ulna. The diaphyseal ends lose their sharp, clear outline; they are cup-shaped and show a spotty or fringy rarefaction. Later, because the ends of the radius and ulna have become noncalcified and radiolucent, the distance between them and the metacarpal bones appears increased. The bone matrix elsewhere also becomes more radiolucent. Characteristic deformities result from the bones bending at the cartilage-shaft junction because the shaft is weak. As healing begins, a thin white
line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds. Later, the bone matrix becomes calcified and opacified at the subperiosteal level.

In adults, bone demineralization, particularly in the spine, pelvis, and lower extremities, can be seen on x-rays; the fibrous lamellae can also be seen, and incomplete ribbonlike areas of demineralization (pseudofractures, Looser’s lines, Milkman’s syndrome) appear in the cortex.

Because levels of serum 25(OH)D reflect body stores of vitamin D and correlate with symptoms and signs of vitamin D deficiency better than levels of other vitamin D metabolites, 25(OH)D (D2+D₃) measurement is generally considered the best way to diagnose deficiency. Goal 25(OH)D levels are 30 to 40 ng/mL (about 75 to 100 nmol/L); whether higher levels may be beneficial remains uncertain.

If the diagnosis is unclear, serum levels of 1,25(OH)₂D and urinary Ca concentration can be measured. In severe deficiency, serum 1,25(OH)₂D is abnormally low, usually undetectable. Urinary Ca is low in all forms of the deficiency except those associated with acidosis.

In vitamin D deficiency, serum Ca may be low or, because of secondary hyperparathyroidism, may be normal. Serum phosphate usually decreases, and serum alkaline phosphatase usually increases. Serum PTH is elevated.

Type I hereditary vitamin D-dependent rickets results in normal serum 25(OH)D, low serum 1,25(OH)₂D and Ca, and normal or low serum phosphate.

Treatment

• Correction of Ca and phosphate deficiencies

• Supplemental vitamin D

Ca deficiency (which is common) and phosphate deficiency should be corrected. As long as Ca and phosphate intake is adequate, adults with osteomalacia and children with uncomplicated rickets can be cured by giving vitamin D 40 µg (1600 IU) po once/day. Serum 25(OH)D and 1,25(OH)₂D begin to increase within 1 or 2 days. Serum Ca and phosphate increase and serum alkaline phosphatase decreases within about 10 days. During the 3rd wk, enough Ca and phosphate are deposited in bones to be visible on x-rays. After about 1 mo, the dose can usually be reduced gradually to the usual maintenance level of 10 to 15 µg (400 to 600 IU) once/day. If tetany is present, vitamin D should be supplemented with IV Ca salts for up to 1 wk (see p. 841). Elderly patients may need 25 to ≥ 50 µg (1000 to ≥ 2000 IU) daily to maintain a 25(OH)D level > 30 ng/mL (> 75 nmol/L); this dose is higher than the recommended daily allowance (RDA) for people > 70 yr (600 IU) and may exceed the current upper limit of 2000 IU/day.

Because rickets and osteomalacia due to defective production of vitamin D metabolites are vitamin D-resistant, they do not respond to the doses usually effective for rickets due to inadequate intake. Endocrinologic evaluation is required because treatment depends on the specific defect. When 25(OH)D production is defective, vitamin D 50 µg (2000 IU) once/day increases serum levels and results in clinical improvement. Patients with kidney disorders often need 1,25(OH)₂D supplementation.

Type I hereditary vitamin D-dependent rickets responds to 1,25(OH)₂D 1 to 2 µg po once/day. Some patients with type II hereditary vitamin D-dependent rickets respond to very high doses (eg, 10 to 24 µg/day) of 1,25(OH)₂D; others require long-term infusions of Ca.

Prevention

Dietary counseling is particularly important in communities whose members are at risk of vitamin D deficiency. Fortifying unleavened chapati flour with vitamin D (125 µg/kg) has been effective among Indian immigrants in Britain. The benefits of sunlight exposure for vitamin D status must be weighed against the increased skin damage and skin cancer risks.
All breastfed infants should be given supplemental vitamin D 5 μg (200 IU) once/day from birth to 6 mo; at 6 mo, a more diversified diet is available. For adolescents at risk, a single IM dose of ergocalciferol 2.5 mg (100,000 IU) given in the fall can maintain adequate 25(OH)D levels throughout the winter. The recommended daily allowance (RDA) for vitamin D is 400 IU for people aged 51 to 70 and 600 IU for those >70; many consider this intake too low, and the 2005 Dietary Guidelines for Americans recommends that healthy older adults consume 1000 IU/day.

Vitamin D Toxicity

Usually, vitamin D toxicity results from taking excessive amounts. Marked hypercalcemia commonly causes symptoms. Diagnosis is typically based on elevated blood levels of 25(OH)D. Treatment consists of stopping vitamin D, restricting dietary Ca, restoring intravascular volume deficits, and, if toxicity is severe, giving corticosteroids or bisphosphonates.

Because synthesis of 1,25(OH)2D (the most active metabolite of vitamin D) is tightly regulated, vitamin D toxicity usually occurs only if excessive doses (prescription or megavitamin) are taken. Vitamin D 1000 μg (40,000 IU)/day causes toxicity within 1 to 4 mo in infants. In adults, taking 1250 μg (50,000 IU)/day for several months can cause toxicity. Vitamin D toxicity can occur iatrogenically when hypoparathyroidism is treated too aggressively (see p. 844).

Symptoms and Signs

The main symptoms result from hypercalcemia. Anorexia, nausea, and vomiting can develop, often followed by polyuria, polydipsia, weakness, nervousness, pruritus, and eventually renal failure. Proteinuria, urinary casts, azotemia, and metastatic calcifications (particularly in the kidneys) can develop.

Diagnosis

- Hypercalcemia plus risk factors or elevated serum 25(OH)D levels

A history of excessive vitamin D intake may be the only clue differentiating vitamin D toxicity from other causes of hypercalcemia. Elevated serum Ca levels of 12 to 16 mg/dL (3 to 4 mmol/L) are a constant finding when toxic symptoms occur. Serum 25(OH)D levels are usually elevated > 150 ng/mL (> 375 nmol/L). Levels of 1,25(OH)2D, which need not be measured to confirm the diagnosis, may be normal.

Serum Ca should be measured often (weekly at first, then monthly) in all patients receiving large doses of vitamin D, particularly the potent 1,25(OH)2D.

Treatment

- IV hydration plus corticosteroids or bisphosphonates

After stopping vitamin D intake, hydration with IV normal saline and corticosteroids or bisphosphonates (which inhibit bone resorption) are used to reduce blood Ca levels.

Kidney damage or metastatic calcifications, if present, may be irreversible.

Vitamin E

Vitamin E is a group of compounds (including tocopherols and tocotrienols) that have similar biologic activities. The most biologically active is α-tocopherol, but β-, γ-, and δ-tocopherols, 4 tocotrienols, and several stereoisomers may also have important biologic activity. These compounds act as antioxidants, which prevent lipid peroxidation of polyunsaturated fatty acids in cellular membranes. Plasma tocopherol levels vary with total plasma lipid levels. Normally, the plasma α-tocopherol level is 5 to 20 μg/mL (11.6 to 46.4 μmol/L). High-dose vitamin E supplements do not protect against cardiovascular disorders; whether
supplements can protect against Alzheimer's disease, tardive dyskinesia, and prostate cancer among smokers is controversial.

Although the amount of vitamin E in many fortified foods and supplements is given in IU, current recommendations are to use mg.

**Vitamin E Deficiency**

**Dietary vitamin E deficiency is common in developing countries; deficiency among adults in developed countries is uncommon and usually due to fat malabsorption. The main symptoms are hemolytic anemia and neurologic deficits. Diagnosis is based on measuring the ratio of plasma α-tocopherol to total plasma lipids; a low ratio suggests vitamin E deficiency. Treatment consists of oral vitamin E, given in high doses if there are neurologic deficits or if deficiency results from malabsorption.**

Vitamin E deficiency causes fragility of RBCs and degeneration of neurons, particularly peripheral axons and posterior column neurons.

**Etiology**

In developing countries, the most common cause is inadequate intake of vitamin E. In developed countries, the most common causes are disorders that cause fat malabsorption, including abetalipoproteinemia (Bassen-Kornzweig syndrome, due to genetic absence of apolipoprotein B), chronic cholestatic hepatobiliary disease, pancreatitis, short bowel syndrome, and cystic fibrosis. A rare genetic form of vitamin E deficiency without fat malabsorption results from defective liver metabolism.

**Symptoms and Signs**

The main symptoms are mild hemolytic anemia and nonspecific neurologic deficits. Abetalipoproteinemia results in progressive neuropathy and retinopathy in the first 2 decades of life (see p. 904).

Vitamin E deficiency may contribute to retinopathy of prematurity (also called retrolental fibroplasia) in premature infants and to some cases of intraventricular and subependymal hemorrhage in neonates. Affected premature neonates have muscle weakness.

In children, chronic cholestatic hepatobiliary disease or cystic fibrosis causes neurologic deficits, including spinocerebellar ataxia with loss of deep tendon reflexes, truncal and limb ataxia, loss of vibration and position senses, ophthalmoplegia, muscle weakness, ptosis, and dysarthria.

In adults with malabsorption, vitamin E deficiency very rarely causes spinocerebellar ataxia because adults have large vitamin E stores in adipose tissue.

**Diagnosis**

- Low α-tocopherol level or low ratio of serum α-tocopherol to serum lipids

Without a history of inadequate intake or a predisposing condition, vitamin E deficiency is unlikely. Confirmation usually requires measuring the vitamin level. Measuring RBC hemolysis in response to peroxide can suggest the diagnosis but is nonspecific. Hemolysis increases as vitamin E deficiency impairs RBC stability.

Measuring the serum α-tocopherol level is the most direct method of diagnosis. In adults, vitamin E deficiency is suggested if the α-tocopherol level is < 5 μg/mL (< 11.6 μmol/L). Because abnormal lipid levels can affect vitamin E status, a low ratio of serum α-tocopherol to lipids (< 0.8 mg/g total lipid) is the most accurate indicator in adults with hyperlipidemia.

In children and adults with abetalipoproteinemia, serum α-tocopherol levels are usually undetectable.
Treatment

• Supplemental α-tocopherol

If malabsorption causes clinically evident deficiency, α-tocopherol 15 to 25 mg/kg po once/day should be given. However, larger doses given by injection are required to treat neuropathy during its early stages or to overcome the defect of absorption and transport in abetalipoproteinemia.

Prevention

Although premature neonates may require supplementation, human milk and commercial formulas have enough vitamin E for full-term neonates.

Vitamin E Toxicity

Many adults take relatively large amounts of vitamin E (α-tocopherol 400 to 800 mg/day) for months to years without any apparent harm. Occasionally, muscle weakness, fatigue, nausea, and diarrhea occur. The most significant risk is bleeding. However, bleeding is uncommon unless the dose is > 1000 mg/day or the patient takes oral coumarin or warfarin. Thus, the upper limit for adults aged ≥19 yr is 1000 mg for any form of α-tocopherol. Recent analyses of previous studies report that high vitamin E intakes may increase the risk of hemorrhagic stroke and premature death.

Vitamin K

Vitamin K₁ (phylloquinone) is dietary vitamin K. Dietary fat enhances its absorption. Infant formulas contain supplemental vitamin K. Vitamin K₂ refers to a group of compounds (menaquinones) synthesized by bacteria in the intestinal tract; the amount synthesized does not satisfy the vitamin K requirement.

Vitamin K controls the formation of coagulation factors II (prothrombin), VII, IX, and X in the liver. Other coagulation factors dependent on vitamin K are protein C, protein S, and protein Z; proteins C and S are anticoagulants. Metabolic pathways conserve vitamin K. Once vitamin K has participated in formation of coagulation factors, the reaction product, vitamin K epoxide, is enzymatically converted to the active form, vitamin K hydroquinone.

The actions of vitamin K-dependent proteins require Ca. The vitamin K-dependent proteins, osteocalcin and matrix γ-carboxy-glutamyl (Gla) protein, may have important roles in bone and other tissues. Forms of vitamin K are common therapy for osteoporosis in Japan and other countries.

Vitamin K Deficiency

Vitamin K deficiency results from extremely inadequate intake, fat malabsorption, or use of coumarin anticoagulants. Deficiency is particularly common among breastfed infants. It impairs clotting. Diagnosis is suspected based on routine coagulation study findings and confirmed by response to vitamin K. Treatment consists of vitamin K given orally or, when fat malabsorption is the cause or risk of bleeding is high, parenterally.

Vitamin K deficiency decreases levels of prothrombin and other vitamin K-dependent coagulation factors, causing defective coagulation and, potentially, bleeding.

Etiology

Worldwide, vitamin K deficiency causes infant morbidity and mortality. Vitamin K deficiency causes hemorrhagic disease of the newborn, which usually occurs 1 to 7 days postpartum. In affected neonates, birth trauma can cause intracranial hemorrhage. Neonates are prone to vitamin K deficiency because of the following:

• The placenta transmits lipids and vitamin K relatively poorly.
• The neonatal liver is immature with respect to prothrombin synthesis.

• Breast milk is low in vitamin K, containing about 2.5 μg/L (cow's milk contains 5000 μg/L).

• The neonatal gut is sterile during the first few days of life.

Late hemorrhagic disease (occurring 3 to 8 wk postpartum) is usually associated with breastfeeding, malabsorption, or a liver disorder. If the mother has taken phenytoin anticonvulsants, coumarin anticoagulants, or cephalosporin antibiotics, the risk of both types of hemorrhagic disease is increased.

In healthy adults, dietary vitamin K deficiency is uncommon because vitamin K is widely distributed in green vegetables and the bacteria of the normal gut synthesize menaquinones. However, biliary obstruction, malabsorption, cystic fibrosis, and resection of the small intestine can contribute to vitamin K deficiency.

Coumarin anticoagulants interfere with the synthesis of vitamin K-dependent coagulation proteins (factors II, VII, IX, and X) in the liver. Certain antibiotics (particularly some cephalosporins and other broad-spectrum antibiotics), salicylates, megadoses of vitamin E, and hepatic insufficiency increase risk of bleeding in patients with vitamin K deficiency.

**Symptoms and Signs**

Bleeding is the usual manifestation. Easy bruisability and mucosal bleeding (especially epistaxis, GI hemorrhage, menorrhagia, and hematuria) can occur. Blood may ooze from puncture sites or incisions.

Hemorrhagic disease of the newborn and late hemorrhagic disease in infants may cause cutaneous, GI, intrathoracic, or, in the worst cases, intracranial bleeding. If obstructive jaundice develops, bleeding—if it occurs—usually begins after the 4th or 5th day. It may begin as a slow ooze from a surgical incision, the gums, the nose, or GI mucosa, or it may begin as massive bleeding into the GI tract.

**Diagnosis**

• Usually, prolonged PT that decreases after phytonadione

Vitamin K deficiency or antagonism (due to coumarin anticoagulants) is suspected when abnormal bleeding occurs in a patient at risk. Blood coagulation studies can preliminarily confirm the diagnosis. PT, usually reported as the INR, is prolonged, but PTT, thrombin time, platelet count, bleeding time, and levels of fibrinogen, fibrin-split products, and D-dimer are normal. If phytonadione (USP generic name for vitamin K₁) 1 mg IV significantly decreases PT within 2 to 6 h, a liver disorder is not the likely cause, and the diagnosis of vitamin K deficiency is confirmed. Some centers can detect vitamin K deficiency more directly by measuring the serum vitamin level. The serum level of vitamin K₁ ranges from 0.2 to 1.0 ng/mL in healthy people consuming adequate quantities of vitamin K₁ (50 to 150 μg/day). Knowing vitamin K intake can help interpret serum levels; recent intake affects levels in serum but not in tissues.

More sensitive indicators of vitamin K status, such as PIVKA (Protein Induced in Vitamin K Absence or Antagonism) and under-carboxylated osteocalcin, are under study.

**Treatment**

• Phytonadione

Whenever possible, phytonadione should be given po or sc. The usual adult dose is 5 to 20 mg. (Rarely, even when phytonadione is correctly diluted and given slowly, IV replacement can result in anaphylaxis or anaphylactoid reactions.) INR usually decreases within 6 to 12 h. The dose may be repeated in 6 to 8 h if INR has not decreased satisfactorily. Phytonadione 2.5 to 10 mg po is indicated for nonemergency correction of a prolonged INR in patients taking anticoagulants. Correction usually occurs within 6 to 8 h. When only partial correction of INR is desirable (eg, when INR should remain slightly elevated because of
a prosthetic heart valve), lower doses (eg, 1 to 2.5 mg) of phytonadione can be given.

In infants, bleeding due to deficiency can be corrected by giving phytonadione 1 mg sc or IM once. The dose is repeated if INR remains elevated. Higher doses may be necessary if the mother has been taking oral anticoagulants.

Prevention

Phytonadione 0.5 to 1 mg IM (or 0.3 mg/kg for preterm infants) is recommended for all neonates within 6 h of birth to reduce the incidence of intracranial hemorrhage due to birth trauma and of classic hemorrhagic disease of the newborn (increased bleeding risks 1 to 7 days after birth). It is also used prophylactically before surgery. Some clinicians recommend that pregnant women taking anticonvulsants receive phytonadione 10 mg po once/day for the 1 mo or 20 mg po once/day for the 2 wk before delivery. The low vitamin K\textsubscript{1} content in breast milk can be increased by increasing maternal dietary intake of phylloquinone to 5 mg/day.

Vitamin K Toxicity

Vitamin K\textsubscript{1} (phylloquinone) is not toxic when consumed orally, even in large amounts. However, menadione (a synthetic, water-soluble vitamin K precursor) can cause toxicity and should not be used to treat vitamin K deficiency.
Chapter 5. Mineral Deficiency and Toxicity

Introduction

Six macrominerals are required by people in gram amounts. Four (Na, K, Ca, and Mg) are cations; two (Cl and P) are accompanying anions (see p. 820). Daily requirements range from 0.3 to 2.0 g. Bone, muscle, heart, and brain function depend on these minerals.

Nine trace minerals (microminerals) are required by people in minute amounts: chromium, copper, iodine, iron, fluorine, manganese, molybdenum, selenium, and zinc. (For sources, functions, effects of deficiency and toxicity, and dietary requirements, see Tables 5-1 and 5-2.) All trace minerals are toxic at high levels; some minerals (arsenic, nickel, and chromium) may be carcinogens.

Mineral deficiencies (except of iodine, iron, and zinc) do not often develop spontaneously in adults on ordinary diets; infants are more vulnerable because their growth is rapid and intake varies. Trace mineral imbalances can result from hereditary disorders (eg, hemochromatosis, Wilson's disease), kidney dialysis, parenteral nutrition, or restrictive diets prescribed for people with inborn errors of metabolism.

Chromium

Only 1 to 3% of biologically active trivalent chromium (Cr) is absorbed. Normal plasma levels are 0.05 to 0.50 μg/L (1.0 to 9.6 nmol/L). Chromium potentiates insulin activity and increases the growth rate in undernourished children. Supplements do not enhance muscle size or strength in men.

Deficiency: Four patients receiving long-term TPN developed possible chromium deficiency, with glucose intolerance, weight loss, ataxia, and peripheral neuropathy. Symptoms resolved in 3 who were given trivalent chromium 150 to 250 mg.

Toxicity: High doses of trivalent chromium given parenterally cause skin irritation, but lower doses given orally are not toxic. Exposure to hexavalent chromium (CrO₃) in the workplace may irritate the skin, lungs, and GI tract and may cause perforation of the nasal septum and lung carcinoma.

Copper

Copper is a component of many body proteins; almost all of the body's copper is bound to copper proteins. Unbound (free) copper ions are toxic. Genetic mechanisms control the incorporation of copper into apoproteins and the processes that prevent toxic accumulation of copper in the body. Copper absorbed in excess of metabolic requirements is excreted through bile.

Acquired Copper Deficiency

If the genetic mechanisms controlling copper metabolism are normal, dietary deficiency rarely causes clinically significant copper deficiency. The only reported causes are kwashiorkor, persistent infantile diarrhea (usually associated with a diet limited to milk), severe malabsorption (as in sprue), and excessive zinc intake.

Deficiency may cause neutropenia, impaired bone calcification, and hypochromic anemia not responsive to iron supplements.

Diagnosis is based on low serum levels of copper and ceruloplasmin, although these tests are not always reliable. Treatment is directed at the cause, and copper 1.5 to 3 mg/day po (usually as copper sulfate) is given.
Inherited Copper Deficiency

(Menkes Syndrome)

Inherited copper deficiency occurs in male infants who inherit a mutant X-linked gene. Incidence is about 1 in 50,000 live births. Copper is deficient in the liver, serum, and essential copper proteins, including cytochrome-c oxidase, ceruloplasmin, and lysyl oxidase.

Symptoms are severe intellectual disability, vomiting, diarrhea, protein-losing enteropathy, hypopigmentation, bone changes, and arterial rupture; the hair is sparse, steely, or kinky.

Diagnosis

• Serum copper and ceruloplasmin levels

• Serum levels of dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in infants at risk

Diagnosis is based on low copper and ceruloplasmin levels in serum, although these tests are not always reliable. Because early diagnosis and treatment seem to result in a better prognosis, the disorder is ideally detected before age 2 wk. However, diagnostic accuracy of these tests is limited. Thus, infants at risk (eg, those with a family history) can be screened by measuring dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in serum. A dihydroxyphenylacetic acid:dihydroxyphenylglycol ratio of > 4 seems to indicate deficiency, and a dopamine:norepinephrine ratio of > 0.2 seems to confirm it.

Treatment

• Copper histidine

Parenteral copper is usually given as copper histidine 250 μg sc bid to age 1 yr, then 250 μg sc once/day until age 3 yr; monitoring kidney function is essential during treatment. Despite early treatment, many children have abnormal neurodevelopment.

Acquired Copper Toxicity

Acquired copper toxicity can result from ingesting or absorbing excess copper (eg, from ingesting an acidic food or beverage that has had prolonged contact with a copper container). Self-limited gastroenteritis with nausea, vomiting, and diarrhea may occur.

[Table 5-2, Guidelines for Daily Intake of Minerals]

More severe toxicity results from ingestion (usually with suicidal intent) of gram quantities of a copper salt (eg, copper sulfate) or from absorption of large amounts through the skin (eg, if compresses saturated with a solution of a copper salt are applied to large areas of burned skin). Hemolytic anemia and anuria can result and may be fatal.

Indian childhood cirrhosis, non-Indian childhood cirrhosis, and idiopathic copper toxicity are probably identical disorders in which excess copper causes cirrhosis. All seem to be caused by ingesting milk that has been boiled or stored in corroded copper or brass vessels. Recent studies suggest that idiopathic copper toxicity may develop only in infants with an unknown genetic defect.

Diagnosis usually requires liver biopsy, which shows Mallory hyalin bodies.

Treatment

• Chelation
• Supportive measures

For copper toxicity due to ingesting grams of copper, prompt gastric lavage is done. Copper toxicity that causes complications such as hemolytic anemia, anuria, or hepatotoxicity is also treated with either oral penicillamine 250 mg q 6 h to 750 mg q 12 h (1000 to 1500 mg/day in 2 to 4 doses) or dimercaprol 3 to 5 mg/kg IM q 4 h for 2 days, then q 4 to 6 h (see also Table 340-4 and copper salts in Table 340-8). If used early, hemodialysis may be effective. Occasionally, copper toxicity is fatal despite treatment.

Inherited Copper Toxicity

(Wilson's Disease)

Inherited copper toxicity results in accumulation of copper in the liver and other organs. Hepatic or neurologic symptoms develop. Diagnosis is based on a low serum ceruloplasmin level, high urinary excretion of copper, and sometimes liver biopsy results. Treatment consists of a low-copper diet and chelation, usually with penicillamine or dimercaprol.

Wilson's disease is a progressive disorder of copper metabolism that affects 1 person in 30,000. Affected people are homozygous for the mutant recessive gene, located on chromosome 13. Heterozygous carriers, who constitute about 1.1% of the population, are asymptomatic.

Pathophysiology

The genetic defect impairs copper transport. The impaired transport decreases copper secretion into the bile, thus causing the copper overload and resultant accumulation in the liver, which begins at birth. The impaired transport also interferes with incorporation of copper into the copper protein ceruloplasmin, thus decreasing serum levels of ceruloplasmin.

Hepatic fibrosis develops, ultimately causing cirrhosis. Copper diffuses out of the liver into the blood, then into other tissues. It is most destructive to the brain but also damages the kidneys and reproductive organs and causes hemolytic anemia. Some copper is deposited in Descemet's membrane of the cornea, causing Kayser-Fleischer rings.

Symptoms and Signs

Symptoms usually develop between ages 5 and 40. In almost half of patients, particularly adolescents, the first symptom is hepatitis—acute, chronic active, or fulminant. But hepatitis may develop at any time. In about 40% of patients, particularly young adults, the first symptoms reflect CNS involvement. Motor deficits are common, including any combination of tremors, dystonia, dysarthria, dysphagia, chorea, drooling, and incoordination. Sometimes the first symptoms are cognitive or psychiatric abnormalities. In 5 to 10% of patients, the first symptom is incidentally noted gold or greenish gold Kayser-Fleischer rings or crescents (due to copper deposits in the cornea), amenorrhea or repeated miscarriages, or hematuria.

Diagnosis

• Slit-lamp examination for Kayser-Fleischer rings

• Serum ceruloplasmin and 24-h urinary copper excretion

• Sometimes confirmation by penicillamine provocation test or liver biopsy

Wilson's disease should be suspected in people < 40 with any of the following:

• An unexplained hepatic, neurologic, or psychiatric disorder

• An unexplained persistent elevation in hepatic transaminases
• A sibling, parent, or cousin with Wilson's disease

• Fulminant hepatitis

If Wilson's disease is suspected, slit-lamp examination for Kayser-Fleischer rings is required, and serum ceruloplasmin and copper levels and 24-h urinary copper excretion are measured. Transaminase levels are also often measured; high levels are consistent with the diagnosis.

Kayser-Fleischer rings: These rings plus typical motor neurologic abnormalities or a decrease in ceruloplasmin are nearly pathognomonic for Wilson's disease. Rarely, these rings occur in other liver disorders (eg, biliary atresia, primary biliary cirrhosis), but ceruloplasmin levels should be unaffected.

Ceruloplasmin: Serum ceruloplasmin (normally 20 to 35 mg/dL) is usually low in Wilson's disease but can be normal. It can also be low in heterozygous carriers and those with other liver disorders (eg, viral hepatitis, drug- or alcohol-induced liver disease). A low ceruloplasmin level in a patient with a Kayser-Fleischer ring is diagnostic. Also, a level of < 5 mg/dL is highly suggestive regardless of clinical findings.

Serum copper: Despite the copper accumulation in the body, serum copper levels are decreased because of the decreased ceruloplasmin levels.

Urinary copper excretion: In Wilson's disease, 24-h urinary copper excretion (normally, ≤ 30 μg/day) is usually > 100 μg/day. If serum ceruloplasmin is low and urinary copper excretion is high, diagnosis is clear. If levels are equivocal, measuring urinary copper excretion after penicillamine is given (penicillamine provocation test) may confirm the diagnosis; this test is not usually done in adults because cutoff values are not well-established.

Liver biopsy: In unclear cases (eg, elevated transaminases, no Kayser-Fleischer rings, indeterminate values for ceruloplasmin and urinary copper), the diagnosis is made by doing a liver biopsy to measure hepatic copper concentration. However, false-negative results may occur because of a sampling error (due to large variations in copper concentrations in the liver) or fulminant hepatitis (causing necrosis that releases large amounts of copper).

Screening: Because early treatment is most effective, screening is indicated for anyone who has a sibling, cousin, or parent with Wilson's disease. Screening consists of a slit-lamp examination and measurement of transaminase levels, serum copper and ceruloplasmin, and 24-h urine copper excretion. If any results are abnormal, liver biopsy is done to measure hepatic copper concentration. Infants should not be tested until after age 1 yr because ceruloplasmin levels are low during the first few months of life. Children < 6 yr with normal test results should be retested 5 to 10 yr later.

Genetic testing is under investigation.

Prognosis

Prognosis is usually good, unless disease is advanced before treatment begins. Untreated Wilson's disease is fatal, usually by age 30.

Treatment

• Penicillamine or another chelating drug if needed to remove accumulated copper

• Low-copper diet

• For maintenance, lifelong low-dose chelation therapy or oral zinc

Continual, lifelong treatment is mandatory regardless of whether symptoms are present. Accumulated copper should be removed with chelating drugs. A low-copper diet (eg, avoiding beef liver, cashews, black-eyed peas, vegetable juice, shellfish, mushrooms, and cocoa) and use of either low-dose chelation
therapy or oral zinc can prevent copper from accumulating.

Penicillamine is the most commonly used chelating drug but has considerable toxicity (eg, fever, rash, neutropenia, thrombocytopenia, proteinuria). Cross-reactivity may occur in people with penicillin allergy. Patients > 5 yr are given oral doses of 62.5 mg q 6 h to 250 mg q 12 h (250 to 500 mg/day in 2 to 4 doses) and slowly increased to a maximum of 250 mg q 6 h to 750 mg q 12 h (1000 to 1500 mg/day in 2 to 4 doses). Younger children are given 10 mg/kg bid or 6.7 mg/kg tid (20 mg/kg/d) po. Pyridoxine 25 mg po once/day is given with penicillamine. Occasionally, use of penicillamine is associated with worsening neurologic symptoms.

Trientine hydrochloride is an alternative treatment to penicillamine. Doses are 375 to 750 mg po bid or 250 to 500 mg po tid (750 to 1500 mg/day).

Zinc acetate 50 mg po tid can prevent reaccumulation of copper in patients who cannot tolerate penicillamine or trientine or who have neurologic symptoms that do not respond to the other drugs. (CAUTION: Penicillamine or trientine must not be given with zinc because either drug can bind zinc, forming a compound with no therapeutic effect.)

Poor long-term adherence to drug therapy is common. After 1 to 5 yr of therapy, lower dose maintenance drug therapy can be considered. Regular follow-up care with an expert in liver disease is recommended.

Liver transplantation may be lifesaving for patients who have Wilson's disease and fulminant hepatic failure or severe hepatic insufficiency refractory to drugs.

Fluorine

Most of the body's fluorine (F) is contained in bones and teeth. Fluoride (the ionic form of fluorine) is widely distributed in nature. The main source of fluoride is fluoridated drinking water.

Deficiency: Fluorine deficiency can lead to dental caries and possibly osteoporosis. Fluoridation of water that contains < 1 ppm (the ideal) reduces the incidence of dental caries. If a child's drinking water is not fluoridated, oral fluoride supplements can be prescribed.

Toxicity: Excess fluorine can accumulate in teeth and bones, causing fluorosis. Drinking water containing > 10 ppm is a common cause. Permanent teeth that develop during high fluoride intake are most likely to be affected. Exposure must be much greater to affect deciduous teeth.

The earliest signs are chalky white, irregularly distributed patches on the surface of the enamel; these patches become stained yellow or brown, producing a characteristic mottled appearance. Severe toxicity weakens the enamel, pitting its surface. Bony changes, including osteosclerosis, exostoses of the spine, and genu valgum, can develop but only in adults after prolonged high intake of fluoride.

No tests to diagnose toxicity are available.

Treatment involves reducing fluoride intake; eg, in areas with high fluoride water levels, patients should not drink fluoridated water or take fluoride supplements. Children should always be told not to swallow fluoridated toothpastes.

Iodine

In the body, iodine (I) is involved primarily in the synthesis of 2 thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Iodine occurs in the environment and in the diet primarily as iodide. In adults, about 80% of the iodide absorbed is trapped by the thyroid gland. Most environmental iodine occurs in seawater as iodide; a small amount enters the atmosphere and, through rain, enters ground water and soil near the sea. Thus, people living far from the sea and at higher altitudes are at particular risk of deficiency. Fortifying table salt with iodide (typically 70 μg/g) helps ensure adequate intake (150 μg/day). Requirements are higher for pregnant (220 μg/day) and breastfeeding (290 μg/day) women.
Iodine Deficiency

Deficiency is rare in areas where iodized salt is used but common worldwide. Iodine deficiency develops when iodide intake is < 20 μg/day. In mild or moderate deficiency, the thyroid gland, influenced by thyroid-stimulating hormone (TSH), hypertrophies to concentrate iodide in itself, resulting in colloid goiter. Usually, patients remain euthyroid; however, severe iodine deficiency in adults may cause hypothyroidism (endemic myxedema). It can decrease fertility and increase risk of stillbirth, spontaneous abortion, and prenatal and infant mortality. Severe maternal iodine deficiency retards fetal growth and brain development, sometimes resulting in birth defects, and, in infants, causes cretinism, which may include intellectual disability, deaf-mutism, difficulty walking, short stature, and sometimes hypothyroidism.

Diagnosis

• Assessment of thyroid structure and function

Diagnosis in adults and children is usually based on thyroid function, examination for goiter, and imaging tests identifying abnormalities in thyroid function and structure (see p. 776). All neonates should be screened by measuring the TSH level.

Treatment

• Iodide with or without levothyroxine

Infants with iodine deficiency are given L-thyroxine 3 μg/kg po once/day for a week plus iodide 50 to 90 μg po once/day for several weeks to quickly restore a euthyroid state. Children are treated with iodide 90 to 120 μg once/day. Adults are given iodide 150 μg once/day. Iodine deficiency can also be treated by giving levothyroxine. Serum TSH levels are monitored in all patients until the levels are normal (ie, < 5 μU/mL).

Iodine Toxicity

Chronic toxicity may develop when intake is > 1.1 mg/day. Most people who ingest excess amounts of iodine remain euthyroid. Some people who ingest excess amounts of iodine, particularly those who were previously deficient, develop hyperthyroidism (Jod-Basedow phenomenon). Paradoxically, excess uptake of iodide by the thyroid may inhibit thyroid hormone synthesis (called Wolff-Chaikoff effect). Thus, iodine toxicity can eventually cause iodide goiter, hypothyroidism, or myxedema. Very large amounts of iodide may cause a brassy taste in the mouth, increased salivation, GI irritation, and acneiform skin lesions. Patients exposed to frequent large amounts of radiographic contrast dyes or the drug amiodarone also need to have their thyroid function monitored.

Diagnosis is usually based on thyroid function and imaging test findings (see p. 776), which are correlated with clinical data. Iodine excretion may be more specific but is not usually measured. Treatment consists of correcting thyroid abnormalities and, if intake is excessive, dietary modification.

Iron

Iron (Fe) is a component of hemoglobin, myoglobin, and many enzymes in the body. Heme iron, contained mainly in animal products, is absorbed much better than nonheme iron (eg, in plants and grains), which accounts for > 85% of iron in the average diet. However, absorption of nonheme iron is increased when it is consumed with animal protein and vitamin C.

Deficiency: Iron deficiency is one of the most common mineral deficiencies in the world. It may result from the following:

• Inadequate iron intake, common in infants, adolescent girls, and pregnant women
• Malabsorption (eg, celiac sprue)
Chronic bleeding due to colon cancer is a serious cause in middle-aged people and the elderly.

When deficiency is advanced, microcytic anemia develops (see p. 924).

In addition to anemia, iron deficiency may cause pica (a craving for nonfoods) and spoon nails and is associated with restless leg syndrome. Rarely, iron deficiency causes dysphagia due to postcricoid esophageal web.

Diagnosis involves CBC, serum ferritin, and possibly measurement of transferrin saturation (iron capacity).

All people with moderate or severe iron deficiency and some people with mild deficiency require iron supplementation.

**Toxicity:** Iron may accumulate in the body because of

- Iron therapy given in excessive amounts or for too long
- Repeated blood transfusions
- Chronic alcoholism
- Overdose of iron

Iron overload can also result from an inherited iron overload disease (hemochromatosis—see p. 1032), a potentially fatal but easily treatable genetic disorder in which too much iron is absorbed. Hemochromatosis affects > 1 million Americans.

An overdose of iron is toxic (see p. 3341), causing vomiting, diarrhea, and damage to the intestine and other organs.

Diagnosis is similar to that for iron deficiency.

Treatment often involves deferoxamine, which binds with iron and is excreted in urine.

**Manganese**

Manganese (Mn), necessary for healthy bone structure, is a component of several enzyme systems, including manganese-specific glycosyltransferases and phosphoenolpyruvate carboxykinase. Median intake is between 1.6 and 2.3 mg/day; absorption is 5 to 10%.

Deficiency has not been conclusively documented, although one experimental case in a volunteer resulted in transient dermatitis, hypocholesterolemia, and increased alkaline phosphatase levels.

Toxicity is usually limited to people who mine and refine ore; prolonged exposure causes neurologic symptoms resembling those of parkinsonism or Wilson's disease.

**Molybdenum**

Molybdenum (Mo) is a component of coenzymes necessary for the activity of xanthine oxidase, sulfite oxidase, and aldehyde oxidase.

Genetic and nutritional deficiencies of molybdenum have been reported but are rare. Genetic sulfite oxidase deficiency was described in 1967 in a child. It resulted from the inability to form the molybdenum coenzyme despite the presence of adequate molybdenum. The deficiency caused intellectual disability, seizures, opisthotonus, and lens dislocation.
Molybdenum deficiency resulting in sulfite toxicity occurred in a patient receiving long-term TPN. Symptoms were tachycardia, tachypnea, headache, nausea, vomiting, and coma. Laboratory tests showed high levels of sulfite and xanthine and low levels of sulfate and uric acid in the blood and urine. Ammonium molybdate 300 μg/day IV caused dramatic recovery.

A case of molybdenum toxicity may have occurred in 1961; it caused goutlike symptoms and abnormalities of the GI tract, liver, and kidneys.

### Selenium

Selenium (Se) is a part of the enzyme glutathione peroxidase, which metabolizes hydro-peroxides formed from polyunsaturated fatty acids. Selenium is also a part of the enzymes that deiodinate thyroid hormones. Generally, selenium acts as an antioxidant that works with vitamin E. Some epidemiologic studies associate low selenium levels with cancer. In children with Down syndrome, selenium supplements may help prevent bacterial infections. Plasma levels vary from 8 to 25 μg/dL, depending on selenium intake. Diagnosis is usually clinical; sometimes blood glutathione peroxidase is measured.

**Deficiency:** Deficiency is rare, even in New Zealand and Finland, where selenium intake is 30 to 50 μg/day, compared with 100 to 250 μg/day in the US and Canada. In certain areas of China, where intake averages 10 to 15 μg/day, selenium deficiency predisposes patients to Keshan disease, an endemic viral cardiomyopathy affecting primarily children and young women. This cardiomyopathy can be prevented but not cured by sodium selenite supplements of 50 μg/day po. Patients receiving long-term TPN have developed selenium deficiency with muscle pain and tenderness that responded to a selenomethionine supplement. In Siberian Russia and China, growing children with selenium deficiency may develop chronic osteoarthropathy (Kashin-Beck disease). Selenium deficiency may contribute synergistically with iodine deficiency to the development of goiter and hypothyroidism.

Diagnosis is made clinically or sometimes by measuring glutathione peroxidase activity or plasma selenium, but neither of these tests is readily available. Treatment consists of sodium selenite 100 μg/day po.

**Toxicity:** At high doses (> 900 μg/day), selenium causes toxicity. Manifestations include hair loss, abnormal nails, dermatitis, peripheral neuropathy, nausea, diarrhea, fatigue, irritability, and a garlic odor of the breath. Toxic levels of plasma selenium are not well defined.

### Zinc

Zinc (Zn) is contained mainly in bones, teeth, hair, skin, liver, muscle, leukocytes, and testes. Zinc is a component of several hundred enzymes, including many nicotinamide adenine dinucleotide (NADH) dehydrogenases, RNA and DNA polymerases, and DNA transcription factors as well as alkaline phosphatase, superoxide dismutase, and carbonic anhydrase. A diet high in fiber and phytate (eg, in whole-grain bread) reduces zinc absorption.

**Deficiency:** Dietary deficiency is unlikely in healthy people. Secondary zinc deficiency can develop in the following:

- Some patients with hepatic insufficiency (because the ability to retain zinc is lost)
- Patients taking diuretics
- Patients with diabetes mellitus, sickle cell disease, chronic renal failure, or malabsorption
- Patients with stressful conditions (eg, sepsis, burns, head injury)
- Elderly institutionalized and homebound patients (common)

Maternal zinc deficiency may cause fetal malformations and low birth weight.
Zinc deficiency in children causes impaired growth and impaired taste (hypogeusia). Other symptoms and signs in children include delayed sexual maturation and hypogonadism. In children or adults, symptoms include hypogonadism, alopecia, impaired immunity, anorexia, dermatitis, night blindness, anemia, lethargy, and impaired wound healing.

Zinc deficiency should be suspected in undernourished patients with typical symptoms or signs. However, because many of the symptoms and signs are nonspecific, clinical diagnosis of mild zinc deficiency is difficult. Laboratory diagnosis is also difficult. Low albumin levels, common in zinc deficiency, make serum zinc levels difficult to interpret; diagnosis usually requires the combination of low levels of zinc in serum and increased urinary zinc excretion. If available, isotope studies can measure zinc status more accurately.

Treatment consists of elemental zinc 15 to 120 mg/day po until symptoms and signs resolve.

**Acrodermatitis enteropathica** (a rare, once fatal autosomal recessive disorder) causes malabsorption of zinc. Psoriasiform dermatitis develops around the eyes, nose, and mouth; on the buttocks; and in an acral distribution. The disorder also causes hair loss, paronychia, impaired immunity, recurrent infection, impaired growth, and diarrhea. Symptoms and signs usually develop after infants are weaned from breast milk. In such cases, doctors suspect the diagnosis. If deficiency is diagnosed, zinc sulfate 30 to 150 mg/day po usually results in complete remission.

**Toxicity:** The recommended upper limit for zinc intake is 40 mg/day. Toxicity is rare. Ingesting doses of elemental zinc ranging from 100 to 150 mg/day for prolonged periods interferes with copper metabolism and causes low blood copper levels, RBC microcytosis, neutropenia, and impaired immunity; higher doses should be given only for short periods of time and the patient should be followed closely. Ingesting larger amounts (200 to 800 mg/day), usually by consuming acidic food or drink from a galvanized (zinc-coated) container, can cause anorexia, vomiting, and diarrhea. Metal fume fever, also called brass-founders’ ague or zinc shakes, is caused by inhaling industrial zinc oxide fumes; it results in neurologic damage. Symptoms usually resolve after 12 to 24 h in a zinc-free environment.
Chapter 6. Obesity and the Metabolic Syndrome

Obesity

Obesity is excess body fat; consequences depend not only on the absolute amount but also on the distribution of the fat. Complications include cardiovascular disorders, diabetes mellitus, many cancers, cholelithiasis, fatty liver and cirrhosis, osteoarthritis, reproductive disorders in men and women, psychologic disorders, and premature death. Diagnosis is based on body mass index (BMI—calculated from height and weight) and waist circumference. BP, fasting plasma glucose, and lipid levels should be measured. Treatment includes physical activity, dietary and behavioral modification, and sometimes drugs or surgery.

Prevalence of obesity in the US is high and is increasing, particularly among children and adolescents (see Table 6-1).

Prevalence is more than twice as high at age 55 as at age 20. Obesity is twice as common among women in a lower socioeconomic group as among those in a higher group. Prevalence among black and white men does not differ significantly, but it is higher among black women than white women. More than 50% of black women ≥ 40 yr are obese; > 80% are overweight.

In the US, obesity and its complications cause as many as 300,000 premature deaths each year, making it second only to cigarette smoking as a preventable cause of death.

Table 6-1. Changes in Prevalence of Obesity According to Nhanes

Etiology

Almost all cases of obesity result from a combination of genetic predisposition and a chronic imbalance between energy intake, energy utilization for basic metabolic processes, and energy expenditure from physical activity.

Genetic factors: Heritability of BMI is about 66%. Genetic factors may affect the many signaling molecules and receptors used by parts of the hypothalamus and GI tract to regulate food intake (see Sidebar 6-1). Rarely, obesity results from abnormal levels of peptides that regulate food intake (eg, leptin) or abnormalities in their receptors (eg, melanocortin-4 receptor).

Genetic factors also regulate energy expenditure, including BMR, diet-induced thermogenesis, and nonvoluntary activity-associated thermogenesis. Genetic factors may have a greater effect on the distribution of body fat, particularly abdominal fat (see Metabolic Syndrome on p. 64), than on the amount of body fat.

Environmental factors: Weight is gained when caloric intake exceeds energy needs. Important determinants of energy intake include portion sizes and the energy density of the food. High-fat foods, processed foods, and diets high in refined carbohydrates, soft drinks, fruit juices, and alcohol promote weight gain. Diets high in fresh fruit and vegetables, fiber, and complex carbohydrates, with water as the main fluid consumed, minimize weight gain. A sedentary lifestyle promotes weight gain.

Regulatory factors: Prenatal maternal obesity, prenatal maternal smoking, intrauterine growth restriction, and insufficient sleep can disturb weight regulation. About 15% of women permanently gain ≥ 20 lb with each pregnancy. Obesity that persists beyond early childhood makes weight loss in later life more difficult.

Drugs, including corticosteroids, lithium, traditional antidepressants (tricyclics, tetracyclics, and monoamine oxidase inhibitors [MAOIs]), benzodiazepines, and antipsychotic drugs, often cause weight gain.

Uncommonly, weight gain is caused by one of the following disorders:
Brain damage caused by a tumor (especially a craniopharyngioma) or an infection (particularly those affecting the hypothalamus), which can stimulate consumption of excess calories.

Hyperinsulinism due to pancreatic tumors.

Hypercortisolism due to Cushing's syndrome, which causes predominantly abdominal obesity.

Hypothyroidism (rarely a cause of substantial weight gain).

### Sidebar 6-1 Pathways Regulating Food Intake

Preabsorptive and postabsorptive signals from the GI tract and changes in plasma nutrient levels provide short-term feedback to regulate food intake:

- GI hormones (eg, glucagon-like peptide 1 [GLP-1], cholecystokinin [CCK]) reduce food intake.

- Ghrelin, secreted primarily by the stomach, increases food intake.

- Leptin, secreted from adipose tissue, informs the brain as to how much fat is stored; high leptin levels correlate with increased body fat.

The hypothalamus integrates various signals involved in the regulation of energy balance and then activates pathways that increase or decrease food intake:

- Neuropeptide Y (NPY), agouti-related peptide (ARP), α-melanocyte-stimulating hormone (α-MSH), cocaine- and amphetamine-related transcript (CART), orexin, and melanin-concentrating hormone (MCH) increase food intake.

- Corticotropic hormone (CRH) and urocortin decrease it.

### Eating disorders: At least 2 pathologic eating patterns may be associated with obesity:

- **Binge eating disorder** is consumption of large amounts of food quickly with a subjective sense of loss of control during the binge and distress after it (see p. 1537). This disorder does not include compensatory behaviors, such as vomiting. Prevalence is 1 to 3% among both sexes and 10 to 20% among people entering weight reduction programs. Obesity is usually severe, large amounts of weight are frequently gained or lost, and pronounced psychologic disturbances are present.

- **Night-eating syndrome** consists of morning anorexia, evening hyperphagia, and insomnia. At least 25 to 50% of daily intake occurs after the evening meal. About 10% of people seeking treatment for severe obesity may have this disorder. Rarely, a similar disorder is induced by use of a hypnotic such as zolpidem.

Similar but less extreme patterns, classified as eating disorders not otherwise specified (EDNOS), probably contribute to excess weight gain in more people. For example, nocturnal eating contributes to excess weight gain in many people who do not have night-eating syndrome.

### Complications

Complications of obesity include the following:

- Metabolic syndrome

- Diabetes mellitus
• Cardiovascular disease
• Nonalcoholic steatohepatitis (fatty liver)
• Gallbladder disease
• Gastroesophageal reflux
• Obstructive sleep apnea
• Reproductive system disorders
• Many cancers
• Osteoarthritis
• Social and psychologic problems

Insulin resistance, dyslipidemias, and hypertension (the metabolic syndrome) develop, often leading to diabetes mellitus and coronary artery disease (see p. 64). These complications are more likely in patients with fat that is concentrated abdominally, a high serum triglyceride level, a family history of type 2 diabetes mellitus or premature cardiovascular disease, or a combination of these risk factors.

Obesity is also a risk factor for nonalcoholic steatohepatitis (which may lead to cirrhosis) and for reproductive system disorders, such as a low serum testosterone level in men and polycystic ovary syndrome in women.

Obstructive sleep apnea can result if excess fat in the neck compresses the airway during sleep. Breathing stops for moments, as often as hundreds of times a night (see p. 1903). This disorder, often undiagnosed, can cause loud snoring and excessive daytime sleepiness and increases the risk of hypertension, cardiac arrhythmias, and metabolic syndrome.

Obesity may cause the obesity-hypoventilation syndrome (Pickwickian syndrome). Impaired breathing leads to hypercapnia, reduced sensitivity to CO₂ in stimulating respiration, hypoxia, cor pulmonale, and risk of premature death. This syndrome may occur alone or secondary to obstructive sleep apnea.

Osteoarthritis and tendon and fascial disorders may result from obesity. Skin disorders are common; increased sweat and skin secretions, trapped in thick folds of skin, are conducive to fungal and bacterial growth, making intertriginous infections especially common. Being overweight probably predisposes to cholelithiasis, gout, deep venous thrombosis and pulmonary embolism, and many cancers (especially colon and breast cancers).

Obesity leads to social, economic, and psychologic problems as a result of prejudice, discrimination, poor body image, and low self-esteem. For example, people may be underemployed or unemployed.

**Diagnosis**

• BMI
• Waist circumference
• Sometimes body composition analysis

In adults, BMI, defined as weight (kg) divided by the square of the height (m²), is used to screen for overweight or obesity. BMI of 25 to 29.9 kg/m² indicates overweight; BMI ≥ 30 kg/m² indicates obesity (see Table 6-2). However, BMI is a crude screening tool and has limitations in many subpopulations. BMI is
age- and race-specific; its use is limited in children and the elderly. In children and adolescents, overweight is BMI at the ≥ 95th percentile based on age- and sex-specific Centers for Disease Control and Prevention (CDC) growth charts at the CDC website.

Asians, Japanese, and many aboriginal populations have a lower cut-off (23 kg/m^2) for overweight. In addition, BMI may be high in muscular athletes who lack excess body fat, and normal or low in formerly overweight people who have lost muscle mass.

The risk of metabolic and cardiovascular complications due to obesity is determined more accurately by the following:

- Other risk factors, particularly a family history of type 2 diabetes or premature cardiovascular disease
- Waist circumference
- Serum triglycerides

The waist circumference that increases risk of complications due to obesity varies by ethnic group and sex:

- White men: > 93 cm (> 36.6 in), particularly > 101 cm (> 39.8 in)
- White women: > 79 cm (> 31.1 in), particularly > 87 cm (> 34.2 in)
- Asian Indian men: > 78 cm (> 30.7 in), particularly > 90 cm (> 35.4 in)
- Asian Indian women: > 72 cm (> 28.3 in), particularly > 80 cm (> 31.5 in)

**Body composition analysis:** Body composition—the percentage of body fat and muscle—is also considered when obesity is diagnosed. Although probably unnecessary in routine clinical practice, body composition analysis can be helpful if clinicians question whether elevated BMI is due to muscle or excessive fat.

The percentage of body fat can be estimated by measuring skinfold thickness (usually over the triceps) or determining mid upper arm area (see p. 13).

Bioelectrical impedance analysis (BIA) can estimate percentage of body fat simply and noninvasively. BIA estimates percentage of total body water directly; percentage of body fat is derived indirectly. BIA is most reliable in healthy people and in people with only a few chronic disorders that do not change the percentage of total body water (eg, moderate obesity, diabetes mellitus). Whether measuring BIA poses risks in people with implanted defibrillators is unclear.

Underwater (hydrostatic) weighing is the most accurate method for measuring percentage of body fat. Costly and time-consuming, it is used more often in research than in clinical care. To be weighed accurately while submerged, people must fully exhale beforehand.

Imaging procedures, including CT, MRI, and dual-energy x-ray absorptiometry (DEXA), can also estimate the percentage and distribution of body fat but are usually used only for research.

**Other testing:** Obese patients should be screened for obstructive sleep apnea with an instrument such as the Epworth Sleepiness Scale and often the apnea-hypopnea index (total number of apnea or hypopnea episodes occurring per hour of sleep—see p. 1904). This disorder is often underdiagnosed, and obesity increases the risk.

Fasting glucose and lipid levels should be measured routinely in patients with a large waist circumference or a family history of type 2 diabetes mellitus or premature cardiovascular disease.
Prognosis

Untreated, obesity tends to progress. The probability and severity of complications are proportional to the absolute amount of fat, the distribution of the fat, and absolute muscle mass. After weight loss, most people return to their pretreatment weight within 5 yr, and accordingly, obesity requires a lifelong management program similar to that for any other chronic disorder.

Treatment

- Nutrition management
- Physical activity
- Behavioral therapy
- Drugs (eg, sibutramine, orlistat)
- Bariatric surgery

Weight loss of even 5 to 10% improves overall health and well-being and in particular helps reduce risk of cardiovascular disorders and type 2 diabetes. Weight loss can lead to improvement in patients with obstructive sleep apnea, but sometimes a lot of weight must be lost for the disorder to resolve.

Support from health care practitioners, peers, and family members and various structured programs can help with weight loss and weight maintenance.

Nutrition: A normal eating pattern is important. People who miss breakfast tend to passively consume too many calories later in the day. Patients should eat small meals and avoid or carefully choose snacks. Low-fat (particularly very low saturated fat), high-fiber diets with modest calorie restriction (by 600 kcal/day) and substitution of some protein for carbohydrate seem to have the best long-term outcome. Fresh fruits and vegetables and salads should be substituted for refined carbohydrates and processed food, and water for soft drinks or juices. Alcohol consumption should be limited to moderate levels. Foods with a low glycemic index (see Table 1-1 on p. 3) and marine fish oils or monounsaturated fats derived from plants (eg, olive oil) reduce the risk of cardiovascular disorders and diabetes. Low-fat dairy products are also part of a healthy diet. Patients need an adequate amount of vitamin D, preferably obtained by exercising outdoors in the sunshine.

Use of meal replacements has proven efficacy; use can be ongoing or intermittent. Diets that require unusual eating habits should be avoided. They are unlikely to be maintained, and weight increases when patients resume previous poor eating habits. Diets of < 1200 kcal/day cannot be sustained, but such diets are sometimes needed to achieve rapid short-term weight loss (eg, to prepare for surgery, to lessen obstructive sleep apnea). Diets of < 800 kcal/day do not produce greater weight loss and are less well tolerated.

Physical activity: Exercise increases energy expenditure, BMR, and diet-induced thermogenesis. Exercise also seems to regulate appetite to more closely match caloric needs. Other benefits include

- Increased insulin sensitivity
- Improved lipid profile
- Lower BP
- Better aerobic fitness
• Improved psychologic well-being

Strengthening (resistance) exercises increase muscle mass. Because muscle tissue burns more calories at rest than does fat tissue, increasing muscle mass produces lasting increases in BMR. Exercise that is interesting and enjoyable is more likely to be sustained. A combination of aerobic and resistance exercise is better than either alone.

**Behavioral therapy:** Behavioral therapy aims to improve eating habits and physical activity level. Rigid dieting is discouraged in favor of healthy eating. Common-sense measures include the following:

• Avoiding high-calorie snacks

• Choosing healthful foods when dining out

• Eating slowly

• Substituting a physically active hobby for a passive one

Social support, cognitive therapy, and stress management may help, particularly during the lapses usually experienced during any long-term weight loss program. Self-monitoring is useful, and maintenance of a diet diary is particularly effective.

**Drugs:** Drugs may be used if BMI is > 30 or if BMI is > 27 and patients have complications (eg, hypertension, insulin resistance). Most weight loss due to drug treatment is modest (5 to 10%) at best and occurs during the first 6 mo; not all patients benefit. Drugs are more useful for maintaining weight loss but must be continued indefinitely for weight loss to be maintained. Premenopausal women taking systemically acting drugs for weight control should use contraception.

Sibutramine is a centrally acting appetite suppressant that produces dose-related weight loss. The usual starting dose is 10 mg po once/day; the dose can be decreased to 5 mg or increased to 15 mg. Common adverse effects are headache, dry mouth, insomnia, and constipation; the most common serious one is hypertension. Cardiovascular disorders, particularly poorly controlled hypertension, are contraindications.

Orlistat inhibits intestinal lipase, decreasing fat absorption and improving serum glucose and lipids. Because orlistat is not absorbed, systemic effects are rare. Flatus, oily stools, and diarrhea are common but tend to resolve during the 2nd yr of treatment. A dose of 120 mg po tid should be taken with meals that include fat. A vitamin supplement should be taken at least 2 h before or after taking orlistat. Malabsorption and cholestasis are contraindications; irritable bowel syndrome and other GI disorders may make orlistat difficult to tolerate. Orlistat is available OTC.

Other OTC weight-loss drugs are not recommended. Some (eg, caffeine, ephedrine, guarana, phenylpropanolamine) may be marginally effective, but their adverse effects outweigh their advantages. Others (eg, brindleberry, L-carnitine, chitosan, pectin, grapeseed extract, horse chestnut, chromium picolinate, fucus vesiculosus, ginkgo biloba) have not been shown to be effective and may have adverse effects.

**Surgery:** Surgery is the most effective treatment for extremely obese patients (see p. 61).

**Special Populations**

Obesity is a particular concern in children and the elderly.

**Children:** Childhood obesity is even more worrisome than adult obesity. For obese children, complications are more likely because children are obese longer. About 20 to 25% of children and adolescents are overweight or obese. Risk factors for obesity in infants are low birth weight and maternal obesity, diabetes, and smoking. After puberty, food intake increases; in boys, the extra calories are used to increase protein deposition, but in girls, fat storage is increased.
For obese children, psychologic complications (eg, poor self-esteem, social difficulties, depression) and musculoskeletal complications can develop early. Some musculoskeletal complications, such as slipped capital femoral epiphyses, occur only in children. Other early complications may include obstructive sleep apnea, insulin resistance, hyperlipidemia, and nonalcoholic steatohepatitis. Risk of cardiovascular, respiratory, metabolic, hepatic, and other obesity-related complications increases when these children become adults.

Risk of obesity persisting into adulthood depends partly on when obesity first develops:

- During infancy: Low risk
- Between 6 mo and 5 yr: 25%
- After 6 yr: > 50%
- During adolescence if a parent is obese: > 80%

In children, preventing further weight gain, rather than losing weight, is a reasonable goal. Diet should be modified, and physical activity increased. Increasing general activities and play is more likely to be effective than a structured exercise program. Participating in physical activities during childhood may promote a lifelong physically active lifestyle. Drugs and surgery are avoided but, if complications of obesity are life threatening, may be warranted.

Measures that control weight and prevent obesity in children may benefit public health the most. Such measures should be implemented in the family, schools, and primary care programs.

**The elderly:** In the US, the percentage of obese elderly people has been increasing.

With aging, body fat increases and is redistributed to the abdomen, and muscle mass is lost, largely because of physical inactivity, but decreased androgens and growth hormone (which are anabolic) and inflammatory cytokines produced in obesity may also play a role.

Risk of complications depends on

- Body fat distribution (increasing with a predominantly abdominal distribution)
- Duration and severity of obesity
- Associated sarcopenia

Increased waist circumference, suggesting abdominal fat distribution, predicts morbidity (eg, hypertension, diabetes mellitus, coronary artery disease) and mortality risk better in the elderly than does BMI.

For the elderly, increased physical activity is usually preferable to dietary restriction unless restricted mobility prohibits activity; in such cases, caloric restriction may be needed to reduce weight enough to restore mobility. Physical activity also improves muscle strength, endurance, and overall well-being. Activity should include strengthening and endurance exercises.

Regardless of whether caloric restriction is considered necessary, nutrition should be optimized.

Weight-loss drugs such as sibutramine or fluoxetine are not recommended for the elderly because the possible benefits do not outweigh the adverse effects. However, orlistat may be useful for obese elderly patients, particularly those with diabetes mellitus or hypertension. Surgery is usually best avoided, although it has proven efficacy and benefits outweigh risks in carefully selected patients.

**Prevention**
Regular physical activity and healthy eating improve general fitness, can control weight, and help prevent obesity and diabetes mellitus. Even without weight loss, exercise decreases the risk of cardiovascular disorders. Dietary fiber decreases the risk of colon cancer and cardiovascular disorders. Sufficient and good-quality sleep, management of stress, and moderation of alcohol intake are also important.

**Bariatric Surgery**

**Bariatric surgery is the surgical alteration of the stomach, intestine, or both to cause weight loss.**

In the US, bariatric surgery is done over 200,000 times annually, accounting for almost two thirds of all bariatric operations done worldwide. Development of safer laparoscopic approaches has made this surgery more popular.

**Indications**

To qualify for bariatric surgery, patients should

- Have acceptable operative risk
- Be well-informed and motivated
- Have unsuccessfully tried all reasonable nonsurgical methods to lose weight and manage obesity-associated complications
- Have a BMI of > 40 kg/m\(^2\) or a BMI > 35 kg/m\(^2\) plus a serious complication (eg, diabetes, hypertension, obstructive sleep apnea, high-risk lipid profile) that could be expected to be meaningfully reduced with a weight loss of 5 to 10%

Contraindications include uncontrolled major depression or psychosis, binge eating disorders, current drug or alcohol abuse, severe coagulopathy, and inability to comply with nutritional requirements, including lifelong vitamin replacement (when indicated). Whether bariatric surgery is appropriate for patients < 18 or > 65 yr is controversial.

**Procedures**

- Restrictive procedures (adjustable gastric banding, vertical banded gastroplasty)
- Malabsorptive procedures (Roux-en-Y gastric bypass)

Most procedures can be done laparoscopically, but the approach depends on the type of procedure as well as patient weight. Morbidity and mortality tend to be lower with laparoscopic than with open surgery. However, if patients weigh ≥ 180 kg, open surgery is more likely to be successful. In about 8% of cases overall (fewer with experienced surgeons), surgery begun laparoscopically must be finished as open surgery.

Procedures can be restrictive, malabsorptive, or both.

**Restrictive procedures:** Restrictive procedures limit the volume of the stomach available for ingested food. This limited volume helps restrict food intake, probably because of earlier satiety. The effects can be partially defeated by patients who consume more high-calorie liquid foods (eg, milk shakes, alcohol), which pass through the restricted portion quicker.

Purely restrictive procedures include adjustable gastric banding and vertical banded gastroplasty.

[Fig. 6-1. Adjustable gastric banding.]
Adjustable gastric banding accounts for about 15% of bariatric procedures done in the US; it is much more common in Europe and is growing in popularity in the US. It is the 2nd most common bariatric procedure. A band is placed around the upper part of the stomach to divide the stomach into a small upper pouch and a larger lower pouch. Saline can be injected into the band via a subcutaneous access port. When saline is injected, the band expands, decreasing the size of the passageway through the stomach. As a result, the upper pouch fills more quickly, sending a message to the brain that the stomach is full; patients eat smaller meals and lose substantial amounts of weight over time. This procedure is usually done laparoscopically. Saline can be removed to make the passageway larger. Even though weight loss from gastric banding is slightly less than that from Roux-en-Y, morbidity and mortality are much less and gastric banding can be reversed if necessary.

**Vertical banded gastroplasty** is no longer commonly done. A stapler is used to divide the stomach into a small upper pouch and a larger lower pouch. A nonexpandable plastic band is placed around the opening where the upper pouch empties into the lower pouch.

**Malabsorptive procedures:** Malabsorptive procedures, such as biliopancreatic diversion with a duodenal switch and Roux-en-Y gastric bypass, result in ingested food bypassing parts of the stomach and small intestine, creating malabsorption, which leads to weight loss. These procedures are also restrictive.

**Roux-en-Y gastric bypass surgery** accounts for about 80% of bariatric procedures in the US. It can often be done laparoscopically. A small part of the proximal stomach is detached from the rest, creating a stomach pouch of < 30 mL. Because stomach volume is smaller, satiety occurs earlier. Also, food bypasses part of the stomach and small intestine, where it is normally absorbed, reducing the amount of food and calories absorbed. The pouch is connected to the proximal jejunum with a narrow opening, producing even more restriction. The segment of bypassed proximal small intestine (and thus the bypassed stomach) is attached to the distal small intestine, enabling bile acids and pancreatic enzymes to mix with GI contents; this mixing limits malabsorption and nutritional deficiencies. Because a gastrojejunostomy is created, symptoms similar to the dumping-syndrome may occur after high glycemic loads; symptoms (light-headedness, diaphoresis, nausea, abdominal pain, diarrhea) may inhibit the consumption of such foods by adverse conditioning.

**Biliopancreatic diversion with a duodenal switch** accounts for < 5% of bariatric procedures done in the US. Part of the stomach is removed, causing restriction. The remaining part empties into the duodenum. The duodenum is cut

and attached to the ileum, bypassing much of the small intestine, including the sphincter of Oddi (where bile acids and pancreatic enzymes enter); malabsorption results. This procedure is technically demanding but can sometimes be done laparoscopically. Malabsorption and nutritional deficiencies often develop.

**Preoperative Evaluation**

Evaluation should determine whether patients have a psychologic commitment to the lifestyle changes and whether operative risks are acceptable. Sleep apnea testing is done.

Extensive preoperative evaluation is probably unnecessary. However, for certain morbidly obese patients (BMI > 50 kg/m²), examining the cardiac, pulmonary, GI, metabolic, and psychologic systems helps identify patients with acceptable operative risk and helps select the appropriate procedure. For these patients, routine preoperative tests may include

- **Liver function tests:** Increased liver enzymes, especially ALT, are common but do not contraindicate surgery.

- **Kidney function tests:** If renal blood flow and glomerular filtration rate are increased, proteinuria is
more likely and renal clearance of drugs may be increased. Thus, drug dosages may need to be adjusted.

- **ECG and echocardiography:** These tests are needed because identifying heart failure and pulmonary hypertension clinically in morbidly obese patients is difficult. Signs of heart failure (eg, increased jugular venous pressure, hepatomegaly, pulmonary crackles) are hard to identify when body fat is excessive. Pulmonary hypertension is also difficult to identify because many patients cannot exercise to the point where exertional dyspnea, fatigue, or syncope would result. Pulmonary hypertension is diagnosed if echocardiography shows tricuspid regurgitation and ECG shows tall R waves, right axis deviation, and right ventricular strain.

- **Sleep study:** Polysomnography (see p. 1706) can confirm obstructive sleep apnea, which is common, and determine its severity. An apnea-hypopnea index of > 30 signals high risk of morbidity and premature death. Obstructive sleep apnea does not contraindicate surgery but is done to help plan for use of continuous positive airway pressure (CPAP) postoperatively.

**Risks**

The most common perioperative complication is wound infection (in about 3%); the most common late complication is anastomatic stomach stenosis (in about 5%).

Other early complications include wound infection, incisional hernia, small-bowel obstruction, GI bleeding, ventral hernia, deep venous thrombosis, and pneumonia. These complications can cause significant morbidity, prolong hospitalization, and increase costs.

The most common cause of early (within about 6 wk) postoperative death (in up to 0.5%) is pulmonary embolism, followed by anastomatic leak. Tachycardia may be the only early sign of anastomatic leak. Less common causes of early postoperative death are MI, pneumonia, and bowel obstruction.

Later problems may include prolonged nausea and vomiting secondary to small-bowel obstruction, and anastomatic stenosis. Nutritional deficiencies (eg, protein-energy undernutrition, vitamin B<sub>12</sub> deficiency) may result from inadequate intake, inadequate supplementation, or malabsorption. Malodorous flatulence, diarrhea, or both may develop, particularly after malabsorptive procedures. Ca and vitamin D absorption may be impaired, causing deficiencies and sometimes hypocalcemia and secondary hyperparathyroidism. With prolonged vomiting, thiamin deficiency may occur. After Roux-en-Y gastric bypass, iron deficiency may result. Patients may have symptoms of reflux, especially after biliopancreatic diversion with a duodenal switch. After rapid weight loss, cholelithiasis may develop.

Eating habits may be disordered. Adjusting to new eating habits can be difficult.

**Prognosis**

Overall, 30-day postoperative risk of death is 0.2 to 1%. Risk is higher in elderly patients and in patients who have had an open procedure, who are extremely morbidly obese (> 50 kg), or who have established organ failure. Risk of death may be lowest with laparoscopic adjustable gastric banding. Risk of death is almost 3 times higher in hospitals that do < 50 of these procedures/yr than in those that do >150 procedures/yr. The American Society of Bariatric Surgery may designate hospitals with better results as a Center of Excellence, based on resources and excellent short- and long-term outcomes.

In most patients, comorbidities (eg, insulin insensitivity, dyslipidemias, hypertension, obstructive sleep apnea, polycystic ovary syndrome, nonalcoholic steatohepatitis) tend to resolve.

Average loss of excess weight (real weight minus ideal weight) is about 60%, or about 40 to 60 kg in most patients. Depending on the procedure, excess weight loss can vary between 50% and 70%; loss tends to be lower with gastric banding and somewhat higher with Roux-en-Y gastric bypass. In many patients, weight loss, although initially rapid, plateaus after about 2 yr; then patients may slowly regain weight.
Mood and work and personal relationships usually improve.

Long-term follow-up data are not yet available because these procedures are relatively new.

**Follow-up**

Patients should be monitored every 4 to 6 wk while weight loss is rapid (usually about the first 6 mo after surgery), then every 6 to 12 mo. Weight and BP are checked, and eating habits are reviewed. Blood tests (usually CBC, electrolytes, glucose, BUN, creatinine, albumin, and protein) and liver function tests are done at each visit. If alkaline phosphatase is increased, parathyroid hormone level is measured; if parathyroid hormone level is abnormal, bone density is monitored. If weight loss exceeds about 9 kg (20 lb)/mo, visits should be scheduled at least monthly, and blood tests should include Mg, phosphorus, vitamin B12, and iron levels. Nutritional supplementation is sometimes necessary.

**Metabolic Syndrome**

Metabolic syndrome (syndrome X, insulin resistance syndrome) is characterized by a clustering of risk factors for cardiovascular disease and type 2 diabetes mellitus. They commonly include excess intra-abdominal fat, insulin resistance, and ≥ 1 of the following: elevated serum triglyceride levels, decreased high-density lipoprotein (HDL) cholesterol level, and hypertension. Causes, complications, diagnosis, and treatment are similar to those of obesity.

In developed countries, metabolic syndrome is a serious problem. It is very common; in the US, > 40% of people > 50 yr may have it. Children and adolescents can develop

[Table 6-3. Criteria Often Used for Diagnosis of Metabolic Syndrome*]

metabolic syndrome, but in these age groups, no definition is established.

Development of metabolic syndrome depends on distribution as well as amount of fat. Excess fat in the abdomen (called apple shape), particularly when it results in a high waist-to-hip ratio (reflecting a relatively low muscle-to-fat mass ratio), increases risk. The syndrome is less common among people who have excess subcutaneous fat around the hips (called pear shape) and a low waist-to-hip ratio (reflecting a higher muscle-to-fat mass ratio).

Excess abdominal fat leads to excess free fatty acids in the portal vein, increasing fat accumulation in the liver. Fat also accumulates in muscle cells. Insulin resistance develops, with hyperinsulinemia. Glucose metabolism is impaired, and dyslipidemias and hypertension develop. Serum uric acid levels are typically elevated, and a prothrombotic state (with increased levels of fibrinogen and plasminogen activator inhibitor I) and an inflammatory state develop. Patients have an increased risk of obstructive sleep apnea. Other risks include nonalcoholic steatohepatitis, chronic kidney disease, polycystic ovary syndrome (for women), and low serum testosterone, erectile dysfunction, or both (for men).

**Diagnosis**

- Waist circumference and BP
- Fasting plasma glucose and a lipid profile

Screening is important. A family history plus measurement of waist circumference and BP are part of routine care. If patients with a family history of type 2 diabetes mellitus, particularly those ≥ 40 yr, have a waist circumference greater than that recommended for race and sex, fasting plasma glucose and a lipid profile must be determined.

Metabolic syndrome has many different definitions, but it is most often diagnosed when ≥ 3 of the following are present: excess abdominal fat, a high fasting plasma glucose level, hypertension, a high triglyceride level, and a low HDL cholesterol level (see Table 6-3).
Treatment

• Healthy diet and exercise

• Sometimes metformin

• Management of cardiovascular risk factors

Optimally, the management approach results in weight loss based on a healthy diet and regular physical activity, which includes a combination of aerobic activity and resistance training, reinforced with behavioral therapy. Metformin, an insulin sensitizer, may be useful. Weight loss of ≈ 7% may be sufficient to reverse the syndrome, but if not, each feature of the syndrome should be managed to achieve recommended targets; available drug treatment is very effective.

Other cardiovascular risk factors (eg, smoking cessation) also need to be managed. Increased physical activity has cardiovascular benefits even if weight is not lost.
Chapter 7. Approach to the Patient With Upper GI Complaints

Introduction

Upper GI complaints include chest pain (see p. 2025), chronic and recurrent abdominal pain, dyspepsia, lump in the throat, halitosis (see p. 506), hiccups, nausea and vomiting, and rumination. Some upper GI complaints represent functional illness (ie, no physiologic cause found after extensive evaluation).

History: Using open-ended, interview-style questions, the physician identifies the location and quality of symptoms and any aggravating and alleviating factors. Psychologic stress factors must be specifically sought. Because a psychiatric disorder does not preclude physiologic disease, the significance of vague, dramatic, or bizarre complaints should not be minimized.

Patients report symptoms differently depending on their personality, the impact of the illness on their life, and sociocultural influences. For example, nausea and vomiting may be minimized or reported indirectly by a severely depressed patient but presented with dramatic urgency by a histrionic one.

Physical examination: Inspection of the abdomen with the patient supine may show a convex appearance when bowel obstruction, ascites, or, rarely, a large mass is present. Auscultation to assess bowel sounds and determine presence of bruits should follow. Percussion elicits hyperresonance (tympany) in the presence of bowel obstruction and dullness with ascites and can determine the span of the liver. Palpation proceeds systematically, beginning gently to identify areas of tenderness and, if tolerated, palpating deeper to locate masses or organomegaly. Digital rectal examination with testing for occult blood and (in women) pelvic examination complete the evaluation of the abdomen.

Testing: Patients with acute, nonspecific symptoms (eg, dyspepsia, nausea) and an unremarkable physical examination rarely require testing. Findings suggesting significant disease (alarm symptoms) should prompt further evaluation:

- Anorexia
- Anemia
- Blood in stool (gross or occult)
- Dysphagia
- Fever
- Hepatomegaly
- Pain that awakens patient
- Persistent nausea and vomiting
- Weight loss

Chronic or recurrent symptoms, even with an unremarkable examination, also warrant evaluation. Specific GI tests are discussed in Ch. 9.

Chronic and Recurrent Abdominal Pain

Chronic abdominal pain (CAP) persists for more than 3 mo either continuously or intermittently. Intermittent pain may be referred to as recurrent abdominal pain (RAP). Acute abdominal pain is discussed on p. 105. CAP occurs any time after 5 yr of age. Up to 10% of children require evaluation for RAP. About 2% of adults, predominantly women, have CAP (a much higher percentage of adults have...
some type of chronic GI symptoms, including nonulcer dyspepsia and various bowel disturbances).

Nearly all patients with CAP have had prior medical evaluation that did not yield a diagnosis after history, physical, and basic testing.

**Pathophysiology**

Functional abdominal pain syndrome (FAPS) is pain that persists > 6 mo without evidence of physiologic disease, shows no relationship to physiologic events (eg, meals, defecation, menses), and interferes with daily functioning. FAPS is poorly understood but seems to involve altered nociception. Sensory neurons in the dorsal horn of the spinal cord may become abnormally excitable and hyperalgesic due to a combination of factors. Cognitive and psychologic factors (eg, depression, stress, culture, secondary gain, coping and support mechanisms) may cause efferent stimulation that amplifies pain signals, resulting in perception of pain with low level inputs and persistence of pain long after the stimulus has ceased. Additionally, the pain itself may function as a stressor, perpetuating a positive feedback loop.

In addition, menopause increases GI symptoms in several disorders including irritable bowel syndrome, inflammatory bowel disease, endometriosis, and nonulcer dyspepsia.

**Etiology**

Perhaps 10% of patients have an occult physiologic illness (see Table 7-1); the remainder have a functional process. However, determining whether a particular abnormality (eg, adhesions, ovarian cyst, endometriosis) is the cause of CAP symptoms or an incidental finding can be difficult.

**Evaluation**

**History:** History of present illness should elicit pain location, quality, duration, timing and frequency of recurrence, and factors that worsen or relieve pain (particularly eating or moving bowels). A specific inquiry as to whether milk and milk products cause abdominal cramps, bloating, or distention is needed, because lactose intolerance is common, especially among blacks.

**Review of systems** seeks concomitant GI symptoms such as gastroesophageal reflux, anorexia, bloating or "gas," nausea, vomiting, jaundice, melena, hematuria, hematemesis, weight loss, and mucus or blood in the stool. Bowel symptoms, such as diarrhea, constipation, and changes in stool consistency, color, or elimination pattern, are particularly important.

In adolescents, a diet history is important because ingestion of large amounts of cola beverages and fruit juices (which may contain significant quantities of fructose and sorbitol) can account for otherwise puzzling abdominal pain.

**Past medical history** should include nature and timing of any abdominal surgery and the results of previous tests that have been done and treatments that have been tried. A drug history should include details concerning prescription and illicit drug use as well as alcohol.

Family history of RAP, fevers, or both should be ascertained, as well as known diagnoses of sickle cell trait or disease, familial Mediterranean fever, and porphyria.

**Physical examination:** Review of vital signs should particularly note presence of fever or tachycardia.

General examination should seek presence of jaundice, skin rash, and peripheral edema. Abdominal examination should note areas of tenderness, presence of peritoneal findings (eg, guarding, rigidity, rebound), and any masses or organomegaly. Rectal examination and (in women) pelvic examination to locate tenderness, masses, and blood are essential.

**Red flags:** The following findings are of particular concern:
• Fever
• Anorexia, weight loss
• Pain that awakens patient
• Blood in stool or urine
• Jaundice
• Edema
• Abdominal mass or organomegaly

Interpretation of findings: Clinical examination alone infrequently provides a firm diagnosis.

Determining whether CAP is physiologic or functional can be difficult. Although the presence of red flag findings indicates a high likelihood of a physiologic cause, their absence does not rule it out. Other hints are that physiologic causes usually cause pain that is well localized, especially to areas other than the periumbilical region. Pain that wakes the patient is usually physiologic. Some findings suggestive of specific disorders are listed in Table 7-1.

Functional CAP may result in pain similar to that of physiologic origin. However, there are no associated red flag findings, and psychosocial features are often prominent. A history of physical or sexual abuse or an unresolved loss (eg, divorce, miscarriage, or death of a family member) may be a clue.

The Rome criteria for diagnosis of irritable bowel syndrome are the presence of abdominal pain or discomfort for at least 3 days/mo in the last 3 mo along with at least 2 of the following: (1) improvement with defecation; (2) onset (of each episode of discomfort) associated with a change in frequency of defecation; and (3) change in consistency of stool.

Testing: In general, simple tests (including urinalysis, CBC, liver tests, ESR, amylase, and lipase) should be done. Abnormalities in these tests, the presence of red flag findings, or specific clinical findings mandate further testing, even if previous assessments have been negative. Specific tests depend on the findings (see Table 7-1) but typically include CT of the abdomen and pelvis with contrast, upper GI endoscopy or colonoscopy, and perhaps small-bowel x-rays or stool testing.

The benefits of testing patients with no red flag findings are unclear. Those > 50 should probably have a colonoscopy; those ≤ 50 can be observed or have CT of the abdomen and pelvis with contrast if an imaging study is desired. Magnetic resonance cholangiopancreatography (MRCP), ERCP, and laparoscopy are rarely helpful in the absence of specific indications.

Between the initial evaluation and the follow-up visit, the patient (or family, if the patient is a child) should record any pain, including its nature, intensity, duration, and precipitating factors. Diet, defecation pattern, and any remedies tried (and the results obtained) should also be recorded. This record may reveal inappropriate behavior patterns and exaggerated responses to pain or otherwise suggest a diagnosis.

Treatment

Physiologic conditions are treated.

If the diagnosis of functional CAP is made, frequent examinations and tests should be avoided because they may focus on or magnify the physical complaints or imply that the physician lacks confidence in the diagnosis.
There are no modalities to cure functional CAP; however, many helpful measures are available. These measures rest on a foundation of a trusting, empathic relationship among the physician, patient, and family. Patients should be reassured that they are not in danger; specific concerns should be sought and addressed. The physician should explain the laboratory findings and the nature of the problem and describe how the pain is generated and how the patient perceives it (ie, that there is a constitutional tendency to feel pain at times of stress). It is important to avoid perpetuating the negative psychosocial consequences of chronic pain (eg, prolonged absences from school or work, withdrawal from social activities) and to promote independence, social participation, and self-reliance. These strategies help the patient control or tolerate the symptoms while participating fully in everyday activities.

Drugs such as aspirin, NSAIDs, H$_2$ receptor blockers, proton pump inhibitors, and tricyclic antidepressants can be effective. Opioids should be avoided because they invariably lead to dependency.

Cognitive methods (eg, relaxation training, biofeedback, hypnosis) may help by contributing to the patient's sense of well-being and control. Regular follow-up visits should be scheduled weekly, monthly, or bimonthly, depending on the patient's needs, and should continue until well after the problem has resolved. Psychiatric referral may be required if symptoms persist, especially if the patient is depressed or there are significant psychologic difficulties in the family.

School personnel should become involved for children who have CAP. Children can rest briefly in the nurse's office during the school day, with the expectation that they return to class after 15 to 30 min. The school nurse can be authorized to dispense a mild analgesic (eg, acetaminophen). The nurse can sometimes allow the child to call a parent, who should encourage the child to stay in school. However, once parents stop treating their child as special or ill, the symptoms may worsen before they abate.

**Key Points**

- Most cases represent a functional process.
- Red flag findings indicate a physiologic cause and need for further assessment.
- Testing is guided by clinical features.
- Repeated testing after physiologic causes are ruled out is usually counterproductive.

**Dyspepsia**

Dyspepsia is a sensation of pain or discomfort in the upper abdomen; it often is recurrent. It may be described as indigestion, gassiness, early satiety, postprandial fullness, gnawing, or burning.

**Etiology**

There are several common causes of dyspepsia (see Table 7-2).

Many patients have findings on testing (eg, duodenitis, pyloric dysfunction, motility disturbance, *Heliobacter pylori* gastritis, lactose deficiency, cholelithiasis) that correlate poorly with symptoms (ie, correction of the condition does not alleviate dyspepsia).

**Nonulcer (functional) dyspepsia** is defined as dyspeptic symptoms in a patient who has no abnormalities on physical examination and upper GI endoscopy.

**Evaluation**

**History:** **History of present illness** should elicit a clear description of the symptoms, including whether they are acute or chronic and recurrent. Other elements include timing and frequency of recurrence, any difficulty swallowing, and relationship of symptoms to eating or taking drugs. Factors that worsen
Review of systems seeks concomitant GI symptoms such as anorexia, nausea, vomiting, hematemesis, weight loss, and bloody or black (melanotic) stools. Other symptoms include dyspnea and diaphoresis.

Past medical history should include known GI and cardiac diagnoses, cardiac risk factors (e.g., hypertension, hypercholesterolemia), and the results of previous tests that have been done and treatments that have been tried. Drug history should include prescription and illicit drug use as well as alcohol.

Physical examination: Review of vital signs should note presence of tachycardia or irregular pulse.

General examination should note presence of pallor or diaphoresis, cachexia, or jaundice. Abdomen is palpated for tenderness, masses, and organomegaly. Rectal examination is done to detect gross or occult blood.

Red flags: The following findings are of particular concern:

- Acute episode with dyspnea, diaphoresis, or tachycardia
- Anorexia
- Nausea or vomiting
- Weight loss
- Blood in the stool
- Dysphagia or odynophagia
- Failure to respond to therapy with H₂ blockers or proton pump inhibitors (PPIs)

Interpretation of findings: Some findings are helpful (see Table 7-2).

A patient presenting with a single, acute episode of dyspepsia is of concern, particularly if symptoms are accompanied by dyspnea, diaphoresis, or tachycardia; such patients may have acute coronary ischemia. Chronic symptoms that occur with exertion and are relieved by rest may represent angina.

GI causes are most likely to manifest as chronic complaints. Symptoms are sometimes classified as ulcer-like, dysmotility-like, or reflux-like; these classifications suggest but do not confirm an etiology. Ulcer-like symptoms consist of pain that is localized in the epigastrium, frequently occurs before meals, and is partially relieved by food, antacids, or H₂ blockers. Dysmotility-like symptoms consist of discomfort rather than pain, along with early satiety, postprandial fullness, nausea, vomiting, bloating, and symptoms that are worsened by food. Reflux-like symptoms consist of heartburn or acid regurgitation. However, symptoms often overlap.

Alternating constipation and diarrhea with dyspepsia suggests irritable bowel syndrome or excessive use of OTC laxatives or antidiarrheals.

Testing: Patients in whom symptoms suggest acute coronary ischemia, particularly those with risk factors, should be sent to the emergency department for urgent evaluation, including ECG and serum cardiac markers.
For patients with chronic, nonspecific symptoms, routine tests include CBC (to exclude anemia caused by GI blood loss) and routine blood chemistries. If results are abnormal, additional tests (eg, imaging studies, endoscopy) should be considered. Because of the risk of cancer, patients > 45 and those with new-onset red flag findings should undergo upper GI endoscopy. For patients < 45 with no red flag findings, some authorities recommend empiric therapy for 2 to 4 wk with antisecretory agents followed by endoscopy in treatment failures. Others recommend screening for \( H. pylori \) infection with a \( ^{14} \text{C} \)-urea breath test or stool assay (see p. 129). However, caution is required in using \( H. pylori \) or any other nonspecific findings to explain symptoms.

Esophageal manometry and pH studies are indicated if reflux symptoms persist after upper GI endoscopy and a 2- to 4-wk trial with a PPI.

**Treatment**

Specific conditions are treated. Patients without identifiable conditions are observed over time and reassured. Symptoms are treated with PPIs, \( \text{H}_2 \) blockers, or a cytoprotective agent (see Table 7-3). Prokinetic drugs (eg, metoclopramide, erythromycin) given as a liquid suspension also may be tried in patients with dysmotility-like dyspepsia. However, there is no clear evidence that matching the drug class to the specific symptoms (eg, reflux vs dysmotility) makes a difference. Misoprostol and anticholinergics are not effective in functional dyspepsia. Drugs that alter sensory perception (eg, tricyclic antidepressants) may be helpful.

**Key Points**

• Coronary ischemia is possible in a patient with acute "gas."

• Endoscopy is indicated for those > 45 or with red flag findings.

• Empiric treatment with an acid blocker is reasonable for those < 45 without red flag findings. Those who do not respond in 2 to 4 wk require further evaluation.

**Hiccups**

Hiccups (hiccough, singultus) are repeated involuntary spasms of the diaphragm followed by sudden closure of the glottis, which checks the inflow of air and causes the characteristic sound. Transient episodes are very common. Persistent (> 2 days) and intractable (> 1 mo) hiccups are uncommon but quite distressing.

**Etiology**

Hiccups follow irritation of afferent or efferent diaphragmatic nerves or of medullary centers that control the respiratory muscles, particularly the diaphragm. Hiccups are more common among men.

Cause is generally unknown, but transient hiccups are often caused by the following:

• Gastric distention

• Alcohol consumption

• Swallowing hot or irritating substances

Persistent and intractable hiccups have myriad causes (see Table 7-4).

**Evaluation**

**History:** **History of present illness** should note duration of hiccups, remedies tried, and relationship of
onset to recent illness or surgery.

**Review of systems** seeks concomitant GI symptoms such as gastroesophageal reflux and swallowing difficulties; thoracic symptoms such as cough, fever, or chest pain; and any neurologic symptoms.

**Past medical history** should query known GI and neurologic disorders. A drug history should include details concerning alcohol use.

**Physical examination:** Examination is usually unrewarding but should seek signs of chronic disease (eg, cachexia). A full neurologic examination is important.

**Red flags:** The following is of particular concern:

• Neurologic symptoms or signs

**Interpretation of findings:** Few findings are specific. Hiccups after alcohol consumption or surgery may well be related to those events. Other possible causes (see Table 7-4) are both numerous and rarely a cause of hiccups.

**Testing:** No specific evaluation is required for acute hiccups if routine history and physical examination are unremarkable; abnormalities are pursued with appropriate testing.

Patients with hiccups of longer duration and no obvious cause should have testing, probably including serum electrolytes, BUN and creatinine, chest x-ray, and ECG. Upper GI endoscopy and perhaps esophageal pH monitoring should be considered. If these are unremarkable, brain MRI and chest CT may be done.

[Table 7-4, Some Causes of Intractable Hiccups]

**Treatment**

Identified problems are treated (eg, proton pump inhibitors for gastroesophageal reflux disease, dilation for esophageal stricture).

For symptom relief, many simple measures can be tried, although none are more than slightly effective: PaCO₂ can be increased and diaphragmatic activity can be inhibited by a series of deep breath-holds or by breathing deeply in to and out of a paper bag. (CAUTION: Plastic bags can cling to the nostrils and should not be used.) Vagal stimulation by pharyngeal irritation (eg, swallowing dry bread, granulated sugar, or crushed ice; applying traction on the tongue; stimulating gagging) may work. Numerous other folk remedies exist.

Persistent hiccups are often recalcitrant to treatment. Many drugs have been used in anecdotal series. Baclofen, a γ-aminobutyric acid agonist (5 mg po q 6 h increasing to 20 mg/dose), may be effective. Other drugs include chlorpromazine 10 to 50 mg po tid as needed, metoclopramide 10 mg po bid to qid, and various anticonvulsants (eg, gabapentin). Additionally, an empiric trial of proton pump inhibitors may be given. For severe symptoms, chlorpromazine 25 to 50 mg IM or IV can be given. In intractable cases, the phrenic nerve may be blocked by small amounts of 0.5% procaine solution, with caution being taken to avoid respiratory depression and pneumothorax. Even bilateral phrenicotomy does not cure all cases.

**Key Points**

• The cause is usually unknown.

• Rarely, a serious disorder is present.

• Evaluation is typically unrewarding but should be pursued for hiccups of long duration.

• Numerous remedies exist, none with clear superiority (or perhaps even effectiveness).
Lump in Throat

Lump in the throat (globus sensation, globus hystericus) is the sensation of a lump or mass in the throat, unrelated to swallowing, when no mass is present. (If a mass is present, see p. 461.)

Etiology

No specific etiology or physiologic mechanism has been established. Some studies suggest that elevated cricopharyngeal (upper esophageal sphincter) pressure or abnormal hypopharyngeal motility occur during the time of symptoms. The sensation may also result from gastroesophageal reflux disease (GERD) or from frequent swallowing and drying of the throat associated with anxiety or another emotional state. Although not associated with stress factors or a specific psychiatric disorder, globus sensation may be a symptom of certain mood states (eg, grief, pride); some patients may have a predisposition to this response.

Disorders that can be confused with globus sensation include cricopharyngeal (upper esophageal) webs, symptomatic diffuse esophageal spasm, GERD, skeletal muscle disorders (eg, myasthenia gravis, myotonia dystrophica, polymyositis), and mass lesions in the neck or mediastinum that cause esophageal compression.

Evaluation

The main goal is to distinguish globus sensation from true dysphagia (see p. 120), which suggests a structural or motor disorder of the pharynx or esophagus.

History: History of present illness should elicit a clear description of the symptom, particularly as to whether there is any pain with swallowing, difficulty swallowing (including sensation of food sticking). Timing of symptoms is important, particularly whether it occurs with eating or drinking or is independent of those activities; association with emotional events should be queried specifically.

Review of systems seeks weight loss (as evidence of a swallowing disorder) and symptoms of muscle weakness.

Past medical history should include known neurologic diagnoses, particularly those causing weakness.

Physical examination: The neck and floor of the mouth are palpated for masses. The oropharynx is inspected (including by direct laryngoscopy). Swallowing (of water and a solid food such as crackers) should be observed. Neurologic examination with particular attention to motor function is important.

Red flags: The following findings are of particular concern:

• Neck or throat pain
• Weight loss
• Abrupt onset after age 50
• Pain, choking, or difficulty with swallowing
• Regurgitation of food
• Muscle weakness
• Palpable or visible mass
• Progressive worsening of symptoms
Interpretation of findings: Symptoms unrelated to swallowing, with no pain or difficulty with swallowing, or sensation of food sticking in the throat in a patient with a normal examination imply globus sensation. Any red flag findings or abnormal findings on examination suggest a mechanical or motor disorder of swallowing. Chronic symptoms that occur during unresolved or pathologic grief and that may be relieved by crying suggest globus sensation.

Testing: Those with findings typical of globus sensation need no testing. If the diagnosis is unclear or the clinician cannot adequately visualize the pharynx, testing as for dysphagia is done. Typical tests include plain or video esophagography, measurement of swallowing time, chest x-ray, and esophageal manometry.

Treatment

Treatment involves reassurance and sympathetic concern. No drug is of proven benefit. Underlying depression, anxiety, or other behavioral disturbances should be managed supportively, with psychiatric referral if necessary. At times, communicating to the patient the association between symptoms and mood state can be beneficial.

Key Points

• Globus symptoms are unrelated to swallowing.

• Tests are not needed unless symptoms are related to swallowing, examination is abnormal, or there are red flag findings.

Nausea and Vomiting

(For nausea and vomiting in infants and children, see p. 2746.)

Nausea, the unpleasant feeling of needing to vomit, represents awareness of afferent stimuli (including increased parasympathetic tone) to the medullary vomiting center. Vomiting is the forceful expulsion of gastric contents caused by involuntary contraction of the abdominal musculature when the gastric fundus and lower esophageal sphincter are relaxed.

Vomiting should be distinguished from regurgitation, the spitting up of gastric contents without associated nausea or forceful abdominal muscular contractions. Patients with achalasia or a Zenker's diverticulum may regurgitate undigested food without nausea.

Complications: Severe vomiting can lead to symptomatic dehydration and electrolyte abnormalities (typically a metabolic alkalosis with hypokalemia) or rarely to an esophageal tear, either partial (Mallory-Weiss) or complete (Boerhaave's syndrome). Chronic vomiting can result in undernutrition, weight loss, and metabolic abnormalities.

Etiology

Nausea and vomiting occur in response to conditions that affect the vomiting center. Causes may originate in the GI tract or CNS or may result from a number of systemic conditions (see Table 7-5).

The most common causes are the following:

• Gastroenteritis

• Drugs

• Toxins
Cyclic vomiting syndrome is an uncommon disorder characterized by severe, discrete attacks of vomiting or sometimes only nausea that occur at varying intervals, with normal health between episodes. It is most common in childhood (mean age of onset 5 yr) and tends to remit with adulthood. The condition may be associated with migraine headaches, possibly representing a migraine variant.

**Evaluation**

**History**: History of present illness should elicit frequency and duration of vomiting; its relation to possible precipitants such as drug or toxin ingestion, head injury, and motion (eg, car, plane, boat, amusement rides); and whether vomitus contained bile (bitter, yellow-green) or blood (red or “coffee ground” material). Important associated symptoms include presence of abdominal pain and diarrhea; the last passage of stool and flatus; and presence of headache, vertigo, or both.

**Review of systems** seeks symptoms of causative disorders such as amenorrhea, breast swelling (pregnancy); polyuria, polydipsia (diabetes); and hematuria, flank pain (kidney stones).

**Past medical history** should ascertain known causes such as pregnancy, diabetes, migraine, hepatic or renal disease, cancer (including timing of any chemotherapy or radiation therapy), and previous abdominal surgery (which may cause bowel obstruction due to adhesions). All drugs and substances ingested recently should be ascertained; certain substances may not manifest toxicity until several days after ingestion (eg, acetaminophen, some mushrooms).

Family history of recurrent vomiting should be noted.

**Physical examination**: Vital signs should particularly note presence of fever and signs of hypovolemia (eg, tachycardia, hypotension, or both).

General examination should seek presence of jaundice and skin rash.

On abdominal examination, the clinician should look for distention and surgical scars; listen for presence and quality of bowel sounds (eg, normal, high-pitched); percuss for tympany; and palpate for tenderness, peritoneal findings (eg, guarding, rigidity, rebound), and any masses, organomegaly, or hernias. Rectal examination and (in women) pelvic examination to locate tenderness, masses, and blood are essential.

Neurologic examination should particularly note mental status, nystagmus, meningismus (eg, stiff neck, Kernig’s or Brudzinski’s signs), and ocular signs of increased intracranial pressure (eg, papilledema, absence of venous pulsations, 3rd cranial nerve palsy) or subarachnoid hemorrhage (retinal hemorrhage).

**Red flags**: The following findings are of particular concern:

- Signs of hypovolemia

- Headache, stiff neck, or mental status change

- Peritoneal signs

- Distended, tympanitic abdomen

**Interpretation of findings**: Many findings are suggestive of a cause or group of causes (see Table 7-5). Vomiting occurring shortly after drug or toxin ingestion or exposure to motion in a patient with an unremarkable neurologic and abdominal examination can confidently be ascribed to those causes, as may vomiting in a woman with a known pregnancy and a benign examination. Acute vomiting accompanied by diarrhea in an otherwise healthy patient with a benign examination is highly likely to be infectious gastroenteritis; further
Vomiting that occurs at the thought of food or that is not temporally related to eating suggests a psychogenic cause, as does personal or family history of functional nausea and vomiting. Patients should be questioned about the relationship between vomiting and stressful events because they may not recognize the association or even admit to feeling distress at those times.

**Testing:** All females of childbearing age should have a urine pregnancy test. Patients with severe vomiting, vomiting lasting over 1 day, or signs of dehydration on examination should have other laboratory tests (e.g., electrolytes, BUN, creatinine, glucose, urinalysis, and sometimes liver tests). Patients with red flag findings should have testing appropriate to the symptoms (see Table 7-5).

The assessment of chronic vomiting usually includes the previously listed laboratory tests plus upper GI endoscopy, small-bowel x-rays, and tests to assess gastric emptying and antral-duodenal motility.

**Treatment**

Specific conditions, including dehydration, are treated. Even without significant dehydration, IV fluid therapy (0.9% saline 1 L, or 20 mL/kg in children) often leads to reduction of symptoms. In adults, various antiemetics are effective (see Table 7-6). Choice of agent varies somewhat with the cause and severity of symptoms. Typical use is the following:

- **Motion sickness:** Antihistamines, scopolamine patches, or both
- **Mild to moderate symptoms:** Prochlorperazine or metoclopramide
- **Severe or refractory vomiting and vomiting caused by chemotherapy:** 5-HT3 antagonists

Obviously, only parenteral agents should be used in actively vomiting patients.

For psychogenic vomiting, reassurance indicates awareness of the patient's discomfort and a desire to work toward relief of symptoms, regardless of cause. Comments such as "nothing is wrong" or "the problem is emotional" should be avoided. Brief symptomatic treatment with antiemetics can be tried. If long-term management is necessary, supportive, regular office visits may help resolve the underlying problem.

**Key Points**

- Many episodes have an obvious cause and benign examination and require only symptomatic treatment.
- Physicians should be alert for signs of an acute abdomen or significant intracranial disorder.
- Pregnancy should always be considered in females of childbearing age.

**Rumination**

Rumination is the (usually involuntary) regurgitation of small amounts of food from the stomach (most often 15 to 30 min after eating) that are rechewed and, in most cases, again swallowed. Patients do not complain of nausea or abdominal pain.

Rumination is commonly observed in infants. The incidence in adults is unknown, because it is rarely reported by patients themselves.

**Etiology**
Patients with achalasia or a Zenker’s diverticulum may regurgitate undigested food without nausea. In the majority of patients who do not have these obstructive esophageal conditions, the pathophysiology is poorly understood. The reverse peristalsis in ruminants has not been reported in humans. The disorder is probably a learned, maladaptive habit and may be part of an eating disorder. The person learns to open the lower esophageal sphincter and propel gastric contents into the esophagus and throat by increasing gastric pressure via rhythmic contraction and relaxation of the diaphragm.

**Symptoms**

Nausea, pain, and dysphagia do not occur. During periods of stress, the patient may be less careful about concealing rumination. Seeing the act for the first time, others may refer the patient to a physician. Rarely, patients regurgitate and expel enough food to lose weight.

**Diagnosis**

- Clinical evaluation
- Sometimes endoscopy, esophageal motility studies, or both

Rumination is usually diagnosed through observation. A psychosocial history may disclose underlying emotional stress. Endoscopy or an upper GI series is necessary to exclude disorders causing mechanical obstruction or Zenker’s diverticulum. Esophageal manometry and tests to assess gastric emptying and antral-duodenal motility may be used to identify a motility disturbance.

**Treatment**

- Behavioral techniques

Treatment is supportive. Drug therapy generally does not help. Motivated patients may respond to behavioral techniques (eg, relaxation, biofeedback, training in diaphragmatic breathing [using the diaphragm instead of chest muscles to breathe]). Psychiatric consultation may be helpful.

**Functional GI Illness**

Often, no physiologic cause for GI complaints is found, even after extensive evaluation. Such patients are said to have functional illness, which accounts for 30 to 50% of referrals to gastroenterologists. Functional illness may manifest with upper and/or lower GI symptoms.

The reasons for functional symptoms are not clear. Some evidence suggests that such patients have visceral hypersensitivity, a disturbance of nociception in which they experience discomfort caused by sensations (eg, luminal distention, peristalsis) that other people do not find distressing. In some patients, psychologic conditions such as anxiety (with or without aerophagia), conversion disorder, somatization in depression, or hypochondriasis are associated with GI symptoms. Psychologic theories hold that functional symptoms may satisfy certain psychologic needs. For example, some patients with chronic illness derive secondary benefits from being sick. For such patients, successful treatment of symptoms may lead to development of other symptoms.

Many referring physicians and GI specialists find functional GI complaints difficult to understand and treat, and uncertainty may lead to frustration and judgmental attitudes. Physicians should avoid ordering repeated studies or multiple drug trials for the insistent patient with inexplicable complaints. When symptoms are not suggestive of serious illness, the physician should wait rather than embark on another diagnostic or therapeutic plan. In time, new information may direct evaluation and management. Functional complaints are sometimes present in patients with physiologic disease (eg, peptic ulcer, esophagitis); such symptoms may not remit even when a physiologic illness is addressed.
Chapter 8. Approach to the Patient With Lower GI Complaints

Introduction

Lower GI complaints include constipation, diarrhea, gas and bloating, abdominal pain (see also p. 105), and rectal pain or bleeding (see Ch. 21). As with upper GI complaints, lower GI complaints result from physiologic illness or represent a functional disorder (ie, no radiologic, biochemical, or pathologic abnormalities found even after extensive evaluation). The reasons for functional symptoms are not clear. Evidence suggests that patients with functional symptoms may have disturbances of motility, nociception, or both; ie, they perceive as uncomfortable certain sensations (eg, luminal distention, peristalsis) that other people do not find distressing.

No bodily function is more variable and subject to external influences than defecation. Bowel habits vary considerably from person to person and are affected by age, physiology, diet, and social and cultural influences. Some people have unwarranted preoccupation with bowel habits. In Western society, normal stool frequency ranges from 2 to 3/day to 2 to 3/wk. Changes in stool frequency, consistency, volume, or composition (ie, presence of blood, mucus, pus, or excess fatty material) may indicate disease.

Constipation

Constipation is difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation.

Many people incorrectly believe that daily defecation is necessary and complain of constipation if stools occur less frequently. Others are concerned with the appearance (size, shape, color) or consistency of stools. Sometimes the major complaint is dissatisfaction with the act of defecation or the sense of incomplete evacuation after defecation. Constipation is blamed for many complaints (abdominal pain, nausea, fatigue, anorexia) that are actually symptoms of an underlying problem (eg, irritable bowel syndrome [IBS], depression). Patients should not expect all symptoms to be relieved by a daily bowel movement, and measures to aid bowel habits should be used judiciously.

Obsessive-compulsive patients often feel the need to rid the body daily of "unclean" wastes. Such patients often spend excessive time on the toilet or become chronic users of cathartics.

Etiology

Acute constipation suggests an organic cause, whereas chronic constipation may be organic or functional (see Table 8-1).

In many patients, constipation is associated with sluggish movement of stool through the colon. This delay may be due to drugs, organic conditions, or a disorder of defecatory function (ie, pelvic floor dysfunction). Patients with disordered defecation do not generate adequate rectal propulsive forces, do not relax the puborectalis and the external anal sphincter during defecation, or both. In IBS, patients have symptoms (eg, abdominal discomfort and altered bowel habits) but generally normal colonic transit and anorectal functions. However, IBS-disordered defecation may coexist.

Excessive straining, perhaps secondary to pelvic floor dysfunctions, may contribute to anorectal pathology (eg, hemorrhoids, anal fissures, and rectal prolapse) and possibly even to syncope. Fecal impaction, which may cause or develop from constipation, is also common among elderly patients, particularly with prolonged bed rest or decreased physical activity. It is also common after barium has been given by mouth or enema.

Changes with aging: Constipation is common among elderly people because of low-fiber diets, lack of exercise, coexisting medical conditions, and use of constipating drugs. Many elderly people have misconceptions about normal bowel habits and use laxatives regularly. Other changes that predispose the elderly to constipation include increased rectal compliance and impaired rectal sensation (such that larger rectal volumes are needed to elicit the desire to defecate).
**Evaluation**

**History:** A lifetime history of the patient's stool frequency, consistency, need to strain or use perineal maneuvers (eg, pushing on the perineum, gluteal region, or recto-vaginal wall) during defecation, and satisfaction after defecation should be obtained, including frequency and duration of laxative or enema use. Some patients deny previous constipation

[Table 8-1. Causes of Constipation]

but, when questioned specifically, admit to spending 15 to 20 min per bowel movement. The presence, amount, and duration of blood in the stool should also be elicited.

Symptoms of metabolic (eg, hypothyroidism, diabetes mellitus) and neurologic (eg, spinal cord injury) disorders and systemic symptoms (eg, weight loss) should also be sought. Prescription and nonprescription drug use should be assessed, with specific questioning about anticholinergic and opioid drugs.

**Physical examination:** A general examination is done to look for signs of systemic disease, including fever and cachexia. Abdominal masses should be sought by palpation. A rectal examination should be done not only for fissures, strictures, blood, or masses (including fecal impaction) but also to evaluate anal resting tone (the puborectalis "lift" when patients squeeze the anal sphincter), perineal descent during simulated evacuation, and rectal sensation. Patients with defecatory disorders may have increased anal resting tone (or anismus), reduced (ie, < 2 cm) or increased (ie, > 4 cm) perineal descent, and/or paradoxical contraction of the puborectalis during simulated evacuation.

**Red flags:** Certain findings raise suspicion of a more serious etiology of chronic constipation:

- Distended, tympanic abdomen
- Vomiting
- Blood in stool
- Weight loss
- Severe constipation of recent onset/worsening in elderly patients

**Interpretation of findings:** Certain symptoms (eg, a sense of anorectal blockage, prolonged or difficult defecation), particularly when associated with abnormal (ie, increased or reduced) perineal motion during simulated evacuation, suggest a defecatory disorder. A tense, distended, tympanic abdomen, particularly when there is nausea and vomiting, suggests mechanical obstruction.

Patients with IBS typically have abdominal pain with disordered bowel habits (see p. 162). Chronic constipation with modest abdominal discomfort in a patient who has used laxatives for a long time suggests slow-transit constipation. Acute constipation coincident with the start of a constipating drug in patients without red flag findings suggests the drug is the cause. New-onset constipation that persists for weeks or occurs intermittently with increasing frequency or severity, in the absence of a known cause, suggests colonic tumor or other causes of partial obstruction. Excessive straining or prolonged or unsatisfactory defecation, with or without anal digitation, suggests a defecatory disorder. Patients with fecal impaction may have cramps and may pass watery mucus or fecal material around the impacted mass, mimicking diarrhea (paradoxic diarrhea).

**Testing:** Testing is guided by clinical presentation.

Constipation with a clear etiology (drugs, trauma, bed rest) may be treated symptomatically without further study. Patients with symptoms of bowel obstruction require flat and upright abdominal x-rays, possibly a water-soluble contrast enema to evaluate for colonic obstruction, and possibly a CT scan or barium x-ray
of the small intestine (see also p. 116). Most patients without a clear etiology should have sigmoidoscopy or colonoscopy and a laboratory evaluation (CBC, thyroid-stimulating hormone, fasting glucose, electrolytes, and Ca).

Further tests are usually reserved for patients with abnormal findings on the previously mentioned tests or who do not respond to symptomatic treatment. If the primary complaint is infrequent defecation, colonic transit times should be measured with radiopaque markers or scintigraphy. If the primary complaint is difficulty with defecation, anorectal manometry and rectal balloon expulsion should be assessed.

Treatment

• Possibly discontinuation of causative drugs (some may be necessary)
• Increase in dietary fiber
• Possibly trial with a brief course of osmotic laxatives

Any identified conditions should be treated.

Agents used to treat constipation are summarized in Table 8-2. Laxatives should be used judiciously. Some (eg, phosphate, bran, cellulose) bind drugs and interfere with absorption. Rapid fecal transit may rush some drugs and nutrients beyond their optimal absorptive locus. Contraindications to laxative and cathartic use include acute abdominal pain of unknown origin, inflammatory bowel disorders, intestinal obstruction, GI bleeding, and fecal impaction.

Diet and behavior: The diet should contain enough fiber (typically 15 to 20 g/day) to ensure adequate stool bulk. Vegetable fiber, which is largely indigestible and unabsorbable, increases stool bulk. Certain components of fiber also absorb fluid, making stools softer and facilitating their passage. Fruits and vegetables are recommended sources, as are cereals containing bran. Fiber supplementation is particularly effective in treating normal-transit constipation but is not very effective for slow-transit constipation or defecatory disorders.

Table 8-2. Agents Used to Treat Constipation

Behavioral changes may help. Patients should try to move their bowels at the same time daily, preferably 15 to 45 min after breakfast, because food ingestion stimulates colonic motility. Initial efforts at regular, unhurried bowel movements may be aided by glycerin suppositories.

Explanation is important, but it is difficult to convince obsessive-compulsive patients that their attitude toward defecation is abnormal. Physicians must explain that daily bowel movements are not essential, that the bowel must be given a chance to function, and that frequent use of laxatives or enemas (> once/3 days) denies the bowel that chance.

Types of laxatives: Bulking agents (eg, psyllium, Ca polycarbophil, methylcellulose) act slowly and gently and are the safest agents for promoting elimination. Proper use involves gradually increasing the dose—ideally taken tid or qid with sufficient liquid (eg, 500 mL/day of extra fluid) to prevent impaction—until a softer, bulkier stool results. Bloating may be reduced by gradually titrating the dose of dietary fiber to the recommended dose, or by switching to a synthetic fiber preparation such as methylcellulose.

Osmotic agents contain poorly absorbed polyvalent ions (eg, Mg, phosphate, sulfate), polymers (eg, polyethylene glycol), or carbohydrates (eg, lactulose, sorbitol) that remain in the bowel, increasing intraluminal osmotic pressure and thereby drawing water into the intestine. The increased volume stimulates peristalsis. These agents usually work within 3 h.

In general, osmotic laxatives are reasonably safe even when used regularly. However, Na phosphate should not be used for bowel cleansing because it may rarely cause acute renal failure even after a single use for bowel preparation. These events occurred primarily in elderly patients, those with preexisting renal disease, and those who were taking drugs that affect renal perfusion or function (eg, diuretics, ACE
Secretory or stimulant cathartics (eg, phenolphthalein, bisacodyl, anthraquinones, castor oil, anthraquinones) act by irritating the intestinal mucosa or by directly stimulating the submucosal and myenteric plexus. Although phenolphthalein was withdrawn from the US market after animal studies suggested the compound was carcinogenic, there is no epidemiologic evidence of this in humans. Bisacodyl is an effective rescue drug for chronic constipation. The anthraquinones senna, cascara sagrada, aloe, and rhubarb are common constituents of herbal and OTC laxatives. They pass unchanged to the colon where bacterial metabolism converts them to active forms. Adverse effects include allergic reactions, electrolyte depletion, melanosis coli, and cathartic colon. Melanosis coli is a brownish black colorectal pigmentation of unknown composition. Cathartic colon refers to alterations in colonic anatomy observed on barium enema in patients with chronic stimulant laxative use. It is unclear whether cathartic colon, which has been attributed to destruction of myenteric plexus neurons by anthraquinones, is caused by currently available agents or other neurotoxic agents (eg, podophyllin), which are no longer available. There does not seem to be an increased risk of colon cancer with long-term anthraquinone use.

Enemas can be used, including tap water and commercially prepared hypertonic solutions.

Emollient agents (eg, docusate, mineral oil) act slowly to soften stools, making them easier to pass. However, they are not potent stimulators of defecation. Docusate is a surfactant, which allows water to enter the fecal mass to soften and increase its bulk.

**Fecal impaction:** Fecal impaction is treated initially with enemas of tap water followed by small enemas (100 mL) of commercially prepared hypertonic solutions (eg, Na phosphate). If these do not work, manual fragmentation and disimpaction of the mass is necessary. This procedure is painful, so perirectal and intrarectal application of local anesthetics (eg, lidocaine 5% ointment or dibucaine 1% ointment) is recommended. Some patients require sedation.

**Key Points**

- Drug causes are common (eg, chronic laxative abuse, use of anticholinergic or opioid drugs).
- Clinicians should be wary of bowel obstruction when constipation is acute and severe.
- Symptomatic treatment is reasonable in the absence of red flag findings and after excluding pelvic floor dysfunction.

**Dyschezia**

(Disordered Evacuation; Dysfunction of Pelvic Floor or Anal Sphincters; Functional Defecatory Disorders; Dyssynergia)

**Dyschezia is difficulty defecating. Patients sense the presence of stool and the need to defecate but are unable. It results from a lack of coordination of pelvic floor muscles and anal sphincters. Diagnosis requires anorectal testing. Treatment is difficult, but biofeedback may be of benefit.**

**Etiology**

Normally, when a person tries to defecate, rectal pressure rises in coordination with relaxation of the external anal sphincter. This process may be affected by one or more dysfunctions (eg, impaired rectal contraction, excessive contraction of the abdominal wall, paradoxical anal contraction, failure of anal relaxation) of unclear etiology. Functional defecatory disorders may manifest at any age. In contrast,
Hirschsprung’s disease, which is due to an absent recto-anal inhibitory reflex, is almost always diagnosed in infancy or childhood.

**Symptoms and Signs**

The patient may or may not sense that stool is present in the rectum. Despite prolonged straining, evacuation is tedious or impossible, frequently even for soft stool or enemas. Patients may complain of anal blockage and may digitally remove stool from their rectum or manually support their perineum or splint the vagina to evacuate. Actual stool frequency may or may not be decreased.

**Diagnosis**

Rectal and pelvic examinations may reveal hypertonia of the pelvic floor muscles and anal sphincters. With bearing down, patients may not demonstrate the expected anal relaxation and perineal descent. With excessive straining, the anterior rectal wall prolapses into the vagina in patients with impaired anal relaxation; thus rectoceles are usually a secondary rather than a primary disturbance. Long-standing dyschezia with chronic straining may cause a solitary rectal ulcer or varying degrees of rectal prolapse or excessive perineal descent or an enterocele. Anorectal manometry and rectal balloon expulsion, occasionally supplemented by defecatory or magnetic resonance proctography, are necessary to diagnose the condition.

**Treatment**

Because treatment with laxatives is unsatisfactory, it is important to assess anorectal functions in patients with refractory constipation. Biofeedback therapy can improve coordination between abdominal contraction and pelvic floor relaxation during defecation, thereby alleviating symptoms. However, pelvic floor retraining for defecatory disorders is highly specialized and available at select centers only. A collaborative approach (physiotherapists, dietitians, behavior therapists, gastroenterologists) is necessary.

**Diarrhea**

(See also Chs. 17 and 19. For diarrhea in children, see p. 2737.)

Stool is 60 to 90% water. In Western society, stool amount is 100 to 200 g/day in healthy adults and 10 g/kg/day in infants, depending on the amount of unabsorbable dietary material (mainly carbohydrates). Diarrhea is defined as stool weight > 200 g/day. However, many people consider any increased stool fluidity to be diarrhea. Alternatively, many people who ingest fiber have bulkier but formed stools but do not consider themselves to have diarrhea.

**Complications:** Complications may result from diarrhea of any etiology. Fluid loss with consequent dehydration, electrolyte loss (Na, K, Mg, Cl), and even vascular collapse sometimes occur. Collapse can develop rapidly in patients who have severe diarrhea (eg, patients with cholera) or are very young, very old, or debilitated. HCO₃⁻ loss can cause metabolic acidosis. Hypokalemia can occur when patients have severe or chronic diarrhea or if the stool contains excess mucus. Hypomagnesemia after prolonged diarrhea can cause tetany.

**Etiology**

Normally, the small intestine and colon absorb 99% of fluid resulting from oral intake and GI tract secretions—a total fluid load of about 9 of 10 L daily. Thus, even small reductions (ie, 1%) in intestinal water absorption or increases in secretion can increase water content enough to cause diarrhea.

There are a number of causes of diarrhea (see Table 8-3). Several basic mechanisms are responsible for most clinically significant diarrheas: increased osmotic load, increased secretions, and decreased contact time/surface area. In many disorders, more than one mechanism is active. For example, diarrhea in inflammatory bowel disease results from mucosal destruction, exudation into the lumen, and from multiple secretagogues and bacterial toxins that affect
enterocyte function.

[Table 8-3: Some Causes of Diarrhea*]

**Osmotic load**: Diarrhea occurs when unabsorbable, water-soluble solutes remain in the bowel and retain water. Such solutes include polyethylene glycol, Mg salts (hydroxide and sulfate), and Na phosphate, which are used as laxatives. Osmotic diarrhea occurs with sugar intolerance (eg, lactose intolerance caused by lactase deficiency). Ingesting large amounts of hexitols (eg, sorbitol, mannitol, xylitol) or high fructose corn syrups, which are used as sugar substitutes in candy, gum, and fruit juices, causes osmotic diarrhea because hexitols are poorly absorbed. Lactulose, which is used as a laxative, causes diarrhea by a similar mechanism. Overingesting certain foodstuffs (see Table 8-4) can cause osmotic diarrhea.

**Increased secretions**: Diarrhea occurs when the bowels secrete more electrolytes and water than they absorb. Causes of increased secretions include infections, unabsorbed fats, certain drugs, and various intrinsic and extrinsic secretagogues.

Infections (eg, gastroenteritis; discussed in Ch. 16) are the most common causes of secretory diarrhea. Infections combined with food poisoning are the most common causes of acute diarrhea (< 4 days in duration). Most enterotoxins block Na\(^+\)-H\(^+\) exchange, which is an important driving force for fluid absorption in the small bowel and colon.

Unabsorbed dietary fat and bile acids (as in malabsorption syndromes and after ileal resection) can stimulate colonic secretion and cause diarrhea.

Drugs may stimulate intestinal secretions directly (eg, quinidine, quinine, colchicine, anthraquinone cathartics, castor oil, prostaglandins) or indirectly by impairing fat absorption (eg, orlistat).

Various endocrine tumors produce secretagogues, including vipomas (vasoactive intestinal peptide), gastrinomas (gastrin), mastocytosis (histamine), medullary carcinoma of the thyroid (calcitonin and prostaglandins), and carcinoid tumors (histamine, serotonin, and polypeptides). Some of these mediators (eg, prostaglandins, serotonin, related compounds) also accelerate intestinal transit, colonic transit, or both.

**Reduced contact time/surface area**: Rapid intestinal transit and diminished surface area impair fluid absorption and cause diarrhea. Common causes include small-bowel or large-bowel resection or bypass, gastric resection,

[Table 8-4: Dietary Factors that May Worsen Diarrhea]

and inflammatory bowel disease. Other causes include microscopic colitis (collagenous or lymphocytic colitis) and celiac sprue.

Stimulation of intestinal smooth muscle by drugs (eg, Mg-containing antacids, laxatives, cholinesterase inhibitors, SSRIs) or humoral agents (eg, prostaglandins, serotonin) also can speed transit.

**Evaluation**

**History**: Duration and severity of diarrhea, circumstances of onset (including recent travel, food ingested, source of water), drug use (including any antibiotics within the previous 3 mo), abdominal pain or vomiting, frequency and timing of bowel movements, changes in stool characteristics (eg, presence of blood, pus, or mucus; changes in color or consistency; evidence of steatorrhea), associated changes in weight or appetite, and rectal urgency or tenesmus should be noted. Simultaneous occurrence of diarrhea in close contacts should be ascertained.

**Physical examination**: Fluid and hydration status should be evaluated. A full examination with attention to the abdomen and a digital rectal examination for sphincter competence and occult blood testing are important.
**Red flags:** Certain findings raise suspicion of an organic or more serious etiology of diarrhea:

- Blood or pus
- Fever
- Signs of dehydration
- Chronic diarrhea
- Weight loss

**Interpretation of findings:** Acute, watery diarrhea in an otherwise healthy person is likely to be of infectious etiology, particularly when travel, possibly tainted food, or an outbreak with a point-source is involved. Acute bloody diarrhea with or without hemodynamic instability in an otherwise healthy person suggests an enteroinvasive infection. Diverticular bleeding and ischemic colitis also manifest with acute bloody diarrhea. Recurrent bouts of bloody diarrhea in a younger person suggest inflammatory bowel disease. In the absence of laxative use, large-volume diarrhea (eg, daily stool volume > 1 L/day) strongly suggests an endocrine cause in patients with normal GI anatomy. A history of oil droplets in stool, particularly if associated with weight loss, suggests malabsorption.

Diarrhea that consistently follows ingestion of certain foods (eg, fats) suggests food intolerance. Recent antibiotic use should raise suspicion for antibiotic-associated diarrhea, including *Clostridium difficile* colitis.

The symptoms can help identify the affected part of the bowel. Generally, in small-bowel diseases, stools are voluminous and watery or fatty. In colonic diseases, stools are frequent, sometimes small in volume, and possibly accompanied by blood, mucus, pus, and abdominal discomfort. In irritable bowel syndrome (IBS), abdominal discomfort is relieved by defecation, associated with more loose or frequent stools, or both. However, these symptoms alone do not discriminate IBS from other diseases (eg, inflammatory bowel disease). Patients with IBS or rectal mucosal involvement often have marked urgency, tenesmus, and small, frequent stools (see p. 163).

Extra-abdominal findings that suggest an etiology include skin lesions or flushing (mastocytosis), thyroid nodules (medullary carcinoma of the thyroid), right-sided heart murmur (carcinoid), lymphadenopathy (lymphoma, AIDS), and arthritis (inflammatory bowel disease, celiac disease).

**Testing:** Acute diarrhea (< 4 days) typically does not require testing. Exceptions are patients with signs of dehydration, bloody stool, fever, severe pain, hypotension, or toxic features—particularly those who are very young or very old. These patients should have a CBC and measurement of electrolytes, BUN, and creatinine. Stool samples should be collected for microscopy, culture, fecal leukocyte testing, and, if antibiotics have been taken recently, *C. difficile* toxin assay.

Chronic diarrhea (> 4 wk) requires evaluation, as does a shorter (1 to 3 wk) bout of diarrhea in immunocompromised patients or those who appear significantly ill. Initial stool testing should include culture, fecal leukocytes (detected by smear or measurement of fecal lactoferrin), microscopic examination for ova and parasites, pH (bacterial fermentation of unabsorbed carbohydrate lowers stool pH < 6.0), fat (by Sudan stain), and electrolytes (Na and K). If no standard pathogens are found, specific tests for *Giardia* antigen and *Aeromonas, Plesiomonas*, coccidia, and microsporidia should be requested. Sigmoidoscopy or colonoscopy with biopsies should follow to look for inflammatory causes.

If no diagnosis is apparent and Sudan stain is positive for fat, fecal fat excretion should be measured, followed by small-bowel enteroclysis or CT enterography (structural disease) and endoscopic small-bowel biopsy (mucosal disease). If evaluation still yields negative findings, assessment of pancreatic structure and function (see p. 142) should be considered for patients who have unexplained steatorrhea. Infrequently, capsule endoscopy may uncover lesions, predominantly Crohn's disease or NSAID enteropathy, not identified by other modalities.
The stool osmotic gap, which is calculated 290 - 2 × (stool Na + stool K), indicates whether diarrhea is secretory or osmotic. An osmotic gap < 50 mEq/L indicates secretory diarrhea; a larger gap suggests osmotic diarrhea. Patients with osmotic diarrhea may have covert Mg laxative ingestion (detectable by stool Mg levels) or carbohydrate malabsorption (diagnosed by hydrogen breath test, lactase assay, and dietary review).

Undiagnosed secretory diarrhea requires testing (eg, plasma gastrin, calcitonin, vasoactive intestinal peptide levels, histamine, urinary 5-hydroxyindole acetic acid [5-HIAA]) for endocrine-related causes. A review for symptoms and signs of thyroid disease and adrenal insufficiency should be done. Surreptitious laxative abuse must be considered; it can be ruled out by a fecal laxative assay.

**Treatment**

- Fluid and electrolytes for dehydration
- Possibly antidiarrheals for nonbloody diarrhea in patients without systemic toxicity

Severe diarrhea requires fluid and electrolyte replacement to correct dehydration, electrolyte imbalance, and acidosis. Parenteral fluids containing NaCl, KCl, and glucose are generally required. Salts to counteract acidosis (Na lactate, acetate, HCO₃⁻) may be indicated if serum HCO₃⁻ is < 15 mEq/L. An oral glucose-electrolyte solution can be given if diarrhea is not severe and nausea and vomiting are minimal (see p. 2809). Oral and parenteral fluids are sometimes given simultaneously when water and electrolytes must be replaced in massive amounts (eg, in cholera).

Diarrhea is a symptom. When possible, the underlying disorder should be treated, but symptomatic treatment is often necessary. Diarrhea may be decreased by oral loperamide 2 to 4 mg tid or qid (preferably given 30 min before meals), diphenoxylate 2.5 to 5 mg (tablets or liquid) tid or qid, codeine phosphate 15 to 30 mg bid or tid, or paregoric (camphorated opium tincture) 5 to 10 mL once/day to qid.

Because antidiarrheals may exacerbate *C. difficile* colitis or increase the likelihood of hemolytic-uremic syndrome in *Shiga* toxin-producing *Escherichia coli* infection, they should not be used in bloody diarrhea of unknown cause. Their use should be restricted to patients with watery diarrhea and no signs of systemic toxicity. However, there is little evidence to justify previous concerns about prolonging excretion of possible bacterial pathogens with antidiarrheals.

Psyllium or methylcellulose compounds provide bulk. Although usually prescribed for constipation, bulking agents given in small doses decrease the fluidity of liquid stools. Kaolin, pectin, and activated attapulgite adsorb fluid. Osmotically active dietary substances (see Table 8-4) and stimulatory drugs should be avoided.

**Key Points**

- In patients with acute diarrhea, stool examination (cultures, ova and parasites, *C. difficile* cytotoxin) is only necessary for those who have prolonged symptoms (ie, > 1 wk) or red flag findings.
- Antidiarrheals should be used cautiously if there is a possibility of *C. difficile*, *Salmonella*, or shigellosis.

**Gas-Related Complaints**

The gut contains < 200 mL of gas, whereas daily gas expulsion averages 600 to 700 mL after consuming a standard diet plus 200 g of baked beans. About 75% of flatus is derived from colonic bacterial fermentation of ingested nutrients and endogenous glycoproteins. Gases include hydrogen (H₂), methane (CH₄), and carbon dioxide (CO₂). Flatus odor correlates with H₂ sulphide concentrations. Swallowed air (aerophagia) and diffusion from the blood into the lumen also contribute to intestinal gas. Gas diffuses between the lumen and the blood in a direction that depends on the difference in partial
pressures. Thus, most nitrogen (N₂) in the lumen originates from the bloodstream, and most H₂ in the bloodstream originates from the lumen.

**Etiology**

There are 3 main gas-related complaints: excessive belching, distention (bloating), and excessive flatus, each with a number of causes (see Table 8-5). Infants 2 to 4 mo of age with recurrent crying spells often appear to observers to be in pain, which in the past has been attributed to abdominal cramping or gas and termed colic. However, studies show no increase in H₂ production or in mouth-to-cecum transit times in colicky infants. Hence, the cause of infantile colic remains unclear (see p. 2725).

**Excessive belching:** Belching (eructation) results from swallowed air or from gas generated by carbonated beverages. Aerophagia occurs normally in small amounts during eating and drinking, but some people unconsciously swallow air repeatedly while eating or smoking and at other times, especially when anxious or in an attempt to induce belching. Excessive salivation increases aerophagia and may be associated with various GI disorders (eg, gastroesophageal reflux disease), ill-fitting dentures, certain drugs, gum chewing, or nausea of any cause.

Most swallowed air is eructated. Only a small amount of swallowed air passes into the small bowel; the amount is apparently influenced by position. In an upright person, air is readily belched; in a supine person, air trapped above the stomach fluid tends to be propelled into the duodenum. Excessive eructation may also be voluntary; patients who belch after taking antacids may attribute the relief of symptoms to belching rather than to antacids and may intentionally belch to relieve distress.

**Distention (bloating):** Abdominal bloating may occur in isolation or along with other GI symptoms in patients with functional disorders (eg, aerophagia, nonulcer dyspepsia, gastroparesis, irritable bowel syndrome) or organic disorders (eg, ovarian cancer, colon cancer). However, excessive intestinal gas is not clearly linked to these complaints. In most healthy people, 1 L/h of gas can be infused into the gut with minimal symptoms. It is likely that many symptoms are incorrectly attributed to "too much gas."

On the other hand, some patients with recurrent GI symptoms often cannot tolerate small quantities of gas: Retrograde colonic distention by balloon inflation or air instillation during colonoscopy often elicits severe discomfort in some patients (eg, those with irritable bowel syndrome) but minimal symptoms in others. Similarly, patients with eating disorders (eg, anorexia nervosa, bulimia) often misperceive and are particularly stressed by symptoms such as bloating. Thus, the basic abnormality in patients with gas-related symptoms may be a hypersensitive intestine. Altered motility may contribute further to symptoms.

**Excessive flatus:** There is great variability in the quantity and frequency of rectal gas passage. As with stool frequency, people who complain of flatulence often have a misconception of what is normal. The average number of gas passages is about 13 to 21/day. Objectively recording flatus frequency (using a diary kept by the patient) is a first step in evaluation.

Flatus is a metabolic byproduct of intestinal bacteria; almost none originates from swallowed air or back-diffusion of gases (primarily N₂) from the bloodstream. Bacterial metabolism yields significant volumes of H₂, CH₄, and CO₂.

H₂ is produced in large quantities in patients with malabsorption syndromes and after ingestion of certain fruits and vegetables containing indigestible carbohydrates (eg, baked beans), sugars (eg, fructose), or sugar alcohols (eg, sorbitol). In patients with disaccharidase deficiencies (most commonly lactase deficiency), large amounts of disaccharides pass into the colon and are fermented to H₂. Celiac disease, tropical sprue, pancreatic insufficiency, and other causes of carbohydrate malabsorption should also be considered in cases of excess colonic gas.

CH₄ is also produced by colonic bacterial metabolism of the same foods (eg, dietary fiber). However, about 10% of people have bacteria that produce CH₄ but not H₂.
CO₂ is also produced by bacterial metabolism and generated in the reaction of HCO₃⁻ and H⁺. H⁺ may come from gastric HCl or from fatty acids released during digestion of fats—the latter sometimes produces several hundred mEq of H⁺. The acid products released by bacterial fermentation of unabsorbed carbohydrates in the colon may also react with HCO₃⁻ to produce CO₂. Although bloating may occasionally occur, the rapid diffusion of CO₂ into the blood generally prevents distention.

[Table 8-5. Some Causes of Gas-Related Complaints]

Diet accounts for much of the variation in flatus production among individuals, but poorly understood factors (eg, differences in colonic flora and motility) may also play a role.

Despite the flammable nature of the H₂ and CH₄ in flatulence, working near open flames is not hazardous. However, gas explosion, even with fatal outcome, has been reported during jejunal and colonic surgery and colonoscopy, when diathermy was used during procedures in patients with incomplete bowel cleaning.

Evaluation

History: Patients with belching should have the history directed at finding the cause of aerophagia, especially dietary causes.

In patients complaining of gas, bloating, or flatus, the relationship between symptoms and meals (both timing and type and amount of food), bowel movements, and exertion should be explored. Certain patients, particularly in the acute setting, may use the term "gas" to describe their symptoms of coronary ischemia. Changes in frequency and color and consistency of stool are sought. History of weight loss is noted.

Physical examination: The examination is generally normal, but in patients with bloating or flatus, signs of an underlying organic disorder should be sought on abdominal, rectal, and (for women) pelvic examination.

Red flags: The following findings are of concern:

- Weight loss

- Blood in stool (occult or gross)

Interpretation of findings: Chronic, recurrent bloating or distention relieved by defecation and associated with change in frequency or consistency of stool but without red flag findings suggests irritable bowel syndrome.

Long-standing symptoms in an otherwise well young person who has not lost weight are unlikely to be caused by serious physiologic disease, although an eating disorder should be considered, particularly in young women. Bloating accompanied by diarrhea, weight loss, or both (or only after ingestion of certain foods) suggests a malabsorption syndrome.

Testing: Testing is not indicated for belching unless other symptoms suggest a particular disorder. Testing for carbohydrate intolerance (eg, lactose, fructose) with breath tests should be considered particularly when the history suggests significant consumption of these sugars. Testing for small-bowel bacterial overgrowth should also be considered, particularly in patients who also have diarrhea, weight loss, or both, preferably by aerobic and anaerobic culture of small-bowel aspirates obtained during upper GI endoscopy. Testing for bacterial overgrowth with H₂ breath tests, generally glucose-H₂ breath tests, is prone to false-positive (ie, with rapid transit) and false-negative (ie, when there are no H₂-producing bacteria) results. New, persistent bloating in middle-aged or older women (or those with an abnormal pelvic examination) should prompt pelvic ultrasonography to rule out ovarian cancer.
Treatment

Belching and bloating are difficult to relieve because they are usually caused by unconscious aerophagia or increased sensitivity to normal amounts of gas. Aerophagia may be reduced by eliminating gum and carbonated beverages, cognitive behavioral techniques to prevent air swallowing, and management of associated upper GI diseases (eg, peptic ulcer). Foods containing unabsorbable carbohydrates should be avoided. Even lactose-intolerant patients generally tolerate up to 1 glass of milk drunk in small amounts throughout the day. The mechanism of repeated belching should be explained and demonstrated. When aerophagia is troublesome, behavioral therapy to encourage open-mouth, diaphragmatic breathing and minimize swallowing may be effective.

Sidebar 8-1 Essay on Flatulence

(First printed in the 14th Edition of The Merck Manual)

Flatulence, which can cause great psychosocial distress, is unofficially described according to its salient characteristics: (1) the "slider" (crowded elevator type), which is released slowly and noiselessly, sometimes with devastating effect; (2) the open sphincter, or "pooh" type, which is said to be of higher temperature and more aromatic; (3) the staccato or drumbeat type, pleasantly passed in privacy; and (4) the "bark" type (described in a personal communication) is characterized by a sharp exclamatory eruption that effectively interrupts (and often concludes) conversation. Aromaticity is not a prominent feature. Rarely, this usually distressing symptom has been turned to advantage, as with a Frenchman referred to as "Le Petomane," who became affluent as an effluent performer who played tunes with the gas from his rectum on the Moulin Rouge stage.

Drugs provide little benefit. Results with simethicone, an agent that breaks up small gas bubbles, and various anticholinergics are poor. Some patients with dyspepsia and postprandial upper abdominal fullness benefit from antacids, a low dose of tricyclic antidepressants (eg, nortriptyline 10 to 50 mg po once/day), or both to reduce visceral hypersensitivity.

Complaints of excess flatus are treated with avoidance of triggering substances (see Table 8-5). Roughage (eg, bran, psyllium seed) may be added to the diet to try to increase colonic transit; however, in some patients, worsening of symptoms may result. Activated charcoal can sometimes help reduce gas and unpleasant odor; however, it stains clothing and the oral mucosa. Charcoal-lined undergarments are available. Probiotics (eg, VSL#3) may also reduce bloating and flatulence by modulating intestinal bacterial flora. Antibiotics are useful in patients with documented bacterial overgrowth.

Functional bloating, distention, and flatus may run an intermittent, chronic course that is only partially relieved by therapy. When appropriate, reassurance that these problems are not detrimental to health is important.

Key Points

• Testing should be guided by the clinical features.

• Clinicians should be wary of new-onset, persistent symptoms in older patients.
Chapter 9. Diagnostic and Therapeutic GI Procedures

Introduction

Diagnostic tests and therapeutic procedures available for patients with GI disorders include acid-related tests, endoscopy, laparoscopy, manometry, nuclear scans, x-ray contrast studies, nasogastric or intestinal intubation, anoscopy and sigmoidoscopy, abdominal paracentesis, electrogastrography, and electrical impedance testing. CT, MRI, and ultrasonography are also commonly done for GI disorders, and sometimes angiography is used. The selection of procedures is discussed in subsequent chapters. ERCP, percutaneous transhepatic cholangiography, and liver biopsy are discussed in Ch. 24.

Acid-Related Tests

Acid-related tests are used to ascertain the effectiveness of acid-blocking drugs. All require nasogastric or nasoesophageal intubation. Complications are very rare. Patients must have nothing by mouth (npo) after midnight.

Ambulatory pH Monitoring

Ambulatory 24-h esophageal pH monitoring is currently the best available test for quantifying esophageal acid exposure. The principal indications are

• To document excessive acid exposure in patients without endoscopic evidence of esophagitis

• To evaluate the effectiveness of medical or surgical treatments

A thin tube containing a pH probe is positioned 5 cm above the lower esophageal sphincter. The patient records symptoms, meals, and sleep for 24 h. Esophageal acid exposure is defined by the percentage of the 24-h recording time that the pH is < 4.0. Values > 3.5% are considered abnormal. However, symptoms may not correlate with acid exposure or the presence of esophagitis. This may be because symptoms may result from nonacidic as well as acidic refluxate. Multichannel intraluminal impedance testing allows for recognition of major acid, minor acid, nonacid, and gas reflux, all of which can cause reflux symptoms.

Gastric Analysis

Samples of stomach contents obtained via NGT are used to measure gastric acid output in a basal and stimulated state. This information may be useful in a patient who develops a recurrent ulcer after surgical vagotomy for peptic ulcer disease. In this case, a positive acid response to stimulation (sham feeding) indicates an incomplete vagotomy. The test also is used to evaluate a patient with elevated serum gastrin levels. Hyperchlorhydria in the presence of elevated gastrin usually indicates Zollinger-Ellison syndrome. Hypochlorhydria in the presence of elevated gastrin indicates impairment of acid output, such as occurs in pernicious anemia, atrophic gastritis, and Menetrier's disease and after inhibition of gastric acid secretion by potent antisecretory drugs.

To do gastric analysis, an NGT is inserted and the gastric contents are aspirated and discarded. Gastric juice is then collected for 1 h, divided into four 15-min samples. These samples represent basal acid output.

Endoscopy

Flexible endoscopes equipped with video cameras can be used to view the upper GI tract from pharynx to upper duodenum and the lower GI tract from anus to cecum (and, sometimes, terminal ileum). Several other diagnostic and therapeutic interventions also can be done endoscopically. The potential to combine diagnosis and therapy in one procedure gives endoscopy a significant advantage over procedures that provide only imaging (eg, x-ray contrast studies, CT, MRI) and often outweighs endoscopy's higher cost and need for sedation.

Diagnostic procedures include the use of ultrasound-equipped endoscopes to evaluate blood flow or
provide imaging of lesions. Endoscopic ultrasound can provide information (eg, the depth and extent of lesions) that is not available via conventional endoscopy. Other diagnostic procedures include cell and tissue sample collection by brush or biopsy forceps.

Screening colonoscopy is recommended for patients at high risk of colon cancer and for everyone ≥ 50. Colonoscopy should be done every 10 yr for patients with no risk factors and with a normal initial colonoscopy. CT colonography (see p. 98) is an alternative to colonoscopy for screening for colonic tumors.

Therapeutic endoscopic procedures include removal of foreign bodies; hemostasis by thermal coagulation, laser photoacoagulation, variceal banding, or sclerotherapy; debulking of tumors by laser or bipolar electrocoagulation; dilation of webs or strictures; stent placement; reduction of volvulus or intussusception; and decompression of acute or subacute colonic dilatation.

**Absolute contraindications** to endoscopy include

- Shock
- Acute MI
- Peritonitis
- Acute perforation
- Fulminant colitis

Relative contraindications include poor patient cooperation, coma (unless the patient is intubated), and cardiac arrhythmias or recent myocardial ischemia.

Patients taking anticoagulants or chronic NSAID therapy can safely undergo diagnostic endoscopy. However, if there is a possibility that biopsy or photoacoagulation will be done, these drugs should be stopped for an appropriate interval before the procedure. Oral iron-containing drugs should be stopped 4 to 5 days before colonoscopy, because certain green vegetables interact with iron to form a sticky residue that is difficult to remove with a bowel preparation and interferes with visualization. The American Heart Association no longer recommends endocarditis prophylaxis for patients having GI endoscopy.

Routine preparations for endoscopy include no solids for 6 to 8 h and no liquids for 4 h before the procedure. Additionally, colonoscopy requires cleansing of the colon. A variety of regimens may be used, but all typically include a full or clear liquid diet for 24 to 48 h and some type of laxative, with or without an enema. A common laxative preparation involves having the patient drink a high-volume (4 L) balanced electrolyte solution over a period of 3 to 4 h before the procedure. Patients who cannot tolerate this solution may be given Mg citrate, Na phosphate, lactulose, or other laxatives. Enemas can be done with either Na phosphate or tap water. Phosphate preparations should not be used in patients with renal insufficiency.

Endoscopy generally requires IV sedation and, for upper endoscopy, topical anesthesia of the throat. Exceptions are anoscopy and sigmoidoscopy (see p. 98), which generally require nothing. The overall complication rate of endoscopy is 0.1 to 0.2%; mortality is about 0.03%. Complications are usually drug related (eg, respiratory depression); procedural complications (eg, aspiration, perforation, significant bleeding) are less common.

**Video capsule endoscopy:** In video capsule endoscopy (wireless video endoscopy), patients swallow a capsule containing a camera that transmits images to an external recorder. This noninvasive technology provides diagnostic imaging of the small bowel that is otherwise difficult to obtain. This procedure is particularly useful in patients with occult GI bleeding. Capsule endoscopy is more difficult in the colon; products and procedures are under development.

**Laparoscopy**
Diagnostic laparoscopy is a surgical procedure used to evaluate intra-abdominal or pelvic pathology (eg, tumor, endometriosis) in patients with acute or chronic abdominal pain and operability in patients with cancer. It also is used for lymphoma staging and liver biopsy.

**Absolute contraindications** include

- A coagulation or bleeding disorder
- Poor patient cooperation
- Peritonitis
- Intestinal obstruction
- Infection of the abdominal wall

Relative contraindications include severe cardiac or pulmonary disease, large abdominal hernias, multiple abdominal operations, and tense ascites.

CBC, coagulation studies, and type and Rh testing are done before laparoscopy. X-rays of the chest and abdomen (kidneys, ureters, and bladder) are also taken. Laparoscopy is done with sterile technique in an operating room or a well-equipped endoscopy suite. The patient is given local anesthesia plus IV sedation and analgesia with an opioid and short-acting sedative (eg, midazolam, propofol).

The procedure involves insertion of a pneumoperitoneum needle into the peritoneal cavity and infusion of nitrous oxide to distend the abdomen. After the opening is enlarged, a peritoneoscope is inserted into the abdomen and the abdominal contents are examined. Surgical instruments for biopsy and other procedures are inserted through separate openings. When the procedure is completed, the nitrous oxide is expelled by the patient with a Valsalva maneuver and the cannula is removed. Complications can include bleeding, bacterial peritonitis, and perforation of a viscus.

**Manometry**

Manometry is measurement of pressure within various parts of the GI tract. It is done by passing a catheter containing solid-state or liquid-filled pressure transducers through the mouth or anus into the lumen of the organ to be studied. Manometry typically is done to evaluate motility disorders in patients in whom structural lesions have been ruled out by other studies. Manometry is used in the esophagus, stomach and duodenum, sphincter of Oddi, and rectum. Aside from minor discomfort, complications are very rare. Patients must have nothing by mouth (npo) after midnight.

**Esophageal manometry:** This test is used to evaluate patients with dysphagia, heartburn, or chest pain. It measures the pressure in the upper and lower esophageal sphincters through the mouth or anus into the lumen of the organ to be studied. Manometry typically is done to evaluate motility disorders in patients in whom structural lesions have been ruled out by other studies. Manometry is used to diagnose achalasia, diffuse spasm, systemic sclerosis, and lower esophageal sphincter hypotension and hypertension. It also is used to evaluate esophageal function before certain therapeutic procedures (eg, antireflux surgery, pneumatic dilation for achalasia).

**Gastroduodenal manometry:** In this test, transducers are placed in the gastric antrum, duodenum, and proximal jejunum. Pressure is monitored for 5 to 24 h in both fasting and fed states. This test is used mainly in patients who have symptoms suggestive of dysmotility but normal gastric emptying studies.

**Barostat:** This is a pressure-sensing device that is placed in the stomach to measure gastric accommodation. The device consists of a plastic balloon and an electronic controller that varies the amount of air in the balloon to maintain constant pressure. This device is used mainly in research studies assessing sensory threshold and altered visceral perception, particularly in functional GI disorders.

**Anorectal manometry:** This test evaluates the anorectal sphincter mechanism and rectal sensation in
patients with incontinence (and sometimes constipation) by means of a pressure transducer in the anus. It can help diagnose Hirschsprung's disease and provide biofeedback training for fecal incontinence.

**Nuclear Scans**

**Gastric emptying** can be measured by having the patient ingest a radiolabeled meal (solid or liquid) and observing its passage out of the stomach with a gamma camera. Because this test cannot differentiate physical obstruction from gastroparesis, further diagnostic studies typically are done if emptying is delayed. The test also is useful in monitoring response to promotility drugs (eg, metoclopramide, erythromycin).

**Bleeding scans** use $^{99m}$Tc-labeled RBCs, or occasionally $^{99m}$Tc-labeled colloid, to determine the origin of lower GI hemorrhage before surgery or angiography. Active bleeding sites are identified by focal areas of tracer that conform to bowel anatomy, increase with time, and move with peristalsis. Bleeding scans are useful mainly for colonic bleeding in patients with significant hemorrhage and an unprepared bowel, in whom endoscopic visualization is difficult.

A **Meckel scan** identifies ectopic gastric mucosa (as in a Meckel's diverticulum) by using an injection of $^{99m}$Tc pertechnetate, which is taken up by mucus-secreting cells of the gastric mucosa. Focal uptake outside of the stomach and in the small bowel indicates a Meckel's diverticulum.

**X-Ray and Other Imaging Contrast Studies**

X-ray and other imaging contrast studies visualize the entire GI tract from pharynx to rectum and are most useful for detecting mass lesions and structural abnormalities (eg, tumors, strictures). Single-contrast studies fill the lumen with radiopaque material, outlining the structure. Better, more detailed images are obtained from double-contrast studies, in which a small amount of high-density barium coats the mucosal surface and gas distends the organ and enhances contrast. The gas is injected by the operator in double-contrast barium enema, whereas in other studies, intrinsic GI tract gas is adequate. In all cases, patients turn themselves to properly distribute the gas and barium. Fluoroscopy can monitor the progress of the contrast material. Either video or plain films can be taken for documentation, but video is particularly useful when assessing motor disorders (eg, cricopharyngeal spasm, achalasia).

The main contraindication to x-ray contrast studies is suspected perforation, because free barium is highly irritating to the mediastinum and peritoneum; water-soluble contrast is less irritating and may be used if perforation is possible. Older patients may have difficulty turning themselves to properly distribute the barium and intraluminal gas.

Patients having upper GI x-ray contrast studies must have nothing by mouth (npo) after midnight. Patients having barium enema follow a clear liquid diet the day before, take an oral Na phosphate laxative in the afternoon, and take a bisacodyl suppository in the evening. Other laxative regimens are effective.

Complications are rare. Perforation can occur if barium enema is done in a patient with toxic megacolon. Barium impaction may be prevented by postprocedure oral fluids and sometimes laxatives.

An **upper GI examination** is best done as a biphasic study beginning with a double-contrast examination of the esophagus, stomach, and duodenum, followed by a single-contrast study using low-density barium. Glucagon 0.5 mg IV can facilitate the examination by causing gastric hypotonia.

A **small-bowel meal** is done by using fluoroscopy and provides a more detailed evaluation of the small bowel. Shortly before the examination, the patient is given metoclopramide 20 mg po to hasten transit of the contrast material.

**Enteroclysis** (small-bowel enema) provides still better visualization of the small bowel but requires intubation of the duodenum with a flexible, balloon-tipped catheter. A barium suspension is injected, followed by a solution of methylcellulose, which functions as a double-contrast agent that enhances visualization of the small-bowel mucosa.
A barium enema can be done as a single-or double-contrast study. Single-contrast barium enemas are used for potential obstruction, diverticulitis, fistulas, and megacolon. Double-contrast studies are preferred for detection of tumors.

CT scanning of the abdomen: CT scanning using oral and IV contrast allows excellent visualization of both the small bowel and colon as well as of other intra-abdominal structures.

CT enterography provides optimal visualization of the small-bowel mucosa; it is preferably done by using a multidetector CT (MDCT) scanner. Patients are given a large volume (1350 mL) of 0.1% barium sulfate before imaging. For certain indications (eg, obscure GI bleeding, small-bowel tumors, chronic ischemia), a biphasic contrast-enhanced MDCT study is done.

CT colonography (virtual colonoscopy) generates 3D and 2D images of the colon by using MDCT and a combination of oral contrast and gas distention of the colon. Viewing the high-resolution 3D images somewhat simulates the appearance of optical endoscopy, hence the name. Optimal CT colonography technique requires careful cleansing and distention of the colon. Residual stool causes problems similar to those encountered with barium enema because it simulates polyps or masses. Three-dimensional endoluminal images are useful to confirm the presence of a lesion and to improve diagnostic confidence.

CT enterography and CT colonoscopy have largely supplanted standard small-bowel series and barium enema examinations.

GI Procedures for the Generalist

Nasogastric or Intestinal Intubation

Nasogastric or intestinal intubation is used to decompress the stomach. It is used to treat gastric atony, ileus, or obstruction; remove ingested toxins, give antidotes (eg, activated charcoal), or both; obtain a sample of gastric contents for analysis (volume, acid content, blood); and supply nutrients.

Contraindications include

- Nasopharyngeal or esophageal obstruction
- Severe maxillofacial trauma
- Uncorrected coagulation abnormalities

Esophageal varices previously have been considered a contraindication, but evidence of adverse effects is lacking.

Several types of tubes are available. A Levin or Salem sump tube is used for gastric decompression or analysis and rarely for short-term feeding. A variety of long, thin, intestinal tubes are used for long-term enteral feeding (see p. 21).

For intubation, the patient sits upright or, if unable, lies in the left lateral decubitus position. A topical anesthetic sprayed in the nose and pharynx helps reduce discomfort. With the patient's head partially flexed, the lubricated tube is inserted through the nares and aimed back and then down to conform to the nasopharynx. As the tip reaches the posterior pharyngeal wall, the patient should sip water through a straw. Violent coughing with flow of air through the tube during respiration indicates that the tube is misplaced in the trachea. Aspiration of gastric juice verifies entry into the stomach. The position of larger tubes can be confirmed by instilling 20 to 30 mL of air and listening with the stethoscope under the left subcostal region for a rush of air.

Some smaller, more flexible intestinal feeding tubes require the use of stiffening wires or stylets. These tubes usually require fluoroscopic or endoscopic assistance for passage through the pylorus.
Complications are rare and include nasopharyngeal trauma with or without hemorrhage, pulmonary aspiration, traumatic esophageal or gastric hemorrhage or perforation, and (very rarely) intracranial or mediastinal penetration.

**Anoscopy and Sigmoidoscopy**

Anoscopy and sigmoidoscopy are used to evaluate symptoms referable to the rectum or anus (eg, bright rectal bleeding, discharge, protrusions, pain). There are no absolute contraindications. Patients with cardiac arrhythmias or recent myocardial ischemia should have the procedure postponed until the comorbid conditions improve; otherwise, patients will need cardiac monitoring. Per changes in American Heart Association guidelines, these procedures no longer require endocarditis prophylaxis.

The perianal area and distal rectum can be examined with a 7-cm anoscope, and the rectum and sigmoid with either a rigid 25-cm or a flexible 60-cm instrument. Flexible sigmoidoscopy is much more comfortable for the patient and readily permits photography and biopsy of tissue. Considerable skill is required to pass a rigid sigmoidoscope beyond the rectosigmoid junction (15 cm) without causing discomfort.

Sigmoidoscopy is done after giving an enema to empty the rectum. IV drugs are usually not needed. The patient is placed in the left lateral position. After external inspection and digital rectal examination, the lubricated instrument is gently inserted 3 to 4 cm past the anal sphincter. At this point, the obturator of the rigid sigmoidoscope is removed, and the instrument is inserted further under direct vision.

Anoscopy may be done without preparation. The anoscope is inserted its full length as described above for rigid sigmoidoscopy, usually with the patient in the left lateral position. Complications are exceedingly rare when the procedure is done properly.

**Abdominal Paracentesis**

Abdominal paracentesis is used to obtain ascitic fluid for testing. It also can be used to remove tense ascites causing respiratory difficulties or pain or as a treatment for chronic ascites.

**Absolute contraindications** include

- Severe, uncorrectable disorders of blood coagulation
- Intestinal obstruction
- An infected abdominal wall

Poor patient cooperation, surgical scarring over the puncture area, and severe portal hypertension with abdominal collateral circulation are relative contraindications.

CBC, platelet count, and coagulation studies are done before the procedure. After emptying the bladder, the patient sits in bed with the head elevated 45 to 90°. In patients with obvious and marked ascites, a point is located at the midline between the umbilicus and the pubic bone and is cleaned with an antiseptic solution and alcohol. In patients with moderate ascites, precise location of ascitic fluid by abdominal ultrasound is indicated. Under sterile technique, the area is anesthetized to the peritoneum with lidocaine 1%. For diagnostic paracentesis, an 18-gauge needle attached to a 50-mL syringe is inserted through the peritoneum (generally a popping sensation is noted). Fluid is gently aspirated and sent for cell count, protein or amylase content, cytology, or culture as needed. For therapeutic (large-volume) paracentesis, a 14-gauge cannula attached to a vacuum aspiration system is used to collect up to 8 L of ascitic fluid. Postprocedure hypotension caused by fluid redistribution is rare as long as interstitial (leg) edema is present.

Hemorrhage is the most common complication. Occasionally, with tense ascites, prolonged leakage of ascitic fluid occurs through the needle site.

**Other Testing Procedures**
Electrogastrography measures gastric electrical activity with adhesive cutaneous electrodes. This procedure is useful in patients with gastroparesis.

In electrical impedance testing, an electrical sensor is placed in the distal esophagus to assess nonacid reflux, which is common among patients receiving gastric antisecretory drugs and among infants with reflux disease.
Chapter 10. GI Bleeding

Introduction

GI bleeding can originate anywhere from the mouth to the anus and can be overt or occult. The manifestations depend on the location and rate of bleeding.

Hematemesis is vomiting of red blood and indicates upper GI bleeding, usually from an arterial source or varix. Coffee-ground emesis is vomiting of dark brown, granular material that resembles coffee grounds. It results from upper GI bleeding that has slowed or stopped, with conversion of red Hb to brown hematin by gastric acid.

Hematochezia is the passage of gross blood from the rectum and usually indicates lower GI bleeding but may result from vigorous upper GI bleeding with rapid transit of blood through the intestines.

Melena is black, tarry stool and typically indicates upper GI bleeding, but bleeding from a source in the small bowel or right colon may also be the cause. About 100 to 200 mL of blood in the upper GI tract is required to cause melena, which may persist for several days after bleeding has ceased. Black stool that does not contain occult blood may result from ingestion of iron, bismuth, or various foods and should not be mistaken for melena.

Chronic occult bleeding can occur from anywhere in the GI tract and is detectable by chemical testing of a stool specimen. Acute, severe bleeding also can occur from anywhere in the GI tract. Patients may present with signs of shock. Those with underlying ischemic heart disease may develop angina or MI because of hypoperfusion.

GI bleeding may precipitate portal-systemic encephalopathy (see p. 220) or hepatorenal syndrome (kidney failure secondary to liver failure—see p. 223).

Etiology

There are many possible causes (see Table 10-1), which are divided into upper GI (above the ligament of Treitz), lower GI, and small bowel.

Bleeding of any cause is more likely, and potentially more severe, in patients with chronic liver disease (eg, caused by alcohol abuse or chronic hepatitis), in those with hereditary coagulation disorders, or in those taking certain drugs. Drugs associated with GI bleeding include anticoagulants (eg, heparin, warfarin), those affecting platelet function (eg, aspirin and certain other NSAIDs, clopidogrel, SSRIs), and those affecting mucosal defenses (eg, NSAIDs).

Evaluation

Stabilization with airway management, IV fluids, or transfusions is essential before and during diagnostic evaluation.

History: History of present illness should attempt to ascertain quantity and frequency of blood passage. However, quantity can be difficult to assess because even small amounts (5 to 10 mL) of blood turn water in a toilet bowl an opaque red, and modest amounts of vomited blood appear huge to an anxious patient. However, most can distinguish among blood streaks, a few teaspoons, and clots.

Patients with hematemesis should be asked whether blood was passed with initial vomiting or only after an initial (or several) nonbloody emesis.

Patients with rectal bleeding should be asked whether pure blood was passed; whether it was mixed with stool, pus, or mucus; or whether blood simply coated the stool. Those with bloody diarrhea should be asked about travel or other possible exposure to GI pathogens.

[Table 10-1. Common Causes of GI Bleeding]
Review of symptoms should include presence of abdominal discomfort, weight loss, easy bleeding or bruising, previous colonoscopy results, and symptoms of anemia (eg, weakness, easy fatigability, dizziness).

Past medical history should inquire about previous GI bleeding (diagnosed or undiagnosed); known inflammatory bowel disease, bleeding diatheses, and liver disease; and use of any drugs that increase the likelihood of bleeding or chronic liver disease (eg, alcohol).

Physical examination: General examination focuses on vital signs and other indicators of shock or hypovolemia (eg, tachycardia, tachypnea, pallor, diaphoresis, oliguria, confusion) and anemia (eg, pallor, diaphoresis). Patients with lesser degrees of bleeding may simply have mild tachycardia (heart rate > 100). Orthostatic changes in pulse (a change of > 10 beats/min) or BP (a drop of ≥ 10 mm Hg) often develop after acute loss of ≥ 2 units of blood. However, orthostatic measurements are unwise in patients with severe bleeding (possibly causing syncope) and generally lack sensitivity and specificity as a measure of intravascular volume, especially in elderly patients.

External stigmata of bleeding disorders (eg, petechiae, ecchymoses) are sought, as are signs of chronic liver disease (eg, spider angiomas, ascites, palmar erythema) and portal hypertension (eg, splenomegaly, dilated abdominal wall veins).

A digital rectal examination is necessary to search for stool color, masses, and fissures. Anoscopy is done to diagnose hemorrhoids. Chemical testing of a stool specimen for occult blood completes the examination if gross blood is not present.

Red flags: Several findings suggest hypovolemia or hemorrhagic shock:

- Syncope
- Hypotension
- Pallor
- Diaphoresis
- Tachycardia

Interpretation of findings: The history and physical examination suggest a diagnosis in about 50% of patients, but findings are rarely diagnostic and confirmatory testing is required.

Epigastric abdominal discomfort relieved by food or antacids suggests peptic ulcer disease. However, many patients with bleeding ulcers have no history of pain. Weight loss and anorexia, with or without a change in stool, suggest a GI cancer. A history of cirrhosis or chronic hepatitis suggests esophageal varices. Dysphagia suggests esophageal cancer or stricture. Vomiting and retching before the onset of bleeding suggests a Mallory-Weiss tear of the esophagus, although about 50% of patients with Mallory-Weiss tears do not have this history.

A history of bleeding (eg, purpura, ecchymosis, hematuria) may indicate a bleeding diathesis (eg, hemophilia, hepatic failure). Bloody diarrhea, fever, and abdominal pain suggest ischemic colitis, inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease), or an infectious colitis (eg, Shigella, Salmonella, Campylobacter, amebiasis). Hematochezia suggests diverticulosis or angiodysplasia. Fresh blood only on toilet paper or the surface of formed stools suggests internal hemorrhoids or fissures, whereas blood mixed with the stool indicates a more proximal source. Occult blood in the stool may be the first sign of colon cancer or a polyp, particularly in patients > 45 yr.

Blood in the nose or trickling down the pharynx suggests the nasopharynx as the source. Spider angiomas, hepatosplenomegaly, or ascites is consistent with chronic liver disease and hence possible esophageal varices. Arteriovenous malformations, especially of the mucous membranes, suggest...
hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Cutaneous nail bed and GI telangiectasia may indicate systemic sclerosis or mixed connective tissue disease.

Testing: Several tests are done to help confirm the suspected diagnosis.

• CBC and often other laboratory studies
• NGT for all but those with minimal rectal bleeding
• Upper endoscopy for suspected upper GI bleeding
• Colonoscopy for lower GI bleeding (unless clearly caused by hemorrhoids)

CBC should be obtained in patients with occult blood loss. Those with more significant bleeding also require coagulation studies (eg, platelet count, PT, PTT) and liver function tests (eg, bilirubin, alkaline phosphatase, albumin, AST, ALT). Type and crossmatch are done if bleeding is ongoing. Hb and Hct may be repeated up to every 6 h in patients with severe bleeding. Additionally, one or more diagnostic procedures are typically required.

Nasogastric aspiration and lavage should be done in all patients with suspected upper GI bleeding (eg, hematemesis, coffee-ground emesis, melena, massive rectal bleeding). Bloody nasogastric aspirate indicates active upper GI bleeding, but about 10% of patients with upper GI bleeding have no blood in the nasogastric aspirate. Coffee-ground material indicates bleeding that is slow or stopped. If there is no sign of bleeding, and bile is returned, the NGT is removed; otherwise, it is left in place to monitor continuing or recurrent bleeding. Nonbloody, nonbilious return is considered a nondiagnostic aspirate.

Upper endoscopy (examination of the esophagus, stomach, and duodenum) should be done for upper GI bleeding. Because endoscopy may be therapeutic as well as diagnostic, it should be done rapidly for significant bleeding but may be deferred for 24 h if bleeding stops or is minimal. Upper GI barium x-rays have no role in acute bleeding, and the contrast used may obscure subsequent attempts at angiography. Angiography is useful in the diagnosis of upper GI bleeding and permits certain therapeutic maneuvers (eg, embolization, vasoconstrictor infusion).

Flexible sigmoidoscopy and anoscopy may be all that is required acutely for patients with symptoms typical of hemorrhoidal bleeding. All other patients with hematochezia should have colonoscopy, which can be done electively after routine preparation unless there is significant ongoing bleeding. In such patients, a rapid prep (5 to 10 L of polyethylene glycol solution delivered via NGT or by mouth over 3 to 4 h) often allows adequate visualization. If colonoscopy cannot visualize the source and ongoing bleeding is sufficiently rapid (> 0.5 to 1 mL/min), angiography may localize the source. Some angiographers first take a radionuclide scan to focus the examination, because angiography is less sensitive than the radionuclide scan.

Diagnosis of occult bleeding can be difficult, because heme-positive stools may result from bleeding anywhere in the GI tract. Endoscopy is the preferred method, with symptoms determining whether the upper or lower GI tract is examined first. Double-contrast barium enema and sigmoidoscopy can be used for the lower tract when colonoscopy is unavailable or the patient refuses it. If the results of upper endoscopy and colonoscopy are negative and occult blood persists in the stool, an upper GI series with small-bowel follow-through, small-bowel endoscopy (enteroscopy), capsule endoscopy, technetium-labeled colloid or RBC scan, and angiography should be considered.

Treatment

• Secure airway if needed
• IV fluid resuscitation
• Blood transfusion if needed
Hematemesis, hematochezia, or melena should be considered an emergency. Admission to an ICU, with consultation by both a gastroenterologist and a surgeon, is recommended for all patients with severe GI bleeding. General treatment is directed at maintenance of the airway and restoration of circulating volume. Hemostasis and other treatment depend on the cause of the bleeding.

**Airway:** A major cause of morbidity and mortality in patients with active upper GI bleeding is aspiration of blood with subsequent respiratory compromise. To prevent these problems, endotracheal intubation should be considered in patients who have inadequate gag reflexes or are obtunded or unconscious—particularly if they will be undergoing upper endoscopy.

**Fluid resuscitation:** IV fluids are initiated as for any patient with hypovolemia or hemorrhagic shock (see p. 2297): healthy adults are given normal saline IV in 500- to 1000-mL aliquots until signs of hypovolemia remit—up to a maximum of 2 L (for children, 20 mL/kg, that may be repeated once). Patients requiring further resuscitation should receive transfusion with packed RBCs. Transfusions continue until intravascular volume is restored and then are given as needed to replace ongoing blood loss. Transfusions in older patients or those with coronary artery disease may be stopped when Hct is stable at 30 unless the patient is symptomatic. Younger patients or those with chronic bleeding are usually not transfused unless Hct is < 23 or they have symptoms such as dyspnea or coronary ischemia.

Platelet count should be monitored closely; platelet transfusion may be required with severe bleeding. Patients who are taking antiplatelet drugs (eg, clopidogrel, aspirin) have platelet dysfunction, often resulting in increased bleeding. Platelet transfusion should be considered when patients taking these drugs have severe ongoing bleeding, although a residual circulating drug (particularly clopidogrel) may inactivate transfused platelets. Fresh frozen plasma should be transfused after every 4 units of packed RBCs.

**Hemostasis:** GI bleeding stops spontaneously in about 80% of patients. The remaining patients require some type of intervention. Specific therapy depends on the bleeding site. Early intervention to control bleeding is important to minimize mortality, particularly in elderly patients.

For peptic ulcer, ongoing bleeding or rebleeding is treated with endoscopic coagulation (with bipolar electrocoagulation, injection sclerotherapy, heater probes, or laser). Non-bleeding vessels that are visible within an ulcer crater are also treated. If endoscopy does not stop the bleeding, surgery is required to oversew the bleeding site. If medical management does not control gastric acid secretion, surgeons do acid-reduction surgery (see p. 136) at the same time.

Active variceal bleeding can be treated with endoscopic banding, injection sclerotherapy, or a transjugular intrahepatic portosystemic shunting (TIPS) procedure.

Severe, ongoing lower GI bleeding caused by diverticula or angiomas can sometimes be controlled colonoscopically by electrocauterity, coagulation with a heater probe, or injection with dilute epinephrine. Polyps can be removed by snare or cautery. If these methods are ineffective or unfeasible, angiography with embolization or vasopressin infusion may be successful. However, because collateral blood flow to the bowel is limited, angiographic techniques have a significant risk of bowel ischemia or infarction unless super-selective catheterization techniques are used. In most series, the rate of ischemic complications is < 5%. Vasopressin infusion has about an 80% success rate for stopping bleeding, but bleeding recurs in about 50% of patients. Also, there is a risk of hypertension and coronary ischemia. Furthermore, angiography can be used to localize the source of bleeding more accurately. Surgery may be used in patients with continued bleeding (requiring > 4 units transfusion/24 h), but localization of the bleeding site is very important. Blind hemicolectomy (with no preoperative identification of the bleeding site) carries a much higher mortality risk than does directed segmental resection. However, assessment must be expeditious so that surgery is not unnecessarily delayed.

Acute or chronic bleeding of internal hemorrhoids stops spontaneously in most cases. Patients with refractory bleeding are treated via anoscopy with rubber band ligation, injection, coagulation, or surgery.
Geriatrics Essentials

In the elderly, hemorrhoids and colorectal cancer are the most common causes of minor bleeding. Peptic ulcer, diverticular disease, and angiodysplasia are the most common causes of major bleeding. Variceal bleeding is less common than in younger patients.

Massive GI bleeding is tolerated poorly by elderly patients. Diagnosis must be made quickly, and treatment must be started sooner than in younger patients, who can better tolerate repeated episodes of bleeding.

Key Points

• Rectal bleeding may result from upper or lower GI bleeding.

• Orthostatic changes in vital signs are unreliable markers for serious bleeding.

• About 80% of patients stop bleeding spontaneously; various endoscopic techniques are usually the first choice for the remainder.

Varices

Varices are dilated veins in the distal esophagus or proximal stomach caused by elevated pressure in the portal venous system, typically from cirrhosis. They may bleed massively but cause no other symptoms. Diagnosis is by upper endoscopy. Treatment is primarily with endoscopic banding and IV octreotide. Sometimes a transjugular intrahepatic portosystemic shunting procedure is needed.

Portal hypertension (see p. 218) results from a number of conditions, predominantly liver cirrhosis. If portal pressure remains higher than inferior vena caval pressure for a significant period, venous collaterals develop. The most dangerous collaterals occur in the distal esophagus and gastric fundus, causing engorged, serpentine submucosal vessels known as varices. These varices partially decompress portal hypertension but can rupture, causing massive GI bleeding. The trigger for variceal rupture is unknown, but bleeding almost never occurs unless the portal/systemic pressure gradient is > 12 mm Hg. Coagulopathies caused by liver disease may facilitate bleeding. NGT passage in a patient with varices has not been shown to trigger bleeding.

Symptoms and Signs

Patients typically present with sudden, painless, upper GI bleeding, often massive. Signs of shock may be present. Bleeding is usually from the distal esophagus, less often from the gastric fundus. Bleeding from gastric varices also may be acute but is more often subacute or chronic.

Bleeding into the GI tract may precipitate portal-systemic encephalopathy in patients with impaired hepatic function.

Diagnosis

• Endoscopy

• Evaluation for coagulopathy

Both esophageal and gastric varices are best diagnosed by endoscopy, which may also identify varices at high risk of bleeding (eg, those with red markings). Endoscopy is also critical to exclude other causes of acute bleeding (eg, peptic ulcer), even in patients known to have varices; perhaps as many as one third of patients with known varices who have upper GI bleeding have a nonvariceal source.

Because varices are typically associated with significant hepatic disease, evaluation for possible coagulopathy is important. Laboratory tests include CBC with platelets, PT, PTT, and liver function tests.
Bleeding patients should have type and crossmatch for 6 units of packed RBCs.

Prognosis

In about 80% of patients, variceal bleeding stops spontaneously. Nevertheless, mortality is high, often > 50%. Mortality depends primarily on severity of the associated liver disease rather than on the bleeding itself. Bleeding is often fatal in patients with severe hepatocellular impairment (eg, advanced cirrhosis), whereas patients with good hepatic reserve usually recover.

Surviving patients are at high risk of further variceal bleeding; typically, 50 to 75% have recurrence within 1 to 2 yr. Ongoing endoscopic or drug therapy significantly lowers this risk, but the overall effect on long-term mortality seems to be marginal, probably because of the underlying hepatic disease.

Treatment

• Fluid resuscitation
• Endoscopic banding (sclerotherapy second choice)
• IV octreotide
• Possibly a transjugular intrahepatic portosystemic shunting (TIPS) procedure

Management of hypovolemia and hemorrhagic shock is as described above and in Ch. 226. Patients with coagulation abnormalities (eg, elevated INR) should be given 1 to 2 units of fresh frozen plasma and 2.5 to 10 mg vitamin K IM (or IV if severe).

Because varices are invariably diagnosed during endoscopy, primary treatment is endoscopic. Endoscopic banding of varices is preferred over injection sclerotherapy. At the same time, IV octreotide (a synthetic analog of somatostatin, which may also be used) should be given. Octreotide increases splanchnic vascular resistance by inhibiting the release of splanchnic vasodilator hormones (eg, glucagon, vasoactive intestinal peptide). The usual dose is a 50 μg IV bolus, followed by infusion of 50 μg/h. Octreotide is preferred over previously used agents such as vasopressin and terlipressin, because it has fewer adverse effects.

If bleeding continues or recurs despite these measures, emergency techniques to shunt blood from the portal system to the vena cava can lower portal pressure and diminish bleeding. A TIPS procedure is the emergency intervention of choice. TIPS is an invasive radiologic procedure in which a guidewire is passed from the vena cava through the liver parenchyma into the portal circulation. The resultant passage is dilated by a balloon catheter, and a metallic stent is inserted, creating a bypass between the portal and hepatic venous circulations. Stent size is crucial. If the stent is too large, portal-systemic encephalopathy results because of diversion of too much portal blood flow from the liver. If the stent is too small, it is more likely to occlude. Surgical portacaval shunts, such as the distal spleno-renal shunt, work by a similar mechanism but are more invasive and have a higher immediate mortality.

Mechanical compression of bleeding varices with a Sengstaken-Blakemore tube or one of its variants causes considerable morbidity and should not be used as primary management. However, such a tube may provide life-saving tamponade pending decompression with a TIPS or surgical procedure. The tube is a flexible NGT with one gastric balloon and one esophageal balloon. After insertion, the gastric balloon is inflated with a fixed volume of air, and traction is applied to the tube to pull the balloon snugly against the gastroesophageal junction. This balloon is often sufficient to control bleeding, but if not, the esophageal balloon is inflated to a pressure of 25 mm Hg. The procedure is quite uncomfortable and may result in esophageal perforation and aspiration; thus, endotracheal intubation and IV sedation are often recommended.

Liver transplantation can also decompress the portal system but is a practical option only for patients already on a transplant list.
Long-term medical therapy of portal hypertension (with β-blockers and nitrates) is discussed elsewhere (see p. 219). Treatment of portal-systemic encephalopathy may be needed (see p. 220).

Vascular GI Lesions

Several distinct congenital or acquired syndromes involve abnormal mucosal or submucosal blood vessels in the GI tract. These vessels may cause recurrent bleeding, which is rarely massive. Diagnosis is by endoscopy and sometimes angiography. Treatment is endoscopic hemostasis; occasionally, angiographic embolization or surgical resection may be needed.

**Vascular ectasias** (angiodysplasias, arteriovenous malformations) are dilated, tortuous vessels that typically develop in the cecum and ascending colon. They occur mainly in people > 60 and are the most common cause of lower GI bleeding in that age group. They are thought to be degenerative and do not occur in association with other vascular abnormalities. Most patients have 2 or 3 lesions, which are typically 0.5 to 1.0 cm, bright red, flat or slightly raised, and covered by very thin epithelium. Vascular ectasias also occur in association with a number of systemic diseases (eg, renal failure, cirrhosis, CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias]—see p. 310) and after radiation to the bowel.

**Gastric antral vascular ectasia** (watermelon stomach) consists of large dilated veins running linearly along the stomach, creating a striped appearance suggestive of a watermelon. The condition occurs mainly in older women and is of unknown etiology.

**Hereditary hemorrhagic telangiectasia** (Rendu-Osler-Weber syndrome—see also p. 982) is an autosomal dominant disorder that causes multiple vascular lesions in various parts of the body, including the entire GI tract. GI bleeding rarely occurs before age 40.

**Dieulafoy's lesion** is an abnormally large artery that penetrates the gut wall, occasionally eroding through the mucosa and causing massive bleeding. It occurs mainly in the proximal stomach.

**Arteriovenous malformations** and **hemangiomas**, both congenital disorders of blood vessels, can occur in the GI tract but are rare.

Symptoms and Signs

Vascular lesions are painless. Patients often present with heme-positive stools or modest amounts of bright red blood from the rectum. Bleeding is often intermittent, sometimes with long periods between episodes. Patients with upper GI lesions may present with melena. Major bleeding is unusual.

Diagnosis

- Endoscopy

Vascular lesions are most commonly diagnosed endoscopically. If routine endoscopy is nondiagnostic, small-bowel endoscopy, capsule endoscopy, intraoperative endoscopy, or visceral angiography may be required. 99mTc-labeled RBC scans are less specific but may help localize the lesion enough to facilitate endoscopy or angiography.

Treatment

- Endoscopic coagulation

Endoscopic coagulation (with heater probe, laser, argon plasma, or bipolar electrocoagulation) is effective for many vascular lesions. Vascular ectasias often recur, although there is some evidence that oral estrogen-progesterone combinations may limit recurrence.

Mild recurrent bleeding can be treated simply with chronic iron therapy. More significant bleeding that is
unresponsive to endoscopic measures may require angiographic embolization or surgical resection. However, rebleeding occurs in about 15 to 25% of surgically treated patients.
Acute abdomen refers to abdominal symptoms and signs of such severity or concern that disorders requiring surgery should be considered. The primary symptom is acute abdominal pain. Chronic abdominal pain is discussed in Ch. 7.

**Acute Abdominal Pain**

Abdominal pain is common and often inconsequential. Acute and severe abdominal pain, however, is almost always a symptom of intra-abdominal disease. It may be the sole indicator of the need for surgery and must be attended to swiftly: Gangrene and perforation of the gut can occur < 6 h from onset of symptoms in certain conditions (eg, interruption of the intestinal blood supply caused by a strangulating obstruction or an arterial embolus). Abdominal pain is of particular concern in patients who are very young or very old and those who have HIV infection or are taking immunosuppressants.

Textbook descriptions of abdominal pain have limitations because people react to pain differently. Some, particularly elderly people, are stoic, whereas others exaggerate their symptoms. Infants, young children, and some elderly people may have difficulty localizing the pain.

**Pathophysiology**

**Visceral pain** comes from the abdominal viscera, which are innervated by autonomic nerve fibers and respond mainly to the sensations of distention and muscular contraction—not to cutting, tearing, or local irritation. Visceral pain is typically vague, dull, and nauseating. It is poorly localized and tends to be referred to areas corresponding to the embryonic origin of the affected structure. Foregut structures (stomach, duodenum, liver, and pancreas) cause upper abdominal pain. Midgut structures (small bowel, proximal colon, and appendix) cause periumbilical pain. Hindgut structures (distal colon and GU tract) cause lower abdominal pain.

**Somatic pain** comes from the parietal peritoneum, which is innervated by somatic nerves, which respond to irritation from infectious, chemical, or other inflammatory processes. Somatic pain is sharp and well localized.

**Referred pain** is pain perceived distant from its source and results from convergence of nerve fibers at the spinal cord. Common examples of referred pain are scapular pain due to biliary colic, groin pain due to renal colic, and shoulder pain due to blood or infection irritating the diaphragm.

**Peritonitis:** Peritonitis is inflammation of the peritoneal cavity. The most serious cause is perforation of the GI tract (see p. 111), which causes immediate chemical inflammation followed shortly by infection from intestinal organisms. Peritonitis can also result from any abdominal condition that causes marked inflammation (eg, appendicitis, diverticulitis, strangulating intestinal obstruction, pancreatitis, pelvic inflammatory disease, mesenteric ischemia). Intraperitoneal blood from any source (eg, ruptured aneurysm, trauma, surgery, ectopic pregnancy) is irritating and results in peritonitis. Barium causes severe peritonitis and should never be given to a patient with suspected GI tract perforation. Peritoneovenous shunts, drains, and dialysis catheters in the peritoneal cavity predispose a patient to infectious peritonitis, as does ascitic fluid. Rarely, spontaneous bacterial peritonitis occurs, in which the peritoneal cavity is infected by blood-borne bacteria.

Peritonitis causes fluid shift into the peritoneal cavity and bowel, leading to severe dehydration and electrolyte disturbances. Adult respiratory distress syndrome can develop rapidly. Kidney failure, liver failure, and disseminated intravascular coagulation follow. The patient's face becomes drawn into the masklike appearance typical of hippocratic facies. Death occurs within days.

**Etiology**

Many intra-abdominal disorders cause abdominal pain (see
Abdominal pain in neonates, infants, and young children has numerous causes not encountered in adults, including meconium peritonitis, pyloric stenosis, esophageal webs, volvulus of a gut with a common mesentery, imperforate anus, intussusception, and intestinal obstruction caused by atresia.

**Evaluation**

Evaluation of mild and severe pain follows the same process, although with severe abdominal pain, therapy sometimes proceeds simultaneously and involves early consultation with a surgeon. History and physical examination usually exclude all but a few possible causes, with final diagnosis confirmed by judicious use of laboratory and imaging tests. Life-threatening causes should always be ruled out before focusing on less serious diagnoses. In seriously ill patients with severe abdominal pain, the most important diagnostic measure may be expeditious surgical exploration. In mildly ill patients, watchful waiting may be best.

**History:** A thorough history usually suggests the diagnosis (see Table 11-2). Of particular importance are pain location (see Fig. 11-1) and characteristics, history of similar symptoms, and associated symptoms. Concomitant symptoms such as gastroesophageal reflux, nausea, vomiting, diarrhea, constipation, jaundice, melena, hematuria, hematemesis, weight loss, and mucus or blood in the stool help direct subsequent evaluation. A drug history should include details concerning prescription and illicit drug use as well as alcohol. Many drugs cause GI upset. Prednisone or immunosuppressants may inhibit the inflammatory response to perforation or peritonitis and result in less pain and leukocytosis than might otherwise be expected. Anticoagulants can increase the chances of bleeding and hematoma formation. Alcohol predisposes to pancreatitis.

Known medical conditions and previous abdominal surgeries are important to ascertain. Women should be asked whether they are pregnant.

**Physical examination:** The general appearance is important. A happy, comfortable-appearing patient rarely has a serious problem, unlike one who is anxious, pale, diaphoretic, or in obvious pain. BP, pulse, state of consciousness, and other signs of peripheral perfusion must be evaluated. However, the focus of the examination is the abdomen, beginning with inspection and auscultation, followed by palpation and percussion. Rectal examination and pelvic examination (for women) to locate tenderness, masses, and blood are essential.

Palpation begins gently, away from the area of greatest pain, detecting areas of particular tenderness, as well as the presence of guarding, rigidity, and rebound (all suggesting peritoneal irritation) and any masses. Guarding is an involuntary contraction of the abdominal muscles that is slightly slower and more sustained than the rapid, voluntary flinch exhibited by sensitive or anxious patients. Rebound is a distinct flinch upon brisk withdrawal of the examiner's hand. The inguinal area and all surgical scars should be palpated for hernias.

**Red flags:** Certain findings raise suspicion of a more serious etiology:

- Severe pain
- Signs of shock (eg, tachycardia, hypotension, diaphoresis, confusion)
• Signs of peritonitis

• Abdominal distention

**Interpretation of findings:** Distention, especially when surgical scars, tympany to percussion, and high-pitched peristalsis or borborygmi in rushes are present, strongly suggests bowel obstruction. Severe pain in a patient with a silent abdomen who is lying as still as possible suggests peritonitis; location of tenderness suggests etiology (eg, right upper quadrant suggests cholecystitis, right lower quadrant suggests appendicitis) but may not be diagnostic. Back pain with shock suggests ruptured AAA, particularly if there is a tender, pulsatile mass. Shock and vaginal bleeding in a pregnant woman suggest ruptured ectopic pregnancy. Ecchymoses of the costovertebral angles (Grey Turner’s sign) or around the umbilicus (Cullen’s sign) suggest hemorrhagic pancreatitis but are not very sensitive for this disorder.

History is often suggestive (see **Table 11-2**). Mild to moderate pain in the presence of active peristalsis of normal pitch suggests a nonsurgical disease (eg, gastroenteritis) but may also be the early manifestations of a more serious disorder. A patient who is writhing around trying to get comfortable is more likely to have an obstructive mechanism (eg, renal or biliary colic).

Previous abdominal surgery makes obstruction from adhesions more likely. Generalized atherosclerosis increases the possibility of MI, AAA, and mesenteric ischemia. HIV infection makes infectious causes and drug adverse effects likely.

**Testing:** Tests are selected based on clinical suspicion.

• Urine pregnancy test for all women of childbearing age

• Selected imaging tests based on suspected diagnosis

Standard tests (eg, CBC, chemistries, urinalysis) are often done but are of little value due to poor specificity; patients with significant disease may have normal results. Abnormal results do not provide a specific diagnosis (the urinalysis in particular may show pyuria or hematuria in a wide variety of conditions), and they can also occur in the absence of significant disease. An exception is serum lipase, which strongly suggests a diagnosis of acute pancreatitis. A bedside urine pregnancy test should be done for all women of childbearing age because a negative result effectively excludes ruptured ectopic pregnancy.

An abdominal series, consisting of flat and upright abdominal x-rays and upright chest x-rays (left lateral recumbent abdomen and anteroposterior chest x-ray for patients unable to stand), should be done when perforation or obstruction is suspected. However, these plain x-rays are seldom diagnostic for other conditions and need not be automatically done. Ultrasound should be done for suspected biliary tract disease or ectopic pregnancy (transvaginal probe). Ultrasound can also detect AAA but cannot reliably identify rupture. Noncontrast helical CT is the modality of choice for suspected renal stones. CT with oral contrast is diagnostic in about 95% of patients with significant abdominal pain and has markedly lowered the negative laparotomy rate. However, advanced imaging must not be allowed to delay surgery in patients with definitive symptoms and signs.

**Treatment**

Some clinicians feel that providing pain relief before a diagnosis is made interferes with their ability to evaluate. However, moderate doses of IV analgesics (eg, fentanyl 50 to 100 μg, morphine 4 to 6 mg) do not mask peritoneal signs and, by diminishing anxiety and discomfort, often make examination easier.

**Key Points**
• Life-threatening causes should be looked for first.

• Pregnancy should be ruled out in women of childbearing age.

• Signs of peritonitis, shock, and obstruction should be sought.

• Blood tests are of minimal value.

**Acute Mesenteric Ischemia**

Acute mesenteric ischemia is interruption of intestinal blood flow by embolism, thrombosis, or a low-flow state. It leads to mediator release, inflammation, and ultimately infarction. Abdominal pain is out of proportion to physical findings. Early diagnosis is difficult, but angiography and exploratory laparotomy have the most sensitivity; other imaging modalities often become positive only late in the disease. Treatment is by embolectomy, revascularization of viable segments, or resection; sometimes vasodilator therapy is successful. Mortality is high.

**Pathophysiology**

The intestinal mucosa has a high metabolic rate and, accordingly, a high blood flow requirement (normally receiving 20 to 25% of cardiac output), making it very sensitive to the effects of decreased perfusion. Ischemia disrupts the mucosal barrier, allowing release of bacteria, toxins, and vasoactive mediators, which in turn leads to myocardial depression, systemic inflammatory response syndrome (see p. 2299), multisystem organ failure, and death. Mediator release may occur even before complete infarction. Necrosis can occur as soon as 10 to 12 h after the onset of symptoms.

Three major vessels serve the abdominal contents: the celiac trunk, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA). The celiac trunk supplies the esophagus, stomach, proximal duodenum, liver, gallbladder, pancreas, and spleen. The SMA supplies the distal duodenum, jejunum, ileum, and colon to the splenic flexure. The IMA supplies the descending colon and sigmoid colon and the rectum. Collateral vessels are abundant in the stomach, duodenum, and rectum; these areas rarely develop ischemia. The splenic flexure is a watershed between the SMA and IMA and is at particular risk of ischemia.

**Etiology**

Mesenteric blood flow may be disrupted on either the venous or arterial sides. In general, patients > 50 are at greatest risk and have the types of occlusions and risk factors shown in Table 11-3. However, many patients have no identifiable risk factors.

**Symptoms and Signs**

The early hallmark of mesenteric ischemia is severe pain but minimal physical findings. The abdomen remains soft, with little or no tenderness. Mild tachycardia may be present. Later, as necrosis develops, signs of peritonitis appear, with marked abdominal tenderness, guarding, rigidity, and no bowel sounds. The stool may be heme-positive (increasingly likely as ischemia progresses). The usual signs of shock develop and are frequently followed by death.

Sudden onset of pain suggests but is not diagnostic of an arterial embolism, whereas a more gradual onset is typical of venous thrombosis. Patients with a history of postprandial abdominal discomfort (which suggests intestinal angina) may have arterial thrombosis.

[Table 11-3. Causes of Acute Mesenteric Ischemia]

**Diagnosis**

• Clinical diagnosis more important than diagnostic tests
Mesenteric angiography if diagnosis unclear

Early diagnosis is particularly important because mortality increases significantly once intestinal infarction has occurred. Mesenteric ischemia must be considered in any patient > 50 with known risk factors or predisposing conditions who develops sudden, severe abdominal pain.

Patients with clear peritoneal signs should proceed directly to the operating room for both diagnosis and treatment. For others, selective mesenteric angiography is the diagnostic procedure of choice. Other imaging studies and serum markers can show abnormalities but lack sensitivity and specificity early in the course of the disease when diagnosis is most critical. Plain abdominal x-rays are useful mainly in ruling out other causes of pain (eg, perforated viscus), although portal venous gas or pneumatosis intestinalis may be seen late in the disease. These findings also appear on CT, which may also directly visualize vascular occlusion—more accurately on the venous side. Doppler ultrasonography can sometimes identify arterial occlusion, but sensitivity is low. MRI is very accurate in proximal vascular occlusion, less so in distal vascular occlusion. Serum markers (eg, creatine kinase, lactate) rise with necrosis but are nonspecific findings that are seen later. Intestinal fatty acid binding protein in the urine may prove valuable in the future as an early marker.

Prognosis

If diagnosis and treatment take place before infarction occurs, mortality is low; after intestinal infarction, mortality approaches 70 to 90%. For this reason, clinical diagnosis of mesenteric ischemia should supersede diagnostic tests, which may delay treatment.

Treatment

- Surgical: Embolectomy, revascularization, or resection
- Angiographic: Vasodilators or thrombolysis
- Long-term anticoagulation or antiplatelet therapy

If diagnosis is made during exploratory laparotomy, options are surgical embolectomy, revascularization, and resection. A "second look" laparotomy may be needed to reassess the viability of questionable areas of bowel. If diagnosis is made by angiography, infusion of the vasodilator papaverine through the angiography catheter may improve survival in both occlusive and nonocclusive ischemia. A 60-mg bolus is given over 2 min, followed by an infusion of 30 to 60 mg/h. Papaverine is useful even when surgical intervention is planned and is sometimes given during and after surgical intervention as well. In addition, for arterial occlusion, thrombolysis or surgical embolectomy may be done. The development of peritoneal signs at any time during the evaluation suggests the need for immediate surgery. Mesenteric venous thrombosis without signs of peritonitis can be treated with papaverine followed by anticoagulation with heparin and then warfarin.

Patients with arterial embolism or venous thrombosis require long-term anticoagulation with warfarin. Patients with nonocclusive ischemia may be treated with antiplatelet therapy.

Acute Perforation

Any part of the GI tract may become perforated, releasing gastric or intestinal contents into the peritoneal space. Causes vary. Symptoms develop suddenly, with severe pain followed shortly by signs of shock. Diagnosis is usually made by the presence of free air in the abdomen on imaging studies. Treatment is with fluid resuscitation, antibiotics, and surgery. Mortality is high, varying with the underlying disorder and the patient's general health.

Etiology

Both blunt and penetrating trauma can result in perforation of any part of the GI tract (see Table 11-4). Swallowed foreign bodies, even sharp ones, rarely cause perforation unless they become
impacted, causing ischemia and necrosis from local pressure. Foreign bodies inserted via the anus may perforate the rectum.

**Symptoms and Signs**

Esophageal, gastric, and duodenal perforation tends to manifest suddenly and catastrophically, with abrupt onset of acute abdomen with severe generalized abdominal pain, tenderness, and peritoneal signs. Pain may radiate to the shoulder.

Perforation at other GI sites often occurs in the setting of other painful, inflammatory conditions. Because such perforations are often small initially and frequently walled off by the omentum, pain often develops gradually and may be localized. Tenderness also is more focal. Such findings can make it difficult to distinguish perforation from worsening of the underlying disorder or lack of response to treatment.

In all types of perforation, nausea, vomiting, and anorexia are common. Bowel sounds are quiet to absent.

**Diagnosis**

- Abdominal series

- If nondiagnostic, abdominal CT

An abdominal series (supine and upright abdominal x-rays and chest x-rays) may be diagnostic, showing free air under the diaphragm in 50 to 75% of cases. As time passes, this sign becomes more common. A lateral chest x-ray is more sensitive for free air than a posteroanterior x-ray. If the abdominal series is nondiagnostic, abdominal CT usually with oral and IV and/or rectal contrast may be helpful. Barium should not be used if perforation is suspected.

**Treatment**

- Surgery

- IV fluids and antibiotics

[Table 11-4. Some Causes of GI Tract Perforation]

If a perforation is noted, immediate surgery is necessary because mortality caused by peritonitis increases rapidly the longer treatment is delayed. If an abscess or an inflammatory mass has formed, the procedure may be limited to drainage of the abscess.

An NGT is inserted before operation. Patients with signs of volume depletion should have urine output monitored with a catheter. Fluid status is maintained by adequate IV fluid and electrolyte replacement. IV antibiotics effective against intestinal flora should be given (eg, cefotetan 1 to 2 g bid, or amikacin 5 mg/kg tid plus clindamycin 600 to 900 mg qid).

**Appendicitis**

Appendicitis is acute inflammation of the vermiform appendix, typically resulting in abdominal pain, anorexia, and abdominal tenderness. Diagnosis is clinical, often supplemented by CT or ultrasound. Treatment is surgical removal.

In the US, acute appendicitis is the most common cause of acute abdominal pain requiring surgery. Over 5% of the population develops appendicitis at some point. It most commonly occurs in the teens and 20s but may occur at any age.

Other conditions affecting the appendix include carcinoids, cancer, villous adenomas, and diverticula. The appendix may also be affected by Crohn's disease or ulcerative colitis with pancolitis.
Etiology

Appendicitis is thought to result from obstruction of the appendiceal lumen, typically by lymphoid hyperplasia, but occasionally by a fecalith, foreign body, or even worms. The obstruction leads to distention, bacterial overgrowth, ischemia, and inflammation. If untreated, necrosis, gangrene, and perforation occur. If the perforation is contained by the omentum, an appendiceal abscess results.

Symptoms and Signs

The classic symptoms of acute appendicitis are epigastric or periumbilical pain followed by brief nausea, vomiting, and anorexia; after a few hours, the pain shifts to the right lower quadrant. Pain increases with cough and motion. Classic signs are right lower quadrant direct and rebound tenderness located at McBurney’s point (junction of the middle and outer thirds of the line joining the umbilicus to the anterior superior spine). Additional signs are pain felt in the right lower quadrant with palpation of the left lower quadrant (Rovsing sign), an increase in pain from passive extension of the right hip joint that stretches the iliopsoas muscle (psoas sign), or pain caused by passive internal rotation of the flexed thigh (obturator sign). Low-grade fever (rectal temperature 37.7 to 38.3°C [100 to 101°F]) is common.

Unfortunately, these classic findings appear in < 50% of patients. Many variations of symptoms and signs occur. Pain may not be localized, particularly in infants and children. Tenderness may be diffuse or, in rare instances, absent. Bowel movements are usually less frequent or absent; if diarrhea is a sign, a retrocecal appendix should be suspected. RBCs or WBCs may be present in the urine. Atypical symptoms are common among elderly patients and pregnant women; in particular, pain is less severe and local tenderness is less marked.

Diagnosis

- Clinical evaluation
- Abdominal CT if necessary
- Ultrasound an option to CT

When classic symptoms and signs are present, the diagnosis is clinical. In such patients, delaying laparotomy to do imaging tests only increases the likelihood of perforation and subsequent complications. In patients with atypical or equivocal findings, imaging studies should be done without delay. Contrast-enhanced CT has reasonable accuracy in diagnosing appendicitis and can also reveal other causes of an acute abdomen. Graded compression ultrasound can usually be done quickly and uses no radiation (of particular concern in children); however, it is occasionally limited by the presence of bowel gas and is less useful for recognizing nonappendiceal causes of pain. Appendicitis remains primarily a clinical diagnosis. Selective and judicious use of radiographic studies may reduce the rate of negative laparotomy.

Laparoscopy can be used for diagnosis as well as definitive treatment; it may be especially helpful in women with lower abdominal pain of unclear etiology. Laboratory studies typically show leukocytosis (12,000 to 15,000/μL), but this finding is highly variable; a normal WBC count should not be used to exclude appendicitis.

Prognosis

Without surgery or antibiotics, mortality is > 50%.

With early surgery, the mortality rate is < 1%, and convalescence is normally rapid and complete. With complications (rupture and development of an abscess or peritonitis), the prognosis is worse: Repeat operations and a long convalescence may follow.

Treatment
• Surgical removal

• IV fluids and antibiotics

Treatment of acute appendicitis is open or laparoscopic appendectomy; because treatment delay increases mortality, a negative appendectomy rate of 15% is considered acceptable. The surgeon can usually remove the appendix even if perforated. Occasionally, the appendix is difficult to locate: In these cases, it usually lies behind the cecum or the ileum and mesentery of the right colon. A contraindication to appendectomy is inflammatory bowel disease involving the cecum. However, in cases of terminal ileitis and a normal cecum, the appendix should be removed.

Appendectomy should be preceded by IV antibiotics. Third-generation cephalosporins are preferred. For nonperforated appendicitis, no further antibiotics are required. If the appendix is perforated, antibiotics should be continued until the patient's temperature and WBC count have normalized or continued for a fixed course, according to the surgeon's preference. If surgery is impossible, antibiotics—although not curative—markedly improve the survival rate. When a large inflammatory mass is found involving the appendix, terminal ileum, and cecum, resection of the entire mass and ileocolostomy are preferable. In late cases in which a pericolic abscess has already formed, the abscess is drained either by an ultrasound-guided percutaneous catheter or by open operation (with appendectomy to follow at a later date). A Meckel's diverticulum in a patient under the age of 40 should be removed concomitantly with the appendectomy unless extensive inflammation around the appendix prevents the procedure.

Hernias of the Abdominal Wall

A hernia of the abdominal wall is a protrusion of the abdominal contents through an acquired or congenital area of weakness or defect in the wall. Many hernias are asymptomatic, but some become incarcerated or strangulated, causing pain and requiring immediate surgery. Diagnosis is clinical. Treatment is elective surgical repair.

Abdominal hernias are extremely common, particularly among males, necessitating about 700,000 operations each year in the US.

Classification

Abdominal hernias are classified as either abdominal wall or groin hernias. Strangulated hernias are ischemic from physical constriction of their blood supply. Gangrene, perforation, and peritonitis may develop. Incarcerated and strangulated hernias cannot be reduced manually.

Abdominal wall hernias include umbilical hernias, epigastric hernias, Spigelian hernias, and incisional (ventral) hernias. Umbilical hernias (protrusions through the umbilical ring) are mostly congenital, but some are acquired in adulthood secondary to obesity, ascites, pregnancy, or chronic peritoneal dialysis. Epigastric hernias occur through the linea alba. Spigelian hernias occur through defects in the transversus abdominis muscle lateral to the rectus sheath, usually below the level of the umbilicus. Incisional hernias occur through an incision from previous abdominal surgery.

Groin hernias include inguinal hernias and femoral hernias. Inguinal hernias occur above the inguinal ligament. Indirect inguinal hernias traverse the internal inguinal ring into the inguinal canal, and direct inguinal hernias extend directly forward and do not pass through the inguinal canal. Femoral hernias occur below the inguinal ligament and go into the femoral canal.

About 75% of all abdominal hernias are inguinal. Incisional hernias comprise another 10 to 15%. Femoral and unusual hernias account for the remaining 10 to 15%.

Symptoms and Signs

Most patients complain only of a visible bulge, which may cause vague discomfort or be asymptomatic. Most hernias, even large ones, can be manually reduced with persistent gentle pressure; placing the patient in the Trendelenburg position may help. An incarcerated hernia cannot be reduced but has no
additional symptoms. A strangulated hernia causes steady, gradually increasing pain, typically with nausea and vomiting. The hernia itself is tender, and the overlying skin may be erythematous; peritonitis may develop depending on location, with diffuse tenderness, guarding, and rebound.

**Diagnosis**

- **Clinical evaluation**

The diagnosis is clinical. Because the hernia may be apparent only when abdominal pressure is increased, the patient should be examined in a standing position. If no hernia is palpable, the patient should cough or perform a Valsalva maneuver as the examiner palpates the abdominal wall. Examination focuses on the umbilicus, the inguinal area (with a finger in the inguinal canal in males), the femoral triangle, and any incisions that are present.

Inguinal masses that resemble hernias may be the result of adenopathy (infectious or malignant), an ectopic testis, or lipoma. These masses are solid and are not reducible. A scrotal mass may be a varicocele, hydrocele, or testicular tumor. Ultrasound may be done if physical examination is equivocal.

**Prognosis**

Congenital umbilical hernias rarely strangulate and are not treated; most resolve spontaneously within several years. Very large defects may be repaired electively after age 2 yr. Umbilical hernias in adults cause cosmetic concerns and can be electively repaired; strangulation and incarceration are unusual but, if happen, usually contain omentum rather than intestine.

**Treatment**

- **Surgical repair**

Groin hernias should be repaired electively because of the risk of strangulation, which results in higher morbidity (and possible mortality in elderly patients). Repair may be through a standard incision or laparoscopy.

An incarcerated or strangulated hernia of any kind requires urgent surgical repair.

**Ileus**

(Paralytic Ileus; Adynamic Ileus; Paresis)

Ileus is a temporary arrest of intestinal peristalsis. It occurs most commonly after abdominal surgery, particularly when the intestines have been manipulated. Symptoms are nausea, vomiting, and vague abdominal discomfort. Diagnosis is based on x-ray findings and clinical impression. Treatment is supportive, with nasogastric suction and IV fluids.

**Etiology**

In addition to postoperative causes, ileus also results from intraperitoneal or retroperitoneal inflammation (eg, appendicitis, diverticulitis, perforated duodenal ulcer), retroperitoneal or intra-abdominal hematomas (eg, ruptured abdominal aortic aneurysm, lumbar compression fracture), metabolic disturbances (eg, hypokalemia), or drugs (eg, opioids, anticholinergics, sometimes Ca channel blockers). Ileus sometimes occurs in association with renal or thoracic disease (eg, lower rib fractures, lower lobe pneumonias, MI).

Gastric and colonic motility disturbances after abdominal surgery are common. The small bowel is typically least affected, with motility and absorption returning to normal within hours after surgery. Stomach emptying is usually impaired for about 24 h or more. The colon is often most affected and may remain inactive for 48 to 72 h or more.

**Symptoms and Signs**
Symptoms and signs include abdominal distention, vomiting, and vague discomfort. Pain rarely has the classic colicky pattern present in mechanical obstruction. There may be obstipation or passage of slight amounts of watery stool. Auscultation reveals a silent abdomen or minimal peristalsis. The abdomen is not tender unless the underlying cause is inflammatory.

**Diagnosis**

- Clinical evaluation
- Sometimes x-rays

The most essential task is to distinguish ileus from intestinal obstruction. In both conditions, x-rays show gaseous distention of isolated segments of intestine. In postoperative ileus, however, gas may accumulate more in the colon than in the small bowel. Postoperative accumulation of gas in the small bowel often implies development of a complication (eg, obstruction, peritonitis). In other types of ileus, x-ray findings are similar to obstruction; differentiation can be difficult unless clinical features clearly favor one or the other. Water-soluble contrast studies may help differentiate.

**Treatment**

- NGT
- IV fluids

Treatment involves continuous nasogastric suction, npo status, IV fluids and electrolytes, a minimal amount of sedatives, and avoidance of opioids and anticholinergic drugs. Maintaining an adequate serum K level (> 4 mEq/L [> 4 mmol/L]) is especially important. Ileus persisting > 1 wk probably has a mechanical obstructive cause, and laparotomy should be considered. Sometimes colonic ileus can be relieved by colonoscopic decompression; rarely, cecostomy is required. Colonoscopic decompression is helpful in treating pseudo-obstruction (Ogilvie's syndrome), which consists of apparent obstruction at the splenic flexure, although no cause can be found by contrast enema or colonoscopy for the failure of gas and feces to pass this point. Some clinicians use IV neostigmine (requires cardiac monitoring) to treat Ogilvie's syndrome.

**Intestinal Obstruction**

Intestinal obstruction is significant mechanical impairment or complete arrest of the passage of contents through the intestine. Symptoms include cramping pain, vomiting, obstipation, and lack of flatus. Diagnosis is clinical, confirmed by abdominal x-rays. Treatment is fluid resuscitation, nasogastric suction, and, in most cases of complete obstruction, surgery.

Mechanical obstruction is divided into obstruction of the small bowel (including the duodenum) and obstruction of the large bowel. Obstruction may be partial or complete. About 85% of partial small-bowel obstructions resolve with nonoperative treatment, whereas about 85% of complete small-bowel obstructions require operation.

**Etiology**

Overall, the most common causes of mechanical obstruction are adhesions, hernias, and tumors. Other general causes are diverticulitis, foreign bodies (including gallstones), volvulus (twisting of bowel on its mesentery), intussusception (telescoping of one segment of bowel into another—see p. 2801), and fecal impaction. Specific segments of the intestine are affected differently (see Table 11-5).

**Pathophysiology**

In simple mechanical obstruction, blockage occurs without vascular compromise. Ingested fluid and food,
digestive secretions, and gas accumulate above the obstruction. The proximal bowel distends, and the distal segment collapses. The normal secretory and absorptive functions of the mucosa are depressed, and the bowel wall becomes edematous and congested. Severe intestinal distention is self-perpetuating and progressive, intensifying

[Table 11-5, Causes of Intestinal Obstruction]

the peristaltic and secretory derangements and increasing the risks of dehydration and progression to strangulating obstruction.

Strangulating obstruction is obstruction with compromised blood flow; it occurs in nearly 25% of patients with small-bowel obstruction. It is usually associated with hernia, volvulus, and intussusception. Strangulating obstruction can progress to infarction and gangrene in as little as 6 h. Venous obstruction occurs first, followed by arterial occlusion, resulting in rapid ischemia of the bowel wall. The ischemic bowel becomes edematous and infarcts, leading to gangrene and perforation. In large-bowel obstruction, strangulation is rare (except with volvulus).

Perforation may occur in an ischemic segment (typically small bowel) or when marked dilation occurs. The risk is high if the cecum is dilated to a diameter ≥ 13 cm. Perforation of a tumor or a diverticulum may also occur at the obstruction site.

Symptoms and Signs

**Obstruction of the small bowel** causes symptoms shortly after onset: abdominal cramps centered around the umbilicus or in the epigastrium, vomiting, and—in patients with complete obstruction—obstipation. Patients with partial obstruction may develop diarrhea. Severe, steady pain suggests that strangulation has occurred. In the absence of strangulation, the abdomen is not tender. Hyperactive, high-pitched peristalsis with rushes coinciding with cramps is typical. Sometimes, dilated loops of bowel are palpable. With infarction, the abdomen becomes tender and auscultation reveals a silent abdomen or minimal peristalsis. Shock and oliguria are serious signs that indicate either late simple obstruction or strangulation.

**Obstruction of the large bowel** usually causes milder symptoms that develop more gradually than those caused by small-bowel obstruction. Increasing constipation leads to obstipation and abdominal distention. Vomiting may occur (usually several hours after onset of other symptoms) but is not common. Lower abdominal cramps unproductive of feces occur. Physical examination typically shows a distended abdomen with loud borborygmi. There is no tenderness, and the rectum is usually empty. A mass corresponding to the site of an obstructing tumor may be palpable. Systemic symptoms are relatively mild, and fluid and electrolyte deficits are uncommon.

**Volvulus** often has an abrupt onset. Pain is continuous, sometimes with superimposed waves of colicky pain.

Diagnosis

• Abdominal series

Supine and upright abdominal x-rays should be taken and are usually adequate to diagnose obstruction. Although only laparotomy can definitively diagnose strangulation, careful serial clinical examination may provide early warning. Elevated WBCs and acidosis may indicate that strangulation has already occurred.

On plain x-rays, a ladderlike series of distended small-bowel loops is typical of small-bowel obstruction but may also occur with obstruction of the right colon. Fluid levels in the bowel can be seen in upright views. Similar, although perhaps less dramatic, x-ray findings and symptoms occur in ileus (paralysis of the intestine without obstruction)—see p. 114; differentiation can be difficult. Distended loops and fluid levels may be absent with an obstruction of the upper jejunum or with closed-loop strangulating obstructions (as may occur with volvulus). Infarcted bowel may produce a mass effect on x-ray. Gas in the bowel wall (pneumatosis intestinalis) indicates gangrene.
In large-bowel obstruction, abdominal x-ray shows distention of the colon proximal to the obstruction. In cecal volvulus, there may be a large gas bubble in the mid-abdomen or left upper quadrant. With both cecal and sigmoidal volvulus, a contrast enema shows the site of obstruction by a typical “bird-beak” deformity at the site of the twist; the procedure may actually reduce a sigmoid volvulus. If contrast enema is not done, colonoscopy can be used to decompress a sigmoid volvulus but rarely works with a cecal volvulus.

**Treatment**

- Nasogastric suction
- IV fluids
- IV antibiotics if bowel ischemia suspected

Patients with possible intestinal obstruction should be hospitalized. Treatment of acute intestinal obstruction must proceed simultaneously with diagnosis. A surgeon should always be involved.

Supportive care is similar for small- and large-bowel obstruction: nasogastric suction, IV fluids (0.9% saline or lactated Ringer's solution for intravascular volume repletion), and a urinary catheter to monitor fluid output. Electrolyte replacement should be guided by test results, although in cases of repeated vomiting serum Na and K are likely to be depleted. If bowel ischemia or infarction is suspected, antibiotics should be given (eg, a 3rd-generation cephalosporin, such as cefotetan 2 g IV) before laparotomy.

**Specific measures:** Obstruction of the duodenum in adults is treated by resection or, if the lesion cannot be removed, palliative gastrojejunostomy (for treatment in children, see p. 2978).

Complete obstruction of the small bowel is preferentially treated with early laparotomy, although surgery can be delayed 2 or 3 h to improve fluid status and urine output in a very ill, dehydrated patient. The offending lesion is removed whenever possible. If a gallstone is the cause of obstruction, it is removed through an enterotomy, and cholecystectomy need not be done. Procedures to prevent recurrence should be done, including repair of hernias, removal of foreign bodies, and lysis of the offending adhesions. In some patients with early postoperative obstruction or repeated obstruction caused by adhesions, simple intubation with a long intestinal tube (many consider a standard NGT to be equally effective), rather than surgery, may be attempted in the absence of peritoneal signs.

Disseminated intraperitoneal cancer obstructing the small bowel is a major cause of death in adult patients with GI tract cancer. Bypassing the obstruction, either surgically or with endoscopically placed stents, may palliate symptoms briefly.

Obstructing colon cancers can often be treated by a single-stage resection and anastomosis. Other options include a diverting ileostomy and distal anastomosis. Occasionally, a diverting colostomy with delayed resection is required.

When diverticulitis causes obstruction, perforation is often present. Removal of the involved area may be very difficult but is indicated if perforation and general peritonitis are present. Resection and colostomy are done, and anastomosis is postponed.

Fecal impaction usually occurs in the rectum and can be removed digitally and with enemas. However, a fecal concretion alone or in a mixture (ie, with barium or antacids) that causes complete obstruction (usually in the sigmoid) requires laparotomy.

Treatment of cecal volvulus consists of resection and anastomosis of the involved segment or fixation of the cecum in its normal position by cecostomy in the frail patient. In sigmoidal volvulus, an endoscope or a long rectal tube can often decompress the loop, and resection and anastomosis may be deferred for a few days. Without a resection, recurrence is almost inevitable.
Abscesses can occur anywhere in the abdomen and retroperitoneum. They mainly occur after surgery, trauma, or conditions involving abdominal infection and inflammation, particularly when peritonitis or perforation occurs. Symptoms are malaise, fever, and abdominal pain. Diagnosis is by CT. Treatment is with drainage, either surgical or percutaneous. Antibiotics are ancillary.

**Etiology**

Intra-abdominal abscesses are classified as intraperitoneal, retroperitoneal, or visceral (see Table 11-6). Many intra-abdominal abscesses develop after perforation of a hollow viscus or colonic cancer. Others develop by extension of infection or inflammation resulting from conditions such as appendicitis, diverticulitis, Crohn's disease, pancreatitis, pelvic inflammatory disease, or indeed any condition causing generalized peritonitis. Abdominal surgery, particularly that involving the digestive or biliary tract, is another significant risk factor: The peritoneum may be contaminated during or after surgery from such events as anastomotic leaks. Traumatic abdominal injuries—particularly lacerations and hematomas of the liver, pancreas, spleen, and intestines—may develop abscesses, whether treated operatively or not.

The infecting organisms typically reflect normal bowel flora and are a complex mixture of anaerobic and aerobic bacteria. Most frequent isolates are aerobic gram-negative bacilli (eg, *Escherichia coli* and *Klebsiella*) and anaerobes (especially *Bacteroides fragilis*).

Undrained abscesses may extend to contiguous structures, erode into adjacent vessels (causing hemorrhage or thrombosis), rupture into the peritoneum or bowel, or form a cutaneous fistula. Subdiaphragmatic abscesses may extend into the thoracic cavity, causing an empyema, lung abscess, or pneumonia. An abscess in the lower abdomen may track down into the thigh or perirectal fossa. Splenic abscess is a rare cause of sustained bacteremia in endocarditis that persists despite appropriate antimicrobial therapy.

**Symptoms and Signs**

Abscesses may form within 1 wk of perforation or significant peritonitis, whereas postoperative abscesses may not occur until 2 to 3 wk after operation and, rarely, not for several months. Although manifestations vary, most abscesses cause fever and abdominal discomfort ranging from minimal to severe (usually near the abscess). Paralytic ileus, either generalized or localized, may develop. Nausea, anorexia, and weight loss are common.

Abscesses in Douglas' cul-de-sac, adjacent to the colon, may cause diarrhea. Contiguity to the bladder may result in urinary urgency and frequency and, if caused by diverticulitis, may create a colovesical fistula.

Subphrenic abscesses may cause chest symptoms such as nonproductive cough, chest pain, dyspnea, and shoulder pain. Rales, rhonchi, or a friction rub may be audible. Dullness to percussion and decreased breath sounds are typical when basilar atelectasis, pneumonia, or pleural effusion occurs.

Generally, there is tenderness over the location of the abscess. Large abscesses may be palpable as a mass.

**Diagnosis**

- Abdominal CT
- Rarely, radionuclide scanning
CT of the abdomen and pelvis with oral contrast is the preferred diagnostic modality for suspected abscess. Other imaging studies, if done, may show abnormalities; plain abdominal x-rays may reveal extraintestinal gas in the abscess, displacement of adjacent organs, a soft-tissue density representing the abscess, or loss of the psoas muscle shadow. Abscesses near the diaphragm may result in chest x-ray abnormalities such as ipsilateral pleural effusion, elevated or immobile hemidiaphragm, lower lobe infiltrates, and atelectasis.

CBC and blood cultures should be done. Leukocytosis occurs in most patients, and anemia is common.

Occasionally, radionuclide scanning with indium$^{111}$-labeled leukocytes may be helpful in identifying intra-abdominal abscesses.

**Prognosis**

Intra-abdominal abscesses have a mortality rate of 10 to 40%. Outcome depends mainly on the patient's primary illness or injury and general medical condition rather than on the specific nature and location of the abscess.

**Treatment**

- IV antibiotics
- Drainage: Percutaneous or surgical

All intra-abdominal abscesses require drainage, either by percutaneous catheters or surgery. Drainage through catheters (placed with CT or ultrasound guidance) may be appropriate given the following conditions: Few abscess cavities are present; the drainage route does not traverse bowel or uncontaminated organs, pleura, or peritoneum; the source of contamination is controlled; and the pus is thin enough to pass through the catheter.

Antibiotics are not curative but may limit hematogenous spread and should be given before and after intervention. Therapy requires drugs active against bowel flora, such as a combination of an aminoglycoside (eg, gentamicin 1.5 mg/kg q 8 h) and metronidazole 500 mg q 8 h. Single-agent therapy with cefotetan 2 g q 12 h is also reasonable. Patients previously given antibiotics or those who have hospital-acquired infections should receive drugs active against resistant aerobic gram-negative bacilli (eg, *Pseudomonas*) and anaerobes.

Nutritional support is important, with the enteral route preferred. Parenteral nutrition should begin early if the enteral route is not feasible.

**Ischemic Colitis**

*Ischemic colitis is a transient reduction in blood flow to the colon.*

Necrosis may occur but is usually limited to the mucosa and submucosa, only occasionally causing full-thickness necrosis necessitating surgery. It occurs mainly in older people (> 60) and is thought to be caused by small-vessel atherosclerosis.

Symptoms are milder and of slower onset than those of acute mesenteric ischemia and consist of left lower quadrant pain followed by rectal bleeding. Diagnosis is made by colonoscopy; angiography or magnetic resonance angiography is not indicated. Treatment is supportive with IV fluids, bowel rest, and antibiotics. Surgery is rarely required. About 5% of patients have a recurrence. Occasionally, strictures develop at the site of the ischemia several weeks later, necessitating surgical resection.
Chapter 12. Esophageal and Swallowing Disorders

Introduction

(See also Esophageal Cancer on p. 186 and Esophageal Atresia on p. 2975.)

The swallowing apparatus consists of the pharynx, upper esophageal (cricopharyngeal) sphincter, the body of the esophagus, and the lower esophageal sphincter (LES). The upper third of the esophagus and the structures proximal to it are composed of skeletal muscle; the distal esophagus and LES are composed of smooth muscle. These components work as an integrated system that transports material from the mouth to the stomach and prevents its reflux into the esophagus. Physical obstruction or disorders that interfere with motor function (motility disorders) can affect the system.

The patient's history suggests the diagnosis almost 80% of the time. The only physical findings in esophageal disorders are cervical and supraclavicular lymphadenopathy caused by metastasis, swellings in the neck caused by large pharyngeal diverticula or thyromegaly, and prolonged swallowing time (the time from the act of swallowing to the sound of the bolus of fluid and air entering the stomach—normally ≤ 12 sec—heard by auscultation with the stethoscope over the epigastrium). Watching the patient swallow may help diagnose aspiration or nasal regurgitation. Most esophageal disorders require specific tests for diagnosis.

Dysphagia

Dysphagia is difficulty swallowing. The condition results from impeded transport of liquids, solids, or both from the pharynx to the stomach. Dysphagia should not be confused with globus sensation (see p. 78), a feeling of having a lump in the throat, which is unrelated to swallowing and occurs without impaired transport.

Complications: Dysphagia can lead to tracheal aspiration of ingested material, oral secretions, or both. Aspiration can cause acute pneumonia; recurrent aspiration may eventually lead to chronic lung disease. Prolonged dysphagia often leads to inadequate nutrition and weight loss.

Etiology

Dysphagia is classified as oropharyngeal or esophageal, depending on where it occurs.

Oropharyngeal dysphagia: Oropharyngeal dysphagia is difficulty emptying material from the oropharynx into the esophagus; it results from abnormal function proximal to the esophagus. Patients complain of difficulty initiating swallowing, nasal regurgitation, and tracheal aspiration followed by coughing.

Most often, oropharyngeal dysphagia occurs in patients with neurologic conditions or muscular disorders that affect skeletal muscles (see Table 12-1).

Esophageal dysphagia: Esophageal dysphagia is difficulty passing food down the esophagus. It results from either a motility disorder or a mechanical obstruction (see Table 12-2).

Evaluation

History: History of present illness begins with duration of symptoms and acuity of onset. Patients should describe what substances cause difficulty and where they feel the disturbance is located. Specific concerns include whether patients have difficulty swallowing solids, liquids, or both; whether food comes out their nose; whether they drool or have food spill from their mouth; and whether they cough or choke while eating.

[Table 12-1. Some Causes of Oropharyngeal Dysphagia]
**Review of symptoms** should focus on symptoms suggestive of neuromuscular, GI, and connective tissue disorders and on the presence of complications. Important neuromuscular symptoms include weakness and easy fatigability, gait or balance disturbance, tremor, and difficulty speaking. Important GI symptoms include heartburn or other chest discomfort suggestive of reflux. Symptoms of connective tissue disorders include muscle and joint pain, Raynaud's phenomenon, and skin changes (eg, rash, swelling, thickening).

**Past medical history** should ascertain known diseases that may cause dysphagia (see Tables 12-1 and 12-2).

**Physical examination:** Examination focuses on findings suggestive of neuromuscular, GI, and connective tissue disorders and on the presence of complications.

General examination should evaluate nutritional status (including body weight). A complete neurologic examination is essential, with attention to any resting tremor, the cranial nerves (note the gag reflex may normally be absent; this absence is thus not a good marker of swallowing dysfunction), and muscle strength. Patients who describe easy fatigability should be observed performing a repetitive action (eg, blinking, counting aloud) for a rapid decrement in performance.

[Table 12-2. Some Causes of Esophageal Dysphagia]

The patient's gait should be observed, and balance should be tested. Skin is examined for rash and thickening or texture changes, particularly on the fingertips. Muscles are inspected for wasting and fasciculations and are palpated for tenderness. The neck is evaluated for thyromegaly or other mass.

**Red flags:** Any dysphagia is of concern, but certain findings are more urgent:

- Symptoms of complete obstruction (eg, drooling, inability to swallow anything)
- Dysphagia resulting in weight loss
- New focal neurologic deficit, particularly any objective weakness

**Interpretation of findings:** Dysphagia that occurs in conjunction with an acute neurologic event is likely the result of that event; new dysphagia in a patient with a stable, long-standing neurologic disorder may have another etiology. Dysphagia for solids alone suggests mechanical obstruction; however, a problem with both solids and liquids is nonspecific. Drooling and spilling food from the mouth while eating or nasal regurgitation suggests an oropharyngeal disorder. Regurgitation of a small amount of food on lateral compression of the neck is virtually diagnostic of pharyngeal diverticulum.

Patients who complain of difficulty getting food to leave the mouth or of food sticking in the lower esophagus are usually correct about the condition's location; the sensation of dysphagia in the upper esophagus is less specific.

Many findings suggest specific disorders (see Table 12-3) but are of varying sensitivity and specificity and thus do not rule in or out a given cause; however, they can guide testing.

**Testing:** A barium swallow (with a solid bolus, usually a marshmallow or tablet) should be done. If this test shows obstruction, endoscopy (and possibly biopsy) should be done to rule out malignancy. If the barium swallow is negative or suggestive of a motility disorder, esophageal motility studies should be done. Other tests for specific causes are done as suggested by findings.

**Treatment**

Treatment is directed at the specific cause. If complete obstruction occurs, emergent upper endoscopy is essential. If a stricture, ring, or web is found, careful endoscopic dilation is performed. Pending resolution,
patients with oropharyngeal dysphagia may benefit

from evaluation by a rehabilitation specialist. Sometimes patients benefit from changing head position while eating, retraining the swallowing muscles, doing exercises that improve the ability to accommodate a food bolus in the oral cavity, or doing strength and coordination exercises for the tongue. Patients with severe dysphagia and recurrent aspiration may require a gastrostomy tube.

Geriatrics Essentials

Chewing, swallowing, tasting, and communicating require intact, coordinated neuromuscular function in the mouth, face, and neck. Oral motor function in particular declines measurably with aging, even in healthy people. Decline in function may have many manifestations:

- Reduction in masticatory muscle strength and coordination is common, especially among patients with partial or complete dentures, and may lead to a tendency to swallow larger food particles, which can increase the risk of choking or aspiration.

- Drooping of the lower face and lips caused by decreased circumoral muscle tone and, in edentulous people, reduced bone support, is an aesthetic concern and can lead to drooling, spilling of food and liquids, and difficulty closing the lips while eating, sleeping, or resting. Sialorrhea (saliva leakage) is often the first symptom.

- Swallowing difficulties increase. It takes longer to move food from mouth to oropharynx, which increases the likelihood of aspiration.

After age-related changes, the most common causes of oral motor disorders are neuromuscular disorders (eg, cranial neuropathies caused by diabetes, stroke, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis). Iatrogenic causes also contribute. Drugs (eg, anticholinergics, diuretics), radiation therapy to the head and neck, and chemotherapy can greatly impair saliva production. Hyposalivation is a major cause of delayed and impaired swallowing.

Oral motor dysfunction is best managed with a multidisciplinary approach. Coordinated referrals to specialists in prosthetic dentistry, rehabilitative medicine, speech pathology, otolaryngology, and gastroenterology may be needed.

Key Points

- All patients complaining of esophageal dysphagia should undergo upper endoscopy to rule out cancer.

- If the upper endoscopy is normal, biopsies should be obtained to rule out eosinophilic esophagitis.

- Treatment is geared toward the cause.

Cricopharyngeal Incoordination

In cricopharyngeal incoordination, the cricopharyngeal muscle (the upper esophageal sphincter) is uncoordinated. It can cause a Zenker's diverticulum (see p. 125). Repeated aspiration of material from the diverticulum can lead to chronic lung disease. The condition can be treated by surgical section of the cricopharyngeal muscle.

Obstructive Disorders

(See also Benign Esophageal Tumors and Esophageal Cancer on p. 186.)

Lower Esophageal Ring
A lower esophageal ring is a 2- to 4-mm mucosal stricture, probably congenital, causing a ringlike narrowing of the distal esophagus at the squamocolumnar junction.

These rings cause intermittent dysphagia for solids. This symptom can begin at any age but usually does not begin until after age 25. The swallowing difficulty comes and goes and is especially aggravated by meat and dry bread. Symptoms usually occur only when the esophageal lumen is < 12 mm in diameter and never when it is > 20 mm. If the distal esophagus is adequately distended, barium x-rays usually show the ring. Instructing the patient to chew food thoroughly is usually the only treatment required in wider rings, but narrow-lumen rings require dilation by endoscopy or bougienage. Surgical resection is rarely required.

Esophageal Web

An esophageal web is a thin mucosal membrane that grows across the lumen.

Rarely, webs develop in patients with untreated severe iron-deficiency anemia; they develop even more rarely in patients without anemia. Webs usually occur in the upper esophagus, causing dysphagia for solids. They are best diagnosed by barium swallow. Webs resolve with treatment of the anemia but can be easily ruptured during esophagoscopy.

Dysphagia Lusoria

Dysphagia lusoria is caused by compression of the esophagus from any of several congenital vascular abnormalities.

The vascular abnormality is usually an aberrant right subclavian artery arising from the left side of the aortic arch, a double aortic arch, or a right aortic arch with left ligamentum arteriosum. The dysphagia may develop in childhood or later in life as a result of arteriosclerotic changes in the aberrant vessel. Barium swallow shows the extrinsic compression, but arteriography is necessary for absolute diagnosis. Most patients require no treatment, but surgical repair is sometimes done.

Motility Disorders

Achalasia

Achalasia is a neurogenic esophageal motility disorder characterized by impaired esophageal peristalsis, a lack of lower esophageal sphincter relaxation during swallowing, and an elevation of lower esophageal sphincter resting pressure. Symptoms are slowly progressive dysphagia, usually to both liquids and solids, and regurgitation of undigested food. Evaluation typically includes barium swallow, endoscopy, and sometimes manometry. Treatments include dilation, chemical denervation, and surgical myotomy.

Achalasia is thought to be caused by a loss of ganglion cells in the myenteric plexus of the esophagus, resulting in denervation of esophageal muscle. Etiology of the denervation is unknown, although a viral cause is suspected, and certain tumors may cause achalasia either by direct obstruction or as a paraneoplastic process. Chagas disease, which causes destruction of autonomic ganglia, may result in achalasia.

Increased pressure at the lower esophageal sphincter (LES) causes obstruction with secondary dilation of the esophagus. Esophageal retention of undigested food is common.
Achalasia occurs at any age but usually begins between ages 20 and 60. Onset is insidious, and progression is gradual over months or years. Dysphagia for both solids and liquids is the major symptom. Nocturnal regurgitation of undigested food occurs in about 33% of patients and may cause cough and pulmonary aspiration. Chest pain is less common but may occur on swallowing or spontaneously. Mild to moderate weight loss occurs; when weight loss is pronounced, particularly in elderly patients whose symptoms of dysphagia developed rapidly, achalasia secondary to a tumor of the gastroesophageal junction should be considered.

**Diagnosis**

- Barium swallow
- Esophageal manometry

The preferred test is barium swallow, which shows absence of progressive peristaltic contractions during swallowing. The esophagus is dilated, often enormously, but is narrowed and beaklike at the LES. If esophagoscopy is done, there is dilation but no obstructing lesion. The esophagoscope usually passes readily into the stomach; resistance raises the possibility of an inapparent cancer or stricture. To exclude cancer, a retroflexed view of the gastric cardia, biopsies, and brushings for cytology should be obtained. Esophageal manometry is usually done and typically shows aperistalsis, increased LES pressure, and incomplete sphincteric relaxation during swallowing.

Achalasia must be differentiated from a distal stenosing carcinoma and a peptic stricture, particularly in patients with systemic sclerosis (see p. 309), in whom esophageal manometry may also show aperistalsis. Systemic sclerosis is usually accompanied by a history of Raynaud's phenomenon and symptoms of gastroesophageal reflux disease (GERD), due to low or absent LES pressure.

Achalasia due to cancer at the gastroesophageal junction can be diagnosed by CT of the chest and abdomen or by endoscopic ultrasound.

**Prognosis**

Pulmonary aspiration and the presence of cancer are the determining prognostic factors. Nocturnal regurgitation and coughing suggest aspiration. Pulmonary complications secondary to aspiration are difficult to manage. Incidence of esophageal cancer in patients with achalasia may be increased; this point is controversial.

**Treatment**

- Balloon dilation of the LES
- Alternatively, botulinum toxin injection or surgical myotomy

No therapy restores peristalsis; treatment aims at reducing the pressure (and thus the obstruction) at the LES. Pneumatic balloon dilation of the LES is indicated initially. Results are satisfactory in about 85% of patients, but repeated dilations may be needed. Esophageal rupture and secondary mediastinitis requiring surgical repair occur in < 2% of patients. Nitrates (eg, isosorbide dinitrate 5 to 10 mg sublingually before meals) or Ca channel blockers (eg, nifedipine 10 mg po tid) are of limited effectiveness but may reduce LES pressure enough to prolong the time between dilations.

Achalasia can also be treated by chemical denervation of cholinergic nerves in the distal esophagus by direct injection of botulinum toxin type A into the LES. Clinical improvement occurs in 70 to 80% of patients, but results may last only 6 mo to 1 yr.

A Heller myotomy, in which the muscular fibers in the LES are cut, is usually reserved for patients who do not respond to dilation; its success rate is about 85%. It can be done via laparoscopy or thoracoscopy and may be a viable alternative to dilation as primary therapy. Symptomatic GERD occurs after surgery in
about 15% of patients.

**Symptomatic Diffuse Esophageal Spasm**

(Spastic Pseudodiverticulosis; Rosary Bead or Corkscrew Esophagus)

Symptomatic diffuse esophageal spasm is part of a spectrum of motility disorders characterized variously by nonpropulsive contractions, hyperdynamic contractions, or elevated lower esophageal sphincter pressure. Symptoms are chest pain and sometimes dysphagia. Diagnosis is by barium swallow or manometry. Treatment is difficult but includes nitrates, Ca channel blockers, botulinum toxin injection, and antireflux therapy.

Abnormalities in esophageal motility correlate poorly with patient symptoms; similar abnormalities may cause different or no symptoms in different people. Furthermore, neither symptoms nor abnormal contractions are definitively associated with histopathologic abnormalities of the esophagus.

**Symptoms and Signs**

Diffuse esophageal spasm typically causes substernal chest pain with dysphagia for both liquids and solids. The pain may waken the patient from sleep. Very hot or cold liquids may aggravate the pain. Over many years, this disorder may evolve into achalasia.

Esophageal spasms can cause severe pain without dysphagia. This pain is often described as a substernal squeezing pain and may occur in association with exercise. Such pain may be indistinguishable from angina pectoris.

Some patients have symptoms that combine those of achalasia and diffuse spasm. One such combination has been called vigorous achalasia because it features both the food retention and aspiration of achalasia and the severe pain and spasm of diffuse spasm.

**Diagnosis**

- Barium swallow
- Esophageal manometry
- Possibly testing for coronary ischemia

Alternative diagnoses include coronary ischemia. Definitive confirmation of an esophageal origin for symptoms is difficult. Barium swallow may show poor progression of a bolus and disordered, simultaneous contractions or tertiary contractions. Severe spasms may mimic the radiographic appearance of diverticula but vary in size and position. Esophageal manometry (see p. 96) provides the most specific description of the spasms. Contractions are usually simultaneous, prolonged or multiphasic, and possibly of very high amplitude ("nutcracker esophagus"). However, spasms may not occur during testing. Lower esophageal sphincter (LES) pressure elevation or impaired relaxation is present in 30% of patients. Esophageal scintigraphy and provocative tests with drugs (eg, edrophonium chloride 10 mg IV) have not proved helpful.

**Treatment**

- Ca channel blockers
- Botulinum toxin injection

Esophageal spasms are often difficult to treat, and controlled studies of treatment methods are lacking. Anticholinergics, nitroglycerin, and long-acting nitrates have had limited success. Ca channel blockers given orally (eg, verapamil 80 mg tid, nifedipine 10 mg tid) may be useful, as may injection of botulinum toxin type A into the LES.
Medical management is usually sufficient, but pneumatic dilation and bougienage, or even surgical myotomy along the full length of the esophagus, may be tried in intractable cases.

**Esophageal Diverticula**

An esophageal diverticulum is an outpouching of mucosa through the muscular layer of the esophagus. It can be asymptomatic or cause dysphagia and regurgitation. Diagnosis is made by barium swallow; surgical repair is rarely required.

There are several types of esophageal diverticula, each of different origin.

- Zenker’s (pharyngeal) diverticula are posterior outpouchings of mucosa and submucosa through the cricopharyngeal muscle, probably resulting from an incoordination between pharyngeal propulsion and cricopharyngeal relaxation.

- Midesophageal (traction) diverticula are caused by traction from mediastinal inflammatory lesions or, secondarily, by motility disorders.

- Epiphrenic diverticula occur just above the diaphragm and usually accompany a motility disorder (achalasia, diffuse esophageal spasm).

**Symptoms and Signs**

A Zenker’s diverticulum fills with food that might be regurgitated when the patient bends or lies down. Aspiration pneumonitis may result if regurgitation is nocturnal. Rarely, the pouch becomes large, causing dysphagia and sometimes a palpable neck mass.

Traction and epiphrenic diverticula are rarely symptomatic, although their underlying cause may be.

**Diagnosis**

All diverticula are diagnosed by videotaped barium swallow.

**Treatment**

- Usually none

- Sometimes surgical resection

Specific treatment is usually not required, although resection is occasionally necessary for large or symptomatic diverticula. Diverticula associated with motility disorders require treatment of the primary disorder. For example, case reports suggest doing a cricopharyngeal myotomy when resecting a Zenker’s diverticulum.

**Gastroesophageal Reflux Disease**

Incompetence of the lower esophageal sphincter allows reflux of gastric contents into the esophagus, causing burning pain. Prolonged reflux may lead to esophagitis, stricture, and rarely metaplasia or cancer. Diagnosis is clinical, sometimes with endoscopy, with or without acid testing. Treatment involves lifestyle modification, acid suppression using proton pump inhibitors, and sometimes surgical repair.

Gastroesophageal reflux disease (GERD) is common, occurring in 30 to 40% of adults. It also occurs frequently in infants, typically beginning at birth.

**Etiology**

The presence of reflux implies lower esophageal sphincter (LES) incompetence, which may result from a generalized loss of intrinsic sphincter tone or from recurrent inappropriate transient relaxations (ie, unrelated to swallowing). Transient LES relaxations are triggered by gastric distention or subthreshold pharyngeal stimulation.

Factors that contribute to the competence of the gastroesophageal junction include the angle of the cardioesophageal junction, the action of the diaphragm, and gravity (ie, an upright position). Factors contributing to reflux include weight gain, fatty foods, caffeinated or carbonated beverages, alcohol, tobacco smoking, and drugs. Drugs that lower LES pressure include anticholinergics, antihistamines, tricyclic antidepressants, Ca channel blockers, progesterone, and nitrates.

Complications: GERD may lead to esophagitis, peptic esophageal ulcer, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma (see p. 186). Factors that contribute to the development of esophagitis include the caustic nature of the refluxate, the inability to clear the refluxate from the esophagus, the volume of gastric contents, and local mucosal protective functions. Some patients, particularly infants, aspirate the reflux material.

Symptoms and Signs

The most prominent symptom of GERD is heartburn, with or without regurgitation of gastric contents into the mouth. Infants present with vomiting, irritability, anorexia, and sometimes symptoms of chronic aspiration. Both adults and infants with chronic aspiration may have cough, hoarseness, or wheezing.

Esophagitis may cause odynophagia and even esophageal hemorrhage, which is usually occult but can be massive. Peptic stricture causes a gradually progressive dysphagia for solid foods. Peptic esophageal ulcers cause the same type of pain as gastric or duodenal ulcers, but the pain is usually localized to the xiphoid or high substernal region. Peptic esophageal ulcers heal slowly, tend to recur, and usually leave a stricture on healing.

Diagnosis

• Clinical diagnosis
• Endoscopy for those not responding to empiric treatment
• 24-h pH testing for those with typical symptoms but normal endoscopy

A detailed history points to the diagnosis. Patients with typical symptoms of GERD may be given a trial of therapy. Patients who do not improve, or have long-standing symptoms or symptoms of complications, should be studied. Endoscopy, with cytologic washings and biopsy of abnormal areas, is the test of choice. Endoscopic biopsy is the only test that consistently detects the columnar mucosal changes of Barrett's esophagus. Patients with unremarkable endoscopy findings who have typical symptoms despite treatment with proton pump inhibitors should undergo 24-h pH testing (see p. 95). Although barium swallow readily shows esophageal ulcers and peptic strictures, it is less useful for mild to moderate reflux; in addition, most patients with abnormalities require subsequent endoscopy. Esophageal manometry may be used to guide pH probe placement and to evaluate esophageal peristalsis before surgical treatment.

Treatment

• Head of bed elevated
• Coffee, alcohol, fats, and smoking avoided
• Proton pump inhibitors

Management of uncomplicated GERD consists of elevating the head of the bed about 15 cm (6 in) and avoiding the following: eating within 2 to 3 h of bedtime, strong stimulants of acid secretion (eg, coffee, alcohol), certain drugs (eg, anticholinergics), specific foods (eg, fats, chocolate), and smoking.
Drug therapy is with a proton pump inhibitor. For example, adults can be given omeprazole 20 mg, lansoprazole 30 mg, or esomeprazole 40 mg 30 min before breakfast. In some cases, proton pump inhibitors may be given bid. Infants and children may be given these drugs at an appropriate lower single daily dose (ie, omeprazole 20 mg in children > 3 yr, 10 mg in children < 3 yr; lansoprazole 15 mg in children ≤ 30 kg, 30 mg in children > 30 kg). These drugs may be continued long-term, but the dose should be adjusted to the minimum required to prevent symptoms. H2 blockers (eg, ranitidine 150 mg at bedtime) or promotility agents (eg, metoclopramide 10 mg po 30 min before meals and at bedtime) are less effective.

Antireflux surgery (usually via laparoscopy) is done on patients with serious esophagitis, large hiatal hernias, hemorrhage, stricture, or ulcers. Esophageal strictures are managed by repeated balloon dilation.

Barrett's esophagus may or may not regress with medical or surgical therapy. Because Barrett's esophagus is a precursor to adenocarcinoma, endoscopic surveillance for malignant transformation is recommended every 1 to 2 yr. Surveillance has uncertain cost-effectiveness in patients with low-grade dysplasia but is important in high-grade dysplasia in patients who are unable to undergo surgical resection. Alternatively, Barrett's esophagus may be treated with endoscopic mucosal resection, photodynamic therapy, cryotherapy, or laser ablation.

**Hiatus Hernia**

Hiatus hernia is a protrusion of the stomach through the diaphragmatic hiatus. Most hernias are asymptomatic, but an increased incidence of acid reflux may lead to symptoms of gastroesophageal reflux disease (GERD). Diagnosis is by barium swallow. Treatment is directed at symptoms of GERD if present.

**Etiology**

Etiology is usually unknown, but a hiatus hernia is thought to be acquired through stretching of the fascial attachments between the esophagus and diaphragm at the hiatus (the opening through which the esophagus traverses the diaphragm).

**Pathophysiology**

In a sliding hiatus hernia (the most common type), the gastroesophageal junction and a portion of the stomach are above the diaphragm. In a paraesophageal hiatus hernia, the gastroesophageal junction is in the normal location, but a portion of the stomach is adjacent to the esophagus in the diaphragmatic hiatus. Hernias may also occur through other parts of the diaphragm (see p. 2977).

A sliding hiatus hernia is common and is an incidental finding on x-ray in > 40% of the population; therefore, the relationship of hernia to symptoms is unclear. Although most patients with GERD have some degree of hiatus hernia, < 50% of patients with hiatus hernia have GERD.

**Symptoms and Signs**

Most patients with a sliding hiatus hernia are asymptomatic, but chest pain and other reflux symptoms can occur. A paraesophageal hiatus hernia is generally asymptomatic but, unlike a sliding hiatus hernia, may incarcerate and strangulate. Occult or massive GI hemorrhage may occur with either type.

**Diagnosis**

- Barium swallow

A large hiatus hernia is often discovered incidentally on chest x-ray. Smaller hernias are diagnosed with a barium swallow.
Treatment

• Sometimes a proton pump inhibitor

An asymptomatic sliding hiatus hernia requires no specific therapy. Patients with accompanying GERD should be treated with a proton pump inhibitor. A paraesophageal hernia should be reduced surgically because of the risk of strangulation.

Infectious Esophageal Disorders

Esophageal infection occurs mainly in patients with impaired host defenses. Primary agents include *Candida albicans*, herpes simplex virus, and cytomegalovirus. Symptoms are odynophagia and chest pain. Diagnosis is by endoscopic visualization and culture. Treatment is with antifungal or antiviral drugs.

Esophageal infection is rare in patients with normal host defenses. Primary esophageal defenses include saliva, esophageal motility, and cellular immunity. Thus, at-risk patients include those with AIDS, organ transplants, alcoholism, diabetes, undernutrition, cancer, and motility disorders. *Candida* infection may occur in any of these patients. Herpes simplex virus (HSV) and cytomegalovirus (CMV) infections occur mainly in AIDS and transplant patients.

*Candida*: Patients with *Candida* esophagitis usually complain of odynophagia and, less commonly, dysphagia. About two thirds of patients have signs of oral thrush (thus its absence does not exclude esophageal involvement). Patients with odynophagia and typical thrush may be given empiric treatment, but if significant improvement does not occur in 5 to 7 days, endoscopic evaluation is required. Barium swallow is less accurate.

Treatment is with fluconazole 200 mg po or IV for one dose, then 100 mg po or IV q 24 h for 14 to 21 days. Alternatives include the azoles (eg, itraconazole, voriconazole, ketoconazole) or echinocandins (eg, caspofungin). Topical therapy has no role.

*HSV and CMV*: These infections are equally likely in transplant patients, but HSV occurs early after transplantation (reactivation) and CMV occurs 2 to 6 mo after. Among AIDS patients, CMV is much more common than HSV, and viral esophagitis occurs mainly when the CD4+ count is < 200/μL. Severe odynophagia results from either infection.

Endoscopy, with cytology or biopsy, is usually necessary for diagnosis. HSV is treated with IV acyclovir 5 mg/kg q 8 h for 7 days or valacyclovir 1 g po tid. CMV is treated with ganciclovir 5 mg/kg IV q 12 h for 14 to 21 days with maintenance at 5 mg/kg IV 5 days/wk in immunocompromised patients. Alternatives include foscarnet and cidofovir.

Mallory-Weiss Syndrome

*Mallory-Weiss syndrome* is a nonpenetrating mucosal laceration of the distal esophagus and proximal stomach caused by vomiting, retching, or hiccuping.

Initially described in alcoholics, Mallory-Weiss syndrome can occur in any patient who vomits forcefully. It is the cause of about 5% of episodes of upper GI hemorrhage. Most episodes of bleeding stop spontaneously; severe bleeding occurs in about 10% of patients who require significant intervention, such as transfusion or endoscopic hemostasis (by injection of ethanol, polidocanol, or epinephrine or by electrocautery). Intra-arterial infusion of pitressin or therapeutic embolization into the left gastric artery during angiography may also be used to control bleeding. Surgical repair is rarely required.

Esophageal Rupture

*Esophageal rupture* may be iatrogenic during endoscopic procedures or other instrumentation or may be spontaneous (Boerhaave's syndrome). Patients are seriously ill, with symptoms of mediastinitis. Diagnosis is by esophagography with a water-soluble contrast agent. Immediate
surgical repair and drainage are required.

Endoscopic procedures are the primary cause of esophageal rupture, but spontaneous rupture may occur, typically related to vomiting, retching, or swallowing a large food bolus. The most common site of rupture is the distal esophagus on the left side. Acid and other stomach contents cause a fulminant mediastinitis and shock. Pneumomediastinum is common.

Symptoms and Signs

Symptoms include chest and abdominal pain, vomiting, hematemesis, and shock. Subcutaneous emphysema is palpable in about 30% of patients. Mediastinal crunch (Hamman’s sign), a crackling sound synchronous with the heartbeat, may be present.

Diagnosis

- Chest and abdominal x-rays
- Esophagography

Chest and abdominal x-rays showing mediastinal air, pleural effusion, or mediastinal widening suggest the diagnosis. Diagnosis is confirmed by esophagography with a water-soluble contrast agent, which avoids potential mediastinal irritation from barium. CT of the thorax detects mediastinal air and fluid but does not localize the perforation well. Endoscopy may miss a small perforation.

Treatment

- Surgical repair

Pending surgical repair, patients should receive broad-spectrum antibiotics (eg, gentamicin plus metronidazole or piperacillin/tazobactam) and fluid resuscitation as needed for shock. Even with treatment, mortality is high.
Chapter 13. Gastritis and Peptic Ulcer Disease

Introduction

Acid is secreted by parietal cells in the proximal two thirds (body) of the stomach. Gastric acid aids digestion by creating the optimal pH for pepsin and gastric lipase and by stimulating pancreatic bicarbonate secretion. Acid secretion is initiated by food: the thought, smell, or taste of food effects vagal stimulation of the gastrin-secreting G cells located in the distal one third (antrum) of the stomach. The arrival of protein to the stomach further stimulates gastrin output. Circulating gastrin triggers the release of histamine from enterochromaffin-like cells in the body of the stomach. Histamine stimulates the parietal cells via their H₂ receptors. The parietal cells secrete acid, and the resulting drop in pH causes the antral D cells to release somatostatin, which inhibits gastrin release (negative feedback control).

Acid secretion is present at birth and reaches adult levels (on a weight basis) by age 2. There is a decline in acid output in elderly patients who develop chronic gastritis, but acid output is otherwise maintained throughout life.

Normally, the GI mucosa is protected by several distinct mechanisms: (1) Mucosal production of mucus and HCO₃⁻ creates a pH gradient from the gastric lumen (low pH) to the mucosa (neutral pH). The mucus serves as a barrier to the diffusion of acid and pepsin. (2) Epithelial cells remove excess hydrogen ions (H⁺) via membrane transport systems and have tight junctions, which prevent back diffusion of H⁺ ions. (3) Mucosal blood flow removes excess acid that has diffused across the epithelial layer. Several growth factors (eg, epidermal growth factor, insulin-like growth factor I) and prostaglandins have been linked to mucosal repair and maintenance of mucosal integrity.

Factors that interfere with these mucosal defenses (particularly NSAIDs and Helicobacter pylori infection) predispose to gastritis and peptic ulcer disease.

NSAIDs promote mucosal inflammation and ulcer formation (sometimes with GI bleeding) both topically and systemically. By inhibiting prostaglandin production via blockage of the enzyme cyclooxygenase (COX), NSAIDs reduce gastric blood flow, reduce mucus and HCO₃⁻ secretion, and decrease cell repair and replication. Also, because NSAIDs are weak acids and are nonionized at gastric pH, they diffuse freely across the mucus barrier into gastric epithelial cells, where H⁺ ions are liberated, leading to cellular damage. Because gastric prostaglandin production involves the COX-1 isoform, NSAIDs that are selective COX-2 inhibitors have fewer adverse gastric effects than other NSAIDs.

Helicobacter pylori Infection

H. pylori is a common gastric pathogen that causes gastritis, peptic ulcer disease, gastric adenocarcinoma, and low-grade gastric lymphoma. Infection may be asymptomatic or result in varying degrees of dyspepsia. Diagnosis is by urea breath test and testing of endoscopic biopsy samples. Treatment is with a proton pump inhibitor plus two antibiotics.

H. pylori is a spiral-shaped, gram-negative organism that has adapted to thrive in acid. In developing countries, it commonly causes chronic infections and is usually acquired during childhood. In the US, infection is less common among children but increases with age: by age 60, about 50% of people are infected. Infection is most common among blacks, Hispanics, and Asians.

The organism has been cultured from stool, saliva, and dental plaque, which suggests oral-oral or fecal-oral transmission. Infections tend to cluster in families and in residents of custodial institutions. Nurses and gastroenterologists seem to be at high risk because bacteria can be transmitted by improperly disinfected endoscopes.

Pathophysiology

Effects of H. pylori infection vary depending on the location within the stomach. Antral-predominant
infection results in increased gastrin production, probably via local impairment of somatostatin release. Resultant hypersecretion of acid predisposes to prepyloric and duodenal ulcer. Body-predominant infection leads to gastric atrophy and decreased acid production, possibly via increased local production of IL-1β. Patients with body-predominant infection are predisposed to gastric ulcer and adenocarcinoma. Some patients have mixed infection of both antrum and body with varying clinical effects. Many patients with *H. pylori* infection have no noticeable clinical effects.

Ammonia produced by *H. pylori* enables the organism to survive in the acidic environment of the stomach and may erode the mucus barrier. Cytotoxins and mucolytic enzymes (eg, bacterial protease, lipase) produced by *H. pylori* may play a role in mucosal damage and subsequent ulcerogenesis.

Infected people are 3 to 6 times more likely to develop stomach cancer. *H. pylori* infection is associated with intestinal-type adenocarcinoma of the gastric body and antrum but not cancer of the gastric cardia. Other associated cancers include gastric lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma, a monoclonally restricted B-cell tumor.

**Diagnosis**

- For initial diagnosis: Serologic tests
- For confirmation of cure: Urea breath test or stool antigen assay

Screening of asymptomatic patients is not warranted. Tests are done during evaluation for peptic ulcer and gastritis. Posttreatment testing is typically done to confirm eradication of the organism. Different tests are preferred for initial diagnosis and posttreatment.

**Noninvasive tests:** Laboratory and office-based serologic assays for antibodies to *H. pylori* have sensitivity and specificity of > 85% and are considered the noninvasive tests of choice for initial documentation of *H. pylori* infection. However, because qualitative assays remain positive for up to 3 yr after successful treatment and because quantitative antibody levels do not decline significantly for 6 to 12 mo after treatment, serologic assays are not usually used to assess cure.

Urea breath tests use an oral dose of $^{13}$C- or $^{14}$C-labeled urea. In an infected patient, the organism metabolizes the urea and liberates labeled CO$_2$, which is exhaled and can be quantified in breath samples taken 20 to 30 min after ingestion of the urea. Sensitivity and specificity are > 90%. Urea breath tests are well suited for confirming eradication of the organism after therapy. False-negative results are possible with recent antibiotic use or concomitant proton pump inhibitor therapy; therefore, follow-up testing should be delayed ≥ 4 wk after antibiotic therapy and 1 wk after proton pump inhibitor therapy. H$_2$ blockers do not affect the test.

Stool antigen assays seem to have a sensitivity and specificity near that of urea breath tests, particularly for initial diagnosis; an office-based test is under development.

**Invasive tests:** Endoscopy is used to obtain mucosal biopsy samples for a rapid urease test (RUT) or histologic staining. Bacterial culture is of limited use because of the fastidious nature of the organism. Endoscopy is not recommended solely for diagnosis of *H. pylori*; noninvasive tests are preferred unless endoscopy is indicated for other reasons.

The RUT, in which presence of bacterial urease in the biopsy sample causes a color change on a special medium, is the diagnostic method of choice on tissue samples. Histologic staining of biopsy samples should be done for patients with negative RUT results but suspicious clinical findings, recent antibiotic use, or treatment with proton pump inhibitors. RUT and histologic staining each have a sensitivity and specificity of > 90%.

**Treatment**

- Antibiotics (various regimens) plus a proton pump inhibitor
Patients with complications (eg, gastritis, ulcer, cancer) should have the organism eradicated. Eradication of *H. pylori* can even cure some cases of MALT lymphoma (but not other infection-related cancers). Treatment of asymptomatic infection has been controversial, but the recognition of the role of *H. pylori* in cancer has led to a recommendation for treatment. Vaccines, both preventive and therapeutic (ie, as an adjunct to treatment of infected patients), are under development.

*H. pylori* eradication requires multidrug therapy, typically antibiotics plus acid suppressants. Proton pump inhibitors suppress *H. pylori*, and the increased gastric pH accompanying their use can enhance tissue concentration and efficacy of antimicrobials, creating a hostile environment for *H. pylori*.

Triple therapy is recommended. Oral omeprazole 20 mg bid or lansoprazole 30 mg bid, plus clarithromycin 500 mg bid, plus amoxicillin 1 g bid (or, for penicillin-allergic patients, metronidazole 500 mg bid) for 14 days, cures infection in >95% of cases. This regimen has excellent tolerability. Ranitidine bismuth citrate 400 mg po bid may be substituted for the proton pump inhibitor.

Quadruple therapy with a proton pump inhibitor bid, tetracycline 500 mg and bismuth subsalicylate or subcitrate 525 mg qid, and metronidazole 500 mg tid is also effective but more cumbersome.

Infected patients with duodenal or gastric ulcer require continuation of the acid suppression for at least 4 wk.

Treatment is repeated if *H. pylori* is not eradicated. If two courses are unsuccessful, some authorities recommend endoscopy to obtain cultures for sensitivity testing.

**Gastritis**

Gastritis is inflammation of the gastric mucosa caused by any of several conditions, including infection (*Helicobacter pylori*), drugs (NSAIDs, alcohol), stress, and autoimmune phenomena (atrophic gastritis). Many cases are asymptomatic, but dyspepsia and GI bleeding sometimes occur. Diagnosis is by endoscopy. Treatment is directed at the cause but often includes acid suppression and, for *H. pylori* infection, antibiotics.

Gastritis is classified as erosive or nonerosive based on the severity of mucosal injury. It is also classified according to the site of involvement (ie, cardia, body, antrum). Gastritis can be further classified histologically as acute or chronic based on the inflammatory cell type. No classification scheme matches perfectly with the pathophysiology; a large degree of overlap exists. Some forms of gastritis involve acid-peptic and *H. pylori* disease. Additionally, the term is often loosely applied to nonspecific (and often undiagnosed) abdominal discomfort and gastroenteritis.

Acute gastritis is characterized by PMN infiltration of the mucosa of the antrum and body.

Chronic gastritis implies some degree of atrophy (with loss of function of the mucosa) or metaplasia. It predominantly involves the antrum (with subsequent loss of G cells and decreased gastrin secretion) or the corpus (with loss of oxyntic glands, leading to reduced acid, pepsin, and intrinsic factor).

**Erosive Gastritis**

Erosive gastritis is gastric mucosal erosion caused by damage to mucosal defenses. It is typically acute, manifesting with bleeding, but may be subacute or chronic with few or no symptoms. Diagnosis is by endoscopy. Treatment is supportive, with removal of the inciting cause. Certain ICU patients (eg, ventilator-bound, head trauma, burn, multisystem trauma) benefit from prophylaxis with acid suppressants.

Causes of erosive gastritis include NSAIDs, alcohol, stress, and less commonly radiation, viral infection (eg, cytomegalovirus), vascular injury, and direct trauma (eg, nasogastric tubes).

Superficial erosions and punctate mucosal lesions occur. These may develop as soon as 12 h after the
Acute stress gastritis, a form of erosive gastritis, occurs in about 5% of critically ill patients. The incidence increases with duration of ICU stay and length of time the patient is not receiving enteral feeding. Pathogenesis likely involves hypoperfusion of the GI mucosa, resulting in impaired mucosal defenses. Patients with head injury or burns may also have increased secretion of acid.

**Symptoms and Signs**

Patients with mild erosive gastritis are often asymptomatic, although some complain of dyspepsia, nausea, or vomiting. Often, the first sign is hematemesis, melena, or blood in the nasogastric aspirate, usually within 2 to 5 days of the inciting event. Bleeding is usually mild to moderate, although it can be massive if deep ulceration is present, particularly in acute stress gastritis. Acute and chronic erosive gastritis are diagnosed endoscopically.

**Diagnosis**

Acute and chronic erosive gastritis are diagnosed endoscopically.

**Treatment**

- For bleeding: Endoscopic hemostasis
- For acid suppression: A proton pump inhibitor or H$_2$ blocker

In severe gastritis, bleeding is managed with IV fluids and blood transfusion as needed. Endoscopic hemostasis should be attempted, with surgery (total gastrectomy) a fallback procedure. Angiography is unlikely to stop severe gastric bleeding because of the many collateral vessels supplying the stomach. Acid suppression should be started if the patient is not already receiving it.

For milder gastritis, removing the offending agent and using drugs to reduce gastric acidity (see p. 136) may be all that is required.

**Prevention**

Prophylaxis with acid-suppressive drugs can reduce the incidence of acute stress gastritis. However, it mainly benefits certain high-risk ICU patients, including those with severe burns, CNS trauma, coagulopathy, sepsis, shock, multiple trauma, mechanical ventilation for > 48 h, hepatic or renal failure, multiorgan dysfunction, and history of peptic ulcer or GI bleeding.

Prophylaxis consists of IV H$_2$ blockers, proton pump inhibitors, or oral antacids to raise intragastric pH > 4.0. Repeated pH measurement and titration of therapy are not required. Early enteral feeding also can decrease the incidence of bleeding.

Acid suppression is not recommended for patients simply taking NSAIDs unless they have previously had an ulcer.

**Nonerosive Gastritis**

Nonerosive gastritis refers to a variety of histologic abnormalities that are mainly the result of *H. pylori* infection. Most patients are asymptomatic. Diagnosis is by endoscopy. Treatment is eradication of *H. pylori* and sometimes acid suppression.

**Pathology**

**Superficial gastritis:** Lymphocytes and plasma cells mixed with neutrophils are the predominant infiltrating inflammatory cells. Inflammation is superficial and may involve the antrum, body, or both. It is
usually not accompanied by atrophy or metaplasia. Prevalence increases with age.

**Deep gastritis:** Deep gastritis is more likely to be symptomatic (eg, vague dyspepsia). Mononuclear cells and neutrophils infiltrate the entire mucosa to the level of the muscularis, but exudate or crypt abscesses seldom result, as might be expected by such infiltration. Distribution may be patchy. Superficial gastritis may be present, as may partial gland atrophy and metaplasia.

**Gastric atrophy:** Atrophy of gastric glands may follow in gastritis, most often longstanding antral (sometimes referred to as type B) gastritis. Some patients with gastric atrophy have autoantibodies to parietal cells, usually in association with corpus (type A) gastritis and pernicious anemia.

Atrophy may occur without specific symptoms. Endoscopically, the mucosa may appear normal until atrophy is advanced, when submucosal vascularity may be visible. As atrophy becomes complete, secretion of acid and pepsin diminishes and intrinsic factor may be lost, resulting in vitamin B\textsubscript{12} malabsorption.

**Metaplasia:** Two types of metaplasia are common in chronic nonerosive gastritis: mucous gland and intestinal.

Mucous gland metaplasia (pseudopyloric metaplasia) occurs in the setting of severe atrophy of the gastric glands, which are progressively replaced by mucous glands (antral mucosa), especially along the lesser curve. Gastric ulcers may be present (typically at the junction of antral and corpus mucosa), but whether they are the cause or consequence of these metaplastic changes is not clear.

Intestinal metaplasia typically begins in the antrum in response to chronic mucosal injury and may extend to the body. Gastric mucosa cells change to resemble intestinal mucosa—with goblet cells, endocrine (enterochromaffin or enterochromaffin-like) cells, and rudimentary villi—and may even assume functional (absorptive) characteristics. Intestinal metaplasia is classified histologically as complete (most common) or incomplete. With complete metaplasia, gastric mucosa is completely transformed into small-bowel mucosa, both histologically and functionally, with the ability to absorb nutrients and secrete peptides. In incomplete metaplasia, the epithelium assumes a histologic appearance closer to that of the large intestine and frequently exhibits dysplasia. Intestinal metaplasia may lead to stomach cancer.

**Symptoms and Signs**

Most patients with *H. pylori*-associated gastritis are asymptomatic, although some have mild dyspepsia or other vague symptoms.

**Diagnosis**

• Endoscopy

Often, the condition is discovered during endoscopy done for other purposes. Testing of asymptomatic patients is not indicated. Once gastritis is identified, testing for *H. pylori* is appropriate.

**Treatment**

• Eradication of *H. pylori*

• Sometimes acid-suppressive drugs

Treatment of chronic nonerosive gastritis is *H. pylori* eradication (see p. 130). Treatment of asymptomatic patients is somewhat controversial given the high prevalence of *H. pylori*-associated superficial gastritis and the relatively low incidence of clinical sequelae (ie, peptic ulcer disease). However, *H. pylori* is a class J carcinogen; eradication removes the cancer risk. In *H. pylori*-negative patients, treatment is directed at symptoms using acid-suppressive drugs (eg, H\textsubscript{2} blockers, proton pump inhibitors) or antacids.
Postgastrectomy Gastritis

Postgastrectomy gastritis is gastric atrophy developing after partial or subtotal gastrectomy (except in cases of gastrinoma).

Metaplasia of the remaining corpus mucosa is common. The degree of gastritis is usually greatest at the lines of anastomosis.

Several mechanisms are responsible: bile reflux, which is common after such surgery, damages the gastric mucosa; loss of antral gastrin decreases stimulation of parietal and peptic cells, causing atrophy; and vagotomy may result in a loss of vagal trophic action.

There are no specific symptoms of gastritis. Postgastrectomy gastritis often progresses to severe atrophy and achlorhydria. Production of intrinsic factor may cease with resultant vitamin B$_{12}$ deficiency (which may be worsened by bacterial overgrowth in the afferent loop). The relative risk of gastric adenocarcinoma seems to increase 15 to 20 yr after partial gastrectomy; however, given the low absolute incidence of postgastrectomy cancer, routine endoscopic surveillance is probably not cost effective, but upper GI symptoms or anemia in such patients should prompt endoscopy.

Uncommon Gastritis Syndromes

Menetrier's disease: This rare idiopathic disorder affects adults aged 30 to 60 and is more common among men. It manifests as a significant thickening of the gastric folds of the gastric body but not the antrum. Gland atrophy and marked foveolar pit hyperplasia occur, often accompanied by mucous gland metaplasia and increased mucosal thickness with little inflammation. Hypoalbuminemia (the most consistent laboratory abnormality) caused by GI protein loss may be present (protein-losing gastropathy). As the disease progresses, the secretion of acid and pepsin decreases, causing hypochlorhydria.

Symptoms are nonspecific and commonly include epigastric pain, nausea, weight loss, edema, and diarrhea. Differential diagnosis includes (1) lymphoma, in which multiple gastric ulcers may occur; (2) mucosa-associated lymphoid tissue (MALT) lymphoma, with extensive infiltration of monoclonal B lymphocytes; (3) Zollinger-Ellison syndrome with associated gastric fold hypertrophy; and (4) Cronkhite-Canada syndrome, a mucosal polyloid protein-losing syndrome associated with diarrhea. Diagnosis is made by endoscopy with deep mucosal biopsy or full-thickness laparoscopic gastric biopsy.

Various treatments have been used, including anticholinergics, antisecretory drugs, and corticosteroids, but none have proved fully effective. Partial or complete gastric resection may be necessary in cases of severe hypoalbuminemia.

Eosinophilic gastritis: Extensive infiltration of the mucosa, submucosa, and muscle layers with eosinophils often occurs in the antrum. It is usually idiopathic but may result from nematode infestation. Symptoms include nausea, vomiting, and early satiety. Diagnosis is by endoscopic biopsy of involved areas. Corticosteroids can be successful in idiopathic cases; however, if pyloric obstruction develops, surgery may be required.

Mucosa-associated lymphoid tissue (MALT) lymphoma: This rare condition is characterized by massive lymphoid infiltration of the gastric mucosa, which can resemble Menetrier's disease.

Gastritis caused by systemic disorders: Sarcoïdosis, TB, amyloidosis, and other granulomatous diseases can cause gastritis, which is seldom of primary importance.

Gastritis caused by physical agents: Radiation and ingestion of corrosives (especially acidic compounds) can cause gastritis. Exposure to > 16 Gy of radiation causes marked deep gastritis, usually involving the antrum more than the corpus. Pyloric stenosis and perforation are possible complications of radiation-induced gastritis.

Infectious (septic) gastritis: Except for H. pylori infection, bacterial invasion of the stomach is rare and mainly occurs after ischemia, ingestion of corrosives, or exposure to radiation. On x-ray, gas outlines the...
mucosa. The condition can manifest as an acute surgical abdomen and has a very high mortality rate. Surgery is often necessary.

Debilitated or immunocompromised patients may develop viral or fungal gastritis with cytomegalovirus, *Candida*, histoplasmosis, or mucormycosis; these diagnoses should be considered in patients with exudative gastritis, esophagitis, or duodenitis.

**Autoimmune Metaplastic Atrophic Gastritis**

Autoimmune metaplastic atrophic gastritis (AMAG) is an inherited autoimmune disease that attacks parietal cells, resulting in hypochlorhydria and decreased production of intrinsic factor. Consequences include atrophic gastritis, B₁₂ malabsorption, and, frequently, pernicious anemia. Risk of gastric adenocarcinoma increases 3-fold. Diagnosis is by endoscopy. Treatment is with parenteral vitamin B₁₂.

Patients with AMAG have antibodies to parietal cells and their components (which include intrinsic factor and the proton pump H⁺,K⁺-ATPase). AMAG is inherited as an autosomal dominant trait. Some patients also develop Hashimoto's thyroiditis and 50% have thyroid antibodies; conversely, parietal cell antibodies are found in 30% of patients with thyroiditis.

The lack of intrinsic factor leads to vitamin B₁₂ deficiency that can result in a megaloblastic anemia (pernicious anemia—see p. 932) or neurologic symptoms (subacute combined degeneration—see p. 38).

Hypochlorhydria leads to G-cell hyperplasia and elevated serum gastrin levels (often >1000 pg/mL). Elevated gastrin levels lead to enterochromaffin-like cell hyperplasia, which occasionally undergoes transformation to a carcinoid tumor.

In some patients, AMAG may be associated with chronic *Helicobacter pylori* infection, although the relationship is not clear. Gastrectomy and chronic acid suppression with proton pump inhibitors cause similar deficiencies of intrinsic factor secretion.

The areas of atrophic gastritis in the body and fundus may manifest metaplasia. Patients with AMAG have a 3-fold increased relative risk of developing gastric adenocarcinoma.

Diagnosis is made by endoscopic biopsy. Serum B₁₂ levels should be obtained. Parietal cell antibodies can be detected but are not measured routinely. The issue of surveillance endoscopy for cancer screening is unsettled; follow-up examinations are unnecessary unless histologic abnormalities (eg, dysplasia) are present on initial biopsy or symptoms develop. No treatment is needed other than parenteral replacement of vitamin B₁₂.

**Peptic Ulcer Disease**

A peptic ulcer is an erosion in a segment of the GI mucosa, typically in the stomach (gastric ulcer) or the first few centimeters of the duodenum (duodenal ulcer), that penetrates through the muscularis mucosae. Nearly all ulcers are caused by *Helicobacter pylori* infection or NSAID use. Symptoms typically include burning epigastric pain that is often relieved by food. Diagnosis is by endoscopy and testing for *H. pylori*. Treatment involves acid suppression, eradication of *H. pylori* (if present), and avoidance of NSAIDs.

Ulcers may range in size from several millimeters to several centimeters. Ulcers are delineated from erosions by the depth of penetration; erosions are more superficial and do not involve the muscularis mucosae. Ulcers can occur at any age, including infancy and childhood, but are most common among middle-aged adults.

**Etiology**
H. pylori and NSAIDs disrupt normal mucosal defense and repair, making the mucosa more susceptible to acid. H. pylori infection is present in 50 to 70% of patients with duodenal ulcers and 30 to 50% of patients with gastric ulcers. If H. pylori is eradicated, only 10% of patients have recurrence of peptic ulcer disease, compared with 70% recurrence in patients treated with acid suppression alone. NSAIDs now account for > 50% of peptic ulcers.

Cigarette smoking is a risk factor for the development of ulcers and their complications. Also, smoking impairs ulcer healing and increases the incidence of recurrence. Risk correlates with the number of cigarettes smoked per day. Although alcohol is a strong promoter of acid secretion, no definitive data link moderate amounts of alcohol to the development or delayed healing of ulcers. Very few patients have hypersecretion of gastrin (Zollinger-Ellison syndrome—see p. 200).

A family history exists in 50 to 60% of children with duodenal ulcer.

**Symptoms and Signs**

Symptoms depend on ulcer location and patient age; many patients, particularly elderly patients, have few or no symptoms. Pain is most common, often localized to the epigastrium and relieved by food or antacids. The pain is described as burning or gnawing, or sometimes as a sensation of hunger. The course is usually chronic and recurrent. Only about half of patients present with the characteristic pattern of symptoms.

**Gastric ulcer** symptoms often do not follow a consistent pattern (eg, eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (eg, bloating, nausea, vomiting) caused by edema and scarring.

**Duodenal ulcers** tend to cause more consistent pain. Pain is absent when the patient awakens but appears in mid-morning, is relieved by food, but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer. In neonates, perforation and hemorrhage may be the first manifestation of duodenal ulcer. Hemorrhage may also be the first recognized sign in later infancy and early childhood, although repeated vomiting or evidence of abdominal pain may be a clue.

**Diagnosis**

- Endoscopy
- Sometimes serum gastrin levels

Diagnosis of peptic ulcer is suggested by patient history and confirmed by endoscopy. Empiric therapy is often begun without definitive diagnosis. However, endoscopy allows for biopsy or cytologic brushing of gastric and esophageal lesions to distinguish between simple ulceration and ulcerating stomach cancer. Stomach cancer may manifest with similar manifestations and must be excluded, especially in patients who are > 45, have lost weight, or report severe or refractory symptoms. The incidence of malignant duodenal ulcer is extremely low, so biopsies of lesions in that area are generally not warranted.

Endoscopy can also be used to definitively diagnose H. pylori infection, which should be sought when an ulcer is detected.

Gastrin-secreting cancer and Zollinger-Ellison syndrome should be considered when there are multiple ulcers, when ulcers develop in atypical locations (eg, postbulbar) or are refractory to treatment, or when the patient has prominent diarrhea or weight loss. Serum gastrin levels should be measured in these patients.

**Complications**

**Hemorrhage:** Mild to severe hemorrhage is the most common complication of peptic ulcer disease. Symptoms include hematemesis (vomiting of fresh blood or "coffee ground" material); passage of bloody stools (hematochezia) or black tarry stools (melena); and weakness, orthostasis, syncope, thirst, and sweating caused by blood loss.
Penetration (confined perforation): A peptic ulcer may penetrate the wall of the stomach. If adhesions prevent leakage into the peritoneal cavity, free penetration is avoided and confined perforation occurs. Still, the ulcer may penetrate into the duodenum and enter the adjacent confined space (lesser sac) or another organ (eg, pancreas, liver). Pain may be intense, persistent, referred to sites other than the abdomen (usually the back when caused by penetration of a posterior duodenal ulcer into the pancreas), and modified by body position. CT or MRI is usually needed to confirm the diagnosis. When therapy does not result in healing, surgery is required.

Free perforation: Ulcers that perforate into the peritoneal cavity unchecked by adhesions are usually located in the anterior wall of the duodenum or, less commonly, in the stomach. The patient presents with an acute abdomen. There is sudden, intense, continuous epigastric pain that spreads rapidly throughout the abdomen, often becoming prominent in the right lower quadrant and at times referred to one or both shoulders. The patient usually lies still because even deep breathing worsens the pain. Palpation of the abdomen is painful, rebound tenderness is prominent, abdominal muscles are rigid (boardlike), and bowel sounds are diminished or absent. Shock may ensue, heralded by increased pulse rate and decreased BP and urine output. Symptoms may be less striking in elderly or moribund patients and those receiving corticosteroids or immunosuppressants.

Diagnosis is confirmed if an x-ray or CT shows free air under the diaphragm or in the peritoneal cavity. Upright views of the chest and abdomen are preferred. The most sensitive view is the lateral x-ray of the chest. Severely ill patients may be unable to sit upright and should have a lateral decubitus x-ray of the abdomen. Failure to detect free air does not exclude the diagnosis.

Immediate surgery is required. The longer the delay, the poorer is the prognosis. When surgery is contraindicated, the alternatives are continuous nasogastric suction and broad-spectrum antibiotics.

Gastric outlet obstruction: Obstruction may be caused by scarring, spasm, or inflammation from an ulcer. Symptoms include recurrent, large-volume vomiting, occurring more frequently at the end of the day and often as late as 6 h after the last meal. Loss of appetite with persistent bloating or fullness after eating also suggests gastric outlet obstruction. Prolonged vomiting may cause weight loss, dehydration, and alkalosis.

If the patient's history suggests obstruction, physical examination, gastric aspiration, or x-rays may provide evidence of retained gastric contents. A succussion splash heard > 6 h after a meal or aspiration of fluid or food residue > 200 mL after an overnight fast suggests gastric retention. If gastric aspiration shows marked retention, the stomach should be emptied and endoscopy done or x-rays taken to determine site, cause, and degree of obstruction.

Edema or spasm caused by an active pyloric channel ulcer is treated with gastric decompression by nasogastric suction and acid suppression (eg, IV H₂ blockers). Dehydration and electrolyte imbalances resulting from protracted vomiting or continued nasogastric suctioning should be vigorously sought and corrected. Prokinetic agents are not indicated. Generally, obstruction resolves within 2 to 5 days of treatment. Prolonged obstruction may result from peptic scarring and may respond to endoscopic pyloric balloon dilation. Surgery is necessary to relieve obstruction in selected cases.

Recurrence: Factors that affect recurrence of ulcer include failure to eradicate H. pylori, continued NSAID use, and smoking. Less commonly, a gastrinoma (Zollinger-Ellison syndrome) may be the cause. The 3-yr recurrence rate for gastric and duodenal ulcers is < 10% when H. pylori is successfully eradicated but > 50% when it is not. Thus, a patient with recurrent disease should be tested for H. pylori and treated again if the tests are positive.

Although long-term treatment with H₂ blockers, proton pump inhibitors, or misoprostol reduces the risk of recurrence, their routine use for this purpose is not recommended. However, patients who require NSAIDs after having had a peptic ulcer are candidates for long-term therapy, as are those with a marginal ulcer or prior perforation or bleeding.
Stomach cancer: Patients with \textit{H. pylori}-associated ulcers have a 3- to 6-fold increased risk of gastric cancer later in life. There is no increased risk of cancer with ulcers of other etiology.

Treatment

- Eradication of \textit{H. pylori} (when present)

- Acid-suppressive drugs

Treatment of gastric and duodenal ulcers requires eradication of \textit{H. pylori} when present (see p. 130) and a reduction of gastric acidity. For duodenal ulcers, it is particularly important to suppress nocturnal acid secretion.

Methods of decreasing acidity include a number of drugs, all of which are effective but which vary in cost, duration of therapy, and convenience of dosing. In addition, mucosal protective drugs (eg, sucralfate) and acid-reducing surgical procedures may be used. Drug therapy is discussed on p. 136.

Adjuncts: Smoking should be stopped, and alcohol consumption stopped or limited to small amounts of dilute alcohol. There is no evidence that changing the diet speeds ulcer healing or prevents recurrence. Thus, many physicians recommend eliminating only foods that cause distress.

Surgery: With current drug therapy, the number of patients requiring surgery has declined dramatically. Indications include perforation, obstruction, uncontrolled or recurrent bleeding, and, although rare, symptoms that do not respond to drug therapy.

Surgery consists of a procedure to reduce acid secretion, often combined with a procedure to ensure gastric drainage. The recommended operation for duodenal ulcer is highly selective, or parietal cell, vagotomy (which is limited to nerves at the gastric body and spares antral innervation, thereby obviating the need for a drainage procedure). This procedure has a very low mortality rate and avoids the morbidity associated with resection and traditional vagotomy. Other acid-reducing surgical procedures include antrectomy, hemigastrectomy, partial gastrectomy, and subtotal gastrectomy (ie, resection of 30 to 90% of the distal stomach). These are typically combined with truncal vagotomy. Patients who undergo a resective procedure or who have an obstruction require gastric drainage via a gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II).

The incidence and type of postsurgical symptoms vary with the type of operation. After resective surgery, up to 30% of patients have significant symptoms, including weight loss, maldigestion, anemia, dumping syndrome, reactive hypoglycemia, bilious vomiting, mechanical problems, and ulcer recurrence.

Weight loss is common after subtotal gastrectomy; the patient may limit food intake because of early satiety (because the residual gastric pouch is small) or to prevent dumping syndrome and other postprandial syndromes. With a small gastric pouch, distention or discomfort may occur after a meal of even moderate size; patients should be encouraged to eat smaller and more frequent meals.

Maldigestion and steatorrhea caused by pancreaticobiliary bypass, especially with Billroth II anastomosis, may contribute to weight loss.

Anemia is common (usually from iron deficiency, but occasionally from vitamin B\textsubscript{12} deficiency caused by loss of intrinsic factor or bacterial overgrowth) in the afferent limb, and osteomalacia may occur. IM vitamin B\textsubscript{12} supplementation is recommended for all patients with total gastrectomy but may also be given to patients with subtotal gastrectomy if deficiency is suspected.

Dumping syndrome may follow gastric surgical procedures, particularly resections. Weakness, dizziness, sweating, nausea, vomiting, and palpitation occur soon after eating, especially hyperosmolar foods. This phenomenon is referred to as early dumping, the cause of which remains unclear but likely involves autonomic reflexes, intravascular volume contraction, and release of vasoactive peptides from the small intestine. Dietary modifications, with smaller, more frequent meals and decreased carbohydrate
intake, usually help.

**Reactive hypoglycemia** or **late dumping** (another form of the syndrome) results from rapid emptying of carbohydrates from the gastric pouch. Early high peaks in blood glucose stimulate excess release of insulin, which leads to symptomatic hypoglycemia several hours after the meal. A high-protein, low-carbohydrate diet and adequate caloric intake (in frequent small feedings) are recommended.

**Mechanical problems** (including gastroparesis and bezoar formation—see p. 138) may occur secondary to a decrease in phase III gastric motor contractions, which are altered after antrectomy and vagotomy. Diarrhea is especially common after vagotomy, even without a resection (pyloroplasty).

**Ulcer recurrence**, according to older studies, occurs in 5 to 12% after highly selective vagotomy and in 2 to 5% after resective surgery. Recurrent ulcers are diagnosed by endoscopy and generally respond to either proton pump inhibitors or H₂ blockers. For ulcers that continue to recur, the completeness of vagotomy should be tested by gastric analysis, *H. pylori* eliminated if present, and Zollinger-Ellison syndrome ruled out by serum gastrin studies.

**Drug Treatment of Gastric Acidity**

Drugs for decreasing acidity are used for peptic ulcer, gastroesophageal reflux disease (GERD—see p. 125), and many forms of gastritis. Some drugs are used in regimens for treating *H. pylori* infection. Drugs include proton pump inhibitors, H₂ blockers, antacids, and prostaglandins.

**Proton pump inhibitors**: These drugs are potent inhibitors of H⁺,K⁺-ATPase. This enzyme, located in the apical secretory membrane of the parietal cell, plays a key role in the secretion of H⁺ (protons). These drugs can completely inhibit acid secretion and have a long duration of action. They promote ulcer healing and are also key components of *H. pylori* eradication regimens. Proton pump inhibitors have replaced H₂ blockers in most clinical situations because of greater rapidity of action and efficacy.

Proton pump inhibitors include esomeprazole, lansoprazole, and pantoprazole, all available orally and IV, and omeprazole and rabeprazole, available only orally in the US (see Table 13-1). Omeprazole is available without a prescription in the US. For uncomplicated duodenal ulcers, omeprazole 20 mg po once/day or lansoprazole 30 mg po once/day is given for 4 wk. Complicated duodenal ulcers (ie, multiple ulcers, bleeding ulcers, those > 1.5 cm, or those occurring in patients with serious underlying illness) respond better to higher doses (omeprazole 40 mg once/day, lansoprazole 60 mg once/day or 30 mg bid). Gastric ulcers require treatment for 6 to 8 wk. Gastritis and GERD require 8 to 12 wk of therapy; GERD additionally requires long-term maintenance.

Long-term proton pump inhibitor therapy produces elevated gastrin levels, which lead to enterochromaffin-like cell hyperplasia. However, there is no evidence of dysplasia or malignant transformation in patients receiving this treatment. Some may develop vitamin B₁₂ malabsorption.

**H₂ blockers**: These drugs (cimetidine, ranitidine, famotidine, available IV and orally; and nizatidine available orally) are competitive inhibitors of histamine at the H₂ receptor, thus suppressing gastrin-stimulated acid secretion and proportionately reducing gastric juice volume. Histamine-mediated pepsin secretion is also decreased.

H₂ blockers are well absorbed from the GI tract, with onset of action 30 to 60 min after ingestion and peak effects at 1 to 2 h. IV administration produces a more rapid onset of action. Duration of action is proportional to dose and ranges from 6 to 20 h. Doses should often be reduced in elderly patients.

For duodenal ulcers, once daily oral administration of cimetidine 800 mg, ranitidine 300 mg, famotidine 40
mg, or nizatidine 300 mg given at bedtime or after dinner for 6 to 8 wk is effective. Gastric ulcers may respond to the same regimen continued for 8 to 12 wk, but because nocturnal acid secretion is less important, morning administration may be equally or more effective. Children ≥ 40 kg may receive adult doses. Below that weight, the oral dosage is ranitidine 2 mg/kg q 12 h and cimetidine 10 mg/kg q 12 h. For GERD, H₂ blockers are now mostly used for pain management. Gastritis heals with famotidine or ranitidine given bid for 8 to 12 wk.

Cimetidine has minor antiandrogen effects expressed as reversible gynecomastia and, less commonly, erectile dysfunction with prolonged use. Mental status changes, diarrhea, rash, drug fever, myalgias, thrombocytopenia, and sinus bradycardia and hypotension after rapid IV administration have been reported with all H₂ blockers, generally in < 1% of treated patients but more commonly in elderly patients.

Cimetidine and, to a lesser extent, other H₂ blockers interact with the P-450 microsomal enzyme system and may delay metabolism of other drugs eliminated through this system (eg, phenytoin, warfarin, theophylline, diazepam, lidocaine).

**Antacids:** These agents neutralize gastric acid and reduce pepsin activity (which diminishes as gastric pH rises to > 4.0). In addition, some antacids adsorb pepsin. Antacids may interfere with the absorption of other drugs (eg, tetracycline, digoxin, iron).

Antacids relieve symptoms, promote ulcer healing, and reduce recurrence. They are relatively inexpensive but must be taken 5 to 7 times/day. The optimal antacid regimen for ulcer healing seems to be 15 to 30 mL of liquid or 2 to 4 tablets 1 h and 3 h after each meal and at bedtime. The total daily dosage of antacids should provide 200 to 400 mEq neutralizing capacity. However, antacids have been superseded by acid-suppressive therapy in the treatment of peptic ulcer and are used only for short-term symptom relief.

In general, there are 2 types of antacids: absorbable and nonabsorbable. Absorbable antacids (eg, Na bicarbonate, Ca carbonate) provide rapid, complete neutralization but may cause alkalosis and should be used only briefly (1 or 2 days). Nonabsorbable antacids (eg, aluminum or Mg hydroxide) have fewer systemic adverse effects and are preferred.

Aluminum hydroxide is a relatively safe, commonly used antacid. With chronic use, phosphate depletion occasionally develops as a result of binding of phosphate by aluminum in the GI tract. The risk of phosphate depletion increases in alcoholics, undernourished patients, and patients with renal disease (including those receiving hemodialysis). Aluminum hydroxide causes constipation.

Mg hydroxide is a more effective antacid than aluminum but may cause diarrhea. To limit diarrhea, many proprietary antacids combine Mg and aluminum antacids. Because small amounts of Mg are absorbed, Mg preparations should be used with caution in patients with renal disease.

**Prostaglandins:** Certain prostaglandins (especially misoprostol) inhibit acid secretion by decreasing the generation of cyclic AMP that is triggered by histamine stimulation of the parietal cell, and enhance mucosal defense. Synthetic prostaglandin derivatives are used predominantly to decrease the risk of NSAID-induced mucosal injury. Patients at high risk of NSAID-induced ulcers (ie, elderly patients, those with a history of ulcer or ulcer complication, those also taking corticosteroids) are candidates to take misoprostol 200 μg po qid with food along with their NSAID. Common adverse effects of misoprostol are abdominal cramping and diarrhea, which occur in 30% of patients. Misoprostol is a powerful abortifacient and is absolutely contraindicated in women of childbearing age who are not using contraception.

**Sucralfate:** This drug is a sucrose-aluminum complex that dissociates in stomach acid and forms a physical barrier over an inflamed area, protecting it from acid, pepsin, and bile salts. It also inhibits pepsin-substrate interaction, stimulates mucosal prostaglandin production, and binds bile salts. It has no effect on acid output or gastrin secretion. Sucralfate seems to have trophic effects on the ulcerated mucosa, possibly by binding growth factors and concentrating them at an ulcer site. Systemic absorption of sucralfate is negligible. Constipation occurs in 3 to 5% of patients. Sucralfate may bind to other drugs and interfere with their absorption.
Chapter 14. Bezoars and Foreign Bodies

Introduction

Food and other ingested materials may collect and form solid masses within the GI tract.

Bezoars

A bezoar is a tightly packed collection of partially digested or undigested material that is unable to exit the stomach. It often occurs in patients with abnormal gastric emptying, especially those that have diabetic gastroparesis, as well as after gastric surgery. Many bezoars are asymptomatic, but some cause symptoms of gastric outlet obstruction. Some can be dissolved enzymatically, others removed endoscopically, and some require surgery.

Partially digested agglomerations of vegetable matter are called phytobezoars; agglomerations of hair are called trichobezoars. Pharmacobezoars are concretions of medication (particularly common with sucralfate and aluminum hydroxide gel). Many other substances have been found in bezoars.

Etiology

Trichobezoars, which can weigh several kg, most commonly occur in patients with psychiatric disturbances who chew and swallow their own hair. Phytobezoars often occur in patients who have undergone a Billroth I or II partial gastrectomy, especially when accompanied by vagotomy. Hypochlorhydria, diminished antral motility, and incomplete mastication are the main predisposing factors; these factors are more common among the elderly, who are thus at higher risk of bezoar formation. Others include diabetic gastroparesis and gastroplasty for morbid obesity. Consumption of persimmons (a fruit containing the tannin shibuol, which polymerizes in the stomach) has been known to cause bezoars that require surgery in > 90% of cases. Persimmon bezoars often occur in epidemics in regions where the fruit is grown.

Symptoms and Signs

Most bezoars cause no symptoms, although postprandial fullness, nausea and vomiting, pain, and GI bleeding may occur.

Diagnosis

• Endoscopy

Bezoars are detectable as a mass lesion on most tests (eg, x-ray, ultrasound, CT) that may be done to evaluate upper GI symptoms. They may be mistaken for tumors; upper endoscopy is usually done. On endoscopy, bezoars have an unmistakable irregular surface and may range in color from yellow-green to gray-black. An endoscopic biopsy that yields hair or plant material is diagnostic.

Treatment

• Observation

• Sometimes manual removal via endoscopy

• Sometimes enzymatic therapy

If initial diagnosis is made by endoscopy, removal can be attempted at that time. Fragmentation with forceps, wire snare, jet spray, or even laser may break up bezoars, allowing them to pass or be extracted. Metoclopramide 40 mg IV over 24 h or 10 mg IM q 4 h for several days may increase peristalsis and aid gastric emptying of fragmented material.

If endoscopy was not initially done, treatment is based on symptoms. Asymptomatic patients that have a
Bezoar discovered incidentally during testing for other reasons do not necessarily require intervention. In some cases, a trial of enzymatic therapy can be attempted. Enzymes include papain (10,000 U with each meal), meat tenderizer (5 mL [1 tsp] in 8 oz of clear liquid before each meal), or cellulase (10 g dissolved in 1 L water, consumed over 24 h for 2 to 3 days). If enzymatic therapy is unsuccessful, or if patients are symptomatic, endoscopic removal may be tried. Rocklike concretions and trichobezoars usually require laparotomy.

Foreign Bodies

A variety of foreign bodies may enter the GI tract. Many pass spontaneously, but some become impacted, causing symptoms of obstruction. Perforation may occur. The esophagus is the most common (75%) site of impaction. Nearly all impacted objects can be removed endoscopically, but surgery is occasionally necessary.

Undigestible objects may be intentionally swallowed by children and demented adults. Denture wearers, the elderly, and inebriated people are prone to accidentally swallowing inadequately masticated food (particularly meat), which may become impacted in the esophagus. Smugglers who swallow drug-filled balloons, vials, or packages to escape detection (body packers or body stuffers) may develop intestinal obstruction. The packaging may rupture, leading to drug overdose.

Esophageal foreign bodies: Foreign bodies usually lodge in an area of esophageal narrowing such as at the cricopharyngeus or aortic arch or just above the gastroesophageal junction. If obstruction is complete, patients retch or vomit. Some patients drool because they are unable to swallow secretions. Immediate endoscopic removal is required for sharp objects, coins in the proximal esophagus, and any obstruction causing significant symptoms. Also, button batteries lodged in the esophagus may cause direct corrosive damage, low-voltage burns, and pressure necrosis and thus require prompt removal. Other esophageal foreign bodies may be observed for a maximum of 12 to 24 h. Glucagon 1 mg IV sometimes relaxes the esophagus enough to allow spontaneous passage. Other methods, such as use of effervescent agents, meat tenderizer, and bougienage, are not recommended. Endoscopic removal is the treatment of choice. Removal is best achieved using a forceps, basket, or snare with an overtube placed in the esophagus to prevent aspiration.

Sometimes, foreign bodies scratch the esophagus but do not become lodged. In such cases, patients may report a foreign body sensation even though no foreign body is present.

Gastric and intestinal foreign bodies: Foreign bodies that pass through the esophagus are asymptomatic unless obstruction or perforation occurs. Of the foreign bodies that reach the stomach, 80 to 90% pass spontaneously, 10 to 20% require nonoperative intervention, and ≤ 1% require surgery. Thus, most intragastric foreign bodies can be ignored. However, objects larger than 5 × 2 cm rarely pass the stomach. Sharp objects should be retrieved from the stomach because 15 to 35% will cause intestinal perforation, but small round objects (eg, coins and button batteries) can simply be observed. The patient's stools should be searched, and if the object does not appear, x-rays are taken at 48-h intervals. A coin that remains in the stomach for > 4 wk or a battery showing signs of corrosion on x-ray that remains in the stomach for > 48 h should be removed. A hand-held metal detector can localize metallic foreign bodies and provide information comparable to that yielded by plain x-rays.

Patients with symptoms of obstruction or perforation require laparotomy. Ingested drug packages are of great concern because of the risk of leakage and consequent drug overdose. Patients with symptoms of drug toxicity should have immediate laparotomy with interim medical management of symptoms (eg, benzodiazepines for cocaine toxicity). Asymptomatic patients should be admitted to the hospital. Some clinicians advocate oral polyethylene glycol solution as a cathartic to enhance passage of the material; others suggest surgical removal. The best practice is unclear.

Most foreign objects that have passed into the small intestine usually traverse the GI tract without problem, even if they take weeks or months to do so. They tend to be held up just before the ileocecal valve or at any site of narrowing, as is present in Crohn's disease. Sometimes objects such as toothpicks
remain within the GI tract for many years, only to turn up in a granuloma or abscess.

**Rectal foreign bodies:** Gallstones, fecoliths, and swallowed foreign bodies (including toothpicks and chicken and fish bones) may lodge at the anorectal junction. Urinary calculi, vaginal pessaries, or surgical sponges or instruments may erode into the rectum. Foreign bodies, sometimes bizarre and/or related to sexual play, may be introduced intentionally but become lodged unintentionally. Some objects are caught in the rectal wall, and others are trapped just above the anal sphincter.

Sudden, excruciating pain during defecation should arouse suspicion of a penetrating foreign body, usually lodged at or just above the anorectal junction. Other manifestations depend on the size and shape of the foreign body, its duration in situ, and the presence of infection or perforation.

Foreign bodies usually become lodged in the mid rectum, where they cannot negotiate the anterior angulation of the rectum. They can be felt on digital examination. Abdominal examination and chest x-rays may be necessary to exclude possible intraperitoneal rectal perforation.

If the object can be palpated, a local anesthetic is given by sc and submucosal injections of 0.5% lidocaine or bupivacaine. The anus is dilated with a rectal retractor, and the foreign body is grasped and removed. If the object cannot be palpated, the patient should be hospitalized. Peristalsis usually moves the foreign body down to the mid rectum, and the above routine can be followed. Removal via a sigmoidoscope or proctoscope is rarely successful, and sigmoidoscopy usually forces the foreign body proximally, delaying its extraction. Regional or general anesthesia is infrequently necessary, and laparotomy with milking of the foreign body toward the anus or colotomy with extraction of the foreign body is rarely necessary. After extraction, sigmoidoscopy should be done to rule out significant rectal trauma or perforation. Removal of a rectal foreign body may be of high risk and should be done by a surgeon or gastroenterologist skilled in foreign body removal.
Chapter 15. Pancreatitis

Introduction

Pancreatitis is classified as either acute or chronic. Acute pancreatitis is inflammation that resolves both clinically and histologically. Chronic pancreatitis is characterized by histologic changes that are irreversible and progressive and that result in considerable loss of exocrine and endocrine pancreatic function. Patients with chronic pancreatitis may have a flare-up of acute disease.

Pancreatitis can affect both the exocrine and endocrine functions of the pancreas. Pancreatic acinar cells secrete bicarbonate and digestive enzymes into ducts that connect the pancreas to the duodenum at the ampulla of Vater (exocrine function). Pancreatic β-cells secrete insulin directly into the bloodstream (endocrine function).

Acute Pancreatitis

Acute pancreatitis is inflammation of the pancreas (and, sometimes, adjacent tissues) caused by the release of activated pancreatic enzymes. The most common triggers are biliary tract disease and chronic heavy alcohol intake. The condition ranges from mild (abdominal pain and vomiting) to severe (pancreatic necrosis and a systemic inflammatory process with shock and multiorgan failure). Diagnosis is based on clinical presentation and serum amylase and lipase levels. Treatment is supportive, with IV fluids, analgesics, and fasting.

Etiology

Biliary tract disease and alcoholism account for ≥ 80% of acute pancreatitis cases. The remaining 20% result from myriad causes (see Table 15-1).

Pathophysiology

The precise mechanism by which obstruction of the sphincter of Oddi by a gallstone or microlithiasis (sludge) causes pancreatitis is unclear, although it probably involves increased ductal pressure. Prolonged alcohol intake (> 100 g/day for > 3 to 5 yr) may cause the protein of pancreatic enzymes to precipitate within small pancreatic ductules. Ductal obstruction by these protein plugs may cause premature activation of pancreatic enzymes. An alcohol binge in such patients can trigger pancreatitis, but the exact mechanism is not known.

A number of genetic mutations predisposing to pancreatitis have been identified. One, an autosomal dominant mutation of the cationic trypsinogen gene, causes pancreatitis in 80% of carriers; an obvious familial pattern is present. Other mutations have lesser penetrance and are not readily apparent clinically except through genetic testing. The genetic abnormality responsible for cystic fibrosis increases the risk of recurrent acute as well as chronic pancreatitis.

Regardless of the etiology, pancreatic enzymes (including trypsin, phospholipase A₂, and elastase) become activated within the gland itself. The enzymes can damage tissue and activate complement and the inflammatory cascade, producing cytokines. This process causes inflammation, edema, and sometimes necrosis. In mild pancreatitis, inflammation is confined to the pancreas; the mortality rate is < 5%. In severe pancreatitis, there is significant inflammation, with necrosis and hemorrhage of the gland and a systemic inflammatory response; the mortality rate is 10 to 50%. After 5 to 7 days, necrotic pancreatic tissue may become infected by enteric bacteria.

[Table 15-1. Some Causes of Acute Pancreatitis]

Activated enzymes and cytokines that enter the peritoneal cavity cause a chemical burn and third spacing of fluid; those that enter the systemic circulation cause a systemic inflammatory response that can result in acute respiratory distress syndrome and renal failure. The systemic effects are mainly the result of
increased capillary permeability and decreased vascular tone, which result from the released cytokines and chemokines. Phospholipase A\textsubscript{2} is thought to injure alveolar membranes of the lungs.

In about 40\% of patients, collections of enzyme-rich pancreatic fluid and tissue debris form in and around the pancreas. In about half, the collections resolve spontaneously. In others, the collections become infected or form pseudocysts. Pseudocysts have a fibrous capsule without an epithelial lining. Pseudocysts may hemorrhage, rupture, or become infected.

Death during the first several days is usually caused by cardiovascular instability (with refractory shock and renal failure) or respiratory failure (with hypoxemia and at times adult respiratory distress syndrome). Occasionally, death results from heart failure secondary to an unidentified myocardial depressant factor. Death after the first week is usually caused by multiorgan system failure.

Symptoms and Signs

An acute attack causes steady, boring upper abdominal pain, typically severe enough to require large doses of parenteral opioids. The pain radiates through to the back in about 50\% of patients; rarely, pain is first felt in the lower abdomen. Pain usually develops suddenly in gallstone pancreatitis; in alcoholic pancreatitis, pain develops over a few days. The pain usually persists for several days. Sitting up and leaning forward may reduce pain, but coughing, vigorous movement, and deep breathing may accentuate it. Nausea and vomiting are common.

The patient appears acutely ill and sweaty. Pulse rate is usually 100 to 140 beats/min. Respiration is shallow and rapid. BP may be transiently high or low, with significant postural hypotension. Temperature may be normal or even subnormal at first but may increase to 37.7 to 38.3°C (100 to 101°F) within a few hours. Sensorium may be blunted to the point of semiconscious. Scleral icterus is occasionally present. The lungs may have limited diaphragmatic excursion and evidence of atelectasis.

About 20\% of patients experience upper abdominal distention caused by gastric distention or displacement of the stomach by a pancreatic inflammatory mass. Pancreatic duct disruption may cause ascites (pancreatic ascites). Marked abdominal tenderness occurs, most often in the upper abdomen. There may be mild tenderness in the lower abdomen, but the rectum is not tender and the stool is usually negative for occult blood. Mild-to-moderate muscular rigidity may be present in the upper abdomen but is rare in the lower abdomen. Rarely, severe peritoneal irritation results in a rigid and boardlike abdomen. Bowel sounds may be hypoactive. Grey Turner's sign (ecchymoses of the flanks) and Cullen's sign (ecchymoses of the umbilical region) indicate extravasation of hemorrhagic exudate.

Infection in the pancreas or in an adjacent fluid collection should be suspected if the patient has a generally toxic appearance with elevated temperature and WBC count or if deterioration follows an initial period of stabilization.

Diagnosis

- Serum markers (amylase, lipase)
- Once pancreatitis is diagnosed, CT usually done

Pancreatitis is suspected whenever severe abdominal pain occurs, especially in a patient with significant alcohol use or known gallstones. Conditions causing similar symptoms include perforated gastric or duodenal ulcer, mesenteric infarction, strangulating intestinal obstruction, dissecting aneurysm, biliary colic, appendicitis, diverticulitis, inferior wall MI, and hematoma of the abdominal muscles or spleen.

Diagnosis is made by clinical suspicion, serum markers (amylase and lipase), and the absence of other causes for the patient's symptoms. Thus, a broad range of tests is done, typically including CBC, electrolytes, Ca, Mg, glucose, BUN, creatinine, amylase, and lipase. Other routine tests include ECG and an abdominal series (chest, flat, and upright abdomen). A urine dipstick for trypsinogen-2 has sensitivity and specificity of > 90\% for acute pancreatitis. Ultrasound and CT are not generally done specifically to diagnose pancreatitis but are often used to evaluate acute abdominal pain (see p.
Laboratory tests: Serum amylase and lipase concentrations increase on the first day of acute pancreatitis and return to normal in 3 to 7 days. Lipase is more specific for pancreatitis, but both enzymes may be increased in renal failure and various abdominal conditions (eg, perforated ulcer, mesenteric vascular occlusion, intestinal obstruction). Other causes of increased serum amylase include salivary gland dysfunction, macroamylasemia, and tumors that secrete amylase. Both amylase and lipase levels may remain normal if destruction of acinar tissue during previous episodes precludes release of sufficient amounts of enzymes. The serum of patients with hypertriglyceridemia may contain a circulating inhibitor that must be diluted before an elevation in serum amylase can be detected.

Amylase:creatinine clearance ratio does not have sufficient sensitivity or specificity to diagnose pancreatitis. It is generally used to diagnose macroamylasemia when no pancreatitis exists. In macroamylasemia, amylase bound to serum immunoglobulin falsely elevates the serum amylase level.

Fractionation of total serum amylase into pancreatic type (p-type) isoamylase and salivary-type (s-type) isoamylase increases the accuracy of serum amylase. However, the level of p-type also increases in renal failure and in other severe abdominal conditions in which amylase clearance is altered.

The WBC count usually increases to 12,000 to 20,000/μL. Third-space fluid losses may increase the Hct to as high as 50 to 55%, indicating severe inflammation. Hyperglycemia may occur. Serum Ca concentration falls as early as the first day because of the formation of Ca "soaps" secondary to excess generation of free fatty acids, especially by pancreatic lipase. Serum bilirubin increases in 15 to 25% of patients because pancreatic edema compresses the common bile duct.

Imaging: Plain x-rays of the abdomen may disclose calcifications within pancreatic ducts (evidence of prior inflammation and hence chronic pancreatitis), calcified gallstones, or localized ileus in the left upper quadrant or the center of the abdomen (a "sentinel loop" of small bowel, dilation of the transverse colon, or duodenal ileus). Chest x-ray may reveal atelectasis or a pleural effusion (usually left-sided or bilateral but rarely confined to the right pleural space).

Ultrasound should be done if gallstone pancreatitis is suspected (and another etiology is not obvious) to detect gallstones or dilation of the common bile duct (which indicates biliary tract obstruction). Edema of the pancreas may be visualized, but overlying gas frequently obscures the pancreas.

CT with IV contrast is generally done to identify necrosis, fluid collections, or pseudocysts once pancreatitis has been diagnosed. It is particularly recommended for severe pancreatitis or if a complication ensues (eg, hypotension or progressive leukocytosis and elevation of temperature). IV contrast facilitates the recognition of pancreatic necrosis; however, it may cause pancreatic necrosis in areas of low perfusion (ie, ischemia). Thus, contrast-enhanced CT should be done only after the patient has been adequately hydrated.

If pancreatic infection is suspected, fluid obtained by percutaneous CT-guided needle aspiration of cysts or areas of fluid collection or necrosis may reveal organisms on Gram stain or culture. The diagnosis is supported by positive blood cultures and, particularly, by the presence of air bubbles in the retroperitoneum on abdominal CT. The advent of magnetic resonance cholangiopancreatography (MRCP) may make the selection of pancreatic imaging simpler.

Prognosis

In edematous pancreatitis, mortality is < 5%. In pancreatitis with necrosis and hemorrhage, mortality is 10 to 50%. In pancreatic infection, mortality is usually 100% without extensive surgical debridement or drainage of the infected area.

CT findings correlate with prognosis. If CT is normal or shows only mild pancreatic edema (Balthazar class A or B), the prognosis is excellent. Patients with peripancreatic inflammation or one area of fluid collection (classes C and D) have a 10 to 15% incidence of abscess formation; the incidence is over 60% in patients with two or more areas of fluid collection (class E).
Ranson’s prognostic signs help predict the prognosis of acute pancreatitis. Five of Ranson's signs can be documented at admission:

- Age > 55 yr
- Plasma glucose > 200 mg/dL (> 11.1 mmol/L)
- Serum LDH > 350 IU/L
- AST > 250 UL
- WBC count > 16,000/μL

The rest of Ranson’s signs are determined within 48 h of admission:

- Hct decrease > 10%
- BUN increase > 5 mg/dL (> 1.78 mmol/L)
- Serum Ca < 8 mg/dL (< 2 mmol/L)
- Pao2 < 60 mm Hg (< 7.98 kPa)
- Base deficit > 4 mEq/L (> 4 mmol/L)
- Estimated fluid sequestration > 6 L

Mortality increases with the number of positive signs: If < 3 signs are positive, the mortality rate is < 5%; if ≥ 3 are positive, mortality is 15 to 20%.

The APACHE II index (see Table 222-4 on p. 2248), calculated on the second hospital day, also correlates with prognosis.

Treatment

- Fluid resuscitation
- Fasting
- Drugs, including adequate analgesia and acid blockers
- Antibiotics for pancreatic necrosis
- Drainage of infected pseudocysts or areas of necrosis

Adequate fluid resuscitation is essential; up to 6 to 8 L/day of fluid containing appropriate electrolytes may be required. Inadequate fluid therapy increases the risk of pancreatic necrosis.

Fasting is indicated until acute inflammation subsides (ie, cessation of abdominal tenderness and pain, normalization of serum amylase, return of appetite, feeling better). Fasting can last from a few days in mild pancreatitis to several weeks. TPN should be initiated in severe cases within the first few days to prevent undernutrition.

Pain relief requires parenteral opioids, which should be given in adequate doses. Although morphine may cause the sphincter of Oddi to contract, this is of doubtful clinical significance. Antiemetic agents (eg, prochlorperazine 5 to 10 mg IV q 6 h) should be given to alleviate vomiting. An NGT is required only if significant vomiting persists or ileus is present.
Parenteral H₂ blockers or proton pump inhibitors are given. Efforts to reduce pancreatic secretion with drugs (eg, anticholinergics, glucagon, somatostatin, octreotide) have no proven benefit.

Severe acute pancreatitis should be treated in an ICU, particularly in patients with hypotension, oliguria, Ranson's score ≥ 3, APACHE II ≥ 8, or pancreatic necrosis on CT > 30%. In the ICU, vital signs and urine output are monitored hourly; metabolic parameters (Hct, glucose, and electrolytes) are reassessed every 8 h; ABG is determined as needed; central venous pressure line or Swan-Ganz catheter measurements are determined every 6 h if the patient is hemodynamically unstable or if fluid requirements are unclear. CBC, platelet count, coagulation parameters, total protein with albumin, BUN, creatinine, Ca, and Mg are measured daily.

Hypoxemia is treated with humidified O₂ via mask or nasal prongs. If hypoxemia persists or adult respiratory distress syndrome develops, assisted ventilation may be required. Glucose > 170 to 200 mg/dL (9.4 to 11.1 mmol/L) should be treated cautiously with sc or IV insulin and carefully monitored. Hypocalcemia generally is not treated unless neuromuscular irritability occurs; 10 to 20 mL of 10% Ca gluconate in 1 L of IV fluid is given over 4 to 6 h. Chronic alcoholics and patients with documented hypomagnesemia should receive Mg sulfate 1 g/L of replacement fluid for a total of 2 to 4 g, or until levels normalize. If renal failure occurs, serum Mg levels are monitored and IV Mg is given cautiously. With restoration of normal Mg levels, serum Ca levels usually return to normal.

Heart failure should be treated (see p. 2126). Prerenal azotemia should be treated by increased fluid replacement. Renal failure may require dialysis (usually peritoneal).

Antibiotic prophylaxis with imipenem can prevent infection of sterile pancreatic necrosis, although the effect on reducing mortality is unclear. Infected areas of pancreatic necrosis require surgical debridement, but infected fluid collections outside the pancreas may be drained percutaneously. A pseudocyst that is expanding rapidly, infected, bleeding, or likely to rupture requires drainage. Whether drainage is percutaneous, surgical, or endoscopic depends on location of the pseudocyst and institutional expertise. Peritoneal lavage to wash out activated pancreatic enzymes and inflammatory mediators has no proven benefit.

Surgical intervention during the first several days is justified for severe blunt or penetrating trauma or uncontrolled biliary sepsis. Although > 80% of patients with gallstone pancreatitis pass the stone spontaneously, ERCP with sphincterotomy and stone removal is indicated for patients who do not improve after 24 h of treatment. Patients who spontaneously improve generally undergo elective laparoscopic cholecystectomy. Elective cholangiography remains controversial.

### Chronic Pancreatitis

Chronic pancreatitis is persistent inflammation of the pancreas that results in permanent structural damage with fibrosis and ductal strictures, followed by a decline in exocrine and endocrine function. It can occur as the result of chronic alcohol abuse but may be idiopathic. Initial symptoms are recurrent attacks of pain. Later in the disease, some patients develop malabsorption and glucose intolerance. Diagnosis is usually made by imaging studies such as ERCP, endoscopic ultrasound, or secretin pancreatic function testing. Treatment is supportive, with dietary modification, analgesics, and enzyme supplements. In some cases, surgical treatment is helpful.

#### Etiology

In the US, 70 to 80% of cases result from alcoholism, and 15 to 25% are idiopathic. However, recent data suggest that alcohol is becoming less of a cause. Less common causes include hereditary pancreatitis, hyperparathyroidism, and obstruction of the main pancreatic duct caused by stenosis, stones, or cancer. In India, Indonesia, and Nigeria, idiopathic calcific pancreatitis occurs among children and young adults (tropical pancreatitis).

#### Pathophysiology
Similar to acute pancreatitis, the mechanism of disease may be ductal obstruction by protein plugs. The protein plugs may result from excess secretion of glycoprotein-2 or a deficiency of lithostatin, a protein in pancreatic fluid that inhibits Ca precipitation. If obstruction is chronic, persistent inflammation leads to fibrosis and alternating areas of ductal dilatation and stricture, which may become calcified. Neuronal sheath hypertrophy and perineural inflammation occur and may contribute to chronic pain.

After several years, progressive fibrosis leads to loss of exocrine and endocrine function. Diabetes develops in 20 to 30% of patients within 10 to 15 yr of onset.

**Symptoms and Signs**

Most patients present with episodic abdominal pain. About 10 to 15% have no pain and present with malabsorption. Pain is epigastric, severe, and may last many hours or several days. Episodes typically subside spontaneously after 6 to 10 yr as the acinar cells that secrete pancreatic digestive enzymes are progressively destroyed. When lipase and protease secretions are reduced to < 10% of normal, the patient develops steatorrhea, passing greasy stools or even oil droplets, and creatorrhea (the presence of undigested muscle fibers in the feces). Symptoms of glucose intolerance may appear at this time.

**Diagnosis**

- Clinical suspicion
- Abdominal CT
- Sometimes magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography, or ERCP

Diagnosis can be difficult because amylase and lipase levels are frequently normal because of significant loss of pancreatic function. In a patient with a typical history of alcohol abuse and recurrent episodes of acute pancreatitis, detection of pancreatic calcification on plain x-ray of the abdomen may be sufficient. However, such calcifications typically occur late in the disease and then are visible in only about 30% of patients. In patients without a typical history, pancreatic cancer must be excluded as the cause of pain: abdominal CT is recommended. CT can show calcifications and other pancreatic abnormalities (eg, pseudocyst or dilated ducts) but still may be normal early in the disease.

The primary options for patients with normal CT findings include ERCP, endoscopic ultrasonography, and secretin pancreatic function testing. These tests are quite sensitive, but ERCP precipitates acute pancreatitis in about 5% of patients. MRCP may prove an acceptable alternative.

Late in the disease, tests of pancreatic exocrine function become abnormal. A 72-h test for stool fat is diagnostic for steatorrhea but cannot establish a cause. The secretin test collects pancreatic secretions via a duodenal tube for analysis but is done in only a few centers. Levels of serum trypsinogen and fecal chymotrypsin and elastase may be decreased. In the bentiromide test and the pancreolauryl test, substances are given orally, and urine is analyzed for cleavage products generated by pancreatic enzymes. All such exocrine tests are less sensitive than ERCP or endoscopic ultrasonography early in the disease.

**Treatment**

- IV fluids
- Fasting
- Drugs, including adequate analgesia and acid blockers
- Pancreatic enzyme supplements
Sometimes drainage of pseudocysts (surgical or endoscopic)

A relapse requires treatment similar to acute pancreatitis with fasting, IV fluids, and analgesics. When feeding resumes, the patient must eschew alcohol and consume a low-fat (< 25 g/day) diet (to reduce secretion of pancreatic enzymes). An H2 blocker or proton pump inhibitor may reduce acid-stimulated release of secretin, thereby decreasing the flow of pancreatic secretions. Too often, these measures do not relieve pain, requiring increased amounts of opioids, with the threat of addiction. Medical treatment of chronic pancreatic pain is often unsatisfactory.

Pancreatic enzyme supplementation may reduce chronic pain by inhibiting the release of cholecystokinin, thereby reducing the secretion of pancreatic enzymes. Supplementation is more likely to be successful in mild idiopathic pancreatitis than in alcoholic pancreatitis. Enzymes are also used to treat steatorrhea. Various preparations are available, and a dose providing at least 30,000 U of lipase should be used. Non-enteric coated tablets should be used, and they should be taken with meals. An H2 blocker or proton pump inhibitor should be given to prevent acid breakdown of the enzymes.

Favorable clinical responses include weight gain, fewer bowel movements, elimination of oil droplet seepage, and improved well-being. Clinical response can be documented by showing a decrease in stool fat after enzyme therapy. If steatorrhea is particularly severe and refractory to these measures, medium-chain triglycerides can be provided as a source of fat (they are absorbed without pancreatic enzymes), reducing other dietary fats proportionally. Supplementation with fat-soluble vitamins (A, D, K) should be given, including vitamin E, which may minimize inflammation.

Surgical treatment may be effective for pain relief. A pancreatic pseudocyst, which may cause chronic pain, can be decompressed into a nearby structure to which it firmly adheres (eg, the stomach) or into a defunctionalized loop of jejunum (via a Roux-en-Y cystojejunostomy). If the main pancreatic duct is dilated > 5 to 8 mm, a lateral pancreaticojejunostomy (Puestow procedure) relieves pain in about 70 to 80% of patients. If the duct is not dilated, a partial resection is similarly effective; either distal pancreatectomy (for extensive disease at the tail of the pancreas) or Whipple procedure (for extensive disease at the head of the pancreas) is done. Operative approaches should be reserved for patients who have stopped using alcohol and who can manage diabetes that may be intensified by pancreatic resection.

Some pseudocysts can be drained endoscopically. Endoscopic ultrasound-guided denervation of the celiac plexus with alcohol and bupivacaine may provide pain relief. If there is significant stricture at the papilla or distal pancreatic duct, ERCP with sphincterotomy, stent placement, or dilatation may be effective.

Oral hypoglycemic drugs rarely help treat diabetes caused by chronic pancreatitis. Insulin should be given cautiously because the coexisting deficiency of glucagon secretion by α-cells means that the hypoglycemic effects of insulin are unopposed and prolonged hypoglycemia may occur.

Patients are at increased risk of pancreatic cancer. Worsening of symptoms, especially with development of a pancreatic duct stricture, should prompt an evaluation for cancer. Evaluation may include brushing strictures for cytologic analysis or measuring serum markers (eg, CA 19-9, carcinoembryonic antigen).
Chapter 16. Gastroenteritis

Introduction

(See also Food Allergy on p. 1118 and Mushroom Poisoning on p. 3336.)

Gastroenteritis is inflammation of the lining of the stomach and small and large intestines. Most cases are infectious, although gastroenteritis may occur after ingestion of drugs and chemical toxins (eg, metals, plant substances). Symptoms include anorexia, nausea, vomiting, diarrhea, and abdominal discomfort. Diagnosis is clinical or by stool culture, although immunoassays are increasingly used. Treatment is symptomatic, although parasitic and some bacterial infections require specific anti-infective therapy.

Gastroenteritis is usually uncomfortable but self-limited. Electrolyte and fluid loss is usually little more than an inconvenience to an otherwise healthy adult but can be grave for people who are very young (see p. 2806), elderly, or debilitated or who have serious concomitant illnesses. Worldwide, an estimated 3 to 6 million children die each year from infectious gastroenteritis.

Etiology

Infectious gastroenteritis may be caused by viruses, bacteria, or parasites. Many specific organisms are discussed further in the Infectious Diseases section.

Viruses: The viruses most commonly implicated are

- Rotavirus
- Norovirus

Viruses are the most common cause of gastroenteritis in the US. They infect enterocytes in the villous epithelium of the small bowel. The result is transudation of fluid and salts into the intestinal lumen; sometimes, malabsorption of carbohydrates worsens symptoms by causing osmotic diarrhea. Diarrhea is watery. Inflammatory diarrhea (dysentery), with fecal WBCs and RBCs or gross blood, is uncommon. Four categories of viruses cause most gastroenteritis: rotavirus and calicivirus (predominantly the norovirus [formerly Norwalk virus]) cause the majority of viral gastroenteritis, followed by astrovirus and enteric adenovirus.

Rotavirus is the most common cause of sporadic, severe, dehydrating diarrhea in young children (peak incidence, 3 to 15 mo). Rotavirus is highly contagious; most infections occur by the fecal-oral route. Adults may be infected after close contact with an infected infant. The illness in adults is generally mild. Incubation is 1 to 3 days. In temperate climates, most infections occur in the winter. Each year in the US, a wave of rotavirus illness begins in the Southwest in November and ends in the Northeast in March.

Norovirus most commonly infects older children and adults. Infections occur year-round. Norovirus is the principal cause of sporadic viral gastroenteritis in adults and of epidemic viral gastroenteritis in all age groups; large waterborne and food-borne outbreaks occur. Person-to-person transmission also occurs because the virus is highly contagious. Incubation is 24 to 48 h.

Astrovirus can infect people of all ages but usually infects infants and young children. Infection is most common in winter. Transmission is by the fecal-oral route. Incubation is 3 to 4 days.

Adenoviruses are the 4th most common cause of childhood viral gastroenteritis. Infections occur year-round, with a slight increase in summer. Children < 2 yr are primarily affected. Transmission is by the fecal-oral route. Incubation is 3 to 10 days.

In immunocompromised patients, additional viruses (eg, cytomegalovirus, enterovirus) can cause gastroenteritis.
**Bacteria:** The bacteria most commonly implicated are

- *Salmonella*
- *Campylobacter*
- *Shigella*
- *Escherichia coli* (especially serotype O157:H7)

Bacterial gastroenteritis is less common than viral. Bacteria cause gastroenteritis by several mechanisms. Certain species (eg, *Vibrio cholerae*, enterotoxigenic strains of *E. coli*) adhere to intestinal mucosa without invading and produce enterotoxins. These toxins impair intestinal absorption and cause secretion of electrolytes and water by stimulating adenylate cyclase, resulting in watery diarrhea. *Clostridium difficile* produces a similar toxin when overgrowth follows antibiotic use (see p. 1292).

Some bacteria (eg, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*) produce an exotoxin that is ingested in contaminated food. The exotoxin can cause gastroenteritis without bacterial infection. These toxins generally cause acute nausea, vomiting, and diarrhea within 12 h of ingestion of contaminated food. Symptoms abate within 36 h.

Other bacteria (eg, *Shigella*, *Salmonella*, *Campylobacter*, some *E. coli* subtypes) invade the mucosa of the small bowel or colon and cause microscopic ulceration, bleeding, exudation of protein-rich fluid, and secretion of electrolytes and water. The invasive process and its results can occur whether or not the organism produces an enterotoxin. The resulting diarrhea contains WBCs and RBCs and sometimes gross blood.

*Salmonella* and *Campylobacter* are the most common bacterial causes of diarrheal illness in the US. Both infections are most frequently acquired through undercooked poultry; unpasteurized milk is also a possible source. *Campylobacter* is occasionally transmitted from dogs or cats with diarrhea. *Salmonella* can be transmitted by undercooked eggs and by contact with reptiles. Species of *Shigella* are the 3rd most common bacterial cause of diarrhea in the US and are usually transmitted person to person, although food-borne epidemics occur. *Shigella dysenteriae* type 1 (not present in the US) produces Shiga toxin, which can cause hemolytic-uremic syndrome (see p. 961).

Several different subtypes of *E. coli* cause diarrhea. The epidemiology and clinical manifestations vary greatly depending on the subtype: (1) Enterohemorrhagic *E. coli* is the most clinically significant subtype in the US. It produces Shiga toxin, which causes bloody diarrhea (hemorrhagic colitis). *E. coli* O157:H7 is the most common strain of this subtype in the US. Undercooked ground beef, unpasteurized milk and juice, and contaminated water are possible sources. Person-to-person transmission is common in the day care setting. Hemolytic-uremic syndrome is a serious complication that develops in 2 to 7% of cases, most commonly among the young and old. (2) Enterotoxigenic *E. coli* produces two toxins (one similar to cholera toxin) that cause watery diarrhea. This subtype is the most common cause of traveler's diarrhea. (3) Enteropathogenic *E. coli* causes watery diarrhea. Once a common cause of diarrhea outbreaks in nurseries, this subtype is now rare. (4) Enteroinvasive *E. coli* causes bloody or nonbloody diarrhea, primarily in the developing world. It is rare in the US.

Several other bacteria cause gastroenteritis, but most are uncommon in the US. *Yersinia enterocolitica* can cause gastroenteritis or a syndrome that mimics appendicitis. It is transmitted by undercooked pork, unpasteurized milk, or contaminated water. Several *Vibrio* species (eg, *V. parahaemolyticus*) cause diarrhea after ingestion of undercooked seafood. *V. cholerae* sometimes causes severe dehydrating diarrhea in the developing world. *Listeria* causes food-borne gastroenteritis. *Aeromonas* is acquired from swimming in or drinking contaminated fresh or brackish water. *Plesiomonas shigelloides* can cause diarrhea in patients who have eaten raw shellfish or traveled to tropical regions of the developing world.

**Parasites:** The parasites most commonly implicated are
Certain intestinal parasites, notably *Giardia intestinalis* (*lamblia*—see p. 1371), adhere to or invade the intestinal mucosa, causing nausea, vomiting, diarrhea, and general malaise. Giardiasis occurs in every region of the US and throughout the world. The infection can become chronic and cause a malabsorption syndrome. It is usually acquired via person-to-person transmission (often in day care centers) or from contaminated water.

*Cryptosporidium parvum* causes watery diarrhea sometimes accompanied by abdominal cramps, nausea, and vomiting. In healthy people, the illness is self-limited, lasting about 2 wk. In immunocompromised patients, illness may be severe, causing substantial electrolyte and fluid loss. *Cryptosporidium* is usually acquired through contaminated water.

Other parasites that can cause symptoms similar to those of cryptosporidiosis include *Cyclospora cayetanensis* and, in immunocompromised patients, *Cystoisospora* (*Isospora*) *belli*, and a collection of organisms referred to as microsporidia (eg, *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis*). *Entamoeba histolytica* (amebiasis) is a common cause of subacute bloody diarrhea in the developing world and occasionally occurs in the US.

### Symptoms and Signs

The character and severity of symptoms vary. Generally, onset is sudden, with anorexia, nausea, vomiting, borborygmi, abdominal cramps, and diarrhea (with or without blood and mucus). Malaise, myalgias, and prostration may occur. The abdomen may be distended and mildly tender; in severe cases, muscle guarding may be present. Gas-distended intestinal loops may be palpable. Borborygmi are present even without diarrhea (an important differential feature from paralytic ileus). Persistent vomiting and diarrhea can result in intravascular fluid depletion with hypotension and tachycardia. In severe cases, shock, with vascular collapse and oliguric renal failure, occurs.

If vomiting is the main cause of fluid loss, metabolic alkalosis with hypochloremia can occur. If diarrhea is more prominent, acidosis is more likely. Both vomiting and diarrhea can cause hypokalemia. Hyponatremia may develop, particularly if hypotonic fluids are used in replacement therapy.

In viral infections, watery diarrhea is the most common symptom; stools rarely contain mucus or blood. Rotavirus gastroenteritis in infants and young children may last 5 to 7 days. Vomiting occurs in 90% of patients, and fever > 39° C (> 102.2° F) occurs in about 30%. Norovirus typically causes acute onset of vomiting, abdominal cramps, and diarrhea, with symptoms lasting only 1 to 2 days. In children, vomiting is more prominent than diarrhea, whereas in adults, diarrhea usually predominates. Patients may also experience fever, headache, and myalgias. The hallmark of adenovirus gastroenteritis is diarrhea lasting 1 to 2 wk. Affected infants and children may have mild vomiting that typically starts 1 to 2 days after the onset of diarrhea. Low-grade fever occurs in about 50% of patients. Astrovirus causes a syndrome similar to mild rotavirus infection.

Bacteria that cause invasive disease (eg, *Shigella*, *Salmonella*) are more likely to result in fever, prostration, and bloody diarrhea. Bacteria that produce an enterotoxin (eg, *S. aureus*, *B. cereus*, *C. perfringens*) usually cause watery diarrhea.

Parasitic infections typically cause subacute or chronic diarrhea. Most cause nonbloody diarrhea; an exception is *E. histolytica*, which causes amebic dysentery. Fatigue and weight loss are common when diarrhea is persistent.

### Diagnosis

- Clinical evaluation
• Stool testing in select cases

Other GI disorders that cause similar symptoms (eg, appendicitis, cholecystitis, ulcerative colitis) must be excluded. Findings suggestive of gastroenteritis include copious, watery diarrhea; ingestion of potentially contaminated food (particularly during a known outbreak), untreated surface water, or a known GI irritant; recent travel; or contact with similarly ill people. *E. coli* O157:H7-induced diarrhea is notorious for appearing to be a hemorrhagic rather than an infectious process, manifesting as GI bleeding with little or no stool. Hemolyticuremic syndrome may follow as evidenced by renal failure and hemolytic anemia (see p. 961). Recent oral antibiotic use (within 3 mo) must raise suspicion for *C. difficile* infection (see p. 1292).

**Stool testing:** If a rectal examination shows occult blood or if watery diarrhea persists > 48 h, stool examination (fecal WBCs, ova, parasites) and culture are indicated. However, for the diagnosis of giardiasis or cryptosporidiosis, stool antigen detection using an enzyme immunoassay has a higher sensitivity. Rotavirus and enteric adenovirus infections can be diagnosed using commercially available rapid assays that detect viral antigen in the stool, but these are usually done only to document an outbreak.

All patients with grossly bloody diarrhea should be tested for *E. coli* O157:H7, as should patients with nonbloody diarrhea during a known outbreak. Specific cultures must be requested because this organism is not detected on standard stool culture media. Alternatively, a rapid enzyme assay for the detection of Shiga toxin in stool can be done; a positive test indicates infection with *E. coli* O157:H7 or one of the other serotypes of enterohemorrhagic *E. coli*. (NOTE: *Shigella* species in the US do not produce Shiga toxin.)

Adults with grossly bloody diarrhea should usually have sigmoidoscopy with cultures and biopsy. Appearance of the colonic mucosa may help diagnose amebic dysentery, shigellosis, and *E. coli* O157:H7 infection, although ulcerative colitis may cause similar lesions. Patients with recent antibiotic use should have a stool assay for *C. difficile* toxin.

**General tests:** Serum electrolytes, BUN, and creatinine should be obtained to evaluate hydration and acid-base status in patients who appear seriously ill. CBC is nonspecific, although eosinophilia may indicate parasitic infection.

**Treatment**

• Oral or IV rehydration

• Consideration of antidiarrheal agents if there is no suspicion of *C. difficile* or *E. coli* O157:H7 infection

• Antibiotics only in select cases

Supportive treatment is all that is needed for most patients. Bed rest with convenient access to a toilet or bedpan is desirable. Oral glucose-electrolyte solutions, broth, or bouillon may prevent dehydration or treat mild dehydration. Even if vomiting, the patient should take frequent small sips of such fluids: vomiting may abate with volume replacement. For patients with *E. coli* O157:H7 infection, rehydration with isotonic IV fluids may attenuate the severity of any renal injury should hemolytic-uremic syndrome develop. Children may become dehydrated more quickly and should be given an appropriate rehydration solution (several are available commercially—see also p. 2809). Carbonated beverages and sports drinks lack the correct ratio of glucose to Na and thus are not appropriate for children < 5 yr. If the child is breastfed, breastfeeding should continue. If vomiting is protracted or if severe dehydration is prominent, IV replacement of volume and electrolytes is necessary (see p. 2297).

When the patient can tolerate fluids without vomiting and the appetite has begun to return, food may be gradually restarted. There is no demonstrated benefit from restriction to bland food (eg, cereal, gelatin, bananas, toast). Some patients have temporary lactose intolerance.
Antidiarrheal agents are safe for patients > 5 yr with watery diarrhea (as shown by heme-negative stool). However, antidiarrheals may cause deterioration of patients with *C. difficile* or *E. coli* O157:H7 infection and thus should not be given to any patient with recent antibiotic use or heme-positive stool, pending specific diagnosis. Effective antidiarrheals include loperamide 4 mg po initially, followed by 2 mg po for each subsequent episode of diarrhea (maximum of 6 doses/day or 16 mg/day), or diphenoxylate 2.5 to 5 mg tid or qid in tablet or liquid form.

If vomiting is severe and a surgical condition has been excluded, an antiemetic may be beneficial. Agents useful in adults include prochlorperazine 5 to 10 mg IV tid or qid, or 25 mg per rectum bid; and promethazine 12.5 to 25 mg IM tid or qid, or 25 to 50 mg per rectum qid. These drugs are usually avoided in children because of lack of demonstrated efficacy and the high incidence of dystonic reactions.

**Antimicrobials:** Empiric antibiotics are generally not recommended except for certain cases of traveler’s diarrhea or when suspicion of *Shigella* or *Campylobacter* infection is high (eg, contact with a known case). Otherwise, antibiotics should not be given until stool culture results are known, particularly in children, who have a higher rate of infection with *E. coli* O157:H7 (antibiotics increase the risk of hemolytic-uremic syndrome in patients infected with *E. coli* O157:H7).

In proven bacterial gastroenteritis, antibiotics are not always required. They do not help with *Salmonella* and prolong the duration of shedding in the stool. Exceptions include immunocompromised patients, neonates, and patients with *Salmonella* bacteremia. Antibiotics are also ineffective against toxic gastroenteritis (eg, *S. aureus*, *B. cereus*, *C. perfringens*). Indiscriminate use of antibiotics fosters the emergence of drug-resistant organisms. However, certain infections do require antibiotics (see Table 16-1).

The use of probiotics, such as lactobacillus, is generally safe and may have some benefit in relieving symptoms. They can be given in the form of yogurt with active cultures.

**Table 16-1.** Selected Oral Antibiotics for Infectious Gastroenteritis*

For cryptosporidiosis, nitazoxanide may be helpful in immunocompetent patients. The dose is 100 mg po bid for children 1 to 3 yr, 200 mg po bid for children 4 to 11 yr, and 500 mg po bid for children ≥ 12 yr and adults.

**Prevention**

A new oral pentavalent rotavirus vaccine is available that is safe and effective against the majority of strains responsible for disease. This vaccine is now part of the recommended infant vaccination schedule and is given at 2, 4, and 6 mo of age (see p. 2718).

Prevention of infection is complicated by the frequency of asymptomatic infection and the ease with which many agents, particularly viruses, are transmitted from person to person. In general, proper procedures for handling and preparing food must be followed. Travelers must avoid potentially contaminated food and drink.

Breastfeeding affords some protection to neonates and infants. Caregivers should wash their hands thoroughly with soap and water after changing diapers, and diaper-changing areas should be disinfected with a freshly prepared solution of 1:64 household bleach (one fourth cup diluted in 1 gallon of water). Children with diarrhea should be excluded from child care facilities for the duration of symptoms. Children infected with enterohemorrhagic *E. coli* or *Shigella* should also have two negative stool cultures before readmission to the facility.

**Traveler's Diarrhea**

(Turista)

**Traveler's diarrhea is gastroenteritis that is usually caused by bacteria endemic to local water.**
Symptoms include vomiting and diarrhea. Diagnosis is mainly clinical. Treatment is with ciprofloxacin or azithromycin, loperamide, and replacement fluids.

**Etiology**

Traveler's diarrhea may be caused by any of several bacteria, viruses, or, less commonly, parasites. However, enterotoxigenic *Escherichia coli* is most common. *E. coli* is common in the water supplies of areas that lack adequate purification. Infection is common among people traveling to developing countries. Norovirus infection has been a particular problem on some cruise ships.

Both food and water can be the source of infection. Travelers who avoid drinking local water may still become infected by brushing their teeth with an improperly rinsed toothbrush, drinking bottled drinks with ice made from local water, or eating food that is improperly handled or washed with local water. People taking drugs that decrease stomach acid (antacids, H₂ blockers, and proton pump inhibitors) are at risk of more severe illness.

**Symptoms and Signs**

Nausea, vomiting, borborygmi, abdominal cramps, and diarrhea begin 12 to 72 h after ingesting contaminated food or water. Severity is variable. Some people develop fever and myalgias. Most cases are mild and self-limited, although dehydration can occur, especially in warm climates.

**Diagnosis**

- Clinical evaluation

Specific diagnostic measures are usually not necessary. However, fever, severe abdominal pain, and bloody diarrhea suggest more serious disease and should prompt immediate evaluation.

**Treatment**

- Fluid replacement
- Sometimes antimotility drugs
- Rarely antibiotics (e.g., ciprofloxacin, azithromycin)

The mainstay of treatment is fluid replacement and an antimotility drug such as loperamide 4 mg po initially, followed by 2 mg po for each subsequent episode of diarrhea (maximum of 6 doses/day or 16 mg/day), or diphenoxylate 2.5 to 5 mg po tid or qid in tablet or liquid form. Antimotility drugs are contraindicated in patients with fever or bloody stools and in children < 2 yr. Iodochlorhydroxyquin, which may be available in some developing countries, should not be used because it may cause neurologic damage.

Generally, antibiotics are not necessary for mild diarrhea. In patients with moderate to severe diarrhea (≥ 3 loose stools over 8 h), antibiotics are given, especially if vomiting, abdominal cramps, fever, or bloody stools are present. For adults, ciprofloxacin 500 mg po bid for 3 days or levofloxacin 500 mg po once/day for 3 days is recommended. Azithromycin 250 mg po once/day for 3 days or rifaximin 200 mg po tid for 3 days may also be used. For children, azithromycin 5 to 10 mg/kg po once/day for 3 days is preferred.

**Prevention**

Travelers should dine at restaurants with a reputation for safety and avoid foods and beverages from street vendors. They should consume only cooked foods that are still steaming hot, fruit that can be peeled, and carbonated beverages without ice served in sealed bottles (bottles of noncarbonated beverages can contain tap water added by unscrupulous vendors); uncooked vegetables should be avoided. Buffets and fast food restaurants pose an increased risk.
Prophylactic antibiotics are effective in preventing diarrhea, but because of concerns about adverse effects and development of resistance, they should probably be reserved for immunocompromised patients.

Drug- and Chemical-Related Gastroenteritis

Many drugs cause nausea, vomiting, and diarrhea as adverse effects. A detailed drug history must be obtained. In mild cases, cessation followed by reuse of the drug may establish a causal relationship. Commonly responsible drugs include antacids containing Mg, antibiotics, antihelminthics, cytotoxics (used in cancer therapy), colchicine, digoxin, heavy metals, laxatives, and radiation therapy. Use of antibiotics may lead to Clostridium difficile-induced diarrhea (see p. 1292).

Iatrogenic, accidental, or intentional heavy-metal poisoning frequently causes nausea, vomiting, abdominal pain, and diarrhea.

Laxative abuse, sometimes denied by patients, may lead to weakness, vomiting, diarrhea, electrolyte depletion, and metabolic disturbances.

Various plants and mushrooms cause a syndrome of gastroenteritis (see p. 3336).
Chapter 17. Malabsorption Syndromes

Introduction

Malabsorption is inadequate assimilation of dietary substances due to defects in digestion, absorption, or transport. Malabsorption can affect macronutrients (eg, proteins, carbohydrates, fats), micronutrients (eg, vitamins, minerals), or both, causing excessive fecal excretion, nutritional deficiencies, and GI symptoms.

Pathophysiology

Digestion and absorption occur in three phases: (1) intraluminal hydrolysis of fats, proteins, and carbohydrates by enzymes—bile salts enhance the solubilization of fat in this phase; (2) digestion by brush border enzymes and uptake of end-products; and (3) lymphatic transport of nutrients. Malabsorption occurs when any of these phases is impaired.

Fats: Pancreatic enzymes split long-chain triglycerides into fatty acids and monoglycerides, which combine with bile acids and phospholipids to form micelles that pass through jejunal enterocytes. Absorbed fatty acids are resynthesized and combined with protein, cholesterol, and phospholipid to form chylomicrons, which are transported by the lymphatic system. Medium-chain triglycerides are absorbed directly.

Unabsorbed fats trap fat-soluble vitamins (A, D, E, K) and possibly some minerals, causing deficiency. Bacterial overgrowth results in deconjugation and dehydroxylation of bile salts, limiting the absorption of fats. Unabsorbed bile salts stimulate the colon, causing diarrhea.

Carbohydrates: Enzymes on microvilli lyse carbohydrates and disaccharides into constituent monosaccharides. Colonic bacteria ferment unabsorbed carbohydrates into CO₂, methane, H₂, and short-chain fatty acids (butyrate, propionate, acetate, and lactate). These fatty acids cause diarrhea. The gases cause abdominal distention and bloating.

Proteins: Enterokinase, a brush border enzyme, activates trypsinogen into trypsin, which converts many pancreatic proteases into their active forms. Active pancreatic enzymes hydrolyze proteins into oligopeptides, which are absorbed directly or hydrolyzed into amino acids.

Etiology

Malabsorption has many causes (see Table 17-1). Some malabsorptive disorders (eg, celiac sprue) impair the absorption of most nutrients, vitamins, and trace minerals (global malabsorption); others (eg, pernicious anemia) are more selective.

Table 17-1. Causes of Malabsorption

PANCREATIC INSUFFICIENCY

Pancreatic insufficiency causes malabsorption if > 90% of function is lost. Increased luminal acidity (eg, Zollinger-Ellison syndrome) inhibits lipase and fat digestion. Cirrhosis and cholestasis reduce hepatic bile synthesis or delivery of bile salts to the duodenum, causing malabsorption. Other causes are discussed elsewhere in this chapter.

Symptoms and Signs

The effects of unabsorbed substances include diarrhea, steatorrhea, abdominal bloating, and gas. Other symptoms result from nutritional deficiencies. Patients often lose weight despite adequate food intake.

Chronic diarrhea is the most common symptom and is what usually prompts evaluation of the patient. Steatorrhea—fatty stool, the hallmark of malabsorption—occurs when > 7 g/day of fat are excreted. Steatorrhea causes foul-smelling, pale, bulky, and greasy stools.

Severe vitamin and mineral deficiencies occur in advanced malabsorption; symptoms are related to the
specific nutrient deficiency (see Table 17-2). Vitamin B₁₂ deficiency may occur in blind loop syndrome or after extensive resection of the distal ileum or stomach.

Amenorrhea may result from undernutrition and is an important manifestation of celiac sprue in young women.

Diagnosis

• Diagnosis typically clinically apparent

• Blood tests to screen for consequences of malabsorption

• Stool fat testing to confirm malabsorption (if unclear)

• Cause diagnosed with endoscopy, contrast x-rays, or other tests based on findings

Malabsorption is suspected in a patient with chronic diarrhea, weight loss, and anemia. The etiology is sometimes obvious. For example, those with malabsorption due to chronic pancreatitis usually have had prior bouts of acute pancreatitis. Patients with celiac sprue can present with classic lifelong diarrhea exacerbated by gluten products and may have dermatitis herpetiformis. Those with cirrhosis and pancreatic cancer can present with jaundice. Abdominal distention, excessive flatus, and watery diarrhea occurring 30 to 90 min after carbohydrate ingestion suggest deficiency of a disaccharidase enzyme, usually lactase. Previous extensive abdominal operations suggest short bowel syndrome.

If the history suggests a specific cause, testing should be directed to that condition (see Fig. 17-1). If no cause is readily apparent, blood tests can be used as screening tools (e.g., CBC, RBC indices, ferritin, vitamin B₁₂, folate, Ca, albumin, cholesterol, PT). These results may suggest a diagnosis and direct further investigation.

Macrocytic anemia should prompt measurement of serum folate and B₁₂ levels. Folate deficiency is common in mucosal disorders involving the proximal small bowel (e.g., celiac sprue, tropical sprue, Whipple's disease). Low B₁₂ levels can occur in pernicious anemia, chronic pancreatitis, bacterial overgrowth, and terminal ileal disease. A combination of low B₁₂ and high folate levels is suggestive of bacterial overgrowth, because intestinal bacteria use vitamin B₁₂ and synthesize folate.

Microcytic anemia suggests iron deficiency, which may occur with celiac sprue. Albumin is a general indicator of nutritional state. Low albumin can result from poor intake, decreased synthesis in cirrhosis, or protein wasting. Low serum carotene (a precursor of vitamin A) suggests malabsorption if intake is adequate.

Confirming malabsorption: Tests to confirm malabsorption are appropriate when symptoms are vague and the etiology is not apparent. Most tests for malabsorption assess fat malabsorption because it is relatively easy to measure. Confirmation of carbohydrate malabsorption is not helpful once steatorrhea is documented. Tests for protein malabsorption are rarely used because fecal nitrogen is difficult to measure.

Direct measurement of fecal fat from a 72-h stool collection is the gold standard for establishing steatorrhea but unnecessary with gross steatorrhea of obvious cause. However, this test is available routinely in only a few centers. Stool is collected for a 3-day period during which the patient consumes ≥
100 g fat/day. Total fat in the stool is measured. Fecal fat > 7 g/day is abnormal. Although severe fat malabsorption (fecal fat ≥ 40 g/day) suggests pancreatic insufficiency or small-bowel mucosal disease, this test cannot determine the specific cause of malabsorption. Because the test is messy, unpleasant, and time consuming, it is unacceptable to most patients and difficult to do.

Sudan III staining of a stool smear is a simple and direct, but nonquantitative, screening test for fecal fat. Acid steatocrit is a gravimetric assay done on a single stool sample; it has a reported high sensitivity and specificity (using 72-h collection as the standard). Near-infrared reflectance analysis (NIRA) simultaneously tests stool for fat, nitrogen, and carbohydrates and may become the preferred test in the future.

Measurement of elastase and chymotrypsin in the stool can also help differentiate pancreatic and intestinal causes of malabsorption; both are decreased in pancreatic exocrine insufficiency.

The D-xylose absorption test, if available, can be done if the etiology is not obvious. It is the best noninvasive test to assess intestinal mucosal integrity and differentiate mucosal from pancreatic disease. This test has a reported specificity of 98% and sensitivity of 91% for small-bowel malabsorption.

D-Xylose is absorbed by passive diffusion and does not require pancreatic enzymes for digestion. A normal D-xylose test in the presence of moderate to severe steatorrhea indicates pancreatic exocrine insufficiency rather than small-bowel mucosal disease. Bacterial overgrowth syndrome can cause abnormal results because the enteric bacteria metabolize pentose, thus decreasing the D-xylose available for absorption.

After fasting, the patient is given 25 g of D-xylose in 200 to 300 mL of water po. Urine is collected over 5 h, and a venous sample is obtained after 1 h. Serum D-xylose < 20 mg/dL or < 4 g in the urine sample indicates abnormal absorption. Falsely low levels can also occur in renal diseases, portal hypertension, ascites, or delayed gastric emptying time. This test is rarely used today. In addition, an abnormal D-xylose test will require an endoscopic examination with biopsies of the small-bowel mucosa. As a result, small-bowel biopsy has replaced this test to establish intestinal mucosal disease.

**Diagnosing the cause of malabsorption:** More specific diagnostic tests (eg, upper endoscopy, colonoscopy, barium x-rays) are indicated to diagnose several causes of malabsorption.

Endoscopy with small-bowel biopsy is done when mucosal disease of the small bowel is suspected or if the D-xylose test is abnormal in a patient with massive steatorrhea. Aspirate from the small bowel can be sent for bacterial culture and colony count to document bacterial overgrowth. Histologic features on small-bowel biopsy (see Table 17-3) can establish the specific mucosal disease.

Small-bowel x-rays (eg, small-bowel follow-through, enteroclysis) can detect anatomic conditions that predispose to bacterial overgrowth. These include jejunal diverticula, fistulas, surgically created blind loops and anastomoses, ulcerations, and strictures. Abdominal flat plate x-ray may show pancreatic calcifications indicative of chronic pancreatitis. Barium contrast studies of the small bowel are neither sensitive nor specific but may have findings suggestive of mucosal disease (eg, dilated small-bowel loops, thinned or thickened mucosal folds, coarse fragmentation of the barium column).

Tests for pancreatic insufficiency (eg, secretin stimulation test, bentiromide test, pancreolauryl test, serum trypsinogen, fecal elastase, fecal chymotrypsin—see p. 145) are done if history is suggestive but are not sensitive for mild pancreatic disease.

The $^{14}$C-xylose breath test helps diagnose bacterial overgrowth. $^{14}$C-xylose is given orally, and the exhaled $^{14}$CO$_2$ concentration is measured. Catabolism of ingested xylose by the overgrowth flora causes $^{14}$CO$_2$ to appear in exhaled breath.

The H$_2$ breath test measures the exhaled H$_2$ produced by the bacterial degradation of carbohydrates. In patients with disaccharidase deficiencies, enteric bacteria degrade nonabsorbed carbohydrates in the
colon, increasing exhaled H₂. The lactose-H₂ breath test is useful only to confirm lactase deficiency (see p. 158) and is not used as an initial diagnostic test in the work-up of malabsorption.

The Schilling test assesses malabsorption of vitamin B₁₂. Its 4 stages determine whether the deficiency results from pernicious anemia, pancreatic exocrine insufficiency, bacterial overgrowth, or ileal disease.

• Stage 1: The patient is given 1 μg of radiolabeled cyanocobalamin po concurrent with 1000 μg of nonlabeled cobalamin IM to saturate hepatic binding sites. A 24-h urine collection is analyzed for radioactivity; urinary excretion of < 8% of the oral dose indicates malabsorption of cobalamin.

• Stage 2: If stage 1 is abnormal, the test is repeated with the addition of intrinsic factor. Pernicious anemia is present if this normalizes absorption.

• Stage 3: Stage 3 is done after adding pancreatic enzymes; normalization in this stage indicates cobalamin malabsorption secondary to pancreatic insufficiency.

• Stage 4: Stage 4 is done after antimicrobial therapy with anaerobic coverage; normalization after antibiotics suggests bacterial overgrowth.

Cobalamin deficiency secondary to ileal disease or ileal resection results in abnormalities in all stages.

Tests for less common causes of malabsorption include serum gastrin (Zollinger-Ellison syndrome), intrinsic factor and parietal cell antibodies (pernicious anemia), sweat chloride (cystic fibrosis), lipoprotein electrophoresis (abetalipoproteinemia), and serum cortisol (Addison’s disease).

**Bacterial Overgrowth Syndrome**

Small-bowel bacterial overgrowth can occur from alterations in intestinal anatomy or GI motility, or lack of gastric acid secretion. This condition can lead to vitamin deficiencies, fat malabsorption, and undernutrition. Diagnosis is by breath test or quantitative culture of intestinal fluid aspirate. Treatment is with oral antibiotics.

Under normal conditions, the proximal small bowel contains < 10⁵ bacteria/mL, mainly gram-positive aerobic bacteria. This low bacterial count is maintained by normal peristalsis, normal gastric acid secretion, mucus, secretory IgA, and an intact ileocecal valve.

**Etiology**

Usually, bacterial overgrowth occurs when anatomic alterations promote stasis of intestinal contents. These conditions include small-bowel diverticulosis, surgical blind loops, postgastrectomy states (especially in the afferent loop of a Billroth II), strictures, or partial obstruction. Intestinal motility disorders associated with diabetic neuropathy, systemic sclerosis, amyloidosis, and idiopathic intestinal pseudo-obstruction can also impair bacterial clearance. Achlorhydria and idiopathic changes in intestinal motility may cause bacterial overgrowth in elderly people.

**Pathophysiology**

The excess bacteria consume nutrients, including vitamin B₁₂ and carbohydrates, leading to caloric deprivation and vitamin B₁₂ deficiency. However, because the bacteria produce folate, this deficiency is rare. The bacteria deconjugate bile salts, causing failure of micelle formation and subsequent fat malabsorption. Severe bacterial overgrowth also damages the intestinal mucosa. Fat malabsorption and mucosal damage can cause diarrhea.

**Symptoms and Signs**

Many patients are asymptomatic and present with only weight loss or nutrient deficiencies. Some have significant diarrhea or steatorrhea.
Diagnosis

- $^{14}\text{C}$-xylose breath test or quantitative culture of intestinal aspirate

- Upper GI series with small-bowel follow-through

Some clinicians advocate response to empiric antibiotic therapy as a diagnostic test. However, because bacterial overgrowth can mimic other malabsorptive disorders (eg, Crohn's disease) and adverse effects of the antibiotics can worsen symptoms, establishing a definitive etiology is preferred.

The standard for diagnosis is quantitative culture of intestinal fluid aspirate showing bacterial count $>10^5$/mL. This method, however, requires endoscopy. Breath tests, using substrates like glucose, lactulose, and xylose, are noninvasive and easy to do. The $^{14}\text{C}$-xylose breath test seems to perform better than the other breath tests. In addition, an upper GI series with small-bowel follow-through should be done to identify predisposing anatomic lesions.

Treatment

- Oral antibiotics (various)

Treatment is with 10 to 14 days of oral antibiotics. Empiric regimens include tetracycline 250 mg qid, amoxicillin/clavulanic acid 250 to 500 mg tid, cephalexin 250 mg qid, trimethoprim/sulfamethoxazole 160/800 mg bid, and metronidazole 250 to 500 mg tid or qid. Antibiotics should be changed based on culture and sensitivity results. Underlying conditions and nutritional deficiencies (eg, vitamin B$_12$) should be corrected.

Carbohydrate Intolerance

Carbohydrate intolerance is the inability to digest certain carbohydrates due to a lack of one or more intestinal enzymes. Symptoms include diarrhea, abdominal distention, and flatulence. Diagnosis is clinical and by an $\text{H}_2$ breath test. Treatment is removal of the causative disaccharide from the diet.

Pathophysiology

Disaccharides are normally split into monosaccharides by disaccharidases (eg, lactase, maltase, isomaltase, sucrase [invertase]) located in the brush border of small-bowel enterocytes. Undigested disaccharides cause an osmotic load that attracts water and electrolytes into the bowel, causing watery diarrhea. Bacterial fermentation of carbohydrates in the colon produces gases ($\text{H}_2$, $\text{CO}_2$, and methane), resulting in excessive flatus, bloating and distention, and abdominal pain.

Etiology

Enzyme deficiencies can be congenital, acquired (primary), or secondary. Congenital deficiencies are rare.

Acquired lactase deficiency (primary adult hypolactasia) is the most common form of carbohydrate intolerance. Lactase levels are high in neonates, permitting digestion of milk; in most ethnic groups (80% of blacks and Hispanics, almost 100% of Asians), the levels decrease in the post-weaning period rendering older children and adults unable to digest significant amounts of lactose. However, 80 to 85% of whites of Northwest European descent produce lactase throughout life and are thus able to digest milk and milk products. It is unclear why the normal state of $>75\%$ of the world's population should be labeled a "deficiency."

Secondary lactase deficiency occurs in conditions that damage the small-bowel mucosa (eg, celiac sprue,
tropical sprue, acute intestinal infections). In infants, temporary secondary disaccharidase deficiency may complicate enteric infections or abdominal surgery. Recovery from the underlying disease is followed by an increase in activity of the enzyme.

**Symptoms and Signs**

Symptoms and signs are similar in all disaccharidase deficiencies. A child who cannot tolerate lactose develops diarrhea after ingesting significant amounts of milk and may not gain weight. An affected adult may have watery diarrhea, bloating, excessive flatus, nausea, borborygmi, and abdominal cramps after ingesting lactose. The patient often recognizes this early in life and avoids eating dairy products. Symptoms typically require ingestion of more than the equivalent of 8 to 12 oz of milk. Diarrhea may be severe enough to purge other nutrients before they can be absorbed. Symptoms may be similar to and can be confused with irritable bowel syndrome (see p. 162).

**Diagnosis**

- Clinical diagnosis
- H₂ breath test for confirmation

Lactose intolerance can usually be diagnosed with a careful history supported by dietary challenge. Patients usually have a history of intolerance to milk and dairy foods. The diagnosis is also suggested if the stool from chronic or intermittent diarrhea is acidic (pH < 6) and can be confirmed by an H₂ breath or a lactose tolerance test.

In the H₂ breath test, 50 g of lactose is given orally and the H₂ produced by bacterial metabolism of undigested lactose is measured with a breath meter at 2, 3, and 4 h postingestion. Most affected patients have an increase in expired H₂ of > 20 ppm over baseline. Sensitivity and specificity are > 95%.

The lactose tolerance test is less specific. Oral lactose (1.0 to 1.5 g/kg body weight) is given. Serum glucose is measured before ingestion and 60 and 120 min after. Lactose-intolerant patients develop diarrhea, abdominal bloating, and discomfort within 20 to 30 min, and their serum glucose levels do not rise > 20 mg/dL (< 1.1 mmol/L) above baseline. Low lactase activity in a jejunal biopsy specimen is diagnostic, but endoscopy is needed to obtain a specimen and is not routine.

**Treatment**

- Dietary restriction

Carbohydrate malabsorption is readily controlled by avoiding dietary sugars that cannot be absorbed (ie, following a lactose-free diet in cases of lactase deficiency). However, because the degree of lactose malabsorption varies greatly, many patients can ingest up to 12 oz (18 g of lactose) of milk daily without symptoms. Yogurt is usually tolerated because it contains an appreciable amount of lactase produced by intrinsic *Lactobacilli*.

For symptomatic patients wishing to drink milk, lactose in milk can be predigested by the addition of a commercially prepared lactase, and pretreated milk is now available. Enzyme supplements should be an adjunct to, not a substitute for, dietary restriction. Lactose-intolerant patients must take Ca supplements (1200 to 1500 mg/day).

**Celiac Sprue**

(Nontropical Sprue; Gluten Enteropathy; Celiac Disease)

Celiac sprue is an immunologically mediated disease in genetically susceptible people caused by intolerance to gluten, resulting in mucosal inflammation, which causes malabsorption. Symptoms usually include diarrhea and abdominal discomfort. Diagnosis is by small-bowel
biopsies showing characteristic though not specific pathologic changes of villous atrophy that resolve with a strict gluten-free diet.

Etiology

Celiac sprue is a hereditary disorder caused by sensitivity to the gliadin fraction of gluten, a protein found in wheat; similar proteins are present in rye and barley. In a genetically susceptible person, gluten-sensitive T cells are activated when gluten-derived peptide epitopes are presented. The inflammatory response causes characteristic mucosal villous atrophy in the small bowel.

Epidemiology: Celiac sprue mainly affects whites of northern European descent. Prevalence estimates based on serologic screens (sometimes confirmed by biopsy) indicate the disorder is present in about 1/300 in Europe and perhaps 1/250 in the US overall (but there may be significant variation among regions in the US).

The disease affects about 10 to 20% of 1st-degree relatives. Female: male ratio is 2:1. Onset is generally in childhood but may occur later.

Symptoms and Signs

The clinical presentation varies; no typical presentation exists. Some patients are asymptomatic or have only signs of nutritional deficiency. Others have significant GI symptoms.

Celiac sprue can manifest in infancy and childhood after introduction of cereals into the diet. The child has failure to thrive, apathy, anorexia, pallor, generalized hypotonia, abdominal distention, and muscle wasting. Stools are soft, bulky, clay-colored, and offensive. Older children may present with anemia or failure to grow normally.

In adults, lassitude, weakness, and anorexia are most common. Mild and intermittent diarrhea is sometimes the presenting symptom. Steatorrhea ranges from mild to severe (7 to 50 g fat/day). Some patients have weight loss, rarely enough to become underweight. Anemia, glossitis, angular stomatitis, and aphthous ulcers are usually seen in these patients. Manifestations of vitamin D and Ca deficiencies (eg, osteomalacia, osteopenia, osteoporosis) are common. Both men and women may have reduced fertility.

About 10% have dermatitis herpetiformis, an intensely pruritic papulovesicular rash that is symmetrically distributed over the extensor areas of the elbows, knees, buttocks, shoulders, and scalp. This rash can be induced by a high-gluten diet. Celiac sprue is also associated with diabetes mellitus, autoimmune thyroid disease, and Down syndrome.

Diagnosis

• Serologic markers

• Small-bowel biopsy

The diagnosis is suspected clinically and by laboratory abnormalities suggestive of malabsorption. Family incidence is a valuable clue. Celiac sprue should be strongly considered in a patient with iron deficiency without obvious GI bleeding.

Confirmation requires a small-bowel biopsy from the second portion of the duodenum. Findings include lack or shortening of villi (villous atrophy), increased intraepithelial cells, and crypt hyperplasia. However, such findings can also occur in tropical sprue, severe intestinal bacterial overgrowth, eosinophilic ententitis, lactose intolerance, and lymphoma.

Because biopsy lacks specificity, serologic markers can aid diagnosis. Anti-tissue transglutaminase antibody (AGA) and anti-endomysial antibody (EMA—an antibody against an intestinal connective tissue protein) each have sensitivity and specificity > 90%. These markers can also be used to screen
populations with high prevalence of celiac sprue, including 1st-degree relatives of affected patients and patients with diseases that occur at a greater frequency in association with celiac sprue. If either test is positive, the patient should have a diagnostic small-bowel biopsy. If both are negative, celiac sprue is extremely unlikely. These antibodies decrease in titer in patients on a gluten-free diet and thus are useful in monitoring dietary compliance.

Other laboratory abnormalities often occur and should be sought. They include anemia (iron-deficiency anemia in children and folate-deficiency anemia in adults); low albumin, Ca, K, and Na; and elevated alkaline phosphatase and PT.

Malabsorption tests are not specific for celiac sprue. If done, common findings include steatorrhea of 10 to 40 g/day and abnormal results with D-xylose and (in severe ileal disease) Schilling tests.

Prognosis

Mortality is 10 to 30% without a gluten-free diet. With proper diet, mortality is < 1%, mainly in adults who have severe disease at the outset. Complications include refractory sprue, collagenous sprue, and intestinal lymphomas. Intestinal lymphomas affect 6 to 8% of patients with celiac sprue, usually manifesting after 20 to 40 yr of disease. The incidence of other GI cancers (eg, carcinoma of the esophagus or oropharynx, small-bowel adenocarcinoma) also increases. Adherence to a gluten-free diet can significantly reduce the risk of cancer.

Treatment

• Gluten-free diet

• Supplements to replace any serious deficiencies

Treatment is a gluten-free diet (avoiding foods containing wheat, rye, or barley). Gluten is so widely used (eg, in commercial soups, sauces, ice creams, hot dogs) that a patient needs a detailed list of foods to avoid. Patients are encouraged to consult a dietitian and join a celiac support group. The response to a gluten-free diet is usually rapid, and symptoms resolve in 1 to 2 wk. Ingesting even small amounts of food containing gluten may prevent remission or induce relapse.

Small-bowel biopsy should be repeated after 3 to 4 mo of a gluten-free diet. If abnormalities persist, other causes of villous atrophy (eg, lymphoma) should be considered. Lessening of symptoms and improvement in small-bowel morphology are accompanied by a decrease in AGA and EMA titers.

Supplementary vitamins, minerals, and hematins may be given, depending on the deficiencies. Mild cases may not require supplementation, whereas severe cases may require comprehensive replacement. For adults, replacement includes ferrous sulfate 300 mg po once/day to tid, folate 5 to 10 mg po once/day, Ca supplements, and any standard multivitamin. Sometimes children (but rarely adults) who are seriously ill on initial diagnosis require bowel rest and TPN.

If a patient responds poorly to gluten withdrawal, either the diagnosis is incorrect or the disease has become refractory. Corticosteroids can control symptoms in the latter case.

Infection and Infestation

Acute bacterial, viral, and parasitic infections may cause transient malabsorption, probably as a result of temporary, superficial damage to the villi and microvilli. Chronic bacterial infections of the small bowel are uncommon, apart from blind loops, systemic sclerosis, and diverticula. Intestinal bacteria may use up dietary vitamin B<sub>12</sub> and other nutrients, perhaps interfere with enzyme systems, and cause mucosal injury.

Intestinal Lymphangiectasia

(Idiopathic Hypoproteinemia)
Intestinal lymphangiectasia is obstruction or malformation of the intramucosal lymphatics of the small bowel. It primarily affects children and young adults. Symptoms include those of malabsorption, with edema and growth retardation. Diagnosis is by small-bowel biopsy. Treatment is usually supportive.

Malformation of the lymphatic system is congenital or acquired. Congenital cases usually manifest in children and young adults (mean age of onset: 11 yr). Males and females are equally affected. In acquired cases, the defect may be secondary to retroperitoneal fibrosis, constrictive pericarditis, pancreatitis, neoplastic tumors, and infiltrative disorders that block the lymphatics.

Impaired lymphatic drainage leads to increased pressure and leakage of lymph into the intestinal lumen. Impairment of chylomicron and lipoprotein absorption results in malabsorption of fats and protein. Because carbohydrates are not absorbed through the lymphatic system, their uptake is not impaired.

Symptoms and Signs

Early manifestations include massive and often asymmetric peripheral edema, intermittent diarrhea, nausea, vomiting, and abdominal pain. Some patients have mild to moderate steatorrhea. Chylous pleural effusions (chylothorax) and chylous ascites may be present. Growth is retarded if onset is in the first decade of life.

Diagnosis

- Endoscopic small-bowel biopsy
- Sometimes contrast lymphangiography

Diagnosis usually requires endoscopic small-bowel biopsy, which shows marked dilation and ectasia of the mucosal and submucosal lymphatic vessels. Alternatively, contrast lymphangiography (injection of contrast material via the pedal vein) can show abnormal intestinal lymphatics.

Laboratory abnormalities include lymphocytopenia and low levels of serum albumin, cholesterol, IgA, IgM, IgG, transferrin, and ceruloplasmin. Barium studies may show thickened, nodular mucosal folds that resemble stacked coins. D-Xylose absorption is normal. Intestinal protein loss can be shown by using chromium-51-labeled albumin.

Treatment

- Supportive care
- Sometimes surgical resection or repair

Abnormal lymphatics cannot be corrected. Supportive treatment includes a low-fat (< 30 g/day), high-protein diet containing medium-chain triglyceride supplements. Supplemenal Ca and fat-soluble vitamins are given. Intestinal resection or anastomosis of the abnormal lymphatics to the venous channels may be beneficial. Pleural effusions should be drained by thoracentesis.

Short Bowel Syndrome

Short bowel syndrome is malabsorption resulting from extensive resection of the small bowel. Symptoms depend on the length and function of the remaining small bowel, but diarrhea can be severe, and nutritional deficiencies are common. Treatment is with small feedings, antidiarrheals, and sometimes TPN or intestinal transplantation.

Common reasons for extensive resection are Crohn's disease, mesenteric infarction, radiation enteritis, cancer, volvulus, and congenital anomalies.
Because the jejunum is the primary digestive and absorptive site for most nutrients, jejunal resection significantly reduces nutrient absorption. In response, the ileum adapts by increasing the length and absorptive function of its villi, resulting in gradual improvement of nutrient absorption.

The ileum is the site of vitamin B\textsubscript{12} and bile acid absorption. Severe diarrhea and bile acid malabsorption result when > 100 cm of the ileum is resected. Notably, there is no compensatory adaptation of the remaining jejunum. Consequently, malabsorption of fat, fat-soluble vitamins, and vitamin B\textsubscript{12} occurs. In addition, unabsorbed bile acids in the colon result in secretory diarrhea. Preservation of the colon can significantly reduce water and electrolyte losses. Resection of the terminal ileum and ileocecal valve can predispose to bacterial overgrowth.

**Treatment**

- TPN

- Eventual oral feeding if > 100 cm of jejunum remain

- Antidiarrheals, cholestyramine, proton pump inhibitors, vitamin supplements

In the immediate postoperative period, diarrhea is typically severe, with significant electrolyte losses. Patients typically require TPN and intensive monitoring of fluid and electrolytes (including Ca and Mg). An oral iso-osmotic solution of Na and glucose (similar to WHO oral rehydration formula—see p. 2809) is slowly introduced in the postoperative phase once the patient stabilizes and stool output is < 2 L/day.

Patients with extensive resection (< 100 cm of remaining jejunum) and those with excessive fluid and electrolyte losses require TPN for life.

Patients with > 100 cm of jejunum left can achieve adequate nutrition through oral feeding. Fat and protein in the diet are usually well tolerated, unlike carbohydrates, which contribute a significant osmotic load. Small feedings reduce the osmotic load. Ideally, 40% of calories should consist of fat.

Patients who have diarrhea after meals should take antidiarrheals (eg, loperamide) 1 h before eating. Cholestyramine 2 to 4 g taken with meals reduces diarrhea associated with bile acid malabsorption. Monthly IM injections of vitamin B\textsubscript{12} should be given to patients with a documented deficiency. Most patients should take supplemental vitamins, Ca, and Mg.

Gastric acid hypersecretion can develop, which can deactivate pancreatic enzymes; thus, most patients are given H\textsubscript{2} blockers or proton pump inhibitors.

Small-bowel transplantation is advocated for patients who are not candidates for long-term TPN and in whom adaptation does not occur.

**Tropical Sprue**

Tropical sprue is an acquired disease, probably of infectious etiology, characterized by malabsorption and megaloblastic anemia. Diagnosis is clinical and by small-bowel biopsy. Treatment is with tetracycline and folate for 6 mo.

**Etiology**

Tropical sprue occurs chiefly in the Caribbean, southern India, and Southeast Asia, affecting both natives and visitors. The illness is rare in visitors spending < 1 mo in areas where the disease is endemic. Although etiology is unclear, it is thought to result from chronic infection of the small bowel by toxigenic strains of coliform bacteria. Malabsorption of folate and vitamin B\textsubscript{12} deficiency result in megaloblastic anemia. The incidence of tropical sprue is decreasing, perhaps because of increasing use of antibiotics for acute traveler's diarrhea.
Symptoms and Signs

Patients commonly have acute diarrhea with fever and malaise. A chronic phase of milder diarrhea, nausea, anorexia, abdominal cramps, and fatigue follows. Steatorrhea is common. Nutritional deficiencies, especially of folate and vitamin B₁₂, eventually develop after several months to years. The patient may also have weight loss, glossitis, stomatitis, and peripheral edema.

Diagnosis

- Endoscopy with small-bowel biopsy
- Blood tests to screen for consequences of malabsorption

Tropical sprue is suspected in people who live in or have visited areas where the disease is endemic and who have megaloblastic anemia and symptoms of malabsorption. The definitive test is upper GI endoscopy with small-bowel biopsy. Characteristic histologic changes (see Table 17-3) usually involve the entire small bowel and include blunting of the villi with infiltration of chronic inflammatory cells in the epithelium and lamina propria. Celiac disease and parasitic infection must be ruled out.

Additional laboratory studies (eg, CBC; albumin; Ca; PT; iron, folate, and B₁₂ levels) help evaluate nutritional status. Barium small-bowel follow-through may show segmentation of the barium, dilation of the lumen, and thickening of the mucosal folds. D-Xylose absorption is abnormal in > 90% of cases. However, these tests are not specific or essential for diagnosis.

Treatment

- Long-term tetracycline

Treatment is tetracycline 250 mg po qid for 1 or 2 mo, then bid for up to 6 mo, depending on disease severity and response to treatment. Folate 5 to 10 mg po once/day should be given for the first month along with vitamin B₁₂ 1 mg IM weekly for several weeks. Megaloblastic anemia promptly abates, and the clinical response is dramatic. Other nutritional replacements are given as needed. Relapse may occur in 20%. Failure to respond after 4 wk of therapy suggests another condition.

Whipple's Disease

(Intestinal Lipodystrophy)

Whipple's disease is a rare systemic illness caused by the bacterium *Tropheryma whippelii*. Main symptoms are arthritis, weight loss, and diarrhea. Diagnosis is by small-bowel biopsy. Treatment is with a minimum 1 yr of trimethoprim/sulfamethoxazole.

Whipple's disease predominately affects white men aged 30 to 60. Although it affects many parts of the body (eg, heart, lung, brain, serous cavities, joints, eye, GI tract), the mucosa of the small bowel is almost always involved. Affected patients may have subtle defects of cell-mediated immunity that predispose to infection with *T. whippelii*. About 30% of patients have HLA-B27.

Symptoms and Signs

Clinical presentation varies depending on the organ systems affected. Usually, the first symptoms are arthritis and fever. Intestinal symptoms (eg, watery diarrhea, steatorrhea, abdominal pain, anorexia, weight loss) usually manifest later, sometimes years after the initial complaint. Gross or occult intestinal bleeding may occur. Severe malabsorption may be present in patients diagnosed late in the clinical course. Other findings include increased skin pigmentation, anemia, lymphadenopathy, chronic cough, serositis, peripheral edema, and CNS symptoms.
Diagnosis

• Endoscopy with small-bowel biopsy

The diagnosis may be missed in patients without prominent GI symptoms. Whipple's disease should be suspected in middle-aged white men who have arthritis and abdominal pain, diarrhea, weight loss, or other symptoms of malabsorption. Such patients should have upper endoscopy with small-bowel biopsy; the intestinal lesions are specific and diagnostic. The most severe and consistent changes are in the proximal small bowel. Light microscopy shows periodic acid-Schiff-positive macrophages that distort the villus architecture. Gram-positive, acid fast-negative bacilli (*T. whippelii*) are seen in the lamina propria and in the macrophages. Confirmation by electron microscopy is recommended.

Whipple's disease should be differentiated from intestinal infection with *Mycobacterium avium-intracellulare* (MAI), which has similar histologic findings. However, MAI stains positive with acid fast. PCR testing may be useful for confirmation.

Treatment

• Antibiotics

• Late relapse a possibility

Untreated disease is progressive and fatal. Many antibiotics are curative (eg, tetracycline, trimethoprim/sulfamethoxazole, chloramphenicol, ampicillin, penicillin, cephalosporins). Treatment is initiated with ceftriaxone (2 g IV daily) or with procaine (1.2 million units IM once/day) or penicillin G (1.5 to 6 million units IV q 6 h) plus streptomycin (1.0 g IM once/day for 10 to 14 days). This regimen is followed by a long-term course of trimethoprim/sulfamethoxazole (160/800 mg po bid for 1 yr). Sulfa-allergic patients may substitute oral penicillin VK or ampicillin. Prompt clinical improvement occurs, with fever and joint pains resolving in a few days. Intestinal symptoms usually abate within 1 to 4 wk.

Some authorities do not recommend repeat small-bowel biopsies because macrophages may persist for years after treatment. However, others recommend repeat biopsy after 1 yr. In the latter approach, electron microscopy is needed to document bacilli (not just macrophages). Relapses are common and may occur years later. If relapse is suspected, small-bowel biopsies should be done (regardless of affected organ systems) to determine presence of free bacilli.
Chapter 18. Irritable Bowel Syndrome

(Spas tic Colon)

Irritable bowel syndrome (IBS) is characterized by abdominal discomfort or pain that is accompanied by at least two of the following: relief by defecation, change in frequency of stool, or change in consistency of stool. The cause is unknown, and the pathophysiology is incompletely understood. Diagnosis is clinical. Treatment is symptomatic, consisting of dietary management and drugs, including anticholinergics and agents active at serotonin receptors.

**Etiology**

The cause of IBS is unknown. No anatomic cause can be found on laboratory tests, x-rays, and biopsies. Emotional factors, diet, drugs, or hormones may precipitate or aggravate GI symptoms. Historically, the disorder was often considered as purely psychosomatic. Although psychosocial factors are involved, IBS is better understood as a combination of psychosocial and physiologic factors.

**Psychosocial factors:** Psychologic distress is common among patients with IBS, especially among those who seek medical care. Some patients have anxiety disorders, depression, or a somatization disorder. Sleep disturbances also coexist. However, stress and emotional conflict do not always coincide with symptom onset and recurrence. Some patients with IBS seem to have a learned aberrant illness behavior (ie, they express emotional conflict as a GI complaint, usually abdominal pain). The physician evaluating patients with IBS, particularly those with refractory symptoms, should investigate for unresolved psychologic issues, including the possibility of sexual or physical abuse. Psychosocial factors also affect the outcome in IBS.

**Physiologic factors:** A variety of physiologic factors seem to be involved in IBS symptoms. Factors include altered motility, visceral hyperalgesia, and various genetic and environmental factors.

Visceral hyperalgesia refers to hypersensitivity to normal amounts of intraluminal distention and heightened perception of pain in the presence of normal quantities of intestinal gas; it may result from remodeling of neural pathways in the brain-gut axis. Some patients (perhaps 1 in 7) have reported their IBS symptoms began after an episode of acute gastroenteritis (termed postinfectious IBS). A subset of patients with IBS has autonomic dysfunctions. However, many patients have no demonstrable physiologic abnormalities, and even in those that do, the abnormalities may not correlate with symptoms.

Constipation may be explained by slower colonic transit, and diarrhea may be explained by faster colonic transit. Some patients with constipation have fewer colonic high amplitude-propagated contractions, which propel colonic contents over several segments. Conversely, excess sigmoid motor activity may retard transit in functional constipation.

Postprandial abdominal discomfort may be attributed to an exaggerated gastro-colonic reflex (the colonic contractile response to a meal), the presence of colonic high amplitude-propagated contractions, increased intestinal sensitivity (visceral hyperalgesia), or a combination of these. Fat ingestion may exaggerate hypersensitivity.

Hormonal fluctuations affect bowel functions in women. Rectal sensitivity is increased during menses but not during other phases of the menstrual cycle. The effects of sex steroids on GI transit are subtle. The role of small-bowel bacterial overgrowth in IBS is controversial.

**Symptoms and Signs**

IBS tends to begin in the teens and 20s, causing bouts of symptoms that recur at irregular periods. Onset in late adult life is less common but not rare. Symptoms rarely rouse the sleeping patient. Symptoms are often triggered by food, particularly fats, or by stress.

Patients have abdominal discomfort, which varies considerably but is often located in the lower quadrant, steady or cramping in nature, and relieved by defecation. In addition, abdominal discomfort is temporally
associated with alterations in stool frequency (increased in diarrhea-predominant IBS and decreased in constipation-predominant IBS) and consistency (i.e., loose or lumpy and hard). Pain or discomfort related to defecation is likely to be of bowel origin; that associated with exercise, movement, urination, or menstruation usually has a different cause. Although bowel patterns are relatively consistent in most patients, it is not unusual for patients to alternate between constipation and diarrhea. Patients may also have symptoms of abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), pass mucus, or complain of bloating or abdominal distention. Many patients also have symptoms of dyspepsia. Extraintestinal symptoms (e.g., fatigue, fibromyalgia, sleep disturbances, chronic headaches) are common.

**Diagnosis**

- Clinical evaluation, based on Rome criteria
- Screening for organic causes with basic laboratory tests and sigmoidoscopy or colonoscopy
- Other tests for patients with red flag findings (rectal blood, weight loss, fever)

Diagnosis is based on characteristic bowel patterns, time and character of pain, and exclusion of other disease processes through physical examination and routine diagnostic tests. Diagnostic testing should be more intensive when the following red flag findings are present either at initial presentation or at any time after diagnosis: older age, fever, weight loss, rectal bleeding, vomiting. Because patients with IBS can develop organic conditions, testing for other conditions should also be considered in patients who develop alarm symptoms or markedly different symptoms during the course of IBS. Common illnesses that may be confused with IBS include lactose intolerance, drug-induced diarrhea, post-cholecystectomy diarrhea, laxative abuse, parasitic diseases (e.g., giardiasis), eosinophilic gastritis or enteritis, microscopic colitis, and early inflammatory bowel disease. However, uninfamed colonic diverticula do not cause symptoms, and their presence should not be considered explanatory.

The bimodal age distribution of patients with inflammatory bowel disease makes it imperative to evaluate both younger and older patients. In patients > 60 with acute symptoms, ischemic colitis should be considered. Patients with constipation and no anatomic lesion should be evaluated for hypothyroidism and hyperparathyroidism. If the patient's symptoms suggest malabsorption, tropical sprue, celiac disease, and Whipple's disease must be considered. Defecatory disorders should be considered as a cause of constipation in patients who report symptoms of difficult defecation. Rare causes of diarrhea include hyperthyroidism, medullary cancer of the thyroid, or carcinoid syndrome, gastrinoma, vipoma, and Zollinger-Ellison syndrome. However, secretory diarrhea caused by vasoactive intestinal peptide (VIP), calcitonin, or gastrin is typically accompanied by stool volumes > 1000 mL daily.

**History:** Particular attention should be given to the character of the pain, bowel habits, familial interrelationships, and drug and dietary histories. Equally important are the patient's overall emotional state, interpretation of personal problems and quality of life. The quality of the patient-physician interaction is key to diagnostic and therapeutic efficacy.

The Rome criteria are standardized symptom-based criteria for diagnosing IBS. The Rome criteria require the presence of abdominal pain or discomfort for at least 3 days/mo in the last 3 mo along with ≥ 2 of the following: (1) improvement with defecation, (2) onset (of each episode of discomfort) associated with a change in frequency of defecation, or (3) change in consistency of stool.

**Physical examination:** Patients generally appear to be healthy. Palpation of the abdomen may reveal tenderness, particularly in the left lower quadrant, at times associated with a palpable, tender sigmoid. A digital rectal examination, including a test for occult blood, should be done on all patients. In women, a pelvic examination helps rule out ovarian tumors and cysts or endometriosis, which may mimic IBS.

**Testing:** The diagnosis of IBS can reasonably be made using the Rome criteria as long as patients have no red flag findings, such as rectal bleeding, weight loss, and fever, or other findings that might suggest another etiology. Many patients with IBS are overtested; however, CBC, biochemical profile (including liver tests), ESR, stool examination for ova and parasites (in those with diarrhea predominance), thyroid-stimulating hormone and Ca for those with constipation, and flexible sigmoidoscopy or colonoscopy
should be done. During flexible fiber-optic proctosigmoidoscopy, introduction of the instrument and air insufflation frequently trigger bowel spasm and pain. The mucosal and vascular patterns in IBS usually appear normal. Colonoscopy is preferred for patients > 50 with a change in bowel habits, particularly those with no previous IBS symptoms, to exclude colonic polyps and tumors. In patients with chronic diarrhea, particularly older women, mucosal biopsy can rule out possible microscopic colitis.

Additional studies (such as ultrasound, CT, barium enema x-ray, upper GI esophagastroduodenoscopy, and small-bowel x-rays) should be undertaken only when there are other objective abnormalities. Fecal fat excretion should be measured when there is a concern about steatorrhea. Testing for celiac sprue and small-bowel x-rays are recommended when malabsorption is suspected. Testing for carbohydrate intolerance should be considered in appropriate circumstances.

**Intercurrent disease:** Patients with IBS may subsequently develop additional GI disorders, and the clinician must not summarily dismiss their complaints. Changes in symptoms (eg, in the location, type, or intensity of pain; in bowel habits; in constipation and diarrhea) and new symptoms or complaints (eg, nocturnal diarrhea) may signal another disease process. Other symptoms that require investigation include fresh blood in the stool, weight loss, very severe abdominal pain or unusual abdominal distention, steatorrhea or noticeably foul-smelling stools, fever or chills, persistent vomiting, hematemesis, symptoms that wake the patient from sleep (eg, pain, the urge to defecate), and a steady progressive worsening of symptoms. Patients > 40 are more likely than younger patients to develop an intercurrent physiologic illness.

**Treatment**

- Support and understanding
- Normal diet, avoiding gas-producing and diarrhea-producing foods
- Increased fiber intake constipation
- Loperamide for diarrhea
- Possibly tricyclic antidepressants

Therapy is directed at specific symptoms. An effective therapeutic relationship is essential for effectively managing IBS. Patients should be invited to express not only their symptoms but also their understanding of their symptoms and the reasons prompting a visit to the health care practitioner (eg, fear of serious disease). Patients should be educated about the disorder (eg, normal bowel physiology and the bowel's hypersensitivity to stress and food) and reassured, after appropriate tests, about the absence of a serious or life-threatening disease. Appropriate therapeutic goals (eg, expectations regarding the normal course or variability in symptoms, adverse effects of drugs, the appropriate and available working relationship between the physician and the patient) should be established. Finally, patients can benefit by being actively involved in the management of their condition. When successful, this can enhance the patient's motivation to adhere to treatment, foster a more positive physician-patient relationship, and mobilize the coping resources of even the most chronically passive patients. Psychologic stress, anxiety, or mood disorders should be identified, evaluated, and treated. Regular physical activity helps relieve stress and assists in bowel function, particularly in patients with constipation.

**Diet:** In general, a normal diet should be followed. Meals should not be overly large, and eating should be slow and paced. Patients with abdominal distention and increased flatulence may benefit from reducing or eliminating beans, cabbage, and other foods containing fermentable carbohydrates. Reduced intake of sweeteners (eg, sorbitol, mannitol, fructose), which are constituents of natural and processed foods (eg, apple and grape juice, bananas, nuts, and raisins), may alleviate flatulence, bloating, and diarrhea. Patients with evidence of lactose intolerance should reduce their intake of milk and dairy products. A low-fat diet may reduce postprandial abdominal symptoms.

Dietary fiber supplements may soften stool and improve the ease of evacuation. A bland bulk-producing agent may be used (eg, raw bran, starting with 15 mL [1 tbsp] with each meal, supplemented with
increased fluid intake). Alternatively, psyllium hydrophilic mucilloid with two glasses of water may be used. However, excessive use of fiber can lead to bloating and diarrhea, so fiber doses must be individualized. Occasionally, flatulence may be reduced by switching to a synthetic fiber preparation (eg, methylcellulose).

**Drug therapy:** Drug therapy is directed toward the dominant symptoms. Anticholinergic drugs (eg, hyoscyamine 0.125 mg po 30 to 60 min before meals) may be used for their antispasmodic effects.

Serotonin receptor modulation may be of benefit. Tegaserod, a 5HT4 agonist, stimulates motility and alleviates constipation. In 2007, tegaserod was withdrawn from the market because, in clinical trials, it slightly increased the incidence of cardiovascular ischemic events (ie, MI, unstable angina pectoris, stroke) compared with placebo. Tegaserod has since been reintroduced under a restricted program. The chloride channel activator lubiprostone may help patients with constipation.

In patients with diarrhea, oral diphenoxylate 2.5 to 5 mg or loperamide 2 to 4 mg may be given before meals. The dose of loperamide should be titrated upward to reduce diarrhea while avoiding constipation. For many patients, tricyclic antidepressants (TCAs) help relieve symptoms of diarrhea, abdominal pain, and bloating. These drugs are thought to reduce pain by down-regulating the activity of spinal cord and cortical afferent pathways arriving from the intestine. Secondary amine TCAs (eg, nortriptyline, desipramine) are often better tolerated than parent tertiary amines (eg, amitriptyline, imipramine, doxepin) because of fewer anticholinergic, sedating antihistaminic, and α-adrenergic adverse effects. Treatment should begin with a very low dose of a TCA (eg, desipramine 10 to 25 mg once/day at bedtime), increasing as necessary and tolerated up to about 100 to 150 mg once/day at bedtime. SSRIs are also useful, particularly for patients with anxiety or an affective disorder, but may exacerbate diarrhea. 5HT3 antagonists (eg, alosetron) may benefit female patients with severe diarrhea refractory to other drugs. Because alosetron is associated with ischemic colitis, its use is restricted.

Preliminary data suggest that certain probiotics (eg, *Bifidobacterium infantis*) alleviate IBS symptoms, particularly bloating. The beneficial effects of probiotics are not generic to the entire species but specific to certain strains. Certain aromatic oils (carminatives) can relax smooth muscle and relieve pain caused by cramps in some patients. Peppermint oil is the most commonly used agent in this class.

**Psychologic therapies:** Cognitive-behavioral therapy, standard psychotherapy, and hypnotherapy may help some IBS patients.
Chapter 19. Inflammatory Bowel Disease

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis (UC), is a relapsing and remitting condition characterized by chronic inflammation at various sites in the GI tract, which results in diarrhea and abdominal pain.

Inflammation results from a cell-mediated immune response in the GI mucosa. The precise etiology is unknown, but evidence suggests that the normal intestinal flora trigger an immune reaction in patients with a multifactorial genetic predisposition (perhaps involving abnormal epithelial barriers and mucosal immune defenses). No specific environmental, dietary, or infectious causes have been identified. The immune reaction involves the release of inflammatory mediators, including cytokines, interleukins, and tumor necrosis factor (TNF).

Although Crohn's disease and UC are similar, they can be distinguished in most cases (see Table 19-1). About 10% of colitis cases are considered indeterminate. The term colitis applies only to inflammatory disease of the colon (eg, ulcerative, granulomatous, ischemic, radiation-induced, infectious). Spastic (mucous) colitis is a misnomer sometimes applied to a functional disorder, irritable bowel syndrome (see p. 162).

Epidemiology: IBD affects people of all ages but usually begins before age 30, with peak incidence from 14 to 24. IBD may have a second smaller peak between ages 50 and 70; however, this later peak may include some cases of ischemic colitis.

IBD is most common among people of Northern European and Anglo-Saxon origin and is 2 to 4 times more common among Ashkenazi Jews than in non-Jewish whites. The incidence is lower in central and southern Europe and lower still in South America, Asia, and Africa. However, the incidence is increasing among blacks and Latin Americans living in North America. Both sexes are equally affected. First-degree relatives of patients with IBD have a 4- to 20-fold increased risk; their absolute risk may be as high as 7%. Familial tendency is much higher in Crohn's disease than in UC.

Several gene mutations conferring a higher risk of Crohn's disease (and some possibly related to UC) have been identified.

Cigarette smoking seems to contribute to development or exacerbation of Crohn's disease but decreases risk of UC. NSAIDs may exacerbate IBD.

Extraintestinal Manifestations

Crohn's disease and UC both affect organs other than the intestines. Most extraintestinal manifestations are more common in UC and Crohn's colitis than in Crohn's disease limited to the small bowel. Extraintestinal manifestations are categorized in 3 ways:

1. Disorders that usually parallel (ie, wax and wane with) IBD flare-ups. These disorders include peripheral arthritis, episcleritis, aphthous stomatitis, erythema nodosum, and pyoderma gangrenosum. Arthritis tends to involve large joints and be migratory and transient. One or more of these parallel disorders develops in more than one third of patients hospitalized with IBD.

2. Disorders that are clearly associated with IBD but appear independently of IBD activity. These disorders include ankylosing spondylitis, sacroilitis, uveitis, and primary sclerosing cholangitis. Ankylosing spondylitis occurs more commonly in IBD patients with the HLA-B27 antigen. Most patients with spinal or sacroiliac involvement have evidence of uveitis and vice versa. Primary sclerosing cholangitis, which is a risk factor for cancer of the biliary tract, is strongly associated with UC or Crohn's colitis. Cholangitis may appear before or concurrently with the bowel disease or even 20 yr after colectomy. Liver disease (eg, fatty liver, autoimmune hepatitis, pericholangitis, cirrhosis) occurs in 3 to
5% of patients, although minor abnormalities in liver function tests are more common. Some of these conditions (eg, primary sclerosing cholangitis) may precede IBD by many years and, when diagnosed, should prompt an evaluation for IBD.

3. Disorders that are consequences of disrupted bowel physiology. These disorders occur mainly in severe Crohn's disease of the small bowel. Malabsorption may result from extensive ileal resection and cause deficiencies of fat-soluble vitamins, vitamin B₁₂, or minerals, resulting in anemia, hypocalcemia, hypomagnesemia, clotting disorders, and bone demineralization. In children, malabsorption retards growth and development. Other disorders include kidney stones from excessive dietary oxalate absorption, hydroureter and hydronephrosis from ureteral compression by the intestinal inflammatory process, gallstones from impaired ileal reabsorption of bile salts, and amyloidosis secondary to longstanding inflammatory and suppurative disease.

Thromboembolic disease may occur as a result of multiple factors in all 3 categories.

**Treatment**

- Supportive care
- 5-Aminosalicylic acid
- Corticosteroids
- Immunomodulating drugs
- Anticytokine drugs
- Sometimes antibiotics (eg, metronidazole, ciprofloxacin) and probiotics

Several classes of drugs are helpful for IBD. Details of their selection and use are discussed under each disorder.

**5-Aminosalicylic acid (5-ASA, mesalamine):** 5-ASA blocks production of prostaglandins and leukotrienes and has other beneficial effects on the inflammatory cascade. Because 5-ASA is active only intraluminally and is rapidly absorbed by the proximal small bowel, it must be formulated for delayed absorption when given orally. Sulfasalazine, the original agent in this class, delays absorption by complexing 5-ASA with a sulfa moiety, sulfapyridine. The complex is cleaved by bacterial flora in the lower ileum and colon, releasing the 5-ASA. The sulfa moiety, however, causes numerous adverse effects (eg, nausea, dyspepsia, headache), interferes with folate (folic acid) absorption, and occasionally causes serious adverse reactions (eg, hemolytic anemia or agranulocytosis and, rarely, hepatitis or pneumonitis). Reversible decreases in sperm count and motility occur in up to 80% of men. If used, sulfasalazine should be given with food, initially in a low dosage (eg, 0.5 g po bid) and gradually increased over several days to 1 to 2 g bid to tid. Patients should take daily folate supplements 1 mg po and have CBC and liver tests every 6 to 12 mo. Acute interstitial nephritis secondary to mesalamine occurs rarely; periodic monitoring of renal function is advisable because most cases are reversible if recognized early.

Newer drugs that complex 5-ASA with other vehicles seem almost equally effective but have fewer adverse effects. Olsalazine (a 5-ASA dimer) and balsalazide (5-ASA conjugated to an inactive compound) are cleaved by bacterial azoreductases (as is sulfasalazine). These drugs are activated mainly in the colon and are less effective for proximal small-bowel disease. Olsalazine dosage is 500 to 1500 mg po bid, and balsalazide is 2.25 g po tid. Olsalazine sometimes causes diarrhea, especially in patients with pancolitis. This problem is minimized by gradual escalation of dose and administration with meals.

Other forms of 5-ASA use delayed-release coatings. Asacol (typical dose 800 to 1200 mg po tid) is 5-ASA coated with an acrylic polymer whose pH solubility delays release of the drug until entry into the distal ileum and colon. Pentasa (1 g po qid) is 5-ASA encapsulated in ethylcellulose microgranules that release 35% of the drug in the small bowel. Two once/day formulations of mesalamine (Lialda, Apriso) are available; this less frequent dosing may improve adherence.
5-ASA is also available as a suppository (500 or 1000 mg at bedtime or bid) or enema (4 g at bedtime or bid) for proctitis and left-sided colon disease. These rectal preparations are effective for both acute treatment and long-term maintenance in proctitis and left-sided colon disease, and they have incremental benefit in combination with oral 5-ASA.

**Corticosteroids:** Corticosteroids are useful for acute flare-ups of most forms of IBD when 5-ASA compounds are inadequate. However, corticosteroids are not appropriate for maintenance. IV hydrocortisone 300 mg/day or methylprednisolone 60 to 80 mg/day by continuous drip or in divided doses is used for severe disease; oral prednisone or prednisolone 40 to 60 mg once/day may be used for moderate disease. Treatment is continued until symptoms remit (usually 7 to 28 days) and then tapered by 5 to 10 mg weekly to 20 mg once/day. Treatment is then further tapered by 2.5 to 5 mg weekly while instituting maintenance therapy with 5-ASA or immunomodulators. Adverse effects of short-term corticosteroids in high doses include hyperglycemia, hypertension, insomnia, hyperactivity, and acute psychotic episodes.

Hydrocortisone enemas or foam may be used for proctitis and left-sided colon disease; as an enema, 100 mg in 60 mL of isotonic solution is given once/day or bid. The enema should be retained in the bowel as long as possible; instillation at night, with the patient lying on the left side with hips elevated, may prolong retention and extend distribution. Treatment, if effective, should be continued daily for about 2 to 4 wk, then every other day for 1 to 2 wk, and then gradually discontinued over 1 to 2 wk.

Budesonide is a corticosteroid with a high (> 90%) first-pass liver metabolism; thus, oral administration may have a significant effect on GI tract disease but minimal adrenal suppression. Oral budesonide has fewer adverse effects than prednisolone but is not as rapidly effective and is typically used for less severe disease. Budesonide may be effective in maintaining remission for 3 to 6 mo but has not yet proved effective for long-term maintenance. Dosage is 9 mg once/day. It is also available outside the US as an enema.

**Immunomodulating drugs:** Azathioprine and its metabolite 6-mercaptopurine inhibit T-cell function. They are effective long-term and may diminish corticosteroid requirements and maintain remission for years. These drugs often require 1 to 3 mo to produce clinical benefits, so corticosteroids cannot be withdrawn until at least the 2nd month. Dosage of azathioprine is usually 2.5 to 3.0 mg/kg po once/day and 6-mercaptopurine 1.5 to 2.5 mg/kg po once/day but varies depending on individual metabolism. Signs of bone marrow suppression must be monitored with regular WBC count (biweekly for 1 mo, then every 1 to 2 mo). Pancreatitis or high fever occurs in about 3 to 5% of patients; either is an absolute contraindication to rechallenge. Hepatotoxicity is rarer and can be screened by blood tests every 6 to 12 mo. Newly available blood tests that measure the activity of one of the enzymes that metabolize azathioprine and 6-mercaptopurine and that directly measure metabolite levels may sometimes be helpful in ensuring safe and effective drug dosages.

Methotrexate 15 to 25 mg po or sc weekly is of benefit to many patients with corticosteroid-refractory or corticosteroid-dependent Crohn's disease, even those who have not responded to azathioprine or 6-mercaptopurine. Adverse effects include nausea, vomiting, and asymptomatic liver function test abnormalities. Folate 1 mg po once/day may diminish some of the adverse effects. Alcohol use, obesity, diabetes, and possibly psoriasis are risk factors for hepatotoxicity. Patients with these conditions should have a liver biopsy after a total dose of 1.5 g, but otherwise, concerns over hepatotoxicity are too often exaggerated. Pulmonary toxicity can also occur with methotrexate therapy.

Cyclosporine, which blocks lymphocyte activation, may benefit patients with severe UC unresponsive to corticosteroids and who may otherwise require colectomy. Its only well-documented use in Crohn's disease is for patients with refractory fistulas or pyoderma. Initial dose is 4 mg/kg IV in continuous infusion over 24 h; responders are converted to an oral dose of 6 to 8 mg/kg once/day with early introduction of azathioprine or 6-mercaptopurine. Long-term use (> 6 mo) is contraindicated by multiple adverse effects (eg, renal toxicity, seizures, opportunistic infections, hypertension, neuropathy). Generally, patients are not offered cyclosporine unless there is a reason to avoid the safer curative option of colectomy. If the drug is used, trough blood levels should be kept between 200 to 400 ng/mL and Pneumocystis jirovecii prophylaxis should be considered during the period of concomitant corticosteroid, cyclosporine, and...
Antimetabolite treatment. Tacrolimus, an immunosuppressant also used in transplant patients, seems as effective as cyclosporine.

Anticytokine drugs: Infliximab, certolizumab, and adalimumab are antibodies to TNF. These agents may be useful in Crohn's disease; additionally infliximab may be beneficial in UC for refractory or corticosteroid-dependent disease. Several anti-interleukin antibodies and interleukins may decrease the inflammatory response and are being studied for Crohn's disease. An antibody to leukocyte adhesion molecules (natalizumab) is approved as monotherapy for the most refractory cases of Crohn's disease; other analogs (eg, vedolizumab) are also being studied.

Infliximab is given as a single IV infusion of 5 mg/kg over 2 h. Monotherapy with infliximab is clearly effective for both induction and maintenance of remission, but some studies suggest better short-term results when infliximab is initiated in combination with a thiopurine (eg, azathioprine). Ideally, infliximab would eventually be stopped and patients would be maintained on the antimetabolite, but this strategy has not been validated in controlled studies. Corticosteroid tapering may begin after 2 wk. The initial infliximab infusion is usually followed by repeat infusions at weeks 2 and 6. Subsequently, it is given every 8 wk or at intervals determined by the patient's clinical course. Adverse effects during infusion (infusion reaction) include immediate hypersensitivity reactions (eg, rash, itching, sometimes anaphylactoid reactions), fever, chills, headache, and nausea. Delayed hypersensitivity reactions have also occurred. Anti-TNF drugs given subcutaneously (eg, adalimumab) do not cause infusion reactions, although they may cause local erythema, pain, and itching (injection site reaction). Patients who are intolerant or who have lost their initial response to infliximab may respond to adalimumab therapy.

Several patients have died of sepsis after infliximab use, so it is contraindicated when uncontrolled bacterial infection is present. Furthermore, TB reactivation has been attributed to this drug; therefore, screening by PPD and chest x-ray is required before its use. Lymphoma, demyelinating disease, and liver and hematologic toxicity are other potential concerns with anti-TNF antibody treatment. Other anticytokine, anti-integrin, and growth factors are under investigation, as is leukopheresis therapy to deplete activated immunocytes.

Antibiotics and probiotics: Antibiotics may be helpful in Crohn's disease but are of limited use in UC. Metronidazole 500 to 750 mg po tid for 4 to 8 wk may control mild Crohn's disease and help heal fistulas. However, adverse effects (particularly neurotoxicity) often preclude completion of treatment. Ciprofloxacin 500 to 750 mg po bid may prove less toxic. Many experts recommend metronidazole and ciprofloxacin in combination. Rifaximin, a nonabsorbable antibiotic, at a dose of 200 mg po tid is also being studied as treatment for active Crohn's disease.

Various nonpathogenic microorganisms (eg, commensal Escherichia coli, Lactobacillus species, Saccharomyces) given daily serve as probiotics and may be effective in preventing pouchitis (see p. 176), but other therapeutic roles have yet to be clearly defined. Therapeutic infestation with the parasite Trichuris suis has been tried in an effort to stimulate T2-helper cell immunity and may decrease disease activity in UC.

Supportive care: Most patients and their families are interested in diet and stress management. Although there are anecdotal reports of clinical improvement on certain diets, including one with rigid carbohydrate restrictions, controlled trials have shown no benefit. Stress management may be helpful.

Crohn's Disease

(Regional Enteritis; Granulomatous Ileitis or Ileocolitis)

Crohn's disease is a chronic transmural inflammatory disease that usually affects the distal ileum and colon but may occur in any part of the GI tract. Symptoms include diarrhea and abdominal pain. Abscesses, internal and external fistulas, and bowel obstruction may arise. Extraintestinal symptoms, particularly arthritis, may occur. Diagnosis is by colonoscopy and barium contrast studies. Treatment is with 5-aminosalicylic acid, corticosteroids, immunomodulators, anticytokines, antibiotics, and often surgery.
Pathophysiology

Crohn's disease begins with crypt inflammation and abscesses, which progress to tiny focal aphthoid ulcers. These mucosal lesions may develop into deep longitudinal and transverse ulcers with intervening mucosal edema, creating a characteristic cobblestoned appearance to the bowel.

Transmural spread of inflammation leads to lymphedema and thickening of the bowel wall and mesentery. Mesenteric fat typically extends onto the serosal surface of the bowel. Mesenteric lymph nodes often enlarge. Extensive inflammation may result in hypertrophy of the muscularis mucosae, fibrosis, and stricture formation, which can lead to bowel obstruction. Abscesses are common, and fistulas often penetrate into adjoining structures, including other loops of bowel, the bladder, or psoas muscle. Fistulas may even extend to the skin of the anterior abdomen or flanks. Independently of intra-abdominal disease activity, perianal fistulas and abscesses occur in 25 to 33% of cases; these complications are frequently the most troublesome aspects of Crohn's disease.

Noncaseating granulomas can occur in lymph nodes, peritoneum, the liver, and all layers of the bowel wall. Although pathognomonic when present, granulomas are not detected in about half of patients with Crohn's disease. The presence of granulomas does not seem to be related to the clinical course.

Segments of diseased bowel are sharply demarcated from adjacent normal bowel ("skip areas"); hence, the name regional enteritis. About 35% of Crohn's disease cases involve the ileum alone (ileitis); about 45% involve the ileum and colon (ileocolitis), with a predilection for the right side of the colon; and about 20% involve the colon alone (granulomatous colitis), most of which, unlike ulcerative colitis (UC), spare the rectum. Occasionally, the entire small bowel is involved (jejunoileitis). The stomach, duodenum, or esophagus is clinically involved only rarely, although microscopic evidence of disease is often detectable in the gastric antrum, especially in younger patients. In the absence of surgical intervention, the disease almost never extends into areas of small bowel that are not involved at first diagnosis.

There is an increased risk of cancer in affected small-bowel segments. Patients with colonic involvement have a long-term risk of colorectal cancer equal to that of UC, given the same extent and duration of disease.

Symptoms and Signs

The most common initial manifestation is chronic diarrhea with abdominal pain, fever, anorexia, and weight loss. The abdomen is tender, and a mass or fullness may be palpable. Gross rectal bleeding is unusual except in isolated colonic disease, which may manifest similarly to UC. Some patients present with an acute abdomen that simulates acute appendicitis or intestinal obstruction. About 33% of patients have perianal disease (especially fissures and fistulas), which is sometimes the most prominent or even initial complaint. In children, extraintestinal manifestations frequently predominate over GI symptoms; arthritis, FUO, anemia, or growth retardation may be a presenting symptom, whereas abdominal pain or diarrhea may be absent.

With recurrent disease, symptoms vary. Pain is most common and occurs with both simple recurrence and abscess formation. Patients with severe flare-up or abscess are likely to have marked tenderness, guarding, rebound, and a general toxic appearance. Stenotic segments may cause bowel obstruction, with colicky pain, distention, obstipation, and vomiting. Adhesions from previous surgery may also cause bowel obstruction, which begins rapidly, without the prodrome of fever, pain, and malaise typical of obstruction due to a Crohn's disease flare-up. An enterovesical fistula may produce air bubbles in the urine (pneumaturia). Draining cutaneous fistulas may occur. Free perforation into the peritoneal cavity is unusual.

Chronic disease causes a variety of systemic symptoms, including fever, weight loss, undernutrition, and extraintestinal manifestations (see p. 166).

The Vienna Classification and its recent Montreal modification categorize Crohn's disease into 3 principal patterns: (1) primarily inflammatory, which after several years commonly evolves into either (2) primarily stenotic or obstructing or (3) primarily penetrating or fistulizing. These different clinical patterns dictate
different therapeutic approaches. Some genetic studies suggest a molecular basis for this classification.

**Diagnosis**

- Barium x-rays of the stomach, small bowel, and colon
- Abdominal CT (conventional or CT enterography)
- Sometimes magnetic resonance (MR) enterography, upper endoscopy, and/or colonoscopy

Crohn's disease should be suspected in a patient with inflammatory or obstructive symptoms or in a patient without prominent GI symptoms but with perianal fistulas or abscesses or with otherwise unexplained arthritis, erythema nodosum, fever, anemia, or (in a child) stunted growth. A family history of Crohn's disease also increases the index of suspicion. Similar symptoms and signs (eg, abdominal pain, diarrhea) may be caused by other GI disorders. Differentiation from UC (see Table 19-1) may be an issue in the 20% of cases in which Crohn's disease is confined to the colon. However, because treatment is similar, this distinction is critical only when surgery or experimental therapy is contemplated.

Patients presenting with an acute abdomen (either initially or on relapse) should have flat and upright abdominal x-rays and an abdominal CT scan. These studies may show obstruction, abscesses or fistulas, and other possible causes of an acute abdomen (eg, appendicitis). Ultrasound may better delineate gynecologic pathology in women with lower abdominal and pelvic pain.

If initial presentation is less acute, an upper GI series with small-bowel follow-through and spot films of the terminal ileum is preferred over conventional CT. However, newer techniques of CT or MR enterography, which combine high-resolution CT or MR imaging with large volumes of ingested contrast, are becoming the procedures of choice in some centers. These imaging studies are virtually diagnostic if they show characteristic strictures or fistulas with accompanying separation of bowel loops. If findings are questionable, CT enteroclysis or video capsule enteroscopy may show superficial aphthous and linear ulcers. Barium enema x-ray may be used if symptoms seem predominantly colonic (eg, diarrhea) and may show reflux of barium into the terminal ileum with irregularity, nodularity, stiffness, wall thickening, and a narrowed lumen. Differential diagnoses in patients with similar x-ray findings include cancer of the cecum, ileal carcinoid, lymphoma, systemic vasculitis, radiation enteritis, ileocecal TB, and ameboma.

In atypical cases (eg, predominantly diarrhea, with minimal pain), evaluation is similar to suspected UC, with colonoscopy (including biopsy, sampling for enteric pathogens, and, when possible, visualization of the terminal ileum). Upper GI endoscopy may identify subtle gastroduodenal involvement even in the absence of upper GI symptoms.

Laboratory tests should be done to screen for anemia, hypoalbuminemia, and electrolyte abnormalities. Liver function tests should be done; elevated alkaline phosphatase and γ-glutamyl transpeptidase levels in patients with major colonic involvement suggest possible primary sclerosing cholangitis. Leukocytosis or increased levels of acute-phase reactants (eg, ESR, C-reactive protein) are nonspecific but may be used serially to monitor disease activity.

Perinuclear antineutrophil cytoplasmic antibodies are present in 60 to 70% of patients with UC and in only 5 to 20% of patients with Crohn's disease. Anti-*Saccharomyces cerevisiae* antibodies are relatively specific for Crohn's disease. However, these tests do not reliably separate the 2 diseases. They have uncertain value in cases of indeterminate colitis and are not recommended for routine diagnosis.

**Prognosis**

Established Crohn's disease is rarely cured but is characterized by intermittent exacerbations and remissions. Some patients have severe disease with frequent, debilitating periods of pain. However, with judicious medical therapy and, where appropriate, surgical therapy, most patients function well and adapt successfully. Disease-related mortality is very low. GI cancer, including cancer of the colon and small bowel, is the leading cause of excess Crohn's disease-related mortality.
Treatment

• Loperamide or antispasmodics for symptom relief

• 5-Aminosalicylic acid (5-ASA) or antibiotics

• Other drugs depending on symptoms and severity

• Sometimes surgery

Details of specific drugs and dosages are discussed on p. 167.

**General management:** Cramps and diarrhea may be relieved by oral administration of loperamide 2 to 4 mg or antispasmodic drugs up to 4 times/day (ideally before meals). Such symptomatic treatment is safe, except in cases of severe, acute Crohn’s colitis, which may progress to toxic megacolon as in UC. Hydrophilic muciloids (eg, methylcellulose or psyllium preparations) sometimes help prevent anal irritation by increasing stool firmness. Dietary roughage is to be avoided in strictureing disease or active colonic inflammation.

**Mild to moderate disease:** This category includes ambulatory patients who tolerate oral intake and have no signs of toxicity, tenderness, mass, or obstruction. 5-ASA (mesalamine) is commonly used as first-line treatment, although its benefits for small-bowel disease are modest at best. Pentasa is the most effective formulation for disease proximal to the terminal ileum; Asacol is effective in distal ileal disease. All formulations are roughly equivalent for Crohn’s colitis, although none of the newer preparations rival sulfasalazine for efficacy on a dose-for-dose basis.

Antibiotics are considered a first-line agent by some clinicians, or they may be reserved for patients not responding to 4 wk of 5-ASA; their use is strictly empiric. With any of these drugs, 8 to 16 wk of treatment may be required.

Responders should receive maintenance therapy.

**Moderate to severe disease:** Patients without fistulas or abscesses but with significant pain, tenderness, fever, or vomiting, or those who have not responded to treatment for mild disease, require corticosteroids, either oral or parenteral, depending on severity of symptoms and frequency of vomiting. Oral prednisone or prednisolone may act more rapidly and reliably than oral budesonide, but budesonide has somewhat fewer adverse effects and is considered the corticosteroid of choice in many centers, especially in Europe. Patients not responding to corticosteroids, or those whose doses cannot be tapered, should receive azathioprine, 6-mercaptopurine, or possibly methotrexate. Infliximab is preferred by some as a second-line agent after corticosteroids, and even as a first-line agent in preference to corticosteroids, but it is contraindicated in active uncontrolled infection.

Obstruction is managed initially with nasogastric suction and IV fluids. Obstruction due to uncomplicated Crohn’s disease should resolve within a few days and therefore does not require parenteral nutrition; absence of prompt response indicates a complication or another etiology and demands immediate surgery.

**Fulminant disease or abscess:** Patients with toxic appearance, high fever, persistent vomiting, rebound, or a tender or palpable mass must be hospitalized for administration of IV fluids and antibiotics. Abscesses must be drained, either percutaneously or surgically. IV corticosteroids should be given only when infection has been ruled out or controlled. If there is no response to corticosteroids and antibiotics within 5 to 7 days, surgery is usually indicated.

**Fistulas:** Fistulas are treated initially with metronidazole and ciprofloxacin. Patients who do not respond in 3 to 4 wk may receive an immunomodulator (eg, azathioprine, 6-mercaptopurine), with or without an induction regimen of infliximab for more rapid response. Cyclosporine is an alternative, but fistulas often relapse after treatment. Severe refractory perianal fistulas may require temporary diverting colostomy but almost invariably recur after reconnection; hence, diversion is more appropriately considered a
preparation for definitive surgery or at best an adjunct to infliximab rather than a primary treatment.

**Maintenance therapy:** Patients who require only 5-ASA or an antibiotic to achieve remission can be maintained on this drug. Patients requiring acute treatment with corticosteroids or infliximab generally require azathioprine, 6-mercaptopurine, methotrexate, or infliximab for maintenance. Systemically active corticosteroids are neither safe nor effective for long-term maintenance, although budesonide has been shown to delay relapse with fewer adverse effects. Patients who respond to infliximab for acute disease but who are not well maintained on antimetabolites may stay in remission with repeat doses of infliximab 5 to 10 mg/kg at 8-wk intervals. Monitoring during remission can be done by following symptoms and blood tests and does not require routine x-rays or colonoscopy (other than regular surveillance for dysplasia after 7 to 8 yr of disease).

**Surgery:** Even though about 70% of patients ultimately require an operation, surgery is always done reluctantly. It is best reserved for recurrent intestinal obstruction or intractable fistulas or abscesses. Resection of the involved bowel may ameliorate symptoms but does not cure the disease, which is likely to recur even after resection of all clinically apparent lesions. The recurrence rate, defined by endoscopic lesions at the anastomotic site, is > 70% at 1 yr and > 85% at 3 yr; defined by clinical symptoms, it is about 25 to 30% at 3 yr and 40 to 50% at 5 yr. Ultimately, further surgery is required in nearly 50% of cases. However, recurrence rates seem to be reduced by early postoperative prophylaxis with 6-mercaptopurine, metronidazole, or possibly infliximab or 5-ASA. Moreover, when surgery is done for appropriate indications, almost all patients have improved quality of life.

**Ulcerative Colitis**

Ulcerative colitis (UC) is a chronic inflammatory and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea. Extraintestinal symptoms, particularly arthritis, may occur. Long-term risk of colon cancer is high. Diagnosis is by colonoscopy. Treatment is with 5-aminosalicylic acid, corticosteroids, immunomodulators, anticytokines, antibiotics, and occasionally surgery.

**Pathophysiology**

UC usually begins in the rectum. It may remain localized to the rectum (ulcerative proctitis) or extend proximally, sometimes involving the entire colon. Rarely, it involves most of the large bowel at once.

The inflammation caused by UC affects the mucosa and submucosa, and there is a sharp border between normal and affected tissue. Only in severe disease is the muscularis involved. In early cases, the mucous membrane is erythematous, finely granular, and friable, with loss of the normal vascular pattern and often with scattered hemorrhagic areas. Large mucosal ulcers with copious purulent exudate characterize severe disease. Islands of relatively normal or hyperplastic inflammatory mucosa (pseudopolyps) project above areas of ulcerated mucosa. Fistulas and abscesses do not occur.

**Toxic or fulminant colitis** occurs when transmural extension of ulceration results in localized ileus and peritonitis. Within hours to days, the colon loses muscular tone and begins to dilate. The terms toxic megacolon or toxic dilation are discouraged because the toxic inflammatory state and its complications can occur without frank megacolon (defined as transverse colon > 6 cm diameter during an exacerbation). Toxic colitis is a medical emergency that usually occurs spontaneously in the course of very severe colitis but is sometimes precipitated by opioid or anticholinergic antidiarrheal drugs. Colonic perforation may occur, which increases mortality significantly.

**Symptoms and Signs**

Bloody diarrhea of varied intensity and duration is interspersed with asymptomatic intervals. Usually an attack begins insidiously, with increased urgency to defecate, mild lower abdominal cramps, and blood and mucus in the stools. Some cases develop after an infection (eg, amebiasis, bacillary dysentery).

When ulceration is confined to the rectosigmoid, the stool may be normal or hard and dry, but rectal discharges of mucus loaded with RBCs and WBCs accompany or occur between bowel movements.
Systemic symptoms are absent or mild. If ulceration extends proximally, stools become looser and the patient may have > 10 bowel movements per day, often with severe cramps and distressing rectal tenesmus, without respite at night. The stools may be watery or contain mucus and frequently consist almost entirely of blood and pus.

Toxic or fulminant colitis manifests initially with sudden violent diarrhea, fever to 40° C (104° F), abdominal pain, signs of peritonitis (eg, rebound tenderness), and profound toxemia.

Systemic symptoms and signs, more common with extensive UC, include malaise, fever, anemia, anorexia, and weight loss. Extraintestinal manifestations (particularly joint and skin complications—see p. 167) are most common when systemic symptoms are present.

Diagnosis

• Stool cultures and microscopy (to exclude infectious causes)

• Sigmoidoscopy with biopsy

**Initial presentation:** Diagnosis is suggested by typical symptoms and signs, particularly when accompanied by extraintestinal manifestations or a history of previous similar attacks. UC should be distinguished from Crohn's disease (see Table 19-1) but more importantly from other causes of acute colitis (eg, infection; in elderly patients, ischemia).

In all patients, stool cultures for enteric pathogens should be done, and *Entamoeba histolytica* should be excluded by examination of fresh stool specimens. When amebiasis is suspected because of epidemiologic or travel history, serologic titers and biopsies should be done. History of prior antibiotic use or recent hospitalization should prompt stool assay for *Clostridium difficile* toxin. Patients at risk should be tested for HIV, gonorrhea, herpesvirus, chlamydia, and amebiasis. Opportunistic infections (eg, cytomegalovirus, *Mycobacterium avium-intracellulare*) or Kaposi's sarcoma must also be considered in immunosuppressed patients. In women using oral contraceptives, contraceptive-induced colitis is possible; it usually resolves spontaneously after hormone therapy is stopped.

Sigmoidoscopy should be done; it allows visual confirmation of colitis and permits direct sampling of stool or mucus for culture and microscopic evaluation, as well as biopsy of affected areas. Although visual inspection and biopsies may be nondiagnostic, because there is much overlap in appearance among different types of colitis, acute, self-limited, infectious colitis can usually be distinguished histologically from chronic idiopathic UC or Crohn's colitis. Severe perianal disease, rectal sparing, absence of bleeding, and asymmetric or segmental involvement of the colon indicate Crohn's disease rather than UC (see Table 19-1). Colonoscopy is usually unnecessary initially but should be done electively if inflammation has extended proximal to the reach of the sigmoidoscope.

Laboratory tests should be done to screen for anemia, hypoalbuminemia, and electrolyte abnormalities. Liver function tests should be done; elevated alkaline phosphatase and γ-glutamyl transpeptidase levels suggest possible primary sclerosing cholangitis. Perinuclear antineutrophil cytoplasmic antibodies are relatively specific (60 to 70%) for UC. Anti-*Saccharomyces cerevisiae* antibodies are relatively specific for Crohn's disease. However, these tests do not reliably separate the 2 diseases and are not recommended for routine diagnosis. Other possible laboratory abnormalities include leukocytosis, thrombocytosis, and elevated acute-phase reactants (eg, ESR, C-reactive protein).

X-rays are not diagnostic but occasionally show abnormalities. Plain X-rays of the abdomen may show mucosal edema, loss of haustration, and absence of formed stool in the diseased bowel. Barium enema shows similar changes, albeit more clearly, and may also show ulcerations, but the enema should not be done during an acute presentation. A shortened, rigid colon with an atrophic or pseudopolypoid mucosa is often seen after several years' illness. X-ray findings of thumbprinting and segmental distribution are more suggestive of intestinal ischemia or possibly Crohn's colitis rather than of UC.

**Recurrent symptoms:** Patients with known disease and a recurrence of typical symptoms should be examined, but extensive testing is not always required. Depending on duration and severity of symptoms,
Sigmoidoscopy or colonoscopy may be done and a CBC obtained. Cultures, ova and parasite examination, and C. difficile toxin assay should be done when there are atypical features to the relapse or when there is an exacerbation after prolonged remission, during a contagious outbreak, after antibiotic exposure, or whenever the clinician is suspicious.

**Fulminant symptoms:** Patients require further evaluation during severe flare-ups. Flat and upright abdominal x-rays should be taken; they may show megacolon or intraluminal gas accumulated over a long, continuous, paralyzed segment of colon—a result of lost muscle tone. Colonoscopy and barium enema should be avoided because of the risk of perforation. CBC, ESR, electrolytes, PT, PTT, and type and crossmatch should be obtained.

The patient must be watched closely for progressive peritonitis or perforation. Percussion over the liver is important because loss of hepatic dullness may be the first clinical sign of free perforation, especially in a patient whose peritoneal signs are suppressed by high-dose corticosteroids. Abdominal x-rays are taken every 1 or 2 days to follow the course of colonic distention and to detect free or intramural air.

**Prognosis**

Usually, UC is chronic with repeated exacerbations and remissions. In about 10% of patients, an initial attack becomes fulminant with massive hemorrhage, perforation, or sepsis and toxemia. Complete recovery after a single attack occurs in another 10%.

Patients with localized ulcerative proctitis have the best prognosis. Severe systemic manifestations, toxic complications, and malignant degeneration are unlikely, and late extension of the disease occurs in only about 20 to 30%. Surgery is rarely required, and life expectancy is normal. The symptoms, however, may prove stubborn and refractory. Moreover, because extensive UC may begin in the rectum and spread proximally, proctitis should not be considered localized until it has been observed for ≥ 6 mo. Localized disease that later extends is often more severe and more refractory to therapy.

**Colon cancer:** The risk of colon cancer is proportional to the duration of disease and amount of colon affected, but not necessarily to the clinical severity of the attacks. Some recent studies suggest that sustained microscopic inflammation is a risk factor, and that use of aminosalicylate to control inflammation is protective. Cancer begins to appear by 7 yr from onset of illness in patients with extensive colitis. The cumulative likelihood of cancer is about 3% at 15 yr, 5% at 20 yr, and 9% at 25 yr, representing an annual risk of about 0.5 to 1% after the 10th yr. There is probably no higher absolute cancer risk among patients with childhood-onset colitis independent of the longer duration of disease. However, patients who have inflammatory bowel disease and primary sclerosing cholangitis are at a higher risk of cancer from the time of colitis diagnosis.

Regular colonoscopic surveillance, preferably during remission, is advised for patients with disease duration > 8 to 10 yr (except for those with isolated proctitis). Endoscopic biopsies should be taken every 10 cm throughout the colon. Newer techniques, especially chromoendoscopy, may better identify areas of suspicion in preference to totally random biopsies. Any grade of definite dysplasia within an area affected by colitis is liable to progress to more advanced neoplasia and even cancer and is a strong indication for total colectomy unless the dysplasia is strictly confined to a discrete, completely excisable polyp. It is important to distinguish definite neoplastic dysplasia from reactive or regenerative atypia secondary to inflammation. However, if the dysplasia is unequivocal, delaying colectomy in favor of repeated follow-up surveillance is a risky strategy. Pseudopolyps have no prognostic significance but may be difficult to distinguish from neoplastic polyps; thus, any suspect polyp should undergo excision biopsy.

The optimal frequency of colonoscopic surveillance has not been established, but some authorities recommend every 2 yr during the 2nd decade of disease and annually thereafter.

Long-term survival after diagnosis of colitis-related cancer is about 50%, a figure comparable to that for colorectal cancer in the general population.

**Treatment**
• Loperamide and dietary management for symptom relief
• 5-Aminosalicylic acid (5-ASA)
• Corticosteroids and other drugs depending on symptoms and severity
• Anticytokine drugs
• Sometimes surgery

Details of specific drugs and regimens are discussed on p. 167.

**General management:** Avoiding raw fruits and vegetables limits trauma to the inflamed colonic mucosa and may lessen symptoms. A milk-free diet may help but need not be continued if no benefit is noted. Loperamide 2 mg po bid to qid is indicated for relatively mild diarrhea; higher oral doses (4 mg in the morning and 2 mg after each bowel movement) may be required for more intense diarrhea. Antidiarrheal drugs must be used with extreme caution in severe cases because they may precipitate toxic dilation.

**Mild left-sided disease:** Patients with proctitis, or colitis that does not extend proximally beyond the splenic flexure, are treated with 5-ASA (mesalamine) enemas once/day or bid depending on severity. Suppositories are effective for more distal disease and are usually preferred by patients. Corticosteroid and budesonide enemas are slightly less effective but should be used if 5-ASA is unsuccessful or not tolerated. Once remission is achieved, dosage is slowly tapered to maintenance levels. Oral 5-ASA drugs theoretically have some incremental benefit in lessening the probability of proximal spread of disease.

**Moderate or extensive disease:** Patients with inflammation proximal to the splenic flexure or left-sided disease unresponsive to topical agents should receive an oral 5-ASA formulation in addition to 5-ASA enemas. High-dose corticosteroids are added for more severe symptoms; after 1 to 2 wk, the daily dose is reduced by about 5 to 10 mg each wk. Immunomodulater therapy with azathioprine or 6-mercaptopurine can be used in patients who are refractory to maximal doses of 5-ASA and would otherwise need long-term corticosteroid therapy. Additionally, infliximab is beneficial in some patients and may be considered for those refractory to immunomodulator or corticosteroid therapy as well as those who are corticosteroid dependent.

**Severe disease:** Patients with > 10 bloody bowel movements per day, tachycardia, high fever, or severe abdominal pain require hospitalization to receive high-dose IV corticosteroids. 5-ASA may be continued. IV fluids and blood transfusion are given as needed for dehydration and anemia. The patient must be observed closely for the development of toxic megacolon. Parenteral hyperalimentation is sometimes used for nutritional support but is of no value as primary therapy; patients who can tolerate food should eat.

Patients who do not respond within 3 to 7 days should be considered for IV cyclosporine or infliximab or else for surgery. Patients who do respond to a corticosteroid regimen are switched within a week or so to prednisone 60 mg po once/day, which may be gradually reduced at home based on clinical response. Patients who are started on IV cyclosporine and respond to therapy are switched to oral cyclosporine and concomitant azathioprine or 6-mercaptopurine. Oral cyclosporine is continued for about 3 to 4 mo, during which time corticosteroids are tapered and cyclosporine levels are closely monitored. Some clinicians recommend prophylaxis against *Pneumocystis jirovecii* pneumonia during the interval of overlapping treatment with corticosteroids, cyclosporine, and an antimetabolite.

**Fulminant colitis:** If fulminant colitis or toxic megacolon is suspected, the patient should (1) stop all antidiarrheal drugs; (2) take nothing by mouth and have inserted a long intestinal tube attached to intermittent suction; (3) receive aggressive IV fluid and electrolyte therapy with 0.9% NaCl, and potassium chloride and blood as needed; (4) be treated with high-dose IV corticosteroid or cyclosporine; and (5) receive antibiotics (eg, metronidazole 500 mg IV q 8 h and ciprofloxacin 500 mg IV q 12 h).

Having the patient roll over in bed from the supine to prone position every 2 to 3 h may help redistribute colonic gas and prevent progressive distention. Passage of a soft rectal tube may also be helpful but
must be done with extreme caution to avoid bowel perforation.

If intensive medical measures do not produce definite improvement within 24 to 48 h, immediate surgery is required or the patient may die of sepsis caused by bacterial translocation or even perforation.

**Maintenance therapy:** After effective treatment of a flare-up, corticosteroids are tapered based on clinical response and then stopped because they are ineffective as maintenance. Patients should remain on 5-ASA drugs indefinitely—oral or rectal, depending on location of disease—because stopping maintenance therapy often allows disease relapse. Dosage intervals for rectal preparations may be gradually lengthened to every 2nd or 3rd day.

Patients who cannot be withdrawn from corticosteroids should be given azathioprine or 6-mercaptopurine. Also, infliximab is becoming more widely accepted as maintenance therapy for UC as well as for Crohn's disease.

**Surgery:** Nearly one third of patients with extensive UC ultimately require surgery. Total proctocolectomy is curative: Life expectancy and quality of life are restored to normal, the disease does not recur (unlike Crohn's disease), and the risk of colon cancer is eliminated.

Emergency colectomy is indicated for massive hemorrhage, fulminating toxic colitis, or perforation. Subtotal colectomy with ileostomy and rectosigmoid closure or mucous fistula is usually the procedure of choice because most critically ill patients cannot tolerate more extensive surgery. The rectosigmoid stump may be electively removed later or may be used for ileoanal anastomosis with a pouch. The intact rectal stump should not be allowed to remain indefinitely because of the risk of disease activation and malignant transformation.

Elective surgery is indicated for cancer, symptomatic strictures, growth retardation in children, or, most commonly, intractable chronic disease resulting in invalidism or corticosteroid dependence. Colectomy is also done for high-grade and perhaps even low-grade mucosal dysplasia confirmed on pathologic consultation, unless the dysplasia is limited exclusively to a completely excisable polyp. Severe colitis-related extraintestinal manifestations (eg, pyoderma gangrenosum), now better controlled by intensive medical therapies, are only rarely indications for surgery.

The elective procedure of choice in patients with normal sphincter function is restorative proctocolectomy with ileoanal anastomosis. This procedure creates a pelvic reservoir or pouch from distal ileum, which is connected to the anus. The intact sphincter allows continence, typically with 8 to 10 bowel movements/day. Pouchitis is an inflammatory reaction occurring after this procedure in about 50% of patients. It is thought to be related to bacterial overgrowth and is treated with antibiotics (eg, quinolones). Probiotics may be protective. Most cases of pouchitis are readily controlled, but 5 to 10% prove refractory to all medical therapy and require conversion to a conventional (Brooke) ileostomy. For a minority of patients who are older, who have well-established families and lifestyles, who have poor sphincter tone or cannot tolerate frequent bowel movements, or who are simply unable or unwilling to face the consequences of frequent or chronic pouchitis, the Brooke ileostomy remains the procedure of choice.

In any event, the physical and emotional burdens imposed by any form of colon resection must be recognized, and care should be taken to see that the patient receives all the instructions and all the medical and psychologic support that is necessary before and after surgery.
Chapter 20. Diverticular Disease

Introduction

Diverticula are saclike mucosal outpouchings that protrude from a tubular structure. True diverticula contain all layers of the parent structure. False or pseudodiverticula are mucosal projections through the muscular layer. Esophageal (see p. 125) and Meckel's diverticula are true diverticula. Colonic diverticula are pseudodiverticula; they cause symptoms by trapping feces and becoming inflamed or infected, bleeding, or rupturing.

Diverticulosis

Diverticulosis is the presence of multiple diverticula in the colon, probably resulting from a lifelong low-fiber diet. Most diverticula are asymptomatic, but some become inflamed or bleed. Diagnosis is by colonoscopy or barium enema. Treatment varies depending on manifestation.

Diverticula occur anywhere in the large bowel—usually in the sigmoid but rarely below the peritoneal reflection of the rectum. They vary in diameter from 3 mm to > 3 cm. Patients with diverticula usually have several of them. Diverticulosis is uncommon in people < 40 but becomes common rapidly thereafter; essentially every 90-yr-old person has many diverticula. Giant diverticula, which are rare, range in diameter from 3 to 15 cm and may be single.

Pathophysiology

Diverticula are probably caused by increased intraluminal pressure leading to mucosal extrusion through the weakest points of the muscular layer of the bowel—areas adjacent to intramural blood vessels. Diverticula are more common among people who eat a low-fiber diet; however, the mechanism is not clear. One theory is that increased intraluminal pressure is required to move low-bulk stool through the colon. Another theory is that low-stool bulk causes a smaller diameter colon, which by Laplace's law would have increased pressure.

The etiology of giant diverticula is unclear. One theory is that a valvelike abnormality exists at the base of the diverticulum, so bowel gas can enter but escapes less freely.

Symptoms and Signs

Most (70%) diverticula are asymptomatic, 15 to 25% become painfully inflamed (diverticulitis), and 10 to 15% bleed painlessly. The bleeding is probably caused by erosion of the adjacent vessel by local trauma from impacted feces in the diverticulum. Although most diverticula are distal, 75% of bleeding occurs from diverticula proximal to the splenic flexure. In 33% of patients (5% overall), bleeding is serious enough to require transfusion.

Diagnosis

• Usually colonoscopy

Asymptomatic diverticula are usually found incidentally during barium enema or colonoscopy. Diverticulosis is suspected when painless rectal bleeding develops, particularly in an elderly patient. Evaluation of rectal bleeding typically includes colonoscopy, which can be done electively after routine preparation unless there is significant ongoing bleeding. In such patients, a rapid preparation (5 to 10 L of polyethylene glycol solution delivered via NGT over 3 to 4 h) often allows adequate visualization. If colonoscopy cannot visualize the source and ongoing bleeding is sufficiently rapid (> 0.5 to 1 mL/min), angiography may localize the source. Some angiographers first do a radionuclide scan to focus the examination.

Treatment

• High-fiber diet
• Sometimes angiographic or endoscopic treatment of bleeding

Treatment of diverticulosis aims at reducing segmental spasm. A high-fiber diet helps and may be supplemented by psyllium seed preparations or bran. Low-fiber diets are contraindicated. The intuitive injunction to avoid seeds or other dietary material that might become impacted in a diverticulum has no established medical basis. Antispasmodics (eg, belladonna) are not of benefit and may cause adverse effects. Surgery is unwarranted for uncomplicated disease. Giant diverticula, however, require surgery.

Diverticular bleeding stops spontaneously in 75% of patients. Treatment is often given during diagnostic procedures. If angiography was done for diagnosis, ongoing bleeding can be controlled in 70 to 90% of patients by intraarterial injection of vasopressin. In some cases, bleeding recurs within a few days and requires surgery. Angiographic embolization effectively stops bleeding but leads to bowel infarction in up to 20% of patients and is not recommended. Colonoscopy allows heat or laser coagulation of vessels or injection of epinephrine. If these measures fail to stop bleeding, segmental resection or subtotal colectomy is indicated.

**Diverticulitis**

*Diverticulitis is inflammation of a diverticulum, which can result in phlegmon of the bowel wall, peritonitis, perforation, fistula, or abscess. The primary symptom is abdominal pain. Diagnosis is by CT. Treatment is with antibiotics (ciprofloxacin, or a 3rd-generation cephalosporin plus metronidazole) and occasionally surgery.*

Diverticulitis occurs when a micro or macro perforation develops in a diverticulum, releasing intestinal bacteria. The resultant inflammation remains localized in about 75% of patients. The remaining 25% may develop abscess, free intraperitoneal perforation, bowel obstruction, or fistulas. The most common fistulas involve the bladder but may also involve the small bowel, uterus, vagina, abdominal wall, or even the thigh.

Diverticulitis is most serious in elderly patients, especially those taking prednisone or other drugs that increase the risk of infection. Nearly all serious diverticulitis occurs in the sigmoid.

**Symptoms and Signs**

Diverticulitis usually manifests with pain or tenderness in the left lower quadrant of the abdomen and fever. Peritoneal signs (eg, rebound or guarding) may be present, particularly with abscess or free perforation. Fistulas may manifest as pneumaturia, feculent vaginal discharge, or a cutaneous or myofascial infection of the abdominal wall, perineum, or upper leg. Patients with bowel obstruction have nausea, vomiting, and abdominal distention. Bleeding is uncommon.

**Diagnosis**

• Abdominal CT

• Colonoscopy after resolution

Clinical suspicion is high in patients with known diverticulosis. However, because other disorders (eg, appendicitis, colon or ovarian cancer) may cause similar symptoms, testing is required. Abdominal CT with oral and IV contrast is preferred, although findings in about 10% of patients cannot be distinguished from colon cancer. Colonoscopy, after resolution of the acute infection, is necessary for definitive diagnosis.

**Treatment**

• Varies with severity

• Liquid diet, oral antibiotics for mild disease
• IV antibiotics, npo for more severe disease

• CT-guided percutaneous drainage of abscess

• Sometimes surgery

A patient who is not very ill is treated at home with rest, a liquid diet, and oral antibiotics (eg, ciprofloxacin 500 mg bid amoxicillin/clavulanate 500 mg tid plus metronidazole 500 mg qid). Symptoms usually subside rapidly. The patient gradually advances to a soft low-fiber diet and a daily psyllium seed preparation. The colon should be evaluated after 2 to 4 wk with a colonoscopy or barium enema. After 1 mo, a high-fiber diet is resumed.

Patients with more severe symptoms (eg, pain, fever, marked leukocytosis) should be hospitalized, as should patients taking prednisone (who are at higher risk of perforation and general peritonitis). Treatment is bed rest, npo, IV fluids, and IV antibiotics (eg, ceftazidime 1 g IV q 8 h plus metronidazole 500 mg IV q 6 to 8 h).

About 80% of patients can be treated successfully without surgery. An abscess may respond to percutaneous drainage (CT guided). If response is satisfactory, the patient remains hospitalized until symptoms are relieved and a soft diet is resumed. A colonoscopy or barium enema is done ≥ 2 wk after symptoms have resolved.

Surgery: Surgery is required immediately for patients with free perforation or general peritonitis and for patients with severe symptoms that do not respond to nonsurgical treatment within 48 h. Increasing pain, tenderness, and fever are other signs that surgery is needed. Surgery should also be considered in patients with any of the following: ≥ 2 previous attacks of mild diverticulitis (or one attack in a patient < 50); a persistent tender mass; clinical, endoscopic, or x-ray signs suggestive of cancer; and dysuria associated with diverticulitis in men (or in women who have had a hysterectomy), because this symptom may presage perforation into the bladder.

The involved section of the colon is resected. The ends can be reanastomosed immediately in healthy patients without perforation, abscess, or significant inflammation. Other patients have a temporary colostomy with anastomosis carried out in a subsequent operation after inflammation resolves and the patient's general condition improves.

Meckel's Diverticulum

Meckel's diverticulum is a congenital sacculation of the distal ileum occurring in 2 to 3% of people. It is usually located within 100 cm of the ileocecal valve and often contains heterotopic gastric tissue, pancreatic tissue, or both. Symptoms are uncommon but include bleeding, bowel obstruction, and inflammation (diverticulitis). Diagnosis is difficult and often involves radionuclide scanning and barium studies. Treatment is surgical resection.

Pathophysiology

In early fetal life, the vitelline duct running from the terminal ileum to the umbilicus and yolk sac is normally obliterated by the 7th wk. If the portion connecting to the ileum fails to atrophy, a Meckel's diverticulum results. This congenital diverticulum arises from the antimesenteric margin of the intestine and contains all layers of the normal bowel. About 50% of diverticula also contain heterotopic tissue of the stomach (and thus contain parietal cells that secrete HCl), pancreas, or both.

Only about 2% of people with Meckel's diverticulum develop complications. Although diverticula are equally common among males and females, males are 2 to 3 times more likely to have complications. Complications include the following:

• Bleeding
Bleeding is more common among young children (< 5 yr) and occurs when acid secreted from ectopic gastric mucosa in the diverticulum ulcerates the adjacent ileum. Obstruction can occur at any age but is more common among older children and adults. In children, obstruction is most likely caused by intussusception of the diverticulum. Obstruction may also result from adhesions, volvulus, retained foreign bodies, tumors, or incarceration in a hernia (Littre's hernia). Acute Meckel's diverticulitis can occur at any age, but its incidence peaks in older children. Tumors, including carcinoids, are rare and occur mainly in adults.

**Symptoms and Signs**

In all ages, intestinal obstruction is manifested by cramping abdominal pain, nausea, and vomiting. Acute Meckel's diverticulitis is characterized by abdominal pain and tenderness typically localized below or to the left of the umbilicus; it is often accompanied by vomiting and is similar to appendicitis except for location of pain.

Children may present with repeated episodes of painless, bright red rectal bleeding, which is usually not severe enough to cause shock. Adults may also bleed, typically resulting in melena rather than frank blood.

**Diagnosis**

- Based on symptoms
- Radionuclide scan for bleeding
- CT for pain

Diagnosis is difficult, and tests are chosen based on presenting symptoms. If rectal bleeding is suspected to originate from a Meckel's diverticulum, a $^{99m}$Tc pertechnetate scan may identify ectopic gastric mucosa and hence the diverticulum. Patients presenting with abdominal pain and focal tenderness should have a CT scan with oral contrast. If vomiting and signs of obstruction are predominant, flat and upright x-rays of the abdomen are done. Sometimes diagnosis is made only during surgical exploration for presumed appendicitis; whenever a normal appendix is found, Meckel's diverticulum should be suspected.

**Treatment**

- Surgery

Patients with intestinal obstruction caused by Meckel's diverticulum require early surgery. For detailed treatment of intestinal obstruction, see p. 117.

A bleeding diverticulum with an indurated area in the adjacent ileum requires resection of this section of the bowel and the diverticulum. A bleeding diverticulum without ileal induration requires only resection of the diverticulum.

Meckel's diverticulitis also requires resection. Small, asymptomatic diverticula encountered incidentally at laparotomy need not be removed.

**Diverticular Disease of the Stomach and Small Bowel**

Diverticula rarely involve the stomach but occur in the duodenum in up to 25% of people. Most duodenal
diverticula are solitary and occur in the second portion of the duodenum near the ampulla of Vater (periampullary). Jejunal diverticula occur in about 0.26% of patients and are more common among patients with disorders of intestinal motility. Meckel's diverticulum occurs in the distal ileum.

Duodenal and jejunal diverticula are asymptomatic in > 90% of cases and are usually detected incidentally during radiologic or endoscopic investigation of the upper GI tract for an unrelated disease. Rarely, small-bowel diverticula bleed or become inflamed, causing pain and nausea. Some even perforate. For poorly understood reasons, patients with periampullary diverticula are at increased risk of gallstones and pancreatitis. Treatment is surgical resection; however, the clinician should be cautious of recommending surgery for patients with a diverticulum and vague GI symptoms (eg, dyspepsia).
Chapter 21. Anorectal Disorders

Introduction

(See also Foreign Bodies on p. 139 and Anorectal Cancer on p. 195.)

The anal canal begins at the anal sphincter and ends at the anorectal junction (pectinate line, mucocutaneous junction, dentate line), where there are 8 to 12 anal crypts and 5 to 8 papillae. The canal is lined with anoderm, a continuation of the external skin. The anal canal and adjacent skin are innervated by somatic sensory nerves and are highly susceptible to painful stimuli. Venous drainage from the anal canal occurs through the caval system, but the anorectal junction can drain into both the portal and caval systems. Lymphatics from the anal canal pass to the internal iliac nodes, the posterior vaginal wall, and the inguinal nodes. The venous and lymphatic distributions determine how malignant disease and infection spread.

The rectum is a continuation of the sigmoid colon beginning at the level of the 3rd sacral vertebra and continuing to the anorectal junction. The rectal lining consists of red, glistening glandular mucosa, which has an autonomic nerve supply and is relatively insensitive to pain. Venous drainage occurs through the portal system. Lymphatic return from the rectum occurs along the superior hemorrhoidal vascular pedicle to the inferior mesenteric and aortic nodes.

The sphincteric ring encircling the anal canal is composed of the internal sphincter, the central portion of the levators, and components of the external sphincter. Anteriorly, it is more vulnerable to trauma, which can result in incontinence. The puborectalis forms a muscular sling around the rectum for support and assistance in defecation.

History: History should include the details of bleeding, pain, protrusion, discharge, swelling, abnormal sensations, bowel movements, incontinence, stool characteristics, use of cathartics and enemas, and abdominal and urinary symptoms. All patients should be asked about anal intercourse and other possible causes of trauma and infection.

Physical examination: Examination should be done gently and with good lighting. It consists of external inspection, perianal and intrarectal digital palpation, abdominal examination, and rectovaginal bidigital palpation. Anoscopy and rigid or flexible sigmoidoscopy to 15 to 60 cm above the anal verge are often included (see p. 98). Inspection, palpation, and anoscopy and sigmoidoscopy are best done with the patient in the left lateral (Sims') position or inverted on a tilt table. In cases of painful anal lesions, topical (lidocaine 5% ointment), regional, or even general anesthesia may be required. If it can be tolerated, a cleansing phosphate enema may facilitate sigmoidoscopy. Biopsies, smears, and cultures may be taken, and x-ray examination done if indicated.

Anal Fissure

(Fissure in Ano; Anal Ulcer)

An anal fissure is an acute longitudinal tear or a chronic ovoid ulcer in the squamous epithelium of the anal canal. It causes severe pain, sometimes with bleeding, particularly with defecation. Diagnosis is by inspection. Treatment is local hygiene, stool softeners, and sometimes botulinum toxin injection.

Anal fissures are believed to result from laceration by a hard or large stool, with secondary infection. Trauma (eg, anal intercourse) is a rare cause. The fissure may cause internal sphincter spasm, decreasing blood supply and perpetuating the fissure.

Symptoms and Signs

Anal fissures usually lie in the posterior midline but may occur in the anterior midline. Those off the midline may have specific etiologies, particularly Crohn's disease. An external skin tag (the sentinel pile) may be present at the lower end of the fissure, and an enlarged (hypertrophic) papilla may be present at...
Infants may develop acute fissures, but chronic fissures are rare. Chronic fissures must be differentiated from cancer, primary lesions of syphilis, TB, and ulceration caused by Crohn's disease.

Fissures cause pain and bleeding. The pain typically occurs with or shortly after defecation, lasts for several hours, and subsides until the next bowel movement. Examination must be gentle but with adequate spreading of the buttocks to allow visualization.

Diagnosis

Diagnosis is made by inspection. Unless findings suggest a specific cause, further studies are not required.

Treatment

• Stool softeners
• Protective ointments, sitz baths
• Nitroglycerin ointment or botulinum toxin type A injection

Fissures often respond to conservative measures that minimize trauma during defecation (eg, stool softeners, psyllium, fiber). Healing is aided by use of protective zinc oxide ointments or bland suppositories (eg, glycerin) that lubricate the lower rectum and soften stool. Topical anesthetics (eg, benzocaine, lidocaine) and warm (not hot) sitz baths for 10 or 15 min after each bowel movement and prn give temporary relief.

Topical nitroglycerin 0.2% ointment, nifedipine cream 0.2% or 0.3%, arginine gel, and injections of botulinum toxin type A into the internal sphincter relax the anal sphincter and decrease maximum anal resting pressure, allowing healing. When conservative measures fail, surgery (internal anal sphincterotomy or controlled anal dilation) is needed to interfere with the cycle of internal anal sphincter spasm.

Anorectal Abscess

An anorectal abscess is a localized collection of pus in the perirectal spaces. Abscesses usually originate in an anal crypt. Symptoms are pain and swelling. Diagnosis is primarily by examination and CT or pelvic MRI for deeper abscesses. Treatment is surgical drainage.

An abscess may be located in various spaces surrounding the rectum and may be superficial or deep. A perianal abscess is superficial and points to the skin. An ischiorectal abscess is deeper, extending across the sphincter into the ischiorectal space below the levator ani; it may penetrate to the contralateral side, forming a "horseshoe" abscess. An abscess above the levator ani (ie, supralelevator abscess) is quite deep and may extend to the peritoneum or abdominal organs; this abscess often results from diverticulitis or pelvic inflammatory disease. Crohn's disease (especially of the colon) sometimes causes anorectal abscess. A mixed infection usually occurs, with Escherichia coli, Proteus vulgaris, Bacteroides, streptococci, and staphylococci predominating.

Symptoms and Signs

Superficial abscesses can be very painful; perianal swelling, redness, and tenderness are characteristic. Deeper abscesses may be less painful but cause toxic symptoms (eg, fever, chills, malaise). There may be no perianal findings, but digital rectal examination may reveal a tender, fluctuant swelling of the rectal wall. High pelvirectal abscesses may cause lower abdominal pain and fever without rectal symptoms. Sometimes fever is the only symptom.

Diagnosis
• Clinical evaluation

• Rarely examination under anesthesia or CT

Patients who have a pointing cutaneous abscess, a normal digital rectal examination, and no signs of systemic illness do not require imaging. Those with any findings suggestive of a deeper abscess or Crohn's disease should have an examination under anesthesia at the time of drainage. Higher (supraleveloper) abscesses require CT to determine the intra-abdominal source of sepsis.

Treatment

• Incision and drainage

• Antibiotics for high-risk patients

Prompt incision and adequate drainage are required and should not wait until the abscess points. Many abscesses can be drained as an in-office procedure; deeper abscesses may require drainage in the operating room. Febrile, neutropenic, or diabetic patients or those with marked cellulitis should also receive antibiotics (eg, ciprofloxacin 500 mg IV q 12 h and metronidazole 500 mg IV q 8 h, ampicillin/sulbactam 1.5 g IV q 8 h). Antibiotics are not indicated for healthy patients with superficial abscesses. Anorectal fistulas may develop after drainage.

Anorectal Fistula

(Fistula in Ano)

An anorectal fistula is a tubelike tract with one opening in the anal canal and the other usually in the perianal skin. Symptoms are discharge and sometimes pain. Diagnosis is by examination and sigmoidoscopy. Treatment often requires surgery.

Fistulas arise spontaneously or occur secondary to drainage of a perirectal abscess. Predisposing causes include Crohn's disease and TB. Most fistulas originate in the anorectal crypts; others may result from diverticulitis, tumors, or trauma. Fistulas in infants are congenital and are more common among boys. Rectovaginal fistulas may be secondary to Crohn's disease, obstetric injuries, radiation therapy, or cancer.

Symptoms and Signs

A history of recurrent abscess followed by intermittent or constant discharge is usual. Discharge material is purulent, serosanguineous, or both. Pain may be present if there is infection. On inspection, one or more secondary openings can be seen. A cordlike tract can often be palpated. A probe inserted into the tract can determine the depth and direction and often the primary opening.

Diagnosis

• Clinical evaluation

• Sigmoidoscopy

Diagnosis is by examination. Sigmoidoscopy should follow to rule out Crohn's disease. Hidradenitis suppurativa, pilonidal sinus, dermal suppurative sinuses, and urethro-perineal fistulas must be differentiated from cryptogenic fistulas.

Treatment

• Various surgical procedures
Medical treatment if caused by Crohn's disease

In the past, the only effective treatment was surgery, in which the primary opening and the entire tract are unroofed and converted into a "ditch." Partial division of the sphincters may be necessary. Some degree of incontinence may occur if a considerable portion of the sphincteric ring is divided. Alternatives to conventional surgery include advancement flaps, biologic plugs, and fibrin glue instillations into the fistulous tract.

If diarrhea or Crohn's disease is present, fistulotomy is inadvisable because of delayed wound healing. For patients with Crohn's disease, metronidazole, other appropriate antibiotics, and suppressive therapies can be given (see p. 171). Infliximab is very effective in closing fistulas caused by Crohn's disease.

Fecal Incontinence

Fecal incontinence is involuntary defecation.

Fecal incontinence can result from injuries or diseases of the spinal cord, congenital abnormalities, accidental injuries to the rectum and anus, procidentia, diabetes, severe dementia, fecal impaction, extensive inflammatory processes, tumors, obstetric injuries, and operations involving division or dilation of the anal sphincters.

Physical examination should evaluate gross sphincter function and perianal sensation and rule out fecal impaction. Anal sphincter ultrasonography, pelvic and perineal MRIs, pelvic floor electromyography, and anorectal manometry are also useful.

Treatment

- Program of stool regulation
- Perineal exercises, sometimes with biofeedback
- Sometimes a surgical procedure

Treatment includes a bowel management program to develop a predictable pattern of defecation. The program includes intake of adequate fluid and sufficient dietary bulk. Sitting on a toilet or using another customary defecatory stimulant (eg, coffee) encourages defecation. A suppository (eg, glycerin, bisacodyl) or a phosphate enema may also be used. If a regular defecatory pattern does not develop, a low-residue diet and oral loperamide may reduce the frequency of defecation.

Simple perineal exercises, in which the patient repeatedly contracts the sphincters, perineal muscles, and buttocks, may strengthen these structures and contribute to continence, particularly in mild cases. Biofeedback (to train the patient to use the sphincters maximally and to better appreciate physiologic stimuli) should be considered before recommending surgery in well-motivated patients who can understand and follow instructions and who have an anal sphincter capable of recognizing the cue of rectal distention. About 70% of such patients respond to biofeedback.

A defect in the sphincter can be sutured directly. When there is insufficient residual sphincter for repair, particularly in patients < 50 yr of age, a gracilis muscle can be transposed. Some centers attach a pacemaker to the gracilis muscle, as well as an artificial sphincter; these or other experimental procedures are available in only a few centers in the US, as research protocols. Alternatively, a Thiersch wire or other material can be used to encircle the anus. When all else fails, a colostomy can be considered.

Hemorrhoids

(Piles)

Hemorrhoids are dilated veins of the hemorrhoidal plexus in the lower rectum. Symptoms
include irritation and bleeding. Thrombosed hemorrhoids are painful. Diagnosis is by inspection or anoscopy. Treatment is symptomatic or with endoscopic banding, injection sclerotherapy, or sometimes surgery.

External hemorrhoids are located below the dentate line and are covered by squamous epithelium. Internal hemorrhoids are located above the dentate line and are lined by rectal mucosa. Hemorrhoids typically occur in the right anterior, right posterior, and left lateral zones. They occur in adults and children.

Symptoms and Signs

Hemorrhoids are often asymptomatic, or they may simply protrude. Pruritus ani is not commonly caused by hemorrhoids.

External hemorrhoids may become thrombosed, resulting in a painful, purplish swelling. Rarely, they ulcerate and cause minor bleeding. Cleansing the anal region may be difficult.

Internal hemorrhoids typically manifest with bleeding after defecation; blood is noted on toilet tissue and sometimes in the toilet bowl. Internal hemorrhoids may be uncomfortable but are not as painful as thrombosed external hemorrhoids. Internal hemorrhoids sometimes cause mucus discharge and a sensation of incomplete evacuation.

Strangulated hemorrhoids occur when protrusion and constriction occlude the blood supply. They cause pain that is occasionally followed by necrosis and ulceration.

Diagnosis

- Anoscopy
- Sometimes sigmoidoscopy or colonoscopy

Most painful hemorrhoids, thrombosed, ulcerated or not, are seen on inspection of the anus and rectum. Anoscopy is essential in evaluating painless or bleeding hemorrhoids. Rectal bleeding should be attributed to hemorrhoids only after more serious conditions are excluded (eg, by sigmoidoscopy or colonoscopy).

Treatment

- Stool softeners, sitz baths
- Rarely excision for thrombosed external hemorrhoids
- Injection sclerotherapy or rubber band ligation for internal hemorrhoids

Symptomatic treatment is usually all that is needed. It is accomplished with stool softeners (eg, docusate, psyllium), warm sitz baths (ie, sitting in a tub of tolerably hot water for 10 min) after each bowel movement and pm, anesthetic ointments containing lidocaine, or witch hazel (hamamelis) compresses (which soothe by an unknown mechanism). Pain caused by a thrombosed hemorrhoid can be treated with NSAIDs. Infrequently, simple excision of the hemorrhoid may relieve pain rapidly; after infiltration with 1% lidocaine, the thrombosed portion of the hemorrhoid is excised, and the defect is closed with an absorbable suture. Bleeding hemorrhoids can be treated by injection sclerotherapy with 5% phenol in vegetable oil. Bleeding should cease at least temporarily.

Rubber band ligation is used for larger, prolapsing internal hemorrhoids or those that do not respond to conservative management. With mixed internal and external hemorrhoids, only the internal component should be rubber band ligated. The internal hemorrhoid is grasped and withdrawn through a stretched 1/2-cm diameter band, which is released to ligate the hemorrhoid, resulting in its necrosis and sloughing. One hemorrhoid is ligated every 2 wk; 3 to 6 treatments may be required. Sometimes, multiple
hemorrhoids can be ligated at a single visit.

Infrared photocoagulation is useful for ablating small internal hemorrhoids, hemorrhoids that cannot be rubber band ligated because of pain sensitivity, or hemorrhoids that are not cured with rubber band ligation. Laser destruction, cryotherapy, and various types of electrodestruction are of unproven efficacy. Surgical hemorrhoidectomy is required for patients who do not respond to other forms of therapy. Significant postoperative pain is common, as is urinary retention and constipation. Stapled hemorrhoidopexy is an alternative procedure for circumferential hemorrhoids, although its advantages and the indications have yet to be defined.

**Levator Syndrome**

Episodic rectal pain caused by spasm of the levator ani muscle.

*Proctalgia fugax* (fleeting pain in the rectum) and *coccydynia* (pain in the coccygeal region) are variants of levator syndrome. Rectal spasm causes pain, typically unrelated to defecation, usually lasting < 20 min. The pain may be brief and intense or a vague ache high in the rectum. It may occur spontaneously or with sitting and can awaken the patient from sleep. The pain may feel as if it would be relieved by the passage of gas or a bowel movement. In severe cases, the pain can persist for many hours and recur frequently. The patient may have undergone various rectal operations for these symptoms, with no benefit.

**Diagnosis**

- Clinical evaluation

Physical examination can exclude other painful rectal conditions (eg, thrombosed hemorrhoids, fissures, abscesses). Physical examination is often normal, although tenderness or tightness of the levator muscle, usually on the left, may be present. Occasional cases are caused by low back or prostate disorders.

**Treatment**

- Analgesics, sitz baths
- Sometimes electrogalvanic stimulation

Treatment consists of explanations to the patient of the benign nature of the condition. An acute episode may be relieved by the passage of gas or a bowel movement, by a sitz bath, or by a mild analgesic. When the symptoms are more intense, physical therapy with electrogalvanic stimulation applied to the lower rectum is usually effective. Skeletal muscle relaxants or anal sphincter massage under local or regional anesthesia can be tried, but the benefit is unclear.

**Pilonidal Disease**

*Pilonidal disease refers to an acute abscess or chronic draining sinus in the sacrococcygeal area.*

Pilonidal disease usually occurs in young, hirsute, white males but can also occur in women. One or several midline or adjacent-to-the-midline pits or sinuses occur in the skin of the sacral region and may form a cavity, often containing hair. The lesion is usually asymptomatic; infected lesions are painful.

Treatment of an acute abscess is by incision and drainage. Usually, one or more chronic draining sinuses persist and must be extirpated by excision and primary closure or, preferably, by an open technique (eg, cystotomy, marsupialization). Antibiotics are generally not needed.

**Proctitis**
Proctitis is inflammation of the rectal mucosa, which may result from infection, inflammatory bowel disease, or radiation. Symptoms are rectal discomfort and bleeding. Diagnosis is by sigmoidoscopy, usually with cultures and biopsy. Treatment depends on etiology.

Proctitis may be a manifestation of sexually transmitted disease, certain enteric infections (e.g., Campylobacter, Shigella, Salmonella), inflammatory bowel disease, or radiation treatments; it may be associated with prior antibiotic use. Sexually transmitted pathogens cause proctitis more commonly among homosexual men. Immunocompromised patients are at particular risk of infections with herpes simplex and cytomegalovirus.

**Symptoms and Signs**

Typically, patients report rectal bleeding or passage of mucus. Proctitis resulting from gonorrhea, herpes simplex, or cytomegalovirus may cause intense anorectal pain.

**Diagnosis**

- Proctoscopy or sigmoidoscopy
- Tests for syphilis and *Clostridium difficile*

Diagnosis requires proctoscopy or sigmoidoscopy, which may reveal an inflamed rectal mucosa. Small discrete ulcers and vesicles suggest herpes infection. Smears should be sent for culture of *Neisseria gonorrhoeae*, *Chlamydia* sp, enteric pathogens, and viral pathogens. Serologic tests for syphilis and stool tests for *C. difficile* toxin are done. Sometimes mucosal biopsy is needed. Colonoscopy may be valuable in some patients.

**Treatment**

- Various treatments depending on cause

Infective proctitis can be treated with antibiotics. Homosexual men with nonspecific proctitis may be treated empirically with ceftriaxone 125 mg IM once (or ciprofloxacin 500 mg po bid for 7 days), plus doxycycline 100 mg po bid for 7 days. Antibiotic-associated proctitis is treated with metronidazole (250 mg po qid) or vancomycin (125 mg po qid) for 7 to 10 days.

Radiation proctitis is usually effectively treated with topical formalin carefully applied to the affected mucosa. Alternative treatments include topical corticosteroids as foam (hydrocortisone 90 mg) or enemas (hydrocortisone 100 mg or methylprednisolone 40 mg) bid for 3 wk, or mesalamine (4 g) enema at bedtime for 3 to 6 wk. Mesalamine suppositories 500 mg once/day or bid, mesalamine 800 mg po tid, or sulfasalazine 500 to 1000 mg po qid for ≥ 3 wk alone or in combination with topical therapy may also be effective. Patients unresponsive to these forms of therapy may benefit from a course of systemic corticosteroids.

**Pruritus Ani**

**Pruritus ani is anal and perianal itching.**

The perianal skin tends to itch, which can result from numerous causes (see Table 21-1).

[Table 21-1. Causes of Pruritus Ani]

Occasionally, the irritation is misinterpreted by the patient as pain, so other causes of perianal pain (e.g., abscess) should be ruled out.

Diagnosis is based on the appearance of the anal skin and relevant information from the history. The skin typically shows dullness and thickening, although the underlying pathology is often obscured by
excoriation caused by scratching and secondary infection. A scraping of local skin is taken to rule out a fungal infection, and a stool sample should be examined for ova and parasites. Visible lesions should be biopsied.

Foods suspected of causing pruritus ani should be eliminated from the diet. Clothing should be loose, and bed clothing light. After bowel movements, the patient should cleanse the anal area with absorbent cotton or plain soft tissue moistened with water. Liberal, frequent dusting with nonmedicated talcum powder or cornstarch helps combat moisture. Hydrocortisone acetate 1% ointment, applied sparingly qid, may relieve symptoms. Systemic causes and parasitic or fungal infections must be treated specifically.

Rectal Prolapse and Procidentia

Rectal prolapse is painless protrusion of the rectum through the anus. Procidentia is complete prolapse of the entire thickness of the rectum. Diagnosis is by inspection. Surgery is usually required in adults.

Transient, minor prolapse of just the rectal mucosa often occurs in otherwise normal infants. Mucosal prolapse in adults persists and may progressively worsen.

Procidentia is complete prolapse of the entire thickness of the rectum. The primary cause is unclear. Most patients are women > 60.

Symptoms and Signs

The most prominent symptom is protrusion. It may only occur while straining or while walking or standing. Rectal bleeding can occur, and incontinence is frequent. Pain is uncommon unless incarceration occurs.

Diagnosis

• Clinical evaluation

• Sigmoidoscopy, colonoscopy, or barium enema

To determine the full extent of the prolapse, the clinician should examine the patient while the patient is standing or squatting and straining. Rectal procidentia can be distinguished from hemorrhoids by the presence of circumferential mucosal folds. Anal sphincter tone is usually diminished. Sigmoidoscopy, colonoscopy, or barium enema x-rays of the colon must be done to search for other disease. Primary neurologic disorders (eg, spinal cord tumors) must be ruled out.

Treatment

• Elimination of causes of straining

• For infants and children: Sometimes strapping buttocks together

• For adults: Sometimes surgery

In infants and children, conservative treatment is most satisfactory. Causes of straining should be eliminated. Firmly strapping the buttocks together with tape between bowel movements usually facilitates spontaneous resolution of the prolapse. For simple mucosal prolapse in adults, the excess mucosa can be excised. For procidentia, an abdominal operation may be required. In patients who are very old or in poor health, a wire or synthetic plastic loop can encircle the sphincteric ring (Thiersch’s procedure). Other perineal operations (eg, Delorme or Altemeier procedure) can be considered.
Chapter 22. Tumors of the GI Tract

Introduction

Various benign and malignant tumors can develop anywhere in the GI tract. Tumors of the mouth are discussed in Ch. 55.

Benign Esophageal Tumors

Although there are many types of benign esophageal tumors, most are of little consequence except for causing annoying swallowing symptoms (see p. 120) and rarely ulceration or bleeding. Leiomyoma, the most common, may be multiple but usually has an excellent prognosis.

Esophageal Cancer

The most common malignant tumor in the proximal two thirds of the esophagus is squamous cell carcinoma; adenocarcinoma is the most common in the distal one third. Symptoms are progressive dysphagia and weight loss. Diagnosis is by endoscopy, followed by CT and endoscopic ultrasound for staging. Treatment varies with stage and generally includes surgery with or without chemotherapy and radiation. Long-term survival is poor except for those with local disease.

Esophageal cancer accounts for an estimated 15,500 cases and 13,900 deaths in the US annually.

Squamous cell carcinoma: About 8000 cases occur annually in the US. It is more common in parts of Asia and in South Africa. In the US, it is 4 to 5 times more common among blacks than whites, and 2 to 3 times more common among men than women.

The primary risk factors are alcohol ingestion and tobacco use (in any form). Other factors include achalasia, human papillomavirus, lye ingestion (resulting in stricture), sclerotherapy, Plummer-Vinson syndrome, irradiation of the esophagus, and esophageal webs. Genetic causes are unclear, but 50% of patients with tylosis (hyperkeratosis palmaris et plantaris), an autosomal dominant disorder, have esophageal cancer by age 45, and 95% have it by age 55.

Adenocarcinoma: Adenocarcinoma occurs in the distal esophagus. Its incidence is increasing; it accounts for 50% of esophageal carcinoma in whites. It is 4 times more common among whites than blacks. Alcohol is not an important risk factor, but smoking is contributory. Adenocarcinoma of the distal esophagus is difficult to distinguish from adenocarcinoma of the gastric cardia invading the distal esophagus.

Most adenocarcinomas arise in Barrett's esophagus, which results from chronic gastroesophageal reflux disease and reflux esophagitis. In Barrett's esophagus, a metaplastic, columnar, glandular, intestine-like mucosa with brush border and goblet cells replaces the normal stratified squamous epithelium of the distal esophagus during the healing phase of acute esophagitis when healing takes place in the continued presence of stomach acid.

Other malignant tumors: Less common malignant tumors include spindle cell carcinoma (a poorly differentiated variant of squamous cell carcinoma), verrucous carcinoma (a well-differentiated variant of squamous cell carcinoma), pseudosarcoma, mucoepidermoid carcinoma, adenosquamous carcinoma, cylindroma (adenoid cystic carcinoma), primary oat cell carcinoma, choriocarcinoma, carcinosarcoma, and primary malignant melanoma.

Metastatic cancer constitutes 3% of esophageal cancer. Melanoma and breast cancer are most likely to metastasize to the esophagus; others include cancers of the head and neck, lung, stomach, liver, kidney, prostate, testis, and bone. These tumors usually seed the loose connective tissue stroma around the esophagus, whereas primary esophageal cancers begin in the mucosa or submucosa.

Symptoms and Signs
Early-stage esophageal cancer tends to be asymptomatic. When the lumen of the esophagus becomes constricted to < 14 mm, dysphagia commonly occurs. The patient first has difficulty swallowing solid food, then semisolid food, and finally liquid food and saliva; this steady progression suggests a growing malignant process rather than a spasm, benign ring, or peptic stricture. Chest pain may be present, usually radiating to the back.

Weight loss, even when the patient maintains a good appetite, is almost universal. Compression of the recurrent laryngeal nerve may lead to vocal cord paralysis and hoarseness. Compression of sympathetic nerves may lead to Horner's syndrome, and nerve compression elsewhere may cause spinal pain, hiccups, or paralysis of the diaphragm. Malignant pleural effusions or pulmonary metastasis may cause dyspnea. Intraluminal tumor involvement may cause odynophagia, vomiting, hematemesis, melena, iron deficiency anemia, aspiration, and cough. Fistulas between the esophagus and tracheobronchial tree may cause lung abscess and pneumonia. Other findings may include superior vena cava syndrome, malignant ascites, and bone pain.

Lymphatic spread to internal jugular, cervical, supraclavicular, mediastinal, and celiac nodes is common. The tumor usually metastasizes to lung and liver and occasionally to distant sites (eg, bone, heart, brain, adrenal glands, kidneys, peritoneum).

**Diagnosis**

- Endoscopy with biopsy
- Then CT and endoscopic ultrasound

There are no screening tests. Patients suspected of having esophageal cancer should have endoscopy with cytology and biopsy. Although barium x-ray may show an obstructive lesion, endoscopy is required for biopsy and tissue diagnosis.

Patients in whom esophageal cancer is identified require CT of the chest and abdomen to determine extent of tumor spread. If CT results are negative for metastasis, endoscopic ultrasound should be done to determine the depth of the tumor in the esophageal wall and regional lymph node involvement. Findings guide therapy and help determine prognosis.

Basic blood tests, including CBC, electrolytes, and liver function, should be done.

**Prognosis**

Prognosis depends greatly on stage, but overall is poor (5-yr survival: < 5%) because many patients present with advanced disease. Patients with cancer restricted to the mucosa have about an 80% survival rate, which drops to < 50% with submucosal involvement, 20% with extension to the muscularis propria, 7% with extension to adjacent structures, and < 3% with distant metastases.

**Treatment**

- Surgical resection, often combined with chemotherapy and radiation

Treatment decisions depend on tumor staging, size, location, and the patient's wishes (many choose to forgo aggressive treatment).

**General principles:** Patients with stage 0, I, or IIA disease (see Table 22-1) respond well to surgical resection; preoperative chemotherapy and radiation provide additional benefit. Those with stage IIB and III have poor survival with surgery alone; response and survival are enhanced by preoperative (neoadjuvant) use of radiation and chemotherapy to reduce tumor volume before surgery. Patients unable or unwilling to undergo surgery may receive some benefit from combined radiation and chemotherapy. Radiation or chemotherapy alone is of little benefit. Patients with stage IV disease require palliation and should not undergo surgery.
After treatment, patients are screened for recurrence by endoscopy and CT of the neck, chest, and abdomen at 6-mo intervals for 3 yr and annually thereafter.

Patients with Barrett’s esophagus require intense long-term treatment for gastroesophageal reflux disease (see p. 125) and endoscopic surveillance for malignant transformation at 3- to 12-mo intervals depending on the degree of metaplasia.

**Surgery:** En bloc resection for cure requires removal of the entire tumor, proximal and distal margins of normal tissue, all potentially malignant lymph nodes, and a portion of the proximal stomach sufficient to contain the distal draining lymphatics. The procedure requires gastric pull-up with esophagogastric anastomosis, small-bowel interposition, or colonic interposition. Pyloroplasty is required to ensure proper gastric drainage because esophagectomy necessarily results in bilateral vagotomy. This extensive surgery may be poorly tolerated by patients > 75 yr, particularly those with underlying cardiac or pulmonary disease (ejection fraction < 40%, or forced expiratory volume in 1 sec [FEV₁] < 1.5 L/min). Overall, operative mortality is about 5%.

Complications of surgery include anastomotic leaks, fistulas, and strictures; bilious gastroesophageal reflux; and dumping syndrome. The burning chest pain of bile reflux after distal esophagectomy can be more annoying than the original symptom of dysphagia and may require subsequent Roux-en-Y jejunostomy for bile diversion. An interposed segment of small bowel or colon in the chest has a tenuous blood supply, and torsion, ischemia, or gangrene of the interposed bowel may result.

**Table 22-1. Staging Esophageal Cancer***

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the esophagus</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the esophagus but is limited to the mediastinum</td>
</tr>
<tr>
<td>III</td>
<td>Tumor extends beyond the mediastinum to regional lymph nodes or involves adjacent structures</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor has metastasized to distant sites</td>
</tr>
</tbody>
</table>

External beam radiation therapy: Radiation is usually used in combination with chemotherapy for patients who are poor candidates for curative surgery, including those with advanced disease. Radiation is contraindicated in patients with tracheoesophageal fistula because tumor shrinkage enlarges the fistula. Similarly, patients with vascular encasement by tumor may experience massive hemorrhage with tumor shrinkage. During the early stages of radiation therapy, edema may worsen esophageal obstruction, dysphagia, and odynophagia. This problem may require esophageal dilation or preradiation placement of a percutaneous gastrostomy feeding tube. Other adverse effects of radiation therapy include nausea, vomiting, anorexia, fatigue, esophagitis, excess esophageal mucus production, xerostomia, stricture, radiation pneumonitis, radiation pericarditis, myocarditis, and myelitis (spinal cord inflammation).

Chemotherapy: Tumors are poorly responsive to chemotherapy alone. Response rates (defined as ≥ 50% reduction in all measurable areas of tumor) vary from 10 to 40%, but responses generally are incomplete (minor shrinkage of tumor) and temporary. No drug is notably more effective than another.

Most commonly, cisplatin and 5-fluorouracil are used in combination. However, several other drugs, including mitomycin, doxorubicin, vindesine, bleomycin, and methotrexate, also are active against squamous cell carcinoma.

Palliation: Palliation is directed at reducing esophageal obstruction sufficiently to allow oral intake. Suffering caused by esophageal obstruction can be significant, with salivation and recurrent aspiration. Options include manual dilation procedures (bougienage), orally inserted stents, radiation therapy, laser photocoagulation, and photodynamic therapy. In some cases, cervical esophagostomy with feeding jejunostomy is required.

Relief provided by esophageal dilation rarely lasts more than a few days. Flexible metal mesh stents are more effective at maintaining esophageal patency. Some plastic-coated models can also be used to occlude tracheoesophageal fistulas, and some are available with a valve that prevents reflux when the stent must be placed near the lower esophageal sphincter.

Endoscopic laser therapy can palliate dysphagia by burning a central channel through the tumor and can be repeated if needed. Photodynamic therapy uses an injection of porfimer sodium, a hematoporphyrin...
A derivative that is taken up by tissues and acts as a photosensitizer. When activated by a laser beam directed on the tumor, this substance releases cytotoxic oxygen singlets that destroy tumor cells. Patients receiving this treatment must avoid sun exposure for 6 wk after treatment because the skin is also sensitized to light.

**Supportive care:** Nutritional support by enteral or parenteral supplementation enhances the tolerability and feasibility of all treatments. An endoscopically or surgically placed feeding tube provides a more distal route for feeding when the esophagus is obstructed.

Because nearly all cases of esophageal cancer are fatal, end-of-life care should always aim to control symptoms, especially pain and inability to swallow secretions (see also p. 3483). At some point, many patients need substantial doses of opioids. Patients should be advised to make end-of-life care decisions early in the course of disease and to record their wishes in an advance directive (see p. 3471).

**Stomach Cancer**

**Etiology of stomach cancer is multifactorial, but *Helicobacter pylori* plays a significant role.** Symptoms include early satiety, obstruction, and bleeding but tend to occur late in the disease. Diagnosis is by endoscopy, followed by CT and endoscopic ultrasound for staging. Treatment is mainly surgery; chemotherapy may provide a temporary response. Long-term survival is poor except for those with local disease.

Stomach cancer accounts for an estimated 21,000 cases and over 11,000 deaths in the US annually. Gastric adenocarcinoma accounts for 95% of malignant tumors of the stomach; less common are localized gastric lymphomas (see p. 1016) and leiomyosarcomas. Stomach cancer is the 2nd most common cancer worldwide, but the incidence varies widely; incidence is extremely high in Japan, China, Chile, and Iceland. In the US, incidence has declined in recent decades to the 7th most common cause of death from cancer. In the US, it is most common among blacks, Hispanics, and American Indians. Its incidence increases with age; > 75% of patients are > 50 yr.

**Etiology**

*Helicobacter pylori* infection is the cause of most stomach cancer. Autoimmune atrophic gastritis (see p. 133) and various genetic factors (see Gastrointestinal Stromal Tumors on p. 190) are also risk factors. Dietary factors are not proven causes.

Gastric polyps can be precursors of cancer. Inflammatory polyps may develop in patients taking NSAIDs, and fundic foveolar polyps are common among patients taking proton pump inhibitors. Adenomatous polyps, particularly multiple ones, although rare, are the most likely to develop cancer. Cancer is particularly likely if an adenomatous polyp is > 2 cm in diameter or has a villous histology. Because malignant transformation cannot be detected by inspection, all polyps seen at endoscopy should be removed. The incidence of stomach cancer is generally decreased in patients with duodenal ulcer.

**Pathophysiology**

Gastric adenocarcinomas can be classified by gross appearance:

- **Protruding:** The tumor is polypoid or fungating.
- **Penetrating:** The tumor is ulcerated.
- **Superficial spreading:** The tumor spreads along the mucosa or infiltrates superficially within the wall of the stomach.
- **Linitis plastica:** The tumor infiltrates the stomach wall with an associated fibrous reaction that causes a rigid "leather bottle" stomach.
- **Miscellaneous:** The tumor shows characteristics of ≥ 2 of the other types; this classification is the
Prognosis is better with protruding tumors than with spreading tumors because protruding tumors become symptomatic earlier.

### Symptoms and Signs

Initial symptoms are nonspecific, often consisting of dyspepsia suggestive of peptic ulcer. Patients and physicians alike tend to dismiss symptoms or treat the patient for acid disease. Later, early satiety (fullness after ingesting a small amount of food) may occur if the cancer obstructs the pyloric region or if the stomach becomes nondistensible secondary to linitis plastica. Dysphagia may result if cancer in the cardiac region of the stomach obstructs the esophageal outlet. Loss of weight or strength, usually resulting from dietary restriction, is common. Massive hematemesis or melena is uncommon, but secondary anemia may follow occult blood loss. Occasionally, the first symptoms are caused by metastasis (eg, jaundice, ascites, fractures).

Physical findings may be unremarkable or limited to heme-positive stools. Late in the course, abnormalities include an epigastric mass; umbilical, left supraclavicular, or left axillary lymph nodes; hepatomegaly; and an ovarian or rectal mass. Pulmonary, CNS, and bone lesions may occur.

### Diagnosis

- Endoscopy with biopsy
- Then CT and endoscopic ultrasound

Differential diagnosis commonly includes peptic ulcer and its complications.

Patients suspected of having stomach cancer should have endoscopy with multiple biopsies and brush cytology. Occasionally, a biopsy limited to the mucosa misses tumor tissue in the submucosa. X-rays, particularly double-contrast barium studies, may show lesions but rarely obviate the need for subsequent endoscopy.

Patients in whom cancer is identified require CT of the chest and abdomen to determine extent of tumor spread. If CT is negative for metastasis, endoscopic ultrasound should be done to determine the depth of the tumor and regional lymph node involvement. Findings guide therapy and help determine prognosis.

Basic blood tests, including CBC, electrolytes, and liver function tests, should be done to assess anemia, hydration, general condition, and possible liver metastases. Carcinoembryonic antigen (CEA) should be measured before and after surgery.

**Screening:** Screening with endoscopy is used in high-risk populations (eg, Japanese) but is not recommended in the US. Follow-up screening for recurrence in treated patients consists of endoscopy and CT of the chest, abdomen, and pelvis. If an elevated CEA dropped after surgery, follow-up should include CEA levels; a rise signifies recurrence.

### Prognosis

Prognosis depends greatly on stage but overall is poor (5-yr survival: < 5 to 15%) because most patients present with advanced disease. If the tumor is limited to the mucosa or submucosa, 5-yr survival may be as high as 80%. For tumors involving local lymph nodes, survival is 20 to 40%. More widespread disease is almost always fatal within 1 yr. Gastric lymphomas have a better prognosis and are discussed in Ch. 118.

### Treatment

- Surgical resection, sometimes combined with chemotherapy, radiation, or both
Treatment decisions depend on tumor staging and the patient's wishes (some may choose to forgo aggressive treatment—see p. 3471).

Curative surgery involves removal of most or all of the stomach and adjacent lymph nodes and is reasonable in patients with disease limited to the stomach and perhaps the regional lymph nodes (< 50% of patients). Adjuvant chemotherapy or combined chemotherapy and radiation therapy after surgery may be beneficial if the tumor is resectable.

Resection of locally advanced regional disease results in a 10-mo median survival (vs 3 to 4 mo without resection).

Metastasis or extensive nodal involvement precludes curative surgery, and at most, palliative procedures should be undertaken. However, the true extent of tumor spread often is not recognized until curative surgery is attempted. Palliative surgery typically consists of a gastroenterostomy to bypass a pyloric obstruction and should be done only if the patient's quality of life can be improved. In patients not undergoing surgery, combination chemotherapy regimens (5-fluorouracil, doxorubicin, mitomycin, cisplatin, or leucovorin in various combinations) may produce temporary response but little improvement in 5-yr survival. Radiation therapy is of limited benefit.

**Gastrointestinal Stromal Tumors**

Gastrointestinal stromal tumors are tumors of the GI tract derived from mesenchymal precursor cells in the gut wall. They result from mutations of a growth factor receptor gene, *CKIT*. Some are caused by previous radiation therapy to the abdomen for other tumors.

Tumors are slow growing, and malignant potential varies from minimal to significant. Most (60 to 70%) occur in the stomach, 20 to 25% in the small bowel, and a small number in the esophagus, colon, and rectum. Average age at presentation is 50 to 60.

Symptoms vary with location but include bleeding, dyspepsia, and obstruction. Diagnosis is usually by endoscopy, with biopsy and endoscopic ultrasound for staging. Treatment is surgical removal. The role of radiation and chemotherapy is unclear, but the tyrosine kinase inhibitor imatinib has been beneficial.

**Small-Bowel Tumors**

Small-bowel tumors account for 1 to 5% of GI tumors (over 5000 cases in the US annually).

**Benign tumors** include leiomyomas, lipomas, neurofibromas, and fibromas. All may cause abdominal distention, pain, bleeding, diarrhea, and, if obstruction develops, vomiting. Polyps are not as common as in the colon.

**Adenocarcinoma**, a malignant tumor, is uncommon. Usually it arises in the duodenum or proximal jejunum and causes minimal symptoms. In patients with Crohn's disease, the tumors tend to occur distally and in bypassed or inflamed loops of bowel; adenocarcinoma occurs more often in Crohn's disease of the small bowel than in Crohn's disease of the colon.

Primary malignant **lymphoma** (see p. 1016) arising in the ileum may cause a long, rigid segment. Small-bowel lymphomas arise often in long-standing untreated celiac sprue.

**Carcinoid tumors** (see p. 907) occur most often in the small bowel, particularly the ileum, and the appendix, and in these locations are often malignant. Multiple tumors occur in 50% of cases. Of those > 2 cm in diameter, 80% have metastasized locally or to the liver by the time of operation. About 30% of small-bowel carcinoids cause obstruction, pain, bleeding, or carcinoid syndrome. Treatment is surgical resection; repeat operations may be required.

**Kaposi's sarcoma** (see p. 753), first described as a disease of elderly Jewish and Italian men, occurs in an aggressive form in Africans, transplant recipients, and AIDS patients, who have GI tract involvement 40 to 60% of the time. Lesions may occur anywhere in the GI tract but usually in the stomach, small bowel,
or distal colon. GI lesions usually are asymptomatic, but bleeding, diarrhea, protein-losing enteropathy, and intussusception may occur. A second primary intestinal cancer occurs in ≤ 20% of patients; most often it is lymphocytic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, or adenocarcinoma of the GI tract. Treatment depends on the cell type and location and extent of the lesions.

**Diagnosis**

- Enteroclysis
- Sometimes push endoscopy or capsule video endoscopy

Enteroclysis (sometimes CT enteroclysis) is probably the most common study for mass lesions of the small bowel. Push endoscopy of the small bowel with an enteroscope may be used to visualize and biopsy tumors. Capsule video endoscopy can help identify small-bowel lesions, particularly bleeding sites; a swallowed capsule transmits 2 images/sec to an external recorder. The original capsule is not useful in the stomach or colon because it tumbles in these larger organs; a colon capsule camera with better optics and illumination is under development for use in these larger-diameter organs.

**Treatment**

- Surgical resection

Treatment is surgical resection. Electrocautery, thermal obliteration, or laser phototherapy at the time of enteroscopy or surgery may be an alternative to resection.

**Polyps of the Colon and Rectum**

An intestinal polyp is any mass of tissue that arises from the bowel wall and protrudes into the lumen. Most are asymptomatic except for minor bleeding, which is usually occult. The main concern is malignant transformation; most colon cancers arise in a previously benign adenomatous polyp. Diagnosis is by endoscopy. Treatment is endoscopic removal.

Polyps may be sessile or pedunculated and vary considerably in size. Incidence of polyps ranges from 7 to 50%; the higher figure includes very small polyps (usually hyperplastic polyps or adenomas) found at autopsy. Polyps, often multiple, occur most commonly in the rectum and sigmoid and decrease in frequency toward the cecum. Multiple polyps may represent familial adenomatous polyposis (see p. 192). About 25% of patients with cancer of the large bowel also have satellite adenomatous polyps.

**Adenomatous (neoplastic) polyps** are of greatest concern. Such lesions are classified histologically as tubular adenomas, tubulo-villous adenomas (villoglandular polyps), or villous adenomas. The likelihood of cancer in an adenomatous polyp at the time of discovery is related to size, histologic type, and degree of dysplasia; a 1.5-cm tubular adenoma has a 2% risk of containing a cancer vs a 35% risk in 3-cm villous adenomas. Serrated adenomas, a somewhat more aggressive type of adenoma, may develop from hyperplastic polyps.

**Nonadenomatous (nonneoplastic) polyps** include hyperplastic polyps, hamartomas, juvenile polyps, pseudopolyps, lipomas, leiomyomas, and other rarer tumors. Juvenile polyps occur in children, typically outgrow their blood supply, and autoamputate some time during or after puberty. Treatment is required only for uncontrollable bleeding or intussusception. Inflammatory polyps and pseudopolyps occur in chronic ulcerative colitis and in Crohn's disease of the colon. Multiple juvenile polyps (but not sporadic ones) convey an increased cancer risk. The specific number of polyps resulting in increased risk is not known.

**Symptoms and Signs**

Most polyps are asymptomatic. Rectal bleeding, usually occult and rarely massive, is the most frequent complaint. Cramps, abdominal pain, or obstruction may occur with a large lesion. Rectal polyps may be palpable by digital examination. Occasionally, a polyp on a long pedicle may prolapse through the anus.
Large villous adenomas may rarely cause watery diarrhea that may result in hypokalemia.

**Diagnosis**

- Colonoscopy

Diagnosis is usually made by colonoscopy. Barium enema, particularly double-contrast examination, is effective, but colonoscopy is preferred because polyps also may be removed during that procedure. Because rectal polyps are often multiple and may coexist with cancer, complete colonoscopy to the cecum is mandatory even if a distal lesion is found by flexible sigmoidoscopy.

**Treatment**

- Complete removal during colonoscopy
- Sometimes follow with surgical resection
- Follow-up surveillance colonoscopy

Polyps should be removed completely with a snare or electrosurgical biopsy forceps during total colonoscopy; complete excision is particularly important for large villous adenomas, which have a high potential for cancer. If colonoscopic removal is unsuccessful, laparotomy should be done.

Subsequent treatment depends on the histology of the polyp. If dysplastic epithelium does not invade the muscularis mucosa, the line of resection in the polyp's stalk is clear, and the lesion is well differentiated, endoscopic excision and close endoscopic follow-up should suffice. Patients with deeper invasion, an unclear resection line, or a poorly differentiated lesion should have segmental resection of the colon. Because invasion through the muscularis mucosa provides access to lymphatics and increases the potential for lymph node metastasis, such patients should have further evaluation (as in colon cancer—see p. 193).

The scheduling of follow-up examinations after polypectomy is controversial. Most authorities recommend total colonoscopy annually for 2 yr (or barium enema if total colonoscopy is impossible), with removal of newly discovered lesions. If 2 annual examinations are negative for new lesions, colonoscopy is recommended every 2 to 3 yr.

**Prevention**

Aspirin and COX-2 inhibitors may help prevent formation of new polyps in patients with polyps or colon cancer.

**Familial Adenomatous Polyposis**

Familial adenomatous polyposis (FAP) is a hereditary disorder causing numerous colonic polyps and resulting in colon carcinoma by age 40. Patients are usually asymptomatic but may have heme-positive stool. Diagnosis is by colonoscopy and genetic testing. Treatment is colectomy.

FAP is an autosomal dominant disease in which ≥ 100 adenomatous polyps carpet the colon and rectum. The disorder occurs in 1 in 8,000 to 14,000 people. Polyps are present in 50% of patients by age 15, and 95% by 35. Cancer develops before age 40 in nearly all untreated patients.

Patients also can develop various extracolonic manifestations (previously termed Gardner's syndrome), both benign and malignant. Benign manifestations include desmoid tumors, osteomas of the skull or mandible, sebaceous cysts, and adenomas in other parts of the GI tract. Patients are at increased risk of cancer in the duodenum (5 to 11%), pancreas (2%), thyroid (2%), brain (medulloblastoma in < 1%), and liver (hepatoblastoma in 0.7% of children < 5).
Symptoms and Signs

Many patients are asymptomatic, but rectal bleeding, typically occult, occurs.

Diagnosis

- Colonoscopy
- Genetic testing of patient and 1st-degree relatives
- Offspring screened for hepatoblastoma

Diagnosis is made by finding > 100 polyps on colonoscopy. Diagnosed patients should have genetic testing to identify the specific mutation, which should then be sought in 1st-degree relatives. If genetic testing is unavailable, relatives should be screened with annual sigmoidoscopy beginning at age 12, reducing frequency with each decade. If no polyps are evident by age 50, screening frequency is then the same as for average-risk patients.

Children of parents with FAP should be screened for hepatoblastoma from birth to age 5 yr with annual serum fetoprotein levels and possibly liver ultrasound.

Treatment

- Colectomy
- Endoscopic surveillance of remainder of GI tract
- Perhaps aspirin or coxibs

Colectomy should be done at the time of diagnosis. Total proctocolectomy, either with ileostomy or mucosal proctectomy and ileoanal pouch, eliminates the risk of cancer. If subtotal colectomy (removal of most of the colon, leaving the rectum) with ileorectal anastomosis is done, the rectal remnant must be inspected every 3 to 6 mo; new polyps must be excised or fulgurated. Aspirin or coxibs may inhibit new polyp formation. If new ones appear too rapidly or prolifically to remove, excision of the rectum and permanent ileostomy are needed.

After colectomy, patients should have upper endoscopy every 6 mo to 4 yr, depending on the number of polyps (if any) in the stomach and duodenum. Annual physical examination of the thyroid, and possibly ultrasound, also is recommended.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disease with multiple hamartomatous polyps in the stomach, small bowel, and colon along with distinctive pigmented skin lesions.

Patients are at a significantly increased risk of GI and non-GI cancers; possibly the genetic defect involves a tumor suppressor gene. GI cancers include those of the pancreas, small intestine, and colon. Non-GI cancers include those of the breast, lung, uterus, and ovaries.

The skin lesions are melanotic macules of the skin and mucous membranes, especially of the perioral region, lips and gums, hands, and feet. All but the buccal lesions tend to fade by puberty. Polyps may bleed and often cause obstruction or intussusception.

Diagnosis is suggested by the clinical picture. Genetic testing is not routinely available but should be considered. First-degree relatives should be evaluated and have routine surveillance for cancers, but there is no firm consensus on specific tests and intervals.

Colonic polyps larger than 1 cm typically are removed.
**Colorectal Cancer**

Colorectal cancer (CRC) is extremely common. Symptoms include blood in the stool or change in bowel habits. Screening is with fecal occult blood testing. Diagnosis is by colonoscopy. Treatment is surgical resection and chemotherapy for nodal involvement.

CRC accounts for an estimated 153,000 cases and 52,000 deaths in the US annually. In Western countries, the colon and rectum account for more new cases of cancer per year than any anatomic site except the lung. Incidence begins to rise at age 40 and peaks at age 60 to 75. Overall, 70% of cases occur in the rectum and sigmoid, and 95% are adenocarcinomas. Colon cancer is more common among women; rectal cancer is more common among men. Synchronous cancers (more than one) occur in 5% of patients.

**Etiology**

CRC most often occurs as transformation within adenomatous polyps. Serrated adenomas are particularly aggressive in their malignant transformation. About 80% of cases are sporadic, and 20% have an inheritable component. Predisposing factors include chronic ulcerative colitis and granulomatous colitis; the risk of cancer increases with the duration of these disorders.

Populations with a high incidence of CRC eat low-fiber diets that are high in animal protein, fat, and refined carbohydrates. Carcinogens may be ingested in the diet but are more likely produced by bacterial action on dietary substances or biliary or intestinal secretions. The exact mechanism is unknown.

CRC spreads by direct extension through the bowel wall, hematogenous metastasis, regional lymph node metastasis, perineural spread, and intraluminal metastasis.

**Symptoms and Signs**

Colorectal adenocarcinoma grows slowly, and a long interval elapses before it is large enough to cause symptoms. Symptoms depend on lesion location, type, extent, and complications.

The right colon has a large caliber, a thin wall, and its contents are liquid; thus, obstruction is a late event. Bleeding is usually occult. Fatigue and weakness caused by severe anemia may be the only complaints. Tumors sometimes grow large enough to be palpable through the abdominal wall before other symptoms appear.

The left colon has a smaller lumen, the feces are semisolid, and cancer tends to encircle the bowel, causing alternating constipation and increased stool frequency or diarrhea. Partial obstruction with colicky abdominal pain or complete obstruction may be the initial manifestation. The stool may be streaked or mixed with blood. Some patients present with symptoms of perforation, usually walled off (focal pain and tenderness), or rarely with diffuse peritonitis.

In rectal cancer, the most common initial symptom is bleeding with defecation. Whenever rectal bleeding occurs, even with obvious hemorrhoids or known diverticular disease, coexisting cancer must be ruled out. Tenesmus or a sensation of incomplete evacuation may be present. Pain is common with perirectal involvement.

Some patients first present with symptoms and signs of metastatic disease (eg, hepatomegaly, ascites, supraclavicular lymph node enlargement).

**Diagnosis**
**Colonoscopy**

**Screening tests**: Early diagnosis depends on routine examination, particularly fecal occult blood (FOB) testing. Cancer detected by this method tends to be at an earlier stage and hence more curable. For average-risk patients, FOB testing should be done annually after age 50, with flexible sigmoidoscopy every 5 yr. Some authorities recommend colonoscopy every 10 yr instead of sigmoidoscopy. Colonoscopy every 3 yr may be even better. Screening of patients with high-risk conditions (eg, ulcerative colitis) is discussed under the specific condition.

CT colonography (virtual colonoscopy) generates 3D and 2D images of the colon using multidetector row CT and a combination of oral contrast and gas distention of the colon. Viewing the high-resolution 3D images somewhat simulates the appearance of optical endoscopy, hence the name. It has some promise as a screening test for people who are unable or unwilling to undergo endoscopic colonoscopy but is less sensitive and highly interpreter dependent. It avoids the need for sedation but still requires thorough bowel preparation, and the gas distention may be uncomfortable. Additionally, unlike with optical colonoscopy, lesions cannot be biopsied during the diagnostic procedure.

Video capsule endoscopy of the colon has many technical problems and is not currently acceptable as a screening test.

**Diagnostic tests**: Patients with positive FOB tests require colonoscopy, as do those with lesions seen on sigmoidoscopy or imaging study. All lesions should be completely removed for histologic examination. If a lesion is sessile or not removable at colonoscopy, surgical excision should be strongly considered.

Barium enema x-ray, particularly a double-contrast study, can detect many lesions but is somewhat less accurate than colonoscopy and is not preferred as follow up to a positive FOB test.

Once cancer is diagnosed, patients should have abdominal CT, chest x-ray, and routine laboratory tests to seek metastatic disease and anemia and to evaluate overall condition.

Elevated serum carcinoembryonic antigen (CEA) levels are present in 70% of patients with CRC, but this test is not specific and therefore is not recommended for screening. However, if CEA is high preoperatively and low after removal of a colon tumor, monitoring CEA may help to detect recurrence earlier. CA 199 and CA 125 are other tumor markers that may be similarly used.

**Prognosis**

Prognosis depends greatly on stage (see Table 22-2). The 10-yr survival rate for cancer limited to the mucosa approaches 90%; with extension through the bowel wall, 70 to 80%; with positive lymph nodes, 30 to 50%; and with metastatic disease, < 20%.

**Treatment**

- **Surgical resection**, sometimes combined with chemotherapy, radiation, or both

**Surgery**: Surgery for cure can be attempted in the 70% of patients presenting without metastatic disease. Attempt to cure consists of wide resection of the tumor and its regional lymphatic drainage with reanastomosis of bowel segments. If there is ≤ 5 cm of normal bowel present between the lesion and the anal verge, an abdominoperineal resection is done, with permanent colostomy.

Resection of a limited number (1 to 3) of liver metastases is recommended in select nondebilitated patients as a subsequent procedure. Criteria include those whose primary tumor has been resected, whose liver metastases are in one hepatic lobe, and who have no extrahepatic metastases. Only a small number of patients with liver metastases meet these criteria, but 5-yr postoperative survival is 25%.

**Adjuvant therapy**: Chemotherapy (typically 5-fluorouracil and leucovorin) improves survival by 10 to 30% in colon cancer patients with positive lymph nodes. Rectal cancer patients with 1 to 4 positive lymph nodes benefit from combined radiation and chemotherapy; when > 4 positive lymph nodes are found,
combined modalities are less effective. Preoperative radiation therapy and chemotherapy to improve the resectability rate of rectal cancer or decrease the incidence of lymph node metastasis are gaining favor.

**Follow-up:** Postoperatively, colonoscopy should be done annually for 5 yr and every 3 yr thereafter if no polyps or tumors are found. If preoperative colonoscopy was incomplete because of an obstructing cancer, a "completion" colonoscopy should be done 3 mo after surgery.

Additional screening for recurrence should include history, physical examination, and laboratory tests (eg, CBC, liver function tests) every 3 mo for 3 yr and then every 6 mo for 2 yr. Imaging studies (CT or MRI) are often recommended at 1-yr intervals but are of uncertain benefit for routine follow up in the absence of abnormalities on examination or blood tests.

**Palliation:** When curative surgery is not possible or the patient is an unacceptable surgical risk, limited palliative surgery (eg, to relieve obstruction or resect a perforated area) may be indicated; median survival is 7 mo. Some obstructing tumors can be debulked by endoscopic laser treatment or electrocoagulation or held open by stents. Chemotherapy may shrink tumors and prolong life for several months.

Newer drugs used singly or in drug combinations include capecitabine (a 5-fluorouracil precursor), irinotecan, and oxaliplatin. Monoclonal antibodies such as bevacizumab, cetuximab, and panitumumab are also being used with some effectiveness. No regimen is clearly more effective for prolonging life in patients with metastatic CRC, although some have been shown to delay disease progression. Chemotherapy for advanced colon cancer should be managed by an experienced chemotherapist who has access to investigational drugs.

When metastases are confined to the liver, ambulatory hepatic artery infusion with floxuridine or radioactive microspheres via an implantable sc pump or an external pump worn on the belt may offer more benefit than systemic chemotherapy; however, these therapies are of uncertain benefit. When metastases are also extrahepatic, intrahepatic arterial chemotherapy offers no advantage over systemic chemotherapy.

**Anorectal Cancer**

The most common anorectal cancer is adenocarcinoma. Squamous cell (nonkeratinizing squamous cell or basaloid) carcinoma of the anorectum accounts for 3 to 5% of distal large-bowel cancers. Basal cell carcinoma, Bowen’s disease (intradermal carcinoma), extramammary Paget’s disease, cloacogenic carcinoma, and malignant melanoma are less common. Other tumors include lymphoma and various sarcomas. Metastasis occurs along the lymphatics of the rectum and into the inguinal lymph nodes.

Risk factors include infection with human papillomavirus (HPV), chronic fistulas, irradiated anal skin, leukoplasia, lymphogranuloma venereum, and condyloma acuminatum. Gay men practicing receptive anal intercourse are at increased risk. Patients with HPV infection may manifest dysplasia in slightly abnormal or normal-appearing anal epithelium (anal intraepithelial neoplasia—histologically graded I, II, or III). These changes are more common among HIV-infected patients, particularly gay men. Higher grades may progress to invasive carcinoma. It is unclear whether early recognition and eradication improve long-term outcome; hence, screening recommendations are unclear.

Wide local excision is often satisfactory treatment of perianal carcinomas. Combination chemotherapy and radiation therapy result in a high rate of cure when used for anal squamous and cloacogenic tumors. Abdominoperineal resection is indicated when radiation and chemotherapy do not result in complete regression of tumor and there are no metastases outside of the radiation field.

**Hereditary Nonpolyposis Colorectal Carcinoma**

Hereditary nonpolyposis colorectal carcinoma (HNPCC) is an autosomal dominant disorder responsible for 3 to 5% of cases of colorectal cancer (CRC). Symptoms, initial diagnosis, and treatment are similar to other forms of CRC. HNPCC is suspected by history and is confirmed by genetic testing. Patients also require surveillance for other cancer, particularly endometrial and
ovarian cancer.

Patients with one of several known mutations have a 70 to 80% lifetime risk of developing CRC. Compared to sporadic forms of colon cancer, HNPCC occurs at a younger age (mid 40s), and the lesion is more likely to be proximal to the splenic flexure. The precursor lesion is usually a single colonic adenoma, unlike the multiple adenomas present in patients with familial adenomatous polyposis (FAP), the other main hereditary form of CRC.

However, similar to FAP, numerous extracolonic manifestations occur. Nonmalignant disorders include cafe-au-lait spots, sebaceous gland tumors, and keratoacanthomas. Common associated cancers include endometrial and ovarian tumors (39% risk of endometrial and 9% risk of ovarian by age 70). Patients also have an elevated risk of cancer of the ureter, renal pelvis, stomach, biliary tree, and small bowel.

**Symptoms and Signs**

Symptoms and signs are similar to other forms of CRC, and diagnosis and management of the tumor itself are the same. The specific diagnosis of HNPCC is confirmed by genetic testing. However, deciding who to test is difficult because (unlike FAP) there is no typical clinical appearance. Thus, suspicion of HNPCC requires a detailed family history, which should be obtained in all younger patients identified with CRC.

**Diagnosis**

- Clinical criteria followed by testing for microsatellite instability (MSI)
- Genetic testing for confirmation

To meet the Amsterdam II criteria for HNPCC, all three of the following historical elements must be present:

- Three or more relatives with CRC or an HNPCC-associated cancer
- CRC involving at least two generations
- At least one case of CRC before age 50

Patients meeting these criteria should have their tumor tissue tested for MSI, a DNA abnormality. If MSI is present, genetic testing for specific HNPCC mutations is indicated. Other authorities use additional criteria (eg, Bethesda criteria) to initiate MSI testing. If MSI testing is not available locally, the patient should be referred to an appropriate center.

Patients with confirmed HNPCC require ongoing screening for other cancers. For endometrial cancer, annual endometrial aspiration or transvaginal ultrasound is recommended. For ovarian cancer, options include annual transvaginal ultrasound and serum CA 125 levels. Prophylactic hysterectomy and oophorectomy are also options. Urinalysis may be used to screen for renal tumors.

First-degree relatives of patients with HNPCC should have colonoscopy every 1 to 2 yr beginning in their 20s, and annually after age 40. Female 1st-degree relatives should be tested annually for endometrial and ovarian cancer. More distant blood relatives should have genetic testing; if results are negative, they should have colonoscopy at the frequency for average-risk patients.

**Treatment**

- Surgical resection

The most common treatment is resection of the index lesion with frequent surveillance for another colon cancer and any associated tumors in other organs. Because most HNPCC tumors occur proximal to the splenic flexure, subtotal colectomy, leaving the rectosigmoid intact, has been suggested as an alternative.
In either case, close follow up is needed.

Pancreatic Cancer

Pancreatic cancer, primarily ductal adenocarcinoma, accounts for an estimated 37,000 cases and 33,000 deaths in the US annually. Symptoms include weight loss, abdominal pain, and jaundice. Diagnosis is by CT. Treatment is surgical resection and adjuvant chemotherapy and radiation therapy. Prognosis is poor because disease is often advanced at the time of diagnosis.

Most pancreatic cancers are exocrine tumors that develop from ductal and acinar cells. Pancreatic endocrine tumors are discussed below.

Adenocarcinomas of the exocrine pancreas arise from duct cells 9 times more often than from acinar cells; 80% occur in the head of the gland. Adenocarcinomas appear at the mean age of 55 yr and occur 1.5 to 2 times more often in men. Prominent risk factors include smoking, a history of chronic pancreatitis, and possibly long-standing diabetes mellitus (primarily in women). Heredity plays some role. Alcohol and caffeine consumption do not seem to be risk factors.

Symptoms and Signs

Symptoms occur late. By diagnosis, 90% of patients have locally advanced tumors that have involved retroperitoneal structures, spread to regional lymph nodes, or metastasized to the liver or lung.

Most patients have severe upper abdominal pain, which usually radiates to the back. The pain may be relieved by bending forward or assuming the fetal position. Weight loss is common. Adenocarcinomas of the head of the pancreas cause obstructive jaundice (often causing pruritus) in 80 to 90% of patients. Cancer in the body and tail may cause splenic vein obstruction, resulting in splenomegaly, gastric and esophageal varices, and GI hemorrhage. The cancer causes diabetes in 25 to 50% of patients, leading to symptoms of glucose intolerance (eg, polyuria and polydipsia).

Diagnosis

• CT or magnetic resonance cholangiopancreatography (MRCP)

• CA 19-9 antigen to follow (not for screening)

The preferred tests are an abdominal helical CT or MRCP. If CT or MRCP shows apparent unresectable or metastatic disease, a percutaneous needle aspiration of an accessible lesion might be considered to obtain a tissue diagnosis. If CT shows a potentially resectable tumor or no tumor, MRCP or endoscopic ultrasound may be used to stage disease or detect small tumors not visible with CT. Patients with obstructive jaundice may have ERCP as the first diagnostic procedure.

Routine laboratory tests should be done. Elevation of alkaline phosphatase and bilirubin indicate bile duct obstruction or liver metastases. Pancreas-associated antigen CA 19-9 may be used to monitor patients diagnosed with pancreatic carcinoma and to screen those at high risk. However, this test is not sensitive or specific enough to be used for population screening. Elevated levels should drop with successful treatment; subsequent increases indicate progression. Amylase and lipase levels are usually normal.

Prognosis

Prognosis varies with stage but overall is poor (5-yr survival: < 2%), because many patients have advanced disease at the time of diagnosis.

Treatment

• Whipple procedure

• Adjuvant chemotherapy and radiation therapy
Symptom control

About 80 to 90% of cancers are considered surgically unresectable at time of diagnosis because of metastases or invasion of major blood vessels. Depending on location of the tumor, the procedure of choice is most commonly a Whipple procedure (pancreatoduodenectomy). Adjuvant therapy with 5-fluorouracil (5-FU) and external beam radiation therapy is typically given, resulting in about 40% 2-yr and 25% 5-yr survival. This combination is also used for patients with localized but unresectable tumors and results in median survival of about 1 yr. Newer drugs (eg, gemcitabine, irinotecan, paclitaxel, oxaliplatin, carboplatin) may be more effective than 5-FU-based chemotherapy, but no drug, singly or in combination, is clearly superior in prolonging survival. Patients with hepatic or distant metastases may be offered chemotherapy as part of an investigational program, but the outlook is dismal with or without such treatment and some patients may choose to forego it.

If an unresectable tumor is found at operation and gastroduodenal or bile duct obstruction is present or pending, a double gastric and biliary bypass operation is usually done to relieve obstruction. In patients with inoperable lesions and jaundice, endoscopic placement of a bile duct stent relieves jaundice. However, surgical bypass should be considered in patients with unresectable lesions if life expectancy is > 6 to 7 mo because of complications associated with stents.

Symptomatic treatment: Ultimately, most patients experience pain and die. Thus, symptomatic treatment is as important as controlling disease. Appropriate end-of-life care should be discussed (see also p. 3480).

Patients with moderate to severe pain should receive an oral opioid in doses adequate to provide relief. Concern about addiction should not be a barrier to effective pain control. For chronic pain, long-acting preparations (eg, transdermal fentanyl, oxycodone, oxymorphone) are usually best. Percutaneous or operative splanchnic (celiac) block effectively controls pain in most patients. In cases of intolerable pain, opioids given sc or by IV, epidural, or intrathecal infusion provides additional relief.

If palliative surgery or endoscopic placement of a biliary stent fails to relieve pruritus secondary to obstructive jaundice, the patient can be managed with cholestyramine (4 g po once/day to qid). Phenobarbital 30 to 60 mg po tid to qid may be helpful.

Exocrine pancreatic insufficiency is treated with tablets of porcine pancreatic enzymes (pancrelipase). The patient should take enough to supply 16,000 to 20,000 lipase units before each meal or snack. If a meal is prolonged (as in a restaurant), some of the tablets should be taken during the meal. Optimal intraluminal pH for the enzymes is 8; thus, some clinicians give a proton pump inhibitor or H₂ blocker 2 times/day. Diabetes mellitus should be closely monitored and controlled.

Cystadenocarcinoma

Cystadenocarcinoma is a rare adenomatous pancreatic cancer that arises as a malignant degeneration of a mucous cystadenoma and manifests as upper abdominal pain and a palpable abdominal mass. Diagnosis is made by abdominal CT or MRI, which typically shows a cystic mass containing debris; the mass may be misinterpreted as necrotic adenocarcinoma or pancreatic pseudocyst. Unlike ductal adenocarcinoma, cystadenocarcinoma has a relatively good prognosis. Only 20% of patients have metastasis at the time of operation; complete excision of the tumor by distal or total pancreatectomy or by a Whipple procedure results in a 65% 5-yr survival.

Intraductal Papillary-Mucinous Tumor

Intraductal papillary-mucinous tumor (IPMT) is a rare cancer resulting in mucus hypersecretion and ductal obstruction. Histology may be benign, borderline, or malignant. Most (80%) occur in women and in the tail of the pancreas (66%).

Symptoms consist of pain and recurrent bouts of pancreatitis. Diagnosis is made by CT, sometimes along with endoscopic ultrasonography, magnetic resonance cholangiopancreatography, or ERCP. Benign and
malignant disease cannot be differentiated without surgical removal, which is the treatment of choice. With surgery, 5-yr survival is > 95% for benign or borderline cases, but 50 to 75% for malignant tumors.

**Pancreatic Endocrine Tumors**

Pancreatic endocrine tumors arise from islet and gastrin-producing cells and often produce many hormones. They have 2 general manifestations. Nonfunctioning tumors may cause obstructive symptoms of the biliary tract or duodenum, bleeding into the GI tract, or abdominal masses. Functioning tumors hypersecrete a particular hormone, causing various syndromes (see Table 22-3). These clinical syndromes can also occur in multiple endocrine neoplasia, in which tumors or hyperplasia affects two or more endocrine glands, usually the parathyroid, pituitary, thyroid, or adrenals (see p. 909).

Treatment for functioning and nonfunctioning tumors is surgical resection. If metastases preclude curative surgery, various antihormone treatments may be tried for functioning tumors. Because of tumor rarity, chemotherapy trials have not identified definitive treatment. However, streptozotocin has selective activity against pancreatic islet cells and is commonly used, either alone or in combination with 5-fluorouracil or doxorubicin. Some centers use chlorozotocin and interferon.

**Insulinoma**

An insulinoma is a rare pancreatic β-cell tumor that hypersecretes insulin. The main symptom is fasting hypoglycemia. Diagnosis is by a 48- or 72-h fast with measurement of glucose and insulin levels, followed by endoscopic ultrasound. Treatment is surgery when possible. Drugs that block insulin secretion (eg, diazoxide, octreotide, Ca channel blockers, β-blockers, phenytoin) are used for patients not responding to surgery.

Of all insulinomas, 80% are single and may be curatively resected if identified. Only 10% of insulinomas are malignant. Insulinoma occurs in 1/250,000 at a median age of 50 yr, except in multiple endocrine neoplasia (MEN) type I (about 10% of insulinomas), when it occurs in the 20s. Insulinomas associated with MEN type I are more likely to be multiple.

Surreptitious administration of exogenous insulin can cause episodic hypoglycemia mimicking insulinoma.

**Symptoms and Signs**

Hypoglycemia secondary to an insulinoma occurs during fasting. Symptoms are insidious and may mimic various psychiatric and neurologic disorders. CNS disturbances include headache, confusion, visual disturbances, motor weakness, palsy, ataxia, marked personality changes, and possible progression to loss of consciousness, seizures, and coma. Symptoms of sympathetic stimulation (faintness, weakness, tremulousness, palpitation, sweating, hunger, nervousness) are often present.

**Diagnosis**

- Insulin level
- Sometimes C-peptide or proinsulin levels
- Endoscopic ultrasound

Plasma glucose should be measured during symptoms. If hypoglycemia is present (glucose < 40 mg/dL, 2.78 mmol/L), an insulin level should be measured on a simultaneous sample. Hyperinsulinemia of > 6 μU/mL (42 pmol/L) suggests an insulin-mediated cause, as does a serum insulin to plasma glucose ratio > 0.3 (μU/mL)/(mg/dL).
Insulin is secreted as proinsulin, consisting of an α chain and β chain connected by a C peptide. Because pharmaceutical insulin consists only of the β chain, surreptitious insulin administration can be detected by measuring C-peptide and proinsulin levels. In patients with insulinoma, C peptide is ≥ 0.2 nmol/L and proinsulin is ≥ 5 pmol/L. These levels are normal or low in patients with surreptitious insulin administration.

Because many patients have no symptoms (and hence no hypoglycemia) at the time of evaluation, diagnosis requires admission to the hospital for a 48- or 72-h fast. Nearly all (98%) with insulinoma develop symptoms within 48 h of fasting; 70 to 80% within 24 h. Hypoglycemia as the cause of the symptoms is established by Whipple's triad: (1) Symptoms occur during the fast; (2) symptoms occur in the presence of hypoglycemia; and (3) ingestion of carbohydrates relieves the symptoms. Hormone levels are obtained as described above when the patient is having symptoms.

If Whipple's triad is not observed after prolonged fasting and the plasma glucose after an overnight fast is > 50 mg/dL (> 2.78 mmol/L), a C-peptide suppression test can be done. During insulin infusion (0.1 U/kg/h), patients with insulinoma fail to suppress C peptide to normal levels (≤ 1.2 ng/mL [≤ 0.40 nmol/L]). Endoscopic ultrasonography has > 90% sensitivity and helps localize the tumor. PET also may be used. CT has not proved useful, and arteriography or selective portal and splenic vein catheterization is generally unnecessary.

**Treatment**

- Surgical resection
- Diazoxide or sometimes octreotide for hypoglycemia

Overall surgical cure rates approach 90%. A small, single insulinoma at or near the surface of the pancreas can usually be enucleated surgically. If a single large or deep adenoma is within the pancreatic body or tail, if there are multiple lesions of the body or tail (or both), or if no insulinoma is found (an unusual circumstance), a distal, subtotal pancreatectomy is done. In < 1% of cases, the insulinoma is ectopically located in peripancreatic sites of the duodenal wall or periduodenal area and can be found only by diligent search during surgery. Pancreatoduodenectomy (Whipple procedure) is done for resectable malignant insulinomas of the proximal pancreas. Total pancreatectomy is done if a previous subtotal pancreatectomy proves inadequate.

If hypoglycemia continues, diazoxide starting at 1.5 mg/kg po bid with a natriuretic can be used. Doses can be increased up to 4 mg/kg. A somatostatin analog, octreotide (100 to 500 μg sc bid to tid), is variably effective and should be considered for patients with continuing hypoglycemia refractory to diazoxide. Patients who respond may be converted to a long-acting octreotide formulation given as 20 to 30 mg IM once/mo. Patients using octreotide may also need to take supplemental pancreatic enzymes because octreotide suppresses pancreatic enzyme secretion. Other drugs that have modest and variable effect on insulin secretion include verapamil, diltiazem, and phenytoin.

If symptoms are not controlled, chemotherapy may be tried, but response is limited. Streptozotocin has a 30 to 40% response rate, and when combined with 5-fluorouracil, a 60% response rate lasting up to 2 yr. Other agents include doxorubicin, chlorozotocin, and interferon.

**Zollinger-Ellison Syndrome**

*(Z-E Syndrome; Gastrinoma)*

Zollinger-Ellison syndrome is caused by a gastrin-producing tumor usually located in the pancreas or the duodenal wall. Gastric acid hypersecretion and peptic ulceration result. Diagnosis is by measuring serum gastrin levels. Treatment is proton pump inhibitors and surgical removal.
Gastrinomas occur in the pancreas or duodenal wall 80 to 90% of the time. The remainder occur in the splenic hilum, mesentery, stomach, lymph node, or ovary. About 50% of patients have multiple tumors. Gastrinomas usually are small (< 1 cm in diameter) and grow slowly. About 50% are malignant. About 40 to 60% of patients with gastrinoma have multiple endocrine neoplasia (see p. 909).

Symptoms and Signs

Zollinger-Ellison syndrome typically manifests as aggressive peptic ulcer disease, with ulcers occurring in atypical locations (up to 25% are located distal to the duodenal bulb). However, as many as 25% do not have an ulcer at diagnosis. Typical ulcer symptoms and complications (e.g., perforation, bleeding, obstruction) can occur. Diarrhea is the initial symptom in 25 to 40% of patients.

Diagnosis

- Serum gastrin level
- CT, scintigraphy, or PET to localize

The syndrome is suspected by history, particularly when symptoms are refractory to standard acid suppressant therapy.

The most reliable test is serum gastrin. All patients have levels > 150 pg/mL; markedly elevated levels of > 1000 pg/mL in a patient with compatible clinical features and gastric acid hypersecretion of > 15 mEq/h establish the diagnosis. However, moderate hypergastrinemia can occur with hypochlorhydric states (e.g., pernicious anemia, chronic gastritis, use of proton pump inhibitors), in renal insufficiency with decreased clearance of gastrins, in massive intestinal resection, and in pheochromocytoma.

A secretin provocative test may be useful in patients with gastrin levels < 1000 pg/mL. An IV bolus of secretin 2 μg/kg is given with serial measurements of serum gastrin (10 and 1 min before, and 2, 5, 10, 15, 20, and 30 min after injection). The characteristic response in gastrinoma is an increase in gastrin levels, the opposite of what occurs in those with antral G-cell hyperplasia or typical peptic ulcer disease. Patients also should be evaluated for *Helicobacter pylori* infection, which commonly results in peptic ulceration and moderate excess gastrin secretion.

Once the diagnosis has been established, the tumor or tumors must be localized. The first test is abdominal CT or somatostatin receptor scintigraphy, which may identify the primary tumor and metastatic disease. PET or selective arteriography with magnification and subtraction is also helpful. If no signs of metastases are present and the primary is uncertain, endoscopic ultrasonography should be done. Selective arterial secretin injection is an alternative.

Prognosis

Five- and 10-yr survival is > 90% when an isolated tumor is removed surgically vs 43% at 5 yr and 25% at 10 yr with incomplete removal.

Treatment

- Acid suppression
- Surgical resection for localized disease
- Chemotherapy for metastatic disease

**Acid suppression:** Proton pump inhibitors are the drugs of choice: omeprazole or esomeprazole 40 mg po bid. The dose may be decreased gradually once symptoms resolve and acid output declines. A maintenance dose is needed; patients need to take these drugs indefinitely unless they undergo surgery.

Octreotide injections, 100 to 500 μg sc bid to tid, may also decrease gastric acid production and may be
palliative in patients not responding well to proton pump inhibitors. A long-acting form of octreotide can be used 20 to 30 mg IM once/mo.

**Surgery:** Surgical removal should be attempted in patients without apparent metastases. At surgery, duodenotomy and intraoperative endoscopic transillumination or ultrasound help localize tumors. Surgical cure is possible in 20% of patients if the gastrinoma is not part of a multiple endocrine neoplasia syndrome.

**Chemotherapy:** In patients with metastatic disease, streptozocin in combination with 5-fluorouracil or doxorubicin is the preferred chemotherapy for islet cell tumors. It may reduce tumor mass (in 50 to 60%) and serum gastrin levels and is a useful adjunct to omeprazole. Patients with metastatic disease are not cured by chemotherapy.

**Vipoma**

A vipoma is a non-β pancreatic islet cell tumor secreting vasoactive intestinal peptide (VIP), resulting in a syndrome of watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome). Diagnosis is by serum VIP levels. Tumor is localized with CT and endoscopic ultrasound. Treatment is surgical resection.

Of these tumors, 50 to 75% are malignant, and some may be quite large (7 cm) at diagnosis. In about 6%, vipoma occurs as part of multiple endocrine neoplasia (see p. 909).

**Symptoms and Signs**

The major symptoms are prolonged massive watery diarrhea (fasting stool volume > 750 to 1000 mL/day and nonfasting volumes of > 3000 mL/day) and symptoms of hypokalemia, acidosis, and dehydration. In half, diarrhea is constant; in the rest, diarrhea severity varies over time. About 33% have diarrhea < 1 yr before diagnosis, but 25% have diarrhea ≥ 5 yr before diagnosis. Lethargy, muscular weakness, nausea, vomiting, and crampy abdominal pain occur frequently. Flushing similar to the carcinoid syndrome occurs in 20% of patients during attacks of diarrhea.

**Diagnosis**

- Confirmation of secretory diarrhea
- Serum VIP levels
- Endoscopic ultrasonography, PET, or scintigraphy can localize

Diagnosis requires demonstration of secretory diarrhea (stool osmolality is close to plasma osmolality, and twice the sum of Na and K concentration in the stool accounts for all measured stool osmolality). Other causes of secretory diarrhea and, in particular, laxative abuse must be excluded (see p. 88). In such patients, serum VIP levels should be measured (ideally during a bout of diarrhea). Markedly elevated levels establish the diagnosis, but mild elevations may occur with short bowel syndrome and inflammatory diseases. Patients with elevated VIP levels should have tumor localization studies, such as endoscopic ultrasonography, PET, and octreotide scintigraphy or arteriography to localize metastases.

Electrolytes and CBC should be measured. Hyperglycemia and impaired glucose tolerance occur in ≤ 50% of patients. Hypercalcemia occurs in 50% of patients.

**Treatment**

- Fluid and electrolyte replacement
- Octreotide
- Surgical resection for localized disease
Initially, fluids and electrolytes must be replaced. Bicarbonate must be given to replace fecal loss and avoid acidosis. Because fecal losses of water and electrolytes increase as rehydration is achieved, continual IV replacement may become difficult.

Octreotide usually controls diarrhea, but large doses may be needed. Responders may benefit from a long-acting octreotide formulation given 20 to 30 mg IM once/mo. Patients using octreotide may also need to take supplemental pancreatic enzymes because octreotide suppresses pancreatic enzyme secretion.

Tumor resection is curative in 50% of patients with a localized tumor. In those with metastatic tumor, resection of all visible tumor may provide temporary relief of symptoms. The combination of streptozocin and doxorubicin may reduce diarrhea and tumor mass if objective response occurs (in 50 to 60%). Chemotherapy is not curative.

**Glucagonoma**

*Glucagonoma* is a pancreatic α-cell tumor that secretes glucagon, causing hyperglycemia and a characteristic skin rash. Diagnosis is by elevated glucagon levels and imaging studies. Tumor is localized with CT and endoscopic ultrasound. Treatment is surgical resection.

Glucagonomas are very rare but similar to other islet cell tumors in that the primary and metastatic lesions are slow-growing: 15-yr survival is common. Eighty percent of glucagonomas are malignant. The average age at symptom onset is 50 yr; 80% of patients are women. A few patients have multiple endocrine neoplasia type I.

**Symptoms and Signs**

Because glucagonomas produce glucagon, the symptoms are the same as those of diabetes. Frequently, weight loss, normochromic anemia, hypoaaminoacidemia, and hypolipidemia are present, but the most distinctive clinical feature is a chronic eruption involving the extremities, often associated with a smooth, shiny, vermilion tongue and cheilitis. The exfoliating, brownish red, erythematous lesion with superficial necrolysis is termed necrolytic migratory erythema.

**Diagnosis**

- Serum glucagon level
- CT and endoscopic ultrasonography to localize

Most patients with glucagonoma have glucagon levels > 1000 pg/mL (normal < 200). However, moderate elevations occur in renal insufficiency, acute pancreatitis, severe stress, and fasting. Correlation with symptoms is required. Patients should have abdominal CT followed by endoscopic ultrasonography; MRI or PET may be used if CT is unrevealing.

**Treatment**

- Surgical resection for localized disease
- Chemotherapy for metastatic disease
- Octreotide to suppress glucagon production

Resection of the tumor alleviates all symptoms. Unresectable, metastatic, or recurrent tumors are treated with combination streptozocin and doxorubicin, which may decrease levels of circulating immunoreactive glucagon, lessen symptoms, and improve response rates (50%) but are unlikely to improve survival. Octreotide injections partially suppress glucagon production and relieve the erythema, but glucose tolerance may also decrease because octreotide decreases insulin secretion. Octreotide may quickly reverse anorexia and weight loss caused by the catabolic effect of glucagon excess. Patients who
respond may be converted to a long-acting octreotide formulation given 20 to 30 mg IM once/mo. Patients using octreotide may also need to take supplemental pancreatic enzymes because octreotide suppresses pancreatic enzyme secretion.

Locally applied, oral, or parenteral zinc may cause the erythema to disappear, but resolution may occur after simple hydration or IV administration of amino or fatty acids, suggesting that the erythema is not solely caused by zinc deficiency.
Chapter 23. Approach to the Patient With Liver Disease

Introduction

The liver is the most metabolically complex organ. Hepatocytes (liver parenchymal cells) perform the liver's metabolic functions:

- Formation and excretion of bile during bilirubin metabolism (see Sidebar 23-1)
- Regulation of carbohydrate homeostasis
- Lipid synthesis and secretion of plasma lipoproteins
- Control of cholesterol metabolism
- Formation of urea, serum albumin, clotting factors, enzymes, and numerous other proteins
- Metabolism or detoxification of drugs and other foreign substances

At the cellular level, portal triads consist of adjacent and parallel terminal branches of bile ducts, portal veins, and hepatic arteries that border the hepatocytes (see Fig. 23-1). Terminal branches of the hepatic veins are in the center of hepatic lobules. Because blood flows from the portal triads past the hepatocytes and drains via vein branches in the center of the lobule, the center of the lobule is the area most susceptible to ischemia.

Pathophysiology

Liver disorders can result from a wide variety of insults, including infections, drugs, toxins, ischemia, and autoimmune disorders. Occasionally, liver disorders occur postoperatively (see p. 223). Most liver disorders cause some degree of hepatocellular injury and necrosis, resulting in various abnormal laboratory test results and, sometimes, symptoms.

Symptoms may be due to liver disease itself (eg, jaundice due to acute hepatitis) or to complications of liver disease (eg, acute GI bleeding due to cirrhosis and portal hypertension).

Sidebar 23-1 Overview of Bilirubin Metabolism

The breakdown of heme produces bilirubin (an insoluble waste product) and other bile pigments. Bilirubin must be made water soluble to be excreted. This transformation occurs in 5 steps: formation, plasma transport, liver uptake, conjugation, and biliary excretion.

Formation: About 250 to 350 mg of unconjugated bilirubin forms daily; 70 to 80% derives from the breakdown of degenerating RBCs, and 20 to 30% (early-labeled bilirubin) derives primarily from other heme proteins in the bone marrow and liver. Hb is degraded to iron and biliverdin, which is converted to bilirubin.

Plasma transport: Unconjugated (indirect-reacting) bilirubin is not water soluble and so is transported in the plasma bound to albumin. It cannot pass through the glomerular membrane into the urine. Albumin binding weakens under certain conditions (eg, acidosis), and some substances (eg, salicylates, certain antibiotics) compete for the binding sites.

Liver uptake: The liver takes up bilirubin rapidly but does not take up the attached serum albumin.
**Conjugation:** Unconjugated bilirubin in the liver is conjugated to form mainly bilirubin diglucuronide, or conjugated (direct-reacting) bilirubin. This reaction, catalyzed by the microsomal enzyme glucuronyl transferase, renders the bilirubin water soluble.

**Biliary excretion:** Tiny canaliculi formed by adjacent hepatocytes progressively coalesce into ductules, interlobular bile ducts, and larger hepatic ducts. Outside the porta hepatis, the main hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum at the ampulla of Vater.

Conjugated bilirubin is secreted into the bile canaliculus with other bile constituents. In the intestine, bacteria metabolize bilirubin to form urobilinogen, much of which is further metabolized to stercobilins, which render the stool brown. In complete biliary obstruction, stools lose their normal color and become light gray (clay-colored stool). Some urobilinogen is reabsorbed, extracted by hepatocytes, and re-excreted in bile (enterohepatic circulation). A small amount is excreted in urine.

Because conjugated bilirubin is excreted in urine and unconjugated bilirubin is not, only conjugated hyperbilirubinemia (eg, due to hepatocellular or cholestatic jaundice) causes bilirubinuria.

Despite necrosis, the liver can regenerate itself. Even extensive patchy necrosis can resolve completely (eg, in acute viral hepatitis). Incomplete regeneration and fibrosis, however, may result from injury that bridges entire lobules or from less pronounced but ongoing damage.

Specific diseases preferentially affect certain hepatobiliary structures or functions (eg, acute viral hepatitis is primarily manifested by damage to hepatocytes or hepatocellular injury; primary biliary cirrhosis, by impairment of biliary secretion; and cryptogenic cirrhosis, by liver fibrosis and resultant portal venous hypertension). The part of the hepatobiliary system affected determines the symptoms, signs, and laboratory abnormalities (see also Ch. 24). Some disorders (eg, severe alcoholic liver disease) affect multiple liver structures, resulting in a combination of patterns of symptoms, signs, and laboratory abnormalities.

The prognosis of serious complications is worse in older adults, who are less able to recover from severe physiologic stresses and to tolerate toxic accumulations.

**Evaluation**

**History:** Various symptoms may develop, but few are specific for liver disorders:

- Common nonspecific symptoms include fatigue, anorexia, nausea, and, occasionally, vomiting, particularly in severe disorders.
- Loose, fatty stools (steatorrhea) can occur when cholestasis prevents sufficient bile from reaching the intestines. Patients with steatorrhea are at risk of deficiencies of fat-soluble vitamins (A, D, E, K). Common clinical consequences may include osteoporosis and bleeding.
- Fever can develop in viral or alcoholic hepatitis.
- Jaundice (see p. 212), occurring in both hepatocellular dysfunction and cholestatic disorders, is the most specific symptom. It is often accompanied by dark urine and light stools.
- Right upper quadrant pain due to liver disorders usually results from distention (eg, by passive venous congestion or tumor) or inflammation of the liver capsule.
- Erectile dysfunction and feminization develop; however, these symptoms may reflect the effects of alcohol more than liver disorders.

Family history, social history, and drug and substance use history should note risk factors for liver disorders (see...
Physical examination: Abnormalities detectable on a physical examination usually do not develop until late in the course of the disease. Some common findings suggest a cause (see Table 23-2).

Ascites

Ascites is free fluid in the peritoneal cavity. The most common cause is portal hypertension. Symptoms usually result from abdominal distention. Diagnosis is based on physical examination and often ultrasonography or CT. Treatments include bed rest, dietary Na restriction, diuretics, and therapeutic paracentesis. Ascitic fluid can become infected (spontaneous bacterial peritonitis), often with pain and fever. Diagnosis of infection involves analysis and culture of ascitic fluid. Infection is treated with antibiotics.

<table>
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<th>Table 23-1. Risk Factors for Liver Disorders</th>
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**Etiology**

Ascites can result from chronic, but not acute, liver diseases.

**Hepatic causes** include the following:

- Portal hypertension (accounts for > 90% of hepatic cases), usually due to cirrhosis
- Chronic hepatitis
- Severe alcoholic hepatitis without cirrhosis
- Hepatic vein obstruction (Budd-Chiari syndrome)

Portal vein thrombosis does not usually cause ascites unless hepatocellular damage is also present.

**Nonhepatic causes** include the following:

- Generalized fluid retention associated with systemic diseases (eg, heart failure, nephrotic syndrome, severe hypoalbuminemia, constrictive pericarditis)
- Peritoneal disorders (eg, carcinomatous or infectious peritonitis, biliary leak due to surgery or another medical procedure)
- Less common causes, such as renal dialysis, pancreatitis, SLE, and endocrine disorders (eg, myxedema)

**Pathophysiology**

Mechanisms are complex and incompletely understood. Factors include altered Starling’s forces in the portal vessels (low oncotic pressure due to hypoalbuminemia plus increased portal venous pressure), avid renal Na retention (urinary Na concentration is typically < 5 mEq/L), and possibly increased hepatic lymph formation.

Mechanisms that seem to contribute to renal Na retention include activation of the renin-angiotensin-aldosterone system; increased sympathetic tone; intrarenal shunting of blood away from the cortex; increased formation of nitric oxide; and altered formation or metabolism of ADH, kinins, prostaglandins, and atrial natriuretic factor. Vasodilation in the splanchnic arterial circulation may be a trigger, but the specific roles and interrelationships of these abnormalities remain uncertain.

**Symptoms and Signs**
Small amounts of ascitic fluid cause no symptoms. Moderate amounts cause increased abdominal girth and weight gain. Massive amounts may cause nonspecific diffuse abdominal pressure, but actual pain is uncommon and suggests another cause of acute abdominal pain (see p. 106). If ascites results in elevation of the diaphragm, dyspnea may occur. Symptoms of spontaneous bacterial peritonitis (SBP) may include new abdominal discomfort and fever.

Signs include shifting dullness on abdominal percussion and a fluid wave. Volumes < 1500 mL may not cause physical findings. Massive ascites causes tautness of the abdominal wall and flattening of the umbilicus. In liver diseases or peritoneal disorders, ascites is usually isolated or disproportionate to peripheral edema; in systemic diseases (eg, heart failure), the reverse is usually true.

**Diagnosis**

- Ultrasonography or CT unless physical findings make diagnosis obvious
- Often tests of ascitic fluid

Diagnosis may be based on physical examination if there is a large amount of fluid, but imaging tests are more sensitive. Ultrasonography and CT reveal much smaller volumes of fluid (100 to 200 mL) than does physical examination. SBP is suspected if a patient with ascites also has abdominal pain, fever, or unexplained deterioration.

**Diagnostic paracentesis** (see p. 99) should be done if any of the following occur:

- Ascites is newly diagnosed.
- Its cause is unknown.
- SBP is suspected.

**Table 23-2. Interpretation of Some Physical Findings**

About 50 to 100 mL of fluid is removed and analyzed for gross appearance, protein content, cell count and differential, cytology, culture, and, as clinically indicated, acid-fast stain, amylase, or both. In contrast to ascites due to inflammation or infection, ascites due to portal hypertension produces fluid that is clear and straw-colored, has a low protein concentration, a low PMN count (< 250 cells/μL), and, most reliably, a high serum-to-ascites albumin concentration gradient, which is the serum albumin concentration minus the ascitic albumin concentration. Gradients > 1.1 g/dL are relatively specific for ascites due to portal hypertension. In ascitic fluid, turbidity and a PMN count > 250 cells/μL indicate SBP, whereas bloody fluid can suggest a tumor or TB. The rare milky (chylous) ascites is most common with lymphoma.

**Treatment**

- Bed rest and dietary Na restriction
- Sometimes spironolactone, possibly plus furosemide
- Sometimes therapeutic paracentesis

Bed rest and dietary Na restriction (2000 mg/day) are the first and least risky treatments for ascites due to portal hypertension. Diuretics should be used if rigid Na restriction fails to initiate diuresis within a few days. Spironolactone is usually effective (in oral doses ranging from 50 mg once/day to 200 mg bid). A loop diuretic (eg, furosemide 20 to 160 mg po usually once/day or 20 to 80 mg po bid) should be added if spironolactone is insufficient. Because spironolactone can cause K retention and furosemide K depletion, the combination of these drugs often provides optimal diuresis with a lower risk of K abnormalities. Fluid restriction is indicated only for treatment of hyponatremia (serum Na < 120 mEq/L). Changes in body weight and urinary Na determinations reflect response to treatment. Weight loss of about 0.5 kg/day is
optimal because the ascitic compartment cannot be mobilized much more rapidly. More aggressive diuresis depletes fluid from the intravascular compartment, especially when peripheral edema is absent; this depletion may cause renal failure or electrolyte imbalance (eg, hypokalemia) that may precipitate portal-systemic encephalopathy. Inadequate dietary Na restriction is the usual cause of persistent ascites.

Therapeutic paracentesis is an alternative. Removal of 4 L/day is safe; many clinicians infuse IV salt-poor albumin (about 40 g/paracentesis) at about the same time to prevent intravascular volume depletion. Even single total paracentesis may be safe. Therapeutic paracentesis shortens the hospital stay with relatively little risk of electrolyte imbalance or renal failure; nevertheless, patients require ongoing diuretics and tend to reaccumulate fluid more rapidly than those treated without paracentesis.

Techniques for the autologous infusion of ascitic fluid (eg, the LeVeen peritoneovenous shunt) often cause complications and are generally no longer used. Transjugular intrahepatic portosystemic shunting (TIPS) can lower portal pressure and successfully treat ascites resistant to other treatments, but TIPS is invasive and may cause complications, including portal-systemic encephalopathy and worsening hepatocellular function.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is infection of ascitic fluid without an apparent source. Manifestations may include fever, malaise, and symptoms of ascites and worsening hepatic failure. Diagnosis is by examination of ascitic fluid. Treatment is with cefotaxime or another antibiotic.

SBP is particularly common in cirrhotic ascites, especially among alcoholics. This infection can cause serious sequelae or death. The most common bacteria causing SBP are gram-negative Escherichia coli and Klebsiella pneumoniae and gram-positive Streptococcus pneumoniae; usually only a single organism is involved.

Symptoms and Signs

Patients have symptoms and signs of ascites. Discomfort is usually present; it typically is diffuse, constant, and mild to moderate in severity.

Signs of SBP may include fever, malaise, encephalopathy, worsening hepatic failure, and unexplained clinical deterioration. Peritoneal signs (eg, abdominal tenderness and rebound) are present but may be somewhat diminished by the presence of ascitic fluid.

Diagnosis

• Diagnostic paracentesis

Clinical diagnosis of SBP can be difficult; diagnosis requires a high index of suspicion and liberal use of diagnostic paracentesis, including culture. Transferring ascitic fluid to blood culture media before incubation increases the sensitivity of culture to almost 70%. PMN count of > 250 cells/μL is diagnostic of SBP. Blood cultures are also indicated. Because SBP usually results from a single organism, finding mixed flora on culture suggests a perforated abdominal viscus or contaminated specimen.

Treatment

• Cefotaxime or another antibiotic

If SBP is diagnosed, an antibiotic such as cefotaxime 2 g IV q 4 to 8 h (pending Gram stain and culture results) is given for at least 5 days and until ascitic fluid shows < 250 PMNs/μL. Antibiotics increase the chance of survival. Because SBP recurs within a year in up to 70% of patients, prophylactic antibiotics are indicated; quinolones (eg, norfloxacin 400 mg po once/day) are most widely used.

Antibiotic prophylaxis in ascitic patients with variceal hemorrhage decreases the risk of SBP.
Fatty Liver

(Hepatic Steatosis)

Fatty liver is excessive accumulation of lipid in hepatocytes, the most common liver response to injury.

Fatty liver develops for many reasons, involves many different biochemical mechanisms, and causes different types of liver damage. Clinically, it is most useful to distinguish fatty liver due to pregnancy or alcoholic liver disease (see p. 235) from that occurring in the absence of pregnancy and alcoholism (nonalcoholic fatty liver disease [NAFLD]). NAFLD includes simple fatty infiltration (a benign condition) and nonalcoholic steatohepatitis, a less common but more important variant.

(See also the American Gastroenterological Association's Medical Position Statement and Technical Review on nonalcoholic fatty liver disease.)

Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a syndrome that develops in patients who are not alcoholics; it causes liver damage that is histologically indistinguishable from alcoholic hepatitis. It develops most often in patients with at least one of the following risk factors: obesity, dyslipidemia, and glucose intolerance. Pathogenesis is poorly understood but seems to be linked to insulin resistance (eg, as in obesity or metabolic syndrome). Most patients are asymptomatic. Laboratory findings include elevations in aminotransferase levels. Biopsy is required to confirm the diagnosis. Treatment includes elimination of causes and risk factors.

NASH (sometimes called steatonecrosis) is diagnosed most often in patients between 40 yr and 60 yr but can occur in all age groups. Many affected patients have obesity, type 2 diabetes mellitus, or dyslipidemia.

Pathophysiology

Pathophysiology involves fat accumulation (steatosis), inflammation, and, variably, fibrosis. Steatosis results from hepatic triglyceride accumulation. Possible mechanisms for steatosis include reduced synthesis of very low density lipoprotein (VLDL) and increased hepatic triglyceride synthesis (possibly due to decreased oxidation of fatty acids or increased free fatty acids being delivered to the liver). Inflammation may result from lipid peroxidative damage to cell membranes. These changes can stimulate hepatic stellate cells, resulting in fibrosis. If advanced, NASH can cause cirrhosis and portal hypertension.

Symptoms and Signs

Most patients are asymptomatic. However, some have fatigue, malaise, or right upper quadrant abdominal discomfort. Hepatomegaly develops in about 75% of patients. Splenomegaly may develop if advanced hepatic fibrosis is present and is usually the first indication that portal hypertension has developed. Patients with cirrhosis due to NASH can be asymptomatic and may lack the usual signs of chronic liver disease.

Diagnosis

- Presence of risk factors
- Absence of hepatitis B and C and excessive alcohol intake
- Liver biopsy

The diagnosis should be suspected in patients with risk factors such as obesity, type 2 diabetes mellitus, or dyslipidemia and in patients with unexplained laboratory abnormalities suggesting liver disease. The
most common laboratory abnormalities are elevations in aminotransferase levels. Unlike in alcoholic liver disease, the ratio of AST/ALT in NASH is usually < 1. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) occasionally increase. Hyperbilirubinemia, prolongation of PT, and hypoalbuminemia are uncommon.

For diagnosis, strong evidence (such as a history corroborated by friends and relatives) that alcohol intake is not excessive (eg, is < 20 g/day) is needed. Serologic tests should show absence of hepatitis B and C infection (ie, hepatitis B surface antigen and hepatitis C virus antibody should be negative). Liver biopsy should reveal damage similar to that seen in alcoholic hepatitis, usually including large fat droplets (macrovesicular fatty infiltration). Indications for biopsy include unexplained signs of portal hypertension (including splenomegaly or cytopenia) and unexplained elevations in aminotransferase levels that persist for > 6 mo in a patient with diabetes, obesity, or dyslipidemia.

Imaging tests, including ultrasonography, CT, and particularly MRI, may identify hepatic steatosis. However, these tests cannot identify the inflammation typical of NASH and cannot differentiate NASH from other causes of hepatic steatosis.

Prognosis

Prognosis is controversial. Probably, most patients do not develop hepatic insufficiency or cirrhosis. However, some drugs (eg, cytotoxic drugs) and metabolic disorders are associated with acceleration of NASH. Prognosis is often good unless complications (eg, variceal hemorrhage) develop.

Treatment

• Elimination of causes and control of risk factors

The only widely accepted treatment goal is to eliminate potential causes and risk factors. Such a goal may include discontinuation of drugs or toxins, weight loss, and treatment for dyslipidemia or hyperglycemia. Preliminary evidence suggests that thiazolidinediones can help correct biochemical and histologic abnormalities in NASH. Many other treatments (eg, ursodeoxycholic acid, vitamin E, metronidazole, metformin, betaine, glucagon, glutamine infusion) have not been proved effective.

Jaundice

Jaundice is a yellowish discoloration of the skin and mucous membranes caused by hyperbilirubinemia. Jaundice becomes visible when the bilirubin level is about 2 to 3 mg/dL (34 to 51 μmol/L).

Pathophysiology

Most bilirubin is produced when Hb is broken down into unconjugated bilirubin (and other substances). Unconjugated bilirubin binds to albumin in the blood for transport to the liver, where it is taken up by hepatocytes and conjugated with glucuronic acid to make it water soluble. Conjugated bilirubin is excreted in bile into the duodenum. In the intestine, bacteria metabolize bilirubin to form urobilinogen. Some urobilinogen is eliminated in the feces, and some is reabsorbed, extracted by hepatocytes, reprocessed, and re-excreted in bile (enterohepatic circulation—see p. 205).

Mechanisms of hyperbilirubinemia: Hyperbilirubinemia may involve predominantly unconjugated or conjugated bilirubin.

Unconjugated hyperbilirubinemia is most often caused by ≥ 1 of the following:

• Increased production

• Decreased hepatic uptake

• Decreased conjugation
Conjugated hyperbilirubinemia is most often caused by ≥ 1 of the following:

- Dysfunction of hepatocytes (hepatocellular dysfunction)
- Slowing of bile egress from the liver (intrahepatic cholestasis)
- Obstruction of extrahepatic bile flow (extra-hepatic cholestasis)

**Consequences:** Outcome is determined primarily by the cause of jaundice and the presence and severity of hepatic dysfunction. Hepatic dysfunction can result in coagulopathy, encephalopathy, and portal hypertension (which can lead to GI bleeding).

**Etiology**

Although hyperbilirubinemia can be classified as predominantly unconjugated or conjugated, many hepatobiliary disorders cause both forms.

Many conditions (see Table 23-3), including use of certain drugs (see Table 23-4), can cause jaundice, but the most common causes overall are

- Inflammatory hepatitis (viral hepatitis, autoimmune hepatitis, toxic hepatic injury)
- Alcoholic liver disease
- Biliary obstruction

**Evaluation**

**History:** History of present illness should include onset and duration of jaundice. Hyperbilirubinemia can cause urine to darken before jaundice is visible. Therefore, the onset of dark urine indicates onset of hyperbilirubinemia more accurately than onset of jaundice. Important associated symptoms include fever, prodromal symptoms (eg, fever, malaise, myalgias) before jaundice, urine and stool color, pruritus, steatorrhea, and abdominal pain (including location, severity, duration, and radiation). Important symptoms suggesting severe disease include nausea and vomiting, weight loss, and possible symptoms of coagulopathy (eg, easy bruising or bleeding, tarry or bloody stools).

**Review of systems** should seek symptoms of possible causes, including weight loss and abdominal pain (cancer); joint pain and swelling

(autoimmune or viral hepatitis, hemochromatosis, primary sclerosing cholangitis, sarcoidosis); and missed menses (pregnancy).

**Past medical history** should identify known causative disorders, such as hepatobiliary disease (eg, gallstones, hepatitis, cirrhosis); disorders that can cause hemolysis (eg, hemoglobinopathy, G6PD deficiency); and disorders associated with liver or biliary disease, including inflammatory bowel disease, infiltrative disorders (eg, amyloidosis, lymphoma, sarcoidosis, TB), and HIV infection or AIDS.

Drug history should include questions about use of drugs or exposure to toxins known to affect the liver (see Table 23-4) and about vaccination against hepatitis.
Surgical history should include questions about previous surgery on the biliary tract (a potential cause of strictures).

Social history should include questions about risk factors for hepatitis (see Table 23-5), amount and duration of alcohol use, injection drug use, and sexual history.

Family history should include questions about recurrent, mild jaundice in family members and diagnosed hereditary liver disorders. The patient's history of recreational drug and alcohol use should be corroborated by friends or family members when possible.

**Physical examination:** Vital signs are reviewed for fever and signs of systemic toxicity (eg, hypotension, tachycardia).

General appearance is noted, particularly for cachexia and lethargy.

Head and neck examination includes inspection of the sclerae and tongue for icterus and the eyes for Kayser-Fleischer rings. Mild jaundice is best seen by examining the sclerae in natural light; it is usually detectable when serum bilirubin reaches 2 to 2.5 mg/dL (34 to 43 μmol/L). Breath odor should be noted (eg, for fetor hepaticus).

The abdomen is inspected for collateral vasculature, ascites, and surgical scars. The liver is palpated for hepatomegaly, masses, nodularity, and tenderness. The spleen is palpated for splenomegaly. The abdomen is examined for umbilical hernia, shifting dullness, fluid wave, masses, and tenderness. The rectum is examined for gross or occult blood.

Men are checked for testicular atrophy and gynecomastia.

The upper extremities are examined for Dupuytren's contractures.

Neurologic examination includes mental status assessment and evaluation for asterixis.

The skin is examined for jaundice, palmar erythema, needle tracks, vascular spiders, excoriations, xanthomas (consistent with primary biliary cirrhosis), paucity of axillary and pubic hair, hyperpigmentation, ecchymoses, petechiae, and purpura.

**Red flags:** The following findings are of particular concern:

- Marked abdominal pain and tenderness
- Altered mental status
- GI bleeding (occult or gross)
- Ecchymoses, petechiae, or purpura

**Interpretation of findings:** Severity of illness is indicated mainly by the degree (if any) of hepatic dysfunction. Ascending cholangitis is a concern because it requires emergency treatment.

Severe hepatic dysfunction is indicated by encephalopathy (eg, mental status change, asterixis) or coagulopathy (eg, easy bleeding, purpura, tarry or heme-positive stool), particularly in patients with signs of portal hypertension

[Table 23-5, Some Risk Factors for Hepatitis]

(eg, abdominal collateral vasculature, ascites, splenomegaly). Massive upper GI bleeding suggests variceal bleeding due to portal hypertension (and possibly coagulopathy).

Ascending cholangitis is suggested by fever and marked, continuous right upper quadrant abdominal
pain; acute pancreatitis with biliary obstruction (eg, due to a common duct stone or pancreatic pseudocyst) may manifest similarly.

**Cause of jaundice** may be suggested by the following:

- Acute jaundice in the young and healthy suggests acute viral hepatitis, particularly when a viral prodrome, risk factors, or both are present; however, acetaminophen overdose is also common.

- Acute jaundice after acute drug or toxin exposure in healthy patients is likely due to that substance.

- A long history of heavy alcohol use suggests alcoholic liver disease, particularly when typical stigmata are present.

- A personal or family history of recurrent, mild jaundice without findings of hepatobiliary dysfunction suggests a hereditary disorder, usually Gilbert syndrome.

- Gradual onset of jaundice with pruritus, weight loss, and clay-colored stools suggests intrahepatic or extrahepatic cholestasis.

- Painless jaundice in elderly patients with weight loss and a mass but with minimal pruritus suggests biliary obstruction caused by cancer.

Other examination findings can also be helpful (see Table 23-6).

**Testing:** The following are done:

- Blood tests (bilirubin, aminotransferase, alkaline phosphatase)

- Usually imaging

- Sometimes biopsy or laparoscopy

Blood tests include measurement of total and direct bilirubin, aminotransferase, and alkaline phosphatase levels in all patients. Results help differentiate cholestasis from hepatocellular dysfunction (important because patients with cholestasis usually require imaging tests):

- Hepatocellular dysfunction: Marked aminotransferase elevation (> 500 U/L) and moderate alkaline phosphatase elevation (< 3 times normal)

- Cholestasis: Moderate aminotransferase elevation (< 200 U/L) and marked alkaline phosphatase elevation (> 3 times normal)

- Hyperbilirubinemia without hepatobiliary dysfunction: Mild hyperbilirubinemia (eg, < 3.5 mg/dL [< 59 μmol/L]) with normal aminotransferase and alkaline phosphatase levels

Also, patients with hepatocellular dysfunction or cholestasis have dark urine due to bilirubinuria because conjugated bilirubin is excreted in urine; unconjugated bilirubin is not. Bilirubin fractionation also differentiates conjugated from unconjugated forms. When aminotransferase and alkaline phosphatase levels are normal, fractionation of bilirubin can help suggest causes, such as Gilbert syndrome or hemolysis (unconjugated) vs Dubin-Johnson syndrome or Rotor's syndrome (conjugated).

Other blood tests are done based on clinical suspicion and initial test findings, as for the following:

- Signs of hepatic insufficiency (eg, encephalopathy, ascites, ecchymoses) or GI bleeding: Coagulation profile (PT/PTT)

- Hepatitis risk factors (see Table 23-5) or a hepatocellular mechanism suggested by blood test results:
Hepatitis viral and autoimmune serologic tests

- Fever, abdominal pain, and tenderness: CBC and, if patients appear ill, blood cultures

[Table 23-6. Findings Suggesting a Cause of Jaundice]

Suspicion of hemolysis can be confirmed by a peripheral blood smear.

Imaging is done if pain suggests extrahepatic obstruction or cholangitis or if blood test results suggest cholestasis.

Abdominal ultrasonography usually is done first; usually, it is highly accurate in detecting extrahepatic obstruction. CT and MRI are alternatives. Ultrasonography is usually more accurate for gallstones, and CT is more accurate for pancreatic lesions. All these tests can detect abnormalities in the biliary tree and focal liver lesions but are less accurate in detecting diffuse hepatocellular disorders (eg, hepatitis, cirrhosis).

If ultrasonography shows extrahepatic cholestasis, other tests may be necessary to determine the cause; usually, magnetic resonance cholangiopancreatography (MRCP) or ERCP is used. ERCP is more invasive but allows treatment of some obstructive lesions (eg, stone removal, stenting of strictures).

Liver biopsy is not commonly required but can help diagnose certain disorders (eg, disorders causing intrahepatic cholestasis, some kinds of hepatitis, some infiltrative disorders, Dubin-Johnson syndrome, hemochromatosis, Wilson's disease). Biopsy can also help when liver enzyme abnormalities are unexplained by other tests.

Laparoscopy (peritoneoscopy) allows direct inspection of the liver and gallbladder without the trauma of a full laparotomy. Unexplained cholestatic jaundice warrants laparoscopy occasionally and diagnostic laparotomy rarely.

Treatment

The cause and any complications are treated. Jaundice itself requires no treatment in adults (unlike in neonates—see p. 2788). Itching, if bothersome, may be relieved with cholestyramine 2 to 8 g po bid. However, cholestyramine is ineffective in patients with complete biliary obstruction.

Geriatrics Essentials

Symptoms may be attenuated or missed in the elderly; eg, abdominal pain may be mild or absent in acute viral hepatitis. A sleep disturbance or mild confusion resulting from portosystemic encephalopathy may be misattributed to dementia.

Key Points

- Acute jaundice, particularly with a viral prodrome, in the young and healthy suggests acute viral hepatitis.

- Painless jaundice in elderly patients with weight loss, an abdominal mass, and minimal pruritus suggests biliary obstruction caused by cancer.

- Aminotransferase levels of > 500 U/L and alkaline phosphatase elevation < 3 times normal suggest hepatocellular dysfunction.

- Aminotransferase levels of < 200 U/L and alkaline phosphatase elevation > 3 times normal suggest cholestasis.

- Significant hepatic dysfunction is indicated by altered mental status and coagulopathy.
Inborn Metabolic Disorders Causing Hyperbilirubinemia

Hereditary or inborn metabolic disorders may cause unconjugated or conjugated hyperbilirubinemia.

• Unconjugated hyperbilirubinemia: Gilbert syndrome, Crigler-Najjar syndrome, and primary shunt hyperbilirubinemia

• Conjugated hyperbilirubinemia: Dubin-Johnson syndrome and Rotor's syndrome

Gilbert Syndrome

Gilbert syndrome is a presumably lifelong disorder in which the only significant abnormality is asymptomatic, mild, unconjugated hyperbilirubinemia. It can be mistaken for chronic hepatitis or other liver disorders. Gilbert syndrome may affect as many as 5% of people. Although family members may be affected, a clear genetic pattern is difficult to establish.

Pathogenesis may involve complex defects in the liver's uptake of bilirubin. Glucuronyl transferase activity is low, though not as low as in Crigler-Najjar syndrome type II. In many patients, RBC destruction is also slightly accelerated, but this acceleration does not explain hyperbilirubinemia. Liver histology is normal.

Gilbert syndrome is most often detected in young adults serendipitously by finding an elevated bilirubin level, which usually fluctuates between 2 and 5 mg/dL (34 and 86 μmol/L) and tends to increase with fasting and other stresses.

Gilbert syndrome is differentiated from hepatitis by fractionation that shows predominantly unconjugated bilirubin, otherwise normal liver function test results, and absence of urinary bilirubin. It is differentiated from hemolysis by the absence of anemia and reticulocytosis. Treatment is unnecessary. Patients should be reassured that they do not have liver disease.

Crigler-Najjar Syndrome

This rare inherited disorder is caused by deficiency of the enzyme glucuronyl transferase. Patients with autosomal recessive type I (complete) disease have severe hyperbilirubinemia. They usually die of kernicterus by age 1 yr but may survive into adulthood. Treatment may include phototherapy and liver transplantation. Patients with autosomal dominant type II (partial) disease (which has variable penetrance) often have less severe hyperbilirubinemia (< 20 mg/dL [< 342 μmol/L]) and usually live into adulthood without neurologic damage. Phenobarbital 1.5 to 2 mg/kg po tid, which induces the partially deficient glucuronyl transferase, may be effective.

Primary Shunt Hyperbilirubinemia

This rare, familial, benign condition is characterized by overproduction of early-labeled bilirubin.

Dubin-Johnson Syndrome and Rotor's Syndrome

Dubin-Johnson syndrome and Rotor's syndrome cause conjugated hyperbilirubinemia, but without cholestasis, causing no symptoms or sequelae other than jaundice. In contrast to unconjugated hyperbilirubinemia in Gilbert syndrome (which also causes no other symptoms), bilirubin may appear in the urine. Aminotransferase and alkaline phosphatase levels are usually normal. Treatment is unnecessary.

Dubin-Johnson syndrome: This rare autosomal recessive disorder involves impaired excretion of bilirubin glucuronides. It is usually diagnosed by liver biopsy; the liver is deeply pigmented as a result of an intracellular melanin-like substance but is otherwise histologically normal.

Rotor's syndrome: This rare disorder is clinically similar to Dubin-Johnson syndrome, but the liver is not pigmented, and other subtle metabolic differences are present.
Portal Hypertension

Portal hypertension is caused most often by cirrhosis (in developed countries), schistosomiasis (in endemic areas), or hepatic vascular abnormalities. Consequences include esophageal varices and portal-systemic encephalopathy. Diagnosis is based on clinical criteria, often in conjunction with imaging tests and endoscopy. Treatment involves prevention of GI bleeding with endoscopy, drugs, or both and sometimes with portocaval shunting.

The portal vein, formed by the superior mesenteric and splenic veins, drains blood from the abdominal GI tract, spleen, and pancreas into the liver. Within reticuloendothelium-lined blood channels (sinusoids), blood from the terminal portal venules merges with hepatic arterial blood. Blood flows out of the sinusoids via the hepatic veins into the inferior vena cava.

Normal portal pressure is 5 to 10 mm Hg (7 to 14 cm H₂O), which exceeds inferior vena caval pressure by 4 to 5 mm Hg (portal venous gradient). Higher values are defined as portal hypertension.

Etiology

Portal hypertension results mainly from increased resistance to flow, which commonly arises from disease within the liver itself or uncommonly from blockage of the splenic or portal vein or impaired hepatic venous outflow (see Table 23-7). Increased flow volume is a rare cause, although it often contributes to portal hypertension in cirrhosis and in hematologic disorders that cause massive splenomegaly.

Pathophysiology

In cirrhosis, tissue fibrosis and regeneration increase resistance in the sinusoids and terminal portal venules. However, other potentially reversible factors contribute; they include contractility of sinusoidal lining cells, production of vasoactive substances (eg, endothelins, nitric oxide), various systemic mediators of arteriolar resistance, and possibly swelling of hepatocytes.

Over time, portal hypertension creates portal-systemic venous collaterals. They may slightly decrease portal vein pressure but can cause complications. Engorged serpentine submucosal vessels (varices) in the distal esophagus and sometimes in the gastric fundus can rupture, causing sudden, catastrophic GI bleeding. Bleeding rarely occurs unless the portal pressure gradient is > 12 mm Hg. Gastric mucosal vascular congestion (portal hypertensive gastropathy) can cause acute or chronic bleeding independent of varices. Visible abdominal wall collaterals are common; veins radiating from the umbilicus (caput medusae) are much rarer and indicate extensive flow in the umbilical and periumbilical veins.

[Table 23-7. Most Common Causes of Portal Hypertension]

Collaterals around the rectum can cause rectal varices that can bleed.

Portal-systemic collaterals shunt blood away from the liver. Thus, less blood reaches the liver when portal flow increases (diminished hepatic reserve). In addition, toxic substances from the intestine are shunted directly to the systemic circulation, contributing to portal-systemic encephalopathy (see p. 220). Venous congestion within visceral organs due to portal hypertension contributes to ascites via altered Starling's forces. Splenomegaly and hypersplenism (see p. 984) commonly occur as a result of increased splenic vein pressure. Thrombocytopenia, leukopenia, and, less commonly, hemolytic anemia may result.

Portal hypertension is often associated with a hyperdynamic circulation. Mechanisms are complex and seem to involve altered sympathetic tone, production of nitric oxide and other endogenous vasodilators, and enhanced activity of humoral factors (eg, glucagon).

Symptoms and Signs

Portal hypertension is asymptomatic; symptoms and signs result from its complications. The most dangerous is acute variceal bleeding (see p. 103). Patients typically present with sudden painless upper
GI bleeding, often massive. Bleeding from portal hypertensive gastropathy is often subacute or chronic. Ascites, splenomegaly, or portal-systemic encephalopathy may be present.

**Diagnosis**

- Usually, clinical evaluation

Portal hypertension is inferred in a patient with chronic liver disease by the presence of collateral circulation, splenomegaly, ascites, or portal-systemic encephalopathy. Proof requires direct portal pressure measurement by a transjugular catheter, which is invasive and usually not done. Imaging may help when cirrhosis is suspected. Ultrasonography or CT often reveals dilated intra-abdominal collaterals, and Doppler ultrasonography can determine portal vein patency and flow.

Esophagogastric varices and portal hypertensive gastropathy are best diagnosed by endoscopy, which may also identify predictors of esophagogastric variceal bleeding (eg, red markings on a varix).

**Prognosis**

Mortality during acute variceal hemorrhage may exceed 50%. Prognosis is predicted by the degree of hepatic reserve and the degree of bleeding. For survivors, the bleeding risk within the next 1 to 2 yr is 50 to 75%. Ongoing endoscopic or drug therapy lowers the bleeding risk but decreases long-term mortality only marginally. For treatment of acute bleeding, see pp. 102 and 104.

**Treatment**

- Ongoing endoscopic therapy and surveillance
- β-Blockers with or without isosorbide mononitrate
- Sometimes portal vein shunting

When possible, the underlying disorder is treated. Long-term treatment of esophagogastric varices that have bled is a series of endoscopic banding sessions to obliterate residual varices, then periodic surveillance endoscopy for recurrent varices.

Long-term drug therapy for varices that have bled involves β-blockers; these drugs lower portal pressure primarily by diminishing portal flow, although the effects vary. Propranolol (40 to 80 mg po bid) or nadolol (40 to 160 mg po once/day) is preferred, with dosage titrated to decrease heart rate by about 25%. Adding isosorbide mononitrate 10 to 20 mg po bid may further reduce portal pressure. Combined long-term endoscopic and drug therapy may be slightly more effective than either alone. Patients who do not adequately respond to either treatment should be considered for transjugular intrahepatic portosystemic shunting (TIPS) or, less frequently, a surgical portocaval shunt. TIPS creates a stent between the portal and hepatic venous circulation within the liver. Although TIPS may result in fewer immediate deaths than surgical shunting, particularly during acute bleeding, maintenance of patency may require repeat procedures because the stent may become stenosed or occluded over time. Long-term benefits are unknown. Liver transplantation may help some patients.

For patients with varices that have not yet bled, β-blockers lower the risk of bleeding.

For bleeding due to portal hypertensive gastropathy, drugs can be used to decrease portal pressure. A shunt should be considered if drugs are ineffective, but results may be less successful than for esophageal variceal bleeding.

Because it rarely causes clinical problems, hypersplenism requires no specific treatment, and splenectomy should be avoided.

**Portal-Systemic Encephalopathy**
Portal-systemic encephalopathy is a neuropsychiatric syndrome. It most often results from high gut protein or acute metabolic stress (e.g., GI bleeding, infection, electrolyte abnormality) in a patient with portal-systemic shunting. Symptoms are mainly neuropsychiatric (e.g., confusion, flapping tremor, coma). Diagnosis is based on clinical findings. Treatment usually is correction of the acute cause, restriction of dietary protein, and oral lactulose.

Portal-systemic encephalopathy better describes the pathophysiology than hepatic encephalopathy or hepatic coma, but all 3 terms are used interchangeably.

**Etiology**

Portal-systemic encephalopathy may occur in fulminant hepatitis caused by viruses, drugs, or toxins, but it more commonly occurs in cirrhosis or other chronic disorders when extensive portal-systemic collaterals have developed as a result of portal hypertension. Encephalopathy also follows portal-systemic anastomoses, such as surgically created anastomoses connecting the portal vein and vena cava (portacaval shunts, transjugular intrahepatic portosystemic shunting [TIPS]).

**Precipitants:** In patients with chronic liver disease, acute episodes of encephalopathy are usually precipitated by reversible causes. The most common are the following:

- Metabolic stress (e.g., infection; electrolyte imbalance, especially hypokalemia; dehydration; use of diuretic drugs)
- Disorders that increase gut protein (e.g., GI bleeding, high-protein diet)
- Nonspecific cerebral depressants (e.g., alcohol, sedatives, analgesics)

**Pathophysiology**

In portal-systemic shunting, absorbed products that would otherwise be detoxified by the liver enter the systemic circulation, where they may be toxic to the brain, particularly the cerebral cortex. The substances causing brain toxicity are not precisely known. Ammonia, a product of protein digestion, is an important cause, but other factors (e.g., alterations in cerebral benzodiazepine receptors and neurotransmission by γ-aminobutyric acid [GABA]) may also contribute. Aromatic amino acid levels in serum are usually high and branched-chain levels are low, but these levels probably do not cause encephalopathy.

**Symptoms and Signs**

Symptoms and signs of encephalopathy tend to develop in progressive stages (see Table 23-8).

Symptoms usually do not become apparent until brain function is moderately impaired. Constructional apraxia, in which patients cannot reproduce simple designs (e.g., a star), develops early. Agitation and mania can develop but are uncommon. A characteristic flapping tremor (asterixis) is elicited when patients hold their arms outstretched with wrists dorsiflexed. Neurologic deficits are symmetric. Neurologic signs in coma usually reflect bilateral diffuse hemispheric dysfunction. Signs of brain stem dysfunction develop only in advanced coma, often during the hours or days before death. A musty, sweet breath odor (fetor hepaticus) can occur regardless of the stage of encephalopathy.

**Diagnosis**

- Clinical evaluation
- Often adjunctive testing with psychometric evaluation, ammonia level, EEG, or a combination
- Exclusion of other treatable disorders
Diagnosis is ultimately based on clinical findings, but testing may help:

- Psychometric testing may reveal subtle neuropsychiatric deficits, which can help confirm early encephalopathy.
- Ammonia levels are usually done.
- An EEG usually shows diffuse slow-wave activity, even in mild cases, and may be sensitive but is not specific for early encephalopathy.

CSF examination is not routinely necessary; the only usual abnormality is mild protein elevation.

Other potentially reversible disorders that could cause similar manifestations (eg, infection, subdural hematoma, hypoglycemia, intoxication) should be ruled out. If portal-systemic encephalopathy is confirmed, the precipitating cause should be sought.

Prognosis

In chronic liver disease, correction of the precipitating cause usually causes encephalopathy to regress without permanent neurologic sequelae. Some patients, especially those with portacaval shunts or TIPS, require continuous therapy, and irreversible extrapyramidal signs or spastic paraparesis rarely develops. Coma (stage 4 encephalopathy) associated with fulminant hepatitis is fatal in up to 80% of patients despite intensive therapy; the combination of advanced chronic liver failure and portal-systemic encephalopathy is often fatal.

Treatment

- Treatment of the cause
- Bowel cleansing using oral lactulose or enemas
- Dietary protein restriction

Treating the cause usually reverses mild cases. Eliminating toxic enteric products is the other goal and is accomplished using several methods. The bowels should be cleared using enemas or, more often, oral lactulose syrup, which can be tube-fed to comatose patients. This synthetic disaccharide is an osmotic cathartic. It also lowers colonic pH, decreasing fecal ammonia production. The initial dosage, 30 to 45 mL po tid, should be adjusted to produce 2 or 3 soft stools daily. Dietary protein should be about 1.0 mg/kg/day, primarily from vegetable sources. Oral nonabsorbable antibiotics such as neomycin and rifaximin are effective for hepatic encephalopathy. Rifaximin is usually preferred because neomycin is an aminoglycoside, which can precipitate ototoxicity or nephrotoxicity.

Sedation deepens encephalopathy and should be avoided whenever possible. For coma caused by fulminant hepatitis, meticulous supportive and nursing care coupled with prevention and treatment of complications increase the chance of survival. High-dose corticosteroids, exchange transfusion, and other complex procedures designed to remove circulating toxins generally do not improve outcome. Patients deteriorating because of fulminant hepatic failure may be saved by liver transplantation.

Other potential therapies, including levodopa, bromocriptine, flumazenil, Na benzoate, infusions of branched-chain amino acids, keto-analogs of essential amino acids, and prostaglandins, have not proved effective. Complex plasma-filtering systems (artificial liver) show some promise but require much more study.

Systemic Abnormalities in Liver Disease

Liver disease often causes systemic symptoms and abnormalities (see Portal-Systemic Encephalopathy).
Circulatory Abnormalities

Hypotension in advanced liver failure may contribute to renal dysfunction. The pathogenesis of the hyperdynamic circulation (increased cardiac output and heart rate) and hypotension that develop in advanced liver failure or cirrhosis is poorly understood. However, peripheral arterial vasodilation probably contributes to both. Factors that may contribute in cirrhosis may include altered sympathetic tone, production of nitric oxide and other endogenous vasodilators, and enhanced activity of humoral factors (eg, glucagon).

For specific disorders of hepatic circulation (eg, Budd-Chiari syndrome), see Ch. 29.

Endocrine Abnormalities

Glucose intolerance, hyperinsulinism, insulin resistance, and hyperglucagonemia are often present in patients with cirrhosis; the elevated insulin levels reflect decreased hepatic degradation rather than increased secretion, whereas the opposite is true for hyperglucagonemia. Abnormal thyroid function tests may reflect altered hepatic handling of thyroid hormones and changes in plasma binding proteins rather than thyroid abnormalities.

Sexual effects are common. Chronic liver disease commonly impairs menstruation and fertility. Males with cirrhosis, especially alcoholics, often have both hypogonadism (including testicular atrophy, erectile dysfunction, decreased spermatogenesis) and feminization (gynecomastia, female habitus). The biochemical basis is not fully understood. Gonadotropin reserve of the hypothalamic-pituitary axis is often blunted. Circulating testosterone levels are low, resulting mainly from decreased synthesis but also from increased peripheral conversion to estrogens. Levels of estrogens other than estradiol are usually increased, but the relationship between estrogens and feminization is complex. These changes are more prevalent in alcoholic liver disease than in cirrhosis of other etiologies, suggesting that alcohol, rather than liver disease, may be the cause. In fact, evidence indicates that alcohol itself is toxic to the testes.

Hematologic Abnormalities

Anemia is common among patients with liver disease. Contributing factors may include blood loss, folate (folic acid) deficiency, hemolysis, marrow suppression by alcohol, and a direct effect of chronic liver disease.

Leukopenia and thrombocytopenia often accompany splenomegaly in advanced portal hypertension.

Clotting and coagulation abnormalities are common and complex. Hepatocellular dysfunction and inadequate absorption of vitamin K may impair liver synthesis of clotting factors. An abnormal PT, depending on the severity of hepatocellular dysfunction, may respond to parenteral phytonadione (vitamin K$_1$) 5 to 10 mg once/day for 2 to 3 days. Thrombocytopenia, disseminated intravascular coagulation, and fibrinogen abnormalities also contribute to clotting disturbances in many patients.

Renal and Electrolyte Abnormalities

Renal and electrolyte abnormalities are common, especially among patients with ascites.

Hypokalemia may result from excess urinary K loss due to increased circulating aldosterone, renal retention of ammonium ion in exchange for K, secondary renal tubular acidosis, or diuretic therapy. Management consists of giving oral KCl supplements and withholding K-wasting diuretics.

Hyponatremia is common even though the kidneys may avidly retain Na (see Ascites on p. 206); it usually occurs with advanced hepatocellular disease and is difficult to correct. Relative water overload is more often responsible than total body Na depletion; K depletion may also contribute. Water restriction and K supplements may help; use of diuretics that increase free water clearance is controversial. Saline solution IV is indicated only if profound hyponatremia causes seizures or if total body Na depletion is
suspected; it should be avoided in patients with cirrhosis and fluid retention because it worsens ascites and only temporarily increases serum Na levels.

Advanced liver failure can alter acid-base balance, usually causing metabolic alkalosis. BUN levels are often low because of impaired liver synthesis; GI bleeding causes elevations because of an increased enteric load rather than renal impairment. When GI bleeding elevates BUN, normal creatinine values tend to confirm normal kidney function.

Renal failure in liver disease may reflect

- Rare disorders that directly affect both the kidneys and the liver (eg, carbon tetrachloride toxicity)
- Circulatory failure with decreased renal perfusion, with or without frank acute tubular necrosis
- Functional renal failure, often called hepatorenal syndrome

**Hepatorenal syndrome:** This syndrome consists of progressive oliguria and azotemia in the absence of structural damage to the kidney; it usually occurs in patients with fulminant hepatitis or advanced cirrhosis with ascites. Its unknown pathogenesis probably involves extreme vasodilation of the splanchnic arterial circulation, leading to decreased central arterial volume. Neural or humoral reductions in renocortical blood flow follow, resulting in a diminished glomerular filtration rate. Low urinary Na concentration and benign sediment usually distinguish it from tubular necrosis, but prerenal azotemia may be more difficult to distinguish; in equivocal cases, response to a volume load should be assessed.

Once established, renal failure due to hepatorenal syndrome is usually rapidly progressive and fatal (type 1 hepatorenal syndrome), although some cases are less severe, with stable low-grade renal insufficiency (type 2).

Liver transplantation is the only accepted treatment for type 1 hepatorenal syndrome; transjugular intrahepatic portosystemic shunting (TIPS) and vasoconstrictors show some promise, but more study is needed.

**The Asymptomatic Patient With Abnormal Laboratory Test Results**

Because aminotransferases and alkaline phosphatase are included in commonly done laboratory test panels, abnormalities are often detected in patients without symptoms or signs of liver disease. In such patients, the physician should obtain a history of exposure to possible liver toxins, including alcohol, prescription and nonprescription drugs, herbal teas and remedies, and occupational or other chemical exposures.

**Aminotransferases:** Mild isolated elevations of ALT or AST (< 2 times normal) may require only repeat testing; they resolve in about one third of cases. If abnormalities are present in other laboratory tests, are severe, or persist on subsequent testing, further evaluation is indicated as follows:

- Fatty liver should be considered; it can often be recognized clinically (see p. 211).
- Patients should be screened for hepatitis B and C (see p. 251).
- Patients > 40 should be screened for hemochromatosis (see p. 1032).
- Patients < 30 should be screened for Wilson's disease (see p. 51).
- Most patients, especially young or middle-aged women, should be screened for autoimmune disorders.
- Patients at risk should be screened for malaria and schistosomiasis.

If at this point the results are negative, screening for α1-antitrypsin deficiency (see p. 1901) is indicated. If the entire evaluation reveals no cause, liver biopsy may be warranted.
Alkaline phosphatase: Isolated elevation of alkaline phosphatase levels in an asymptomatic patient requires confirmation of hepatic origin by showing elevation of 5’-nucleotidase or γ-glutamyl transpeptidase. If hepatic origin is confirmed, liver imaging, usually with ultrasonography or magnetic resonance cholangiopancreatography, is indicated. If no structural abnormality is found on imaging, intrahepatic cholestasis is possible and may be suggested by a history of exposure to drugs or toxins. Infiltrative diseases and liver metastases (eg, due to colon cancer) should also be considered. In women, antimitochondrial antibody should be obtained. Persistent unexplained elevations or suspicion of intrahepatic cholestasis warrants consideration of liver biopsy.

Postoperative Liver Dysfunction

Mild liver dysfunction sometimes occurs after major surgery even in the absence of preexisting liver disorders. This dysfunction usually results from hepatic ischemia or poorly understood effects of anesthesia. Patients with preexisting well-compensated liver disease (eg, cirrhosis with normal liver function) usually tolerate surgery well. However, surgery can increase the severity of some preexisting liver disorders; eg, laparotomy may precipitate acute liver failure in a patient with viral or alcoholic hepatitis.

Postoperative jaundice: Diagnosis of postoperative jaundice requires liver laboratory tests. Timing of symptoms also aids in diagnosis.

Multifactorial mixed hyperbilirubinemia is the most common reason for postoperative jaundice. It is caused by increased formation of bilirubin and decreased hepatic clearance. This disorder most often occurs after major surgery or trauma requiring multiple transfusions. Hemolysis, sepsis, resorption of hematomas, and blood transfusions can increase the bilirubin load; simultaneously, hypoxemia, hepatic ischemia, and other poorly understood factors impair hepatic function. This condition is usually maximal within a few days of operation. Hepatic insufficiency is rare, and hyperbilirubinemia typically resolves slowly but completely. Liver laboratory tests can often differentiate multifactorial mixed hyperbilirubinemia from hepatitis. In multifactorial mixed hyperbilirubinemia, severe hyperbilirubinemia with mild aminotransferase and alkaline phosphatase elevations are common. In hepatitis, aminotransferase levels are usually very high.

Postoperative hepatitis: Ischemic postoperative "hepatitis" results from insufficient liver perfusion, not inflammation. The cause is transient perioperative hypotension or hypoxia. Typically, aminotransferase levels increase rapidly (often > 1000 units/L), but bilirubin is only mildly elevated. Ischemic hepatitis is usually maximal within a few days of operation and resolves within a few days.

Halothane-related hepatitis can result from use of anesthetics containing halothane or related agents. It usually develops within 2 wk, is often preceded by fever, and is sometimes accompanied by a skin rash and eosinophilia.

True postoperative hepatitis is now rare. It used to result mainly from transmission of hepatitis C virus during blood transfusion.

Postoperative cholestasis: The most common cause of postoperative cholestasis is extrahepatic biliary obstruction due to intra-abdominal complications or drugs given postoperatively. Intrahepatic cholestasis occasionally develops after major surgery, especially after abdominal or cardiovascular procedures (benign postoperative intrahepatic cholestasis). The pathogenesis is unknown, but the condition usually resolves slowly and spontaneously. Occasionally, postoperative cholestasis results from acute acalculous cholecystitis or pancreatitis.
Chapter 24. Testing for Hepatic and Biliary Disorders

Introduction

Diagnosis of liver and biliary system disorders may include laboratory tests, imaging tests, and liver biopsy. Individual tests, particularly those of liver biochemistry and excretion, often have limited sensitivity and specificity. A combination of tests often best defines the cause and severity of disease. Useful algorithms (eg, Model of End-Stage Liver Disease [MELD], Child-Pugh score) have incorporated clinical and laboratory features to predict survival in patients with decompensated cirrhosis.

Laboratory Tests

Laboratory tests are generally effective for the following:

• Detecting hepatic dysfunction
• Assessing the severity of liver injury
• Monitoring the course of liver diseases and the response to treatment
• Refining the diagnosis

Many tests of liver biochemistry and excretory performance are called liver function tests. However, rather than assessing liver function, several of these tests measure liver enzymes that are released into the bloodstream (eg, release of aminotransferases from injured liver cells or of alkaline phosphatase due to cholestasis). Only certain tests actually assess liver function by evaluating hepatobiliary excretion (eg, bilirubin) or the liver's synthetic capability (eg, PT, usually reported as the INR; albumin).

The most useful laboratory tests to screen for liver disorders are serum aminotransferases (the most commonly used liver function tests), bilirubin, and alkaline phosphatase. Certain patterns of biochemical abnormalities help distinguish hepatocellular injury from impaired bile excretion (cholestasis—see Table 24-1). Tests that detect viral hepatitis, liver inflammation, or altered immunoregulation include hepatitis serologic tests (see p. 251) and measurement of immunoglobulins, antibodies, and autoantibodies.

A few laboratory tests are diagnostic by themselves; they include the following:

• IgM antibody to hepatitis A virus (anti-HAV) for acute hepatitis A
• Hepatitis B surface antigen (HBsAg) for hepatitis B
• Antibody to hepatitis C virus (anti-HCV) and HCV-RNA for hepatitis C
• Antimitochondrial antibody for primary biliary cirrhosis
• Serum ceruloplasmin (reduced) and urinary copper (elevated) for Wilson's disease
• Serum α1-antitrypsin for α1-antitrypsin deficiency
• α1-Fetoprotein for hepatocellular carcinoma

Tests for Liver Injury

Aminotransferases: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) leak from damaged cells; thus, these enzymes are sensitive indicators of liver injury. Markedly high values (> 500 IU/L; normal, ≤ 40 IU/L), which indicate acute hepatocellular necrosis or injury, usually result from the following:
• Acute viral hepatitis
• Toxin- or drug-induced hepatitis
• Ischemic hepatitis or hepatic infarction

High levels continue usually for days or, in viral hepatitis, for weeks. The degree of elevation may not reflect the extent of liver injury. Serial measurements better reflect severity and prognosis than does a single measurement. A fall to normal indicates recovery unless accompanied by an increase in bilirubin and in PT or INR (which indicates fulminant liver failure). Fulminant liver failure results in fewer liver cells that can leak enzymes.

Aminotransferase levels may also be markedly high in the following:
• Acute exacerbation of autoimmune hepatitis
• Reactivation of chronic hepatitis B
• Acute Budd-Chiari syndrome
• Acute fatty liver of pregnancy
• Passage of a common duct stone

Modest elevations (300 to 500 IU/L) persist in chronic liver disorders (eg, chronic hepatitis, alcoholic hepatitis) and in biliary obstruction, except when passage of a common duct stone can transiently result in markedly high levels, sometimes into the thousands.

Mild increases (< 300 IU/L) are nonspecific and often present in disorders such as

[Table 24-1. Common Patterns of Laboratory Test Abnormalities]

• Cirrhosis secondary to viral hepatitis
• Nonalcoholic fatty liver disease (NAFLD)
• Cholestatic liver disorders
• Hepatocellular cancer

Aminotransferases can be normal in certain liver disorders, such as
• Hemochromatosis
• Methotrexate- or amiodarone-induced liver injury
• Chronic hepatitis C
• NAFLD

Elevated ALT is somewhat specific for liver injury. Because AST is present in the heart, skeletal muscle, kidneys, and pancreas, elevated AST may reflect rhabdomyolysis or injury to one of these organs. In most liver disorders, the ratio of AST to ALT is < 1. However, in alcohol-related liver disease, the ratio is characteristically > 2 because pyridoxal-5’-phosphate is deficient in alcoholic patients; it is required for ALT synthesis but is less essential for AST synthesis. This deficiency also explains why elevations of ALT and AST are low (< 300 IU/L) in alcoholic patients.
Lactate dehydrogenase: LDH, commonly included in routine analysis, is present in many other tissues and is insensitive and nonspecific for hepatocellular injury. LDH is typically elevated in ischemic hepatitis and cancers that extensively infiltrate the liver.

Tests for Cholestasis

Bilirubin: Bilirubin, the pigment in bile, is produced from the breakdown of heme proteins, mostly from the heme moiety of hemoglobin in senescent RBCs. Unconjugated (free) bilirubin is insoluble in water and thus cannot be excreted in urine; most unconjugated bilirubin is bound to albumin in plasma. Bilirubin is conjugated in the liver with glucuronic acid to form the more water-soluble bilirubin diglucuronide. Conjugated bilirubin is then excreted through the biliary tract into the duodenum, where it is metabolized into urobilinogens (some of which are reabsorbed and resecreted into bile), then into orange-colored urobilins (most of which are eliminated in feces). These bile pigments give stool its typical color.

Hyperbilirubinemia results from one or more of the following:

• Increased bilirubin production

• Decreased liver uptake or conjugation

• Decreased biliary excretion (see p. 212)

Normally, total bilirubin is mostly unconjugated, with values of < 1.2 mg/dL (< 20 μmol/L). Fractionation measures the proportion of bilirubin that is conjugated (ie, direct, so-called because it is measured directly, without the need for solvents). Fractionation is most helpful for evaluating neonatal jaundice and for evaluating elevated bilirubin when other liver test results are normal, suggesting that hepatobiliary dysfunction is not the cause.

Unconjugated hyperbilirubinemia (indirect bilirubin fraction > 85%) reflects increased bilirubin production (eg, in hemolysis) or defective liver uptake or conjugation (eg, in Gilbert syndrome). Such increases in unconjugated bilirubin are usually < 5 times normal (to < 6 mg/dL [<100 μmol/L]) unless there is concurrent liver injury.

Conjugated hyperbilirubinemia (direct bilirubin fraction > 50%) results from decreased bile formation or excretion (cholestasis). When associated with other liver function test abnormalities, a high serum bilirubin indicates hepatocellular dysfunction. Serum bilirubin is somewhat insensitive for liver dysfunction. However, the development of severe hyperbilirubinemia in primary biliary cirrhosis, alcoholic hepatitis, and acute liver failure suggests a poor prognosis.

Bilirubinuria reflects the presence of conjugated bilirubin in urine; bilirubin spills into urine because blood levels are markedly elevated, indicating severe disease. Unconjugated bilirubin is water insoluble and bound to albumin and so cannot be excreted in urine. Bilirubinuria can be detected at the bedside with commercial urine test strips in acute viral hepatitis or other hepatobiliary disorders, even before jaundice appears. However, the diagnostic accuracy of such urine tests is limited. Results can be falsely negative when the urine specimen has been stored a long time, vitamin C has been ingested, or urine contains nitrates (eg, due to UTIs). Similarly, increases in urobilinogen are neither specific nor sensitive.

Alkaline phosphatase: Increased levels of this hepatocyte enzyme suggest cholestasis. Results may not be specific because alkaline phosphatase consists of several isoenzymes and has a widespread extrahepatic distribution (eg, in the placenta, the small intestine, WBCs, kidneys, and particularly bone).

Alkaline phosphatase levels increase to ≥ 4 times normal 1 to 2 days after onset of biliary obstruction, regardless of the site of obstruction. Levels may remain elevated for several days after the obstruction resolves because the half-life of alkaline phosphatase is about 7 days. Increases of up to 3 times normal occur in many liver disorders, including

• Hepatitis
• Cirrhosis

• Space-occupying lesions (eg, carcinoma)

• Infiltrative disorders (eg, amyloidosis, sarcoidosis, TB, metastases, abscesses)

• Syphilitic hepatitis (alkaline phosphatase may be disproportionately elevated compared with the modest changes in other liver tests)

Isolated elevations (ie, when other liver test results are normal) may accompany

• Focal liver lesions (eg, abscess, tumor)

• Partial or intermittent bile duct obstruction (eg, stone, stricture, cholangiocarcinoma)

• Syphilitic hepatitis

• Occasionally, infiltrative disorders

Isolated elevations also occur in the absence of any apparent liver or biliary disorder, as in the following:

• Some cancers without apparent liver involvement (eg, bronchogenic carcinoma, Hodgkin lymphoma, renal cell carcinoma)

• After ingestion of fatty meals (because of an enzyme produced in the small intestine)

• Pregnancy (because of an enzyme produced in the placenta)

• Children and adolescents who are still growing (because of bone growth)

• Chronic renal failure (because of an enzyme produced in the intestine and bone)

Levels of γ-glutamyl transpeptidase or 5′-nucleotidase, which are more specific to the liver, can differentiate hepatic from extrahepatic sources of alkaline phosphatase better than fractionation of alkaline phosphatase, which is technically difficult. Also, in otherwise asymptomatic elderly people, an increase in alkaline phosphatase usually originates in bone (eg, in Paget's disease) and does not require further investigation for liver injury.

5′-Nucleotidase: Increases in levels of this enzyme are as sensitive as alkaline phosphatase for detecting cholestasis and biliary obstruction but are more specific, almost always indicating hepatobiliary dysfunction. Because levels of alkaline phosphatase and 5′-nucleotidase do not always correlate, one can be normal while the other is increased.

γ-Glutamyl transpeptidase (GGT): Levels of this enzyme increase in hepatobiliary dysfunction, especially cholestasis, and correlate loosely with levels of alkaline phosphatase and 5′-nucleotidase. Levels do not increase because of bone lesions, during childhood, or during pregnancy. However, alcohol and certain drugs (eg, some anticonvulsants, warfarin) can induce hepatic microsomal (cytochrome P-450) enzymes, markedly increasing GGT and thus somewhat limiting its specificity.

Tests of Hepatic Synthetic Capacity

PT and INR: PT may be expressed in time (sec) or, preferably, as a ratio of the patient's measured PT to the laboratory's control value (INR—see p. 971). The INR is more accurate than PT for monitoring anticoagulation. PT or INR is a valuable measure of the liver's ability to synthesize fibrinogen and vitamin K-dependent clotting factors: factors II (prothrombin), V, VII, and X. Changes can occur rapidly because some of the involved clotting factors have short biologic half-lives (eg, 6 h for factor VII). Abnormalities indicate severe hepatocellular dysfunction, an ominous sign in acute liver disorders. In chronic liver disorders, an increasing PT or INR indicates progression to liver failure. The PT or INR does not increase
in mild hepatocellular dysfunction and is often normal in cirrhosis.

A prolonged PT and an abnormal INR can result from coagulation disorders such as a consumptive coagulopathy or vitamin K deficiency. Fat malabsorption, including cholestasis, can cause vitamin K deficiency. In chronic cholestasis, marked hepatocellular dysfunction can be ruled out if vitamin K replacement (10 mg sc) corrects PT by ≥ 30% within 24 h.

**Serum proteins:** Hepatocytes synthesize most serum proteins, including α- and β-globulins, albumin, and most clotting factors (but not factor VIII, produced by the vascular endothelium, or γ-globulin, produced by B cells). Hepatocytes also make proteins that aid in the diagnosis of specific disorders:

- α1-Antitrypsin (absent in α1-antitrypsin deficiency)
- Ceruloplasmin (reduced in Wilson’s disease)
- Transferrin (saturated with iron in hemochromatosis)
- Ferritin (greatly increased in hemochromatosis)

These proteins usually increase in response to damage (eg, inflammation) to various tissues, so that elevations may not specifically reflect liver disorders.

**Serum albumin** commonly decreases in chronic liver disorders because of an increase in volume of distribution (eg, due to ascites), a decrease in hepatic synthesis, or both. Values < 3 g/dL (< 30 g/L) suggest decreased synthesis, caused by one of the following:

- Advanced cirrhosis (the most common cause)
- Alcoholism
- Chronic inflammation
- Protein undernutrition

Hypoalbuminemia can also result from excessive loss of albumin from the kidneys (ie, nephrotic syndrome), gut (eg, due to proteinlosing gastroenteropathies), or skin (eg, due to burns or exfoliative dermatitis).

Because albumin has a half-life of about 20 days, serum levels take weeks to increase or decrease.

**Other Laboratory Tests**

**Ammonia:** Nitrogen compounds that enter the colon (eg, ingested protein, secreted urea) are degraded by resident bacteria, liberating ammonia. The ammonia is then absorbed and transported via the portal vein to the liver. The healthy liver readily clears the ammonia from the portal vein and converts it to glutamine, which is metabolized by the kidneys into urea to be excreted. In patients with portal-systemic shunting, the diseased liver does not clear ammonia, which then enters the systemic circulation, possibly contributing to portal-systemic (hepatic) encephalopathy. Elevated ammonia levels occur in hepatic encephalopathy, but levels may be falsely low or high. In advanced liver disorders, the following may increase ammonia levels:

- High-protein meals
- GI bleeding
- Hypokalemia
- Metabolic alkalosis
• Certain drugs (eg, alcohol, barbiturates, diuretics, opioids, valproate)
• High-dose chemotherapy
• Parenteral nutrition
• Renal insufficiency
• Extreme muscle exertion and muscle wasting
• Salicylate intoxication
• Shock
• Ureterosigmoidostomy

UTI with a urease-producing organism (eg, *Proteus mirabilis*)

Because the degree of elevation in the ammonia level correlates poorly with severity of hepatic encephalopathy, this level has limited usefulness in monitoring therapy.

**Serum immunoglobulins:** In chronic liver disorders, serum immunoglobulins often increase. However, elevations are not specific and are usually not helpful clinically. Levels increase slightly in acute hepatitis, moderately in chronic active hepatitis, and markedly in autoimmune hepatitis. The pattern of immunoglobulin elevation adds little information, although different immunoglobulins are usually very high in different disorders:

• IgM in primary biliary cirrhosis
• IgA in alcoholic liver disease
• IgG in autoimmune hepatitis

**Antimitochondrial antibodies:** These heterogeneous antibodies are positive, usually in high titers, in > 95% of patients with primary biliary cirrhosis. They are also occasionally present in the following:

• Autoimmune hepatitis
• Drug-induced hepatitis
• Other autoimmune disorders, such as connective tissue disorders, myasthenia gravis, autoimmune thyroiditis, Addison's disease, and autoimmune hemolytic anemia

Antimitochondrial antibodies can help determine the cause of cholestasis because they are usually absent in extrahepatic biliary obstruction and primary sclerosing cholangitis.

**Other antibodies:** Other antibodies may help in diagnosis of the following:

• Autoimmune hepatitis: Smooth muscle antibodies against actin, antinuclear antibodies (ANA) that provide a homogeneous (diffuse) fluorescence, and antibodies to liver-kidney microsome type 1 (anti-LKM1) are often present.

• Primary biliary cirrhosis: Antimitochondrial antibody is key to the diagnosis.

• Primary sclerosing cholangitis: Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) can help raise the index of suspicion.
Isolated abnormalities of any of these antibodies are never diagnostic and do not elucidate pathogenesis.

**α-Fetoprotein (AFP):** AFP, a glycoprotein normally synthesized by the yolk sac in the embryo and then by the fetal liver, is elevated in neonates and hence the pregnant mother. AFP decreases rapidly during the first year of life, reaching adult values (normally, < 10 to 20 ng/mL or < 10 to 20 mg/L depending on the laboratory) by the age of 1 yr. An increase in AFP, no matter how small, should prompt consideration of primary hepatocellular carcinoma (HCC). Serum AFP generally correlates with tumor size, differentiation and metastatic involvement. Because small tumors may produce low levels of AFP, increasing values suggest the presence of HCC, especially when tumors are > 3 cm diameter. AFP also helps predict prognosis.

Mild AFP elevations also occur in acute and chronic hepatitis, probably reflecting liver regeneration; AFP can occasionally increase to 500 ng/mL in fulminant hepatitis. High AFP levels can occur in a few other disorders (eg, embryonic teratocarcinomas, hepatoblastomas in children, some hepatic metastases from GI tract cancers, some cholangiocarcinomas), but these circumstances are not common and usually can be differentiated based on clinical and histopathologic grounds.

Sensitivity, specificity, and peak levels of AFP in patients with HCC vary by population, reflecting differences in factors such as hepatitis prevalence and ethnicity. In areas with a relatively low prevalence of hepatitis (eg, North America and western Europe), AFP cutoff values of 20 ng/mL have a sensitivity of 39 to 64% and a specificity of 76 to 91%. However, not all HCCs produce AFP. Thus, AFP is not an ideal screening test but does have a role in detecting HCC. Levels exceeding normal (> 20 ng/mL), especially when increasing, strongly suggest HCC. In cirrhotic patients with a mass and a high value (eg, > 200 ng/mL), the predictive value is high. The combined use of AFP and ultrasonography currently provides the best surveillance.

**Imaging Tests**

Imaging is essential for accurately diagnosing biliary tract disorders and is important for detecting focal liver lesions (eg, abscess, tumor). It is limited in detecting and diagnosing diffuse hepatocellular disease (eg, hepatitis, cirrhosis).

**Ultrasonography:** Ultrasonography, traditionally done transabdominally and requiring a period of fasting, provides structural, but not functional, information. It is the least expensive, safest, and most sensitive technique for imaging the biliary system, especially the gallbladder. Ultrasonography is the procedure of choice for

- Screening for biliary tract abnormalities
- Evaluating the hepatobiliary tract in patients with right upper quadrant abdominal pain
- Differentiating intrahepatic from extrahepatic causes of jaundice
- Detecting liver masses

The kidneys, pancreas, and blood vessels are also often visible on hepatobiliary ultrasounds. Ultrasonography can measure spleen size and thus help diagnose splenomegaly, which suggests portal hypertension.

Use of endoscopic ultrasonography may further refine the approaches to hepatobiliary abnormalities.

Ultrasonography can be difficult in patients with intestinal gas or obesity and is operator-dependent. Endoscopic ultrasonography incorporates an ultrasound transducer into the tip of an endoscope and thus provides greater image resolution even when intestinal gas is present.

**Gallstones** cast intense echoes with distal acoustic shadowing that move with gravity. Transabdominal ultrasonography is extremely accurate (sensitivity > 95%) for gallstones > 2 mm in diameter. Endoscopic ultrasonography can detect stones as small as 0.5 mm (microlithiasis) in the gallbladder or biliary system.
Transabdominal and endoscopic ultrasonography can also identify biliary sludge (a mixture of particulate material and bile) as low-level echoes that layer in the dependent portion of the gallbladder without acoustic shadowing.

**Cholecystitis** typically causes

- A thickened gallbladder wall (> 3 mm)
- Pericholecystic fluid
- An impacted stone in the gallbladder neck
- Tenderness on palpation of the gallbladder with the ultrasound probe (ultrasonographic Murphy’s sign)

**Extrahepatic obstruction** is indicated by dilated bile ducts. On transabdominal and endoscopic ultrasounds, bile ducts stand out as echo-free tubular structures. The diameter of the common duct is normally < 6 mm, increases slightly with age, and can reach 10 mm after cholecystectomy. Dilated ducts are virtually pathognomonic for extrahepatic obstruction in the appropriate clinical setting. Ultrasonography can miss early or intermittent obstruction that does not dilate the ducts. Transabdominal ultrasonography may not reveal the level or cause of biliary obstruction (eg, sensitivity for common duct stones is < 40%). Endoscopic ultrasonography has a better yield.

**Focal liver lesions** > 1 cm in diameter can usually be detected by transabdominal ultrasonography. In general, cysts are echo-free; solid lesions (eg, tumors, abscesses) tend to be echogenic. Carcinoma appears as a nonspecific solid mass. Ultrasonography has been used to screen for hepatocellular carcinoma in patients at high risk (eg, with chronic hepatitis B, cirrhosis, or hemochromatosis). Because ultrasonography can localize focal lesions, it can be used to guide aspiration and biopsy.

**Diffuse disorders** (eg, cirrhosis, sometimes fatty liver) can be detected with ultrasonography. Ultrasound elastography can measure liver stiffness as an index of hepatic fibrosis. In this procedure, the transducer emits a vibration that induces an elastic shear wave. The rate at which the wave is propagated through the liver is measured; liver stiffness speeds this propagation.

**Doppler ultrasonography:** This noninvasive method is used to assess direction of blood flow and patency of blood vessels around the liver, particularly the portal vein. Clinical uses include

- Detecting portal hypertension, (eg, indicated by significant collateral flow and the direction of flow)
- Assessing the patency of liver shunts (eg, surgical portocaval, percutaneous transhepatic)
- Evaluating portal vein patency before liver transplantation and detecting hepatic artery thrombosis after transplantation
- Detecting unusual vascular structures (eg, cavernous transformation of the portal vein)
- Assessing tumor vascularity before surgery

**CT:** CT is commonly used to identify hepatic masses, particularly small metastases, with an accuracy of about 80%. It is considered the most accurate imaging technique. CT with IV contrast is accurate for diagnosing cavernous hemangiomas of the liver as well as differentiating them from other abdominal masses. Neither obesity nor intestinal gas obscures CT images. CT can detect fatty liver and the increased hepatic density that occurs with iron overload. CT is less helpful than ultrasonography in identifying biliary obstruction but often provides the best assessment of the pancreas.

**Cholescintigraphy:** After patients fast, an IV technetium-labeled iminodiacetic compound (eg, hydroxy or diisopropyl iminodiacetic acid [HIDA or DISIDA]) is injected; these substances are taken up by the liver and excreted in bile, then enter the gallbladder.
In acute calculous cholecystitis, which is usually caused by impaction of a stone in the cystic duct, the gallbladder does not appear on a scintigraphic scan because the radionuclide cannot enter the gallbladder. Such nonvisualization is diagnostically quite accurate (except for false-positive results in some critically ill patients). However, cholescintigraphy is rarely needed clinically to diagnose acute cholecystitis.

If acalculous cholecystitis is suspected, the gallbladder is scanned before and after administration of cholecystokinin (used to initiate gallbladder contraction). The decrease in scintigraphic counts indicates the gallbladder ejection fraction. Reduced emptying, measured as the ejection fraction, suggests acalculous cholecystitis.

Cholescintigraphy also detects bile leaks (eg, after surgery or trauma) and anatomic abnormalities (eg, congenital choledochal cysts, choledochoenteric anastomoses). After cholecystectomy, cholescintigraphy can quantitate biliary drainage; biliary drainage helps identify sphincter of Oddi dysfunction.

Radionuclide liver scanning: Ultrasonography and CT have largely supplanted radionuclide scanning, which had been used to diagnose diffuse liver disorders and mass lesions of the liver. Radionuclide scanning shows the distribution of an injected radioactive tracer, usually technetium ($^{99m}$Tc sulfur colloid), which distributes uniformly within the normal liver. Space-occupying lesions > 4 cm, such as liver cysts, abscesses, metastases, and tumors, appear as defects. Diffuse liver disorders (eg, cirrhosis, hepatitis) decrease liver uptake of the tracer, with more appearing in the spleen and bone marrow. In hepatic vein obstruction (Budd-Chiari syndrome), liver uptake is decreased except in the caudate lobe because its drainage into the inferior vena cava is preserved.

Plain x-ray of the abdomen: Plain x-rays are not usually useful for diagnosis of hepatobiliary disorders. They are insensitive for gallstones unless the gallstones are calcified and large. Plain x-rays can detect a calcified (porcelain) gallbladder. Rarely, in gravely ill patients, x-rays show air in the biliary tree, which suggests emphysematous cholangitis.

MRI: MRI images blood vessels (without using contrast), ducts, and hepatic tissues. Its clinical uses are still evolving. MRI is superior to CT and ultrasonography for diagnosing diffuse liver disorders (eg, fatty liver, hemochromatosis) and for clarifying some focal defects (eg, hemangiomas). MRI also shows blood flow and therefore complements Doppler ultrasonography and CT angiography in the diagnosis of vascular abnormalities and in vascular mapping before liver transplantation.

Magnetic resonance cholangiopancreatography (MRCP) is more sensitive than CT or ultrasonography in diagnosing common bile duct abnormalities, particularly stones. Its images of the biliary system and pancreatic ducts are comparable to those obtained with ERCP and percutaneous transhepatic cholangiography, which are more invasive. Thus, MRCP is a useful screening tool when biliary obstruction is suspected and before therapeutic ERCP (eg, for simultaneous imaging and stone removal) is done.

ERCP: ERCP combines endoscopy through the second portion of the duodenum with contrast imaging of the biliary and pancreatic ducts. The papilla of Vater is cannulated through an endoscope placed in the descending duodenum, and the pancreatic and biliary ducts are then injected with a contrast agent.

ERCP provides detailed images of much of the upper GI tract and the periampullary area, biliary tract, and pancreas. ERCP can also be used to obtain tissue for biopsy. ERCP is the best test for diagnosis of ampullary cancers. ERCP is as accurate as endoscopic ultrasonography for diagnosis of common duct stones. Because it is invasive, ERCP is used more for treatment (including simultaneous diagnosis and treatment) than for diagnosis alone. ERCP is the procedure of choice for treating biliary and pancreatic obstructing lesions, as for

- Removal of bile duct stones
- Stenting of strictures (inflammatory or malignant)
- Sphincterotomy (eg, for sphincter of Oddi dysfunction)
Morbidity from a diagnostic ERCP with only injection of contrast material is about 1%. Adding sphincterotomy raises morbidity to 4 to 9% (mainly due to pancreatitis and bleeding). ERCP with manometry to measure sphincter of Oddi pressure causes pancreatitis in up to 25% of patients.

**Percutaneous transhepatic cholangiography (PTC):** With fluoroscopic or ultrasound guidance, the liver is punctured with a needle, the peripheral intrahepatic bile duct system is cannulated above the common hepatic duct, and a contrast agent is injected.

PTC is highly accurate in diagnosing biliary disorders and can be therapeutic (eg, decompression of the biliary system, insertion of an endoprosthesis). However, ERCP is usually preferred because PTC causes more complications (eg, sepsis, bleeding, bile leaks).

**Operative cholangiography:** A contrast agent is directly injected during laparotomy to image the bile duct system.

Operative cholangiography is indicated when jaundice occurs and noninvasive procedures are equivocal, suggesting common duct stones. The procedure can be followed by common duct exploration for removal of biliary stones. Technical difficulties have limited its use, particularly during laparoscopic cholecystectomy.

**Liver Biopsy**

Liver biopsy provides histologic information about liver structure and evidence of liver injury (type and degree, any fibrosis); this information can be essential not only to diagnosis but also to staging, prognosis, and management. Although only a small core of tissue is obtained, it is usually representative, even for focal lesions.

Liver biopsy is usually done percutaneously at the bedside or with ultrasound guidance. Ultrasound guidance is preferred because its complication rate is slightly lower and it provides opportunity to visualize the liver and target focal lesions.

**Indications:** Generally, biopsy is indicated for suspected liver abnormalities that are not identified by less invasive methods or that require histopathology for staging (see Table 24-2). Biopsy is especially valuable for detecting TB or other granulomatous infiltrations and for clarifying graft problems (ischemic injury, rejection, biliary tract disorders, viral hepatitis) after liver transplantation. Serial biopsies, commonly done over years, may be necessary to monitor disease progression.

Gross examination and histopathology are often definitive. Cytology (fine-needle aspiration), frozen section, and culture may be useful for selected patients. Metal content (eg, copper in suspected Wilson's disease, iron in hemochromatosis) can be measured in the biopsy specimen.

Limitations of liver biopsy include

- Sampling error
- Occasional errors or uncertainty in cases of cholestasis
- Need for a skilled histopathologist (some pathologists have little experience with needle specimens)

**Contraindications:** Absolute contraindications to liver biopsy include

- Patient's inability to remain still and to maintain brief expiration for the procedure
- Suspected vascular lesion (e.g., hemangioma)
- Bleeding tendency (e.g., INR > 1.2 despite receiving vitamin K, bleeding time > 10 min)
- Severe thrombocytopenia (< 50,000/mL)

Relative contraindications include profound anemia, peritonitis, marked ascites, high-grade biliary obstruction, and a subphrenic or right pleural infection or effusion. Nonetheless, percutaneous liver biopsy is sufficiently safe to be done on an outpatient basis. Mortality is 0.01%. Major complications (e.g., intra-abdominal hemorrhage, bile peritonitis, lacerated liver) develop in about 2% of patients. Complications usually become evident within 3 to 4 h—the recommended period for monitoring patients.

Other routes: Transjugular venous biopsy of the liver is more invasive than the percutaneous route; it is reserved for patients with a severe coagulopathy. The procedure involves cannulating the right internal jugular vein and passing a catheter through the inferior vena cava into the hepatic vein. A fine needle is then advanced through the hepatic vein into the liver. Biopsy is successful in > 95% of patients. Complication rate is low; 0.2% bleed from puncture of the liver capsule.

Occasionally, liver biopsy is done during surgery (e.g., laparoscopy); a larger, more targeted tissue sample can then be obtained.
Chapter 25. Drugs and the Liver

Introduction

Interaction between drugs and the liver can be categorized as follows:

• Effects of liver disease on drug metabolism
• Liver injury caused by drugs
• Effects of hepatic drug metabolism (eg, induction of hepatic enzymes, see p. 3177)

The number of possible interactions is vast.

Effects of Liver Disease on Drug Metabolism

Liver disease may have complex effects on drug clearance, biotransformation, and pharmacokinetics. Pathogenetic factors include alterations in intestinal absorption, plasma protein binding, hepatic extraction ratio, liver blood flow, portal-systemic shunting, biliary excretion, enterohepatic circulation, and renal clearance. Sometimes alterations increase levels of bioavailable drug, causing normal drug doses to have toxic effects. However, levels and effects for an individual drug are unpredictable and do not correlate well with the type of liver injury, its severity, or liver function test results. Thus, no general rules are available for modifying drug dosage in patients with liver disease.

Clinical effects can vary independent of drug bioavailability, especially in chronic liver disease; eg, cerebral sensitivity to opioids and sedatives is often enhanced in patients with chronic liver disease. Thus, seemingly small doses of these drugs given to cirrhotic patients may precipitate encephalopathy. The mechanism of this effect probably involves alterations in cerebral drug receptors.

Adverse drug reactions do not appear to be more likely in patients with advanced liver disease; however, such patients may tolerate any hepatic adverse effects of drugs less well.

Liver Injury Caused by Drugs

Many drugs (eg, statins) commonly cause asymptomatic elevation of hepatic enzymes (ALT, AST, alkaline phosphatase). However, clinically significant liver injury (eg, with jaundice, abdominal pain, or pruritus) or impaired liver function—ie, resulting in deficient protein synthesis (eg, with prolonged PT or with hypoalbuminemia)—is rare.

The term drug-induced liver injury (DILI) may be used to mean clinically significant liver injury or all (including asymptomatic) liver injury. DILI includes injury caused by medicinal herbs, plants, and nutritional supplements as well as drugs.

Pathophysiology

The pathophysiology of DILI varies depending on the drug (or other hepatotoxin) and, in many cases, is not entirely understood. Drug-induced injury mechanisms include covalent binding of the drug to cellular proteins resulting in immune injury, inhibition of cell metabolic pathways, blockage of cellular transport pumps, induction of apoptosis, and interference with mitochondrial function.

In general, the following are thought to increase risk of DILI:

• Age ≥ 18 yr
• Obesity
• Pregnancy
• Concomitant alcohol consumption

• Genetic polymorphisms (increasingly recognized)

**Patterns of liver injury:** DILI can be predictable (when injury usually occurs shortly after exposure and is dose-related) or unpredictable (when injury develops after a period of latency and has no relation to dose). Predictable DILI (commonly, acetaminophen-induced) is a common cause of acute jaundice and acute liver failure in the US. Unpredictable DILI is a rare cause of severe liver disease. Subclinical DILI may be underreported.

Biochemically, 3 types of liver injury are generally noted (see **Table 25-1**):

• **Hepatocellular:** Hepatocellular hepatotoxicity generally manifests as malaise and right upper quadrant abdominal pain, associated with marked elevation in aminotransferase levels (ALT, AST, or both), which may be followed by hyperbilirubinemia in severe cases. Hyperbilirubinemia in this setting is known as hepatocellular jaundice and, according to Hy's law, is associated with mortality rates as high as 50%. If hepatocellular liver injury is accompanied by jaundice, impaired hepatic synthesis, and encephalopathy, chance of spontaneous recovery is low, and liver transplantation should be considered. This type of injury can result from drugs such as acetaminophen and isoniazid.

• **Cholestatic:** Cholestatic hepatotoxicity is characterized by development of pruritus and jaundice accompanied by marked elevation of serum alkaline phosphatase levels. Usually, this type of injury is less serious than severe hepatocellular syndromes, but recovery may be protracted. Substances known to lead to this type of injury include amoxicillin/clavulanate and chlorpromazine. Rarely, cholestatic hepatotoxicity leads to chronic liver disease and vanishing bile duct syndrome (progressive destruction of intrahepatic bile ducts).

• **Mixed:** In these clinical syndromes, neither aminotransferase nor alkaline phosphatase elevations are clearly predominant. Symptoms may also be mixed. Drugs such as phenytoin can cause this type of injury.

**Diagnosis**

• Identification of characteristic patterns of laboratory abnormalities

• Exclusion of other causes

Presentation varies widely, ranging from absent or nonspecific symptoms (eg, malaise, nausea, anorexia) to jaundice, impaired hepatic synthesis, and encephalopathy. Early recognition of DILI improves prognosis.

Identification of a potential hepatotoxin and a pattern of liver test abnormalities that is characteristic of the substance (its signature) make the diagnosis likely.

Because there is no confirmatory diagnostic test, other causes of liver disease, especially viral, biliary, alcoholic, autoimmune, and metabolic causes, need to be excluded. Drug rechallenge, although it can strengthen evidence for the diagnosis, should usually be avoided. Suspected cases of DILI should be reported to MedWatch (the FDA's adverse drug reaction monitoring program).

**Treatment**

• Early drug withdrawal

Management emphasizes drug withdrawal, which, if done early, usually results in recovery. In severe
Cases, consultation with a specialist is indicated, especially if patients have hepatocellular jaundice and impaired liver function, because liver transplantation may be required. Antidotes for DILI are available for only a few hepatotoxins; such antidotes include N-acetylcysteine for acetaminophen toxicity and silymarin or penicillin for *Amanita phalloides* toxicity.

**Prevention**

Efforts to avoid DILI begin during the drug development process, although apparent safety in small preclinical trials does not ensure eventual safety of the drug after it is in widespread use. Postmarketing surveillance, although often voluntary in the US, can call attention to potentially hepatotoxic drugs. Routine monitoring of liver enzymes has not been shown to decrease the incidence of hepatotoxicity. Use of pharmacogenomics may allow tailoring of drug use and avoidance of potential toxicities in susceptible patients.
Alcohol consumption is high in most Western countries. In the US, > 10% of people abuse or are dependent on alcohol. The male:female ratio is about 2:1. Disorders that occur in alcohol abusers, often in sequence, include

- Fatty liver (in > 90%)
- Alcoholic hepatitis (in 10 to 35%)
- Cirrhosis (in 10 to 20%)

Hepatocellular carcinoma may also develop, especially in association with iron accumulation.

Risk Factors

The main causative factors in alcoholic liver disease are

- Quantity and duration of alcohol use (usually > 8 yr)
- Sex
- Genetic and metabolic traits
- Nutritional status

Quantity of alcohol: Among susceptible people, a linear correlation generally exists between the amount and duration of alcohol use and the development of liver disease.

Alcohol content is estimated to be the beverage volume (in mL) multiplied by its percentage of alcohol. For example, the alcohol content of 40 mL of an 80-proof (40% alcohol) beverage is 16 mL by volume. Each mL contains about 0.79 g of alcohol. Although values can vary, the percentage of alcohol averages 2 to 7% for most beers and 10 to 15% for most wines. Thus, a 12-oz glass of beer contains about 3 to 10 g of alcohol, and an 8-oz glass of wine contains about 10 to 15 g.

Risk increases markedly for men who drink > 40 g, particularly > 80 g, of alcohol/day for > 10 yr (eg, 3 to 6 cans of beer, 3 to 6 shots of hard liquor, 4 to 8 glasses of wine). For cirrhosis to develop, consumption must usually be > 80 g/day for > 10 yr. If consumption exceeds 230 g/day for 20 yr, risk of cirrhosis is about 50%. But only some chronic alcohol abusers develop liver disease. Thus, variations in alcohol intake do not fully explain variations in susceptibility, indicating that other factors are involved.

Sex: Women are more susceptible to alcoholic liver disease, even after adjustment for body size. Women require only 20 to 40 g of alcohol to be at risk—half of that for men. Risk in women may be increased because they have less alcohol dehydrogenase in their gastric mucosa; thus, first-pass oxidation of alcohol is decreased.

Genetic factors: Alcoholic liver disease often runs in families, suggesting genetic factors (eg, deficiency of cytoplasmic enzymes that eliminate alcohol).

Nutritional status: Undernutrition, particularly protein-energy undernutrition, increases susceptibility, as does a diet high in unsaturated fat and obesity.

Other factors: Other risk factors include iron accumulation in the liver (not necessarily related to iron intake) and concomitant hepatitis C.

Pathophysiology

Alcohol absorption and metabolism: Alcohol (ethanol) is readily absorbed from the stomach, but most
is absorbed from the small intestine. Alcohol cannot be stored. A small amount is degraded in transit through the gastric mucosa, but most is catabolized in the liver, primarily by alcohol dehydrogenase (ADH) but also by cytochrome P-450 2E1 (CYP2E1) and the microsomal enzyme oxidation system (MEOS).

Metabolism via the ADH pathway involves the following:

- **ADH**, a cytoplasmic enzyme, oxidizes alcohol into acetaldehyde. Genetic polymorphisms in ADH account for some individual differences in blood alcohol levels after the same alcohol intake but not in susceptibility to alcoholic liver disease.

- **Acetaldehyde dehydrogenase (ALDH)**, a mitochondrial enzyme, then oxidizes acetaldehyde to acetate. Chronic alcohol consumption enhances acetate formation. Asians, who have lower levels of ALDH, are more susceptible to toxic acetaldehyde effects (eg, flushing); the effects are similar to those of disulfiram, which inhibits ALDH.

- These oxidative reactions generate hydrogen, which converts nicotinamide-adenine dinucleotide (NAD) to its reduced form (NADH), increasing the redox potential (NADH/NAD) in the liver.

- The increased redox potential inhibits fatty acid oxidation and gluconeogenesis, promoting fat accumulation in the liver.

Chronic alcoholism induces the MEOS (mainly in endoplasmic reticulum), increasing its activity. The main enzyme involved is CYP2E1. When induced, the MEOS pathway can account for 20% of alcohol metabolism. This pathway generates harmful reactive O\(_2\) species, increasing oxidative stress and formation of O\(_2\)-free radicals.

**Hepatic fat accumulation:** Fat (triglycerides) accumulates throughout the hepatocytes for the following reasons:

- Export of fat from the liver is decreased because hepatic fatty acid oxidation and lipoprotein production decrease.

- Input of fat is increased because the decrease in hepatic fat export increases peripheral lipolysis and triglyceride synthesis, resulting in hyperlipidemia.

Hepatic fat accumulation may predispose to subsequent oxidative damage.

**Endotoxins in the gut:** Alcohol changes gut permeability, increasing absorption of endotoxins released by bacteria in the gut. In response to the endotoxins (which the impaired liver can no longer detoxify), liver macrophages (Kupffer cells) release free radicals, increasing oxidative damage.

**Oxidative damage:** Oxidative stress is increased by

- Liver hypermetabolism, caused by alcohol consumption

- Free radical-induced lipid peroxidative damage

- Reduction in protective antioxidants (eg, glutathione, vitamins A and E), caused by alcohol-related undernutrition

- Binding of alcohol oxidation products, such as acetaldehyde, to liver cell proteins, forming neoantigens and resulting in inflammation

- Accumulation of neutrophils and other WBCs, which are attracted by lipid peroxidative damage and neoantigens

- Inflammatory cytokines secreted by WBCs
Accumulation of hepatic iron, if present, aggravates oxidative damage. Iron can accumulate in alcoholic liver disease through ingestion of iron-containing fortified wines; most often, the iron accumulation is modest. This condition must be differentiated from hereditary hemochromatosis.

**Resultant inflammation, cell death, and fibrosis:** A vicious circle of worsening inflammation occurs: Cell necrosis and apoptosis result in hepatocyte loss, and subsequent attempts at regeneration result in fibrosis. Stellate (Ito) cells, which line blood channels (sinusoids) in the liver, proliferate and transform into myofibroblasts, producing an excess of type I collagen and extracellular matrix. As a result, the sinusoids narrow, limiting blood flow. Fibrosis narrows the terminal hepatic venules, compromising hepatic perfusion and thus contributing to portal hypertension. Extensive fibrosis is associated with an attempt at regeneration, resulting in liver nodules. This process culminates in cirrhosis.

**Pathology**

Fatty liver, alcoholic hepatitis, and cirrhosis are often considered separate, progressive manifestations of alcoholic liver disease. However, their features often overlap.

**Fatty liver** (steatosis) is the initial and most common consequence of excessive alcohol consumption. Fatty liver is potentially reversible. Macrovesicular fat accumulates as large droplets of triglyceride and displaces the hepatocyte nucleus, most markedly in perivenular hepatocytes. The liver enlarges.

**Alcoholic hepatitis** (steatohepatitis) is a combination of fatty liver, diffuse liver inflammation, and liver necrosis (often focal)—all in various degrees of severity. The damaged hepatocytes are swollen with a granular cytoplasm (balloon degeneration) or contain fibrillar protein in the cytoplasm (Mallory or alcoholic hyaline bodies). Severely damaged hepatocytes become necrotic. Sinusoids and terminal hepatic venules are narrowed. Cirrhosis may also be present.

**Alcoholic cirrhosis** is advanced liver disease characterized by extensive fibrosis that disrupts the normal liver architecture. The amount of fat present varies. Alcoholic hepatitis may coexist. The feeble compensatory attempt at hepatic regeneration produces relatively small nodules (micronodular cirrhosis). As a result, the liver usually shrinks. In time, even with abstinence, fibrosis forms broad bands, separating liver tissue into large nodules (macronodular cirrhosis—see p. 241).

**Symptoms and Signs**

Symptoms usually become apparent in patients during their 30s or 40s; severe problems appear about a decade later.

**Fatty liver** is often asymptomatic. In one third of patients, the liver is enlarged and smooth, but it is not usually tender.

**Alcoholic hepatitis** ranges from mild and reversible to life threatening. Most patients with moderate disease are undernourished and present with fatigue, fever, jaundice, right upper quadrant pain, tender hepatomegaly, and sometimes a hepatic bruit. About 40% deteriorate soon after hospitalization, with consequences ranging from mild (eg, increasing jaundice) to severe (eg, ascites, portal-systemic encephalopathy, variceal bleeding, liver failure with hypoglycemia, coagulopathy). Other manifestations of cirrhosis may be present.

**Cirrhosis**, if compensated, may be asymptomatic. The liver is usually small; when the liver is enlarged, fatty liver or hepatoma should be considered. Symptoms range from those of alcoholic hepatitis to the complications of end-stage liver disease, such as portal hypertension (often with esophageal varices and upper GI bleeding, splenomegaly, ascites, and portal-systemic encephalopathy). Portal hypertension may lead to intrapulmonary arteriovenous shunting with hypoxemia (hepatopulmonary syndrome), which may cause cyanosis and nail clubbing. Acute renal failure secondary to progressively decreasing renal blood flow (hepatorenal syndrome) may develop. Hepatocellular carcinoma develops in 10 to 15% of patients with alcoholic cirrhosis.

**Chronic alcoholism**, rather than liver disease, causes Dupuytren's contracture of the palmar fascia,
vascular spiders, and peripheral neuropathy. In men, chronic alcoholism causes signs of hypogonadism and feminization (eg, smooth skin, lack of male-pattern baldness, gynecomastia, testicular atrophy, changes in pubic hair). Undernutrition may lead to multiple vitamin deficiencies (eg, of folate and thiamin), enlarged parotid glands, and white nails. In alcoholics, Wernicke's encephalopathy and Korsakoff's psychosis result mainly from thiamin deficiency. Hepatitis C occurs in > 25% of alcoholics; this combination markedly worsens the progression of liver disease.

Rarely, patients with fatty liver or cirrhosis present with Zieve's syndrome (hyperlipidemia, hemolytic anemia, and jaundice).

**Diagnosis**

- Confirmed history of alcohol use
- Liver function tests and CBC
- Sometimes liver biopsy

Alcohol is suspected as the cause of liver disease in any patient who chronically consumes excess alcohol, particularly > 80 g/day. History should be confirmed by family members. Patients can be screened for alcoholism using the CAGE questionnaire (need to Cut down, Annoyed by criticism, Guilty about drinking, and need for a morning Eye-opener). There is no specific test for alcoholic liver disease, but if the diagnosis is suspected, liver function tests (PT; serum bilirubin, aminotransferase, and albumin levels) and CBC are done to detect signs of liver injury and anemia.

Elevations of aminotransferases are moderate (< 300 IU/L) and do not reflect the extent of liver damage. The ratio of AST to ALT is ≥ 2. The basis for low ALT is a dietary deficiency of pyridoxal phosphate (vitamin B₆), which is needed for ALT to function. Its effect on AST is less pronounced. Serum γ-glutamyl transpeptidase (GGT) increases, more because ethanol induces this enzyme than because patients have cholestasis or liver injury or use other drugs. Serum albumin may be low, usually reflecting undernutrition but occasionally reflecting otherwise obvious liver failure with deficient synthesis. Macrocytosis with an MCV > 100 fl reflects the direct effect of alcohol on bone marrow as well as macrocytic anemia resulting from folate deficiency, which is common among undernourished alcoholics. Indexes of the severity of liver disease are

- Serum bilirubin, which represents secretory function
- PT or INR, which reflects synthetic ability

Thrombocytopenia can result from the direct toxic effects of alcohol on bone marrow or from splenomegaly, which accompanies portal hypertension. Neutrophilic leukocytosis may result from alcoholic hepatitis, although coexisting infection (particularly pneumonia and spontaneous bacterial peritonitis) should also be suspected.

Imaging tests are not routinely needed for diagnosis. If done for other reasons, abdominal ultrasonography or CT may suggest fatty liver or show evidence of splenomegaly, portal hypertension, or ascites. Ultrasound elastography measures liver stiffness and thus detects advanced fibrosis. This valuable adjunct can obviate the need for liver biopsy to check for cirrhosis and help assess prognosis. Its exact role is under study.

If abnormalities suggest alcoholic liver disease, screening tests for other treatable forms of liver disease, especially viral hepatitis, should be done. Because features of fatty liver, alcoholic hepatitis, and cirrhosis overlap, describing the precise findings is more useful than assigning patients to a specific category, which can only be determined by liver biopsy.

Not all experts agree on the indications for liver biopsy. Proposed indications include the following:

- Unclear clinical diagnosis (eg, equivocal clinical and laboratory findings, unexplained persistent
• Clinical suspicion of > 1 cause of liver disease (eg, alcohol plus viral hepatitis)

• Desire for a precise prediction of prognosis

Liver biopsy confirms liver disease, helps identify excessive alcohol use as the likely cause, and establishes the stage of liver injury. If iron accumulation is observed, measurement of the iron content and genetic testing can eliminate hereditary hemochromatosis (see p. 1032) as the cause.

For stable patients with cirrhosis, α-fetoprotein measurement and liver ultrasonography should be done to screen for hepatocellular carcinoma (see p. 265).

Prognosis

Prognosis is determined by the degree of hepatic fibrosis and inflammation. Fatty liver and alcoholic hepatitis without fibrosis are reversible if alcohol is avoided. With abstinence, fatty liver completely resolves within 6 wk. Fibrosis and cirrhosis are irreversible.

Certain biopsy findings (eg, neutrophils, perivenular fibrosis) indicate a worse prognosis. Proposed quantitative indexes to predict severity and mortality use primarily laboratory features of liver failure such as prothrombin time, creatinine (for hepatorenal syndrome) and bilirubin levels. The Maddrey discriminant function is calculated from the formula:

\[ 4.6 \times (\text{PT} - \text{control PT}) + \text{serum bilirubin} \]

For this formula, bilirubin level is measured in mg/dL (converted from bilirubin in μmol/L by dividing by 17). A value of > 32 is associated with a high short-term mortality rate (eg, after 1 mo, 35% without encephalopathy and 45% with encephalopathy). Other indexes include the Model for End-Stage Liver Disease (MELD), Glasgow alcoholic hepatitis score, and Lille model.

Once cirrhosis and its complications (eg, ascites, bleeding) develop, the 5-yr survival rate is about 50%; survival is higher in patients who abstain and lower in patients who continue drinking.

Coexisting iron accumulation or chronic hepatitis C increases risk of hepatocellular carcinoma.

Treatment

• Abstinence

• Supportive care

• Corticosteroids and enteral nutrition for severe alcoholic hepatitis

• Sometimes transplantation

Restricting alcohol intake: Abstinence is the mainstay of treatment; it prevents further damage from alcoholic liver disease and thus prolongs life. Because compliance is problematic, a compassionate team approach is essential. Behavioral and psychosocial interventions can help motivated patients; they include rehabilitation programs and support groups (see p. 1521), brief interventions by primary care physicians, and therapies that explore and clarify the motivation to abstain (motivational enhancement therapy).

Drugs, if used, should only supplement other interventions. Opioid antagonists (naltrexone or nalmefene) and drugs that modulate γ-aminobutyric acid receptors (baclofen or acamprosate) appear to have a short-
term benefit by reducing the craving and withdrawal symptoms. Disulfiram inhibits aldehyde dehydrogenase, allowing acetaldehyde to accumulate; thus, drinking alcohol within 12 h of taking disulfiram causes flushing and has other unpleasant effects. However, disulfiram has not been shown to promote abstinence and consequently is recommended only for certain patients.

Supportive care: General management emphasizes supportive care. A nutritious diet and vitamin supplements (especially B vitamins) are important during the first few days of abstinence. Alcohol withdrawal requires use of benzodiazepines (eg, diazepam). In patients with advanced alcoholic liver disease, excessive sedation can precipitate hepatic encephalopathy and thus must be avoided.

Severe acute alcoholic hepatitis commonly requires hospitalization, often in an intensive care unit, to facilitate enteral feeding (which can help manage nutritional deficiencies) and to manage specific complications (eg, infection, bleeding from esophageal varices, specific nutritional deficiencies, Wernicke's encephalopathy, Korsakoff's psychosis, electrolyte abnormalities, portal hypertension, ascites, portal-systemic encephalopathy—see elsewhere in THE MANUAL).

Specific treatment: Corticosteroids (eg, prednisolone 40 mg/day po for 4 wk, followed by tapered doses improve outcome in patients who have severe acute alcoholic hepatitis and who do not have infection, GI bleeding, renal failure, or pancreatitis.

Other than corticosteroids and enteral feeding, few specific treatments are clearly established. Antioxidants (eg, S-adenosyl-L-methionine, phosphatidylcholine, metadoxine) show promise in ameliorating liver injury during early cirrhosis but require further study. Therapies directed at cytokines, particularly tumor necrosis factor-α (TNF-α), and aiming to reduce inflammation have had mixed results in small trials. Pentoxifylline, a phosphodiesterase inhibitor that inhibits TNF-α synthesis, has some benefit. In contrast, when biologic agents that inhibit TNF-α (eg, infliximab, etanercept) are used, risk of infection outweighs benefit. Drugs given to decrease fibrosis (eg, colchicine, penicillamine) and drugs given to normalize the hypermetabolic state of the alcoholic liver (eg, propylthiouracil) have no proven benefit. Antioxidant remedies, such as silymarin (milk thistle) and vitamins A and E, are ineffective.

Liver transplantation can be considered if disease is severe. With transplantation, 5-yr survival rates are comparable to those for nonalcoholic liver disease—as high as 80% in patients without active liver disease and 50% in those with acute alcoholic hepatitis. Because up to 50% of patients resume drinking after transplantation, most programs require 6 mo of abstinence before transplantation is done.
Chapter 27. Fibrosis and Cirrhosis

Introduction

In hepatic fibrosis, excessive connective tissue accumulates in the liver; this tissue represents scarring in response to chronic, repeated liver cell injury. Commonly, fibrosis progresses, disrupting hepatic architecture and eventually function, as regenerating hepatocytes attempt to replace and repair damaged tissue. When such disruption is widespread, cirrhosis is diagnosed. To develop, cirrhosis usually requires > 6 mo of liver disease but can occur more rapidly (eg, during infancy with biliary atresia, after liver transplantation for severe liver disease secondary to chronic hepatitis B or C).

Fibrosis

Hepatic fibrosis is overly exuberant wound healing in which excessive connective tissue builds up in the liver. The extracellular matrix is overproduced, degraded deficiently, or both. The trigger is chronic injury, especially if there is an inflammatory component. Fibrosis itself causes no symptoms but can lead to portal hypertension (the scarring distorts blood flow through the liver) or cirrhosis (the scarring results in disruption of normal hepatic architecture and liver dysfunction). Diagnosis is based on liver biopsy. Treatment involves correcting the underlying condition when possible.

Various types of chronic liver injury can cause fibrosis (see Table 27-1). Self-limited, acute liver injury (eg, acute viral hepatitis A), even when fulminant, does not necessarily distort the scaffolding architecture and hence does not cause fibrosis, despite loss of hepatocytes. In its initial stages, hepatic fibrosis can regress if the cause is reversible (eg, with viral clearance). After months or years of chronic or repeated injury, fibrosis becomes permanent. Fibrosis develops even more rapidly in mechanical biliary obstruction.

Pathophysiology

Activation of the hepatic perivascular stellate cells (Ito cells, which store fat) initiates fibrosis. These and adjacent cells proliferate, becoming contractile cells termed myofibroblasts. These cells produce excessive amounts of abnormal matrix (consisting of collagen, other glycoproteins, and glycans) and matricellular proteins. Kupffer cells (resident macrophages), injured hepatocytes, platelets, and leukocytes aggregate. As a result, reactive O_2 species and inflammatory mediators (eg, platelet-derived growth factor, transforming growth factors, and connective tissue growth factor) are released. Thus, stellate cell activation results in abnormal extracellular matrix, both in quantity and composition.

Myofibroblasts, stimulated by endothelin-1, contribute to increased portal vein resistance and increase the density of the abnormal matrix. Fibrous tracts join branches of afferent portal veins and efferent hepatic veins, bypassing the hepatocytes and limiting their blood supply. Hence, fibrosis contributes both to hepatocyte ischemia (causing hepatocellular dysfunction) and portal hypertension. The extent of the ischemia and portal hypertension determines how the liver is affected. For example, congenital hepatic fibrosis affects portal vein branches, largely sparing the parenchyma. The result is portal hypertension with sparing of hepatocellular function.

Symptoms and Signs

Hepatic fibrosis itself does not cause symptoms. Symptoms may develop secondary to the primary disorder or to portal hypertension. Portal hypertension with splenomegaly is often asymptomatic unless complications, such as variceal GI bleeding, ascites, or portal-systemic encephalopathy, develop. Eventually, cirrhosis supervenes.

Diagnosis
Biopsy

Hepatic fibrosis is suspected in patients who have an underlying disorder or take a drug that could cause fibrosis or who have unexplained abnormalities in liver function or enzymes. Noninvasive tests (eg, serologic markers) are under study but are not yet ready for routine clinical use. Imaging tests such as ultrasonography, CT, and MRI may detect findings associated with fibrosis (eg, portal hypertension, splenomegaly, cirrhosis) but are not sensitive to parenchymal fibrosis itself. Liver biopsy is currently the only means of detecting hepatic fibrosis. Biopsy is indicated to clarify the diagnosis (eg, nonalcoholic steatohepatitis, primary biliary cirrhosis) and stage its progress (eg, in chronic hepatitis C to determine whether fibrosis is present or whether it has progressed to cirrhosis).

Treatment

Treatment of cause

Because fibrosis represents a response to hepatic damage, primary treatment should focus on the cause (removing the basis of the liver injury). Such treatment may include eliminating HBC or HCV in chronic viral hepatitis, abstaining from alcohol in alcoholic liver disease, removing heavy metals such as iron in hemochromatosis or copper in Wilson's disease, and decompressing bile ducts in biliary obstruction.

Treatments aimed at reversing the fibrosis are usually too toxic for long-term use (eg, corticosteroids, penicillamine) or have no proven efficacy (eg, colchicine). Other antifibrotic treatments are under study. Simultaneous use of multiple antifibrotic drugs may eventually prove most beneficial.

Cirrhosis

Cirrhosis is a late stage of hepatic fibrosis that has resulted in widespread distortion of normal hepatic architecture. Cirrhosis is characterized by regenerative nodules surrounded by dense fibrotic tissue. Symptoms may not develop for years and are often nonspecific (eg, anorexia, fatigue, weight loss). Late manifestations include portal hypertension, ascites, and, when decompensation occurs, liver failure. Diagnosis often requires liver biopsy. Cirrhosis is usually considered irreversible. Treatment is supportive.

Cirrhosis is a leading cause of death worldwide. The causes of cirrhosis are the same as those of fibrosis (see Table 27-1). In developed countries, most cases result from chronic alcohol abuse or chronic hepatitis C. In parts of Asia and Africa, cirrhosis often results from chronic hepatitis B. Cirrhosis of unknown etiology (cryptogenic cirrhosis) is becoming less common as many specific causes (eg, chronic hepatitis C, steatohepatitis) are identified. Injury to the bile ducts also can result in cirrhosis, as occurs in mechanical bile duct obstruction, primary biliary cirrhosis (see p. 244), and primary sclerosing cholangitis (see p. 278).

Pathophysiology

There are 2 primary factors:

• Hepatic fibrosis

• Regenerating liver cells

In response to injury and loss, growth regulators induce hepatocellular hyperplasia (producing regenerating nodules) and arterial growth (angiogenesis). Among the growth regulators are cytokines and hepatic growth factors (eg, epithelial growth factor, hepatocyte growth factor, transforming growth factor-α, tumor necrosis factor). Insulin, glucagon, and patterns of intrahepatic blood flow determine how and where nodules develop.

Angiogenesis produces new vessels within the fibrous sheath that surrounds nodules. These vessels connect the hepatic artery and portal vein to hepatic venules, restoring the intrahepatic circulatory
pathways. Such interconnecting vessels provide relatively low-volume, high-pressure venous drainage that cannot accommodate as much blood volume as normal. As a result, portal vein pressure increases. Such distortions in blood flow contribute to portal hypertension, which increases because the regenerating nodules compress hepatic venules.

The progression rate from fibrosis to cirrhosis and the morphology of cirrhosis vary from person to person. Presumably, the reason for such variation is the extent of exposure to the injurious stimulus and the individual's response.

**Complications:** Portal hypertension (see p. 218) is the most common serious complication; it can manifest as GI bleeding from esophageal, gastric, or rectal varices or portal hypertensive gastropathy. Portal hypertension can be massive. Cirrhosis can cause other cardiovascular complications. Vasodilation and intrapulmonary right-to-left shunting and ventilation/perfusion mismatch can result in hypoxia (hepatopulmonary syndrome). A cardiac myopathy can also accompany cirrhosis.

Ascites can develop, with a risk of spontaneous bacterial peritonitis. Splenic congestion with hypersplenism may occur, resulting in splenomegaly, platelet sequestration, and consequent cytopenia.

Progressive loss of hepatic architecture impairs function, leading to hepatic insufficiency; it manifests as coagulopathy, renal failure (hepatorenal syndrome—see p. 223), and hepatic encephalopathy. Hepatocytes secrete less bile, contributing to cholestasis and jaundice. Less bile in the intestine causes malabsorption of dietary fat (triglycerides) and fat-soluble vitamins. Malabsorption of vitamin D may contribute to osteoporosis. Undernutrition is common. It may result from anorexia with reduced food intake or, in patients with alcoholic liver disease, from malabsorption due to pancreatic insufficiency.

Blood disorders are common. Anemia results from hypersplenism, chronic GI bleeding, folate deficiency (particularly in patients with alcoholism), and hemolysis. Clotting may be impaired because of coagulopathy or thrombocytopenia. Coagulopathy results from impaired hepatic synthesis of the factors necessary for clotting, malabsorption of vitamin K due to impaired bile secretion into the duodenum, or both. Thrombocytopenia may be caused by hypersplenism (platelet sequestration), alcohol excess (directly inhibiting the bone marrow), or both. Pancytopenia also occurs with alcoholism.

Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B and C viruses, hemochromatosis, alcohol-related liver disease, α₁ antitrypsin deficiency, or glycogen storage disease.

**Histopathology:** Cirrhosis is characterized by regenerating nodules and fibrosis. Incompletely formed liver nodules, nodules without fibrosis (nodular regenerative hyperplasia), and congenital hepatic fibrosis (ie, widespread fibrosis without regenerating nodules) are not true cirrhosis.

Cirrhosis can be micronodular or macronodular. Micronodular cirrhosis is characterized by uniformly small nodules (< 3 mm in diameter) and thick regular bands of connective tissue. Typically, nodules lack lobular organization; terminal (central) hepatic venules and portal triads are distorted. With time, macronodular cirrhosis often develops. The nodules vary in size (3 mm to 5 cm in diameter) and have some rather normal lobular organization of portal triads and terminal hepatic venules. Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal hepatic architecture is suggested by the concentration of portal triads within the fibrous scars. Mixed cirrhosis (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Differentiation between these morphologic types of cirrhosis has limited clinical value.

**Symptoms and Signs**

Cirrhosis may be asymptomatic for years. One third of patients never develop symptoms. Often, the first symptoms are nonspecific; they include generalized fatigue (due to cytokine release), anorexia, malaise, and weight loss (see Table 27-2). The liver is typically palpable and firm, with a blunt edge, but is sometimes small and difficult to palpate. Nodules usually are not palpable.
Clinical signs that suggest a chronic liver disorder or chronic alcohol use but are not specific for cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, clubbing, Dupuytren's contracture, spider angiomas (< 10 may be normal), gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy.

Once complications of cirrhosis develop, decompensation inexorably ensues.

**Diagnosis**

- Liver function tests, coagulation tests, CBC, and serologic tests for viral cause
- Sometimes biopsy
- Identification of cause based on clinical evaluation and selective testing

**General approach:** Cirrhosis is suspected in patients with manifestations of any of its complications (see Table 27-2), particularly portal hypertension or ascites. Early cirrhosis should be considered in patients with nonspecific symptoms or characteristic laboratory abnormalities detected incidentally during laboratory testing, particularly in patients who have a disorder or take a drug that might cause fibrosis.

Testing seeks to detect cirrhosis and any complications and to determine its cause.

**Laboratory tests:** Diagnostic testing begins with liver function tests, coagulation tests, CBC, and serologic tests for viral causes (eg, hepatitis B and C). Laboratory tests alone may increase suspicion for cirrhosis but cannot confirm or exclude it. Liver biopsy becomes necessary if a clear diagnosis would lead to better management and outcome.

Test results may be normal or may indicate nonspecific abnormalities due to complications of cirrhosis or alcoholism. ALT and AST levels are often modestly elevated. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are often normal; elevated levels indicate cholestasis or biliary obstruction. Bilirubin is usually normal but increases when cirrhosis progresses, particularly in primary biliary cirrhosis (see p. 244). Decreased serum albumin and a prolonged PT directly reflect impaired hepatic synthesis —usually an end-stage event. Albumin can also be low when nutrition is poor. Serum globulin increases in cirrhosis and in most liver disorders with an inflammatory component. Anemia is common and usually normocytic with a high RBC distribution width. Anemia is often multifactorial; contributing factors may include chronic GI bleeding (usually causing microcytic anemia), folate nutritional deficiency (causing macrocytic anemia, especially in alcohol abuse), hemolysis, and hypersplenism. CBC may detect leukopenia, thrombocytopenia, or pancytopenia.

**Diagnostic imaging:** Imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. In advanced cirrhosis, ultrasonography shows a small, nodular liver. Ultrasonography also detects portal hypertension and ascites.

CT can detect a nodular texture, but it has no advantage over ultrasonography. Radionuclide liver scans using technetium-99m sulfur colloid may show irregular liver uptake and increased spleen and bone marrow uptake. MRI is more expensive than other imaging tests and has little advantage.

**Identification of the cause:** Determining the specific cause of cirrhosis requires key clinical information from the history and examination, as well as selective testing. Alcohol is the likely cause in patients with a documented history of alcoholism and clinical findings such as gynecomastia, spider angiomas (telangiectasia), and testicular atrophy plus laboratory confirmation of liver damage (AST elevated more than ALT) and liver enzyme induction (a greatly increased GGT). Fever, tender hepatomegaly, and jaundice suggest the presence of alcoholic hepatitis.
Detecting hepatitis B surface antigen (HBsAg) and IgG antibodies to hepatitis B (IgG anti-HBc) confirms chronic hepatitis B. Identifying serum antibody to hepatitis C (anti-HCV) and HCV-RNA points to hepatitis C.

If common causes such as alcohol or viral hepatitis are not confirmed, other less common causes are sought:

- Presence of antimitochondrial antibodies (in 95%) suggests primary biliary cirrhosis.
- Strictures and dilations of the intrahepatic and extrahepatic bile ducts seen on magnetic resonance cholangiopancreatography (MRCP) suggest primary sclerosing cholangitis.
- Increased serum Fe and transferrin and possibly results of genetic testing suggest hemochromatosis.
- Decreased serum ceruloplasmin and characteristic copper test results suggest Wilson's disease.
- Hypergammaglobulinemia and presence of autoantibodies (eg, antinuclear or anti-smooth muscle antibodies) indicate autoimmune hepatitis.

Liver biopsy: If clinical criteria and noninvasive testing are inconclusive, liver biopsy is usually done. Its sensitivity approaches 100%. Nonalcoholic steatohepatitis (NASH), often associated with obesity, diabetes, or the metabolic syndrome, may be evident on ultrasound scans but requires liver biopsy for confirmation. In obvious cases of cirrhosis with a marked coagulopathy, portal hypertension, ascites, and liver failure, biopsy is not required when results would not change management.

Monitoring: Patients with cirrhosis, particularly if due to chronic viral hepatitis B or C or hemochromatosis, should be screened for hepatocellular carcinoma (eg, measuring α-fetoprotein levels and ultrasonography every 6 to 12 mo—see p. 266).

Prognosis

Prognosis is often unpredictable. It depends on factors such as etiology, severity, presence of complications, comorbid conditions, host factors, and effectiveness of therapy. Patients who continue to drink alcohol, even small amounts, have a very poor prognosis. The Child-Turcotte-Pugh scoring system uses clinical and laboratory information to stratify disease severity, surgical risk, and overall prognosis (see Tables 27-3 and 27-4).

Treatment

- Supportive care

In general, treatment is supportive and includes stopping injurious drugs, providing nutrition (including supplemental vitamins), and treating the underlying disorders and complications. Doses of drugs metabolized in the liver should be reduced. All alcohol and hepatotoxic substances must be avoided. Withdrawal symptoms during hospitalization should be anticipated in patients who have cirrhosis and have continued to abuse alcohol.

Patients with varices need therapy to prevent bleeding (see p. 219). Liver transplantation is indicated for end-stage liver failure in suitable candidates.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune liver disorder characterized by the progressive destruction of intrahepatic bile ducts, leading to cholestasis, cirrhosis, and liver failure. Patients usually are asymptomatic at presentation but may experience fatigue or have symptoms of cholestasis (eg, pruritus, steatorrhea) or cirrhosis (eg, portal hypertension,
ascites). Laboratory tests reveal cholestasis, increased IgM, and, characteristically, antimitochondrial antibodies in the serum. Liver biopsy may be necessary for diagnosis and staging. Treatment includes ursodeoxycholic acid, cholestyramine (for pruritus), supplementary fat-soluble vitamins, and, ultimately for advanced disease, liver transplantation.

Etiology

PBC is the most common liver disease associated with chronic cholestasis in adults. Most (95%) cases occur in women aged 35 to 70. PBC also clusters in families. A genetic predisposition, perhaps involving the X chromosome, probably contributes. There may be an inherited abnormality of immune regulation. An autoimmune mechanism has been implicated; antibodies to antigens located on the inner mitochondrial membranes occur in > 95% of cases. These antimitochondrial antibodies (AMAs), the serologic hallmarks of PBC, are not cytotoxic and are not involved in bile duct damage. PBC is associated with other autoimmune disorders, such as RA, systemic sclerosis, Sjogren's syndrome, CREST syndrome, autoimmune thyroiditis, and renal tubular acidosis.

T cells attack the small bile ducts. CD4 and CD8 T lymphocytes directly target biliary epithelial cells. The trigger for the immunologic attack on bile ducts is unknown. Exposure to foreign antigens, such as an infectious (bacterial or viral) or toxic agent, may be the instigating event. These foreign antigens might be structurally similar to endogenous proteins (molecular mimicry); then the subsequent immunologic reaction would be autoimmune and self-perpetuating. Destruction and loss of bile ducts lead to impaired bile formation and secretion (cholestasis). Retained toxic materials such as bile acids then cause further damage, particularly to hepatocytes. Chronic cholestasis thus leads to liver cell inflammation and scarring in the perportal areas. Eventually, hepatic inflammation decreases as hepatic fibrosis progresses to cirrhosis.

Autoimmune cholangitis is sometimes considered to be a separate disorder. It is characterized by autoantibodies, such as antinuclear antibodies (ANAs), anti-smooth muscle antibodies, or both and has a clinical course and response to treatment that are similar to PBC. However, in autoimmune cholangitis, AMAs are absent.

Symptoms and Signs

About half of patients present without symptoms. Symptoms or signs may develop during any stage of the disease and may include fatigue or reflect cholestasis (and the resulting fat malabsorption, which may lead to vitamin deficiencies and osteoporosis), hepatocellular dysfunction, or cirrhosis.

Symptoms usually develop insidiously. Pruritus, fatigue, and dry mouth and eyes are the initial symptoms in > 50% of patients and can precede other symptoms by months or years. Other initial manifestations include right upper quadrant discomfort (10%); an enlarged, firm, nontender liver (25%); splenomegaly (15%); hyperpigmentation (25%); xanthelasmas (10%); and jaundice (10%). Eventually, all the features and complications of cirrhosis occur. Peripheral neuropathy and other autoimmune disorders associated with PBC may also develop.

Diagnosis

- Liver function tests
- Antimitochondrial antibodies
- Ultrasonography and often MRCP
- Liver biopsy
In asymptomatic patients, PBC is detected incidentally when liver function tests detect abnormalities, typically elevated levels of alkaline phosphatase and \( \gamma \)-glutamyl transpeptidase (GGT). PBC is suspected in middle-aged women with classic symptoms (eg, unexplained pruritus, fatigue, right upper quadrant discomfort, jaundice) or laboratory results suggesting cholestatic liver disease: elevated alkaline phosphatase and GGT but minimally abnormal aminotransferases (ALT, AST). Serum bilirubin is usually normal in the early stages; elevation indicates disease progression and a worsening prognosis.

If PBC is suspected, liver function tests and tests to measure serum IgM (increased in PBC) and AMA should be done. ELISA tests are 95% sensitive and 98% specific for PBC; false-positive results can occur in autoimmune hepatitis (type 1). Other autoantibodies (eg, ANAs, anti-smooth muscle antibodies, rheumatoid factor) may be present. Extrahepatic biliary obstruction should be ruled out. Ultrasonography is often done first, but ultimately MRCP and sometimes ERCP are necessary. Unless life expectancy is short or there is a contraindication, liver biopsy is usually done. Liver biopsy confirms the diagnosis; it may detect pathognomonic bile duct lesions, even in early stages. As PBC progresses, it becomes morphologically indistinguishable from other forms of cirrhosis. Liver biopsy also helps stage PBC, which has 4 histologic stages:

- **Stage 1:** Inflammation, abnormal connective tissue, or both, confined to the portal areas
- **Stage 2:** Inflammation, fibrosis, or both, confined to the portal and periportal areas
- **Stage 3:** Bridging fibrosis
- **Stage 4:** Cirrhosis

Autoimmune cholangitis is diagnosed when AMAs are absent in a patient who otherwise would be diagnosed with PBC.

**Prognosis**

Usually, PBC progresses to terminal stages over 15 to 20 yr, although the rate of progression varies. PBC may not diminish quality of life for many years. Patients who present without symptoms tend to develop symptoms over 2 to 7 yr but may not do so for 10 to 15 yr. Once symptoms develop, median life expectancy is 10 yr. Predictors of rapid progression include the following:

- Rapid worsening of symptoms
- Advanced histologic changes
- Older patient age
- Presence of edema
- Presence of associated autoimmune disorders
- Abnormalities in bilirubin, albumin, PT, or INR

The prognosis is ominous when pruritus disappears, xanthomas shrink, jaundice develops, and serum cholesterol decreases.

**Treatment**

- Arresting or reversing liver damage
- Treating complications (chronic cholestasis and liver failure)
- Eventually, doing liver transplantation
All alcohol use and hepatotoxic drugs should be stopped. Ursodeoxycholic acid (15 mg/kg po once/day) decreases liver damage, prolongs survival, and delays the need for liver transplantation. About 20% of patients do not have biochemical improvement after ≥ 4 mo; they may have advanced disease and require liver transplantation in a few years. Other drugs proposed to decrease liver damage have not improved overall clinical outcomes or are controversial.

Pruritus may be controlled with cholestyramine 6 to 8 g po bid. This anionic-binding drug binds bile salts and thus may aggravate fat malabsorption. If cholestyramine is taken long-term, supplements of fat-soluble vitamins should be considered. Cholestyramine can decrease absorption of ursodeoxycholic acid, so these drugs should not be given simultaneously.

Some patients with pruritus respond to ursodeoxycholic acid and ultraviolet light; others may warrant a trial of rifampin or an opioid antagonist, such as naltrexone. Patients with fat malabsorption due to bile salt deficiency should be treated with vitamins A, D, E, and K. For osteoporosis, weight-bearing exercises, bisphosphonates, or raloxifene may be needed in addition to Ca and vitamin D supplements. In later stages, portal hypertension (see p. 218) or complications of cirrhosis (see p. 241) require treatment.

Liver transplantation has excellent results. The general indication is decompensated liver disease (uncontrolled variceal bleeding, refractory ascites, intractable pruritus, and hepatic encephalopathy). Survival rates after liver transplantation are > 90% at 1 yr, > 80% at 5 yr, and > 65% at 10 yr. AMAs tend to persist after transplantation. PBC recurs in 15% of patients in the first few years and in > 30% by 10 yr. So far, recurrent PBC after liver transplantation has a benign course. Cirrhosis rarely occurs.
Chapter 28. Hepatitis

Introduction

Hepatitis is an inflammation of the liver characterized by diffuse or patchy necrosis. Major causes are specific hepatitis viruses, alcohol, and drugs. Less common causes include other viral infections (e.g., infectious mononucleosis, yellow fever, cytomegalovirus infection) and leptospirosis. Parasitic infections (e.g., schistosomiasis, malaria, amebiasis), pyogenic infections, and abscesses that affect the liver are not considered hepatitis. Liver involvement with TB and other granulomatous infiltrations is sometimes called granulomatous hepatitis, but the clinical, biochemical, and histologic features differ from those of diffuse hepatitis.

Various systemic infections and other illnesses may produce small focal areas of hepatic inflammation or necrosis. This nonspecific reactive hepatitis can cause minor liver function abnormalities but is usually asymptomatic.

Some types of infectious and noninfectious liver inflammation are summarized (see Table 28-1).

Acute Viral Hepatitis

Acute viral hepatitis is diffuse liver inflammation caused by specific hepatotropic viruses that have diverse modes of transmission and epidemiologies. A nonspecific viral prodrome is followed by anorexia, nausea, and often fever or right upper quadrant pain. Jaundice often develops, typically as other symptoms begin to resolve. Most cases resolve spontaneously, but some progress to chronic hepatitis. Occasionally, acute viral hepatitis progresses to acute hepatic failure (fulminant hepatitis). Diagnosis is by liver function tests and serologic tests to identify the virus. Good hygiene can prevent acute viral hepatitis. Depending on the specific virus, preexposure and postexposure prophylaxis may be possible using vaccines or serum globulins. Treatment is usually supportive.

(See also Neonatal Hepatitis B Virus Infection on p. 2825.)

Acute viral hepatitis is a common, worldwide disease that has different causes; each type shares clinical, biochemical, and morphologic features. Liver infections caused by nonhepatitis viruses (e.g., Epstein-Barr virus, yellow fever virus, cytomegalovirus) generally are not termed acute viral hepatitis.

Etiology

At least 5 specific viruses appear to be responsible (see Table 28-2). Other unidentified viruses probably also cause acute viral hepatitis.

Hepatitis A virus (HAV): HAV is a single-stranded RNA picornavirus. It is the most common cause of acute viral hepatitis and is particularly common among children and young adults. In some countries, >75% of adults have been exposed. HAV spreads primarily by fecal-oral contact and thus may occur in areas of poor hygiene. Waterborne and food-borne epidemics occur, especially in underdeveloped countries. Eating contaminated raw shellfish is sometimes responsible. Sporadic cases are also common, usually as a result of person-to-person contact. Fecal shedding of the virus occurs before symptoms develop and usually ceases a few days after symptoms begin; thus, infectivity often has already ceased when hepatitis becomes clinically evident. HAV has no known chronic carrier state and does not cause chronic hepatitis or cirrhosis.

Hepatitis B virus (HBV): HBV is the most thoroughly characterized and complex hepatitis virus. The infective particle consists of a viral core plus an outer surface coat. The core contains circular double-stranded DNA and DNA polymerase, and it replicates within the nuclei of infected hepatocytes. A surface coat is added in the cytoplasm and, for unknown reasons, is produced in great excess.

HBV is the 2nd most common cause of acute viral hepatitis. Prior unrecognized infection is common but is
much less widespread than that with HAV. HBV is often transmitted parenterally, typically by contaminated blood or blood products. Routine screening of donor blood for hepatitis B surface antigen (HBsAg) has nearly eliminated the previously common posttransfusion transmission, but transmission through needles shared by drug users remains common. Risk of HBV is increased for patients in renal dialysis and oncology units and for hospital personnel in contact with blood. The virus may be spread through contact with other body fluids (eg, between sex partners, both heterosexual and homosexual; in closed institutions, such as mental health institutions and prisons), but infectivity is far lower than that of HAV, and the means of transmission is often unknown. The role of insect bites in transmission is unclear. Many cases of acute hepatitis B occur sporadically without a known source.

HBV, for unknown reasons, is sometimes associated with several primarily extrahepatic disorders, including polyarteritis nodosa, other connective tissue diseases, membranous glomerulonephritis, and essential mixed cryoglobulinemia. The pathogenic role of HBV in these disorders is unclear, but autoimmune mechanisms are suggested.

Chronic HBV carriers provide a worldwide reservoir of infection. Prevalence varies widely according to several factors, including geography (eg, < 0.5% in North America and northern Europe, > 10% in some regions of the Far East). Vertical transmission from mother to infant is common (see p. 2644).

Table 28-1. Selected Diseases or Organisms Associated with Liver Inflammation

Hepatitis C virus (HCV): HCV is a single-stranded RNA flavivirus. Six major HCV subtypes exist with varying amino acid sequences (genotypes); these subtypes vary geographically and in virulence and response to therapy. HCV can also alter its amino acid pattern over time in an infected person, producing quasispecies. Infection is most commonly transmitted through blood, primarily when parenteral drug users share needles, but also through tattoos or body piercing. Sexual transmission and vertical transmission from mother to infant are relatively rare. Transmission through blood transfusion has become very rare since the advent of screening tests for donated blood. Some sporadic cases occur in patients without apparent risk factors. HCV prevalence varies with geography and other risk factors.

HCV infection sometimes occurs simultaneously with specific systemic disorders, including essential mixed cryoglobulinemia, porphyria cutanea tarda (about 60 to 80% of porphyria patients have HCV infection, but only a few patients infected with HCV develop porphyria), and glomerulonephritis; the mechanisms are uncertain. In addition, up to 20% of patients with alcoholic liver disease harbor HCV. The reasons for this high association are unclear because concomitant alcohol and drug use accounts for only a portion of cases. In these patients, HCV and alcohol act synergistically to exacerbate liver damage.

Hepatitis D virus (HDV): HDV, or delta agent, is a defective RNA virus that can replicate only in the presence of HBV. It occurs uncommonly as a co-infection with acute hepatitis B or as a superinfection in chronic hepatitis B. Infected hepatocytes contain delta particles coated with HBsAg. Prevalence of HDV varies widely geographically, with endemic pockets in several countries. Parenteral drug users are at relatively high risk, but HDV (unlike HBV) has not widely permeated the homosexual community.

Hepatitis E virus (HEV): HEV is an enterically transmitted RNA virus. Outbreaks of acute HEV infection, often waterborne and linked to fecal contamination of the water supply, have occurred in China, India, Mexico, Pakistan, Peru, Russia, and central and northern Africa. These outbreaks have epidemiologic characteristics similar to HAV epidemics. Sporadic cases also occur. No outbreaks have occurred in the US or in Western Europe. Like HAV, HEV does not cause chronic hepatitis or cirrhosis, and there is no chronic carrier state.

Symptoms and Signs

General: Acute infection tends to develop in predictable phases. Infection begins with an incubation period (see Table 28-2), during which the virus multiplies and spreads without symptoms. The prodromal, or pre-icteric, phase follows, causing nonspecific symptoms, such as profound anorexia, malaise, nausea and vomiting, and often fever or right upper quadrant abdominal pain. Urticaria and arthralgias
occasionally occur, especially in HBV infection. After 3 to 10 days, the urine darkens, followed by jaundice (the icteric phase). Systemic symptoms often regress, and the patient feels better despite worsening jaundice. During the icteric phase, the liver is usually enlarged and tender, but the edge of the liver remains soft and smooth. Mild splenomegaly occurs in 15 to 20% of patients. Jaundice usually peaks within 1 to 2 wk and then fades during a 2- to 4-wk recovery phase. Appetite usually returns after the first week. Acute viral hepatitis usually resolves spontaneously 4 to 8 wk after symptom onset.

Sometimes anicteric hepatitis, a minor flulike illness without jaundice, is the only manifestation. It occurs more often than icteric hepatitis in patients with HCV infection and in children with HAV infection.

Recrudescent hepatitis occurs in a few patients and is characterized by recurrent manifestations during the recovery phase. Manifestations of cholestasis may develop during the icteric phase (called cholestatic hepatitis) but usually resolve. When they persist, they cause prolonged jaundice, elevated alkaline phosphatase, and pruritus, despite general regression of inflammation.

**Virus-specific:** HAV often does not cause jaundice and may not cause any symptoms. It almost invariably resolves after the acute infection, although there can be early recrudescence.

HBV causes a wide spectrum of liver diseases, from a subclinical carrier state to severe or fulminant acute hepatitis, particularly in the elderly, in whom mortality can reach 10 to 15%. Five to 10% of all patients with HBV develop chronic hepatitis or become inactive carriers. Cirrhosis can develop. Hepatocellular carcinoma can ultimately develop in chronic HBV infection, even without being preceded by cirrhosis.

HCV may be asymptomatic during the acute infection. Its severity often fluctuates, sometimes with recrudescent hepatitis and

Table 28-2. Characteristics of Hepatitis Viruses

roller-coaster aminotransferase levels for many years or even decades. HCV has the highest rate of chronicity (about 75%). The resultant chronic hepatitis is usually asymptomatic or benign but progresses to cirrhosis in 20 to 30% of patients; cirrhosis often takes decades to appear. Hepatocellular carcinoma can result from HCV-induced cirrhosis but results only rarely from chronic infection without cirrhosis (unlike in HBV infection).

Acute HDV infection typically manifests as unusually severe acute HBV infection (co-infection), an acute exacerbation in chronic HBV carriers (superinfection), or a relatively aggressive course of chronic HBV infection.

HEV may be severe, especially in pregnant women.

**Diagnosis**

- Liver function tests (AST and ALT elevated out of proportion to alkaline phosphatase, usually with hyperbilirubinemia)
- Viral serologic testing
- PT measurement

**Initial diagnosis:** Acute hepatitis must first be differentiated from other disorders that cause similar symptoms. In the prodromal phase, hepatitis mimics various nonspecific viral illnesses and is difficult to diagnose. Anicteric patients suspected of having hepatitis based on risk factors are tested initially with nonspecific liver function tests, including aminotransferases, bilirubin, and alkaline phosphatase. Usually, acute hepatitis is suspected only during the icteric phase. Thus, acute hepatitis should be differentiated from other disorders causing jaundice (see Fig. 28-1 and p. 212).
Acute hepatitis can usually be differentiated from other causes of jaundice by its marked elevations of AST and ALT (typically ≥ 400 IU/L). ALT is typically higher than AST, but absolute levels correlate poorly with clinical severity. Values increase early in the prodromal phase, peak before jaundice is maximal, and fall slowly during the recovery phase. Urinary bilirubin usually precedes jaundice. Hyperbilirubinemia in acute viral hepatitis varies in severity, and fractionation has no clinical value. Alkaline phosphatase is usually only moderately elevated; marked elevation suggests extrahepatic cholestasis and prompts imaging tests (eg, ultrasonography). Liver biopsy generally is not needed unless the diagnosis is uncertain. If laboratory results suggest acute hepatitis, particularly if ALT and AST are > 1000 IU/L, PT is measured. Manifestations of portal-systemic encephalopathy, bleeding diathesis, or prolongation of INR suggest fulminant hepatitis (see p. 254).

If acute hepatitis is suspected, efforts are next directed toward identifying its cause. A history of exposure may provide the only clue of drug-induced or toxic hepatitis. The history should also elicit risk factors for viral hepatitis. Prodromal sore throat and diffuse adenopathy suggest infectious mononucleosis rather than viral hepatitis. Alcoholic hepatitis is suggested by a history of drinking, more gradual onset of symptoms, and presence of vascular spiders or signs of chronic alcohol use or chronic liver disease (see also p. 235); aminotransferase levels rarely exceed 300 IU/L, even in severe cases. Also, unlike in viral hepatitis, AST is typically higher than ALT, although this difference by itself does not reliably differentiate the two. In uncertain cases, liver biopsy usually distinguishes alcoholic from viral hepatitis.

Serology: In patients with findings suggesting acute viral hepatitis, the following studies are done to screen for hepatitis viruses A, B, and C:

- IgM antibody to HAV (IgM anti-HAV)
- HBsAg
- IgM antibody to hepatitis B core (IgM anti-HBc)
- Antibody to HCV (anti-HCV)

If any are positive, further serologic testing may be necessary to differentiate acute from past or chronic infection (see Tables 28-3, 28-4, and 28-5). If serology suggests hepatitis B, testing for hepatitis B e antigen (HBeAg) and antibody to hepatitis B e antigen (anti-HBe) is usually done to help determine the prognosis and to guide antiviral therapy. If serologically confirmed HBV is severe, anti-HDV is measured. If the patient has recently traveled to an endemic area, IgM anti-HEV should be measured if the test is available.

HAV is present in serum only during acute infection and cannot be detected by clinically available tests. IgM antibody typically develops early in the infection and peaks about 1 to 2 wk after the development of jaundice. It diminishes within several weeks, followed by the development of protective IgG antibody (IgG anti-HAV), which persists usually for life. Thus, IgM antibody is a marker of acute infection, whereas IgG anti-HAV indicates only previous exposure to HAV and immunity to recurrent infection.

HBV has at least 3 distinct antigen-antibody systems that can be tested: HBsAg, hepatitis B core antigen (HBcAg), and HBeAg. HBV-DNA can also be tested. HBV surface coat can be detected in serum as HBsAg. HBsAg characteristically appears during the incubation period, usually 1 to 6 wk before clinical or biochemical

[Fig. 28-1. Simplified diagnostic approach to possible acute viral hepatitis.]

illness develops, and implies infectivity of the blood. It disappears during convalescence. However, HBsAg is occasionally transient. The corresponding protective antibody (anti-HBs) appears weeks or months later, after clinical recovery, and usually persists for life; thus, its detection indicates past HBV infection and relative immunity. In 5 to 10% of patients, HBsAg persists and antibodies do not develop; these patients become asymptomatic carriers of the virus or develop chronic hepatitis.
HBcAg reflects the viral core. It is detectable in infected liver cells but not in serum except by special techniques. Antibody to HBcAg (anti-HBc) generally appears at the onset of clinical illness; thereafter, titers gradually diminish, usually over years or life. Its presence with anti-HBs indicates recovery from previous HBV infection. Anti-HBc is also present in chronic HBsAg carriers, who do not mount an anti-HBs response. In acute infection, anti-HBc is mainly of the IgM class, whereas in chronic infection, IgG anti-HBc predominates. IgM anti-HBc is a sensitive marker of acute HBV infection and occasionally is the only marker of recent infection, reflecting a window between disappearance of HBsAg and appearance of anti-HBs.

HBcAg is a protein derived from the viral core (not to be confused with hepatitis E virus).

**[Table 28-3. Hepatitis A Serology]**

Present only in HBsAg-positive serum, HBeAg tends to suggest more active viral replication and greater infectivity. In contrast, presence of the corresponding antibody (anti-HBe) suggests lower infectivity. Thus, e antigen markers are more helpful in prognosis than in diagnosis. Chronic liver disease develops more often among patients with HBeAg and less often among patients with anti-HBe.

In patients with active HBV infection, HBV-DNA can be detected in the serum with special testing, although this testing is not routinely available.

In **HCV**, serum antibody to HCV (anti-HCV) almost always implies active infection; it is not protective. Anti-HCV usually appears within 2 wk of acute infection but is sometimes delayed; however, HCV-RNA is positive. In a small proportion of patients, anti-HCV merely reflects prior exposure with clearance of the virus rather than active infection. In such cases, ALT and AST levels are usually normal. In unclear cases, HCV-RNA is measured.

**[Table 28-4. Hepatitis B Serology*]**

**[Table 28-5. Hepatitis C Serology]**

In **HDV**, anti-HDV implies active infection. It may not be detectable until weeks after the acute illness.

In **HEV**, the test for IgM anti-HEV is not routinely available. In a patient with endemic exposure and compatible clinical findings, anti-HEV suggests acute HEV infection.

**Biopsy:** Biopsy is usually unnecessary but, if done, usually reveals similar histopathology regardless of the specific virus: patchy cell dropout, acidophilic hepatocellular necrosis, mononuclear inflammatory infiltrate, histologic evidence of regeneration, and preservation of the reticulin framework. HBV can occasionally be diagnosed based on the presence of ground-glass hepatocytes (caused by HBsAg-packed cytoplasm) and using special immunologic stains for the viral components. However, these findings are unusual in acute HBV and are much more common in chronic HBV infection. HCV causation can sometimes be inferred from subtle morphologic clues. Liver biopsy may help predict prognosis in acute hepatitis but is rarely done solely for this purpose. Complete histologic recovery occurs unless extensive necrosis bridges entire acini (bridging necrosis). Most patients with bridging necrosis recover fully. However, some cases progress to chronic hepatitis.

**Treatment**

- **Supportive care**

- **Occasionally postexposure prophylaxis**

No treatments attenuate acute viral hepatitis except, occasionally, postexposure immunoprophylaxis. Alcohol should be avoided because it can increase liver damage. Restrictions on diet or activity, including commonly prescribed bed rest, have no scientific basis. Most patients may safely return to work after jaundice resolves, even if AST or ALT levels are slightly elevated. For cholestatic hepatitis,
cholestyramine 8 g po once/day or bid can relieve itching. Viral hepatitis should be reported to the local or state health department.

**Prevention**

Because treatments have limited efficacy, prevention of viral hepatitis is very important. Good personal hygiene helps prevent transmission, particularly fecal-oral transmission, as occurs with HAV and HEV. Blood and other body fluids (eg, saliva, semen) of patients with acute HBV and HCV and stool of patients with HAV are considered infectious. Barrier protection is recommended, but isolation of patients does little to prevent spread of HAV and is of no value in HBV or HCV infection. Posttransfusion infection is minimized by avoiding unnecessary transfusions and screening all donors for HBsAg and anti-HCV. Screening has decreased the incidence of posttransfusion hepatitis, probably to about 1/100,000 units of blood component transfused.

Immunoprophylaxis can involve active immunization using vaccines and passive immunization.

**HAV:** Preexposure HAV prophylaxis should be provided for travelers to highly endemic areas. It should also be considered for military personnel, day-care center employees, diagnostic laboratory workers, and, because they have an increased risk of fulminant hepatitis from HAV, patients with chronic liver disorders (including chronic hepatitis C). Several vaccines against HAV are available, each with different doses and schedules; they are safe, provide protection within about 4 wk, and provide prolonged protection (probably for > 20 yr).

Standard immune globulin, formerly immune serum globulin, prevents or decreases the severity of HAV infection and should be given to family members and close contacts of patients for postexposure prophylaxis; 0.02 mL/kg IM is generally recommended, but some experts advise 0.06 mL/kg (3 to 5 mL for adults).

**HBV:** Vaccination in endemic areas has dramatically reduced local prevalence. Pre-exposure immunization has long been recommended for people at high risk. However, selective vaccination of high-risk groups in the US and other nonendemic areas has not substantially decreased the incidence of HBV; thus, vaccination is now recommended for all US residents < 18 beginning at birth. Universal worldwide vaccination is desirable but is too expensive to be feasible.

Two recombinant vaccines are available; both are safe, even during pregnancy. Three IM deltoid injections are given: at baseline, at 1 mo, and at 6 mo. Children are given lower doses, and immunosuppressed patients and patients receiving hemodialysis are given higher doses.

After vaccination, levels of anti-HBs remain protective for 5 yr in 80 to 90% of immunocompetent recipients and for 10 yr in 60 to 80%. Booster doses of vaccine are recommended for patients receiving hemodialysis and immunosuppressed patients whose anti-HBs is < 10 mIU/mL.

HBV postexposure immunoprophylaxis combines vaccination with hepatitis B immune globulin (HBIG), a product with high titers of anti-HBs. HBIG probably does not prevent infection but prevents or attenuates clinical illness. For infants born to HBsAg-positive mothers, an initial dose of vaccine plus 0.5 mL of HBIG is given IM in the thigh immediately after birth. For anyone having sexual contact with an HBsAg-positive person or percutaneous or mucous membrane exposure to HBsAg-positive blood, 0.06 mL/kg of HBIG is given IM within days, along with vaccine. Any previously vaccinated patient sustaining a percutaneous HBsAg-positive exposure is tested for anti-HBs; if titers are < 10 mIU/mL, a booster dose of vaccine is given.

**HCV, HDV, and HEV:** A vaccine is now available for hepatitis E; it appears to have about 95% efficacy in preventing symptomatic infection in males and is safe. Efficacy in other groups, duration of protection, and efficacy in preventing asymptomatic infection are unknown. No product exists for immunoprophylaxis of HCV or HDV. However, prevention of HBV prevents HDV. The propensity of HCV for changing its genome hampers vaccine development.

**Fulminant Hepatitis**
**Fulminant hepatitis** is a rare syndrome of massive necrosis of liver parenchyma and a decrease in liver size (acute yellow atrophy) that usually occurs after infection with certain hepatitis viruses, exposure to toxic agents, or drug-induced injury. HBV is sometimes responsible, and up to 50% of cases of fulminant hepatitis B involve HDV coinfection. Fulminant hepatitis with HAV is rare but may be more likely in people with preexisting liver disorders. The role of HCV remains uncertain.

Patients rapidly deteriorate because portal-systemic encephalopathy develops, often followed by coma within hours or a few days, sometimes with cerebral edema. Bleeding commonly results from hepatic failure or disseminated intravascular coagulation, and functional renal failure (hepatorenal syndrome—see p. 223) may develop. Increasing PT, portal-systemic encephalopathy, and particularly renal failure are ominous.

Meticulous nursing care and aggressive treatment of complications improve the outcome. However, emergency liver transplantation provides the best hope for survival. Survival in adults is uncommon without transplantation; children tend to do better. Patients who survive usually recover fully.

**Chronic Hepatitis**

Chronic hepatitis is hepatitis that lasts > 6 mo. Common causes include hepatitis B and C viruses, autoimmune mechanisms (autoimmune hepatitis), and drugs. Many patients have no history of acute hepatitis, and the first indication is discovery of asymptomatic aminotransferase elevations. Some patients present with cirrhosis or its complications (eg, portal hypertension). Biopsy is necessary to confirm the diagnosis and to grade and stage the disease. Treatment is directed toward complications and the underlying condition (eg, corticosteroids for autoimmune hepatitis, antiviral therapy for viral hepatitis). Liver transplantation is often indicated for end-stage disease.

**Etiology**

Hepatitis lasting > 6 mo is generally defined as chronic, although this duration is arbitrary. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequent causes of chronic hepatitis; 5 to 10% of cases of HBV infection, with or without hepatitis D virus (HDV) co-infection, and about 75% of cases of HCV infection become chronic. Hepatitis A and E viruses are not causes. Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.

Many cases are idiopathic. A high proportion of idiopathic cases have prominent features of immune-mediated hepatocellular injury (autoimmune hepatitis), including the following:

- The presence of serologic immune markers
- An association with histocompatibility haplotypes common in autoimmune disorders (eg, HLA-B1, HLA-B8, HLA-DR3, HLA-DR4)
- A predominance of T lymphocytes and plasma cells in liver histologic lesions
- Complex in vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders (eg, RA, autoimmune hemolytic anemia, proliferative glomerulonephritis)
- A response to therapy with corticosteroids or immunosuppressants

Sometimes chronic hepatitis has features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cirrhosis, chronic viral hepatitis). These conditions are called overlap syndromes.
Many drugs, including isoniazid, methyldopa, nitrofurantoin, and, rarely, acetaminophen, can cause chronic hepatitis. The mechanism varies with the drug and may involve altered immune responses, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

Other causes of chronic hepatitis include alcoholic hepatitis and nonalcoholic steatohepatitis. Less often, chronic hepatitis results from α1-antitrypsin deficiency or Wilson's disease.

Cases were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. A more useful recent classification system specifies the etiology, the intensity of histologic inflammation and necrosis (grade), and the degree of histologic fibrosis (stage). Inflammation and necrosis are potentially reversible; fibrosis generally is not.

**Symptoms and Signs**

Clinical features vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo. Many patients are asymptomatic, especially in chronic HCV infection. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent. Often, particularly with HCV, the first findings are signs of chronic liver disease (eg, splenomegaly, spider nevi, palmar erythema). A few patients with chronic hepatitis develop manifestations of cholestasis. In the autoimmune variant, especially in young women, manifestations may involve virtually any body system and can include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.

Chronic HCV is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, and perhaps non-Hodgkin B-cell lymphoma. About 1% of patients develop symptomatic cryoglobulinemia with fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and skin rashes (urticaria, purpura, or leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

**Diagnosis**

- Liver function test results compatible with hepatitis
- Viral serologic tests
- Possibly autoantibodies, immunoglobulins, α1-antitrypsin level, and other tests
- Usually biopsy
- Serum albumin and PT

The diagnosis is suspected in patients with suggestive symptoms and signs, incidentally noted elevations in aminotransferase levels, or previously diagnosed acute hepatitis. Liver function tests are needed if not previously done and include serum ALT, AST, alkaline phosphatase, and bilirubin. Aminotransferase elevations are the most characteristic laboratory abnormalities. Although levels can vary, they are typically 100 to 500 IU/L. ALT is usually higher than AST. Amino-transferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV. Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high. Bilirubin is usually normal unless the disease is severe or advanced. However, abnormalities in these laboratory tests are not specific and can result from other disorders, such as alcoholic liver disease, recrudescence acute viral hepatitis, and primary biliary cirrhosis.

If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV (see Tables 28-4 and 28-5). Unless these tests indicate viral etiology, further testing is required. The first tests done include autoantibodies, immunoglobulins, and α1-antitrypsin level. Children and young adults are screened for Wilson's disease with a ceruloplasmin level. Marked elevations in serum immunoglobulins suggest chronic autoimmune hepatitis but are not conclusive. Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti-smooth muscle, or anti-liver/kidney
microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children).

Unlike in acute hepatitis, biopsy is necessary. Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases rarely develop into clinically important liver disease or cirrhosis. In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation. The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis. Biopsy is also used to grade and stage the disease.

In most cases, the specific cause of chronic hepatitis cannot be discerned via biopsy alone, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells. In patients with histologic but not serologic criteria for chronic autoimmune hepatitis, variant autoimmune hepatitis is diagnosed; many have overlap syndromes.

Serum albumin and PT should be measured to determine severity; hepatic insufficiency is suggested by low serum albumin or prolonged PT. If symptoms or signs of cryoglobulinemia develop during chronic hepatitis, particularly with HCV, cryoglobulinin levels and rheumatoid factor should be measured; high levels of rheumatoid factor and low levels of complement suggest cryoglobulinemia.

Patients with chronic HBV infection should be screened annually for hepatocellular cancer with ultrasonography and serum α-fetoprotein measurement, although the cost-effectiveness of this practice is debated. Patients with chronic HCV infection should be similarly screened only if cirrhosis is present.

**Prognosis**

Prognosis is highly variable. Chronic hepatitis caused by a drug often regresses completely when the offending drug is withdrawn. Without treatment, cases caused by HBV can resolve (uncommon), progress rapidly, or progress slowly to cirrhosis over decades. Resolution often begins with a transient increase in disease severity and results in seroconversion from hepatitis B e antigen (HBeAg) to antibody to hepatitis B e antigen (anti-HBe). Co-infection with HDV causes the most severe form of chronic HBV infection; without treatment, cirrhosis develops in up to 70% of patients. Untreated chronic hepatitis due to HCV produces cirrhosis in 20 to 30% of patients, although development may take decades. Chronic autoimmune hepatitis usually responds to therapy but sometimes causes progressive fibrosis and eventual cirrhosis.

Chronic HBV infection increases the risk of hepatocellular cancer. The risk is also increased in chronic HCV infection, but only if cirrhosis has already developed (see p. 265).

**Treatment**

- Supportive care

- Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antivirals for HBV, interferons for HCV)

Treatment goals include management of complications (eg, ascites, encephalopathy) and treatment of the cause. Drugs that cause hepatitis should be stopped. Underlying disorders, such as Wilson's disease, should be treated. In chronic hepatitis due to HBV, prophylaxis for contacts of patients may be helpful (see p. 254); corticosteroids and immunosuppressive drugs should be avoided because they enhance viral replication. No prophylactic measures are required for contacts of patients with HCV infection.

**Autoimmune hepatitis:** Corticosteroids, with or without azathioprine, prolong survival. Prednisone is usually started at 30 to 40 mg po once/day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. Some experts give concomitant azathioprine 1 to 1.5 mg/kg po once/day; others add azathioprine only if low-dose prednisone fails to maintain suppression. Most patients require long-term, low-dose maintenance treatment. Liver transplantation may be required for end-stage disease.
**HBV:** Antiviral treatment is indicated for patients with elevated aminotransferase levels, clinical or biopsy evidence of progressive disease, or both. The goal is to eliminate HBV-DNA. Treatment may need to be continued indefinitely and thus may be very expensive; stopping treatment prematurely can lead to relapse, which may be severe. However, treatment may be stopped if HBeAg converts to anti-HBe or if tests for HBsAg become negative. Drug resistance is also a concern. Six antiviral drugs—entecavir, adefovir, lamivudine, interferon-α (INF-α), pegylated INF-α2a (peginterferon-α2a), and telbivudine—are available (see Table 28-6).

First-line treatment is usually with an oral antiviral drug, such as entecavir (a nucleoside analogue) or adefovir (a nucleotide analogue). Combination therapy has not proved superior to monotherapy.

Entecavir appears to have higher antiviral potency than other commonly used drugs. Resistance to entecavir is uncommon, but the drug has not been in widespread clinical use for very long. Dosage is 0.5 mg po once/day; however, patients who have previously taken a nucleoside analogue should take 1 mg po once/day. Dose reduction is required in patients with renal insufficiency. Serious adverse effects appear to be uncommon so far, although the drug can induce tumors in animals.

Adefovir is also relatively potent. Dosage is 10 mg po once/day. Adefovir may cause renal dysfunction, so serum creatinine level must be measured periodically and the dose reduced if necessary.

Alternatively, lamivudine (a nucleoside analogue) 100 mg po once/day is given. It has few adverse effects, which is one of its advantages over other antiviral drugs used to treat chronic HBV infection. INF-α (usually IFN-α2b), formerly first-line treatment, can be used. Dosage is 5 million IU sc once/day or 10 million IU sc 3 times/wk for 4 mo. In about 40% of patients, this regimen eliminates HBV-DNA and causes seroconversion to anti-HBe; a successful response is usually presaged by a temporary increase in aminotransferase levels. The drug must be given by injection and is often poorly tolerated. The first 1 or 2 doses cause an influenza-like syndrome. Later, fatigue, malaise, depression, bone marrow suppression, and, rarely, bacterial infections or autoimmune disorders can occur. In patients with advanced cirrhosis, INF-α can precipitate hepatic failure and is therefore contraindicated. Other contraindications include renal failure, immunosuppression, solid organ transplantation, cytopenia, and substance abuse. In a few patients, treatment must be stopped because of intolerable adverse effects. The drug should be given cautiously or not at all to patients with ongoing substance abuse or a major psychiatric disorder.

Pegylated INF-α2 can also be given. Dosage is 180 μg sc once/wk. Adverse effects are similar to those of INF-α but may be less severe.

Telbivudine is a new drug that has greater efficacy than lamivudine but has high rates of resistance.

Liver transplantation should be considered for end-stage liver disease caused by HBV, but the infection aggressively attacks the graft, and prognosis is less favorable than when liver transplantation is done for other indications. Long-term posttransplantation therapy with lamivudine improves the outcome.

**HCV:** For chronic hepatitis due to HCV, treatment is indicated if aminotransferase levels are elevated and biopsy shows active inflammatory disease with evolving fibrosis. Treatment aims to permanently eliminate HCV-RNA (sustained response), which is associated with permanent normalization of aminotransferase and cessation of histologic progression.

Combination therapy with pegylated IFN-α plus ribavirin has the best results. Pegylated IFN-α2b 1.5 μg/kg sc once/wk and pegylated IFN-α2a 180 μg sc once/wk have comparable results. Ribavirin 500 to 600 mg po bid is usually given, although 400 mg bid may be sufficient for viral genotypes 2 and 3.

HCV genotype and viral load are determined before treatment because results influence treatment.
Genotype 1 is the most common type but is relatively resistant to treatment. Combination therapy is given for 1 yr; a sustained response rate of about 45 to 50% overall occurs. Results are more favorable in patients with early disease and less favorable in those who already have cirrhosis. HCV viral load should be measured at 3 mo and treatment stopped if RNA has not declined by at least 2 log levels compared with pretreatment values.

Less common genotypes 2 and 3 respond more favorably. Combination therapy is required for only 6 mo and gives an overall sustained response rate of about 75%. Longer treatment does not improve the results.

Adverse effects of pegylated IFN are similar to those of IFN-α but may be less severe; contraindications are also similar (see above).

Ribavirin is usually well tolerated but commonly causes anemia due to hemolysis; dosage should be decreased if hemoglobin falls to < 10 g/dL. Ribavirin is teratogenic for both men and women, necessitating contraception until 6 mo after completion of treatment. Patients who cannot tolerate ribavirin should be given pegylated IFN-α, but results are not as good as with combination treatment. Ribavirin monotherapy is of no value.

In most adult transplantation centers, advanced cirrhosis due to HCV is now the most common indication for liver transplantation. Although HCV recurs in the graft, the course is usually indolent, and long-term survival rates are relatively high.
Chapter 29. Vascular Disorders of the Liver

Introduction

The liver has a dual blood supply. The portal vein (which is rich in nutrients and relatively high in O\textsubscript{2}) provides two thirds of blood flow to the liver. The hepatic artery (which is O\textsubscript{2}-rich) supplies the rest. The hepatic veins drain the liver into the inferior vena cava. When portal vein blood flow increases, hepatic artery flow decreases and vice versa (the hepatic arterial buffer response). This dual, reciprocally compensatory blood supply provides some protection from hepatic ischemia in healthy people.

Despite its dual blood supply, the liver, a metabolically active organ, can be injured by

- **Ischemia**: Ischemia results from reduced blood flow, reduced O\textsubscript{2} delivery, increased metabolic activity, or all three.

- **Insufficient venous drainage**: The cause may be focal or diffuse obstruction. Manifestations of focal venous obstruction depend on the location. Diffuse venous congestion causes congestive hepatopathy. Reduced venous outflow from the liver (originating in the hepatic veins or within the liver itself, usually from cirrhosis) results in portal hypertension.

- **Specific vascular lesions**: The hepatic artery, hepatic vein, or portal vein may be involved. In peliosis hepatis, the vascular lesion occurs in the sinusoids (microvascular anastomoses between the portal and hepatic veins).

**Hepatic Ischemia**

Diffuse ischemia can cause ischemic hepatitis; focal ischemia can cause hepatic infarction or ischemic cholangiopathy. Hepatic infarction results from hepatic artery disorders.

**Ischemic Hepatitis**

(Acute Hepatic Infarction; Hypoxic Hepatitis; Shock Liver)

Ischemic hepatitis is diffuse liver damage due to an inadequate blood or O\textsubscript{2} supply.

Causes are most often systemic:

- Impaired hepatic perfusion (eg, due to heart failure or acute hypotension)
- Hypoxemia (eg, due to respiratory failure or carbon monoxide toxicity)
- Increased metabolic demand (eg, due to sepsis)

Focal lesions of the hepatic vasculature are less common causes. Ischemic hepatitis may develop when hepatic artery thrombosis occurs during liver transplantation or when a sickle cell crisis is associated with portal vein thrombosis (thus compromising the dual blood supply to the liver). Centrizonal necrosis develops without liver inflammation (ie, not a true hepatitis).

Symptoms may include nausea, vomiting, and tender hepatomegaly.

**Diagnosis**

- Clinical evaluation and liver function tests
- Doppler ultrasonography, MRI, or arteriography

Ischemic hepatitis is suspected in patients who have risk factors and laboratory abnormalities:
• Serum aminotransferase increases dramatically (eg, to 1000 to 3000 IU/L).

• LDH increases within hours of ischemia (unlike acute viral hepatitis).

• Serum bilirubin increases modestly, only to ≤ 4 times its normal level.

• PT/INR increases.

Diagnostic imaging helps define the cause: Doppler ultrasonography, MRI, or arteriography can identify an obstructed hepatic artery or portal vein thrombosis.

**Treatment**

• Hepatic reperfusion

Treatment is directed at the cause, aiming to restore hepatic perfusion, particularly by improving cardiac output and reversing any hemodynamic instability.

If perfusion is restored, aminotransferase decreases over 1 to 2 wk. In most cases, liver function is fully restored. Fulminant liver failure, although uncommon, can occur in patients with preexisting cirrhosis.

**Ischemic Cholangiopathy**

**Ischemic cholangiopathy is focal damage to the biliary tree due to disrupted flow from the hepatic artery via the peribiliary arterial plexus.**

Common causes of ischemic cholangiopathy include vascular injury during orthotopic liver transplantation or laparoscopic cholecystectomy, graft-rejection injury, chemoembolization, radiation therapy, and thrombosis resulting from hypercoagulability disorders. Bile duct injury (ischemic necrosis) results, causing cholestasis, cholangitis, or biliary strictures (often multiple).

Symptoms (eg, pruritus, dark urine, pale stools), laboratory tests, and imaging studies indicate cholestasis.

The diagnosis is suspected when cholestasis is evident in patients at risk, particularly after liver transplantation. Ultrasonography is the 1st-line diagnostic imaging test for cholestasis, but most patients require magnetic resonance cholangiopancreatography, ERCP, or both to rule out other causes such as cholelithiasis or cholangiocarcinoma.

Treatment is directed at the cause. After liver transplantation, such treatment includes antirejection therapy and possible retransplantation. Biliary strictures warrant endoscopic balloon dilation and stenting.

**Congestive Hepatopathy**

(Passive Hepatic Congestion)

**Congestive hepatopathy is diffuse venous congestion within the liver that results from right-sided heart failure (usually due to a cardiomyopathy, tricuspid regurgitation, mitral insufficiency, cor pulmonale, or constrictive pericarditis).**

Moderate or severe right-sided heart failure increases central venous pressure, which is transmitted to the liver via the inferior vena cava and hepatic veins. Chronic congestion leads to atrophy of hepatocytes, distention of sinusoids, and centrizonal fibrosis, which, if severe, progresses to cirrhosis (cardiac cirrhosis). The basis for liver cell death is probably sinusoidal thrombosis that propagates to the central veins and branches of the portal vein, causing ischemia.

Most patients are asymptomatic. However, moderate congestion causes right upper quadrant discomfort.
(due to stretching of the liver capsule) and tender hepatomegaly. Severe congestion leads to massive hepatomegaly and jaundice. Ascites may result from the transmitted central venous hypertension; infrequently, splenomegaly results. With transmitted central venous hypertension, the hepatojugular reflex is present, unlike in hepatic congestion due to Budd-Chiari syndrome.

**Diagnosis**

- **Clinical evaluation**

Congestive hepatopathy is suspected in patients who have right-sided heart failure, jaundice, and tender hepatomegaly. Liver biochemistries are modestly abnormal: unconjugated hyperbilirubinemia (total bilirubin < 3 mg/dL), elevated (usually < 2 to 3 fold) aminotransferases, and prolonged PT/INR. Any ascitic fluid has a high albumin content (> 25 g/L) and serum ascites/albumin gradient (≥ 1.1). Because the laboratory abnormalities are nonspecific, recognition of congestive hepatopathy is ultimately clinical. The liver disorder is more important as an index of the severity of heart failure than as a diagnosis by itself.

**Treatment**

Treatment is directed at the underlying heart failure.

**Hepatic Artery Disorders**

The hepatic artery may be occluded. Uncommonly, aneurysms develop.

**Hepatic Artery Occlusion**

Causes of hepatic artery occlusion include thrombosis (eg, due to hypercoagulability disorders, severe arteriosclerosis, or vasculitis), emboli (eg, due to endocarditis, tumors, therapeutic embolization, or chemoembolization), iatrogenic causes (eg, ligation during surgery), vasculitis (via nonthrombotic mechanisms), structural arterial abnormalities (eg, hepatic artery aneurysm), eclampsia, cocaine use, and sickle cell crisis. Usually, the result is an hepatic infarct. In patients with a liver transplant or preexisting portal vein thrombosis, hepatic artery thrombosis causes ischemic hepatitis (see p. 259). Because of the liver's dual blood supply, the liver is somewhat resistant to ischemic hepatitis and infarction.

Hepatic artery occlusion does not elicit symptoms without hepatic infarction or ischemic hepatitis. Hepatic infarction may be asymptomatic or cause right upper quadrant pain, fever, nausea, vomiting, and jaundice. Leukocytosis and a high aminotransferase level are common.

**Diagnosis**

- **Vascular imaging**

Diagnosis of hepatic artery occlusion is confirmed by imaging with Doppler ultrasonography, usually followed by angiography. The choice between CT angiography, magnetic resonance angiography, and celiac arteriography largely depends on availability and expertise. CT may detect a wedge-shaped area of low attenuation.

**Treatment**

Treatment is directed at the cause.

**Aneurysms**

Aneurysms of the hepatic artery are uncommon. They tend to be saccular and multiple. Causes include infection, arteriosclerosis, trauma, and vasculitis. Untreated aneurysms may cause death by rupturing into the common bile duct (causing hemobilia), peritoneum (causing peritonitis), or adjacent hollow viscera. Hemobilia may cause jaundice, upper GI bleeding, and abdominal pain in the right upper quadrant.
Diagnosis is suspected if typical symptoms occur or if imaging tests detect an aneurysm. Doppler ultrasonography, followed by contrast CT, is required for confirmation.

Treatment is embolization or surgical ligation.

**Hepatic Vein Disorders**

Obstruction of hepatic venous outflow can occur in extrahepatic vessels (Budd-Chiari syndrome) or intrahepatic vessels (veno-occlusive disease) but often occurs in both. Obstruction results in congestion of the sinusoids, hepatomegaly, portal hypertension, reduced portal blood flow, ascites, and splenomegaly.

**Budd-Chiari Syndrome**

Budd-Chiari syndrome is obstruction of hepatic venous outflow that originates anywhere from the small hepatic veins inside the liver to the inferior vena cava and right atrium. Manifestations range from no symptoms to fulminant liver failure. Diagnosis is based on ultrasonography. Treatment includes supportive medical therapy and measures to establish and maintain venous patency, such as thrombolysis, decompression with shunts, and long-term anticoagulation.

**Etiology**

In the Western world, the most common cause is a clot obstructing the hepatic veins and the adjacent inferior vena cava. Clots commonly result from the following:

- Thrombotic conditions (eg, protein C or S deficiency, antiphospholipid syndrome, antithrombin III deficiency, factor V Leiden mutation, pregnancy, oral contraceptive use)
- Hematologic disorders (eg, myeloproliferative disorders such as polycythemia and paroxysmal nocturnal hemoglobinopathy)
- Inflammatory bowel disease
- Connective tissue disorders
- Trauma
- Infection (eg, hydatid cyst, amebiasis)
- Tumor invasion of the hepatic vein (eg, hepatocellular or renal cell carcinoma)

Sometimes Budd-Chiari syndrome begins during pregnancy and unmasks a previously asymptomatic hypercoagulability disorder.

The cause of obstruction is often unknown. In Asia and South Africa, the basic defect is often a membranous obstruction (webs) of the inferior vena cava above the liver, likely representing recanalization of a prior thrombus in adults or a developmental flaw (eg, venous stenosis) in children. This type of obstruction is called obliterative hepatocavopathy.

Budd-Chiari syndrome usually develops over weeks or months. When it does, cirrhosis and portal hypertension tend to develop.

**Symptoms and Signs**

Manifestations range from none (asymptomatic) to fulminant liver failure or cirrhosis. Symptoms vary depending on whether the obstruction occurs acutely or over time.

**Acute obstruction** (in about 20%) causes fatigue, right upper quadrant pain, nausea, vomiting, mild
jaundice, tender hepatomegaly, and ascites. It typically occurs during pregnancy. Fulminant liver failure with encephalopathy is rare. Aminotransferase levels are quite high.

Chronic outflow obstruction (developing over weeks to months) may be rather asymptomatic in some patients until it progresses or may cause fatigue, abdominal pain, and hepatomegaly. Lower-extremity edema and ascites may result from venous obstruction, even in the absence of cirrhosis. Cirrhosis may develop, leading to variceal bleeding, massive ascites, splenomegaly, hepatopulmonary syndrome (see p. 1988), or a combination. Complete obstruction of the inferior vena cava causes edema of the abdominal wall and legs plus visibly tortuous superficial abdominal veins from the pelvis to the costal margin.

Diagnosis

• Clinical evaluation and liver function tests
• Vascular imaging

Budd-Chiari syndrome is suspected in patients with:

• Hepatomegaly, ascites, liver failure, or cirrhosis when there is no obvious cause (eg, alcohol abuse, hepatitis) or when the cause is unexplained
• Abnormal liver function test results and risk factors for thrombosis

Liver function tests are usually abnormal; the pattern is variable and nonspecific. Imaging usually begins with abdominal Doppler ultrasonography, which can show the direction of blood flow and the site of obstruction. Magnetic resonance angiography and CT are useful if ultrasonography is not diagnostic. Conventional angiography (venography with pressure measurements and arteriography) is necessary if therapeutic or surgical intervention is planned. Liver biopsy is done occasionally to diagnose the acute stages and determine whether cirrhosis has developed.

Prognosis

Without treatment, most patients with complete venous obstruction die of liver failure within 3 yr. For patients with incomplete obstruction, the course varies.

Treatment

• Supportive care
• Restoration and maintenance of adequate venous outflow

Treatment varies according to its onset (acute vs chronic) and severity (fulminant liver failure vs decompensated cirrhosis vs stable or asymptomatic). The cornerstones of management are:

• Giving supportive therapy directed at complications (eg, ascites, liver failure, esophageal varices)
• Decompressing the congested liver (ie, maintaining venous outflow)
• Preventing propagation of the clot

Aggressive interventions (eg, thrombolysis, stents) are used when the disease is acute (eg, within 4 wk and in the absence of cirrhosis). Thrombolysis can dissolve acute clots, allowing recanalization and so relieving hepatic congestion. Radiologic procedures have a major role using angioplasty, stenting, and portosystemic shunts. For caval webs or hepatic venous stenosis, decompression via percutaneous transluminal balloon angioplasty with intraluminal stents can maintain hepatic outflow. When dilation of a hepatic outflow narrowing is not technically feasible, transjugular intrahepatic portosystemic shunting (TIPS) and various surgical shunts can provide decompression by diversion into the systemic circulation. Portosystemic shunts are generally not used if hepatic encephalopathy is present; such shunts worsen
liver function. Further, shunts tend to thrombose, especially when associated with hematologic disorders. Long-term anticoagulation is often necessary to prevent recurrence. Liver transplantation may be lifesaving in patients with fulminant disease or decompensated cirrhosis.

**Veno-Occlusive Disease**

*(Sinusoidal Obstruction Syndrome)*

Hepatic veno-occlusive disease is caused by endothelial injury, leading to nonthrombotic occlusion of the terminal hepatic venules and hepatic sinusoids, rather than of the hepatic veins or inferior vena cava (as in Budd-Chiari syndrome).

Venous congestion causes portal hypertension and ischemic necrosis (which leads to cirrhosis).

Common causes include

- Irradiation
- Graft-vs-host disease resulting from bone marrow or hematopoietic cell transplantation
- Pyrrolizidine alkaloids in crotalaria and senecio plants (eg, medicinal bush teas) and other herbs (eg, comfrey)
- Other hepatotoxins (eg, dimethylnitrosamine, aflatoxin, azathioprine, some anticancer drugs)

Initial manifestations include sudden jaundice, ascites, and tender, smooth hepatomegaly. Onset is within the first 3 wk of transplantation in bone marrow or hematopoietic cell recipients, who either recover spontaneously within a few weeks (or sometimes, with mild cases, after an increase in immunosuppressant therapy) or die of fulminant liver failure. Other patients have recurrent ascites, portal hypertension, splenomegaly, and, eventually, cirrhosis.

**Diagnosis**

- Clinical evaluation and liver function tests
- Ultrasonography
- Sometimes invasive tests (eg, liver biopsy, measurement of portal-hepatic venous pressure gradient)

The diagnosis is suspected in patients with unexplained clinical or laboratory evidence of liver disease, particularly in those with known risk factors, such as bone marrow or hematopoietic cell transplantation. Laboratory results are nonspecific: elevated aminotransferase and conjugated bilirubin levels. PT/INR becomes abnormal when disease is severe. Ultrasonography shows retrograde flow in the portal vein. If the diagnosis is unclear, invasive tests become necessary—eg, liver biopsy or measurement of the portal-hepatic venous pressure gradient (a pressure gradient > 10 mm Hg suggests veno-occlusive disease). Measuring the pressure across the liver entails inserting a catheter percutaneously into a hepatic vein and then wedging it into the liver. This wedged pressure reflects portal vein pressure. (An exception is portal vein thrombosis; in this case, the pressure is normal despite portal hypertension.)

**Treatment**

- Supportive care
- Treatment of cause
- For progressive disease, transjugular intrahepatic portosystemic shunting or transplantation
Ursodeoxycholic acid helps prevent graft-vs-host disease in bone marrow or hematopoietic cell transplant recipients. Management includes withdrawing the causative agent (such as herbal teas) and providing supportive therapy. Most patients have mild to moderate disease and do quite well. Those that progress may require transjugular intrahepatic portosystemic shunting (TIPS) for relief of portal hypertension. However, in 25%, veno-occlusive disease is severe, accompanied by fulminant liver failure. Liver transplantation is a last resort.

**Portal Vein Disorders**

Nearly all portal vein disorders obstruct portal vein blood flow and cause portal hypertension (see p. 218). Obstruction can be

- Extrahepatic—portal vein thrombosis due to a hypercoagulable state, vessel wall lesion (eg, pylephlebitis, omphalitis), an adjacent lesion (eg, pancreatitis, tumor), or congenital atresia of the portal vein

- Intrahepatic (eg, microvascular portal vein obstruction as in schistosomiasis, primary biliary cirrhosis, sarcoidosis, noncirrhotic portal hypertension)

**Portal Vein Thrombosis**

Portal vein thrombosis causes portal hypertension and consequent GI bleeding from varices, usually in the lower esophagus or stomach. Diagnosis is based on ultrasonography. Treatment involves control of variceal bleeding (usually with endoscopic banding, IV octreotide, or both), prevention of recurrence using β-blockers and sometimes surgical shunts and thrombolysis for acute thrombosis.

**Etiology**

Common causes vary by age group (see Table 29-1).

**Symptoms and Signs**

Acute portal vein thrombosis is commonly asymptomatic unless associated with another event, such as pancreatitis (the cause), or another complication, such as mesenteric venous thrombosis. Most often, clinical features—splenomegaly (especially in children) and variceal hemorrhage—develop chronically secondary to portal hypertension. Ascites is uncommon (10%) in postsinusoidal portal hypertension. Ascites may be precipitated when cirrhosis is also present or when serum albumin (and thus oncotic pressure) decreases after high-volume fluid resuscitation for a major GI bleed.

**Diagnosis**

- Clinical evaluation and liver function tests
- Doppler ultrasonography

Portal vein thrombosis is suspected in patients with the following:

- Manifestations of portal hypertension without cirrhosis
- Mild abnormalities in liver function or enzymes plus risk factors such as neonatal umbilical infection, childhood appendicitis, or a hypercoagulability disorder

Doppler ultrasonography is usually diagnostic, showing diminished or absent portal vein flow and sometimes the thrombus. Difficult cases may require MRI or CT with contrast. Angiography may be required to guide shunt surgery.
Table 29-1. Common Causes of Portal Vein Thrombosis*

Treatment

- For some acute cases, thrombolysis
- Long-term anticoagulation
- Management of portal hypertension and its complications

In acute cases, thrombolysis is sometimes successful, best reserved for recent occlusion, particularly in hypercoagulable states. Anticoagulation does not lyse clots but has some value for long-term prevention in hypercoagulable states despite the risk of variceal bleeding. In neonates and children, treatment is directed at the cause (eg, omphalitis, appendicitis). Otherwise, management is directed at the portal hypertension and its complications (see p. 218); treatment can include octreotide IV (a synthetic analog of somatostatin) and endoscopic banding to control variceal bleeding and nonselective β-blockers to prevent rebleeding. These therapies have decreased the use of surgical shunts (eg, mesocaval, splenorenal), which can become occluded and have an operative mortality rate of 5 to 50%. Transjugular intrahepatic portosystemic shunting (TIPS) is not recommended. TIPS requires monitoring (including frequent angiography) to assess patency, may become blocked, and may not adequately decompress the liver.

Peliosis Hepatis

Peliosis hepatis is typically an asymptomatic disorder in which multiple blood-filled cystic spaces develop randomly in the liver.

Measuring a few millimeters to about 3 cm in diameter, the cysts of peliosis hepatis often lack a cell lining and are surrounded by hepatocytes. Some have an endothelial cell lining, accompanied by dilated hepatic sinusoids. The cause is probably damage to the sinusoidal lining cells. Peliosis hepatis is associated with use of hormones (eg, anabolic steroids, oral contraceptives, glucocorticoids), tamoxifen, vinyl chloride, vitamin A, and, particularly in kidney transplant recipients, azathioprine.

Peliosis hepatis is usually asymptomatic, but occasionally cysts rupture, resulting in hemorrhage and sometimes causing death. Some patients develop overt liver disease, characterized by jaundice, hepatomegaly, and liver failure.

Mild cases may be detected incidentally during imaging tests done because liver function test results are slightly abnormal or for other reasons. Ultrasonography or CT can detect cysts.
Chapter 30. Liver Masses and Granulomas

Introduction

Liver masses include cysts, benign tumors, primary liver cancers, and metastatic liver cancer. Certain drugs and disorders can result in granuloma formation in the liver.

Hepatic Cysts

Isolated cysts are commonly detected incidentally on abdominal ultrasonography or CT. These cysts are usually asymptomatic and have no clinical significance. The rare congenital polycystic liver is commonly associated with polycystic disease of the kidneys (see p. 2385) and other organs. It causes progressive nodular hepatomegaly (sometimes massive) in adults. Nevertheless, hepatocellular function is remarkably well preserved, and portal hypertension rarely develops.

Other hepatic cysts include the following:

- Hydatid (echinococcal) cysts (see p. 1362)
- Caroli’s disease, which is rare, autosomal recessive, and characterized by segmental cystic dilation of intrahepatic bile ducts (often becoming symptomatic in adulthood, with stone formation, cholangitis, and sometimes cholangiocarcinoma)
- True cystic tumors (rare)

Benign Liver Tumors

Benign liver tumors are relatively common. Most are asymptomatic, but some cause hepatomegaly, right upper quadrant discomfort, or intraperitoneal hemorrhage. Most are detected incidentally on ultrasound or other scans. Liver function tests are usually normal or only slightly abnormal. Diagnosis is usually possible with imaging tests but may require biopsy. Treatment is needed only in a few specific circumstances.

Hepatocellular adenoma: Hepatocellular adenoma is the most important benign tumor to recognize. It occurs primarily in women of childbearing age, particularly those taking oral contraceptives, possibly via estrogen’s effects. Most adenomas are asymptomatic, but large ones may cause right upper quadrant discomfort. Rarely, adenomas manifest as peritonitis and shock due to rupture and intraperitoneal hemorrhage. Rarely, they become malignant.

Diagnosis is often suspected based on ultrasound or CT results, but biopsy is sometimes needed for confirmation.

Adenomas due to contraceptive use often regress if the contraceptive is stopped. If the adenoma does not regress or if it is subcapsular or > 5 cm, surgical resection is often recommended.

Focal nodular hyperplasia: This localized hamartoma may resemble macronodular cirrhosis histologically. Diagnosis is usually based on MRI or CT with contrast, but biopsy may be necessary. Treatment is rarely needed.

Hemangiomas: Hemangiomas are usually small and asymptomatic; they occur in 1 to 5% of adults. These tumors often have a characteristic highly vascular appearance. Rupture is rare, even when tumors are large. Hemangiomas are found incidentally during ultrasonography, CT, or MRI. Treatment is usually not indicated.

In infants, hemangiomas often regress spontaneously by age 2 yr. However, large hemangiomas occasionally cause arteriovenous shunting sufficient to cause heart failure and sometimes consumption coagulopathy. In these cases, treatment may include high-dose corticosteroids, sometimes diuretics and digoxin to improve heart function, interferon-α (given sc), surgical removal, selective hepatic artery
Other benign tumors: Lipomas (usually asymptomatic) and localized fibrous tumors (eg, fibromas) rarely occur in the liver.

Benign bile duct adenomas are rare, inconsequential, and usually detected incidentally. They are sometimes mistaken for metastatic cancer.

Primary Liver Cancer

Primary liver cancer is usually hepatocellular carcinoma. The first manifestations of liver cancer are usually nonspecific, delaying the diagnosis. Prognosis is usually poor.

Hepatocellular Carcinoma

Hepatocellular carcinoma (hepatoma) usually occurs in patients with cirrhosis and is common in areas where infection with hepatitis B and C viruses is prevalent. Symptoms and signs are usually nonspecific. Diagnosis is based on α-fetoprotein (AFP) levels, imaging tests, and sometimes liver biopsy. Screening with periodic AFP measurement and ultrasonography is sometimes recommended for high-risk patients. Prognosis is poor when cancer is advanced, but for small tumors that are confined to the liver, ablative therapies are palliative and surgical resection or liver transplantation is sometimes curative.

Hepatocellular carcinoma is the most common type of primary liver cancer and results in about 14,000 deaths annually in the US. However, it is more common outside the US, particularly in East Asia and sub-Saharan Africa; incidence generally parallels geographic prevalence of chronic hepatitis B virus (HBV) infection.

Etiology

Hepatocellular carcinoma is usually a complication of cirrhosis.

The presence of HBV increases risk of hepatocellular carcinoma by > 100-fold among HBV carriers. Incorporation of HBV-DNA into the host's genome may initiate malignant transformation, even in the absence of chronic hepatitis or cirrhosis.

Other disorders that cause hepatocellular carcinoma include cirrhosis due to chronic hepatitis C virus (HCV) infection, hemochromatosis, and alcoholic cirrhosis. Patients with cirrhosis due to other conditions are also at increased risk.

Environmental carcinogens may play a role; eg, ingestion of food contaminated with fungal aflatoxins is believed to contribute to the high incidence of hepatocellular carcinoma in subtropical regions.

Symptoms and Signs

Most commonly, previously stable patients with cirrhosis present with abdominal pain, weight loss, right upper quadrant mass, and unexplained deterioration. Fever may occur. In a few patients, the first manifestation of hepatocellular carcinoma is bloody ascites, shock, or peritonitis, caused by hemorrhage of the tumor. Occasionally, a hepatic friction rub or bruit develops.

Occasionally, systemic metabolic complications, including hypoglycemia, erythrocytosis, hypercalcemia, and hyperlipidemia, occur. These complications may manifest clinically.

Diagnosis

• α-Fetoprotein (AFP) measurement
• Imaging (CT, ultrasonography, or MRI)
Diagnosis is based on AFP measurement and an imaging test. In adults, AFP signifies dedifferentiation of hepatocytes, which most often indicates hepatocellular carcinoma; 40 to 65% of patients with the cancer have high AFP levels (> 400 μg/L). High levels are otherwise rare, except in teratocarcinoma of the testis, a much less common tumor. Lower values are less specific and can occur with hepatocellular regeneration (eg, in hepatitis). Other blood tests, such as AFP-L3 (an AFP isoform) and des-y-carboxyprothrombin, are being studied as markers to be used for early detection of hepatocellular carcinoma.

Depending on local preferences and capabilities, the first imaging test may be contrast-enhanced CT, ultrasonography, or MRI. Hepatic arteriography is occasionally helpful in equivocal cases and can be used to outline the vascular anatomy when ablation or surgery is planned.

If imaging shows characteristic findings and AFP is elevated, the diagnosis is clear. Liver biopsy, often guided by ultrasonography or CT, is sometimes indicated for definitive diagnosis.

**Staging:** If a hepatocellular carcinoma is diagnosed, evaluation usually includes chest CT without contrast, imaging of the portal vein (if not already done) by MRI or CT with contrast to exclude thrombosis, and sometimes bone scanning.

Hepatocellular carcinoma is staged based on the following (American Cancer Society classification system—see Table 30-1):

- **T:** How many primary tumors, how big they are, and whether the cancer has spread to adjacent organs
- **N:** Whether the cancer has spread to nearby lymph nodes
- **M:** Whether the cancer has metastasized to other organs of the body

Numbers (0 to 4) are added after T, N, and M to indicate increasing severity. The letter X means no assessment is possible.

**Screening:** An increasing number of hepatocellular carcinomas are being detected through screening programs. Screening patients with cirrhosis is reasonable, although this measure is controversial and has not been shown to reduce mortality. One common screening method is AFP measurement and ultrasonography every 6 or 12 mo. Many experts advise screening patients with longstanding hepatitis B even when cirrhosis is absent.

**Treatment**

- Transplantation if tumors are small and few

[Table 30-1, Staging Hepatocellular Carcinoma*]

For single tumors < 5 cm or ≤ 3 tumors ≤ 3 cm that are limited to the liver, liver transplantation results in as good a prognosis as liver transplantation done for noncancerous disorders. Alternatively, surgical resection may be done; however, the cancer usually recurs.

Ablative treatments (eg, hepatic arterial chemoembolization, intratumoral ethanol injection, cryoablation, radiofrequency ablation) provide palliation and slow tumor growth; they are used when patients are awaiting liver transplantation.

If the tumor is large (> 5 cm), is multifocal, has invaded the portal vein, or is metastatic (ie, stage III or higher), prognosis is much less favorable (eg, 5-yr survival rates of about 5% or less). Radiation therapy is usually ineffective. Some newer chemotherapeutic regimens are promising.

**Prevention**
Use of vaccine against HBV eventually decreases the incidence, especially in endemic areas. Preventing the development of cirrhosis of any cause (eg, via treatment of chronic hepatitis C, early detection of hemochromatosis, management of alcoholism) can also have a significant effect.

**Other Primary Liver Cancers**

Other primary liver cancers are uncommon or rare. Diagnosis usually requires biopsy. Prognosis is typically poor. Some cancers, if localized, can be resected. With resection or liver transplantation, survival may be prolonged.

**Fibrolamellar carcinoma:** This distinct variant of hepatocellular carcinoma has a characteristic morphology of malignant hepatocytes enmeshed in lamellar fibrous tissue. It usually occurs in young adults and has no association with preexisting cirrhosis, HBV, HCV, or other known risk factors. AFP levels are rarely elevated. Prognosis is better than that for hepatocellular carcinoma, and many patients survive several years after tumor resection.

**Cholangiocarcinoma:** This tumor originates in the biliary epithelium. It is common in China, where underlying infestation with liver flukes is believed to contribute. Elsewhere, it is less common than hepatocellular carcinoma; histologically, the two may overlap. Primary sclerosing cholangitis greatly increases risk of cholangiocarcinoma.

**Hepatoblastoma:** Although rare, hepatoblastoma is one of the most common primary liver cancers in infants, particularly those with a family history of familial adenomatous polyposis (see p. 192). It can also develop in children. Some patients with hepatoblastoma present with precocious puberty caused by ectopic gonadotropin production, but the cancer is usually detected because of deteriorating general health and a right upper quadrant mass. An elevated AFP level and abnormal imaging test results may help in the diagnosis.

**Angiosarcoma:** This rare cancer is associated with specific chemical carcinogens, including industrial vinyl chloride.

**Metastatic Liver Cancer**

Liver metastases are common in many types of cancer, especially those of the GI tract, breast, lung, and pancreas. The first symptoms of metastases are usually nonspecific (eg, weight loss, right upper quadrant discomfort); they are sometimes the first symptoms of the primary cancer. Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. Diagnosis is usually supported by an imaging test, most often ultrasonography, spiral CT with contrast, or MRI with contrast. Treatment usually involves palliative chemotherapy.

Metastatic liver cancer is more common than primary liver cancer and is sometimes the initial clinical manifestation of cancer originating in the GI tract, breast, lung, or pancreas.

**Symptoms and Signs**

Early liver metastases may be asymptomatic. Nonspecific symptoms of cancer (eg, weight loss, anorexia, fever) often develop first. The liver may be enlarged, hard, or tender; massive hepatomegaly with easily palpable nodules signifies advanced disease. Hepatic bruits and pleuritic-type pain with an overlying friction rub are uncommon but characteristic. Splenomegaly is occasionally present, especially when the primary cancer is pancreatic. Concomitant peritoneal tumor seeding may produce ascites, but jaundice is usually absent or mild initially unless a tumor causes biliary obstruction.

In the terminal stages, progressive jaundice and hepatic encephalopathy presage death.

**Diagnosis**
Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. If metastases are suspected, liver function tests are often done, but results are usually not specific for the diagnosis. Alkaline phosphatase, γ-glutamyl transpeptidase, and sometimes LDH typically increase earlier or to a greater degree than do other test results; aminotransferase levels vary. Imaging tests have good sensitivity and specificity. Ultrasonography is usually helpful, but CT with contrast or MRI with contrast is often more accurate.

Liver biopsy guided by imaging provides the definitive diagnosis and is done if other tests are equivocal or if histologic information (e.g., cell type of the liver metastasis) may help determine the treatment plan.

**Hematologic Cancers and the Liver**

The liver is commonly involved in advanced leukemia and related blood disorders. Liver biopsy is not needed. In hepatic lymphoma, especially Hodgkin lymphoma, the extent of liver involvement determines staging and treatment but may be difficult to assess. Hepatomegaly and abnormal liver function tests may reflect a systemic reaction to Hodgkin lymphoma rather than spread to the liver, and biopsy often shows nonspecific focal mononuclear infiltrates or granulomas of uncertain significance. Treatment is directed at the hematologic cancer.

**Hepatic Granulomas**

Hepatic granulomas have numerous causes and are usually asymptomatic. However, the underlying disorder may cause extrahepatic manifestations, hepatic inflammation, fibrosis, portal hypertension, or a combination. Diagnosis is based on liver biopsy, but biopsy is necessary only if a treatable underlying disorder (e.g., infection) is suspected or if other liver disorders need to be ruled out. Treatment depends on the underlying disorder.

Hepatic granulomas, although sometimes insignificant, more often reflect clinically relevant disease. The term granulomatous hepatitis is often used to describe the condition, but the disorder is not true hepatitis, and the presence of granulomas does not imply hepatocellular inflammation.

**Etiology**

Hepatic granulomas have many causes (see Table 30-2); drugs and systemic disorders (often infections) are more common causes than primary liver disorders. Infections must be identified because they require specific treatments. TB and schistosomiasis are the most common infectious causes worldwide; fungal and viral causes are less common. Sarcoidosis is the most common noninfectious cause; the liver is involved in about two thirds of patients, and occasionally, clinical manifestations of sarcoidosis are predominantly hepatic.

Granulomas are much less common in primary liver disorders; primary biliary cirrhosis is the only important cause. Small granulomas occasionally occur in other liver disorders but are not clinically significant.
**Idiopathic granulomatous hepatitis** is a rare syndrome of hepatic granulomas with recurrent fever, myalgias, fatigue, and other systemic symptoms, which often occur intermittently for years. Some experts believe it is a variant of sarcoidosis.

**Pathophysiology**

A granuloma is a localized collection of chronic inflammatory cells with epithelioid cells and giant multinucleated cells. Caseation necrosis or foreign body tissue (eg, schistosome eggs) may be present. Most granulomas occur in the parenchyma, but in primary biliary cirrhosis, granulomas may occur in the hepatic triads.

Granuloma formation is incompletely understood. Granulomas may develop in response to poorly soluble exogenous or endogenous irritants. Immunologic mechanisms are involved.

Hepatic granulomas rarely affect hepatocellular function. However, when granulomas are part of a broader inflammatory reaction involving the liver (eg, drug reactions, infectious mononucleosis), hepatocellular dysfunction is present. Sometimes inflammation causes progressive hepatic fibrosis and portal hypertension, typically with schistosomiasis and occasionally with extensive sarcoideal infiltration.

**Symptoms and Signs**

Granulomas themselves are typically asymptomatic; even extensive infiltration usually causes only minor hepatomegaly and little or no jaundice. Symptoms, if they occur, reflect the underlying condition (eg, constitutional symptoms in infections, hepatosplenomegaly in schistosomiasis).

[Table 30-2. Causes of Hepatic Granulomas]

**Diagnosis**

- Liver function tests
- Imaging
- Biopsy

Hepatic granulomas are suspected in patients with

- Conditions that commonly cause granulomas
- Unexplained hepatic masses found during imaging tests
- Occasionally, when an imaging test is done to evaluate asymptomatic elevations in liver enzymes, particularly alkaline phosphatase

When granulomas are suspected, liver function tests are usually done, but results are nonspecific and are rarely helpful in diagnosis. Alkaline phosphatase (and \( \gamma \)-glutamyltransferase) is often mildly elevated but occasionally may be markedly elevated. Other test results may be normal or abnormal, reflecting additional hepatic damage (eg, widespread hepatic inflammation due to a drug reaction). Usually, imaging tests, such as ultrasonography, CT, or MRI, are not diagnostic; they may show calcification (if granulomas are long-standing) or filling defects, particularly with confluent lesions.

Diagnosis is based on liver biopsy. However, biopsy is usually indicated only to diagnose treatable causes (eg, infections) or to rule out nongranulomatous disorders (eg, chronic viral hepatitis). Biopsy sometimes detects evidence of the specific cause (eg, schistosome eggs, caseation of TB, fungal organisms). However, other tests (eg, cultures, skin tests, laboratory tests, imaging tests, other tissue specimens) are often needed.
In patients with constitutional or other symptoms suggesting infection (eg, FUO), specific measures are taken to increase the diagnostic sensitivity of biopsy for infections; eg, a portion of the fresh biopsy specimen is sent for culture, or special stains for acid-fast bacilli, fungi, and other organisms are used. Often, cause cannot be established.

**Prognosis**

Hepatic granulomas caused by drugs or infection regress completely after treatment. Sarcoid granulomas may disappear spontaneously or persist for years, usually without causing clinically important liver disease. Progressive fibrosis and portal hypertension (sarcoidal cirrhosis) rarely develop.

In schistosomiasis, progressive portal scarring (pipestem fibrosis) is typical; liver function is usually preserved, but marked splenomegaly and variceal hemorrhage can occur.

**Treatment**

- **Treatment of cause**

  Treatment is directed at the underlying disorder. When the cause is unknown, treatment is usually withheld, and follow-up with periodic liver function tests is instituted. However, if symptoms of TB (eg, prolonged fever) and deteriorating health occur, empiric antituberculous therapy may be justified.

  Corticosteroids may benefit patients with progressive hepatic sarcoidosis, although whether these drugs prevent hepatic fibrosis is unclear. However, corticosteroids are not indicated for most patients with sarcoidosis and are warranted only if TB and other infections can be excluded confidently.
Chapter 31. Gallbladder and Bile Duct Disorders

Introduction

The liver produces about 500 to 600 mL of bile each day. Bile is isosmotic with plasma and consists primarily of water and electrolytes but also organic compounds: bile salts, phospholipids (mostly lecithin), cholesterol, bilirubin, and other endogenously produced or ingested compounds, such as proteins that regulate GI function and drugs or their metabolites. Bilirubin is a degradation product of heme compounds from worn-out RBCs and is the pigment that gives bile its yellow-green color.

Bile salts (bile acids) are the major organic component in bile. The liver uses active transport to secrete bile salts into the canaliculus, the cleft between adjacent hepatocytes. Canalicular transport is the rate-limiting step in bile formation. Once secreted, bile salts draw other bile components (particularly Na\(^+\) and water) into the canaliculus by osmosis. Bile salts are also biologic detergents that enable the body to excrete cholesterol and potentially toxic compounds (eg, bilirubin, drug metabolites). The function of bile salts in the duodenum is to solubilize ingested fat and fat-soluble vitamins, facilitating their digestion and absorption. From the liver, bile flows from the intrahepatic collecting system into the right or left hepatic duct.

During fasting, about 75% of the bile secreted passes from the common hepatic duct into the gallbladder via the cystic duct. The rest flows directly into the common bile duct (formed by the junction of the common hepatic and cystic ducts) into the duodenum. During fasting, the gallbladder absorbs up to 90% of bile water, concentrating and storing bile.

Bile empties from the gallbladder into the common bile duct. The common bile duct joins with the pancreatic duct to form the ampulla of Vater, which empties into the duodenum. Before joining the pancreatic duct, the common bile duct tapers to a diameter of ≤ 0.6 cm.

The sphincter of Oddi, which surrounds both the pancreatic duct and the common bile duct, includes a sphincter for each duct. Bile does not normally flow retrograde into the pancreatic duct. These sphincters are highly sensitive to cholecystokinin and other gut hormones (eg, gastrin-releasing peptide) and to alterations in cholinergic tone (eg, by anticholinergic drugs).

Eating releases gut hormones and stimulates cholinergic nerves, causing the gallbladder to contract and the sphincter of Oddi to relax. As a result, the gallbladder empties 50 to 75% of its contents into the duodenum. Conversely, during fasting, an increase in sphincter tone facilitates gallbladder filling.

Bile salts are poorly absorbed by passive diffusion in the proximal small bowel; most intestinal bile salts reach the terminal ileum, which actively absorbs 90% into the portal venous circulation. Returned to the liver, bile salts are efficiently extracted, promptly modified (eg, conjugated if they arrive in the free form), and secreted back into bile. Bile salts circulate through this pathway from liver to gut to liver—the enterohepatic circulation—10 to 12 times/day.

Cholelithiasis

Cholelithiasis is the presence of one or more calculi (gallstones) in the gallbladder. In developed countries, about 10% of adults and 20% of people > 65 yr have gallstones. Gallstones tend to be asymptomatic. The most common symptom is biliary colic; gallstones do not cause dyspepsia or fatty food intolerance. More serious complications include cholecystitis; biliary tract obstruction (from stones in the bile ducts or cholecolithiasis), sometimes with infection (cholangitis); and gallstone pancreatitis. Diagnosis is usually by ultrasonography. If cholelithiasis causes symptoms or complications, cholecystectomy is necessary.

Risk factors for gallstones include female sex, obesity, increased age, American Indian ethnicity, a Western diet, and a family history. Most disorders of the biliary tract result from gallstones.

Pathophysiology
**Biliary sludge** is often a precursor of gallstones. It consists of Ca bilirubinate (a polymer of bilirubin), cholesterol microcrystals, and mucin. Sludge develops during gallbladder stasis, as occurs during pregnancy or use of TPN. Most sludge is asymptomatic and disappears when the primary condition resolves. Alternatively, sludge can evolve into gallstones or migrate into the biliary tract, obstructing the ducts and leading to biliary colic, cholangitis, or pancreatitis.

There are several types of gallstones.

**Cholesterol stones** account for > 85% of gallstones in the Western world. For cholesterol gallstones to form, the following is required:

- Bile must be supersaturated with cholesterol. Normally, water-insoluble cholesterol is made water soluble by combining with bile salts and lecithin to form mixed micelles. Supersaturation of bile with cholesterol most commonly results from excessive cholesterol secretion (as occurs in obesity or diabetes) but may result from a decrease in bile salt secretion (eg, in cystic fibrosis because of bile salt malabsorption) or in lecithin secretion (eg, in a rare genetic disorder that causes a form of progressive intrahepatic familial cholestasis).

- The excess cholesterol must precipitate from solution as solid microcrystals. Such precipitation in the gallbladder is accelerated by mucin, a glycoprotein, or other proteins in bile.

- The microcrystals must aggregate and grow. This process is facilitated by the binding effect of mucin forming a scaffold and by retention of microcrystals in the gallbladder with impaired contractility due to excess cholesterol in bile.

**Black pigment stones** are small, hard gallstones composed of Ca bilirubinate and inorganic Ca salts (eg, Ca carbonate, Ca phosphate). Factors that accelerate stone development include alcoholic liver disease, chronic hemolysis, and older age.

**Brown pigment stones** are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation (eg, liver flukes in Asia).

Gallstones grow at about 1 to 2 mm/yr, taking 5 to 20 yr before becoming large enough to cause problems. Most gallstones form within the gallbladder, but brown pigment stones form in the ducts. Gallstones may migrate to the bile duct after cholecystectomy or, particularly in the case of brown pigment stones, develop behind strictures as a result of stasis and infection.

**Symptoms and Signs**

About 80% of people with gallstones are asymptomatic. The remainder have symptoms ranging from biliary-type pain (biliary colic) to cholecystitis to life-threatening cholangitis. Biliary colic is the most common symptom.

Stones occasionally traverse the cystic duct without causing symptoms. However, most gallstone migration leads to cystic duct obstruction, which, even if transient, causes biliary colic. Biliary colic characteristically begins in the right upper quadrant but may occur elsewhere in the abdomen. It is often poorly localized, particularly in diabetics and the elderly. The pain may radiate into the back or down the arm. Episodes begin suddenly, become intense within 15 min to 1 h, remain at a steady intensity (not colicky) for up to 12 h (usually < 6 h), and then gradually disappear over 30 to 90 min, leaving a dull ache. The pain is usually severe enough to send patients to the emergency department for relief. Nausea and some vomiting are common, but fever and chills do not occur unless cholecystitis has developed. Mild right upper quadrant or epigastric tenderness may be present; peritoneal findings are absent. Between episodes, patients feel well.

Although biliary-type pain can follow a heavy meal, fatty food is not a specific precipitating factor. Nonspecific GI symptoms, such as gas, bloating, and nausea, have been inaccurately ascribed to gallbladder disease. These symptoms are common, having about equal prevalence in cholelithiasis,
peptic ulcer disease, and functional GI disorders.

Little correlation exists between the severity and frequency of biliary colic and pathologic changes in the gallbladder. Biliary colic can occur in the absence of cholecystitis. If colic lasts > 12 h, particularly if it is accompanied by vomiting or fever, acute cholecystitis or pancreatitis is likely.

**Diagnosis**

- **Ultrasonography**

Gallstones are suspected in patients with biliary colic. Abdominal ultrasonography is the method of choice for detecting gallbladder stones; sensitivity and specificity are 95%. Ultrasonography also accurately detects sludge. CT, MRI (see p. 230), and oral cholecystography (rarely available now, although quite accurate) are alternatives. Endoscopic ultrasonography accurately detects small gallstones (< 3 mm) and may be needed if other tests are equivocal. Laboratory tests usually are not helpful; typically, results are normal unless complications develop. Asymptomatic gallstones and biliary sludge are often detected incidentally when imaging, usually ultrasonography, is done for other reasons. About 10 to 15% of gallstones are calcified and visible on plain x-rays.

**Prognosis**

Patients with asymptomatic gallstones become symptomatic at a rate of about 2%/yr. The symptom that develops most commonly is biliary colic rather than a major biliary complication. Once biliary symptoms begin, they are likely to recur; pain returns in 20 to 40% of patients/yr, and about 1 to 2% of patients/yr develop complications such as cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis.

**Treatment**

- **Laparoscopic cholecystectomy for symptomatic stones**

- **Expectant for asymptomatic stones; sometimes stone dissolution**

Most asymptomatic patients decide that the discomfort, expense, and risk of elective surgery are not worth removing an organ that may never cause clinical illness. However, if symptoms occur, gallbladder removal (cholecystectomy) is indicated because pain is likely to recur and serious complications can develop.

**Surgery:** Surgery can be done with an open or laparoscopic technique.

Open cholecystectomy, which involves a large abdominal incision and direct exploration, is safe and effective. Its overall mortality rate is about 0.1% when done electively during a period free of complications.

Laparoscopic cholecystectomy is the treatment of choice. Using video endoscopy and instrumentation through small abdominal incisions, the procedure is less invasive than open cholecystectomy. The result is a much shorter convalescence, decreased postoperative discomfort, improved cosmetic results, yet no increase in morbidity or mortality. Laparoscopic cholecystectomy is converted to an open procedure in 2 to 5% of patients, usually because biliary anatomy cannot be identified or a complication cannot be managed. Older age typically increases the risks of any type of surgery.

Cholecystectomy effectively prevents future biliary colic but is less effective for preventing atypical symptoms such as dyspepsia. Cholecystectomy does not result in nutritional problems or a need for dietary limitations. Some patients develop diarrhea, often because bile salt malabsorption in the ileum is unmasked. Prophylactic cholecystectomy is warranted in asymptomatic patients with cholelithiasis only if they have large gallstones (> 3 cm) or a calcified gallbladder (porcelain gallbladder); these conditions increase the risk of gallbladder carcinoma.

**Stone dissolution:** For patients who decline surgery or who are at high surgical risk (eg, because of
concomitant medical disorders or advanced age), gallbladder stones can sometimes be dissolved by ingesting bile acids orally for many months. The best candidates for this treatment are those with small, radiolucent stones (more likely to be composed of cholesterol) in a functioning nonobstructed gallbladder (indicated by normal filling detected during cholecintigraphy or oral cholecystography or by absence of stones in the neck).

Ursodeoxycholic acid 8 to 10 mg/kg/day po dissolves 80% of tiny stones < 0.5 cm in diameter within 6 mo. For larger stones (the majority), the success rate is much lower, even with higher doses of ursodeoxycholic acid. Further, after successful dissolution, stones recur in 50% within 5 yr. Most patients are thus not candidates and prefer laparoscopic cholecystectomy. However, ursodeoxycholic acid can help prevent stone formation in morbidly obese patients who are losing weight rapidly after bariatric surgery or while on a very low calorie diet.

Stone fragmentation (extracorporeal shock wave lithotripsy) to assist stone dissolution and clearance is now unavailable.

Cholecystitis

Cholecystitis, which is inflammation of the gallbladder, can be acute or chronic.

Acute Cholecystitis

Acute cholecystitis is inflammation of the gallbladder that develops over hours, usually because a gallstone obstructs the cystic duct. Symptoms include right upper quadrant pain and tenderness, sometimes accompanied by fever, chills, nausea, and vomiting. Abdominal ultrasonography detects the gallstone and sometimes the associated inflammation. Treatment usually involves antibiotics and cholecystectomy.

Acute cholecystitis is the most common complication of cholelithiasis. Conversely, ≥ 95% of patients with acute cholecystitis have cholelithiasis. When a stone becomes impacted in the cystic duct and persistently obstructs it, acute inflammation results. Bile stasis triggers release of inflammatory enzymes (eg, phospholipase A, which converts lecithin to lysolecithin, which then may mediate inflammation). The damaged mucosa secretes more fluid into the gallbladder lumen than it absorbs. The resulting distention further releases inflammatory mediators (eg, prostaglandins), worsening mucosal damage and causing ischemia, all of which perpetuate inflammation. Bacterial infection can supervene. The vicious circle of fluid secretion and inflammation, when unchecked, leads to necrosis and perforation. If acute inflammation resolves, the gallbladder becomes fibrotic and contracted and does not concentrate bile or empty normally—features of chronic cholecystitis.

Acute acalculous cholecystitis: Acalculous cholecystitis is cholecystitis without stones. It accounts for 5 to 10% of cholecystectomies done for acute cholecystitis. Risk factors include the following:

- Critical illness (eg, major surgery, burns, sepsis, or trauma)
- Prolonged fasting or TPN (both predispose to bile stasis)
- Shock
- Immune deficiency
- Vasculitis (eg, SLE, polyarteritis nodosa)

The mechanism probably involves inflammatory mediators released because of ischemia, infection, or bile stasis. Sometimes an infecting organism can be identified (eg, Salmonella sp or cytomegalovirus in immunodeficient patients). In young children, acute acalculous cholecystitis tends to follow a febrile illness without an identifiable infecting organism.

Symptoms and Signs
Most patients have had prior attacks of biliary colic or acute cholecystitis. The pain of cholecystitis is similar in quality and location to biliary colic but lasts longer (ie, > 6 h) and is more severe. Vomiting is common, as is right subcostal tenderness. Within a few hours, Murphy's sign (deep inspiration exacerbates the pain during palpation of the right upper quadrant and halts inspiration) develops along with involuntary guarding of upper abdominal muscles on the right side. Fever, usually low grade, is common.

In the elderly, the first or only symptoms may be systemic and nonspecific (eg, anorexia, vomiting, malaise, weakness, fever). Sometimes fever does not develop.

Acute cholecystitis begins to subside in 2 to 3 days and resolves within 1 wk in 85% of patients.

**Complications:** Without treatment, 10% of patients develop localized perforation, and 1% develop free perforation and peritonitis. Increasing abdominal pain, high fever, and rigors with rebound tenderness or ileus suggest empyema (pus in the gallbladder), gangrene, or perforation. When acute cholecystitis is accompanied by jaundice or cholestasis, partial common duct obstruction is likely, usually due to stones or inflammation. Other complications include the following:

- **Mirizzi's syndrome:** Rarely, a gallstone becomes impacted in the cystic duct or Hartman's pouch and compresses and obstructs the common bile duct, causing cholestasis.

- **Gallstone pancreatitis:** Gallstones pass from the gallbladder into the biliary tract and block the pancreatic duct.

- **Cholecystoenteric fistula:** Infrequently, a large stone erodes the gallbladder wall, creating a fistula into the small bowel (or elsewhere in the abdominal cavity); the stone may pass freely or obstruct the small bowel (gallstone ileus).

**Acute acalculous cholecystitis:** The symptoms are similar to those of acute cholecystitis with gallstones but may be difficult to identify because patients tend to be severely ill (eg, ICU setting) and may be unable to communicate clearly. Abdominal distention or unexplained fever may be the only clue. Untreated, the disease can rapidly progress to gallbladder gangrene and perforation, leading to sepsis, shock, and peritonitis; mortality approaches 65%.

**Diagnosis**

- Ultrasonography

- Cholescintigraphy if ultrasonography results are equivocal or if acalculous cholecystitis is suspected

Acute cholecystitis is suspected based on symptoms and signs.

Transabdominal ultrasonography is the best test to detect gallstones. The test may also elicit local abdominal tenderness over the gallbladder (ultrasonographic Murphy's sign). Pericholecystic fluid or thickening of the gallbladder wall indicates acute inflammation.

Cholescintigraphy is useful when results are equivocal; failure of the radionuclide to fill the gallbladder suggests an obstructed cystic duct (ie, an impacted stone). False-positive results may be due to the following:

- A critical illness

- Receiving TPN and no oral foods (because gallbladder stasis prevents filling)

- Severe liver disease (because the liver does not secrete the radionuclide)

- Previous sphincterotomy (which facilitates exit into the duodenum rather than the gallbladder)
Morphine provocation, which increases tone in the sphincter of Oddi and enhances filling, helps eliminate false-positive results.

Abdominal CT identifies complications such as gallbladder perforation or pancreatitis.

Laboratory tests are done but are not diagnostic. Leukocytosis with a left shift is common. In uncomplicated acute cholecystitis, liver function tests are normal or only slightly elevated. Mild cholestatic abnormalities (bilirubin up to 4 mg/dL and mildly elevated alkaline phosphatase) are common, probably indicating inflammatory mediators affecting the liver rather than mechanical obstruction. More marked increases, especially if lipase (amylase is less specific) is elevated > 2-fold, suggest bile duct obstruction. Passage of a stone through the biliary tract increases aminotransferases (ALT, AST).

Acute acalculous cholecystitis: Acute acalculous cholecystitis is suggested if a patient has no gallstones but has ultrasonographic Murphy's sign or a thickened gallbladder wall and pericholecystic fluid. A distended gallbladder, biliary sludge, and a thickened gallbladder wall without pericholecystic fluid (due to low albumin or ascites) may result simply from a critical illness. CT identifies extrabiliary abnormalities. Cholescintigraphy is more helpful; failure of a radionuclide to fill may indicate edematous cystic duct obstruction. Giving morphine helps eliminate a false-positive result due to gallbladder stasis.

Treatment

- Supportive care (hydration, analgesics, antibiotics)
- Cholecystectomy

Management includes hospital admission, IV fluids, and analgesia with an NSAID (ketorolac) or an opioid. Nothing is given orally, and nasogastric suction is instituted if vomiting or an ileus is present. Parenteral antibiotics are usually initiated to treat possible infection, but evidence of benefit is lacking. Empiric coverage, directed at gram-negative enteric organisms, involves IV regimens such as ceftriaxone 2 g q 24 h plus metronidazole 500 mg q 8 h, piperacillin/tazobactam 4 g q 6 h, or ticarcillin/clavulanate 4 g q 6 h.

Cholecystectomy cures acute cholecystitis and relieves biliary pain. Early cholecystectomy is generally preferred, best done during the first 24 to 48 h in the following situations:

- The diagnosis is clear and patients are at low surgical risk.
- Patients are elderly or have diabetes and are thus at higher risk of infectious complications.
- Patients have empyema, gangrene, perforation, or acalculous cholecystitis.

Surgery may be delayed when patients have an underlying severe chronic disorder (eg, cardiopulmonary) that increases the surgical risks. In such patients, cholecystectomy is deferred until medical therapy stabilizes the comorbid disorders or until cholecystitis resolves. If cholecystitis resolves, cholecystectomy may be done ≥ 6 wk later. Delayed surgery carries the risk of recurrent biliary complications. Percutaneous cholecystostomy is an alternative to cholecystectomy for patients at very high surgical risk, such as the elderly, those with acalculous cholecystitis, and those in an ICU because of burns, trauma, or respiratory failure.

Chronic Cholecystitis

Chronic cholecystitis is long-standing gallbladder inflammation almost always due to gallstones.

Chronic cholecystitis almost always results from gallstones and prior episodes of acute cholecystitis (even if mild). Damage ranges from a modest infiltrate of chronic inflammatory cells to a fibrotic, shrunken gallbladder. Extensive calcification due to fibrosis is called porcelain gallbladder.

Symptoms and Signs
Gallstones intermittently obstruct the cystic duct and so cause recurrent biliary colic. Such episodes of pain are not necessarily accompanied by overt gallbladder inflammation; the extent of inflammation does not correlate with the intensity or frequency of biliary colic. Upper abdominal tenderness may be present, but usually fever is not. Fever suggests acute cholecystitis. Once episodes begin, they are likely to recur.

**Diagnosis**

• Ultrasonography

Chronic cholecystitis is suspected in patients with recurrent biliary colic plus gallstones. Ultrasonography or another imaging test usually shows gallstones and sometimes a shrunken, fibrotic gallbladder. The diagnosis is made in patients with a history of recurrent biliary colic and evidence of gallstones on ultrasonography. Cholescintigraphy may show nonvisualization of the gallbladder but is less accurate.

**Treatment**

Laparoscopic cholecystectomy is indicated to prevent symptom recurrence and further biliary complications. This procedure is particularly valid for the porcelain gallbladder associated with gallbladder carcinoma.

**Acalculous Biliary Pain**

Acalculous biliary pain is biliary colic without gallstones, resulting from structural or functional disorders; it is sometimes treated with laparoscopic cholecystectomy.

Biliary colic can occur in the absence of gallstones, particularly in young women. Acalculous biliary pain accounts for up to 15% of laparoscopic cholecystectomies. Common causes of such biliary pain include the following:

• Microscopic stones—not detected by routine abdominal ultrasonography

• Abnormal gallbladder emptying

• An overly sensitive biliary tract

• Sphincter of Oddi dysfunction

• Hypersensitivity of the adjacent duodenum

• Possibly gallstones that have spontaneously passed

Some patients eventually develop other functional GI disorders.

**Diagnosis**

Acalculous biliary pain is suspected in patients with biliary colic when diagnostic imaging cannot detect gallstones. Imaging should include ultrasonography and, where available, endoscopic ultrasonography (for small stones < 1 cm). Abnormal laboratory tests may reveal evidence of a biliary tract abnormality (eg, elevated alkaline phosphatase, bilirubin, ALT, or AST) or a pancreatic abnormality (eg, elevated lipase) during an episode of acute pain. Cholescintigraphy with cholecystokinin infusion measures gallbladder emptying (ejection fraction); potentially interfering drugs such as Ca channel blockers, opioids, and anticholinergics should not be used. ERCP with biliary manometry detects sphincter of Oddi dysfunction. The best diagnostic approach remains problematic.

**Treatment**

Laparoscopic cholecystectomy improves outcomes for patients with microscopic stones and possibly
abnormal gallbladder motility. The role of laparoscopic cholecystectomy or endoscopic sphincterotomy remains problematic. Drug therapies have no proven benefit.

Postcholecystectomy Syndrome

Postcholecystectomy syndrome is occurrence of abdominal symptoms after cholecystectomy.

Postcholecystectomy syndrome occurs in 5 to 40% of patients. It refers to presumed gallbladder symptoms that continue or that develop after cholecystectomy or to other symptoms that result from cholecystectomy. Removal of the gallbladder, the storage organ for bile, normally has few consequences on biliary tract function or pressures. In about 10%, biliary colic appears to result from functional or structural abnormalities of the sphincter of Oddi, resulting in altered biliary pressures or heightened sensitivity.

The most common symptoms are dyspepsia or otherwise nonspecific symptoms rather than true biliary colic. Papillary stenosis, which is rare, is fibrotic narrowing around the sphincter, perhaps caused by trauma and inflammation due to pancreatitis, instrumentation (eg, ERCP), or prior passage of a stone. Other causes include a retained bile duct stone, pancreatitis, and gastroesophageal reflux.

Diagnosis

• ERCP with biliary manometry or biliary nuclear scanning
• Exclusion of extrabiliary pain

Patients with postcholecystectomy pain should be evaluated as indicated for extra-biliary as well as biliary causes. If the pain suggests biliary colic, alkaline phosphatase, bilirubin, ALT, amylase, and lipase should be measured, and ERCP with biliary manometry or biliary nuclear scanning should be done. Elevated liver enzymes suggest sphincter of Oddi dysfunction; elevated amylase and lipase suggest dysfunction of the sphincter's pancreatic portion.

Dysfunction is best detected by biliary manometry done during ERCP, although ERCP has a risk of inducing pancreatitis. Manometry shows increased pressure in the biliary tract when pain is reproduced. A slowed hepatic hilum-duodenal transit time on a scan also suggests sphincter of Oddi dysfunction. Diagnosis of papillary stenosis is based on a clear-cut history of recurrent episodes of biliary pain and abnormal liver (or pancreatic) enzyme tests.

Treatment

Endoscopic sphincterotomy can relieve recurrent pain due to sphincter of Oddi dysfunction, especially if due to papillary stenosis. It is controversial for patients who have postcholecystectomy pain and no objective abnormalities.

Choledocholithiasis and Cholangitis

Choledocholithiasis is the presence of stones in bile ducts; the stones can form in the gallbladder or in the ducts themselves. These stones cause biliary colic, biliary obstruction, gallstone pancreatitis, or cholangitis (bile duct infection and inflammation). Cholangitis, in turn, can lead to strictures, stasis, and choledocholithiasis. Diagnosis usually requires visualization by magnetic resonance cholangiopancreatography or ERCP. Early endoscopic or surgical decompression is indicated.

Stones may be described as

• Primary stones (usually brown pigment stones), which form in the bile ducts
• Secondary stones (usually cholesterol), which form in the gallbladder but migrate to the bile ducts
Residual stones, which are missed at the time of cholecystectomy (evident < 3 yr later)

- Recurrent stones, which develop in the ducts > 3 yr after surgery

In developed countries, > 85% of common duct stones are secondary; affected patients have additional stones located in the gallbladder. Up to 10% of patients with symptomatic gallstones also have associated common bile duct stones. After cholecystectomy, brown pigment stones may result from stasis (eg, due to a postoperative stricture) and the subsequent infection. The proportion of ductal stones that are pigmented increases with time after cholecystectomy.

Bile duct stones may pass into the duodenum asymptptomatically. Biliary colic occurs when the ducts become partially obstructed. More complete obstruction causes duct dilation, jaundice, and, eventually, cholangitis (a bacterial infection). Stones that obstruct the ampulla of Vater can cause gallstone pancreatitis. Some patients (usually the elderly) present with biliary obstruction due to stones that have caused no symptoms previously.

In acute cholangitis, bile duct obstruction allows bacteria to ascend from the duodenum. Most (85%) cases result from common bile duct stones, but bile duct obstruction can result from tumors or other conditions (see Table 31-1). Common infecting organisms include gram-negative bacteria (eg, Escherichia coli, Klebsiella sp, Enterobacter sp); less common are gram-positive bacteria (eg, Enterococcus sp) and mixed anaerobes (eg, Bacteroides sp, Clostridia sp). Symptoms include abdominal pain, jaundice, and fever or chills (Charcot's triad). The abdomen is tender, and often the liver is tender and enlarged (often containing abscesses). Confusion and hypotension predict about a 50% mortality rate and high morbidity.

Recurrent pyogenic cholangitis (Oriental cholangiohepatitis, hepatolithiasis) is characterized by intrahepatic brown pigment stone formation. This disorder occurs in Southeast Asia. It consists of sludge and bacterial debris in the bile ducts. Undernutrition and parasitic infestation (eg, Clonorchis sinensis, Opisthorchis viverrini) increase susceptibility. Parasitic infestation can cause obstructive jaundice with intrahepatic ductal inflammation, proximal stasis, stone formation, and cholangitis. Repeating cycles of obstruction, infection, and inflammation lead to bile duct strictures and biliary cirrhosis. The extrahepatic ducts tend to be dilated, but the intrahepatic ducts appear straight because of periductal fibrosis.

In AIDS-related cholangiopathy or cholangitis, direct cholangiography may show abnormalities similar to those in primary sclerosing cholangitis or papillary stenosis (ie, multiple strictures and dilations involving the intrahepatic and extrahepatic bile ducts). Etiology is probably infection, most likely with cytomegalovirus, Cryptosporidium sp, or microsporidia.

**Diagnosis**

- Liver function tests
- Ultrasonography

Common duct stones should be suspected in patients with jaundice and biliary colic. Fever and leukocytosis further suggest acute cholangitis. Elevated levels of bilirubin, alkaline phosphatase, ALT, and \( \gamma \)-glutamyltransferase are consistent with extrahepatic obstruction, suggesting stones, particularly in patients with features of acute cholecystitis or cholangitis.

Ultrasonography may show stones in the gallbladder and occasionally in the common duct (less accurate). The common duct is dilated (> 6 mm in diameter if the gallbladder is intact; > 10 mm after a cholecystectomy). If the ducts are not dilated early in the presentation (eg, first day), stones have probably passed. If doubt exists, magnetic resonance cholangiopancreatography (MRCP) is highly accurate for retained stones. ERCP is done if MRCP is equivocal; it can be therapeutic as well as
diagnostic. CT, though less accurate than ultrasonography, can detect liver abscesses.

For suspected acute cholangitis, CBC and blood cultures are essential. Leukocytosis is common, and aminotransferases may reach 1000 IU/L, suggesting acute hepatic necrosis, often due to microabscesses. Blood cultures guide antibiotic choice.

**Treatment**

- **ERCP and sphincterotomy**

If biliary obstruction is suspected, ERCP and sphincterotomy are necessary to remove the stone. Success rate exceeds 90%; up to 7% of patients have complications (eg, bleeding pancreatitis, infection with fibrosis and subsequent duct stricture). Laparoscopic cholecystectomy, which is not as well suited for operative cholangiography or common duct exploration, can be done electively following ERCP and sphincterotomy. Mortality and morbidity after open cholecystectomy with common duct exploration are higher. In patients at high risk of complications with cholecystectomy (eg, the elderly), sphincterotomy alone is an alternative.

Acute cholangitis is an emergency requiring aggressive supportive care and urgent removal of the stones, endoscopically or surgically. Antibiotics are given, similar to those used for acute cholecystitis (see p. 274). An alternative regimen for very ill patients is imipenem and ciprofloxacin, plus metronidazole to cover anaerobes.

For recurrent pyogenic cholangitis, management aims to provide supportive care (eg, broad-spectrum antibiotics), eradicate any parasites, and mechanically clear the ducts of stones and debris endoscopically (via ERCP) or surgically.

**Sclerosing Cholangitis**

Sclerosing cholangitis refers to chronic cholestatic syndromes characterized by patchy inflammation, fibrosis, and strictures of the intrahepatic and extrahepatic bile ducts. Progression obliterates the bile ducts and leads to cirrhosis, liver failure, and sometimes cholangiocarcinoma.

Sclerosing cholangitis may be primary (with no known cause) or secondary due to immune deficiencies (congenital in children, acquired in adults as AIDS cholangiopathy) often associated with superimposed infections (eg, cytomegalovirus, Cryptosporidium), histiocytosis X, or use of drugs (eg, intraarterial 5-fluorouracil). Both primary and secondary sclerosing cholangitis cause similar inflammatory and fibrosing lesions scarifying the bile ducts. Other causes of bile duct strictures are choledocholithiasis, postoperative biliary stricture, ischemic bile duct injury (during liver transplantation), congenital biliary abnormalities, cholangiocarcinoma, and parasitic infestations.

Diagnosis of biliary strictures and dilations requires imaging techniques such as ultrasonography and cholangiography. Treatment focuses on relieving biliary obstruction (eg, dilating and stenting strictures) and, when possible, eradicating responsible organisms or treating the cause (eg, HIV).

**Primary Sclerosing Cholangitis**

Primary sclerosing cholangitis (PSC), the most common form of sclerosing cholangitis, has no known cause. However, 80% of patients have inflammatory bowel disease, most often ulcerative colitis. Other associated conditions include connective tissue disorders, alloimmune disorders, and immunodeficiency syndromes, sometimes complicated by opportunistic infections. Fatigue and pruritus develop insidiously and progressively. Diagnosis is by cholangiography (magnetic resonance cholangiopancreatography or ERCP). Liver transplantation is indicated for advanced disease.

Most (70%) patients with PSC are men. Mean age at diagnosis is 40 yr.
Etiology

Although the cause is unknown, PSC is associated with inflammatory bowel disease, which is present in 80% of patients. About 5% of patients with ulcerative colitis and about 1% with Crohn's disease develop PSC. This association and the presence of several autoantibodies (eg, anti-smooth muscle and perinuclear antineutrophilic antibodies [pANCA]) suggest immune-mediated mechanisms. T cells appear to be involved in the destruction of the bile ducts, implying disordered cellular immunity. A genetic predisposition is suggested by a tendency for the disorder to develop in multiple family members and a higher frequency in people with HLAB8 and HLADR3, which are often correlated with autoimmune disorders. An unknown trigger (eg, bacterial infection, ischemic duct injury) probably causes PSC to develop in genetically predisposed people.

Symptoms and Signs

Onset is usually insidious, with progressive fatigue and then pruritus. Jaundice tends to develop later. About 10 to 15% of patients present with repeated episodes of right upper quadrant pain and fever, possibly due to ascending bacterial cholangitis. Steatorrhea and deficiencies of fat-soluble vitamins can develop. Persistent jaundice harbingers advanced disease. Symptomatic gallstones and choledocholithiasis tend to develop in about 75% of patients. Some patients, asymptomatic until late in the course, first present with hepatosplenomegaly or cirrhosis. PSC tends to slowly and inexorably progress. The terminal phase involves decompensated cirrhosis, portal hypertension, ascites, and liver failure. The time from diagnosis to liver failure is about 12 yr.

Despite the association between PSC and inflammatory bowel disease, the two diseases tend to run separate courses. Ulcerative colitis may appear years before PSC yet tends to have a milder course when associated with PSC. Similarly, total colectomy does not change the course of PSC. The presence of both diseases increases the risk of colorectal carcinoma, regardless of whether a liver transplantation has been done for PSC. Cholangiocarcinoma develops in 10 to 15% of patients.

Diagnosis

- Magnetic resonance cholangiopancreatography (MRCP)

PSC is suspected in patients with unexplained abnormalities in liver biochemical tests, particularly in those with inflammatory bowel disease. A cholestatic pattern is typical: elevated alkaline phosphatase and γ-glutamyltransferase (GGT) rather than aminotransferases. Gamma globulin and IgM levels tend to be increased. Anti-smooth muscle antibodies and pANCA are usually positive. Antimitochondrial antibody, positive in primary biliary cirrhosis, is characteristically negative.

Imaging of the hepatobiliary system begins with ultrasonography to exclude extrahepatic biliary obstruction. Although ultrasonography or CT can show ductal dilation, diagnosis requires cholangiography to show multiple strictures and dilations in the intrahepatic and extrahepatic bile ducts. Imaging should begin with MRCP. ERCP is usually a 2nd choice because it is invasive. Liver biopsy is generally not required for diagnosis; when done, it shows bile duct proliferation, periductal fibrosis, inflammation, and loss of bile ducts. With disease progression, periductal fibrosis extends from the portal regions and eventually leads to secondary biliary cirrhosis.

Measurement of serum tumor markers and ERCP surveillance with brush cytology should be done regularly to check for cholangiocarcinoma.

Treatment

- Supportive care
- ERCP dilation for major (dominant) strictures
- Transplantation for recurrent bacterial cholangitis or complications of end-stage liver disease
Asymptomatic patients usually require only monitoring (eg, physical examination and liver biochemical tests twice/yr). Ursodeoxycholic acid (up to 15 mg/kg/day reduces itching and improve biochemical markers but not survival. Chronic cholestasis (see p. 212) and cirrhosis require supportive treatment. Episodes of bacterial cholangitis warrant antibiotics and therapeutic ERCP, as needed. If a single stricture appears to be the major cause of obstruction (a dominant stricture, found in about 20% of patients), ERCP dilation (with brush cytology to check for tumors) and stenting can relieve symptoms.

Liver transplantation is the only treatment that improves life expectancy in patients with PSC and offers a cure. Recurrent bacterial cholangitis or complications of end-stage liver disease (eg, intractable ascites, portal-systemic encephalopathy, bleeding esophageal varices) are reasonable indications for liver transplantation.

**AIDS Cholangiopathy**

AIDS cholangiopathy is biliary obstruction secondary to biliary tract strictures caused by various opportunistic infections.

Before the advent of highly active antiretroviral therapy, cholangiopathy occurred in 25% of patients with AIDS, especially in those with a low CD4 count (< 100/μL). The most common pathogen is *Cryptosporidium parvum*. Others include cytomegalovirus, microsporidia, and *Cyclospora* sp. Papillary stenosis or intrahepatic or extrahepatic sclerosing cholangitis develops in most patients. Over half have both.

Common symptoms include right upper quadrant and epigastric pain and diarrhea. A few patients have fever and jaundice. Severe pain usually indicates papillary stenosis. Milder pain suggests sclerosing cholangitis. The diarrhea reflects small-bowel infection, often cryptosporidiosis.

**Diagnosis**

- Usually ERCP and ultrasonography

ERCP provides the diagnosis, identification of the causal organism by small-bowel biopsy, and a therapeutic opportunity to relieve strictures. Ultrasonography is noninvasive and very accurate (> 95%). CT and magnetic resonance cholangiopancreatography likely have supportive roles.

Liver biochemistry is consistent with cholestasis, especially a high alkaline phosphatase level.

**Treatment**

- Endoscopic procedures

Endoscopic sphincterotomy can markedly relieve pain, jaundice, and cholangitis in patients with papillary stenosis. Isolated or dominant strictures can be stented endoscopically. Although the cause is an infectious agent, antimicrobial therapy alone does not relieve the biliary tract damage or its sequelae. Because of its use in primary sclerosing cholangitis, ursodeoxycholic acid may have a role in treating intrahepatic ductal sclerosis and cholestasis.

**Tumors of the Gallbladder and Bile Ducts**

Gallbladder and bile duct tumors can cause extrahepatic biliary obstruction. Symptoms may be absent but often are constitutional or reflect biliary obstruction. Diagnosis is based on ultrasonography plus CT cholangiography or magnetic resonance cholangiopancreatography. Prognosis is grim. Mechanical bile drainage can often relieve pruritus, recurrent sepsis, and pain due to biliary obstruction.

**Cholangiocarcinomas** and other bile duct tumors are rare (1 to 2/100,000 people) but are usually malignant. Cholangiocarcinomas occur predominantly in the extrahepatic bile ducts: 60 to 70% in the perihilar region (Klatskin tumors), about 25% in the distal ducts, and the rest in the liver. Risk factors
include primary sclerosing cholangitis, older age, infestation with liver flukes, and a choledochal cyst.

**Gallbladder carcinoma** is uncommon (2.5/100,000). It is more common among American Indians, patients with large gallstones (> 3 cm), and those with extensive gallbladder calcification due to chronic cholecystitis (porcelain gallbladder). Nearly all (70 to 90%) patients also have gallstones. Median survival is 3 mo. Cure is possible when cancer is found early (eg, incidentally at cholecystectomy).

**Gallbladder polyps** are usually asymptomatic benign mucosal projections that develop in the lumen of the gallbladder. Most are < 10 mm in diameter and composed of cholesterol ester and triglycerides; the presence of such polyps is called cholesterolosis. They are found in about 5% of people during ultrasonography. Other, much less common benign polyps include adenomas (causing adenomyomatosis) and inflammatory polyps. Small gallbladder polyps are incidental findings that do not require treatment.

**Symptoms and Signs**

Most patients with cholangiocarcinomas present with pruritus and painless obstructive jaundice, typically at age 50 to 70 yr. Early perihilar tumors may cause only vague abdominal pain, anorexia, and weight loss. Other features include acholic stool, a palpable mass, hepatomegaly, or a distended gallbladder (Courvoisier's sign, with distal cholangiocarcinoma). Pain may resemble that of biliary colic (reflecting biliary obstruction) or may be constant and progressive. Sepsis (acute cholangitis), though unusual, may be induced by ERCP.

Manifestations of gallbladder carcinoma may range from incidental findings at cholecystectomy done for biliary pain to cholelithiasis to advanced disease with constant pain, weight loss, and an abdominal mass or obstructive jaundice.

**Diagnosis**

Cholangiocarcinomas are suspected when extrahepatic biliary obstruction is unexplained. Laboratory test results reflect the degree of cholestasis. In patients with primary sclerosing cholangitis, serum carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 levels are used for surveillance to detect the development of cholangiocarcinoma. Diagnosis is based on ultrasonography (or endoscopic ultrasonography) and CT cholangiography or magnetic resonance cholangiopancreatography. When these methods are inconclusive, ERCP with percutaneous transhepatic cholangiography (PTC) becomes necessary. ERCP not only detects the tumor but also, with brushings, can provide a tissue diagnosis, sometimes making ultrasonography- or CT-guided needle biopsy unnecessary. Contrast-enhanced CT assists in staging.

Gallbladder carcinomas are better defined by CT than by ultrasonography. Open laparotomy is necessary to determine disease extent, which guides treatment.

**Treatment**

- For cholangiocarcinomas, stenting (or another bypass procedure) or occasionally resection

For cholangiocarcinoma, stenting or surgically bypassing the obstruction relieves pruritus, jaundice, and perhaps fatigue.

Hilar cholangiocarcinomas with CT evidence of spread are stented via PTC or ERCP. Distal duct cholangiocarcinomas are stented endoscopically with ERCP. If cholangiocarcinoma appears localized, surgical exploration determines resectability by hilar resection or pancreaticoduodenectomy. However, successful resection is uncommon.

Liver transplantation is not indicated because of the high recurrence rate. Effectiveness of adjuvant chemotherapy and radiation therapy for cholangiocarcinomas is unproved as yet.
Many gallbladder carcinomas are treated symptomatically.
Chapter 32. Approach to the Patient With Joint Disease

Introduction

Some musculoskeletal disorders affect primarily the joints, causing arthritis. Others affect primarily the bones (eg, fractures, Paget's disease, tumors), muscles or other extra-articular soft tissues (eg, fibromyalgia), or periarticular soft tissues (eg, polymyalgia rheumatica, bursitis, tendinitis, sprain). Arthritis has myriad possible causes, including infection, autoimmune disorders, crystal-induced inflammation, and noninflammatory tissue degeneration (eg, osteoarthritis). Arthritis may affect single joints (monarthritis) or multiple joints (polyarthritis) in a symmetric or asymmetric manner. Joints may suffer fractures or sprains (see elsewhere in THE MANUAL).

History

The clinician should focus on systemic and extra-articular symptoms as well as joint symptoms. Many symptoms, including fever, chills, malaise, weight loss, Raynaud's syndrome, mucocutaneous symptoms (eg, rash, eye irritation or pain, photosensitivity), and GI or cardiopulmonary symptoms, can be associated with various joint disorders.

Pain is the most common symptom of joint disorders. The history should address the character, location, severity, factors that aggravate or relieve pain, and time frame (new-onset or recurrent). The clinician must determine whether pain is worse when first moving a joint or after prolonged use and whether it is present upon waking or develops during the day. Usually, pain originating from superficial structures is better localized than pain originating from deeper structures. Pain originating in small distal joints tends to be better localized than pain originating in large proximal joints. Joint pain can be referred from extra-articular structures or from other joints. Arthritis often causes aching pain, whereas neuropathies often cause burning pain.

Stiffness may mean weakness, fatigue, or fixed limitation of motion to patients. The clinician must separate the inability to move a joint from reluctance to move a joint because of pain. Characteristics of stiffness may suggest a cause, as in the following:

- Discomfort that occurs with motion when attempting to move a joint after a period of rest occurs in rheumatic disease. Duration of stiffness after beginning joint motion reflects its severity.
- The theater sign (stiffness upon standing that necessitates walking slowly after sitting for several hours) is common in osteoarthritis.
- Stiffness is more severe and prolonged in inflammatory joint disorders.
- Morning stiffness in peripheral joints that lasts > 1 h can be an important early symptom of RA (see Table 32-1).
- In the low back, morning stiffness that lasts > 1 h may reflect spondylitis.

Fatigue is a desire to rest that reflects exhaustion. It differs from weakness, inability to move, and reluctance to move due to pain with movement.

Instability (buckling of a joint) may suggest weakness of the ligaments or other structures that stabilize the joint, which are assessed by stress testing. Buckling occurs most often in the knee and most often results from an internal joint derangement.

Physical Examination

Each involved joint should be inspected and palpated, and the range of motion should be estimated. With polyarticular disease, certain nonarticular signs (eg, fever, wasting, rash) may reflect systemic disorders.
The rest position of joints is noted, along with any erythema, swelling, deformity, and skin abrasions or punctures. Involved joints are compared with their uninvolved opposites or with those of the examiner.

Joints are gently palpated, noting the presence and location of tenderness, warmth, and swelling. Determining whether tenderness is present along the joint line or over tendon insertions or bursae is particularly important. Soft masses, bulges, or tissues that fill normal concavities or spaces (representing joint effusion or synovial proliferation) are noted. Palpation of

**Table 32-1. Distinguishing Inflammatory vs Noninflammatory Features in Joint Disease by Features**

swollen joints can sometimes differentiate among joint effusion, synovial thickening, and capsular or bony enlargement. Small joints (eg, the acromioclavicular, tibiofibular, radioulnar) can be the source of pain that was initially believed to arise from a nearby major joint. Bony enlargement (often due to osteophytes) is noted.

Active range of motion (the maximum range through which the patient can move the joint) is measured first, using a goniometer; limitation may reflect weakness, pain, or stiffness as well as mechanical abnormalities. Then passive range of motion (the maximum range through which the examiner can move the joint) is assessed; passive limitation generally reflects mechanical abnormalities (eg, scarring, swelling, deformities) rather than weakness or pain. Active and passive movement of an inflamed joint (eg, due to infection or gout) may be very painful.

Patterns of joint involvement should be noted. Symmetric involvement of multiple joints is common in systemic diseases (eg, RA); monarticular (involving one joint) or asymmetric oligoarticular (involving ≤ 4) joint involvement is more common in osteoarthritis and psoriatic arthritis. Small peripheral joints are commonly affected in RA, and the larger joints and spine are affected more in spondyloarthropathies. However, a pattern of involvement may not be apparent in early disease.

Crepitus, a palpable or audible grinding produced by motion, is noted. It may be caused by roughened articular cartilage or by tendons; crepitus-causing motions should be determined and may suggest which structures are involved.

Specific features should be sought at each joint.

**Elbow:** Synovial swelling and thickening caused by joint disease occur in the lateral aspect between the radial head and olecranon, causing a bulge. Full 180° extension of the joint should be attempted. Although full extension is possible with nonarthritic or extra-articular problems such as tendinitis, its loss is an early change in arthritis. The area around the joint is examined for swellings. Rheumatoid nodules are firm, occurring especially along the extensor surface of the forearm. Tophi are sometimes visible under the skin as cream-colored aggregates and indicate gout. Swelling of the olecranon bursa occurs over the tip of the olecranon, is cystic, and does not limit joint motion; infection, trauma, gout, and RA are possible causes. Epitrochlear nodes occur above the medial epicondyle; they can result from inflammation in the hand but can also suggest sarcoidosis or lymphoma.

**Shoulder:** Because pain can be referred to areas around the shoulder, shoulder palpation should include the glenohumeral, acromioclavicular, and sternoclavicular joints, the coracoid process, clavicle, acromion process, subacromial bursa, biceps tendon, and greater and lesser tuberosities of the humerus, as well as the neck. Glenohumeral joint effusions may cause a bulge between the coracoid process and the humeral head. Possible causes include RA, osteoarthritis, septic arthritis, Milwaukee shoulder (see p. 355), and other arthropathies.

Limited motion, weakness, pain, and other disturbances of mobility caused by rotator cuff impairment can be quickly identified by having the patient attempt to abduct and raise both arms above the head and then to slowly lower them. Muscle atrophy and neurologic abnormalities should be sought.

**Knee:** At the knee, gross deformities such as swelling (eg, joint effusion, popliteal cysts), quadriceps muscle atrophy, and joint instability may be obvious when the patient stands and walks. With the patient
supine, the examiner should palpate the knee, identifying the patella, femoral condyles, tibial tuberosity, tibial plateau, fibular head, medial and lateral joint lines, popliteal fossa, and quadriiceps and patellar tendons. The medial and lateral joint lines correspond to locations of the medial and lateral menisci and can be located by palpation while slowly flexing and extending the knee. Tender extra-articular bursae such as the anserine bursa below the medial joint line should be differentiated from true intra-articular disturbances.

Detection of small knee effusions is often difficult and is best accomplished using the bulge sign. The knee is fully extended and the leg slightly externally rotated while the patient is supine with muscles relaxed. The medial aspect of the knee is stroked to express any fluid away from this area. Placement of one hand on the suprapatellar pouch and gentle stroking or pressing on the lateral aspect of the knee can create a fluid wave or bulge, visible medially when an effusion is present. Larger effusions can be identified visually or by balloting the patella. Joint effusion can result from many joint diseases, including RA, osteoarthritis, gout, and trauma.

Full 180° extension of the knee is attempted to detect flexion contractures. The patella is tested for free, painless motion.

**Hip:** Examination begins with gait evaluation. A limp is common in patients with significant hip arthritis. It may be caused by pain, leg shortening, flexion contracture, muscle weakness, or knee problems. Loss of internal rotation (often the earliest change in hip osteoarthritis or any hip synovitis), flexion, extension, or abduction can usually be demonstrated. Placement of one hand on the patient's iliac crest detects pelvic movement that might be mistaken for hip movement. Flexion contracture can be identified by attempting leg extension with the opposite hip maximally flexed to stabilize the pelvis. Tenderness over the femoral greater trochanter suggests bursitis (which is extra-articular) rather than an intra-articular disorder. Pain with passive range of motion (assessed by internal and external rotation with the patient supine and the hip and knee flexed to 90°) suggests intra-articular origin. However, patients may have simultaneous intra-articular and extra-articular disorders.

**Other:** Hand examination is discussed elsewhere (see p. 385 and *Polyarticular Joint Pain* on p. 292). Foot and ankle examination is discussed in Ch. 44. Examination of the neck and back is discussed on p. 379.

**Testing**

Laboratory testing and imaging studies often provide less information than do the history and physical examination. While some testing may be warranted in some patients, extensive testing is often not.

**Blood tests:** Some tests, although not specific, can be helpful in supporting the possibility of certain systemic rheumatic diseases, as for the following:

- Antinuclear antibodies (ANA) and complement in SLE
- Rheumatoid factor and anticitrullinated peptide (CCP) in RA
- HLA-B27 in spondyloarthropathy (occasionally useful)
- Antineutrophil cytoplasmic antibodies (ANCA) in certain vasculitides (occasionally useful)

Tests such as WBC count, ESR, and C-reactive protein may help determine the likelihood that arthritis is inflammatory due to infectious or other systemic disorders, but these tests are not highly specific or sensitive. For example, an elevated ESR or C-reactive protein level suggests inflammation or may be due to aging or a large number of nonarticular inflammatory conditions (eg, infection, cancer). Also, such markers may not be elevated in all inflammatory disorders.

**Imaging studies:** Imaging studies are often unnecessary. Plain x-rays in particular reveal mainly bony abnormalities, and most joint disorders do not affect bone primarily. However, imaging may help in the initial evaluation of relatively localized, unexplained persistent or severe joint and particularly spine
abnormalities; they may reveal primary or metastatic tumors, osteomyelitis, bone infarctions, periarticular calcifications (as in calcific tendinitis), or other changes in deep structures that may escape physical examination. If chronic RA, gout, or osteoarthritis is suspected, erosions, cysts, and joint space narrowing with osteophytes may be visible. In pseudogout, Ca pyrophosphate deposition may be visible in intra-articular cartilage.

For musculoskeletal imaging, plain x-rays may be obtained first, but they are often less sensitive, particularly during early disease, than MRI, CT, or ultrasonography. MRI is the most accurate study for fractures not visible on plain x-rays, particularly in the hip and pelvis, and for soft tissues and internal derangements of the knee. CT is useful if MRI is contraindicated or unavailable. Ultrasonography, arthrography, and bone scanning may help in certain conditions, as can biopsy of bone, synovium, or other tissues.

**Arthrocentesis:** Arthrocentesis is the process of puncturing the joint with a needle to withdraw fluid. If there is an effusion and arthrocentesis is done correctly, fluid can generally be withdrawn. Examination of synovial fluid is the most accurate way to exclude infection, diagnose crystal-induced arthritis, and otherwise determine the cause of joint effusions. It is indicated in all patients with severe or unexplained monarticular joint effusions and in patients with unexplained polyarticular effusions.

Arthrocentesis is done using strictly sterile technique. Infection or other rash over the site used to enter the joint is a contraindication. Preparations for collecting samples should be made before doing the procedure. Local anesthesia, with lidocaine or difluoroethane spray, is often used. Many joints are punctured on the extensor surface to avoid nerves, arteries, and veins, which are usually on the joint's flexor surface. A 20-gauge needle can be used for most larger joints. Smaller joints of the upper and lower extremities are probably easier to access using a 22- or 23-gauge needle. As much fluid as is possible should be removed. Specific anatomic landmarks are used (see **Figs. 32-1, 32-2, and 32-3**).

Metacarpophalangeal joints, metatarsophalangeal joints, and interphalangeal joints of the hands and feet are punctured similarly to each other, using a 22- or 23-gauge needle. The needle is inserted dorsally, to either side of the extensor tendon. Distraction of the joint is sometimes useful to open the joint space and allow easier access.

[**Fig. 32-1.** Arthrocentesis of the shoulder.]

**Synovial fluid examination:** At the bedside, gross characteristics of the fluid are assessed, such as its color, turbidity, and viscosity. Viscosity can be assessed using the string sign. The length of a viscous string of joint fluid dropped from the syringe is normally > 3 cm. Inflammation decreases viscosity, shortening the length of the string.

Gross characteristics allow many effusions to be tentatively classified as noninflammatory, inflammatory, or infectious (see **Table 32-2**). Effusions can also be hemorrhagic. Each type of effusion suggests certain joint diseases (see **Table 32-3**). So-called noninflammatory effusions are actually mildly inflammatory but tend to suggest diseases such as osteoarthritis, in which inflammation is not severe.

Laboratory tests commonly done on joint fluid include cell count, leukocyte differential, Gram stain and culture (if infection is a concern—see p. 365), and wet drop examination for cells and crystals. However, the exact tests often depend on which diagnoses are suspected.

Microscopic examination of a wet drop preparation of synovial fluid for crystals (only a single drop of fluid from a joint is needed), using polarized light, is essential for definitive diagnosis of gout, pseudogout, and other crystal-induced arthritides (see p. 349). A polarizer over the light source and another polarizer between the specimen and the examiner's eye allow visualization of crystals with a shiny white birefringence. Compensated polarized light is provided by inserting a first-order red plate, as is found in
commercially available microscopes. The effects of a compensator can be reproduced by placing 2 strips of clear adhesive tape on a glass slide and placing this slide over the lower polarizer. Such a homemade system should be tested against a commercial polarizing microscope. The most common crystals seen are those diagnostic of gout (monosodium urate, negatively birefringent needle-shaped crystals) and pseudogout (Ca pyrophosphate, positively birefringent square-ended crystals). If crystals appear atypical in a wet drop, several less common crystals (cholesterol, liquid lipid crystals, oxalate, cryoglobulins) or artifacts (eg, depot corticosteroid crystals) should be considered.

Other synovial fluid findings that occasionally make or suggest a specific diagnosis include the following:

- Specific organisms (identifiable by Gram or acid-fast stain)
- Marrow spicules or fat globules (caused by fracture)
- Reiter's cells (monocytes on Wright's-stained smears that have phagocytized PMNs), which appear most often in reactive arthritis
- Amyloid fragments (identifiable by Congo red stain)
- Sickled RBCs (caused by sickle cell hemoglobinopathies)

[Fig. 32-2. Arthrocentesis of the elbow.]

[Table 32-2. Classification of Synovial Effusions]

Monarticular Joint Pain

Monarticular pain may originate from the joint itself or surrounding structures. There may be pain (arthralgia) or also inflammation (arthritis) with redness, warmth, and swelling. Pain may occur only with use, suggesting a mechanical problem (eg, osteoarthritis, tendinitis), or also at rest, suggesting inflammation (eg, crystal disease, septic arthritis). There may or may not be fluid within the joint (effusion). Prompt assessment is essential to exclude infection. It is important to remember that acute monarticular arthritis is sometimes the initial manifestation of some types of polyarticular arthritis (eg, psoriatic arthritis, RA).

Pathophysiology

Monarticular pain may originate

- Within a joint (intra-articular)
- Around a joint (periarticular)

Intra-articular disorders may be inflammatory (eg, infectious, rheumatoid, crystal deposition arthritis) or noninflammatory (eg, osteoarthritis, internal derangement).

Periarticular disorders include bursitis and tendinitis.

Crystal-induced arthritis is usually caused by monosodium urate crystals (gout) or Ca pyrophosphate dihydrate crystals (pseudogout).

Etiology

At all ages, injury is the most common cause of acute monarticular joint pain; history of trauma is usually obvious.

[Fig. 32-3. Arthrocentesis of the knee.]
Among young adults, the most common nontraumatic causes are the following:

• Disseminated gonococcal infection
• Periarticular syndromes

Among older adults, the most common nontraumatic causes are the following:

• Osteoarthritis
• Crystal-induced disease (gout or pseudogout)
• Periarticular syndromes

The most dangerous cause at any age is acute infectious arthritis, because it requires acute operative intervention (saline washout of the joint) and antibiotics to minimize permanent damage to the joint and to prevent sepsis and death.

At all ages, rare causes include adjacent osteomyelitis, avascular necrosis, pigmented villonodular synovitis, hemarthrosis (eg, in hemophilia or coagulopathies), and tumors (see Table 32-4).

### Evaluation

Acute monarticular joint pain requires especially rapid diagnosis because some of its causes, particularly infectious (septic) arthritis and crystal-induced arthritis, require rapid treatment.

Evaluation should determine whether the joint or periarticular structures are the cause of symptoms and whether there is inflammation. If inflammation is present or the diagnosis is unclear, symptoms and signs of polyarticular and systemic disorders should be sought and all joints should be examined.

**History:** History of present illness should focus on the acuity of onset (eg, abrupt, gradual), whether the problem is new or recurrent, and whether other joints have caused pain in the past. Also, temporal patterns (eg, diurnal variation, persistent vs intermittent), exacerbating and mitigating factors (eg, cold weather, activity), and any recent or past trauma to the joint should be noted. Patients should be specifically asked about unprotected sexual contact (possible gonococcal infection), tick bites, and residence in or travel to an area where Lyme disease is endemic.

**Review of systems** should seek symptoms of causative disorders, including fever (infection), urethritis (gonococcal arthritis), and previous unexplained illness with rash (Lyme arthritis).

**Past medical history** should identify known joint disorders (particularly gout, osteoarthritis) and any known conditions that may cause monarticular joint pain (eg, coagulopathy, bursitis, tendinitis, hemoglobinopathy). Drug history should be reviewed for any use of anticoagulants or diuretics and for chronic corticosteroid use. A family history should also be obtained.

**Physical examination:** Vital signs are reviewed for fever. Examination of the head, neck, and skin should note any signs of conjunctivitis, psoriatic plaques, mucosal lesions, ecchymoses, or malar rash. Genital examination should note any discharge or other findings consistent with sexually transmitted diseases.

Joints are inspected for deformities, erythema, and swelling. Range of motion is assayed, first actively and then passively; any crepitus on joint motion is noted.
Palpation is done to detect warmth, identify any effusion, and localize the area of tenderness. Of particular importance is whether the tenderness is directly over the joint line or adjacent to it (helping to differentiate an intra-articular from a periarticular disorder). Sometimes, compression of the joint without flexing or extending it (eg, pushing on the end of the great toe for patients with pain in the 1st metatarsophalangeal joint), sometimes with slight rotation, also helps differentiate intra-articular from periarticular disorders; this maneuver is not particularly painful for patients with tendinitis or bursitis but is quite painful for those with arthritis. If the patient can tolerate it, the joint is stressed with various maneuvers to identify disruption of cartilage or ligaments (eg, in the knee, valgus and varus tests, anterior and posterior drawer tests, Lachman's test, and McMurray's test). Comparison with the contralateral unaffected joint often helps detect more subtle changes.

Large effusions in the knee are typically readily apparent. The examiner can check for minor knee effusions by pushing the suprapatellar pouch inferiorly and then pressing medially on the lateral side of the patella on an extended knee. This maneuver causes swelling to appear on the medial side.

Periarticular structures also should be examined to look for discrete soft swelling at the site of a bursa (bursitis), point tenderness at the insertion of a tendon (tendinitis), and point tenderness over a tendon with fine crepitus (tenosynovitis).

**Red flags:** The following findings are of particular concern:

- Erythema, warmth, effusion, and decreased range of motion
- Fever
- Acute-onset joint pain in a sexually active young adult
- Skin breaks with cellulitis adjacent to the affected joint
- Underlying bleeding disorder, hemoglobinopathy, or anticoagulation
- Extra-articular or systemic symptoms

**Interpretation of findings:** Antecedent trauma suggests a fracture, meniscal tear, or hemarthrosis. In the absence of trauma, history and physical examination may suggest a cause, but testing is often necessary to rule out serious causes.

Acuteness of onset is a very important feature. Severe joint pain that develops over hours suggests crystal-induced arthritis or, less often, infectious arthritis. A previous attack of crystal-induced arthritis with development of similar symptoms suggests recurrence. Gradual onset of pain is typical of RA or noninfectious arthritis but can result from certain infectious arthritides (eg, mycobacterial, fungal).

Pain during rest and on initiating activity suggests inflammatory arthritis, whereas pain worsened by movement and relieved by rest suggests mechanical disorders (eg, osteoarthritis).

Pain worse with active than with passive joint motion may indicate tendinitis or bursitis; intra-articular inflammation generally restricts active and passive range of joint motion severely.

Increased warmth and erythema suggest inflammation, but erythema is often absent during inflammation. Tenderness or swelling at only one side of a joint, or away from the joint line, suggests an extra-articular origin (eg, in ligaments, tendons, or bursae); findings on several aspects of the joint suggest an intra-articular cause.

Although gout can involve many different single joints or combinations of joints, acute, painful monarticular arthritis of the metatarsophalangeal joint of a great toe (podagra) is especially suggestive.

The presence of systemic findings can help narrow the diagnosis. Urethritis can suggest gonococcal infection (although gonococcal arthritis often develops in patients without symptoms of urethritis). Fever is
indicative of septic joint, crystal-induced arthropathy, or osteomyelitis. Symptoms indicating dermatologic, cardiac, or pulmonary involvement suggest diseases that are more commonly associated with polyarticular joint pain.

**Testing:** Joint aspiration (arthrocentesis) should be done in patients with an effusion or other signs of inflammation (eg, erythema, warmth, fever). Studies of the joint fluid should include WBC count with differential (to determine whether the effusion is bloody or inflammatory), Gram stain and cultures, and microscopic examination for crystals. Finding crystals in synovial fluid confirms crystal-induced arthritis but does not rule out coexisting infection. A noninflammatory synovial fluid (eg, < 2000/μL WBCs or < 75% neutrophils) should lead to consideration of osteoarthritis, soft-tissue injury, or viral infection.

X-rays usually are done unless the cause is clearly a flare-up of a known disorder (eg, gout) or is a clinically obvious bursitis or tendinitis, which can often be diagnosed without further testing.

Other imaging tests (eg, CT, MRI, bone scan) are adjunctive and are done depending on what diagnoses are being considered (see Table 32-4).

Blood tests (eg, ESR, antinuclear antibodies, rheumatoid factor, anticyclic citrullinated peptide [CCP] antibody, HLA-B27 testing) may help support an early diagnosis of a noninfectious inflammatory arthritis.

**Treatment**

Overall treatment is directed at the underlying disorder.

Joint inflammation is usually treated symptomatically with NSAIDs. Pain without inflammation is usually more safely treated with acetaminophen. Joint immobilization with a splint or sling can sometimes relieve pain. Heat therapy may relieve muscle spasm around joints. Cold therapy may be analgesic in inflammatory joint diseases.

Physical therapy after the acute symptoms have lessened is useful to maintain range of motion and strengthen surrounding muscles.

**Key Points**

- Atraumatic joint pain should prompt consideration of degenerative disease, crystal-induced arthropathy, infection, or cancer.

- Arthrocentesis is mandatory to rule out infection in a joint that is red, warm, and swollen.

- Disseminated gonococcal infection is the most common cause of acute nontraumatic monarthritis in young adults, whereas osteoarthritis is the most common cause in older adults.

- Crystals in synovial fluid confirm crystal-induced arthritis but do not rule out coexisting infection.

- Joint pain that is still unexplained after arthrocentesis and x-ray should be evaluated with MRI to rule out uncommon etiologies (eg, occult fracture, avascular necrosis, pigmented villonodular synovitis).

**Polyarticular Joint Pain**

Joints may simply be painful (arthralgia) or also inflamed (arthritis), with redness, warmth, and swelling. Pain may occur only with use or also at rest, and there may or may not be fluid within the joint (effusion).

A useful initial distinction is whether pain is present in one joint (monarticular) or multiple joints (polyarticular). When multiple joints are affected, different terms can be used:

- Arthritis involving ≤ 4 joints, particularly when it occurs in an asymmetric fashion, is oligoarticular or pauciarticular arthritis.
Arthritis involving > 4 joints, usually in a symmetric fashion, is polyarticular arthritis.

**Pathophysiology**

Polyarticular arthralgia can originate from arthritis or from extra-articular disorders (eg, polymyalgia rheumatica, fibromyalgia). Pain caused by intra-articular disorders may be secondary to an inflammatory arthritis (eg, infection, RA, crystal deposition) or a noninflammatory process (eg, osteoarthritis).

Inflammatory arthritis may involve peripheral joints only (eg, hands, knees, feet) or both peripheral and axial joints (eg, sacroiliac, apophyseal, discovertebral, costovertebral).

**Etiology**

Peripheral oligoarticular and polyarticular arthritis have specific, likely causes (see Table 32-5); the presence or absence of axial involvement helps limit possibilities. However, in many patients, arthritis is often transient and resolves without diagnosis or may not fulfill the criteria for any defined rheumatic disease.

Acute polyarticular arthritis is most often due to the following:

- Infection (usually viral)
- Flare of a rheumatic disease

Chronic polyarticular arthritis in adults is most often due to the following:

- RA (inflammatory)
- Osteoarthritis (noninflammatory)

Chronic polyarticular arthritis in children is most often due to the following:

- Juvenile idiopathic arthritis

**Evaluation**

Evaluation should determine whether the joints or periarticular structures are the cause of symptoms and whether there is inflammation or effusion. If inflammation is present or the diagnosis is unclear, symptoms and signs of systemic disorders should be sought.

**History:** History of present illness should identify the acuity of onset (eg, abrupt, gradual), temporal patterns (eg, diurnal variation, persistent vs intermittent), chronicity (eg, acute vs longstanding), and exacerbating factors (eg, cold weather, activity). Patients should be specifically asked about unprotected sexual contact (possible gonococcal infection) and tick bites or residence in a Lyme-endemic area.

**Review of systems** should seek symptoms and signs of causative disorders (see Tables 32-5 and 32-6).

**Past medical history** and family history should identify known rheumatic disorders and other conditions capable of causing joint symptoms (see Table 32-5).

**Physical examination:** Vital signs are reviewed for fever.

Examination of the head, neck, and skin should note any signs of conjunctivitis, iritis, mucosal lesions,
sino-nasal abnormalities, lymphadenopathy, ecchymoses, skin ulcers, psoriatic plaques, purpura, or malar rash.

Cardiopulmonary examination should note any signs of acute inflammatory disease or serositis (eg, murmur, pericardial rub, muffled heart sounds, bibasilar dullness consistent with pleural effusion).

Genital examination should note any discharge, ulcers, or other findings consistent with sexually transmitted diseases.

Musculoskeletal examination should note muscular point tenderness associated with fibromyalgia. Joint examination begins with inspection for deformities, erythema, swelling, or effusion and then proceeds to palpation and estimation of pain and crepitus with active and passive range of motion. Comparison with the contralateral unaffected joint often helps detect more subtle changes. Examination should note whether the distribution of affected joints is symmetric.

Periarticular structures also should be examined for discrete, soft swelling at the site of a bursa (bursitis), point tenderness at the insertion of a tendon (tendinitis), and point tenderness over a tendon with fine crepitus (tenosynovitis).

Red flags: The following findings are of particular concern:

- Hot, swollen, red joints
- Any extra-articular symptoms (eg, fever, rash, plaques, ulcers, conjunctivitis, iritis, murmur, purpura)

Interpretation of findings: An important initial element is whether pain originates in the joints, spine, or both or in other structures such as bones, tendons, bursae, muscles, other soft-tissue structures, or nerves. Pain that worsens with active rather than passive joint motion may indicate tendinitis or bursitis; intra-articular inflammation generally restricts active and passive range of joint motion severely. Tenderness or swelling at only one side of a joint, or away from the joint line, suggests an extra-articular origin (eg, in ligaments, tendons, or bursae); findings on several aspects of the joint suggest an intra-articular cause. Pain that is diffuse and described inconsistently or vaguely may result from fibromyalgia or functional disorders.

If the joints, spine, or both are involved, differentiating inflammatory from noninflammatory disorders may help. Clinical findings of prominent morning stiffness, nontraumatic joint swelling, and fever or weight loss are suggestive of an inflammatory disorder, but testing is often helpful.

Examination of the hand joints may yield other clues (see Table 32-6) and may help differentiate osteoarthritis from RA (see Table 32-7).

Back pain with arthritis suggests ankylosing spondylitis, a reactive or psoriatic arthritis, or fibromyalgia.

[Table 32-7. Differential Features of the Hand in RA and Osteoarthritis]

Testing: The following tests are of particular importance:

- Arthrocentesis
- Serologic testing
- Usually ESR

Arthrocentesis is mandatory in most patients with a new effusion and can help rule out infection and crystal arthropathy as well as distinguish between an inflammatory and noninflammatory process. Other tests may be needed to identify specific disorders (see Table 32-5).
If the specific diagnosis cannot be established clinically and if determining whether arthritis is inflammatory may help determine the diagnosis, ESR and C-reactive protein may be done. A low ESR makes inflammatory causes (e.g., rheumatic disease, gout, infection, vasculitis) less likely but does not rule them out. Elevated results argue more strongly for inflammation, but they are very nonspecific, particularly in older adults.

Once a diagnosis of a systemic disease is thought to be most likely, supportive serologic testing for antinuclear antibodies, double-stranded DNA, rheumatoid factor, anticyclic citrullinated peptide, and antineutrophil cytoplasmic antibodies may assist in making the diagnosis.

**Treatment**

The underlying disorder is treated. Systemic diseases may require either immunosuppression or antibiotics as determined by the diagnosis. Joint inflammation is usually treated symptomatically with NSAIDs. Pain without inflammation is usually more safely treated with acetaminophen. Joint immobilization with a splint or sling can sometimes relieve pain. Heat therapy may relieve muscle spasm around joints, and cold therapy may be analgesic in inflammatory joint diseases. For cases of chronic arthritis, continued physical activity is encouraged.

**Geriatrics Essentials**

Osteoarthritis is by far the most common cause of arthritis in older people. RA most commonly begins between ages 30 and 40, but in up to one third of patients, it develops after the age of 60. Because paraneoplastic phenomena also can cause inflammatory polyarthritis, cancer should be considered in older adults in whom new-onset RA is suspected.

**Key Points**

- The differential diagnosis of polyarticular joint pain can be narrowed by considering how many joints are affected, whether inflammation is present, and whether any extra-articular signs are present.

- Chronic arthritis is most often caused by juvenile idiopathic arthritis in children and osteoarthritis and RA in adults.

- Acute polyarticular arthritis is most often due to infection, gout, or a flare of rheumatic disease.

- Arthrocentesis is mandatory in most cases of a new effusion and can help rule out infection and crystal-induced arthropathy as well as distinguish between an inflammatory and noninflammatory process.
Chapter 33. Autoimmune Rheumatic Disorders

Introduction

Autoimmune rheumatic disorders include eosinophilic fasciitis, mixed connective tissue disease, polymyositis and dermatomyositis, relapsing polychondritis, Sjogren's syndrome, SLE, and systemic sclerosis. RA and the spondyloarthropathies and their variants (see Ch. 35) are also immune mediated. The triggers and precise pathophysiology remain unknown for all these disorders, although many aspects of pathogenesis are becoming clearer. Patients with most autoimmune rheumatic disorders are at increased risk of atherosclerosis.

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF) is an uncommon disorder characterized by symmetric and painful inflammation, swelling, and induration of the arms and legs. Diagnosis is by biopsy of skin and fascia. Treatment is with corticosteroids.

The cause of EF is unknown. The disorder occurs mostly in middle-aged men but can occur in women and children.

Symptoms and Signs

The disease often begins after strenuous physical activity (eg, chopping wood). The initial features are pain, swelling, and inflammation of the skin and subcutaneous tissues, followed by induration, creating a characteristic orange-peel configuration most evident over the anterior surfaces of the extremities. The face and trunk are occasionally involved. Restriction of arm and leg movement usually develops insidiously. Contractures commonly evolve, secondary to induration and thickening of the fascia, but the process may also involve tendons, synovial membranes, and muscle. Typically, EF does not involve the fingers and toes (acral areas). Muscle strength is unimpaired, but myalgia and arthritis may occur. Carpal tunnel syndrome may also occur.

Fatigue and weight loss are common. Rarely, aplastic anemia, thrombocytopenia, and lymphoproliferative processes develop.

Diagnosis

• Biopsy

EF should be suspected in patients with typical symptoms. The cutaneous manifestations may suggest systemic sclerosis; however, patients with systemic sclerosis usually also have Raynaud's syndrome, acral involvement, telangiectasia, and visceral changes (eg, esophageal dysmotility). All of these are absent in EF.

Diagnosis is confirmed by en bloc biopsy, which should be deep enough to include fascia and adjacent muscle fibers. Characteristic findings are inflammation of the fascia, with or without eosinophils.

Blood tests are not diagnostic, but CBC shows eosinophilia (in early active disease), and serum protein electrophoresis shows polyclonal hypergamma globulinemia. CBC should be done in all patients because the presence of eosinophilia helps in the diagnosis. Autoantibodies are usually absent. MRI, although not specific, can show thickened fascia, the increased signal intensity in the superficial muscle fibers correlating with the inflammation.

Prognosis

Although the long-term outcome varies, EF is often self-limited and uncomplicated.

Treatment
• Oral prednisone

Most patients respond rapidly to high doses of prednisone (40 to 60 mg po once/day followed by gradual reduction to 5 to 10 mg/day as soon as the fascitis resolves). Continued low doses may be required for 2 to 5 yr. Some patients require longer courses and possibly other drugs (eg, hydroxychloroquine, cyclosporine). NSAIDs and H₂ blockers (eg, cimetidine) also have been used to treat EF.

Monitoring with CBCs is advised because of the occasional hematologic complications.

**Mixed Connective Tissue Disease**

Mixed connective tissue disease (MCTD) is an uncommon, specifically defined, overlap syndrome characterized by clinical features of SLE, systemic sclerosis, and polymyositis with very high titers of circulating antinuclear antibody to a ribonucleoprotein antigen. Hand swelling, Raynaud’s syndrome, polyarthritis, inflammatory myopathy, esophageal hypomotility, and pulmonary dysfunction are common. Diagnosis is by the combination of clinical features, antibodies to ribonucleoprotein, and absence of antibodies specific for other autoimmune diseases. Treatment varies with disease severity and organ involvement but usually includes corticosteroids and sometimes additional immunosuppressants.

MCTD occurs worldwide and in all races, with a peak incidence in the teens and 20s. About 80% of people who have this disease are women. The cause is unknown. In some patients, the disorder evolves into classic systemic sclerosis or SLE.

**Symptoms and Signs**

Raynaud’s syndrome may precede other manifestations by years. Frequently, the first manifestations resemble early SLE, systemic sclerosis, polymyositis, dermatomyositis, or even RA. Whatever the initial manifestation, limited disease tends to progress and become widespread, and the clinical pattern changes over time.

The most frequent finding is swelling of the hands that eventually causes a sausage-like appearance of the fingers. Skin findings include lupus or dermatomyositis-like rashes. Diffuse systemic sclerosis-like skin changes and ischemic necrosis or ulceration of the fingertips may occasionally develop.

Almost all patients have polyarthritis, and 75% have frank arthritis. Often the arthritis is nondeforming, but erosive changes and deformities similar to those in RA (eg, boutonniere and swan-neck deformities) may be present. Proximal muscle weakness with or without tenderness is common.

Renal disease occurs in about 10% and is often mild but occasionally causes morbidity or mortality. Sometimes pulmonary involvement is the most serious complication. Heart failure can occur. Sjögren’s syndrome may develop. A trigeminal sensory neuropathy develops more frequently in MCTD than in other systemic autoimmune diseases. It may be the presenting feature and is considered the most frequent CNS manifestation.

**Diagnosis**

• Testing for antinuclear antibodies (ANA), extractable nuclear antigen (ENA), and ribonucleoprotein (RNP)

• Organ involvement determined as clinically indicated

MCTD should be suspected when additional overlapping features are present in patients appearing to have SLE, systemic sclerosis, polymyositis, or RA.

Tests for ANA and antibody to ENA and RNP antigen are done first. If results of these tests are compatible with MCTD (eg, RNP antibodies very high, positive ANA), tests for rheumatoid factors, anti Jo-1 (anti-histidyl t-RNA synthetase), antibodies to the ribonucleoside-resistant Smith (Sm) component of ENA,
and double-stranded DNA are done to exclude other possible diagnoses.

Further evaluation depends on symptoms and signs; manifestations of myositis, renal involvement, or pulmonary involvement prompt tests of those organs (eg, CK, MRI, electromyogram, or muscle biopsy for diagnosis of myositis).

Almost all patients have high titers (often > 1:1000) of fluorescent ANA that produce a speckled pattern. Antibodies to ENA are usually present at very high titers (> 1:100,000). Antibody to RNP is present, whereas antibody to the ribonuclease-resistant Sm component of ENA is absent.

Rheumatoid factors are frequently positive, and titers are often high. The ESR is frequently elevated.

**Prognosis**

The overall 10-yr survival rate is 80%, but prognosis depends largely on which manifestations predominate. Patients with features of systemic sclerosis and polymyositis have a worse prognosis. Patients are at increased risk of atherosclerosis. Causes of death include pulmonary hypertension, renal failure, MI, colonic perforation, disseminated infection, and cerebral hemorrhage. Some patients have sustained remissions for many years without treatment.

**Treatment**

- NSAIDs or antimalarials for mild disease
- Corticosteroids for moderate to severe disease
- Sometimes other immunosuppressants

General management and initial drug therapy are tailored to the specific clinical problem and are similar to those of SLE. Most patients with moderate or severe disease respond to corticosteroids, particularly if treated early. Mild disease is often controlled by NSAIDs, antimalarials, or sometimes low-dose corticosteroids. Severe major organ involvement usually requires higher doses of corticosteroids (eg, prednisone 1 mg/kg po once/day) and additional immunosuppressants. If patients develop features of myositis or systemic sclerosis, treatment is as for those diseases.

All patients should be closely monitored for atherosclerosis. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

**Polymyositis and Dermatomyositis**

Polymyositis and dermatomyositis are uncommon systemic rheumatic disorders characterized by inflammatory and degenerative changes in the muscles (polymyositis) or in the skin and muscles (dermatomyositis). The most specific skin signs are Gottron's papules over the knuckles and a periorbital heliotropic rash. Manifestations include symmetric weakness, some tenderness, and later atrophy, principally of the proximal limb girdle muscles. Complications can include visceral involvement and cancer. Diagnosis is by clinical findings and abnormalities on muscle tests, which may include muscle enzymes, MRI, electromyography, and muscle biopsy. Treatment is with corticosteroids, sometimes combined with immunosuppressants or IV immune globulin.

The female:male ratio is 2:1. These disorders may appear at any age but occur most commonly from age 40 to 60 or, in children, from age 5 to 15.

**Etiology**

The cause seems to be an autoimmune reaction to muscle tissue in genetically susceptible people. Familial clustering occurs, and HLA subtypes DR3, DR52, DR6 seem to be the genetic predisposition. Possible inciting events include viral myositis and underlying cancer. Picornavirus-like structures have
been found in muscle cells, but their significance is not known, and viruses can trigger similar disorders in animals. The association of cancer with dermatomyositis (much less so with polymyositis) suggests that a tumor may incite myositis as the result of an autoimmune reaction against a common antigen in muscle and tumor.

Pathophysiology

Pathologic changes in both disorders include cellular damage and atrophy, with variable degrees of inflammation. Muscles in the hands, feet, and face are affected less than other skeletal muscles. Involvement of visceral muscles in the pharynx and upper esophagus and occasionally the heart, stomach, or intestines can impair the functions of those organs. High blood levels of myoglobin from rhabdomyolysis can damage the kidneys. Inflammation may occur in joints and lungs, especially in patients with antisynthetase antibodies.

Dermatomyositis is characterized by immune complex deposition in the vessels and is considered a complement-mediated vasculopathy. In contrast, the main pathophysiologic abnormality in polymyositis is direct T cell-mediated muscle injury.

Classification

Myositis has been divided into several subtypes:

- Primary idiopathic polymyositis can occur at any age and does not involve the skin.
- Primary idiopathic dermatomyositis is similar to primary idiopathic polymyositis but also involves the skin.
- Polymyositis or dermatomyositis associated with cancer can occur at any age but is most common among older adults; the cancer can develop up to 2 yr before or after the myositis.
- Childhood dermatomyositis can be associated with systemic vasculitis.
- Polymyositis or dermatomyositis can occur with an associated disorder such as progressive systemic sclerosis, mixed connective tissue disease, RA, SLE, or sarcoidosis.

Inclusion body myositis is a separate disorder that has clinical manifestations similar to chronic idiopathic polymyositis; however, it develops at an older age, frequently involves distal muscles (eg, hand and feet muscles), has a longer duration, responds poorly to therapy, and has a different histologic appearance.

Symptoms and Signs

Onset of polymyositis may be acute (particularly in children) or insidious (particularly in adults). Polyarthralgias, Raynaud’s syndrome, dysphagia, pulmonary symptoms, and constitutional complaints (notably fever, fatigue, and weight loss) may also occur.

Muscle weakness may progress over weeks to months. However, it takes destruction of 50% of muscle fibers to cause symptomatic weakness (ie, muscle weakness indicates advanced myositis). Patients may have difficulty raising their arms above their shoulders, climbing steps, or rising from a sitting position. Patients may become wheelchair-bound or bedridden because of weakness of pelvic and shoulder girdle muscles. The flexors of the neck may be severely affected, causing an inability to raise the head from the pillow. Involvement of pharyngeal and upper esophageal muscles may impair swallowing and predispose to aspiration. Muscles of the hands, feet, and face escape involvement. Limb contractures may eventually develop.

Joint manifestations include polyarthralgia or polyarthritis, often with swelling, effusions, and other characteristics of nondeforming arthritis, which occur in about 30% of patients. However, joint manifestations tend to be mild. They occur more often in a subset with Jo-1 or other antisynthetase antibodies.
Visceral involvement (except that of the pharynx and upper esophagus) is less common in polymyositis than in some other rheumatic disorders (eg, SLE, systemic sclerosis). Occasionally, and especially in patients with antisynthetase antibodies, interstitial pneumonitis (manifested by dyspnea and cough) is the most prominent manifestation. Cardiac arrhythmias (including conduction disturbances and abnormal systolic time intervals) can occur but are often asymptomatic. GI symptoms, more common among children with associated vasculitis, may include hematemesis, melena, and ischemic bowel perforation.

Skin changes, which occur in dermatomyositis, tend to be dusky and erythematous. Periorbital edema with a purplish appearance (heliotrope rash) is specific for dermatomyositis. The rash may be slightly elevated and smooth or scaly; it may appear on the forehead, V of the neck and shoulders, chest and back, forearms and lower legs, elbows and knees, medial malleoli, and radiodorsal aspects of the proximal interphalangeal and metacarpophalangeal joints (Gottron's papules—also a relatively specific finding). The base and sides of the fingernails may be hyperemic or thickened. Desquamating dermatitis with splitting of the skin may evolve over the radial aspects of the fingers. The primary skin lesions frequently fade completely but may be followed by secondary changes (eg, brownish pigmentation, atrophy, scarring, vitiligo). Subcutaneous calcification may occur, particularly in children.

Diagnosis

- Clinical criteria

- Muscle biopsy (definitive)

Polymyositis should be suspected in patients with proximal muscle weakness with or without muscle tenderness. Dermatomyositis should be suspected in patients with a heliotropic rash or Gottron's papules, even without polymyositis, and in patients with symptoms of polymyositis and any skin findings compatible with dermatomyositis. Polymyositis and dermatomyositis share certain clinical findings with systemic sclerosis or, less frequently, with SLE or vasculitis. Establishing the diagnosis requires as many as possible of the following 5 criteria:

- Proximal muscle weakness
- Characteristic rash
- Elevated serum muscle enzymes (CK, or if this is not elevated, aminotransferases or aldolase)
- Characteristic electromyographic or MRI abnormalities
- Muscle biopsy changes (the definitive test)

Muscle biopsy excludes some similar conditions such as inclusion body myositis and postviral rhabdomyolysis. Biopsy findings can be variable, but chronic inflammation and muscle degeneration and regeneration are typical. A definite diagnosis made by muscle biopsy is recommended before treatment of polymyositis to exclude other muscle disorders. To increase the sensitivity of the biopsy results, the biopsy sample should be obtained from a muscle that has one or more of the following characteristics:

- Weakness on clinical examination
- Inflammation identified on MRI
- Contralateral pair of a muscle shown to be abnormal on electromyography

Laboratory studies can increase or decrease suspicion for the disorder, assess its severity, identify overlaps, and help detect complications. Autoantibodies should be tested. Antinuclear antibodies are positive in up to 80% of patients. Detailed testing of the antinuclear antibodies (ANA), when present, is important in identifying other overlap syndromes, most often those with another autoimmune disorder. About 30% of patients have myositis-specific autoantibodies: antibodies to aminoacyl-tRNA synthetases (anti-synthetase antibodies), including anti-Jo-1; antibodies to signal recognition particle (SRP—anti-SRP.
antibodies); and antibodies to Mi-2, a nuclear helicase. The relationship between these autoantibodies and disease pathogenesis remains unclear, although antibody to Jo-1 is a significant marker for fibrosing alveolitis, pulmonary fibrosis, arthritis, and Raynaud's syndrome.

Periodic measurement of CK is helpful in monitoring treatment. However, in patients with widespread muscle atrophy, levels are occasionally normal despite chronic, active myositis. Muscle biopsy, MRI, or high CK levels can often differentiate a relapse of polymyositis from corticosteroid-induced myopathy. Aldolase is a less specific marker for muscle injury than CK.

**Cancer screening** is recommended by some authorities for any adult who has dermatomyositis or for patients ≥ 60 yr who have polymyositis because these patients often have unsuspected cancers. Screening should include a physical examination that includes breast, pelvis, and rectum (with occult blood testing); CBC; biochemical profile; mammogram; carcinoembryonic antigen; urinalysis; chest x-ray; and any other tests appropriate based on patient's age. Additional investigation should be based on history and physical examination findings. Some authorities recommend CT of the chest, abdomen, and pelvis. Younger patients without symptoms of cancer need not undergo screening.

**Prognosis**

Long remissions (even apparent recovery) occur in up to 50% of treated patients within 5 yr, more often in children. Relapse, however, may still occur at any time. Overall 5-yr survival rate is 75% and is higher in children. Death in adults is preceded by severe and progressive muscle weakness, dysphagia, undernutrition, aspiration pneumonia, or respiratory failure with superimposed pulmonary infection. Polymyositis tends to be more severe and resistant to treatment in patients with cardiac or pulmonary involvement. Death in children may be a result of bowel vasculitis. Cancer, if present, generally determines the overall prognosis.

**Treatment**

- **Corticosteroids**

- Sometimes immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, IV immune globulin)

Physical activities should be modestly curtailed until the inflammation subsides. Corticosteroids are the drugs of choice initially. For acute disease, adults receive prednisone ≥ 40 to 60 mg po once/day. Serial measurements of CK provide the best early guide of therapeutic effectiveness, falling toward or reaching normal in most patients in 6 to 12 wk, followed by improved muscle strength. Once enzyme levels have returned to normal, prednisone can be gradually reduced. If muscle enzyme levels rise, the dose is increased. Patients who seem to recover can have treatment gradually withdrawn with close monitoring, but most adults require chronic maintenance with prednisone (up to 10 to 15 mg/day). Children require initial doses of prednisone of 30 to 60 mg/m² once/day. In children, it may be possible to stop prednisone after ≥ 1 yr of remission.

Occasionally, patients treated chronically with high-dose corticosteroids become increasingly weak because of a superimposed corticosteroid myopathy.

If a patient does not respond to corticosteroids, depends on a high to moderate dose of corticosteroids, or develops a corticosteroid myopathy or another complication that necessitates stopping or decreasing prednisone, immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, IV immune globulin) should be tried. Some patients have received only methotrexate (generally in higher doses than used for RA) for ≥ 5 yr. IV immune globulins can be effective in some patients refractory to drug treatment, but the prohibitive cost has precluded comparative trials. Some clinicians combine prednisone with an immunosuppressant. Other possible emerging therapies include anti-tumor necrosis factor (TNF) agents and rituximab.

Myositis associated with tumors, metastatic disease, or inclusion body myositis usually is more refractory to corticosteroids. Cancer-associated myositis may remit if the tumor is removed.
People with an autoimmune disorder are at higher risk of atherosclerosis and should be closely monitored. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

**Relapsing Polychondritis**

Relapsing polychondritis is an episodic, inflammatory, and destructive disorder involving primarily cartilage of the ear and nose but also potentially affecting the eyes, tracheobronchial tree, heart valves, kidneys, joints, skin, and blood vessels. Diagnosis is by a combination of clinical, laboratory, imaging, and sometimes biopsy findings. Treatment usually requires prednisone and other immunosuppressants.

Relapsing polychondritis affects men and women equally; onset typically is in middle age. An association with RA, systemic vasculitis, SLE, and other connective tissue disorders suggests an autoimmune etiology.

**Symptoms and Signs**

Acute pain, erythema, and swelling most commonly affect the pinna cartilage. Nasal cartilage inflammation is the next most common, followed by arthritis that varies from arthralgias to symmetric or asymmetric nondeforming arthritis involving large and small joints, with a predilection for the costochondral joints. The next most common manifestations, in decreasing order of frequency, are inflammation of the eye (eg, conjunctivitis, scleritis, iritis, keratitis, chorioretinitis); cartilaginous tissue of the larynx, trachea, or bronchi (causing hoarseness, cough, and tenderness over the laryngeal cartilage); internal ear; cardiovascular system (eg, aortic regurgitation, mitral regurgitation, pericarditis, myocarditis, aortic aneurysms, aortitis); kidney; and skin. Bouts of acute inflammation heal over weeks to months, with recurrences over several years. Various rashes can develop.

Advanced disease can lead to destruction of supporting cartilage, causing floppy ears; saddle nose; pectus excavatum; and visual, auditory, and vestibular abnormalities. Tracheal narrowing can lead to dyspnea, pneumonia, or even tracheal collapse. Coexisting systemic vasculitis (leukocytoclastic vasculitis or polyarteritis nodosa), myelodysplastic syndrome, or cancer is possible.

**Diagnosis**

- Clinical criteria
- Sometimes biopsy

Diagnosis is established if the patient develops at least 3 of the following:

- Bilateral chondritis of the external ears
- Inflammatory polyarthritis
- Nasal chondritis
- Ocular inflammation
- Respiratory tract chondritis
- Auditory or vestibular dysfunction

Biopsy of involved cartilage, most often the pinna, is helpful if clinical diagnosis is not clear-cut.

Laboratory tests are done. They are not specific but may help to exclude other disorders. Synovial fluid analysis reveals mild inflammatory changes that are nonspecific but help to rule out an infectious process. Blood tests may show normocytic-normochromic anemia, leukocytosis, elevated ESR or γ-globulin levels, and occasionally positive rheumatoid factor, antinuclear antibodies (ANA), or, in up to 25%, antineutrophil...
cytoplasmic antibodies (ANCA). Abnormal renal function may indicate an associated vasculitis. A positive c-ANCA test (ANCA that are reactive mainly to proteinase-3) suggests Wegener's granulomatosis, which can cause similar findings (see p. 329).

The upper and lower airways should be evaluated, including complete spirometric testing and chest CT, when the diagnosis is made.

Prognosis

Mortality after 5 yr is 30%, from collapse of laryngeal and tracheal structures or from cardiovascular complications such as large-vessel aneurysm, cardiac valvular insufficiency, or systemic vasculitis.

Treatment

• NSAIDs or dapsone for mild ear disease

• Corticosteroids

• Sometimes methotrexate or other immunosuppressants (eg, cyclosporine, cyclophosphamide, azathioprine)

Mild recurrent ear disease may respond to NSAIDs in anti-inflammatory doses, or dapsone (50 to 100 mg po once/day). However, most patients are treated with prednisone 30 to 60 mg po once/day, with tapering of the dose as soon as there is a clinical response. Some patients require chronic use. In such patients, methotrexate 7.5 to 20 mg po once/wk can reduce the requirement for corticosteroids. Very severe cases may require other immunosuppressants, such as cyclosporine, cyclophosphamide, or azathioprine (see p. 337). None of these therapies has been tested in controlled trials or has been shown to decrease mortality. If tracheal narrowing causes stridor, a tracheostomy or stent may be needed. More extensive tracheobronchial collapse may require tracheal reconstruction. Eye disease may sometimes be recalcitrant to treatment, especially when involving the sclera, and carries a poor prognosis.

All patients should be closely monitored for atherosclerosis given the risk of premature atherosclerosis in systemic vasculitides. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Sjogren's Syndrome

Sjogren's syndrome (SS) is a relatively common chronic, autoimmune, systemic, inflammatory disorder of unknown cause. It is characterized by dryness of the mouth, eyes, and other mucous membranes due to lymphocytic infiltration of the exocrine gland and secondary gland dysfunction. Sjogren's syndrome can affect various exocrine glands or other organs. Diagnosis is by specific criteria relating to eye, mouth, and salivary gland involvement, autoantibodies, and (occasionally) histopathology. Treatment is symptomatic.

SS occurs most frequently among middle-aged women. SS is classified as primary when there is no other associated disease. In about 30% of patients with autoimmune disorders such as RA, SLE, systemic sclerosis, mixed connective tissue disease, Hashimoto's thyroiditis, primary biliary cirrhosis, or chronic autoimmune hepatitis, SS develops and, in such cases, is classified as secondary. Genetic associations have been found (eg, HLADR3 antigens in whites with primary SS).

Pathophysiology

Salivary, lacrimal, and other exocrine glands become infiltrated with CD4+ T cells and with some B cells. The T cells produce inflammatory cytokines (eg, IL-2, interferon-γ). Salivary duct cells also produce cytokines, eventually damaging the secretory ducts. Atrophy of the secretory epithelium of the lacrimal glands causes desiccation of the cornea and conjunctiva (keratoconjunctivitis sicca—see p. 592). Lymphocytic infiltration and intraductal cellular proliferation in the parotid gland cause luminal narrowing and in some cases formation of compact cellular structures termed myoepithelial islands; atrophy of the
gland can result. Dryness and GI mucosal or submucosal atrophy and diffuse infiltration by plasma cells and lymphocytes may cause symptoms (eg, dysphagia).

**Symptoms and Signs**

**Glandular manifestations:** SS often affects the eyes or mouth initially and sometimes exclusively. Dry eyes can cause irritation and photosensitivity. In advanced cases, the cornea is severely damaged, epithelial strands hang from the corneal surface (keratitis filiformis), and vision can be impaired. Diminished saliva (xerostomia) results in difficulty chewing and swallowing, secondary Candida infection, tooth decay, and calculi in the salivary ducts. Taste and smell may be diminished. Dryness may also develop in the skin and in mucous membranes of the nose, throat, larynx, bronchi, vulva, and vagina. Dryness of the respiratory tract may cause cough. Alopecia may occur. Parotid glands enlarge in 33% of patients and are usually firm, smooth, and mildly tender. Chronic salivary gland enlargement is rarely painful unless there is obstruction or infection.

**Extraglandular manifestations:** Joint disease in SS is typically nonerosive and nondeforming. Arthralgias occur in about 50% of patients. Arthritis occurs in about 33% of patients and is similar in distribution to RA but is not erosive.

Other common extraglandular manifestations include generalized lymphadenopathy, Raynaud's syndrome, parenchymal lung involvement (which is common but infrequently serious), and vasculitis. Vasculitis can occasionally affect the peripheral nerves (causing peripheral polyneuropathy or mononeuritis multiplex) or CNS or cause rashes (including purpura) and glomerulonephritis. Kidney involvement can cause renal tubular acidosis, impaired concentrating ability, kidney stones, or interstitial nephritis. Pseudolymphoma, malignant lymphoma, or Waldenstrom's macroglobulinemia can develop; patients develop non-Hodgkin lymphoma at 40 times the normal rate. Chronic hepatobiliary disease and pancreatitis (exocrine pancreatic tissue is similar to that of salivary glands) may also occur.

**Diagnosis**

- Eye symptoms, oral symptoms, and eye and salivary gland testing
- Autoantibodies
- Sometimes salivary gland biopsy

SS should be suspected in patients with gritty or dry eyes or dry mouth, enlarged salivary glands, peripheral neuropathy, purpura, or unexplained renal tubular acidosis. Such patients should receive diagnostic tests that can include evaluation of the eyes and salivary glands and serologic tests. Different criteria have been proposed for classification of SS. The latest modifications to the American-European classification criteria for SS were proposed in 2002. These criteria were not developed for use in routine clinical practice, and not every patient who receives a clinical diagnosis of SS fulfills the proposed criteria (usually > 3 of 6 manifestations). The 6 manifestations are eye symptoms, oral symptoms, positive eye tests, salivary gland involvement, autoantibodies, and histopathology.

**Eye symptoms** are ≥ 3 mo of either dry eyes or use of tear substitutes ≥ 3 times/day; slit-lamp examination may also confirm dry eyes.

**Oral symptoms** are > 3 mo of daily dry mouth sensation, daily use of liquids to aid in swallowing, or swollen salivary glands.

**Eye signs** include evaluation by Schirmer's test, which measures the quantity of tears secreted in 5 min after irritation from a filter paper strip placed under each lower eyelid. A young person normally moistens 15 mm of each paper strip. Most people with SS moisten < 5 mm, although about 15% of test results are false-positive and 15% are false-negative. Ocular staining with an eyedrop of rose bengal or lissamine green solution is highly specific. Slit-lamp examination showing a fluorescein tear breakup in < 10 sec is also suggestive.
Salivary gland involvement can be confirmed by abnormally low saliva production (≤ 1.5 mL/15 min) as measured by salivary flow, sialography, or salivary scintiscanning, although these tests are used less often.

Autoantibodies (serologic criteria) have limited sensitivity and specificity. They include antibodies to Ro (SS-A autoantibodies—see Systemic Lupus Erythematosus on p. 305) or to nuclear antigens (termed La or SS-B autoantibodies), antinuclear antibodies, or an elevated level of antibodies against γ-globulin. Rheumatoid factor is present in > 70% of patients. ESR is elevated in 70%, 33% have anemia, and up to 25% have leukopenia.

Histopathology is assessed by biopsy of minor salivary glands in the buccal mucosa. Salivary gland biopsy is usually reserved for patients in whom the diagnosis cannot be established by autoantibody testing or when a major organ is involved. Histopathologic involvement is confirmed if labial minor salivary glands show multiple large foci of lymphocytes with atrophy of acinar tissue.

Most common causes of dry eyes and dry mouth (sicca symptoms) are aging and drugs, but when parotid enlargement occurs in addition to sicca symptoms, diseases such as hepatitis C, HIV, bulimia, and sarcoidosis should be differentiated from SS.

Prognosis

SS is chronic, and death may occasionally result from pulmonary infection and, rarely, from renal failure or lymphoma. Associated systemic autoimmune disorders may dictate prognosis.

Treatment

• Symptomatic treatment for sicca symptoms

• Avoidance of aggravating factors

• Occasionally oral corticosteroids or cyclophosphamide

SS should be initially managed by topical therapy of dry eyes and dry mouth. Other systemic manifestations of SS should be treated depending on the severity and the involved organ. Recognition of therapies for other conditions that can exacerbate dryness complaints is crucial. Hydroxychloroquine 200 to 400 mg po once/day is usually given to halt the progression of the disease and for the treatment of arthralgias.

Dry eyes should be treated with lubricating eye preparations (initially drops such as hypromellose or methylcellulose and an OTC ointment at bedtime). Other treatments include drainage (punctal) duct closure and topical cyclosporine. Skin and vaginal dryness can be treated with lubricants.

Mouth dryness may be avoided by sipping fluids throughout the day, chewing sugarless gum, and using a saliva substitute containing carboxymethylcellulose as a mouthwash. Drugs that decrease salivary secretion (eg, antihistamines, antidepressants, other anticholinergics) should be avoided. Fastidious oral hygiene and regular dental visits are essential. Stones must be promptly removed, preserving viable salivary tissue. The pain of suddenly enlarged salivary glands is generally best treated with warm compresses and analgesics. Pilocarpine 5 mg po tid to qid or cevimeline HCl 30 mg po tid can stimulate salivary production but should be avoided in patients with bronchospasm and closed-angle glaucoma.

Aggressive systemic treatment is occasionally indicated. It is usually reserved for patients with associated diseases (eg, severe vasculitis or visceral involvement); corticosteroids (eg, prednisone 1 mg/kg po once/day) or cyclophosphamide 5 mg/kg po once/day may be used.

Systemic Lupus Erythematosus

(Disseminated Lupus Erythematosus)
Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory disorder of autoimmune etiology, occurring predominantly in young women. Common manifestations may include arthralgias and arthritis; malar and other skin rashes; pleuritis or pericarditis; renal or CNS involvement; and hematologic cytopenias. Diagnosis requires clinical and serologic criteria. Treatment of severe ongoing active disease requires corticosteroids, often hydroxychloroquine, and sometimes immunosuppressants.

Of all cases, 70 to 90% occur in women (usually of child-bearing age). SLE is more common among blacks and Asians than whites. It can affect patients of any age, including neonates. Increased awareness of mild forms has resulted in a worldwide rise in reported cases. In some countries, the prevalence of SLE rivals that of RA. SLE may be precipitated by currently unknown environmental triggers that cause autoimmune reactions in genetically predisposed people. Some drugs (eg, hydralazine, procainamide, isoniazid) cause a reversible lupus-like syndrome.

### Symptoms and Signs

Clinical findings vary greatly. SLE may develop abruptly with fever or insidiously over months or years with episodes of arthralgias and malaise. Vascular headaches, epilepsy, or psychoses may be initial findings. Manifestations referable to any organ system may appear. Periodic exacerbations (flares) may occur.

**Joint manifestations:** Joint symptoms, ranging from intermittent arthralgias to acute polyarthritis, occur in about 90% of patients and may precede other manifestations by years. Most lupus polyarthritis is nondestructive and nondeforming. However, in long-standing disease, deformities without bone erosions may develop (eg, the metacarpophalangeal and interphalangeal joints may rarely develop ulnar drift or swan-neck deformities without bony or cartilaginous erosions [Jaccoud's arthritis]).

**Skin and mucous membrane manifestations** (see also p. 309): Skin lesions include malar butterfly erythema (flat or raised) that generally spares the nasolabial folds. The absence of papules and pustules helps distinguish SLE from rosacea. A variety of other erythematous, firm, maculopapular lesions can occur elsewhere, including exposed areas of the face and neck, upper chest, and elbows. Skin blistering and ulceration are rare, although recurrent ulcers on mucous membranes (particularly the central portion of the hard palate near the junction of the hard and soft palate, the buccal and gum mucosa, and the anterior nasal septum) are common. Generalized or focal alopecia is common during active phases of SLE. Panniculitis can cause subcutaneous nodular lesions. Vasculitic skin lesions may include mottled erythema on the palms and fingers, periungual erythema, nail-fold infarcts, urticaria, and palpable purpura. Petechiae may develop secondary to thrombocytopenia. Photosensitivity occurs in most patients.

**Cardiopulmonary manifestations:** Cardiopulmonary symptoms commonly include recurrent pleurisy, with or without pleural effusion. Pneumonitis is rare, although minor impairments in pulmonary function are common. Severe pulmonary hemorrhage occasionally occurs. Prognosis has traditionally been poor but seems to be improving, possibly because of better early, aggressive, critical care. Other complications include pulmonary emboli, pulmonary hypertension, and shrinking lung syndrome. Cardiac complications include pericarditis (most commonly), pericardial effusion, and myocarditis. Serious, rare complications are coronary artery vasculitis, valvular involvement, and Libman-Sacks endocarditis. Accelerated atherosclerosis is an increasing cause of morbidity and mortality. Congenital heart block can develop in neonates.

**Adenopathy and splenic manifestations:** Generalized adenopathy is common, particularly among children, young adults, and blacks. Splenomegaly occurs in 10% of patients. The spleen may develop periarterial fibrosis.

**Neurologic manifestations:** Neurologic symptoms can result from involvement of any part of the central or peripheral nervous system or meninges. Mild cognitive impairment is common. There may also be headaches, personality changes, ischemic stroke, subarachnoid hemorrhage, seizures, psychoses, organic brain syndrome, aseptic meningitis, peripheral neuropathies, transverse myelitis, or cerebellar dysfunction.
Renal manifestations: Renal involvement can develop at any time and may be the only manifestation of SLE. It may be benign and asymptomatic or progressive and fatal. Renal lesions can range in severity from a focal, usually benign, glomerulitis to a diffuse, potentially fatal, membranoproliferative glomerulonephritis. Common manifestations include proteinuria (most often), an abnormal urinary sediment manifested by RBC casts and leukocytes, hypertension, and edema.

Obstetric manifestations: Obstetric manifestations include early and late fetal loss. In patients with antiphospholipid antibodies, the risk of recurrent miscarriages is increased. Pregnancy can be successful (see p. 2636), particularly after 6 to 12 mo of remission, but SLE flares are common during pregnancy. Pregnancy should be timed for when disease is in remission. During pregnancy, the patient should be monitored closely for any disease flare or thrombotic events by a multidisciplinary team that includes a rheumatologist, an obstetrician who specializes in high-risk pregnancies, and a hematologist.

Hematologic manifestations: Hematologic manifestations include anemia (often autoimmune hemolytic), leukopenia (usually lymphopenia, with < 1500 cells/μL), and thrombocytopenia (sometimes life-threatening autoimmune thrombocytopenia). Recurrent arterial or venous thrombosis, thrombocytopenia, and a high probability of obstetric complications occur in patients with antiphospholipid antibodies. Thromboses probably account for many of the complications of SLE, including obstetric complications.

GI manifestations: GI manifestations can result from bowel vasculitis or impaired bowel motility. In addition, pancreatitis can result from SLE or from its treatment with corticosteroids or azathioprine. Manifestations may include abdominal pain from serositis, nausea, vomiting, manifestations of bowel perforation, and pseudo-obstruction. SLE rarely causes parenchymal liver disease.

Diagnosis

• Clinical criteria

• Cytopenias

• Autoantibodies

SLE should be suspected in patients, particularly young women, with any of the symptoms and signs. However, early-stage SLE can mimic other connective (or nonconnective) tissue disorders, including RA if arthritic symptoms predominate. Mixed connective tissue disease can mimic SLE but also may involve features of systemic sclerosis, rheumatoid-like polyarthritis, and polymyositis or dermatomyositis. Infections (eg, bacterial endocarditis, histoplasmosis) can mimic SLE and may develop as a result of treatment-caused immunosuppression. Disorders such as sarcoidosis and paraneoplastic syndromes can also mimic SLE.

Laboratory testing differentiates SLE from other connective tissue disorders. Routine testing should include the following:

• Antinuclear antibodies (ANA)

• CBC

• Urinalysis

• Chemistry profile including renal and liver enzymes

The diagnosis is especially likely if ≥ 4 of the criteria in Table 33-1 are present at any time but is still possible if < 4 criteria are present. If the diagnosis is suspected but not established, additional testing for autoantibodies can be useful. Establishing the diagnosis may require repeated evaluations over months or years.
Fluorescent ANA: The fluorescent test for ANA is the best screen for SLE; positive ANA tests (usually in high titer: > 1:80) occur in > 98%. However, positive ANA tests can also occur in RA, other connective tissue disorders, cancers, and even in the general population. The false-positive rate varies from about 3% for ANA titers of 1:320 to about 30% for ANA titers of 1:40 among healthy controls. Drugs such as hydralazine, procainamide, and tumor necrosis factor (TNF)-α antagonists can produce positive ANA results as well as a lupus-like syndrome; the ANA eventually becomes negative if the drug is stopped. Positive ANA should prompt more specific testing such as anti-double-stranded DNA antibodies; high titers are highly specific for SLE but occur in only 25 to 30% of people with SLE.

Other ANA and anticytoplasmic antibodies: The ANA test is very sensitive, but it is not specific for SLE; thus, evidence of other autoantibodies is needed to establish the diagnosis. They include Ro [SSA], La [SSB], Smith [Sm], ribonucleoprotein [RNP], and double-stranded DNA. Ro is predominantly cytoplasmic; anti-Ro antibodies are occasionally present in ANA-negative SLE patients presenting with chronic cutaneous lupus. Anti-Ro is the causal antibody for neonatal lupus and congenital heart block. Anti-Sm is highly specific for SLE but, like anti-double-stranded DNA, is not sensitive. Anti-RNP occurs in patients with SLE, mixed connective tissue disease, and occasionally other systemic autoimmune disorders and systemic sclerosis.

[Table 33-1. Criteria for the Classification of SLE*]

Other blood tests: Leukopenia (usually lymphopenia) is common. Hemolytic anemia may occur. Thrombocytopenia in SLE may be difficult or impossible to differentiate from idiopathic thrombocytopenic purpura except that patients have other features of SLE. False-positive serologic tests for syphilis occur in 5 to 10% of SLE patients. These test results may be associated with the lupus anticoagulant and a prolonged PTT. Abnormal values in one or more of these assays suggest the presence of antiphospholipid antibodies (eg, anticardiolipin antibodies), which should then be measured directly by enzyme-linked immunosorbent assay (ELISA). Antiphospholipid antibodies are associated with arterial or venous thrombosis, thrombocytopenia, and, during pregnancy, spontaneous abortion or late fetal death but may be present in asymptomatic patients.

Other tests help monitor disease severity and determine the need for treatment. Serum complement levels (C3, C4) are often depressed in active disease and are usually lowest in patients with active nephritis. ESR is elevated frequently during active disease. C-reactive protein levels are not necessarily elevated.

Renal involvement: Screening for renal involvement begins with urinalysis. RBC and WBC casts suggest active nephritis. Urinalysis should be done at regular intervals, even for patients in apparent remission, because kidney disease may be asymptomatic. Renal biopsy is usually not necessary for diagnosis of SLE or to confirm renal involvement but is helpful in evaluating the status of renal disease (ie, active inflammation vs postinflammatory scarring) and guide therapy. Patients with chronic renal insufficiency and mostly sclerotic glomeruli are not likely to benefit from aggressive immunosuppressive therapy.

Prognosis

The course is usually chronic, relapsing, and unpredictable. Remissions may last for years. If the initial acute phase is controlled, even if very severe (eg, with cerebral thrombosis or severe nephritis), the long-term prognosis is usually good. The 10-yr survival in most developed countries is > 95%. Improved prognosis is in part due to earlier diagnosis and more effective therapies. More severe disease requires more toxic therapies, which increase risk of mortality. Examples of such complications include infection from immunosuppression or osteoporosis from long-term corticosteroid use. Increased risk of coronary artery disease can contribute to premature death.

Treatment

- NSAIDs and often antimalarials for mild disease
- Corticosteroids and often immunosuppressants for severe disease
To simplify therapy, SLE should be classified as mild (eg, fever, arthritis, pleurisy, pericarditis, headache, rash) or severe (eg, hemolytic anemia, thrombocytopenic purpura, massive pleural and pericardial involvement, significant renal damage, acute vasculitis of the extremities or GI tract, florid CNS involvement).

**Mild or remittent disease:** Little or no therapy may be needed. Arthralgias are usually controlled with NSAIDs. Antimalarials help, particularly when joint and skin manifestations are prominent. Hydroxychloroquine 200 mg po once/day or bid reduces the frequency of SLE flares. Alternatives include chloroquine 250 mg po once/day and quinacrine 50 to 100 mg po once/day. Hydroxychloroquine can rarely cause retinal toxicity. The eyes should be examined at 12-mo intervals.

**Severe disease:** Corticosteroids are first-line therapy. A combination of prednisone and immunosuppressants is recommended in active, serious CNS lupus, vasculitis especially affecting viscera or nerves, or active lupus nephritis. Prednisone is usually given in doses of 40 to 60 mg po once/day, but the dose may vary according to the manifestation of SLE. Oral azathioprine 1 to 2.5 mg/kg once/day or oral cyclophosphamide 1 to 4 mg/kg once/day can be used as an immunosuppressant. For renal involvement, cyclophosphamide is usually given in intermittent IV pulses instead of daily oral doses; eg, about 500 mg to 1 g/m² IV (together with mesna and fluid loading to protect the bladder) monthly for 6 mo and then once q 3 mo for 18 mo (less frequently if there is renal or hematologic toxicity—see Table 33-2).

In CNS lupus or other critical crises, methylprednisolone 1 g by slow (1-h) IV infusion on 3 successive days is often the initial treatment, followed by IV cyclophosphamide, as mentioned previously. Mycophenolate mofetil is an alternative to cyclophosphamide therapy for patients with active kidney disease who have preserved kidney function. IgG 400 mg/kg IV once/day for 5 consecutive days may be useful for refractory thrombocytopenia. Patients

[Table 33-2. Protocol for Chemotherapy with Cyclophosphamide and IV Mesna]

with end-stage renal disease can undergo kidney transplantation, as an alternative to dialysis, with a successful outcome, especially if their disease has been in remission.

Improvement of severe SLE often takes 4 to 12 wk. Thrombosis or embolism of cerebral, pulmonary, or placental vessels requires short-term treatment with heparin and longer treatment with warfarin, if the diagnosis of antiphospholipid syndrome is confirmed. The target INR is usually 3.

**Suppressive therapy:** For most patients, the risk of flares can be decreased without prolonged high-dose corticosteroids. Chronic disease should be treated with the lowest dose of corticosteroids and other drugs that control inflammation (eg, antimalarials, low-dose immunosuppressants). Treatment should be guided by clinical features primarily, although anti-double-stranded DNA antibody titers or serum complement levels may be followed. Other pertinent blood and urine tests may be used to assess specific organ involvement. Anti-double-stranded DNA antibody titers or serum complement levels may not parallel nonrenal disease flares. If a patient needs long-term high-dose corticosteroids, alternative oral immunosuppressants should be considered. Ca, vitamin D, and bisphosphonate therapy should be considered in patients taking corticosteroids long term.

**Focal complications and coexisting medical conditions:** All patients should be closely monitored for atherosclerosis. Long-term anticoagulation is vital in patients with antiphospholipid antibodies and recurrent thrombosis (see p. 2228).

If a pregnant patient has antiphospholipid antibodies, thrombotic complications can be limited with corticosteroids (prednisone ≤ 30 mg po once/day), low-dose aspirin, or anticoagulation with heparin. Daily heparin given subcutaneously with or without one baby aspirin throughout the 2nd and 3rd trimesters may be the most successful prophylactic measure.

**Variant Forms of Lupus**

**Discoid lupus erythematosus (DLE):** DLE, also sometimes called chronic cutaneous lupus
Erythematous, is a set of skin changes that can occur as part of lupus, with or without systemic involvement. Skin lesions begin as erythematous plaques and progress to atrophic scars. They cluster in light-exposed areas of the skin, such as the face, scalp, and ears. Untreated, lesions extend and develop central atrophy and scarring. There may be widespread scarring alopecia. Mucous membrane involvement may be prominent, especially in the mouth.

Patients presenting with typical discoid lesions should be evaluated for SLE. Antibodies against double-stranded DNA are almost invariably absent in DLE. Although it does not differentiate DLE from SLE, biopsy can rule out other disorders (eg, lymphoma or sarcoidosis). Biopsy should be done from the active margin of a skin lesion.

Early treatment can prevent permanent atrophy. Exposure to sunlight or ultraviolet light should be minimized (eg, using potent sunscreens when outdoors). Topical corticosteroid ointments (particularly for dry skin) or creams (less greasy than ointments) tid to qid (eg, triamcinolone acetonide 0.1 or 0.5%, fluocinolone 0.025 or 0.2%, flurandrenolide 0.05%, betamethasone valerate 0.1%, and, particularly betamethasone dipropionate 0.05%) usually cause involution of small lesions; they should not be used excessively or on the face (where they cause skin atrophy). Resistant lesions can be covered with plastic tape coated with flurandrenolide. Alternatively, intradermal injection with triamcinolone acetonide 0.1% suspension (< 0.1 mL per site) may resolve lesions, but secondary atrophy frequently follows. Antimalarials (eg, hydroxychloroquine 200 mg po once/day or bid) can help, including for facial lesions. In resistant cases, combinations (eg, hydroxychloroquine 200 mg/day plus quinacrine 50 to 100 mg po once/day) may be required for months to years.

Subacute cutaneous lupus erythematosus (SCLE): SCLE is a variant form of SLE in which skin involvement is prominent. Patients with SCLE develop extensive recurring rashes. Annular or papulosquamous lesions may develop on the face, arms, and trunk. Lesions are usually photosensitive and can develop hypopigmentation but rarely scar. Arthritis and fatigue are common in SCLE, but neurologic and renal manifestations are not. Patients may be ANA-positive or ANA-negative. Most have antibodies to Ro (SSA). Infants whose mothers have Ro antibodies may have congenital SCLE or congenital heart block. SCLE should be treated similarly to SLE.

Systemic Sclerosis

(Scleroderma)

Systemic sclerosis (SSc) is a rare chronic disease of unknown cause characterized by diffuse fibrosis, degenerative changes, and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower GI tract, lungs, heart, and kidneys). Common symptoms include Raynaud's syndrome, polyarthritis, dysphagia, heartburn, and swelling and eventually skin tightening and contractures of the fingers. Lung, heart, and kidney involvement accounts for most deaths. Diagnosis is clinical, but laboratory tests help with confirmation. Specific treatment is difficult, and emphasis is often on treatment of complications.

SSc is about 4 times more common among women than men. It is most common among people aged 20 to 50 and is rare in children. SSc can develop as part of mixed connective tissue disease.

Etiology

Immunologic mechanisms and heredity (certain HLA subtypes) play a role in etiology. SSc-like syndromes can result from exposure to vinyl chloride, bleomycin, pentazocine, epoxy and aromatic hydrocarbons, contaminated rapeseed oil, or L-tryptophan.

Pathophysiology

Pathophysiology involves vascular damage and activation of fibroblasts; collagen and other extracellular proteins in various tissues are overproduced.

In SSc, the skin develops more compact collagen fibers in the reticular dermis, epidermal thinning, loss of
rete pegs, and atrophy of dermal appendages. T cells may accumulate, and extensive fibrosis in the dermal and subcutaneous layers develops. In the nail folds, capillary loops dilate and some microvascular loops are lost. In the extremities, chronic inflammation and fibrosis of the synovial membrane and surfaces and periarticular soft tissues occur.

Esophageal motility becomes impaired, and the lower esophageal sphincter becomes incompetent; gastroesophageal reflux and secondary strictures can develop. The intestinal muscularis mucosa degenerates, leading to pseudodiverticula in the colon and ileum. Interstitial and peribronchial fibrosis or intimal hyperplasia of small pulmonary arteries can develop; if long-standing, pulmonary hypertension can result. Diffuse myocardial fibrosis or cardiac conduction abnormalities occur. Intimal hyperplasia of interlobular and arcuate arteries can develop within the kidneys, causing renal ischemia and hypertension.

SSc varies in severity and progression, ranging from generalized skin thickening with rapidly progressive and often fatal visceral involvement (SSc with diffuse scleroderma) to isolated skin involvement (often just the fingers and face) and slow progression (often several decades) before visceral disease develops. The latter form is termed limited cutaneous scleroderma or CREST syndrome (calcinosis cutis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasias). In addition, SSc can overlap with other autoimmune rheumatic disorders—eg, sclerodermatomyositis (tight skin and muscle weakness indistinguishable from polymyositis) and mixed connective tissue disease.

**Symptoms and Signs**

The most common initial symptoms and signs are Raynaud's syndrome and insidious swelling of the distal extremities with gradual thickening of the skin of the fingers. Polyarthralgia is also prominent. GI disturbances (eg, heartburn, dysphagia) or respiratory complaints (eg, dyspnea) are occasionally the first manifestations.

**Skin and nail manifestations:** Swelling of the skin is usually symmetric and progresses to induration. It may be confined to the fingers (sclerodactyly) and hands, or it may affect most or all of the body. The skin eventually becomes taut, shiny, and hypopigmented or hyperpigmented; the face becomes masklike; and telangiectases may appear on the fingers, chest, face, lips, and tongue. Subcutaneous calcifications may develop, usually on the fingertips (pulps) and over bony eminences. Trophic ulcers are common, especially on the fingertips, overlying the finger joints, or over calcinotic nodules. Abnormal capillary and microvascular loops in the nails can be seen with an ophthalmoscope or dissecting microscope.

**Joint manifestations:** Polyarthralgias or mild arthritis can be prominent. Flexion contractures may develop in the fingers, wrists, and elbows. Friction rubs may develop over the joints, tendon sheaths, and large bursae.

**GI manifestations:** Esophageal dysfunction is the most frequent visceral disturbance and occurs in most patients. Dysphagia (usually retrosternal) usually develops first. Acid reflux can cause heartburn and stricture. Barrett's esophagus occurs in one third of patients and predisposes to complications (eg, stricture, adenocarcinoma). Hypomotility of the small bowel causes anaerobic bacterial overgrowth that can lead to malabsorption. Air may penetrate the damaged bowel wall and be visible on x-rays (pneumatosis intestinalis). Leakage of bowel contents into the peritoneal cavity can cause peritonitis. Distinctive wide-mouthed diverticula can develop in the colon. Biliary cirrhosis may develop in patients with CREST syndrome.

**Cardiopulmonary manifestations:** Lung involvement generally progresses indolently, with substantial individual variability, but is a common cause of death. Lung fibrosis can impair gas exchange, leading to exertional dyspnea and restrictive disease with eventual respiratory failure. Acute alveolitis (potentially responsive to therapy) can develop. Esophageal dysfunction can lead to aspiration pneumonia. Pulmonary hypertension may develop, as can heart failure, both of which are poor prognostic findings. Pericarditis with effusion or pleurisy can occur. Cardiac arrhythmias are common.

**Renal manifestations:** Severe, often sudden renal disease (renal crisis) may occur, most commonly in the first 4 to 5 yr and in patients with diffuse scleroderma. It is usually heralded by sudden, severe
hypertension.

Diagnosis

• Clinical evaluation

• Usually antinuclear antibodies (ANA), Scl-70 (topoisomerase I), and anticentromere antibodies

SSc should be considered in patients with Raynaud's syndrome, typical musculoskeletal or skin manifestations, or unexplained dysphagia, malabsorption, pulmonary fibrosis, pulmonary hypertension, cardiomyopathies, or conduction disturbances. Diagnosis can be obvious in patients with combinations of classic manifestations, such as Raynaud's syndrome, dysphagia, and tight skin. However, in some patients, the diagnosis cannot be made clinically, and confirmatory laboratory tests can increase the probability of disease but do not rule it out.

Serum ANA and Scl-70 antibody should be obtained. ANA are present in ≥ 90%, often with an antinucleolar pattern. Antibody to centromeric protein (anticentromere antibody) occurs in the serum of a high proportion of patients with CREST syndrome and is detectable on the ANA. Scl-70 antigen is a DNA-binding protein sensitive to nucleases. Patients with diffuse scleroderma are more likely than those with CREST to have anti-Scl-70 antibodies. Rheumatoid factor also is positive in one third of patients.

If lung involvement is suspected, pulmonary function testing, chest CT, and echocardiography can begin to define its severity. Acute alveolitis is often detected by high-resolution chest CT.

Prognosis

The course depends on the type of SSc but is often unpredictable. Typically, progression is slow. Overall 10-yr survival is about 65%. Most patients with diffuse skin disease eventually develop visceral complications, which are the usual causes of death. Prognosis is poor if cardiac, pulmonary, or renal manifestations are present early. Heart failure may be intractable. Ventricular ectopy, even if asymptomatic, increases the risk of sudden death. Acute renal insufficiency, if untreated, progresses rapidly and causes death within months. Patients with CREST syndrome may have disease that is limited and nonprogressive for long periods; visceral changes (eg, pulmonary hypertension caused by vascular disease of the lung, a peculiar form of biliary cirrhosis) eventually develop, but the course is often remarkably benign.

Treatment

• Treatment directed at symptoms and dysfunctional organs

No drug significantly influences the natural course of SSc overall, but various drugs are of value in treating specific symptoms or organ systems. NSAIDs can help arthritis. Corticosteroids may be helpful if there is overt myositis or mixed connective tissue disease but may predispose to renal crisis. Penicillamine, long used for treatment of skin thickening, has not shown clear efficacy in recent trials.

Various immunosuppressants, including methotrexate, azathioprine, and cyclophosphamide, may help pulmonary alveolitis. Successful lung transplantation has been reported. Epoprostenol (prostacyclin) and bosentan may be helpful for pulmonary hypertension. Ca channel blockers, such as nifedipine 20 mg po tid or as an extended-release formulation, or angiotensin receptor blockers, such as losartan 50 mg po once/day, may help Raynaud's syndrome. Patients should dress warmly. IV infusions of prostaglandin E1 (alprostadil) or epoprostenol or sympathetic blockers can be used for digital ischemia. Reflux esophagitis is relieved by frequent small feedings, high-dose proton pump inhibitors, and sleeping with the head of the bed elevated. Esophageal strictures may require periodic dilation; gastroesophageal reflux may possibly require gastroplasty. Tetracycline 500 mg po bid or another broad-spectrum antibiotic can suppress overgrowth of intestinal flora and may alleviate malabsorption symptoms. Physiotherapy may help preserve muscle strength but is ineffective in preventing joint contractures. No treatment affects calcinosis.
For acute renal crisis, prompt treatment with an ACE inhibitor can dramatically prolong survival. Blood pressure is usually, but not always, controlled. The mortality rate of renal crisis remains high. If end-stage renal disease develops, it may be reversible, but dialysis and transplantation may be necessary.
**Chapter 34. Vasculitis**

**Introduction**

Vasculitis is inflammation of blood vessels, often with ischemia, necrosis, and occlusive changes. It can affect any blood vessel—arteries, arterioles, veins, venules, or capillaries. Most damage results when inflammation narrows vessels and causes tissue necrosis. Clinical manifestations of specific vasculitic disorders are diverse and depend on the size of the involved vessels and the organs affected by ischemia.

**Etiology**

Vasculitis may be primary or secondary. Primary vasculitis results from an inflammatory response that targets the vessel walls and has no known cause. Secondary vasculitis may be triggered by an infection, a drug, or a toxin or may occur as part of another inflammatory disorder or cancer.

**Pathophysiology**

Histologic description of an affected vessel should include the following:

- A description of vessel wall damage
- The nature of the inflammatory infiltrate in the vessel wall (eg, granulomatous, nongranulomatous, leukocytoclastic vasculitis)
- A description of healing responses (eg, intimal hypertrophy, fibrosis)

Certain features (eg, predominant inflammatory cells, location of inflammation) suggest particular vasculitic processes and may aid in the diagnosis (see Table 34-1). For example, in many acute lesions, the predominant inflammatory cells are PMNs; in chronic lesions, lymphocytes predominate.

Inflammation may be segmental or involve the entire vessel. At sites of inflammation, varying degrees of cellular inflammation and necrosis or scarring occur in one or more layers of the vessel wall. Inflammation in the media of a muscular artery tends to destroy the internal elastic lamina.

Leukocytoclastic vasculitis is a histopathologic term used to describe findings in small-vessel vasculitis. It refers to breakdown of inflammatory cells that leaves small nuclear fragments (nuclear debris) in and around the vessels. Inflammation is transmural, rarely necrotizing, and nongranulomatous. PMNs predominate early; later, lymphocytes predominate. Resolution of the inflammation tends to result in fibrosis and intimal hypertrophy. Intimal hypertrophy or secondary clot formation can narrow the arterial lumen and accounts for tissue ischemia or necrosis.

**Classification**

Vasculitic disorders can be classified according to the size of the predominant vessel affected (see Table 34-2). However, there is often substantial overlap.

**Symptoms and Signs**

Size of the affected vessels helps determine clinical presentation (see Table 34-2).
Regardless of the size of the vessels involved, patients can present with symptoms and signs of systemic inflammation (eg, fever, night sweats, fatigue, anorexia, weight loss, arthralgias, arthritis). Some manifestations are life- or organ-threatening and require immediate treatment. They include alveolar hemorrhage, rapidly progressive glomerulonephritis, mesenteric ischemia, orbital pseudotumor threatening the optic nerve (in Wegener's granulomatosis), and vision loss in patients with giant cell arteritis.

**Diagnosis**

- Clinical evaluation
- Antineutrophil cytoplasmic antibodies (ANCA) tests
- Biopsy
- Angiography

Systemic vasculitis is suspected in patients with the following:

- Symptoms or signs characteristic of vasculitis (eg, mononeuritis multiplex, leukocytoclastic vasculitis)
- Ischemic manifestations (eg, ischemic stroke, limb claudication, mesenteric ischemia) out of proportion to a patient's risk factors for atherosclerosis
- Unexplained combinations of symptoms in more than one organ system that are compatible with vasculitis (eg, hypertension, myalgias), particularly when symptoms of a systemic illness are present

Primary vasculitic disorders are diagnosed based on the presence of characteristic symptoms, physical findings, compatible laboratory test results, and exclusion of other causes (ie, secondary vasculitis). Histologic examination is done whenever possible and may point to a particular vasculitic disorder (see Table 34-1).

Routine laboratory tests are done. Most results are nonspecific but can help support the diagnosis. Tests usually include CBC, ESR or C-reactive protein, serum albumin and total protein, and tests for ANCA. Often, patients present with elevated ESR or C-reactive protein, anemia due to chronic inflammation, elevated platelets, and low serum albumin and total protein. Freshly voided urine must be tested for RBCs, RBC casts, and protein to identify renal involvement. Serum creatinine levels should be checked and monitored. Leukopenia and thrombocytopenia are uncommon.

Detection of ANCA may support the diagnosis of Wegener's granulomatosis, Churg-Strauss syndrome, or microscopic polyangiitis. Standardized tests for ANCA include immunofluorescence staining and enzyme-linked immunosorbent assay (ELISA). Immunofluorescence staining of ethanol-fixed neutrophils can detect the cytoplasmic pattern of cANCA or the perinuclear pattern of pANCA. Then solid-phase ELISA is used to check for antibodies specific for the major autoantigens: proteinase-3 (PR3), which correlates with the cANCA staining pattern, or myeloperoxidase (MPO), which correlates with the pANCA staining pattern. Because false-positives occur, ANCA should be measured only when one of these vasculitic disorders is clinically suspected.

Other useful laboratory tests include hepatitis B and C serologic testing, testing for the presence of cryoglobulins, and complement levels to diagnose viral or cryoglobulinemic vasculitis. Further testing is determined by clinical findings. A chest x-ray should be done to check for infiltrates, but high-resolution noncontrast CT of the chest may be needed to check for subtle findings, such as small nodules or cavities. Bilateral diffuse infiltrates suggest possible alveolar hemorrhage, which requires immediate diagnosis and treatment. Other imaging tests may be required. For example, magnetic resonance angiography of large blood vessels and the aorta is useful for diagnosis and monitoring when such vessels appear affected. If symptoms suggest mononeuritis multiplex, electromyography is done.
Because vasculitic disorders are rare and treatment may have severe adverse effects, tissue biopsy is done to confirm the diagnosis whenever possible. Usually, clinical findings suggest the best site for biopsy. For example, if clinical and electromyographic findings suggest mononeuritis multiplex with dysfunction of a specific peripheral nerve, tissue around arteries supplying the nerve is biopsied. Usually, biopsies of unaffected tissue are much less likely to provide positive results.

Because vasculitis is often segmental or focal, biopsy may not show inflammation even when a vessel is affected. Sampling from multiple areas or long segments of a vessel may increase diagnostic sensitivity.

**Treatment**

- Corticosteroids and cyclophosphamide to induce remission of life- or organ-threatening disorders
- Tapering or elimination of corticosteroids and substitution of methotrexate or azathioprine to maintain remission

Treatment depends on the etiology and extent and severity of disease. For secondary vasculitic disorders, removing the cause (eg, infection, drug, cancer) can help.

For primary vasculitic disorders, treatment aims to induce and maintain remission. Remission is induced by using cytotoxic immunosuppressants and high-dose corticosteroids, usually for 3 to 6 mo, until remission occurs or disease activity is acceptably reduced. Adjusting treatment to maintain remission usually takes longer, on average > 1 or 2 yr. During this period, the goal is to eliminate corticosteroids or reduce their dose and to use less potent immunosuppressants as long as needed.

**Induction of remission:** For less severe forms of vasculitis, low doses of corticosteroids and less potent immunosuppressants (eg, methotrexate, azathioprine, mycophenolate mofetil) may be used.

Severe, rapidly progressive and life- or organ-threatening vasculitis (eg, causing alveolar hemorrhage, rapidly progressive glomerulonephritis, or mesenteric ischemia) is a medical emergency requiring hospital admission and immediate treatment. Treatment consists of the following:

- **Corticosteroids:** High-dose corticosteroids (also called pulse corticosteroids) are often prescribed. Methylprednisolone 15 mg/kg or 1 g IV once/day for 3 days may be used. Oral prednisone is given concurrently. A dose of 1 mg/kg once/day is given for about 4 wk until patients improve. The dose is then tapered slowly, as tolerated, usually by 10 mg every week to 40 mg/day, by 5 mg every 2 wk to 20 mg/day, by 2.5 mg every 2 wk to 10 mg/day, and by 1 mg every month from there on until the drug is stopped. Changes in this tapering schedule may be necessary if the patient fails to improve or relapses.

- **Cyclophosphamide:** A dose of 2 mg/kg po once/day is usually recommended for at least 3 mo or until remission occurs. The WBC count must be closely monitored, and the dose must be adjusted to avoid leukopenia. (WBC count should be maintained at > 3500/µL.) If patients cannot tolerate oral cyclophosphamide, are unlikely to take oral drugs as directed, or have a high risk of bladder cancer, IV cyclophosphamide may be used. The recommended cumulative dose of cyclophosphamide is 0.75 to 1 g/m² monthly. The dose should be reduced in patients with significant renal insufficiency. Patients taking cyclophosphamide should also be given prophylactic treatment against *Pneumocystis jirovecii*.

Acrolein, a product of cyclophosphamide degradation, is toxic to the bladder epithelium and can lead to hemorrhagic cystitis. For patients who have taken cyclophosphamide long term, risk of cystitis is increased, and some develop transitional cell carcinoma of the bladder. During cyclophosphamide therapy, careful hydration is needed to reduce the risk of bladder hemorrhage, cystitis, and bladder cancer. Mesna binds acrolein and is mixed together with the IV cyclophosphamide infusion. One milligram of mesna is added for each milligram of cyclophosphamide. Recurrence of hematuria, especially without casts and dysmorphic red cells, should prompt a referral for urologic evaluation. Cystoscopy and renal imaging should be done to exclude cancer.

**Remission maintenance:** Corticosteroids are tapered to zero or to the lowest dose that can maintain remission. Usually, methotrexate (with folate) or azathioprine is prescribed to replace cyclophosphamide.
because these drugs have a better adverse effects profile. The duration of this treatment varies, from one year to several years. Patients with frequent relapses may need to take immunosuppressants indefinitely.

Long-term use of corticosteroids can have significant adverse effects. Patients who are taking such therapy should be given Ca and vitamin D supplements and bisphosphonates to help prevent or minimize osteoporosis; bone density should be monitored yearly.

**Behcet's Syndrome**

*Behcet's syndrome is a multisystem, relapsing, chronic vasculitic disorder with prominent mucosal inflammation. Common manifestations include recurrent oral ulcers, ocular inflammation, genital ulcers, and skin lesions. The most serious manifestations are blindness, neurologic or GI manifestations, venous thromboses, and arterial aneurysms. Diagnosis is clinical, using international criteria. Treatment is mainly symptomatic but may involve corticosteroids for acute severe ocular or neurologic manifestations or immunosuppressants for severe chronic lesions.*

Behcet's syndrome involves small and large arteries and veins. Arterial thrombosis and superficial and deep venous thrombosis often occur.

The syndrome occurs nearly equally in men and women, typically beginning during their 20s. Occasionally, the syndrome develops in children. Incidence varies by location. Behcet's syndrome is most common along the silk route from the Mediterranean to China; it is uncommon in the US.

The cause is unknown. Immunologic (including autoimmune) and viral or bacterial triggers have been suggested, and HLA-B51 is associated with cases from Turkey, Iran, China, Korea, and Japan.

Neutrophil infiltration is detected in biopsy specimens from oral aphthous ulcers and erythema nodosum and pathergy lesions, but no histologic changes are pathognomonic.

**Symptoms and Signs**

**Mucocutaneous:** Almost all patients have recurrent painful oral ulcers resembling those of aphthous stomatitis; in most, these ulcers are the first manifestations. The ulcers are round or oval, 2 to 10 mm in diameter, and shallow or deep with a central yellowish necrotic center; they can occur anywhere in the oral cavity, often in clusters. Ulcers last 1 to 2 wk. Similar ulcers occur on the penis and scrotum, on the vulva where they are painful, or in the vagina where they may cause little or no pain.

Cutaneous lesions are common and may include acneiform lesions, nodules, erythema nodosum, superficial thrombophlebitis, pyoderma gangrenosum-type lesions, and palpable purpura.

Pathergy (an erythematous papular or pustular response to local skin injury) is defined as a papule > 2 mm that appears 24 to 48 h after oblique insertion of a 20- to 25-gauge needle into the skin. Pathergy has occurred in many parts of the world but is less common among North American and northern European patients than among Middle Eastern and Asian patients.

**Ocular:** The eyes are affected in 25 to 75% of patients. The following may occur:

- Relapsing uveitis or iridocyclitis (most common) often manifests as pain, photophobia, and red eye.
- Hypopyon (a layer of pus visible in the anterior chamber) may occur.
- Uveitis is typically bilateral and episodic, often involves the entire uveal tract (panuveitis), and may not resolve completely between episodes.
- Choroiditis, retinal vasculitis, vascular occlusion, and optic neuritis may irreversibly impair vision and even progress to blindness.
Musculoskeletal: Relatively mild, self-limiting, and nondestructive arthralgias or frank arthritis, especially in the knees and other large joints, occur in 50% of patients. Sacroiliac inflammation can occur.

Vascular: Superficial and deep venous thromboses are common. Large vessels are affected in about one third of patients. Perivascular and endovascular inflammation may lead to hemorrhage, stenosis, aneurysms, and thrombosis in arteries and veins. Superior and inferior vena cava occlusion, Budd-Chiari syndrome, and other venous obstructive lesions can also occur.

Disease of the aorta and large blood vessels may be life threatening. Hemoptysis may occur if fistulas between the pulmonary artery and bronchus develop.

Neurologic and psychiatric: CNS involvement is less common but is serious. Onset may be sudden or gradual. The first manifestations may be parenchymal involvement with pyramidal signs, small-vessel disease with a multiple sclerosis-like pattern, aseptic meningitis or meningoencephalitis, or dural sinus thrombosis.

Psychiatric disorders including personality changes and dementia may develop years later. Peripheral neuropathy, common in other vasculitic disorders, is uncommon in Behcet's syndrome.

GI: Abdominal discomfort, abdominal pain, and diarrhea with intestinal ulcers, occurring primarily in the ileum and colon and closely resembling Crohn's disease, may occur.

Diagnosis

• Clinical criteria

Behcet's syndrome should be suspected in young adults with recurrent oral aphthous ulcers, unexplained ocular findings, or genital ulcers. Diagnosis is clinical and may require months because many of the manifestations are nonspecific and can be insidious.

International criteria for diagnosis include recurrent oral ulcers (3 times in 1 yr) and 2 of the following:

• Recurrent genital ulcers
• Eye lesions
• Skin lesions
• Positive pathergy test with no other clinical explanation

Laboratory tests (eg, CBC, ESR or C-reactive protein, serum albumin and total protein levels) are done. Results are nonspecific but characteristic of inflammatory disease (elevated ESR, C-reactive protein, and α2- and γ-globulins; mild leukocytosis).

Differential diagnosis includes reactive arthritis, SLE, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and herpes simplex infection. Behcet's syndrome has no single pathognomonic finding but may be distinguished by its combinations of relapsing symptoms with spontaneous remissions and multiple organ involvement, particularly in patients with recurrent, deep mucosal ulcers.

Prognosis

Behcet's syndrome typically has a waxing and waning course characterized by exacerbations and remissions. Mucocutaneous and ocular lesions and arthralgias are often worse early in the disease. CNS and large-vessel manifestations, if they develop, typically occur later. Occasionally, the syndrome results in death, usually due to neurologic, vascular (eg, aneurysms), or GI manifestations. Many patients eventually go into remission.

Treatment
• Colchicine, thalidomide, etanercept, and interferon for mucosal disease

• Azathioprine or cyclosporine for eye disease

• Cyclophosphamide and chlorambucil for refractory or life-threatening disease

Treatment depends on the clinical manifestations.

Mucosal disease can be managed symptomatically. Colchicine 0.6 mg po bid may decrease the frequency and severity of oral or genital ulcers and may be effective for erythema nodosum and arthralgias. Thalidomide 100 to 300 mg po once/day may be used to treat oral, genital, and skin lesions, but lesions may recur when treatment is stopped. Etanercept 50 mg sc once/wk or 25 mg sc twice/wk may suppress mucocutaneous lesions. Etanercept can be given if colchicine is ineffective. Interferon alfa-2a 6 million units sc 3 times/wk can also be given if colchicine is ineffective.

Azathioprine 2.5 mg/kg po once/day helps preserve visual acuity and prevent new eye lesions. Azathioprine is also useful for mucocutaneous lesions and arthralgia. Cyclosporine 5 to 10 mg/kg po once/day may be reserved for patients with severe ocular manifestations and may be used with azathioprine to treat refractory uveitis. Interferon alfa-2a 6 million units sc 3 times/wk and infliximab (a tumor necrosis factor inhibitor) 3 to 10 mg/kg IV at 0, 2, 4, and then every 8 wk show promise for patients with ocular manifestations.

Cyclophosphamide and chlorambucil are used in patients with refractory disease, life-threatening conditions (eg, pulmonary aneurysms), or CNS manifestations.

The efficacy of corticosteroids is unsubstantiated, despite their wide use. Topical corticosteroids may temporarily relieve ocular manifestations and most oral lesions. However, topical or systemic corticosteroids do not alter the frequency of relapses. A few patients with severe uveitis or CNS manifestations respond to high-dose systemic corticosteroids (eg, prednisone 60 to 80 mg po once/day).

Whether immunosuppressants should be added to anticoagulation therapy when patients have thromboses has not been established.

**Churg-Strauss Syndrome**

(Allergic Angitis and Granulomatosis)

Churg-Strauss syndrome is a pulmonary and systemic small-vessel necrotizing vasculitis, characterized by extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils. It tends to occur in people with adult-onset asthma, allergic rhinitis, nasal polyposis, or a combination. Diagnosis is best confirmed by biopsy. Treatment is primarily with corticosteroids and, for severe disease, addition of other immunosuppressants.

Churg-Strauss syndrome occurs in about 3 people/million. Mean age at onset is 48.

Churg-Strauss syndrome is characterized by extravascular necrotizing granulomas (usually containing eosinophilic infiltrates), eosinophilia, and tissue infiltration by eosinophils. However, these abnormalities rarely coexist. The vasculitis typically affects pulmonary and systemic arteries and veins. Any organ can be affected, but the lungs, skin, cardiovascular system (eg, as coronary artery vasculitis), kidneys, peripheral nervous system, sinuses, joints, and GI tract are most commonly affected. Occasionally, pulmonary capillaritis may cause alveolar hemorrhage.

**Etiology**

The cause is unknown. However, an allergic mechanism, with tissue directly injured by eosinophils and neutrophil degranulation products, may be involved. Activation of T lymphocytes seems to help maintain eosinophilic inflammation. The syndrome occurs in patients who have adult-onset asthma, allergic rhinitis,
nasal polyposis, or a combination. Antineutrophil cytoplasmic autoantibodies (ANCA) are sometimes present.

**Symptoms and Signs**

The syndrome has 3 phases, which may overlap:

- **Prodromal:** This phase may persist for years. Patients have allergic rhinitis, nasal polyposis, asthma, or a combination.

- **2nd phase:** Peripheral blood and tissue eosinophilia is typical. Clinical presentation, which may resemble Loffler's syndrome, includes chronic eosinophilic pneumonia and eosinophilic gastroenteritis.

- **3rd phase:** Potentially life-threatening vasculitis develops. Systemic symptoms (eg, fever, malaise, weight loss, fatigue) are common.

However, the phases do not necessarily follow one another consecutively, and the time interval between them varies greatly.

Various organs and systems may be affected:

- **Respiratory:** Asthma, often with onset during adulthood, occurs in most patients. Sinusitis is common, typically without severe necrotizing inflammation. Sinusitis causes facial pain and increases nasal discharge. Patients may be short of breath. Cough and hemoptysis, due to alveolar hemorrhage, may be present. Transient patchy pulmonary infiltrates are common.

- **Neurologic:** Neurologic manifestations are common. Mononeuritis multiplex occurs in up to three fourths of patients. CNS involvement is rare but can include confusion, seizures, and coma, with or without cranial nerve palsies or evidence of cerebral infarction.

- **Cutaneous:** The skin is affected in about one half of patients. Nodules and papules appear on extensor surfaces of extremities. They are caused by extravascular palisading granulomatous lesions with central necrosis. Purpura or erythematous papules, due to leukocytoclastic vasculitis with or without prominent eosinophilic infiltration, may develop.

- **Musculoskeletal:** Occasionally, arthralgias, myalgias, or even arthritis can occur, usually during the vasculitic phase.

- **Cardiac:** Heart failure, MI, coronary artery vasculitis (possibly with MI), valvular disorders, or pericarditis may develop. The predominant histopathologic finding is eosinophilic myocarditis.

- **GI:** Up to one third of patients present with GI symptoms (eg, abdominal pain, diarrhea, bleeding) due to eosinophilic gastroenteritis or mesenteric ischemia due to vasculitis.

- **Renal:** The kidneys are affected less often than in other vasculitic disorders associated with ANCA. Typically, pauci-immune (few if any immune complexes), focal segmental necrotizing glomerulonephritis with crescent formation is present; eosinophilic or granulomatous inflammation of the kidneys is rare.

Renal, cardiac, or neurologic involvement indicates a worse prognosis.

**Diagnosis**

- **Clinical criteria**

- **Routine laboratory tests**

- **Biopsy**
Criteria for classification from the American College of Rheumatology consist of the following:

- Asthma
- Eosinophilia of > 10% in peripheral blood
- Paranasal sinusitis
- Pulmonary infiltrates, sometimes transient
- Histologic evidence of vasculitis with extravascular eosinophils
- Mononeuritis multiplex or polyneuropathy

If ≥ 4 criteria are present, sensitivity is 85%, and specificity is 99.7%.

Testing aims to establish the diagnosis and the extent of organ involvement and to distinguish Churg-Strauss syndrome from other eosinophilic disorders (eg, parasitic infections, drug reactions, acute and chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, idiopathic hypereosinophilic syndrome). Diagnosis is suggested by clinical findings and results of routine laboratory tests but should usually be confirmed by biopsy of lung or other affected tissue.

Blood tests and chest x-rays are done, but results are not diagnostic. CBC with differential is done to check for eosinophilia. Peripheral blood eosinophilia is also a marker of disease activity. IgE and C-reactive protein levels and ESR are determined periodically to evaluate inflammatory activity. Electrolyte levels are measured and urinalysis is done to check for evidence of renal involvement and to follow its severity.

Serologic testing is done. It detects ANCA in up to 50%; if ANCA is detected, enzyme-linked immunosorbent assay (ELISA) is done to check for specific antibodies. Perinuclear ANCA (p-ANCA) with antibodies against myeloperoxidase is the most common result, but ANCA is not specific for Churg-Strauss syndrome.

Chest x-ray often shows transient patchy pulmonary infiltrates.

Biopsy of the most accessible affected tissue should be done if possible.

Treatment

- Corticosteroids

Systemic corticosteroids are the mainstay of treatment. When to add other immunosuppressants is not clear, but Churg-Strauss syndrome is generally treated the same way as Wegener's granulomatosis (see p. 329) or microscopic polyangiitis (see p. 322). Recombinant interferon alfa-2a 3 million units sc daily has been used when the syndrome is refractory to other drugs or when eosinophilic inflammation is difficult to control.

Cutaneous Vasculitis

Cutaneous vasculitis affects small or medium-sized vessels in the skin and subcutaneous tissue. This disorder may be limited to the skin or be part of systemic vasculitis. Purpura, ulcers, livedo reticularis, or nodules may develop. Diagnosis requires biopsy. Treatment depends on etiology and extent of disease.

Common causes include serum sickness, infections (eg, hepatitis C), cancers, rheumatologic or other autoimmune disorders, and hypersensitivity to drugs.

Vessel inflammation often results from immune complex deposition, but other pathogenetic mechanisms
may be involved. Predominantly cutaneous vasculitis is a leukocytoclastic vasculitis, so-called because inflammation disrupts leukocytes, resulting in deposition of nuclear debris (leukocytoclasis) in the vessel wall.

**Symptoms and Signs**

Patients may present with skin symptoms such as lesions, including palpable purpura, urticaria, ulcers, livedo reticularis, and nodules. If cutaneous vasculitis occurs as part of a systemic vasculitis, symptoms may also include fever, arthralgias, other organ involvement, or a combination.

**Diagnosis**

- Exclusion of systemic vasculitis clinically and by routine tests (eg, CBC, ESR, urinalysis, chest x-ray, serum creatinine)

- Biopsy

- Tests for the cause of vasculitis (eg, cryoglobulins, antineutrophil cytoplasmic antibodies [ANCA], hepatitis B and C antibodies, complement levels)

A diagnosis of vasculitis limited to the skin requires a complete history and physical examination, focusing on excluding manifestations of inflammation or vasculitis in other organs, as in the following:

- Lungs: Shortness of breath, cough, hemoptysis, and signs of consolidation

- Kidneys: New-onset hypertension or edema

- Nerves: New-onset asymmetric weakness or paresthesias

- Intestine: New-onset abdominal pain, diarrhea, and bloody stools

Urinalysis should exclude blood, protein, and RBC casts. A chest x-ray is needed to check for infiltrates (suggesting alveolar hemorrhage). CBC and other blood tests are needed to check for anemia, to determine platelet count and serum creatinine level, and to check for elevated levels of acute-phase reactants (eg, ESR, C-reactive protein).

A skin biopsy is done, optimally within 24 to 48 h after vasculitic lesions appear. Diagnostic yield depends on the depth of the biopsy. Generally, punch biopsy or excision biopsy into the subcutis is preferred; these biopsies can sample small and medium-sized vessels. Shave biopsy is usually inadequate.

If histologic examination detects the following, cutaneous vasculitis is confirmed:

- Infiltration of the vessel wall by inflammatory cells, resulting in disruption and destruction of the vessel wall

- Intramural and intraluminal fibrin deposition (fibrinoid necrosis)

- Extravasation of RBCs

- Nuclear debris (leukocytoclasis)

Direct immunofluorescence staining is needed to check for IgA, IgM, and IgG and complement deposition in and around the vessel wall, which suggests an immune complex-mediated process and supports the diagnosis. Further testing to establish the cause of vasculitis includes checking for cryoglobulins, ANCA, and hepatitis B and C antibodies, measuring complement levels, and tests for any clinically suspected disorders that can cause vasculitis.

**Treatment**
• Antihistamines and sometimes low-dose corticosteroids to treat skin lesions

• Trial of colchicine, hydroxychloroquine, or dapsone to prevent recurrences

Treatment is first directed at any identified cause. If no cause is identified and vasculitis is limited to the skin, treatment is minimal and conservative. Support hose and antihistamines may be sufficient. If this treatment is ineffective, low-dose corticosteroids can be tried.

If lesions recur, colchicine, hydroxychloroquine, or dapsone may prevent further recurrences. Rarely, stronger immunosuppressants (eg, azathioprine, methotrexate) are used, particularly if lesions ulcerate.

**Giant Cell Arteritis**

(Temporal Arteritis; Cranial Arteritis; Horton's Disease)

Giant cell arteritis involves predominantly the thoracic aorta, large arteries emerging from the aorta in the neck, and extracranial branches of the carotid arteries. Simultaneous polymyalgia rheumatica is common. Focal symptoms and signs may include headaches, visual disturbances, temporal artery tenderness, and pain in the jaw muscles during chewing. Fever, weight loss, malaise, and fatigue are also common. ESR and C-reactive protein are typically elevated. Diagnosis is clinical and confirmed by temporal artery biopsy. Treatment with high-dose corticosteroids and aspirin is usually effective and prevents vision loss.

Giant cell arteritis is a relatively common form of vasculitis in the US and Europe. Incidence varies depending on ethnic background. Autopsy studies suggest that the disorder may be more common than is clinically apparent. Women are affected more often. Mean age at onset is about 70, with a range of 50 to > 90. About 40 to 60% of patients with giant cell arteritis have polymyalgia rheumatica. The intracranial vessels are usually not affected.

**Pathophysiology**

Vasculitis may be localized, multifocal, or widespread. The disorder tends to affect arteries containing elastic tissue, most often the temporal, cranial, or other carotid system arteries. The aortic arch branches, coronary arteries, and peripheral arteries can also be affected. Mononuclear cell infiltrates in the adventitia form granulomas containing activated T cells and macrophages. Multinucleated giant cells, when present, cluster near the disrupted elastic lamina. The intimal layer is markedly thickened, with concentric narrowing and occlusion of the lumen.

**Symptoms and Signs**

Symptoms may begin gradually over several weeks or abruptly.

Patients may present with systemic symptoms such as fever (usually low-grade), fatigue, malaise, unexplained weight loss, and sweats. Some patients are initially diagnosed as having FUO. Eventually, most patients develop symptoms related to the affected arteries.

Severe, sometimes throbbing headache (temporal, occipital, frontal, or diffuse) is the most common symptom. It may be accompanied by scalp pain elicited by touching the scalp or combing the hair.

Visual disturbances include diplopia, scotomas, ptosis, blurred vision, and loss of vision (which is an ominous sign). Brief periods of partial or complete vision loss (amaurosis fugax) in one eye may be rapidly followed by permanent irreversible loss of vision. If untreated, the other eye may also be affected. However, complete bilateral blindness is uncommon. Vision loss is caused by arteritis of branches of the ophthalmic artery or posterior ciliary arteries, which leads to ischemia of the optic nerve. Funduscopic findings may include ischemic optic neuritis with pallor and edema of the optic disk, scattered cotton-wool patches, and small hemorrhages. Later, the optic nerve atrophies. Rarely, central blindness results from infarction in the occipital cortex caused by arterial lesions in the distal cervical region or base of the brain.
Intermittent claudication (ischemic muscle pain) may occur in jaw muscles and muscles of the tongue or extremities. Jaw claudication is noted especially when firm foods are chewed.

Neurologic manifestations, such as strokes and transient ischemic attacks, can result when the carotid or vertebrobasilar arteries or branches are narrowed or occluded.

Thoracic aortic aneurysms and dissection of the aorta are serious, often late, complications.

**Diagnosis**

- ESR, C-reactive protein, and CBC
- Biopsy, usually of the temporal artery

Giant cell arteritis is suspected in patients > 55 if any of the following develops, especially if they also have symptoms of systemic inflammation:

- A new type of headache
- Any new symptom or sign compatible with ischemia of an artery above the neck
- Jaw pain during chewing
- Temporal artery tenderness
- Unexplained subacute fever or anemia

The diagnosis is more likely if patients also have symptoms of polymyalgia rheumatica.

Physical examination may detect swelling and tenderness, with or without nodularity or erythema, over the temporal arteries. Temporal arteries can become prominent. A temporal artery that rolls under the examiner's fingers, rather than collapses, is abnormal. The large arteries of the neck and limbs and the aorta should be evaluated for bruits.

If the diagnosis is suspected, ESR, C-reactive protein, and CBC are determined. In most patients, ESR and C-reactive protein are elevated; anemia of chronic disease is common. Occasionally, platelets are elevated, and serum albumin and total protein, measured for other reasons, are low. Mild leukocytosis is commonly detected but is nonspecific.

If the diagnosis is suspected, biopsy of an artery is recommended. Because inflamed segments often alternate with normal segments, a segment that appears abnormal should be sampled if possible. Usually, the temporal artery is biopsied, but the occipital artery can also be biopsied if it appears abnormal. The optimal length of the temporal artery to remove is unclear, but 5 cm is recommended if possible. Treatment should not be delayed to do the biopsy. Biopsy can be done up to 2 wk or perhaps more after treatment is started because the inflammatory infiltrate is slow to resolve.

If patients have pulse deficits, the aorta and its branches are imaged (see Table 34-3 on p. 328).

**Treatment**

- Corticosteroids
- Low-dose aspirin

Treatment should be started as soon as giant cell arteritis is suspected, even if biopsy is going to be delayed for several days.
Corticosteroids are the cornerstone of treatment. Corticosteroids rapidly reduce symptoms and prevent vision loss in most patients. The optimal initial dose, tapering schedule, and total length of treatment are debated. For most patients, an initial dose of prednisone 40 to 60 mg po once/day (or equivalent) for 4 wk, followed by gradual tapering, is effective. If patients have visual disturbances, an initial dose of IV methylprednisolone 500 to 1000 mg once/day for 3 to 5 days can be tried in an attempt to help prevent further decline in vision, particularly in the contralateral eye.

If symptoms lessen, prednisone can be tapered gradually from doses of up to 60 mg/day based on the patient's response, usually as follows: by 5 to 10 mg/day every week to 40 mg/day, by 2 to 5 mg/day every week to 10 to 20 mg/day, then by 1 mg/day every month thereafter until the drug is stopped. ESR alone should not be used alone to evaluate patient response (and disease activity). Clinical symptoms must also be used.

Most patients require at least 2 yr of treatment with corticosteroids. Long-term use of corticosteroids can have significant adverse effects and thus should be limited if possible. More than one half of patients taking these drugs have drug-related complications. Consequently, alternative therapies are being studied. If patients cannot tolerate corticosteroids or if symptoms return when the dose is tapered, methotrexate 0.3 mg/kg/wk may be useful.

Tumor necrosis factor inhibitors have not been shown to be effective.

Low-dose aspirin (100 mg po once/day) may help prevent ischemic events and should be prescribed for all patients unless contraindicated.

**Henoch-Schonlein Purpura**

*Henoch-Schonlein purpura is vasculitis that affects primarily small vessels. It occurs most often in children. Common manifestations include palpable purpura, arthralgias, GI symptoms and signs, and glomerulonephritis. Diagnosis is clinical in children but usually warrants biopsy in adults. Disease is usually self-limited. Corticosteroids can relieve arthralgias and GI symptoms but do not alter the course of the disease. Progressive glomerulonephritis may require high-dose corticosteroids and cyclophosphamide.*

In Henoch-Schonlein purpura, IgA-containing immune complexes are deposited in small vessels of the skin and other sites, with consequent activation of complement. Possible inciting antigens include viruses that cause URIs, streptococcal infection, drugs, foods, insect bites, and immunizations. Focal, segmental proliferative glomerulonephritis is typical but mild.

**Symptoms and Signs**

The disease begins with a sudden palpable purpuric rash typically occurring on the feet, legs, and arms and as a strip across the buttocks. The purpura may start as small areas of urticaria that become indurated and palpable. Crops of new lesions may appear over days to several weeks. Many patients also have fever and polyarthralgia with periarticular tenderness and swelling of the ankles, knees, hips, wrists, and elbows.

GI symptoms are common and include colicky abdominal pain, abdominal tenderness, and melena. Intussusception occasionally develops in children. Stool may test positive for occult blood.

Symptoms usually remit after about 4 wk but often recur at least once after a disease-free interval of several weeks. In most patients, the disorder subsides without serious sequelae; however, some patients develop chronic renal failure.

**Diagnosis**

- Biopsy of skin lesions
The diagnosis is suspected in patients, particularly children, with typical skin findings. It is confirmed by biopsy of skin lesions when leukocytoclastic vasculitis with IgA in the vessel walls is identified. Biopsy is unnecessary if clinical diagnosis is clear in children. Urinalysis is done; hematuria, proteinuria, and RBC casts indicate renal involvement. CBC and renal function tests are done.

If renal function is deteriorating, renal biopsy may help define the prognosis. Diffuse glomerular involvement or crescent formation in most glomeruli predicts progressive renal failure.

**Treatment**

- Primarily corticosteroids and symptomatic measures

If the cause is a drug, it has to be stopped. Otherwise, treatment is primarily symptomatic. Corticosteroids (eg, prednisone 2 mg/kg up to a total of 50 mg po once/day) may help control abdominal pain and are occasionally needed to treat severe joint pain or renal disease. Pulse IV methylprednisolone followed by oral prednisone and cyclophosphamide can be given to attempt to control inflammation when the kidneys are severely affected. However, the effects of corticosteroids on renal manifestations are not clear.

**Microscopic Polyangiitis**

Microscopic polyangiitis is a systemic pauci-immune necrotizing vasculitis that affects mainly small vessels. It may begin as a pulmonary-renal syndrome with rapidly progressing glomerulonephritis and alveolar hemorrhage, but the pattern of disease depends on the organs affected. Diagnosis is by biopsy. Treatment, which depends on disease severity, includes corticosteroids and immunosuppressants.

Microscopic polyangiitis is rare (about 13 to 19 cases/million). Pathogenesis is unknown. Like immune complex-associated vasculitis (eg, SLE, cryoglobulinemia, serum sickness, Henoch-Schönlein purpura), microscopic polyangiitis affects small vessels. Polyarteritis nodosa can cause some manifestations similar to the small vessel vasculitides, such as mononeuritis multiplex and bowel ischemia. Microscopic polyangiitis can be distinguished from immune complex-associated vasculitis and polyarteritis nodosa by the following:

- Microscopic polyangiitis affects predominantly small vessels, unlike polyarteritis nodosa, which affects medium-sized muscular arteries.
- Microscopic polyangiitis, unlike polyarteritis nodosa, may cause glomerulonephritis and may affect the lungs and cause alveolar hemorrhage.
- Immune complex deposits are scarce or absent (ie, pauci-immune) in contrast to immune complex-associated vasculitis.

Clinical manifestations resemble those of Wegener's granulomatosis except that granulomatous destructive lesions are absent and the upper respiratory tract is usually not severely affected. In both disorders, antineutrophil cytoplasmic antibodies (ANCA) may be present. Microscopic polyangiitis can occur in patients with viral hepatitis B or C.

**Symptoms and Signs**

Usually, a prodromal illness with systemic symptoms of fever, weight loss, myalgia, and arthralgia occurs. Other symptoms depend on which organs and systems are affected:

- **Renal**: The kidneys are affected in up to 90% of patients. Hematuria, proteinuria (sometimes > 3 g/24 h), and RBC casts are present. Without prompt diagnosis and treatment, renal failure may follow rapidly.
- **Cutaneous**: About one third of patients have a purpuric rash at the time of the diagnosis. Nail bed infarcts and splinter hemorrhages may occur; digital ischemia occurs rarely.
• **Respiratory:** If the lungs are affected, alveolar hemorrhage may occur, followed by pulmonary fibrosis. Rapid-onset dyspnea and anemia, with or without hemoptysis and bilateral patchy infiltrates (seen on chest x-ray) may be due to alveolar hemorrhage, a medical emergency that requires immediate treatment. Mild symptoms of rhinitis, epistaxis, and sinusitis may occur; however, if the upper respiratory tract is severely affected, the cause is more likely to be Wegener's granulomatosis.

• **GI:** GI symptoms include abdominal pain, nausea, vomiting, diarrhea, and bloody stools.

• **Neurologic:** If the nervous system is affected, mononeuritis multiplex that affects peripheral or cranial nerves usually occurs. Cerebral hemorrhage, infarction, seizures, or headache rarely results from cerebral vasculitis.

• **Cardiac:** Rarely, the heart is affected.

• **Ocular:** If the eyes are affected, episcleritis usually results.

**Diagnosis**

• Clinical findings

• Tests for ANCA and C-reactive protein and routine laboratory tests

• Biopsy

Microscopic polyangiitis may mimic many other disorders because its manifestations vary. The disorder should be suspected in patients who have unexplained combinations of GI symptoms or signs, alveolar hemorrhage, episcleritis, and peripheral neuropathy. Laboratory tests and sometimes x-rays are done, but the diagnosis is usually confirmed by biopsy. Tests include CBC, ESR, C-reactive protein, urinalysis, serum creatinine, and tests for ANCA. ESR. C-reactive protein levels, and WBC and platelet counts are elevated, reflecting systemic inflammation. Anemia of chronic disease is common. An acute drop in Hct suggests alveolar hemorrhage or hemorrhage in the GI tract. Urinalysis (to check for hematuria, proteinuria, and cellular casts) should be done, and serum creatinine should be measured periodically to check for renal involvement.

Immunofluorescence staining can detect ANCA; this test is followed by enzyme-linked immunosorbent assay (ELISA) to check for specific antibodies. At least 60% of patients have ANCA, usually perinuclear ANCA (p-ANCA) with antibodies against myeloperoxidase. Biopsy of the most accessible involved tissue should be done to confirm vasculitis. Renal biopsy may detect focal segmental pauci-immune necrotizing glomerulonephritis with fibrinoid necrosis of the glomerular capillary wall, leading to formation of cellular crescents.

In patients with respiratory symptoms, chest x-ray is done to check for infiltrates. Bilateral patchy infiltrates suggest alveolar hemorrhage even in patients without hemoptysis.

If patients have dyspnea and bilateral infiltrates, bronchoscopy should be done immediately to check for alveolar hemorrhages. Blood coming from both lungs and all bronchi, with more blood coming as the bronchoscope goes deeper in the airways, indicates active alveolar hemorrhage. Hemosiderin-laden macrophages appear within 24 to 72 h after onset of hemorrhage and may persist for up to 2 mo.

**Treatment**

• When vital organs are affected, corticosteroids plus cyclophosphamide

• For less severe cases, corticosteroids plus azathioprine or methotrexate
Treatment is similar to that of Wegener's granulomatosis. Cyclophosphamide given daily plus corticosteroids improves survival when vital organs are affected. However, induction and maintenance regimens vary, and adjunctive therapies such as plasma exchange and pulse IV methylprednisolone may or may not be used.

Less severe cases may be managed with corticosteroids plus azathioprine or methotrexate.

**Polyarteritis Nodosa**

(Polyarteritis; Periarteritis Nodosa)

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries and occasionally affects small muscular arteries, resulting in secondary tissue ischemia. The kidneys, skin, joints, muscles, peripheral nerves, and GI tract are most commonly affected, but any organ can be. However, the lungs are usually spared. Patients typically present with systemic symptoms (eg, fever, fatigue). Diagnosis requires a biopsy or arteriography. Treatment with corticosteroids and immunosuppressants is often effective.

PAN is rare (about 2 to 33 cases/million). It affects mainly middle-aged adults, and incidence increases with aging, peaking in people in their 50s.

**Etiology**

Most cases are idiopathic. About 20% of patients have hepatitis B or C.

The cause is unknown, but immune mechanisms appear to be involved. The variety of clinical and pathologic features suggests multiple pathogenic mechanisms. Drugs may be a cause. Usually, no predisposing antigen is identified. Patients with certain lymphomas and leukemias, RA, or Sjogren's syndrome may develop a systemic vasculitis similar to PAN.

**Pathophysiology**

PAN is characterized by segmental, transmural necrotizing inflammation of muscular arteries, most commonly at points of bifurcation. Unlike other vasculitic disorders, PAN does not involve postcapillary venules or veins. Lesions in all stages of development and healing are usually present. Early lesions contain PMNs and occasionally eosinophils; later lesions contain lymphocytes and plasma cells. Granulomatous inflammation does not occur. Intimal proliferation with secondary thrombosis and occlusion leads to organ and tissue infarction. Weakening of the muscular arterial wall may cause small aneurysms and arterial dissection. Healing can result in nodular fibrosis of the adventitia.

Mostly commonly affected are the kidneys, skin, peripheral nerves, joints, muscles, and GI tract. Often affected are the liver and heart. Renal ischemia and infarction occur, but glomerulonephritis is not a feature of PAN. Purpura is not a characteristic of PAN.

**Symptoms and Signs**

PAN mimics many disorders. The course may be acute and prolonged, subacute and fatal after several months, or insidious, chronic, and debilitating. Symptoms depend mainly on location and severity of the arteritis and extent of secondary ischemia. Only one organ or organ system may be affected.

Patients typically present with fever, fatigue, night sweats, loss of appetite, weight loss, and generalized weakness. Myalgias with areas of focal ischemic myositis and arthralgias are common. Affected muscles are tender and weak. Arthritis may occur.

Symptoms and signs vary, depending on organ or organ system predominantly affected:

- **Peripheral nervous system:** Patients usually present with asymmetric peripheral neuropathy, such as mononeuritis multiplex with signs of motor and sensory involvement of the peroneal, median, or ulnar...
nerves. As additional nerve branches are affected, patients may appear to have a distal symmetric polyneuropathy.

• CNS: Headache and seizures can result. In a few patients, ischemic stroke and cerebral hemorrhage occur, sometimes resulting from hypertension.

• Renal: If small and medium-sized arteries in the kidneys are affected, patients may have hypertension, oliguria, uremia, and a nonspecific urinary sediment with hematuria, proteinuria, and no cellular casts. Hypertension may worsen rapidly. Rupture of renal arterial aneurysms can cause perirenal hematomas. In severe cases, multiple renal infarcts with lumbar pain and gross hematuria may occur. Renal ischemia and infarction can lead to renal failure.

• GI: Vasculitis of the liver or gallbladder causes right upper quadrant pain. Perforation of the gallbladder with acute abdomen may occur. Vasculitis of medium-sized mesenteric arteries causes abdominal pain, nausea, vomiting (with or without bloody diarrhea), malabsorption, intestinal perforation, and acute abdomen. Aneurysms may develop in hepatic or celiac arteries.

• Cardiac: Some patients have coronary artery disease, which is usually asymptomatic, but may cause angina. Heart failure may result from ischemic or hypertensive cardiomyopathy

• Cutaneous: Livedo reticularis, skin ulcers, tender erythematous nodules, bullous or vesicular eruptions, infarction and gangrene of fingers or toes, or a combination may occur. The nodules in PAN resemble erythema nodosum (inflammation of subcutaneous fat), but in PAN, necrotizing vasculitis occurs within the walls of medium-sized arteries, usually located in the deep dermis and subcutaneous fat.

• Genital: Orchitis with testicular pain and tenderness can occur.

Diagnosis

• Clinical findings

• Biopsy

• Arteriography if no clinically involved tissue is available for biopsy

PAN may be suspected in patients with unexplained fever, abdominal pain, renal failure, hypertension, arthralgia, muscle tenderness or weakness, subcutaneous nodules, skin ulcers, pain in the abdomen or extremities, or rapidly developing hypertension. If patients have insidious, nonspecific symptoms, diagnosis is much more difficult. The diagnosis is further clarified when clinical findings are combined with certain laboratory results and other causes are excluded. PAN is also suspected in patients with systemic symptoms or signs and peripheral (usually multiple) neuritis involving major nerve trunks (eg, radial, peroneal, sciatic) in a bilaterally symmetric or asymmetric fashion (mononeuritis multiplex).

Diagnosis is confirmed by biopsy showing necrotizing arteritis or by arteriography showing the typical aneurysms in medium-sized arteries. Magnetic resonance angiography may show microaneurysms, but some abnormalities may be too small for it to detect. Thus, magnetic resonance angiography is not the test used primarily for diagnosis. Biopsy of clinically uninvolved tissue is usually useless because the disease is focal; biopsy should target sites suggested by clinical evaluation. Samples of subcutaneous tissue, sural nerve, and muscle, if thought to be involved, are preferred to samples from the kidneys or liver. If clinical findings are absent or minimal, electromyography and nerve conduction studies may help select the site of muscle or nerve biopsy. If skin lesions are present, surgical skin biopsies that include deeper dermis and subcutaneous fat should be done. (Punch biopsies of the skin that sample the epidermis and superficial dermis miss the lesions of PAN.) Even though microscopic lesions in the testes are common, testicular biopsy should not be done if testicular symptoms are absent and if other possible sites are accessible because the yield is low. Also, men may be reluctant to have testicular biopsy.

Laboratory tests are nonspecific. Leukocytosis up to 20,000 to 40,000/μL, proteinuria, and microscopic hematuria are the most common abnormalities. Patients may have thrombocytosis, markedly elevated
ESR, anemia caused by blood loss or renal failure, hypoalbuminemia, and elevated serum immunoglobulins. AST and ALT are often mildly elevated. Testing for hepatitis B and C should be done. Other testing (e.g., antineutrophil cytoplasmic antibodies [ANCA], rheumatoid factor, anticyclic citrullinated peptides [CCP], antinuclear antibodies [ANA], C3 and C4 complement levels, cryoglobulin levels, nuclear antigens and antibodies to extractable nuclear antigens such as anti-Smith, anti-Ro/SSA, anti-La/SSB, and anti-RNP) is done if the clinical presentation suggests other diagnoses, such as RA, SLE, or Sjogren's syndrome.

Prognosis

Without treatment, 5-yr survival is < 15%. With treatment, 5-yr survival is > 80% but may be lower for patients with hepatitis B. Prognosis is better if disease remission is achieved within 18 mo after diagnosis.

The following findings are associated with a poor prognosis:

- Renal insufficiency
- GI involvement
- Neurologic involvement

Treatment

- Corticosteroids alone or with cyclophosphamide, methotrexate, or azathioprine, depending on disease severity
- Addition of lamivudine and plasma exchange for patients with hepatitis B

Hepatitis B-related PAN: Treatment aims at rapidly suppressing inflammation, then eliminating the virus and inducing seroconversion via plasma exchange. A short course of corticosteroids is used for a few weeks. Lamivudine 100 mg po once/day is given for a maximum of 6 mo. A lower dose is used in patients with renal insufficiency. Plasma exchanges are scheduled as follows: 3 times/wk for 3 wk, 2 times/wk for 2 wk and once/wk until hepatitis B e antigen (HBeAg) converts to hepatitis B e antibody (anti-HBe) or until clinical recovery is sustained for 2 to 3 mo. Although this approach has not been proved to improve survival when compared with immunosuppressive therapy only, it may reduce the risk of long-term complications of hepatitis B and suppress the side effects of long-term treatment with corticosteroids and immunosuppressants.

Traditional treatment with corticosteroids, sometimes with cytotoxic immunosuppressants (mainly cyclophosphamide), was often effective in the short term but did not prevent relapses and complications (e.g., chronic hepatitis, cirrhosis) due to persistence of the hepatitis B virus.

Polymyalgia Rheumatica

Polymyalgia rheumatica is a syndrome closely associated with giant cell (temporal) arteritis. It affects adults > 55. It typically causes severe pain and stiffness in proximal muscles, without weakness or atrophy, and nonspecific systemic symptoms. ESR is markedly elevated. Diagnosis is clinical. Treatment with low-dose corticosteroids is effective.

Polymyalgia rheumatica affects adults > 55; the female: male ratio is 2:1.

Because polymyalgia rheumatica is closely associated with giant cell arteritis (see p. 319), some
authorities consider the two disorders to be different phases of the same process. Polymyalgia rheumatica appears to be more common. A few patients with polymyalgia rheumatica develop giant cell arteritis, but 40 to 60% of patients with giant cell arteritis have polymyalgia rheumatica. Polymyalgia rheumatica may precede or occur simultaneously with giant cell arteritis.

Etiology and pathogenesis are unknown. Whether symptoms result from vasculitis is unclear; they probably result from low-grade axial synovitis and bursitis.

**Symptoms and Signs**

Polymyalgia rheumatica is characterized by bilateral proximal aching of the shoulder and hip girdle muscles and the back (upper and lower) and neck muscles. Stiffness in the morning is typical. Shoulder symptoms may reflect proximal bursitis (eg, subdeltoid, subacromial) and less often bicipital tenosynovitis or joint synovitis. Discomfort is worse in the morning and is occasionally severe enough to prevent patients from getting out of bed and from doing simple activities. The pain may make patients feel weak, but objective muscle weakness is not a feature of the disorder.

**Diagnosis**

- Clinical findings
- Exclusion of other causes

Polymyalgia rheumatica is suspected in elderly patients with typical symptoms, but other possible causes must be excluded. Tests include ESR, CBC, thyroid-stimulating hormone levels, and CK. In > 80% of patients, ESR is markedly elevated, often > 100 mm/h, usually > 50 mm/h (Westergren method). Electromyography, biopsy, and other tests (eg, rheumatoid factor), which are normal in polymyalgia rheumatica, are sometimes done to rule out other clinically suspected diagnoses.

The following findings in polymyalgia rheumatica distinguish it:

- From RA: Chronic small joint synovitis (although some joint swelling may be present), erosive or destructive lesions, rheumatoid nodules, and rheumatoid factor are absent.
- From polymyositis: Pain rather than weakness predominates; muscle enzyme levels and electromyography and muscle biopsy results are normal.
- From hypothyroidism: Thyroid function test results and muscle enzyme levels are normal.
- From multiple myeloma: Monoclonal gammopathy is absent.
- From fibromyalgia: Symptoms are more localized, and ESR is typically elevated.

**Treatment**

- Prednisone

Prednisone started at 15 to 20 mg po once/day results in dramatic improvement. If giant cell arteritis is thought to be present, the dose should be higher, and temporal artery biopsy should be done. As symptoms subside, corticosteroids are tapered to the lowest clinically effective dose, regardless of ESR. Some patients are able to stop corticosteroids in ≤ 1 yr; others require small doses for years. NSAIDs are rarely sufficient.

In elderly patients, physicians should watch for and treat complications of corticosteroid use (eg, diabetes, hypertension). Patients taking prednisone long term should be given a bisphosphonate to prevent osteoporosis.

Because patients may develop giant cell arteritis, they should be instructed to immediately report...
headache, muscle pain during chewing, and, particularly, visual disturbances to their physician.

**Takayasu's Arteritis**

*(Pulseless Disease; Occlusive Thromboaortopathy; Aortic Arch Syndrome)*

Takayasu's arteritis is an inflammatory disease affecting the aorta, its branches, and pulmonary arteries. It occurs predominantly in young women. Etiology is unknown. Vascular inflammation may cause arterial stenosis, occlusion, dilation, or aneurysms. It causes asymmetric pulses and symptoms and signs of arterial obstruction. Diagnosis is by aortic arteriography or magnetic resonance angiography. Treatment is with corticosteroids and, for organ-threatening ischemia, vascular interventions such as bypass surgery.

Takayasu's arteritis is rare. It is more common among Asians but occurs worldwide. Female: male ratio is 8:1, and age at onset is typically 15 to 30. In North America, annual incidence is estimated to be 2.6 cases/million.

**Etiology**

The cause is unknown. Cell-mediated immune mechanisms may be involved and may be similar to those in giant cell arteritis.

**Pathophysiology**

Takayasu's arteritis affects primarily large elastic arteries. The most commonly affected are the innominate and subclavian arteries, aorta (mainly the ascending aorta and the arch), common carotid arteries, and renal arteries. Most patients have stenoses or occlusions. Aneurysms occur in about one third of patients. Usually, the wall of the aorta or its branches thickens irregularly, with intimal wrinkling. When the aortic arch is affected, orifices of the major arteries emerging from the aorta may be markedly narrowed or even obliterated by intimal thickening. In one half of patients, pulmonary arteries are also affected.

Histologically, early changes consist of adventitial mononuclear infiltrate with perivascular cuffing of the vasa vasorum. Later, intense mononuclear inflammation of the media may occur, sometimes accompanied by granulomatous changes, giant cells, and patchy necrosis of the media. Morphologic changes may be indistinguishable from those of giant cell arteritis. Panarteritic inflammatory infiltrates cause marked thickening of the affected artery and subsequent luminal narrowing and occlusion.

**Symptoms and Signs**

Most patients present with only focal symptoms that reflect hypoperfusion of the affected organ or limb. Takayasu's arteritis may have 3 stages:

• Systemic disease, usually with systemic, nonspecific symptoms (e.g., fever, malaise, night sweats, weight loss, arthralgias, fatigue)

• Vascular inflammatory phase, with ischemic manifestations that may wax and wane

• Inactive (burned-out) disease, sometimes with acute or progressive occlusion (including thrombosis)

Only one third of patients have systemic symptoms at presentation or recall having had such symptoms.

Repetitive arm movements and sustained arm elevation may cause pain and fatigue. Arterial pulses in arms and legs may be diminished and asymmetric. Bruits are often audible over the subclavian arteries, brachial arteries, carotid arteries, abdominal aorta, or femoral arteries. Reduced BP in one or both arms is common.

When the carotid and vertebral arteries are affected, cerebral blood flow decreases, leading to dizziness,
syncope, orthostatic hypotension, headaches, transient visual disturbances, transient ischemic attacks, or strokes. Stenotic lesions in a subclavian artery near the origin of a patent vertebral artery can cause posterior circulation neurologic symptoms or syncope when the arm is used (called subclavian steal syndrome). Retrograde flow through the vertebral artery supplies the subclavian artery distal to the stenosis, and vasodilation of the arterial bed in the upper limb during exercise compromises posterior cerebral blood flow.

Angina pectoris or MI may result from narrowing of the coronary artery orifice due to aortitis or coronary arteritis. Aortic regurgitation may occur if the ascending aorta is markedly dilated. Heart failure can develop.

Obstruction of the descending thoracic aorta sometimes causes signs of aortic coarctation (e.g., hypertension, headache, leg claudication). Renovascular hypertension may develop if the abdominal aorta or renal arteries are narrowed.

Pulmonary arteries are often affected, sometimes causing pulmonary hypertension. Because Takayasu’s arteritis is chronic, collateral circulation can develop. Thus, ischemic ulcerations or gangrene due to obstruction of the arteries to the extremities is rare.

**Diagnosis**

- Aortic arteriography or magnetic resonance angiography
- Monitoring of disease activity

The diagnosis is suspected when symptoms suggest ischemia of organs supplied by the aorta or its branches or when peripheral pulses are decreased or absent in patients at low risk of atherosclerosis and other aortic disorders, especially in young women. In these patients, arterial bruits and right-left or upper extremity-lower extremity discrepancies in pulses or in BP also suggest the diagnosis. Confirmation of the diagnosis requires aortic arteriography or magnetic resonance angiography to evaluate all branches of the aorta. Characteristic findings include stenosis, occlusion, irregularities in arterial lumens, poststenotic dilation, collateral arteries around obstructed vessels, and aneurysms.

BP is measured in both arms. However, measurement can be difficult. If both subclavian arteries are severely affected, systemic BP can be accurately measured only in the legs. If the disorder affects both subclavian arteries in patients with coarctation of the descending aorta or involvement of both iliac or femoral arteries, BP cannot be accurately measured. Then, central arterial pressure must be measured via angiography to detect occult hypertension, which can cause complications.

Laboratory tests are nonspecific and not helpful in diagnosis. Common findings include anemia of chronic disease, elevated platelet levels, occasionally elevated WBC counts, and elevated ESR and C-reactive protein.

Once Takayasu’s arteritis is diagnosed, disease activity must be monitored to look for the following:

- New systemic symptoms, which may reflect active arthritis or infection (secondary to immunosuppression therapy)
- Evidence of inflammation detected by blood tests (although markers of inflammation may miss active arteritis)
- Development of stenosis, aneurysms, or ischemic symptoms in previously unaffected arteries, as assessed with periodic imaging (usually magnetic resonance angiography)

Periodic imaging of the aorta and large arteries is important (see Table 34-3) because the disorder may progress silently, without clinical symptoms or evidence of inflammation in blood. Once the disorder is diagnosed, BP should be measured periodically in an unaffected limb because hypertension must be controlled.
Disorders that mimic Takayasu's arteritis must be excluded. They include inherited connective tissue disorders (eg, Ehlers-Danlos or Marfan syndrome), vascular infections (tuberculous, fungal, or syphilitic), fibromuscular dysplasias, disorders causing arterial thrombosis (eg, hypercoagulable states), and idiopathic inflammatory conditions (eg, ankylosing spondylitis with aortitis, Cogan's or Behcet's syndrome, Kawasaki disease, sarcoidosis); all can affect large vessels.

**Table 34-3. Imaging Tests Used in Takayasu's Arteritis**

dysplasias, disorders causing arterial thrombosis (eg, hypercoagulable states), and idiopathic inflammatory conditions (eg, ankylosing spondylitis with aortitis, Cogan's or Behcet's syndrome, Kawasaki disease, sarcoidosis); all can affect large vessels.

**Prognosis**

For 20% of patients, the course is monophasic. For the rest, the course is relapsing and remitting or chronic and progressive. Even when symptoms and laboratory abnormalities suggest quiescence, new lesions occur and are evident on imaging studies. A progressive course and the presence of complications (eg, hypertension, aortic regurgitation, heart failure, aneurysms) predict a less favorable prognosis.

**Treatment**

- Corticosteroids
- Sometimes immunosuppressants
- Antihypertensives
- Vascular interventions

**Drugs:** Corticosteroids are the cornerstone of treatment. The optimal dose, tapering schedule, and length of treatment have not been determined. Treatment with corticosteroids alone induces remission in most patients. Prednisone is usually used. The starting dose is 1 mg/kg po once/day for 1 to 3 mo; the dose is then tapered slowly over several months. Lower starting doses may also induce remission. About one half of patients relapse when the drug is tapered or stopped, despite initial response.

Methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, and tumor necrosis factor inhibitors (eg, etanercept, infliximab) have been used in some patients. They can be tried if corticosteroids are insufficiently effective or cannot be tapered. Methotrexate is given with a corticosteroid. Often, the starting dose is 0.3 mg/kg once/wk, which is increased up to 25 mg/wk. Mycophenolate mofetil can also be tried. Cyclophosphamide should be considered in patients with coronary vasculitis or other serious complications thought to be due to active arteritis.

An antiplatelet drug (eg, aspirin 325 mg po once/day) is frequently used because platelet-mediated occlusion cannot be excluded. Hypertension should be treated aggressively; ACE inhibitors may be effective.

**Procedures:** Vascular intervention, usually a bypass procedure, may be needed to reestablish blood flow to ischemic tissues if drug therapy is ineffective. Indications include the following:

- Severe hypertension that is refractory to medical management because renal artery stenosis is present (although reocclusion and thrombosis of grafts is common)
- Ischemia in the extremities that interferes with daily activities
- Ischemia of cerebral arteries
- New York Heart Association (NYHA) class II heart failure secondary to a discrete coronary artery stenosis or occlusion
• Cardiac ischemia caused by stenosis of the coronary arteries

• Coarctation of the aorta

• Dissection or enlargement of an aortic aneurysm

Bypass grafting preferably with an autologous graft has the best patency rates. The anastomosis should be made at disease-free sites of the affected arteries to help prevent aneurysm formation and occlusion.

Percutaneous transluminal coronary angioplasty (PTCA) has few risks and may be effective for short lesions. But long-term restenosis rates seem much higher than those with bypass grafting. Vascular stenting is usually not recommended because the restenosis rate is high.

For aortic regurgitation, valvular surgery with aortic root replacement may be necessary.

**Wegener's Granulomatosis**

Wegener's granulomatosis is characterized by necrotizing granulomatous inflammation, small and medium-sized vessel vasculitis, and focal necrotizing glomerulonephritis, often with crescent formation. Typically, the upper and lower respiratory tract and the kidneys are affected, but any organ may be. Symptoms vary depending on the organs and systems affected. Patients may present with upper and lower respiratory tract symptoms (eg, recurrent nasal discharge or epistaxis, cough), followed by hypertension and edema, or with symptoms reflecting multiorgan involvement. Diagnosis usually requires biopsy. Treatment is with corticosteroids plus an immunosuppressant. Remission is usually possible, although relapses are common.

Wegener's granulomatosis occurs in about 1/25,000 people; it is most common among whites but can occur in all ethnic groups and at any age. Mean age at onset is 40.

The cause is unknown, although immunologic mechanisms play a role. Most patients with active generalized disease have antineutrophil cytoplasmic antibodies (ANCA).

**Pathophysiology**

Characteristically, granulomas form with histiocytic epithelioid cells and often with giant cells. Plasma cells, lymphocytes, neutrophils, and eosinophils are present. Inflammation affects tissues as well as vessels; vasculitis may be a small or large component of the disease. Micronecrosis, usually with neutrophils (microabscesses), occurs early. Micronecrosis progresses to macronecrosis. A central area of necrosis (called geographic necrosis) is rimmed by lymphocytes, plasma cells, macrophages, and giant cells. A zone of fibroblastic proliferation with palisading histiocytes may surround the area.

Nonspecific chronic inflammation and tissue necrosis occurs in the nose. The lungs are most likely to display the full spectrum of histopathologic abnormalities. In the kidneys, the most common finding is a proliferative crescentic focal glomerulonephritis with necrosis and thrombosis of individual loops or larger segments of the glomerulus. Vasculitic lesions and disseminated granulomas occur only occasionally.

**Symptoms and Signs**

Onset may be insidious or acute; the full spectrum of the disease may take years to evolve. Some patients present initially with upper and lower respiratory tract symptoms; at some point later, the kidneys are affected. In other patients, onset of systemic manifestations is relatively acute; several organs and systems, such as the upper respiratory tract, peripheral nervous system (causing mononeuritis multiplex), kidneys (causing glomerulonephritis), and lower respiratory tract (causing hemorrhage, lung nodules, cavities, or a combination), are simultaneously affected.

• **Upper respiratory tract:** Sinus pain, serosanguineous or purulent discharge, and epistaxis may occur. The mucosa appears granular (like cobblestones) and is friable; ulcers, thick dark crusts, and septal
perforation are common. Nasal chondritis can occur with swelling, pain, and collapse of the nasal bridge (saddle nose). Patients may report recurrent sinusitis that has responded inadequately to multiple antibiotic regimens and has required one or more sinus operations before diagnosis. Secondary infections (eg, due to *Staphylococcus aureus*) may develop. Subglottic stenosis may develop, causing symptoms such as pain in the larynx, hoarseness, dyspnea, wheezing, and stridor.

**Ears:** Otitis, sensorineural hearing loss, vertigo, and chondritis may occur. The middle ear, inner ear, and mastoids are often affected.

**Eyes:** Eyes may appear red and swollen. Nasolacrimal duct inflammation and obstruction may affect the eye; conjunctivitis, scleritis, uveitis, or retinal vasculitis may also occur. Inflammatory infiltrates in the retro-orbital space (orbital pseudotumor) can cause proptosis, compression of the optic nerve, and blindness. Extension into the extraocular muscles leads to diplopia. If serious eye symptoms develop, evaluation and treatment are required immediately to prevent permanent vision loss.

**Lower respiratory tract:** Respiratory manifestations are common. Inflammation of the major bronchi and branches can cause localized wheezing, postobstructive pneumonia, and atelectasis. Single or multiple pulmonary nodules, with or without cavitation, and parenchymal infiltrates, sometimes cause symptoms, such as chest pain, shortness of breath, and productive cough. Dyspnea with bilateral infiltrates, with or without hemoptysis, may indicate alveolar hemorrhage, and must be evaluated immediately.

**Heart:** Coronary artery disease may occur, but rarely.

**Musculoskeletal system:** Patients may present with myalgias, arthralgias, or nonerosive inflammatory arthritis.

**Skin:** Leukocytoclastic vasculitis, tender subcutaneous nodules, papules, livedo reticularis, or pyoderma gangrenosum may develop.

**Nervous system:** Vasculitis may cause ischemic peripheral neuropathy, brain lesions, or extension of lesions from contiguous sites. Lesions that originate in the sinuses or middle ear may extend directly to the retropharyngeal area and base of the skull, leading to cranial neuropathy, proptosis, diabetes insipidus, or meningitis.

**Kidneys:** Symptoms and signs of glomerulonephritis develop. Urinary sediment may be abnormal, and serum creatinine may increase rapidly. Edema and hypertension may result. Rapidly progressive glomerulonephritis, which is life threatening, can develop.

**Other organs:** Occasionally, an inflammatory mass occurs in the breasts, kidneys, prostate, or other organs.

**Diagnosis**

- Routine laboratory tests, including urinalysis
- Tests for ANCA
- Biopsy for definitive diagnosis

Wegener's granulomatosis should be suspected in patients with chronic, unexplained respiratory symptoms and signs (including otitis media in adults), particularly if manifestations in other organ systems, especially the kidneys, also suggest the disorder. Routine laboratory tests are done, but ANCA testing and biopsy yield the most specific findings.

Routine laboratory tests include ESR or C-reactive protein, CBC with differential, serum albumin and total protein, serum creatinine, urinalysis, 24-h urine protein, and chest x-ray. In most patients with active disease, ESR and C-reactive protein are elevated, and serum albumin and total protein are decreased;
anemia, thrombocytosis, and mild to moderate eosinophilia are detected. Dysmorphic RBCs and RBC casts, detected during urinalysis, indicate glomerular involvement. Proteinuria may be detected. Serum creatinine may be increased.

Serologic testing to detect ANCA is followed by enzyme-linked immunosorbent assay (ELISA) to check for specific antibodies. Most patients with active disease have cytoplasmic ANCA (cANCA), with antibodies against proteinase-3 (PR3); these findings plus characteristic clinical findings suggest Wegener’s granulomatosis.

Some patients with other disorders (eg, bacterial endocarditis, TB) test positive for ANCA. If characteristic clinical findings are absent, a positive ANCA result does not confirm Wegener's granulomatosis. ANCA testing should not be used to guide treatment. During apparent remission, ANCA may increase or ANCA test results may change from negative to positive. In some of these patients, symptoms do not recur; in others, symptoms recur or worsen soon after the test is done or during the next few weeks, months, or sometimes years.

Biopsy should be done if possible to confirm the diagnosis. Clinically abnormal sites may be biopsied first, but lung biopsy is most likely to detect characteristic findings. Open thoracotomy provides the best access to affected tissue. Biopsies of lung or sinus tissue are cultured to exclude infection. Renal biopsy may be necessary to confirm the diagnosis and to exclude other causes, especially if serum creatinine is elevated. Biopsy results may also provide histologic information that can help guide treatment (eg, renal fibrosis, which is irreversible with immunosuppressive treatment).

Differential diagnosis includes other vasculitic disorders that affect small and medium-sized vessels. Polyarteritis nodosa is unlikely if lung involvement is prominent and glomerulonephritis is present. Infections, especially due to slow-growing fungi or acid-fast organisms should be ruled out by staining and by culture of the sampled tissues. RA should not be diagnosed based only on the presence of rheumatoid factor, which is present in one half of patients with Wegener's granulomatosis.

**Prognosis**

Prognosis depends on the extent of the disorder—whether it is limited to nasal and pulmonary lesions, with little or no systemic involvement, or it affects many organs, causing severe systemic vasculitis.

Use of immunosuppressants for severe disease has dramatically improved prognosis. With treatment, complete remission is possible for about 70% of patients, but about one half of them eventually relapse; relapse may occur when treatment is stopped or many years after it is stopped. Resuming or increasing treatment can usually control the disorder. However, the disease or treatment causes significant morbidity in 90% of patients.

**Treatment**

- Emergency treatment with corticosteroids and cyclophosphamide for severe disease
- Corticosteroids and methotrexate for less severe disease
- Kidney transplantation if necessary

Treatment depends on the severity of disease. A multidisciplinary approach is required for multiorgan disease; a rheumatologist, an otorhinolaryngologist, a pulmonologist, and sometimes a nephrologist may be included.

Patients who have severe life- or organ-threatening manifestations (eg, alveolar hemorrhage, rapidly progressive glomerulonephritis, mononeuritis multiplex with motor involvement) require immediate treatment and hospital admission. These patients require high-dose corticosteroids and cyclophosphamide (see p. 314). The role of rituximab in severe or refractory disease is under study.

For less severe disease, corticosteroids and methotrexate are used. Methotrexate or azathioprine is used
to maintain remission.

Irrigation of sinuses with saline, with or without mupirocin 2% nasal ointment, helps minimize crusting and secondary staphylococcal infections.

Treatment of subglottic stenosis is difficult. Systemic immunosuppressants may not be effective. Intralesional injection of long-acting corticosteroids, with gentle progressive dilation, markedly improves outcomes and helps prevent unnecessary tracheostomies.

Patients should be taught about the disorder so that relapses can be detected early. Patients should learn how to test their urine for blood and protein and be instructed to notify their physician at the first sign of hematuria.

Kidney transplantation has been successful; the risk of relapse after transplantation is reduced compared with maintenance dialysis treatment (possibly in part due to use of immunosuppressants to prevent rejection).
Chapter 35. Joint Disorders

Introduction

Joint disorders may be inflammatory (RA, spondyloarthropathies, crystal-induced arthritis) or relatively less inflammatory (osteoarthritis, neurogenic arthropathy). Crystal-induced arthritis and infectious arthritis are discussed elsewhere in THE MANUAL.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily involves the joints. RA causes damage mediated by cytokines, chemokines, and metalloproteases. Characteristically, peripheral joints (eg, wrists, metacarpophalangeal joints) are symmetrically inflamed, leading to progressive destruction of articular structures, usually accompanied by systemic symptoms. Diagnosis is based on specific clinical, laboratory, and imaging features. Treatment involves drugs, physical measures, and sometimes surgery. Disease-modifying antirheumatic drugs help control symptoms and slow disease progression.

RA affects about 1% of the population. Women are affected 2 to 3 times more often than men. Onset may be at any age, most often between 35 yr and 50 yr, but can be during childhood (see Juvenile Idiopathic Arthritis on p. 339) or old age.

Etiology

Although RA involves autoimmune reactions, the precise cause is unknown; many factors may contribute. A genetic predisposition has been identified and, in white populations, localized to a shared epitope in the HLA-DR β1 locus of class II histocompatibility antigens. Unknown environmental factors (eg, viral infections) are thought to play a role.

Pathophysiology

Prominent immunologic abnormalities include immune complexes produced by synovial lining cells and in inflamed blood vessels. Plasma cells produce antibodies (eg, rheumatoid factor [RF]) that contribute to these complexes, but destructive arthritis can occur in the absence of RF. Macrophages also migrate to diseased synovium in early disease; increased macrophage-derived lining cells are prominent along with vessel inflammation. Lymphocytes that infiltrate the synovial tissue are primarily CD4+ T cells. Macrophages and lymphocytes produce pro-inflammatory cytokines and chemokines (eg, tumor necrosis factors [TNF], granulocyte-macrophage colony-stimulating factor [GM-CSF], various ILs, interferon-γ) in the synovium. Release of inflammatory mediators probably contributes to the systemic and joint manifestations of RA.

In chronically affected joints, the normally thin synovium thickens and develops many villous folds. The synovial lining cells produce various materials, including collagenase and stromelysin, which contribute to cartilage destruction, and IL-1 and TNF-α, which stimulate cartilage destruction, osteoclast-mediated bone absorption, synovial inflammation, and prostaglandins (which potentiate inflammation). Fibrin deposition, fibrosis, and necrosis are also present. Hyperplastic synovial tissue (pannus) releases these inflammatory mediators, which erode cartilage, subchondral bone, articular capsule, and ligaments. PMNs on average make up about 60% of WBCs in the synovial fluid.

Rheumatoid nodules develop in about 30% of patients with RA. They are granulomas consisting of a central necrotic area surrounded by palisaded histiocytic macrophages, all enveloped by lymphocytes, plasma cells, and fibroblasts. Nodules and vasculitis can also develop in visceral organs.

Symptoms and Signs

Onset is usually insidious, often beginning with systemic and joint symptoms. Systemic symptoms include early morning stiffness of affected joints, generalized afternoon fatigue and malaise, anorexia, generalized
weakness, and occasionally low-grade fever. Joint symptoms include pain, swelling, and stiffness.

The disease progresses most rapidly during the first 6 yr, particularly the first year; 80% of patients develop some permanent joint abnormalities within 10 yr. The course is unpredictable in individual patients.

Joint symptoms are characteristically symmetric. Typically, stiffness lasts > 60 min after rising in the morning but may occur after any prolonged inactivity. Involved joints become tender, with erythema, warmth, swelling, and limitation of motion. The joints involved include the following:

• Wrist and the index and middle metacarpophalangeal joints (most commonly involved)
• Proximal interphalangeal joints
• Metatarsophalangeal joints
• Shoulders
• Elbows
• Hips
• Knees
• Ankles

However, virtually any joint except uncommonly the distal interphalangeal (DIP) joints may be involved. The axial skeleton is rarely involved except for the upper cervical spine. Synovial thickening is detectable. Joints are often held in flexion to minimize pain, which results from joint capsular distention.

Fixed deformities, particularly flexion contractures, may develop rapidly; ulnar deviation of the fingers with an ulnar slippage of the extensor tendons off the metacarpophalangeal joints is typical, as are swan-neck and boutonniere deformities (see Fig. 43-2 on p. 387). Joint instability can also occur. Carpal tunnel syndrome can result from wrist synovitis compressing the median nerve. Popliteal (Baker's) cysts can develop, causing calf swelling and tenderness suggestive of deep venous thrombosis.

Extra-articular manifestations: Subcutaneous rheumatoid nodules are not usually an early sign but eventually develop in up to 30% of patients, usually at sites of pressure and chronic irritation (eg, the extensor surface of the forearm, metacarpophalangeal joints, occiput). Visceral nodules, usually asymptomatic, are common in severe RA. Other extra-articular signs include vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, pulmonary nodules, pulmonary infiltrates or fibrosis, pericarditis, myocarditis, lymphadenopathy, Felty's syndrome, Sjogren's syndrome, scleromalacia, and episcleritis. Involvement of the cervical spine can cause atlantoaxial subluxation (see p. 385) and spinal cord compression (see p. 1810); it may worsen with extension of the neck (eg, during endotracheal intubation).

Diagnosis

• Clinical criteria

• Serum rheumatoid factor (RF) or anticyclic citrullinated peptide antibody (anti-CCP)

• X-rays

RA should be suspected in patients with polyarticular, symmetric arthritis, particularly if the wrists and 2nd and 3rd metacarpophalangeal joints are involved. Criteria for the diagnosis of RA are listed in Table 35-1. The presence of ≥ 4 criteria suggests the diagnosis. Other causes of symmetric polyarthritis,
particularly hepatitis C, must be excluded. Patients should have a serum RF test, hand and wrist x-rays, and baseline x-rays of affected joints to document future erosive changes.

[Table 35-1. Diagnosing Rheumatoid Arthritis*]

RFs, antibodies to human γ-globulin, are present in about 70% of patients with RA. However, RF, often in low titers, occurs in patients with other diseases, including other connective tissue diseases (eg, SLE), granulomatous diseases, chronic infections (eg, viral hepatitis, subacute bacterial endocarditis, TB), and cancers. Low RF titers can also occur in 3% of the general population and 20% of the elderly. An RF titer measured by latex agglutination of > 1:80 or a positive anti-CCP test supports the diagnosis of RA.

Anti-CCP antibodies have high specificity (90%) and sensitivity (96%) for RA and, like RF, predict a worse prognosis.

X-rays show only soft-tissue swelling during the first months of disease. Subsequently, periarticular osteoporosis, joint space (articular cartilage) narrowing, and marginal erosions may become visible. Erosions often develop within the first year but may occur any time. MRI seems to be more sensitive and detects earlier articular inflammation and erosions. In addition, abnormal subchondral bone signals (eg, bone marrow lesions, bone marrow edema) around the knee suggest progressive disease.

If RA is diagnosed, additional tests help detect complications and unexpected abnormalities. CBC with differential should be obtained. A normochromic (or slightly hypochromic)-normocytic anemia occurs in 80%; Hb is usually > 10 g/dL. If Hb is ≤ 10 g/dL, superimposed iron deficiency or other causes of anemia should be considered. Neutropenia occurs in 1 to 2% of cases, often with splenomegaly (Felty's syndrome). Acute-phase reactants (eg, thrombocytosis, elevated ESR, elevated C-reactive protein) reflect disease activity. A mild polyclonal hypergammaglobulinemia often occurs. ESR is elevated in 90% of patients with active disease.

Synovial fluid examination is necessary with any new-onset effusion to rule out other disorders and differentiate RA from other inflammatory arthritides (eg, septic and crystal-induced arthritis). In RA, during active joint inflammation, synovial fluid is turbid, yellow, and sterile, with reduced viscosity and usually 10,000 to 50,000 WBCs/μL; PMNs typically predominate, but > 50% may be lymphocytes and other mononuclear cells. Crystals are absent.

**Differential diagnosis:** Many disorders can simulate RA:

- Crystal-induced arthritis
- Osteoarthritis
- SLE
- Sarcoidosis
- Reactive arthritis
- Psoriatic arthritis
- Ankylosing spondylitis

RF can be nonspecific and is often present in several autoimmune diseases; the presence of anti-CCP antibodies is more specific for RA.

Some patients with crystal-induced arthritis may meet criteria for RA; however, synovial fluid examination should clarify the diagnosis. The presence of crystals makes RA unlikely. Joint involvement and subcutaneous nodules can result from gout, cholesterol, and amyloidosis as well as RA; aspiration or biopsy of the nodules may occasionally be needed.
SLE usually can be distinguished if there are skin lesions on light-exposed areas, hair loss, oral and nasal mucosal lesions, absence of joint erosions in even long-standing arthritis, joint fluid that often has < 2000 WBCs/μL (predominantly mononuclear cells), antibodies to double-stranded DNA, renal disease, and low serum complement levels. In contrast to RA, deformities in SLE are usually reducible because of the lack of erosions and bone or cartilage damage. Arthritis similar to RA can also occur in other rheumatic disorders (eg, polyarthritis, systemic sclerosis, dermatomyositis, or polymyositis) or there can be features of more than one disease, which suggests an overlap syndrome or mixed connective tissue disease.

Sarcoidosis, Whipple's disease, multicentric reticulohistiocytosis, and other systemic diseases may involve joints; other clinical features and tissue biopsy sometimes help differentiate these conditions.

Acute rheumatic fever has a migratory pattern of joint involvement and evidence of antecedent streptococcal infection (culture or changing antistreptolysin-O titer); in contrast, RA has an additive arthritis.

Reactive arthritis (see p. 343) can be differentiated by antecedent GI or GU symptoms; asymmetric involvement and pain at the Achilles insertion of the heel, sacroiliac joints, and large joints of the leg; conjunctivitis; iritis; painless buccal ulcers; balanitis circinata; or keratoderma blennorrhagicum on the soles and elsewhere.

Psoriatic arthritis (see p. 344) tends to be asymmetric and is not usually associated with RF, but differentiation may be difficult in the absence of nail or skin lesions. DIP joint involvement and severely mutilating arthritis (arthritis mutilans) is strongly suggestive, as is the presence of a diffusely swollen (sausage) digit. Ankylosing spondylitis (see p. 341) may be differentiated by spinal and axial joint involvement, absence of subcutaneous nodules, and negative RF test.

Osteoarthritis (see p. 345) can be differentiated by the joints involved; the absence of rheumatoid nodules, systemic manifestations, or significant amounts of RF; and synovial fluid WBC counts < 2000/μL. Osteoarthritis of the hands most typically involves the DIP and proximal interphalangeal joints. RA does not affect the DIP joints.

Prognosis

RA decreases life expectancy by 3 to 7 yr, with heart disease, infection, and GI bleeding accounting for most excess mortality; drug treatment, cancer, as well as the underlying disease may be responsible.

At least 10% of patients eventually are severely disabled despite full treatment. Whites and women have a poorer prognosis, as do patients with subcutaneous nodules, advanced age at disease onset, inflammation in ≥ 20 joints, early erosions, cigarette smoking, high ESR, and high levels of RF or anti-CCP.

Treatment

- Supportive measures (eg, nutrition, rest, physical measures, analgesics)
- NSAIDs
- Drugs that modify disease progression

Treatment involves a balance of rest and exercise, adequate nutrition, physical measures, drugs, and sometimes surgery.

Rest and nutrition: Complete bed rest is rarely indicated, even for a short time; however, a program including judicious rest should be prescribed. An ordinary nutritious diet is generally sufficient. Rarely, patients have food-associated exacerbations; no specific foods have been noted to exacerbate RA. Food and diet quackery is common and should be discouraged. Substituting ω-3 fatty acids (in fish oils) for dietary ω-6 fatty acids (in meats) may partially relieve symptoms by transiently decreasing production of inflammatory prostaglandins.
Physical measures: Joint splinting reduces local inflammation and may relieve severe symptoms. Cold may be applied to reduce pain from temporary worsening in one joint. Orthopedic or athletic shoes with good heel and arch support are frequently helpful; metatarsal supports placed posteriorly to painful metatarsophalangeal joints decrease the pain of weight bearing. Molded shoes may be needed for severe deformities. Self-help devices enable many patients with debilitating RA to perform activities of daily living.

Exercise should proceed as tolerated. During acute inflammation, passive range-of-motion exercise helps prevent flexion contractures. Heat therapy can be helpful. Range-of-motion exercises done in warm water are helpful because heat improves muscle function by reducing stiffness and muscle spasm. However, contractures can be prevented and muscle strength can be restored more successfully after inflammation begins to subside; active exercise (including walking and specific exercises for involved joints) to restore muscle mass and preserve range of joint motion should not be fatiguing. Flexion contractures may require intensive exercise, casting, or immobilization (eg, splinting) in progressively more stretched-open positions. Paraffin baths can warm digits and facilitate finger exercise. Massage by trained therapists, traction, and deep heat treatment with diathermy or ultrasonography may be useful.

Surgery: Surgery must always be considered in terms of the total disease and patient expectations. For example, deformed hands and arms limit crutch use during rehabilitation; seriously affected knees and feet limit benefit from hip surgery. Reasonable objectives for each patient must be determined, and function must be considered. Surgery may be done while the disease is active.

Arthroplasty with prosthetic joint replacement is indicated if damage severely limits function; total hip and knee replacements are most consistently successful. Prosthetic hips and knees cannot tolerate vigorous activity (eg, competitive athletics). Excision of subluxed painful metatarsophalangeal joints may greatly aid walking. Thumb fusions may provide stability for pinch. Neck fusion may be needed for C1-2 subluxation with severe pain or potential for spinal cord compression. Arthroscopic or open synovectomy can relieve joint inflammation but only temporarily unless disease activity can be controlled.

Drugs for RA

The goal is to reduce inflammation as a means of preventing erosions and progressive deformity. Disease-modifying antirheumatic drugs (DMARDs) are used early, often in combination. Other drug classes, including biologic agents, TNF-α antagonists, and IL-1 receptor antagonists, seem to slow the progression of RA. NSAIDs are of some help for the pain of RA but do not prevent erosions or disease progression. Sometimes low-dose systemic corticosteroids (prednisone < 10 mg daily) are added to control severe polyarticular symptoms, usually with the objective of replacement with a DMARD. Intra-articular depot corticosteroids can control severe monarticular or even oligoarticular symptoms. The optimal combinations of drugs are not yet clear. However, some data suggest that certain combinations of drugs from different classes (eg, methotrexate plus other DMARDs, a rapidly tapered corticosteroid plus a DMARD, methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist, a TNF-α antagonist or an IL-1 receptor antagonist plus a DMARD) are more effective than using DMARDs alone sequentially or in combination.

NSAIDs: Aspirin is no longer used for RA, as effective doses are often toxic. Only one NSAID should be given at a time (see Table 35-2), although patients may also take aspirin at ≤ 325 mg/day for its antiplatelet cardioprotective effect. Because the maximal response for NSAIDs can take up to 2 wk, doses should be increased no more frequently than this. Doses of drugs with flexible dosing can be increased until response is maximal or maximum dosage is reached. All NSAIDs treat the symptoms of RA and decrease inflammation but do not alter the course of the disease.

NSAIDs inhibit cyclooxygenase (COX) enzymes and thus decrease production of prostaglandins. Some prostaglandins under COX-1 control have important effects in [Table 35-2, NSAID Treatment of Rheumatoid Arthritis]
many parts of the body (ie, they protect gastric mucosa and inhibit platelet adhesiveness). Other
prostaglandins are induced by inflammation and are produced by COX-2. Selective COX-2 inhibitors, also
called coxibs (eg, celecoxib), seem to have efficacy comparable to nonselective NSAIDs and are less
likely to cause GI toxicity; however, they do not seem less likely to cause renal toxicity.

NSAIDs other than coxibs should be avoided in patients with previous peptic ulcer disease or dyspepsia.
Other possible adverse effects of all NSAIDs include headache, confusion and other CNS symptoms,
increased BP worsening of hypertension, edema, and decreased platelet function. The effect of NSAIDs
on cardiovascular risk is still unclear. Creatinine levels can rise reversibly because of inhibited renal
prostaglandins; less frequently, interstitial nephritis can occur. Patients with urticaria, rhinitis, or asthma
from aspirin can have the same problems with these other NSAIDs.

Traditional DMARDs: (See
Table 35-3
for specific dosage information and adverse effects of other drugs used to treat RA.)

These drugs seem to slow the progression of RA and are indicated in nearly all patients with RA. They
differ from each other chemically and pharmacologically. Many take weeks or months to have an effect.
About two thirds of patients improve overall, but complete remissions are uncommon. Many result in
evidence of decreased damage on imaging studies, presumably reflecting decreased disease activity.
They have minimal immediate analgesic effects, so NSAIDs or low-dose corticosteroids must often be
continued. Patients should be fully apprised of the risks of DMARDs and monitored carefully for evidence
of toxicity.

Combinations of DMARDs may be more effective than single drugs. For example, hydroxychloroquine,
sulfasalazine, and methotrexate together are more effective than methotrexate alone or the other two
together. Also, combining a DMARD with another drug, such as methotrexate plus a TNF-α antagonist or
an IL-1 receptor antagonist or a rapidly tapered corticosteroid, may be more effective than using DMARDs
alone.

Methotrexate is a folate antagonist with immunosuppressive effects at high dose. It is anti-inflammatory
at doses used in RA. It is very effective and has a relatively rapid onset (clinical benefit often within 3 to 4
wk). Methotrexate should be used with caution, if at all, in patients with hepatic dysfunction or renal
failure. Alcohol should be avoided. Supplemental folate, 1 mg po once/day, reduces the likelihood of
adverse effects. CBC, AST, ALT, and albumin and creatinine levels should be determined about every 8
wk. Rarely, a liver biopsy is needed if liver function test findings are persistently twice the upper limit of
normal or more and the patient needs to continue to use methotrexate. Severe relapses of arthritis can
occur after withdrawal of methotrexate. Paradoxically, rheumatoid nodules may enlarge with methotrexate
therapy.

Hydroxychloroquine can also control symptoms of mild RA. Funduscopic examination should be done
and visual fields should be assessed before and every 12 mo during treatment. The drug should be
stopped if no improvement occurs after 9 mo.

Sulfasalazine can alleviate symptoms and slow development of joint damage. It is usually given as
enteric-coated tablets. Benefit should occur within 3 mo. Enteric coating or dose reduction may increase
tolerability. CBCs should be obtained after 1 to 2 wk and then about every 12 wk during therapy. AST and
ALT should be obtained at about 6-mo intervals and whenever the dose is increased.

Leflunomide interferes with an enzyme involved with pyrimidine metabolism. It is about as effective as
methotrexate but is less likely to suppress bone marrow, cause abnormal liver function, or cause
pneumonitis.

Parenteral gold compounds are not commonly used anymore.

Corticosteroids: Systemic corticosteroids decrease inflammation and other symptoms more rapidly and
to a greater degree than other drugs. They also seem to slow bone erosion. However, they do not
prevent joint destruction, and their clinical benefit often diminishes with time. Furthermore, rebound often
follows the withdrawal of corticosteroids in active disease. Because of their long-term adverse effects,
Corticosteroids may be used for severe joint or systemic manifestations of RA (eg, vasculitis, pleurisy, pericarditis). Relative contraindications include peptic ulcer disease, hypertension, untreated infections, diabetes mellitus, and glaucoma. The risk of latent TB should be considered before corticosteroid therapy is begun.

**Intra-articular injections** of depot corticosteroids may temporarily help control pain and swelling in particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time. Triamcinolone acetonide and methylprednisolone acetate are also effective. No single joint should be injected with a corticosteroid more than 3 to 4 times a year, as too-frequent injections may accelerate joint destruction (although there are no specific data from humans to support this effect). Because injectable corticosteroid esters are crystalline, local inflammation transiently increases within a few hours in < 2% of injections. Although infection occurs in only < 1:40,000, it must be considered if pain occurs > 24 h after injection.

**Immunomodulatory, cytotoxic, and immunosuppressive drugs:** Treatment with azathioprine, cyclosporine (an immunomodulatory drug), or cyclophosphamide provides efficacy similar to DMARDs. However, these drugs are more toxic, particularly cyclophosphamide. Thus, they are used only for patients in whom treatment with DMARDs has failed or to decrease the need for corticosteroids. They are used infrequently unless there are extra-articular complications. For maintenance therapy with azathioprine, the lowest effective dose should be used. Low-dose cyclosporine may be effective alone or when combined with methotrexate. It may be less toxic than azathioprine and cyclophosphamide.

**Biologic agents:** Biologic response modifiers other than TNF-α antagonists can be used to target B cells or T cells.

**Rituximab** is an anti-CD 20 antibody that depletes B cells. It can be used in refractory patients. Response is often delayed but may last 6 mo. The course can be repeated in 6 mo. Mild adverse effects are common, and analgesia, corticosteroids, diphenhydramine, or a combination may need to be given concomitantly. Rituximab is given only to patients who have not improved after using a TNF inhibitor and methotrexate.

**Abatacept**, a soluble fusion cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) Ig, is indicated for patients with RA with an inadequate response to other DMARDs.

[Table 35-3, Other Drugs Used to Treat RA]

**Other agents: Anakinra** is a recombinant IL-1 receptor antagonist. IL-1 is heavily involved in the pathogenesis of RA. Infection and leukopenia can be a problem, particularly when given in combination with a TNF antagonist.

**TNF-α antagonists** (eg, adalimumab, etanercept, and infliximab) reduce the progression of erosions and reduce the number of new erosions. Although not all patients respond, many have a prompt, dramatic feeling of well being, sometimes with the first injection. Inflammation is often dramatically reduced.

Although there are some differences among agents, the most serious problem is infection, particularly with reactivated TB. Patients should be screened for TB with PPD. Etanercept, infliximab, and adalimumab can and probably should be used with methotrexate. High-dose infliximab should not be used in patients with severe heart failure.

**Juvenile Idiopathic Arthritis**

Juvenile idiopathic arthritis (JIA) is a group of rheumatic diseases that begins at or before age 16. Arthritis, fever, rash, adenopathy, splenomegaly, and iridocyclitis are typical of some forms. Diagnosis is clinical. Treatment involves NSAIDs and disease-modifying antirheumatic drugs.
JIA is uncommon. The cause is unknown, but there seems to be a genetic predisposition and an autoimmune pathophysiology. JIA may be similar to adult RA (see p. 332), but most forms are slightly different.

**Symptoms and Signs**

Patients with JIA can have joint stiffness, swelling, effusion, pain, and tenderness. JIA may interfere with growth and development. Micrognathia (receded chin) due to early closure of mandibular epiphyses may occur. Iridocyclitis may develop, which may cause conjunctival injection, pain, and photophobia but can be asymptomatic; scarring and glaucoma with band keratopathy can result. The initial symptoms and signs of JIA tend to fall into 3 possible patterns.

**Systemic onset** (Still's disease) occurs in about 20% of patients. High fever, rash, splenomegaly, generalized adenopathy, and serositis with pericarditis or pleuritis are common. These symptoms may precede the development of arthritis. Fever (quotidian) is often highest in the afternoon or evening and may persist for up to 2 wk. A typical transient rash often appears with the fever or may be diffuse and migratory, with urticarial or macular lesions.

**Pauciarticular onset** is characterized by involvement of ≤ 4 joints. It occurs in about 40% of patients, usually young girls. Iridocyclitis is most common in pauciarticular JIA, developing in nearly 20%. Many affected older boys have the HLA-B27 allele. Most of these boys subsequently develop classic features of one of the spondyloarthropathies (eg, ankylosing spondylitis, psoriatic arthritis, reactive arthritis).

**Polyarticular onset** involves ≥ 5 joints, often ≥ 20. It occurs in the remaining 40% of patients and is often similar to adult RA. Arthritis tends to be symmetric and develop slowly.

**Diagnosis**

- Clinical criteria
- Rheumatoid factor (RF) and antinuclear antibodies (ANA)

JIA should be suspected in children with symptoms of arthritis, signs of iridocyclitis, generalized adenopathy, splenomegaly, or unexplained rash or fever lasting more than a few days. Diagnosis is primarily clinical. Patients suspected of having JIA should be tested for RF, ANA, and ESR because these tests may be helpful in diagnosing JIA and distinguishing its subtypes. In Still's disease, RF and ANA are absent. In pauciarticular-onset JIA, ANA are present in up to 75% and RF is absent. In polyarticular-onset JIA, RF usually is negative, but in some patients, mostly adolescent girls, it can be positive.

To diagnose iridocyclitis, slit-lamp examination should be done, even in the absence of ocular symptoms. A recently diagnosed patient with pauciarticular onset should have an eye examination every 3 to 4 mo, and a patient with polyarticular onset should have an eye examination about every 6 mo.

**Prognosis**

Complete remissions occur in 50 to 75% of treated patients. Patients with polyarticular onset and a positive RF have a less favorable prognosis.

**Treatment**

- Drugs that slow disease progression
- Usually NSAIDs

Similar to the therapy of patients with adult RA, disease-modifying antirheumatic drugs (DMARDs), particularly the biologic agents, have dramatically changed the therapeutic approach.

Symptoms may be reduced with NSAIDs. Naproxen 5 to 10 mg/kg po bid, ibuprofen 5 to 10 mg/kg po qid,
and indomethacin 0.5 to 1.0 mg/kg po tid are among the most useful. Salicylates are rarely used because of their possible role in causing Reye’s syndrome (see p. 2937). Excerpt for severe systemic disease, systemic corticosteroids can usually be avoided. When necessary, the lowest possible dose is used (eg, oral prednisone, 0.0125 to 0.5 mg/kg qid, or the same daily dose given once or twice daily). Growth retardation, osteoporosis, and osteonecrosis are the major hazards of prolonged corticosteroid use in children. Intra-articular depot corticosteroids can be given. The dosage for children is adjusted based on weight. Children may need to be sedated for intra-articular injection. Methotrexate is useful for pauciarticular and polyarticular disease. Adverse effects are monitored as in adults. Bone marrow depression and hepatic toxicity are monitored with CBC, AST, ALT, and albumin. Occasionally, sulfasalazine is used, especially in cases of suspected spondyloarthropathy. IM gold and penicillamine are rarely used. Etanercept, used as in adults, blocks tumor necrosis factor-α (TNF-α) and is often effective; 0.4 mg/kg sc (up to a maximum of 25 mg) is given twice/wk. Anakinra is particularly effective in some patients with systemic-onset disease. Physical therapy, exercises, splints, and other supportive measures help prevent flexion contractures. Adaptive devices can improve function and minimize unnecessary stresses on inflamed joints. Iridocyclitis is treated with ophthalmic corticosteroid drops and mydriatics (see p. 609).

**Seronegative Spondyloarthropathies**

(Seronegative Spondyloarthritides)

Seronegative spondyloarthropathies share certain clinical characteristics (eg, back pain, uveitis, GI symptoms, rashes). Some are strongly associated with the HLA-B27 allele. Clinical and genetic similarities suggest that they also share similar causes or pathophysiologies. Rheumatoid factor (RF) is negative in the spondyloarthropathies (hence, why they are called seronegative spondyloarthropathies). They include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and other disorders.

**Ankylosing Spondylitis**

Ankylosing spondylitis (AS) is a systemic disorder characterized by inflammation of the axial skeleton, large peripheral joints, and digits; nocturnal back pain; back stiffness; accentuated kyphosis; constitutional symptoms; aortitis; cardiac conduction abnormalities; and anterior uveitis. Diagnosis requires showing sacroiliitis on x-ray. Treatment is with NSAIDs or tumor necrosis factor antagonists and physical measures that maintain joint flexibility.

AS is 3 times more frequent in men than in women and begins most often between ages 20 and 40. It is 10 to 20 times more common among 1st-degree relatives of AS patients than in the general population. The risk of AS in 1st-degree relatives with the HLA-B27 allele is about 20%. Increased prevalence of HLA-B27 in whites or HLA-B7 in blacks supports a genetic predisposition. However, the concordance rate in identical twins is only about 50%, suggesting that environmental factors contribute. The pathophysiology probably involves immune-mediated inflammation.

**Symptoms and Signs**

The most frequent manifestation is back pain, but disease can begin in peripheral joints, especially in children and women, and rarely with acute iridocyclitis (iritis or anterior uveitis). Other early symptoms and signs are diminished chest expansion from diffuse costovertebral involvement, low-grade fever, fatigue, anorexia, weight loss, and anemia.

Back pain—often nocturnal and of varying intensity—eventually becomes recurrent. Morning stiffness, typically relieved by activity, and paraspinal muscle spasm develop. A flexed or bent-over posture eases back pain and paraspinal muscle spasm; thus, kyphosis is common in untreated patients. Severe hip arthritis can eventually develop. In late stages, the patient has accentuated kyphosis, loss of lumbar
lordosis, and fixed bent-forward posturing, with compromised pulmonary function and inability to lie flat. There may be peripheral potentially deforming joint involvement, sometimes involving the digits (dactylitis). Achilles tendinitis can occur.

Systemic manifestations occur in one third of patients. Recurrent, acute anterior uveitis is common but usually self-limited; uncommonly it becomes protracted and severe enough to impair vision. Neurologic signs occasionally result from compression radiculitis or sciatica, vertebral fracture or subluxation, or cauda equina syndrome (see p. 1806). Cardiovascular manifestations can include aortic insufficiency, aortitis, angina, pericarditis, and cardiac conduction abnormalities (which may be asymptomatic). Dyspnea, cough, or hemoptysis can result from nontuberculous fibrosis or cavitation of an upper lobe of the lung; secondary infection with Aspergillus can develop. Rarely, AS results in secondary amyloidosis. Subcutaneous nodules do not develop.

Diagnosis

- Lumbosacral spine imaging
- Blood tests (ESR, C-reactive protein, and CBC) or explicit clinical criteria (modified New York criteria)

AS should be suspected in patients, particularly young men, with nocturnal back pain and kyphosis, diminished chest expansion, Achilles tendinitis, or unexplained anterior uveitis. A 1st-degree relative with AS should heighten suspicion. Patients should generally be tested with ESR, C-reactive protein, and CBC. IgM, RF, and antinuclear antibodies are needed only if peripheral arthritis suggests other diagnoses. No laboratory test is diagnostic, but results can increase suspicion for the disorder or rule out other disorders than can simulate AS. If, after these tests, AS is still suspected, patients should undergo imaging of the lumbosacral spine; demonstration of sacroiliitis on x-ray strongly supports the diagnosis.

Alternatively, AS can be diagnosed by the modified New York criteria. Using these criteria, the patient must have imaging study evidence of sacroiliitis and one of the following:

- Restriction of lumbar spinal motion in both the sagittal (looking from the side) and frontal (looking from the back) planes
- Restriction of chest expansion, adjusted for age
- A history of inflammatory back pain

Historical features that distinguish inflammatory back pain from noninflammatory back pain include onset at ≤ 40 yr, gradual onset, morning stiffness, improvement with activity, and duration ≥ 3 mo before seeking medical attention.

ESR and other acute-phase reactants (eg, C-reactive protein) are inconsistently elevated in patients with active AS. Tests for RF and antinuclear antibodies are negative. The HLA-B27 genetic marker is not of diagnostic value.

The earliest x-ray abnormalities are pseudowidening from subchondral erosions, followed by sclerosis or later narrowing and eventually fusion in the sacroiliac joints. Changes are symmetric. Early changes in the spine are upper lumbar vertebral squaring with sclerosis at the corners; spotty ligamentous calcification; and one or two evolving syndesmophytes. Late changes result in a "bamboo spine" appearance, resulting from prominent syndesmophytes, diffuse paraspinal ligamentous calcification, and osteoporosis; these changes develop in some patients on average over 10 yr.

Changes typical of AS may not become visible on plain x-rays for years. CT and MRI show changes earlier, but there is no consensus regarding their role in routine diagnosis.

A herniated intervertebral disk can cause back pain and radiculopathy similar to AS, but the pain is limited to the spine, usually causes more sudden symptoms, and causes no systemic manifestations or
laboratory test abnormalities. If necessary, CT or MRI can differentiate it from AS. Involvement of a single sacroiliac joint suggests a different spondyloarthropathy, possibly infection. Tuberculous spondylitis can simulate AS (see p. 1313).

**Diffuse idiopathic skeletal hyperostosis (DISH)** occurs primarily in men > 50 yr and may resemble AS clinically and on x-ray. Patients uncommonly have spinal pain, stiffness, and insidious loss of motion. X-ray findings in DISH include large ossifications anterior to spinal ligaments (the calcification appears as if someone poured candle wax in front and on the sides of the vertebrae), bridging several vertebrae and usually starting at the lower thoracic spine, eventually affecting the cervical and lumbar spine. There is often subperiosteal bone growth along the pelvic brim and at insertion of tendons (such as the Achilles tendon insertion). However, the anterior spinal ligament is intact and frequently bulging, and sacroiliac and spinal apophyseal joints are not eroded. Additional differentiating features are stiffness that is not accentuated in the morning and a normal ESR.

**Prognosis**

AS is characterized by mild or moderate flares of active inflammation alternating with periods of little or no inflammation. Proper treatment in most patients results in minimal or no disability and in a full, productive life despite back stiffness. Occasionally, the course is severe and progressive, resulting in pronounced incapacitating deformities.

**Treatment**

- **NSAIDs**
- **Sulfasalazine, methotrexate, or tumor necrosis factor (TNF) antagonists**
- **Exercises and supportive measures**

The goals of treatment are relieving pain, maintaining joint range of motion, and preventing end-organ damage. Because the condition may cause lung fibrosis, cigarette smoking is discouraged.

NSAIDs reduce pain and suppress joint inflammation and muscle spasm, thereby increasing range of motion, which facilitates exercise and prevents contractures. Most NSAIDs work in AS, and tolerance and toxicity dictate drug choice. The daily dose of NSAIDs should be as low as possible, but maximum doses may be needed with active disease. Drug withdrawal should be attempted only slowly, after systemic and joint signs of active disease have been suppressed for several months.

Sulfasalazine may help reduce peripheral joint symptoms and laboratory markers of inflammation. Dosage should be started at 500 mg/day and increased by 500 mg/day at 1-wk intervals to 1 to 1.5 g bid maintenance. Peripheral joint symptoms may also abate with methotrexate (see p. 337). Systemic corticosteroids, immunosuppressants, and most disease-modifying antirheumatic drugs have no proven benefit and should generally not be used. TNF-α antagonists (eg, etanercept, infliximab, adalimumab) are effective treatments for inflammatory back pain.

For proper posture and joint motion, daily exercise and other supportive measures (eg, postural training, therapeutic exercise) are vital to strengthen muscle groups that oppose the direction of potential deformities (ie, the extensor rather than flexor muscles). Reading while lying prone and pushing up on the elbows or pillows and thus extending the back may help keep the back flexible. Because chest wall motion can be restricted, which impairs lung function, cigarette smoking, which also impairs lung function, is strongly discouraged.

Intra-articular depot corticosteroids may be beneficial, particularly when one or two peripheral joints are more severely inflamed than others, thereby compromising exercise and rehabilitation. They may also help if systemic drugs are ineffective. Corticosteroids injected into the sacroiliac joints may occasionally help severe sacroiliitis.

For acute uveitis, topical corticosteroids and mydriatics are usually adequate. If severe hip arthritis
develops, total hip arthroplasty may lessen pain and improve flexibility dramatically.

Reactive Arthritis

Reactive arthritis is an acute spondyloarthropathy that often seems precipitated by an infection, usually GU or GI. Common manifestations include asymmetric arthritis of variable severity that tends to affect the lower extremities, sausage-shaped deformities of fingers or toes or both, constitutional symptoms, enthesitis, tendinitis, and mucocutaneous ulcers, including hyperkeratotic or crusted vesicular lesions (keratoderma blennorrhagicum). Diagnosis is clinical. Treatment involves NSAIDs and sometimes sulfasalazine or immunosuppressants.

Spondyloarthropathy associated with urethritis or cervicitis, conjunctivitis, and mucocutaneous lesions (previously called Reiter’s syndrome) is one type of reactive arthritis.

Etiology

Two forms of reactive arthritis are common: sexually transmitted and dysenteric. The sexually transmitted form occurs primarily in men aged 20 to 40. Genital infections with *Chlamydia trachomatis* are most often implicated. Men or women can acquire the dysenteric form after enteric infections, primarily *Shigella, Salmonella, Yersinia*, or *Campylobacter*. Reactive arthritis probably results from joint infection or postinfectious inflammation. Although there is evidence of microbial antigens in the synovium, organisms cannot be cultured from joint fluid.

Epidemiology: The prevalence of the HLA-B27 allele in patients is 63 to 96% vs 6 to 15% in healthy white controls, thus supporting a genetic predisposition.

Symptoms and Signs

Reactive arthritis can range from transient monarticular arthritis to a severe, multisystem disorder. Constitutional symptoms may include fever, fatigue, and weight loss. Arthritis may be mild or severe. Joint involvement is generally asymmetric and oligoarticular or polyarticular, occurring predominantly in the large joints of the lower extremities and in the toes. Back pain may occur, usually with severe disease. Enthesopathy (inflammation at tendinous insertion into bone—eg, plantar fasciitis, digital periostitis, Achilles tendinitis) is common and characteristic. Mucocutaneous lesions—small, transient, relatively painless, superficial ulcers—commonly occur on the oral mucosa, tongue, and glans penis (balanitis circinata). Particularly characteristic are vesicles (sometimes identical to pustular psoriasis) of the palms and soles and around the nails that become hyperkeratotic and form crusts (keratoderma blennorrhagicum). Rarely, cardiovascular complications (eg, aortitis, aortic insufficiency, cardiac conduction defects), pleuritis, and CNS or peripheral nervous system symptoms develop.

Urethritis may develop 7 to 14 days after sexual contact (or occasionally after dysentery); low-grade fever, conjunctivitis, and arthritis develop over the next few weeks. Not all features may occur, so incomplete forms need to be considered. In men, the urethritis is less painful and productive of purulent discharge than acute gonococcal urethritis and may be associated with hemorrhagic cystitis or prostatitis. In women, urethritis and cervicitis may be mild (with dysuria or slight vaginal discharge) or asymptomatic. Conjunctivitis is the most common eye lesion. It usually causes eye redness and grittiness, but keratitis and anterior uveitis can develop also, causing eye pain, photophobia, and tearing.

Diagnosis

- Typical arthritis
- Symptoms of GI or GU infection
- One other extra-articular feature

Reactive arthritis should be suspected in patients with acute, asymmetric arthritis affecting the large joints of the lower extremities or toes, particularly if there is tendinitis or a history of an antecedent diarrhea or...
dysuria. Diagnosis is ultimately clinical and requires the typical peripheral arthritis with symptoms of GU or GI infection or one of the other extra-articular features. Because these features may manifest at different times, definitive diagnosis may require several months. Serum and synovial fluid complement levels are high, but these findings are not usually diagnostic and need not be measured.

Disseminated gonococcal infection can closely simulate reactive arthritis (see p. 1472). Arthrocentesis may fail to differentiate them, owing to inflammatory characteristics of synovial fluid in both disorders and the difficulty of culturing gonococci from this fluid. Clinical characteristics may help; disseminated gonococcal infection tends to involve upper and lower extremities equally, be more migratory, and not produce back pain, and vesicles tend not to be hyperkeratotic. A positive gonococcal culture from blood or skin lesions helps differentiate the two disorders, but a positive culture from the urethra or cervix does not. If differentiation is still difficult, ceftriaxone may be required for simultaneous diagnosis and treatment.

Psoriatic arthritis can simulate reactive arthritis, causing similar skin lesions, uveitis, and asymmetric arthritis. However, psoriatic arthritis often affects mostly the upper extremities and especially the distal interphalangeal joints, may be abrupt in onset but may also develop gradually, causes less enthesopathy, and tends not to cause mouth ulcers or symptoms of GU or GI infection.

**Prognosis**

Reactive arthritis often resolves in 3 to 4 mo, but up to 50% of patients experience recurrent or prolonged symptoms over several years. Joint, spinal, or sacroiliac inflammation or deformity may occur with chronic or recurrent disease. Some patients are disabled.

**Treatment**

- **NSAIDs**
- **Sometimes sulfasalazine, doxycycline, azathioprine or methotrexate, or a combination**
- **Supportive measures**

NSAIDs (eg, indomethacin 25 to 50 mg po tid) usually help relieve symptoms. If induced by infection with *C. trachomatis*, doxycycline 100 mg po bid for up to 3 mo may accelerate recovery, but this is controversial. Sulfasalazine as used to treat RA may also be helpful (see p. 337). If symptoms are severe despite NSAIDs and sulfasalazine, azathioprine or methotrexate may be considered. Systemic corticosteroids have no proven value.

Local injection of depot corticosteroids for enthesopathy or resistant oligoarthritis may relieve symptoms. Physical therapy aimed at maintaining joint mobility is helpful during the recovery phase. Anterior uveitis is treated as usual, with corticosteroid and mydriatic eye drops to prevent scarring. Conjunctivitis and mucocutaneous lesions require only symptomatic treatment.

**Psoriatic Arthritis**

Psoriatic arthritis is a chronic inflammatory arthritis that occurs in people with psoriasis of the skin or nails. The arthritis is often asymmetric, and some forms involve the distal interphalangeal joints. Diagnosis is clinical. Treatment is usually similar to that of RA but can also involve phototherapy.

Psoriatic arthritis develops in 5 to 40% of patients with psoriasis. Prevalence is increased in patients with AIDS. Risk of some involvement is increased in patients with HLA-B27 or some other specific alleles and in family members. Etiology and pathophysiology are unknown.

**Symptoms and Signs**

Psoriasis of the skin or nails may precede or follow joint involvement. Skin lesions may be hidden in the scalp, gluteal folds, or umbilicus and go unrecognized by the patient.
The distal interphalangeal (DIP) joints of fingers and toes are especially affected. Asymmetric involvement of large and small joints, including the sacroiliacs and spine, is common. Joint and skin symptoms may lessen or worsen simultaneously. Inflammation of the fingers, toes, or both may lead to sausage-shaped deformities. Rheumatoid nodules are absent. Arthritic remissions tend to be more frequent, rapid, and complete than in RA, but progression to chronic arthritis and crippling may occur. There may be arthritis mutilans (destruction of multiple hand joints with telescoping of the digits).

Back pain may be present. It is often accompanied by asymmetric syndesmophytes of the spine.

**Diagnosis**

- Clinical evaluation
- RF

Psoriatic arthritis should be suspected in patients with both psoriasis and arthritis. Because psoriasis may be overlooked or hidden or develop only after arthritis occurs, psoriatic arthritis should be considered in any patient with seronegative inflammatory arthritis; these patients should be examined for psoriasis and nail pitting and should be questioned about a family history of psoriasis. Patients suspected of having psoriatic arthritis should be tested for rheumatoid factor, which can coexist. Psoriatic arthritis is diagnosed clinically and by excluding other disorders that can cause such similar manifestations. X-ray findings common in psoriatic arthritis include DIP involvement; resorption of terminal phalanges; arthritis mutilans; and extensive destruction, proliferative bone reaction, and dislocation of large and small joints.

**Treatment**

- Arthritis treated generally similarly to RA
- Phototherapy

Treatment is directed at control of skin lesions (see p. 677) and at joint inflammation. Drug therapy is similar to that for RA, particularly methotrexate. Hydroxychloroquine is inconsistently of benefit and may cause exfoliative dermatitis or aggravate underlying psoriasis. Benefit may be gained from NSAIDs, cyclosporine, and TNF antagonists (see p. 335 under Drugs for RA); TNF antagonists have been particularly effective.

Phototherapy using long-wave psoralen plus ultraviolet A (PUVA) combined with oral methoxsalen 600 μg/kg po 2 h before PUVA twice/wk seems to be highly effective for psoriatic lesions and somewhat effective for peripheral arthritis, but not for spine involvement.

**Other Spondyloarthropathies**

Spondyloarthropathy can develop in association with GI conditions (sometimes called enteropathic arthritis) such as inflammatory bowel disease, intestinal bypass surgery, or Whipple's disease.

Juvenile-onset spondyloarthropathy is an asymmetric, mostly lower extremity spondyloarthropathy that begins most commonly in boys aged 7 to 16.

Spondyloarthropathy can also develop in people without characteristics of other specific spondyloarthropathy (undifferentiated spondyloarthropathy). Treatment of the arthritis of these other spondyloarthropathies is similar to that of treatment of reactive arthritis (see p. 344).

**Osteoarthritis**

(Degenerative Joint Disease; Osteoarthrosis; Hypertrophic Osteoarthritis)

Osteoarthritis (OA) is a chronic arthropathy characterized by disruption and potential loss of
joint cartilage along with other joint changes, including bone hypertrophy (osteophyte formation). Symptoms include gradually developing pain aggravated or triggered by activity, stiffness lasting < 30 min on awakening and after inactivity, and occasional joint swelling. Diagnosis is confirmed by x-rays. Treatment includes physical measures (including rehabilitation), patient education, and drugs.

OA, the most common joint disorder, often becomes symptomatic in the 40s and 50s and is nearly universal (although not always symptomatic) by age 80. Only half of patients with pathologic changes of OA have symptoms. Below age 40, most OA is in men and results from trauma. Women predominate from age 40 to 70, after which men and women are equally affected.

Classification

OA is classified as primary (idiopathic) or secondary to some known cause.

Primary OA may be localized to certain joints (eg, chondromalacia patellae is a mild OA that occurs in young people). Primary OA is usually subdivided by the site of involvement (eg, hands and feet, knee, hip). If primary OA involves multiple joints, it is classified as primary generalized OA.

Secondary OA results from conditions that change the microenvironment of the cartilage. These conditions include significant trauma, congenital joint abnormalities, metabolic defects (eg, hemochromatosis, Wilson's disease), infections (causing postinfectious arthritis), endocrine and neuropathic diseases, and disorders that alter the normal structure and function of hyaline cartilage (eg, RA, gout, chondrocalcinosis).

Pathophysiology

Normal joints have little friction with movement and do not wear out with typical use, overuse, or trauma. Hyaline cartilage is avascular, aneural, and alymphatic. It is 95% water and extracellular cartilage matrix and only 5% chondrocytes. Chondrocytes have the longest cell cycle in the body (similar to CNS and muscle cells). Cartilage health and function depend on compression and release of weight bearing and use (ie, compression pumps fluid from the cartilage into the joint space and into capillaries and venules, whereas release allows the cartilage to reexpand, hyperhydrate, and absorb necessary electrolytes and nutrients).

OA begins with tissue damage from mechanical injury (eg, torn meniscus), transmission of inflammatory mediators from the synovium into cartilage, or defects in cartilage metabolism. The tissue damage stimulates chondrocytes to attempt repair, which increases production of proteoglycans and collagen. However, efforts at repair also stimulate the enzymes that degrade cartilage, as well as inflammatory cytokines, which are normally present in small amounts. Inflammatory mediators trigger an inflammatory cycle that further stimulates the chondrocytes and synovial lining cells, eventually breaking down the cartilage. Chondrocytes undergo programmed cell death (apoptosis). Once cartilage is destroyed, exposed bone becomes eburnated and sclerotic.

All articular and some periarticular tissues become involved in OA. Subchondral bone stiffens, then undergoes infarction, and develops subchondral cysts. Attempts at bony repair cause subchondral sclerosis and osteophytes at the joint margins. The osteophytes seem to develop in an attempt to stabilize the joint. The synovium becomes inflamed and thickened and produces synovial fluid with less viscosity and greater volume. Periarticular tendons and ligaments become stressed, resulting in tendinitis and contractures. As the joint becomes less mobile, surrounding muscles thin and become less supportive. Menisci fissure and may fragment.

OA of the spine can, at the disk level, cause marked thickening and proliferation of the posterior longitudinal ligaments, which are posterior to the vertebral body but anterior to the spinal cord. The result can be transverse bars that encroach on the anterior spinal cord. Hypertrophy and hyperplasia of the ligamenta flava, which are posterior to the spinal cord, often compress the posterior canal, causing lumbar spinal stenosis. In contrast, the anterior and posterior nerve roots, ganglia, and common spinal nerve are relatively well protected in the intervertebral foramina, where they occupy only 25% of the
Symptoms and Signs

Onset is most often gradual, usually beginning with one or a few joints. Pain is the earliest symptom, sometimes described as a deep ache. Pain is usually worsened by weight bearing and relieved by rest but can eventually become constant. Stiffness follows awakening or inactivity but lasts < 30 min and lessens with movement. As OA progresses, joint motion becomes restricted, and tenderness and crepitus or grating sensations develop. Proliferation of cartilage, bone, ligament, tendon, capsules, and synovium, along with varying amounts of joint effusion, ultimately cause the joint enlargement characteristic of OA. Flexion contractures may eventually develop. Acute and severe synovitis is uncommon.

Tenderness on palpation and pain on passive motion are relatively late signs. Muscle spasm and contracture add to the pain. Mechanical block by intra-articular loose bodies or abnormally placed menisci can occur and cause locking or catching. Deformity and subluxations can also develop.

The joints most often affected in generalized OA include the following:

- Distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints (causing Heberden's and Bouchard's nodes)
- Thumb carpometacarpal joint
- Intervertebral disks and zygapophyseal joints in the cervical and lumbar vertebrae
- First metatarsophalangeal joint
- Hip
- Knee

Cervical and lumbar spinal OA may lead to myelopathy or radiculopathy. However, the clinical signs of myelopathy are usually mild. Lumbar spinal stenosis may cause lower back or leg pain that is worsened by walking or back extension. Radiculopathy can be prominent but is less common because the nerve roots and ganglia are well protected. Insufficiency of the vertebral arteries, infarction of the spinal cord, and dysphagia due to esophageal impingement by osteophytes occasionally occur. Symptoms and signs from OA in general may also derive from subchondral bone, ligamentous structures, synovium, periarticular bursae, capsules, muscles, tendons, disks, and periostium, all of which are pain sensitive. Venous pressure may increase within the subchondral bone marrow and cause pain (sometimes called bone angina).

Hip OA causes gradual loss of range of motion. Pain may be felt in the inguinal area or greater trochanter or referred to the knee.

Knee OA causes cartilage to be lost (medial loss occurs in 70% of cases). The ligaments become lax and the joint becomes less stable, with local pain arising from the ligaments and tendons.

Erosive OA causes synovitis and cysts in the hand. It primarily affects the DIP or PIP joints. The thumb carpometacarpal joints are involved in 20% of hand OA, but the metacarpophalangeal joints and wrists are usually spared. At this time, it is uncertain whether erosive interphalangeal OA is a variant of hand OA or whether it represents a separate entity.

OA is usually sporadically progressive but occasionally, with no predictability, stops or reverses.

Diagnosis

- X-rays
OA should be suspected in patients with gradual onset of symptoms and signs, particularly in older adults. If OA is suspected, plain x-rays should be taken of the most symptomatic joints. X-rays generally reveal marginal osteophytes, narrowing of the joint space, increased density of the subchondral bone, subchondral cyst formation, bony remodeling, and joint effusions. Standing x-rays of knees are more sensitive in detecting joint space narrowing.

Laboratory studies are normal in OA but may be required to rule out other disorders (eg, RA) or to diagnose an underlying disorder causing secondary OA. If OA causes joint effusions, synovial fluid analysis can help differentiate it from inflammatory arthritides; in OA, synovial fluid is usually clear, viscous, and has ≤ 2000 WBC/μL.

OA involvement outside the usual joints suggests secondary OA; further evaluation may be required to determine the underlying primary disorder (eg, endocrine, metabolic, neoplastic, biomechanical disorders).

Treatment

- Rehabilitative and supportive measures

- Adjunctive drug therapy

Treatment goals are relieving pain, maintaining joint flexibility, and optimizing joint and overall function. Primary treatments include physical measures that involve rehabilitation; support devices; exercise for strength, flexibility, and endurance; patient education; and modifications in activities of daily living. Adjunctive therapies include drug treatment and surgery.

Physical measures: Rehabilitation techniques are best begun before disability develops. Exercises (range of motion, isometric, isotonic, isokinetic, postural, strengthening—see p. 3453) maintain range of motion and increase the capacity for tendons and muscles to absorb stress during joint motion. Exercise can sometimes arrest or even reverse hip and knee OA. Stretching exercises should be done daily. Immobilization for any prolonged period of time can promote contractures and worsen the clinical course. However, a few minutes of rest (every 4 to 6 h in the daytime) can help if balanced with exercise and use.

Modifying activities of daily living can help. For example, a patient with lumbar spine, hip, or knee OA should avoid soft deep chairs and recliners in which posture is poor and from which rising is difficult. The regular use of pillows under the knees while reclining encourages contractures and should also be avoided. Patients should sit in straight-back chairs without slumping, sleep on a firm bed, perhaps with a bed board, use a car seat shifted forward and designed for comfort, do postural exercises, wear well-supported shoes or athletic shoes, and continue employment and physical activity.

In OA of the spine, knee, or thumb carpometacarpal joint, various supports can relieve pain and increase function, but to preserve flexibility, they should be accompanied by specific exercise programs. In erosive OA, range-of-motion exercises done in warm water can help prevent contractures.

Drugs: Drug therapy is an adjunct to the physical program. Acetaminophen in doses of up to 1 g po qid may relieve pain and is safe. More potent analgesia may be required.

NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors or coxibs, may be considered if patients have refractory pain or signs of inflammation (eg, redness, warmth). NSAIDs may be used simultaneously with other analgesics (eg, tramadol, opioids) to provide better relief of symptoms.

Muscle relaxants (usually in low doses) occasionally relieve pain that arises from muscles strained by attempting to support OA joints. In the elderly, however, they may cause more adverse effects than relief.

Oral corticosteroids have no role. However, intra-articular depot corticosteroids help relieve pain and increase joint flexibility.

Synthetic hyaluronans (similar to hyaluronic acid, a normal component of the joint) can be injected into
the knee, with pain relief for prolonged periods of time (up to a year). However, the effect seems to be small. The treatment is a series of 3 to 5 weekly injections.

Glucosamine sulfate 1500 mg po once/day has been suggested to relieve pain and slow joint deterioration; chondroitin sulfate 1200 mg once/day has also been suggested for pain relief. Studies to date have shown mixed results in terms of pain relief.

Other adjunctive and experimental therapies: Other adjunctive measures can relieve pain, including massage, heating pads, weight loss, acupuncture, transcutaneous electrical nerve stimulation, and local rubs (eg, with capsaicin). Laminectomy, osteotomy, and total joint replacement should be considered if all nonsurgical approaches fail. (See also the Agency for Healthcare Research and Quality's Evidence-Based Practice Program's evidence report.)

Experimental therapies that may preserve cartilage or allow chondrocyte grafting are being studied. It is not clear whether using a lidocaine 5% patch relieves pain. Flavocoxid, a new drug, can be tried.

**Neurogenic Arthropathy**

(Neuropathic Arthropathy; Charcot's Joints)

**Neurogenic arthropathy is a rapidly destructive arthropathy due to impaired pain perception and position sense, which can result from various underlying disorders, most commonly diabetes and stroke. Common manifestations include joint swelling, effusion, deformity, and instability. Pain may be disproportionately mild due to the underlying neuropathy. Diagnosis requires x-ray confirmation. Treatment consists of joint immobilization, which slows disease progression, and sometimes surgery if the disease is advanced.**

**Pathophysiology**

Many conditions predispose to neurogenic arthropathy (see Table 35-4). Impaired deep pain sensation or proprioception affects the joint's normal protective reflexes, often allowing trauma (especially repeated minor episodes) and small periarticular fractures to go unrecognized. Increased blood flow to bone from reflex vasodilation, resulting in active bone resorption, contributes to bone and joint damage. Each new injury sustained by the joint causes more distortion as it heals. Hemorrhagic joint effusions and multiple small fractures can occur, accelerating disease progression. Ligamentous laxity, muscular hypotonia, and rapid destruction of joint cartilage are common, predisposing to joint dislocations, which also accelerate disease progression. Advanced neurogenic arthropathy can cause hypertrophic changes, destructive changes, or both.

[Table 35-4. Conditions Underlying Neurogenic Arthropathy]

**Symptoms and Signs**

Arthropathy does not usually develop until years after onset of the neurologic condition but can then progress rapidly and lead to complete joint disorganization in a few months. Pain is a common early symptom. However, because the ability to sense pain is commonly impaired, the degree of pain is often unexpectedly mild for the degree of joint damage. A prominent, often hemorrhagic, effusion and subluxation and instability of the joint are usually present during early stages. Acute joint dislocation sometimes occurs also.

During later stages, pain may be more severe if the disease has caused rapid joint destruction (eg, periarticular fractures or tense hematomas). During advanced stages, the joint is swollen from bony overgrowth and massive synovial effusion. Deformity results from dislocations and displaced fractures. Fractures and bony healing may produce many loose pieces of cartilage or bone that can slough into the joint, causing a coarse, grating, often audible crepitus usually more unpleasant for the observer than for the patient. The joint may feel like a "bag of bones."

Although many joints can be involved, the knee and the ankle are most often affected. Distribution
depends largely on the underlying disease. Thus, tabes dorsalis affects the knee and hip, and diabetes mellitus affects the foot and ankle. Syringomyelia commonly affects the spine and upper limb joints, especially the elbow and shoulder. Frequently, only one joint is affected and usually no more than two or three (except for the small joints of the feet), in an asymmetric distribution.

Infectious arthritis may develop with or without systemic symptoms (eg, fever, malaise), particularly with diabetes. Structures such as blood vessels, nerves, and the spinal cord can become compressed due to the tissue overgrowth.

**Diagnosis**

- **X-rays**

The diagnosis should be considered in a patient with a predisposing neurologic disorder who develops a destructive but unexpectedly painless arthropathy, usually several years after the onset of the underlying neurologic condition. If neurogenic arthropathy is suspected, x-rays should be taken. Diagnosis is established by characteristic x-ray abnormalities in a patient with a predisposing condition and typical symptoms and signs.

X-ray abnormalities in early neurogenic arthropathy are often similar to those in osteoarthritis (OA). The cardinal signs are bone fragmentation, bone destruction, new bone growth, and loss of joint space. There may also be synovial effusion and joint subluxation. Later, the bones are deformed, and new bone forms adjacent to the cortex, starting within the joint capsule and often extending up the shaft, particularly in long bones. Rarely, calcification and ossification occur in the soft tissues. Large, bizarrely shaped osteophytes may be present at the joint margins or within joints. Large curved (parrot's beak) osteophytes frequently develop in the spine in the absence of clinical spinal disease.

In its early stages, neurogenic arthropathy can simulate OA. However, neurogenic arthropathy progresses more rapidly than OA and frequently causes proportionately less pain.

**Treatment**

- **Treatment of cause**

- **Sometimes surgery**

Early diagnosis of asymptomatic or minimally symptomatic fractures facilitates early treatment; immobilization (with splints, special boots, or calipers) protects the joint from further injury, possibly stopping disease evolution. Prevention of neurogenic arthropathy may even be possible in a patient at risk.

Treatment of the underlying neurologic condition may slow progression of the arthropathy and, if joint destruction is still in the early stages, partially reverse the process. For a grossly disorganized joint, arthrodesis using internal fixation, compression, and an adequate bone graft may be successful. For grossly disorganized hip and knee joints, if neurogenic arthropathy is not expected to be progressive, good results can be obtained with total hip and knee replacements. However, loosening and dislocation of the prosthesis are major hazards.
Chapter 36. Crystal-Induced Arthritides

Introduction

Arthritis can result from intra-articular deposition of crystals: monosodium urate, Ca pyrophosphate dihydrate, basic Ca phosphate (apatite), and, rarely, others such as Ca oxalate crystals. Diagnosis requires synovial fluid analysis (see p. 287). Polarized light microscopy is used to specifically identify most crystals; basic Ca phosphate crystals are of ultramicroscopic size and require other methods. Crystals may be engulfed in WBCs or may be extracellular. The presence of crystals does not exclude the possibility of simultaneous infectious or other inflammatory forms of arthritis.

Gout

Gout is precipitation of monosodium urate crystals into tissue, usually in and around joints, most often causing recurrent acute or chronic arthritis. Acute arthritis is initially monarticular and often involves the 1st metatarsophalangeal joint. Symptoms include acute pain, tenderness, warmth, redness, and swelling. Diagnosis requires identification of crystals in synovial fluid. Treatment of acute attacks is with anti-inflammatory drugs. The frequency of attacks can be reduced by regular use of NSAIDs, colchicine, or both and by treating hyperuricemia with allopurinol or uricosuric drugs.

Gout is more common among men than women. Usually, gout develops during middle age in men and after menopause in women. Gout is rare in younger people but is often more severe in people who develop the disorder before age 30. Gout often runs in families.

Pathophysiology

The greater the degree and duration of hyperuricemia, the greater is the likelihood of gout and the more severe are the symptoms. Urate levels can be elevated because of

- Decreased excretion
- Increased production
- Increased purine intake

Why only some people with elevated serum uric acid (urate) levels develop gout is not known.

Decreased renal excretion is by far the most common cause of hyperuricemia. It may be hereditary and also occurs in patients receiving diuretics and in those with diseases that decrease GFR. Ethanol increases purine catabolism in the liver and increases the formation of lactic acid, which blocks urate secretion by the renal tubules. Lead poisoning and cyclosporine, usually given to transplant patients, irreversibly damage renal tubules, leading to urate retention.

Increased production of urate may be caused by increased nucleoprotein turnover in hematologic conditions (eg, lymphoma, leukemia, hemolytic anemia) and in conditions with increased rates of cellular proliferation and cell death (eg, psoriasis, cytotoxic cancer therapy, radiation therapy). Increased urate production may also occur as a primary hereditary abnormality and in obesity, because urate production correlates with body surface area. In most cases, the cause is unknown, but a few cases are attributable to enzyme abnormalities; deficiency of hypoxanthine-guanine phosphoribosyltransferase (complete deficiency is Lesch-Nyhan syndrome) is a possible cause, as is overactivity of phosphoribosylpyrophosphate synthetase.

Increased intake of purine-rich foods (eg, liver, kidney, anchovies, asparagus, consomme, herring, meat gravies and broths, mushrooms, mussels, sardines, sweetbreads) can contribute to hyperuricemia. However, a strict low-purine diet lowers serum urate by only about 1 mg/dL.

Urate precipitates as needle-shaped monosodium urate (MSU) crystals, which are deposited
extracellularly in avascular tissues (eg, cartilage) or in relatively avascular tissues (eg, tendons, tendon sheaths, ligaments, walls of bursae) and skin around cooler distal joints and tissues (eg, ears). In severe, longstanding hyperuricemia, MSU crystals may be deposited in larger central joints and in the parenchyma of organs such as the kidney. At the acid pH of urine, urate precipitates readily as small platelike or irregular crystals that may aggregate to form gravel or stones, which may cause obstruction. Tophi are MSU crystal aggregates that most often develop in joint and cutaneous tissue.

Acute gouty arthritis may be triggered by trauma, medical stress (eg, pneumonia or other infection), and especially vascular occlusions (eg, stroke or MI), or by surgery, use of thiazide diuretics or drugs with uricosuric activity (eg, allopurinol), or indulgence in purine-rich food or alcohol. Attacks are often precipitated by a sudden increase or, more commonly, a sudden decrease in serum urate levels. Why acute attacks follow some of these precipitating conditions is unknown. Tophi in and around joints can limit motion and cause deformities, called chronic tophaceous gouty arthritis.

Symptoms and Signs

Acute gouty arthritis usually begins with sudden onset of pain (often nocturnal). The metatarsophalangeal joint of a great toe is most often involved (podagra), but the instep, ankle, knee, wrist, and elbow are also common sites. Rarely, the hip, shoulder, sacroiliac, sternoclavicular, or cervical spine joints are involved. The pain becomes progressively more severe, usually over a few hours, and is often excruciating. Swelling, warmth, redness, and exquisite tenderness may suggest infection. The overlying skin may become tense, warm, shiny, and red or purplish. Fever, tachycardia, chills, and malaise sometimes occur. Coexisting hypertension, hyperlipidemia, and obesity are common.

Course: The first few attacks usually affect only a single joint and last only a few days. Later attacks may affect several joints simultaneously or sequentially and persist up to 3 wk if untreated. Subsequent attacks develop after progressively shorter symptom-free intervals. Eventually, several attacks may occur each year.

Tophi: Tophi develop most often in patients with chronic gout, but they can occur in patients who have never had acute gouty arthritis. They are usually firm yellow or white papules or nodules, single or multiple. They can develop in various locations, commonly the fingers, hands, feet, and around the olecranon or Achilles tendon. Tophi can also develop in the kidneys and other organs and under the skin on the ears. Patients with osteoarthritic Heberden's nodes may develop tophi in the nodes. This development occurs most often in elderly women taking diuretics. Normally painless, tophi, especially in the olecranon bursae, can become acutely inflamed and painful. Tophi may even erupt through the skin, discharging chalky masses of urate crystals. Tophi may eventually cause deformities.

Chronic gout: Chronic gouty arthritis can cause pain, deformity, and limited joint motion. Inflammation can be flaring in some joints while subsiding in others. About 20% of patients with gout develop urolithiasis with uric acid stones or Ca oxalate stones. Complications include obstruction and infection, with secondary tubulointerstitial disease. Untreated progressive renal dysfunction, most often related to coexisting hypertension or, less often, some other cause of nephropathy, further impairs excretion of urate, accelerating crystal deposition in tissues.

Cardiovascular disease and the metabolic syndrome are common among patients with gout.

Diagnosis

• Clinical criteria

• Synovial fluid analysis

Gout should be suspected in patients with acute monarticular or oligoarthritis, particularly older adults or those with other risk factors. Podagra and recurrent instep inflammation are particularly suggestive. Similar symptoms can result from

• Ca pyrophosphate dihydrate (CPPD) crystal deposition disease (see p. 354) (however, CPPD generally
attacks larger joints and its clinical course is usually milder)

- Acute rheumatic fever with joint involvement and juvenile RA (however, these disorders occur mostly in young people, who rarely get gout)

- RA (however, in RA, all affected joints flare and subside together, whereas in gout, inflammation is usually flaring in some joints while subsiding in others)

- Acute fracture in patients unable to provide a history of injury

- Infectious arthritis (see pp. 365 and 369; differentiation may require synovial fluid analysis)

- Palindromic rheumatism

Palindromic rheumatism is characterized by acute, recurrent attacks of inflammation in or near one or occasionally several joints with spontaneous resolution; pain and erythema can be as severe as in gout. Attacks subside spontaneously and completely in 1 to 3 days. Such attacks may herald the onset of RA, and rheumatoid factor tests can help in differentiation; they are positive in about 50% of patients (these tests are positive in 10% of gouty patients also).

**Synovial fluid analysis:** If acute gouty arthritis is suspected, arthrocentesis and synovial fluid analysis should be done at the initial presentation. A typical recurrence in a patient with known gout does not mandate arthrocentesis, but it should be done if there is any question of the diagnosis or if the patient's risk factors or any clinical characteristics suggest infectious arthritis. Synovial fluid analysis can confirm the diagnosis by identifying needle-shaped, strongly negatively birefringent urate crystals that are free in the fluid or engulfed by phagocytes. Synovial fluid during attacks has inflammatory characteristics (see Table 36-1), usually 2,000 to 100,000 WBCs/μL, with > 80% polymorphonuclear WBCs. These findings overlap considerably with infectious arthritis, which must be excluded by Gram stain and culture.

**Serum urate level:** An elevated serum urate level supports the diagnosis of gout but is neither specific nor sensitive; at least 30% of patients have a normal serum urate level during an acute attack. However, the serum urate level reflects the size of the extracellular miscible urate pool. The level should be measured on 2 or 3 occasions in patients with newly proven gout to establish a baseline; if elevated (> 7 mg/dL [> 0.41 mmol/L]), 24-h urinary urate excretion can also be measured. Normal 24-h excretion in people eating a regular diet is about 600 to 900 mg. Quantification of urinary uric acid can indicate whether hyperuricemia results from impaired excretion or increased production and help guide any serum urate-lowering therapy. Patients with elevated urine excretion of urate are at increased risk of urolithiasis.

**X-rays:** X-rays of the affected joint may be taken to look for bony tophi but are probably unnecessary if the diagnosis has been established by synovial fluid analysis. In CPPD, radiopaque deposits are present in fibrocartilage, hyaline articular cartilage (particularly the knee), or both.

**Diagnosis of chronic gouty arthritis:** Chronic gouty arthritis should be suspected in patients with persistent joint disease or subcutaneous or bony tophi. Plain x-rays of the 1st metatarsophalangeal joint or other affected joint may be useful. These x-rays may show punched-out lesions of subchondral bone with overhanging bony margins, most commonly in the 1st metatarsophalangeal joint; lesions must be ≥ 5 mm in diameter to be visible on x-ray.

Bone lesions are not specific or diagnostic but nearly always precede the appearance of subcutaneous tophi.

**Prognosis**

With early diagnosis, therapy enables most patients to live a normal life. For many patients with advanced disease, aggressive lowering of the serum urate level can resolve tophi and improve joint function. Gout
is generally more severe in patients whose initial symptoms appear before age 30. The metabolic syndrome and cardiovascular disease probably increase mortality in patients with gout.

Some patients do not improve sufficiently with treatment. The usual reasons include nonadherence, alcoholism, and undertreatment by physicians.

**Treatment**

- Termination of an acute attack with NSAIDs or corticosteroids
- Prevention of recurrent acute attacks with daily colchicine or an NSAID
- Prevention of further deposition of MSU crystals and resolution of existing tophi by lowering the serum urate level
- Treatment of coexisting hypertension, hyperlipidemia, and obesity

**Treatment of acute attacks:** **NSAIDs** are effective in treating acute attacks and are generally well tolerated. However, they can still cause adverse effects, including GI upset, hyperkalemia, increases in creatinine, and fluid retention. Elderly and dehydrated patients are at particular risk, especially if there is a history of renal disease. Virtually any NSAID used in anti-inflammatory (high) doses is effective and is likely to exert an analgesic effect in a few hours (see Table 35-2 on p. 336). Treatment should be continued for several days after the pain and signs of inflammation have resolved to prevent relapse.

**Oral colchicine,** a traditional therapy, often produces a dramatic response if begun soon after the onset of symptoms. Joint pain generally begins to subside after 12 to 24 h of treatment and ceases within 3 to 7 days. One regimen is colchicine 0.6 mg po q 1 h until symptoms abate to a maximum total dose of 4 to 5 mg or until diarrhea or vomiting occurs. However, diarrhea, sometimes severe, develops in up to 80% of patients given this regimen of oral colchicine for an acute attack. If treatment is started very early, regimens such as 0.6 to 1.2 mg bid to tid for 1 to 2 days are better tolerated and may be effective. If colchicine is tolerated, 0.6 to 1.2 mg once/day can be continued as the attack subsides.

**IV colchicine** is much less likely to cause GI symptoms and provides an alternative, particularly for postoperative patients. Colchicine 1 mg is diluted with 0.9% saline to 20 mL and injected slowly (over 2 to 5 min); a second 1-mg dose can be given in 12 h if needed; no more than 2 mg is given in 24 h (and no more than 4 mg over 7 days). **IV colchicine should not be given to patients with renal or liver disease or those receiving prophylactic oral colchicine, because severe bone marrow suppression, shock, and death may occur.** IV colchicine is also locally irritating, particularly if extravasated. Although effective and perhaps the option of choice in certain specific situations, IV colchicine should only be used with careful adherence to prescribing indications and contraindications.

**Corticosteroids** are sometimes used to treat acute attacks; however, this use is controversial because inflammation may continue while symptoms are masked. Aspiration of affected joints, followed by instillation of corticosteroid ester crystal suspension, is very effective, particularly for monarticular symptoms; prednisolone tebutate 4 to 40 mg or prednisolone acetate 5 to 25 mg can be used, with dose depending on the size of the affected joint. Oral prednisone (about 40 mg once/day), IM or IV corticosteroids, or single-dose ACTH 80 U IM is also very effective, particularly if multiple joints are involved. As with NSAID therapy, corticosteroids should be continued until after the attack fully resolves to prevent relapse.

In addition to NSAIDs or corticosteroids, supplementary analgesics, rest, ice application, and splinting of the inflamed joint may be helpful. Because lowering the serum urate level during an attack prolongs the attack or predisposes to recurrence, drugs that lower the serum urate level should not be initiated until acute symptoms have been completely controlled.

**Prevention of recurrent attacks:** The frequency of acute attacks is reduced by taking one to two 0.6-mg tablets of colchicine daily (depending on tolerance and severity). An extra two or three 0.6-mg tablets...
of colchicine taken at the first suggestion of an attack may abort flares. A (reversible) neuropathy or myopathy can develop during chronic colchicine ingestion. This condition may occur in patients with renal insufficiency, in patients also receiving a statin or macrolide, or in patients with none of these risk factors. Attack frequency can also be decreased with daily low-dose NSAIDs.

**Lowering the serum urate level:** Colchicine, NSAIDs, and corticosteroids do not retard the progressive joint damage caused by tophi. Such damage can be prevented and, if present, reversed with urate-lowering drugs. Tophaceous deposits are resorbed by lowering serum urate. Lowering serum urate may also decrease the frequency of acute arthritic attacks. This decrease is accomplished by

- Blocking urate production with allopurinol
- Increasing urate excretion with a uricosuric drug
- Using both types of drugs together in severe tophaceous gout

Uricase can also be given but is not yet routinely used. Uricase is an enzyme that converts urate to allantoin, which is more soluble. IV uricase transiently lowers serum urate by a large amount.

Hypouricemic therapy is indicated for patients with

- Tophaceous deposits
- Frequent or disabling attacks of gouty arthritis (eg, more than 2 attacks/yr or very severe attacks) despite prophylactic colchicine, an NSAID, or both
- Gout with persistent serum urate ≥ 9 mg/dL
- Urolithiasis
- Multiple comorbidities (eg, peptic ulcer disease, chronic kidney disease) that are relative contraindications to the drugs used to treat acute attacks (NSAIDs or corticosteroids)

Hyperuricemia is not usually treated in the absence of gout.

If the goal of hypouricemic therapy is to dissolve tophi, the serum urate level should be lowered to 4.5 mg/dL (0.26 mmol/L), the saturation level at the normal temperature (31°C) of the bunion joint, or even lower. If tophi do not need to be dissolved, a level of 5 to 6 mg/dL (0.30 to 0.36 mmol/L), which is below the level of saturation (> 7.0 mg/dL [> 0.41 mmol/L] at normal core body temperature and pH), is acceptable. These target levels should be maintained indefinitely. Low levels are often difficult to maintain.

Drugs are effective in lowering serum urate; dietary restriction of purines is less effective, but high intake of high-purine food and alcohol (beer in particular) should be avoided. Carbohydrate restriction and weight loss can lower serum urate in patients with insulin resistance because high insulin levels suppress urate excretion. Because acute attacks tend to develop during the first months of hypouricemic therapy, such therapy should be started in conjunction with once or twice daily colchicine or NSAIDs and during a symptom-free period. Resolution of tophi may take many months even with maintenance of serum urate at low levels. Serum urate should be measured periodically, usually monthly while determining required drug dosage and then yearly to confirm the effectiveness of therapy.

**Allopurinol**, which inhibits urate synthesis, is the most commonly prescribed hypouricemic therapy. It is especially helpful in treating patients who repeatedly pass uric acid or Ca oxalate stones or who have severe renal dysfunction. Uric acid stones or gravel may dissolve during allopurinol treatment. Treatment begins with 100 mg po once/day and can be increased up to 800 mg po once/day, or even higher, to achieve target urate levels; however, the dose must be decreased in patients with renal insufficiency. The most common daily dose is 300 mg. Adverse effects include mild GI distress and skin rash, which can be a harbinger of Stevens-Johnson syndrome, life-threatening hepatitis, vasculitis, or leukopenia. Adverse
effects are more common among patients with renal dysfunction.

**Uricosuric therapy** is preferred to allopurinol as initial therapy for patients ≤ 60 yr with normal renal function, no history of urolithiasis, and decreased renal urate excretion. Probenecid or sulfinpyrazone can be used. Probenecid treatment begins with 250 mg po bid, with doses increased as needed, to a maximum of 1 g po tid. Sulfinpyrazone treatment begins with 50 to 100 mg po bid, with doses increased as needed, to a maximum of 100 mg po qid. Sulfinpyrazone is more potent than probenecid but is more toxic. Salicylates at low doses antagonize both drugs and can increase urate levels. Low doses may worsen hyperuricemia, but a therapeutic trial of a cardioprotective dose while monitoring urate levels may be indicated for patients at high risk of cardiovascular disease. Acetaminophen provides comparable analgesia without interfering with drug efficacy.

**Other treatments:** Fluid intake ≥ 3 L/day is desirable for all patients, especially those who chronically pass urate gravel or stones. Alkalization of urine (with K citrate 20 to 40 mEq po bid or acetazolamide 500 mg po at bedtime) is also occasionally effective for patients with persistent uric acid urolithiasis despite hypouricemic therapy and adequate hydration. However, excessive urine alkalization may cause deposition of Ca oxalate crystals. Extracorporeal shock wave lithotripsy may be needed to disintegrate renal stones. Large tophi in areas with healthy skin may be removed surgically; all others should slowly resolve under adequate hypouricemic therapy. Losartan, which has uricosuric effects, can be considered as an alternative to thiazide diuretics.

**Asymptomatic Hyperuricemia**

Asymptomatic hyperuricemia is elevation of serum urate > 7 mg/dL (> 0.42 mmol/L) in the absence of clinical gout. Generally, treatment is not required. However, patients with overexcretion of urate who are at risk of urolithiasis may receive allopurinol.

**Calcium Pyrophosphate Dihydrate Crystal Deposition Disease**

(Pseudogout)

Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease involves intra-articular and/or extra-articular deposition of CPPD crystals. Manifestations are protean and may be minimal or include intermittent attacks of acute arthritis and a degenerative arthropathy that is often severe. Diagnosis requires identification of CPPD crystals in synovial fluid. Treatment is with intra-articular corticosteroids or oral NSAIDs or colchicine.

CPPD crystal deposition (chondrocalcinosis), whether symptomatic and asymptomatic, becomes more common with age.

The incidence of radiologic (usually asymptomatic) chondrocalcinosis in patients aged 70 is about 3%, reaching nearly 50% in patients aged 90. Asymptomatic chondrocalcinosis is common in the knee, hip, anulus fibrosus, and symphysis pubis. Men and women are affected equally.

**Etiology**

The cause is unknown. Frequent association with other conditions, such as trauma (including surgery), amyloidosis, myxedema, hypomagnesemia, hyperparathyroidism, gout, hemochromatosis, and old age, suggests that CPPD crystal deposits are secondary to degenerative or metabolic changes in the affected tissues. Some cases are familial, usually transmitted in an autosomal dominant pattern, with complete penetration by age 40.

**Symptoms and Signs**

Acute, subacute, or chronic arthritis can occur, usually in the knee or other large peripheral joints, which can mimic many other forms of arthritis. Attacks are sometimes similar to gout but are usually less severe. There may be no symptoms between attacks or continuous low-grade symptoms in multiple joints, similar to RA or osteoarthritis. These patterns tend to persist for life.
Diagnosis

- Synovial fluid analysis
- Identification of crystals microscopically

CPPD crystal deposition disease should be suspected in older patients with arthritis, particularly inflammatory arthritis. Diagnosis is established by identifying rhomboid or rod-shaped, weakly positively birefringent crystals on polarized light microscopy of synovial fluid (see Table 36-1). Coincident infectious arthritis must be ruled out by Gram stain and culture. X-rays are indicated if synovial fluid cannot be obtained for analysis; findings of multiple linear or punctate calcification in articular cartilage, especially fibrocartilages, support the diagnosis but do not exclude gout or infection.

Prognosis

The prognosis for individual attacks is usually excellent. However, chronic arthritis can occur, and severe destructive arthropathy resembling neuropathic (Charcot's) joints occasionally occurs.

Treatment

- Intra-articular corticosteroids
- NSAIDs
- Colchicine maintenance

Symptoms of acute synovial effusion abate with synovial fluid drainage and instillation of a microcrystalline corticosteroid ester suspension into the joint space (eg, 40 mg prednisolone acetate or prednisolone tertiary butylacetate into a knee). Indomethacin, naproxen, or another NSAID given at anti-inflammatory doses (see Table 35-2 on p. 336) often stops acute attacks promptly. Colchicine 0.6 mg po once/day or bid may decrease the number of acute attacks.

Basic Calcium Phosphate and Calcium Oxalate Crystal Deposition Diseases

Basic Ca phosphate (apatite) and Ca oxalate crystal disorders tend to cause clinical manifestations similar to other crystal-induced arthritides.

Basic Ca phosphate crystal deposition disease: Most pathologic calcifications throughout the body contain mixtures of carbonate-substituted hydroxyapatite and octacalcium phosphate. Because these ultramicroscopic crystals are nonacidic Ca phosphates, the term basic Ca phosphate (BCP) is much more precise than apatite. These ultramicroscopic crystals occur in snowball-like clumps in rheumatic conditions (eg, calcific tendinitis, calcific periarthritis, some cases of progressive systemic sclerosis and dermatomyositis). They also occur in joint fluids of patients with all degenerative arthropathies sufficiently advanced to cause joint space narrowing on x-ray.

BCP crystals can destroy joints and can cause severe intra-articular or periarticular inflammation. Milwaukee shoulder syndrome is one example, a profoundly destructive arthropathy affecting predominantly elderly women that usually develops in the shoulders and (often) knees.

Acute podagra due to periarticular BCP deposition can mimic gout; it occurs as a discrete syndrome in young women (less often in young men) and is treated the same as acute gout.

Besides synovial fluid analysis, x-rays should be taken of symptomatic joints. On x-ray, BCP crystals may be visible as periarticular cloudlike opacities. Definitive assay for BCP crystals in synovial fluid is not readily available. Clumped crystals can be identified only with transmission electron microscopy. The clumps are not birefringent under polarized light.
Treatment with oral or IV colchicine, an NSAID, or, if a large joint is involved, intra-articular corticosteroid ester crystal suspension is helpful. Treatment is the same as that for acute gout (see p. 352).

**Ca oxalate crystal deposition disease:** Ca oxalate crystal deposition is rare. It occurs most often in azotemic patients receiving hemodialysis or peritoneal dialysis, particularly those treated with ascorbic acid (vitamin C), which is metabolized to oxalate. Crystals may deposit in blood vessel walls and skin, as well as joints. The crystals appear as birefringent bipyramidal structures (see Table 36-1). Synovial fluid may have > 2000 WBC/μL. On x-ray, Ca oxalate crystals are indistinguishable from BCP periarticular calcifications or Ca pyrophosphate dihydrate (CPPD) crystal deposits in cartilage. Treatment is the same as that for CPPD crystals (see above).
Chapter 37. Osteoporosis

Introduction

Osteoporosis is a progressive metabolic bone disease that decreases bone density (bone mass per unit volume), with deterioration of bone structure. Skeletal weakness leads to fractures with minor or inapparent trauma, particularly in the thoracic and lumbar spine, wrist, and hip. Acute or chronic back pain is common. Diagnosis is by dual-energy x-ray absorptiometry. Prevention and treatment involve Ca and vitamin D supplements, exercises to maximize bone and muscle strength and minimize the risk of falls, and drug therapy to preserve bone mass or stimulate new bone formation.

Pathophysiology

Normally, bone formation and resorption are closely coupled. Osteoblasts (cells that make the organic matrix of bone and then mineralize bone) and osteoclasts (cells that resorb bone) are regulated by parathyroid hormone (PTH), calcitonin, estrogen, vitamin D, various cytokines, and other local factors such as prostaglandins.

Peak bone mass in men and women occurs by the mid 20s. Blacks reach higher bone mass than whites and Asians, whereas Hispanics have intermediate values. Men have higher bone mass than women. Bone mass plateaus for about 10 yr, during which time bone formation approximately equals bone resorption. After this, bone loss occurs at a rate of about 0.3 to 0.5%/yr. Beginning with menopause, bone loss accelerates in women to about 3 to 5%/yr for about 5 to 7 yr.

Osteoporotic bone loss affects cortical and trabecular (cancellous) bone. Cortical thickness and the number and size of trabeculae decrease, resulting in increased porosity. Trabeculae may be disrupted or entirely absent.

Classification

Osteoporosis can develop as a primary disorder or secondarily due to some other factor.

Primary osteoporosis: More than 95% of osteoporosis in women and probably about 80% in men is primary. Most cases occur in postmenopausal women and older men. The terms postmenopausal, involutional, senile, and age-related osteoporosis have been used to describe primary osteoporosis in elderly patients. Estrogen deficiency is an important factor in men as well as women. Other contributing factors may include decreased Ca intake, low vitamin D levels, and secondary hyperparathyroidism.

The major mechanism is increased bone resorption, which results in decreased bone mass and microarchitectural deterioration, but other mechanisms also contribute not only in primary osteoporosis but also in the various secondary forms of osteoporosis. The mechanisms of bone loss may involve the following:

• Local changes in the production of bone-resorbing cytokines, such as increases in cytokines that stimulate bone resorption

• Impaired formation response during bone remodeling (probably caused by age-related decline in the number and activity of osteoblasts)

• Other factors such as a decline in local and systemic growth factors

Trabecular bone loss occurs more rapidly than cortical bone loss because trabecular bone is more porous and bone turnover is high. However, loss of both types contributes to skeletal fragility.

The most common sites for fragility fractures are the distal radius (dorsally displaced fractures), spine (vertebral compression fractures), femoral neck, and greater trochanter. Other sites include the proximal humerus and pelvis. Fragility fractures rarely occur in children or young adults with normal gonadal
function and no detectable secondary cause. This condition is called idiopathic osteoporosis.

**Secondary osteoporosis:** Secondary osteoporosis accounts for < 5% of osteoporosis cases in women but probably more in men. The causes (see Table 37-1) may also aggravate bone loss and increase fracture risk in patients with primary osteoporosis.

**Risk Factors**

Because stress, including weight bearing, is necessary for bone growth, immobilization or extended sedentary periods result in bone loss. Being thin predisposes to decreased bone mass. Insufficient dietary intake of Ca, P, and vitamin D predisposes to bone loss, as does endogenous acidosis (eg, high-protein diets). Cigarette smoking and excessive caffeine or alcohol use also adversely affect bone mass. Whites and Asians are at higher risk. A family history of osteoporosis also increases risk. Other risk factors (eg, decreasing amounts of sex hormones) predispose to specific types of osteoporosis. Patients who have had one fragility fracture are at increased risk of having other clinical (symptomatic) fractures as well as clinically asymptomatic vertebral compression fractures.

**Symptoms and Signs**

Most of the chronic pain typical of osteoporosis results from fractures, which may develop after minimal, inapparent, or no trauma. Patients may be asymptomatic for years, until fractures begin to occur. Eventually, patients often develop pain in the bones or muscles, particularly of the back. Vertebral compression fractures are common, usually in weight-bearing vertebrae (T6 and below). The pain begins acutely, usually does not radiate, is aggravated by weight bearing, may cause local tenderness, and generally begins to subside in 1 wk. However, residual pain may last for months or be constant.

Multiple thoracic compression fractures eventually cause dorsal kyphosis, with exaggerated cervical lordosis (dowager's hump). Abnormal stress on the spinal muscles and ligaments may cause chronic, dull, aching pain, particularly in the lower back. Fractures can develop at other sites, commonly the hip or wrist, usually from falls.

**Diagnosis**

- Dual-energy x-ray absorptiometry (DEXA)

Osteoporosis should be suspected in patients who sustain fractures after only mild or trivial trauma; older adults, particularly those with risk factors and unexplained back pain; patients with decreased bone density that is incidentally noted on imaging studies; and patients at risk of secondary osteoporosis. If imaging studies have been done or are necessary to evaluate symptoms (eg, back pain), osteoporosis may be obvious. However, imaging studies are often equivocal, and the diagnosis should be established by bone density measurement.

**Plain x-rays:** Bones show decreased radiodensity and loss of trabecular structure, but not until about 30% of bone has been lost. A loss of horizontally oriented trabeculae increases the prominence of the cortical end plates and of vertically oriented, weight-bearing trabeculae. Loss of height and increased biconcavity characterize vertebral compression fractures. Thoracic vertebral fractures may cause anterior wedging. In long bones, although the cortices may be thin, the periosteal surface remains smooth. Vertebral fractures at T4 or above suggest cancer rather than osteoporosis.

Corticosteroid-induced osteoporosis is likely to cause rib fractures and exuberant callus formation at sites of healing fractures. Osteomalacia may cause abnormalities on imaging tests similar to those of osteoporosis (see Sidebar 37-1). Hyperparathyroidism can be differentiated when it causes subperiosteal resorption or cystic bone lesions, but these are uncommon.
Bone density measurement: DEXA is used to measure bone density. DEXA is diagnostic for osteoporosis, predicts the risk of fracture, and can be used to follow treatment response. Bone density of the lumbar spine, hip, distal radius or ulna, or the entire body can be measured. (Quantitative CT scanning can produce similar measurements in the spine or hip.) Usually, the lumbar spine, total proximal femur, or femoral neck is measured. DEXA results are reported as T scores. A T score corresponds to the number of standard deviations by which bone density differs from a healthy, young person of the same sex and race. A DEXA result of > 1 is defined as osteopenia and suggests an increased risk of osteoporosis; > 2.5 is diagnostic for osteoporosis.

If DEXA scanning of the central skeleton is unavailable, portable, less expensive systems such as peripheral DEXA or quantitative ultrasonography of the heel can be used. However, monitoring the response to treatment with serial measurements of bone density should be done only with central DEXA scanning.

Sidebar 37-1 Osteopenia: Differentiating Osteoporosis and Osteomalacia

Osteopenia is decreased bone mass. Two metabolic bone diseases decrease bone mass: osteoporosis and osteomalacia. In osteoporosis, bone mass decreases, but the ratio of bone mineral to bone matrix is normal. In osteomalacia, the ratio of bone mineral to bone matrix is low.

Osteoporosis results from a combination of low peak bone mass, increased bone resorption, and impaired bone formation. Osteomalacia is due to impaired mineralization, usually because of severe vitamin D deficiency or abnormal vitamin D metabolism (see p. 41). Osteoporosis is much more common than osteomalacia in the US. The 2 disorders may coexist, and their clinical expression is similar; moreover, mild to moderate vitamin D deficiency can occur in osteoporosis.

Current central DEXA systems can also assess vertebral deformities in the lower thoracic and lumbar spine, a procedure termed vertebral fracture analysis (VFA). Vertebral deformities, even those clinically silent, may indicate increased risk of future fractures. VFA is more likely to be useful in patients with loss of ≥ 3 cm in height.

Other testing: Once osteoporosis is diagnosed, patients should be checked for causes of secondary osteoporosis. Serum Ca should be measured to rule out asymptomatic hyperparathyroidism. PTH levels may be increased in patients with decreased Ca absorption or hypercalciiuria. Other tests such as thyroid-stimulating hormone or free thyroxine to check for hyperthyroidism, vitamin D levels, measurements of urinary free cortisol, and blood counts and other tests to rule out cancer, especially myeloma (eg, serum protein electrophoresis), should be considered depending on the clinical findings. Serum alkaline phosphatase is usually normal but may be elevated by recent fracture.

Patients with weight loss should be screened for GI disorders as well as cancer. Bone biopsy is reserved for unusual cases (eg, young patients with pathologic fractures and no apparent cause). Levels of serum or urine N-telopeptide crosslinks (NTX) or free deoxypyridinoline (DPYR) may reflect increased breakdown of collagen. These tests are not sufficiently accurate for routine clinical use but may be used to assess the effectiveness of therapy.

Screening

DEXA screening is recommended for all women > 65. Bone density should also be measured in women between 50 and 65 who have risk factors, including a family history of osteoporosis, a history of fragility fractures, and low body weight. Screening is also recommended for both men and women who have had fragility fractures, even at younger ages.

Treatment

• Risk factor modification
• Ca and vitamin D supplements

• Bisphosphonates or sometimes other antiresorptive drugs

The goals of treatment are to preserve bone mass, prevent fractures, decrease pain, and maintain function.

Preserving bone mass: The rate of bone loss can be slowed with drugs and, when possible, modification of risk factors. Ca and vitamin D intake and physical activity must be adequate for drug treatment to be effective.

Risk factor modification can include maintaining adequate body weight, increasing weight-bearing exercise, minimizing caffeine and alcohol intake, and stopping smoking. The optimal amount of weight-bearing exercise is not established, but an average of 30 min/day is recommended. A physical therapist can develop a safe exercise program.

All men and women should consume at least 1000 mg of elemental Ca daily. An intake of 1200 to 1500 mg/day is recommended for postmenopausal women and older men and for periods of increased requirements, such as pubertal growth, pregnancy, and lactation. Diet alone is rarely adequate; Ca supplements are needed, most commonly as Ca carbonate or Ca citrate. Supplements differ in their elemental Ca concentration. Ca citrate is better absorbed in patients with achlorhydria, but both are well absorbed when taken with meals. Ca should be taken in divided doses of 500 to 600 mg bid or tid.

Vitamin D in doses of 800 U once/day is generally recommended, but up to 2000 U/day is safe and may be helpful in osteoporotic patients. Patients with vitamin D deficiency may need even higher doses. Supplemental vitamin D is usually given as cholecalciferol, the natural form of vitamin D, although ergocalciferol, the synthetic plant derived form, is probably also acceptable.

Bisphosphonates are first-line drug therapy. By inhibiting bone resorption, bisphosphonates preserve bone mass and can decrease vertebral and hip fractures by 50%. To treat osteoporosis, bisphosphonates can be given orally. Alendronate can be given at doses of 10 mg po once/day or 70 mg po once/wk, ibandronate 2.5 mg po once/day or 150 mg once/mo, or risedronate at 5 mg po once/day or 35 mg once/wk. All increase bone mineral density and decrease risk of at least vertebral fractures. Oral bisphosphonates must be taken on an empty stomach with a full glass of water, and the patient must remain upright for ≥ 30 min. They can cause esophageal irritation. Esophageal disorders that delay transit time and symptoms of upper GI disorders are relative contraindications to oral bisphosphonates. Weekly or monthly therapy is generally preferred for its greater convenience and probably fewer adverse effects.

Parenteral zolendronate is an alternative to oral bisphosphonates. Doses of 5 mg IV once/year increase bone mass and decrease risk of vertebral and nonvertebral fractures. Pamidronate can also be given IV but has not yet been shown to prevent fractures.

Osteonecrosis of the jaw has been associated with use of bisphosphonates; however, this condition is rare in patients taking oral bisphosphonates. Risk factors include IV bisphosphonate use and cancer. Bisphosphonates may also be associated with atrial fibrillation, but the mechanism is not clear and there has been no association with increased cardiovascular mortality.

Salmon calcitonin is less effective than bisphosphonates for treating osteoporosis. The subcutaneous dose is 100 IU/day or every other day; the nasal spray dose is 200 U/day in alternating nostrils (1 spray). Salmon calcitonin may provide short-term analgesia after an acute fracture.

Estrogen can preserve bone density and prevent fractures. Most effective if started within 4 to 6 yr of menopause, estrogen may slow bone loss and possibly reduce fractures even when started much later. It is usually given as conjugated estrogen 0.625 to 1.25 mg po once/day. However, 0.3 mg po once/day may be as effective. Use of estrogen increases the risk of thromboembolism and endometrial cancer and may increase the risk of breast cancer. The risk of endometrial cancer can be reduced in women with an intact uterus by taking a progestin with estrogen (see p. 2519). However, taking a combination of a progestin
and estrogen increases the risk of breast cancer, coronary artery disease, stroke, and biliary disease.

Raloxifene is a selective estrogen receptor modulator (SERM) that may be appropriate for treatment of osteoporosis in women who cannot take bisphosphonates. It reduces vertebral fractures by about 50% but has not been shown to reduce nonvertebral fractures. Raloxifene does not stimulate the uterus and antagonizes estrogen effects in the breast, probably reducing the risk of breast cancer.

PTH, which stimulates new bone formation, is generally reserved for patients who have the following characteristics:

- Cannot tolerate antiresorptive drugs or have contraindications to their use
- Fail to respond to antiresorptive drugs, as well as Ca, vitamin D, and exercise, developing new fractures and loss of bone mineral density
- Possibly have severe osteoporosis (eg, T score < 3.5)

When given daily by injection for an average of 20 mo, synthetic PTH (PTH 1-34; teriparatide) increases bone mass and reduces risk of fractures.

**Preventing fractures:** Many elderly patients are at risk of falls because of poor coordination, poor vision, muscle weakness, confusion, and use of drugs that cause postural hypotension or alter the sensorium. Educating patients about the risks of falls and fractures and developing individualized programs to increase physical stability and attenuate risk can help. Strengthening exercises may increase stability. Hip pads can reduce the incidence of hip fracture despite continued falls.

**Treating pain and maintaining function:** Acute back pain from a vertebral compression fracture should be treated with orthopedic support, analgesics, and (when muscle spasm is prominent) heat and massage (see p. 3459). Chronic backache may be relieved by an orthopedic garment and exercises to strengthen paravertebral muscles. Avoiding heavy lifting can help. Bed rest should be minimized, and consistent, carefully designed weight-bearing exercise should be encouraged.

In some cases, vertebroplasty, sometimes preceded by kyphoplasty, can relieve severe pain. In vertebroplasty, methyl methacrylate is injected into the vertebral body. In kyphoplasty, the vertebral body is expanded with a balloon. These procedures may reduce deformity in the injected vertebrae but do not reduce and may even increase the risk of fractures in adjacent vertebrae. Other risks may include rib fractures, cement leakage, and pulmonary edema or MI.

**Prevention**

The goals of prevention are to preserve bone mass and prevent fractures. Preventive measures are indicated in postmenopausal women and older men, patients taking long-term systemic corticosteroids, and patients at high risk (eg, osteopenia with multiple risk factors or secondary causes).

Preventive measures are similar to treatment measures, including those aimed at preserving bone mass. Bisphosphonates and other drugs can be given as for treatment of osteoporosis, but alendronate is given at a reduced dose (5 mg po once/day or 35 mg once/wk). Measures to prevent fractures are also indicated.
Chapter 38. Paget's Disease of Bone

Introduction

(Osteitis Deformans)

Paget's disease of bone is a chronic disorder of the adult skeleton in which bone turnover is accelerated in localized areas. Normal matrix is replaced with softened and enlarged bone. The disease may be asymptomatic or cause gradual onset of bone pain or deformity. Diagnosis is by x-ray. Treatment includes symptomatic measures and often drugs, usually bisphosphonates.

About 1% of adults in the US > 40 have Paget's disease, with a 3:2 male predominance. Prevalence increases with aging. However, overall prevalence seems to be decreasing. The disease is most common in Europe (except Scandinavia), Australia, and New Zealand. It is particularly common in England.

Etiology

Several genetic abnormalities, many affecting osteoclast generation and activity, have been identified. Mutations of the Sequestrum 1 gene from chromosome 6 are commonly related to Paget's disease. Appearance of involved bone on electron microscopy suggests a viral infection, but a viral cause has not been established.

Pathophysiology

Any bone can be involved. The bones most commonly affected are, in decreasing order, the pelvis, femur, skull, tibia, vertebrae, clavicle, and humerus.

Bone turnover is accelerated at involved sites. Pagetic lesions are metabolically active and highly vascular. Excessively active osteoclasts are often large and contain many nuclei. Osteoblastic repair is also hyperactive, causing coarsely woven, thickened lamellae and trabeculae. This abnormal structure weakens the bone, despite bone enlargement and heavy calcification.

Complications: Overgrown bone may compress nerves and other structures passing through small foramina. Spinal stenosis or spinal cord compression may develop. Osteoarthritis may develop in joints adjacent to involved bone.

In about 10 to 15% of patients, increased bone formation and Ca requirement leads to secondary hyperparathyroidism; if this need is not matched by an increase in Ca intake, hypocalcemia may occur. Hypercalcemia (see p. 843) occasionally develops in patients who are immobile. It also occurs in patients with Paget's disease who develop secondary hyperparathyroidism.

Large or numerous lesions may lead to high-output heart failure.

Symptoms and Signs

There are usually no symptoms for a prolonged period. If symptoms occur, they develop insidiously, with pain, stiffness, fatigue, and bone deformity. Bone pain is aching, deep, and occasionally severe, sometimes worse at night. Pain also may arise from compression neuropathy or osteoarthritis. If the skull is involved, there may be headaches and hearing impairment.

Signs may include skull enlargement bitemporally and frontally (frontal bossing); dilated scalp veins; nerve deafness in one or both ears; angioid streaks in the fundus of the eye; a short kyphotic trunk with simian appearance; hobbling gait; and anterolateral angulation (bowing) of the thigh or leg, often with warmth and tenderness. Deformities may develop from bowing of the long bones or osteoarthritis. Pathologic fractures may be the presenting manifestation. Sarcomatous degeneration develops in < 1% and is often suggested by increasingly severe pain.

Diagnosis
Diagnosis

• Plain x-rays
• Serum alkaline phosphatase, Ca, and PO₄
• Bone scan after the diagnosis is established

Paget's disease should be suspected in patients with the following:

• Unexplained bone pain or deformity
• Suggestive findings on x-ray
• Unexplained elevation of serum alkaline phosphatase on laboratory tests done for other reasons, particularly if γ-glutamyl-transpeptidase (GGT) is normal
• Hypercalcemia that develops during bed rest, particularly among elderly patients
• Bone sarcoma in elderly patients

If Paget's disease is suspected, plain x-rays and serum alkaline phosphatase, Ca, and PO₄ levels should be obtained. Confirmation on x-ray is required to establish the diagnosis. Characteristic x-ray findings include the following:

• Increased bone sclerosis
• Abnormal architecture with coarse cortical trabeculation or cortical thickening
• Bowing
• Bone enlargement

There may be stress microfractures of the tibia or femur.

Characteristic laboratory findings include elevated serum alkaline phosphatase (increased anabolic activity of bone) but usually normal GGT and serum PO₄ levels. Serum Ca is usually normal but can increase because of immobilization or hyperparathyroidism or decrease (often transiently) because of increased bone synthesis. If alkaline phosphatase is not elevated or it is unclear whether the increased serum alkaline phosphatase is of bony origin (ie, if GGT is increased in proportion to alkaline phosphatase), a bone-specific fraction can be measured.

Occasionally, increased catabolic activity of bone, as demonstrated by elevated urine markers of bone collagen turnover (eg, pyridinoline crosslinks), supplements the findings.

Radionuclide bone scan using technetium-labeled phosphonates should be done at baseline to determine the extent of bone involvement.

Treatment

• Supportive care for symptoms and complications
• Bisphosphonates

Localized, asymptomatic disease requires no treatment. Symptomatic treatment includes

[Table 38-1. Drug Therapy for Paget's Disease]
analgesics or NSAIDs for pain. Orthotics help correct abnormal gait caused by bowed lower extremities. Some patients require orthopedic surgery (eg, hip or knee replacement, decompression of the spinal cord). Weight bearing should be encouraged, and bed rest should be avoided.

Drug therapy: Drug therapy suppresses osteoclast activity. It is indicated for the following:

- To prevent or reduce bleeding during orthopedic surgery
- To prevent or retard progression of complications (eg, hearing loss, deformity, osteoarthritis, paraparesis or paraplegia related to vertebral Paget's disease, or other neurologic deficits, particularly in a poor surgical candidate)
- To treat pain clearly related to the pagetic process and not to another source (eg, osteoarthritis)
- When serum alkaline phosphatase (of bony origin) is > 2 times the normal level, even in the absence of symptoms

Although disease progression can be retarded, existing deficits (eg, deformity, osteoarthritis, hearing loss, neural impingement) are not reversed.

Several bisphosphonates are available and are the drugs of choice (see Table 38-1 on p. 361). Synthetic salmon calcitonin is an alternative to bisphosphonates for patients intolerant of or resistant to them. The newer bisphosphonates (amino-containing bisphosphonates, eg, zolendronate) seem to provide more prolonged response.
Chapter 39. Osteonecrosis

Introduction

(Avascular Necrosis; Aseptic Necrosis; Ischemic Necrosis of Bone)

Osteonecrosis (ON) is a focal infarct of bone that may be caused by specific etiologic factors or may be idiopathic. It can cause pain, limitation of motion, joint collapse, and osteoarthritis. Diagnosis is by x-rays and MRI. In early stages, surgical procedures may slow or prevent progression. In later stages, joint replacement may be required for relief of pain and maintenance of function.

In the US, ON affects about 20,000 new patients annually. The hip (femoral head) is most commonly affected, followed by the knee and shoulder (humeral head). The wrist and ankle are less often involved. It is unusual for ON to involve the shoulder or other less commonly affected sites without the hip also being involved.

Etiology

The most common cause of ON is trauma. Nontraumatic ON affects men more often than women, is bilateral in > 60% of cases, and occurs primarily in patients between ages 30 and 50.

Traumatic ON: The most common cause of traumatic ON is a displaced subcapital fracture of the hip (see p. 321); ON is uncommon after intertrochanteric fractures. The incidence of ON after hip dislocation is high without prompt reduction; the sooner reduction occurs, the lower the incidence. Fracture or dislocation may cause ON by grossly disrupting or compressing nearby blood vessels.

Spontaneous ON of the knee (SPONK) is localized ON of the femoral condyle or tibial plateau in elderly women (occasionally men). SPONK is thought to be caused by an insufficiency fracture (a type of fragility fracture caused by normal wear and tear on osteoporotic bone that occurs without direct trauma).

Nontraumatic ON: Factors causing or contributing to nontraumatic ON are listed in Table 39-1. The most common factors are the following:

• Chronic corticosteroid use
• Excessive alcohol consumption

The risk of ON is increased when the dose of prednisone or an equivalent corticosteroid is > 25 mg/day for several weeks or months, resulting in a cumulative dose usually > 3000 mg. The risk of ON also is increased when > 3 drinks/day (> 500 mL ethanol/wk) are consumed for several years. Some genetic factors increase susceptibility to ON. Subtle clotting abnormalities due to deficiencies in protein C, protein S, or antithrombin III or to anticardiolipin antibodies (see Ch. 110) can be detected in a high percentage of patients with ON. Some disorders that are themselves associated with ON are treated with corticosteroids (eg, SLE), so it is not clear whether risk is increased because of corticosteroid use or the disorder. About 20% of cases are idiopathic.

[Table 39-1, Nontraumatic Risk Factors for Osteonecrosis]

ON of the jaw has recently been reported in several patients who have received high-dose IV bisphosphonate therapy (see Sidebar 39-1). Nontraumatic ON of the hip is bilateral in 60% of patients.

Pathophysiology

ON involves the death of osteocytes and bone marrow. Mechanisms of nontraumatic ON may include embolization by blood clots or lipid droplets, intravascular thrombosis, and extravascular compression. After the vascular insult, the repair processes attempt to remove necrotic bone and marrow and replace them with viable tissue. If the infarct is small, particularly if it is not subject to major weight bearing, this
process may succeed. However, in about 80% of patients, the process is not successful and the infarct gradually collapses. The overlying articular surface becomes flattened and irregular, causing increased pain and eventually leading to osteoarthritis.

**Symptoms and Signs**

**General symptoms:** Affected areas may remain asymptomatic for weeks to months after the vascular insult. Usually pain then develops gradually, although it may be acute. With progressive collapse of the joint, pain increases and is exacerbated by motion and weight bearing and is relieved by rest.

**Joint-specific symptoms:** ON of the hip causes groin pain that may radiate down the thigh or into the buttock. Motion becomes limited, and a limp usually develops. SPONK usually causes sudden knee pain without preceding trauma. This pain is most often on the medial side of the femoral condyle or tibial plateau and manifests with tenderness, joint effusion, painful motion, and a limp. ON of the humeral head often causes less pain and disability than hip and knee involvement. With advanced disease, patients have pain and decreased motion, although passive range of motion is less affected than active range of motion.

**Sidebar 39-1 Osteonecrosis of the Jaw**

Osteonecrosis of the jaw (ONJ) has no unanimously accepted definition but is generally held to be an oral lesion involving bare mandibular or maxillary bone, which usually manifests with pain and purulent discharge, although it may be asymptomatic. ONJ may occur spontaneously or after dental extraction or trauma, radiation therapy to the head and neck (osteoradionecrosis), or high-dose IV bisphosphonate therapy (e.g., for cancer treatment). It is not clear whether routine use of oral bisphosphonates for treatment or prevention of osteoporosis increases risk of ONJ. Currently, otherwise appropriate bisphosphonate use should not be discouraged. However, it seems reasonable to do any necessary oral surgery before beginning bisphosphonate therapy and to encourage good oral hygiene while patients are taking bisphosphonates.

Once established, ONJ is challenging to treat and should be managed by an oral surgeon with experience treating ONJ. Treatment typically involves limited debridement, antibiotics, and oral rinses. Surgical resection of the affected area may worsen the condition and should not be the initial treatment.

**Diagnosis**

- X-rays
- MRI

ON should be suspected in patients with the following:

- Fractures associated with an increased incidence of ON, particularly if pain persists or worsens
- Persistent spontaneous hip, knee, or shoulder pain, particularly if risk factors for ON are present

Plain x-rays should be done initially. They may show no abnormalities for months. The earliest findings are localized areas of sclerosis and lucency. Later, a subchondral crescent sign may appear. Then, gross collapse and flattening of the articular surface is seen, followed by advanced degenerative changes.

When x-rays are normal or nondiagnostic, an MRI, which is much more sensitive and more specific, should be done. Both hips should be imaged. Bone scans are less sensitive and less specific than MRI. CT is rarely needed, although it may occasionally be of value to detect joint collapse, which does not appear on plain x-rays.

Laboratory studies are usually normal and of little value in detecting ON. However, they might help detect
an underlying disorder (eg, coagulation defects, hemoglobinopathies, lipid abnormalities).

**Treatment**

- Symptomatic measures (eg, rest, physical therapy, NSAIDs)
- Surgical decompression or other procedures to stimulate healing
- Hip replacement

**Nonsurgical treatments:** Small, asymptomatic lesions may heal spontaneously and may not need treatment.

Larger lesions, both symptomatic and asymptomatic, have a poor prognosis if untreated, especially when in the femoral head. Therefore, early treatment to slow or prevent progression and save the joint is desirable. No completely effective treatment is yet available. Nonsurgical treatments include drugs (eg, bisphosphonates) and physical modalities (eg, electromagnetic fields and acoustic waves). Drug therapy and physical modalities have shown promise in limited studies but are not currently in general use.

**Surgical treatments:** Surgical treatments are most effective when done before joint collapse. They have been used most often in treating ON of the hip when the prognosis without treatment is worse than that for other regions. Core decompression is the procedure most frequently done; one or more cores of bone are removed from the necrotic region or multiple small tracks or perforations are made in an attempt to decrease intraosseous pressure and stimulate repair. Core decompression is technically simple, and the complication rate is very low if the procedure is done correctly. Protected weight bearing is needed for about 6 wk. Most reports indicate satisfactory or good results in 65% of patients, including those whose hips have some degree of collapse, and in 80% of patients whose hips have small, early lesions. Other established procedures include various proximal femoral osteotomies and bone grafting, both vascularized and nonvascularized. These procedures are technically demanding, require protected weight bearing for up to 6 mo, and have not been done often in the US. Reports vary as to their indications and effectiveness. They should be done primarily at selected centers that have the surgical experience and facilities to achieve optimal results. An approach currently being evaluated is injection of autologous marrow into the necrotic lesion.

If extensive collapse of the femoral head and degenerative changes in the acetabulum cause sufficient pain and disability, an arthroplasty usually is the only way to effectively relieve pain and increase range of motion. The conventional approach is total hip replacement. Good to excellent results are achieved in 95% of total hip and total knee replacements, complication rates are low, and patients resume most activities of daily living within 3 mo. Most prosthetic hips and knees last > 15 to 20 yr.

Two alternatives under investigation include surface replacement arthroplasty (SRA) and hemi-SRA. SRA, which can be done instead of total hip replacement, involves the insertion of 2 metal caps, one into the acetabulum and one onto the femoral head, producing a metal-on-metal articulation. Hemi-SRA involves placement of a metal cap onto only the femoral head. It is done only if disease is limited to the femoral head and is considered a temporizing procedure.

ON of the knee and shoulder can be managed nonsurgically more often than ON of the hip. Limited experience with core decompression has been promising. In advanced stages, partial or total joint replacement may be indicated.

**Prevention**

Risk of ON caused by corticosteroids can be minimized by using them only when essential and by giving them in as low a dose as needed and for as short a duration as possible. To prevent ON caused by decompression sickness, people should follow accepted rules for decompression when diving and when working in pressurized environments. Excessive alcohol use and smoking should be discouraged. Various drugs (eg, anticoagulants, vasodilators, lipid-lowering drugs) are being evaluated for prevention of ON in patients at high risk.
Chapter 40. Infections of Joints and Bones

Acute Infectious Arthritis

Acute infectious arthritis is a joint infection that evolves over hours or days. The infection resides in synovial or periarticular tissues and is usually bacterial—in younger adults, frequently *Neisseria gonorrhoeae*. However, nongonococcal bacterial infections can also occur and can rapidly destroy joint structures. Symptoms include rapid onset of pain, effusion, and restriction of both active and passive range of motion, usually within a single joint. Diagnosis requires synovial fluid analysis and culture. Treatment is IV antibiotics and drainage of pus from joints.

Acute infectious arthritis may occur in children. About 50% of children with joint infection are <3 yr. However, routine childhood vaccination for *Haemophilus influenzae* and *Streptococcus pneumoniae* is decreasing the incidence in this age group.

Risk factors are listed in Table 40-1. Risk is substantially increased in patients with RA and other disorders causing chronic joint damage, a past history of joint infection, IV drug abuse, or a prosthetic joint (see p. 370). RA patients are at particular risk of bacterial arthritis (prevalence 0.3 to 3.0%; annual incidence 0.5%). Most children who develop infectious arthritis do not have identified risk factors.

**Etiology**

Infectious organisms reach joints by direct penetration (eg, trauma, surgery, arthrocentesis, bites), extension from an adjacent infection (eg, osteomyelitis, a soft-tissue abscess, an infected wound), or hematogenous spread from a remote site of infection.

[Table 40-1. Risk Factors for Infectious Arthritis]

Common organisms are listed in Table 40-2. In adults, most cases result from bacteria and are classified as gonococcal or nongonococcal. In adults overall, *Staphylococcus aureus* tends to be the most frequent cause of infectious arthritis. Methicillin resistance has become more common among community isolates of *S. aureus*. In young adults and adolescents, *Neisseria gonorrhoeae* is the most common cause and results when *N. gonorrhoeae* spreads from infected mucosal surfaces (cervix, urethra, rectum, pharynx) via the bloodstream. Affected patients often have simultaneous genital infections with *Chlamydia trachomatis* (see p. 1468). *Streptococcus* species are also frequent causes, particularly in patients with polyarticular infections.

[Table 40-2. Organisms that Commonly Cause Acute Infectious Arthritis]

Infecting organisms multiply in the synovial fluid and synovial lining. Some bacteria (eg, *S. aureus*) produce virulence factors (adhesins), which allow bacteria to penetrate, remain within, and infect joint tissues. Other bacterial products (eg, endotoxin from gram-negative organisms, cell wall fragments, exotoxins from gram-positive organisms, immune complexes formed by bacterial antigens and host antibodies) augment the inflammatory reaction.

PMNs migrate into the joint and phagocytose the infecting organisms. Phagocytosis of bacteria also results in PMN autolysis with release of lysosomal enzymes into the joint, which damage synovia, ligaments, and cartilage. Therefore, PMNs are both the major host defense system and the cause of joint damage. Articular cartilage can be destroyed within hours or days. Inflammatory synovitis may occasionally persist even after the infection has been eradicated by antibiotics. Particularly in gonococcal cases, persistent antigen debris from bacteria or infection may alter cartilage, causing it to become antigenic, and—together with the adjuvant effects of bacterial components—immune-mediated, “sterile”
chronic inflammatory synovitis results.

**Symptoms and Signs**

Over a few hours to a few days, patients develop moderate to severe joint pain, warmth, tenderness, effusion, restricted active and passive motion, and sometimes redness. Systemic symptoms may be minimal or absent. Infants and children may present with limited spontaneous movement of a limb (pseudoparalysis), irritability, feeding disturbances, and a high, low-grade, or no fever.

**Gonococcal arthritis:** Gonococcal arthritis can cause a distinctive dermatitis-polyarthritistenosynovitis syndrome. Classic manifestations are fever (for 5 to 7 days); shaking chills; multiple skin lesions (petechiae, papules, pustules, hemorraghic vesicles or bullae, necrotic lesions) on mucosal surfaces and on the skin of the trunk, hands, or lower extremities; and migratory arthralgias, arthritis, and tenosynovitis, which evolves into persistent inflammatory arthritis in one or more joints, most often the small joints of the hands, wrists, elbows, knees, and ankles, and rarely the axial skeletal joints. Symptoms of the original mucosal infection (eg, urethritis, cervicitis) may not be present.

**Nongonococcal bacterial arthritis:** Nongonococcal bacterial arthritis causes progressive moderate to severe joint pain that is markedly worsened by movement or palpation. Most infected joints are swollen, red, and warm. Fever is absent or low grade in up to 50% of patients; 20% of patients report a shaking chill. Virulent organisms (eg, *S. aureus*, *Pseudomonas aeruginosa*) generally cause a more fulminant arthritis, whereas less virulent organisms (eg, coagulase-negative staphylococci, *Propionibacterium acnes*) cause a less fulminant arthritis. In 80% of adults, nongonococcal bacterial arthritis is monarticular and usually occurs in a peripheral joint: knee, hip, shoulder, wrist, ankle, or elbow. In children, ≥ 90% is monarticular: knee (39%), hip (26%), and ankle (13%). Polyarticular involvement is somewhat more common among patients who are immunosuppressed or have an underlying chronic arthritis (eg, RA, osteoarthritis). In IV drug users and patients with indwelling vascular catheters, axial joints (eg, sternoclavicular, costochondral, hip, shoulder, vertebral, symphysis pubis, sacroiliac) are often involved.

**Infectious arthritis secondary to bite wounds:** Infection due to human, dog, or cat bites usually develops within 48 h. Rat bites cause systemic symptoms such as fever, rash, and joint pain or true arthritis with regional adenopathy within about 2 to 10 days.

**Viral infectious arthritis:** Viral infectious arthritis sometimes causes symptoms similar to acute nongonococcal bacterial arthritis and is more likely to be polyarticular than bacterial arthritis.

**Borrelia burgdorferi arthritis:** Patients with *B. burgdorferi* arthritis may have other symptoms of Lyme disease (see p. 1269) or present only with acute monarthritis or oligoarthritis.

**Diagnosis**

- Arthrocentesis with synovial fluid examination and culture
- Blood culture
- Sometimes imaging studies
- Often CBC and ESR (or C-reactive protein)

Infectious arthritis is suspected in patients with acute monarticular arthritis and in patients with other combinations of symptoms characteristic of particular infectious arthritis syndromes (eg, migratory polyarthritis, tenosynovitis and skin lesions typical of disseminated gonococcal infection; erythema migrans or other symptoms and signs of Lyme disease—see p. 1269). Even mild monarticular joint symptoms should arouse suspicion in patients with risk factors (eg, RA, a prosthetic joint, or an extra-articular infection capable of spreading to a joint (eg, genital gonococcal infection, bacteremia, any anaerobic infection).

**General arthritis:** Synovial fluid examination is the cornerstone of diagnosis. Fluid is examined
grossly and sent for cell count and differential, Gram stain, aerobic and anaerobic culture, and crystals. Foul-smelling synovial fluid suggests anaerobic infection. Fluid from an acutely infected joint usually reveals a WBC count > 20,000/μL (often > 100,000/μL) consisting of > 95% PMNs. WBC counts tend to be higher in nongonococcal bacterial than in gonococcal infectious arthritis. WBC counts may also be lower in early or partially treated infections. Gram stain reveals organisms in only 50 to 75% of joints with acute bacterial arthritis, most often with staphylococci. If positive, Gram stain is usually relatively specific, but cultures are definitive. The presence of crystals does not exclude infectious arthritis. Sometimes synovial fluid analysis cannot differentiate between infectious and other inflammatory synovial fluid. If differentiation is impossible by clinical means or synovial fluid examination, infectious arthritis is assumed, pending culture results.

**Blood tests**, such as blood cultures, CBC, and ESR (or C-reactive protein), are usually obtained. However, normal results do not exclude infection. Likewise, WBC count, ESR, or C-reactive protein may be increased in noninfectious as well as infectious joint inflammation.

**Plain x-rays** of the involved joint are not diagnostic of acute infection but can exclude other conditions under consideration (eg, fractures). Abnormalities in early acute bacterial arthritis are limited to soft-tissue swelling and signs of synovial effusions. After 10 to 14 days of untreated bacterial infection, destructive changes of joint space narrowing (reflecting cartilage destruction) and erosions or foci of subchondral osteomyelitis may appear. Gas visible within the joints suggests infection with *Escherichia coli* or anaerobes.

**MRI** is considered if the joint is not easily accessible for examination and aspiration (eg, an axial joint). MRI or ultrasonography can identify sites of effusion or abscess that can be aspirated or drained for both diagnosis and therapy. MRI can provide early suggestion of associated osteomyelitis. Bone scans using technetium-99m can be falsely negative in infectious arthritis. Also, because they show increased uptake with increased blood flow in inflamed synovial membranes and in metabolically active bone, they can be falsely positive in noninfectious inflammatory arthritis. Nuclear imaging and MRI do not distinguish infection from crystal-induced arthritis.

**Gonococcal arthritis:** If gonococcal arthritis is suspected, blood and synovial fluid samples should be immediately plated on nonselective chocolate agar, and specimens from the urethra, endocervix, rectum, and pharynx should be plated on selective Thayer-Martin medium. Genital chlamydial cultures are also done. Blood cultures are positive in 60 to 75% of cases during the first week and may be the only method by which to identify the organism; cultures from joints with early tenosynovitis or arthritis are often negative. Synovial fluid cultures from joints with frank purulent arthritis are usually positive, and fluid from skin lesions may be positive. If disseminated gonococcal infection is suspected based on clinical criteria, it is assumed to be present even if all gonococcal cultures are negative. Clinical response to antibiotics (anticipated within 5 to 7 days) can help confirm the diagnosis.

**Prognosis**

Acute nongonococcal bacterial arthritis can destroy articular cartilage, permanently damaging the joint within hours or days. Gonococcal arthritis does not usually damage joints permanently. Factors that increase susceptibility to infectious arthritis may also increase disease severity. In patients with RA, functional outcome is particularly poor, and the mortality rate is increased.

**Treatment**

- IV antibiotics
- Drainage of pus from infected joints (for acute nongonococcal bacterial arthritis or any septic arthritis with persistent effusion)

**Antibiotic therapy:** Initial antibiotic selection is directed at the most likely pathogens. The regimen is adjusted based on the results of culture and susceptibility testing.

Gonococcal arthritis is treated with ceftriaxone 1 g IV once/day until at least 24 h after symptoms and
signs resolve, followed by cefixime 400 mg po bid for 7 days. Joint drainage and debridement may be unnecessary. Coexisting genital infection with *C. trachomatis* is also treated, often with doxycycline 100 mg po bid for 7 days, and sexual contacts of the patient are treated as necessary (see p. 1470).

If nongonococcal gram-positive infection is suspected by Gram stain in an adult, the empiric choice is one of the following: a semisynthetic penicillin (eg, nafcillin 2 g IV q 4 h), a cephalosporin (eg, cefazolin 2 g IV q 8 h), or vancomycin 1 g IV q 12 h (if methicillin resistance is common among local community isolates of *S. aureus*). If gram-negative infection is suspected, empiric treatment includes a parenteral 3rd-generation cephalosporin with antipseudomonal activity (eg, ceftazidime 2 g IV q 8 h) and, if infection is severe, an aminoglycoside.

Parenteral antibiotics are continued until clinical improvement is clear (usually 2 to 4 wk), and oral antibiotics should be given at high doses for another 2 to 6 wk according to the clinical response. Infections caused by streptococci and *Haemophilus* are usually eradicated after 2 wk of oral antibiotics after IV treatment. Staphylococcal infections require at least 3 wk and often 6 wk or longer, especially in patients with prior arthritis.

**Other therapies:** In addition to antibiotics, acute nongonococcal bacterial arthritis requires large-bore needle aspiration of intra-articular pus at least once/day, or tidal irrigation lavage, arthroscopic lavage, or arthroscopy for debridement. Infected RA joints should generally undergo even earlier and more aggressive surgical debridement and drainage. For gonococcal arthritis with persistent effusion, pus is aspirated and drainage may need to be repeated as necessary. Acute bacterial arthritis requires joint splinting for the first few days to reduce pain, followed by passive and active range-of-motion exercises to limit contractures, with muscle strengthening as soon as tolerated. NSAIDs can help decrease pain and inflammation.

**Viral arthritis and arthritis secondary to bite wounds:** Viral arthritis is treated supportively. Bite wounds are treated with antibiotics and surgical drainage as necessary (see p. 3307).

**Chronic Infectious Arthritis**

Chronic infectious arthritis develops over weeks and is usually caused by mycobacteria, fungi, or bacteria with low pathogenicity.

Chronic infectious arthritis accounts for 5% of infectious arthritis. It can develop in healthy people, but patients at increased risk include those with

- RA
- HIV infection
- Immunosuppression (eg, hematologic or other cancers, immunosuppressive drug use)
- Prosthetic joints (see p. 370)

Examples of possible causes are *Mycobacterium tuberculosis*, *M. marinum*, *M. kansasii*, *Candida* sp, *Coccidioides immitis*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Aspergillus fumigatus*, *Actinomyces israelii*, and *Brucella* sp. The arthritis of Lyme disease is usually acute but may be chronic and recurrent. Unusual opportunistic organisms are possible in patients with hematologic cancers or HIV infection or who are taking immunosuppressive drugs. In chronic infectious arthritis, the synovial membrane can proliferate and can erode articular cartilage and subchondral bone.

Onset is often indolent, with gradual swelling, mild warmth, minimal or no redness of the joint area, and aching pain that may be mild. Usually a single joint is involved. A prolonged duration and lack of response to conventional antibiotics suggest a mycobacterial or fungal cause.

Patients should have fungal and mycobacterial cultures taken of synovial fluid or synovial tissue, as well
as routine studies. Plain x-ray findings may differ from those of acute infectious arthritis in that joint space is preserved longer, and marginal erosions and bony sclerosis may occur. Mycobacterial and fungal joint infections require prolonged treatment. Mycobacterial infections are often treated with multiple antibiotics, guided by sensitivity testing results.

**Prosthetic Joint Infectious Arthritis**

Prosthetic joints are at risk of acute and chronic infection, which can cause sepsis, morbidity, or mortality.

**Etiology**

Infections are more common in prosthetic joints. They are frequently caused by perioperative inoculations of bacteria into the joint or by postoperative bacteremia resulting from skin infection, pneumonia, dental procedures, invasive instrumentation, UTI, or possibly falls. They develop within 1 yr of surgery in two thirds of cases. During the first few months after surgery, the causes are *Staphylococcus aureus* in 50% of cases, mixed flora in 35%, gram-negative organisms in 10%, and anaerobes in 5%.

**Symptoms and Signs**

There is a history of a fall within 2 wk of symptom onset in about 25% of patients and of prior surgical revisions in about 20%. Some patients have had a postoperative wound infection that appeared to resolve, satisfactory postoperative recovery for many months, and then development of persistent joint pain at rest and during weight bearing. Symptoms and signs may include pain, swelling, and limited motion; temperature may be normal.

**Diagnosis**

- Clinical, microbiologic, pathologic, and radiographic criteria

The diagnosis often uses a combination of clinical, microbiologic, pathologic, and radiographic criteria. Communication between a sinus tract and the prosthesis may also be considered diagnostic of infection. Synovial fluid should be sampled for cell count and culture. X-rays may show loosening of the prosthesis or periosteal reaction but are not diagnostic. Technetium-99m bone scanning and indium-labeled WBC scanning are more sensitive than plain x-rays but may lack specificity in the immediate postoperative period. Ultimately, periprosthetic tissue collected at the time of surgery may be sent for culture and histologic analysis.

**Treatment**

- Arthrotomy with debridement
- Long-term systemic antibiotic therapy

Treatment must be prolonged and usually involves arthrotomy for prosthesis removal with meticulous debridement of all cement, abscesses, and devitalized tissues. Debridement is followed by immediate prosthesis revision or placement of an antibiotic-impregnated spacer and then delayed (2 to 4 mo) implantation of a new prosthesis using antibiotic-impregnated cement. Long-term systemic antibiotic therapy is used in either case; empiric therapy is initiated after intraoperative culture is done and usually combines coverage for methicillin-resistant gram-positive organisms (eg, vancomycin 1 g IV q 12 h) and aerobic gram-negative organisms (eg, piperacillin/tazobactam 3.375 g IV q 6 h or ceftazidime 2 g IV q 8 h) and is revised based on results of culture and sensitivity testing. Infection develops in 38% of new implants, whether replaced immediately or after delay.

If patients cannot tolerate surgery, long-term antibiotic therapy alone can be tried. Excision arthroplasty with or without fusion usually is reserved for patients with uncontrolled infection and insufficient bone stock.
Prevention

In the absence of other indications (eg, valvular heart disease), patients with prosthetic joints do not need prophylactic antibiotics before procedures such as dental work and urologic instrumentation. Detailed recommendations are available at www.aaos.org.

Osteomyelitis

Osteomyelitis is inflammation and destruction of bone caused by bacteria, mycobacteria, or fungi. Common symptoms are localized bone pain and tenderness with constitutional symptoms (in acute osteomyelitis) or without constitutional symptoms (in chronic osteomyelitis). Diagnosis is by imaging studies and cultures. Treatment is with antibiotics and sometimes surgery.

Etiology

Osteomyelitis is caused by

• Contiguous spread (from infected tissue or an infected prosthetic joint)

• Bloodborne organisms (hematogenous osteomyelitis)

• Open wounds (from contaminated open fractures or bone surgery)

Trauma, ischemia, and foreign bodies predispose to osteomyelitis. Osteomyelitis may form under deep decubitus ulcers.

About 80% of osteomyelitis results from contiguous spread or from open wounds; it is often polymicrobial. *Staphylococcus aureus* (including both methicillin-sensitive and methicillin-resistant strains) is present in ≥50%; other common bacteria include streptococci, gram-negative enteric organisms, and anaerobic bacteria. Osteomyelitis that results from contiguous spread is common in the feet (in patients with diabetes or peripheral vascular disease), at sites where bone was penetrated during trauma or surgery, at sites damaged by radiation therapy, and in bones contiguous to decubitus ulcers, such as the hips and sacrum. A sinus, gum, or tooth infection may spread to the skull.

Hematogenously spread osteomyelitis usually results from a single organism. In children, gram-positive bacteria are most common, usually affecting the metaphyses of the tibia, femur, or humerus. Hematogenously spread osteomyelitis in adults usually affects the vertebrae. Risk factors in adults are older age, debilitation, hemodialysis, sickle cell disease, and IV drug use. Common infecting organisms include *S. aureus* (methicillin-resistant *S. aureus* [MRSA] is common) and enteric gram-negative bacteria (in adults who are older, debilitated, or receiving hemodialysis); *S. aureus*, *Pseudomonas aeruginosa*, and *Serratia* sp (in IV drug users); and *Salmonella* sp (in patients with sickle cell disease). Fungi and mycobacteria can cause hematogenous osteomyelitis, usually in immunocompromised patients or in areas of endemic infection with histoplasmosis, blastomycosis, or coccidioidomycosis. The vertebrae are often involved.

Pathophysiology

Osteomyelitis tends to occlude local blood vessels, which causes bone necrosis and local spread of infection. Infection may expand through the bone cortex and spread under the periosteum, with formation of subcutaneous abscesses that may drain spontaneously through the skin. In vertebral osteomyelitis, paravertebral or epidural abscess can develop.

If treatment of acute osteomyelitis is only partially successful, low-grade chronic osteomyelitis develops.

Symptoms and Signs

Patients with acute osteomyelitis of peripheral bones usually experience weight loss, fatigue, fever, and
localized warmth, swelling, erythema, and tenderness.

Vertebral osteomyelitis causes localized back pain and tenderness with paravertebral muscle spasm that is unresponsive to conservative treatment. Patients are usually afebrile.

Chronic osteomyelitis causes intermittent (months to many years) bone pain, tenderness, and draining sinuses.

**Diagnosis**

- ESR or C-reactive protein
- X-rays, MRI, or radioisotopic bone scanning
- Culture of bone, abscess, or both

Acute osteomyelitis is suspected in patients with localized peripheral bone pain, fever, and malaise or with localized refractory vertebral pain, particularly in patients with recent risk factors for bacteremia. Chronic osteomyelitis is suspected in patients with persistent localized bone pain, particularly if they have risk factors.

If osteomyelitis is suspected, CBC and ESR or C-reactive protein, as well as plain x-rays of the affected bone, are obtained. The WBC count may not be elevated, but the ESR and C-reactive protein usually are. X-rays become abnormal after 2 to 4 wk, showing periosteal elevation, bone destruction, soft-tissue swelling, and, in the vertebrae, loss of vertebral body height or narrowing of the adjacent infected intervertebral disk space and destruction of the end plates above and below the disk.

If x-rays are equivocal or symptoms are acute, CT and MRI are the current imaging techniques of choice to define abnormalities and reveal abscesses (eg, paravertebral or epidural abscesses). Alternatively, a radioisotope bone scan with technetium-99m can be done. The bone scan shows abnormalities earlier than plain x-rays but does not distinguish among infection, fractures, and tumors. A white blood cell scan using indium-111-labeled cells may help to better identify areas of infection seen on bone scan. Bacteriologic diagnosis is necessary for optimal therapy of osteomyelitis; bone biopsy with a needle or surgical excision and aspiration or debridement of abscesses provides tissue for culture and antibiotic sensitivity testing. Culture of sinus drainage does not necessarily reveal the bone pathogen. Biopsy and culture should precede antibiotic therapy unless the patient is in shock or has neurologic dysfunction.

**Treatment**

- Antibiotics
- Surgery for abscess, constitutional symptoms, potential spinal instability, or much necrotic bone

Antibiotics effective against both gram-positive and gram-negative organisms are given until culture results and sensitivities are available. Initial antibiotic treatment for acute hematogenous osteomyelitis should include a penicillinase-resistant semisynthetic penicillin (eg, nafcillin or oxacillin 2 g IV q 4 h) or vancomycin 1 g IV q 12 h (when MRSA is prevalent in a community) and a 3rd- or 4th-generation cephalosporin (such as ceftazidime 2 g IV q 8 h or cefepime 2 g IV q 12 h). Empiric treatment of chronic osteomyelitis arising from a contiguous soft-tissue focus, particularly in patients with diabetes, must be effective against anaerobic organisms in addition to gram-positive and gram-negative aerobes. Ampicillin/sulbactam 3 g IV q 6 h or piperacillin/tazobactam 3.375 g IV q 6 h is commonly used; vancomycin 1 g IV q 12 h is added when infection is severe or MRSA is prevalent. Antibiotics must be given parenterally for 4 to 8 wk and tailored to results of appropriate cultures. If any constitutional findings (eg, fever, malaise, weight loss) persist or if large areas of bone are destroyed, necrotic tissue is debrided surgically. Surgery may also be needed to drain coexisting paravertebral or epidural abscesses or to stabilize the spine to prevent injury. Skin or pedicle grafts may be needed to close large surgical defects. Broad-spectrum antibiotics should be continued for > 3 wk after surgery. In chronic osteomyelitis, long-term antibiotic therapy may be needed.
Chapter 41. Bursa, Muscle, and Tendon Disorders

Introduction

Often, muscles, bursae, and tendons are injured during sports activities. Injury, overuse, infection, and occasionally disease can temporarily or permanently damage these structures. Damage can cause pain, limit control of movement, and reduce range of motion.

Bursitis

Bursitis is acute or chronic inflammation of a bursa. The cause is usually unknown, but trauma, repetitive or acute, may contribute, as may infection and crystal-induced disease. Symptoms include pain (particularly with motion or pressure), swelling, and tenderness. Diagnosis is usually clinical; however, ultrasonography may be needed to evaluate deep bursae. Diagnosis of infection and crystal-induced disease requires analysis of bursal fluid. Treatment includes splinting, NSAIDs, sometimes corticosteroid injections, and treatment of the cause.

Bursae are fluid-filled sac-like cavities or potential cavities that are located where friction occurs (eg, where tendons or muscles pass over bony prominences). Bursae minimize friction between moving parts and facilitate movement. Some communicate with joints.

Bursitis may occur in the shoulder (subacromial or subdeltoid bursitis), particularly in patients with rotator cuff tendinitis, which is usually the primary lesion in the shoulder. Other commonly affected bursae include olecranon (miners’ or barfly’s elbow), prepatellar (housemaid’s knee), suprapatellar, retrocalcaneal, iliopsoas, ischial (tailor’s or weaver’s bottom), greater trochanteric, pes anserine, and first metatarsal head (bunion) bursae. Occasionally, bursitis causes inflammation in a communicating joint.

Etiology

Bursitis may be caused by the following:

• Injury

• Chronic overuse

• Inflammatory arthritis (eg, gout, RA)

• Acute or chronic infection (eg, pyogenic organisms, particularly *Staphylococcus aureus*)

Idiopathic and traumatic causes are by far the most common. Acute bursitis may follow unusual exercise or strain and usually causes bursal effusion. Infection most often affects olecranon and prepatellar bursae.

Chronic bursitis may develop after previous attacks of bursitis or repeated trauma. The bursal wall is thickened, with proliferation of its synovial lining; bursal adhesions, villus formation, tags, and chalky deposits may develop.

Symptoms and Signs

Acute bursitis causes pain, particularly when the bursa is compressed or stretched during motion. Swelling, sometimes with other signs of inflammation, is common if the bursa is superficial (eg, prepatellar, olecranon). Swelling may be more prominent than pain in olecranon bursitis. Crystal- or bacterial-induced bursitis is usually accompanied by erythema, pitting edema, pain, and warmth in the area over the bursa.

Chronic bursitis may last for several months and may recur frequently. Bouts may last a few days to several weeks. If inflammation persists near a joint, the joint's range of motion may be limited.
motion may lead to muscle atrophy.

**Diagnosis**

- Clinical evaluation
- Ultrasonography or MRI for deep bursitis
- Aspiration for suspected infection or crystal-induced bursitis

Superficial bursitis should be suspected in patients with swelling or signs of inflammation over bursae. Deep bursitis is suspected in patients with unexplained pain worsened by motion in a location compatible with bursitis. Usually, bursitis can be diagnosed clinically. Ultrasonography or MRI can help confirm the diagnosis when deep bursae are not readily accessible for inspection, palpation, or aspiration. These tests are done to confirm or exclude a suspected diagnosis. These imaging techniques increase the accuracy of identifying the involved structures.

If bursal swelling is particularly painful, red, or warm or if the olecranon or prepatellar bursa is affected, infection and crystal-induced disease should be excluded by bursal aspiration. After a local anesthetic is injected, fluid is withdrawn from the bursa using sterile techniques; analysis includes cell count, Gram stain and culture, and microscopic search for crystals. Gram stain, although helpful, may not be specific, and WBC counts in infected bursae are usually lower than those in septic joints. Urate crystals are easily seen with polarized light, but the apatite crystals typical of calcific tendinitis appear only as shiny chunks that are not birefringent. X-rays should be taken if bursitis is persistent or if calcification is suspected.

Acute bursitis should be distinguished from hemorrhage into a bursa, which can cause similar manifestations because blood is inflammatory. Fluid in traumatic bursitis is serosanguineous. Cellulitis can cause signs of inflammation but does not normally cause bursal effusion; cellulitis overlying the bursa is a relative contraindication to bursal puncture through the cellulitis, but if septic bursitis is strongly suspected, aspiration must occasionally be done.

**Treatment**

- Rest
- High-dose NSAIDs
- Treatment of crystal-induced disease or infection

Crystal-induced disease (see p. 349) or infection should be treated if present. For infection, choice of antibiotic is determined by results of Gram stain and culture. Empiric antibiotics effective against *S. aureus* should be given. Infectious bursitis requires drainage or excision in addition to antibiotics.

Acute nonseptic bursitis is treated with temporary rest or immobilization and high-dose NSAIDs and sometimes with other analgesics. Voluntary movement should be increased as pain subsides. Pendulum exercises are helpful for the shoulder joint.

If oral drugs and rest are inadequate, aspiration and intrabursal injection of depot corticosteroids 0.5 to 1 mL (eg, triamcinolone acetonide 40 mg/mL) are the treatment of choice. About 1 mL of local anesthetic (eg, 2% lidocaine) can be injected before the corticosteroid injection. The same needle is used; it is kept in place and the syringes are changed. Dose and volume of the corticosteroid may vary according to the size of the bursa. Infrequently, a flare-up occurs within several hours of injection of a depot corticosteroid; the flare-up is probably a form of crystal-induced synovitis. It usually lasts ≤ 24 h and responds to cold compresses plus analgesics. Oral corticosteroids (eg, prednisone) can be used if a local injection is not feasible.

Chronic bursitis is treated the same as acute bursitis, except that splinting and rest are less likely to help and range-of-motion exercises are especially important. Rarely, the bursa needs to be excised.
**Tendinitis and Tenosynovitis**

Tendinitis is inflammation of a tendon, often developing after degeneration (tendinopathy); tenosynovitis is tendinitis with inflammation of the tendon sheath lining. Symptoms usually include pain with motion and tenderness with palpation. Chronic deterioration or inflammation can cause scars that restrict motion. Diagnosis is clinical, sometimes supplemented with imaging. Treatment includes rest, NSAIDs, and sometimes corticosteroid injections.

Tendinopathy usually results from repeated small tears or degenerative changes (sometimes with Ca deposit) that occur over years in the tendon.

Tendinitis and tenosynovitis most commonly affect tendons associated with the shoulder (rotator cuff), the tendon of the long head of the biceps muscle (bicipital tendon), flexor carpi radialis or ulnaris, flexor digitorum (for infectious flexor tenosynovitis, see p. 390), popliteus tendon, Achilles tendon (see p. 3304), and the abductor pollicis longus and extensor pollicis brevis, which share a common fibrous sheath (the resulting disorder is de Quervain's syndrome—see p. 393).

**Etiology**

The cause of tendinitis is often unknown. It usually occurs in people who are middle-aged or older as the vascularity of tendons decreases; repetitive microtrauma may contribute. Repeated or extreme trauma (short of rupture), strain, and excessive or unaccustomed exercise probably also contribute. Some quinolone antibiotics may increase the risk of tendinopathy and tendon rupture.

Risk of tendinitis may be increased by certain systemic disorders—most commonly RA, systemic sclerosis, gout, reactive arthritis, and diabetes or, very rarely, amyloidosis or markedly elevated blood cholesterol levels. In younger adults, particularly women, disseminated gonococcal infection may cause acute migratory tenosynovitis.

**Symptoms and Signs**

Affected tendons are usually painful when moved. Occasionally, tendon sheaths become swollen and fluid accumulates, usually when patients have infection, RA, or gout. Swelling may be visible or only palpable. Along the tendon, palpation elicits localized tenderness of varying severity.

In systemic sclerosis, the tendon sheath may remain dry, but movement of the tendon in its sheath causes friction, which can be felt, or heard with a stethoscope.

**Diagnosis**

- Clinical evaluation
- Sometimes imaging

Usually, the diagnosis can be based on symptoms and physical examination, including palpation or specific maneuvers to assess pain. MRI or ultrasonography may be done to confirm the diagnosis or rule out other disorders. MRI can detect tendon tears and inflammation (as can ultrasonography).

- **Rotator cuff tendinitis:** This disorder is the most common cause of shoulder pain. Active abduction in an arc of 40 to 120° and internal rotation cause pain (see p. 3298). Passive abduction causes less pain. Ca deposits in the tendon just below the acromion are sometimes visible on x-ray. Ultrasonography or MRI may help with further evaluation and with treatment decisions.

- **Bicipital tendinitis:** Pain in the biceps tendon is aggravated by shoulder flexion or resisted supination of the forearm. Examiners can elicit tenderness proximally over the bicipital groove of the humerus by rolling (flipping) the bicipital tendon under their thumb.
• **Volar flexor tenosynovitis** (digital tendinitis): This common musculoskeletal disorder is often overlooked (see p. 393). Pain occurs in the palm on the volar aspect of the thumb or other digits and may radiate distally. Palpation of the tendon and sheath elicits tenderness; swelling and sometimes a nodule are present. In later stages, the digit may lock when it is flexed, then extend suddenly with a snap (trigger finger).

• **Gluteus medius tendinitis**: Patients with trochanteric bursitis almost always have gluteus medius tendinitis. In patients with trochanteric bursitis, palpation over the lateral prominence of the greater trochanter elicits tenderness. Patients often have a history of chronic pressure on the joint, trauma, a change in gait (eg, due to osteoarthritis, stroke, or leg-length discrepancy), or inflammation at this site (eg, in RA).

### Treatment

- Rest or immobilization, heat or cold, followed by exercise
- High-dose NSAIDs
- Sometimes corticosteroid injection

Symptoms are relieved by rest or immobilization (splint or sling) of the tendon, application of heat (usually for chronic inflammation) or cold (usually for acute inflammation), and high-dose NSAIDs (see Table 35-2 on p. 336) for 7 to 10 days. Indomethacin or colchicine may be helpful if gout is the cause (see p. 349). After inflammation is controlled, exercises that gradually increase range of motion should be done several times a day, especially for the shoulder, which can develop contractures rapidly.

Injecting a sustained-release corticosteroid (eg, betamethasone 6 mg/mL, triamcinolone 40 mg/mL, methylprednisolone 20 to 40 mg/mL) in the tendon sheath may help; injection is usually indicated if pain is severe or if the problem has been chronic. Injection volume may range from 0.3 mL to 1 mL, depending on the site. An injection through the same needle of an equal or double volume of local anesthetic (eg, 1 to 2% lidocaine) confirms the diagnosis if pain is relieved immediately. Clinicians should be careful not to inject the tendon (which can be recognized by marked resistance to injection); doing so may weaken it, increasing risk of rupture. Patients are advised to rest the injected joint to reduce the slight risk of rupture. Infrequently, symptoms can worsen for up to 24 h after the injection.

Repeat injections and symptomatic treatment may be required. Rarely, for persistent cases, particularly rotator cuff tendinitis, surgical exploration with removal of Ca deposits or tendon repair, followed by graded physical therapy, is needed. Occasionally, patients require surgery to release scars that limit function or tenosynovectomy to relieve chronic inflammation.

### Fibromyalgia

(Myofascial Pain Syndrome; Fibrositis; Fibromyositis)

**Fibromyalgia is a common nonarticular disorder of unknown cause characterized by generalized aching (sometimes severe); widespread tenderness of muscles, areas around tendon insertions, and adjacent soft tissues; muscle stiffness; fatigue; and poor sleep.**

**Diagnosis is clinical. Treatment includes exercise, local heat, stress management, drugs to improve sleep, and analgesics.**

In fibromyalgia, any fibromuscular tissues may be involved, especially those of the occiput, neck, shoulders, thorax, low back, and thighs. There is no specific histologic abnormality. Symptoms and signs are generalized, in contrast to localized soft-tissue pain and tenderness (myofascial pain syndrome—see also p. 533), which is often related to overuse or microtrauma.

Fibromyalgia is common; it is about 7 times more common among women, usually young or middle-aged women, but can occur in men, children, and adolescents. Because of the sex difference, it is sometimes overlooked in men. It sometimes occurs in patients with systemic rheumatic disorders.
The cause is unknown, but disruption of stage 4 sleep may contribute, as can emotional stress. Patients may tend to be perfectionists. Fibromyalgia may be precipitated by a viral or other systemic infection (eg, Lyme disease) or a traumatic event.

**Symptoms and Signs**

Stiffness and pain frequently begin gradually and diffusely and have an achy quality. Symptoms can be exacerbated by environmental or emotional stress, poor sleep, trauma, or exposure to dampness or cold or by a physician who implies that the disorder is "all in the head."

Patients tend to be stressed, tense, anxious, fatigued, ambitious, and sometimes depressed. Many patients also have irritable bowel syndrome symptoms or migraine or tension headaches. Pain may worsen with fatigue, muscle strain, or overuse. Specific, discrete areas of muscle (tender points) may be tender when palpated.

**Diagnosis**

- Clinical criteria

Fibromyalgia is suspected in patients with the following:

- Generalized pain and tenderness, especially if disproportionate to physical findings
- Negative laboratory results despite widespread symptoms
- Fatigue as the predominant symptom

Tests should include ESR or C-reactive protein, CK, and probably tests for hypothyroidism and hepatitis C (which can cause fatigue and generalized myalgias). The diagnosis is based on clinical criteria, including tenderness at some of the 18 specified tender points (see Fig. 41-1). Most experts no longer require a specific number of tender points to make the diagnosis, as originally proposed (≥ 11 of 18). Patients with only some of the specified features may still have fibromyalgia.

[Fig. 41-1, Diagnosing fibromyalgia.]

To avoid potential pitfalls, clinicians should consider the following:

- Fibromyalgia is often overlooked in men, children, and adolescents.
- Chronic fatigue syndrome (see p. 3442) can cause similar generalized myalgias and fatigue and typically produces normal laboratory test results.
- Polymyalgia rheumatica (see p. 325) can cause generalized myalgias, particularly in older adults; it can be distinguished because it tends to affect proximal muscles selectively and ESR is high.
- In patients with systemic rheumatic disorders, diagnosing fibromyalgia may be difficult. For example, fibromyalgia may be misinterpreted as an exacerbation of RA or SLE.

**Prognosis**

Fibromyalgia tends to be chronic but may remit spontaneously if stress decreases. It can also recur at frequent intervals. Functional prognosis is usually favorable for patients being treated with a comprehensive, supportive program, although symptoms tend to persist to some degree.

**Treatment**
• Stretching and aerobic exercise, local heat, and massage

• Stress management

• Tricyclic antidepressants or cyclobenzaprine to improve sleep

• Analgesics

Stretching exercises, aerobic exercises, sufficient sound sleep, local applications of heat, and gentle massage may provide relief. Overall stress management (eg, deep breathing exercises, meditation, psychologic support, counseling if necessary) is important.

Exercises to gently stretch the affected muscles should be done daily; stretches should be held for about 30 sec and repeated about 5 times. Aerobic exercise (eg, fast walking, swimming, exercise bicycle) can lessen symptoms.

Improving sleep is critical. Low-dose oral tricyclic antidepressants at bedtime (eg, amitriptyline 10 to 50 mg, trazodone 50 to 150 mg, doxepin 10 to 25 mg) or the pharmacologically similar cyclobenzaprine 10 to 40 mg may promote deeper sleep and decrease muscle pain. The lowest effective dose should be used. Drowsiness, dry mouth, and other adverse effects may make some or all of these drugs intolerable, particularly for the elderly.

Nonopioid analgesics (eg, tramadol, propoxyphene, acetaminophen, NSAIDs) may help some patients but on average are not effective. Opioids should be avoided. Pregabalin, used as an adjunct to exercise, measures to improve sleep, and stress management, may help reduce pain.

Rarely, injections of 0.5% bupivacaine or 1% lidocaine 1 to 5 mL are used to treat incapacitating areas of focal tenderness, but such injections should not be relied on as primary treatment.

Drugs taken by the patient should be reviewed to identify those that may aggravate sleep problems. Such drugs should be stopped, and future use should be avoided. Anxiety or depression, if present, may require treatment.

**Muscle Cramps**

A muscle cramp is a sudden, brief, painful contraction of a muscle or group of muscles.

Cramps (charley horses) can occur in healthy people (usually middle-aged and elderly people), sometimes during rest, but particularly during or after exercise. Leg cramps can occur during sleep, causing pain and plantar flexion of the foot and toes.

Tight calf muscles (eg, from lack of stretching, inactivity, or sometimes chronic lower leg edema) are a common cause of leg cramps. Cramps may also be caused by electrolyte abnormalities (eg, hypokalemia). Exertional muscle pain from ischemia due to peripheral arterial disease (claudication) may cause similar calf pain, but this pain is due to inadequate blood flow to muscles and not to a muscle contraction as with a cramp.

**Treatment**

• Stretching

If a cramp occurs, stretching the affected muscle often relieves the cramp. For example, for a calf cramp, the person could use a hand to pull the foot and toes upward (dorsiflexion) or do the runner's stretch.

**Prevention**

Measures to prevent cramps include the following:
• Not exercising immediately after eating

• Gently stretching the muscles before exercising or going to bed

• Drinking plenty of fluids (particularly beverages that contain potassium) after exercise

• Not consuming stimulants (eg, caffeine, nicotine, ephedrine, pseudoephedrine)

The runner's stretch is most useful. A person stands with one leg forward and bent at the knee and the other leg behind and the knee straight—a lunge position. The hands can be placed on the wall for balance. Both heels remain on the floor. The knee of the front leg is bent further until a stretch is felt along the back of the other leg. The greater the distance between the two feet and the more the front knee is bent, the greater the stretch. The stretch is held for 30 sec and repeated 5 times. The set of stretches is repeated on the other side.

Most of the drugs prescribed to prevent cramps (eg, quinine, magnesium, benzodiazepines) have no demonstrated efficacy and are not recommended. Mexiletine sometimes helps, but whether using it is worth the risk of adverse effects is unclear. These adverse effects include nausea, vomiting, heartburn, dizziness, and tremor. Ca supplements are safe and have few adverse effects but have not proved effective.
Chapter 42. Neck and Back Pain

Introduction

Neck pain and back pain are among the most common reasons for physician visits. This discussion covers neck pain involving the posterior neck (not pain limited to the anterior neck) and does not cover most major traumatic injuries (eg, fractures, dislocations, subluxations).

Pathophysiology

Depending on the cause, neck or back pain may be accompanied by neurologic symptoms.

If a nerve root is affected, pain may radiate distally along the distribution of that root (called radicular pain or, in the low back, sciatica). Strength, sensation, and reflexes of the area innervated by that root may be impaired.

If the spinal cord is affected, strength, sensation, and reflexes may be impaired at the affected spinal cord level and all levels below (called segmental neurologic deficits).

If the cauda equina is affected, segmental deficits develop in the lumbosacral region, typically with loss of bowel and bladder function, loss of perianal sensation, erectile dysfunction, urinary retention, and loss of rectal tone and sphincter (eg, bulbocavernosus, anal wink) reflexes.

Any painful disorder of the spine may also cause reflex tightening (spasm) of paraspinal muscles, which can be excruciating.

Etiology

Most neck and back pain is caused by disorders of the spine. Fibromyalgia is also a common cause. Occasionally, pain is referred from extraspinal disorders (particularly vascular, GI, or GU disorders). Some uncommon causes—spinal and extraspinal—are serious.

Most spinal disorders are mechanical. Only a few involve infection, inflammation, or cancer (considered nonmechanical).

Common causes: Most mechanical spine disorders that cause neck or back pain involve a nonspecific mechanical derangement:

• Muscle strain, ligament sprain, spasm, or a combination

Only about 15% involve specific structural lesions that clearly cause the symptoms, primarily the following:

• Disk herniation
• Compression fracture
• Lumbar spinal stenosis
• Osteoarthritis
• Spondylolisthesis

In the other mechanical disorders, there are no specific lesions, or the findings (eg, disk bulging or degeneration, osteophytes, spondylolysis, congenital facet abnormalities) are common among people without neck or back pain, and thus are questionable as the etiology of pain. However, etiology of back pain, particularly if mechanical, is often multifactorial, with an underlying disorder exacerbated by fatigue, physical deconditioning, and sometimes psychosocial stress or psychiatric abnormality. Thus, identifying
a single cause is often difficult or impossible.

**Serious uncommon causes:** Serious causes may require timely treatment to prevent disability or death.

Serious **extraspinal** disorders include the following:

- Abdominal aortic aneurysm
- Aortic dissection
- Carotid or vertebral artery dissection
- Acute meningitis
- Angina or MI
- Certain GI disorders (eg, cholecystitis, diverticulitis, diverticular abscess, pancreatitis, penetrating peptic ulcer, retrocecal appendicitis)
- Certain pelvic disorders (eg, ectopic pregnancy, ovarian cancer, salpingitis)
- Certain pulmonary disorders (eg, pleuritis, pneumonia)
- Certain urinary tract disorders (eg, prostatitis, pyelonephritis)

Serious **spinal** disorders include the following:

- Infections (eg, diskitis, epidural abscess, osteomyelitis)
- Primary tumors (of spinal cord or vertebrae)
- Metastatic vertebral tumors (most often from breasts, lungs, or prostate)

Mechanical spine disorders can be serious if they compress the spinal nerve roots or, particularly, the spinal cord. Spinal cord compression may result from disorders such as tumors and spinal epidural abscess or hematoma.

**Other uncommon causes:** Neck or back pain can result from many other disorders, such as Paget’s disease of bone, torticollis, thoracic outlet syndrome, temporomandibular joint syndrome, herpes zoster, and spondyloarthropathies (ankylosing spondylitis most often, but also enteropathic arthritis, psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthropathy).

**Evaluation**

**General:** Because the cause is often multifactorial, a definitive diagnosis cannot be established in many patients. However, clinicians should determine the following if possible:

- Whether pain has a spinal or extraspinal cause
- Whether the cause is a serious disorder

**History:** **History of present illness** should include quality, onset, duration, severity, location, radiation, and time course of pain, as well as modifying factors such as rest, activity, changes in position, weight bearing, and time of day (eg, at night, when awakening). Accompanying symptoms to note include stiffness, numbness, paresthesias, weakness, urinary retention, and incontinence.

**Review of systems** should note symptoms suggesting a cause, including fever and chills (infection); weight loss and poor appetite (infection or cancer); fatigue, depressive symptoms, and headaches.
(multifactorial mechanical back pain); worsening of neck pain during swallowing (esophageal disorders); anorexia, nausea, vomiting, and change in bowel function or stool (GI disorders); urinary symptoms and flank pain (urinary tract disorders); cough, dyspnea, and worsening during inspiration (pulmonary disorders); vaginal bleeding or discharge and pain related to menstrual cycle phase (pelvic disorders).

### Past medical history
Includes known neck or back disorders (including osteoporosis, osteoarthritis, disk disorders, recent or remote injury) and surgery, risk factors for back disorders (eg, cancer, osteoporosis), risk factors for aneurysm (eg, smoking, hypertension), and risk factors for infection (eg, immunosuppression; IV drug use; recent surgery, penetrating trauma, or bacterial infection).

### Physical examination
Temperature and general appearance are noted. When possible, patients should be unobtrusively observed as they move into the examination room, undress, and climb onto the table. If symptoms are exacerbated by psychologic issues, true functional level can be assessed more accurately when patients are not aware they are being evaluated.

The examination focuses on the spine and the neurologic examination. If no mechanical spinal source of pain is obvious, patients are checked for sources of referred pain.

In the spinal examination, the back and neck are inspected for any visible deformity, area of erythema, or vesicular rash. The spine and paravertebral muscles are palpated for tenderness and muscle spasm. Gross range of motion is tested.

In the neurologic examination, strength and deep tendon reflexes are tested. In patients with neurologic symptoms, sensation and sacral nerve function (eg, rectal tone, anal wink reflex, bulbocavernosus reflex) are tested. These tests are among the most reliable physical tests for confirming normal spinal cord function. Corticospinal tract dysfunction is indicated by the extensor plantar response and Hoffman's sign. To test for Hoffman's sign, clinicians tap the nail or flick the volar surface of the 3rd finger; if the distal phalanx of the thumb flexes, the test is positive, usually indicating corticospinal tract dysfunction caused by stenosis of the cervical cord. Sensory findings are subjective and may be unreliable.

The straight leg raise test helps confirm sciatica. The patient is supine with both knees extended and the ankles dorsiflexed. The clinician raises the affected leg, keeping the knee extended. If sciatica is present, 10 to 60° of elevation typically causes symptoms. For the crossed straight leg raise test, the unaffected leg is raised; the test is positive if sciatica occurs in the affected leg. A positive straight leg test is sensitive but not specific for herniated disk; the crossed straight leg raise test is less sensitive but 90% specific. The seated straight leg raise test is done while patients are seated with the hip joint flexed at 90°; the lower leg is slowly raised until the knee is fully extended. If sciatica is present, the pain occurs as the leg is extended.

In the general examination, the lungs are auscultated. The abdomen is checked for tenderness, masses, and, particularly in patients > 55, a pulsatile mass (which suggests abdominal aortic aneurysm). With a fist, clinicians percuss the costovertebral angle for tenderness, suggesting pyelonephritis.

Rectal examination, including stool testing for occult blood and, in men, prostate examination, is done. In women with symptoms suggesting a pelvic disorder or with unexplained fever, pelvic examination is done.

Lower-extremity pulses are checked.

### Red flags
The following findings are of particular concern:

- Abdominal aorta that is > 5 cm (particularly if tender) or lower-extremity pulse deficits
- Acute, tearing mid-back pain
- Cancer, diagnosed or suspected
- Duration of pain > 6 wk
• Neurologic deficit

• Fever

• GI findings such as localized abdominal tenderness, peritonitis, melena, or hematochezia

• Infection risk factors (eg, immunosuppression; IV drug use; recent surgery, penetrating trauma, or bacterial infection)

• Meningismus

• Severe nocturnal or disabling pain

• Unexplained pain after age 55

• Unexplained weight loss

**Interpretation of findings:** Although serious extraspinal disorders (eg, cancers, aortic aneurysms, epidural abscesses, osteomyelitis) are uncommon causes of back pain, they are not rare, particularly in high-risk groups.

A spinal cause is more likely (but not definitive) than referred pain from an extraspinal cause when

• Pain is worsened by movement or weight bearing and is relieved by rest or recumbency

• Vertebral or paravertebral tenderness is present

Red flag findings should heighten suspicion of a serious cause (see Table 42-1).

Other findings are also helpful. Erythema and tenderness over the spine suggests infection, particularly in patients with risk factors. Worsening of pain with flexion is consistent with intervertebral disk disease; worsening with extension suggests spinal stenosis, arthritis affecting the facet joints, or retroperitoneal inflammation or infiltration (eg, pancreatic or kidney inflammation or tumor). Tenderness over certain specific trigger points suggests fibromyalgia. Deformities of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) finger joints and stiffness that lessens within 30 min after awakening suggest osteoarthritis. Neck pain that is unrelated to swallowing and is exertional may indicate angina.

**Testing:** Usually, if duration of pain is short (< 4 to 6 wk), no testing is required unless red flag findings are present, patients have had a serious injury (eg, vehicular crash, fall from a height, penetrating trauma), or evaluation suggests a specific nonmechanical cause (eg, pyelonephritis).

Plain x-rays can identify most osteoporotic fractures and osteoarthritis. However, they do not identify abnormalities in soft tissue (the most common cause of back and neck pain) or nerve tissue (as occurs in many serious disorders). Thus, x-rays are usually unnecessary and do not change management. Sometimes

**[Table 42-1. Interpretation of Red Flag Findings in Patients with Back Pain]**

x-rays are done to identify obvious bone abnormalities (eg, those due to infection or tumors) and to avoid MRI and CT, which are harder to obtain but which are much more accurate and usually necessary.

Testing is guided by findings and suspected cause:

• Neurologic deficits, particularly those consistent with spinal cord compression: MRI or CT myelography, done as soon as possible

• Possible infection: WBC count, ESR, imaging (usually MRI or CT), and culture of infected tissue
• Possible cancer: CT or MRI and possibly biopsy
• Possible aneurysm: CT, angiography, or sometimes ultrasonography
• Possible aortic dissection: Angiography, CT, or MRI
• Symptoms that are disabling or that persist > 6 wk: Imaging (usually MRI or CT) and, if infection is suspected, WBC count and ESR
• Other extraspinal disorders: Testing as appropriate (eg, chest x-ray for pulmonary disorders, urinalysis for urinary tract disorders)

Treatment

Underlying disorders are treated.

Acute musculoskeletal pain (with or without radiculopathy) is treated with

• Analgesics
• Heat and cold
• Early mobilization followed by stabilization exercises

Acetaminophen or NSAIDs are the initial choice of analgesics, but opioids may be necessary for severe pain. Adequate analgesia is important immediately after acute injury to help limit the cycle of pain and spasm.

Acute muscle spasms may also be relieved by cold or heat. Cold is usually preferred to heat during the first 2 days after an injury. Ice and cold packs should not be applied directly to the skin. They should be enclosed (eg, in plastic) and placed over a towel or cloth. The ice is removed after 20 min, then later reapplied for 20 min over a period of 60 to 90 min. This process can be repeated several times during the first 24 h. Heat, using a heating pad, can be applied for the same periods of time. Because the skin on the back may be insensitive to heat, heating pads must be used cautiously to prevent burns. Patients are advised not to use a heating pad at bedtime to avoid prolonged exposure due to falling asleep with the pad still on their back. Diathermy may help reduce muscle spasm and pain after the acute stage.

Oral muscle relaxants (eg, cyclobenzaprine, methocarbamol, metaxalone) are controversial. Benefits of these drugs should be weighed against their CNS and other adverse effects, particularly in elderly patients, who may have more severe adverse effects.

Although a brief initial period (eg, 1 to 2 days) of decreased activity is sometimes needed for comfort, prolonged bed rest, spinal traction, and corsets are not beneficial. Patients with severe torticollis may benefit from a cervical collar and contour pillow until pain is relieved and they can participate in a stabilization program.

Spinal manipulation may help relieve pain caused by muscle spasm or an acute neck or back injury; however, some forms of manipulation may have risks for patients with disk disorders or osteoporosis.

When acute pain decreases enough that motion is possible, a lumbar stabilization program is begun. This program includes exercises that strengthen abdominal and low back muscles plus instruction in work posture; the aim is to strengthen the supporting structures of the back and reduce the likelihood of the condition becoming chronic or recurrent.

Clinicians should reassure patients with acute nonspecific musculoskeletal back pain that the prognosis is good and that activity and exercise are safe even when they cause some discomfort. Clinicians should be thorough, kind, firm, and nonjudgmental. If depression or secondary gain persists for several months,
psychologic evaluation should be considered.

**Geriatrics Essentials**

Low back pain affects 50% of adults > 60.

Abdominal aortic aneurysm (and CT or ultrasonography to detect it) should be considered in elderly patients with atraumatic low back pain, even if no physical findings suggest this diagnosis.

Imaging of the spine may be appropriate for elderly patients (eg, to rule out cancer) even when the cause appears to be uncomplicated musculoskeletal back pain.

Oral muscle relaxants (eg, cyclobenzaprine, methocarbamol, metaxalone) are controversial; anticholinergic, CNS, and other adverse effects may outweigh potential benefits in elderly patients.

**Key Points**

- Most neck and back pain is caused by mechanical spinal disorders, usually nonspecific, self-limited musculoskeletal derangements.
- Most mechanical disorders are treated with analgesics, early mobilization, and exercises; prolonged bed rest and immobilization are avoided.
- Back pain is often multifactorial, making diagnosis difficult.
- Serious spinal or extraspinal disorders are unusual causes.
- Red flag findings often indicate a serious disorder and the need for testing.
- Patients with segmental neurologic deficits suggesting spinal cord compression require MRI or CT myelography as soon as possible.
- Normal spinal cord function during physical examination is best confirmed by tests of sacral nerve function (eg, rectal tone, anal wink reflex, bulbocavernosus reflex).
- Pain not worsened by movement is often extraspinal, particularly if no vertebral or paravertebral tenderness is detected.
- Abdominal aortic aneurysm should be considered in any elderly patient with low back pain, even if no physical findings suggest this diagnosis.

**Spasmodic Torticollis**

Spasmodic torticollis is characterized by involuntary tonic contractions or intermittent spasms of neck muscles. The cause is unknown. Diagnosis is clinical. Treatment can include physical therapy, drugs, and selective denervation of neck muscles with surgery or locally injected botulinum toxin.

In torticollis, contraction of the neck muscles causes the neck to turn from its usual position. It is the most common dystonia (see p. 1760).

Spasmodic (or adult-onset) torticollis is usually idiopathic. About 5% of patients with spasmodic torticollis have a family history. One third of these patients have other dystonias (eg, eyelids, face, jaw, hand). Torticollis can also be congenital or secondary to other conditions such as lesions of the brain stem and basal ganglia.

**Symptoms and Signs**
Symptoms may begin at any age but usually begin between age 20 and 60, with a peak between age 30 and 50.

Symptoms usually begin gradually but may begin suddenly. Painful tonic contractions or intermittent spasms of the sternocleidomastoid, trapezius, and other neck muscles occur, usually unilaterally, and result in abnormal head position. Sternocleidomastoid muscle contraction causes the head to rotate to the opposite side and the neck to flex laterally to the same side. Rotation may involve any plane but almost always has a horizontal component. Besides rotational tilting (torticollis), the head can tilt laterally (laterocollis), forward (anterocollis), or backward (retrocollis). During sleep, muscle spasms disappear.

Spasmodic torticollis ranges from mild to severe. Usually, it progresses slowly for 1 to 5 yr, then plateaus. About 10 to 20% of patients recover spontaneously within 5 yr of onset (usually in milder cases with younger age onset). However, it may persist for life and can result in restricted movement and postural deformity.

**Diagnosis**

- Clinical evaluation

The diagnosis is based on characteristic symptoms and signs and exclusion of alternative diagnoses, such as the following:

- Tardive dyskinesia can cause torticollis but can usually be distinguished by a history of chronic antipsychotic use and involuntary movements in muscles outside of the neck.

- Basal ganglia disease and occasionally CNS infections can cause movement disorders but usually also involve other muscles. Also, CNS infections are usually acute and cause other symptoms.

- Neck infections or tumors are usually differentiated by features of the primary process.

- Antipsychotics and other drugs can cause acute torticollis, but the symptoms usually develop in hours and resolve within days.

**Treatment**

- Physical measures

- Sometimes botulinum toxin or oral drugs

Spasms can sometimes be temporarily inhibited by physical therapy and massage, including sensory biofeedback techniques (slight tactile pressure to the jaw on the same side as head rotation) and any light touch.

Injections of botulinum toxin type A into the dystonic muscles can reduce painful spasms for 1 to 3 mo in about 70% of patients, restoring a more neutral position of the head. However, this treatment can lose effectiveness with repeated injections because antibodies develop against the toxin. Drugs can usually relieve pain, but they suppress dystonic movements in only about 25 to 33% of patients. Anticholinergics such as trihexyphenidyl 10 to 25 mg po once/day or bid may help, but adverse effects may limit their use; benzodiazepines (particularly clonazepam 0.5 mg po bid) and baclofen and carbamazepine may help. All drugs should be started in low doses. Doses should be increased until symptoms are controlled or intolerable adverse effects (particularly likely in the elderly) develop.

Surgery is controversial. The most successful surgical approach selectively severs nerves to affected neck muscles, permanently weakening or paralyzing them. Results are favorable when the procedure is done at centers with extensive experience.

Rarely, an emotional problem contributes to spasmodic torticollis; psychiatric treatment is indicated.
Psychiatric prognosis is best if symptom onset coincided with exogenous stress.

**Sciatica**

Sciatica is pain along the sciatic nerve. It usually results from compression of nerve roots in the lower back. Common causes include intervertebral disk herniation, osteophytes, and narrowing of the spinal canal (spinal stenosis). Symptoms include pain radiating from the buttocks down the leg. Diagnosis sometimes involves MRI or CT. Electromyography and nerve conduction studies can identify the affected level. Treatment includes symptomatic measures and sometimes surgery, particularly if there is a neurologic deficit.

**Etiology**

Sciatica is typically caused by nerve root compression, usually due to intervertebral disk herniation (see p. 1810), bony irregularities (eg, osteoarthritic osteophytes, spondylolisthesis), or, much less often, intraspinal tumor or abscess. Compression may occur within the spinal canal or intervertebral foramen. The nerves can also be compressed outside the vertebral column, in the pelvis or buttocks. L5-S1, L4-L5, and L3-L4 nerve roots are most often affected (see Table 186-1 on p. 1805).

**Symptoms and Signs**

Pain radiates along the course of the sciatic nerve, most often down the buttocks and posterior aspect of the leg to below the knee. The pain is typically burning, lancinating, or stabbing. It may occur with or without low back pain. The Valsalva maneuver or coughing may worsen pain due to disk herniation. Patients may complain of numbness and sometimes weakness in the affected leg.

Nerve root compression can cause sensory, motor, or, the most objective finding, reflex deficits (see p. 1810). L5-S1 disk herniation may affect the ankle jerk reflex; L3-L4 herniation may affect the knee jerk. Straight leg raising may cause pain that radiates down the leg when the leg is raised above 60° and sometimes less. This finding is sensitive for sciatica; pain radiating down the affected leg when the contralateral leg is lifted (crossed straight leg raising) is more specific for sciatica.

**Diagnosis**

- Clinical evaluation
- Sometimes MRI, electrodiagnostic studies, or both

Sciatica is suspected based on the characteristic pain. If it is suspected, strength, reflexes, and sensation should be tested. If there are neurologic deficits or if symptoms persist for > 6 wk, imaging and electrodiagnostic studies should be done. Structural abnormalities causing sciatica (including spinal stenosis) are most accurately diagnosed by MRI or CT. Electrodiagnostic studies can confirm the presence and degree of nerve root compression and can exclude conditions that may mimic sciatica, such as polyneuropathy. These studies may help determine whether the lesion involves single or multiple nerve levels and whether the clinical findings correlate with MRI abnormalities (especially valuable before surgery). However, abnormalities may not be evident on electrodiagnostic studies for up to a few weeks after symptoms begin.

**Treatment**

- Bed rest (brief), analgesics, and sometimes drugs that relieve neuropathic pain
- Surgery for severe cases

Acute pain relief can come from 24 to 48 h of bed rest in a recumbent position with the head of the bed elevated about 30° (semi-Fowler's position). Measures used to treat low back pain, including nonopioid analgesics (eg, NSAIDs, acetaminophen), can be tried for up to 6 wk. Drugs that decrease neuropathic
pain (see p. 1633), such as gabapentin or other anticonvulsants or low-dose tricyclic antidepressants (no tricyclic is superior to another), may relieve symptoms. Gabapentin 100 to 300 mg po at bedtime is used initially, but doses typically have to be much higher, up to 3600 mg/day. As with all sedating drugs, care should be taken in the elderly, patients at risk of falls, and those with arrhythmias. Muscle spasm may be relieved with therapeutic heat or cold (see p. 3459), and physical therapy may be useful. Whether corticosteroids should be used to treat acute radicular pain is controversial. Given epidurally, corticosteroids may accelerate pain relief, but they probably should not be used unless pain is severe or persistent.

Surgery is indicated only for unequivocal disk herniation plus one of the following:

- Muscular weakness
- Progressive neurologic deficit
- Intolerable, intractable pain that interferes with job or personal functions in an emotionally stable patient and that has not lessened after 6 wk of conservative treatment

Some of these patients benefit from epidural corticosteroids instead of surgery.

Classic diskectomy with limited laminotomy for intervertebral disk herniation is the standard procedure. If herniation is localized, microdiskectomy may be done; with it, the skin incision and laminotomy can be smaller. Chemonucleolysis, using intradiskal injection of chymopapain, is no longer used.

Predictors of poor surgical outcome include

- Prominent psychiatric factors
- Persistence of symptoms for > 6 mo
- Heavy manual labor
- Prominence of back pain (nonradicular)
- Secondary gain (ie, litigation and compensability)

**Lumbar Spinal Stenosis**

Lumbar spinal stenosis (LSS) is narrowing of the lumbar spinal canal, which puts pressure on the sciatic nerve roots (or sometimes the cord) before their exit from the foramina. It causes positional back pain, symptoms of nerve root compression, and lower-extremity pain during walking or weight bearing.

Spinal stenosis can be congenital or acquired. It may involve the cervical or lumbar spine. Acquired LSS is a common cause of sciatica in middle-aged or elderly patients. The most common causes of LSS are osteoarthritis, degenerative disk disorders, and spondylolisthesis with compression of the cauda equina. Other causes include Paget's disease of bone, RA, and ankylosing spondylitis.

**Symptoms and Signs**

Pain occurs in the buttocks, thighs, or calves during walking, running, climbing stairs, or even standing. The pain is not relieved by standing still but by flexing the back or by sitting (although paresthesias may continue). Walking up hills is less painful than walking down because the back is slightly flexed. Patients may have pain, paresthesias, weakness, and diminished reflexes in the affected nerve root distribution. Rarely, spinal cord compression may cause cauda equina syndrome (see p. 1806).
Diagnosis

• Clinical evaluation

• Sometimes MRI, electrodiagnostic studies, or both

Spinal stenosis is suspected based on characteristic symptoms. Diagnostic tests are the same as for sciatica (see p. 383). Calf symptoms may simulate those of intermittent claudication. Claudication can be differentiated by relief with rest (not position change), skin atrophy, and abnormalities in pulses, capillary refill, and vascular tests.

Treatment

• Bed rest (brief), analgesics, and sometimes drugs that relieve neuropathic pain

• Surgery for severe cases

Conservative treatments and indications for surgery are similar to those for sciatica. For advanced spinal stenosis, surgery involves decompression of nerve root entrapment by vertebral canal and foraminal encroachments, which sometimes requires laminectomy at 2 or 3 levels plus foraminotomies.

Spinal stability must be preserved. Spinal fusion is indicated if there is instability or severe, well-localized arthritic changes in 1 or 2 vertebral interspaces.

Nontraumatic Subluxation

Spinal dislocation and subluxation (partial dislocation) are usually due to trauma. For example, atlantoaxial subluxation and spondylolisthesis can result from obvious major trauma, such as a high-speed deceleration injury. However, these disorders can occur with minimal, unrecognized, or no trauma. Rarely, cervical disk disorders can cause nontraumatic spinal subluxation.

Atlantoaxial Subluxation

(C1-C2 Subluxation)

Atlantoaxial subluxation is misalignment of the 1st and 2nd cervical vertebrae, which may occur only with neck flexion.

Atlantoaxial subluxation can result from major trauma or can occur without trauma in patients with RA, juvenile RA, or ankylosing spondylitis.

Atlantoaxial subluxation is usually asymptomatic but may cause vague neck pain, occipital headache, or occasionally intermittent (and potentially fatal) cervical spinal cord compression.

Diagnosis

• Plain x-rays

• MRI if cord compression suspected

It is usually diagnosed with plain cervical x-rays; however, flexion views may be required to show intermittent subluxation. Views during flexion, done by the patient, show dynamic instability of the entire cervical spine. If x-rays are normal and subluxation is still suspected, MRI, which is more sensitive, should be done. MRI also provides the most sensitive evaluation of spinal cord compression and is done immediately if cord compression is suspected.

Treatment
Indications for treatment include pain, neurologic deficits, and potential spinal instability. Treatment includes symptomatic measures and cervical immobilization, usually beginning with a rigid cervical collar. Surgery may be needed to stabilize the spine.

**Spondylolisthesis**

Spondylolisthesis is subluxation of lumbar vertebrae, usually occurring during adolescence. It usually results from a congenital defect in the pars interarticularis (spondylolysis).

Spondylolisthesis is usually fixed. It usually involves the L3-L4, L4-L5, or L5-S1 vertebrae. Spondylolisthesis often occurs in adolescents or young adults who are athletes and who have had only minimal trauma; the cause is a lumbar vertebra weakened by a congenital defect in the pars interarticularis. This defect is easily fractured; separation of the fracture fragments causes the subluxation. Spondylolisthesis can also occur with minimal trauma in patients who are > 60 and have osteoarthritis. If mild to moderate (subluxation of ≤ 50%), spondylolisthesis, particularly in the young, may cause little or no pain. Spondylolisthesis can predispose to later development of spinal stenosis. If due to major trauma, spondylolisthesis can cause spinal cord compression or other neurologic deficits (see p. 1810); these deficits rarely occur.

Spondylolisthesis is staged according to the degree of subluxation of adjacent vertebral bodies:

- **Stage I:** 0 to 25%
- **Stage II:** 25 to 50%
- **Stage III:** 50 to 75%
- **Stage IV:** 75 to 100%

Spondylolisthesis is evident on plain lumbar x-rays. The lateral view is usually used for staging.

Treatment is usually symptomatic.
### Chapter 43. Hand Disorders

#### Introduction

Common hand disorders include a variety of deformities, ganglia, infections, Kienbock's disease, nerve compression syndromes, noninfectious tenosynovitis, and osteoarthritis. Complex regional pain syndrome (reflex sympathetic dystrophy) is discussed on p. 1633, and hand injuries are discussed in Ch. 323.

#### Evaluation

History and physical examination findings are often diagnostic in hand disorders.

**History:** The history should include information about the trauma or other events that may be associated with symptoms. The presence and duration of deformity and difficulty with motion are noted. The presence, duration, severity, and factors that exacerbate or relieve pain are elicited. Associated symptoms, such as fever, swelling, rashes, Raynaud's syndrome (see p. 2221), paresthesias, and weakness, are also recorded.

**Physical examination:** Examination should include inspection for redness, swelling, or deformity and palpation for tenderness. Active range of motion should be tested for any possible tendon injury. Passive range of motion can assess whether specific motions aggravate pain. Sensation is tested most accurately by 2-point discrimination, using 2 ends of a paper clip. Motor function testing involves muscles innervated by the radial, median, and ulnar nerves. Vascular examination should include evaluation of capillary refill, radial and ulnar pulses, and Allen's test (see p. 1856). Stress testing is helpful when specific ligament injuries are suspected (eg, ulnar collateral ligament in gamekeeper's thumb—see p. 3216). Provocative testing can aid in the diagnosis of tenosynovitis and nerve compression syndromes.

**Laboratory testing:** Laboratory testing has a limited role. Plain x-rays and MRI are helpful for injuries, arthritis, and Kienbock's disease or to rule out hidden foreign bodies that could be sources of infections. Nerve conduction testing can help diagnose nerve compression syndromes. Bone scans may assist in diagnosing occult fractures and reflex sympathetic dystrophy.

#### Deformities

Deformities can result from generalized disorders (eg, arthritis) or dislocations, fractures, and other localized disorders. Most nontraumatic localized disorders can be diagnosed by physical examination. Once a hand deformity becomes firmly established, it cannot be significantly altered by splinting, exercise, or other nonsurgical treatment.

#### Mallet Finger

**Mallet finger is a flexion deformity of the distal interphalangeal joint preventing extension (see Fig. 43-1).**

This deformity results from an extensor tendon rupture or an avulsion fracture of the distal phalanx. The deformity may not be obvious immediately after injury, but on examination, patients cannot fully extend the distal interphalangeal (DIP) joint. Closed injuries may be treated with splinting that holds the DIP joint in extension and leaves the proximal interphalangeal (PIP) joint free. Avulsion fractures are usually united after 6 wk, but pure tendon injuries require an additional 2 to 4 wk of nighttime splinting. Surgery may be required if there is a fracture that involves a large proportion of the articular surface or if the joint is subluxated.

#### Swan-Neck Deformity

**A swan-neck deformity consists of hyperextension of the PIP joint, flexion of the DIP joint, and sometimes flexion of the metacarpophalangeal joint (see Fig. 43-2).**
Although characteristic in RA, swan-neck deformity has several causes, including untreated mallet finger, laxity of the ligaments of the volar aspect of the PIP joint, spasticity of intrinsic hand muscles, rupture of the flexor tendon of the PIP joint, and malunion of a fracture of the middle or proximal phalanx. The inability to correct or compensate for hyperextension of the PIP joint makes finger closure impossible and can cause severe disability. Treatment is aimed at correcting the underlying disorder when possible (eg, correcting the mallet finger or any bony malalignment, releasing spastic intrinsic muscles). Mild deformities in patients with RA may be treated with a functional ring splint.

True swan-neck deformity does not affect the thumb, which has only one interphalangeal joint. However, severe hyperextension of the interphalangeal joint of the thumb with flexion of the metacarpophalangeal (MCP) joint can occur; this is called a duck bill, Z (zigzag) type, or 90°-angle deformity. With simultaneous thumb instability, pinch is greatly impaired. This deformity can usually be corrected by interphalangeal arthrodesis along with tendon reconstruction at the MCP joint.

**Boutonniere Deformity**

(Buttonhole Deformity)

A boutonniere deformity consists of flexion of the PIP joint accompanied by hyperextension of the DIP joint (see Fig. 43-2).

This deformity can result from tendon laceration, dislocation, fracture, osteoarthritis, or RA. Classically, the deformity is caused by disruption of the central slip attachment of the extensor tendon to the base of the middle phalanx, allowing the proximal phalanx to protrude ("buttonhole") between the lateral bands of the extensor tendon. Initial treatment consists of splinting, but it must occur before scarring and fixed deformities develop. Surgical reconstruction often cannot restore normal motion but may decrease the deformity and improve hand function.

**Dupuytren's Contracture**

(Palmar Fibromatosis)

Dupuytren's contracture is progressive contracture of the palmar fascial bands, causing flexion deformities of the fingers.

Dupuytren's contracture is one of the more common hand deformities; the incidence is higher among men and increases after age 45. This autosomal dominant condition with variable penetrance may occur more commonly among patients with diabetes, alcoholism, or epilepsy. However, the specific factor that causes the palmar fascia to thicken and contract is unknown.

**Symptoms and Signs**

The earliest manifestation is usually a tender nodule in the palm, most often near the middle or ring finger; it gradually becomes painless. Next, a superficial cord forms and contracts the MCP joints and interphalangeal joints of the fingers. The hand eventually becomes arched. The disease is occasionally associated with fibrous thickening of the dorsum of the PIP joints (Garrod's pads), Peyronie's disease (penile fibromatosis) in about 7 to 10% of patients, and rarely nodules on the plantar surface of the feet (plantar fibromatosis). Other types of flexion deformities of the fingers can also occur in diabetes, systemic sclerosis, and chronic reflex sympathetic dystrophy, which need to be differentiated.

**Treatment**

- Corticosteroid injection (before contractures develop)
• Surgery for disabling contractures

Injection of a corticosteroid suspension into the nodule can relieve local tenderness if begun before contractures develop. If the hand cannot be placed flat on a table or, especially, when significant contracture develops at the PIP joints, surgery is usually indicated. Excision of the diseased fascia must be meticulous because it surrounds neurovascular bundles and tendons. Incomplete excision or new disease results in recurrent contracture, especially in patients who are young at disease onset or who have a family history, Garrod's pads, Peyronie's disease, or plantar foot involvement. Injectable collagenase may reverse some contractures, although this treatment is not yet in widespread clinical use.

Ganglia

(Ganglion Cysts)

Ganglia are cystic swellings occurring usually on the hands, especially on the dorsal aspect of the wrists. Aspiration or excision is indicated for symptomatic ganglia.

Ganglia constitute about 60% of chronic soft-tissue swellings affecting the hand and wrist. They usually develop spontaneously in adults aged 20 to 50, with a female:male preponderance of 3:1.

Etiology

The cause of most ganglia is unknown. The cystic structures are near or attached (often by a pedicle) to tendon sheaths and joint capsules. The wall of the ganglion is smooth, fibrous, and of variable thickness. The cyst is filled with clear gelatinous, sticky, or mucoid fluid of high viscosity. The fluid in the cyst is sometimes almost pure hyaluronic acid.

Most ganglia are isolated abnormalities. The dorsal wrist ganglion arises from the scapholunate joint and constitutes about 65% of ganglia of the wrist and hand. The volar wrist ganglion arises over the distal aspect of the radius and constitutes about 20 to 25% of ganglia. Flexor tendon sheath ganglia and mucous cysts (arising from dorsal distal interphalangeal joint) make up the remaining 10 to 15%. Ganglia may spontaneously regress.

Diagnosis

• Examination

Ganglia are evident on examination. Another type of ganglion on the dorsal wrist occurs in patients with RA; it is easily differentiated by its soft irregular appearance and association with proliferative rheumatoid extensor tenosynovitis.

Treatment

• Aspiration or excision if troublesome

Most ganglia do not require treatment. However, if the patient is disturbed by its appearance or if the ganglion is painful or tender, a single aspiration with a large-bore needle is effective in about 50% of patients. Attempting to rupture the ganglion by hitting it with a hard object risks local injury without likely benefit. Nonsurgical treatment fails in about 40 to 70% of patients, necessitating surgical excision. Recurrence rates after surgical removal are about 5 to 15%.

Infections

Common bacterial hand infections include paronychia (see p. 735), infected bite wounds, felon, palm abscess, and infectious flexor tenosynovitis. Herpetic whitlow is a viral hand infection. Infections often begin with constant, intense, throbbing pain and are usually diagnosed by physical examination. X-rays are taken in some infections (eg, bite wounds, infectious flexor tenosynovitis) to detect occult foreign
bodies but may not detect small or radiolucent objects.

**Treatment**

- Surgical measures and antibiotics

The increased incidence of community-acquired and nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) should be taken into consideration. Uncomplicated MRSA infections are best treated with incision and drainage. If there is a high incidence of MRSA and the infection is severe, hospitalization and vancomycin or daptomycin (for IV therapy) are recommended, as is consultation with an infectious disease specialist. For outpatients, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid (for oral therapy) can be given. Once culture and sensitivity results rule out MRSA, nafcillin, cloxacillin, dicloxacillin, or a 1st- or 2nd-generation cephalosporin can be given.

**Infected Bite Wounds**

A small puncture wound, particularly from a human or cat bite, may involve significant injury to the tendon, joint capsule, or articular cartilage. The most common cause of human bites is a tooth-induced injury to the metacarpophalangeal joint as a result of a punch to the mouth (clenched fist injury). The oral flora of humans includes *Eikenella corrodens*, staphylococci, streptococci, and anaerobes. Patients with clenched fist injuries tend to wait hours or days after the wound occurs before seeking medical attention, which increases the severity of the infection. Animal bites usually contain multiple potential pathogens, including *Pasteurella multocida* (particularly in cat bites), staphylococci, streptococci, and anaerobes. Serious complications include infectious arthritis and osteomyelitis.

**Diagnosis**

- Clinical evaluation
- X-rays

Erythema and pain localized to the bite suggest infection. Tenderness along the course of a tendon suggests spread to the tendon sheath. Pain worsening significantly with motion suggests infection of a joint or tendon sheath.

The diagnosis is clinical, but if the skin is broken, x-rays should be taken to detect fracture or teeth or other foreign bodies that could be a nidus of continuing infection.

**Treatment**

- Debridement
- Antibiotics

Treatment includes surgical debridement, with the wound left open, and antibiotics. For outpatient treatment, empiric antibiotics usually include monotherapy with amoxicillin/clavulanate 500 mg po tid or combined therapy with a penicillin 500 mg po qid (for *E. corrodens*, *P. multocida*, streptococci, and anaerobes) plus a cephalosporin (eg, cepalexin 500 mg po qid) or semisynthetic penicillin (eg, dicloxacillin 500 mg po qid) for staphylococci. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin. If the patient is allergic to penicillin, clindamycin 300 mg po q 6 h can be used. The hand should be splinted in the functional position and elevated (see Fig. 43-3).
Noninfected bites may require surgical debridement and prophylaxis with 50% of the dose of antibiotic used to treat infected wounds.

**Felon**

A felon is an infection of the pulp space of the fingertip, usually with staphylococci and streptococci.

The most common site is the distal pulp, which may be involved centrally, laterally, or apically. The septa between pulp spaces ordinarily limit the spread of infection, resulting in an abscess, which creates pressure and necrosis of adjacent tissues. The underlying bone, joint, or flexor tendons may become infected. There is intense throbbing pain and a swollen, warm, extremely tender pulp. Treatment involves prompt incision and drainage (using a mid-lateral incision that adequately divides the fibrous septa) and oral antibiotic therapy. Empiric treatment with a cephalosporin is adequate. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

**Palm Abscess**

A palm abscess is a purulent infection of deep spaces in the palm, typically with staphylococci or streptococci.

Palm abscesses can include collar-button abscesses, thenar space abscesses, and midpalmar space abscesses. An abscess can occur in any of the deep palmar compartments and spread between the metacarpals, from the midpalmar space to the dorsum, manifesting as an infection on the dorsum of the hand. Intense throbbing pain occurs with swelling and severe tenderness on palpation. X-rays should be taken to detect occult foreign bodies. Incision and drainage in the operating room (with cultures), with care to avoid the many important anatomic structures, and antibiotics (eg, a cephalosporin) are required. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

**Infectious Flexor Tenosynovitis**

Infectious flexor tenosynovitis is an acute infection within the flexor tendon sheath.

The usual cause is a penetration and bacterial inoculation of the sheath.

**Diagnosis**

- Kanavel's signs
- X-rays

Infectious flexor tenosynovitis causes Kanavel's signs:

- Flexed resting position of the digit
- Fusiform swelling
- Tenderness along the flexor tendon sheath
- Pain with passive extension of the digit

X-rays should be taken to detect occult foreign bodies. Acute calcific tendinitis and RA can restrict motion and cause pain in the tendon sheath but can usually be differentiated from infectious flexor tenosynovitis by a more gradual onset and the absence of some of Kanavel's signs. Disseminated gonococcal infection can cause tenosynovitis but often involves multiple joints (particularly those of the wrists, fingers, ankles,
and toes), and patients often have recent fever, rash, polyarthralgias, and often risk factors for an STD. Infection of the tendon sheath may involve atypical mycobacteria, but these infections are usually indolent and chronic.

**Treatment**

- Surgical drainage and antibiotics

Treatment is surgical drainage (eg, irrigation of the tendon sheath by inserting a cannula into one end and allowing the irrigating fluid to pass along the tendon sheath to the other end). Antibiotic therapy (beginning empirically with a cephalosporin) and cultures are also required. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

**Herpetic Whitlow**

**Herpetic whitlow is a cutaneous infection of the distal aspect of the finger caused by herpes simplex virus.**

Herpetic whitlow may cause intense pain. The digital pulp is not very tense. Vesicles develop on the volar or dorsal distal phalanx but often not until 2 to 3 days after pain begins. The intense pain can simulate a felon, but herpetic whitlow can usually be differentiated by the absence of tenseness in the pulp or the presence of vesicles. The condition is self-limited but may recur. Incision and drainage are contraindicated. Topical acyclovir 5% can shorten the duration of a first episode. Oral acyclovir (800 mg po bid) may prevent recurrences if given immediately after onset of recurrent symptoms. Open or draining vesicles should be covered to prevent transmission.

**Kienbock's Disease**

**Kienbock's disease is avascular necrosis of the lunate bone.**

Kienbock's disease occurs most commonly in the dominant hand of men aged 20 to 45, usually in workers doing heavy manual labor. Overall, Kienbock's disease is relatively rare. Its cause is unknown. The lunate can eventually collapse and cause fixed rotation of the scaphoid and subsequent degeneration of the carpal joints.

**Symptoms and Signs**

Symptoms generally start with insidious onset of wrist pain, localized to the region of the lunate carpal bone; patients have no recollection of trauma. Kienbock's disease is bilateral in 10% of cases. There is localized tenderness in the lunate bone.

**Diagnosis**

- Imaging

MRI and CT are the most sensitive; plain x-rays show abnormalities later, usually beginning with a sclerotic lunate, then later cystic changes, fragmentation, and collapse.

**Treatment**

- Surgical procedures

Treatment is aimed at relieving pressure on the lunate by surgically shortening the radius or lengthening the ulna. Alternative treatments attempt to revascularize the lunate (eg, implanting a blood vessel or bone graft on a vascular pedicle). Salvage procedures (eg, proximal row carpectomy or intercarpal fusions) may help preserve some wrist function if the carpal joints have degenerated. Total wrist arthrodesis can be done as a last resort to relieve pain. Nonsurgical treatments are not effective.
Nerve Compression Syndromes

Common nerve compression syndromes include carpal tunnel syndrome, cubital tunnel syndrome, and radial tunnel syndrome. Compression of nerves often causes paresthesias; these paresthesias can often be reproduced by tapping the compressed nerve, usually with the examiner's fingertip (Tinel's sign). Suspected nerve compression can be confirmed by testing nerve conduction velocity and distal latencies, which accurately measure motor and sensory nerve conduction. Initial treatment is usually conservative, but surgical decompression may be necessary if conservative measures fail or if there are significant motor or sensory deficits.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is compression of the median nerve as it passes through the carpal tunnel in the wrist. Symptoms include pain and paresthesias in the median nerve distribution. Diagnosis is suggested by symptoms and signs and is confirmed by nerve conduction velocity testing. Treatments include ergonomic improvements, analgesia, splinting, and sometimes corticosteroid injection or surgery.

Carpal tunnel syndrome is very common and most often occurs in women aged 30 to 50. Risk factors include RA or other wrist arthritis (sometimes the presenting manifestation), diabetes mellitus, hypothyroidism, acromegaly, amyloidosis, hemodialysis, and pregnancy-induced edema in the carpal tunnel. Activities or jobs that require repetitive flexion and extension of the wrist may contribute, but rarely. Most cases are idiopathic.

Symptoms and Signs

Symptoms include pain of the hand and wrist associated with tingling and numbness, classically distributed along the median nerve (the palmar side of the thumb, the index and middle fingers, and the radial half of the ring finger) but possibly involving the entire hand. Typically, the patient wakes at night with burning or aching pain and with numbness and tingling and shakes the hand to obtain relief and restore sensation. Thenar atrophy and weakness of thumb opposition and abduction may develop late.

Diagnosis

• Clinical evaluation

• Nerve conduction testing

The diagnosis is strongly suggested by Tinel's sign, in which median nerve paresthesias are reproduced by tapping at the volar surface of the wrist over the site of the median nerve in the carpal tunnel. Reproduction of tingling with wrist flexion (Phalen's sign) is also suggestive. However, clinical differentiation from other types of peripheral neuropathy may sometimes be difficult. If symptoms are severe or the diagnosis is uncertain, nerve conduction testing should be done on the affected arm for diagnosis and to exclude a more proximal neuropathy.

Treatment

• Splinting

• Sometimes corticosteroid/anesthetic injection

• Sometimes surgical decompression

Changing the position of computer keyboards and making other ergonomic corrections may occasionally provide relief. Otherwise, treatment includes wearing a lightweight neutral wrist splint (see Fig. 43-4), especially at night, and taking mild analgesics (eg, acetaminophen, NSAIDs). If these measures do not control symptoms, a mixture of a corticosteroid and an anesthetic (eg, 1.5 mL of a 4-
mg/mL dexamethasone solution mixed with 1.5 mL of 1% lidocaine) should be injected into the carpal tunnel at a site just ulnar to the palmaris longus tendon and proximal to the distal crease at the wrist. If bothersome symptoms persist or recur or if hand weakness and thenar wasting develop, the carpal tunnel can be surgically decompressed by using an open or endoscopic technique.

[Fig. 43-4. Neutral wrist splint.]

### Cubital Tunnel Syndrome

(Ulnar Neuropathy)

**Cubital tunnel syndrome is compression or traction of the ulnar nerve at the elbow.**

The ulnar nerve is commonly irritated at the elbow or, rarely, the wrist. Cubital tunnel syndrome is most often caused by leaning on the elbow or by prolonged and excessive elbow flexion. It is less common than carpal tunnel syndrome. Baseball pitching (particularly sliders), which can injure the medial elbow ligaments, confers risk.

### Symptoms and Signs

Symptoms include numbness and paresthesia along the ulnar nerve distribution (in the ring and little fingers and the ulnar aspect of the hand) and elbow pain. In advanced stages, weakness of the intrinsic muscles of the hand and the flexors of the ring and little fingers may develop. Weakness interferes with pinch between the thumb and index finger and with hand grip.

### Diagnosis

- Clinical evaluation
- Sometimes nerve conduction studies

Diagnosis is often possible clinically. However, if clinical diagnosis is equivocal and when surgery is being considered, nerve conduction studies are done. Cubital tunnel syndrome is differentiated from ulnar nerve entrapment at the wrist (in Guyon's canal) by the presence of sensory deficits (on sensory testing or with Tinel's sign) over the ulnar dorsal hand and by the presence of ulnar nerve deficits proximal to the wrist on muscle testing or nerve conduction velocity testing.

### Treatment

Treatment involves splinting at night, with the elbow extended at 45°, and use of an elbow pad during the day. Surgical decompression can help if conservative treatment fails.

### Radial Tunnel Syndrome

(Posterior Interosseous Nerve Syndrome)

**Radial tunnel syndrome is compression of the radial nerve in the proximal forearm.**

Compression at the elbow can result from trauma, ganglia, lipomas, bone tumors, or radiocapitellar (elbow) synovitis.

### Symptoms and Signs

Symptoms include lancinating pain in the dorsum of the forearm and lateral elbow. Pain is precipitated by attempted extension of the wrist and fingers and forearm supination. Sensory loss is rare because the radial nerve is principally a motor nerve at this level. This disorder is sometimes confused with backhand tennis elbow (lateral epicondylitis). When weakness of the extensor muscles is the primary finding, the condition is referred to as posterior interosseous nerve palsy.
Diagnosis

- Clinical evaluation

Lateral epicondylitis can cause similar tenderness around the lateral epicondyle but does not cause Tinel's sign or tenderness along the course of the radial nerve.

Treatment

- Splinting

Splinting allows avoidance of the forceful or repeated motion of supination or wrist dorsiflexion, reducing pressure on the nerve. If wristdrop or weakened digital extension develops, or conservative treatment fails to provide relief after 3 mo, surgical decompression may be needed.

Noninfectious Tenosynovitis

(See also p. 374.)

Although the digital flexor tendons and extensor pollicis brevis are commonly affected, tenosynovitis may involve any of the tendons in or around the hand.

Digital Flexor Tendinitis and Tenosynovitis

(Trigger Finger)

Digital flexor tendinitis and tenosynovitis are inflammation, sometimes with subsequent fibrosis, of tendons and tendon sheaths of the digits.

These conditions are idiopathic but are common among patients with RA or diabetes mellitus. Repetitive use of the hands (as may occur when using heavy gardening shears) may contribute. In diabetes, they often coexist with carpal tunnel syndrome and occasionally with fibrosis of the palmar fascia. Pathologic changes begin with a thickening or nodule within the tendon; when located at the site of the tight first annular pulley, the thickening or nodule blocks smooth extension or flexion of the finger. The finger may lock in flexion, or "trigger," suddenly extending with a snap.

Treatment

- Conservative measures

- Sometimes corticosteroid injection

Treatment of acute inflammation and pain includes splinting, moist heat, and anti-inflammatory doses of NSAIDs (see p. 335). If these measures fail, injection of a corticosteroid suspension into the flexor tendon sheath, along with splinting, may provide safe, rapid relief of pain and triggering. Operative release can be done if corticosteroid therapy fails.

De Quervain's Syndrome

(Washerwoman's Sprain)

De Quervain's syndrome is stenosing tenosynovitis of the short extensor (extensor pollicis brevis) and long abductor tendon (abductor pollicis longus) of the thumb within the first extensor compartment.

De Quervain's syndrome usually occurs after repetitive use (especially wringing) of the wrist, although it occasionally occurs in association with RA. The major symptom is aching pain at the wrist and thumb,
aggravated by motion. Tenderness can be elicited just proximal to the radial styloid process over the site of the involved tendon sheaths. Diagnosis is highly suggested by the Finkelstein test. The patient adducts the involved thumb into the palm and wraps the fingers over the thumb. The test is positive if gentle passive ulnar deviation of the wrist provokes severe pain at the affected tendon sheaths.

**Treatment**

- Corticosteroid injection
- Thumb spica splint

Rest, warm soaks, and NSAIDs may help in very mild cases. Local corticosteroid injections and a thumb spica splint help 70 to 80% of cases. Tendon rupture is a rare complication of injection and can be prevented by confining infiltration to the tendon sheath and avoiding injection of the corticosteroid into the tendon. Intratendinous location of the needle is likely if injection is met with moderate or severe resistance. Surgical release of the first extensor compartment is very effective when conservative therapy fails.

**Osteoarthritis of the Hand**

**Hand involvement is extremely common in osteoarthritis.**

Osteoarthritis affecting the hand may be asymptomatic enlargement of nodules at the proximal interphalangeal joint (Bouchard's nodules) or distal interphalangeal joint (Heberden's nodes) or angulation at these joints. Pain and stiffness of these joints and the base of the thumb are also common. The wrist usually is spared, and there is usually minimal or no metacarpophalangeal joint involvement unless the patient also has a metabolic disorder (eg, hemochromatosis). Differentiation of hand changes in osteoarthritis from those in RA is discussed in Table 32-7 on p. 296.

**Treatment**

- Conservative measures
- Occasionally corticosteroid injection or surgery

Treatment is symptomatic with analgesics, appropriate rest, splinting, and occasionally corticosteroid injection as needed. Surgical procedures can help relieve pain and correct deformity for severe changes at the base of the thumb and, less commonly, for advanced degeneration of the interphalangeal joints.
Chapter 44. Foot and Ankle Disorders

Introduction

Most foot problems result from anatomic disorders or abnormal function of articular or extra-articular structures (see Fig. 44-1). Less commonly, foot problems reflect a systemic disorder (see Table 44-1).

In people with diabetes and people with peripheral vascular disease, careful examination of the feet, with evaluation of vascular sufficiency and neurologic integrity, should be done at least twice/yr. People with these diseases should examine their own feet at least once/day.

The feet are also common sites for corns and calluses (see p. 660) and infections by fungus (see Tinea Pedis on p. 708), bacteria (see p. 694), and viruses (see Warts on p. 715).

Table 44-2 lists foot and ankle disorders according to anatomic site.
Table 44-3 lists common causes of heel pain according to location.

Tibialis Posterior Tendinosis

Tibialis posterior tendinosis, degeneration of the tibialis posterior tendon, is the most common cause of pain behind the medial malleolus.

The posterior tibial tendon lies immediately behind the medial malleolus. Degeneration results from long-standing biomechanical problems, such as excessive pronation often in obese people. The tendon can also be involved by primary inflammatory disorders, such as RA or gout.

Symptoms and Signs

Early on, patients experience occasional pain behind the medial malleolus. Over time, the pain becomes severe, with painful swelling behind the medial malleolus. Normal standing, walking, and standing on the toes become difficult.

Diagnosis

• MRI

Clinical findings suggest the diagnosis. Palpation of the tendon in an inverted-plantar flexed position usually elicits pain. Standing on the toes is usually painful and may not be possible if the tendon is ruptured. Pain and swelling behind the medial malleolus, especially with tibialis posterior tendon pain on palpation, are highly suggestive. MRI or ultrasonography can confirm injury to the tendon and its extent.

Treatment

• Orthotics and braces or surgery

Complete rupture requires surgery if normal function is the goal. Surgery is especially important in young active patients with acute tears. Conservative therapy consists of mechanically off-loading the tendon by using orthotics and ankle braces. Corticosteroid injections exacerbate the degenerative process (see Sidebar 44-1). If the tendon is inflamed, rest and aggressive anti-inflammatory therapy are warranted.
Tarsal Tunnel Syndrome

(Posterior Tibial Nerve Neuralgia)

Tarsal tunnel syndrome is pain along the course of the posterior tibial nerve, usually resulting from nerve compression within the tarsal tunnel.

At the level of the ankle, the posterior tibial nerve passes through a fibro-osseous canal and divides into the medial and lateral plantar nerves. Tarsal tunnel syndrome refers to compression of the nerve within this canal, but the term has been loosely applied to neuralgia of the posterior tibial nerve resulting from any cause. Synovitis of the flexor tendons of the ankle caused by abnormal foot function, inflammatory arthritis (eg, RA), fracture, and ankle venous stasis edema are contributing factors. Patients with hypothyroidism may develop tarsal tunnel-like symptoms as a result of perineural mucin deposition.

Symptoms and Signs

Pain (occasionally burning and tingling) is usually retromalleolar and sometimes in the plantar medial heel and may extend along the plantar surface as far as the toes. Although the pain is worse during standing and walking, pain at rest may occur as the disorder progresses.

Diagnosis

• Examination and electrodiagnostic testing

Tapping or palpating the posterior tibial nerve below the medial malleolus at a site of compression or injury often causes distal tingling (Tinel's sign). While false-negative results on electrodiagnostic tests are somewhat common, a positive history combined with supportive physical findings and positive electrodiagnostic results makes the diagnosis of tarsal tunnel syndrome highly likely. The cause of any swelling near the nerve should be determined.

Treatment

• Foot inversion, injection, surgery, or a combination

Strapping the foot in a neutral or slightly inverted position or wearing an orthotic that keeps the foot inverted reduces nerve tension. Local infiltration of a mixture of an insoluble corticosteroid and an anesthetic may be effective if the cause is inflammation or fibrosis. Surgical decompression may be necessary to relieve suspected fibro-osseous compression with recalcitrant symptoms.

Metatarsalgia

Metatarsalgia is a general term for pain in the area of the metatarsophalangeal joints (ball of the foot). Most common causes include Freiberg's disease, interdigital nerve pain (Morton's neuroma), metatarsophalangeal joint pain, and sesamoiditis.

Freiberg's Disease

Freiberg's disease is avascular necrosis of the metatarsal head.

Freiberg's disease is caused by microtrauma at the metaphysis and growth plate. Avascular necrosis flattens the metatarsal head. The 2nd metatarsal head is most often affected. Freiberg's disease occurs more frequently among pubertal females and among people who have a short 1st metatarsal bone, which increases stress on the 2nd metatarsal head and joint.

Symptoms and Signs
The pain is most pronounced in the forefoot at the metatarsal head with weight bearing, particularly when pushing off or when wearing high-heeled footwear. The metatarsophalangeal joint may also be swollen and have limited and painful passive range of motion.

**Diagnosis**

- **X-rays**

The diagnosis is confirmed with x-rays. Typically, the head of the 2nd metatarsal is widened and flattened, and the metatarsal joint is sclerotic and irregular.

**Sidebar 44-1 Considerations for Using Corticosteroid Injections**

Corticosteroid injections should be used judiciously to avoid adverse effects. Injectable corticosteroids should be reserved for inflammation, which is not present in most foot disorders. Because the tarsus, ankle, retrocalcaneal space, and dorsum of the toes have little connective tissue between the skin and underlying bone, injection of insoluble corticosteroids into these structures may cause depigmentation, atrophy, or ulceration, especially in elderly patients with peripheral arterial disease.

Insoluble corticosteroids can be given deeply rather than superficially with greater safety (eg, in the heel pad, tarsal canal, or metatarsal interspaces). The foot should be immobilized for a few days after tendon sheaths are injected. Unusual resistance to injection suggests injection into a tendon. Repeated injection into a tendon should be avoided because the tendon may weaken (partially tear), predisposing to subsequent rupture.

**Treatment**

- **Immobilization and weight unloading if acute, then modification of footwear**

Corticosteroid injections and immobilization may help to alleviate acutely painful flare-ups. Long-term management may require orthoses with metatarsal bars and low-heeled footwear to reduce stress on the 2nd metatarsal head and joint. Corticosteroid injections can be tried, and, rarely, surgical excision of the metatarsal head may be necessary to relieve recalcitrant pain.

**Interdigital Nerve Pain**

*(Morton's Neuroma/Neuralgia)*

**Interdigital nerve irritation (neuralgia) or persistent benign enlargement of the perineurium (neuroma) can cause pain, which may be nonspecific, burning, or lancinating, or a foreign body sensation. Diagnosis is usually clinical. Treatment may involve correction of footwear, local injection, or sometimes surgical excision.*

The interdigital nerves of the foot travel beneath and between the metatarsals, extending distally to innervate the toes. Neuralgia of the interdigital nerve along its distal innervation near the ball of the foot develops primarily as a result of improper or constrictive footwear or, less commonly, nerve traction resulting from abnormal foot structure. As a result of chronic repetitive trauma, a benign thickening of the nerve develops (Morton's neuroma).

**Symptoms and Signs**

Interdigital neuralgia is characterized by pain around the metatarsal heads or the toes. Early interdigital neuralgia often causes an occasional mild ache or discomfort in the ball of the foot, usually when wearing a specific shoe, such as those that are too narrow at the front. Neuralgia is usually unilateral. As the condition progresses, the nerve thickens. The pain becomes worse, often with a burning or lancinating
quality or paresthesias. In time, patients are unable to wear most shoes. While walking, patients often falsely sense a pebble in their shoes, which they take off for relief. Neuroma most frequently affects the 3rd interspace. Only slightly less common is involvement of the 2nd interspace. Sometimes both interspaces or feet are involved simultaneously.

Diagnosis

- Clinical evaluation

The symptoms are often specific, and the diagnosis is confirmed by tenderness on plantar palpation of the interdigital space and reproduction of the radiating burning pain by squeezing the space. Although MRI does not usually confirm neuroma, it may be useful to rule out other interspace lesions or arthritis causing similar symptoms.

Treatment

- Modification of footwear and injection

Neuralgia of recent onset usually resolves quickly with properly fitting shoes and insoles or with local anesthetic injection. In contrast, neuromas may require one or more perineural infiltrations of long-acting corticosteroids with a local anesthetic. Injection is at a 45° angle to the foot, into the interspace at the level of the dorsal aspect of the metatarsophalangeal joints. An appropriate orthotic often relieves symptoms. If conservative therapy is ineffective, excision often brings complete relief. However, another neuroma occasionally develops at the site of nerve excision (amputation or stump neuroma).

Metatarsophalangeal Joint Pain

Metatarsophalangeal joint pain usually results from tissue changes due to aberrant foot biomechanics. Symptoms and signs include pain with walking and tenderness. Diagnosis is clinical; however, infection or systemic rheumatic diseases (eg, RA) may need to be excluded by testing. Treatment includes orthotics, sometimes local injection, and occasionally surgery.

Metatarsophalangeal joint pain most commonly results from misalignment of the joint surfaces with altered foot biomechanics, causing joint subluxations, capsular impingement, and joint cartilage destruction (osteoarthrosis). Misaligned joints may cause synovial impingement, with minimal if any heat and swelling (osteoarthritic synovitis).

Metatarsophalangeal joint subluxations also occur as a result of inflammatory arthropathy, particularly RA. Inflammatory synovitis and interosseous muscle atrophy in RA lead to subluxations of the lesser metatarsophalangeal joints as well, resulting in hammer toe deformities. Consequently, the metatarsal fat pad, which usually cushions the stress between the metatarsals and interdigital nerves during walking, moves distally under the toes; interdigital neuralgia or Morton's neuroma may result. To compensate for the loss of cushioning, adventitial calluses and bursae may develop.

Metatarsophalangeal joint pain may also result from functional hallux limitus, which limits passive and active joint motion and usually occurs at the 1st metatarsophalangeal joint. Patients usually have foot pronation disorders that result in elevation of the 1st ray with lowering of the medial longitudinal arch during weight bearing. As a result of the 1st ray elevation, the proximal phalanx of the great toe cannot freely extend on the 1st metatarsal head; the result is jamming at the dorsal joint leading to osteoarthritic changes and loss of joint motion. Over time, pain may develop, and the joint may become less mobile with an arthrosis (hallux rigidus), which can be debilitating.

Symptoms and Signs

Symptoms include pain on walking. Dorsal and plantar joint tenderness is usually present on palpation and during passive range of motion. Mild swelling with minimal heat occurs in osteoarthritic synovitis. Significant warmth, swelling, or redness suggests inflammatory arthropathies or infection.
Diagnosis

- Mainly clinical evaluation
- Exclusion of infection or arthropathy if signs of inflammation

Metatarsophalangeal joint pain can usually be differentiated from neuralgia or neuroma of the interdigital nerves by the absence of burning, numbness, and tingling and interspace pain, although these symptoms may develop from joint inflammation; if so, palpation can help with differentiation.

Monarticular heat, redness, and swelling indicate infection until proven otherwise, although gout is more likely. When warmth, redness, and swelling involve multiple joints, evaluation for a systemic cause of joint inflammation (eg, gout, RA, viral-associated arthritis, enteropathic arthritis) with a rheumatic disease assessment (eg, antinuclear antibodies, rheumatoid factor, ESR) is indicated.

Treatment

- Orthoses

Foot orthoses may help to redistribute and relieve pressure from the noninflamed joints. With excess subtalar eversion or when the feet are highly arched, an orthotic that corrects these abnormal motions should be prescribed. For functional hallux limitus, orthosis modifications may further help to plantarflex the 1st ray to improve metatarsophalangeal joint motion and reduce pain. For more severe limitation of 1st metatarsophalangeal motion or pain, the use of rigid orthoses, carbon fiber plates, or external shoe bars or rocker soles may be necessary to reduce motion at the joint. Surgery may be needed if conservative therapies are ineffective. If inflammation (synovitis) is present, injection of a local corticosteroid/anesthetic mixture may be useful.

Sesamoiditis

Sesamoiditis is pain at the sesamoid bones beneath the head of the 1st metatarsal, with or without inflammation or fracture. Diagnosis is usually clinical. Treatment is usually modification of footwear.

The 2 semilunar-shaped sesamoid bones aid the foot in locomotion. The medial bone is the tibial sesamoid, and the lateral bone is the fibular sesamoid. Direct trauma or positional change of the sesamoids due to alterations in foot structure (eg, lateral displacement of a sesamoid due to lateral deviation of the great toe) can make the sesamoids painful. Sesamoiditis is particularly common among dancers, joggers, and those who have high-arched feet or wear high heels. Many people with sesamoiditis have bunions.

Symptoms and Signs

The pain of sesamoiditis is beneath the head of the 1st metatarsal; the pain is usually made worse by walking and may be worse when wearing certain shoes. Occasionally, inflammation occurs, causing mild warmth and swelling or occasionally redness that may extend medially and appear to involve the 1st metatarsophalangeal joint. Sesamoid fracture can also cause pain, moderate swelling, and possibly inflammation.

Diagnosis

- Clinical evaluation
- Imaging if fracture, infection, or gout is suspected

With the foot and 1st (big) toe dorsiflexed, the examiner inspects the metatarsal head and palpates each sesamoid. Tenderness is localized to a sesamoid, usually the tibial sesamoid. Hyperkeratotic tissue may indicate that a wart or corn is causing pain. If inflammation causes swelling around the 1st
metatarsophalangeal joint, arthrocentesis is usually indicated to exclude gout and infectious arthritis. If fracture, osteoarthritis, or displacement is suspected, x-rays are taken. Sesamoids separated by cartilage or fibrous tissue (bipartite sesamoids) may appear fractured on x-rays. If plain x-rays are equivocal, MRI may be ordered.

Treatment

- New shoes, orthotics, or both

Simply not wearing the shoes that cause pain may be sufficient. If symptoms persist, shoes with a thick sole and orthotics are prescribed and help by reducing sesamoid pressure. If fracture without displacement is present, conservative therapy may be sufficient and may also involve immobilization of the joint with the use of a flat, rigid, surgical shoe. NSAIDs and injections of a corticosteroid/local anesthetic solution can be helpful. Although surgery may help in recalcitrant cases, it is controversial because of the potential for disturbing biomechanics and locomotion of the foot. If inflammation is present, treatment includes conservative measures plus local infiltration of a corticosteroid/anesthetic solution to help reduce symptoms.

**Plantar Fasciosis**

(Plantar Fasciitis)

Plantar fasciosis is pain at the site of the attachment of the plantar fascia and the calcaneus, with or without accompanying pain along the medial band of the plantar fascia. Diagnosis is mainly clinical. Treatment involves calf muscle and plantar soft-tissue foot-stretching exercises, night splints, and orthotics.

 Syndromes of pain in the plantar fascia have been called plantar fasciitis; however, because there is usually no inflammation, plantar fasciosis is more correct. Other terms used include calcaneal enthesopathy pain or calcaneal spur syndrome; however, there may be no bone spurs on the calcaneus. Plantar fasciosis may involve acute or chronic stretching, tearing, and degeneration of the fascia at its attachment site.

Etiology

Recognized causes include shortening or contracture of the calf muscles and plantar fascia. Risk factors for such shortening include a sedentary lifestyle, occupations requiring sitting, very high or low arches in the feet, and wearing high-heel shoes. The disorder is also common among runners and dancers and may occur in people whose occupations involve standing or walking on hard surfaces for prolonged periods. Disorders that may be associated with plantar fasciosis are obesity, RA, reactive arthritis, and psoriatic arthritis. Multiple injections of corticosteroids may contribute by causing degenerative changes of the fascia and possible loss of the cushioning subcalcaneal fat pad.

Symptoms and Signs

Plantar fasciosis is characterized by pain at the bottom of the heel on weight bearing, particularly when first arising in the morning; pain usually improves within 5 to 10 min, only to return later in the day. It is often worse when pushing off of the heel (the propulsive phase of gait). Acute severe heel pain, especially with mild local puffiness, may indicate an acute tear. Some patients describe burning or sticking pain along the plantar medial border of the foot when walking.

Diagnosis

- Pain reproduced by calcaneal pressure during dorsiflexion

Other disorders causing heel pain can mimic plantar fasciosis:

- Throbbing heel pain, particularly when the shoes are removed or when mild heat and puffiness are
present, is more suggestive of calcaneal bursitis (see p. 401).

- Acute severe retrocalcaneal pain, with redness and heat, may indicate gout.
- Pain that radiates from the low back to the heel may be an S1 radiculopathy due to an L5 disk herniation.

Plantar fasciosis is confirmed if firm thumb pressure applied to the calcaneus when the foot is dorsiflexed elicits pain. Fascial pain along the plantar medial border of the fascia may also be present. If findings are equivocal, demonstration of a heel spur on x-ray may support the diagnosis; however, absence does not rule out the diagnosis, and visible spurs are not generally the cause of symptoms. Also, infrequently, calcaneal spurs appear ill defined on x-ray, exhibiting fluffy new bone formation, suggesting spondyloarthropathy (eg, ankylosing spondylitis, reactive arthritis). If an acute fascial tear is suspected, MRI is done.

**Treatment**

- Splinting, stretching, and cushioning or orthotics

To alleviate the stress and pain on the fascia, the person can take shorter steps and avoid walking barefoot. Activities that involve foot impact, such as jogging, should be avoided. The most effective treatments include the use of in-shoe heel and arch cushioning with calf-stretching exercises and night splinting devices that stretch the calf and plantar fascia while the patient sleeps. Prefabricated or custom-made foot orthotics may also alleviate fascial tension and symptoms. Other treatments may include activity modifications, NSAIDs, weight loss in obese patients, cold and ice massage therapy, and occasional corticosteroid injections. However, because corticosteroid injections can predispose to plantar fasciosis, many clinicians limit these injections. For recalcitrant cases, physical medicine, oral corticosteroids, and cast immobilization should be used before surgical intervention is considered.

**Inferior Calcaneal Bursitis**

Bursitis can develop at the inferior calcaneus, near the insertion of the plantar fascia. Symptoms and signs include throbbing heel pain, particularly when the shoes are removed; mild warmth; and swelling. The pain is most pronounced when the heel first contacts the ground during walking or running activity. Treatment is injection of a local anesthetic/corticosteroid mixture and soft-soled shoes with added protective heel cushion padding.

**Achilles Tendon Enthesopathy**

Achilles tendon enthesopathy is pain at the insertion of the Achilles tendon at the posterosuperior aspect of the calcaneus.

The cause is chronic traction of the Achilles tendon on the calcaneus. Contracted or shortened calf muscles (resulting from a sedentary lifestyle and obesity) and athletic overuse are factors. Enthesopathy may be caused by a spondyloarthropathy.

Pain at the posterior heel below the top of the shoe counter during ambulation is characteristic. Pain on palpation of the tendon at its insertion is diagnostic. Manual dorsiflexion of the ankle during palpation usually exacerbates the pain. Recurrent and especially multifocal enthesitis should prompt evaluation (history and examination) for a spondyloarthropathy.

**Treatment**

- Stretching, splinting, and heel lifts

Physical therapy aimed at calf muscle stretching should be done 10 min three times/day. The patient can exert pressure posteriorly to stretch the calf muscle while facing a wall at arms’ length, with knees extended and foot dorsiflexed. To minimize stress to the Achilles tendon with weight bearing, the patient
should move the foot and ankle actively through their range of motion for about 1 min when rising after extended periods of rest. Night splints may also be prescribed to provide passive stretch during sleep and help prevent contractures. Heel lifts should be used temporarily to decrease tendon stress during weight bearing and relieve pain. Heel lifts should be used bilaterally to prevent gait disturbance even if pain is only in one heel.

**Anterior Achilles Tendon Bursitis**

(Albert's Disease; Retromalleolar Bursitis)

**Anterior Achilles tendon bursitis is inflammation of the retromalleolar (retrocalcaneal) bursa, located anterior (deep) to the attachment of the Achilles tendon to the calcaneus.**

Bursitis is due to trauma (eg, from rigid or poorly fitting shoes) or inflammatory arthritis (eg, RA, gout). On occasion, small calcaneal erosions may develop from severe inflammation.

**Symptoms and Signs**

Symptoms and signs caused by trauma or gout develop rapidly; those caused by another systemic disorder develop gradually. Pain, swelling, and warmth around the heel are common, as are difficulty walking and wearing shoes. The bursa is tender. Initially, the swelling is localized anterior to the Achilles tendon but in time extends medially and laterally.

Using the thumb and index finger, side-to-side compression anterior to the Achilles tendon causes pain.

**Diagnosis**

- Clinical evaluation and x-rays

Fracture of the posterolateral talus tubercle also causes tenderness anterior to the insertion of the Achilles tendon. Bursitis is often differentiated from the fracture by the localization of warmth and swelling contiguous to the tendon and pain localized primarily in the soft tissue. Also, x-rays are taken to rule out fracture as well as erosive calcaneal changes characteristic of chronic RA or other rheumatic disorders.

**Treatment**

- Intrabursal injection of a soluble corticosteroid/anesthetic solution

A corticosteroid/anesthetic injection, NSAIDs, and warm or cold compresses may be effective. Care must be taken to inject only the bursal sac and not the tendon proper because tendon injection may lead to tendon weakening or tearing, predisposing to subsequent rupture.

**Posterior Achilles Tendon Bursitis**

**Posterior Achilles tendon bursitis is inflammation of a bursa that forms in response to shoe pressure and is located at the top edge of the posterior shoe counter between the skin and Achilles tendon.**

This disorder occurs mainly in young women. Wearing high-heeled shoes is a risk factor. Many patients have a bony prominence (Haglund's deformity) on the calcaneus.

**Symptoms and Signs**

Symptoms and signs develop at the top edge of the posterior shoe counter. Early symptoms may be limited to redness, pain, and warmth. Later, superficial skin erosion may occur. After months or longer, a fluctuant, tender, cystic nodule 1- to 3-cm in diameter develops. It is red or flesh-colored. In chronic cases, the bursa becomes fibrotic.
Diagnosis

• Symptoms and a small, tender, flesh-colored or red nodule

The presence of the small, tender, flesh-colored or red nodule in a patient with compatible symptoms is diagnostic. Rarely, an Achilles tendon xanthoma develops at the top edge of the posterior shoe counter but tends to be pink and asymptomatic. Achilles tendon enthesopathy causes pain mainly at the tendon's insertion but may also cause pain at the top edge of the posterior shoe counter. Enthesopathy is differentiated by the absence of a soft-tissue lesion.

Treatment

• Modification of footwear

Properly fitting shoes with low heels are essential. A foam rubber or felt heel pad may be needed to lift the heel high enough so that the bursa does not hit the shoe counter. Padding around the bursa or the wearing of a backless shoe until inflammation subsides is indicated. Foot orthotics may enhance rear foot stability and help reduce irritating motion on the posterior calcaneus while walking. Warm or cool compresses, NSAIDs, and intrabursal injection of a local anesthetic/corticosteroid solution offer temporary relief; the Achilles tendon itself must not be injected. Surgical removal of a portion of the underlying bone may rarely be necessary to reduce soft-tissue impingement.

Epiphysitis of the Calcaneus

(Sever's Disease)

Epiphysitis of the calcaneus is painful disruption between the calcaneal apophysis and the body of the heel that occurs before calcaneal ossification is complete.

The calcaneus develops from two centers of ossification: one begins at birth, the other usually after age 8. Ossification is usually complete by age 15. The cartilaginous disruption in calcaneal epiphysitis may result from an excessive pull on the apophysis by contracted or shortened calf muscles. Bone growth spurts without adaptive calf muscle lengthening may play a role.

Pain develops in a patient (usually aged 9 to 14) with a history of athletic activity; it affects the sides or margins of the heel and is aggravated by standing on tip toes or running. Warmth and swelling are occasionally present.

The diagnosis is clinical. X-rays are not helpful.

Treatment

• Heel pads and splinting or casting

Heel pads relieve symptoms by reducing the pull of the Achilles tendon on the heel. Night splints may be used to passively stretch the calf muscles, helping maintain flexibility. In more severe or recalcitrant cases, cast immobilization may be used to relieve pain and stretch the calf muscles. Reassurance is important because symptoms may last several months.

Medial Plantar Nerve Entrapment

Medial plantar nerve entrapment is symptomatic compression of the medial branch of the posterior tibial nerve at the medial heel.

Symptoms include almost constant pain, with and without weight bearing. Simple standing is often difficult. Burning, numbness, and paresthesias are usually absent.

Diagnosis
Clinical evaluation

Medial plantar nerve entrapment may be confused with plantar fasciosis and heel spur pain as well as tarsal tunnel syndrome. In medial plantar nerve entrapment, the following are present:

• Tenderness is at the medial heel.

• Other signs of tarsal tunnel syndrome are absent.

• Symptoms can be reproduced by palpation over the proximal aspect of the abductor hallucis, the origin of the plantar fascia, or both at the medial tubercle of the calcaneus.

Treatment

• Orthoses, immobilization, and physical therapy

Immobilization and foot orthoses to prevent irritating motion and pressure may be helpful, as may physical therapy and cryotherapy. If these treatments are ineffective, injection with a sclerosing agent that contains alcohol or careful surgical decompression of the nerve may help relieve pain.

Plantar Fibromatosis

Plantar fibromatosis is a benign proliferative neoplasia of the plantar fascia.

In plantar fibromatosis, nodules are displayed most easily when the foot is dorsiflexed against the leg. Most patients also have palmar nodules, usually located at the 4th metacarpophalangeal joint. Reported associations with diabetes, epilepsy, and alcoholism may be anecdotal. Treatment is usually not indicated unless the nodules become large enough to cause pressure-related pain with weight bearing. If so, orthoses can help redistribute pressure away from the fibrotic nodular lesions. Surgery usually results in recurrence and may also result in unintentional instability of the foot when fascial removal is excessive.

Hammer Toe Deformity

Hammer toe is a C-shaped deformity caused by dorsal subluxation at the metatarsophalangeal joint.

[Fig. 44-2. Hammer toe.]

The usual cause is misalignment of the joint surfaces due to a genetic predisposition toward aberrant foot biomechanics and tendon contractures. RA and neurologic disorders such as Charcot-Marie-Tooth disease are other causes. The 2nd toe is the most common digit to develop a hammer toe deformity (see Fig. 44-2). Second toe hammer toes commonly result from an elongated 2nd metatarsal and from pressure due to an excessively abducted great toe (hallux valgus deformity) causing a bunion (see below). Painful corns (see p. 660) often develop in hammer toe deformity, particularly of the 5th toe. Reactive adventitial bursas often develop beneath corns, which may become inflamed.

Symptoms include pain while wearing shoes, especially shoes with low and narrow toe boxes, and sometimes metatarsalgia. Diagnosis is clinical. Joints are examined for coexistent arthritis (eg, RA).

Treatment

• Wide toe box, toe pads, orthotics, or a combination

Shoes should have a wide toe box. Toe pads sold in pharmacies also help by shielding the affected toes from the overlying shoe. If these measures are ineffective, surgical correction of the deformity often relieves symptoms. If there is accompanying metatarsalgia, OTC or prescription orthotic devices with
metatarsal pads and cushioning may help alleviate the pain.

**Bunion**

**Bunion** is a prominence of the medial portion of the head of the 1st metatarsal bone. The cause is often variations in position of the 1st metatarsal bone or great toe, such as lateral angulation of the great toe (hallux valgus). Secondary osteoarthritis and spur formation are common. Symptoms may include pain and redness, bursitis medial to the joint, and mild synovitis. Diagnosis is usually clinical. Treatment is usually a shoe with a wide toe box, protective pads, and orthotics. For bursitis or synovitis, corticosteroid injection may be helpful.

Contributing factors may include excessive turning in (pronation) of the ankles, wearing tight and pointed-toe shoes, and occasionally trauma. Joint misalignment causes osteoarthritis with cartilage erosion and exostosis formation, resulting in joint motion being limited (hallux limitus) or eliminated (hallux rigidus). In late stages, synovitis occurs, causing joint swelling. In reaction to pressure from tight shoes, an adventitious bursa can develop medial to the joint prominence, which can become painful, swollen, and inflamed (see [Fig. 44-3](#)).

**Symptoms and Signs**

The initial symptom may be pain at the joint prominence when wearing certain shoes. The joint capsule may be tender at any stage. Later symptoms may include a painful, warm, red, cystic, movable, fluctuant swelling located medially (adventitial bursitis) and swellings and mild inflammation affecting the entire joint (osteoarthritic synovitis), which is more circumferential. With hallux limitus or rigidus, there is restriction of passive joint motion, tenderness of the lateral aspect of the joint, and increased dorsiflexion of the distal phalanx.

[Fig. 44-3, Bunion.]

**Diagnosis**

- Clinical evaluation

Clinical findings are usually specific. Acute circumferential intense pain, warmth, swelling, and redness suggest gouty arthritis or infectious arthritis, mandating examination of synovial fluid. If multiple joints are affected, gout or another systemic rheumatic disease should be considered. If clinical diagnosis of osteoarthritic synovitis is equivocal, x-rays are taken. Suggestive findings include joint space narrowing and bony spurs extending from the metatarsal head or sometimes from the base of the proximal phalanx. Periarticular erosions (Martel's sign) seen on imaging studies suggest gout.

**Treatment**

- Wide toe box, bunion pads, orthotics, or a combination

Mild discomfort may lessen by wearing a shoe with a wide toe box. If not, bunion pads purchased in most pharmacies can shield the painful area. Orthotics can also be prescribed to redistribute and relieve pressure from the affected articulation. If conservative therapy fails or if the patient is unwilling to wear large, wide shoes and orthotics because they are unattractive, surgery aimed at correcting abnormal bony alignments and restoring joint mobility should be strongly considered. For bursitis, bursal aspiration and injection of a corticosteroid are indicated. For osteoarthritic synovitis, oral NSAIDs or an intra-articular injection of a corticosteroid/anesthetic solution reduces symptoms. For hallux limitus or hallux rigidus, treatment aims to preserve joint mobility by using passive stretching exercises, which occasionally require injection of a local anesthetic to relieve muscle spasm. Sometimes surgical release of contractures is necessary.
Chapter 45. Tumors of Bones and Joints

Introduction

Bone tumors may be primary or metastatic and benign or malignant.

In children, most bone tumors are primary and benign; some are malignant primary tumors (eg, osteosarcoma, Ewing's sarcoma). Very few are metastatic tumors (eg, neuroblastoma, Wilms' tumor). Bone also can be affected by childhood leukemia and lymphomas.

In adults, especially those over age 40, metastatic tumors are about 100 times more common than primary malignant tumors. Excluding marrow cell tumors (eg, multiple myeloma), there are only about 2500 cases of primary malignant bone tumors in the US each year among children and adults.

Synovial tumors are extremely rare in both children and adults. Pigmented villonodular synovitis is a benign but at times destructive tumor of synovial cells. Synovial sarcoma (often with both spindle cell and glandular-like components) is a malignant soft-tissue tumor not of synovial origin, which seldom occurs inside of a joint.

Symptoms and Signs

Bone tumors typically cause unexplained, progressive pain and swelling. Pain can occur without weight bearing or bone stress and can occur at rest and at night.

Diagnosis

- Plain x-rays
- MRI usually and sometimes CT
- Bone scan if multicentric or metastatic tumors are suspected
- Biopsy unless imaging studies clearly show benign characteristics

The most common reason that diagnosis of bone tumors is delayed is that physicians fail to suspect the tumor and order appropriate imaging studies. Persistent or progressive unexplained pain of the trunk or extremities, particularly if associated with a mass, is suggestive. Plain x-rays are the first test. Tumors should also be suspected if a radiographic study shows an unexplained abnormality consistent with a tumor. Lesions suggestive of tumors usually require further assessment, often with additional imaging studies and a biopsy.

Characteristic findings: Some tumors (eg, Paget's disease, nonossifying fibroma, fibrous dysplasia, enchondromas) may have characteristic radiographic findings and can be diagnosed without biopsy.

Radiographic findings that suggest cancer include the following:

- A lytic, destructive, or permeative appearance
- Irregular tumor borders
- Areas, especially multiple areas, of bone destruction (moth-eaten appearance)
- Cortical destruction
- Soft-tissue extension
- Pathologic fracture
A lytic appearance is characterized by clear areas of bone destruction that are sharply demarcated. A permeative appearance is characterized by a faint, gradual loss of bone or an infiltrating pattern without clear borders. Certain tumors have a characteristic appearance (eg, Ewing's sarcoma typically shows permeative-type bone destruction, including a large soft-tissue mass with periosteal onion-skin reactive bone often before there is an extensive, lytic, destructive appearance; giant cell tumor has a cystic appearance without a sclerotic interface between the tumor and normal bone). The tumor's location may narrow diagnostic possibilities (eg, Ewing's sarcoma commonly appears in the shaft of a long bone; osteosarcoma usually appears in the metaphyseal-diaphyseal region toward the end of a long bone; giant cell tumor usually occurs in the epiphysis).

Some benign conditions, however, can mimic a malignant tumor:

- Heterotopic ossification (myositis ossificans) and exuberant callus formation after fracture can cause mineralization around bony cortices and in adjacent soft tissues, mimicking malignant tumors.

- Langerhans' cell histiocytosis (histiocytosis X, Letterer-Siwe disease, Hand-Schuller-Christian disease, eosinophilic granuloma) can cause solitary or multiple bone lesions that are usually distinguishable on x-ray. In solitary lesions, there may be periosteal new bone formation, suggesting a malignant bone tumor.

- Osteopoikilosis (spotted bones) is an asymptomatic condition of no clinical consequence but can simulate osteoblastic bone metastases of breast cancer. It is characterized by multiple small, round, or oval foci of bony sclerosis, usually in the tarsal, carpal, or pelvic bones or the metaphyseal-epiphyseal regions of tubular bones.

**Other testing:** CT and MRI may help define the location and extent of a bone tumor and sometimes suggest a specific diagnosis. MRI is usually done if cancer is suspected. If tumors are suspected of being metastatic or involving multiple foci (multicentric), then radioisotopic technetium bone scanning should be done to search for all tumors.

Biopsy is usually essential for diagnosis of malignant tumors, unless the imaging studies have a classically benign appearance. The pathologist should be given pertinent details of the clinical history and should review imaging studies. Histopathologic diagnosis may be difficult and requires sufficient viable tissue from a representative portion of the tumor (usually the soft portion). The best results are obtained in centers with extensive experience in bone biopsies. Immediate, accurate, definitive diagnosis is possible in > 90% of cases. If a malignant diagnosis is suspected on frozen section histology, often the surgeon will wait upon permanent histology before treating definitively. Mistakes occur more frequently in hospitals that infrequently encounter patients with malignant primary tumors.

**Benign Bone Tumors**

**Osteochondroma:** Osteochondromas (osteocartilaginous exostoses), the most common benign bone tumors, may arise from any bone but tend to occur near the ends of long bones. These tumors manifest most often in people aged 10 to 20 and may be single or multiple. Multiple osteochondromas tend to run in families. Secondary malignant chondrosarcoma develops in about 10% of patients with multiple osteochondromas and in well < 1% of those with single osteochondromas. Osteochondromas rarely cause the bone to fracture.

On imaging studies, the lesion appears as a bony prominence with a cartilage cap (< 2 cm) off the surface of the bone with no underlying cortex under the prominence.

Excision is needed if the tumor is compressing a large nerve; causes pain (especially when impinging on muscle and creating an inflammatory bursa); disturbs growth; or on imaging study has a destructive appearance, soft-tissue mass, or thickened cartilaginous cap (> 2 cm) suggesting transformation into malignant chondrosarcoma.

**Enchondroma:** Enchondromas may occur at any age but tend to be recognized in patients aged 10 to 40. They are usually located within the medullary bone metaphyseal-diaphyseal region. These tumors are
usually asymptomatic but may enlarge and become painful. They are often found when x-rays are taken for another reason.

On x-ray, the tumor may appear as a lobulated calcified area within bone; some lesions are less calcified, with areas of stippled calcification either on plain films or CT. If adjacent to the cortex, enchondromas show minor endosteal scalloping. Almost all enchondromas have increased uptake on a bone scan and thus create concern of cancer. X-ray findings, including MRI and CT, may be diagnostic; if they are not, and especially if the tumor (not the associated joint) is painful, the diagnosis should be confirmed by biopsy. To help differentiate bone pain from joint pain, the joint can be injected, usually with a long-lasting anesthetic (eg, bupivacaine); if pain persists, it may be caused by the bone lesion.

An asymptomatic enchondroma does not need biopsy, excision, or other treatment (usually curettage); however, follow-up imaging studies are indicated to rule out disease progression. These are done at 6 mo and again at 1 yr or whenever symptoms develop.

**Chondroblastoma:** Chondroblastoma is rare and occurs most commonly among people aged 10 to 20. Arising in the epiphysis, this tumor may continue to grow and destroy bone and the joint. It appears on imaging studies as a sclerotic margined cyst containing spots of punctate calcification. MRI can help diagnostically by showing characteristic changes well away from the lesion.

The tumor must be surgically removed by curettage, and the cavity must be bone grafted. Local recurrence rate is about 10 to 20%, and recurrent lesions often resolve with repeat bone curettage and bone grafting.

**Chondromyxofibroma:** Chondromyxofibroma is very rare and usually occurs before age 30. The appearance on imaging studies (usually eccentric, sharply circumscribed, lytic, and located near the end of long bones) suggests the diagnosis. Treatment after biopsy is surgical excision or curettage.

**Osteoid osteoma:** Osteoid osteoma, which tends to affect young people (commonly aged 10 to 35), can occur in any bone but is most common among long bones. It can cause pain (usually worse at night) that is typically relieved by mild analgesics, particularly aspirin or other NSAIDs. In growing children, the inflammatory response and associated hyperemia, if close to the open growth plate, may cause overgrowth and limb length discrepancy. Physical examination may reveal atrophy of regional muscles because the pain causes muscle disuse.

Characteristic appearance on imaging studies is a small radiolucent zone surrounded by a larger sclerotic zone. If a tumor is suspected, a technetium-99m bone scan should be done; an osteoid osteoma appears as an area of increased uptake. CT with fine image sequences is also done and is most helpful in distinguishing the lesion.

Removal of the small radiolucent zone with percutaneous radiofrequency ablation provides permanent relief. Most osteoid osteomas are treated by an interventional musculoskeletal radiologist using percutaneous techniques and anesthesia. Less often, osteoid osteomas are surgically curetted or excised.

**Benign giant cell tumor:** These tumors, which most commonly affect people in their 20s and 30s, occur in the epiphyses and may eventually erode the rest of the bone and extend into the soft tissues. They may cause pain. Giant cell tumors are notorious for their tendency to recur. Rarely, a giant cell tumor may metastasize to the lung, even though it remains histologically benign.

Benign giant cell tumors appear as expansile lytic lesions on imaging. On imaging studies, there is a margin without a sclerotic rim where the tumor ends and normal trabecular bone begins.

Most benign giant cell tumors are treated by curettage and packing with methyl methacrylate or by bone graft. To reduce recurrence rate, surgeons often prefer using an adjuvant such as thermal heat (provided by the hardening of methyl methacrylate) or chemically by phenol or freezing with liquid nitrogen. If a tumor is very large and destructive to the joint, complete excision with joint reconstruction may be necessary.
Primary Malignant Bone Tumors

(See also Ch. 117.)

Multiple myeloma: Multiple myeloma is the most common primary malignant bone tumor but is often considered a marrow cell tumor within the bone rather than a bone tumor. It is of hematopoietic derivation (see also p. 1029) and occurs mostly in older adults. The neoplastic process is usually multicentric and often involves the bone marrow so diffusely that bone marrow aspiration is diagnostic. Imaging studies usually show sharply circumscribed lytic lesions or diffuse demineralization. Rarely, the lesion can appear as sclerotic or as diffuse osteopenia, especially in a vertebral body. An isolated single myeloma lesion without systemic marrow involvement is called a plasmacytoma.

Osteosarcoma: Osteosarcoma (osteogenic sarcoma) is the 2nd most common primary bone tumor and is highly malignant. It is most common among people aged 10 to 25, although it can occur at any age. Osteosarcoma produces malignant osteoid (immature bone) from tumor bone cells. Osteosarcoma usually develops around the knee (distal femur more often than proximal tibia) or in other long bones, particularly the metaphyseal-diaphyseal area, and may metastasize, usually to lung or other bone. Pain and swelling are the usual symptoms.

Findings on imaging studies vary and may include sclerotic or lytic features. Diagnosis requires biopsy. Patients need a chest x-ray and CT to detect lung metastases and a bone scan to detect bone metastases.

Treatment is a combination of chemotherapy and surgery. Use of adjuvant chemotherapy increases survival from < 20% to > 65% at 5 yr. Chemotherapy usually begins before any surgery. Decreased tumor size on x-ray, decreased pain level, and decreased serum alkaline phosphatase indicate some response, but the desired response is for > 95% tumor necrosis on mapping of the resected specimen. After several courses of chemotherapy (over several months), limb-sparing surgery and limb reconstruction can proceed. In limb-sparing surgery, the tumor is resected en bloc, including all surrounding reactive tissue and a rim of surrounding normal tissue; to avoid microscopic spillage of tumor cells, the tumor is not violated. More than 80% of patients can be treated with limb-sparing surgery without decreasing long-term survival rate. Continuation of chemotherapy after surgery is usually necessary. If there is nearly complete tumor necrosis (about 99%) from preoperative chemotherapy, 5-yr survival rate is > 90%.

Fibrosarcoma: Fibrosarcomas have similar characteristics to osteosarcomas but produce fibrous tumor cells (rather than bone tumor cells), affect the same age group, and pose similar problems.

Malignant fibrous histiocytoma: This tumor is clinically similar to osteosarcoma and fibrosarcoma, although malignant fibrous histiocytomas have been classified as different from the osteosarcoma group because of a different histology (no tumor bone production). Malignant fibrous histiocytomas tend to occur in children and teenagers but can also occur in older adults as secondary lesions in bone infarcts and radiation fields. Treatment is similar to that of osteosarcoma.

Chondrosarcoma: Chondrosarcomas are malignant tumors of cartilage. They differ from osteosarcomas clinically, therapeutically, and prognostically. Of chondrosarcomas, 90% are primary tumors. Chondrosarcomas arise in other pre-existing conditions, particularly multiple osteochondromas and multiple enchondromatosis (eg, in Ollier's disease and Maffucci's syndrome). Chondrosarcomas tend to occur in older adults. They often develop in flat bones (eg, pelvis, scapula) but can develop in any portion of any bone and can implant in surrounding soft tissues.

X-rays often reveal punctate calcifications. Primary chondrosarcomas often also exhibit cortical bone destruction and loss of normal bone trabeculae. Secondary chondrosarcoma may be suggested by the appearance of punctate calcifications or an increase in size of an osteochondroma. Technetium-99m bone scintigraphy is a helpful screening study; all cartilaginous lesions show increased uptake on the scan, although chondrosarcomas exhibit particularly high uptake. Biopsy is required for diagnosis and can also determine the tumor's grade (probability of metastasizing).
Low-grade chondrosarcomas (grade 1/2 or grade 1) are often treated intralesionally (wide curettage) with addition of an adjuvant (often freezing liquid nitrogen; argon beam; heat of methyl methacrylate; radiofrequency; or phenol). Other tumors are treated with total surgical resection. When surgical resection with maintenance of function is impossible, amputation may be necessary. Because of the potential to implant the tumor, meticulous care must be taken to avoid spillage of tumor cells into the soft tissues during biopsy or surgery. Recurrence is inevitable if tumor cells spill. If no spillage occurs, the cure rate depends on the tumor grade. Low-grade tumors are nearly all cured with adequate treatment. Because these tumors have limited vascularity, chemotherapy and radiation therapy have little efficacy.

**Ewing’s sarcoma of bone:** Ewing's sarcoma is a round-cell bone tumor with a peak incidence between 10 and 25 yr. Most develop in the extremities, but any bone may be involved. Ewing's sarcoma tends to be extensive, sometimes involving the entire bone shaft, most often the diaphyseal region. About 15 to 20% occur around the metaphyseal region. Pain and swelling are the most common symptoms. Lytic destruction, particularly a permeative infiltrating pattern without clear borders, is the most common finding on imaging, but multiple layers of subperiosteal reactive new bone formation may give an onion-skin appearance. X-rays do not usually reveal the full extent of bone involvement, and a large soft-tissue mass usually surrounds the affected bone. MRI better defines disease extent, which can help guide treatment. Many other benign and malignant tumors can appear very similar, so diagnosis is made by biopsy. At times this tumor may be confused with an infection. Accurate histologic diagnosis can be accomplished with molecular markers, including evaluation for a typical clonal chromosomal abnormality.

Treatment includes various combinations of surgery, chemotherapy, and radiation therapy. Currently, > 60% of patients with primary localized Ewing's sarcoma may be cured by this multimodal approach. Cure is sometimes possible even with metastatic disease. Chemotherapy in conjunction with surgical en bloc resection, if applicable, often yields better long-term results.

**Lymphoma of bone:** Lymphoma of bone (previously known as reticulum cell sarcoma) affects adults, usually in their 40s and 50s. It may arise in any bone. The tumor consists of small round cells, often with a mixture of reticulum cells, lymphoblasts, and lymphocytes. It can develop as an isolated primary bone tumor, in association with similar tumors in other tissues, or as a metastasis from known soft-tissue lymphomatous disease. Pain and swelling are the usual symptoms. Pathologic fracture is common. Imaging studies reveal bone destruction, which may be in a mottled or patchy or even infiltrating, permeative pattern, often with a clinical and radiographic large soft-tissue mass. In advanced disease, the entire outline of the affected bone may be lost.

In isolated primary bone lymphoma, the 5-yr survival rate is ≥ 50%. Combination radiation therapy and chemotherapy is as curative as amputation or other extensive ablative surgery. Stabilization of long bones is often necessary to prevent pathologic fracture. Amputation is indicated only rarely, when function is lost because of pathologic fracture or extensive soft-tissue involvement that cannot be managed otherwise.

**Malignant giant cell tumor:** Malignant giant cell tumor, which is rare, is usually located at the extreme end of a long bone. X-ray reveals classic features of malignant destruction (predominantly lytic destruction, cortical destruction, soft-tissue extension, and pathologic fracture). A malignant giant cell tumor that develops in a previously benign giant cell tumor is characteristically radioresistant. Treatment is similar to that of osteosarcoma, but the cure rate is low.

**Chordoma:** Chordoma, which is rare, develops from the remnants of the primitive notochord. It tends to occur at the ends of the spinal column, usually in the middle of the sacrum or near the base of the skull. A chordoma in the sacrococcygeal region causes nearly constant pain. A chordoma in the base of the skull can cause deficits in a cranial nerve, most commonly in nerves to the eye.

Symptoms may exist for months to several years before diagnosis. A chordoma appears on imaging studies as an expansile, destructive bone lesion that may be associated with a soft-tissue mass. Metastasis is unusual, but local recurrence is not. Chordomas in the sacrococcygeal region may be cured by radical en bloc excision. Chordomas in the base of the skull are usually inaccessible to surgery but may respond to radiation therapy.
Metastatic Bone Tumors

Any cancer may metastasize to bone, but metastases from carcinomas are the most common, particularly those arising in the following areas:

- Breast
- Lung
- Prostate
- Kidney
- Thyroid
- Colon

Prostate cancer in men and breast cancer in women are the most common types of cancers. Lung cancer is the most common cause of cancer death in both sexes. Breast cancer is the most common cancer to metastasize to bone. Any bone may be involved with metastases. Metastatic disease does not commonly spread to bone below the mid forearm or mid calf, but when it occurs in those sites, it results most often from lung or sometimes kidney cancer.

Symptoms and Signs

Metastases manifest as bone pain, although they may remain asymptomatic for some time. Bone metastases may cause symptoms before the primary tumor is suspected or may appear in patients with a known diagnosis of cancer.

Diagnosis

- X-ray
- Radionuclide scanning to identify all metastases
- Clinical evaluation and testing to diagnose the primary tumor (if unknown)
- Often biopsy if the primary tumor is unknown after assessment

Metastatic bone tumors are considered in all patients with unexplained bone pain, but particularly in patients who have

- Known cancer
- Pain at more than one site
- Findings on imaging studies that suggest metastases

Prostate cancer is most often blastic, lung cancer is most often lytic, and breast cancer may be blastic or lytic.

CT and MRI are highly sensitive for specific metastases. However, if metastases are suspected, a radionuclide whole-body scan, which is not quite as sensitive, is usually done. Bone scan is more sensitive for early and asymptomatic metastases than plain x-rays and can be used to scan the entire body. Lesions on the scan are usually presumed to be metastases if the patient has a known primary cancer. Metastases should be suspected in patients who have multiple lesions on bone scan. Although metastases are suspected in patients with known cancer and a single bone lesion, the lesion may not be
If bone metastases are suspected because multiple lytic lesions are found, assessment for the primary tumor can begin with clinical evaluation for primary cancers (particularly focused on the breast, prostate, and thyroid), chest x-ray, mammography, and measurement of prostate-specific antigen level. Initial CT of the chest, abdomen, and pelvis may also reveal the primary tumor. However, bone biopsy, especially fine-needle or core biopsy, is necessary if metastatic tumor is suspected and the primary tumor has not been otherwise diagnosed. Biopsy with use of immunohistologic stains may give clues to the primary tumor type.

Treatment

• Usually radiation therapy

• Surgery to stabilize bone at risk of pathologic fracture

• Kyphoplasty or vertebroplasty for certain painful vertebral fractures

Treatment depends on the type of tissue involved (which organ tissue type). Radiation therapy, combined with selected chemotherapeutic or hormonal drugs, is the most common treatment modality. Early use of radiation (30 Gy) and bisphosphonates (eg, zoledronate, pamidronate) slows bone destruction. Some tumors are more likely to heal after radiation therapy; for example, blastic lesions of prostate and breast cancer are more likely to heal than lytic destructive lesions of lung cancer and renal cell carcinoma.

If bone destruction is extensive, resulting in imminent or actual pathologic fracture, surgical fixation or resection and reconstruction may be required to provide stabilization and help minimize morbidity. When the primary cancer has been removed and only a single bone metastasis remains (especially if the metastatic lesion appears ≥ 1 yr after the primary tumor), en bloc excision sometimes combined with radiation therapy, chemotherapy, or both rarely may be curative. Insertion of methyl methacrylate into the spine (kyphoplasty or vertebroplasty) relieves pain and expands and stabilizes compression fractures that do not have epidural soft-tissue extension.

Other Bone Lesions

Many nonneoplastic conditions of bone may clinically or radiologically mimic solitary bone tumors.

Unicameral bone cyst: Simple unicameral bone cysts occur in the long bones starting distal to the epiphyseal plate in children. The cyst causes the cortex to thin and predisposes the area to a buckle-like pathologic fracture, which is usually how the cyst is recognized. Cysts < 5 cm may heal and may disappear as the fracture heals. Cysts > 5 cm, particularly in children, may require excision or curettage and bone grafting; however, many respond to injections of corticosteroids, demineralized bone matrix, or synthetic bone substitutes. The response may be variable and may require multiple injections. Regardless of treatment, cysts persist in about 10 to 15% of patients.

Fibrous dysplasia: Fibrous dysplasia involves abnormal bone development during childhood. It may affect one or several bones. Cutaneous pigmentation and endocrine abnormalities may be present (Albright's syndrome). The abnormal bone lesions of fibrous dysplasia commonly stop developing at puberty. They rarely undergo malignant degeneration. On x-ray, the lesions can appear cystic and may be extensive and deforming. Calcitonin may help relieve pain. Progressive deformities, fractures that do not heal with immobilization, or intractable pain may be effectively treated with orthopedic surgery.

Aneurysmal bone cyst: An aneurysmal bone cyst is an idiopathic expansile lesion that usually develops before age 25 yr. This cystic lesion usually occurs in the metaphyseal region of the long bones, but almost any bone may be affected. It tends to grow slowly. A periosteal new bone shell forms around the expansile lesion and is often wider than the original bone. Pain and swelling are common. The lesion may be present for a few weeks to a year before diagnosis. The appearance on x-ray is often characteristic: The rarefied area is usually well circumscribed and eccentric; the periosteum bulges, extending into the
soft tissues, and may be surrounded by new bone formation.

Surgical removal of the entire lesion is the most successful treatment; regression after incomplete removal sometimes occurs. Radiation should be avoided when possible because sarcomas occasionally develop. However, radiation may be the treatment of choice in completely surgically inaccessible vertebral lesions that are compressing the spinal cord.

**Joint Tumors**

Tumors rarely affect joints, unless by direct extension of an adjacent bone or soft-tissue tumor. However, 2 conditions—synovial chondromatosis and pigmented villonodular synovitis—occur in the lining (synovium) of joints. These conditions are benign but locally aggressive. Both usually affect one joint, most often the knee and second most often the hip, and can cause pain and effusion. Both are treated by synovectomy and removal of any intra-articular bodies.

**Synovial chondromatosis:** Synovial chondromatosis (previously called synovial osteochondromatosis) is considered metaplastic. It is characterized by numerous calcified cartilaginous bodies in the synovium, which often become loose. Each body may be no larger than a grain of rice, in a swollen, painful joint. Malignant change is very rare. Recurrence is common.

**Pigmented villonodular synovitis:** Pigmented villonodular synovitis is considered neoplastic. The synovium becomes thickened and contains hemosiderin, which gives the tissue its blood-stained appearance and characteristic appearance on MRI. This tissue tends to invade adjacent bone, causing cystic destruction and damage to the cartilage. Pigmented villonodular synovitis is usually monarticular but may be polyarticular. Late management, especially after recurrence, may require total joint replacement. On rare occasions after several synovectomies, radiation therapy can be used.
Chapter 46. Approach to the Patient With Ear Problems

Introduction

Earache, hearing loss, otorrhea, tinnitus, and vertigo are the principal symptoms of ear problems. Hearing loss is discussed in Ch. 47.

In addition to the ears, nose, nasopharynx, and paranasal sinuses, the teeth, tongue, tonsils, hypopharynx, larynx, salivary glands, and temporomandibular joint are examined; pain and discomfort may be referred from them to the ears. It is important to examine cranial nerve function (see pp. 1587 and 1745) and to perform tests of hearing (see p. 431) and of the vestibular apparatus. The patient is also examined for nystagmus (a rhythmic movement of the eyes—see Sidebar 46-1).

Testing

Patients with abnormal hearing on history or physical examination or with tinnitus or vertigo undergo an audiogram (see p. 433). Patients with nystagmus or altered vestibular function may benefit from computerized electrònystagmography (ENG), which quantifies spontaneous, gaze, or positional nystagmus that might not be visually detectable. Computerized ENG caloric testing quantifies the strength of response of the vestibular system to cool and warm irrigations in each ear, enabling the physician to discriminate unilateral weakness. Different components of the vestibular system can be tested by varying head and body position or by presenting visual stimuli.

Sidebar 46-1 Nystagmus

Nystagmus is a rhythmic movement of the eyes that can have various causes. Vestibular disorders can result in nystagmus because the vestibular system and the oculomotor nuclei are interconnected. The presence of vestibular nystagmus helps identify vestibular disorders and sometimes distinguishes central from peripheral vertigo. Vestibular nystagmus has a slow component caused by the vestibular input and a quick, corrective component that causes movement in the opposite direction. The direction of the nystagmus is defined by the direction of the quick component because it is easier to see. Nystagmus may be rotary, vertical, or horizontal and may occur spontaneously, with gaze, or with head motion.

Initial inspection for nystagmus is done with the patient lying supine with unfocused gaze (±30 diopter or Frenzel lenses can be used to prevent gaze fixation). The patient is then slowly rotated to a left and then to a right lateral position. The direction and duration of nystagmus are noted. If nystagmus is not detected, the Dix-Hallpike (or Barany) maneuver is done. In this maneuver, the patient sits erect on a stretcher so that when lying back, the head extends beyond the end. With support, the patient is rapidly lowered to horizontal, and the head is extended back 45° below horizontal and rotated 45° to the left. Direction and duration of nystagmus and development of vertigo are noted. The patient is returned to an upright position, and the maneuver is repeated with rotation to the right. Any position or maneuver that causes nystagmus should be repeated to see whether it fatigues.

Nystagmus secondary to peripheral nervous system disorders has a latency period of 3 to 10 sec and fatigues rapidly, whereas nystagmus secondary to CNS has no latency period and does not fatigue. During induced nystagmus, the patient is instructed to focus on an object. Nystagmus caused by peripheral disorders is inhibited by visual fixation. Because Frenzel lenses prevent visual fixation, they must be removed to assess visual fixation.

Nystagmus is a rhythmic movement of the eyes. It is caused by the vestibular system and the oculomotor nuclei. Vestibular nystagmus helps identify vestibular disorders and distinguishes central from peripheral vertigo. Nystagmus may be rotary, vertical, or horizontal and may occur spontaneously, with gaze, or with head motion.

Caloric stimulation of the ear canal induces nystagmus in a person with an intact vestibular system. Failure to induce nystagmus or > 20% difference in duration between sides suggests a lesion on the side of the decreased response. Quantification of caloric response is best done with formal (computerized) electrònystagmography.

Ability of the vestibular system to respond to peripheral stimulation can be assessed at the bedside. Care
should be taken not to irrigate an ear with a known tympanic membrane perforation or chronic infection. With the patient supine and the head elevated 30°, each ear is irrigated sequentially with 3 mL of ice water. Alternatively, 240 mL of warm water (40 to 44°C) may be used, taking care not to burn the patient with overly hot water. Cold water causes nystagmus to the opposite side; warm water causes nystagmus to the same side. A mnemonic device is COWS (Cold to the Opposite and Warm to the Same).

Primary imaging tests include CT of the temporal bone with or without radiopaque dye and gadolinium-enhanced MRI of the brain, with attention paid to the internal auditory canals to rule out an acoustic neuroma. These tests may be indicated in cases of trauma to the ear, head, or both; chronic infection; hearing loss; vertigo; facial paralysis; and otalgia of obscure origin.

Earache

(Otalgia)

Earache may occur in isolation or along with discharge or, rarely, hearing loss.

Pathophysiology

Pain may come from a process within the ear itself or may be referred to the ear from a nearby nonotologic disorder.

**Pain from the ear itself** may result from a pressure gradient between the middle ear and outside air, from local inflammation, or both. A middle ear pressure gradient usually involves eustachian tube obstruction, which inhibits equilibration between middle ear pressure and atmospheric pressure and also allows fluid to accumulate in the middle ear. Otitis media causes painful inflammation of the tympanic membrane (TM) as well as pain from increased middle ear pressure (causing bulging of the TM).

**Referred pain** can result from disorders in areas innervated by cranial nerves responsible for sensation in the external and middle ear (5th, 9th, and 10th). Specific areas include the nose, paranasal sinuses, nasopharynx, teeth, gingiva, temporomandibular joint (TMJ), mandible, parotid glands, tongue, palatine tonsils, pharynx, larynx, trachea, and esophagus. Disorders in these areas sometimes also obstruct the eustachian tube, causing pain from a middle ear pressure gradient.

Etiology

Earache results from otologic causes (involving the middle ear or external ear) or from nonotologic causes referred to the ear from nearby disease processes (see Table 46-1).

With **acute pain**, the most common causes are

- Middle ear infection
- External ear infection

With **chronic pain** (> 2 to 3 wk), the most common causes are

- TMJ dysfunction
- Chronic eustachian tube dysfunction
- Chronic otitis externa

Also with chronic pain, a tumor must be considered, particularly in elderly patients and if the pain is associated with ear drainage. People with diabetes or in other immunocompromised states may develop a particularly severe form of external otitis termed malignant or necrotizing external otitis. In this situation, if
abnormal soft tissue is found on examination of the ear canal, the tissue must be biopsied to rule out cancer.

TMJ dysfunction is a common cause of earache in patients with a normal ear examination.

**Evaluation**

**History:** History of present illness should assess the location, duration, and severity of pain and whether it is constant or intermittent. If intermittent, it is important to determine whether it is random or occurs mainly with swallowing or jaw movement. Important associated symptoms include ear drainage, hearing loss, and sore throat. The patient should be asked about any attempts at cleaning the ear canal (e.g., with cotton swab) or other recent instrumentation, foreign bodies, recent air travel or scuba diving, and swimming or other recurrent water exposure to ears.

**Review of systems** should ask about symptoms of chronic illness, such as weight loss and fevers.

**Past medical history** should ask about known diabetes or other immunocompromised state, previous ear disorders (particularly infections), and amount and duration of tobacco and alcohol use.

**Physical examination:** Vital signs should be checked for fever.

Examination focuses on the ears, nose, and throat.

The pinna and area over the mastoid process should be inspected for redness and swelling. The ear canal should be examined for redness, discharge, cerumen or foreign body, and any other lesions. The TM should be examined for redness, perforation, and signs of middle ear fluid collection (e.g., bulging, distortion, change in normal light reflex). A brief bedside test of hearing (see p. 431) should be conducted.

The throat should be examined for erythema, tonsillar exudate, peritonsillar swelling, and any mucosal lesions suggesting cancer.

TMJ function should be assessed by palpation of the joints on opening and closing of the mouth, and notation should be made of trismus or evidence of bruxism.

The neck should be palpated for lymphadenopathy. In-office fiberoptic examination of the pharynx and larynx should be considered, particularly if no cause for the pain is identified on routine examination and if nonotologic symptoms such as hoarseness, difficulty swallowing, or nasal obstruction are reported.

**Red flags:** The following findings are of particular concern:

- Diabetes or immunocompromised state
- Redness and fluctuance over mastoid and protrusion of auricle
- Severe swelling at external auditory canal meatus
- Chronic pain, especially if associated with other head/neck symptoms

**Interpretation of findings:** An important differentiator is whether the ear examination is normal; middle and external ear disorders cause abnormal physical findings, which, when combined with history, usually suggest an etiology (see Table 46-1). For example, those with chronic eustachian tube dysfunction have abnormalities of the TM, typically a retraction pocket.

Those with a normal ear examination may have a visible oropharyngeal cause, such as tonsillitis or peritonsillar abscess. Ear pain due to neuralgia has a classic manifestation as brief (usually seconds,
always < 2 min) episodes of extremely severe, sharp pain. Chronic ear pain without abnormality on ear examination might be due to a TMJ disorder, but patients should have a thorough head and neck examination (including fiberoptic examination) to rule out cancer.

**Testing:** Most cases are clear after history and physical examination. Depending on clinical findings, nonotologic causes may require testing (see Table 46-1). Those with a normal ear examination, particularly with chronic or recurrent pain, may warrant evaluation with an MRI to rule out cancer.

**Treatment**

Underlying disorders are treated.

Pain is treated with oral analgesics; usually an NSAID or acetaminophen is adequate, but sometimes a brief course of an oral opioid is necessary, particularly for cases of severe otitis externa. In cases of severe otitis externa, effective treatment requires suction of debris from the ear canal and insertion of a wick to allow for delivery of antibiotic ear drops to the infected tissue. Topical analgesics (eg, antipyrine-benzocaine combinations) are generally not very effective but can be used on a limited basis.

Patients should be instructed to avoid digging in their ears with any objects (no matter how soft the objects are or how careful the patient claims to be). Also, patients should not irrigate their ears unless instructed by a physician to do so, and then only gently. An oral irrigator should never be used to irrigate the ear.

**Key Points**

• Most cases are due to infection of the middle or external ear.

• History and physical examination are usually adequate for diagnosis.

• Nonotologic causes should be considered when ear examination is normal.

**Otorrhea**

Ear discharge (otorrhea) is drainage exiting the ear. It may be serous, serosanguineous, or purulent. Associated symptoms may include ear pain, fever, pruritus, vertigo, tinnitus, and hearing loss.

**Etiology**

Causes may originate from the ear canal, the middle ear, or the cranial vault. Certain causes tend to manifest acutely because of the severity of their symptoms or associated conditions. Others usually have a more indolent, chronic course but sometimes manifest acutely (see Table 46-2).

Overall, the most common causes are

• Acute otitis media with perforation

• Chronic otitis media (with a perforation of the eardrum, cholesteatoma, or both)

• Otitis externa

The most serious causes are necrotizing external otitis and cancer of the ear.

**Evaluation**

**History:** History of present illness should cover duration of symptoms and whether symptoms have been recurrent. Important associated symptoms include pain, itching, decreased hearing, vertigo, and tinnitus. Patients are questioned about activities that can affect the canal or tympanic membrane (TM...
—eg, swimming; insertion of objects, including cotton swabs; use of ear drops). Head trauma sufficient to cause a CSF leak is readily apparent.

**Review of systems** should seek symptoms of cranial nerve deficit and systemic symptoms suggesting Wegener's granulomatosis (eg, nasal discharge, cough, joint pains).

**Past medical history** should note any previous known ear disorders, ear surgery (particularly tympanostomy tube placement), and diabetes or immunodeficiency.

**Physical examination:** Examination begins with a review of vital signs for fever.

Ear and surrounding tissues (particularly the area over the mastoid) are inspected for erythema and edema. The pinna is pulled and the tragus is pushed gently to see whether pain is worsened. The ear canal is inspected with an otoscope; the character of discharge and presence of canal lesions, granulation tissue, or foreign body are noted. Edema and discharge may block visualization of all but the distal canal (irrigation should not be used in case there is a TM perforation), but when

[Table 46-2. Some Causes of Ear Discharge]

possible, the TM is inspected for inflammation, perforation, distortion, and signs of cholesteatoma (eg, canal debris, polypoid mass from TM).

When the ear canal is severely swollen at the meatus (eg, as with severe otitis externa) or there is copious drainage, careful suctioning can permit an adequate examination and also allow treatment (eg, application of drops, with or without a wick).

The cranial nerves are tested. The nasal mucosa is examined for raised, granular lesions, and the skin is inspected for vasculitic lesions, both of which may suggest Wegener's granulomatosis.

**Red flags:** The following findings are of particular concern:

- Recent major head trauma
- Any cranial nerve dysfunction (including sensorineural hearing loss)
- Fever
- Erythema of ear or periauricular tissue
- Diabetes or immunodeficiency

**Interpretation of findings:** Otoscopic examination can usually diagnose perforated TM, external otitis media, foreign body, or other uncomplicated sources of otorrhea. Some findings are highly suggestive (see Table 46-2). Other findings are less specific but indicate a more serious problem that involves more than a localized external ear or middle ear disorder:

- Vertigo and tinnitus (disorder of the inner ear)
- Cranial nerve deficits (disorder involving the skull base)
- Erythema and tenderness of ear, surrounding tissues, or both (significant infection)

**Testing:** Many cases are clear after clinical evaluation.

If CSF leakage is in question, discharge can be tested for glucose or β2-transferrin; these substances are present in CSF but not in other types of discharge.

Patients without an obvious etiology on examination require audiogram and CT of the temporal bone or
gadolinium-enhanced MRI. Biopsy should be considered when auditory canal granulation tissue is present.

**Treatment**

Treatment is directed at the cause. Most physicians do not treat a suspected CSF leak with antibiotics without a definitive diagnosis because drugs might mask the onset of meningitis.

**Key Points**

- Acute discharge in a patient without chronic ear problems or immunodeficiency is likely the result of otitis externa or perforated otitis media.
- Severe otitis externa may require specialty referral for more extensive cleaning and possible wick placement.
- Those with recurrent ear symptoms (diagnosed or undiagnosed), cranial nerve findings, or systemic symptoms should have specialty referral.

**Tinnitus**

Tinnitus is a noise in the ears. It is experienced by 10 to 15% of the population.

**Subjective tinnitus** is perception of sound in the absence of an acoustic stimulus and is heard only by the patient. Most tinnitus is subjective.

**Objective tinnitus** is uncommon and results from noise generated by structures near the ear. Sometimes the tinnitus is loud enough to be heard by the examiner.

**Characteristics:** Tinnitus may be described as buzzing, ringing, roaring, whistling, or hissing and is sometimes variable and complex. Objective tinnitus typically is pulsatile (synchronous with the heartbeat) or intermittent. Tinnitus is most noticeable in quiet environments and in the absence of distracting stimuli and, thus, frequently seems worse at bedtime.

Tinnitus may be intermittent or continuous. Continuous tinnitus is at best annoying and is often quite distressing. Some patients adapt to its presence better than others; depression occasionally results. Stress generally exacerbates tinnitus.

**Pathophysiology**

**Subjective tinnitus** is thought to be caused by abnormal neuronal activity in the auditory cortex. This activity results when input from the auditory pathway (cochlea, auditory nerve, brain stem nuclei, auditory cortex) is disrupted or altered in some manner. This disruption may cause loss of suppression of intrinsic cortical activity and perhaps creation of new neural connections. Some believe the phenomenon is similar to the development of phantom limb pain after amputation. Conductive hearing loss (eg, caused by cerumen impaction, otitis media, or eustachian tube dysfunction) may also be associated with subjective tinnitus, by altering sound input to the central auditory system.

**Objective tinnitus** represents actual noise generated by physiologic phenomena occurring near the middle ear. Usually the noise comes from blood vessels, either normal vessels in conditions of increased or turbulent flow (eg, caused by atherosclerosis) or abnormal vessels (eg, in tumors or vascular malformations). Sometimes muscle spasms or myoclonus of palatal muscles or muscles in the middle ear (stapedius, tensor tympani) cause clicking sounds.

**Etiology**

Causes may be considered by whether they cause subjective or objective tinnitus (see Table 46-3).
**Subjective tinnitus:** Subjective tinnitus may occur with almost any disorder affecting the auditory pathways.

The most common disorders are those that involve sensorineural hearing loss, particularly

- Acoustic trauma (noise-induced sensorineural hearing loss)
- Aging (presbycusis)
- Ototoxic drugs
- Meniere's disease

Infections and CNS lesions (eg, caused by tumor, stroke, multiple sclerosis) that affect auditory pathways also may be responsible.

Disorders causing conductive hearing loss also may cause tinnitus. These include obstruction of the ear canal by cerumen, a foreign body, or external otitis. Otitis media, barotrauma, eustachian tube dysfunction, and otosclerosis may also be associated with tinnitus.

Temporomandibular joint dysfunction may be associated with tinnitus in some patients.

**Objective tinnitus:** Objective tinnitus usually involves noise from vascular flow, which causes an audible pulsating sound synchronous with the pulse. Causes include

- Turbulent flow through the carotid artery or jugular vein
- Highly vascular middle ear tumors
- Dural arteriovenous malformations (AVMs)

Muscle spasms or myoclonus of palatal muscles or those of the middle ear (stapedius, tensor tympani) may cause perceptible noise, typically a rhythmic clicking. Such spasms may be idiopathic or caused by tumors, head trauma, and infectious or demyelinating diseases (eg, multiple sclerosis). Palatal myoclonus causes visible movement of the palate, tympanic membrane, or both that coincides with tinnitus.

**Evaluation**

**History:** History of present illness should note duration of tinnitus, whether it is in one or both ears, and whether it is a constant tone or intermittent. If intermittent, the clinician should determine whether it is regular and whether it is about the rate of the pulse or sporadic. Any exacerbating or relieving factors (eg, swallowing, head position) should be noted. Important associated symptoms include hearing loss, vertigo, ear pain, and ear discharge.

**Review of systems** should seek symptoms of possible causes, including diplopia and difficulty swallowing or speaking (lesions of the brain stem) and focal weakness and sensory changes (peripheral nervous system disorders). The impact of the tinnitus on the patient also should be assessed. Whether the tinnitus is sufficiently distressing to cause significant anxiety, depression, or sleeplessness should be noted.

**Past medical history** should ask about risk factors for tinnitus, including exposure to loud noise, sudden pressure change (from diving or air travel), history of ear or CNS infections or trauma, radiation therapy to the head, and recent major weight loss (risk of eustachian dysfunction). Drug use should be ascertained, particularly any salicylates, aminoglycosides, or loop diuretics.

**Physical examination:** Physical examination focuses on the ear and the nervous system.
The ear canal should be inspected for discharge, foreign body, and cerumen. The tympanic membrane should be inspected for signs of acute infection (eg, redness, bulging), chronic infection (eg, perforation, cholesteatoma), and tumor (red or bluish mass). A bedside hearing test should be done.

Cranial nerves, particularly vestibular function (see p. 423), are tested along with peripheral strength, sensation, and reflexes. A stethoscope is used to listen for vascular noise over the course of the carotid arteries and jugular veins and over and adjacent to the ear.

**Red flags:** The following findings are of particular concern:

- Bruit, particularly over the ear or skull
- Accompanying neurologic symptoms or signs (other than hearing loss)
- Unilateral tinnitus

**Interpretation of findings:** In some cases, tinnitus may indicate retrocochlear pathology, such as an acoustic neuroma (benign but invasive tumor originating from the vestibular portion of the 8th cranial nerve in the internal auditory canal).

It is important to note whether the tinnitus is unilateral because acoustic neuromas may manifest only with unilateral tinnitus. This diagnosis is more likely if there is also unilateral sensorineural hearing loss or asymmetric hearing loss with worse hearing in the ear with tinnitus.

It also is important to distinguish the uncommon cases of objective tinnitus from the more common cases of subjective tinnitus. Tinnitus that is pulsatile or intermittent is almost always objective (although not always detectable by the examiner), as is that associated with a bruit. Pulsatile tinnitus is nearly always benign. Continuous tinnitus is usually subjective (except perhaps for that caused by a venous hum, which may be identified by presence of a bruit and often by a change in tinnitus with head rotation or jugular vein compression).

Specific causes can often be suspected by findings on examination (see Table 46-3). In particular, exposure to loud noise, barotrauma, or certain drugs before onset suggests those factors as the cause.

**Testing:** All patients with significant tinnitus should be referred for comprehensive audiologic evaluation to determine the presence, degree, and type of hearing loss.

In patients with unilateral tinnitus and hearing loss, acoustic neuroma should be ruled out by gadolinium-enhanced MRI. In those with unilateral tinnitus and normal hearing and physical examination, MRI is not necessary unless tinnitus persists > 6 mo.

Other testing depends on patient presentation (see Table 46-3).

Those with visible evidence of a vascular tumor in the middle ear require CT, gadolinium-enhanced MRI, and referral to a subspecialist if the diagnosis is confirmed.

Those with pulsatile, objective tinnitus and no ear abnormalities on examination or audiology require further investigation of the vascular system (carotid, vertebral, and intracranial vessels). The usual test sequence is to begin with magnetic resonance angiography (MRA). However, because MRA is not very sensitive for dural AVMs, many clinicians then consider doing an arteriogram. However, because dural AVMs are rare, the significant risks of arteriography must be weighed against the potential benefit of diagnosis and treatment (with embolization) of this vascular anomaly.

**Treatment**

Treatment of the underlying disorder may lessen tinnitus. Correcting hearing loss (eg, with a hearing aid) relieves tinnitus in about 50% of patients.
Because stress and other mental factors (eg, depression) can exacerbate symptoms, efforts to recognize and treat these factors may help. Many patients are reassured by learning that their tinnitus does not represent a serious medical problem. Tinnitus also can be worsened by caffeine and other stimulants, so patients should try eliminating use of these substances.

Although no specific medical or surgical therapy is available, many patients find that background sound masks the tinnitus and may help them fall asleep. Some patients benefit from a tinnitus masker, a device worn like a hearing aid that provides a low-level sound that can cover up the tinnitus. Tinnitus retraining therapy, offered by programs that specialize in tinnitus treatment, are helpful for many patients. Electrical stimulation of the inner ear, as with a cochlear implant, occasionally reduces the tinnitus but is appropriate only for patients who are profoundly deaf.

Geriatrics Essentials

One out of 4 people > 65 yr have significant hearing impairment. Because tinnitus is common in people with sensorineural hearing loss, tinnitus is a common complaint among the elderly.

Key Points

• Subjective tinnitus is caused by an abnormality somewhere in the auditory pathway.

• Objective tinnitus is caused by an actual noise produced in a vascular structure near the ear.

• Loud noise, aging, Meniere's disease, and drugs are the most common causes of subjective tinnitus.

• Unilateral tinnitus with hearing loss or dizziness/dysequilibrium warrants gadolinium-enhanced MRI to rule out acoustic neuroma.

• Any tinnitus accompanied by a neurologic deficit is of concern.

Dizziness and Vertigo

Dizziness is an imprecise term patients often use to describe various related sensations, including

• Faintness (a feeling of impending syncope)

• Light-headedness

• Feeling of imbalance or unsteadiness

• A vague spaced-out or swimmy-headed feeling

Vertigo is a false sensation of movement of the self or the environment. Usually the perceived movement is rotary—a spinning or wheeling sensation—but some patients simply feel pulled to one side. Vertigo is not a diagnosis—it is a description of a sensation.

Both sensations may be accompanied by nausea and vomiting or difficulty with balance, gait, or both.

Perhaps because these sensations are hard to describe in words, patients often use "dizziness," "vertigo," and other terms interchangeably and inconsistently. Different patients with the same underlying disorder may describe their symptoms very differently. A patient may even give different descriptions of the same "dizzy" event during a given visit depending on how the question is asked. Because of this discrepancy, even though vertigo seems to be a clearly delineated subset of dizziness, many clinicians prefer to consider the two symptoms together.

[Table 46-3. Some Causes of Tinnitus]
However they are described, dizziness and vertigo may be disturbing and even incapacitating, particularly when accompanied by nausea and vomiting. Symptoms cause particular problems for people doing an exacting or dangerous task, such as driving, flying, or operating heavy machinery.

Dizziness accounts for about 5 to 6% of physician visits. It may occur at any age but becomes more common with increasing age; it affects about 40% of people over 40 yr at some time. Dizziness may be temporary or chronic. Chronic dizziness, defined as lasting > 1 mo, is more common among elderly people.

Pathophysiology

The vestibular system is the main neurologic system involved in balance. This system includes

• The vestibular apparatus of the inner ear

• The 8th (vestibulocochlear) cranial nerve, which conducts signals from the vestibular apparatus to the central components of the system

• The vestibular nuclei in the brain stem and cerebellum

Disorders of the inner ear and 8th cranial nerve are considered peripheral disorders. Those of the vestibular nuclei and their pathways in the brain stem and cerebellum are considered central disorders.

The sense of balance also incorporates visual input from the eyes and proprioceptive input from the peripheral nerves (via the spinal cord). The cerebral cortex receives output from the lower centers and integrates the information to produce the perception of motion.

Vestibular apparatus: Perception of stability, motion, and orientation to gravity originates in the vestibular apparatus, which consists of

• The 3 semicircular canals

• The 2 otolith organs—the saccule and utricle

Rotary motion causes flow of endolymph in the semicircular canal oriented in the plane of motion. Depending on the direction of flow, endolymph movement either stimulates or inhibits neuronal output from hair cells lining the canal. Similar hair cells in the saccule and utricle are embedded in a matrix of Ca carbonate crystals (otoliths). Deflection of the otoliths by gravity stimulates or inhibits neuronal output from the attached hair cells.

Etiology

There are numerous structural (trauma, tumors, degenerative), vascular, infectious, toxic (including drug-related), and idiopathic causes (see Table 46-4), but only about 5% of cases are caused by a serious disorder.

[Table 46-4. Some Causes of Dizziness and Vertigo]

The most common causes of dizziness with vertigo involve some component of the peripheral vestibular system:

• Benign positional vertigo

• Meniere's disease

• Vestibular neuronitis

• Labyrinthitis
Less often, the cause is a central vestibular disorder (most commonly migraine), a disorder with a more global effect on cerebral function, a psychiatric disorder, or a disorder affecting visual or proprioceptive input. Sometimes, no cause can be found.

The most common causes of dizziness without vertigo are less clear cut, but they are usually not otologic and probably are

- Drug effects
- Multifactorial or idiopathic

Nonneurologic disorders with a more global effect on cerebral function sometimes manifest as dizziness and rarely as vertigo. These disorders typically involve inadequate substrate (eg, O₂, glucose) delivery caused by hypotension, hypoxemia, anemia, or hypoglycemia; when severe, some of these disorders may manifest as syncope. Additionally, certain hormonal changes (eg, as with thyroid disease, menstruation, pregnancy) can cause dizziness. Numerous CNS-active drugs can cause dizziness independent of any toxic effect on the vestibular system.

Occasionally, dizziness and vertigo may be psychogenic. Patients with panic disorder, hyperventilation syndrome, anxiety, or depression may present with complaints of dizziness.

In elderly patients, dizziness is often multifactorial secondary to drug adverse effects and age-diminished visual, vestibular, and proprioceptive abilities. Two of the most common specific causes are disorders of the inner ear: benign paroxysmal positional vertigo and Meniere's disease.

**Evaluation**

**History:** History of present illness should cover the sensations felt; an open-ended question is best (eg, "Different people use the word 'dizziness' differently. Can you please describe as thoroughly as you can what you feel?"). Brief, specific questioning as to whether the feeling is faintness, light-headedness, loss of balance, or vertiginous may bring some clarity, but persistent efforts to categorize a patient's sensations are unnecessary. Other elements are more valuable and clear-cut:

- Severity of initial episode
- Severity and characteristics of subsequent episodes
- Symptoms continuous or episodic
- If episodic, frequency and duration
- Triggers and relievers (ie, triggered by head/body position change)
- Associated aural symptoms (eg, hearing loss, ear fullness, tinnitus)
- Severity and related disability

Is the patient having a single, sudden, acute event, or has dizziness been chronic and recurrent? Was the first episode the most severe (vestibular crisis)? How long do episodes last, and what seems to trigger and worsen them? The patient should be asked specifically about movement of the head, arising, being in anxious or stressful situations, and menses. Important associated symptoms include headache, hearing loss, tinnitus, nausea and vomiting, impaired vision, focal weakness, and difficulty walking. The severity of impact on the patient's life should be estimated: Has the patient fallen? Is the patient reluctant to drive or leave the house? Has the patient missed work days?

**Review of systems** should seek symptoms of causative disorders, including URI symptoms (inner ear disorders); chest pain, palpitations, or both (heart disease); dyspnea (lung disease); dark stools (anemia
caused by GI blood loss); and weight change or heat or cold intolerance (thyroid disease).

**Past medical history** should note presence of recent head trauma (usually obvious), migraine, diabetes, heart or lung disease, and drug and alcohol abuse. In addition to identifying all current drugs, drug history should assess recent changes in drugs, doses, or both.

**Physical examination:** Examination begins with a review of vital signs, including presence of fever, rapid or irregular pulse, and supine and standing BP, noting any drop in BP on standing up (orthostatic hypotension) and whether standing provokes symptoms. If standing does provoke symptoms, postural symptoms should be distinguished from those triggered by head movement by returning the patient supine until symptoms dissipate and then rotating the head.

The ENT and neurologic examinations are fundamental. Specifically, with the patient supine, the eyes are checked for presence, direction, and duration of spontaneous nystagmus (for full description of examination for nystagmus, see **Sidebar 46-1**). Direction and duration of nystagmus and development of vertigo are noted.

A gross bedside hearing test is done, the ear canal is inspected for discharge and foreign body, and the tympanic membrane is checked for signs of infection or perforation.

Cerebellar function is tested by assessing gait and doing a finger-nose test and Romberg's test. The remainder of the neurologic examination is done, including testing the rest of the cranial nerves.

**Red flags:** The following findings are of particular concern:

- Head or neck pain
- Ataxia
- Loss of consciousness
- Focal neurologic deficit

**Interpretation of findings:** Traditionally, differential diagnosis has been based on the exact nature of the chief complaint (ie, distinguishing dizziness from light-headedness from vertigo). However, the inconsistency of patients’ descriptions and the poor specificity of symptoms make this unreliable. A better approach places more weight on the onset and timing of symptoms, the triggers, and associated symptoms and findings, particularly otologic and neurologic ones.

Some constellations of findings are highly suggestive (see **Table 46-4**), particularly those that help differentiate peripheral from central vestibular disorders.

- Peripheral: Ear symptoms (eg, tinnitus, fullness, hearing loss) usually indicate a peripheral disorder. They are typically associated with vertigo and not generalized dizziness (unless caused by uncompensated peripheral vestibular weakness). Symptoms are usually paroxysmal, severe, and episodic; continuous dizziness is rarely due to peripheral vertigo. Loss of consciousness is not associated with dizziness due to peripheral vestibular pathology.

- Central: Ear symptoms are rarely present, but gait/balance disturbance is common. Nystagmus is not inhibited by visual fixation.

**Testing:** Patients with a sudden, ongoing attack should have pulse oximetry and finger-stick glucose test. Women should have a pregnancy test. Most clinicians also do an ECG. Other tests are done based on findings (see **Table 46-4**), but generally gadolinium-enhanced MRI is indicated for patients with acute symptoms who have headache, neurologic abnormalities, or any other findings suggestive of a CNS etiology.

Patients with chronic symptoms should have gadolinium-enhanced MRI to look for evidence of stroke,
Patients for whom results of bedside tests of hearing and vestibular function are abnormal or equivocal should undergo formal testing with audiometry and electronystagmography.

Laboratory tests are rarely helpful, except for patients with chronic vertigo and bilateral hearing loss, for whom syphilis serology is indicated.

**Treatment**

Treatment is directed at the cause, including stopping, reducing, or switching any causative drugs. If a vestibular disorder is present and thought to be secondary to active Meniere’s disease or vestibular neuronitis or labyrinthitis, the most effective vestibular nerve suppressants are diazepam (2 to 5 mg po q 6 to 8 h, with higher doses given under supervision for severe vertigo) or oral antihistamine/anticholinergic drugs (eg, meclizine 25 to 50 mg tid). All of these drugs can cause drowsiness, thereby limiting their use for certain patients. Nausea can be treated with prochlorperazine 10 mg IM qid or 25 mg rectally bid. Vertigo associated with benign paroxysmal positional vertigo is treated with the Epley maneuver (otolith repositioning) done by an experienced practitioner (see Fig. 48-1 on p. 443). Meniere’s disease is best managed by an otolaryngologist with training in management of this chronic disorder, but initial management consists of a low-salt diet and a K-sparing diuretic.

Patients with persistent or recurrent vertigo secondary to unilateral vestibular weakness (such as secondary to vestibular neuronitis) usually benefit from vestibular rehabilitation therapy done by an experienced physical therapist. Most patients compensate well, although some, especially the elderly, have more difficulty. Physical therapy can also provide important safety information for elderly or particularly disabled patients.

**Geriatrics Essentials**

As people age, organs involved in balance function less well. For example, seeing in dim light becomes more difficult, inner ear structures deteriorate, proprioception becomes less sensitive, and mechanisms that control BP become less responsive (eg, to postural changes, postprandial demands). Older people also are more likely to have cardiac or cerebrovascular disorders that can contribute to dizziness. They also are more likely to be taking drugs that can cause dizziness, including those for hypertension, angina, heart failure, seizures, and anxiety, as well as certain antibiotics, antihistamines, and sleep aids. Thus, dizziness in elderly patients usually has more than one cause.

Although unpleasant at any age, the consequences of dizziness and vertigo are a particular problem for elderly patients. Those with frailty are at significant risk of falling with consequent fractures; their fear of moving and falling often significantly decreases their ability to do daily activities.

In addition to treatment of specific causes, elderly patients with dizziness or vertigo may benefit from physical therapy and exercises to strengthen muscles and help maintain independent ambulation as long as possible.

**Key Points**

- Vague or inconsistently described symptoms may still be associated with a serious condition.

- Cerebrovascular disease and drug effects should be sought, particularly in elderly patients.

- Peripheral vestibular system disorders should be differentiated from central vestibular system disorders.

- Immediate neuroimaging should be done when symptoms are accompanied by headache, focal neurologic abnormalities, or both.
Chapter 47. Hearing Loss

Introduction

Nearly 10% of people in the US have some degree of hearing loss. About 1/800 to 1/1000 neonates are born with severe to profound hearing loss. Two to 3 times as many are born with lesser hearing loss. During childhood, another 2 to 3/1000 children acquire moderate to severe hearing loss. Adolescents are at risk from excessive exposure to noise, head trauma, or both. Older adults typically experience a progressive decrease in hearing (presbycusis—see p. 438), which is probably related to aging and noise exposure.

Hearing deficits in early childhood can result in lifelong impairments in receptive and expressive language skills. The severity of the handicap is determined by the age at which the hearing loss occurred; the nature of the loss (its duration, the frequencies affected, and the degree); and the susceptibilities of the individual child (eg, coexisting visual impairment, intellectual disability, primary language deficits, inadequate linguistic environment). Children who have other sensory, linguistic, or cognitive deficiencies are affected most severely.

Pathophysiology

Hearing loss can be classified as conductive, sensorineural, or both (mixed loss).

Conductive hearing loss occurs secondary to lesions in the external auditory canal, tympanic membrane (TM), or middle ear. These lesions prevent sound from being effectively conducted to the inner ear.

Sensorineural hearing loss is caused by lesions of either the inner ear (sensory) or the auditory (8th) nerve (neural—see Table 47-1). This distinction is important because sensory hearing loss is sometimes reversible and is seldom life threatening. A neural hearing loss is rarely recoverable and may be due to a potentially life-threatening brain tumor—commonly a cerebellopontine angle tumor.

Mixed loss may be caused by severe head injury with or without fracture of the skull or temporal bone, by chronic infection, or by one of many genetic disorders. It may also occur when a transient conductive hearing loss, commonly due to otitis media, is superimposed on a sensorineural hearing loss.

Etiology

Hearing loss can be congenital (see Table 47-2) or acquired (see Table 47-3), progressive or sudden (see also p. 438), temporary or permanent, unilateral or bilateral, and mild or profound. Drug-induced ototoxicity is discussed elsewhere (see p. 443).

The most common causes overall are the following:

• Cerumen accumulation

• Noise

• Aging

• Infections (particularly among children and young adults)

Cerumen (earwax) accumulation is the most common cause of treatable hearing loss, especially in the
elderly. Foreign bodies obstructing the canal are sometimes a problem in children, both because of their presence and because of any damage inadvertently caused during their removal.

**Noise** can cause sudden or gradual sensorineural hearing loss. In acoustic trauma, hearing loss results from exposure to a single, extreme noise (eg, a nearby gunshot or explosion); some patients have tinnitus as well. The loss is usually temporary (unless there is also blast damage, which may destroy the TM, ossicles, or both). In noise-induced hearing loss, the loss develops over time because of chronic exposure to noise > 85 decibels (dB—see Sidebar 47-1 on p. 434). Although people vary somewhat in susceptibility to noise-induced hearing loss, nearly everyone loses some hearing if they are exposed to sufficiently intense noise for an adequate time. Repeated exposure to loud noise ultimately results in loss of hair cells in the organ of Corti. Hearing loss typically occurs first at 4 kHz and gradually spreads to the lower and higher frequencies as exposure continues. In contrast to most other causes of sensorineural hearing losses, noise-induced hearing loss may be less severe at 8 kHz than at 4 kHz.

**Table 47-2. Congenital Causes of Hearing Loss**

- **Acute otitis media** (AOM—see p. 448) is a common cause of transient mild to moderate hearing loss (mainly in children). However, without treatment, AOM sequelae and chronic otitis media (and the rarer purulent labyrinthitis) can cause permanent loss, particularly if a cholesteatoma forms.

- **Secretory otitis media** (SOM—see p. 450) occurs in several ways. Almost all episodes of AOM are followed by a period of 2 to 4 wk of SOM. SOM can also be caused by eustachian tube dysfunction (eg, resulting from cleft palate, benign or malignant tumors of the nasopharynx, or rapid changes in external air pressure as occur during descent from high altitudes or rapid ascent while scuba diving).

- **Autoimmune disorders** can cause sensorineural hearing loss at all ages and can cause other symptoms and signs as well.

**Evaluation**

Evaluation consists of detecting and quantifying hearing loss and determining etiology (particularly reversible causes).

**Screening:** Most adults and older children notice a sudden hearing loss, and caregivers may suspect that a neonate has a severe hearing loss within the first week of life when the neonate does not respond to voices or other sounds. However, progressive losses and nearly all losses in infants and young children must be detected by screening. Screening should begin at birth (see p. 2717) so that linguistic input can allow optimal language development. Suspected hearing loss at any time should prompt referral to a specialist. If screening is not done, severe bilateral losses may not be recognized until age 2 yr, and mild to moderate or severe unilateral losses are often not recognized until children reach school age.

**History:** History of present illness should note how long hearing loss has been perceived, how it began (eg, gradual, acute), whether it is unilateral or bilateral, and whether sound is distorted (eg, music is off—dull or lifeless) or there is difficulty with speech discrimination. The patient should be asked whether the loss followed any acute event (eg, head injury, barotrauma [particularly a diving injury], starting of a drug). Important accompanying symptoms include other otologic symptoms (eg, ear pain, tinnitus, ear discharge), vestibular symptoms (eg, disorientation in the dark, vertigo), and other neurologic symptoms (eg, headache, weakness or asymmetry of the face, an abnormal sense of taste, fullness of the ear). In children, important associated symptoms include presence of delays in speech or language development and delayed motor development.

**Review of systems** should seek to determine the impact of hearing difficulty on the patient's life.

**Past medical history** should note previous possibly causative disorders, including CNS infection, repeated ear infections, chronic exposure to loud noise, head trauma, rheumatic disorders (eg, RA, lupus), and a family history of hearing loss. Drug history should specifically query current or previous use of ototoxic drugs (see Table 47-3).
**Physical examination:** The focus is examination of the ears and hearing and the neurologic examination. The external ear is inspected for obstruction, infection, congenital malformations, and other lesions. The TM is examined for perforation, drainage, otitis media, and cholesteatoma. During the neurologic examination, particular attention needs to be paid to the 2nd through 7th cranial nerves as well as to vestibular and cerebellar function because abnormalities in these areas often occur with tumors of the brain stem and cerebellopontine angle. Weber's test and the Rinne test require a tuning fork to differentiate conductive from sensorineural hearing loss.

In **Weber's test**, the stem of a vibrating 512-Hz or 1024-Hz tuning fork is placed on the midline of the head, and the patient indicates in which ear the tone is louder. In unilateral conductive hearing loss, the tone is louder in the ear with hearing loss. In unilateral sensorineural hearing loss, the tone is louder in the normal ear because the tuning fork stimulates both inner ears equally and the patient perceives the stimulus with the unaffected ear.

In the **Rinne test**, hearing by bone and by air conduction is compared. Bone conduction bypasses the external and middle ear and tests the integrity of the inner ear, 8th cranial nerve, and central auditory pathways. The stem of a vibrating tuning fork is held against the mastoid (for bone conduction); as soon as the sound is no longer perceived, the fork is removed from the mastoid, and the still-vibrating tines are held close to the pinna (for air conduction). Normally, the fork can once more be heard, indicating that air conduction is better than bone conduction. With conductive hearing loss, the relationship is reversed; bone conduction is louder than air conduction. With sensorineural hearing loss, both air and bone conduction are reduced, but air conduction remains louder.

**Red flags:** Findings of particular concern are

- Unilateral sensorineural hearing loss
- Abnormalities of cranial nerves (other than hearing loss)

**Interpretation of findings:** Many causes of hearing loss (eg, cerumen, injury, significant noise exposure, infectious sequelae, drugs) are readily apparent based on results of the examination (see Table 47-3).

Associated findings are helpful in diagnosing the remaining small number of patients in whom no clear cause can be found. Those who have focal neurologic abnormalities are of particular concern. The 5th or 7th cranial nerve or both are often affected by tumors that involve the 8th nerve, so loss of facial sensation and weak jaw clench (5th) and hemifacial weakness and taste abnormalities (7th) point to a lesion in that area. Signs of autoimmune disorders, maxillofacial malformations, and renal dysfunction may suggest these disorders as a cause.

Any child with delays in speech or language development or difficulty in school should be evaluated for hearing loss. Intellectual disability, aphasia, and autism must also be considered. Delayed motor development may signal vestibular deficit, which is often associated with a sensorineural hearing loss.

**Testing:** Testing includes

- Audiologic tests
- Sometimes MRI or CT

**Audiologic tests** are required for all people who have hearing loss; these tests usually include

- Measurement of pure-tone thresholds with air and bone conduction
- Speech reception threshold
• Speech discrimination
• Tympanometry
• Acoustic reflex testing

Information gained from these tests helps determine whether more definitive differentiation of sensory from neural hearing loss is needed.

Pure-tone audiometry quantifies hearing loss. An audiometer delivers sounds of specific frequencies (pure tones) at different intensities to determine the patient's hearing threshold (how loud a sound must be to be perceived) for each frequency. Hearing in each ear is tested from 125 or 250 to 8000 Hz by air conduction (using earphones) and up to 4 kHz by bone conduction (using an oscillator in contact with the mastoid process or forehead). Test results are plotted on graphs called audiograms (see Fig. 47-1), which show the difference between the patient's hearing threshold and normal hearing at each frequency. The difference is measured in dB (see Sidebar 47-1). The normal threshold is considered 0 dB hearing level (HL); hearing loss is considered present if the patient's threshold is > 25 dB HL. When hearing loss is such as to require loud test tones, intense tones presented to one ear may be heard in the other ear. In such cases, a masking sound, usually narrow band noise, is presented to the ear not being tested to isolate it.

Speech audiometry includes the speech reception threshold (SRT) and the word recognition score. The SRT is a measure of the intensity at which speech is recognized. To determine the SRT, the examiner presents the patient with a list of words at specific sound intensities. These words usually have 2 equally accented syllables (spondees), such as railroad, staircase, and baseball. The examiner notes the intensity at which the patient repeats 50% of the words correctly. The SRT approximates the average hearing level at speech frequencies (eg, 500 Hz, 1000 Hz, 2000 Hz).

Sidebar 47-1 Sound Levels

Sound intensity and pressure (the physical correlates of loudness) are measured in decibels (dB). A dB is a unitless figure that compares 2 values and is defined as the logarithm of the ratio of a measured value to a reference value, multiplied by a constant:

\[ dB = k \log \left( \frac{V_{\text{measured}}}{V_{\text{ref}}} \right) \]

By convention, the reference value for sound pressure level (SPL) is taken as the quietest 1000-Hz sound detectable by young, healthy human ears. The sound may be measured in terms of pressure (N/m²) or intensity (watts/m²).

Because sound intensity equals the square of sound pressure, the constant (k) for SPL is 20; for sound intensity, 10. Thus, each 20-dB increase represents a 10-fold increase in SPL but a 100-fold increase in sound intensity.

The dB values in the table below give only a rough idea of the risk of hearing loss. Some of them are dB SPL values (referenced to N/m²), whereas others represent peak dB or dB on the A-scale (a scale that emphasizes the frequencies that are most hazardous to human hearing).

<table>
<thead>
<tr>
<th>Decibels</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Faintest sound heard by human ear</td>
</tr>
<tr>
<td>30</td>
<td>Whisper, quiet library</td>
</tr>
<tr>
<td>60</td>
<td>Normal conversation, sewing machine, typewriter</td>
</tr>
<tr>
<td>90</td>
<td>Lawnmower, shop tools, truck traffic (8 h/day is the maximum exposure without protection)</td>
</tr>
<tr>
<td>100</td>
<td>Chain saw, pneumatic drill, snowmobile (2 h/day is the maximum exposure without protection)</td>
</tr>
</tbody>
</table>
115  Sandblasting, loud rock concert, automobile horn (15 min/day is the maximum exposure without protection)
140  Gun muzzle blast, jet engine (noise causes pain and even brief exposure injures unprotected ears; injury may occur even with hearing protectors)
180  Rocket launching pad

*In audiometric testing, because human ears respond differently at different frequencies, the reference value changes for each frequency tested. Threshold values reported on audiograms take this into account; the normal threshold is always 0 dB, regardless of the actual SPL.

†Mandatory federal standard, but protection is recommended for more than brief exposure to sound levels > 85 dB.

The word recognition score tests the ability to discriminate among the various speech sounds or phonemes. It is determined by presenting 50 phonetically balanced one-syllable words at an intensity of 35 to 40 dB above the patient's SRT. The word list contains phonemes in the same relative frequency found in conversational English. The score is the percentage of words correctly repeated by the patient and reflects the ability to understand speech.

[Fig. 47-1. Audiogram of right ear in a patient with normal hearing.]

under optimal listening conditions. A normal score ranges from 90 to 100%. The word recognition score is normal with conductive hearing loss, albeit at a higher intensity level, but can be reduced at all intensity levels with sensorineural hearing loss. Discrimination is even poorer in neural than in sensory hearing loss.

Tympanometry measures the impedance of the middle ear to acoustic energy and does not require patient participation. It is commonly used to screen children for middle ear effusions. A probe containing a sound source, microphone, and air pressure regulator is placed snugly with an airtight seal into the ear canal. The probe microphone records the reflected sound from the TM while pressure in the canal is varied. Normally, maximal compliance of the middle ear occurs when the pressure in the ear canal equals atmospheric pressure. Abnormal compliance patterns suggest specific anatomic disruptions. In eustachian tube obstruction and middle ear effusion, maximal compliance occurs with a negative pressure in the ear canal. When the ossicular chain is disrupted, as in necrosis or dislocation of the long process of the incus, the middle ear is excessively compliant. When the ossicular chain is fixed, as in stapedial ankylosis in otosclerosis, compliance may be normal or reduced.

The acoustic reflex is contraction of the stapedius muscle in response to loud sounds, which changes the compliance of the TM, protecting the middle ear from acoustic trauma. The reflex is tested by presenting a tone and measuring what intensity provokes a change in middle ear impedance as noted by movement of the TM. An absent reflex could indicate middle ear disease or a tumor of the auditory nerve.

Advanced testing is sometimes needed. Gadolinium-enhanced MRI of the head to detect lesions of the cerebellopontine angle may be needed in patients with an abnormal neurologic examination or those whose audiologic testing shows poor word recognition, asymmetric sensorineural hearing loss, or a combination when the etiology is not clear.

CT is done if bony tumors or bony erosion is suspected. Magnetic resonance angiography is done if vascular abnormalities such as glomus tumors are suspected.

The auditory brain stem response uses surface electrodes to monitor brain wave response to acoustic stimulation in people who cannot otherwise respond.

Electrocochleography measures the activity of the cochlea and the auditory nerve with an electrode placed on or through the eardrum. It can be used to assess and monitor patients with dizziness, can be used in patients who are awake, and is useful in intraoperative monitoring.
Otoacoustic emissions testing measures sounds produced by outer hair cells of the cochlea in response to a sound stimulus usually placed in the ear canal. It is used to screen neonates and infants for hearing loss and to monitor the hearing of patients who are using ototoxic drugs (eg, gentamicin, cisplatin).

Certain patients, such as children with a reading or other learning problem and elderly people who seem to hear but do not comprehend, should undergo a central auditory evaluation. It measures discrimination of degraded or distorted speech, discrimination in the presence of a competing message in the opposite ear, the ability to fuse incomplete or partial messages delivered to each ear into a meaningful message, and the capacity to localize sound in space when acoustic stimuli are delivered simultaneously to both ears.

**Treatment**

The causes of a hearing loss should be determined and treated. Ototoxic drugs should be stopped or the dose should be lowered unless the severity of the disease being treated (usually cancer or a severe infection) requires that the risk of additional ototoxic hearing loss be accepted. Attention to peak and trough drug levels may help minimize risk.

Fluid from middle ear effusion can be drained by myringotomy and prevented with the insertion of a tympanostomy tube. Benign growths (eg, enlarged adenoids, nasal polyps) and malignant tumors (eg, nasopharyngeal cancers, sinus cancers) blocking the eustachian tube or ear canal can be removed. Hearing loss caused by autoimmune disorders may respond to corticosteroids.

Damage to the TM or ossicles or otosclerosis may require reconstructive surgery. Brain tumors causing hearing loss may in some cases be removed and hearing preserved.

Many causes of hearing loss have no cure, and treatment involves compensating for the hearing loss with hearing aids and, for severe to profound loss, a cochlear implant. In addition, various coping mechanisms may help.

**Hearing aids:** Amplification of sound with a hearing aid helps many people. Although hearing aids do not restore hearing to normal, they can significantly improve communication. Physicians should encourage hearing aid use and help patients overcome a sense of social stigma that continues to obstruct use of these devices, perhaps by making the analogy that a hearing aid is to hearing as eye glasses are to seeing.

All hearing aids have a microphone, amplifier, speaker, earpiece, and volume control, although they differ in the location of these components. An audiologist should be involved in selection and fitting of a hearing aid.

The best models are adjusted to a person's particular pattern of hearing loss. People with mainly high-frequency hearing loss do not benefit from simple amplification, which merely makes the garbled speech they hear sound louder. They usually need a hearing aid that selectively amplifies the high frequencies. Some hearing aids contain vents in the ear mold, which facilitate the passage of high-frequency sound waves. Some use digital sound processing with multiple frequency channels so that amplification more precisely matches hearing loss as measured on the audiogram.

Telephone use can be difficult for people with hearing aids. Typical hearing aids cause squealing when the ear is placed next to the phone handle. Some hearing aids have a phone coil with a switch that turns the microphone off and links the phone coil electromagnetically to the speaker magnet in the phone.

For moderate to severe hearing loss, a postauricular (ear-level) aid, which fits behind the pinna and is coupled to the ear mold with flexible tubing, is appropriate. An in-the-ear aid is contained entirely within the ear mold and fits less conspicuously into the concha and ear canal; it is appropriate for mild to moderate hearing loss. Some people with mild hearing loss limited to high frequencies are most comfortably fitted with postauricular aids and completely open ear canals. Canal aids are contained entirely within the ear canal and are cosmetically acceptable to many people who would otherwise refuse
to use a hearing aid, but they are difficult for some people (especially the elderly) to manipulate. The CROS aid (contralateral routing of signals) is occasionally used for severe unilateral hearing loss; a hearing-aid microphone is placed in the nonfunctioning ear, and sound is routed to the functioning ear through a wire or radio transmitter. This device enables the wearer to hear sounds from the nonfunctioning side, allowing for some limited capacity to localize sound. If the better ear also has some hearing loss, the sound from both sides can be amplified with the binaural CROS (BiCROS) aid. The body aid type is appropriate for profound hearing loss. It is worn in a shirt pocket or a body harness and connected by a wire to the earpiece (the receiver), which is coupled to the ear canal by a plastic insert (ear mold).

A bone conduction aid may be used when an ear mold or tube cannot be used, as in atresia of the ear canal or persistent otorrhea. An oscillator is held against the head, usually over the mastoid, with a spring band, and sound is conducted through the skull to the cochlea. Bone conduction hearing aids require more power, introduce more distortion, and are less comfortable to wear than air conduction hearing aids. Some bone conduction aids (bone-anchored hearing aids or BAHAs) are surgically implanted in the mastoid process, avoiding the discomfort and prominence of the spring band.

Cochlear implants: Profoundly deaf patients, including those with some hearing but who even with a hearing aid cannot understand speech without the assistance of vision (lip-reading or speech-reading), may benefit from a cochlear implant. This device provides electrical signals directly into the auditory nerve via multiple electrodes implanted in the cochlea. An external microphone and processor convert sound waves to electrical impulses, which are transmitted through the skin electromagnetically from an external induction coil to an internal coil implanted in the skull above and behind the ear. The internal coil connects to electrodes inserted in the scala tympani.

Cochlear implants help with speech-reading by providing information about the intonation of words and the rhythm of speech. Many if not most adults with cochlear implants can discriminate words without visual clues, allowing them to talk on the telephone. Cochlear implants enable deaf people to hear and distinguish environmental sounds and warning signals. They also help deaf people modulate their voice and make their speech more intelligible.

Brain stem implants: Patients who have had both acoustic nerves destroyed (eg, by bilateral temporal bone fractures or neurofibromatosis) can have some hearing restored by means of brain stem implants that have electrodes connected to sound-detecting and sound-processing devices similar to those used for cochlear implants.

Coping mechanisms: Alerting systems that use light let people know when the doorbell is ringing, a smoke detector is sounding, or a baby is crying. Special sound systems transmitting infrared or FM radio signals help people hear in theaters, churches, or other places where competing noise exists. Many television programs carry closed captioning. Telephone communication devices are also available.

Lip-reading or speech-reading is particularly important for people who can hear but have trouble discriminating sounds. Most people get useful speech information from lip-reading even without formal training. Even people with normal hearing can better understand speech in a noisy place if they can see the speaker. To use this information the listener must be able to see the speaker's mouth. Health care personnel should be sensitive to this issue and always position themselves appropriately when speaking to the hearing-impaired. Observing the position of a speaker's lips allows recognition of the consonant being spoken, thereby improving speech comprehension in patients with high-frequency hearing loss. Lip-reading may be learned in aural rehabilitation sessions in which a group of age-matched peers meets regularly for instruction and supervised practice in optimizing communication.

People can gain control over their listening environment by modifying or avoiding difficult situations. For example, people can visit a restaurant during off-peak hours, when it is quieter. They can ask for a booth, which blocks out some extraneous sounds. In direct conversations, people may ask the speaker to face them. At the beginning of a telephone conversation, they can identify themselves as being hearing-impaired. At a conference, the speaker can be asked to use an assistive listening system, which makes use of either inductive loop, infrared, or FM technology that sends sound through the microphone to a patient's hearing aid.
People with profound hearing loss often communicate by using sign language. American Sign Language (ASL) is the most common version in the US. Other forms include Signed English, Signing Exact English, and Cued Speech.

**Treatment in Children**

In addition to treatment of any cause and the provision of hearing aids, children with hearing loss require support of language development with appropriate therapy. Because children must hear language to learn it spontaneously, most deaf children develop language only with special training, ideally beginning as soon as the hearing loss is identified (an exception would be a deaf child growing up with deaf parents who are fluent sign language users). Deaf infants must be provided with a form of language input. For example, a visually based sign language can provide a foundation for later development of oral language if a cochlear implant is not available.

If infants as young as 1 mo have profound bilateral hearing loss and cannot benefit from hearing aids, they can be a candidate for a cochlear implant. Although cochlear implants allow auditory communication in many children with either congenital or acquired deafness, they are, in the main, more effective in children who already have developed language. Children who have postmeningitic deafness develop an ossified inner ear; they should receive cochlear implants early to maximize effectiveness. Children whose acoustic nerves have been destroyed by tumors may be helped by implantation of brain stem auditory-stimulating electrodes. Children with cochlear implants may have a slightly greater risk of meningitis than children without cochlear implants or adults with cochlear implants.

Children with unilateral deafness should be allowed to use a special system in the classroom, such as an FM auditory trainer. With these systems, the teacher speaks into a microphone that sends signals to a hearing aid in the child's nonaffected ear, improving the child's greatly impaired ability to hear speech against a noisy background.

**Geriatrics Essentials**

Elderly people typically experience a progressive decrease in hearing (presbycusis). The prevalence of hearing impairment is 30% in people > 65 and is 40 to 50% in those > 75. Nonetheless, hearing loss in the elderly should be evaluated and not ascribed to aging; elderly patients may have a tumor, a neurologic or autoimmune disorder, or an easily correctible conductive hearing loss. Also, hearing loss in the elderly facilitates dementia (which can be mitigated by properly correcting hearing loss).

**Presbycusis:** Presbycusis is sensorineural hearing loss that probably results from a combination of age-related deterioration and cell death in various components of the hearing system and the effects of chronic noise exposure.

Hearing loss usually affects the highest frequencies (18 to 20 kHz) early on and gradually affects the lower frequencies; it usually becomes clinically significant when it affects the critical 2- to 4-kHz range at about age 55 to 65 (sometimes sooner). The loss of high-frequency hearing significantly affects speech comprehension. Although the loudness of speech seems normal, certain consonant sounds (eg, C, D, K, P, S, T) become hard to hear. Consonant sounds are the most important sounds for speech recognition. For example, when "shoe," "blue," "true," "too," or "new" is spoken, many people with presbycusis can hear the "oo" sound, but most have difficulty recognizing which word has been spoken because they cannot distinguish the consonants. This inability to distinguish consonants causes affected people to often think the speaker is mumbling. A speaker attempting to speak louder usually accentuates vowel sounds (which are low frequency), doing little to improve speech recognition. Speech comprehension is particularly difficult when background noise is present.

**Screening:** A screening tool is often helpful for elderly people because many do not complain of hearing loss. One tool is the Hearing Handicap Inventory for the Elderly-Screening Version, which asks

- Does a hearing problem cause you to feel embarrassed when you meet people?
• Does a hearing problem cause you to feel frustrated when talking to a family member?
• Do you have difficulty hearing when someone whispers?
• Do you feel handicapped by a hearing problem?
• Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?
• Does a hearing problem cause you to attend religious services less often than you would like?
• Does a hearing problem cause you to have arguments with family members?
• Does a hearing problem cause you difficulty when listening to the television or radio?
• Do you feel that any difficulty with your hearing hampers your personal or social life?
• Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?

Scoring is "no" = 0 points, "sometimes" = 2 points, and "yes" = 4 points. Scores > 10 suggest significant hearing impairment and necessitate follow-up.

Prevention

Prevention of hearing loss consists mainly of limiting duration and intensity of noise exposure. People required to expose themselves to loud noise must wear ear protectors (eg, plastic plugs in the ear canals or glycerin-filled muffs over the ears). The Occupational Safety and Health Administration (OSHA) of the US Department of Labor and similar agencies in many other countries have standards regarding the length of time that a person can be exposed to a noise. The louder the noise, the shorter the permissible time of exposure.

Key Points

• Cerumen, genetic disorders, infections, aging, and noise exposure are the most common causes.
• All patients with hearing loss should have audiologic testing.
• Cranial nerve deficits and other neurologic deficits should raise concern and warrant imaging tests.

Sudden Deafness

Sudden deafness is severe sensorineural hearing loss that develops within a few hours or is noticed on awakening. It affects about 1/5000 people each year. Initial hearing loss is typically unilateral (unless drug-induced) and may range in severity from mild to profound. Many also have tinnitus, and some have dizziness, vertigo, or both.

Sudden deafness has some causes that differ from chronic hearing loss and must be addressed urgently.

Etiology

The following are common characteristics of sudden deafness:
• Most cases (see Table 47-4) are idiopathic.
• Some occur in the course of an obvious explanatory event.

A few represent the initial manifestation of an occult but identifiable disorder.
**Idiopathic:** There are numerous theories for which some evidence (although conflicting and incomplete) exists. The most promising possibilities include viral infections (particularly involving herpes simplex), autoimmune attacks, and acute microvascular occlusion.

**Obvious event:** Some causes of sudden deafness are readily apparent.

**Blunt head trauma** with temporal bone fracture or severe concussion involving the cochlea can cause sudden hearing loss.

**Large ambient pressure changes** (eg, caused by diving) or strenuous activities (eg, weightlifting) can induce a perilymphatic fistula between the middle and inner ear, causing sudden, severe symptoms. Perilymphatic fistula can also be congenital; it can spontaneously cause a sudden loss or loss may occur after trauma or pressure changes.

Table 47-4. Some Causes of Sudden Deafness

**Ototoxic drugs** can result in hearing loss occurring sometimes within a day, especially with an overdose (systemically or when applied to a large wound area, such as a burn). There is a rare genetic mitochondrial-transmitted disorder that increases the susceptibility to aminoglycoside ototoxicity.

A number of infections cause sudden deafness during or immediately after acute illness. Common causes include bacterial meningitis, Lyme disease, and many viral infections that affect the cochlea (and sometimes the vestibular apparatus). The most common viral causes in the developed world are mumps and herpes. Measles is a very rare cause because most of the population is immunized.

**Occult disorders:** Sudden deafness rarely can be an isolated first manifestation of some disorders that usually have other initial symptoms. Sudden deafness rarely may be the first manifestation of an acoustic neuroma, multiple sclerosis, Meniere’s disease, or a small cerebellar stroke. Syphilis reactivation in HIV-infected patients rarely can cause sudden deafness.

Cogan’s syndrome is a rare autoimmune reaction directed against an unknown common autoantigen in the cornea and inner ear; > 50% of patients present with vestibuloauditory symptoms. About 10 to 30% of patients also have a severe systemic vasculitis, which may include life-threatening aortitis.

Some vasculitic disorders can cause hearing loss, some of which is acute. Hematologic disorders, such as Waldenstrom’s macroglobulinemia, sickle cell disease, and some forms of leukemia, rarely can cause sudden deafness.

**Evaluation**

Evaluation consists of detecting and quantifying hearing loss and determining etiology (particularly reversible causes).

**History:** History of present illness should verify that loss is sudden and not chronic. The history should also note whether loss is unilateral or bilateral and whether there is a current acute event (eg, head injury, barotrauma [particularly a diving injury], infectious illness). Important accompanying symptoms include other otologic symptoms (eg, tinnitus, ear discharge), vestibular symptoms (eg, disorientation in the dark, vertigo), and other neurologic symptoms (eg, headache, weakness or asymmetry of the face, abnormal sense of taste).

**Review of systems** should seek symptoms of possible causes, including transient, migratory neurologic deficits (multiple sclerosis) and eye irritation and redness (Cogan’s syndrome).

**Past medical history** should ask about known HIV or syphilis infection and risk factors for them (eg, multiple sex partners, unprotected intercourse). Family history should note close relatives with hearing loss (suggesting a congenital fistula). Drug history should specifically query current or previous use of ototoxic drugs (see Table 47-4) and whether the patient has known renal insufficiency or renal failure.
Physical examination: The examination focuses on the ears and hearing and on the neurologic examination.

The tympanic membrane is inspected for perforation, drainage, or other lesions. During the neurologic examination, attention should be paid to the cranial nerves (particularly the 5th, 7th, and 8th) and to vestibular and cerebellar function because abnormalities in these areas often occur with tumors of the brain stem and cerebellopontine angle.

Weber's test and the Rinne test require a tuning fork to differentiate conductive from sensorineural hearing loss (see p. 429).

Additionally, the eyes are examined for redness and photophobia (possible Cogan's syndrome), and the skin is examined for rash (eg, viral infection, syphilis).

Red flags: Findings of particular concern are

• Abnormalities of cranial nerves (other than hearing loss)

Interpretation of findings: Traumatic, ototoxic, and some infectious causes are usually apparent clinically. A patient with perilymphatic fistula may hear an explosive sound in the affected ear when the fistula occurs and may also have sudden vertigo, nystagmus, and tinnitus.

Focal neurologic abnormalities are of particular concern. The 5th cranial nerve, 7th cranial nerve, or both are often affected by tumors that involve the 8th cranial nerve, so loss of facial sensation and weak jaw clench (5th) and hemifacial weakness and taste abnormalities (7th) point to a lesion in that area.

Unilateral hearing loss accompanied by tinnitus and vertigo also suggests Meniere's disease. Systemic symptoms suggesting inflammation (eg, fevers, rash, joint pains, mucosal lesions) should raise suspicion of an occult infection or autoimmune disorder.

Testing: Typically, patients should have an audiogram, and unless the diagnosis is clearly an acute infection or drug toxicity, most clinicians do gadolinium-enhanced MRI to diagnose inapparent causes. Patients with an acute traumatic cause also should have MRI. If a perilymphatic fistula is suspected clinically, it may be confirmed by tympanometry and electronystagmography (ENG); CT is usually done to show the bony characteristics of the inner ear.

Patients who have risk factors for or symptoms that suggest causes should have appropriate tests (eg, serologic tests for possible HIV infection or syphilis, CBC and coagulation profile for hematologic disorders, ESR and antinuclear antibodies for vasculitis).

Treatment

Treatment focuses on the causative disorder when known. Fistulas are explored and repaired surgically.

In viral and idiopathic cases, hearing returns to normal in about 50% of patients and is partially recovered in others.

In patients who recover their hearing, improvement usually occurs within 10 to 14 days.

For patients with idiopathic loss, many clinicians empirically give a short course of glucocorticoids and antiviral drugs effective against herpes simplex (eg, valacyclovir, famciclovir). Glucocorticoids can be given orally or by transtympanic injection; it is unclear which route is more effective.

Key Points

• Most cases are idiopathic.

• A few cases have an obvious cause (eg, major trauma, acute infection, drugs).
A very few cases represent unusual manifestations of treatable disorders.
Chapter 48. Inner Ear Disorders

Introduction

(See also Hearing Loss on p. 429.)

The inner ear is in the petrous area of the temporal bone. Within the bone is the osseous labyrinth, which encases the membranous labyrinth. The osseous labyrinth includes the vestibular system (made up of the semicircular canals and the vestibule) and the cochlea. The vestibular system is responsible for balance and posture; the cochlea, for hearing.

Acoustic Neuroma

(Acoustic Neurinoma; 8th Nerve Tumor; Vestibular Schwannoma)

An acoustic neuroma is a Schwann cell-derived tumor of the 8th cranial nerve. Symptoms include unilateral hearing loss. Diagnosis is based on audiology and confirmed by MRI. Treatment is surgical removal, stereotactic radiation therapy, or both.

Acoustic neuromas almost always arise from the vestibular division of the 8th cranial nerve and account for about 7% of all intracranial tumors. As the tumor expands, it projects from the internal auditory meatus into the cerebellopontine angle and compresses the cerebellum and brain stem. The 5th cranial nerve and later the 7th cranial nerve are affected.

Bilateral acoustic neuromas are common in neurofibromatosis type 2.

Symptoms and Signs

Slowly progressive unilateral sensorineural hearing loss is the hallmark symptom. However, the onset of hearing loss may be abrupt, and the degree of impairment may fluctuate. Other early symptoms include unilateral tinnitus, dizziness and dysequilibrium, headache, sensation of pressure or fullness in the ear, otalgia, trigeminal neuralgia, and numbness or weakness of the facial nerve.

Diagnosis

• Audiogram

• If positive, gadolinium-enhanced MRI

An audiogram is the first test done (see p. 433). It usually reveals an asymmetric sensorineural hearing loss and a greater impairment of speech discrimination than would be expected for the degree of hearing loss. Acoustic reflex decay, the absence of waveforms, and increased latency of the 5th waveform in auditory brain stem response testing are further evidence of a neural lesion. Although not usually required in the routine evaluation of a patient with asymmetric sensorineural hearing loss, caloric testing shows marked vestibular hypoaactivity (canal paresis). Such findings indicate the need for imaging tests, preferably gadolinium-enhanced MRI.

Treatment

• Surgical removal

• Sometimes stereotactic radiation therapy

Small tumors may be removed with microsurgery that preserves the facial nerve. A middle cranial fossa or retrosigmoid approach may preserve remaining hearing; a translabyrinthine route may be used if no useful hearing remains. Large tumors are removed with the translabyrinthine approach regardless of the remaining hearing. Stereotactic radiation therapy as the sole treatment modality is used predominantly in the management of small tumors in older patients; its long-term efficacy and adverse effects are under
Benign Paroxysmal Positional Vertigo
(Benign Postural or Positional Vertigo)

In benign paroxysmal positional vertigo (BPPV), short (< 60 sec) episodes of vertigo occur with certain head positions. Nausea and nystagmus develop. Diagnosis is clinical. Treatment involves canalith repositioning maneuvers. Drugs and surgery are rarely, if ever, indicated.

BPPV is the most common cause of relapsing otogenic vertigo. It affects people increasingly as they age and can severely affect balance in the elderly, leading to potentially injurious falls.

Etiology

The condition is thought to be caused by displacement of otoconial crystals (Ca carbonate crystals normally embedded in the saccule and utricle). This displaced material stimulates hair cells in the posterior semicircular canal, creating the illusion of motion. Etiologic factors include spontaneous degeneration of the utricular otolithic membranes, labyrinthine concussion, otitis media, ear surgery, recent viral infection (e.g., viral neuronitis), head trauma, prolonged anesthesia or bed rest, previous vestibular disorders (e.g., Meniere's disease), and occlusion of the anterior vestibular artery.

Symptoms and Signs

Vertigo is triggered when the patient's head moves (e.g., when rolling over in bed or bending over to pick up something). Acute vertigo lasts only a few seconds to minutes; episodes tend to peak in the morning and abate throughout the day. Nausea and vomiting may occur, but hearing loss and tinnitus do not.

Diagnosis

- Clinical evaluation
- Gadolinium-enhanced MRI if findings suggest CNS lesion

Diagnosis is based on characteristic symptoms, on nystagmus as determined by the Dix-Hallpike maneuver (a provocative test for positional nystagmus—see Sidebar 46-1 on p. 414), and on absence of other abnormalities on neurologic examination. Such patients require no further testing. Patients with nystagmus suggesting a CNS lesion undergo gadolinium-enhanced MRI. Unlike the positional nystagmus of BPPV, the positional nystagmus of CNS lesions lacks latency, fatigability, and severe subjective sensation and may continue for as long as the position is maintained. Nystagmus caused by a CNS lesion may be vertical or change direction and, if rotary, is likely to be in the unexpected direction.

Treatment

- Provocative maneuvers to fatigue symptoms
- Canalith repositioning maneuvers
- Drug treatment typically not recommended

BPPV usually subsides spontaneously in several weeks or months but may continue for months or years. Because the condition can be long-lasting, drug treatment (like that used in Meniere's disease—see p. 445) is not recommended. Often, the adverse effects of drugs worsen dysequilibrium.

Because BPPV is fatigable, one therapy is to have the patient perform provocative maneuvers early in the day in a safe environment. Symptoms are then minimal for the rest of the day.

Canalith repositioning maneuvers (Epley maneuver—see
Fig. 48-1—and Semont maneuver) involve moving the head through a series of specific positions intended to return the errant canalith to the utricle. After performing these maneuvers, the patient should remain erect or semi-erect for 1 to 2 days. Both maneuvers can be repeated as necessary.

For the Semont maneuver, the patient is seated upright in the middle of a stretcher. The patient's head is rotated toward the unaffected ear; this rotation is maintained throughout the maneuver. Next, the torso is lowered laterally onto the stretcher so that the patient is lying on the side of the affected ear with the nose pointed up. After 3 min in this position, the patient is quickly moved through the upright position without straightening the head and is lowered laterally to the other side now with the nose pointed down. After 3 min in this position, the patient is slowly returned to the upright position, and the head is rotated back to normal.

Drug-Induced Ototoxicity

A wide variety of drugs can be ototoxic (see Table 48-1).

Factors affecting ototoxicity include dose, duration of therapy, concurrent renal failure,

Table 48-1. Some Drugs that Cause Ototoxicity]

infusion rate, lifetime dose, co-administration with other drugs having ototoxic potential, and genetic susceptibility. Ototoxic drugs should not be used for otic topical application when the tympanic membrane is perforated because the drugs might diffuse into the inner ear.

Streptomycin tends to cause more damage to the vestibular portion than to the auditory portion of the inner ear. Although vertigo and difficulty maintaining balance tend to be temporary, severe loss of vestibular sensitivity may persist, sometimes permanently. Loss of vestibular sensitivity causes difficulty walking, especially in the dark, and oscillopsia (a sensation of bouncing of the environment with each step). About 4 to 15% of patients who receive 1 g/day for > 1 wk develop measurable hearing loss, which usually occurs after a short latent period (7 to 10 days) and slowly worsens if treatment is continued. Complete, permanent deafness may follow.

Neomycin has the greatest cochleotoxic effect of all antibiotics. When large doses are given orally or by colonic irrigation for intestinal sterilization, enough may be absorbed to affect hearing, particularly if mucosal lesions are present. Neomycin should not be used for wound irrigation or for intraperitoneal or intraperitoneal irrigation, because massive amounts of the drug may be retained and absorbed, causing deafness. Kanamycin and amikacin are close to neomycin in cochleotoxic potential and are both capable of causing profound, permanent hearing loss while sparing balance. Viomycin has both cochlear and vestibular toxicity. Gentamicin and tobramycin have vestibular and cochlear toxicity, causing impairment in balance and hearing.

Vancomycin can cause hearing loss, especially in the presence of renal insufficiency.

Chemotherapeutic (antineoplastic) drugs, particularly those containing platinum (cisplatin and carboplatin), can cause tinnitus and hearing loss. Hearing loss can be profound and permanent, occurring immediately after the first dose, or can be delayed until several months after completion of treatment. Sensorineural hearing loss strikes bilaterally, progresses decrementally, and is permanent.

Ethacrynic acid and furosemide given IV have caused profound, permanent hearing loss in patients with renal failure who had been receiving aminoglycoside antibiotics.

Salicylates in high doses (> 12 325-mg tablets of aspirin per day) cause temporary hearing loss and tinnitus. Quinine and its synthetic substitutes can also cause temporary hearing loss.

Prevention
Ototoxic antibiotics should be avoided during pregnancy. The elderly and people with preexisting hearing loss should not be treated with ototoxic drugs if other effective drugs are available. The lowest effective dosage of ototoxic drugs should be used and levels should be closely monitored. If possible before treatment with an ototoxic drug, hearing should be measured and then monitored during treatment; symptoms are not reliable warning signs.

**Herpes Zoster Oticus**

(Geniculate Herpes; Ramsay Hunt Syndrome; Viral Neuronitis)

**Herpes zoster oticus is infection of the 8th cranial nerve ganglia and the geniculate ganglion of the facial nerve by the herpes zoster virus.**

Risk factors for herpes infection include immunodeficiency secondary to cancer, chemotherapy, radiation therapy, and HIV infection.

**Symptoms and Signs**

Symptoms include severe ear pain, transient or permanent facial paralysis (resembling Bell's palsy), vertigo lasting days to weeks, and hearing loss (which may be permanent or which may resolve partially or completely). Vesicles occur on the pinna and in the external auditory canal along the distribution of the sensory branch of the facial nerve. Symptoms of meningoencephalitis (eg, headache, confusion, stiff neck) are uncommon. Sometimes other cranial nerves are involved.

**Diagnosis**

Diagnosis usually is clinical. If there is any question about viral etiology, vesicular scrapings may be collected for direct immunofluorescence or for viral cultures, and MRI is done.

**Treatment**

- Perhaps corticosteroids, antivirals, and surgical decompression

Although there is no reliable evidence that corticosteroids, antiviral drugs, or surgical decompression makes a difference, they are the only possibly useful treatments. Corticosteroids are started with prednisone 60 mg po once/day for 4 days, followed by gradual tapering of the dose over the next 2 wk. Acyclovir 800 mg po q 4 h 5 times/day or valacyclovir 1 g po bid for 10 days may shorten the clinical course. Vertigo is effectively suppressed with diazepam 2 to 5 mg po q 4 to 6 h. Pain may require oral opioids. Postherpetic neuralgia may be treated with amitriptyline. Surgical decompression of the fallopian canal may be indicated if the facial palsy is complete (no visible facial movement). Before surgery, however, electroneurography is done and should show a > 90% decrement.

**Meniere's Disease**

(Endolymphatic Hydrops)

**Meniere's disease is an inner ear disorder that causes vertigo, fluctuating sensorineural hearing loss, and tinnitus. There is no diagnostic test. Vertigo and nausea are treated with anticholinergics or benzodiazepines. Diuretics and a low-salt diet may decrease frequency and severity of episodes. For severe cases, the vestibular system can be ablated with topical gentamicin or surgery.**

In Meniere's disease, pressure and volume changes of the labyrinthine endolymph affect inner ear function. The etiology of endolymphatic fluid buildup is unknown. Risk factors include a family history of Meniere's disease, preexisting autoimmune disorders, allergies, trauma to the head or ear, and, rarely, syphilis (even several decades previously). Peak incidence is between ages 20 and 50.
**Symptoms and Signs**

Patients have sudden attacks of vertigo lasting up to 24 h, usually with nausea and vomiting. Accompanying symptoms include diaphoresis, diarrhea, and gait unsteadiness. Tinnitus may be constant or intermittent, buzzing or roaring; it is not related to position or motion. Hearing impairment, typically affecting low frequencies, may follow. Before an episode, most patients sense fullness or pressure in the affected ear. In 50% of patients, only one ear is affected.

During the early stages, symptoms remit between episodes; symptom-free interludes may last > 1 yr. As the disease progresses, however, hearing impairment persists and gradually worsens, and tinnitus may be constant.

**Diagnosis**

- Clinical evaluation
- Audiogram and gadolinium-enhanced MRI to rule out other causes

The diagnosis, made clinically, is primarily one of exclusion. Similar symptoms can result from viral labyrinthitis or neuritis, a cerebellopontine angle tumor (eg, acoustic neuroma), or a brain stem stroke. Patients with suggestive symptoms should have an audiogram and an MRI (with gadolinium enhancement) of the CNS with attention to the internal auditory canals to exclude other causes. Audiogram typically shows a low-frequency sensorineural hearing loss in the affected ear.

On examination during an acute attack, the patient has nystagmus and falls to the affected side. Between attacks, the Fukada stepping test (marching in place with eyes closed) can be used; a patient with Meniere's disease often turns away from the affected ear, consistent with a unilateral labyrinthine lesion. Additionally, the Rinne test and Weber's test may indicate sensorineural hearing loss (see p. 431).

**Treatment**

- Symptom relief with antiemetics, antihistamines, or benzodiazepines
- Diuretics and low-salt diet
- Rarely vestibular ablation by drugs or surgery

Meniere's disease tends to be self-limited. Treatment of an acute attack is aimed at symptom relief. Anticholinergics (eg, prochlorperazine or promethazine 25 mg rectally or 10 mg po q 6 to 8 h) can minimize vagal-mediated GI symptoms. Antihistamines (eg, diphenhydramine, meclizine, or cyclizine 50 mg po q 6 h) or benzodiazepines (eg, diazepam 5 mg po q 6 to 8 h) are used to sedate the vestibular system. Some physicians also use a corticosteroid burst (eg, prednisone 60 mg once/day for 1 wk, tapered over another wk) for an acute episode.

A low-salt (< 1.5 g/day) diet, avoidance of alcohol and caffeine, and a diuretic (eg, hydrochlorothiazide 25 mg po once/day) may help prevent vertigo and are useful for many patients.

Intratympanic gentamicin (chemical labyrinthectomy) may be used when medical management is unsuccessful. Typical dose is 1 mL (at a 30 mg/mL concentration, made by diluting the commercial 40 mg/mL preparation with bicarbonate) injected through the tympanic membrane. Follow-up with serial audiometry is recommended to distinguish hearing loss from cochleotoxicity. The injection can be repeated in 4 wk if vertigo persists without hearing loss.

Surgery is reserved for patients with frequent, severely debilitating episodes who are unresponsive to other modalities. Endolymphatic sac decompression relieves vertigo in some patients and poses minimal risk of hearing loss. Vestibular neurectomy (an intracranial procedure) relieves vertigo in about 95% of patients and usually preserves hearing. A surgical labyrinthectomy is done only if preexisting hearing loss is profound.
Unfortunately, there is no known way to prevent the natural progression of hearing loss. Most patients sustain moderate to severe sensorineural hearing loss in the affected ear within 10 to 15 yr.

**Purulent Labyrinthitis**

Purulent (suppurative) labyrinthitis is bacterial infection of the inner ear, often causing deafness and loss of vestibular function.

Purulent labyrinthitis usually occurs when bacteria spread to the inner ear during the course of severe acute otitis media, purulent meningitis, or an enlarging cholesteatoma.

Symptoms include severe vertigo and nystagmus, nausea and vomiting, tinnitus, and varying degrees of hearing loss. Pain and fever are common.

Purulent labyrinthitis is suspected if vertigo, nystagmus, sensorineural hearing loss, or a combination occurs during an episode of acute otitis media. CT of the temporal bone is done to identify erosion of the otic capsule bone or other complications of acute otitis media, such as coalescent mastoiditis. MRI may be indicated if symptoms of meningitis or brain abscess, such as altered mental status, meningismus, or high fever, are present; in such cases, a lumbar puncture and blood cultures also are done.

Treatment is with IV antibiotics appropriate for meningitis (eg, ceftriaxone 50 to 100 mg/kg IV once/day to maximum 2 g) adjusted according to results of culture and sensitivity testing. A myringotomy (and sometimes tympanostomy tube placement) is done to drain the middle ear. Mastoidectomy may be required.

**Vestibular Neuronitis**

Vestibular neuronitis causes a self-limited episode of vertigo, presumably due to inflammation of the vestibular division of the 8th cranial nerve; some vestibular dysfunction may persist.

Although etiology is unclear, a viral cause is suspected.

**Symptoms and Signs**

Symptoms include a single attack of severe vertigo, with nausea and vomiting and persistent nystagmus toward the affected side, which lasts 7 to 10 days. The nystagmus is unidirectional, horizontal, and spontaneous, with fast-beat oscillations in the direction of the unaffected ear. The absence of concomitant tinnitus or hearing loss is a hallmark of vestibular neuronitis. The condition slowly subsides after this initial episode. Some patients have residual dysequilibrium, especially with rapid head movements, probably due to permanent vestibular injury.

**Diagnosis**

- Audiology, electronystagmography, and MRI

Patients undergo an audiological assessment, electronystagmography with caloric testing, and gadolinium-enhanced MRI of the head, with attention to the internal auditory canals to exclude other diagnoses, such as cerebellopontine angle tumor, brain stem hemorrhage, or infarction. MRI may show enhancement of the vestibular nerves, consistent with inflammatory neuritis.

**Treatment**

- Symptom relief with antiemetics, antihistamines, or benzodiazepines

Symptoms are addressed as in Meniere’s disease (see p. 445), ie, with anticholinergics, antiemetics (eg, prochlorperazine or promethazine 25 mg rectally or 10 mg po q 6 to 8 h), antihistamines or benzodiazepines, and a corticosteroid burst with rapid taper. If vomiting is prolonged, IV fluids and
electrolytes may be required. Vestibular rehabilitation (usually given by a physical therapist) helps compensate for any residual vestibular deficit.
Chapter 49. Middle Ear and Tympanic Membrane Disorders

Introduction

(See also Otic Tumors on p. 493)

Middle ear disorders may be secondary to infection, eustachian tube obstruction, or trauma. Information about objects placed in the ear and symptoms such as rhinorrhea, nasal obstruction, sore throat, URI, allergies, headache, systemic symptoms, and fever aid diagnosis. The appearance of the external auditory canal and tympanic membrane (see Fig. 49-1) often yields a diagnosis. The nose, nasopharynx, and oropharynx are examined for signs of infection and allergy and for evidence of tumors. Middle ear function is evaluated with use of pneumatic otoscopy, Weber’s tuning fork test and the Rinne tuning fork test, tympanometry, and audiologic tests (see p. 431).

Mastoiditis

Mastoiditis is a bacterial infection of the mastoid air cells, which typically occurs after acute otitis media. Symptoms include redness, tenderness, swelling, and fluctuation over the mastoid process, with displacement of the pinna. Diagnosis is clinical. Treatment is with antibiotics, such as ceftriaxone, and mastoidectomy if drug therapy is not effective.

In acute purulent otitis media, inflammation often extends into the mastoid antrum and air cells, resulting in fluid accumulation. In a few patients, bacterial infection develops in the collected fluid, typically with the same organism causing the otitis media; pneumococcus is most common. Mastoid infection can cause osteitis of the septae, leading to coalescence of the air cells. The infection may decompress through a perforation in the tympanic membrane or extend through the lateral mastoid cortex, forming a postauricular subperiosteal abscess. Rarely, it extends centrally, causing a temporal lobe abscess or a septic thrombosis of the lateral sinus. Occasionally, the infection may erode through the tip of the mastoid and drain into the neck (called a Bezold abscess).

Symptoms and Signs

Symptoms begin days to weeks after onset of acute otitis media and include fever and persistent, throbbing otalgia. Nearly all patients have signs of otitis media (see p. 448) and purulent otorrhea. Redness, swelling,

[Fig. 49-1. Tympanic membrane of right ear (A); tympanic cavity with tympanic membrane removed (B).]

tenderness, and fluctuation may develop over the mastoid process; the pinna is typically displaced laterally and inferiorly.

Diagnosis

• Clinical evaluation

• Rarely CT

Diagnosis is clinical. CT is rarely necessary but can confirm the diagnosis and show the extent of the infection. Any middle ear drainage is sent for culture and sensitivity. Typanocentesis for culture purposes can be done if no spontaneous drainage occurs. CBC and ESR may be abnormal but are neither sensitive nor specific and add little to the diagnosis.

Treatment

• IV ceftriaxone

IV antibiotic treatment is initiated immediately with a drug that provides CNS penetration, such as...
Ceftriaxone 1 to 2 g (children, 50 to 75 mg/kg) once/day continued for ≥ 2 wk. Oral treatment with a quinolone may be acceptable. Subsequent antibiotic choice is guided by culture and sensitivity test results.

A subperiosteal abscess usually requires a simple mastoidectomy, in which the abscess is drained, the infected mastoid cells are removed, and drainage is established from the antrum of the mastoid to the middle ear cavity.

**Myringitis**

*(Bullous Myringitis)*

Myringitis is a form of acute otitis media in which vesicles develop on the tympanic membrane.

Myringitis can develop with viral, bacterial (particularly *Streptococcus pneumoniae*), or mycoplasmal otitis media. Pain occurs suddenly and persists for 24 to 48 h. Hearing loss and fever suggest a bacterial origin. Diagnosis is based on otoscopic visualization of vesicles on the tympanic membrane.

Because differentiation among a viral, bacterial, and mycoplasmal cause is difficult, antibiotics effective against organisms causing otitis media are prescribed (see Table 49-1). Severe, continued pain may be relieved by rupturing the vesicles with a myringotomy knife or by oral analgesics (eg, oxycodone with acetaminophen). Topical analgesics (eg, benzocaine, antipyrine) may also be beneficial.

**Acute Otitis Media**

Acute otitis media (AOM) is a bacterial or viral infection of the middle ear, usually accompanying a URI. Symptoms include otalgia, often with systemic symptoms (eg, fever, nausea, vomiting, diarrhea), especially in the very young. Diagnosis is based on otoscopy. Treatment is with analgesics and sometimes antibiotics.

Although AOM can occur at any age, it is most common between ages 3 mo and 3 yr. At this age, the eustachian tube is structurally and functionally immature; the angle of the eustachian tube is more horizontal; and the angle of the tensor veli palatini muscle and the cartilaginous eustachian tube renders the opening mechanism less efficient.

The etiology may be viral or bacterial. Viral infections are often complicated by secondary bacterial infection. In neonates, gram-negative enteric bacilli, particularly *Escherichia coli*, and *Staphylococcus aureus* cause AOM. In older infants and children < 14 yr, the most common organisms are *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, and nontypeable *Haemophilus influenzae*; less common causes are group Aβ-hemolytic streptococci and *S. aureus*. In patients > 14 yr, *S. pneumoniae*, group Aβ-hemolytic streptococci, and *S. aureus* are most common, followed by *H. influenzae*.

In rare cases, bacterial middle ear infection spreads locally, resulting in acute mastoiditis, petrositis, or labyrinthitis. Intracranial spread is extremely rare and usually causes meningitis, but brain abscess, subdural empyema, epidural abscess, lateral sinus thrombosis, or otitic hydrocephalus may occur. Even with antibiotic treatment, intracranial complications are slow to resolve, especially in immunocompromised patients.

**Symptoms and Signs**

The usual initial symptom is earache, often with hearing loss. Infants may simply be cranky or have difficulty sleeping. Fever, nausea, vomiting, and diarrhea often occur in young children. Otoscopic examination can show a bulging, erythematous tympanic membrane (TM) with indistinct landmarks and displacement of the light reflex. Air insufflation (pneumatic otoscopy) shows poor mobility of the TM. Spontaneous perforation of the TM causes serosanguineous or purulent otorrhea.

Severe headache, confusion, or focal neurologic signs may occur with intracranial spread of infection.
Facial paralysis or vertigo suggests local extension to the fallopian canal or labyrinth.

[Table 49-1, Antibiotics for Otitis Media]

Diagnosis

Diagnosis usually is clinical. Except for fluid obtained during myringotomy, cultures are not generally done.

Treatment

• Analgesics
• Sometimes antibiotics
• Rarely myringotomy

Although 80% of cases resolve spontaneously, in the US, antibiotics are often given (see Table 49-1). Antibiotics relieve symptoms quicker (although results after 1 to 2 wk are similar) and may reduce the chance of residual hearing loss and labyrinthine or intracranial sequelae. However, with the recent emergence of resistant organisms, pediatric organizations have strongly recommended initial antibiotics only for those at highest risk (eg, those who are younger or more severely ill—see Table 49-2) or for those with recurrent AOM (eg, ≥ 4 episodes in 6 mo). Others, provided there is good follow-up, can safely be observed for up to 72 h and given antibiotics only if no improvement is seen; if follow-up by phone is planned, a prescription can be given at the initial visit to save time and expense.

All patients receive analgesics (eg, acetaminophen, ibuprofen). In adults, topical intranasal vasoconstrictors, such as phenylephrine 0.25% 3 drops q 3 h, improve eustachian tube function. To avoid rebound congestion, these preparations should not be used > 4 days. Systemic decongestants (eg, pseudoephedrine 30 to 60 mg po q 6 h prn) may be helpful. Antihistamines (eg, chlorpheniramine 4 mg po q 4 to 6 h for 7 to 10 days) may improve eustachian tube function in people with allergies but should be reserved for the truly allergic. For children, neither vasoconstrictors nor antihistamines are of benefit.

Myringotomy may be done for a bulging TM, particularly if severe or persistent pain, fever, vomiting, or diarrhea is present. The patient's hearing, tympanometry, and TM appearance and movement are monitored until normal.

Prevention

Routine childhood vaccination against pneumococci (with pneumococcal conjugate vaccine), H. influenzae type B, and influenza decreases the incidence of AOM. Infants should not sleep with a bottle, and elimination of household smoking may decrease incidence.

Secretory Otitis Media

(Serous Otitis Media)

Secretory otitis media is an effusion in the middle ear resulting from incomplete resolution of acute otitis media or obstruction of the eustachian tube without infection. Symptoms include hearing loss and a sense of fullness or pressure in the ear. Diagnosis is based on appearance of the tympanic membrane and sometimes on tympanometry. Most cases resolve in 2 to 3 wk. If there is no improvement in 1 to 3 mo, some form of myringotomy is indicated, usually with insertion of a tympanostomy tube. Antibiotics and decongestants are not effective.
Normally, the middle ear is ventilated 3 to 4 times/min as the eustachian tube opens during swallowing, and O₂ is absorbed by blood in the vessels of the middle ear mucous membrane. If patency of the eustachian tube is impaired, a relative negative pressure develops within the middle ear, which can lead to fluid accumulation. This fluid may cause hearing loss.

Secretory otitis media is a common sequela to acute otitis media in children (often identified on routine ear recheck) and may persist for weeks to months. In other cases, eustachian tube obstruction may be secondary to inflammatory processes in the nasopharynx, allergies, hypertrophic adenoids or other obstructive lymphoid aggregations on the torus of the eustachian tube and in Rosenmuller's fossa, or benign or malignant tumors. The effusion may be sterile or (more commonly) contain pathogenic bacteria sometimes as a biofilm, although inflammation is not observed.

**Symptoms and Signs**

Patients may report no symptoms, but some (or their family members) note hearing loss. Patients may experience a feeling of fullness, pressure, or popping in the ear with swallowing. Otalgia is rare.

Various possible changes to the tympanic membrane (TM) include an amber or gray color, displacement of the light reflex, mild to severe retraction, and accentuated landmarks. On air insufflation, the TM may be immobile. An air-fluid level or bubbles of air may be visible through the TM.

**Diagnosis**

Diagnosis is clinical. Tympanometry may be done to confirm middle ear effusion. Adults and adolescents must undergo nasopharyngeal examination to exclude malignant or benign tumors.

**Treatment**

- Observation
- If unresolved, myringotomy with tympanostomy tube insertion
- If recurrent in childhood, sometimes adenoidectomy

For most patients, watchful waiting is all that is required. Antibiotics and decongestants are not helpful. For patients in whom allergies are clearly involved, antihistamines and topical corticosteroids may be helpful.

If no improvement occurs in 1 to 3 mo, myringotomy may be done for aspiration of fluid and insertion of a tympanostomy tube, which allows ventilation of the middle ear and temporarily ameliorates eustachian tube obstruction, regardless of cause. Tympanostomy tubes may be inserted for persistent conductive hearing loss or to help prevent recurrence of acute otitis media.

Occasionally, the middle ear is temporarily ventilated with the Valsalva maneuver or politzerization. To do the Valsalva maneuver, patients keep their mouth closed and try to forcibly blow air out through their pinched nostrils (ie, popping the ear). To do politzerization, the physician blows air with a special syringe (middle ear inflator) into one of the patient's nostrils and blocks the other while the patient swallows. This forces the air into the eustachian tube and middle ear. Neither procedure should be done if the patient has a cold and rhinorrhea.

Persistent, recurrent secretory otitis media may require correction of underlying nasopharyngeal conditions. Children may benefit from adenoidectomy, including the removal of the central adenoid mass as well as lymphoid aggregations on the torus of the eustachian tube and in Rosenmuller's fossa. Antibiotics should be given for bacterial rhinitis, sinusitis, and nasopharyngitis. Demonstrated allergens should be eliminated from the patient's environment and immunotherapy should be considered.

**Chronic Otitis Media**
Chronic otitis media is a persistent, chronically draining (> 6 wk), suppurative perforation of the tympanic membrane. Symptoms include painless otorrhea with conductive hearing loss. Complications include development of aural polyps, cholesteatoma, and other infections. Treatment requires complete cleaning of the ear canal several times daily, careful removal of granulation tissue, and application of topical corticosteroids and antibiotics. Systemic antibiotics and surgery are reserved for severe cases.

Chronic otitis media can result from acute otitis media, eustachian tube obstruction, mechanical trauma, thermal or chemical burns, blast injuries, or iatrogenic causes (eg, after tympanostomy tube placement). Further, patients with craniofacial abnormalities (eg, Down syndrome, cri du chat syndrome, cleft lip and/or cleft palate, velocardiofacial syndrome [Shprintzen's syndrome]) have an increased risk.

Chronic otitis media may become exacerbated after a URI or when water enters the middle ear through a tympanic membrane (TM) perforation during bathing or swimming. Infections often are caused by gram-negative bacilli or *Staphylococcus aureus*, resulting in painless, purulent, sometimes foul-smelling otorrhea. Persistent chronic otitis media may result in destructive changes in the middle ear (such as necrosis of the long process of the incus) or aural polyps (granulation tissue prolapsing into the ear canal through the TM perforation). Aural polyps are a serious sign, almost invariably suggesting cholesteatoma.

A cholesteatoma is an epithelial cell growth that forms in the middle ear, mastoid, or epitympanum after chronic otitis media (see Plate 1). Lytic enzymes, such as collagenases, produced by the cholesteatoma can destroy adjacent bone and soft tissue. The cholesteatoma is also a nidus for infection; purulent labyrinthitis, facial paralysis, or intracranial abscess may develop.

### Symptoms and Signs

Chronic otitis media usually manifests with conductive hearing loss and otorrhea. Pain is uncommon unless an associated osteitis of the temporal bone occurs. The TM is perforated and draining, and the auditory canal is macerated and littered with granulation tissue.

A patient with cholesteatoma has white debris in the middle ear, a draining polypoid mass protruding through the TM perforation, and an ear canal that appears clogged with mucopurulent granulation tissue.

### Diagnosis

Diagnosis is usually clinical. Drainage is cultured. When cholesteatoma or other complications are suspected (as in a febrile patient or one with vertigo or otalgia), CT or MRI is done. These tests may reveal intratemporal or intracranial processes (eg, labyrinthitis, ossicular or temporal erosion, abscesses).

### Treatment

- Irrigation and topical antibiotic drops
- Removal of granulation tissue

The ear canal is irrigated with a bulb syringe 3 times/day with a slightly warmed solution of half vinegar and half sterile water. After the ear drains, 10 drops topical ofloxacin solution are instilled in the affected ear 2 times/day for 14 days.

When granulation tissue is present, it is removed with microinstruments or cauterization with silver nitrate sticks. Ciprofloxacin 0.3% and dexamethasone 0.1% is then instilled into the ear canal for 7 to 10 days.

Severe exacerbations require systemic antibiotic therapy with amoxicillin 250 to 500 mg po q 8 h for 10 days or a 3rd-generation cephalosporin, subsequently modified by culture results and response to therapy.

Tympanoplasty is indicated for patients with marginal or attic perforations and chronic central TM perforations.
perforations. A disrupted ossicular chain may be repaired during tympanoplasty as well.

Cholesteatomas must be removed surgically. Because recurrence is common, reconstruction of the middle ear is usually deferred until a 2nd-look operation is done 6 to 8 mo later.

**Otic Barotrauma**

(Barotitis Media or Aerotitis Media)

Otic barotrauma is ear pain or damage to the tympanic membrane caused by rapid changes in pressure.

To maintain equal pressure on both sides of the tympanic membrane (TM), gas must move freely between the nasopharynx and middle ear. When a URI, allergy, or other mechanism interferes with eustachian tube functioning during changes in environmental pressure, the pressure in the middle ear either falls below ambient pressure, causing retraction of the TM, or rises above it, causing bulging. With negative middle ear pressure, a transudate of fluid may form in the middle ear. As the pressure differential increases, ecchymosis and subepithelial hematoma may develop in the mucous membrane of the middle ear and the TM. A very large pressure differential may cause bleeding into the middle ear, TM rupture, and the development of a perilymph fistula through the oval or round window.

Symptoms are severe pain, conductive hearing loss, and, if there is a perilymph fistula, sensory neural loss. Symptoms usually worsen during rapid increase in external air pressures, such as a rapid ascent (eg, during scuba diving) or descent (eg, during air travel). Sensorineural hearing loss or vertigo during descent suggests the development of a perilymph fistula; the same symptoms during ascent from a deep-sea dive can additionally suggest an air bubble formation in the inner ear.

**Treatment**

- Methods to equalize pressure (eg, yawning, swallowing, chewing gum)

Routine self-treatment of pain associated with changing pressure in an aircraft includes chewing gum, attempting to yawn and swallow, blowing against closed nostrils, and using decongestant nasal sprays.

If hearing loss is sensorineural and vertigo is present, a perilymph fistula is suspected and middle ear exploration to close a fistula is considered. If pain is severe and hearing loss is conductive, myringotomy is helpful.

**Prevention**

A person with nasal congestion due to URI or allergies should avoid flying and diving. When these activities are unavoidable, a topical nasal vasoconstrictor (eg, phenylephrine 0.25 to 1.0%) is applied 30 to 60 min before descent or ascent.

**Otosclerosis**

Otosclerosis is a disease of the bone of the otic capsule that causes an abnormal accumulation of new bone within the oval window.

In otosclerosis, the new bone traps and restricts the movement of the stapes, causing conductive hearing loss (see p. 429). Otosclerosis also may cause a sensorineural hearing loss, particularly when the foci of otosclerotic bone are adjacent to the scala media. Half of all cases are inherited. The measles virus plays an inciting role in patients with a genetic predisposition for otosclerosis.

Although about 10% of white adults have some otosclerosis (compared with 1% of blacks), only about 10% of affected people develop conductive hearing loss. Hearing loss caused by otosclerosis may manifest as early as age 7 or 8, but most cases do not become evident until the late teen or early adult years, when slowly progressive, asymmetric hearing loss is diagnosed. Fixation of the stapes may
progress rapidly during pregnancy.

A hearing aid may restore hearing. Alternatively, microsurgery to remove some or all of the stapes and to replace it with a prosthesis may be beneficial.

**Traumatic Perforation of the Tympanic Membrane**

Traumatic perforation of the tympanic membrane (TM) can cause pain, bleeding, hearing loss, tinnitus, and vertigo. Diagnosis is based on otoscopy. Treatment often is unnecessary. Antibiotics may be needed for infection. Surgery may be needed for perforations persisting > 2 mo, disruption of the ossicular chain, or injuries affecting the inner ear.

Traumatic causes of TM perforation include

- Insertion of objects into the ear canal purposely (eg, cotton swabs) or accidentally
- Concussion caused by an explosion or open-handed slap across the ear
- Head trauma (with or without basilar fracture)
- Sudden negative pressure (eg, strong suction applied to the ear canal)
- Barotrauma (eg, during air travel or scuba diving)
- Iatrogenic perforation during irrigation or foreign body removal

Penetrating injuries of the TM may result in dislocations of the ossicular chain, fracture of the stapedial footplate, displacement of fragments of the ossicles, bleeding, a perilymph fistula from the oval or round window resulting in leakage of perilymph into the middle ear space, or facial nerve injury.

**Symptoms and Signs**

Traumatic perforation of the TM causes sudden severe pain sometimes followed by bleeding from the ear, hearing loss, and tinnitus. Hearing loss is more severe if the ossicular chain is disrupted or the inner ear is injured. Vertigo suggests injury to the inner ear. Purulent otorrhea may begin in 24 to 48 h, particularly if water enters the middle ear.

**Diagnosis**

- Otoscopy
- Audiometry

Perforation is generally evident on otoscopy. Any blood obscuring the ear canal is carefully suctioned. Irrigation and pneumatic otoscopy are avoided. Extremely small perforations may require otomicroscopy or middle ear impedance studies for definitive diagnosis. If possible, audiometric studies are done before and after treatment to avoid confusion between trauma-induced and treatment-induced hearing loss.

Patients with marked hearing loss or severe vertigo are evaluated by an otolaryngologist as soon as possible. Exploratory tympanotomy may be needed to assess and repair damage. Patients with a large TM defect should also be evaluated, because the displaced flaps may need to be repositioned.

**Treatment**

- Ear kept dry
- Oral or topical antibiotics if dirty injury
Often, no specific treatment is needed. The ear should be kept dry; routine antibiotic eardrops are unnecessary. However, prophylaxis with oral broad-spectrum antibiotics or antibiotic eardrops is necessary if contaminants may have entered through the perforation as occurs in dirty injuries.

If the ear becomes infected, amoxicillin 500 mg po q 8 h is given for 7 days.

Although most perforations close spontaneously, surgery is indicated for a perforation persisting > 2 mo. Persistent conductive hearing loss suggests disruption of the ossicular chain, necessitating surgical exploration and repair.
Chapter 50. External Ear Disorders

Introduction

The external ear (pinna and external auditory canal) can be affected by congenital, dermatologic, infectious, neoplastic, obstructive, and traumatic disorders. Congenital defects are discussed on p. 2971. Ear trauma is discussed on p. 3231.

Dermatitis

Dermatitis is inflammation of the ear canal involving itching and skin changes that are caused by exposure to allergens (contact dermatitis) or are spontaneous occurrences (aural eczematoid dermatitis).

Common contact allergens include nickel-containing earrings and numerous beauty products (eg, hairsprays, lotions, hair dye). Aural eczematoid dermatitis is more common among people with a predisposition toward atopy and with other similar dermatitides (eg, seborrhea, psoriasis).

Both contact dermatitis and aural eczematoid dermatitis cause itching, redness, discharge, desquamation, hyperpigmentation, and, sometimes, fissuring. A secondary infection can occur.

Contact dermatitis requires avoidance or withdrawal of allergic triggers. Trial and error may be needed to identify the offending agent. Topical corticosteroids (eg, 1% hydrocortisone cream) can decrease inflammation and itching.

Aural eczematoid dermatitis can be treated with dilute aluminum acetate solution (Burow's solution), which can be applied as often as required for comfort. Itching and inflammation can be reduced with topical corticosteroids. If diffuse external otitis ensues, antibiotic therapy may be required (see p. 455).

External Otitis

External otitis is infection of the ear canal, typically by bacteria. Symptoms include itching, pain, and discharge. Diagnosis is based on inspection. Treatment is with topical drugs, including antibiotics, corticosteroids, and acetic acid or a combination.

External otitis may manifest as a localized furuncle or as a diffuse infection of the entire canal (generalized or diffuse external otitis). This condition is often called swimmer's ear because it sometimes afflicts people who swim. Malignant external otitis (see p. 455) is a severe Pseudomonas infection of the temporal bone and is especially dangerous in diabetics.

Etiology

Diffuse external otitis is usually caused by bacteria, such as Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus, or Escherichia coli. Fungal external otitis (otomycosis), typically caused by Aspergillus niger or Candida albicans, is less common. Furuncles usually are due to S. aureus.

Predisposing conditions include allergies, psoriasis, eczema, seborrheic dermatitis, decreased canal acidity (possibly due to the repeated presence of water), irritants (eg, hair spray, hair dye), and inadvertent injury to the canal caused by excessive cleaning with cotton swabs or other objects. Attempts to clean the ear canal may push debris and cerumen deeper into the canal; these accumulated substances tend to trap water, resulting in skin maceration that sets the stage for bacterial infection.

Symptoms and Signs

Patients have itching and pain. Sometimes, a foul-smelling discharge and hearing loss occur if the canal becomes swollen or filled with purulent debris. Exquisite tenderness accompanies traction of the pinna or pressure over the tragus. Otoscopic examination is painful and difficult to conduct. It shows the ear canal
to be red, swollen, and littered with moist, purulent debris. Otomycosis caused by *A. niger* usually manifests with grayish black or yellow dots (fungal conidiophores) surrounded by a cottonlike material (fungal hyphae). Infection caused by *C. albicans* does not show any visible fungi but usually contains a thickened, creamy white exudate.

Furuncles cause severe pain and may drain sanguineous, purulent material. They appear as a focal, erythematous swelling.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on inspection. When discharge is copious, external otitis can be difficult to differentiate from perforated otitis media; pain with pulling on the pinna may indicate an external otitis. Fungal infection is diagnosed by appearance or culture.

**Treatment**

- Topical acetic acid and corticosteroids

- Sometimes topical antibiotics

In diffuse external otitis, topical antibiotics and corticosteroids are effective. First, the infected debris should be gently and thoroughly removed from the canal with suction or dry cotton wipes. Mild external otitis can be treated by altering the ear canal's pH with 2% acetic acid and by relieving inflammation with topical hydrocortisone; these are given as 5 drops tid for 7 days. Moderate external otitis requires the addition of an antibacterial solution or suspension, such as neomycin, polymyxin, ciprofloxacin, or ofloxacin. When inflammation of the ear canal is relatively severe, an ear wick should be placed into the ear canal and wetted with the necessary drugs 4 times/day. The wick is left in place for 24 to 72 h, after which time the swelling may have receded enough to allow the instillation of drops directly into the canal.

Severe external otitis or the presence of cellulitis extending beyond the ear canal may require systemic antibiotics, such as cephalexin 500 mg po tid for 10 days or ciprofloxacin 500 mg po bid for 10 days. An analgesic, such as an NSAID or even an oral opioid, may be necessary for the first 24 to 48 h. Fungal external otitis requires thorough cleaning of the ear canal and application of an antifungal solution (eg, gentian violet, cresylate acetate, nystatin, clotrimazole). Repeated cleanings and treatments may be needed.

A furuncle, if obviously pointing, should be incised and drained. Incision is of little value, however, if the patient is seen at an early stage. Topical antibiotics are ineffective; oral antistaphylococcal antibiotics should be given. Analgesics, such as oxycodone with acetaminophen, may be necessary for pain relief. Dry heat can also lessen pain and hasten resolution.

**Prevention**

External otitis often can be prevented by irrigating the ears with a 1:1 mixture of rubbing alcohol and vinegar immediately after swimming. The alcohol helps remove water, and the vinegar alters the pH of the canal.

**Malignant External Otitis**

**Malignant external otitis is typically a *Pseudomonas* osteomyelitis of the temporal bone.**

Soft tissue, cartilage, and bone are all affected. The osteomyelitis spreads along the base of the skull and may cross the midline.

Malignant external otitis occurs mainly in elderly patients with diabetes or in immunocompromised patients and is often initiated by *Pseudomonas* external otitis. It is characterized by persistent and severe earache,
foul-smelling purulent otorrhea, and granulation tissue in the ear canal (usually at the junction of the bony and cartilaginous portions of the canal). Varying degrees of conductive hearing loss may occur. In severe cases, facial nerve paralysis may ensue.

Diagnosis is based on a CT scan of the temporal bone, which may show increased radiodensity in the air-cell system and middle ear radiolucency (deminerelization) in some areas. Cultures are done, and the ear canal is biopsied to differentiate the granulation tissue of this disorder from a malignant tumor.

Treatment is with a 6-wk IV course of a fluoroquinolone or an aminoglycoside-semisynthetic penicillin combination. Extensive bone disease may require more prolonged antibiotic therapy. Careful control of diabetes is essential. Surgery usually is not necessary.

**Obstructions**

The ear canal may be obstructed by cerumen (earwax), insertion of a foreign object, or an insect. Itching, pain, and temporary conductive hearing loss may result. Most causes of obstruction are readily apparent during otoscopic examination. Treatment is manual removal.

**Cerumen:** Cerumen may get pushed further into the ear canal and accumulate during ill-advised attempts to clean the ear canal with cotton swabs, resulting in obstruction. Cerumen solvents (hydrogen peroxide, carbamide peroxide, glycerin, triethanolamine) may be used to soften very hard wax before irrigation or direct removal. However, the prolonged use of these agents may lead to canal skin irritation or allergic reactions. Although cerumen may be removed by irrigation, rolling the cerumen out of the ear canal with a blunt curet or loop or removing it with a suction tip (eg, Baron, size 7 French) is quicker, neater, safer, and more comfortable for the patient. Irrigation is contraindicated if the patient has a history of otorrhea or perforation of the tympanic membrane; water entering the middle ear through a perforation may exacerbate chronic otitis media.

**Foreign bodies:** Foreign bodies are common, particularly among children, who often insert objects, particularly beads, erasers, and beans, into the ear canal. Foreign bodies may remain unnoticed until they provoke an inflammatory response, causing pain, itching, infection, and foul-smelling, purulent drainage. A foreign body in the ear canal is best removed by reaching behind it and rolling it out with a blunt hook. Forceps tend to push smooth objects deeper into the canal. Unfortunately, a foreign body lying medial to the isthmus (the bony cartilaginous junction of the external auditory canal) is difficult to remove without injuring the tympanic membrane and ossicular chain. Metal and glass beads can sometimes be removed by irrigation, but hygroscopic foreign bodies (eg, beans or other vegetable matter) swell when water is added, complicating removal. A general anesthetic may be needed when a child cannot remain still or when removal is difficult, threatening injury to the tympanic membrane or ossicles. Further, if manipulating a presumed foreign object results in bleeding, immediate otolaryngologic consultation should be sought. Bleeding may indicate a mucosal polyp originating in the middle ear, which may be attached to the ossicles or facial nerve.

Insects in the canal are most annoying while alive. Filling the canal with viscous lidocaine kills the insect, which provides immediate relief and allows the immobilized insect to be removed with forceps.

**Perichondritis**

Perichondritis is infection of the perichondrium of the pinna in which pus accumulates between the cartilage and the perichondrium.

Causes of perichondritis include trauma, insect bites, body piercings, and incision of superficial infections of the pinna. Because the cartilage's blood supply is provided by the perichondrium, separation of the perichondrium from both sides of the cartilage may lead to avascular necrosis and a deformed pinna. Septic necrosis may also ensue, often with infection by gram-negative bacilli. Symptoms include redness, pain, and swelling. The course of perichondritis tends to be indolent, long-term, and destructive.

The affected area is incised, and a drain is left in place for 24 to 72 h. Systemic antibiotics are initiated with an aminoglycoside and semisynthetic penicillin. Subsequent antibiotic choice is guided by culture.
and sensitivity tests. Warm compresses may help.
Chapter 51. Approach to the Patient With Nasal and Pharyngeal Symptoms

Introduction

The nose and pharynx (consisting of the nasopharynx, oropharynx, and hypopharynx) may be affected by inflammation, infection, trauma, tumors, and several miscellaneous conditions.

Anatomy

**Throat:** The uvula hangs in the midline at the far end of the soft palate. It varies greatly in length. A long uvula and loose or excess velopharyngeal tissue may cause snoring and occasionally contribute to obstructive sleep apnea.

Tonsils and adenoids are patches of lymphoid tissue surrounding the posterior pharynx in an area termed Waldeyer's ring. Their role is to combat infection.

The larynx is discussed in Ch. 54.

**Nose:** The nasal cavity is covered with a highly vascular mucosa that warms and humidifies incoming air. Each lateral wall of the cavity has 3 turbinates, which are bony shelves that increase the surface area, thereby allowing more effective heat and moisture exchange. Nasal mucus traps incoming particulate matter. The space between the middle and inferior turbinate is the middle meatus, into which the maxillary and most of the ethmoid sinuses drain. Polyps may develop between the turbinates, often in association with asthma, allergy, aspirin use, and cystic fibrosis.

**Sinuses:** The paranasal sinuses are mucus-lined bony cavities that connect to the nasopharynx. The 4 types are maxillary, frontal, ethmoid, and sphenoid sinuses. They are located in the facial and cranial bones (see Fig. 51-1). The physiologic role of the sinuses is unclear.

![Fig. 51-1. Paranasal sinuses.](image_url)

Evaluation

Examination of the nose and pharynx is part of every general physical examination.

**History:** General information includes use of alcohol or tobacco (both major risk factors for head and neck cancer) and systemic symptoms, such as fever and weight loss. Oropharyngeal symptoms include pain, ulcers, and difficulty swallowing or speaking. Nasal and sinus symptoms include presence and duration of congestion, discharge, or bleeding.

**Physical examination:** Most physicians use a head-mounted light. However, because the light cannot be precisely aligned on the axis of vision, it is difficult to avoid shadowing in narrow areas (eg, nasal cavity). Better illumination results with a head-mounted convex mirror; the physician looks through a hole in the center of the mirror, so the illumination is always on-axis. The head mirror reflects light from a source (any incandescent light) placed behind the patient and slightly to one side and requires practice to use effectively.

The nose is examined using a nasal speculum, which is held so that the 2 blades open in an anteroposterior (or slightly oblique) direction and do not press against the septum. The physician notes crusting, discharge, septal deviation, or perforation; whether mucosa is erythematous, boggy, or swollen; and presence of polyps. The skin over the frontal and maxillary sinuses is examined for erythema and tenderness, suggesting sinus inflammation.

If necessary, the nasopharynx and hypopharynx can be examined with mirrors, which should be warmed before use to avoid fogging. A small mirror is used for the nasopharynx. It is held just below the uvula, angling upward; the tongue is pushed down with a tongue blade. A larger mirror is used for the hypopharynx and larynx. The tongue is retracted by grasping it with a gauze pad, and the mirror is placed...
against the soft palate, angling downward. If patients do not tolerate mirror examination, a flexible fiberoptic nasopharyngoscope is helpful. A topical anesthetic (eg, lidocaine 4%) is sprayed in the nose and throat, and the nose is also sprayed with a decongestant (eg, phenylephrine 0.5%). After several minutes, the scope is gently passed through the nares, and the nasal cavity, hypopharynx, and larynx are inspected.

Neck examination consists of inspection and palpation for masses. If masses are found, the physician notes whether they are tender; fluctuant, firm, or stony hard; and movable or fixed. Masses caused by infection are tender and mobile; cancers tend to be not tender, hard, and fixed. Particular attention is paid to the cervical lymph nodes and thyroid and parotid glands.

Epistaxis

Epistaxis is nose bleeding. Bleeding can range from a trickle to a strong flow, and the consequences can range from a minor annoyance to life-threatening hemorrhage. Swallowed blood is a gastric irritant, so patients also may describe vomiting blood.

Pathophysiology

Most nasal bleeding is anterior, originating from a plexus of vessels in the anteroinferior septum (Kiesselbach's area).

Less common but more serious are posterior nosebleeds, which originate in the posterior septum overlying the vomer bone, or laterally on the inferior or middle turbinate. Posterior nosebleeds tend to occur in patients who have preexisting atherosclerotic vessels or bleeding disorders and have undergone nasal or sinus surgery.

Etiology

The most common causes of epistaxis are

• Local trauma (eg, nose blowing and picking)

• Drying of the nasal mucosa

There are a number of less common causes (see Table 51-1). Hypertension may contribute to the persistence of a nosebleed that has already begun but is unlikely to be the sole etiology.

Evaluation

History: History of present illness should try to determine which side began bleeding first; although major epistaxis quickly involves both nares, most patients can localize the initial flow to one side, which focuses the physical examination. Also, the duration of bleeding should be established, as well as any triggers (eg, sneezing, nose blowing, picking) and attempts by the patient to stop the bleeding. Important associated symptoms prior to onset include symptoms of a URI, sensation of nasal obstruction, and nasal or facial pain. The time and number of previous nose-bleeding episodes and their resolution should be identified.

[Table 51-1, Some Causes of Epistaxis]

Review of systems should ask about symptoms of excessive bleeding, including easy bruising; bloody or tarry stools; hemoptysis; blood in urine; and excess bleeding with toothbrushing, phlebotomy, or minor trauma.

Past medical history should note presence of known bleeding disorders (including a family history) and conditions associated with defects in platelets or coagulation, particularly cancer, cirrhosis, HIV, and pregnancy. Drug history should specifically query about use of drugs that may promote bleeding,
including aspirin and other NSAIDs, other antiplatelet drugs (eg, clopidogrel), heparin, and warfarin.

**Physical examination:** Vital signs should be reviewed for indications of intravascular volume depletion (tachycardia, hypotension) and marked hypertension. With active bleeding, treatment takes place simultaneously with evaluation.

During active bleeding, inspection is difficult, so attempts are first made to stop the bleeding as described below. The nose is then examined using a nasal speculum and a bright head lamp or head mirror, which leaves one hand free to manipulate suction or an instrument.

Anterior bleeding sites are usually apparent on direct examination. If no site is apparent and there have been only 1 or 2 minor nosebleeds, further examination is not needed. If bleeding is severe or recurrent and no site is seen, fiberoptic endoscopy may be necessary.

The general examination should look for signs of bleeding disorders, including petechiae, purpura, and perioral and oral mucosal telangiectasias as well as any intranasal masses.

**Red flags:** The following findings are of particular concern:

- Signs of hypovolemia or hemorrhagic shock
- Anticoagulant drug use
- Cutaneous signs of a bleeding disorder
- Bleeding not stopped by direct pressure or vasoconstrictor-soaked pledgets
- Multiple recurrences, particularly with no clear cause

**Interpretation of findings:** Many cases have a clear-cut trigger (particularly nose blowing or picking) as suggested by findings (see Table 51-1).

**Testing:** Routine laboratory testing is not required. Patients with symptoms or signs of a bleeding disorder and those with severe or recurrent epistaxis should have CBC, PT, and PTT.

CT may be done if a foreign body, a tumor, or sinusitis is suspected.

**Treatment**

Presumptive treatment for actively bleeding patients is that for anterior bleeding. The need for blood replacement is determined by the Hb level, symptoms of anemia, and vital signs. Any identified bleeding disorders are treated.

**Anterior epistaxis:** Bleeding can usually be controlled by pinching the nasal alae together for 10 min while the patient sits upright (if possible). If this maneuver fails, a cotton pledget impregnated with a vasoconstrictor (eg, phenylephrine 0.25%) and a topical anesthetic (eg, lidocaine 2%) is inserted and the nose pinched for another 10 min. The bleeding point may then be cauterized with electrocautery or silver nitrate on an applicator stick. Cauterizing 4 quadrants immediately adjacent to the bleeding vessel is most effective. Care must be taken to avoid burning the mucous membrane too deeply; therefore, silver nitrate is the preferred method. Alternatively, a nasal tampon of expandable foam may be inserted. Coating the tampon with a topical ointment, such as bacitracin or mupirocin, may help. If these methods are ineffective, various commercial nasal balloons can be used to compress bleeding sites. Alternatively, an anterior nasal pack consisting of 1/2-in petrolatum gauze may be inserted; up to 72 in of gauze may be required. This procedure is painful, and analgesics usually are needed; it should be used only when other methods fail or are not available.

**Posterior epistaxis:** Posterior bleeding may be difficult to control. Commercial nasal balloons are quick and convenient; a gauze posterior pack is effective but more difficult to position. Both are very
uncomfortable; IV sedation and analgesia may be needed, and hospitalization is required.

Commercial balloons are inserted according to the instructions accompanying the product.

The posterior gauze pack consists of 4-in gauze squares folded, rolled, tied into a tight bundle with 2 strands of heavy silk suture, and coated with antibiotic ointment. The ends of one suture are tied to a catheter that has been introduced through the nasal cavity on the side of the bleeding and brought out through the mouth. As the catheter is withdrawn from the nose, the postnasal pack is pulled into place above the soft palate in the nasopharynx. The 2nd suture hangs down the back of the throat and is trimmed below the level of the soft palate so that it can be used to remove the pack. The nasal cavity anterior to this pack is firmly packed with 1/2-in petrolatum gauze, and the 1st suture is tied over a roll of gauze at the anterior nares to secure the postnasal pack. The packing remains in place for 4 to 5 days. An antibiotic (eg, amoxicillin/clavulanate 875 mg po bid for 7 to 10 days) is given to prevent sinusitis and otitis media. Posterior nasal packing lowers the arterial $PO_2$, and supplementary $O_2$ is given while the packing is in place.

Rarely, the internal maxillary artery and its branches must be ligated to control the bleeding. The arteries may be ligated with clips using endoscopic or microscopic guidance and a surgical approach through the maxillary sinus. Alternatively, angiographic embolization may be done by a skilled radiologist.

**Bleeding disorders:** In Rendu-Osler-Weber syndrome, a split-thickness skin graft (septal dermatoplasty) reduces the number of nosebleeds and allows the anemia to be corrected. Laser (Nd:YAG) photocoagulation can be done in the operating room. Selective embolization also is very effective, particularly in patients who cannot tolerate general anesthesia or for whom surgical intervention has not been successful. New endoscopic sinus devices have made transnasal surgery more effective.

Blood may be swallowed in large amounts and, in patients with liver disease, should be eliminated promptly with enemas and cathartics to prevent hepatic encephalopathy. The GI tract should be sterilized with nonabsorbable antibiotics (eg, neomycin 1 g po qid) to prevent the breakdown of blood and the absorption of ammonia.

**Key Points**

- Most nosebleeds are anterior and stop with direct pressure.
- Screening (by history and physical examination) for bleeding disorders is important.
- Patients should always be asked about aspirin or ibuprofen use.

**Nasal Congestion and Rhinorrhea**

Nasal congestion and rhinorrhea (runny nose) are extremely common problems that commonly occur together but occasionally occur alone.

**Etiology**

The most common causes (see Table 51-2) are the following:

- Viral infections
- Allergic reactions

Dry air may provoke congestion. Acute sinusitis is slightly less common, and a nasal foreign body is unusual (and occurs predominantly in children).

Patients who use topical decongestants for > 1 day often experience significant rebound congestion when the effects of the drug wear off, causing them to continue using the decongestant in a vicious circle.
of persistent, worsening congestion. This situation (rhinitis medicamentosa) may persist for some time and may be misinterpreted as a continuation of the original problem rather than a consequence of treatment.

**Evaluation**

**History:** History of present illness should determine the nature of the discharge (eg, watery, mucoid, purulent, bloody) and whether discharge is chronic or recurrent. If recurrent, any relation to patient location, season, or exposure to potential triggering allergens (numerous) should be determined.

**Review of systems** should seek symptoms of possible causes, including fever and facial pain (sinusitis); watery, itchy eyes (allergies); and sore throat, malaise, fever, and cough (viral URI).

**Past medical history** should seek known allergies and existence of diabetes or immunocompromise. Drug history should ask specifically about topical decongestant use.

**Physical examination:** Vital signs are reviewed for fever.

Examination focuses on the nose and area over the sinuses. The face is inspected for focal erythema over the frontal and maxillary sinuses; these areas are also palpated for tenderness. Nasal mucosa is inspected for color (eg, red or pale), swelling, color and nature of discharge, and (particularly in children) presence of any foreign body.

**Red flags:** The following findings are of particular concern:

- Unilateral discharge, particularly if purulent or bloody
- Facial pain, tenderness, or both

**Interpretation of findings:** Symptoms and examination are often enough to suggest a diagnosis (see Table 51-2).

In children, unilateral foul-smelling discharge suggests a nasal foreign body. If no foreign body is seen, sinusitis is suspected when purulent rhinorrhea persists for > 10 days along with fatigue and cough.

**Testing:** Testing is generally not indicated for acute nasal symptoms unless invasive sinusitis is suspected in a diabetic or immunocompromised patient; these patients usually should undergo CT.

[Table 51-2, Some Causes of Nasal Congestion and Rhinorrhea]

**Treatment**

Specific conditions are treated. Symptomatic relief of congestion can be achieved with topical or oral decongestants. Topical decongestants include oxymetazoline, 2 sprays each nostril once/day or bid for 3 days. Oral decongestants include pseudoephedrine 60 mg bid. Prolonged use should be avoided.

Viral rhinorrhea can be treated with oral antihistamines (eg, diphenhydramine 25 to 50 mg po bid), which are recommended because of their anticholinergic properties unrelated to their H2-blocking properties.

Allergic congestion and rhinorrhea can be treated with antihistamines; in such cases, nonanticholinergic antihistamines (eg, fexofenadine 60 mg po bid) as needed provoke fewer adverse effects. Nasal corticosteroids (eg, mometasone 2 sprays each nostril daily) also help allergic conditions.

Antihistamines and decongestants are not recommended for children < 6 yr.

**Geriatrics Essentials**

Antihistamines and can have sedating and anticholinergic effects and should be given in decreased...
dosage in the elderly. Similarly, sympathomimetics should be used with the lowest dosage that is clinically effective.

**Key Points**

- Most nasal congestion and rhinorrhea are caused by URI or allergies.
- A foreign body should be considered in children.
- Rebound from topical decongestant overuse should also be considered.

**Neck Mass**

Patients or their family members may notice a mass on the neck, or one may be discovered during routine examination. A neck mass may be painless or painful depending on the cause. When a neck mass is painless, much time may pass before patients seek medical care.

**Etiology**

There are many causes of neck mass, including infectious, cancerous, and congenital causes (see Table 51-3).

The most common causes in younger patients include the following:

- Reactive adenitis
- Primary bacterial lymph node infection
- Systemic infections

[Table 51-3. Some Causes of Neck Mass]

Reactive adenitis occurs in response to viral or bacterial infection somewhere in the oropharynx. Some systemic infections (eg, mononucleosis, HIV, TB) cause cervical lymph node enlargement—usually generalized rather than isolated.

Congenital disorders may cause a neck mass, typically longstanding. The most common are thyroglossal duct cysts, branchial cleft cysts, and dermoid or sebaceous cysts.

Cancerous masses are more common among older patients but may occur in younger ones. These masses may represent a local primary tumor or lymph node involvement from a local, regional, or distant primary cancer. About 60% of supraclavicular triangle masses are metastases from distant primary sites. Elsewhere in the neck, 80% of cancerous cervical adenopathy originates in the upper respiratory or alimentary tract. Likely sites of origin are the posterior-lateral border of the tongue and the floor of the mouth followed by the nasopharynx, palatine tonsil, laryngeal surface of the epiglottis, and hypopharynx, including the pyriform sinuses.

The thyroid gland may enlarge in various disorders, including simple nontoxic goiter, subacute thyroiditis, and, less often, thyroid cancer.

**Evaluation**

**History: History of present illness** should note how long the mass has been present and whether it is painful. Important associated acute symptoms include sore throat, URI symptoms, and toothache.

**Review of systems** should ask about difficulty swallowing or speaking and symptoms of chronic disease (eg, fever, weight loss, malaise). Regional and distant cancers causing metastases to the neck occasionally cause symptoms in their system of origin (eg, cough in lung cancer, swallowing difficulty in
esophageal cancer). Because numerous cancers can metastasize to the neck, a complete review of systems is important to help identify a source.

**Past medical history** should inquire about known HIV or TB and risk factors for them. Risk factors for cancer are assessed, including consumption of alcohol or use of tobacco (particularly snuff or chewing tobacco), ill-fitting dental appliances, and chronic oral candidiasis. Poor oral hygiene also may be a risk.

**Physical examination:** The neck mass is palpated to determine consistency (ie, whether soft and fluctuant, rubbery, or hard) and presence and degree of tenderness. Whether the mass is freely mobile or appears fixed to the skin or underlying tissue also needs to be determined.

The scalp, ears, nasal cavities, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx are closely inspected for signs of infection and any other visible lesions. Teeth are percussed to detect the exquisite tenderness of root infection. The base of the tongue, floor of the mouth, and the thyroid and salivary glands are palpated for masses.

The breasts and prostate gland are palpated for masses, and the spleen is palpated for enlargement. Stool is checked for occult blood, suggestive of a GI cancer.

Other lymph nodes are palpated (eg, axillary, inguinal).

**Red flags:** The following findings are of particular concern:

- Hard, fixed mass
- Older patient
- Presence of oropharyngeal lesions (other than simple pharyngitis or dental infection)
- A history of persistent hoarseness or dysphagia

**Interpretation of findings:** Important differentiating factors for a neck mass (see also [Table 51-3](#)) include acuity, pain and tenderness, and consistency and mobility.

A new mass (ie, developing over only a few days), particularly after symptoms of a URI or pharyngitis, suggests benign reactive lymphadenopathy. An acute tender mass suggests lymphadenitis or an infected dermoid cyst.

A chronic mass in younger patients suggests a cyst. A non-midline mass in older patients, particularly those with risk factors, should be considered cancer until proven otherwise; a midline mass is likely of thyroid origin (benign or malignant).

Pain, tenderness, or both in the mass suggest inflammation (particularly infectious), whereas a painless mass suggests a cyst or tumor. A hard, fixed, nontender mass suggests cancer, whereas rubbery consistency and mobility suggest otherwise.

Generalized adenopathy and splenomegaly suggest infectious mononucleosis or a lymphoreticular cancer. Generalized adenopathy alone may suggest HIV infection, particularly in those with risk factors.

Red and white mucosal patches (erythroplakia and leukoplakia) in the oropharynx may be malignant lesions responsible for the neck mass.

Difficulty swallowing may be noted with thyroid enlargement or cancer originating in various sites in the neck. Difficulty speaking suggests a cancer involving the larynx or recurrent laryngeal nerve.

**Testing:** If the nature of the mass is readily apparent (eg, lymphadenopathy caused by recent pharyngitis) or is in a healthy young patient with a recent, tender swelling and no other findings, then no immediate testing is required. However, the patient is reexamined regularly; if the mass fails to resolve,
Further evaluation is needed.

Most other patients should have a CBC and chest x-ray. Those with findings suggesting specific causes should also have testing for those disorders (see Table 51-3).

If examination reveals an oral or nasopharyngeal lesion that fails to begin resolving within 2 wk, testing may include CT or MRI and fine-needle biopsy of that lesion.

In young patients with no risk factors for head and neck cancer and no other apparent lesions, the neck mass may be biopsied.

Older patients, particularly those with risk factors for cancer, should first undergo further testing to identify the primary site; biopsy of the neck mass may simply reveal undifferentiated squamous cell carcinoma without illuminating the source. Such patients should have direct laryngoscopy, bronchoscopy, and esophagoscopy with biopsy of all suspicious areas. CT of the head, neck, and chest and possibly a thyroid scan are done. If a primary tumor is not found, fine-needle aspiration biopsy of the neck mass should be done, which is preferable to an incisional biopsy because it does not leave a transected mass in the neck. If the neck mass is cancerous and a primary tumor has not been identified, random biopsy of the nasopharynx, palatine tonsils, and base of the tongue should be considered.

Treatment

Treatment is directed at the cause.

Key Points

• An acute neck mass in younger patients is usually benign.

• Neck mass in an elderly patient raises concern of cancer.

• Thorough oropharyngeal examination is important.

Pharyngitis

Pharyngitis (sore throat) is pain in the posterior pharynx that occurs with or without swallowing. Pain can be severe; many patients refuse oral intake.

Etiology

Sore throat results from infection; the most common cause is

• Tonsillopharyngitis

Rarely, an abscess or epiglottitis is involved; although uncommon, these are of particular concern because they may compromise the airway.

Tonsillopharyngitis: Tonsillopharyngitis is predominantly a viral infection; a lesser number of cases are caused by bacteria.

The respiratory viruses (rhinovirus, adenovirus, influenza, coronavirus, respiratory syncytial virus) are the most common viral causes, but occasionally Epstein-Barr virus (the cause of mononucleosis), herpes simplex, cytomegalovirus, or primary HIV infection is involved.

The main bacterial cause is group Aβ-hemolytic streptococcus (GABHS), which, although estimates vary, causes perhaps 10% of cases in adults and slightly more in children. GABHS is a concern because of the possibility of the poststreptococcal sequelae of rheumatic fever, glomerulonephritis, and abscess. Uncommon bacterial causes include gonorrhea, diphtheria, mycoplasma, and chlamydia.
Abscess: An abscess in the pharyngeal area (peritonsillar, parapharyngeal, and, in children, retropharyngeal) is uncommon but causes significant throat pain. The usual causative organism is *GABHS*.

Epiglottitis: Epiglottitis, perhaps better termed supraglottitis, used to occur primarily in children and usually was caused by *Haemophilus influenzae* type B (HiB). Now, because of widespread childhood vaccination against HiB, supraglottitis/epiglottitis has been almost eradicated in children (more cases occur in adults). Causal organisms in children and adults include *Streptococcus pneumoniae*, *Staphylococcus aureus*, nontypeable *H. influenzae*, *Haemophilus parainfluenzae*, β-hemolytic streptococci, *Branhamella catarrhalis*, and *Klebsiella pneumoniae*. HiB is still a cause in adults and unvaccinated children.

Evaluation

**History:** History of present illness should note the duration and severity of sore throat.

**Review of systems** should seek important associated symptoms, such as runny nose, cough, and difficulty swallowing, speaking, or breathing. The presence and duration of any preceding weakness and malaise (suggesting mononucleosis) are noted.

**Past medical history** should seek history of previous documented mononucleosis (recurrence is highly unlikely). Social history should inquire about close contact with people with documented GABHS infection, risk factors for gonorrhea transmission (e.g., recent oral-genital sexual contact), and risk factors for HIV acquisition (e.g., unprotected intercourse, multiple sex partners, IV drug abuse).

**Physical examination:** General examination should note fever and signs of respiratory distress, such as tachypnea, dyspnea, stridor, and, in children, the tripod position (sitting upright, leaning forward with neck hyperextended and jaw thrust forward).

Pharyngeal examination should not be done in children if supraglottitis/epiglottitis is suspected, because it may trigger complete airway obstruction. Adults with no respiratory distress may be examined but with care. Erythema, exudates, and any signs of swelling around the tonsils or retropharyngeal area should be noted. Whether the uvula is in the midline or appears pushed to one side should also be noted.

The neck is examined for presence of enlarged, tender lymph nodes. The abdomen is palpated for presence of splenomegaly.

**Red flags:** The following findings are of particular concern:

- Stridor or other sign of respiratory distress
- Drooling
- Muffled, "hot potato" voice
- Visible bulge in pharynx

**Interpretation of findings:** Supraglottitis/epiglottitis and pharyngeal abscess pose a threat to the airway and must be differentiated from simple tonsillopharyngitis, which is uncomfortable but not acutely dangerous. Clinical findings help make this distinction.

With supraglottitis/epiglottitis, there is abrupt onset of severe throat pain and dysphagia, usually with no preceding URI symptoms. Children often have drooling and signs of toxicity. Sometimes (more often in children), there are respiratory manifestations, with tachypnea, dyspnea, stridor, and sitting in the tripod position. If examined, the pharynx almost always appears unremarkable.

Pharyngeal abscess and tonsillopharyngitis both may cause pharyngeal erythema, exudate, or both. However, some findings are more likely in one condition or another:
• Pharyngeal abscess: Muffled, "hot potato" voice (speaking as if a hot object is being held in the mouth); visible focal swelling in the posterior pharyngeal area (often with deviation of the uvula)

• Tonsillopharyngitis: Accompanied by URI symptoms (eg, runny nose, cough)

Although tonsillopharyngitis is easily recognized clinically, its cause is not. Manifestations of viral and GABHS infection overlap significantly, although URI symptoms are more common with a viral cause. In adults, clinical criteria that increase suspicion of GABHS as a cause include

• Tonsillar exudate
• Tender lymphadenopathy
• Fever (including history)
• Absence of cough

Those with ≤ 1 criterion reasonably may be presumed to have viral illness. If ≥ 2 criteria are present, the likelihood of GABHS is high enough to warrant testing but probably not high enough to warrant antibiotics, but this decision needs to be patient-specific (ie, threshold for testing and treatment may be lower in those at risk because of diabetes or immunocompromise). In children, testing usually is done.

Regarding rarer causes of tonsillopharyngitis, infectious mononucleosis should be considered when there is posterior cervical or generalized adenopathy, hepatosplenomegaly, and fatigue and malaise for > 1 wk. Those with no URI symptoms but recent oral-genital contact may have pharyngeal gonorrhea. A dirty-gray, thick, tough membrane on the posterior pharynx that bleeds if peeled away indicates diphtheria (rare in the US). HIV infection should be considered in patients with risk factors.

Testing: If supraglottitis/epiglottitis is considered possible after evaluation, testing is required. Patients who do not appear seriously ill and have no respiratory symptoms may have plain lateral neck x-rays to look for an edematous epiglottis. However, a child who appears seriously ill or has stridor or any other respiratory symptoms should not be transported to the x-ray suite. Such patients (and those with positive or equivocal x-ray findings) usually should have flexible fiberoptic laryngoscopy. (CAUTION: Examination of the pharynx and larynx may precipitate complete respiratory obstruction in children, and the pharynx and larynx should not be directly examined except in the operating room, where the most advanced airway intervention is available.)

Many abscesses are managed clinically, but if location and extent are unclear, immediate CT of the neck should be done.

In tonsillopharyngitis, throat culture is the only reliable way to differentiate viral infection from GABHS. To balance timeliness of diagnosis, cost, and accuracy, one strategy in children is to do a rapid strep screen in the office, treat if positive, and send a formal culture if negative. In adults, because other bacterial pathogens may be involved, throat culture for all bacterial pathogens is appropriate for those meeting clinical criteria described previously.

Testing for mononucleosis, gonorrhea, or HIV is done only when clinically suspected.

Treatment

Specific conditions are treated. Those with severe symptoms of tonsillopharyngitis may be started on a broad-spectrum antibiotic (eg, amoxicillin/clavulanate) pending culture results.

Symptomatic treatments such as warm saltwater gargles and topical anesthetics (eg, benzocaine, lidocaine, dyclonine) may help temporarily relieve pain in tonsillopharyngitis. Patients in severe pain (even from tonsillopharyngitis) may require short-term use of opioids.
Key Points

• Most sore throats are caused by viral tonsillopharyngitis.

• It is difficult to clinically distinguish viral from bacterial causes of tonsillopharyngitis.

• Abscess and epiglottitis are rare but serious causes.

• Severe sore throat in a patient with a normal-appearing pharynx should raise suspicion of epiglottitis.

Smell and Taste Abnormalities

Because distinct flavors depend on aromas to stimulate the olfactory chemoreceptors, smell and taste are physiologically interdependent. Dysfunction of one often disturbs the other. Disorders of smell and taste are rarely incapacitating or life threatening, so they often do not receive close medical attention, although their effect on quality of life can be severe.

Taste: Although abnormal taste sensations may be due to mental disorders, local causes should always be sought. Glossopharyngeal and facial nerve integrity can be determined by testing taste on both sides of the dorsum of the tongue with sugar, salt, vinegar (acid), and quinine (bitter).

Drying of the oral mucosa caused by heavy smoking, Sjogren's syndrome, radiation therapy of the head and neck, or desquamation of the tongue can impair taste, and various drugs (eg, those with anticholinergic properties and vincristine) alter taste. In all instances, the gustatory receptors are diffusely involved. When limited to one side of the tongue (eg, in Bell's palsy), ageusia (loss of the sense of taste) is rarely noticed.

Smell: The inability to detect certain odors, such as gas or smoke, may be dangerous, and several systemic and intracranial disorders should be excluded before dismissing symptoms as harmless. Whether brain stem disease (involvement of the nucleus solitarius) can cause disorders of smell and taste is uncertain, because other neurologic manifestations usually take precedence.

Anosmia (loss of the sense of smell) is probably the most common abnormality. Hyperosmia (increased sensitivity to odors) usually reflects a neurotic or histrionic personality but can occur intermittently with seizure disorders. Dysosmia (disagreeable or distorted sense of smell) may occur with infection of the nasal sinuses, partial damage to the olfactory bulbs, or mental depression. Some cases, accompanied by a disagreeable taste, result from poor dental hygiene. Uncinate epilepsy can produce brief, vivid, unpleasant olfactory hallucinations. Hyposmia (diminished sense of smell) and hypogeusia (diminished sense of taste) can follow acute influenza, usually temporarily.

Rarely, idiopathic dysgeusia (distorted sense of taste), hypogeusia, and dysosmia respond to zinc supplementation.

Anosmia

Anosmia is complete loss of smell. Hyposmia is partial loss of smell. Most patients with anosmia have normal perception of salty, sweet, sour, and bitter substances but lack flavor discrimination, which largely depends on olfaction. Therefore, they often complain of losing the sense of taste (ageusia) and of not enjoying food. If unilateral, anosmia is often unrecognized.

Etiology

Anosmia occurs when intranasal swelling or other obstruction prevents odors from gaining access to the olfactory area; when the olfactory neuroepithelium is destroyed; or when the olfactory nerve fila, bulbs, tracts, or central connections are destroyed (see Table 51-4).

Major causes include
• Head trauma (young adults)

• Viral infections and Alzheimer’s disease (older adults)

[Table 51-4. Some Causes of Anosmia]

Prior URI, especially influenza infection, is implicated in 14 to 26% of all presenting cases of hyposmia or anosmia.

Drugs can contribute to anosmia in susceptible patients. Other causes include prior head and neck radiation, recent nasal or sinus surgery, nasal and brain tumors, and toxins. The role of tobacco is uncertain.

**Evaluation**

**History:** History of present illness should assess the time course of symptoms and their relation to any URI or head injury. Important associated symptoms are nasal congestion, rhinorrhea, or both. The nature of rhinorrhea should be assessed (eg, watery, mucoid, purulent, bloody).

**Review of systems** should assess neurologic symptoms, particularly those involving mental status (eg, difficulty with recent memory) and cranial nerves (eg, diplopia, difficulty speaking or swallowing, tinnitus, vertigo).

**Past medical history** should include history of sinus disorders, cranial trauma or surgery, allergies, drugs used, and exposure to chemicals or fumes.

**Physical examination:** The nasal passages should be inspected for swelling, inflammation, discharge, and polyps. Having the patient breathe through each nostril sequentially (while the other is manually occluded) may help identify obstruction.

A complete neurologic examination, particularly of mental status and cranial nerves, is done.

**Red flags:** The following findings are of particular concern:

• Previous head injury

• Neurologic symptoms or signs

• Sudden onset

**Interpretation of findings:** Sudden onset after significant head trauma or toxin exposure strongly implicates that event as the cause.

A history of chronic rhinosinusitis is suggestive, particularly when significant congestion, polyps, or both are visible on examination. However, because these findings are common in the population, the physician should be wary of missing another disorder. Progressive confusion and recent memory loss in an elderly patient suggest Alzheimer’s disease as a cause. Waxing and waning neurologic symptoms affecting multiple areas suggest a neurodegenerative disease such as multiple sclerosis. Slowly progressive anosmia in an elderly patient with no other symptoms or findings suggests normal aging as the cause.

**Testing:** An in-office test of olfaction can help confirm olfactory dysfunction. Commonly, one nostril is pressed shut, and a pungent odor such as from a vial containing coffee, cinnamon, or tobacco is placed under the open nostril; if the patient can identify the substance, olfaction is presumed intact. The test is repeated on the other nostril to determine whether the response is bilateral. Unfortunately, the test is crude and unreliable.

If anosmia is present and no cause is readily apparent on clinical evaluation (see [Table 51-4](#)), patients
should have CT of the head (including sinuses) with contrast to rule out a tumor or unsuspected fracture of the floor of the anterior cranial fossa. MRI is also used to evaluate intracranial disease and may be needed as well, particularly in those patients with no nasal or sinus pathology on CT.

A psychophysical assessment of odor and taste identification and threshold detection is done as well. This assessment commonly involves use of one or several commercially available testing kits. One kit uses a scratch-and-sniff battery of odors, whereas another kit involves sequential dilutions of an odorous chemical.

**Treatment**

Specific causes are treated, although smell does not always recover even after successful treatment of sinusitis.

There are no treatments for anosmia. Patients who retain some sense of smell may find adding concentrated flavoring agents to food improves their enjoyment of eating. Smoke alarms, important in all homes, are even more essential for patients with anosmia. Patients should be cautioned about consumption of stored food and use of natural gas for cooking or heating, because they have difficulty detecting food spoilage or gas leaks.

**Geriatrics Essentials**

There is a significant loss of olfactory receptor neurons with normal aging, leading to a marked diminution of the sense of smell. Changes are usually noticeable by age 60 and can be marked after age 70.

**Key Points**

- Anosmia may be part of normal aging.
- Common causes include URI, sinusitis, and head trauma.
- Cranial imaging is typically required unless the cause is obvious.
Chapter 52. Oral and Pharyngeal Disorders

Introduction

Oral and pharyngeal disorders include adenoid disorders, epiglottitis, parapharyngeal abscess, peritonsillar abscess and cellulitis, retropharyngeal abscess, salivary stones, sialadenitis, submandibular space infection, tonsilloliths, Tornwaldt's cyst, and velopharyngeal insufficiency. Oral, pharyngeal, and salivary gland tumors are discussed in Ch. 55.

Sialadenitis

Sialadenitis is bacterial infection of a salivary gland, usually due to an obstructing stone or gland hyposecretion. Symptoms are swelling, pain, redness, and tenderness. Diagnosis is clinical. CT, ultrasound, and MRI may help identify the cause. Treatment is with antibiotics.

Etiology

Sialadenitis usually occurs after hyposecretion or duct obstruction but may develop without an obvious cause. The major salivary glands are the parotid, submandibular, and sublingual glands. Sialadenitis is most common in the parotid gland and typically occurs in patients in their 50s and 60s, in chronically ill patients with xerostomia, in those with Sjogren's syndrome, and in those who have had radiation therapy to the oral cavity. Teenagers and young adults with anorexia are also prone to this disorder. The most common causative organism is Staphylococcus aureus; others include streptococci, coliforms, and various anaerobic bacteria.

Symptoms and Signs

Fever, chills, and unilateral pain and swelling develop. The gland is firm and diffusely tender, with erythema and edema of the overlying skin. Pus can often be expressed from the duct by compressing the affected gland and should be cultured. Focal enlargement may indicate an abscess.

Diagnosis

CT, ultrasound, and MRI can confirm sialadenitis or abscess that is not obvious clinically, although MRI may miss an obstructing stone.

Treatment

• Antistaphylococcal antibiotics

• Local measures (eg, sialagogues, warm compresses)

Initial treatment is with antibiotics active against S. aureus (eg, dicloxacillin, 250 mg po qid, a 1st-generation cephalosporin, or clindamycin), modified according to culture results. With the increasing prevalence of methicillin-resistant S. aureus, especially among the elderly living in extended-care nursing facilities, vancomycin is often required. Hydration, sialagogues (eg, lemon juice, hard candy, or some other substance that triggers saliva flow), warm compresses, gland massage, and good oral hygiene are also important. Abscesses require drainage. Occasionally, a superficial parotidectomy or submandibular gland excision is indicated for patients with chronic or relapsing sialadenitis.

Other Salivary Gland Infections

Mumps often cause parotid swelling (see Table 155-1 on p. 1462). Patients with HIV infection often have parotid enlargement secondary to one or more lymphoepithelial cysts. Cat-scratch disease caused by Bartonella infection often invades periparotid lymph nodes and may infect the parotid glands by contiguous spread. Although cat-scratch disease is self-limited, antibiotic therapy is often provided, and incision and drainage are necessary if an abscess
develops.

Atypical mycobacterial infections in the tonsils or teeth may spread contiguously to the major salivary glands. The PPD may be negative, and the diagnosis may require biopsy and tissue culture for acid-fast bacteria. Treatment recommendations are controversial. Options include surgical debridement with curettage, complete excision of the infected tissue, and use of anti-TB drug therapy (rarely necessary).

**Salivary Stones**

*(Sialolithiasis)*

Stones composed of Ca salts often obstruct salivary glands, causing pain, swelling, and sometimes infection. Diagnosis is made clinically or with CT, ultrasonography, or sialography. Treatment involves stone expression with saliva stimulants, manual manipulation, a probe, or surgery.

The major salivary glands are the paired parotid, submandibular, and sublingual glands. Stones in the salivary glands are most common among adults. Eighty percent of stones originate in the submandibular glands and obstruct Wharton's duct. Most of the rest originate in the parotid glands and block Stensen's duct. Only about 1% originate in the sublingual glands. Multiple stones occur in about 25% of patients.

**Etiology**

Most salivary stones are composed of Ca phosphate with small amounts of Mg and carbonate. Patients with gout may have uric acid stones. Stone formation requires a nidus on which salts can precipitate during salivary stasis. Stasis occurs in patients who are debilitated, dehydrated, have reduced food intake, or take anticholinergics. Persisting or recurrent stones predispose to infection of the involved gland (sialadenitis—see p. 469).

**Symptoms and Signs**

Obstructing stones cause glandular swelling and pain, particularly after eating, which stimulates saliva flow. Symptoms may subside after a few hours. Relief may coincide with a gush of saliva. Some stones cause intermittent or no symptoms. If a stone is lodged distally, it may be visible or palpable at the duct's outlet.

**Diagnosis**

- Clinical evaluation
- Sometimes imaging (eg, CT, ultrasonography, sialography)

If a stone is not apparent on examination, the patient can be given a sialagogue (eg, lemon juice, hard candy, or some other substance that triggers saliva flow). Reproduction of symptoms is almost always diagnostic of a stone. CT, ultrasonography, and sialography are highly sensitive and are used if clinical diagnosis is equivocal. Contrast sialography may be done through a catheter inserted into the duct and can differentiate between stone, stenosis, and tumor. This technique is occasionally therapeutic. Because 90% of submandibular calculi are radiopaque and 90% of parotid calculi are radiolucent, plain x-rays are not always accurate. MRI is not indicated.

**Treatment**

- Local measures (eg, sialagogues, massage)
- Sometimes manual expression or surgical removal

Analgesics, hydration, and massage can relieve symptoms. Antistaphylococcal antibiotics can be used to prevent acute sialadenitis if started early. Stones may pass spontaneously or when salivary flow is
stimulated by sialagogues; patients are encouraged to suck a lemon wedge or sour candy every 2 to 3 h. Stones right at the duct orifice can sometimes be expressed manually by squeezing with the fingertips. Dilation of the duct with a small probe may facilitate expulsion. Surgical removal of stones succeeds if other methods fail. Stones at or near the orifice of the duct may be removed transorally, whereas those in the hilum of the gland often require complete excision of the salivary gland.

**Submandibular Space Infection**

(Ludwig's Angina)

Submandibular space infection is acute cellulitis of the soft tissues below the mouth. Symptoms include pain, dysphagia, and potentially fatal airway obstruction. Diagnosis usually is clinical. Treatment includes airway management, surgical drainage, and IV antibiotics.

Submandibular space infection is a rapidly spreading, bilateral, indurated cellulitis occurring in the suprahypoid soft tissues, the floor of the mouth, and both sublingual and submaxillary spaces without abscess formation. Although not a true abscess, it resembles one clinically and is treated similarly.

The condition usually develops from an odontogenic infection, especially of the 2nd and 3rd mandibular molars, or as an extension of peritonsillar cellulitis. Contributing factors may include poor dental hygiene, tooth extractions, and trauma (eg, fractures of the mandible, lacerations of the floor of the mouth).

**Symptoms and Signs**

Early manifestations are pain in any involved teeth, with severe, tender, localized submental and sublingual induration. Board-like firmness of the floor of the mouth and brawny induration of the suprahypoid soft tissues may develop rapidly. Drooling, trismus, dysphagia, stridor caused by laryngeal edema, and elevation of the posterior tongue against the palate may be present. Fever, chills, and tachycardia are usually present as well. The condition can cause airway obstruction within hours and does so more often than do other neck infections.

**Diagnosis**

The diagnosis usually is obvious. If not, CT is done.

**Treatment**

- Maintenance of airway patency
- Surgical incision and drainage
- Antibiotics active against oral flora

Maintaining airway patency is of the highest priority. Because swelling makes oral endotracheal intubation difficult, fiberoptic nasotracheal intubation done with topical anesthesia in the operating room or ICU with the patient awake is preferable. Some patients require a tracheotomy. Patients without immediate need for intubation require intense observation and may benefit temporarily from a nasal trumpet.

Incision and drainage with placement of drains deep into the mylohyoid muscles relieve the pressure. Antibiotics should be chosen to cover both oral anaerobes and aerobes (eg, clindamycin, ampicillin/sulbactam, high-dose penicillin).

**Adenoid Disorders**

Hypertrophy or inflammation of the adenoids is common among children. Symptoms include nasal obstruction, sleep disturbances, and middle ear effusions with hearing loss. Diagnosis is enhanced by flexible fiberoptic nasopharyngoscopy. Treatment often includes intranasal corticosteroids, antibiotics, and, for significant nasal obstruction or persistent recurrent acute
Adenoidectomy.

The adenoids are a rectangular mass of lymphatic tissue in the posterior nasopharynx. They are largest in children 2 to 6 yr. Enlargement may be physiologic or secondary to viral or bacterial infection, allergy, irritants, and, possibly, gastroesophageal reflux. Other risk factors include ongoing exposure to bacterial or viral infection (eg, to multiple children at a child care center). Severe hypertrophy can obstruct the eustachian tubes (causing otitis media), posterior choanae (causing sinusitis), or both.

Symptoms and Signs

Although patients with adenoid hypertrophy may not complain of symptoms, they usually have chronic mouth breathing, snoring, sleep disturbance, halitosis, recurrent acute otitis media, conductive hearing loss (secondary to recurrent otitis media or persistent middle ear effusions), and a hyponasal voice quality. Chronic adenoiditis can also cause chronic or recurrent nasopharyngitis, rhinosinusitis, epistaxis, halitosis, and cough.

Diagnosis

• Flexible nasopharyngoscopy

Adenoid hypertrophy is suspected in children and adolescents with characteristic symptoms, persistent middle ear effusions, or recurrent acute otitis media or rhinosinusitis. Similar symptoms and signs in a male adolescent may result from an angiofibroma. The gold standard for office assessment of the nasopharynx is flexible nasopharyngoscopy. X-ray imaging and sleep tape recording, although also often used, are not as accurate. A sleep study may help define the severity of any sleep disturbance due to chronic obstruction.

Treatment

• Treatment of cause

• Sometimes adenoidectomy

Underlying allergy is treated with intranasal corticosteroids, and underlying bacterial infection is treated with antibiotics. In children with persistent middle ear effusions or frequent otitis media, adenoidectomy often limits recurrence. Children > 4 yr who require tympanostomy tubes often undergo adenoidectomy when tubes are placed. Surgery is also recommended for younger children with recurrent epistaxis or significant nasal obstruction (eg, sleep disturbance, voice change). Although it requires general anesthesia, adenoidectomy usually can be done on an outpatient basis with recovery in 48 to 72 h.

Retropharyngeal Abscess

Retropharyngeal abscesses, most common among young children, can cause sore throat, fever, neck stiffness, and stridor. Diagnosis requires lateral neck x-ray or CT. Treatment is with endotracheal intubation, drainage, and antibiotics.

Retropharyngeal abscesses develop in the retropharyngeal lymph nodes at the back of the pharynx, adjacent to the vertebrae. They can be seeded by infection of the pharynx, sinuses, adenoids, or nose. They occur mainly in children 1 to 8 yr, as the retropharyngeal lymph nodes begin to recede by 4 to 5 yr. However, adults may develop infection after foreign body ingestion or after instrumentation. Common organisms include aerobic (Streptococcus and Staphylococcus sp) and anaerobic (Bacteroides and Fusobacterium) bacteria and, increasingly in adults and children, HIV and TB.

The most serious consequences include airway obstruction, septic shock, rupture of the abscess into the airway resulting in aspiration pneumonia or asphyxia, mediastinitis, carotid rupture, and suppurative thrombophlebitis of the internal jugular veins (Lemierre syndrome).
Symptoms and signs are usually preceded in children by an acute URI and in adults by foreign body ingestion or instrumentation. Children may have odynophagia, dysphagia, fever, cervical lymphadenopathy, nuchal rigidity, stridor, dyspnea, snoring or noisy breathing, and torticollis. Adults may have severe neck pain but less often have stridor. The posterior pharyngeal wall may bulge to one side.

**Diagnosis**

- CT

Diagnosis is suspected in patients with severe, unexplained sore throat and neck stiffness; stridor; or noisy breathing. Lateral soft-tissue x-rays of the neck, taken in the maximum possible hyperextension and during inspiration, may show focal widening of the prevertebral soft tissues, reversal of normal cervical lordosis, air in the prevertebral soft tissues, or erosion of the adjacent vertebral body. CT can help diagnose questionable cases, help differentiate cellulitis from an abscess, and assess extent of the abscess.

**Treatment**

- Antibiotics (eg, ceftriaxone, clindamycin)

- Usually surgical drainage

Antibiotics, such as a broad-spectrum cephalosporin (eg, ceftriaxone 50 to 75 mg/kg IV once/day) or clindamycin, may occasionally be sufficient for children with small abscesses. However, most patients also require drainage through an incision in the posterior pharyngeal wall. Endotracheal intubation is done preoperatively and maintained for 24 to 48 h.

**Tornwaldt's Cyst**

*(Pharyngeal Bursa)*

Tornwaldt's cyst is a rare cyst in the midline of the nasopharynx that may become infected.

Tornwaldt's cyst is a remnant of the embryonal notochord superficial to the superior constrictor muscle of the pharynx and is covered by the mucous membrane of the nasopharynx. It may become infected, causing persistent purulent drainage with a foul taste and odor, eustachian tube obstruction, and sore throat.

Purulent exudate may be seen at the opening of the cyst. Diagnosis is based on nasopharyngoscopy supplemented by CT or MRI when the diagnosis is in doubt. Treatment consists of marsupialization or excision.

**Velopharyngeal Insufficiency**

Velopharyngeal insufficiency is incomplete closure of a sphincter between the oropharynx and nasopharynx, often resulting from anatomic abnormalities of the palate and causing hypernasal speech. Treatment is with speech therapy and surgery.

Velopharyngeal insufficiency is incomplete closure of the velopharyngeal sphincter between the oropharynx and the nasopharynx. Closure, normally achieved by the sphincteric action of the soft palate and the superior constrictor muscle, is impaired in patients with cleft palate, repaired cleft palate, congenitally short palate, submucous cleft palate, palatal paralysis, and, sometimes, enlarged tonsils. The condition may also result when adenoidectomy or uvulopalatopharyngoplasty is done in a patient with a congenital underdevelopment (submucous cleft) or paralysis of the palate.

**Symptoms and Signs**
Speech in a patient with velopharyngeal insufficiency is characterized by hypernasal resonant voice, nasal emission of air, nasal turbulence, and inability to produce sounds requiring oral pressure (plosives). Severe velopharyngeal insufficiency results in regurgitation of solid foods and fluids through the nose. Inspection of the palate during phonation may reveal palatal paralysis.

**Diagnosis**

- Direct inspection with a fiberoptic nasoendoscope

The diagnosis is suspected in patients with the typical speech abnormalities. Palpation of the midline of the soft palate may reveal an occult submucous cleft. Direct inspection with a fiberoptic nasoendoscope is the primary diagnostic technique. Multiview videofluoroscopy during connected speech and swallowing (modified barium swallow), done in conjunction with a speech pathologist, can also be used.

**Treatment**

- Surgical repair and speech therapy

Treatment consists of speech therapy and surgical correction by a palatal elongation pushback procedure, posterior pharyngeal wall implant, pharyngeal flap, or pharyngoplasty, depending on the mobility of the lateral pharyngeal walls, the degree of velar elevation, and the size of the defect.

**Tonsillopharyngitis**

(See also p. 1232.)

Tonsillopharyngitis is acute infection of the pharynx, palatine tonsils, or both. Symptoms may include sore throat, dysphagia, cervical lymphadenopathy, and fever. Diagnosis is clinical, supplemented by culture or rapid antigen test. Treatment depends on symptoms and, in the case of group A β-hemolytic streptococcus, involves antibiotics.

The tonsils participate in systemic immune surveillance. In addition, local tonsillar defenses include a lining of antigen-processing squamous epithelium that involves B- and T-cell responses.

Tonsillopharyngitis of all varieties constitutes about 15% of all office visits to primary care physicians.

**Etiology**

Tonsillopharyngitis is usually viral, most often caused by the common cold viruses (adenovirus, rhinovirus, influenza, coronavirus, respiratory syncytial virus), but occasionally by Epstein-Barr virus, herpes simplex virus, cytomegalovirus, or HIV.

In about 30% of patients, the cause is bacterial. Group A β-hemolytic streptococcus (GABHS) is most common (see p. 1232), but Staphylococcus aureus, Streptococcus pneumoniae, Mycoplasma pneumoniae, and Chlamydia pneumoniae are sometimes involved. Rare causes include pertussis, Fusobacterium, diphtheria, syphilis, and gonorrhea.

GABHS occurs most commonly between ages 5 and 15 and is uncommon before age 3.

**Symptoms and Signs**

Pain with swallowing is the hallmark and is often referred to the ears. Very young children who are not able to complain of sore throat often refuse to eat. High fever, malaise, headache, and GI upset are common, as are halitosis and a muffled voice. A scarlatiniform or nonspecific rash may also be present. The tonsils are swollen and red and often have purulent exudates. Tender cervical lymphadenopathy may be present. Fever, adenopathy, palatal petechiae, and exudates are somewhat more common with GABHS than with viral tonsillopharyngitis, but there is much overlap. GABHS usually resolves within 7
days. Untreated GABHS may lead to local suppurative complications (eg, peritonsillar abscess or cellulitis) and sometimes to rheumatic fever or glomerulonephritis.

**Diagnosis**

- Clinical evaluation
- GABHS ruled out by rapid antigen test, culture, or both

Pharyngitis itself is easily recognized clinically. However, its cause is not. Rhinorrhea and cough usually indicate a viral cause. Infectious mononucleosis is suggested by posterior cervical or generalized adenopathy, hepatosplenomegaly, fatigue, and malaise for > 1 wk; a full neck with petechiae of the soft palate; and thick tonsillar exudates. A dirty gray, thick, tough membrane that bleeds if peeled away indicates diphtheria (rare in the US).

Because GABHS requires antibiotics, it must be diagnosed early. Criteria for testing are controversial. Many authorities recommend testing with a rapid antigen test or culture for all children. Rapid antigen tests are specific but not sensitive and may need to be followed by a culture, which is about 90% specific and 90% sensitive. In adults, many authorities recommend using the following 4 criteria:

- History of fever
- Tonsillar exudates
- Absence of cough
- Tender anterior cervical lymphadenopathy

Patients who meet 1 or no criteria are unlikely to have GABHS and should not be tested. Patients who meet 2 criteria can be tested. Patients who meet 3 or 4 criteria can be tested or treated empirically for GABHS.

**Treatment**

- Symptomatic treatment
- Antibiotics for GABHS
- Tonsillectomy considered for recurrent GABHS

Supportive treatments include analgesia, hydration, and rest. Penicillin V is usually considered the drug of choice for GABHS tonsillopharyngitis; dose is 250 mg po bid for 10 days for patients < 27 kg and 500 mg for those > 27 kg (see also p. 1234). Amoxicillin is effective and more palatable if a liquid preparation is required. If adherence is a concern, a single dose of benzathine penicillin 1.2 million units IM (600,000 units for children ≤ 27 kg) is effective. Other oral drugs include macrolides for patients allergic to penicillin, a 1st-generation cephalosporin, and clindamycin.

Treatment may be started immediately or delayed until culture results are known. If treatment is started presumptively, it should be stopped if cultures are negative. Follow-up throat cultures are not done routinely. They are useful in patients with multiple GABHS recurrences or if pharyngitis spreads to close contacts at home or school.

**Tonsillectomy**: Tonsillectomy should be considered if GABHS tonsillitis recurs repeatedly (> 6 episodes/yr, > 4 episodes/yr for 2 yr, > 3 episodes/yr for 3 yr) or if acute infection is severe and persistent despite antibiotics. Other criteria for tonsillectomy include obstructive sleep disorder, recurrent peritonsillar abscess, and suspicion of cancer.

Numerous effective surgical techniques are used to perform tonsillectomy, including electrocautery,
microdebrider, radiofrequency coblation, and sharp dissection. Significant intraoperative or postoperative bleeding occurs in < 2% of patients, usually within 24 h of surgery or after 7 days, when the eschar detaches. Patients with bleeding should go to the hospital. If bleeding continues on arrival, patients generally are examined in the operating room, and hemostasis is obtained. Any clot present in the tonsillar fossa is removed, and patients are observed for 24 h. Postoperative IV rehydration is necessary in ≤ 3% of patients, possibly in fewer patients with use of optimal preoperative hydration, perioperative antibiotics, analgesics, and corticosteroids. Postoperative airway obstruction occurs most frequently in children < 2 yr who have preexisting severe obstructive sleep disorders and in patients who are morbidly obese or have neurologic disorders, craniofacial anomalies, or significant preoperative obstructive sleep apnea. Complications are generally more common and serious among adults.

Peritonsillar Abscess and Cellulitis

Peritonsillar abscess and cellulitis are acute pharyngeal infections most common among adolescents and young adults. Symptoms are severe sore throat, trismus, "hot potato" voice, and uvular deviation. Diagnosis requires needle aspiration. Treatment includes broad-spectrum antibiotics, drainage of any pus, hydration, analgesics, and, occasionally, acute tonsillectomy.

Etiology

Abscess (quinsy) and cellulitis probably represent a spectrum of the same process in which bacterial infection of the tonsils and pharynx spreads to the soft tissues. Infection is virtually always unilateral and is located between the tonsil and the superior pharyngeal constrictor muscle. It usually involves multiple bacteria. Streptococcus and Staphylococcus are the most frequent aerobic pathogens, whereas Bacteroides sp is the predominant anaerobic pathogen.

Symptoms and Signs

Symptoms include gradual onset of severe unilateral sore throat, dysphagia, fever, otalgia, and asymmetric cervical adenopathy. Trismus, "hot potato" voice (speaking as if a hot object was in the mouth), a toxic appearance (see Epiglottitis on p. 475), drooling, severe halitosis, tonsillar erythema, and exudates are common. Abscess and cellulitis both have swelling above the affected tonsil, but with abscess there is more of a discrete bulge, with deviation of the soft palate and uvula and pronounced trismus.

Diagnosis

• Needle aspiration
• Sometimes CT

Peritonsillar cellulitis is recognized in patients with severe sore throat who have trismus, "hot potato" voice, and uvular deviation. All such patients require needle aspiration of the tonsillar mass and cultures. Aspiration of pus differentiates abscess from cellulitis. CT or ultrasound of the neck can help confirm the diagnosis when the physical examination is difficult or the diagnosis is in doubt, particularly when the condition must be differentiated from a parapharyngeal infection or other deep neck infection.

Treatment

• Antibiotics
• Drainage of abscess

Cellulitis subsides, usually within 48 h, with hydration and high-dose penicillin (eg, 2 million units IV q 4 h or 1 g po qid); alternative drugs include a 1st-generation cephalosporin or clindamycin. Culture-directed antibiotics are then prescribed for 10 days. Abscesses are incised and drained in the emergency department using thorough local anesthesia and sometimes procedural sedation; many clinicians believe needle aspiration alone provides adequate drainage. Although most patients can be treated as
outpatients, some need brief hospitalization for parenteral antibiotics, IV hydration, and airway monitoring. Rarely, an immediate tonsillectomy is done, particularly in a young or uncooperative patient who has other indications for elective tonsillectomy (eg, history of frequently recurrent tonsillitis or obstructive sleep apnea). Otherwise, elective tonsillectomy is done 4 to 6 wk out to prevent abscess recurrence.

Parapharyngeal Abscess

A parapharyngeal abscess is a deep neck abscess treated with antibiotics and surgical drainage.

The parapharyngeal (pharyngomaxillary) space is lateral to the superior pharyngeal constrictor and medial to the masseter muscle. This space connects to every other major fascial neck space and is divided into anterior and posterior compartments by the styloid process. The posterior compartment contains the carotid artery, internal jugular vein, and numerous nerves. Infections in the parapharyngeal space usually originate in the tonsils or pharynx, although local spread from odontogenic sources and lymph nodes may occur.

Abscess swelling can compromise the airway. Posterior space abscess can erode into the carotid artery or cause septic thrombophlebitis of the internal jugular vein (Lemierre syndrome).

Symptoms and Signs

Most patients have fever, sore throat, odynophagia, and swelling in the neck down to the hyoid bone. Anterior space abscesses cause trismus and induration along the angle of the mandible, with medial bulging of the tonsil and lateral pharyngeal wall. Posterior space abscesses cause swelling that is more prominent in the posterior pharyngeal wall. Trismus is minimal. Posterior abscesses may involve structures within the carotid sheath, possibly causing rigors, high fever, bacteremia, neurologic deficits, and massive hemorrhage caused by carotid artery rupture.

Diagnosis

• CT

Diagnosis is suspected in patients with poorly defined deep neck infection or other typical symptoms and is confirmed by using contrast-enhanced CT.

Treatment

• Broad-spectrum antibiotics (eg, ceftriaxone, clindamycin)
• Surgical drainage

Treatment may require airway control. Parenteral broad-spectrum antibiotics (eg, ceftriaxone, clindamycin) and surgical drainage are generally needed. Posterior abscesses are drained externally through the submaxillary fossa. Anterior abscesses can often be drained through an intra-oral incision. Several days of parenteral culture-determined antibiotics are required after drainage, followed by 10 to 14 days of oral antibiotics. Occasionally, small abscesses can be treated with IV antibiotics alone.

Epiglottitis

(Supraglottitis)

Epiglottitis is a rapidly progressive bacterial infection of the epiglottis and surrounding tissues that may lead to sudden respiratory obstruction and death. Symptoms include severe sore throat, dysphagia, high fever, drooling, and inspiratory stridor. Diagnosis requires direct visualization of the supraglottic structures, which is not to be done until full respiratory support is available. Treatment includes airway protection and antibiotics.
Epiglottitis used to be primarily a disease of children and usually was caused by *Haemophilus influenzae* type B. Now, because of widespread vaccination, it has been almost eradicated in children (more cases occur in adults). Causal organisms in children and adults include *Streptococcus pneumoniae*, *Staphylococcus aureus*, nontypeable *H. influenzae*, *Haemophilus parainfluenzae*, β-hemolytic streptococci, *Branhamella catarrhalis*, and *Klebsiella pneumoniae*. *H. influenzae* type B is still a cause in adults and unvaccinated children.

Bacteria that have colonized the nasopharynx spread locally to cause supraglottic cellulitis with marked inflammation of the epiglottis, vallecula, aryepiglottic folds, arytenoids, and laryngeal ventricles. With *H. influenzae* type B, infection may spread hematogenously.

The inflamed supraglottic structures mechanically obstruct the airway, increasing the work of breathing, ultimately causing respiratory failure. Clearance of inflammatory secretions is also impaired.

### Symptoms and Signs

In children, sore throat, odynophagia, and dysphagia develop abruptly. Fatal asphyxia may occur within a few hours of onset. Drooling is very common. Additionally, the child has signs of toxicity (poor or absent eye contact, failure to recognize parents, cyanosis, irritability, inability to be consoled or distracted) and is febrile and anxious. Dyspnea, tachypnea, and inspiratory stridor may be present, often causing the child to sit upright, lean forward, and hyperextend the neck with the jaw thrust forward and mouth open in an effort to enhance air exchange (tripod position). Relinquishing this position may herald respiratory failure. Suprasternal, supraclavicular, and subcostal inspiratory retractions may be present.

In adults, symptoms are similar to those of children, including sore throat, fever, dysphagia, and drooling, but peak symptoms usually take > 24 h to develop. Because of the larger diameter of the adult airway, obstruction is less common and less fulminant. Often, there is no visible oropharyngeal inflammation. However, severe throat pain with a normal-appearing pharynx raises suspicion of epiglottitis.

### Diagnosis

- Direct inspection (typically in operating room)
- X-ray in milder cases with low suspicion

Epiglottitis is suspected in patients with severe sore throat and no pharyngitis and also in patients with sore throat and inspiratory stridor. Stridor in children may also result from croup (viral laryngotracheal bronchitis—see Table 52-1 and p. 2879), bacterial tracheitis, and airway foreign body. The tripod position may also occur with peritonsillar or retropharyngeal abscess.

The patient is hospitalized if epiglottitis is suspected. Diagnosis requires direct examination, usually with flexible fiberoptic laryngoscopy. (CAUTION: Examination of the pharynx and larynx may precipitate complete respiratory obstruction in children, and the pharynx and larynx should not be directly examined except in the operating room, where the most advanced airway intervention is available.) Although plain x-rays may be helpful, a child with stridor should not be transported to the x-ray suite. Direct laryngoscopy that reveals a beefy-red, stiff, edematous epiglottis is diagnostic. Cultures from the supraglottic tissues and blood can then be taken to search for the causative organism.

[Table 52-1. Differentiating Epiglottitis from Croup]

Adults may, in some cases, safely undergo flexible fiberoptic laryngoscopy.

### Treatment

- Adequate airway ensured
- Antibiotics (eg, ceftriaxone)
In children, the airway must be secured immediately, preferably by nasotracheal intubation. Securing the airway can be quite difficult and should, if possible, be done by experienced personnel in the operating room. An endotracheal tube is usually required until the patient has been stabilized for 24 to 48 h (usual total intubation time is < 60 h). Alternatively, a tracheotomy is done. If respiratory arrest occurs before an airway is established, bag-mask ventilation may be a life-saving temporary measure. For emergency care of children with epiglottitis, each institution should have a protocol that involves critical care, otolaryngology, anesthesia, and pediatrics.

Adults whose airway is severely obstructed can be endotracheally intubated during flexible fiberoptic laryngoscopy. Other adults may not require immediate intubation but should be observed for airway compromise in an ICU with an intubation set and cricothyrotomy tray at the bedside.

A β-lactamase-resistant antibiotic, such as ceftriaxone 50 to 75 mg/kg IV once/day (maximum 2 g), should be used empirically, pending culture and sensitivity test results.

Epiglottitis caused by *H. influenzae* type B can be effectively prevented with the *H. influenzae* type B (Hib) conjugate vaccine.
Chapter 53. Nose and Paranasal Sinus Disorders

Introduction

(See Ch. 51 for a detailed description of the anatomy of the nose and sinuses.)

Bacterial Infections

Nasal vestibulitis is bacterial infection of the nasal vestibule, typically with *Staphylococcus aureus*. It may result from nose picking or excessive nose blowing and causes annoying crusts and bleeding when the crusts slough off. Bacitracin or mupirocin ointment applied topically bid for 14 days is effective.

Furuncles of the nasal vestibule are usually staphylococcal; they may develop into spreading cellulitis of the tip of the nose. Systemic antistaphylococcal antibiotics (eg, cephalexin 500 mg po qid) are given and warm compresses and topical mupirocin are applied. Furuncles are incised and drained to prevent local thrombophlebitis and subsequent cavernous sinus thrombosis.

Foreign Bodies

Nasal foreign bodies are found occasionally in young children, the intellectually impaired, and psychiatric patients. Common objects pushed into the nose include beads, beans, seeds, nuts, insects, and button batteries (which may cause chemical burns). When mineral salts are deposited on a long-retained foreign body, the object is called a rhinolith.

A nasal foreign body is suspected in any patient with a unilateral, foul-smelling, bloody, purulent rhinorrhea. Diagnosis is often made through another party's observation of the item being pushed into the nose or through visualization with a nasal speculum.

Nasal foreign bodies can sometimes be removed in the office with a nasal speculum and Hartmann's nasal forceps. Pretreatment with topical phenylephrine may aid visualization and removal. To avoid pushing a slippery, round object deeper, it is better to reach behind the object with the bent tip of a blunt probe and pull it forward. Sometimes, general anesthesia is necessary if a rhinolith has formed or if the foreign body may be displaced dorsally and then aspirated, resulting in airway obstruction.

Nasal Polyps

Nasal polyps are fleshy outgrowths of the nasal mucosa that form at the site of dependent edema in the lamina propria of the mucous membrane, usually around the ostia of the maxillary sinuses (see Plate 2).

Allergic rhinitis, acute and chronic infections, and cystic fibrosis all predispose to the formation of nasal polyps. Bleeding polyps occur in rhinosporidiosis. Unilateral polyps occasionally occur in association with or represent benign or malignant tumors of the nose or paranasal sinuses. They can also occur in response to a foreign body. Nasal polyps are strongly associated with aspirin allergy, sinus infections, and asthma.

Symptoms include obstruction and postnasal drainage, congestion, sneezing, rhinorrhea, anosmia, hyposmia, facial pain, and ocular itching.

Diagnosis generally is based on physical examination. A developing polyp is teardrop-shaped; when mature, it resembles a peeled seedless grape.

Treatment

- Topical corticosteroid spray
- Sometimes surgical removal
Corticosteroids (eg, mometasone [30 μg/spray], beclomethasone [42 μg/spray], flunisolide [25 μg/spray] aerosols), given as 1 or 2 sprays bid in each nasal cavity, may shrink or eliminate polyps, as may a 1-wk tapered course of oral corticosteroids. Surgical removal is still required in many cases. Polyps that obstruct the airway or promote sinusitis are removed, as are unilateral polyps that may be obscuring benign or malignant tumors. However, polyps tend to recur unless the underlying allergy or infection is controlled. After removal of nasal polyps, topical beclomethasone or flunisolide therapy tends to retard recurrence. In severe recurrent cases, maxillary sinusotomy or ethmoidectomy may be indicated. These procedures are usually done endoscopically.

**Rhinitis**

(See also Allergic Rhinitis on p. 1117.)

Rhinitis is inflammation of the nasal mucous membrane, with resultant nasal congestion, rhinorrhea, and variable associated symptoms depending on etiology (eg, itching, sneezing, purulence, anosmia, ozena). The cause is usually viral, although irritants can cause it. Diagnosis is usually clinical. Treatment includes humidification of room air, sympathomimetic amines, and antihistamines. Bacterial superinfection requires appropriate antibiotic treatment.

There are several forms of rhinitis.

**Acute rhinitis:** This form of rhinitis, manifesting with edema and vasodilation of the nasal mucous membrane, rhinorrhea, and obstruction, is usually the result of a common cold (see p. 1404); other causes include streptococcal, pneumococcal, and staphylococcal infections.

**Chronic rhinitis:** This form of rhinitis is generally a prolongation of subacute inflammatory or infectious viral rhinitis but may also occur in syphilis, TB, rhinoscleroma, rhinosporidiosis, leishmaniasis, blastomycosis, histoplasmosis, and leprosy—all of which are characterized by granuloma formation and destruction of soft tissue, cartilage, and bone. Nasal obstruction, purulent rhinorrhea, and frequent bleeding result. Rhinoscleroma causes progressive nasal obstruction from indurated inflammatory tissue in the lamina propria. Rhinosporidiosis is characterized by bleeding polyps. Both low humidity and airborne irritants can result in chronic rhinitis.

**Atrophic rhinitis:** This form of rhinitis results in atrophy and sclerosis of mucous membrane; the mucous membrane changes from ciliated pseudostratified columnar epithelium to stratified squamous epithelium, and the lamina propria is reduced in amount and vascularity. Atrophic rhinitis is associated with advanced age, Wegener's granulomatosis, and iatrogenically induced excessive nasal tissue extirpation. Although the exact etiology is unknown, bacterial infection frequently plays a role. Nasal mucosal atrophy often occurs in the elderly.

**Vasomotor rhinitis:** This form of rhinitis is a chronic condition in which intermittent vascular engorgement of the nasal mucous membrane leads to watery rhinorrhea and sneezing. Etiology is uncertain, and no allergy can be identified. A dry atmosphere seems to aggravate the condition.

**Symptoms and Signs**

Acute rhinitis results in cough, low-grade fever, nasal congestion, rhinorrhea, and sneezing. Symptoms and signs of chronic rhinitis are similar but may include purulent rhinorrhea and bleeding.

Atrophic rhinitis results in abnormal patency of the nasal cavities, crust formation, anosmia, and epistaxis that may be recurrent and severe.

Vasomotor rhinitis results in sneezing and watery rhinorrhea. The turgescent mucous membrane varies from bright red to purple. The condition is marked by periods of remission and exacerbation. Vasomotor rhinitis is differentiated from specific viral and bacterial infections of the nose by the lack of purulent exudate and crusting. It is differentiated from allergic rhinitis by the absence of an identifiable allergen.
Diagnosis
The different forms of rhinitis are diagnosed clinically. Testing is unnecessary.

Treatment

• For viral rhinitis, decongestants, antihistamines, or both

• For atrophic rhinitis, topical treatment

• For vasomotor rhinitis, humidification and sometimes topical corticosteroids and oral pseudoephedrine

Viral rhinitis may be treated symptomatically with decongestants (either topical vasoconstriction with a sympathomimetic amine, such as oxymetazoline q 8 to 12 h or phenylephrine 0.25% q 3 to 4 h for not more than 7 days, or systemic sympathomimetic amines, such as pseudoephedrine 30 mg po q 4 to 6 h). Antihistamines (see Table 127-2 on p. 1111) may be helpful. Those with anticholinergic properties dry mucous membranes and therefore may increase irritation. Decongestants also may relieve symptoms of acute bacterial rhinitis and chronic rhinitis, whereas an underlying bacterial infection requires culture or biopsy, pathogen identification, antibiotic sensitivities, and appropriate antimicrobial treatment.

Treatment of atrophic rhinitis is directed at reducing the crusting and eliminating the odor with topical antibiotics (eg, bacitracin), topical or systemic estrogens, and vitamins A and D. Occluding or reducing the patency of the nasal cavities surgically decreases the crusting caused by the drying effect of air flowing over the atrophic mucous membrane.

Treatment of vasomotor rhinitis is by trial and error and is not always satisfactory. Patients benefit from humidified air, which may be provided by a humidified central heating system or a vaporizer in the workroom or bedroom. Systemic sympathomimetic amines (eg, for adults, pseudoephedrine 30 mg po q 4 to 6 h prn) relieve symptoms but are not recommended for long-term use. Topical vasoconstrictors are avoided because they cause the vasculature of the nasal mucous membrane to lose its sensitivity to other vasoconstrictive stimuli—eg, the humidity and temperature of inspired air. Topical corticosteroids (eg, mometasone 2 sprays bid) can be of some benefit.

Septal Deviation and Perforation

Deviations of the nasal septum due to developmental abnormalities or trauma are common but often are asymptomatic and require no treatment. Symptomatic septal deviation causes nasal obstruction and predisposes the patient to sinusitis (particularly if the deviation obstructs the ostium of a paranasal sinus) and to epistaxis due to drying air currents. Other symptoms may include facial pain, headaches, and noisy night breathing. Septal deviation is usually evident on examination, although a flashlight and examination of the anterior nasal passage may not be sufficient. Treatment consists of septoplasty (septal reconstruction).

Septal ulcers and perforations may result from nasal surgery; repeated trauma, such as chronic nose picking; cosmetic piercing; toxic exposures (eg, acids, chromium, phosphorus, copper vapor); chronic cocaine use; chronic nasal spray use (including corticosteroids and OTC phenylephrine or oxymetazoline sprays); transnasal O2 use; or diseases such as TB, syphilis, leprosy, SLE, and Wegener's granulomatosis. Crusting around the margins and repeated epistaxis, which can be severe, may result. Small perforations may whistle. Anterior rhinoscopy or fiberoptic endoscopy can be used to view septal perforations. Topical bacitracin or mupirocin ointment reduces crusting, as may saline nasal spray. Symptomatic septal perforations are occasionally repaired with buccal or septal mucous membrane flaps; closing the perforation with a silicone septal button is a reliable option.

Sinusitis

Sinusitis is inflammation of the paranasal sinuses due to viral, bacterial, or fungal infections or allergic reactions. Symptoms include nasal obstruction and congestion, purulent rhinorrhea,
cough, facial pain, malaise, and sometimes fever. Treatment is with antibiotics, such as amoxicillin, penicillin, erythromycin, or trimethoprim/sulfamethoxazole, given for 12 to 14 days for acute sinusitis and for up to 6 wk for chronic sinusitis. Decongestants and application of heat and humidity may help relieve symptoms and improve sinus drainage. Recurrent sinusitis may require surgery to improve sinus drainage.

Sinusitis may be classified as acute (completely resolved in < 30 days); subacute (completely resolved in 30 to 90 days); recurrent (multiple discrete acute episodes, each completely resolved in < 30 days but recurring in cycles, with at least 10 days between complete resolution of symptoms and initiation of a new episode); and chronic (lasting > 90 days).

Etiology

Acute sinusitis is usually precipitated by viral URI, followed by secondary bacterial colonization with streptococci, pneumococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, or staphylococci. In a URI, the swollen nasal mucous membrane obstructs the ostium of a paranasal sinus, and the O\textsubscript{2} in the sinus is absorbed into the blood vessels of the mucous membrane. The resulting relative negative pressure in the sinus (vacuum sinusitis) is painful. If the vacuum is maintained, a transudate from the mucous membrane develops and fills the sinus; the transudate serves as a medium for bacteria that enter the sinus through the ostium or through a spreading cellulitis or thrombophlebitis in the lamina propria of the mucous membrane. An outpouring of serum and leukocytes to combat the infection results, and painful positive pressure develops in the obstructed sinus. The mucous membrane becomes hyperemic and edematous.

Chronic sinusitis may be exacerbated by gram-negative bacilli or anaerobic micro-organisms. In a few cases, chronic maxillary sinusitis is secondary to dental infection or exposure to environmental pollution. Fungal infections (*Aspergillus*, *Sporothrix*, *Pseudallescheria*) tend to strike the immunocompromised patient, whereas hospital-acquired infections complicate cystic fibrosis, nasogastric and nasotracheal intubation, and debilitated patients. Typical organisms include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterobacter*.

Allergic fungal sinusitis is characterized by diffuse nasal congestion, markedly viscid nasal secretions, and, often, nasal polyps. It is an allergic response to the presence of topical fungi, often *Aspergillus*, and is not caused by an invasive infection.

Symptoms and Signs

Acute and chronic sinusitis cause similar symptoms and signs, including purulent rhinorrhea, pressure and pain in the face, nasal congestion and obstruction, hyposmia, halitosis, and productive cough (especially at night). Often the pain is more severe in acute sinusitis. The area over the affected sinus may be tender, swollen, and erythematous. Maxillary sinusitis causes pain in the maxillary area, toothache, and frontal headache. Frontal sinusitis causes pain in the frontal area and frontal headache. Ethmoid sinusitis causes pain behind and between the eyes, frontal headache often described as splitting, periorbital cellulitis, and tearing. Pain caused by sphenoid sinusitis is less well localized and is referred to the frontal or occipital area. Malaise may be present. Fever and chills suggest an extension of the infection beyond the sinuses.

The nasal mucous membrane is red and turgid; yellow or green purulent rhinorrhea may be present. Seropurulent or mucopurulent exudate may be seen in the middle meatus with maxillary, anterior ethmoid, or frontal sinusitis and in the area medial to the middle turbinate with posterior ethmoid or sphenoid sinusitis.

Diagnosis

- Clinical evaluation
- Sometimes CT

Sinus infections are usually diagnosed clinically. Absence or dullness of light on transillumination may
suggest fluid-filled maxillary or frontal sinuses. In acute and chronic sinusitis, the swollen mucous membranes and retained exudate cause the affected sinus to appear opaque on 4-view x-rays. Plain x-rays are not as valuable as CT, which provides better definition of the extent and degree of sinusitis. X-rays of the apices of the teeth may be required in chronic maxillary sinusitis to exclude a periapical abscess. When questions persist (eg, regarding intracranial extension, treatment failure, or hospital-acquired causes of sinusitis), culture and sensitivity tests can be done on sinus secretions obtained through endoscopy or sinus puncture and aspiration.

Sinusitis in children is suspected when purulent rhinorrhea persists for > 10 days along with fatigue and cough. Fever is uncommon. Local facial pain or discomfort may be present. Nasal examination discloses purulent drainage; CT is confirmatory. CT is of limited cuts in the coronal projection to limit radiation exposure.

**Treatment**

- Local measures to enhance drainage (eg, steam, topical vasoconstrictors)
- Antibiotics (eg, amoxicillin, erythromycin, trimethoprim/sulfamethoxazole)

In acute sinusitis, improved drainage and control of infection are the aims of therapy. Steam inhalation; hot, wet towels over the affected sinuses; and hot beverages alleviate nasal vasoconstriction and promote drainage. Topical vasoconstrictors, such as phenylephrine 0.25% spray q 3 h, are effective but should be used for a maximum of 5 days or for a repeating cycle of 3 days on and 3 days off until the sinusitis is resolved. Systemic vasoconstrictors, such as pseudoephedrine 30 mg po (for adults) q 4 to 6 h, are less effective.

In acute and chronic sinusitis, antibiotics are given for at least 10 days and often for 14 days. In acute sinusitis, amoxicillin 500 mg po q 8 h with or without clavulanate is primary therapy. Erythromycin 250 mg po q 6 h or trimethoprim/sulfamethoxazole 80/400 mg q 6 h can be given to patients allergic to penicillin. Second-line therapy includes cefuroxime 500 mg q 12 h or moxifloxacin 400 mg once/day. For children, similar antibiotics are used, adjusted for the child's weight. Fluoroquinolones, however, are not used in children because of concerns of premature epiphyseal growth plate closure.

In exacerbations of chronic sinusitis in children or adults, a broad-spectrum antibiotic, such as amoxicillin/clavulanate 875 mg po q 12 h (12.5 to 25 mg/kg q 12 h in children), cefuroxime, or, in adults, moxifloxacin, is used. In chronic sinusitis, prolonged antibiotic therapy for 4 to 6 wk often brings complete resolution. The sensitivities of pathogens isolated from the sinus exudate and the patient's response guide subsequent therapy.

Sinusitis unresponsive to antibiotic therapy may require surgery (maxillary sinusotomy, ethmoidectomy, or sphenoid sinusotomy) to improve ventilation and drainage and to remove inspissated mucopurulent material, epithelial debris, and hypertrophic mucous membrane. These procedures usually are done intranasally with the aid of an endoscope. Chronic frontal sinusitis may be managed either with osteoplastic obliteration of the frontal sinuses or endoscopically in selected patients. The use of intraoperative computer-aided surgery to localize disease and prevent injury to surrounding contiguous structures (such as the eye and brain) has become common.

**Sinusitis in Immunocompromised Patients**

Aggressive and even fatal fungal or bacterial sinusitis can occur in patients who are immunocompromised because of poorly controlled diabetes, neutropenia, or HIV infection.

**Mucormycosis:** Mucormycosis (phycomycosis)—a mycosis due to fungi of the order Mucorales, including species of *Mucor, Absidia,* and *Rhizopus*—may develop in patients with poorly controlled diabetes. It is characterized by black, devitalized tissue in the nasal cavity and neurologic signs secondary to retrograde thromboarteritis in the carotid arterial system. Diagnosis is based on histopathologic demonstration of mycelia in the avascularized tissue. Treatment requires control of the underlying condition (such as reversal of ketoacidosis in diabetes) and IV amphotericin B therapy. Prompt
biopsy of intranasal tissue for histology and culture is warranted.

**Aspergillosis and candidiasis:** *Aspergillus* and *Candida* spp may infect the paranasal sinuses of patients who are immunocompromised secondary to therapy with cytotoxic drugs or to immunosuppressive diseases, such as leukemia, lymphoma, multiple myeloma, and AIDS. These infections can appear as polypoid tissue in the nose as well as thickened mucosa; tissue is required for diagnosis. Aggressive paranasal sinus surgery and IV amphotericin B therapy are used to control these often-fatal infections.
Chapter 54. Laryngeal Disorders

Introduction

The larynx contains the vocal cords and serves as the opening to the tracheobronchial tree. Laryngeal disorders include various benign and malignant tumors, contact ulcers, granulomas, laryngitis, laryngoceles, spasmodic dysphonia, vocal cord paralysis, and vocal cord polyps and nodules. For acute laryngotracheobronchitis, see Croup on p. 2879. Laryngeal cancer is discussed on p. 489.

Most laryngeal disorders cause dysphonia, which is impairment of the voice (see Sidebar 54-1). A persistent change in the voice (eg, > 3 wk) requires visualization of the vocal cords, including their mobility. Although the voice changes with advancing age, becoming breathy and aperiodic, acute or prominent changes in the elderly should not be presumed to result from aging, and evaluation is required.

The voice should be assessed and recorded, particularly if surgical procedures are planned. Examination of the larynx includes external inspection and palpation of the neck and internal visualization of the epiglottis, false cords, true cords, arytenoids, pyriform sinuses, and subglottic region below the cords. Internal visualization is accomplished by either indirect mirror examination (see Fig. 54-1) or direct flexible fiberoptic laryngoscopy in an outpatient setting with a topical anesthetic. Rigid laryngoscopy with the patient under general anesthesia allows for biopsy when necessary or assessment of passive mobility of the vocal cords when immobilized by either paralysis or fixation.

Sidebar 54-1 The Professional Voice

People who use their voice professionally for public speaking and singing often experience voice disorders manifesting as hoarseness or breathiness, lowered vocal pitch, vocal fatigue, nonproductive cough, persistent throat clearing, and/or throat ache. These symptoms often have benign causes, such as vocal nodules, vocal fold edema, polyps, or granulomas. Such disorders are usually caused by vocal fold hyperfunction (excessive laryngeal muscular tension when speaking) and possibly laryngopharyngeal reflux.

Treatment in most cases includes the following:

• Voice evaluation by a speech pathologist or experienced physician, including, when available, use of a computer-assisted program to assess pitch and intensity and to determine parameters of vocal acoustics

• Behavioral treatment (decreasing musculoskeletal laryngeal tension when speaking) using the same computer program for visual and auditory biofeedback

• A vocal hygiene program to eliminate vocally abusive behaviors, such as excessive loudness, long duration, vocal tension, and habitual throat clearing

• An antireflux regimen, when appropriate

• Adequate hydration to promote an adequate glottal mucosal wave

• Diet modification before vocal performances, which may include avoidance of dairy products, caffeine, and ambient tobacco smoke and other inhaled irritants

Benign Tumors

Benign laryngeal tumors include juvenile papillomas hemangiomas, fibromas, chondromas, myxomas, and neurofibromas. They may appear in any part of the larynx. Symptoms include hoarseness, breathy voice,
dyspnea, aspiration, dysphagia, pain, otalgia (pain referred to the ear), and hemoptysis. Diagnosis is based on direct or indirect visualization of the larynx, supplemented by CT. Removal restores the voice, the functional integrity of the laryngeal sphincter, and the airway. Smaller lesions may be excised endoscopically by using a CO₂ laser and general anesthesia. Larger lesions extending beyond the laryngeal framework often require pharyngotomy or laryngofissure.

Cancerous tumors are discussed in Ch. 55.

Contact Ulcers

Contact ulcers are unilateral or bilateral erosions of the mucous membrane over the vocal process of the arytenoid cartilage.

Contact ulcers are usually caused by voice abuse in the form of repeated sharp glottal attacks (abrupt loudness at the onset of phonation), often experienced by singers. They may also occur after endotracheal intubation if an oversized tube erodes the mucosa overlying the cartilaginous vocal processes. Gastroesophageal reflux may also cause or aggravate contact ulcers. Symptoms include varying degrees of hoarseness and mild pain with phonation and swallowing. Biopsy to exclude carcinoma or TB is important. Prolonged ulceration leads to nonspecific granulomas that also cause varying degrees of hoarseness.

Treatment consists of ≥ 6 wk of voice rest. Patients must recognize the limitations of their voice and learn to adjust their postrecovery vocal activities to avoid recurrence. Granulomas tend to recur after surgical removal. Risk of recurrence is reduced through vigorous treatment of gastroesophageal reflux (see p. 125). Suppression of bacterial flora by antibiotics during postoperative healing is also recommended.

Laryngitis

Laryngitis is inflammation of the larynx, usually the result of a virus or overuse. The result is acute change in the voice, with decreased volume and hoarseness. Diagnosis is based on clinical findings. Laryngoscopy is required for symptoms persisting > 3 wk. Viral laryngitis is self-limited. Other infectious or irritating causes may require specific treatment.

The most common cause of acute laryngitis is a viral URI. Coughing-induced laryngitis may also occur in bronchitis, pneumonia, influenza, pertussis, measles, and diphtheria.

Excessive use of the voice (especially with loud speaking or singing), allergic reactions, gastroesophageal reflux, bulimia, or inhalation of irritating substances (eg, cigarette smoke or certain aerosolized drugs) can cause acute or chronic laryngitis. Bacterial laryngitis is extremely rare. Smoking can cause Reinke's edema, which is a watery swelling of both vocal cords.

Symptoms and Signs

An unnatural change of voice is usually the most prominent symptom. Volume is typically greatly decreased; some patients have aphonia. Hoarseness, a sensation of tickling, rawness, and a constant urge to clear the throat may occur. Symptoms vary with the severity of the inflammation. Fever, malaise, dysphagia, and throat pain may occur in more severe infections. Laryngeal edema, although rare, may cause dyspnea.

Diagnosis

• Clinical evaluation

• Sometimes direct or indirect laryngoscopy

Diagnosis is based on symptoms. Indirect or direct flexible laryngoscopy is recommended for symptoms
persisting > 3 wk; findings in laryngitis include mild to marked erythema of the mucous membrane, which may also be edematous. With reflux, there is swelling of the inner lining of the larynx and redness of the vocal cords that extends above and below the edges of the back part of the cords. If a pseudomembrane is present, diphtheria is suspected.

**Treatment**

- Symptomatic treatment (eg, cough suppressants, voice rest, steam inhalations)

No specific treatment is available for viral laryngitis. Cough suppressants, voice rest, and steam inhalations relieve symptoms and promote resolution of acute laryngitis. Smoking cessation and treatment of acute or chronic bronchitis may relieve laryngitis. Depending on the presumed cause, specific treatments to control gastroesophageal reflux, bulimia, or drug-induced laryngitis may be beneficial.

**Laryngoceles**

**Laryngoceles are evaginations of the mucous membrane of the laryngeal ventricle.**

Internal laryngoceles displace and enlarge the false vocal cords, resulting in hoarseness and airway obstruction. External laryngoceles extend through the thyrohyoid membrane, causing a mass in the neck. Laryngoceles tend to occur in musicians who play wind instruments. Laryngoceles are filled with air and can be expanded by the Valsalva maneuver. They appear on CT as smooth, ovoid, low-density masses. Laryngoceles may become infected (laryngopyocele) or filled with mucoid fluid. Treatment is excision.

**Spasmodic Dysphonia**

**Spasmodic dysphonia (vocal cord spasms) is intermittent spasm of laryngeal muscles that causes an abnormal voice.**

Cause is unknown. Patients often describe the onset of symptoms following a URI, a period of excessive voice use, or occupational or emotional stress. As a localized form of movement disorder, spasmodic dysphonia has an onset between ages 30 and 50 yr, and about 60% of patients are women.

In the adductor type of spasmodic dysphonia, patients attempt to speak through the spasmodic closure with a voice that sounds squeezed, effortful, or strained. These spasmodic episodes usually occur when vowel sounds are being formed, particularly at the beginning of words. The less common abductor form results in sudden interruptions of sound caused by momentary abduction of the vocal cords accompanied by audible escape of air during connected speech.

Surgery has been more successful than other approaches for adductor spasmodic dysphonia. The use of botulinum toxin injection has restored a normal voice in 70% of patients for up to 3 mo. Because the effect is temporary, injections may be repeated. There is no known temporary alleviation of the abductor form of this disorder.

**Vocal Cord Paralysis**

**Vocal cord paralysis has numerous causes and can affect speaking, breathing, and swallowing. The left vocal cord is affected twice as often as the right, and females are affected more often than males (3:2). Diagnosis is based on direct visualization. An extensive assessment may be necessary to determine the cause. Several direct surgical approaches are available if treating the cause is not curative.**

Vocal cord paralysis may result from lesions at the nucleus ambiguus, its supranuclear tracts, the main trunk of the vagus, or the recurrent laryngeal nerves.

Paralysis is usually unilateral. About one third of unilateral vocal cord paralyses are neoplastic in origin, one third are traumatic, and one third are idiopathic. Intracranial tumors, vascular accidents, and demyelinating diseases cause nucleus ambiguus paralysis. Tumors at the base of the skull and trauma to
Recurrence of laryngeal nerve paralysis is caused by neck or thoracic lesions (e.g., aortic aneurysm; mitral stenosis; mediastinal tuberculous adenitis; tumors of the thyroid gland, esophagus, lung, or mediastinal structures), trauma, thyroidectomy, neurotoxins (e.g., lead, arsenic, mercury), neurotoxic infections (e.g., diphtheria), cervical spine injury or surgery, Lyme disease, and viral illness. Viral neuronitis probably accounts for most idiopathic cases.

Bilateral vocal cord paralysis is a life-threatening disorder caused by thyroid and cervical surgery, tracheal intubation, trauma, and neurodegenerative and neuromuscular diseases.

**Symptoms and Signs**

Vocal cord paralysis results in loss of vocal cord abduction and adduction. Paralysis may affect phonation, respiration, and deglutition, and food and fluids may be aspirated into the trachea. The paralyzed cord generally lies 2 to 3 mm lateral to the midline. In recurrent laryngeal nerve paralysis, the cord may move with phonation but not with inspiration. In unilateral paralysis, the voice may be hoarse and breathy, but the airway is usually not obstructed because the normal cord abducts sufficiently. In bilateral paralysis, both cords generally lie within 2 to 3 mm of the midline, and the voice is of good quality but of limited intensity. The airway, however, is inadequate, resulting in stridor and dyspnea with moderate exertion as each cord is drawn to the midline glottis by an inspiratory Bernoulli effect. Aspiration is also a danger.

**Diagnosis**

- Laryngoscopy
- Various tests for possible causes

Diagnosis is based on laryngoscopy. The cause must always be sought. Evaluation is guided by abnormalities identified on history and physical examination. During the history, the physician asks about all possible causes of peripheral neuropathy, including chronic heavy metal exposure (arsenic, lead, mercury), drug effects from phenytoin and vincristine, and history of connective tissue disorders, Lyme disease, sarcoidosis, diabetes, and alcoholism. Further evaluation may include enhanced CT or MRI of the head, neck, and chest; thyroid scan; barium swallow or bronchoscopy; and esophagoscopy. Cricoarytenoid arthritis, which may cause fixation of the cricoarytenoid joint, must be differentiated from a neuromuscular etiology. Fixation is best documented by absence of passive mobility during rigid laryngoscopy under general anesthesia. Cricoarytenoid arthritis may complicate such conditions as RA, external blunt trauma, and prolonged endotracheal intubation.

**Treatment**

- For unilateral paralysis, surgical procedures to move cords closer together
- For bilateral paralysis, surgical procedures and measures to maintain airway

In unilateral paralysis, treatment is directed at improving voice quality through augmentation, medialization, or reinnervation.

Augmentation involves injecting a paste of plasticized particles, collagen, micronized dermis, or autologous fat into the paralyzed cord, bringing the cords closer together to improve the voice and prevent aspiration.

Medialization is shifting the vocal cord toward the midline by inserting an adjustable spacer laterally to the affected cord. This can be done with a local anesthetic, allowing the position of the spacer to be “tuned” to the patient’s voice. Unlike augmentation with plasticized particles, which permanently fixes the cord, the spacer is both adjustable and removable.

Reinnervation has only rarely been successful.
In bilateral paralysis, an adequate airway must be reestablished. Tracheotomy may be needed permanently or temporarily during a URI. An arytenoidectomy with lateralization of the true vocal cord opens the glottis and improves the airway but may adversely affect voice quality. Posterior laser cordectomy opens the posterior glottis and may be preferred to endoscopic or open arytenoidectomy. Successful laser establishment of a posterior glottic airway usually obviates the need for long-term tracheotomy while preserving a serviceable voice quality.

**Vocal Cord Polyps and Nodules**

Acute trauma or chronic irritation causes changes in the vocal cords that can lead to polyps or nodules. Both cause hoarseness and a breathy voice. Persistence of these symptoms for > 3 wk dictates visualization of the vocal cords. Diagnosis is based on laryngoscopy and on biopsy to rule out cancer. Surgical removal restores the voice, and removal of the irritating source prevents recurrence.

**Etiology**

Polyps and nodules result from injury to the lamina propria of the true vocal cords. Polyps may occur at the mid third of the membranous cords and are more often unilateral. They frequently result from an initiating acute phonatory injury. Nodules usually occur bilaterally at the junction of the anterior and middle third of the cords. Their main cause is chronic voice abuse—yelling, shouting, singing loudly, or using an unnaturally low frequency. Polyps may have several other causes, including gastric reflux, untreated hypothyroid states, chronic laryngeal allergic reactions, or chronic inhalation of irritants, such as industrial fumes or cigarette smoke. Polyps tend to be larger and more protuberant than nodules and often have a dominant surface blood vessel.

**Symptoms and Signs**

Both result in slowly developing hoarseness and a breathy voice.

**Diagnosis**

- Laryngoscopy
- Sometimes biopsy

Diagnosis is based on direct or indirect visualization of the larynx with a mirror or laryngoscope. Biopsy of discrete lesions to exclude carcinoma is done by microlaryngoscopy.

**Treatment**

- Avoidance of cause
- For polyps, usually surgical removal

Correction of the underlying voice abuse cures most nodules and prevents recurrence. Removal of the offending irritants allows healing, and voice therapy with a speech therapist reduces the trauma to the vocal cords caused by improper singing or protracted loud speaking. Nodules usually regress with voice therapy alone.

Most polyps must be surgically removed to restore a normal voice. Cold-knife microsurgical excision during direct microlaryngoscopy is preferable to laser excision, which is more likely to cause collateral thermal injury if improperly applied.

In microlaryngoscopy, an operating microscope is used to examine, biopsy, and operate on the larynx. Images can be recorded on video as well. The patient is anesthetized, and the airway is secured by high-pressure jet ventilation through the laryngoscope, endotracheal intubation, or, for an inadequate upper airway, tracheotomy. Because the microscope allows observation with magnification, tissue can be
removed precisely and accurately, minimizing damage (possibly permanent) to the vocal mechanism. Laser surgery can be done through the optical system of the microscope to allow for precise cuts. Microlaryngoscopy is preferred for almost all laryngeal biopsies, for procedures involving benign tumors, and for many forms of phonosurgery.
Chapter 55. Tumors of the Head and Neck

Introduction

The most common noncutaneous tumor of the head and neck is squamous cell carcinoma of the larynx, followed by squamous cell carcinomas of the tongue, palatine tonsil, and floor of the mouth. Less common are tumors of the salivary glands, jaw, nose and paranasal sinuses, and ear. Tumors of the thyroid gland, eye, and skin are discussed elsewhere in THE MANUAL.

Excluding the skin and thyroid gland, > 90% of head and neck cancers are squamous cell (epidermoid) carcinomas, and 5% are melanomas, lymphomas, and sarcomas. Patients with sarcomas or carcinomas of the salivary glands or paranasal sinuses are often younger than patients with squamous cell carcinoma, who are more commonly in their mid-50s and older.

Etiology

The vast majority of patients, 85% or more, with cancer of the head and neck have a history of alcohol use, smoking, or both. Other suspected causes include use of snuff or chewing tobacco, sunlight exposure, previous x-rays of the head and neck, certain viral infections, ill-fitting dental appliances, chronic candidiasis, and poor oral hygiene. In India, oral cancer is extremely common, probably because of chewing betel quid (a mixture of substances, also called paan). Long-term exposure to sunlight and the use of tobacco products are the primary causes of squamous cell carcinoma of the lower lip.

Patients who in the past were treated with radiation for acne, excess facial hair, enlarged thymus, or hypertrophic tonsils and adenoids are predisposed to thyroid and salivary gland cancers and benign salivary tumors.

Epstein-Barr virus plays a role in the pathogenesis of nasopharyngeal cancer, and serum measures of certain Epstein-Barr virus proteins may be biomarkers of recurrence. Human papillomavirus seems to be associated with head and neck squamous cell carcinoma, particularly oropharyngeal cancer. The mechanism for viral-mediated tumor genesis may be distinct from tobacco-related pathways and seem to have a different, better, prognosis.

Symptoms and Signs

Most head and neck cancers first manifest as an asymptomatic neck mass, painful mucosal ulceration, or visible mucosal lesion (eg, leukoplakia, erythroplakia). Subsequent symptoms depend on location and extent of the tumor and include pain, paresthesia, nerve palsies, trismus, and halitosis. Otalgia is an often overlooked symptom usually representing referred pain from the primary tumor. Weight loss caused by perturbed eating and odynophagia is also common.

Diagnosis

• Clinical evaluation

• Biopsy

• Imaging tests and endoscopy to evaluate extent of disease

Routine physical examination (including a thorough oral examination) is the best way to detect cancers early before they become symptomatic. Commercially available brush biopsy kits help screen for oral cancers. Any head and neck symptom (eg, sore throat, hoarseness, otalgia) lasting > 2 to 3 wk should prompt referral to a head and neck specialist.

Definitive diagnosis usually requires a biopsy. Additional important information is obtained from a combination of imaging tests (eg, CT, MRI, PET/CT), endoscopy, and fine-needle aspiration of any neck mass.
**Staging**

Head and neck cancers may remain localized for months to years. Local tissue invasion eventually is followed by metastasis to regional lymph nodes, related in large part to tumor size and extent, and reduces overall survival by nearly half. Distant metastases tend to occur late, usually in patients with advanced tumor and nodal stages. Metastases occur more commonly among immunocompromised patients. Common sites of distant metastases are the lungs, liver, bone, and brain.

Head and neck cancers are staged (see Table 55-1) according to size and site of the primary tumor (T), number and size of metastases to the cervical lymph nodes (N), and evidence of distant metastases (M). Staging usually requires imaging with CT, MRI, or both, and often PET.

**Prognosis**

Prognosis is favorable if diagnosis is early and treatment is timely and appropriate. In general, the more poorly differentiated the cancer, the greater the chance of regional and distant metastases. The presence of regional nodal spread reduces overall survival by nearly half. Distant metastasis greatly reduces survival, having only rare cures. Local invasion, a criterion for advanced T stage, with invasion of muscle, bone, or cartilage, also significantly decreases cure rate. Perineural spread, as evidenced by pain, paralysis, or numbness, indicates a highly aggressive tumor, is associated with nodal metastasis, and has a less favorable prognosis than a similar lesion without perineural invasion.

With appropriate treatment, 5-yr survival can be as high as 90% for stage I, 75 to 80% for stage II, 45 to 75% for stage III, and up to 40% for stage IV. The survival rates vary greatly depending on the primary site. Stage I laryngeal cancers have an excellent survival rate when compared to other sites.

**Treatment**

- Surgery, radiation therapy, or both
- Sometimes chemotherapy

Many stage I tumors, regardless of location, respond similarly to surgery and to radiation therapy, allowing other factors (eg, patient preference) to determine choice of therapy. Thus, the treating physician should carefully review risks and benefits with the patient. However, at certain locations, there is clear superiority of one modality over another. For example, surgery is the better treatment for early-stage disease involving the oral cavity. In select head and neck cancers, endoscopic surgery has cure rates similar to those of open surgery or radiation, and morbidity is significantly less. However, many physicians still recommend radiation for early-stage laryngeal cancer.

If radiation therapy is chosen for primary therapy, it is delivered to the primary site and sometimes bilaterally to the cervical lymph nodes. The treatment of lymphatics, whether by radiation or surgery, is determined by the primary site, histologic criteria, and risk of nodal disease.

Advanced-stage disease (stages III and IV) often requires multimodality treatment, incorporating some combination of chemotherapy, radiation therapy, and surgery. Bone or cartilage invasion requires surgical resection of the primary site and usually regional lymph nodes because of the high risk of nodal spread. If the primary site is treated surgically, then postoperative radiation to the cervical lymph nodes is delivered if there are high-risk features, such as multiple lymph nodes with cancer or extracapsular extension. Postoperative radiation usually is preferred over preoperative radiation, because radiated tissues heal poorly. Recent studies have shown that adding chemotherapy to adjuvant radiation therapy to the neck improves regional control of the cancer and improves survival. There are significant risks to this approach, so the decision to add chemotherapy should be carefully considered.
Advanced squamous cell carcinoma without bony invasion often is treated with concomitant chemotherapy and radiation therapy. Although advocated as organ-sparing, combining chemotherapy with radiation therapy doubles the rate of acute toxicities, particularly severe dysphagia. Radiation may be used alone for debilitated patients with advanced disease who cannot tolerate the sequelae of chemotherapy and are too high a risk for general anesthesia.

Primary chemotherapy is reserved for chemosensitive tumors, such as Burkitt's lymphoma, or for patients who have widespread metastases (eg, hepatic or pulmonary involvement). Several drugs—cisplatin, fluorouracil, bleomycin, and methotrexate—provide palliation for pain and shrink the tumor in patients who cannot be treated with other methods. Response may be good initially but is not durable, and the cancer will return.

**Tumor recurrence:** Managing recurrent tumors after therapy is complex and has potential complications. A palpable mass or ulcerated lesion with edema or pain at the primary site after therapy strongly suggests a persistent tumor. Such patients require CT (with thin cuts) or MRI. For local recurrence after surgical treatment, all scar planes and reconstructive flaps are excised along with residual cancer. Radiation therapy, chemotherapy, or both may be done but have limited effectiveness. Patients with recurrence after radiation therapy should not receive additional radiation and are best treated with surgery.

**Symptom control:** Pain is a common symptom in patients with head and neck cancer and must be adequately addressed. Palliative surgery or radiation may temporarily alleviate pain, and in 30 to 50% of patients, chemotherapy can produce improvement that lasts a mean of 3 mo. A stepwise approach to pain management, as recommended by the WHO, is critical to controlling pain. Severe pain is best managed in association with a pain and palliative care specialist.

Pain, difficulty eating, choking on secretions, and other problems make adequate symptomatic treatment essential. Patient directives regarding such care should be clarified early (see p. 3471).

**Adverse effects of treatment:** All cancer treatments have potential complications and expected sequelae. Because many treatments have similar cure rates, the choice of modality is based largely on real, or perceived, differences in sequelae.

Although it is commonly thought that surgery requires rehabilitation for swallowing and speaking, many procedures do not require such rehabilitation. Increasingly complex reconstructive procedures and techniques, including prostheses, grafts, regional pedicle flaps, and complex free flaps, can restore function and appearance often to near normal.

Toxic effects of chemotherapy include malaise, severe nausea and vomiting, mucositis, transient hair loss, gastroenteritis, hematopoietic and immune suppression, and infection.

Therapeutic radiation for head and neck cancers has several adverse effects. The function of any salivary gland within the beam is permanently destroyed by a dose of about 40 Gy, resulting in xerostomia, which markedly increases the risk of dental caries. Newer radiation techniques, such as intensity-modulated radiation therapy, can minimize or eliminate toxic doses to the parotid glands in certain patients. Radioprotectant drugs (eg, amifostine) also can help protect salivary function. In addition, the blood supply of bone, particularly in the mandible, is compromised by doses of > 60 Gy, and osteoradionecrosis may occur (see also p. 505). In this condition, tooth extraction sites break down, sloughing bone and soft tissue. Therefore, any needed dental treatment, including scaling, fillings, and extractions, should be done before radiation therapy. Any teeth in poor condition that cannot be rehabilitated should be extracted. Radiation therapy may also cause oral mucositis and dermatitis in the overlying skin, which may result in dermal fibrosis. Loss of taste (ageusia) and impaired smell (dysosmia) often occur but are usually transient.

**Prevention**

Removing risk factors is critical, and all patients should cease tobacco use and limit alcohol consumption. Removing risk factors also helps prevent disease recurrence in those treated for cancer. A new primary
cancer develops in about 5% of patients/yr (to a maximum risk of about 20%); risk is lower in those who stop.

Cancer of the lower lip may be prevented by sunscreen use and tobacco cessation. Because 60% of head and neck cancers are well advanced (stage III or IV) at the time of diagnosis, the most promising strategy for reducing morbidity and mortality is diligent routine examination of the oral cavity.

Jaw Tumors

Numerous tumor types, both benign and malignant, originate in the jaw. Symptoms are swelling, pain, tenderness, and unexplained tooth mobility; some tumors are discovered on routine dental x-rays, whereas others are found on routine examinations of the oral cavity and teeth. Treatment depends on location and tumor type. Benign tumors may be observed and may not need surgical excision, although most tumors require resection with possible reconstruction.

If not initially detected on x-ray, jaw tumors are diagnosed clinically because their growth causes swelling of the face, palate, or alveolar ridge (the part of the jaw supporting the teeth). They can also cause bone tenderness and severe pain.

Bony outgrowths (torus palatinus, torus mandibularis) may develop on the palate or mandible. These are common growths and may prompt concerns about cancer, although they are benign and of concern only if they interfere with dental care or function of the submandibular gland. When on the palate, they are in the midline and have intact, smooth mucosa. Multiple osteomas seen on dental x-ray may suggest Gardner's syndrome.

The most common tumor of the mandible and maxilla is squamous cell carcinoma invading the bone through dental sockets. These can involve any portion of the intraoral mandible or maxilla.

Ameloblastoma, the most common epithelial odontogenic tumor, usually arises in the posterior mandible. It is slowly invasive and rarely metastatic. On x-ray, it typically appears as multiloculated or soap-bubble radiolucency. Treatment is wide surgical excision and reconstruction if appropriate.

Odontoma, the most common odontogenic tumor, affects the dental follicle or the dental tissues and usually appears in the mandibles of young people. Odontomas include fibrous odontomas and cementomas. A clinically absent molar tooth suggests a composite odontoma. Typically, no treatment is indicated. These tumors may be excised when the diagnosis is in doubt.

Osteosarcoma, giant cell tumor, Ewing's tumor, multiple myeloma, and metastatic tumors may affect the jaw. Treatment is the same as for those tumors in other bony sites.

Laryngeal Cancer

Ninety percent of laryngeal cancer is squamous cell carcinoma. Smoking, alcohol abuse, lower socioeconomic status, and being male and > 60 yr increase risk. Early diagnosis is common with vocal cord tumors because vocal, swallowing, or respiratory symptoms develop early. However, supraglottic tumors (above the vocal cords) and subglottic tumors (below the vocal cords) are often very large and at an advanced stage when diagnosed because they are asymptomatic until obstructive symptoms develop. Diagnosis is based on laryngoscopy and biopsy. Treatment of early-stage tumors is with surgery or radiation. Advanced-stage tumors are most often treated with chemotherapy and radiation therapy. Surgery is reserved for salvage treatment or lesions with significant extralaryngeal extension or cartilage destruction. Reestablishment of speaking ability is needed if a total laryngectomy is done.

Squamous cell carcinoma is the most common cancer of the larynx. In the US, it is 4 times more common among men and is more common among those of lower socioeconomic status. Over 95% of patients are smokers; 15 pack-years of smoking increase the risk 30-fold. The incidence of larynx cancer is decreasing, particularly among men, most likely due to changes in smoking habits.
Sixty percent of patients present with localized disease alone; 25% present with local disease and regional nodal metastatic disease; and 15% present with advanced disease, distant metastases, or both. Distant metastases occur most frequently in the lungs and liver.

Common sites of origin are the true vocal cords (glottis) and the supraglottic larynx. The least common site is the subglottic larynx, where only 1% of primary laryngeal cancers originate. Verrucous carcinoma, a rare variant of squamous cell carcinoma, usually arises in the glottic area and has a better survival rate than standard squamous cell carcinoma.

**Symptoms and Signs**

Symptoms and signs differ based on the involved portion of the larynx. Hoarseness is common early in glottic cancers but is a late symptom for supraglottic and subglottic cancers. Supraglottic cancer is often asymptomatic until it manifests as a mass lesion (eg, with airway obstruction, dysphagia, otalgia, or a "hot potato" voice) or with weight loss. Such patients should be referred for indirect laryngoscopy without delay.

**Diagnosis**

- Laryngoscopy
- Operative endoscopy and biopsy
- Imaging tests for staging

All patients who have hoarseness for > 2 to 3 wk should have their larynx examined by a head and neck specialist. Any lesions discovered require further evaluation, usually with operative endoscopy and biopsy, with concomitant evaluation of the upper airway and GI tract for coexisting cancers. The incidence of a synchronous second primary tumor may be as high as 10%.

Patients with confirmed carcinoma typically have neck CT with contrast and a chest x-ray or chest CT. Most clinicians also do PET of the neck and chest at the time of diagnosis.

**Treatment**

- Early-stage: Surgery or radiation therapy
- Advanced: Radiation therapy and sometimes chemotherapy

For early-stage glottic carcinoma, laser excision, radiation therapy, or occasionally open laryngeal surgery results in a 5-yr survival rate of 85 to 95%. Endoscopic laser resection and radiation therapy usually preserve a normal voice and post-treatment function and have similar cure rates.

For advanced glottic carcinoma, defined by a lack of vocal cord mobility, thyroid cartilage invasion, or extension into the tongue, most patients are treated with chemotherapy and radiation therapy. Surgery (followed by radiation therapy) is reserved for salvage situations; most such cases require total laryngectomy, although endoscopic or open partial laryngectomy may sometimes be used. Extensive local invasion, however, usually requires an initial total laryngectomy rather than nonsurgical therapy.

Early supraglottic carcinoma can be effectively treated with radiation therapy or partial laryngectomy. Laser resection has shown considerable success on early-stage supraglottic squamous cell carcinomas and minimizes functional changes after surgery. If the carcinoma is more advanced but does not affect the true vocal cords, a supraglottic partial laryngectomy can be done to preserve the voice and glottic sphincter. If the true vocal cords also are affected, a supracricoid laryngectomy or a total laryngectomy is required if surgery is chosen. As with glottic carcinoma, most advanced-stage supraglottic cancers initially are treated with chemotherapy and radiation therapy.
Treatment of hypopharyngeal carcinomas is similar to that of laryngeal cancer. Early-stage lesions usually are treated with radiation alone, although endoscopic resection is an option. However, the majority of patients with hypopharyngeal cancer have advanced-stage disease, because of the silent nature of the disease and frequent regional lymphatic spread; such patients are treated with chemotherapy and radiation therapy primarily, with surgical salvage.

Rehabilitation: Rehabilitation may be required after either surgical or nonsurgical treatment. Significant swallowing problems are common after chemotherapy and radiation therapy and may require esophageal dilation, swallowing therapy, or, in severe cases, surgical replacement of the pharynx or gastrostomy tube feedings. Swallowing also is affected by surgery and may require swallowing therapy or dilation as well.

Speech, on the other hand, is more significantly affected by surgery. After total laryngectomy, the patient requires creation of a new voice by way of

- Esophageal speech
- A tracheoesophageal puncture
- An electrolarynx

In all 3 techniques, sound is articulated into speech by the pharynx, palate, tongue, teeth, and lips.

Esophageal speech involves taking air into the esophagus during inspiration and gradually eructating the air through the pharyngoesophageal junction to produce a sound.

A tracheoesophageal puncture involves placement of a one-way valve between the trachea and esophagus to facilitate phonation. This valve forces air into the esophagus during expiration to produce a sound. Patients receive physical rehabilitation, speech therapy, and appropriate training in the maintenance and use of this valve and must be cautioned against the possible aspiration of food, fluids, and secretions.

An electrolarynx is a battery-powered sound source that is held against the neck to produce sound. Although it carries a great deal of social stigma for many patients, it has the advantage of being functional immediately with little or no training.

Nasopharyngeal Cancer

Nasopharyngeal cancers are rare in the US but common in the South China Sea region. Symptoms develop late, including unilateral bloody nasal discharge, nasal obstruction, facial swelling, and numbness. Diagnosis is based on inspection and biopsy, with CT, MRI, or PET to evaluate extent. Treatment is with radiation, chemotherapy, and, rarely, surgery.

Squamous cell carcinoma is the most common malignant tumor of the nasopharynx. It can occur in any age group and is rare in North America. It is one of the most common cancers among people of Chinese, especially southern Chinese, and Southeast Asian ancestry, including Chinese immigrants to North America. Over several generations, the prevalence among Chinese-Americans gradually decreases to that among non-Chinese Americans, suggesting an environmental component to etiology. Dietary exposure to nitrites and salted fish also is thought to increase risk. Epstein-Barr virus is a significant risk factor, and there is hereditary predisposition. Other nasopharyngeal cancers include adenoid cystic and mucoepidermoid carcinomas, malignant mixed tumors, adenocarcinomas, lymphomas, fibrosarcomas, osteosarcomas, chondrosarcomas, and melanomas.

Symptoms and Signs

The first symptom is often nasal or eustachian tube obstruction causing hearing loss due to a middle ear effusion. Other symptoms include purulent bloody rhinorrhea, frank epistaxis, cranial nerve palsies, and cervical lymphadenopathy. Cranial nerve palsies most often involve the 6th, 4th, and 3rd cranial nerves due to their location in the cavernous sinus, in close proximity to the foramen lacerum, which is the most
common route of intracranial spread for these tumors. Because lymphatics of the nasopharynx communicate across the midline, bilateral metastases are common.

**Diagnosis**

- Nasopharyngeal endoscopy and biopsy
- Imaging tests for staging

Patients suspected of having nasopharyngeal cancer must undergo examination with a nasopharyngeal mirror or endoscope, and lesions are biopsied. Open cervical node biopsy should not be done as the initial procedure (see Neck Mass on p. 461), although a needle biopsy is acceptable and often recommended. Gadolinium-enhanced MRI (with fat suppression) of the head with attention to the nasopharynx and skull base is done; the skull base is involved in about 25% of patients. CT also is required to accurately assess skull base bony changes, which are less visible on MRI. A PET scan also commonly is done to assess the extent of disease as well as the cervical lymphatics.

**Treatment**

- Chemotherapy plus radiation therapy

Because of the location and extent of involvement, nasopharyngeal cancers often are not amenable to surgical resection. They are typically treated with chemotherapy and radiation therapy, which are often followed by adjuvant chemotherapy.

Recurrent tumors can be treated with another course of radiation, commonly with brachytherapy; radionecrosis of the skull base is a risk. An alternative to radiation is skull base resection.

**Oral Squamous Cell Carcinoma**

Oral squamous cell carcinoma affects about 30,000 Americans each year. Over 95% smoke, drink alcohol, or both. Early, curable lesions are rarely symptomatic; thus, preventing fatal disease requires early detection by screening. Treatment is with surgery, radiation, or both. The overall 5-yr survival rate (all sites and stages combined) is > 50%.

In the US, 3% of cancers in men and 2% in women are oral squamous cell carcinomas, most of which occur after age 50. Squamous cell carcinoma is the most common oral or pharyngeal cancer (and the most common at head and neck sites in general).

The chief risk factors for oral squamous cell carcinoma are smoking (especially > 2 packs/day) and alcohol use. Risk increases dramatically when alcohol use exceeds 6 oz of distilled liquor, 6 oz of wine, or 12 oz of beer/day. The combination of heavy smoking and alcohol abuse is estimated to raise the risk 100-fold in women and 38-fold in men. Squamous cell carcinoma of the tongue may also result from any chronic irritation, such as dental caries, overuse of mouthwash, chewing tobacco, or the use of betel quid. Oral human papillomavirus (HPV), typically acquired via oral-genital contact, may have a role in etiology.

About 40% of intraoral squamous cell carcinomas begin on the floor of the mouth or on the lateral and ventral surfaces of the tongue. About 38% of all oral squamous cell carcinomas occur on the lower lip; these are usually solar-related cancers on the external surface. About 11% begin in the palate and tonsillar area. Squamous cell carcinoma of the tonsil (an oropharyngeal cancer), 2nd in frequency only to carcinoma of the larynx among cancers of the upper respiratory tract, occurs predominantly in males.

**Symptoms and Signs**

Oral lesions are asymptomatic initially, highlighting the need for oral screening. Most dental professionals carefully examine the oral cavity and oropharynx during routine care and may do a brush biopsy of abnormal areas. The lesions may appear as areas of erythroplakia or leukoplakia and may be exophytic.
or ulcerated. Cancers are often indurated and firm with a rolled border. Tonsillar carcinoma usually manifests as an asymmetric swelling and sore throat, with pain often radiating to the ipsilateral ear. A metastatic mass in the neck may be the first symptom, particularly in tonsillar cancer.

**Diagnosis**

- Biopsy
- Endoscopy to detect second primary cancer
- Chest x-ray and CT of head and neck

Biopsy of suspect areas is done. Direct laryngoscopy, bronchoscopy, and esophagoscopy are done to exclude a simultaneous second primary cancer. Head and neck CT usually is done. Chest x-ray is done; chest CT is done if an advanced stage is suspected or confirmed.

**Prognosis**

If carcinoma of the tongue is localized (no lymph node involvement), 5-yr survival is > 50%. For localized carcinoma of the floor of the mouth, 5-yr survival is 65%. Lymph node metastasis decreases survival rate by about 50%. Metastases reach the regional lymph nodes first and later the lungs.

For lower lip lesions, 5-yr survival is 90%, and metastases are rare. Carcinoma of the upper lip tends to be more aggressive and metastatic. For carcinoma of the palate and tonsillar area, 5-yr survival is 68% if patients are treated before lymph node involvement but only 17% after involvement. The prognosis for tonsillar carcinoma is often better stage for stage than that for oral cancers. Oropharyngeal cancer associated with HPV infection may have a better prognosis.

**Treatment**

- Surgery or radiation therapy

Surgery and radiation therapy are the treatments of choice. Regional or distant disease necessitates a more radical treatment approach.

For tongue lesions, surgery is usually the initial treatment, particularly for early-stage disease. Selective neck dissection is indicated if the risk of nodal disease exceeds 15 to 20%. Routine surgical reconstruction is the key to reducing postoperative oral disabilities; procedures range from local tissue flaps to free tissue transfers. Speech and swallowing therapy may be required after significant resections. Radiation therapy is an alternative treatment. Chemotherapy is not used routinely but is recommended on an individual basis; rare distant metastases are present in sites where chemotherapy may be of some palliative value (eg, lung, bone, heart, pericardium).

Treatment of squamous cell carcinoma of the lip is surgical excision with reconstruction to maximize postoperative function. When large areas of the lip exhibit premalignant change, the lip can be surgically shaved, or a laser can remove all affected mucosa. Thereafter, appropriate sunscreen application is recommended.

Treatment of tonsillar carcinoma usually consists of concomitant chemotherapy and radiation therapy. Another option includes radical resection of the tonsillar fossa, sometimes with partial mandibulectomy and neck dissection.

**Otic Tumors**

A number of malignant and benign otic tumors occur, usually manifesting with hearing loss. They may also manifest with dizziness, vertigo, or imbalance. These tumors are rare and can be difficult to diagnose.
Malignant otic tumors: Basal cell and squamous cell carcinomas may arise in the ear canal. Persistent inflammation caused by chronic otitis media may predispose to the development of squamous cell carcinoma. Extensive resection is indicated, followed by radiation therapy. En bloc resection of the ear canal with sparing of the facial nerve is done when lesions are limited to the canal and have not invaded the middle ear. Deeper invasion requires a more significant temporal bone resection.

Rarely, squamous cell carcinoma originates in the middle ear. The persistent otorrhea of chronic otitis media may be a predisposing factor. Resection of the temporal bone and postoperative radiation therapy are necessary.

Nonchromaffin paragangliomas (chemodectomas) arise in the temporal bone from glomus bodies in the jugular bulb (glomus jugulare tumors) or the medial wall of the middle ear (glomus tympanicum tumors). They appear as a pulsatile red mass in the middle ear. The first symptom often is tinnitus that is synchronous with the pulse. Hearing loss develops, followed by vertigo. Cranial nerve palsies of the 9th, 10th, or 11th nerve may accompany glomus jugulare tumors that extend through the jugular foramen. Excision is the treatment of choice, and radiation is used for nonsurgical candidates.

Benign otic tumors: Sebaceous cysts, osteomas, and keloids may arise in and occlude the ear canal, causing retention of cerumen and conductive hearing loss. Excision is the treatment of choice for all benign otic tumors.

Ceruminomas occur in the outer third of the ear canal. These tumors appear benign histologically and do not metastasize regionally or distantly but they are locally invasive and potentially destructive and should be excised widely.

Salivary Gland Tumors

Most salivary gland tumors are benign and occur in the parotid glands. A painless salivary mass is the most common sign and is evaluated by fine-needle aspiration biopsy. Imaging with CT and MRI can be helpful. For malignant tumors, treatment is with excision and radiation. Long-term results are related to the grade of the cancer.

About 85% of salivary gland tumors occur in the parotid glands, followed by the submandibular and minor salivary glands, and about 1% occur in the sublingual glands. About 75 to 80% are benign, slow-growing, movable, painless, usually solitary nodules beneath normal skin or mucosa. Occasionally, when cystic, they are soft but most often they are firm.

Benign tumors: The most common type is a pleomorphic adenoma (mixed tumor). Malignant transformation is possible, resulting in carcinoma ex mixed tumor, but this usually occurs only after the benign tumor has been present for 15 to 20 yr. If malignant transformation occurs, the cure rates are very low, despite adequate surgery and adjuvant therapy.

Other benign tumors include monomorphic adenoma, oncocytoma, and papillary cystadenoma lymphomatosum (previously known as cylindroma). These tumors rarely recur and rarely become malignant.

Malignant salivary gland tumors: Malignant tumors are less common and are characterized by rapid growth or a sudden growth spurt. They are firm, nodular, and can be fixed to adjacent tissue, often with a poorly defined periphery. Pain and neural involvement are common. Eventually, the overlying skin or mucosa may become ulcerated or the adjacent tissues may become invaded. Surgery, followed by radiation therapy, is the treatment of choice for resectable disease. Currently, there is no effective chemotherapy for salivary cancer.

Mucoepidermoid carcinoma is the most common salivary gland cancer, typically occurring in people in their 20s to 50s. It can manifest in any salivary gland, often in a minor salivary gland of the palate, or it can occur deep within the bone, such as in the wall of a dentigerous cyst. Intermediate and high-grade mucoepidermoid carcinomas may metastasize to the regional lymphatics, which must be addressed with surgical dissection or postoperative radiation therapy.
Adenoid cystic carcinoma is the most common malignant tumor of minor salivary glands (and of the trachea). It is a slowly growing malignant transformation of a much more common benign cylindroma. Its peak incidence is between ages 40 and 60, and symptoms include severe pain and, often, facial nerve paralysis. It has a propensity for perineural invasion and spread, with disease potentially extending many centimeters from the main tumor mass. Lymphatic spread is not a common feature of this tumor, so elective nodal treatment is less common. Although the 5- and 10-yr survival rates are quite good, the 15- and 20-yr rates are quite poor, with most patients developing distant metastases. Pulmonary metastases are common, although patients can live quite long with them.

Acinic cell carcinoma, a common parotid tumor, occurs in people in their 40s and 50s. This carcinoma has a more indolent course, as well as an incidence of multifocality.

Carcinoma ex mixed tumor is adenocarcinoma arising in a preexisting benign carcinoma ex mixed tumor. Only the carcinomatous element metastasizes.

**Symptoms and Signs**

Most benign and malignant tumors manifest as a painless mass. However, malignant tumors may invade nerves, causing localized or regional pain, numbness, paresthesia, causalgia, or a loss of motor function.

**Diagnosis**

- Biopsy
- CT and MRI for extent of disease

CT and MRI locate the tumor and describe its extent. Biopsy confirms the cell type. A search for spread to regional nodes or distant metastases in the lung, liver, bone, or brain may be indicated before treatment is selected.

**Treatment**

- Surgery, sometimes plus radiation therapy

Treatment of benign tumors is surgery. The recurrence rate is high when excision is incomplete.

Treatment of mucoepidermoid carcinoma consists of wide excision and postoperative radiation. The 5-yr survival rate is 95% with the low-grade type, primarily affecting mucus cells, and 50% with the high-grade type, primarily affecting epidermoid cells. Treatment of adenoid cystic carcinoma is wide surgical excision, but local recurrence is common. Lung metastases and death are likely, although many years, to a decade or more, after the initial diagnosis and treatment. The prognosis for acinic cell carcinoma is favorable after wide excision. All surgeries are designed to spare the facial nerve, which is sacrificed only in cases of direct tumor involvement with the nerve.
Chapter 56. Approach to Dental and Oral Symptoms

Introduction

A physician should always examine the mouth and be able to recognize major oral disorders, particularly possible cancers. However, consultation with a dentist is needed to evaluate nonmalignant changes as well as patients with tooth problems. Likewise, patients with xerostomia or unexplained swelling or pain in the mouth, face, or neck require a dental consultation. Children with abnormal facies (who also may have dental malformations requiring correction) should be evaluated by a dentist. In FUO or a systemic infection of unknown cause, a dental disorder should be considered. A dental consultation is necessary before head and neck radiation therapy and is advisable before chemotherapy.

Clues suggesting systemic disease may be found in the mouth and adjacent structures (see Table 56-1). A dentist should consult a physician when a systemic disorder is suspected, when the patient is taking certain drugs (eg, warfarin, bisphosphonates), and when a patient's ability to withstand general anesthesia or extensive oral surgery must be evaluated. Patients with certain heart valve abnormalities may require antibiotic prophylaxis to help prevent bacterial endocarditis before undergoing certain dental procedures (see Tables 215-3 and 215-4 on pp. 2199 and 2200).

Common dental disorders are discussed in Ch. 57. Dental emergencies, including toothache, are discussed in Ch. 58.

Anatomy and Development

Teeth: The teeth are categorized as incisors, canines, premolars, and molars and conventionally are numbered beginning with the maxillary right 3rd molar (see Fig. 56-1).

Each tooth has a crown and a root. The canines have the largest and strongest roots. An inner pulp contains blood vessels, lymphatics, and nerves, surrounded by the hard but porous dentin, a very hard enamel coating that covers the crown. The bonelike cementum is over the root, which, when healthy, is covered by gingiva (see Fig. 56-2). Twenty deciduous teeth normally begin appearing at close to age 6 mo and should all be in place by age 30 mo (see Table 271-1 on p. 2757). These teeth are followed by 32 permanent teeth that begin to appear by about age 6. The period from age 6 to 11 is called the mixed dentition stage, in which both deciduous and permanent teeth are present. Timing of tooth eruption is one indicator of skeletal age and may identify growth retardation or establish age for forensic purposes.

Supporting tissues: The gingiva surrounds the teeth at the base of their crown. The alveolar ridges are trabecular bone containing sockets for the teeth. The periodontium consists of the tissues that support the teeth—the gingiva, epithelial attachment, connective tissue attachment, periodontal ligament, and alveolar bone. The mandible and maxilla support the alveolar ridges and house the teeth. Saliva from the salivary glands bathes and protects the teeth. The tongue directs food between the grinding surfaces and helps clean the teeth. The maxilla receives innervation from the maxillary nerve, the 2nd division of the trigeminal nerve (the 5th cranial nerve). The mandibular nerve, which is the 3rd and most inferior division of the trigeminal nerve, innervates the mandible.

In the elderly, or in some periodontal diseases, gingival recession exposes the dental root adjacent to the crown, making root caries common. If tooth destruction results and the tooth must be removed, the mechanical stimulation necessary for maintaining bone integrity ceases. Consequently, atrophy of the alveolar ridge (senile atrophy) begins when teeth are absent.
**Mouth:** Normally, keratinized epithelium occurs on the facial aspect of the lips, dorsum of the tongue, hard palate, and gingiva around the teeth. When healthy, the gingiva extends 5 to 7 mm from the tooth. Nonkeratinized mucosa occurs over alveolar bone further from the teeth, inside the lips and cheeks, on the sides and undersurface of the tongue, on the soft palate, and covering the floor of the mouth. The skin and mucosa of the lips are demarcated by the vermilion border.

The buccal mucosa, including the vestibule and nonkeratinized alveolar mucosa, is usually smooth, moist, and more red than pink (as compared to healthy gingiva). Innocuous entities in this region include linea alba (a thin white line, typically bilateral, on the level of the occlusal plane, where the cheek is bitten), Fordyce's granules (aberrant sebaceous glands appearing as < 1 mm light yellow spots that also may occur on the lips), and white sponge nevus (bilateral thick white folds over most of the buccal mucosa). Recognizing these avoids needless biopsy and apprehension. The orifices of the parotid (Stensen's) ducts are opposite the maxillary 1st molar on the inside of each cheek and should not be mistaken for an abnormality.

The dorsal surface of the tongue is covered with numerous whitish elevations called the filiform papillae. Interspersed among them are isolated reddish prominences called the fungiform papillae, occurring mostly on the anterior part of the tongue. The circumvallate papillae, numbering 8 to 12, are considerably larger and lie posteriorly in a V pattern. The circumvallate papillae do not project from the tongue but instead are surrounded by a trench. The foliate papillae appear as a series of parallel, slitted folds on the lateral borders of the tongue, near the anterior pillars of the fauces. They vary in length and can easily be confused with malignant lesions, as may the foramen cecum, median rhomboid glossitis, and, rarely, a lingual thyroid nodule. Lingual tonsils are components of Waldeyer's ring, are at the back of the tongue, and should not be mistaken for lesions. If an apparent abnormality is bilateral, it is almost always a normal variant.

Innervation is supplied by the lingual nerves (branches of the 5th cranial nerves), for general sensory innervation, and the chorda tympani fibers (of the 7th cranial nerve), which innervate the taste buds of the anterior two thirds of the tongue. Behind the circumvallate papillae, the glossopharyngeal nerves (9th cranial nerves) provide the sensations of touch and taste. The tongue has taste receptors for sweet, salty, sour, bitter, and umami (a savory taste triggered by natural glutamic acid and glutamates such as the flavoring agent monosodium glutamate). Although previously thought to be isolated to particular portions of the tongue, these receptors are now known to be distributed over the surface of the tongue. The hypoglossal nerves (12th cranial nerves) control movement of the tongue.

The major salivary glands are the paired parotid, submandibular, and sublingual glands. Most oral mucosal surfaces contain many minor mucus-secreting salivary glands. Anteriorly and near the midline on each side of the floor of the mouth are the openings of Wharton's ducts, which drain the ipsilateral submandibular and sublingual glands. The parotid glands drain into the cheeks via Stensen's ducts.

**Evaluation**

The first routine dental examination should take place by age 1 yr or when the first tooth erupts. Subsequent evaluations should take place at 6-mo intervals or whenever symptoms develop. Examination of the mouth is part of every general physical examination. Oral findings in many systemic diseases are unique, sometimes pathognomonic, and may be the first sign of disease. Oral cancer may be detected at an early stage.

**History:** Important dental symptoms include bleeding, pain, malocclusion, new growths, numbness or paresthesias, and chewing problems (which may lead to weight loss—see Table 56-2). General information includes use of alcohol or tobacco (both major risk factors for head and
neck cancer) and systemic symptoms, such as fever and weight loss.

**Physical examination:** A thorough inspection requires good illumination, a tongue blade, gloves, and a gauze pad. Complete or partial dentures are removed so that underlying soft tissues can be seen.

Most physicians use a head-mounted light. However, because the light cannot be precisely aligned on the axis of vision, it is difficult to avoid shadowing in narrow areas. Better illumination results with a head-mounted convex mirror; the physician looks through a hole in the center of the mirror, so the illumination is always on-axis. The head mirror reflects light from a source (any incandescent light) placed behind the patient and slightly to one side and requires practice to use effectively.

The examiner initially looks at the face for asymmetry, masses, and skin lesions. Slight facial asymmetry is universal, but more marked asymmetry may indicate an underlying disorder, either congenital or acquired (see Table 56-3).

Teeth are inspected for shape, alignment, defects, mobility, color, and presence of adherent plaque, materia alba (dead bacteria, food debris, desquamated epithelial cells), and calculus (tartar).

Teeth are gently tapped with a tongue depressor or mirror handle to assess tenderness (percussion sensitivity). Tenderness to percussion suggests deep caries that has caused a necrotic pulp with periapical abscess or severe periodontal disease. Percussion sensitivity or pain on biting also can indicate an incomplete (green stick) fracture of a tooth. Percussion tenderness in multiple adjacent maxillary teeth may result from maxillary sinusitis. Tenderness to palpation around the apices of the teeth also may indicate an abscess.

Loose teeth usually indicate severe periodontal disease but can be caused by bruxism (clenching or grinding of teeth—see p. 506) or trauma that damages periodontal tissues. Rarely, teeth become loose when alveolar bone is eroded by an underlying mass (eg, ameloblastoma, eosinophilic granuloma). A tumor or systemic cause of alveolar bone loss (eg, diabetes mellitus, hyperparathyroidism, osteoporosis, Cushing's syndrome) is suspected when teeth are loose and heavy plaque and calculus are absent.

Calculus is mineralized bacterial plaque—a concretion of bacteria, food residue, saliva,

and mucus with Ca and phosphate salts. After a tooth is cleaned, a mucopolysaccharide coating (pellicle) is deposited almost immediately. After about 24 h, bacterial colonization turns the pellicle into plaque. After about 72 h, the plaque starts calcifying, becoming calculus. When present, calculus is deposited most heavily on the lingual (inner, or tongue) surfaces of the mandibular anterior teeth near the submandibular and sublingual duct orifices (Wharton's ducts) and on the buccal (cheek) surfaces of the maxillary molars near the parotid duct orifices (Stensen's ducts).

Caries (tooth decay—see p. 516) first appears as defects in the tooth enamel. Caries then appears as white spots, later becoming brown.

Attrition (wearing of biting surfaces) can result from chewing abrasive foods or tobacco or from the wear that accompanies aging, but it usually indicates bruxism. Another common cause is abrasion of a porcelain crown occluding against opposing enamel, because porcelain is considerably harder than enamel. Attrition makes chewing less effective and causes noncarious teeth to become painful when the eroding enamel exposes the underlying dentin. Dentin is sensitive to touch and to temperature changes. A dentist can desensitize such teeth or restore the dental anatomy by placing crowns or onlays over badly worn teeth. In minor cases of root sensitivity, the exposed root may be desensitized by fluoride application or dentin-bonding agents.
Deformed teeth may indicate a developmental or endocrine disorder. In Down syndrome, teeth are small. In congenital syphilis, the incisors may be small at the incisal third, causing a pegged or screwdriver shape with a notch in the center of the incisal edge (Hutchinson's incisors), and the 1st molar is small, with a small occlusal surface and roughened, lobulated, often hypoplastic enamel (mulberry molar). In ectodermal dysplasia, teeth are absent or conical, so that dentures are needed from childhood. Dentinogenesis imperfecta, an autosomal dominant disorder, causes abnormal dentin that is dull bluish brown and opalescent and does not cushion the overlying enamel adequately. Such teeth cannot withstand occlusal stresses and rapidly become worn. People with pituitary dwarfism or with congenital hypoparathyroidism have small dental roots; people with gigantism have large ones. Acromegaly causes excess cementum in the roots as well as enlargement of the jaws, so teeth may become widely spaced. Acromegaly also can cause an open bite to develop in adulthood. Congenitally narrow lateral incisors occur in the absence of systemic disease. The most commonly congenitally absent teeth are the 3rd molars, followed in frequency by the maxillary lateral incisors and 2nd mandibular premolars.

Defects in tooth color must be differentiated from the darkening or yellowing that is caused by food pigments, aging, and, most prominently, smoking. A tooth may appear gray because of pulpal necrosis, usually due to extensive caries penetrating the pulp or because of hemosiderin deposited in the dentin after trauma, with or without pulpal necrosis. Children's teeth darken appreciably and permanently after even short-term use of tetracyclines by the mother during the 2nd half of pregnancy or by the child during odontogenesis (tooth development), specifically calcification of the crowns, which lasts until age 9. Tetracyclines rarely cause permanent discoloration of fully formed teeth in adults. However, minocycline darkens bone, which can be seen in the mouth when the overlying gingiva and mucosa are thin. Affected teeth fluoresce with distinctive colors under ultraviolet light corresponding to the specific tetracycline taken. In congenital porphyria, both the deciduous and permanent teeth may have red or brownish discoloration but always fluoresce red from the pigment deposited in the dentin. Congenital hyperbilirubinemia causes a yellowish tooth discoloration. Teeth can be whitened (see Table 56-4).

Defects in tooth enamel may be caused by rickets, which results in a rough, irregular band in the enamel. Any prolonged febrile illness during odontogenesis can cause a permanent narrow zone of chalky, pitted enamel or simply white discoloration visible after the tooth erupts. Thus, the age at which the disease occurred and its duration can be estimated from the location and height of the band. Amelogenesis imperfecta, an autosomal dominant disease, causes severe enamel hypoplasia. Chronic vomiting and esophageal reflux can decalcify the dental crowns, primarily the lingual surfaces of the maxillary anterior teeth. Chronic snorting of cocaine can result in widespread decalcification of teeth, because the drug dissociates in saliva into a base and HCl. Chronic use of methamphetamines markedly increases dental caries ("meth mouth").

Swimmers who spend a lot of time in over-chlorinated pools may lose enamel from the outer facial/buccal side of the teeth, especially the maxillary incisors, canines, and 1st premolars. If Na carbonate has been added to the pool water to correct pH, then brown calculus develops but can be removed by a dental cleaning.

Fluorosis is mottled enamel that may develop in children who drink water containing > 1 ppm of fluoride during tooth development. Fluorosis depends on the amount of fluoride ingested. Enamel changes range from irregular whitish opaque areas to severe brown discoloration of the entire crown with a roughened surface. Such teeth are highly resistant to dental caries.

The lips are palpated. With the patient's mouth open, the buccal mucosa and vestibules are examined with a tongue blade; then the hard and soft palates, uvula, and oropharynx are viewed. The patient is asked to extend the tongue as far as possible, exposing the dorsum, and to move the extended tongue as far as possible to each side, so that its posterolateral surfaces can be seen. If a patient does not extend the tongue far enough to expose the circumvallate papillae, the examiner grasps the tip of the tongue with a gauze pad and extends it. Then the tongue is raised to view the ventral surface and the floor of the mouth. The teeth and gingiva are viewed. An abnormal distribution of keratinized or nonkeratinized oral mucosa demands attention. Keratinized tissue that occurs in normally nonkeratinized areas appears white. This abnormal condition, called leukoplakia, requires a biopsy because it may be cancerous or precancerous. More ominous, however, are thinned areas of mucosa. These
[Table 56-4. Tooth Whitening Procedures]

red areas, called erythroplakia, if present for at least 2 wk, especially on the ventral tongue and floor of the mouth, suggest dysplasia, carcinoma in situ, or cancer.

With gloved hands, the examiner palpates the vestibules and the floor of the mouth, including the sublingual and submandibular glands. To make palpation more comfortable, the examiner asks the patient to relax the mouth, keeping it open just wide enough to allow access.

The temporomandibular joint (TMJ) is assessed by looking for jaw deviation on opening and by palpating the head of the condyle anterior to the external auditory meatus. Examiners then place their little fingers into the external ear canals with the pads of the fingertips lightly pushing anteriorly while patients open widely and close 3 times. Patients also should be able to comfortably open wide enough to fit 3 of their fingers vertically between the incisors (typically 4 to 5 cm). Trismus, the inability to open the mouth, may indicate temporomandibular disease (the most common cause), pericoronitis, scleroderma, arthritis, ankylosis of the TMJ, dislocation of the temporomandibular disk, tetanus, or peritonsillar abscess. Unusually wide opening suggests subluxation or type III Ehlers-Danlos syndrome.

Testing: For a new patient or for someone who requires extensive care, the dentist takes a full mouth x-ray series. This series consists of 14 to 16 periapical films to show the roots and bone plus 4 bite-wing films to detect early caries between posterior teeth. Modern techniques reduce radiation exposure to a near-negligible level. Patients at high risk of caries (ie, those who have had caries detected during the clinical examination, have many restorations, or have recurrent caries on teeth previously restored) should undergo bite-wing x-rays every 12 mo. Otherwise, bite-wings are indicated every 2 to 3 yr. A panoramic x-ray can yield useful information about tooth development, cysts or tumors of the jaws, supernumerary or congenitally absent teeth, 3rd molar impaction, Eagle’s syndrome (less frequently), and carotid plaques.

Geriatrics Essentials

With aging, resting salivary secretion diminishes and can be further diminished by drugs, although meal-stimulated salivary flow is usually adequate. The flattened cusps of worn teeth and weakness of the masticatory muscles may make chewing tiresome, impairing food intake. Loss of bone mass in the jaws (particularly the alveolar portion), dryness of the mouth, thinning of the oral mucosa, and impaired coordination of lip, cheek, and tongue movements may make denture retention difficult. The taste buds become less sensitive, so the elderly may add abundant seasonings, particularly salt (which is harmful for some), or they may desire very hot foods for more taste, sometimes burning the often atrophic oral mucosa. Gingival recession and xerostomia contribute to development of root caries. Despite these changes, improved dental hygiene has greatly decreased the prevalence of tooth loss, and most older people can expect to retain their teeth.

Poor oral health contributes to poor nutritional intake, which impairs general health. Dental disease (particularly periodontitis) is associated with a 2-fold increased risk of coronary artery disease. Edentulous patients cannot have periodontitis (because they do not have a periodontium), although periodontitis may have resulted in their tooth loss. Aspiration pneumonia in patients with periodontitis can involve anaerobic organisms and has a high mortality rate. Severe bacteremias secondary to acute or chronic dental infection may contribute to brain abscesses, cavernous sinus thrombosis, endocarditis, prosthetic joint infections, and unexplained fevers.

Dental Care of Patients With Systemic Disorders

Certain medical conditions (and their treatment) predispose patients to dental problems or affect dental care.

Hematologic disorders: People who have disorders that interfere with coagulation (eg, hemophilia, acute leukemia, thrombocytopenia) require medical consultation before undergoing dental procedures that might cause bleeding (eg, extraction, mandibular block). Hemophiliacs should have clotting factors
given before, during, and after an extraction. Such oral surgery should be done in the hospital in consultation with a hematologist. All patients with bleeding disorders should maintain a lifelong routine of regular dental visits, which includes cleanings, fillings, topical fluoride, and preventative sealants, to avoid the need for extractions.

**Cardiovascular disorders:** After an MI, dental procedures should be avoided for 6 mo, if possible, to allow damaged myocardium to become less electrically labile. Patients with pulmonary or cardiac disease who require inhalation anesthesia for dental procedures should be hospitalized.

**Endocarditis prophylaxis** is required before dental procedures only in patients with

- Prosthetic cardiac valves
- Previous history of bacterial endocarditis
- Cyanotic congenital defects of the heart or great vessels (if unrepaired, if completely repaired during first 6 mo after surgery, or if repaired but with residual defects)
- Cardiac transplantation recipients with a valvulopathy

The heart is better protected against low-grade bacteremias, which occur in chronic dental conditions, when dental treatment is received (with prophylaxis) than when it is not received. Patients who are to undergo cardiac valve surgery or repair of congenital heart defects should have any necessary dental treatment completed before surgery.

Although probably of marginal benefit, antibiotic prophylaxis is sometimes recommended for patients with hemodialysis shunts and within 2 yr of receipt of a major prosthetic joint (hip, knee, shoulder, elbow). The organisms causing infections at these sites are almost invariably of dermal rather than oral origin.

Epinephrine and levonordefrin are added to local anesthetics to increase the duration of anesthesia. In some cardiovascular patients, excess amounts of these drugs cause arrhythmias, myocardial ischemia, or hypertension. Plain anesthetic can be used for procedures requiring < 45 min, but in longer procedures or where hemostasis is needed, up to 0.04 mg epinephrine (2 dental cartridges with 1:100,000 epinephrine) is considered safe. Generally, no healthy patient should receive > 0.2 mg epinephrine at any one appointment. Absolute contraindications to epinephrine (any dose) are uncontrolled hyperthyroidism; pheochromocytoma; BP > 200 mm Hg systolic or > 115 mm Hg diastolic; uncontrolled arrhythmias despite drug therapy; and unstable angina, MI, or stroke within 6 mo.

Some electrical dental equipment, such as an electrosurgical cautery, a pulp tester, or an ultrasonic scaler, can interfere with early-generation pacemakers.

**Cancer:** Extracting a tooth adjacent to a carcinoma of the gingiva, palate, or antrum facilitates invasion of the alveolus (tooth socket) by the tumor. Therefore, a tooth should be extracted only during the course of definitive treatment. In patients with leukemia or agranulocytosis, infection may follow an extraction despite the use of antibiotics.

**Immunosuppression:** People with impaired immunity are prone to severe mucosal and periodontal infections by fungi, herpes and other viruses, and, less commonly, bacteria. The infections may cause hemorrhage, delayed healing, or sepsis. Dysplastic or neoplastic oral lesions may develop after a few years of immunosuppression. People with AIDS may develop Kaposi's sarcoma, non-Hodgkin lymphoma, hairy leukoplakia, candidiasis, aphthous ulcers, or a rapidly progressive form of periodontal disease.

**Endocrine disorders:** Dental treatment may be complicated by some endocrine disorders. For example, people with hyperthyroidism may develop tachycardia and excessive anxiety as well as thyroid storm if given epinephrine. Insulin requirements may be reduced on elimination of oral infection in diabetics; insulin dose may require reduction when food intake is limited because of pain after oral surgery. In people with diabetes, hyperglycemia with resultant polyuria may lead to dehydration, resulting in decreased salivary flow (xerostomia), which, along with elevated salivary glucose levels, contributes to
Patients receiving corticosteroids and those with adrenocortical insufficiency may require supplemental corticosteroids during major dental procedures. Patients with Cushing's syndrome or who are taking corticosteroids may have alveolar bone loss, delayed wound healing, and increased capillary fragility.

**Neurologic disorders:** Patients with seizures who require dental appliances should have nonremovable appliances that cannot be swallowed or aspirated. Patients unable to brush or floss effectively may use chlorhexidine 12% rinses in the morning and at bedtime.

**Obstructive sleep apnea:** Patients with obstructive sleep apnea who are unable to tolerate treatment with a positive airway pressure (CPAP, biPAP) mask are sometimes treated with an intraoral device that expands the oropharynx. This treatment is not as effective as CPAP, but more patients tolerate using it.

**Drugs:** Certain drugs, such as corticosteroids, immunosuppressants, and antineoplastics, compromise healing and host defenses. When possible, dental procedures should not be done while these drugs are being given.

Some antineoplastics (eg, doxorubicin, 5-fluorouracil, bleomycin, dactinomycin, cytosine, arabinoside, methotrexate) cause stomatitis, which is worse in patients with preexisting periodontal disease. Before such drugs are prescribed, oral prophylaxis should be completed, and patients should be instructed in proper toothbrushing and flossing.

Drugs that interfere with clotting may need to be reduced or stopped before oral surgery. Patients taking aspirin, NSAIDs, or clopidogrel should stop doing so 4 days before undergoing dental surgery and can resume taking these drugs after bleeding stops. Warfarin should be stopped 2 to 3 days before oral surgery. PT is obtained; INR of 1.5 is considered safe for surgery. For people receiving hemodialysis, dental procedures should be done the day after dialysis, when heparinization has subsided.

Phenytoin and Ca channel blockers, particularly nifedipine, contribute to gingival hyperplasia; however, this hyperplasia is minimized with excellent oral hygiene and frequent oral prophylaxes (cleanings).

Bisphosphonates, primarily when given parenterally for treatment of bone cancer, and to a much lesser degree when used orally to prevent osteoporosis, can result in osteonecrosis after an extraction (see Sidebar 39-1 on p. 363).

**Radiation therapy:** (CAUTION: Extraction of teeth from irradiated tissues [particularly if the total dose was > 65 Gy, especially in the mandible] is commonly followed by osteoradionecrosis of the jaw. This is a catastrophic complication in which extraction sites break down, frequently sloughing bone and soft tissue.) Thus, if possible, patients should have any necessary dental treatment completed before undergoing radiation therapy of the head and neck region, with time allowed for healing. Teeth that may not survive should be extracted. Necessary sealants and topical fluoride should be applied. After radiation, extraction should be avoided, if possible, by using dental restorations and root canal treatment instead.

Head and neck radiation often damages salivary glands, causing xerostomia, which promotes caries. Patients must therefore practice lifelong good oral hygiene. A fluoride gel and fluoride mouth rinse should be used daily. Rinsing with 0.12% chlorhexidine for 30 to 60 sec, if tolerated, can be done in the morning and at bedtime. Viscous lidocaine may enable a patient with sensitive oral tissues to brush and floss the teeth and eat. A dentist must be seen at 3-, 4-, or 6-mo intervals, depending on findings at the last examination. Irradiated tissue under dentures is likely to break down, so dentures should be checked and adjusted whenever discomfort is noted. Early caries may also be reversed by Ca phosphopeptides and amorphous Ca phosphate, which can be applied by a dentist or prescribed to a patient for at-home use.

Patients who undergo radiation therapy may develop oral mucosal inflammation and diminished taste as well as trismus due to fibrosis of the masticatory muscles. Trismus may be minimized by such exercises as opening and closing the mouth widely 20 times 3 or 4 times/day. Extractions of teeth in irradiated bone
should be avoided (because of possible osteoradionecrosis). Sometimes root canal therapy is done, and the tooth is ground down to the gum line. If extraction is required after radiation, 10 to 20 treatments in a hyperbaric O\textsubscript{2} chamber may forestall or prevent osteoradionecrosis.

**Bruxism**

Bruxism is clenching or grinding of teeth. Bruxism can abrade and eventually wear down dental crowns and loosen teeth. In many people, headaches, jaw pain, or both actually are the result of bruxism. The most severe and extensive grinding and clenching occurs during sleep, so the person may be oblivious to it, but family members might notice.

Treatment requires that the patient consciously try to reduce bruxism while awake. Plastic oral appliances (night guards) that prevent occlusal contact by fitting between the teeth can be used while sleeping. When symptoms are severe, a guard can be used also during the day. Usually, such devices are made by dentists. However, if the only problem is tooth wear, OTC heat-moldable devices, fitted at home, are available. Mild anxiolytics, particularly benzodiazepines, may help until a night guard is available but should not be used for extended periods.

**Halitosis**

(Fetor Oris; Oral Malodor)

Halitosis is a frequent or persistent unpleasant odor to the breath.

**Pathophysiology**

Halitosis most often results from fermentation of food particles by anaerobic gram-negative bacteria in the mouth, producing volatile sulfur compounds such as hydrogen sulfide and methyl mercaptan. Causative bacteria may be present in areas of gingival or periodontal disease, particularly when ulceration or necrosis is present. The causative organisms reside deep in periodontal pockets around teeth. In patients with healthy periodontal tissue, these bacteria may deposit on the dorsal posterior tongue.

Factors contributing to the overgrowth of causative bacteria include decreased salivary flow (eg, due to parotid disease, Sjogren's syndrome, use of anticholinergics—see p. 513), salivary stagnation, and increased salivary pH.

Certain foods or spices, after digestion, release the odor of that substance to the lungs; the exhaled odor may be unpleasant to others. For example, the odor of garlic is noted on the breath by others 2 or 3 h after consumption, long after it is gone from the mouth.

**Etiology**

About 85% of cases result from oral conditions. A variety of systemic and extraoral conditions account for the remainder (see Table 56-5).

The most common causes overall are the following:

• Gingival or periodontal disease

• Smoking

• Ingested foods that have a volatile component

GI disorders rarely cause halitosis because the esophagus is normally collapsed. It is a fallacy that breath odor reflects the state of digestion and bowel function.

**Other breath odors:** Several systemic diseases produce volatile substances detectable on the breath,
although not the particularly foul, pungent odors typically considered halitosis. Diabetic ketoacidosis produces a sweet or fruity odor of acetone; liver failure produces a mousy or sometimes faintly sulfurous odor; and renal failure produces an odor of urine or ammonia.

**Evaluation**

**History:** History of present illness should ascertain duration and severity of halitosis (including whether other people have noticed or complained), adequacy of patient's oral hygiene, and the relationship of halitosis to ingestion of causative foods (see Table 56-5).

**Review of systems** should seek symptoms of causative disorders, including nasal discharge and face or head pain (sinusitis, nasal foreign body); productive cough and fevers (pulmonary infection); and regurgitation of undigested food when lying down or bending over (Zenker's diverticulum). Predisposing factors such as dry mouth, dry eyes, or both (Sjogren's syndrome) should be noted.

**Past medical history** should ask about duration and amount of use of alcohol and tobacco. Drug history should specifically ask about use of those that can cause dry mouth.

[Table 56-5. Some Causes of Halitosis]

**Physical examination:** Vital signs are reviewed, particularly for presence of fever.

The nose is examined for discharge and foreign body.

The mouth is examined for signs of gum disease, dental infection, and cancer. Signs of apparent dryness are noted (eg, whether the mucosa is dry, sticky, or moist; whether saliva is foamy, stringy, or normal in appearance).

The pharynx is examined for signs of infection and cancer.

**Sniff test:** A sniff test of exhaled air is conducted. In general, oral causes result in a putrefying, pungent smell, whereas systemic conditions result in a more subtle, abnormal odor. Ideally, for 48 h before the examination, the patient avoids eating garlic or onions, and for 2 h before, the patient abstains from eating, chewing, drinking, gargling, rinsing, or smoking. During the test, the patient exhales 10 cm away from the examiner's nose, first through the mouth and then with the mouth closed. A worse odor through the mouth suggests an oral etiology. A worse odor through the nose suggests a nasal or sinus etiology. Similar odor through both nose and mouth suggests a systemic or pulmonary cause. If site of origin is unclear, the posterior tongue is scraped with a plastic spoon. After 5 sec, the spoon is sniffed 5 cm from the examiner's nose.

**Red flags:** The following findings are of particular concern:

- Fever
- Purulent nasal discharge or sputum
- Visible or palpable oral lesions

**Interpretation of findings:** Because oral causes are by far the most common, any visible oral disease may be presumed to be the cause in patients with no extraoral symptoms or signs. When other disorders are involved, clinical findings often suggest a diagnosis (see Table 56-5).

In patients whose symptoms seem to be related to intake of certain substances and who have no other findings, a trial of avoidance may clarify the diagnosis.

**Testing:** Extensive diagnostic evaluation should not be undertaken unless the history and physical examination suggest an underlying disease (see Table 56-5). Portable sulfur monitors, gas chromatography, and chemical tests of tongue scrapings are available but best left to research protocols.
or the occasional dental office that focuses on halitosis.

**Treatment**

Underlying diseases are treated.

If the cause is oral, the patient should see a dentist for professional cleaning and treatment of gingival disease and caries. Home treatment involves enhanced oral hygiene, including thorough flossing, toothbrushing, and brushing of the tongue with the toothbrush or a scraper. Mouthwashes are of limited benefit except to mask odor for about 20 min. Psychogenic halitosis may require psychiatric consultation.

**Geriatrics Essentials**

Elderly patients are more likely to take drugs that cause dry mouth, which leads to difficulties with oral hygiene and hence to halitosis, but are otherwise not more likely to have halitosis. Also, oral cancers are more common with aging and are more of a concern among elderly than younger patients.

**Key Points**

- Most halitosis comes from fermentation of food particles by anaerobic gram-negative bacteria in the mouth.
- Extraoral disorders may cause halitosis but are often accompanied by suggestive findings.
- It is a fallacy that breath odor reflects the state of digestion and bowel function.
- Mouthwashes provide only brief benefit.

**Malocclusion**

Malocclusion is abnormal contact between the maxillary and mandibular teeth.

Normally, each dental arch consists of teeth in side-by-side contact, forming a smooth curve, with the maxillary anterior teeth overlying the upper third of the mandibular anterior teeth. The buccal (outer) cusps of the maxillary posterior teeth are external to the corresponding cusps of the mandibular posterior teeth. On each side of the mouth, the anterior buccal cusp of the maxillary 1st permanent molar fits into the anterior buccal groove of the mandibular 1st molar. Because the outer parts of all maxillary teeth are normally external to the mandibular teeth, the lips and cheeks are displaced from between the teeth so that they are not bitten. The lingual (inner) surfaces of the lower teeth form a smaller arc than those of the upper teeth, confining the tongue and minimizing the likelihood of its being bitten. All the maxillary teeth should contact the corresponding mandibular teeth, so that the masticatory forces (which may be > 150 lb in the molar region and 250 lb when clenching during sleep) are widely distributed. If these forces are applied to only a few teeth, those teeth will eventually loosen.

**Etiology**

Malocclusion often results from jaw and tooth size discrepancies (ie, the jaw is too small or the teeth are too large for the jaw to accommodate them in proper alignment) but may be caused by a number of congenital deformities and disorders or by tooth loss. When permanent teeth are lost, adjacent teeth shift and opposing teeth extrude, causing malocclusion unless a bridge, implant, or partial denture is worn to prevent these movements. When children lose deciduous teeth prematurely, the teeth more posterior in the arch or the permanent 1st molars often drift forward, leaving insufficient space for other permanent teeth to erupt. Malocclusion after facial trauma may indicate tooth displacement or jaw fracture. In ectodermal dysplasia, malocclusion results from having too few teeth.

**Evaluation**

Occlusion is checked on both sides of the mouth by retracting each cheek with a tongue depressor while
telling the patient to close on the back teeth. Malocclusion sometimes is identified as early as the first dental visit. Early identification may make later treatment easier and more effective.

**Treatment**

Malocclusions are corrected primarily for aesthetic and psychologic reasons. However, in some cases, treatment may increase resistance to caries (in specific teeth), to anterior tooth fracture, and, possibly, to periodontal disease or stripping of the gingiva on the palate. Treatment may improve speech and mastication as well. Occlusion can be improved by aligning teeth properly, by selectively grinding teeth and restorations that contact prematurely, and by inserting crowns or onlays to build up tooth surfaces that are below the plane of occlusion.

Orthodontic appliances (braces) apply a continuous mild force to teeth to gradually remodel the surrounding alveolar bone. Extraction of one or more permanent teeth (usually a 1st premolar) may be needed to allow other teeth to be repositioned or to erupt into a stable alignment. After the teeth are properly aligned, the patient wears a plastic-and-wire retainer 24 h/day initially, then only at night for 2 to 3 yr.

When orthodontic treatment alone is insufficient, surgical correction of jaw abnormalities contributing to malocclusion (orthognathic surgery) may be indicated.

**Stomatitis**

Oral inflammation and ulcers, known as stomatitis, may be mild and localized or severe and widespread. They are invariably painful. Stomatitis may involve swelling and redness of the oral mucosa or discrete, painful ulcers (single or multiple). Less commonly, whitish lesions form, and, rarely, the mouth appears normal (burning mouth syndrome) despite significant symptoms. Symptoms hinder eating, sometimes leading to dehydration and malnutrition. Secondary infection occasionally occurs. Some conditions are recurrent.

**Etiology**

Stomatitis may be caused by local infection, systemic disease, a physical or chemical irritant, or an allergic reaction (see Table 56-6); many cases are idiopathic. Because the normal flow of saliva protects the mucosa against many insults, xerostomia predisposes the mouth to stomatitis of any cause.

The **most common specific causes** overall include

- Recurrent aphthous stomatitis (RAS)—also called recurrent aphthous ulcers (RAU)
- Viral infections, particularly herpes simplex and herpes zoster
- Other infectious agents (*Candida albicans* and bacteria)
- Trauma
- Tobacco
- Chemotherapy and radiation therapy

**Evaluation**

**History:** **History of present illness** should ascertain the duration of symptoms and whether the patient ever had them previously. Presence and severity of pain should be noted. The relation of symptoms to food, drugs, and other substances (particularly occupational exposure to chemicals, metals, fumes, or dust) is sought.
**Review of systems** seeks symptoms of possible causes, including chronic diarrhea and weakness (inflammatory bowel disease, celiac sprue); genital lesions (Behcet's syndrome, syphilis); eye irritation (Behcet's syndrome); and weight loss, malaise, and fever (nonspecific chronic illness).

**Past medical history** should ascertain known conditions that cause oral lesions, including herpes simplex, Behcet's syndrome, inflammatory bowel disease, and risk factors for oral lesions, including immunocompromised state (eg, cancer, diabetes, organ transplant, use of immunosuppressants, HIV infection). Whether chemotherapy or radiation therapy has ever been used to manage cancer needs to be determined. Drug history should note all recent drugs used. History of tobacco use should be noted. Social history should include sexual contact, particularly oral sex, unprotected sex, and sex with multiple partners.

**Physical examination:** Vital signs are reviewed for fever. The patient's general appearance is noted for lethargy, discomfort, or other signs of significant systemic illness.

The mouth is inspected for the location and nature of any lesions.

The skin and other mucosal surfaces (including the genitals) are inspected for any lesions, rash, petechiae, or desquamation. Any bullous lesions are rubbed for Nikolsky's sign (peeling of epithelium with lateral pressure).

**Red flags:** The following findings are of particular concern:

- Fever
- Cutaneous bullae
- Ocular inflammation
- Immunocompromise

**Interpretation of findings:** Occasionally, causes are obvious in the history (eg, cytotoxic chemotherapy; significant occupational exposure to chemicals, fumes, or dust). Recurrent episodes of oral lesions occur with RAS, herpes simplex, and Behcet's syndrome. History of diabetes, HIV infection or other immunocompromise, or recent antibiotic use should increase suspicion of *Candida* infection. Recent drug use (particularly sulfa drugs, other antibiotics, and antiepileptics) should increase suspicion of Stevens-Johnson syndrome (SJS).

Some causes typically have **extraoral, noncutaneous findings**, some of which suggest a cause. Recurrent GI symptoms suggest inflammatory bowel disease or celiac sprue. Ocular symptoms can occur with Behcet's syndrome and SJS. Genital lesions may occur with Behcet's syndrome and primary syphilis.

Some causes usually also have **extraoral, cutaneous findings**.

Cutaneous bullae suggest SJS, pemphigus vulgaris, or bullous pemphigoid. Prodrome of malaise, fever, conjunctivitis, and generalized macular target lesions suggests SJS. Pemphigus vulgaris starts with oral lesions, then progresses to flaccid cutaneous bullae. Bullous pemphigoid has tense bullae on normal-appearing skin. Nikolsky's sign is usually positive in SJS and pemphigus vulgaris.

Cutaneous vesicles are typical with chickenpox or herpes zoster. Unilateral lesions in a band after a dermatome suggest herpes zoster. Diffuse, scattered vesicular and pustular lesions in different stages suggest chickenpox.

Kawasaki disease usually has a macular rash, desquamation of hands and feet, and conjunctivitis; it occurs in children, usually those < 5 yr. Oral findings include erythema of the lips and oral mucosa.
Other cutaneous lesions may implicate erythema multiforme, hand-foot-and-mouth disease (from coxsackievirus), or secondary syphilis.

Some causes have isolated oral findings, including RAS, most viral infections, acute necrotizing ulcerative gingivitis, primary syphilis, gonorrhea, and Candida.

Location of oral lesions may help identify the cause. Interdental ulcers occur with primary herpes simplex or acute necrotizing ulcerative gingivitis. Lesions on keratinized surfaces suggest herpes simplex, RAS, or physical injury. Physical injury typically has an irregular appearance and occurs near projections of teeth, dental appliances, or where biting can injure the mucosa. An aspirin burn next to a tooth and pizza burn on the palate are common.

Primary herpes simplex infection causes multiple vesicular lesions on the intraoral mucosa on both keratinized and nonkeratinized surfaces and always includes the gingiva. These lesions rapidly ulcerate. Clinical manifestation occurs most often in children. Subsequent reactivations (secondary herpes simplex, cold sore) usually appear starting in puberty on the lip at the vermilion border and, rarely, on the hard palate.

Acute necrotizing ulcerative gingivitis causes severe inflammation and punched-out ulcers on the dental papillae and marginal gingivae. A severe variant called noma (gangrenous stomatitis) can cause full-thickness tissue destruction (sometimes involving the lips or cheek), typically in a debilitated patient. It begins as a gingival, buccal, or palatal (midline lethal granuloma) ulcer that becomes necrotic and spreads rapidly. Tissue sloughing may occur.

Isolated oral gonorrhea very rarely causes burning ulcers and erythema of the gingiva and tongue, as well as the more common pharyngitis. Primary syphilis chancres may appear in the mouth. Tertiary syphilis may cause oral gummata or a generalized glossitis and mucosal atrophy. The site of a gumma is the only time that squamous cell carcinoma develops on the dorsum of the tongue. A common sign of HIV becoming AIDS is hairy leukoplakia (vertical white lines on the lateral border of the tongue).

C. albicans and related species, which are normal oral flora, can overgrow in people who have taken antibiotics or corticosteroids or who are immunocompromised, such as patients with AIDS. C. albicans can cause whitish, cheesy plaques that leave erosions when wiped off. Sometimes only flat, erythematous areas appear (erosive form of Candida).

**Testing:** Patients with acute stomatitis and no symptoms, signs, or risk factors for systemic illness probably require no testing.

If stomatitis is recurrent, viral and bacterial cultures, CBC, serum iron, ferritin, vitamin B₁₂, folate, zinc, and endomysial antibody (for sprue) are done. Biopsy at the periphery of normal and abnormal tissue can be done for persistent lesions that do not have an obvious etiology.

Systematically eliminating foods from the diet can be useful, as can changing brands of toothpaste, chewing gum, or mouthwash.

**Treatment**

Specific disorders are treated, and any causative substances or drugs are avoided.

Meticulous oral hygiene (using a soft toothbrush) may help prevent secondary infection. A soft diet that does not include acidic or salty foods is followed.

**Topical measures:** Numerous topical treatments, alone or in combination, are used to ease symptoms. These treatments include

- Anesthetics
For topical anesthesia of discomfort that may interfere with eating and drinking, the following may be effective:

- Lidocaine rinse
- Sucralfate plus aluminum-magnesium antacid rinse

A 2-min rinse is done with 15 mL (1 tbsp) 2% viscous lidocaine q 3 h prn; patient expectorates when done (no rinsing with water and no swallowing unless the pharynx is involved). A soothing coating may be prepared with sucralfate (1-g pill dissolved in 15 mL water) plus 30 mL of aluminum-magnesium liquid antacid; the patient should rinse with or without swallowing. Many institutions and pharmacies have their own variation of this formulation (magic mouthwash), which sometimes also contains an antihistamine.

If the physician is certain the inflammation is not caused by an infectious organism, the patient can

- Rinse and expectorate after meals with dexamethasone elixir 0.5 mg/5 mL (1 tsp)
- Apply a paste of 0.1% triamcinolone in an oral emollient
- Wipe amlexanox over the ulcerated area with the tip of a finger

Chemical or physical cautery can ease pain of localized lesions. Silver nitrate sticks are not as effective as low-power (2- to 3-watt), defocused, pulsed-mode CO₂ laser treatments, after which pain relief is immediate and lesions tend not to recur locally.

**Key Points**

- Isolated stomatitis in patients with no other symptoms and signs or risk factors for systemic illness is usually caused by a viral infection or RAS.
- Extraoral symptoms, skin rash, or both suggest more immediate need for diagnosis.

**Recurrent Aphthous Stomatitis**

Recurrent aphthous stomatitis is a common condition in which round or ovoid painful ulcers recur on the oral mucosa. Etiology is unclear. Diagnosis is clinical. Treatment is symptomatic and usually includes topical corticosteroids.

Recurrent aphthous stomatitis (RAS) affects 20 to 30% of adults and a greater percentage of children at some time in their life.

**Etiology**

Etiology is unclear, but RAS tends to run in families. The damage is predominately cell-mediated. Cytokines, such as IL-2, IL-10, and, particularly, tumor necrosis factor-α, play a role.

**Predisposing factors** include

- Oral trauma
• Stress

• Foods, particularly chocolate, coffee, peanuts, eggs, cereals, almonds, strawberries, cheese, and tomatoes

Allergy does not seem to be involved.

Factors that may, for unknown reasons, be protective include oral contraceptives, pregnancy, and tobacco, including smokeless tobacco and nicotine-containing tablets.

Symptoms and Signs

Symptoms and signs usually begin in childhood (80% of patients are < 30 yr) and decrease in frequency and severity with aging. Symptoms may involve as few as one ulcer 2 to 4 times/yr or almost continuous disease, with new ulcers forming as old ones heal. A prodrome of pain or burning for 1 to 2 days precedes ulcers, but there are no antecedent vesicles or bullae. Severe pain, disproportionate to the size of the lesion, can last from 4 to 7 days.

Ulcers are well-demarcated, shallow, ovoid, or round and have a necrotic center with a yellow-gray pseudomembrane, a red halo, and slightly raised red margins.

Minor aphthae (Mikulicz's disease) account for 85% of cases. They occur on the floor of the mouth, lateral and ventral tongue, buccal mucosa, and pharynx; are < 8 mm (typically 2 to 3 mm); and heal in 10 days without scarring.

Major aphthae (Sutton's disease, periadenitis mucosa necrotica recurrens) constitute 10% of cases. Appearing after puberty, the prodrome is more intense and the ulcers are deeper, larger (> 1 cm), and longer lasting (weeks to months) than minor aphthae. They appear in the lips, soft palate, and throat. Fever, dysphagia, malaise, and scarring may occur.

Herpetiform ulcers (morphologically resembling but unrelated to herpesvirus) account for 5% of cases. They begin as multiple (up to 100) 1- to 3-mm crops of small, painful clusters of ulcers on an erythematous base. They coalesce to form larger ulcers that last 2 wk. They tend to occur in women and at a later age of onset than do other forms of RAS.

Diagnosis

• Clinical evaluation

Evaluation proceeds as described previously under stomatitis (see p. 509). Diagnosis is based on appearance and on exclusion, because there are no definitive histologic features or laboratory tests.

Primary oral herpes simplex may mimic RAS but usually occurs in younger children, always involves the gingiva and may affect any keratinized mucosa (hard palate, attached gingiva, dorsum of tongue), and is associated with systemic symptoms. Viral culture can be done to identify herpes simplex. Recurrent herpetic lesions are usually unilateral.

Similar recurrent episodes can occur with Behcet's syndrome, inflammatory bowel disease, sprue, HIV infection, and nutritional deficiencies; these conditions generally have systemic symptoms and signs. Isolated recurrent oral ulcers can occur with herpes infection, HIV, and, rarely, nutritional deficiency. Viral testing and serum hematologic tests can identify these conditions.

Drug reactions may mimic RAS but are usually temporally related to ingestion. However, reactions to foods or dental products may be difficult to identify; sequential elimination may be necessary.

Treatment

• Topical chlorhexidine and corticosteroids
General treatments for stomatitis (see p. 512) may help patients with RAS. Chlorhexidine gluconate mouthwashes and topical corticosteroids, the mainstays of therapy, should be used during the prodrome, if possible. The corticosteroid can be dexamethasone 0.5 mg/5 mL tid used as a rinse and then expectorated or clobetasol ointment 0.05% or fluocinonide ointment 0.05% in carboxymethylcellulose mucosal protective paste (1:1) applied tid. Patients using these corticosteroids should be monitored for candidiasis. If topical corticosteroids are ineffective, prednisone (eg, 40 mg po once/day) may be needed for ≤ 5 days. Continuous or particularly severe RAS is best treated by a specialist in oral medicine. Treatment may require prolonged use of systemic corticosteroids, azathioprine or other immunosuppressants, pentoxifylline, or thalidomide. Intralesional injections can be done with betamethasone, dexamethasone, or triamcinolone. Supplemental B₁, B₂, B₆, B₁₂, folate, or iron lessens RAS in some patients.

**Xerostomia**

Xerostomia is dry mouth caused by reduced or absent flow of saliva. This condition can result in discomfort, interfere with speech and swallowing, make wearing dentures difficult, cause halitosis, and impair oral hygiene by causing a decrease in oral pH and an increase in bacterial growth. Longstanding xerostomia can result in severe tooth decay and oral candidiasis. Xerostomia is a common complaint among older adults, affecting about 20% of the elderly.

**Pathophysiology**

Stimulation of the oral mucosa signals the salivatory nuclei in the medulla, triggering an efferent response. The efferent nerve impulses release acetylcholine at salivary gland nerve terminals, activating muscarinic receptors (M₃), which increase saliva production and flow. Medullary signals responsible for salivation may also be modulated by cortical inputs from other stimuli (eg, taste, smell, anxiety).

**Etiology**

Xerostomia is usually caused by the following:

- Drugs
- Radiation to the head and neck (for cancer treatment)

Systemic disorders are less commonly the cause, but xerostomia is common in Sjogren's syndrome and may occur in HIV/AIDS, uncontrolled diabetes, and certain other disorders.

**Drugs**: Drugs are the most common cause (see Table 56-7); about 400 prescription drugs

[Table 56-7, Some Causes of Xerostomia]

and many OTC drugs cause decreased salivation. The most common include the following:

- Anticholinergics
- Antiparkinsonians
- Antineoplastics (chemotherapy)

Chemotherapy drugs cause severe dryness and stomatitis while they are being taken; these problems usually end after therapy is stopped.

Other common drug classes that cause xerostomia include antihypertensives, anxiolytics, and antidepressants (less severe with SSRIs than with tricyclics).
The rise of illicit methamphetamine use has resulted in an increasing incidence of meth mouth, which is severe tooth decay caused by methamphetamine-induced xerostomia. The damage is exacerbated by the bruxing and clenching caused by the drug. This combination causes very rapid destruction of teeth. Tobacco use usually causes a decrease of saliva.

**Radiation:** Incidental radiation to the salivary glands during radiation therapy for head and neck cancer often causes severe xerostomia (5200 cGy causes severe, permanent dryness, but even low doses can cause temporary drying).

**Evaluation**

**History:** History of present illness should include acuity of onset, temporal patterns (eg, constant vs intermittent, presence only on awakening), provoking factors, including situational or psychogenic factors (eg, whether xerostomia occurs only during periods of psychologic stress or certain activities), assessment of fluid status (eg, fluid intake habits, recurrent vomiting or diarrhea), and sleeping habits. Use of recreational drugs should be specifically elicited.

**Review of systems** should seek symptoms of causative disorders, including dry eyes, dry skin, rashes, and joint pain (Sjogren's syndrome).

**Past medical history** should inquire about conditions associated with xerostomia, including Sjogren's syndrome, history of radiation treatment, head and neck trauma, and a diagnosis of or risk factors for HIV infection. Drug profiles should be reviewed for potential offending drugs (see Table 56-7).

**Physical examination:** Physical examination is focused on the oral cavity, specifically any apparent dryness (eg, whether the mucosa is dry, sticky, or moist; whether saliva is foamy, stringy, or normal in appearance), the presence of any lesions caused by *Candida albicans*, and the condition of the teeth.

The presence and severity of xerostomia can be assessed at the bedside in several ways. For example, a tongue blade can be held against the buccal mucosa for 10 sec. If the tongue blade falls off immediately when released, salivary flow is normal. The more difficulty encountered removing the tongue blade, the more severe the xerostomia. In women, the lipstick sign, where lipstick adheres to the front teeth, may be a useful indicator of xerostomia.

If there appears to be dryness, the submandibular, sublingual, and parotid glands should be palpated while observing the ductal openings for saliva flow. The openings are at the base of the tongue anteriorly for the submandibular glands and on the middle of the inside of the cheek for the parotid glands. Drying the duct openings with a gauze square before palpation aids observation. If a graduated container is available, the patient can expectorate once to empty the mouth and then expectorate all saliva into the container. Normal production is 0.3 to 0.4 mL/min. Significant xerostomia is 0.1 mL/min.

Dental caries may be sought at the margins of restorations or in unusual places (eg, at the neck or tip of the tooth).

The most common manifestation of *C. albicans* infection is areas of erythema and atrophy (eg, on the dorsum of the tongue). Less common is the better-known white, cheesy curd that bleeds when wiped off.

**Red flags:** The following findings are of particular concern:

- Extensive tooth decay
- Concomitant dry eyes, dry skin, rash, or joint pain
- Risk factors for HIV

**Interpretation of findings:** Xerostomia is diagnosed by symptoms, appearance, and absence of salivary flow when massaging the salivary glands.
No further assessment is required when xerostomia occurs after initiation of a new drug and stops after cessation of that drug or when symptoms appear within several weeks of irradiation of the head and neck. Xerostomia that occurs with abrupt onset after head and neck trauma is caused by nerve damage.

Concomitant presence of dry eyes, dry skin, rash, or joint pain, particularly in a female patient, suggests a diagnosis of Sjogren's syndrome. Severe tooth decay, out of proportion to expected findings, may be indicative of illicit drug use, particularly methamphetamines. Xerostomia that occurs only during nighttime or that is noted only on awakening may be indicative of excessive mouth breathing in a dry environment.

Testing: For those in whom the presence of xerostomia is unclear, sialometry can be conducted by placing collection devices over the major duct orifices and then stimulating salivary production with citric acid or by chewing paraffin. Normal parotid flow is 0.4 to 1.5 mL/min/gland. Flow monitoring can also help determine response to therapy.

The cause of xerostomia is often apparent, but if the etiology is unclear and systemic disease is considered possible, further assessment should be pursued with biopsy of a minor salivary gland (for detection of Sjogren's syndrome, sarcoidosis, amyloidosis, TB, or cancer) and HIV testing.

Treatment

When possible, the cause of xerostomia should be addressed and treated.

For patients with drug-related xerostomia whose therapy cannot be changed to another drug, drug schedules should be modified to achieve maximum drug effect during the day, because nighttime xerostomia is more likely to cause caries. For all drugs, easy-to-take formulations, such as liquids, should be considered, and sublingual dosage forms should be avoided. The mouth and throat should be lubricated with water before swallowing capsules and tablets or before using sublingual nitroglycerin. Patients should avoid decongestants and antihistamines.

Patients using continuous positive airway pressure for obstructive sleep apnea may benefit from humidifying the source air (room humidifier for those using oral appliance therapy).

Symptom control: Symptomatic treatment consists of measures that do the following:

• Increase existing saliva
• Replace lost secretions
• Control caries

Drugs that augment saliva production include cevimeline and pilocarpine, both cholinergic agonists. Cevimeline (30 mg po tid) has less M₂ (cardiac) receptor activity than pilocarpine and a longer half-life. The main adverse effect is nausea. Pilocarpine (5 mg po tid) may be given after ophthalmologic and cardiorespiratory contraindications are excluded; adverse effects include sweating, flushing, and polyuria.

Sipping sugarless fluids frequently, chewing xylitol-containing gum, and using an OTC saliva substitute containing carboxymethylcellulose or hydroxyethylcellulose may help. Petroleum jelly can be applied to the lips and under dentures to relieve drying, cracking, soreness, and mucosal trauma. A cold-air humidifier may aid mouth breathers who typically have their worst symptoms at night.

Meticulous oral hygiene is essential. Patients should brush and floss regularly and use fluoride rinses or gels daily; using newer toothpastes with added Ca and phosphorous also may help avoid rampant caries. An increased frequency of preventive dental visits with plaque removal is advised. The most effective way to prevent caries is to sleep with individually fitted carriers containing 1.1% Na fluoride or 0.4% stannous fluoride. If 2 carriers cannot be worn at once, then each arch should be covered every other night. In addition, a dentist can apply a 5% Na fluoride varnish 2 to 4 times/yr.

Patients should avoid sugary or acidic foods and beverages and any irritating foods that are dry, spicy,
astringent, or excessively hot or cold.

**Geriatrics Essentials**

Although dry mouth becomes more common among the elderly, this is probably due to the many drugs typically used by the elderly rather than aging itself.

**Key Points**

- Drugs are the most common cause, but systemic diseases (most commonly Sjogren’s syndrome or HIV) and radiation therapy also can cause xerostomia.

- Symptomatic treatment includes increasing existing saliva flow with stimulants or drugs, and artificial saliva replacement. Xylitol-containing gum and candy may be useful.

- Patients with xerostomia are at high risk of tooth decay; meticulous oral hygiene and professionally applied fluorides are essential.
Common dental disorders include caries, gingivitis, periodontitis, and pulpitis. Dental emergencies, such as toothache, fractured or avulsed teeth, and postextraction complications, are discussed in Ch. 58.

Caries is tooth decay, commonly called cavities. The symptoms—tender, painful teeth—appear late. Diagnosis is based on inspection, probing of the enamel surface with a fine metal instrument, and dental x-rays. Treatment involves removing affected tooth structure and restoring it with various materials. Fluoride, diligent dental hygiene, sealants, and proper diet can prevent virtually all caries.

Etiology

Caries is caused by acids produced by bacteria in dental plaque. Plaque is, at first, a soft, thin film of bacteria, mucin, dead epithelial cells, and food debris that develops on the tooth surface within about 24 h after the tooth is cleaned. *Mutans streptococci* is a group of related bacteria that grow in plaque and can cause caries. Some strains are more cariogenic than others. Eventually (commonly, after 72 h), soft plaque mineralizes, mainly with Ca, phosphate, and other minerals, becoming calculus (hard plaque or tartar), which cannot easily be removed with a toothbrush.

Risk factors: There are several risk factors for caries:

- Dental defects
- High-acid or low-fluoride environment
- Reduced salivary flow

Many teeth have open enamel pits, fissures, and grooves, which may extend from the surface to the dentin. These defects may be wide enough to harbor bacteria but too narrow to clean effectively. They predispose teeth to caries. Large amounts of sugar in the diet provide nutrients for plaque-forming bacteria.

A tooth surface is more susceptible to caries when it is poorly calcified, has low fluoride exposure, or is in an acidic environment. Typically, decalcification begins when the pH at the tooth falls below 5.5 (eg, when lactic acid-producing bacteria colonize the area or when people drink cola beverages, which contain phosphoric acid).

Rampant caries in deciduous teeth suggests prolonged contact with infant formula, milk, or juice, typically when an infant goes to bed with a bottle (baby or nursing bottle caries). Thus, bedtime bottles should contain only water.

The elderly often take drugs that reduce salivary flow, predisposing to caries. The elderly also have a higher incidence of root caries because of gingival recession, exposure of root surfaces, and declining manual dexterity.

Complications: Untreated caries leads to tooth destruction, infections, and the need for extractions and replacement prostheses. Premature loss of deciduous teeth may shift the adjacent teeth, hindering eruption of their permanent successors.

Symptoms and Signs

Caries initially involves only the enamel and causes no symptoms. A cavity that invades the dentin causes pain, first when hot, cold, or sweet foods or beverages contact the involved tooth, and later with chewing.
or percussion. Pain can be intense and persistent when the pulp is severely involved (see Pulpitis on p. 522).

**Diagnosis**

- Direct inspection
- Sometimes use of x-rays or special testing instruments

Routine, frequent (q 6 to 12 mo) clinical evaluation identifies early caries at a time when minimal intervention prevents its progression. A thin probe, sometimes special dyes, and transillumination by fiberoptic lights are used, frequently supplemented by new devices that detect caries by changes in electrical conductivity or laser reflectivity. However, x-rays are still important for detecting caries, determining the depth of involvement, and identifying caries under existing restorations.

**Treatment**

- Restorative therapy
- Sometimes a root canal and crown

Incipient caries (which is confined to the enamel) should be remineralized through improved home care (brushing and flossing), cleanings, prescriptions for high-fluoride toothpastes, and multiple fluoride applications at the dental office.

The primary treatment of caries that has entered dentin is removal by drilling, followed by filling of the resultant defect. For very deep cavities, a temporary filling may be left in place 6 to 10 wk in the hope that a tooth will deposit reparative dentin, preventing exposure of the pulp, which necessitates root canal treatment.

Fillings for occlusal surfaces of posterior teeth, which bear the brunt of mastication, must be composed of strong materials. The most common material has been silver amalgam, which combines silver, mercury, copper, tin, and, occasionally, zinc, palladium, or indium. Amalgam is inexpensive and lasts an average of 14 yr. However, if oral hygiene is good and if amalgam was placed using a rubber dam for isolation from saliva, many amalgam fillings last > 40 yr. Although concern has been raised about mercury poisoning, the number of amalgam fillings a person has bears no relationship to blood mercury levels. Replacing amalgam is not recommended because it is expensive, damages tooth structure, and actually increases patient exposure to mercury.

Composite resins, which have a more acceptable appearance, have long been used in anterior teeth, where aesthetics are primary and the forces of chewing are minimal. Some patients request them in posterior teeth as well, and they are becoming common there. However, composite resins under high occlusal stress generally last less than half as long as amalgam and tend to develop recurrent decay because the composite resin shrinks when it hardens and expands and contracts with heat and cold more than the tooth or other filling materials. The current generation of composites also closely resemble enamel but do not appear to have the same incidence of recurrent caries as earlier materials and may also last longer. However, although long-term results with these newer amalgam substitutes appear good, data equivalent in numbers and duration to those with amalgam are not yet available.

If decay leaves too little dentin to hold a restoration, a dentist replaces the missing dentin with cement, amalgam, composite, or other materials. Sometimes a post must be inserted into one or more roots to support a gold, silver, or composite core, which replaces the coronal dentin. This procedure necessitates a root canal filling, in which an opening is made in the tooth and the pulp is removed. The root canal system is thoroughly debrided, shaped, and then filled with gutta-percha. The outer tooth surfaces (what would have been the enamel) are then reduced so that an artificial crown, usually made of gold, porcelain, or both, can be placed. Crowns for anterior teeth consist of, or are covered with, porcelain.

**Prevention**
• Regular brushing and flossing
• Fluoride in water, toothpaste, or both
• Regular professional cleanings
• Rarely chlorhexidine rinses and topical fluoride applications

For most people, caries is preventable. Cavities first form on permanent teeth in the early teens to late 20s. Caries-prone people typically have low exposure to fluoride and a relatively cariogenic microflora acquired from their mothers and through social contact. Maintaining good oral hygiene and minimizing sugar intake are especially important.

Removal of plaque at least q 24 h, usually by brushing and flossing, helps prevent dental caries. The gingival third of the tooth is the most important area to clean but is the area most often neglected. Electric and electronic toothbrushes are excellent, but a manual soft toothbrush, used for an average of 3 to 4 min, suffices. Using excess toothpaste, particularly an abrasive type, may erode the teeth. Dental floss is placed between each of the teeth, curved against the side of each tooth, and moved up and down 3 times, going just beneath the gingival margin. Flosses that are very thin (dental tape) or coated with wax or polytetraethylene can be used for exceptionally tight contacts between teeth or rough filling margins.

Teeth with fluoride incorporated into their enamel are more resistant to acidic decalcification and more readily recalculate when pH increases. If drinking water is not adequately fluoridated, fluoride supplements are recommended for children from shortly after birth through age 8 yr and for pregnant women beginning at 3 mo gestation (when teeth are forming in the fetus). The dose must be selected according to the amount of fluoride present in the drinking water and the age of the child. The total dose should not be so high as to cause dental fluorosis (see p. 52). Fluoridated toothpaste should also be used by people of all ages.

Fluoridation offers less protection against caries in pits and fissures than against those on smooth surfaces. Pits and fissures require use of sealants (plastic materials that adhere tightly to the surface of the enamel) to prevent nutrients from reaching bacteria, reducing their growth and acid production.

If these measures do not decrease cavity formation, more intensive therapy is aimed at changing the flora. After cavities are treated, pits and fissures, which can harbor *M. streptococci*, are sealed. This treatment is followed by 60-sec mouth rinses using 0.12% chlorhexidine bid for 2 wk, which may reduce the cariogenic bacteria in plaque and allow repopulation with less cariogenic strains of *M. streptococci*. To encourage this repopulation, xylitol in the form of hard candy or chewing gum is used for 5 min tid. Additionally, topical fluoride may be applied by a dentist or used at night in a custom-made fluoride carrier.

For pregnant women with a history of severe caries, the above regimen may be used before the child's teeth erupt. If this is not feasible, the mother can use xylitol, as mentioned above, from the time of the baby's birth to the age at which the mother no longer samples the child's food (the hypothesized mode of transfer).

For prevention of caries in deciduous teeth (once they have erupted) in infants, bedtime bottles should contain only water.

**Gingivitis**

Gingivitis is inflammation of the gingivae, causing bleeding with swelling, redness, exudate, a change of normal contours, and, occasionally, discomfort. Diagnosis is based on inspection. Treatment involves professional teeth cleaning and intensified home dental hygiene. Advanced cases may require antibiotics or surgery.

Normally, the gingivae are firm, tightly adapted to the teeth, and contoured to a point. Keratinized gingiva near the crowns is pink stippled tissue. This tissue should fill the entire space between the crowns. The
gingiva farther from the crowns, called alveolar mucosa, is nonkeratinized, highly vascular, red, movable, and continuous with the buccal mucosa. A tongue depressor should express no blood or pus from normal gingiva.

Inflammation, or gingivitis, the most common gingival problem, may evolve into periodontitis (see p. 520).

**Etiology**

The most common cause of gingivitis is poor oral hygiene.

Poor oral hygiene allows plaque to accumulate between the gingiva and the teeth; gingivitis does not occur in edentulous areas. Irritation due to plaque deepens the normal crevice between the tooth and gingiva, creating gingival pockets. These pockets contain bacteria that may cause both gingivitis and root caries. Other local factors, such as malocclusion, dental calculus, food impaction, faulty dental restorations, and xerostomia, play a secondary role.

**Systemic causes:** Gingivitis also commonly occurs at puberty, during menstruation and pregnancy, and at menopause, presumably because of hormonal changes. Similarly, oral contraceptives may exacerbate inflammation.

Gingivitis may be an early sign of a systemic disorder, particularly those that affect the response to infection (eg, diabetes, AIDS, vitamin deficiency, leukopenia), particularly if it occurs in patients with minimal dental plaque. Some patients with Crohn's disease have a cobblestone area of granulomatous gingival hypertrophy when intestinal flare-ups occur. Exposure to heavy metals (eg, lead, bismuth) may cause gingivitis and a dark line at the gingival margin. Severe deficiency of niacin or vitamin C can cause gingivitis.

**Symptoms and Signs**

Simple gingivitis first causes a deepening of the sulcus (gingival crevice) between the tooth and the gingiva, followed by a band of red, inflamed gingiva along one or more teeth, with swelling of the interdental papillae and easy bleeding. Pain is usually absent. It may resolve, remain superficial for years, or occasionally progress to periodontitis.

Pericoronitis is acute, painful inflammation of the gingival flap over a partly erupted tooth, usually around mandibular 3rd molars (wisdom teeth). Infection is common, and an abscess may develop. Pericoronitis often recurs as food gets trapped beneath the flap. The gingival flap disappears when the tooth is fully erupted.

Desquamative gingivitis may occur during menopause. It is characterized by deep red, painful gingival tissue that bleeds easily. Vesicles may precede desquamation. The gingivae are soft because the keratinized cells that resist abrasion by food particles are absent. A similar gingival lesion may be associated with pemphigus vulgaris, bullous pemphigoid, benign mucous membrane pemphigoid, or atrophic lichen planus.

During pregnancy, swelling, especially of the interdental papillae, is likely to occur. Pedunculated gingival growths often arise in the interdental papillae during the 1st trimester, may persist throughout pregnancy, and may or may not subside after delivery. Pregnancy tumors are soft reddish masses that are, histologically, pyogenic granulomas. They develop rapidly and then remain static. An underlying irritant is common, such as calculus or a restoration with a rough margin.

Uncontrolled diabetes can exaggerate the effects of gingival irritants, making secondary infections and acute gingival abscesses common.

In leukemia, the gingivae may become engorged with a leukemic infiltrate, exhibiting clinical symptoms of edema, pain, and easily induced bleeding.

In scurvy (vitamin C deficiency), the gingivae are inflamed, hyperplastic, and engorged, bleeding easily.
Petechiae and ecchymoses may appear throughout the mouth.

In pellagra (niacin deficiency), the gingivae are inflamed, bleed easily, and are susceptible to secondary infection. Additionally, the lips are reddened and cracked, the mouth feels scalded, the tongue is smooth and bright red, and the tongue and mucosa may have ulcerations.

**Diagnosis**

- Clinical evaluation

Finding erythematous, friable tissue at the gum lines confirms the diagnosis. To detect early gingival disease, some dentists frequently measure the depth of the pocket around each tooth. Depths < 3 mm are normal; deeper pockets are at high risk of gingivitis and periodontitis.

**Treatment**

- Regular oral hygiene and professional cleaning

Simple gingivitis is controlled by proper oral hygiene with or without an antibacterial mouth rinse. Thorough scaling (professional cleaning with hand or ultrasonic instruments) should be done. If appropriate, poorly contoured restorations are reshaped or replaced and local irritants are removed. Excess gingiva, if present, can be excised. Drugs causing gingival hyperplasia should be stopped if possible; if not, improved home care and more frequent professional cleanings (at least every 3 mo) usually reduce the hyperplasia. Pregnancy tumors are excised.

Treatment of pericoronitis consists of

- Removal of debris from under the gingival flap
- Irrigation with saline, 1.5% hydrogen peroxide, or 0.12% chlorhexidine
- Particularly when episodes recur, extraction

If severe infection develops, antibiotics may be given for a day before extraction and continued during healing. A common regimen is amoxicillin 500 mg po q 6 h for 10 days (or until 3 days after all inflammation has subsided). Abscesses associated with pericoronitis require localized incision and drainage, a periodontal flap and root debridement, or extraction.

In gingivitis caused by systemic disorders, treatment is directed at the cause. In desquamative gingivitis during menopause, sequential administration of estrogens and progestins may be beneficial, but adverse effects of this therapy (see p. 2519) limit recommendations for its use. Otherwise, dentists may prescribe a corticosteroid rinse or a corticosteroid paste that is applied directly to the gums. Gingivitis caused by pemphigus vulgaris (see p. 658) and similar mucocutaneous conditions may require systemic corticosteroid therapy.

**Prevention**

Daily removal of plaque with dental floss and a toothbrush and routine cleaning by a dentist or hygienist at 6-mo to 1-yr intervals can help minimize gingivitis. Patients with systemic disorders predisposing to gingivitis require more frequent professional cleanings (from q 2 wk to 4 times/yr).

**Acute Necrotizing Ulcerative Gingivitis**

(Fusospirochetosis; Trench Mouth; Vincent's Infection or Angina)

Acute necrotizing ulcerative gingivitis is a painful infection of the gums. Symptoms are acute pain, bleeding, and foul breath. Diagnosis is based on clinical findings. Treatment is gentle debridement, improved oral hygiene, mouth rinses, supportive care, and, if debridement must
Acute necrotizing ulcerative gingivitis occurs most frequently in smokers and debilitated patients who are under stress. Other risk factors are poor oral hygiene, nutritional deficiencies, and sleep deprivation.

**Symptoms and Signs**

The usually abrupt onset may be accompanied by malaise or fever. The chief manifestations are acutely painful, bleeding gingivae; excessive salivation; and overwhelmingly foul breath (fetor oris). Ulcerations, which are pathognomonic, are present on the dental papillae and marginal gingiva; these have a characteristically punched-out appearance and are covered by a gray pseudomembrane. Similar lesions on the buccal mucosa and tonsils are rare. Swallowing and talking may be painful. Regional lymphadenopathy often is present.

**Diagnosis**

- Clinical evaluation

Rarely, tonsillar or pharyngeal tissues are affected, and diphtheria or infection due to agranulocytosis must be ruled out by throat culture and CBC.

**Treatment**

- Debridement
- Rinses (eg, hydrogen peroxide, chlorhexidine)
- Improved oral hygiene
- Sometimes oral antibiotics

Treatment consists of gentle debridement with a hand scaler or ultrasonic device. Debridement is done over several days. The patient uses a soft toothbrush to wipe the teeth. Rinses at hourly intervals with warm normal saline or twice/day with 1.5% hydrogen peroxide or 0.12% chlorhexidine may help during the first few days after initial debridement. Essential supportive measures include improved oral hygiene (done gently at first), adequate nutrition, high fluid intake, rest, analgesics as needed, and avoiding irritation (eg, caused by smoking or hot or spicy foods). Marked improvement usually occurs within 24 to 48 h, after which debridement can be completed. If debridement is delayed (eg, if a dentist or the instruments necessary for debridement are unavailable), oral antibiotics (eg, amoxicillin 500 mg, erythromycin 250 mg, or tetracycline 250 mg q 6 h) provide rapid relief and can be continued until 72 h after symptoms resolve. If the gingival contour inverts (ie, if the tips of papillae are lost) during the acute phase, surgery is eventually required to prevent subsequent periodontitis.

**Other Gingival Disorders**

Hyperplasia of gingival tissues may occur without inflammation in response to various drugs, particularly phenytoin, cyclosporine, and nifedipine or, less commonly, other Ca channel blockers. Hyperplasia is characterized by diffuse, relatively avascular smooth or nodular enlargement of the gingiva, which may almost cover some teeth. The hypertrophied tissue is often excised. If possible, substitutions are made for the offending drugs. Scrupulous oral hygiene may minimize recurrence.

Carcinoma can also originate in the gingiva and spread to regional lymph nodes.

**Periodontitis**

Periodontitis is an infection of the periodontium—causing inflammation of the periodontal ligament, gingiva, cementum, and alveolar bone. It usually manifests as a worsening of gingivitis. Symptoms are rare except with HIV or when abscesses develop, in which case pain
and swelling are common. Diagnosis is based on inspection, periodontal probing, and x-rays. Treatment involves dental cleaning that extends under the gums and a vigorous home hygiene program. Advanced cases may require antibiotics and surgery.

**Etiology**

Periodontitis usually develops when gingivitis, usually with abundant plaque and calculus beneath the gingival margin, has not been adequately treated. In periodontitis, the deep pockets can harbor anaerobic organisms that do more damage than those usually present in simple gingivitis. The gingiva progressively loses its attachment to the teeth, periodontal pockets deepen, and bone loss begins. With progressive bone loss, teeth may loosen, and gingiva recedes. Tooth migration is common in later stages.

**Systemic causes:** Systemic diseases that predispose patients to periodontitis include diabetes (especially type 1); acquired, familial, and cyclic neutropenia; leukemia; Down syndrome; leukocyte adhesion deficiency syndromes; Papillon-Lefevre syndrome; Crohn's disease; histiocytosis syndromes; agranulocytosis; lazy leukocyte syndrome; hypogammaglobulinemia; Chediak-Higashi syndrome; glycogen storage disease; infantile genetic agranulocytosis; Ehlers-Danlos syndrome (types IV and VIII); vitamin C deficiency (scurvy); and hypophosphatasia. Faulty occlusion, causing an excessive functional load on teeth, may contribute to progression of a particular type of periodontitis characterized by angular bony defects.

**Pathophysiology**

Periodontitis is usually chronic and characterized by periods of exacerbation and remission. Chronic periodontitis (formerly adult periodontitis) occurs in localized and generalized forms, and people with significant disease tend to be > 35 yr. About 85% of the population is affected to a mild degree, but the most advanced cases are seen in less than 5% of the population.

**Aggressive periodontitis:** Several more rapidly progressive subtypes of chronic periodontitis exist, collectively known as aggressive periodontitis. Aggressive periodontitis may develop as early as childhood, sometimes before age 3 yr. Patients may have severe bone loss, even tooth loss, by age 20. Neutrophil function may be defective in aggressive periodontitis; its clinical significance is unknown.

In one type of aggressive periodontitis that occurs in healthy adolescents (formerly called localized juvenile periodontitis), patients often have significant colonization of *Actinobacillus actinomycetemcomitans.* Typically, the signs of inflammation are minor. The disease is detected by periodontal probing or x-rays, which show localized, deep (vertical) bone loss, commonly limited to the 1st molars and incisors. Bone loss progresses faster than in adult periodontitis, often at a rate of 3 to 4 μm/day.

An uncommon type of aggressive periodontitis (formerly called prepubertal periodontitis) affects deciduous teeth, usually shortly after eruption. Generalized acute proliferative gingivitis and rapid alveolar bone destruction are its hallmarks. Patients also have frequent bouts of otitis media and are usually diagnosed by age 4 yr. In some patients, the disease resolves before the permanent teeth erupt. Treatment regimens are under study.

Prototypical aggressive periodontitis (formerly called rapidly progressive periodontitis) occurs in patients aged 20 to 35 yr. It is often associated with *A. actinomycetemcomitans,* *Porphyromonas gingivalis,* *Eikenella corrodens,* and many gram-negative bacilli, but cause and effect are not clear. Some cases result from undiagnosed localized juvenile periodontitis or prepubertal periodontitis, but others appear independently.

HIV-associated periodontitis is a particularly virulent, rapidly progressing disease. Clinically, it resembles acute necrotizing ulcerative gingivitis (see p. 520) combined with rapidly progressive periodontitis. Patients may lose 9 to 12 mm of attachment in as little as 6 mo.

**Symptoms and Signs**
Pain is usually absent unless an acute infection forms in one or more periodontal pockets or if HIV-associated periodontitis is present. Impaction of food in the pockets can cause pain at meals. Abundant plaque along with redness, swelling, and exudate are characteristic. Gums may be tender and bleed easily, and breath may be foul.

**Diagnosis**

- Clinical evaluation
- Sometimes dental x-rays

Inspection of the teeth and gingiva combined with probing of the pockets and measurement of their depth are usually sufficient for diagnosis. Pockets deeper than 4 mm indicate periodontitis. Dental x-rays reveal alveolar bone loss adjacent to the periodontal pockets.

**Treatment**

- Scaling and root planing
- Sometimes oral antibiotics, antibiotic packs, or both
- Surgery or extraction

For all forms of periodontitis, the first phase of treatment consists of thorough scaling and root planing (ie, removal of diseased or toxin-affected cementum and dentin followed by smoothing of the root) to remove plaque and calculus deposits. Thorough home oral hygiene is necessary. The patient is reevaluated after 3 wk. If pockets are no deeper than 4 mm at this point, the only treatment needed is regular cleanings.

If deeper pockets persist, systemic antibiotics can be used. A common regimen is amoxicillin 500 mg po qid for 10 days. In addition, a gel containing doxycycline or microspheres of minocycline can be placed into isolated recalcitrant pockets. These are resorbed in 2 wk.

Another approach is to surgically eliminate the pocket and recontour the bone so that the patient can clean the depth of the sulcus (pocket reduction/elimination surgery). In selected situations, regenerative surgery and bone grafting are done to encourage alveolar bone growth. Splinting of loose teeth and selective reshaping of tooth surfaces to eliminate traumatic occlusion may be necessary. Extractions are often necessary in advanced disease. Contributing systemic factors should be controlled before initiating periodontal therapy.

Ninety percent of patients with HIV-associated periodontitis respond to irrigation of the sulcus with povidone-iodine (which the dentist applies with a syringe), regular use of chlorhexidine mouth rinses, and systemic antibiotics, usually metronidazole 250 mg po tid for 14 days.

Localized juvenile periodontitis requires periodontal surgery plus oral antibiotics (eg, amoxicillin 500 mg qid or metronidazole 250 mg tid for 14 days).

**Pulpitis**

Pulpitis is inflammation of the dental pulp resulting from untreated caries, trauma, or multiple restorations. Its principal symptom is pain. Diagnosis is based on clinical findings and is confirmed by x-ray. Treatment involves removing decay, restoring the damaged tooth, and sometimes doing root canal therapy or extracting the tooth.

Pulpitis can occur when

- Caries progresses deeply into the dentin
- A tooth requires multiple invasive procedures
• Trauma disrupts the lymphatic and blood supply to the pulp

Pulpitis begins as a reversible condition in which the tooth can be saved by a simple filling. It becomes irreversible as swelling inside the rigid enencasement of the dentin compromises circulation, making the pulp necrotic, which predisposes to infection.

Complications: Infectious sequelae of pulpitis include apical periodontitis, periapical abscess, cellulitis, and osteomyelitis of the jaw. Spread from maxillary teeth may cause purulent sinusitis, meningitis, brain abscess, orbital cellulitis, and cavernous sinus thrombosis. Spread from mandibular teeth may cause Ludwig's angina, parapharyngeal abscess, mediastinitis, pericarditis, empyema, and jugular thrombophlebitis.

Symptoms and Signs

In reversible pulpitis, pain occurs when a stimulus (usually cold or sweet) is applied to the tooth. When the stimulus is removed, the pain ceases within 1 to 2 sec.

In irreversible pulpitis, pain occurs spontaneously or lingers minutes after the stimulus is removed. A patient may have difficulty locating the tooth from which the pain originates, even confusing the maxillary and mandibular arches (but not the left and right sides of the mouth). The pain may then cease for several days because of pulpal necrosis. As infection develops and extends through the apical foramen, the tooth becomes exquisitely sensitive to pressure and percussion. A periapical (dentoalveolar) abscess elevates the tooth from its socket and feels "high" when the patient bites down.

Diagnosis

• Clinical evaluation

• Sometimes dental x-rays

Diagnosis is based on the history and physical examination, which makes use of provoking stimuli (application of heat, cold, percussion). X-rays help determine whether inflammation has extended beyond the tooth apex and help exclude other conditions.

Treatment

• Drilling and filling for reversible pulpitis

• Root canal and crown or extraction for irreversible pulpitis

• Antibiotics (eg, amoxicillin) for infection

In reversible pulpitis, pulp vitality can be maintained if the tooth is treated, usually by caries removal, and then restored.

Irreversible pulpitis and its sequelae require endodontic (root canal) therapy or tooth extraction. In endodontic therapy, an opening is made in the tooth and the pulp is removed. The root canal system is thoroughly debrided, shaped, and then filled with gutta-percha. After root canal therapy, adequate healing is manifested clinically by resolution of symptoms and radiographically by bone filling in the radiolucent area at the root apex over a period of months. If patients have systemic signs of infection (eg, fever), an oral antibiotic is prescribed (amoxicillin 500 mg q 8 h; for patients allergic to penicillin, clindamycin 150 mg or 300 mg q 6 h). If symptoms persist or worsen, root canal therapy is usually repeated in case a root canal was missed, but alternative diagnoses (eg, temporomandibular disorder, occult tooth fracture, neurologic disorder) should be considered.

Very rarely, subcutaneous or mediastinal emphysema develops after compressed air or a high-speed air turbine dental drill has been used during root canal therapy or extraction. These devices can force air into
the tissues around the tooth socket that dissects along fascial planes. Acute onset of jaw and cervical swelling with characteristic crepitus of the swollen skin on palpation is diagnostic. Treatment usually is not required, although prophylactic antibiotics are sometimes given.

**Dental Appliances**

Teeth may be lost to dental caries, periodontal disease, or trauma or may be removed when treatment fails. Missing teeth may cause cosmetic, phonation, and occlusal problems and may allow movement of remaining teeth.

**Types:** Dental appliances include fixed bridges, removable partial or complete dentures, and osseointegrated implants.

A bridge (fixed partial denture) is composed of false teeth cast or soldered to each other and, at each end, to a crown that is cemented to natural (abutment) teeth, which bear all stress of biting. A bridge is not removed. A bridge is smaller than a removable partial denture, but one or multiple bridges can be made to replace many of the teeth in a dental arch.

A removable partial denture, typically an appliance with clasps that snap over abutment teeth, may be removed for cleaning and during sleep. Part of the occlusal stress may be borne by the soft tissues under the denture, often on both sides of the jaw. This appliance commonly is used when many teeth have to be replaced and bridges or implants are not feasible or affordable.

Complete dentures are removable appliances used when no teeth remain. They help a patient chew and improve speech and appearance but do not provide the efficiency or sensation of natural dentition. When teeth are absent, the mandible slowly resorbs, resulting in ill-fitting dentures that require revision (called reline or rebase) or replacement. Alternatives are oral surgical procedures to enlarge the alveolar ridge or dental implants to replace missing teeth.

An implant is typically a titanium cylinder or screw that replaces a tooth root. One or more implants are placed into the alveolar bone, where they ankylose. After 4 to 6 mo, artificial teeth are attached to the implants. Implants are not readily removable, although the prostheses they support can be. The potential for infection at these sites warrants scrupulous attention to oral hygiene.

**Dental appliances and surgery:** Generally, all removable dental appliances are removed before general anesthesia, throat surgery, or convulsive therapy to prevent their breakage or aspiration. They are stored in water to prevent changes in shape. However, some anesthesiologists believe that leaving appliances in place aids the passage of an airway tube, keeps the face in a more normal shape so that the anesthetic mask fits better, prevents natural teeth from injuring the opposing gingiva of a completely edentulous jaw, and does not interfere with laryngoscopy.

**Denture problems:** Occasionally, the mucosa beneath a denture becomes inflamed (denture sore mouth, inflammatory papillary hyperplasia). Contributing factors to this usually painless condition include candidal infections, poor denture fit, poor hygiene, excessive movement of the denture, and, most frequently, wearing a denture 24 h/day. The mucosa appears red and velvety. Candidal overgrowth may be indicated by adherent cottonlike patches or, more commonly, erosive lesions on the mucosa. The presence of *Candida* can be confirmed by the microscopic appearance of typical branching hyphae. Without *Candida*, inflammatory papillary hyperplasia is unlikely.

A new well-made denture almost always improves the situation. Other treatments consist of improving oral and denture hygiene, refitting the existing denture, removing the denture for extended periods, and using anti-fungal therapy (nystatin rinses for the mouth and overnight nystatin soaks for the denture). Soaking the denture in a commercial cleanser is sometimes helpful. Other options are applying nystatin suspension to the tissue surface of the denture and clotrimazole troches 10 mg 5 times/day. Ketoconazole 200 mg po once/day may be required. If inflammation persists, biopsy is indicated, and systemic conditions should be ruled out.
Chapter 58. Dental Emergencies

Introduction

Emergency dental treatment by a physician is sometimes required when a dentist is unavailable.

Oral analgesics effective for most dental problems include acetaminophen 650 to 1000 mg q 6 h and NSAIDs such as ibuprofen 400 to 800 mg q 6 h. For severe pain, these drugs may be combined with opioids such as codeine 60 mg; hydrocodone 5 mg, 7.5 mg, or 10 mg; or oxycodone 5 mg.

Antibiotics for dental infections include penicillin VK 500 mg po q 6 h and clindamycin 300 mg po q 8 h.


Coverage for dental procedures is recommended only for patients with prosthetic cardiac valves, previous IE, specific congenital heart diseases, and for cardiac transplant recipients with heart valve problems (valvulopathy). Dental procedures requiring prophylaxis are those that require manipulation or perforation of gingival or oral mucosa or that involve the root end area of the teeth (ie, those most likely to cause bacteremia). The preferred drug is amoxicillin 2 g po 30 to 60 min before the procedure. For those who cannot tolerate penicillins, alternatives include clindamycin 600 mg or cephalexin 2 g.

Fractured and Avulsed Teeth

Tooth fracture: Fractures are divided by depth into those that

• Affect only the enamel
• Expose the dentin
• Expose the pulp

If the fracture involves only the enamel, patients notice rough or sharp edges but are asymptomatic. Dental treatment to smooth the edges and improve appearance is elective.

If dentin is exposed but not the dental pulp, patients usually exhibit sensitivity to cold air and water. Treatment is a mild analgesic and referral to a dentist. Dental treatment consists of restoration of the tooth by a composite (white filling) or, if the fracture is extensive, a dental crown, to cover the exposed dentin.

If the pulp is exposed (indicated by bleeding from the tooth) or if the tooth is mobile, dental referral is urgent. Dental treatment usually involves a root canal.

Root fractures and alveolar fractures are not visible, but the tooth (or several teeth) may be mobile. Dental referral is also urgent for stabilization by bonding an orthodontic arch wire or polyethylene line onto several adjacent teeth.

Tooth avulsion: Avulsed primary teeth are not replaced because they typically become necrotic, then infected. They may also become ankylosed and do not exfoliate, thereby interfering with the eruption of the permanent tooth.

If a secondary tooth is avulsed, the patient should replace it in its socket immediately and seek dental care to stabilize it. If this cannot be done, the tooth should be kept immersed in milk or wrapped in a moistened paper towel and brought to a dentist for replacement and stabilization. The tooth should not be scrubbed, because scrubbing may remove viable periodontal ligament fibers, which aid in reattachment. A patient with an avulsed tooth should take an antibiotic for several days. If the avulsed tooth cannot be found, it may have been aspirated, embedded in soft tissue, or swallowed. A chest x-ray may be needed to rule out aspiration, but a swallowed tooth is harmless.
A partially avulsed tooth that is repositioned and stabilized quickly usually is permanently retained. A completely avulsed tooth may be permanently retained if replaced in the socket with minimal handling within 30 min to 1 h. Both partial and complete avulsions usually ultimately require root canal therapy because the pulp tissue becomes necrotic. When replacement of the tooth is delayed, the long-term retention rate drops, and root resorption eventually occurs. Nevertheless, a patient may be able to use the tooth for several years.

Mandibular Dislocation

Spontaneous mandibular dislocation usually occurs in people with a history of such dislocations. Although a dislocated mandible is occasionally caused by trauma, the initiating episode is typically a wide opening followed by biting pressure (eg, biting into a large sandwich with hard bread), a wide yawn, or a dental procedure. People prone to dislocation may have naturally loose temporomandibular joint (TMJ) ligaments.

Patients present with a wide-open mouth that they are unable to close. Pain is secondary to patients’ attempts to close the mouth. If the mandibular midline deviates to one side, the dislocation is unilateral. Although rarely used, a local anesthetic (eg, 2% lidocaine 2 to 5 mL) injected into the ipsilateral joint and into the adjacent area of insertion of the lateral pterygoid muscle may allow the mandible to reduce spontaneously.

Manual reduction may be necessary (see Fig. 58-1). Premedication may be used (eg, diazepam 5 to 10 mg IV at 5 mg/min or midazolam 3 to 5 mg IV at 2 mg/min and an opioid such as meperidine 25 mg IV or fentanyl 0.5 to 1 μg/kg IV) but is usually unnecessary, especially if time will be lost preparing the IV. The longer the mandible is dislocated, the more difficult it is to reduce and the greater the likelihood that dislocation will recur.

Barton's bandage may be needed for 2 or 3 days. Most importantly, the patient must avoid opening the mouth wide for at least 6 wk. When anticipating a yawn, the patient should place a fist under the chin to prevent wide opening. Food must be cut into small pieces. If the patient suffers from chronic dislocations and more conservative treatment modalities have been exhausted, an oral and maxillofacial surgeon may be consulted. As last-resort treatments, the ligaments around the TMJ can be surgically tightened (shortened) in an attempt to stabilize the joint or the articular eminence can be reduced (eminectomy).

Postextraction Problems

Pain and swelling: Swelling is normal after oral surgery and is proportional to the degree of manipulation and trauma. If swelling does not begin to subside by the 3rd postoperative day, infection is likely and an antibiotic may be given (eg, penicillin VK 500 mg po q 6 h until 72 h after symptoms subside).

Postoperative pain varies from moderate to severe and is treated with analgesics (see p. 1623).

Alveolitis and osteomyelitis: Postextraction alveolitis (dry socket) is pain emanating from bare bone if the socket's clot lyses. Although assumed to be due to bacterial action, it is much more common among smokers and oral contraceptive users. It is peculiar to the removal of mandibular molars, usually wisdom teeth. Typically, the pain begins on the 2nd or 3rd postoperative day, is referred to the ear, and lasts from a few days to many weeks. Alveolitis is best treated with topical analgesics: a 1- to 2-in iodoform gauze strip saturated in eugenol or coated with an anesthetic ointment, such as lidocaine 2.5% or tetracaine 0.5%, is placed in the socket. The gauze is changed every 1 to 3 days until symptoms do not return after the gauze is left out for a few hours. This procedure eliminates the need for systemic analgesics.

Osteomyelitis, which in rare cases is confused with alveolitis, is differentiated by fever, local tenderness,
and swelling. If symptoms last a month, a sequestrum, which is diagnostic of osteomyelitis, should be sought by x-ray. Osteomyelitis requires long-term treatment with antibiotics effective against both gram-positive and gram-negative organisms and referral for definitive care.

**Osteonecrosis of the jaw (ONJ):** ONJ (see also Sidebar 39-1 on p. 363) is an oral lesion involving persistent exposure of mandibular or maxillary bone, which usually manifests with pain, loosening of teeth, and purulent discharge. ONJ may occur after dental extraction but also may develop after trauma or radiation therapy to the head and neck. Recently, an association has been discovered between IV bisphosphonate (BP) use and ONJ. However, oral BP therapy seems to pose very low risk of ONJ. Stopping oral BP therapy is unlikely to reduce this already low rate of ONJ, and maintaining good oral hygiene is a more effective preventative measure than stopping oral BP before dental procedures. Management of ONJ is challenging and typically involves limited debridement, antibiotics, and oral rinses.

**Bleeding:** Postextraction bleeding usually occurs in the small vessels. Any clots extending out of the socket are removed with gauze, and a 4-in gauze pad (folded) or a tea bag is placed over the socket. Then the patient is instructed to apply continuous pressure by biting for 1 h. The procedure may have to be repeated 2 or 3 times. Patients are told to wait at least 1 h before checking the site so as not to disrupt clot formation. They also are informed that a few drops of blood diluted in a mouth full of saliva appear to be more blood than is actually present. If bleeding continues, the site may be anesthetized by nerve block or local infiltration with 2% lidocaine containing 1:100,000 epinephrine. The socket is then curetted to remove the existing clot and to freshen the bone and is irrigated with normal saline. Then the area is sutured under gentle tension. Local hemostatic agents, such as oxidized cellulose, topical thrombin on a gelatin sponge, or microfibrillar collagen, may be placed in the socket before suturing.

If possible, patients taking low-dose anticoagulants (eg, aspirin, clopedigrol, warfarin) should stop therapy 3 to 4 days before surgery. Therapy can be reinstated that evening. If these measures fail, a systemic cause (eg, bleeding diathesis) is sought.

**Toothache and Infection**

Pain in and around the teeth is a common problem, particularly among those with poor oral hygiene. Pain may be constant, felt after stimulation (eg, heat, cold, sweet food or drink, chewing, brushing), or both.

**Etiology**

The most common causes of toothache (see Table 58-1) are

- Dental caries
- Pulpitis
- Trauma
- Erupting wisdom tooth (causing pericoronitis)

Toothache is usually caused by dental caries and its consequences.

Caries causes pain when the lesion extends through the enamel into dentin. Pain usually occurs after stimulation from cold, heat, sweet food or drink, or brushing; these stimuli cause fluid to move along dentinal tubules to the pulp. As long as the discomfort does not persist after the stimulus is removed, the pulp is likely healthy enough to be maintained. This is referred to as normal dentinal sensitivity, reversible pulpalgia, or reversible pulpitis.

Pulpitis is inflammation of the pulp, typically due to advancing caries, cumulative minor pulp damage from previous large restorations, a defective restoration, or trauma. It may be reversible or irreversible. Pressure necrosis frequently results from pulpitis, because the pulp is encased in a rigid compartment. Pain may be spontaneous or in response to stimulation. In both cases, pain lingers for a minute or longer.
Once the pulp becomes necrotic, pain ends briefly (hours to weeks). Subsequently, periapical inflammation (apical periodontitis) or an abscess develops. The tooth is exquisitely sensitive to percussion (tapped with a metal dental probe or tongue blade) and chewing.

Periapical abscess may follow untreated caries or pulpitis. The abscess may point intraorally and eventually drain or may become a cellulitis.

Tooth trauma can damage the pulp. The damage may manifest soon after the injury or up to decades later.

Pericoronitis is inflammation and infection of the tissue between the tooth and its overlying flap of gingiva (operculum). It usually occurs in an erupting wisdom tooth (almost always a lower one).

Complications: Rarely, sinusitis results from untreated maxillary dental infection. More commonly, pain from a sinus infection is perceived as originating in the (unaffected) teeth, mistakenly creating the impression of a dental origin.

Rarely, cavernous sinus thrombosis (see p. 624) or Ludwig's angina (submandibular space infection—see p. 470) develops; these conditions are life threatening and require immediate intervention.

Table 58-1. Some Causes of Toothache

| Evaluation |
| History: History of present illness | should identify the location and duration of the pain and whether it is constant or present only after stimulation. Specific triggering factors to review include heat, cold, sweet food or drink, chewing, and brushing. Any preceding trauma or dental work should be noted. |
| Review of systems | should seek symptoms of complications, including face pain, swelling, or both (dental abscess, sinusitis); pain below the tongue and difficulty swallowing (submandibular space infection); pain with bending forward (sinusitis); and retro-orbital headache, fever, and vision symptoms (cavernous sinus thrombosis). |
| Past medical history | should note previous dental problems and treatment. |
| Physical examination: | Vital signs are reviewed for fever. |

The examination focuses on the face and mouth. The face is inspected for swelling and is palpated for induration and tenderness.

The oral examination includes inspection for gum inflammation and caries and any localized swelling at the base of a tooth that may represent a pointing apical abscess. If no tooth is clearly involved, teeth in the area of pain are percussed for tenderness with a tongue depressor. Also, an ice cube can be applied briefly to each tooth, removing it immediately once pain is felt. In healthy teeth, the pain stops almost immediately. Pain lingering more than a few seconds indicates pulp damage (eg, irreversible pulpitis, necrosis). The floor of the mouth is palpated for induration and tenderness, suggesting a deep space infection.

Neurologic examination, concentrating on the cranial nerves, should be done in those with fever, headache, or facial swelling.

Red flags: Findings of particular concern are

- Headache
- Fever
- Swelling or tenderness of floor of the mouth
• Cranial nerve abnormalities

Interpretation of findings: Red flag finding of headache suggests sinusitis, particularly if multiple upper molar and premolar (back) teeth are painful. However, presence of vision symptoms or abnormalities of the pupils or of ocular motility suggests cavernous sinus thrombosis.

Fever is unusual with routine dental infection unless there is significant local extension. Bilateral tenderness of the floor of the mouth suggests Ludwig's angina.

[Table 58-2. Characteristics of Pain in Toothache]

Difficulty opening the mouth (trismus) can occur with any lower molar infection but is common only with pericoronitis.

Isolated dental condition: Patients without red flag findings or facial swelling likely have an isolated dental condition, which, although uncomfortable, is not serious. Clinical findings, particularly the nature of the pain, help suggest a cause (see Tables 58-1 and 58-2). Because of its innervation, the pulp can perceive stimuli (eg, heat, cold, sweets) only as pain. An important distinction is whether there is continuous pain or pain only on stimulation and, if pain is only on stimulation, whether the pain lingers after the stimulus is removed.

Swelling at the base of a tooth, on the cheek, or both indicates infection, either cellulitis or abscess. A tender, fluctuant area at the base of a tooth suggests a pointing abscess.

Testing: Dental x-rays are the mainstay of testing but can be deferred to a dentist.

The rare cases in which cavernous sinus thrombosis or Ludwig's angina are suspected require imaging studies, typically CT or MRI.

Treatment

Analgesics (see p. 1623) are given pending dental evaluation and definitive treatment. A patient who is seen frequently for emergencies but who never receives definitive dental treatment despite availability may be seeking opioids.

Antibiotics directed at oral flora are given for most disorders beyond irreversible pulpitis (eg, necrotic pulp, apical periodontitis, abscess, cellulitis). The patient with pericoronitis also should receive an antibiotic. However, antibiotics can be deferred if the patient can be seen the same day by a dentist, who may be able to treat the infection by removing the source (eg, by extraction, pulpectomy, or curettage). When antibiotics are used, penicillin is preferred, with clindamycin the alternative.

An abscess associated with well-developed (soft) fluctuance is typically drained through an incision with a #15 scalpel blade at the most dependent point of the swelling. A rubber drain, held by a suture, is often placed.

Pericoronitis or erupting 3rd molars are treated with chlorhexidine 0.12% rinses or hypertonic saltwater soaks (1 tbsp salt mixed in a glass of hot water—no hotter than the coffee or tea a patient normally drinks). The salt water is held in the mouth on the affected side until it cools and then is expectorated and immediately replaced with another mouthful. Three or 4 glasses of salt water a day usually control inflammation and pain pending dental evaluation.

Teething pain in young children may be treated with weight-based doses of acetaminophen or ibuprofen. Topical treatments can include chewing hard crackers (eg, biscotti), applying 7.5% or 10% benzocaine gel qid (provided there is no family history of methemoglobinemia), and chewing on anything cold (eg, gel-containing teething rings).
The rare patient with cavernous sinus thrombosis or Ludwig’s angina requires immediate hospitalization, removal of the infected tooth, and culture-guided parenteral antibiotics.

**Geriatrics Essentials**

The elderly are more prone to caries of the root surfaces, usually because of gingival recession. Periodontitis often begins in young adulthood; if untreated, tooth pain and loss are common in old age.

**Key Points**

- Most toothache involves dental caries or its complications (eg, pulpitis, abscess).
- Symptomatic treatment and dental referral are usually adequate.
- Antibiotics are given if signs of a necrotic pulp or more severe conditions are present.
- Very rare but serious complications include extension of dental infection to the floor of the mouth or to the cavernous sinus.
- Dental infections rarely cause sinusitis, but sinus infection may cause pain perceived as originating in the teeth.
Chapter 59. Temporomandibular Disorders

Introduction

(See also Mandibular Dislocation on p. 524, Temporal Bone Fractures on p. 3234, and Jaw Tumors on p. 489.)

The term temporomandibular disorders is an umbrella term for conditions causing dysfunction of the jaw joint or pain in the jaw and face, often in or around the temporomandibular joint (TMJ), including masticatory and other muscles of the head and neck, the fascia, or both. A person is considered to have a temporomandibular disorder only if pain or limitation of motion is severe enough to require professional care.

Temporomandibular disorders typically are multifactorial, but most are related to problems with muscles or joints. Internal derangements of the TMJ cause disturbed movement of the mandibular condyle in the glenoid fossa or against the cartilaginous articular disk (see Fig. 59-1). This disk, shaped like a donut with a closed hole or like a mature red blood cell, serves as a cushion between joint surfaces. Causes for this disturbed movement include clenching and grinding of the teeth, trauma, arthritis, and malocclusion and missing teeth. Even the trauma of persistent gum chewing can be enough to damage the joint.

Diagnosis

Disorders of the TMJ must be distinguished from the many conditions that mimic them (see Table 59-1). Pain exacerbated by finger pressure on the joint when the mouth is opened implicates the TMJ.

Patients are asked to describe the pain and designate painful areas. The cervical and occipital muscles and each of the major muscle groups involved in mastication are palpated for general tenderness and trigger points (spots that radiate pain to another area). Patients are observed opening the mouth as wide as is comfortable. When patients open and close their mouth with the junction of the maxillary and mandibular central incisors (normally in the midline) lined up against a vertical straight edge, the mandibular midline typically deviates toward the painful side. Palpation and auscultation of the joint during opening and closing may reveal tenderness, catching, clicking, or popping. Condylar motion can best be palpated by placing the 5th fingers into the external ear canals and exerting very gentle forward pressure as patients move the jaw. The average-sized patient can open the mouth at least 40 to 45 mm (measured between upper and lower central incisors). To account for differences in patient size, a patient should be able to fit 3 fingers (index, middle, ring) in the mouth on top of each other.

Ankylosis of the Temporomandibular Joint

Ankylosis of the TMJ is immobility or fusion of the joint.

Ankylosis of the TMJ most often results from trauma or infection, but it may be congenital or a result of RA. Chronic, painless limitation of motion occurs. When ankylosis leads to arrest of condylar growth, facial asymmetry is common (see Condylar Hyperplasia on p. 532). Intra-articular (true) ankylosis must be distinguished from extra-articular (false) ankylosis, which may be caused by enlargement of the coronoid process, depressed fracture of the zygomatic arch, or scarring resulting from surgery, irradiation, or infection. In most cases of true ankylosis, x-rays of the joint show loss of normal bony architecture.

Treatment may include a condylectomy if the ankylosis is intra-articular or an ostectomy of part of the ramus if the coronoid process and zygomatic arch are also affected. Jaw-opening exercises must be done for months to years to maintain the surgical correction, but forced opening of the jaws without surgery is generally ineffective because of bony fusion.
Arthritis of the Temporomandibular Joint

Infectious arthritis, traumatic arthritis, osteoarthritis, RA, and secondary degenerative arthritis can affect the TMJ.

**Infectious arthritis:** Infection of the TMJ may result from direct extension of adjacent infection or hematogenous spread of blood-borne organisms (see also Acute Infectious Arthritis on p. 365). The area is inflamed, and jaw movement is limited. Local signs of infection associated with evidence of a systemic disease or with an adjacent infection suggest the diagnosis. X-ray results are negative in the early stages but may show bone destruction later. If suppurative arthritis is suspected, the joint is aspirated to confirm the diagnosis and to identify the causative organism. Diagnosis must be made rapidly to prevent permanent joint damage.

[Table 59-1. Some Conditions that Mimic Temporomandibular Disorders]

Treatment includes antibiotics, proper hydration, pain control, and motion restriction. Parenteral penicillin G is the drug of choice until a specific bacteriologic diagnosis can be made on the basis of culture and sensitivity testing. Suppurative infections are aspirated or incised. Once the infection is controlled, jaw-opening exercises help prevent scarring and limitation of motion.

**Traumatic arthritis:** Rarely, acute injury (eg, due to difficult tooth extraction or endotracheal intubation) may lead to arthritis of the TMJ. Pain, tenderness, and limitation of motion occur. Diagnosis is based primarily on history. X-ray results are negative except when intra-articular edema or hemorrhage widens the joint space. Treatment includes NSAIDs, application of heat, a soft diet, and restriction of jaw movement.

**Osteoarthritis:** The TMJ may be affected, usually in people > 50 yr. Occasionally, patients complain of stiffness, grating, or mild pain. Crepitus results from a hole worn through the disk, causing bone to grate on bone. Joint involvement is generally bilateral. X-rays or CT may show flattening and lipping of the condyle, suggestive of dysfunctional change. Treatment is symptomatic.

**Rheumatoid arthritis:** The TMJ is affected in > 17% of adults and children with RA, but it is usually among the last joints involved. Pain, swelling, and limited movement are the most common findings. In children, destruction of the condyle results in mandibular growth disturbance and facial deformity. Ankylosis may follow. X-rays of the TMJ are usually negative in early stages but later show bone destruction, which may result in an anterior open-bite deformity. The diagnosis is suggested by TMJ inflammation associated with polyarthritis and is confirmed by other findings typical of the disease.

Treatment is similar to that of RA in other joints. In the acute stage, NSAIDs may be given, and jaw function should be restricted. A night guard or splint is often helpful. When symptoms subside, mild jaw exercises help prevent excessive loss of motion. Surgery is necessary if ankylosis develops but should not be done until the condition is quiescent.

**Secondary degenerative arthritis:** This type of arthritis usually develops in people aged 20 to 40 after trauma or in people with persistent myofascial pain syndrome (see p. 533). It is characterized by limited opening of the mouth, unilateral pain during jaw movement, joint tenderness, and crepitus. When it is associated with the myofascial pain syndrome, symptoms wax and wane. Diagnosis is based on x-rays, which generally show condylar flattening, lipping, spurring, or erosion. Unilateral joint involvement helps distinguish secondary degenerative arthritis from osteoarthritis.

Treatment is conservative, as it is for myofascial pain syndrome, although arthroplasty or high condylectomy may be necessary. An occlusal splint (mouth guard) usually relieves symptoms. The splint is worn constantly, except during meals, oral hygiene, and appliance cleaning. When symptoms resolve, the length of time that the splint is worn each day is gradually reduced. Intra-articular injection of corticosteroids may relieve symptoms but may harm the joint if repeated often.

**Condylar Hyperplasia**
Condylar hyperplasia is a disorder of unknown etiology characterized by persistent or accelerated growth of the condyle when growth should be slowing or ended. Growth eventually stops without treatment.

Slowly progressive unilateral enlargement of the head and neck of the condyle causes crossbite malocclusion, facial asymmetry, and shifting of the midpoint of the chin to the unaffected side. The patient may appear prognathic. The lower border of the mandible is often convex on the affected side. Chondroma and osteochondroma may cause similar symptoms and signs, but they grow more rapidly and may cause even greater asymmetric condylar enlargement.

**Diagnosis**

- Plain x-rays
- Usually CT

On x-ray, the temporomandibular joint may appear normal, or the condyle may be proportionally enlarged and the mandibular neck elongated. CT is usually done to determine whether bone growth is generalized, which confirms the diagnosis, or localized to part of the condylar head. If growth is localized, a biopsy may be necessary to distinguish between tumor and hyperplasia.

**Treatment**

- During active growth, usually condylectomy
- After growth cessation, orthodontics or surgical mandibular repositioning

Treatment usually includes condylectomy during the period of active growth. If growth has stopped, orthodontics and surgical mandibular repositioning are indicated. If the height of the mandibular body is greatly increased, facial symmetry can be further improved by reducing the inferior border.

**Condylar Hypoplasia**

Condylar hypoplasia is a facial deformity caused by a short mandibular ramus.

This condition usually results from trauma, infection, or irradiation occurring during the growth period but may be idiopathic. The deformity involves fullness of the face, deviation of the chin to the affected side, an elongated mandible, and flatness of the face on the unaffected side. (The side to which the ramus is short causes muscles to appear fuller; the muscles on the unaffected side are stretched so that side appears flatter.) Mandibular deviation causes malocclusion.

Diagnosis is based on a history of progressive facial asymmetry during the growth period, x-ray evidence of condylar deformity and antegonial notching (a depression in the inferior border of the mandible just anterior to the angle of the mandible), and, frequently, a causative history.

Treatment consists of surgical shortening of the unaffected side of the mandible or lengthening of the affected side. Presurgical orthodontic therapy helps optimize results.

**Internal Joint Derangement**

The most common form of internal joint derangement is anterior misalignment or displacement of the articular disk above the condyle. Symptoms are localized joint pain and popping on jaw movement. Diagnosis is based on history and physical examination. Treatment is with analgesics, jaw rest, muscle relaxation, physical therapy, and bite splinting. If these methods fail, surgery may be necessary. Early treatment greatly improves results.

The superior head of the lateral pterygoid muscle may pull the articular disk out of place when abnormal
Jaw mechanics place unusual stress on the joint. Abnormal jaw mechanics can be due to congenital or acquired asymmetries or to the sequelae of trauma or arthritis. If the disk remains anterior, the derangement is said to be without reduction. Restricted jaw opening (locked jaw) and pain in the ear and around the temporomandibular joint result. If at some point in the joint's excursion the disk returns to the head of the condyle, it is said to be with reduction. Derangement with reduction occurs in about one third of the population at some point. All types of derangement can cause capsulitis (or synovitis), which is inflammation of the tissues surrounding the joint (eg, tendons, ligaments, connective tissue, synovium). Capsulitis can also occur spontaneously or result from arthritis, trauma, or infection.

Symptoms and Signs

Derangement with reduction often causes a clicking or popping sound when the mouth is opened. Pain may be present, particularly when chewing hard foods. Patients are often embarrassed because they think others can hear noise when they chew. Indeed, although the sound seems louder to the patient, others can sometimes hear it.

Derangement without reduction usually causes no sound, but maximum opening between the tips of the upper and lower incisors is reduced from the normal 40 to 45 mm to ≤ 30 mm. Pain and a change in the patients' perception of their bite generally result.

Capsulitis results in localized joint pain, tenderness, and, sometimes, restricted opening.

Diagnosis

- Clinical evaluation

Diagnosis of derangement with reduction requires observation of the jaw when the mouth is opened. When the jaw is opened > 10 mm (measured between upper and lower incisors), a click or pop is heard or a catch is felt as the disk pops back over the head of the condyle. The condyle remains on the disk during further opening. Usually, another click is heard during closing when the condyle slips over the posterior rim of the disk and the disk slips forward (reciprocal clicking).

Diagnosis of derangement without reduction requires that the patient open as wide as possible. The opening is measured, and gentle pressure is then exerted to open the mouth a little wider. Normally, the jaw opens about 45 to 50 mm; if the disk is deranged, it will open about 20 mm. Closing or protruding the jaw against resistance worsens the pain.

MRI is usually done to confirm presence of derangement or to determine why a patient is not responding to treatment.

Capsulitis is often diagnosed based on a history of injury or infection along with exquisite tenderness over the joint and by exclusion when pain remains after treatment for myofascial pain syndrome, disk derangement, arthritis, and structural asymmetries. However, capsulitis may be present with any of these conditions.

Treatment

- Analgesics as needed
- Sometimes repositioning splint or surgery
- Sometimes corticosteroid injection for capsulitis

Derangement with reduction does not require treatment if the patient can open reasonably wide (about 40 mm or the width of the index, middle, and ring fingers) without discomfort. If pain occurs, mild analgesics, such as NSAIDs (ibuprofen 400 mg po q 6 h), can be used. If onset is < 6 mo, an anterior repositioning splint may be used to position the mandible forward and on the disk. The splint is a horseshoe-shaped appliance of hard, transparent acrylic (plastic) made to fit snugly over the teeth of one arch. Its chewing
surface is designed to hold the mandible forward when the patient closes on the splint. In this position, the disk is always on the head of the condyle. The splint is gradually adjusted to allow the mandible to move posteriorly. If the disk stays with the condyle as the superior head of the external pterygoid stretches, the disk is said to be captured. The longer the disk is displaced, the more deformed it becomes and the less likely repositioning will succeed. Surgical plication of the disk may be done, with variable success.

Derangement without reduction may not require treatment other than analgesics. Splints may help if the articular disk has not been significantly deformed, but long-term use may result in irreversible changes in oral architecture. In some cases, the patient is instructed to slowly stretch the disk out of position, which allows the jaw to open normally. Various arthroscopic and open surgical procedures are available when conservative treatment fails.

Capsulitis is initially treated with NSAIDs, jaw rest, and muscle relaxation. If these treatments are unsuccessful, corticosteroids may be injected into the joint, or arthroscopic joint lavage and debridement are used.

Myofascial Pain Syndrome

Myofascial pain syndrome can occur in patients with a normal temporomandibular joint. It is caused by tension, fatigue, or spasm in the masticatory muscles (medial or internal and lateral or external pterygoids, temporalis, and masseter). Symptoms include bruxism, pain and tenderness in and around the masticatory apparatus or referred to other locations in the head and neck, and, often, abnormalities of jaw mobility. Diagnosis is based on history and physical examination. Conservative treatment, including analgesics, muscle relaxation, habit modification, and bite splinting, usually is effective.

This syndrome is the most common disorder affecting the temporomandibular region. It is more common among women and has a bimodal age distribution in the early 20s and around menopause. The muscle spasm causing the disorder usually is the result of nocturnal bruxism (clenching or grinding of the teeth). Whether bruxism is caused by irregular tooth contacts, emotional stress, or sleep disorders is controversial. Bruxism usually has a multifactorial etiology. Myofascial pain syndrome is not limited to the muscles of mastication. It can occur anywhere in the body, most commonly involving muscles in the neck and back.

Symptoms and Signs

Symptoms include pain and tenderness of the masticatory muscles and often pain and limitation of jaw excursion. Nocturnal bruxism may lead to headache that is more severe on awakening and that gradually subsides during the day. Such pain should be distinguished from temporal arteritis. Daytime symptoms, including headache, may worsen if bruxism continues throughout the day.

The jaw deviates when the mouth opens but usually not as suddenly or always at the same point of opening as it does with internal joint derangement (see p. 532). Exerting gentle pressure, the examiner can open the patient’s mouth another 1 to 3 mm beyond unaided maximum opening.

Diagnosis

• Clinical evaluation

A simple test may aid the diagnosis: Tongue blades of 2 or 3 thicknesses are placed between the rear molars on each side, and the patient is asked to bite down gently. The distraction produced in the joint space may ease the symptoms. X-rays usually do not help except to rule out arthritis. If temporal arteritis is suspected, ESR is measured.

Treatment

• Mild analgesics
• Splint or mouth guard

• An anxiolytic at bedtime considered

• Physical therapy modalities considered

A plastic splint or mouth guard from the dentist can keep teeth from contacting each other and prevent the damages of bruxism. Comfortable, heat-moldable splints are available from many sporting goods stores or drugstores. Low doses of a benzodiazepine at bedtime are often effective for acute exacerbations and temporary relief of symptoms. Mild analgesics, such as NSAIDs or acetaminophen, are indicated. Cyclobenzaprine may help muscle relaxation in some people. Because the condition is chronic, opioids should not be used, except perhaps briefly for acute exacerbations. The patient must learn to stop clenching the jaw and grinding the teeth. Hard-to-chew foods and chewing gum should be avoided. Physical therapy, biofeedback to encourage relaxation, and counseling help some patients. Physical modalities include transcutaneous electric nerve stimulation and "spray and stretch," in which the jaw is stretched open after the skin over the painful area has been chilled with ice or sprayed with a skin refrigerant, such as ethyl chloride. Botulinum toxin has recently been used successfully to relieve muscle spasm in myofascial pain syndrome. Most patients, even if untreated, stop having significant symptoms within 2 to 3 yr.
Chapter 60. Approach to the Ophthalmologic Patient

Introduction

The eye can be examined with routine equipment, including a standard ophthalmoscope; thorough examination requires special equipment and evaluation by an ophthalmologist. (See Fig. 60-1 for a cross-section of the eye.)

History

History includes location, speed of onset, and duration of current symptoms and history of previous ocular symptoms; the presence and nature of pain, discharge, or redness; and changes in visual acuity. Worrisome symptoms besides vision loss and eye pain include flashing lights, showers of floaters (both of which may be symptoms of retinal detachment), diplopia, and loss of peripheral vision.

Physical Examination

Visual acuity: The first step is to record visual acuity. Many patients do not give a full effort. Providing adequate time and coaxing patients tend to yield more accurate results. Visual acuity is measured with and without the patient's own glasses. If patients do not have their glasses, a pinhole refractor is used. If a commercial pinhole refractor is unavailable, one can be made at the bedside by poking holes through a piece of cardboard using an 18-gauge needle and varying the diameter of each hole slightly. Patients choose the hole that corrects vision the most. If acuity corrects with pinhole refraction, the problem is a refractive error. Pinhole refraction is a rapid, efficient way to diagnose refractive errors, which are the most common cause of blurred vision. However, with pinhole refraction, best correction is usually to only about 20/30, not 20/20.

Visual acuity in each eye is tested as the opposite eye is covered with a solid object (not the patient's fingers, which may separate during testing). Patients look at an eye chart 20 ft (6 m) away. If this test cannot be done, acuity can be measured using a chart held about 36 cm (14 in) from the eye. Normal and abnormal vision is quantified by Snellen notation. A Snellen notation of 20/40 (6/12) indicates that the smallest letter that can be read by someone with normal vision at 40 ft (12 m) has to be brought to 20 ft (6 m) before it is recognized by the patient. Vision is recorded as the smallest letter patients read correctly, even if patients feel that the letter is blurry or they have to guess. If the patient cannot read the top line of the Snellen chart at 20 ft (6 m), acuity is tested at 10 ft (3 m). If nothing can be read from a chart even at the closest distance, the examiner holds up different numbers of fingers to see whether the patient can accurately count them. If not, the examiner tests whether the patient can perceive hand motion. If not, a light is shined into the eye to see whether light is perceived.

Near vision is checked by asking patients to read a standard near card or newsprint at 14 in (35 cm); patients > 40 yr who require corrective lenses (reading glasses) should wear them during near vision testing.

Refractive error can be estimated roughly with a handheld ophthalmoscope by noting the lens necessary for the examiner to focus on the retina; this procedure requires examiners to use their own corrective lenses and is never a substitute for a comprehensive assessment of refraction. More commonly, refractive error is measured with a standard phoropter or an automated refractor (a device that measures changes in light projected and reflected by the patient's eye). These devices also measure astigmatism (see p. 571).

Eyelid and conjunctival examination: Eyelid margins and periocular cutaneous tissues are examined under a focal light and magnification (eg, provided by loupe, slit lamp, or ophthalmoscope focused at the examiner's working distance). In cases of suspected dacryocystitis or canaliculitis, the lacrimal sacs are palpated and an attempt is made to express any contents through the canaliculi and puncta. After eyelid
eversion, the palpebral and bulbar conjunctivae and the fornices can be inspected for foreign bodies, signs of inflammation (eg, follicular hypertrophy, exudate, hyperemia, edema), or other abnormalities.

**Corneal examination:** Indistinct or blurred edges of the corneal light reflex (reflection of light from the cornea when illuminated) suggest the corneal surface is not intact or is roughened, as occurs with a corneal abrasion or keratitis. Fluorescein staining reveals abrasions and ulcers. Before staining, a drop of topical anesthetic (eg, proparacaine 0.5%, tetracaine 0.5%) may be added to facilitate examination if the patient is in pain or if it is necessary to touch the cornea or conjunctiva (eg, to remove a foreign body or measure intraocular pressure). A sterile, individually packaged fluorescein strip is moistened with 1 drop of sterile saline or topical anesthetic and, with the patient’s eye turned upward, is touched momentarily to the inside of the lower eyelid. The patient blinks several times to spread the dye into the tear film, and then the eye is examined under magnification and cobalt blue illumination. Areas where corneal or conjunctival epithelium is absent (abraded or ulcerated) fluoresce green.

**Pupil examination:** The size and shape of the pupils are noted, and pupillary reaction to light is tested in each eye, one at a time, while the patient looks in the distance. Then the swinging flashlight test is done with a penlight to compare direct and consensual pupillary response. There are 3 steps:

1. One pupil is maximally constricted by being exposed to light from the penlight for 1 to 3 sec.
2. The penlight is rapidly moved to the other eye for 1 to 3 sec.
3. The light is moved back to the first eye.

Normally, a pupil constricts similarly when light is shone on it (direct response) and when light is shone on the other eye (consensual response). However, if one eye has less light perception than the other, as caused by dysfunction of the afferent limb (from the optic nerve to the optic chiasm) or extensive retinal disease, then the consensual response in the affected eye is stronger than the direct response. Thus, on step 3 of the swinging light test, when the light is shined back on the affected eye, it paradoxically appears to dilate. This finding indicates a relative afferent pupillary defect (RAPD, or Marcus Gunn pupil).

**Extraocular muscles:** The examiner guides the patient to look in 8 directions (up, up and right, right, down and right, down, down and left, left, left and up) with a moving finger, penlight, or transillumination light, observing for gaze deviation, limitation of movement, disconjugate gaze, or a combination consistent with cranial nerve palsy, orbital disease, or other abnormalities that restrict movement.

**Ophthalmoscopy:** Ophthalmoscopy can be done directly by using a handheld ophthalmoscope or indirectly by using a head-mounted ophthalmoscope with a handheld lens. With handheld ophthalmoscopy, the examiner dials the ophthalmoscope to zero dioplers, then increases or decreases the setting until the fundus comes into focus. The view of the retina is limited with a handheld ophthalmoscope, whereas indirect ophthalmoscopy gives a 3-dimensional view and is better for visualizing the peripheral retina, where retinal detachment most commonly occurs. The view of the fundus can be improved by dilating the pupils. Before dilation, the anterior chamber depth is estimated because mydriasis can precipitate an attack of acute angle-closure glaucoma if the anterior chamber is shallow. Depth can be estimated with a slit lamp (see below) or less accurately with a penlight held at the temporal limbus parallel to the plane of the iris and pointed toward the nose. If the medial iris is in shadow, the chamber is shallow and dilation should be avoided. Other contraindications to dilation include head trauma, suspicion of a ruptured globe, a narrow angle, and angle-closure glaucoma.

Pupils can be dilated using 1 drop of tropicamide 1%, phenylephrine 2.5%, or both (repeated in 5 to 10 min if necessary); for longer action, a larger dilated pupil, or both, cyclopentolate 1% can be substituted for tropicamide.

Ophthalmoscopy can detect lens or vitreous opacities, assess the optic cup-to-disk ratio, and identify retinal and vascular changes. The optic cup is the central depression, and the optic disk is the entire area of the optic nerve head. The normal ratio of the cup-to-nerve diameters is 0 to 0.4. A ratio of ≥ 0.5 may signify loss of ganglion cells and may be a sign of glaucoma. Retinal changes include hemorrhage, manifested as small or large areas of blood, and drusen (small subretinal yellow-white spots that may
signify dry age-related macular degeneration). Vascular changes include arteriovenous nicking, a sign of chronic hypertension in which retinal veins are compressed by arteries where the two cross; copper wiring, a sign of arteriosclerosis in which thickened arteriolar walls increase the thickness of the light reflex; silver wiring, a sign of hypertension in which thin, fibrotic arteriolar walls decrease the thickness of the light reflex; and loss of venous pulsations, a sign of increased intracranial pressure in patients known to have had pulsations.

**Slit-lamp examination:** A slit lamp focuses the height and width of a beam of light for a precise stereoscopic view of the eyelids, conjunctiva, cornea, anterior chamber, iris, lens, and anterior vitreous. It is especially useful for the following:

- Identifying corneal foreign bodies and abrasions
- Measuring depth of the anterior chamber
- Detecting cells (RBCs or WBCs) and flare (evidence of protein) in the anterior chamber
- Identifying ciliary flush (dilation of blood vessels localized to the limbal region overlying the ciliary body), which occurs with uveitis
- Identifying scleral edema, which is seen as a bowing forward of the slit beam when it is focused beneath the conjunctiva and which is usually a sign of scleritis

Tonometry (see p. 540) and gonioscopy, which quantifies the iridocorneal angle and requires the use of a special lens, may be done.

**Visual field testing:** Visual fields may be impaired by lesions anywhere in the neural visual pathways from the optic nerves to the occipital lobes (see Table 60-1 and Fig. 69-1 on p. 620). Glaucoma causes loss of peripheral vision. Fields can be assessed grossly by direct confrontation testing or by more precise, detailed testing.

In **direct confrontation**, patients maintain a fixed gaze at the examiner's eye or nose. The examiner brings a small target (eg, a match or a finger) from the patients' visual periphery into each of the 4 visual quadrants and asks patients to indicate when they first see the object. Wiggling the small target helps patients separate and define it. Another method of direct confrontation visual field testing is to hold a number of fingers in each quadrant and ask patients how many they see. For both methods, each eye is tested separately. Abnormalities in target detection should prompt detailed testing with more precise instruments.

More detailed methods include use of a tangent screen, Goldmann perimeter, or computerized automated perimetry (in which the visual field is mapped out in detail based on patient response to a series of flashing lights in different locations controlled by a standardized computer program). The Amsler grid is used to test central vision. Distortion of the grid (metamorphopsia) or a missing area (central scotoma) may indicate disease of the macula (eg, choroidal neovascularization), as occurs in age-related macular degeneration.

**Color vision testing:** Twelve to 24 Ishihara color plates, which have colored numbers or symbols hidden in a field of colored dots, are commonly used to test color vision. Colorblind patients or patients with acquired color deficiency (eg, in optic nerve diseases) cannot see some or all of the hidden numbers. Most congenital color blindness is red-green; most acquired (eg, caused by glaucoma or optic nerve disease) is blue-yellow.

[Table 60-1. Types of Field Defects]

Testing
Tonometry: Tonometry measures intraocular pressure by determining the amount of force needed to indent the cornea. Handheld pen-type tonometers are used for screening. This test requires topical anesthesia (eg, proparacaine 0.5%). Office-based screening with noncontact air-puff tonometry also can be used; it requires less training because it makes no direct corneal contact. Goldmann applanation tonometry is the most accurate method but requires more training and typically is used only by ophthalmologists. Measurement of intraocular pressure alone is not adequate screening for glaucoma; the optic nerve also should be examined.

Fluorescein angiography: After IV injection of fluorescein solution, the retinal, choroidal, optic disk, or iris vasculature is photographed in rapid sequence. Fluorescein angiography is used to investigate underperfusion and neovascularization in conditions such as diabetes, age-related macular degeneration, retinal vascular occlusion, and ocular histoplasmosis. It is also useful in preoperative assessment for retinal laser procedures.

Electroretinography: Electrodes are placed on each cornea and on the surrounding skin, and electrical activity in the retina is recorded. This technique evaluates retinal function in patients with retinal degeneration. It does not evaluate vision.

Ultrasonography: B-mode ultrasonography provides 2-dimensional structural information even in the presence of opacities of the cornea and lens. Examples of ophthalmologic applications include assessment of retinal tumors, detachments, and vitreous hemorrhages; location of foreign bodies; detection of posterior scleral edema characteristic of posterior scleritis; and distinction of choroidal melanoma from metastatic carcinoma and subretinal hemorrhage.

A-mode ultrasonography is 1-dimensional ultrasonography used to determine the axial length of the eye, a measurement needed to calculate the power of an intraocular lens for implantation as a part of cataract surgery.

Ultrasonic pachymetry is use of ultrasonography to measure the thickness of the cornea before refractive surgery (eg, LASIK) and in patients with corneal dystrophies.

CT and MRI: These imaging techniques most often are used for evaluation of ocular trauma, particularly if an intraocular foreign body is suspected, and in the evaluation of orbital tumors, optic neuritis, and optic nerve tumors. MRI should not be done when there is suspicion of a metallic intraocular foreign body.

Electronystagmography: See p. 414.

Acute Vision Loss

Loss of vision is usually considered acute if it develops within a few minutes to a couple of days. It may affect one or both eyes and all or part of a visual field. Patients with small visual field defects (eg, caused by a small retinal detachment) may describe their symptoms as blurred vision.

Pathophysiology

Acute loss of vision has 3 general causes:

• Opacification of normally transparent structures through which light rays pass to reach the retina (eg, cornea, vitreous)

• Retinal abnormalities

• Abnormalities affecting the optic nerve or visual pathways

Etiology

The most common causes of acute loss of vision are
• Vascular occlusions of the retina (central retinal artery occlusion, central retinal vein occlusion)

• Ischemic optic neuropathy (often in patients with temporal arteritis)

• Vitreous hemorrhage (caused by diabetic retinopathy or trauma)

• Trauma

In addition, sudden recognition of loss of vision (pseudo-sudden loss of vision) may manifest initially as sudden onset. For example, a patient with long-standing reduced vision in one eye (possibly caused by a dense cataract) suddenly is aware of the reduced vision in the affected eye when covering the unaffected eye.

Presence or absence of pain helps categorize loss of vision (see Table 60-2).

Most disorders that cause total loss of vision when they affect the entire eye may affect only part of the eye and cause only a visual field defect (eg, branch occlusion of the retinal artery or retinal vein, focal retinal detachment).

Less common causes of acute loss of vision include

• Anterior uveitis (a common disorder, but one that usually causes eye pain severe enough to trigger evaluation before vision is lost)

• Highly aggressive retinitis

• Certain drugs (eg, methanol, salicylates, ergot alkaloids, quinine)

**Evaluation**

**History:** *History of present illness* should describe loss of vision in terms of onset, duration, progression, and location (whether it is monocular or binocular and whether it involves the entire visual field or a specific part and which part). Important associated visual symptoms include floaters, flashing lights, halos around lights, distorted color vision, and jagged or mosaic patterns (scintillating scotomata). The patient should be asked about eye pain and whether it is constant or occurs only with eye movement.

**Review of systems** should seek extraocular symptoms of possible causes, including jaw or tongue claudication, temporal headache, proximal muscle pain, and stiffness (giant cell arteritis); and headaches (ocular migraine).

**Past medical history** should seek known risk factors for eye disorders (eg, contact lens use, severe myopia, recent eye surgery or injury), risk factors for vascular disease (eg, diabetes, hypertension), and hematologic disorders (eg, sickle cell anemia or disorders such as Waldenstrom's macroglobulinemia or multiple myeloma that could cause a hyperviscosity syndrome).

Family history should note any family history of migraine headaches.

**Physical examination:** Vital signs, including temperature, are measured.

If the diagnosis of a transient ischemic attack is under consideration, a complete neurologic examination is done. The facial skin is inspected for vesicles or ulcers in the V1 distribution (ophthalmic division of the trigeminal nerve), and the temples are palpated for pulses, tenderness, or nodularity over the course of
the temporal artery. However, most of the examination focuses on the eye.

Eye examination includes the following:

- Visual acuity is measured.
- Peripheral visual fields are assessed by confrontation.
- Central visual fields are assessed by Amsler grid.
- Direct and consensual pupillary light reflexes are examined using the swinging flashlight test.
- Ocular motility is assessed.
- Color vision is tested with color plates.
- The eyelids, sclera, and conjunctiva are examined using a slit lamp if possible.
- The cornea is examined with fluorescein staining.
- The anterior chamber is examined for cells and flare in patients who have eye pain or conjunctival injection.
- The lens is checked for cataracts using a direct ophthalmoscope, slit lamp, or both.
- Intraocular pressure is measured.
- Ophthalmoscopy is done, preferably after dilating the pupil with a drop of a sympathomimetic (eg, 2.5% phenylephrine), cycloplegic (eg, 1% cyclopentolate or 1% tropicamide), or both; dilation is nearly full after about 20 min. The entire fundus, including the retina, macula, fovea, vessels, and optic disk and its margins, is examined.
- If pupillary light responses are normal and functional loss of vision is suspected (rarely), [optokinetic nystagmus is checked. If an optokinetic drum is unavailable, a mirror can be held near the patient's eye and slowly moved. If the patient can see, the eyes usually track movement of the mirror.

Red flags: Acute loss of vision is itself a red flag; most causes are serious.

Interpretation of findings: Diagnosis can be begun systematically. Fig. 60-2 describes a simplified, general approach. Specific patterns of visual field deficit help suggest a cause (see Table 60-1). Other clinical findings also help suggest a cause (see Table 60-2):

- Difficulty seeing the red reflex during ophthalmoscopy suggests opacification of transparent structures (eg, caused by corneal ulcer, vitreous hemorrhage, or severe endophthalmitis).
- Retinal abnormalities that are severe enough to cause acute loss of vision are detectable during ophthalmoscopy, particularly if the pupils are dilated. Retinal detachment may show retinal folds; retinal vein occlusion may show marked retinal hemorrhages; and retinal artery occlusion may show a pale retina with cherry-red fovea.
- An afferent pupillary defect (absence of a direct pupillary light response but a normal consensual response) with an otherwise normal examination (except sometimes an abnormal optic disk) suggests an abnormality of the optic nerve or retina (ie, anterior to the chiasm).
In addition, the following facts may help:

- Monocular symptoms suggest a lesion anterior to the optic chiasm.
- Bilateral, symmetric visual field defects suggest a lesion posterior to the chiasm.
- Constant eye pain suggests a corneal lesion (ulcer or abrasion), anterior chamber inflammation, or increased intraocular pressure, whereas eye pain with movement suggests optic neuritis.
- Temporal headaches suggest giant cell arteritis or migraine.

**Testing:** ESR is done for all patients with symptoms (eg, temporal headaches, jaw claudication, proximal myalgias, stiffness) or signs (eg, temporal artery tenderness or induration, pale retina, papilledema) suggesting optic nerve or retinal ischemia to exclude giant cell arteritis.

Other testing is listed in Table 60-2. The following are of particular importance:

- Ultrasonography is done to view the retina if the retina is not clearly visible with pupillary dilation and indirect ophthalmoscopy done by an ophthalmologist.
- Gadolinium-enhanced MRI is done for patients who have eye pain with movement or afferent pupillary defect, particularly with optic nerve swelling on ophthalmoscopy, to diagnose multiple sclerosis.

**Treatment**

Causative disorders are treated. Treatment should usually commence immediately if the cause is treatable. In many cases (eg, vascular disorders), treatment is unlikely to salvage the affected eye but can decrease the risk of the same process occurring in the contralateral eye.

**Key Points**

- Diagnosis and treatment should occur as rapidly as possible.
- Acute monocular loss of vision with an afferent pupillary defect indicates a lesion of the eye or of the optic nerve anterior to the optic chiasm.
- Optic nerve lesion, particularly ischemia, is considered in patients with acute monocular loss of vision or afferent pupillary defect and in those with or without optic nerve abnormalities on ophthalmoscopy but no other abnormalities on eye examination.
- Corneal ulcer, acute angle-closure glaucoma, endophthalmitis, or severe anterior uveitis is considered in patients with acute monocular loss of vision, afferent pupillary defect, eye pain, and conjunctival injection.

**Anisocoria**

(Unequal Pupils)

Anisocoria is unequal pupil sizes. Anisocoria itself does not cause symptoms.

**Etiology**

The most common cause of anisocoria is

- Physiologic (present in about 20% of people)

See Table 60-3 for other causes of anisocoria.
Many disorders are accompanied by anisocoria due to iris or neurologic dysfunction but usually manifest with other, more bothersome symptoms (eg, uveitis, optic neuritis, stroke, subarachnoid hemorrhage, acute angle-closure glaucoma).

**Evaluation**

The goal of evaluation is to elucidate the physiologic mechanism of anisocoria. By identifying certain mechanisms (eg, Horner's syndrome, 3rd cranial nerve palsy), clinicians can diagnose the occasional serious occult disorder (eg, tumor, aneurysm) manifesting with anisocoria.

**History:** History of present illness includes the presence, nature, and duration of symptoms. Any history of head or ocular trauma is noted.

**Review of systems** seeks symptoms that may suggest a cause, such as birth defects or chromosomal abnormalities (congenital defects); droopy eyelid, cough, chest pain, or dyspnea (Horner's syndrome); genital lesions, adenopathy, rashes, or fever (syphilis); and headaches or other neurologic symptoms (Horner's syndrome or 3rd cranial nerve palsy).

**Past medical history** includes known ocular disorders and surgeries and exposure to drugs.

*[Table 60-3. Some Common Causes of Anisocoria]*

**Physical examination:** Pupillary size and light responses should be examined in lighted and dark rooms. Accommodation and extraocular movements should be tested. Ocular structures are inspected by using a slit lamp or other magnification to identify structural abnormalities and ptosis. Other ocular symptoms are evaluated by eye examination as clinically indicated. An old photograph of the patient or the patient's driver's license should be examined (under magnification if possible) to see whether anisocoria was present previously.

**Testing:** Testing is usually unnecessary but is indicated for clinically suspected disorders. Patients with Horner's syndrome or 3rd cranial nerve palsy usually require brain MRI or CT.

**Red flags:** The following findings are of particular concern:

- Ptosis
- Anhidrosis
- Pupils that respond more to accommodation than light
- Impaired extraocular movements

**Interpretation of findings:** If the difference in size is greater in the dark, the smaller pupil is abnormal. Common causes include Horner's syndrome and physiologic anisocoria. An ophthalmologist can differentiate them because the small pupil in Horner's syndrome does not dilate after instillation of an ocular dilating drop (eg, 10% cocaine).

If the difference in pupillary sizes is greater in light, the larger pupil is abnormal. If extraocular movements are impaired, particularly with ptosis, 3rd cranial nerve palsy is likely. If extraocular movements are intact, an ophthalmologist can further differentiate among causes by instilling a drop of a pupillary constrictor (eg, 0.1% pilocarpine). If the large pupil constricts, the cause is probably Adie's tonic pupil; if the large pupil does not constrict, the cause is probably drugs or structural (eg, traumatic, surgical) damage to the iris.

**Treatment**

Treatment of anisocoria is unnecessary.
Key Points

• Physiologic anisocoria is very common and causes < 1 mm of difference between the pupils in size.

• Examining the pupils in light and dark and inspecting an old photograph or the driver's license of the patient provide a great deal of diagnostic information.

• Serious disorders should be considered in patients with Horner's syndrome or 3rd cranial nerve palsy.

Blurred Vision

Blurred vision is the most common visual symptom. It usually refers to decreased visual acuity of gradual onset. For sudden, complete loss of vision in one or both eyes (blindness), see p. 541. Patients with small visual field defects (eg, caused by a small retinal detachment) may describe their symptoms as blurring.

Etiology

The most common causes of blurred vision (see Table 60-4) include

• Refractive errors (the most common cause overall)

• Age-related macular degeneration

• Cataracts

• Diabetic retinopathy

• Glaucoma

Blurred vision has 4 general mechanisms:

• Opacification of normally transparent ocular structures (cornea, lens, vitreous) through which light rays must pass to reach the retina

• Disorders affecting the retina

• Disorders affecting the optic nerve or its connections

• Refractive errors

Certain disorders can have more than one mechanism. For example, refraction can be impaired by early cataracts or the reversible lens swelling caused by poorly controlled diabetes.

Patients with certain disorders that cause blurred vision (eg, acute corneal lesions [such as abrasions], ulcers, herpes simplex keratitis, herpes zoster ophthalmicus, acute angle-closure glaucoma) are more likely to present with other symptoms such as eye pain and red eye.

Rare disorders that can cause blurred vision include hereditary optic neuropathies (eg, dominant optic atrophy, Leber's hereditary optic neuropathy) and corneal scarring due to vitamin A deficiency or amiodarone toxicity.

Evaluation

**History:** History of present illness should ascertain the onset, duration, and progression of symptoms, as well as whether they are bilateral or unilateral. The symptom should be defined as precisely as possible by asking an open-ended question or request (eg, "Please describe what you mean by blurred..."
vision”). For example, loss of detail is not the same as loss of contrast. Also, visual field defects may not be recognized as such by patients, who may instead describe symptoms such as missing steps or the inability to see words when reading. Important associated symptoms include eye redness, photophobia, floaters, sensation of lightning-like flashes of light (photopsias), and pain at rest or with eye movement. The effects of darkness (night vision), bright lights (ie, causing blur, star bursts, halos, photophobia), distance from an object, and corrective lenses and whether central or peripheral vision seems to be more affected should be ascertained.

**Review of systems** includes questions about symptoms of possible causes, such as increased thirst and polyuria (diabetes).

**Past medical history** should note previous eye injury or other diagnosed eye disorders and ask about disorders known to be risk factors for eye disorders (eg, hypertension, diabetes, HIV/AIDS, SLE, sickle cell anemia, disorders that could cause hyperviscosity syndrome such as multiple myeloma or Waldenstrom's macroglobulinemia). Drug history should include questions about use of drugs that could affect vision (eg, amiodarone, corticosteroids) and treatments for disorders affecting vision (eg, diabetic retinopathy).

**Physical examination:** Nonvisual symptoms are evaluated as needed; however, examination of the eyes may be all that is necessary.

Testing **visual acuity** is key. Many patients do not give a full effort. Providing adequate time and coaxing patients tend to yield more accurate results.

Acuity ideally is measured while the patient stands 6 m (about 20 ft) from a Snellen chart posted on a wall. If this test cannot be done, acuity can be measured using a chart held about 36 cm (14 in) from the eye. Measurement of near vision should be done with reading correction in place for patients > age 40. Each eye is measured separately while the other eye is covered with a solid object (not the patient's fingers, which may separate during testing). If the patient cannot read the top line of the Snellen chart at 6 m, acuity is tested at 3 m. If nothing can be read from a chart even at the closest distance, the examiner holds up different numbers of fingers to see whether the patient can accurately count them. If not, the examiner tests whether the patient can perceive hand motion. If not, a light is shined into the eye to see whether light is perceived.

Visual acuity is measured with and without the patients' own glasses. If acuity is corrected

[Table 60-4. Some Causes of Blurred Vision]

with glasses, the problem is a refractive error. If patients do not have their glasses, a pinhole refractor is used. If a commercial pinhole refractor is unavailable, one can be made at the bedside by poking holes through a piece of cardboard using an 18-gauge needle and varying the diameter of each hole slightly. Patients choose the hole that corrects vision the most. If acuity corrects with pinhole refraction, the problem is a refractive error. Pinhole refraction is a rapid, efficient way to diagnose refractive errors, which are the most common cause of blurred vision. However, with pinhole refraction, best correction is usually to only about 20/30, not 20/20.

**Eye examination** is also important. Direct and consensual pupillary light responses are examined using the swinging flashlight test. Visual fields are checked using confrontation and an Amsler grid.

The cornea is examined for opacification, ideally using a slit lamp. The anterior chamber is examined for cells and flare using a slit lamp if possible, although results of this examination are unlikely to explain visual blurring in patients without eye pain or redness.

The lens is examined for opacities using an ophthalmoscope, slit lamp, or both.

Ophthalmoscopy is done using a direct ophthalmoscope. More detail is visible if the eyes are dilated for ophthalmoscopy with a drop of a sympathomimetic (eg, 2.5% phenylephrine), cycloplegic (eg, 1% tropicamide or 1% cyclopentolate), or both; dilation is nearly full after about 20 min. As much of the fundus
as is visible, including the retina, macula, fovea, vessels, and optic disk and its margins, is examined. To see the entire fundus (ie, to see a peripheral retinal detachment), the examiner, usually an ophthalmologist, must use an indirect ophthalmoscope.

Intraocular pressure is measured.

**Red flags:** The following findings are of particular concern:

- Sudden change in vision
- Eye pain (with or without eye movement)
- Visual field defect (by history or examination)
- Visible abnormality of the retina or optic disk
- HIV/AIDS or other immunosuppressive disorder
- A systemic disorder that could cause retinopathy (eg, sickle cell anemia, possible hyperviscosity syndrome, diabetes, hypertension)

**Interpretation of findings:** Symptoms and signs help suggest a cause (see Table 60-4).

If visual acuity is corrected with glasses or a pinhole refractor, simple refractive error is the cause of blurring. Loss of contrast or glare may still be caused by cataract, which should be considered.

However, red flag findings suggest a more serious ophthalmologic disorder (see Table 60-5) and need for a complete examination, including slit-lamp examination, tonometry, ophthalmoscopic examination with pupillary dilation, and, depending on findings, possibly immediate or urgent ophthalmologic referral.

Specific retinal findings help suggest a cause (see Table 60-6).

**Testing:** If acuity corrects appropriately with refraction, patients are referred to an optometrist or ophthalmologist for routine formal refraction. If visual acuity is not corrected with refraction but there are no red flag findings, patients are referred to an ophthalmologist for routine evaluation. With certain red flag findings, patients are referred for immediate or urgent ophthalmologic evaluation.

Patients with symptoms or signs of systemic disorders should have appropriate testing:

- Diabetes: Fingerstick or random glucose measurement
- Poorly controlled hypertension and acute hypertensive retinopathy (hemorrhages, exudates, or papilledema): Urinalysis, renal function testing, BP monitoring, and possibly ECG
- HIV/AIDS and retinal abnormalities: HIV serology and CD4+ count
- SLE and retinal abnormality: Antinuclear antibodies, ESR, and CBC
- Waldenstrom's macroglobulinemia, multiple myeloma, or sickle cell anemia: CBC with differential count and other testing (eg, serum protein electrophoresis) as clinically indicated

**Treatment**
Underlying disorders are treated. Corrective lenses may be used to improve visual acuity, even when the disorder causing blurring is not purely a refractive error (eg, early cataract).

**Geriatrics Essentials**

Although some decrease in visual acuity normally occurs with aging, acuity normally is correctable to 20/20 with refraction, even in very elderly patients.

**Key Points**

- If visual acuity is corrected with pinhole refraction, refractive error is the problem.
- Because glaucoma is common, intraocular pressure should be measured.
- If pinhole refraction does not correct acuity and there is no obvious cataract or corneal abnormality, ophthalmoscopy should be done after pupillary dilation.
- Many abnormalities on ophthalmoscopy, particularly if symptoms are recently worsening, require urgent or immediate ophthalmologic referral.

**Diplopia**

(Double Vision)

Diplopia is the perception of 2 images of a single object. Diplopia may be monocular or binocular. Monocular diplopia is present when only one eye is open. Binocular diplopia disappears when either eye is closed.

**Etiology**

**Monocular diplopia** can occur when something distorts light transmission through the eye to the retina. There may be > 2 images. One of the images is of normal quality (eg, brightness, contrast, clarity); the rest are of inferior quality. The most common causes of monocular diplopia are

- Cataract
- Corneal shape problems, such as keratoconus or surface irregularity
- Uncorrected refractive error, usually astigmatism

Other causes include corneal scarring and dislocated lens. Complaints also may represent malingering.

**Binocular diplopia** suggests disconjugate alignment of the eyes. There are only 2 images, and they are of equal quality. There are many possible causes of binocular diplopia (see Table 60-7). The most common are

- Cranial nerve (3rd, 4th, or 6th) palsy
- Myasthenia gravis
- Orbital infiltration (eg, thyroid infiltrative ophthalmopathy, orbital pseudotumor)

Most commonly, the eyes are misaligned because of a disorder affecting the cranial nerves innervating the extraocular muscles (3rd, 4th, or 6th cranial nerves). These palsies may be isolated and idiopathic or the result of various disorders involving the cranial nerve nuclei or the infranuclear nerve or nerves. Other causes involve mechanical interference with ocular motion or a generalized disorder of neuromuscular transmission.
Evaluation

History: History of present illness should determine whether diplopia involves one or both eyes, whether diplopia is intermittent or constant, and whether the images are separated vertically, horizontally, or both. Any associated pain is noted, as well as whether it occurs with or without eye movement.

Review of systems should seek symptoms of other cranial nerve dysfunction, such as vision abnormalities (2nd cranial nerve); numbness of forehead and cheek (5th cranial nerve); facial weakness (7th cranial nerve); dizziness, hearing loss, or gait difficulties (8th cranial nerve); and swallowing or speech difficulties (9th and 12th cranial nerves). Other neurologic symptoms, such as weakness and sensory abnormalities, should be sought noting whether these are intermittent or constant. Nonneurologic symptoms of potential causes are ascertained; they include nausea, vomiting, and diarrhea (botulism); palpitations, heat sensitivity, and weight loss (Graves' disease); and difficulty with bladder control (multiple sclerosis).

Past medical history should seek presence of known hypertension, diabetes, or both; atherosclerosis, particularly including cerebrovascular disease; and alcohol abuse.

Physical examination: Examination begins with a review of vital signs for fever and general appearance for signs of toxicity (eg, prostration, confusion).

Eye examination begins with measuring visual acuity (with correction) in each eye and both together, which also helps determine whether diplopia is monocular or binocular. Eye examination should note presence of bulging of one or both eyes, eyelid droop, pupillary abnormalities, and disconjugate eye movement and nystagmus during ocular motility testing. Ophthalmoscopy should be done, particularly noting any abnormalities of the lens (eg, cataract, displacement) and retina (eg, detachment).

Ocular motility is tested by having the patient hold the head steady and track the examiner's finger, which is moved to extreme gaze to the right, left, upward, downward, diagonally to either side, and finally inward toward the patient's nose (convergence). However, mild paresis of ocular motility sufficient to cause diplopia may escape detection by such examination.

If diplopia occurs in one direction of gaze, the eye that produces each image can be determined by repeating the examination with a red glass placed over one of the patient's eyes. The image that is more peripheral originates in the paretic eye; ie, if the more peripheral image is red, the red glass is covering the paretic eye. If a red glass is not available, the paretic eye can sometimes be identified by having the patient close each eye. The paretic eye is the eye that when closed eliminates the more peripheral image.

The other cranial nerves are tested, and the remainder of the neurologic examination, including strength, sensation, reflexes, cerebellar function, and observation of gait, is completed.

Relevant nonneurophtalmologic components of the examination include palpation of the neck for goiter and inspection of the shins for pretibial myxedema (Graves' disease).

Red flags: The following findings are of particular concern:

- More than one cranial nerve deficit
- Pupillary involvement of any degree
- Any neurologic symptoms or signs besides diplopia
- Pain
- Proptosis

Interpretation of findings: Findings sometimes suggest which nerve is involved.
• Nerve III: Eyelid droop, eye deviated laterally and down, sometimes pupillary dilation

[Table 60-7, Some Causes of Binocular Diplopia]

• Nerve IV: Vertical diplopia worse on downward gaze (patient tilts head to improve vision)

• Nerve VI: Eye deviated medially, diplopia worse on lateral gaze (patient turns head to improve vision)

Other findings help suggest a cause (see Table 60-7).

Intermittent diplopia suggests a waxing and waning neurologic disorder, such as myasthenia gravis or multiple sclerosis, or unmasking of a latent phoria (eye deviation). Patients with latent phoria do not have any other neurologic manifestations.

Internuclear ophthalmoplegia (INO) results from a brain stem lesion in the medial longitudinal fasciculus (MLF). INO manifests on horizontal gaze testing with diplopia, weak adduction on the affected side (usually cannot adduct eye past midline), and nystagmus of the contralateral eye. However, the affected eye adducts normally on convergence testing (which does not require an intact MLF).

Pain suggests a compressive lesion or inflammatory disorder.

Testing: Patients with monocular diplopia are referred to an ophthalmologist to evaluate for ocular pathology; no other tests are required beforehand.

For binocular diplopia, patients with a unilateral, single cranial nerve palsy, a normal pupillary light response, and no other symptoms or signs can usually be observed without testing for a few weeks. Many cases resolve spontaneously. Ophthalmologic evaluation may be done to monitor the patient and help further delineate the deficit.

Most other patients require neuroimaging with MRI to detect orbital, cranial, or CNS abnormalities. CT may be substituted if there is concern about a metallic intraocular foreign body or if MRI is otherwise contraindicated or unavailable. Imaging should be done immediately if findings suggest infection, aneurysm, or acute (< 3 h) stroke.

Patients with manifestations of Graves' disease should have thyroid tests (serum thyroxine \([T_4]\) and thyroid-stimulating hormone [TSH] levels). Testing for myasthenia gravis and multiple sclerosis should be strongly considered for those with intermittent diplopia.

Treatment

Treatment is management of the underlying disorder.

Key Points

• Isolated, pupil-sparing nerve palsy in patients with no other symptoms may resolve spontaneously.

• Imaging is required for those with red flag findings.

• Focal weakness (in any muscle) may indicate a disorder of neuromuscular transmission.

Eyelid Swelling

Eyelid swelling can be unilateral or bilateral. It may be asymptomatic or accompanied by itching or pain.

Etiology

Eyelid swelling has many causes (see
Table 60-8). It usually results from an eyelid disorder but may result from disorders in and around the orbit or from systemic disorders that cause generalized edema.

The most common causes are allergic, including

- Local allergy (contact sensitivity)
- Systemic allergy (eg, angioedema, systemic allergy accompanying allergic rhinitis)

Focal swelling of one eyelid is most often caused by a chalazion.

The most immediately dangerous causes are orbital cellulitis and cavernous sinus thrombosis (rare).

[Table 60-8. Some Causes of Eyelid Swelling]

In addition to the disorders listed in Table 60-8, eyelid swelling may result from the following:

- Disorders that may involve the eyelid but do not cause swelling unless very advanced (eg, eyelid tumors, including squamous cell carcinomas and melanoma)
- Disorders (eg, dacryocystitis, canaliculitis) that cause swelling that begins and is usually most severe in structures near, but not part of, the eyelids
- Disorders in which swelling occurs but is not the presenting symptom (eg, basilar skull fracture, burns, trauma, postsurgery)

**Evaluation**

**History:** History of present illness should ascertain how long swelling has been present, whether it is unilateral or bilateral, and whether it has been preceded by any trauma (including insect bites). Important accompanying symptoms to identify include itching, pain, headache, change in vision, fever, and eye discharge.

**Review of systems** should seek symptoms of possible causes, including runny nose, itching, rash, and wheezing (systemic allergic reaction); headache, nasal congestion, and purulent nasal discharge (sinusitis); toothache (dental infection); dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (heart failure); cold intolerance and changes in skin texture (hypothyroidism); and heat intolerance, anxiety, and weight loss (hyperthyroidism).

**Past medical history** should include recent eye injury or surgery; known heart, liver, renal, or thyroid disease; and allergies and exposure to possible allergens. Drug history should specifically include use of ACE inhibitors.

**Physical examination:** Vital signs should be assessed for fever and tachycardia.

Eye inspection should assess the location and color of swelling (erythematous or pale), including whether it is present on one eyelid, both eyelids, or both eyes and whether it is tender, warm, or both. The examiner should observe whether the finding represents edema of the eyelids, protrusion of the globe (proptosis), or both. Eye examination should particularly note visual acuity and range of extraocular motion (full or limited). This examination can be difficult when swelling is marked but is important because deficits suggest an orbital or retro-orbital disorder rather than an eyelid disorder; an assistant may be required to hold the eyelids open. Conjunctivae are examined for injection and discharge. Any eyelid or eye lesions are evaluated using a slit lamp.

General examination should assess signs of toxicity, suggesting a serious infection, and signs of a causative disorder. Facial skin is inspected for dryness and scales (which may suggest hypothyroidism) and greasy scales or other signs of seborrheic dermatitis. Extremities and the presacral area are examined for edema, which suggests a systemic cause. If a systemic cause is suspected, see p. 2031 for
Red flags: The following findings are of particular concern:

- Fever
- Loss of visual acuity
- Impaired extraocular movements
- Proptosis

Interpretation of findings: Some findings help distinguish among categories of disorders. The first important distinction is between inflammation or infection and allergy or fluid overload. Pain, redness, warmth, and tenderness suggest inflammation or infection. Painless, pale swelling suggests angioedema. Itching suggests allergic reaction, and absence of itching suggests cardiac or renal dysfunction.

Swelling localized to one eyelid in the absence of other signs is rarely caused by a dangerous disorder. Massive swelling of the eyelids of one or both eyes should raise suspicion of a serious problem. Signs of inflammation, proptosis, loss of vision, and impaired extraocular movements suggest an orbital disorder (eg, orbital cellulitis, cavernous sinus thrombosis) that may be pushing the globe forward or affecting the nerves or muscles. Other suggestive and specific findings are listed in Table 60-8.

Testing: In most cases, diagnosis can be established clinically and no testing is necessary. If orbital cellulitis or cavernous sinus thrombosis is suspected, diagnosis and treatment should proceed as rapidly as possible. Immediate imaging with CT or MRI should be done. If cardiac, liver, renal, or thyroid dysfunction is suspected, organ function is evaluated with laboratory tests and imaging as appropriate for that system.

Treatment

Treatment is directed at the underlying disorder. There is no specific treatment for the swelling.

Key Points

- Proptosis with impaired vision or extraocular movements suggests orbital cellulitis or cavernous sinus thrombosis, and diagnosis and treatment should proceed as rapidly as possible.
- Eyelid disorders should be differentiated from orbital and systemic causes of swelling.

Eye Pain

Eye pain may be described as sharp, aching, or throbbing and should be distinguished from superficial irritation or a foreign body sensation. In some disorders, pain is worsened by bright light. Eye pain may be caused by a serious disorder and requires prompt evaluation. Many causes of eye pain also cause a red eye.

Pathophysiology

The cornea is richly innervated and highly sensitive to pain. Many disorders that affect the cornea or anterior chamber (eg, uveitis) also cause pain via ciliary muscle spasm; when such spasm is present, bright light causes muscle contraction, worsening pain.

Etiology

Disorders that cause eye pain can be divided into those that affect primarily the cornea, other ocular disorders, and disorders that cause pain referred to the eye (see Table 60-9).
The most common causes overall are

• Corneal abrasion

• Foreign bodies

However, most corneal disorders can cause eye pain.

A feeling of scratchiness or of a foreign body may be caused by either a conjunctival or a corneal disorder.

**Evaluation**

**History:** History of present illness should address the onset, quality, and severity of pain and any history of prior episodes (e.g., daily episodes in clusters). Important associated symptoms include true photophobia (shining a light into the unaffected eye causes pain in the affected eye when the affected eye is shut), decreased visual acuity, foreign body sensation and pain when blinking, and pain when moving the eye.

**Review of systems** should seek symptoms suggesting a cause, including presence of an aura (migraine); fever and chills (infection); and pain when moving the head, purulent rhinorrhea, productive or nocturnal cough, and halitosis (sinusitis).

**Past medical history** should include known disorders that are risk factors for eye pain, including autoimmune disorders, multiple sclerosis, migraine, and sinus infections. Additional risk factors to assess include use (and overuse) of contact lenses (contact lens keratitis), exposure to excessive sunlight or to welding (UV keratitis), hammering or drilling metal (foreign body), and recent eye injury or surgery (endophthalmitis).

**Physical examination:** Vital signs are checked for the presence of fever. The nose is inspected for purulent rhinorrhea, and the face is palpated for tenderness. If the eye is red, the preauricular region is checked for adenopathy. Hygiene during examination must be scrupulous when examining patients who have chemosis, preauricular adenopathy, punctate corneal staining, or a combination; these findings suggest epidemic keratoconjunctivitis, which is highly contagious.

Eye examination should be as complete as possible for patients with eye pain. Best corrected visual acuity is checked. Visual fields are typically tested by confrontation in patients with eye pain, but this test can be insensitive (particularly for small defects) and unreliable because of poor patient cooperation. A light is moved from one eye to the other to check for pupillary size and direct and consensual pupillary light responses. In patients who have unilateral eye pain, a light is shined in the unaffected eye while the affected eye is shut; pain in the affected eye represents true photophobia. Extraocular movements are checked. The orbital and periorbital structures are inspected. Conjunctival injection that seems most intense and confluent around the cornea and limbus is called ciliary flush.

Slit-lamp examination is done if possible. The cornea is stained with fluorescein and examined under magnification with cobalt blue light. If a slit lamp is unavailable, the cornea can be examined after fluorescein staining with a Wood's light using magnification. Ophthalmoscopy is done, and ocular pressures are measured (tonometry). In patients with a foreign body sensation or unexplained corneal abrasions, the eyelids are everted and examined for foreign bodies.

**Red flags:** The following findings are of particular concern:

• Vomiting, halos around lights, or corneal edema

• Signs of systemic infection (e.g., fever, chills)

• Decreased visual acuity
• Proptosis

• Impaired extraocular motility

**Interpretation of findings:** Suggestive findings are listed in Table 60-9. Some findings suggest categories of disorders.

Scratchiness or a foreign body sensation is most often caused by disorders of the eyelids, conjunctivae, or superficial cornea. Photosensitivity is possible.

Surface pain with photophobia is often accompanied by a foreign body sensation and pain when blinking; it suggests a corneal lesion, most often a foreign body or abrasion.

Deeper pain—often described as aching or throbbing—usually indicates a serious disorder such as glaucoma, uveitis, scleritis, endophthalmitis, orbital cellulitis, or orbital pseudotumor. Within this group, eyelid swelling, proptosis, or both and impaired extraocular movements or visual acuity suggest orbital pseudotumor, orbital cellulitis, or possibly severe endophthalmitis. Fever, chills, and tenderness suggest infection (eg, orbital cellulitis, sinusitis).

A red eye suggests that the disorder causing pain is ocular rather than referred.

If pain develops in the affected eye in response to shining light in the unaffected eye when the affected eye is shut (true photophobia), the cause is most often a corneal lesion or uveitis.

If topical anesthetic drops (eg, proparacaine) abolish pain in a red eye, the cause is probably a corneal disorder.

Some findings are more suggestive of particular disorders. Pain and photophobia days after blunt eye trauma suggest uveitis. Hammering or drilling metal is a risk factor for occult metal intraocular foreign body. Pain with movement of extraocular muscles and loss of pupillary light response that is disproportionate to loss of visual acuity suggest optic neuritis.

**Testing:** Testing is not usually necessary, with some exceptions (see Table 60-9). Gonioscopy is done if glaucoma is suspected based on increased intraocular pressure. Imaging, usually with CT or MRI, is done if orbital pseudotumor or orbital cellulitis is suspected or if sinusitis is suspected but the diagnosis is not clinically clear. MRI is often done when optic neuritis is suspected, looking for demyelinating lesions in the brain suggesting multiple sclerosis.

Intraocular fluids (vitreous and aqueous humor) may be cultured for suspected endophthalmitis. Viral cultures can be used to confirm herpes zoster ophthalmicus or herpes simplex keratitis if the diagnosis is not clear clinically.

**Treatment**

The cause of pain is treated. Pain itself is also treated. Systemic analgesics are used as needed. Pain caused by uveitis and many corneal lesions is also relieved with cycloplegic eye drops (eg, homatropine 5% qid).

**Key Points**

• Most diagnoses can be made by clinical evaluation.

• Infection precautions should be maintained when examining patients with bilateral red eyes.
Important danger signs are vomiting, halos around lights, fever, decreased visual acuity, proptosis, and impaired extraocular motility.

Pain in the affected eye in response to shining light in the unaffected eye when the affected eye is shut (true photophobia) suggests a corneal lesion or uveitis.

If a topical anesthetic (eg, proparacaine) relieves pain, the cause of pain is a corneal lesion.

Hammering or drilling on metal is a risk factor for occult intraocular foreign body.

**Proptosis**

(Exophthalmos)

Proptosis is protrusion of the eyeball. Exophthalmos means the same thing, and this term is usually used when describing proptosis due to Grave's disease. Disorders that may cause changes in the appearance of the face and eyes that resemble proptosis but are not include hyperthyroidism without infiltrative eye disease, Cushing's disease, and severe obesity.

**Etiology**

The most common cause is Graves’ disease (see Table 60-10), which causes edema and lymphoid infiltration of the orbital tissues.

**Evaluation**

Rate of onset may provide a clue to diagnosis. Sudden unilateral onset suggests intraorbital hemorrhage (which can occur after surgery, retrobulbar injection, or trauma) or inflammation of the orbit or paranasal sinuses. A 2- to 3-wk onset suggests chronic inflammation or orbital inflammatory pseudotumor (non-neoplastic cellular infiltration and proliferation); slower onset suggests an orbital tumor.

Ocular examination findings typical of hyperthyroidism but unrelated to infiltrative eye disease include eyelid retraction, eyelid lag, temporal flare of the upper eyelid, and staring. Other signs include eyelid erythema and conjunctival hyperemia. Prolonged exposure of larger-than-usual areas of the eyeball to air causes corneal drying and can lead to infection and ulceration.

**Testing:** Proptosis can be confirmed with exophthalmometry, which measures the distance between the lateral angle of the bony orbit and the cornea; normal values are < 20 mm in whites and < 22 mm in blacks. CT or MRI is often useful to confirm the diagnosis and to identify structural causes of unilateral proptosis. Thyroid function testing is indicated when Graves’ disease is suspected.

[Table 60-10, Some Causes of Proptosis]

**Treatment**

Lubrication to protect the cornea is required in severe cases. When lubrication is not sufficient, surgery to provide better coverage of the eye surface or to reduce proptosis may be required. Systemic corticosteroids (eg, prednisone 1 mg/kg po once/day for 1 wk, tapered over ≥ 1 mo) are often helpful in controlling edema and orbital congestion due to thyroid eye disease or inflammatory orbital pseudotumor. Other interventions vary by etiology. Graves’ exophthalmos is not affected by treatment of the thyroid condition but may lessen over time. Tumors must be surgically removed. Selective embolization or, rarely, trapping procedures may be effective in cases of arteriovenous fistulas involving the cavernous sinus.

**Floaters**

Floaters are opacities that move across the visual field and do not correspond to external visual objects.

**Pathophysiology**
With aging, the vitreous humor can contract and separate from the retina. The age at which this change occurs varies but most often is between 50 and 75 yr. During this separation, the vitreous can intermittently tug on the retina. The mechanical traction stimulates the retina, which sends a signal that is perceived by the brain and interpreted as light. Complete separation of the vitreous leads to an increase in floaters, which may last for years.

However, traction on the retina may create a hole (retinal tear), and if fluid leaks behind the tear, the retina may detach. Retinal detachment may also be caused by other factors (eg, trauma, primary retinal disorders). Lightning-like flashes, common in retinal detachment, are called photopsias. Photopsias can also occur when rubbing the eyes or when looking around after awakening.

**Etiology**

The most common cause of vitreous floaters is

- Contraction of the vitreous humor that occurs for unknown reasons (idiopathic)

Less common causes are listed in [Table 60-11](#).

Rare causes of floaters include intraocular tumors (eg, lymphoma). Intraocular foreign bodies can cause floaters but usually manifest with other symptoms, such as loss of vision, eye pain, or redness.

**Evaluation**

The most important goal is to identify serious vitreous and retinal disorders. If these disorders cannot be ruled out, patients should be examined by an ophthalmologist using an indirect ophthalmoscope after pupillary dilation. Recognizing ocular migraine is also helpful.

**History:** History of present illness should ascertain onset and duration of symptoms and the shape and volume of floaters, as well as whether they are unilateral or bilateral and whether they have been preceded by trauma. The patient should try to distinguish floaters from lightning-like flashes of light (as in photopsias) or jagged lines across the visual field (as in migraine). Important associated symptoms include loss of vision (and its distribution in the visual field) and eye pain.

**Review of systems** should seek symptoms of possible causes, such as headaches (ocular migraine) and eye redness (vitreous inflammation).

**Past medical history** should note diabetes (including diabetic retinopathy), migraine headaches, eye surgery, severe myopia, and any disorders that could affect the immune system (eg, AIDS).

**Physical examination:** Eye examination should be reasonably complete. Best corrected visual acuity is measured. The eyes are inspected for redness. Visual fields are assessed in all patients. However, recognition of visual field defects by bedside examination is very insensitive, so inability to show such a defect is not evidence that the patient has full visual fields. Extraocular movements and pupillary light responses are assessed. If patients have a red eye or eye pain, the corneas are examined under magnification after fluorescein staining, and slit-lamp examination is done if possible. Ocular pressure is measured (tonometry).

Ophthalmoscopy is the most important part of the examination. It is done using a direct ophthalmoscope and after dilating the pupils. To dilate the pupils, the physician first makes sure to record pupillary size and light responses, then instills drops, usually 1 drop each of a short-acting α-adrenergic agonist (eg, 2.5% phenylephrine) and a cycloplegic (eg, 1% tropicamide or 1% cyclopentolate). The pupils are fully dilated about 20 min after these drops are instilled.

**Red flags:** The following findings are of particular concern:
Table 60-11. Some Causes of Floaters

- Sudden increase in floaters
- Lightning-like flashes (photopsias)
- Loss of vision, diffuse or focal (visual field defect)
- Recent eye surgery or eye trauma
- Eye pain
- Loss of red reflex
- Abnormal retinal findings

**Interpretation of findings:** Retinal detachment is suggested by sudden increases in floaters, photopsias, or any of its other, more specific characteristics (eg, visual field defects, retinal abnormalities). Bilateral synchronous symptoms suggest ocular migraine, although patients often have difficulty deciphering the laterality of their symptoms (eg, they often interpret scintillating scotoma of the left field of both eyes as left-eyed). Loss of red reflex suggests opacification of the vitreous (eg, vitreous hemorrhage or inflammation), but it also can be caused by advanced cataracts. Loss of vision suggests a serious disorder causing dysfunction of the vitreous or retina.

**Testing:** Patients who require evaluation by an ophthalmologist may need testing. However, tests can be selected by or in conjunction with the ophthalmologist. For example, patients suspected of having chorioretinitis may require microbiologic testing.

**Treatment**

Idiopathic vitreous floaters require no treatment. Other disorders causing symptoms are treated.

**Key Points**

- Floaters by themselves rarely indicate a serious disorder.
- Patients with any abnormal findings on examination require ophthalmologic referral.
- If floaters are accompanied by any other symptoms (eg, persistent flashing lights, visual deficit, sensation of a moving curtain of vision loss), patients require ophthalmologic referral, regardless of examination findings.

**Red Eye**

(Pink Eye)

Red eye refers to a red appearance of the opened eye, reflecting dilation of the superficial ocular vessels.

**Pathophysiology**

Dilation of superficial ocular vessels can result from

- Infection
- Allergy
- Inflammation (noninfectious)
• Elevated intraocular pressure

Several ocular components may be involved, most commonly the conjunctiva, but also the uveal tract, episclera, and sclera.

**Etiology**

The most common causes of red eye include

• Infectious conjunctivitis

• Allergic conjunctivitis

Corneal abrasions and foreign bodies are common causes (see [*Table 60-12*](#)). Although the eye is red, patients usually present with a complaint of injury, eye pain, or both. However, in young children and infants, this information may be unavailable.

**Evaluation**

Most disorders can be diagnosed by a general health care practitioner.

**History:** *History of present illness* should note the onset and duration of redness and presence of any change in vision, itching, scratchy sensation, pain, or discharge. Nature and severity of pain, including whether pain is worsened by light (photophobia), are noted. The clinician should determine whether discharge is watery or purulent. Other questions assess history of injury, including exposure to irritants and use of contact lenses (eg, possible overuse, such as wearing them while sleeping). Prior episodes of eye pain or redness and their time patterns are elicited.

**Review of systems** should seek symptoms suggesting possible causes, including headache, nausea, vomiting, and halos around lights (acute angle-closure glaucoma); runny nose and sneezing (allergies, URI); and cough, sore throat, and malaise (URI).

**Past medical history** includes questions about known allergies and autoimmune disorders. Drug history should specifically ask about recent use of topical ophthalmic drugs (including OTC drugs), which might be sensitizing.

**Physical examination:** General examination should include head and neck examination for signs of associated disorders (eg, URI, allergic rhinitis, zoster rash).

Eye examination involves a formal measure of visual acuity and usually requires a penlight, fluorescein stain, and slit lamp.

Best corrected visual acuity is measured. Pupillary size and reactivity to light are assessed. True photophobia (sometimes called  

[Table 60-12; Some Causes of Red Eye]  

consensual photophobia) is present if shining light into an unaffected eye causes pain in the affected eye when the affected eye is shut. Extraocular movements are assessed, and the eye and periorbital tissues are inspected for lesions and swelling. The tarsal surface is inspected for follicles. The corneas are stained with fluorescein and examined with magnification. If a corneal abrasion is found, the eyelid is everted and examined for hidden foreign bodies. Inspection of the ocular structures and cornea is best done using a slit lamp. A slit lamp is also used to examine the anterior chamber for cells, flare, and pus (hypopyon). Ocular pressure is measured using tonometry, although it may be permissible to omit this test if there are no symptoms or signs suggesting a disorder other than conjunctivitis.

**Red flags:** The following findings are of particular concern:
• Sudden, severe pain and vomiting
• Zoster skin rash
• Decreased visual acuity
• Corneal crater
• Branching, dendritic corneal lesion
• Ocular pressure > 40 mm Hg
• Failure to blanch with phenylephrine eye drop

Interpretation of findings: Conjunctival disorders and episcleritis are differentiated from other causes of red eye by the absence of pain, photophobia, and corneal staining. Among these disorders, episcleritis is differentiated by its focality, and subconjunctival hemorrhage is usually differentiated by the absence of lacrimation, itching, and photosensitivity. Clinical criteria do not accurately differentiate viral from bacterial conjunctivitis.

Corneal disorders are differentiated from other causes of red eye (and usually from each other) by fluorescein staining. These disorders also tend to be characterized by pain and photophobia. If instillation of an ocular anesthetic drop (eg, proparacaine 0.5%), which is done before tonometry and ideally before fluorescein instillation, completely relieves pain, the cause is probably limited to the cornea. If pain is present and is not relieved by an ocular anesthetic, the cause may be anterior uveitis, glaucoma, or scleritis. Because patients may have anterior uveitis secondary to corneal lesions, persistence of pain after instillation of the anesthetic does not exclude a corneal lesion.

Anterior uveitis, glaucoma, acute angle-closure glaucoma, and scleritis can usually be differentiated from other causes of red eye by the presence of pain and the absence of corneal staining. Anterior uveitis is likely in patients with pain, true photophobia, absence of corneal fluorescein staining, and normal intraocular pressure; it is definitively diagnosed based on the presence of cells and flare in the anterior chamber. However, these findings may be difficult for general health care practitioners to discern. Acute angle-closure glaucoma can usually be recognized by the sudden onset of its severe and characteristic symptoms, but tonometry is definitive.

Instillation of phenylephrine 2.5% causes blanching in a red eye unless the cause is scleritis. Phenylephrine is instilled to dilate the pupil in patients needing a thorough retinal examination. However, it should not be used in patients who have the following:

• Suspected acute angle-closure glaucoma
• A history of angle-closure glaucoma
• A narrow anterior chamber

Testing: Testing is usually unnecessary. Viral cultures may help if herpes simplex or herpes zoster is suspected and the diagnosis is not clear clinically. Corneal ulcers are cultured by an ophthalmologist. Gonioscopy is done in patients with glaucoma. Testing for autoimmune disorders may be worthwhile in patients with uveitis and no obvious cause (eg, trauma). Patients with scleritis undergo further testing as directed by an ophthalmologist.

Treatment

The cause is treated. Red eye itself does not require treatment. Topical vasoconstrictors are not recommended.
Key Points

• Most cases are caused by conjunctivitis.

• Pain and true photophobia suggest other, more serious diagnoses.

• In patients with pain, slit-lamp examination with fluorescein staining and tonometry are key.

• Persistence of pain despite an ocular anesthetic in a patient with a normal fluorescein examination suggests anterior uveitis, scleritis, or acute angle-closure glaucoma. These diagnoses should not be missed.

Tearing

(Epiphora)

Excess tearing may cause a sensation of watery eyes or result in tears falling down the cheek (epiphora).

Pathophysiology

Tears are produced in the lacrimal gland and drain through the upper and lower puncta into the canaliculi and then into the lacrimal sac and nasolacrimal duct (see Fig. 60-3). Obstruction of tear drainage can lead to stasis and infection. Recurrent infection of the lacrimal sac (dacryocystitis) can sometimes spread, potentially leading to orbital cellulitis.

Etiology

Overall, the most common causes of tearing are

• URI

• Allergic rhinitis

Tearing can be caused by increased tear production or decreased nasolacrimal drainage.

Increased tear production: The most common causes are

• URI

• Allergic rhinitis

• Allergic conjunctivitis

• Dry eyes (reflex tearing produced in response to dryness of the ocular surface)

• Trichiasis

Any disorder causing conjunctival or corneal irritation can increase tear production (see Table 60-13). However, most patients with corneal disorders that cause excess tearing (eg, corneal abrasion, corneal ulcer, corneal foreign body, keratitis) or with primary angle-closure glaucoma or anterior uveitis present with eye symptoms other than tearing (eg, eye pain, redness). Most people who have been crying do not present for evaluation of tearing.

Decreased nasolacrimal drainage: The most common causes are

• Idiopathic age-related nasolacrimal duct stenosis

• Dacryocystitis
Ectropion

(Fig. 60-3, Anatomy of the lacrimal system.)

Nasolacrimal drainage system obstruction may be caused by strictures, tumors, or foreign bodies (eg, stones, often associated with subclinical infection by *Actinomyces*). Obstruction can also be a congenital malformation. Many disorders and drugs can cause stricture or obstruction of nasolacrimal drainage.

Other causes of nasolacrimal drainage stricture or obstruction include

- Burns
- Chemotherapy drugs
- Eye drops (particularly echothiophate iodide, epinephrine, and pilocarpine)
- Infection, including canaliculitis (eg, caused by *Staphylococcus aureus*, *Actinomyces*, *Streptococcus*, *Pseudomonas*, herpes zoster virus, herpes simplex conjunctivitis, infectious mononucleosis, human papillomavirus, *Ascaris*, leprosy, TB)
- Inflammatory disorders (sarcoidosis, Wegener's granulomatosis)
- Injuries (eg, nasoethmoid fractures; nasal, orbital, or endoscopic sinus surgery)
- Obstruction of nasal outlet despite an intact nasolacrimal system (eg, URI, allergic rhinitis, sinusitis)
- Radiation therapy
- Stevens-Johnson syndrome
- Tumors (eg, primary lacrimal sac tumors, benign papillomas, squamous and basal cell carcinoma, transitional cell carcinoma, fibrous histiocytes, midline granuloma, lymphoma)

Evaluation

**History:** History of present illness addresses the duration, onset, and severity of symptoms, including whether tears drip down the cheek (true epiphora). The effects of weather, environmental humidity, and cigarette smoke are ascertained.

**Review of symptoms** should seek symptoms of possible causes, including itching, rhinorrhea, or sneezing, particularly when occurring perennially or after exposure to specific potential allergens (allergic reaction); eye irritation or pain (blepharitis, corneal abrasion, irritant chemicals); and pain near the medial canthus (dacryocystitis). Other symptoms are of lower yield but should be sought; they include positional headache, purulent rhinorrhea, nocturnal cough, and fever (sinusitis, Wegener's granulomatosis); rash (Stevens-Johnson syndrome); cough, dyspnea, and chest pain (sarcoidosis); and epistaxis, hemoptysis, polyarthralgias, and myalgias (Wegener's granulomatosis).

**Past medical history** asks about known disorders that can cause tearing, including Wegener's granulomatosis, sarcoidosis, and cancer treated with chemotherapy drugs; disorders that cause dry eyes (eg, RA, sarcoidosis, Sjogren's syndrome); and drugs, such as echothiophate, epinephrine, and pilocarpine. Previous ocular and nasal history, including infections, injuries, surgical procedures, and radiation exposure, is ascertained.

**Physical examination:** Examination focuses on the eye and surrounding structures.
The face is inspected; asymmetry suggests congenital or acquired obstruction of nasolacrimal duct drainage. When available, a slit lamp should be used to examine the eyes. The conjunctivae and corneas are inspected for lesions, including punctate spots, and redness. The cornea is stained with fluorescein and examined. The lids are everted to detect hidden foreign bodies. The eyelids, including the lacrimal puncta, are closely inspected for foreign bodies, blepharitis, hordeola, ectropion, entropion, and trichiasis. The lacrimal sac (near the medial canthus) is palpated for warmth, tenderness, and swelling. Any swellings are palpated for consistency and to see whether pus is expressed.

The nose is examined for congestion, purulence, and bleeding.

**Red flags**: The following findings are of particular concern:

- Repeated, unexplained episodes of tearing
- Hard mass in or near the nasolacrimal drainage structures

**Interpretation of findings**: Findings that suggest obstruction of nasolacrimal drainage include

- Tears running down the cheek (true epiphora)
- Absence of signs of a specific cause

A cause is often evident from the clinical evaluation (see Table 60-14).

**Testing**: Testing is often unnecessary because the cause is usually evident from the examination.

Schirmer's test with a large amount of wetting (eg, > 25 mm) suggests an evaporative dry eye as the etiology of tearing. Schirmer's test with very little wetting (< 5.5 mm) suggests an aqueous tear-deficient dry eye. Usually, Schirmer's test is done by an ophthalmologist to ensure it is done and interpreted correctly.

Probing and saline irrigation of the lacrimal drainage system can help detect anatomic obstruction of drainage, as well as stenosis due to complete obstruction of the nasolacrimal drainage system. Irrigation is done with and without fluorescein dye. Reflux through the opposite punctum or canaliculus signals fixed obstruction; reflux and nasal drainage signify stenosis. This test is considered adjunctive and is done by ophthalmologists.

Imaging tests and procedures (dacryocystography, CT, nasal endoscopy) are sometimes useful to delineate abnormal anatomy when surgery is being considered or occasionally to detect an abscess.

**Treatment**

Underlying disorders (eg, allergies, foreign bodies, conjunctivitis) are treated.

The use of artificial tears lessens tearing when dry eyes or corneal epithelial defects are the cause.

Congenital nasolacrimal duct obstruction often resolves spontaneously. In patients < 1 yr, manual compression of the lacrimal sac 4 or 5 times/day may relieve the distal obstruction. After 1 yr, the nasolacrimal duct may need probing with the patient under general anesthesia. If obstruction is recurrent, a temporary drainage tube may be inserted.

In acquired nasolacrimal duct obstruction, irrigation of the nasolacrimal duct may be therapeutic when underlying disorders do not respond to treatment. As a last resort, a passage between the lacrimal sac and the nasal cavity can be created surgically (dacryocystorhinostomy).
In cases of punctal or canalicular stenosis, dilation is usually curative. If canalicular stenosis is severe and bothersome, a surgical procedure that places a glass tube leading from the caruncle into the nasal cavity can be considered.

Geriatrics Essentials

Idiopathic age-related nasolacrimal duct stenosis is the most common cause of unexplained epiphora in elderly patients; however, tumors should also be considered.

Key Points

- If tears do not run down the cheek, dry eyes is often the cause.
- If tears run down the cheek, obstruction of nasolacrimal drainage is likely.
- Testing is often unnecessary but is needed in cases of recurrent infectious dacryocystitis, which can progress to more serious conditions such as orbital cellulitis.

Other Eye Symptoms

Dry eyes are discussed under Keratoconjunctivitis sicca (see p. 592) The disorder is most often idiopathic or associated with older age but can also be caused by connective tissue diseases (eg, Sjogren's syndrome, RA, SLE).

Eye discharge: Discharge is often accompanied by a red eye (see p. 563) and commonly is caused by allergic or infectious conjunctivitis, blepharitis, and, in infants, ophthalmia neonatorum (neonatal conjunctivitis). Infectious discharge may be purulent in bacterial infection, such as staphylococcal conjunctivitis or gonorrhea. Less common causes include dacryocystitis and canaliculitis.

Diagnosis is usually made clinically. Allergic conjunctivitis can often be distinguished from infectious by predominance of itching, clear discharge, and presence of other allergic symptoms (eg, runny nose, sneezing). Clinical differentiation between viral and bacterial conjunctivitis is difficult. Cultures are not usually done, but are indicated for patients with the following:

- Clinically suspected gonococcal or chlamydial conjunctivitis
- Severe symptoms
- Immunocompromise
- A vulnerable eye (eg, after a corneal transplant, in exophthalmos due to Graves' disease)
- Ineffective initial therapy

Halos: Halos around light may result from cataracts; conditions that result in corneal edema, such as acute angle-closure glaucoma or disorders that cause bullous keratopathy; corneal haziness; mucus on the cornea; or drugs, such as digoxin or chloroquine.

Blue hues: Certain conditions may cause a blue tint to the visual field (cyanopsia). Cyanopsia may occur for a few days after cataract removal or as an adverse effect of sildenafil and possibly other phosphodiesterase-5 (PDE5) inhibitors.

Scotomata: Scotomata are visual field deficits and are divided into

- Negative scotoma (blind spots)
- Positive scotoma (light spots or scintillating flashes)
Negative scotomata may not be noticed by patients unless they involve central vision and interfere significantly with visual acuity; the complaint is most often decreased visual acuity (see p. 541). Negative scotomata have multiple causes that can sometimes be distinguished by the specific type of field deficit (see Table 60-1) as identified by use of a tangent screen, Goldmann perimeter, or computerized automated perimetry (in which the visual field is mapped out in detail based on patient response to a series of flashing lights in different locations controlled by a standardized computer program).

Positive scotomata represent a response to abnormal stimulation of some portion of the visual system, as occurs in migraines.
Chapter 61. Refractive Error

Introduction

In the emmetropic (normally refracted) eye, entering light rays are focused on the retina by the cornea and the lens, creating a sharp image that is transmitted to the brain. The lens is elastic, more so in younger people. During accommodation, the ciliary muscles adjust lens shape to properly focus images. Refractive errors are failure of the eye to focus images sharply on the retina, causing blurred vision (see Fig. 61-1).

In myopia (nearsightedness), the point of focus is in front of the retina because the cornea is too steeply curved, the axial length of the eye is too long, or both. Distant objects are blurred, but near objects can be seen clearly. To correct myopia, a concave (minus) lens is used. Myopic refractive errors in children frequently increase until the child stops growing.

In hyperopia (farsightedness), the point of focus is behind the retina because the cornea is too flatly curved, the axial length is too short, or both. In adults, both near and distant objects are blurred. Children and young adults with mild hyperopia may be able to see clearly because of their ability to accommodate. To correct hyperopia, a convex (plus) lens is used.

[Fig. 61-1. Errors of refraction.]

In astigmatism, nonspherical (variable) curvature of the cornea or lens causes light rays of different orientations (e.g., vertical, oblique, horizontal) to focus at different points. To correct astigmatism, a cylindric lens (a segment cut from a cylinder) is used. Cylindric lenses have no refractive power along one axis and are concave or convex along the other axis.

Presbyopia is loss of the lens’ ability to change shape to focus on near objects due to aging. Typically, presbyopia becomes noticeable by the time a person reaches the early or mid 40s. A convex (plus) lens is used for correction when viewing near objects. These lenses may be supplied as separate glasses or built into a lens as bifocals or variable focus lenses.

Anisometropia is a significant difference between the refractive errors of the 2 eyes (usually > 3 diopters). When corrected with eyeglasses, a difference in image size (aniseikonia) is produced; it can lead to difficulties with fusion of the 2 differently sized images and even to suppression of one of the images.

Symptoms and Signs

The primary symptom of refractive errors is blurred vision for distant objects, near objects, or both. Sometimes the excessive ciliary muscle tone can cause headaches. Occasionally, excessive staring can lead to ocular surface desiccation, causing eye irritation, itching, visual fatigue, foreign body sensation, and redness. Frowning when reading and excessive blinking or rubbing of the eyes are symptoms in children.

Diagnosis

Refraction should be checked every 1 or 2 yr. Screening children helps detect refractive errors before they interfere with learning. A comprehensive eye examination (see p. 537) should accompany refraction testing, whether done by an ophthalmologist or an optometrist.

Contact Lenses

Contact lenses often provide better visual acuity and peripheral vision than do eyeglasses and can be prescribed to correct myopia, hyperopia, astigmatism, anisometropia, aniseikonia, aphakia (absence of the lens) after cataract removal, and keratoconus (a conical-shaped cornea). Either soft or rigid lenses are used to correct myopia and hyperopia. Toric soft contact lenses (which have different curvatures molded onto the front lens surface) or rigid lenses are used to correct significant astigmatism; they are...
satisfactory in many cases but require expert fitting.

Presbyopia can also be corrected with contact lenses. In one approach, termed monovision, the nondominant eye is corrected for reading and the dominant eye is corrected for distant vision. Rigid and soft bifocal and multifocal contact lenses can also be successful, but the fitting procedure is time-consuming because precise alignment is essential.

Neither rigid nor soft contact lenses offer the eyes the protection against blunt or sharp injury that eyeglasses do.

**Care and Complications**

Instructions for hygiene and handling lenses must be strictly observed. Poor contact lens hygiene may lead to persistent inflammation or infection of the cornea.

Contact lenses occasionally cause painless superficial corneal changes. Contact lenses can be painful when

- The corneal epithelium is abraded (see p. 3236); the cornea becomes red and inflamed and stains with fluorescein.
- The lenses fit poorly (eg, too tight, too loose, poorly centered).
- There is too little moisture to keep the lens floating above the cornea.
- The lenses are worn in a nonideal environment (eg, O₂-poor, smoky, windy).
- A lens is improperly inserted or removed.
- A small foreign particle (eg, soot, dust) becomes trapped between the lens and the cornea.
- The lenses are worn for a long time (overwear syndrome).

In overwear syndrome, spontaneous healing may occur in a day or so if lenses are not worn. In some cases, active treatment is required—eg, topical antibiotic eyedrops or ointments and dilation of the pupil with a mydriatic to ease photophobia. (Mydriatics work by paralyzing the muscles of the iris and ciliary body [movement of the inflamed muscles causes pain].) Recovery is usually rapid, complete, and without vision impairment. An ophthalmologist should be consulted before lenses are worn again.

Risk factors for contact lens-related corneal infection (keratitis) include the following:

- Poor lens hygiene
- Overnight or extended wear
- Use of tap water in the cleaning regimen
- Eyes with a compromised ocular surface (eg, dryness, poor corneal sensation)

Infections require rapid management by an ophthalmologist.

**Corneal ulcer:** A corneal ulcer, which is a potentially vision-threatening infection of the cornea, is suspected when a contact lens wearer experiences intense eye pain (both foreign body sensation and ache), redness, photophobia, and tearing (see also p. 588).

Diagnosis is by slit-lamp examination and fluorescein staining. A corneal infiltrate (collection of WBCs in the corneal stroma) is present. At times, the corneal infiltrate is large and dense enough to be seen with handheld magnification or even with the naked eye as a white spot on the cornea. Microbiologic analysis
of cultures and smears of the corneal infiltrate, contact lens, and contact lens case is indicated.

Treatment includes cessation of contact lens wear and antibiotic drops. Initial therapy includes broad-spectrum antibiotic coverage using a fluoroquinolone antibiotic drop q 15 to 60 min around the clock for 24 to 72 h, then at gradually longer intervals. Drops of an additional antibiotic, such as cefazolin, vancomycin, or concentrated tobramycin, are used if the ulcer is large, deep, or close to the visual axis. The antibiotic may be changed later based on culture results. Neglected cases may respond poorly or not at all to treatment, and severe vision loss may result.

Rigid Corneal Contact Lenses

Older polymethyl methacrylate rigid contact lenses have been replaced by gas-permeable contact lenses (GPCLs) made of fluorocarbon and polymethyl methacrylate admixtures. GPCLs are 6.5 to 10 mm in diameter and cover part of the cornea, floating on the tear layer overlying it.

Rigid contact lenses can improve vision for people with myopia, hyperopia, and astigmatism. If the corneal surface is irregular, rigid lenses often provide a smooth refracting surface and thus improve visual acuity noticeably more than soft contact lenses or eyeglasses.

For complete wearing comfort, rigid contact lenses require an adaptation period, sometimes as long as 1 wk. During this time, the wearer gradually increases the number of hours the lenses are worn each day. Importantly, no pain should occur at any time. Pain is a sign of an ill-fitting contact lens or corneal irritation. Wearers usually experience temporary (< 2 h) blurred vision (spectacle blur) when wearing eyeglasses after removing rigid contact lenses.

Soft Hydrophilic Contact Lenses

Soft contact lenses are made of poly-2-hydroxyethyl methacrylate and other flexible plastics and are 30 to 79% water. They are 13 to 15 mm in diameter and cover the entire cornea. Soft contact lenses can improve vision for people with myopia and hyperopia. Because soft contact lenses mold to the existing corneal curvature, anything greater than minimal astigmatism cannot be treated unless a special toric lens, which has different curvatures molded onto the front lens surface, is used. Weighting the lower aspect of the lens maintains its orientation.

Soft contact lenses are also prescribed for treatment of recurrent corneal erosions and other corneal disorders (called bandage or therapeutic contact lenses). Prophylactic antibiotic eyedrops (eg, fluoroquinolone qid) may be advisable with a bandage lens. Extended wearing of contact lenses, especially in aphakia after cataract surgery, is practical, but an ophthalmologist should examine the patient at least 4 times/yr. The patient should clean the lenses once/wk.

Because of their larger size, soft contact lenses are easier to handle, are not as likely as rigid lenses to eject spontaneously, and are less likely to allow foreign bodies to lodge beneath them. Immediate wearing comfort allows for a brief adaptation period.

Soft contact lenses have a higher incidence of corneal infections, which increases for every night a person wears them during sleep. When dry, soft contact lenses are brittle and break easily. They absorb a certain amount of moisture (based on the water content) from the tear film to retain adequate shape and pliability. Therefore, patients with dry eye are usually more comfortable wearing lenses that have a low water content.

Refractive Surgery

Corneal refractive surgery alters the curvature of the cornea to focus light more precisely on the retina. The goal of refractive surgery is to decrease dependence on eyeglasses or contact lenses. Most people who undergo refractive surgery achieve this goal; about 95% do not need corrective lenses for distance vision. Ideal candidates for refractive surgery are people with healthy eyes who are not satisfied wearing eyeglasses or contact lenses. Preoperative examination excludes people with active ocular diseases, including severe dry eye. Candidates should not have a history of autoimmune or connective tissue
disease because of potential problems with wound healing. Latent herpes simplex virus may be reactivated after surgery; patients should be advised accordingly. Refraction should be stable for at least 1 yr, and candidates should be > 18 yr. Another contraindication is use of isotretinoin or amiodarone.

Adverse effects of refractive surgery include temporary foreign body sensation, glare, halos, and dryness; occasionally, these symptoms persist. Potential complications include overcorrection and undercorrection, infection, and irregular astigmatism. In excimer laser procedures performed on the superficial corneal stroma, haze formation is possible. If infection, irregular astigmatism, or haze formation causes permanent changes in the central cornea, best-corrected acuity could be lost. The overall complication rate is low; chance of vision loss is < 1% if the patient is considered a good candidate for refractive surgery preoperatively.

Laser In Situ Keratomileusis

In laser in situ keratomileusis (LASIK), a flap of corneal tissue is created with a laser or mechanical microkeratome and turned back, the underlying stromal bed is sculpted (photo-ablated) with the excimer laser, and the flap is replaced without suturing. Because surface epithelium is not disrupted centrally, vision returns rapidly. Most people notice a significant improvement the next day. LASIK can be used to treat myopia, astigmatism, and hyperopia.

Advantages of LASIK over photorefractive keratectomy (PRK) include the desirable lack of healing response (the central corneal epithelium is not removed, thereby decreasing the risk of central haze formation that occurs during healing), the shorter visual rehabilitation period, and minimal postoperative pain. Disadvantages include possible intraoperative and postoperative flap-related complications, such as irregular flap formation, flap dislocation, and the need for adequate corneal thickness to prevent long-term corneal ectasia. Ectasia occurs when the cornea has become so thin that intraocular pressure causes instability and bulging of the thinned and weakened corneal stroma. Blurring, increasing myopia, and irregular astigmatism can result.

Photorefractive Keratectomy

In PRK, the excimer laser is used to sculpt (photoablate) the anterior curvature of the corneal stromal bed to treat myopia, hyperopia, and astigmatism. The corneal epithelium is removed before photoablation and generally takes 3 to 4 days to regenerate; during this time a bandage contact lens is worn. Unlike LASIK, no corneal flap is created.

PRK may be more suitable for patients with thin corneas or anterior basement membrane dystrophy.

Advantages of PRK include an overall thicker residual stromal bed (thereby reducing risk of ectasia) and lack of flap-related complications. Disadvantages include potential for corneal haze formation if a large amount of corneal tissue is ablated and the need for postoperative corticosteroid drops for 3 to 4 mo. More than 95% of patients see 20/40 or better without eyeglasses after surgery.

Intracorneal Ring Segments

Intracorneal ring segments (INTACS) are thin arc-shaped segments of biocompatible plastic that are inserted in pairs through a small radial corneal incision into the peripheral corneal stroma at two-thirds depth. After INTACS are inserted, the central corneal curvature is flattened, reducing myopia. INTACS are used for mild myopia (< 3 diopters) and minimal astigmatism (< 1 diopter). INTACS maintain a central, clear, optical zone because the 2 segments are placed in the corneal periphery. INTACS can be replaced or removed if desired.

Risks include induced astigmatism, undercorrection and overcorrection, infection, glare, halo, and incorrect depth placement. Vision results are very good; in US clinical studies, 97% of patients saw 20/40 or better and 74% of patients saw 20/20 or better.

Conductive Keratoplasty
Conductive keratoplasty (CK) is a thermal technique that can treat spherical hyperopia (ie, hyperopia without associated astigmatism) and presbyopia. CK uses radiofrequency energy applied with a fine probe in a ring pattern to the peripheral cornea to contract the periphery and steepen the center, thereby increasing the refractive power of the cornea. For presbyopic patients who wear only reading glasses, CK is typically done in the nondominant eye (monovision) to induce myopia in that eye and enable the patient to regain reading vision. As the presbyopia progresses, additional rings of treatment are added. Risks of CK include induced astigmatism and regression of effect.

**Phakic Intraocular Lenses**

Phakic intraocular lenses (IOLs) are lens implants that are used to treat severe myopia in patients who are not suitable candidates for laser vision correction. Unlike in cataract surgery, the patient's natural lens is not removed. The phakic IOL is inserted directly anterior or posterior to the iris through an incision in the eye. This procedure is intraocular surgery and must be done in an operating room.

Risks include cataract formation, glaucoma, infection, and loss of corneal endothelial cells.

Because phakic IOLs do not correct astigmatism, patients can undergo subsequent laser vision correction to refine refractive results in a technique known as bioptics. Because the bulk of the myopia is corrected with the phakic IOL, less corneal tissue is removed with LASIK, and the risk of ectasia is thus low.

**Clear Lensectomy**

Clear lensectomy can be considered in patients with high hyperopia who are already presbyopic. This procedure is identical to cataract surgery except the patient's lens is clear and not cataractous. A multifocal intraocular lens, which allows the patient to focus over a wide range of distances without external lens correction, can be inserted.

The main risks of clear lensectomy are infection and rupture of the posterior capsule of the lens, which would necessitate further surgery. Clear lensectomy should be done with great caution in young myopic patients because they have an increased risk of retinal detachment.

**Radial and Astigmatic Keratotomy**

Radial and astigmatic keratotomy procedures change the shape of the cornea by making deep corneal incisions using a diamond blade.

Radial keratotomy has been replaced by laser vision correction and is rarely used because it offers no clear advantages over laser vision correction, has a greater need for subsequent retreatment, leads to visual and refractive results that change through the day, and tends to cause hyperopia in the long term.

Astigmatic keratotomy is used to treat astigmatism at the time of cataract surgery or after corneal transplantation.
Chapter 62. Eyelid and Lacrimal Disorders

Introduction

Common eyelid and lacrimal disorders include blepharitis, blepharospasm, canalicularitis, chalazion and hordeolum, dacryocystitis, dacryostenosis, entropion and ectropion, trichiasis, and tumors.

Blepharitis

Blepharitis is inflammation of the eyelid margins that may be acute or chronic. Symptoms and signs include itching and burning of the eyelid margins with redness and edema. Diagnosis is by history and examination. Acute ulcerative blepharitis is usually treated with topical antibiotics or systemic antivirals. Acute nonulcerative blepharitis is occasionally treated with topical corticosteroids. Chronic disease is treated with tear supplements, warm compresses, and occasionally oral antibiotics (eg, a tetracycline) for meibomian gland dysfunction or with eyelid hygiene and tear supplements for seborrheic blepharitis.

Etiology

Blepharitis may be acute (ulcerative or nonulcerative) or chronic (meibomian gland dysfunction, seborrheic blepharitis).

Acute: Acute ulcerative blepharitis is usually caused by bacterial infection (usually staphylococcal) of the eyelid margin at the origins of the eyelashes; the lash follicles and meibomian glands are also involved. It may also be due to a virus (eg, herpes simplex, varicella zoster).

Acute nonulcerative blepharitis is usually caused by an allergic reaction involving the same area (eg, atopic blepharodermatitis and seasonal allergic blepharoconjunctivitis, which cause intense itching, rubbing, and a rash; contact sensitivity [dermatoblepharo-conjunctivitis]).

Chronic: Chronic blepharitis is noninfectious inflammation of unknown cause. Meibomian glands in the eyelid produce lipids (meibum) that reduce tear evaporation by forming a lipid layer on top of the aqueous tear layer. In meibomian gland dysfunction, the lipid composition is abnormal, and gland ducts and orifices become inspissated with hard, waxy plugs. Many patients have rosacea (see p. 654) and recurrent hordeola or chalazia.

Many patients with seborrheic blepharitis have seborrheic dermatitis of the face and scalp (see p. 671) or acne rosacea. Secondary bacterial colonization often occurs on the scales that develop on the eyelid margin. Meibomian glands can become obstructed.

Most patients with meibomian gland dysfunction or seborrheic blepharitis have increased tear evaporation and secondary keratoconjunctivitis sicca.

Symptoms and Signs

Symptoms common to all forms of blepharitis include itching and burning of the eyelid margins and conjunctival irritation with lacrimation, photosensitivity, and foreign body sensation.

Acute: In acute ulcerative blepharitis, small pustules may develop in eyelash follicles and eventually break down to form shallow marginal ulcers. Tenacious adherent crusts leave a bleeding surface when removed. During sleep, eyelids can become glued together by dried secretions. Recurrent ulcerative blepharitis can cause eyelid scars and loss of eyelashes.

In acute nonulcerative blepharitis, eyelid margins become edematous and erythematous; eyelashes may become crusted with dried serous fluid.

Chronic: In meibomian gland dysfunction, examination reveals dilated, inspissated gland orifices that, when pressed, exude a waxy, thick, yellowish secretion with pressure. In seborrheic blepharitis, greasy...
easily removable scales develop on eyelid margins. Most patients with seborheic blepharitis and meibomian gland dysfunction have symptoms of keratoconjunctivitis sicca, such as foreign body sensation, grittiness, eye strain and fatigue, and blurring with prolonged visual effort.

Diagnosis

Diagnosis is usually by slit-lamp examination. Chronic blepharitis that does not respond to treatment may require biopsy to exclude eyelid tumors that can simulate the condition.

Prognosis

Acute blepharitis most often responds to treatment but may recur, develop into chronic blepharitis, or both. Chronic blepharitis is indolent, recurrent, and resistant to treatment. Exacerbations are inconvenient, uncomfortable, and cosmetically unappealing but do not usually result in corneal scarring or vision loss.

Treatment

Acute: Acute ulcerative blepharitis is treated with an antibiotic ointment (eg, bacitracin/polymyxin B, erythromycin, or gentamicin 0.3% qid for 7 to 10 days). Acute viral ulcerative blepharitis is treated with systemic antivirals (eg, for herpes simplex, acyclovir 400 mg po tid for 7 days; for varicella zoster, famciclovir 500 mg po tid or valacyclovir 1 g po tid for 7 days).

Treatment of acute nonulcerative blepharitis begins with avoiding the offending action (eg, rubbing) or substance (eg, new eye drops). Warm compresses over the closed eyelid may relieve symptoms and speed resolution. If swelling persists > 24 h, topical corticosteroids (eg, fluorometholone ophthalmic ointment 0.1% tid for 7 days) can be used.

Chronic: The initial treatment for both meibomian gland dysfunction and seborrheic blepharitis is directed toward the secondary keratoconjunctivitis sicca (see p. 592). Tear supplements, bland ointments at night, and, if necessary, punctal plugs (inserts that obstruct the puncta and thus decrease tear drainage) are effective in most patients.

If needed, additional treatment for meibomian gland dysfunction includes warm compresses to melt the waxy plugs and occasionally eyelid massage to extrude trapped secretions and coat the ocular surface. A tetracycline (eg, doxycycline 100 mg po bid tapered over 3 to 4 mo) may also be effective because it changes the composition of meibomian gland secretions.

If needed, additional treatment for seborrheic blepharitis includes gentle cleansing of the eyelid margin 2 times a day with a cotton swab dipped in a dilute solution of baby shampoo (2 to 3 drops in 1/2 cup of warm water). A topical antibiotic ointment (bacitracin/polymyxin B or sulfacetamide 10% bid for up to 3 mo) may be added to reduce bacterial counts on the eyelid margin when cases are unresponsive to weeks of eyelid hygiene.

Blepharospasm

Blepharospasm is spasm of muscles around the eye causing involuntary blinking and eye closing.

The cause of blepharospasm is most often unknown. It affects women more than men and tends to occur in families. Blepharospasm may be secondary to eye disorders, including those that cause ocular irritation (eg, trichiasis, corneal foreign body, keratoconjunctivitis sicca) and systemic neurologic diseases that cause spasm (eg, Parkinson's disease).

Symptoms are involuntary blinking and closing of the eyes; in severe cases, people cannot open their eyes. Spasms may be made worse by fatigue, bright light, and anxiety.

Treatment involves injecting botulinum toxin type A into the eyelid muscles; treatment must be repeated in
most instances. Anxiolytics may help. Surgery to cut the periorbital muscles is also effective but, because of potential complications, is considered only if botulinum toxin is ineffective. Sunglasses help decrease the light sensitivity that may cause or accompany blepharospasm.

Canaliculitis

Canaliculitis is inflammation of the canaliculus (see Fig. 60-3 on p. 567).

The most common cause is infection with *Actinomyces israelii*, a gram-positive bacillus with fine branching filaments, but other bacteria, fungi (eg, *Candida albicans*), and viruses (eg, herpes simplex) may be causative. Symptoms and signs are tearing, discharge, red eye (especially nasally), and mild tenderness over the involved side.

Diagnosis is suspected based on symptoms and signs, expression of turbid secretions with pressure over the lacrimal sac, and a gritty sensation caused by necrotic material that can be felt during probing of the lacrimal system. Canaliculitis can be differentiated from dacryocystitis. In canaliculitis, the punctum and canaliculus are red and swollen; in dacryocystitis, the punctum and canaliculus are normal, but a red, swollen, tender mass is located in or near the lacrimal sac.

Treatment is warm compresses, irrigation of the canaliculus with antibiotic solution (by an ophthalmologist), and removal of any concretions, which usually requires surgery. Antibiotic selection is usually empiric with a 1st-generation cephalosporin or penicillinase-resistant synthetic penicillin but may be guided by irrigation samples.

Chalazion and Hordeolum

Chalazia and hordeola are sudden-onset localized swellings of the eyelid. A chalazion is caused by noninfectious meibomian gland occlusion, whereas a hordeolum is caused by infection. Both conditions initially cause eyelid hyperemia and edema, swelling, and pain. With time, a chalazion becomes a small nontender nodule in the eyelid center, whereas a hordeolum remains painful and localizes to an eyelid margin. Diagnosis is clinical. Treatment is with hot compresses. Both conditions improve spontaneously, but incision or, for chalazia, intralesional corticosteroids may be used to hasten resolution.

Chalazion: A chalazion is noninfectious obstruction of a meibomian gland causing extravasation of irritating lipid material in the eyelid soft tissues with focal secondary granulomatous inflammation (see Plate 7). Disorders that cause abnormally thick meibomian gland secretions (eg, meibomian gland dysfunction, acne rosacea) increase the risk of meibomian gland obstruction.

Hordeolum: A hordeolum (stye) is an acute, localized, pyogenic (usually staphylococcal) infection or abscess of the eyelid that may be external or internal (see Plate 16). Most hordeola are external and result from obstruction and infection of an eyelash follicle and adjacent glands of Zeis or Moll's glands. Follicle obstruction may be associated with blepharitis. An internal hordeolum, which is very rare, results from infection of a meibomian gland. Sometimes cellulitis accompanies hordeola.

Symptoms and Signs

Chalazia and hordeola each cause eyelid redness, swelling, and pain.

Chalazion: After 1 or 2 days, a chalazion localizes to the body of the eyelid. Typically, a small nontender nodule or lump develops. A chalazion usually drains through the inner surface of the eyelid or is absorbed spontaneously over 2 to 8 wk; rarely, it persists longer. Vision may be slightly blurred.

Hordeolum: After 1 to 2 days, an external hordeolum localizes to the eyelid margin. There may be tearing, photophobia, and a foreign body sensation. Typically, a small yellowish pustule develops at the base of an eyelash, surrounded by hyperemia, induration, and diffuse edema. Within 2 to 4 days, the
lesion ruptures and discharges pus, thereby relieving pain and resolving the lesion.

Symptoms of an internal hordeolum are the same as those of a chalazion, with pain, redness, and edema localized to the posterior tarsal conjunctival surface. Inflammation may be severe, sometimes with fever or chills. Inspection of the tarsal conjunctivae shows a small elevation or yellow area at the site of the affected gland. Later, an abscess forms. Spontaneous rupture is rare; however, when it does occur, it usually occurs on the conjunctival side of the eyelid and sometimes erupts through the skin side. Recurrence is common.

**Diagnosis**

- Clinical assessment

Diagnosis of chalazion and both kinds of hordeola is clinical; however, during the first 2 days, they may be clinically indistinguishable. Because internal hordeola are so rare, they are not usually suspected unless inflammation is severe or fever or chills are present. If the chalazion or hordeolum lies near the inner canthus of the lower eyelid, it must be differentiated from dacryocystitis (see below), which can usually be excluded by noting the location of maximum induration and tenderness (eg, eyelid for a chalazion, under the medial canthus near the side of the nose for dacryocystitis). Chronic chalazia that do not respond to treatment require biopsy to exclude tumor of the eyelid.

**Treatment**

- Hot compresses
- Sometimes drainage or drug therapy

Hot compresses for 5 to 10 min 2 or 3 times a day can be used to hasten resolution of chalazia and external hordeola.

**Chalazion**: Incision and curettage or intrachalazion corticosteroid therapy (0.05 to 0.2 mL triamcinolone 25 mg/mL) may be indicated if chalazia are large, unsightly, and persist for more than several weeks despite conservative therapy.

**Hordeolum**: An external hordeolum that does not respond to hot compresses can be incised with a sharp, fine-tipped blade. Systemic antibiotics (eg, dicloxacillin or erythromycin 250 mg po qid) are indicated when cellulitis accompanies a hordeolum.

Treatment of internal hordeola is oral antibiotics and incision and drainage if needed. Topical antibiotics are usually ineffective.

**Dacryocystitis**

**Dacryocystitis is infection of the lacrimal sac, usually with staphylococcal or streptococcal species and usually as a consequence of nasolacrimal duct obstruction.**

In acute dacryocystitis, the patient presents with pain, redness, and edema around the lacrimal sac. Diagnosis is suspected based on symptoms and signs and when pressure over the lacrimal sac causes reflux of mucoid material through the puncta. Initial treatment is with warm compresses and oral antibiotics for mild cases or IV antibiotics for more severe cases. The antibiotic is usually a 1st-generation cephalosporin or penicillinase-resistant synthetic penicillin. If the infection does not respond as expected, consideration should be given to methicillin-resistant *Staphylococcus aureus* (MRSA), and antibiotics changed accordingly. The abscess can be drained and the antibiotics can be changed based on culture results if the initial antibiotic proves ineffective.

Patients with chronic dacryocystitis usually present with a mass under the medial canthal tendon and chronic conjunctivitis. Definitive treatment for resolved acute dacryocystitis or chronic conjunctivitis is usually surgery that creates a passage between the lacrimal sac and the nasal cavity.
Dacryostenosis

Dacryostenosis is obstruction or stenosis of the nasolacrimal duct, causing excess tearing.

Nasolacrimal obstruction may be congenital or acquired. One cause of congenital obstruction is inadequate development of any part of the nasolacrimal ducts. Typically, a membrane at the distal end of the nasolacrimal duct persists. There is tearing and purulent discharge; the condition may manifest as chronic conjunctivitis, usually beginning after the age of 2 wk (most often at age 3 to 12 wk).

Causes of acquired nasolacrimal duct obstruction are listed in Table 62-1. The cause is most often age-related stenosis of the nasolacrimal duct. Other causes include past nasal or facial bone fractures and sinus surgery, which disrupt the nasolacrimal duct; inflammatory diseases (e.g., sarcoidosis, Wegener's granulomatosis); and dacryocystitis.

Causes of punctal or canalicular stenosis include chronic conjunctivitis (especially herpetic), certain types of chemotherapy, adverse reactions to eye drops (especially topical echothiophate iodide), and radiation.

Diagnosis

Diagnosis is usually based on clinical criteria. Sometimes ophthalmologists probe and irrigate the lacrimal drainage system with saline, with or without fluorescein dye. Reflux indicates stenosis.

Treatment

Congenital nasolacrimal duct obstruction often resolves spontaneously by about age 6 to 9 mo; before 1 yr, manual compression of the lacrimal sac 4 or 5 times/day may relieve the obstruction. After 1 yr, the nasolacrimal duct may need probing, usually under general anesthesia; if obstruction is recurrent, a temporary silastic tube may be inserted.

[Table 62-1. Causes of Acquired Nasolacrimal Duct Obstruction]

In acquired nasolacrimal duct obstruction, the underlying disorder is treated when possible. If treatment is not possible or is ineffective, a passage between the lacrimal sac and the nasal cavity can be created surgically (dacryocystorhinostomy).

In cases of punctal or canalicular stenosis, dilation is usually curative. If canalicular stenosis is severe and bothersome, a surgical procedure that places a glass tube (Jones tube) leading from the caruncle into the nasal cavity can be considered.

Entropion and Ectropion


Entropion: Entropion (inversion of an eyelid) is caused by age-related tissue relaxation, postinfectious or posttraumatic changes, or blepharospasm. Eyelashes rub against the eyeball and may lead to corneal ulceration and scarring. Symptoms can include foreign body sensation, tearing, and red eye. Diagnosis is clinical. Definitive treatment is surgery.

Ectropion: Ectropion (eversion of the lower eyelid—see Plate 12) is caused by age-related tissue relaxation, cranial nerve VII palsy, and posttraumatic or postsurgical changes. Symptoms are tearing (due to poor drainage of tears through the nasolacrimal system, which may no longer contact the eyeball) and symptoms of dry eyes (see p. 592), possibly due to inadequate blinking. Diagnosis is clinical. Symptomatic treatment can include tear supplements and, at night, ocular lubricants; definitive treatment is surgery.

Trichiasis
Trichiasis is an anatomic misalignment of eyelashes, which rub against the eyeball, in a patient with no entropion.

Trichiasis is most often idiopathic, but known causes include blepharitis, posttraumatic and postsurgical changes, conjunctival scarring (eg, secondary to cicatricial pemphigoid, atopic keratoconjunctivitis, Stevens-Johnson syndrome, or chemical injury), epiblepharon (an extra lower eyelid skinfold that directs lashes into a vertical position), and distichiasis (a congenital extra row of eyelashes). Corneal ulceration and scarring can occur in chronic cases. Symptoms are foreign body sensation, tearing, and red eye. Diagnosis is usually clinical. Trichiasis differs from entropion in that the eyelid position is normal. Evaluation includes fluorescein staining to exclude corneal abrasion or ulceration. Treatment is eyelash removal with forceps. If eyelashes grow back, electrolysis or cryosurgery is more effective at permanently preventing recurrence.

**Tumors**

The skin of the eyelids is a common site for growth of benign and malignant tumors.

**Xanthelasma:** Xanthelasma is a common, benign deposit of yellow-white flat plaques of lipid material that occur subcutaneously on the upper and lower eyelids. Although some people with xanthelasmas have dyslipidemias, most do not. Diagnosis is by appearance. No treatment is necessary, although xanthelasmas can be removed for cosmetic reasons, and underlying dyslipidemias should be treated.

**Basal cell carcinoma:** This skin cancer frequently occurs at the eyelid margins, at the inner canthus, and on the upper cheek (see also p. [749](#)). Metastasis is rare. Biopsy establishes the diagnosis. Treatment is surgical excision using conventional techniques or by Mohs' surgery.

**Other malignant tumors:** These types of tumors are less common; they include squamous cell carcinoma, meibomian gland carcinoma, and melanomas. Eyelid tumors may simulate chronic blepharitis or chronic chalazion. Therefore, chronic blepharitis, chronic chalazion, or similar lesions should be biopsied if unresponsive to initial treatment.
Chapter 63. Conjunctival and Scleral Disorders

Introduction

The conjunctiva lines the back of the eyelids (palpebral or tarsal conjunctiva), crosses the space between the lid and the globe (forniceal conjunctiva), then folds back on itself as it spreads over the sclera to the cornea (bulbar conjunctiva). The conjunctiva helps maintain the tear film and protect the eye from foreign objects and infection.

The sclera is the thick white sphere of dense connective tissue that encloses the eye and maintains its shape. Anteriorly, the sclera fuses with the cornea, and posteriorly it blends with the meninges where the optic nerve penetrates the globe.

The episclera is a thin vascular membrane between the conjunctiva and the sclera.

The most common disorders are inflammatory (eg, conjunctivitis, episcleritis, scleritis). Conjunctivitis can be acute or chronic and is infectious, allergic, or irritant in origin. Scleritis usually results from immune-mediated disease and episcleritis often does as well. Episcleritis usually does not threaten vision, but scleritis can destroy vision and the eye. Major symptoms of conjunctivitis (eg, conjunctival hyperemia) are similar. Early, accurate diagnosis is important.

Select eye findings in conjunctival disorders: Edema of the bulbar conjunctiva results in a translucent, bluish, thickened conjunctiva. Gross edema with ballooning of the conjunctiva, often leading to prolapse of conjunctiva, is known as chemosis.

Edema of the tarsal conjunctiva (typical of allergic conjunctivitis) results in fine, minute projections (papillae), giving the conjunctiva a velvety appearance.

Hyperplasia of lymphoid follicles in the conjunctiva can occur in viral or chlamydial conjunctivitis. It appears as small bumps with pale centers, resembling cobblestones. It occurs most commonly in the inferior tarsal conjunctiva.

Cicatricial Pemphigoid

(Cicatricial Pemphigoid; Benign Mucous Membrane Pemphigoid; Mucous Membrane Pemphigoid; Ocular Cicatricial Pemphigoid)

Cicatricial pemphigoid is a chronic, bilateral, progressive scarring and shrinkage of the conjunctiva with opacification of the cornea. Early symptoms are hyperemia, discomfort, itching, and discharge; progression leads to eyelid and corneal damage and sometimes blindness. Diagnosis may be confirmed by biopsy, but biopsy is often not necessary. Treatment may require systemic immunosuppression.

Cicatricial pemphigoid is an autoimmune disease in which binding of anticonjunctival basement membrane antibodies results in conjunctival inflammation. It is unrelated to bullous pemphigoid.

Symptoms and Signs

Usually beginning as a chronic conjunctivitis, the condition progresses to symblepharon (adhesion between the tarsal and bulbar conjunctiva); trichiasis (in-turning eyelashes); keratoconjunctivitis sicca; corneal neovascularization, opacification, and keratinization; and conjunctival shrinkage and keratinization. Chronic corneal epithelial defects can lead to secondary bacterial ulceration, scarring, and blindness. Oral mucous membrane involvement with ulceration and scarring is common, but skin involvement, characterized by scarring bullae and erythematous plaques, is uncommon.

Diagnosis

• Unexplained symblepharon or biopsy findings
Diagnosis is suspected clinically in patients with conjunctival scarring plus corneal changes, symblepharon, or both. The differential diagnosis of progressive conjunctival scarring includes postradiation and atopic disease. Therefore, the clinical diagnosis of cicatricial pemphigoid is made when there is progression of symblepharon without a history of local radiation or severe perennial allergic conjunctivitis. Diagnosis can be confirmed by conjunctival biopsy showing antibody deposition on the basement membrane.

**Treatment**

- Epilation of in-turning lashes
- Sometimes systemic immunosuppression

Tear substitutes and epilation, cryoepilation, or electroepilation of the in-turning eyelashes may increase patient comfort and reduce the risk of ocular infection and secondary scarring. For progressive scarring or corneal opacification or for nonhealing corneal epithelial defects, systemic immunosuppression with dapsone or cyclophosphamide is indicated.

**Conjunctivitis**

**Conjunctival inflammation typically results from infection, allergy, or irritation. Symptoms are conjunctival hyperemia and ocular discharge and, depending on the etiology, discomfort and itching. Diagnosis is clinical; sometimes cultures are indicated. Treatment depends on etiology and may include topical antibiotics, antihistamines, mast cell stabilizers, and corticosteroids.**

Infectious conjunctivitis is most commonly viral or bacterial and is contagious. Rarely, mixed or unidentifiable pathogens are present. Numerous allergens can cause allergic conjunctivitis (see p. 584). Nonallergic conjunctival irritation can result from foreign bodies; wind, dust, smoke, fumes, chemical vapors, and other types of air pollution; and intense ultraviolet light of electric arcs, sunlamps, and reflection from snow.

Conjunctivitis is typically acute, but both infectious and allergic conditions can be chronic. Conditions that cause chronic conjunctivitis include ectropion, entropion, blepharitis, and chronic dacryocystitis.

**Symptoms and Signs**

Any source of inflammation causes lacrimation or discharge and diffuse conjunctival vascular dilation. Discharge may cause the eyes to crust overnight. Thick discharge may blur vision, but once discharge is cleared, visual acuity should be unaffected.

Itching and watery discharge predominate in allergic conjunctivitis. Chemosis and papillary hyperplasia also suggest allergic conjunctivitis. Irritation or foreign body sensation, photophobia, and discharge suggest infectious conjunctivitis; purulent discharge suggests a bacterial cause. Severe eye pain suggests scleritis (see p. 587).

**Diagnosis**

- Clinical evaluation
- Sometimes culture

Usually, diagnosis is made by history and examination (see also Table 63-1), usually including slit-lamp examination with fluorescein staining of the cornea and, if glaucoma is suspected, measurement of intraocular pressure.

Other disorders can cause a red eye (see p. 563). Deep pain in the affected eye when a light is shone in the unaffected eye (true photophobia) does not occur in uncomplicated conjunctivitis and suggests a disorder of the cornea or anterior uveal tract. Circumcorneal conjunctival hyperemia (sometimes
described as ciliary flush) is caused by dilated, fine, straight, deep vessels that radiate out 1 to 3 mm from the limbus, without significant hyperemia of the bulbar and tarsal conjunctivae. Ciliary flush occurs with uveitis, acute glaucoma, and some types of keratitis.

The cause of conjunctivitis is suggested by clinical findings. However, cultures are indicated for patients with severe symptoms, immunocompromise, a vulnerable eye (eg, after a corneal transplant, in exophthalmos due to Graves' disease), or ineffective initial therapy.

Clinical differentiation between viral and bacterial infectious conjunctivitis is not highly accurate. However, temporarily missing some cases of mild bacterial conjunctivitis is not likely to be harmful because the infection often resolves spontaneously and antibiotics can be prescribed if symptoms persist.

Treatment

- Prevention of spread

- Treatment of symptoms

Most infectious conjunctivitis is highly contagious and spreads by droplet, fomites, and hand-to-eye inoculation. To avoid transmitting infection, physicians must wash their hands thoroughly and disinfect equipment after examining patients. Patients should wash their hands thoroughly after touching their eyes or nasal secretions, avoid touching the noninfected eye after touching the infected eye, avoid sharing towels or pillows, and avoid swimming in pools. Eyes should be kept free of discharge and should not be patched. Small children with conjunctivitis should be kept home from school to avoid spread. Cool washcloths applied to the eyes may help relieve local burning and itching. Antimicrobials are used for certain infections.

Viral Conjunctivitis

Viral conjunctivitis is a highly contagious acute conjunctival infection usually caused by adenovirus. Symptoms include irritation, photophobia, and watery discharge. Diagnosis is clinical. Infection is self-limited, but severe cases sometimes require topical corticosteroids.

Etiology

Conjunctivitis may accompany the common cold and other systemic viral infections (especially measles, but also chickenpox, rubella, and mumps). Isolated viral conjunctivitis usually results from adenoviruses and sometimes enteroviruses.

Epidemic keratoconjunctivitis usually results from adenovirus serotypes Ad 5, 8, 11, 13, 19, and 37. Pharyngoconjunctival fever usually results from serotypes Ad 3, 4, and 7. Outbreaks of acute hemorrhagic conjunctivitis, a rare conjunctivitis associated with infection by enterovirus type 70, have occurred in Africa and Asia.

Symptoms and Signs

After an incubation period of about 5 to 12 days, conjunctival hyperemia, watery discharge, and ocular irritation usually begin in one eye and spread rapidly to the other. Follicles may be present on the palpebral conjunctiva. A preauricular lymph node is often enlarged and painful. Many patients have had contact with someone with conjunctivitis, a recent URI, or both.

In severe adenoviral conjunctivitis, patients may have photophobia and foreign body sensation. Chemosis may be present. Pseudomembranes of fibrin and inflammatory cells on the tarsal conjunctiva, focal corneal inflammation, or both may blur vision. Even after conjunctivitis has resolved, residual corneal subepithelial opacities (multiple, coin-shaped, 0.5 to 1.0 mm in diameter) may be visible with a slit lamp for up to 2 yr. Corneal opacities occasionally result in decreased vision and significant glare.
Diagnosis

• Clinical evaluation

Diagnosis of conjunctivitis and differentiation between bacterial, viral, and noninfectious conjunctivitis are usually clinical; special tissue cultures are necessary for growth of the virus but are rarely indicated. Features that may help differentiate between viral and bacterial conjunctivitis can include purulence of eye discharge, presence of preauricular lymphadenopathy, and, in epidemic keratoconjunctivitis, chemosis. Patients with photophobia are stained with fluorescein and examined with a slit lamp. Epidemic keratoconjunctivitis may cause punctate corneal staining. Secondary bacterial infection of viral conjunctivitis is rare. However, if any signs suggest bacterial conjunctivitis (eg, purulent discharge), smears from the eye may be examined microscopically and cultured for bacteria.

Treatment

• Supportive measures

Viral conjunctivitis is highly contagious, and transmission precautions must be followed (as described previously). Children should generally be kept out of school until resolution.

Viral conjunctivitis is self-limiting, lasting 1 wk in mild cases to up to 3 wk in severe cases. It requires only warm or cool compresses for symptomatic relief. However, patients who have severe photophobia or whose vision is affected may benefit from topical corticosteroids (eg, 1% prednisolone acetate q 6 to 8 h). Corticosteroids, if prescribed, are usually prescribed by an ophthalmologist. Herpes simplex keratitis (see p. 589) must be ruled out first (by fluorescein staining and slit-lamp examination) because corticosteroids can exacerbate it.

Acute Bacterial Conjunctivitis

Acute conjunctivitis can be caused by numerous bacteria. Symptoms are hyperemia, lacrimation, irritation, and discharge. Diagnosis is clinical. Treatment is with topical antibiotics, augmented by systemic antibiotics in more serious cases.

Most bacterial conjunctivitis is acute; chronic bacterial conjunctivitis may be caused by Chlamydia and rarely Moraxella. Chlamydial conjunctivitis includes trachoma and adult or neonatal inclusion conjunctivitis.

Etiology

Bacterial conjunctivitis is usually caused by Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus sp, or, less commonly, Chlamydia trachomatis (see p. 583). Neisseria gonorrhoeae causes gonococcal conjunctivitis, which usually results from sexual contact with a person who has a genital infection.

Ophthalmia neonatorum (see also p. 2824) is conjunctivitis that occurs in 20 to 40% of neonates delivered through an infected birth canal. It can be caused by maternal gonococcal or chlamydial infection.

Symptoms and Signs

Symptoms are typically unilateral but frequently spread to the opposite eye within a few days. Discharge is typically purulent.

The bulbar and tarsal conjunctivae are intensely hyperemic and edematous. Petechial subconjunctival hemorrhages, chemosis, photophobia, and an enlarged preauricular lymph node are typically absent. Eyelid edema is often moderate.
With adult gonococcal conjunctivitis, symptoms develop 12 to 48 h after exposure. Severe eyelid edema, chemosis, and a profuse purulent exudate are typical. Rare complications include corneal ulceration, abscess, perforation, panophthalmitis, and blindness.

Ophthalmia neonatorum caused by gonococcal infection appears 2 to 5 days after delivery. With ophthalmia neonatorum caused by a chlamydial infection, symptoms appear within 5 to 14 days. Symptoms of both are bilateral, intense papillary conjunctivitis with lid edema, chemosis, and mucopurulent discharge.

**Diagnosis**

- Clinical evaluation

Diagnosis of conjunctivitis and differentiation between bacterial, viral, and noninfectious conjunctivitis are usually clinical. Smears and bacterial cultures should be done in patients with severe symptoms, immunocompromise, ineffective initial therapy, or a vulnerable eye (eg, after a corneal transplant, in exophthalmos due to Graves’ disease). Smears and conjunctival scrapings should be examined microscopically and stained with Gram stain to identify bacteria and stained with Giemsa stain to identify the characteristic epithelial cell basophilic cytoplasmic inclusion bodies of chlamydial conjunctivitis.

**Treatment**

- Antibiotics (topical for all causes except gonococcal)

Bacterial conjunctivitis is very contagious, and standard infection control measures (see p. 581) should be followed.

If neither gonococcal nor chlamydial infection is suspected, most clinicians treat presumptively with moxifloxacin 0.5% drops tid for 7 to 10 days or another fluoroquinolone or trimethoprim/polymyxin B qid. A poor clinical response after 2 or 3 days indicates that the cause is resistant bacteria, a virus, or an allergy. Culture and sensitivity studies determine subsequent treatment.

Adult gonococcal conjunctivitis requires a single dose of ceftriaxone 1 g IM. Fluoroquinolones are no longer recommended because resistance is now widespread. Bacitracin 500 U/g or gentamicin 0.3% ophthalmic ointment instilled into the affected eye q 2 h may be used in addition to systemic treatment. Sex partners should also be treated. Because chlamydial genital infection is often present in patients with gonorrhea, patients should also receive a single dose of azithromycin 1 g or doxycycline 100 mg po bid for 7 days.

Ophthalmia neonatorum is prevented by the routine use of silver nitrate eye drops or erythromycin ointment at birth. Infections that develop despite this treatment require systemic treatment. For gonococcal infection, ceftriaxone 25 to 50 mg/kg IV or IM is given once/day for 7 days. Chlamydial infection is treated with erythromycin 12.5 mg/kg po or IV qid for 14 days. The parents should also be treated.

**Adult Inclusion Conjunctivitis**

(About Chlamydial Conjunctivitis; Swimming Pool Conjunctivitis)

Adult inclusion conjunctivitis is caused by sexually transmitted *Chlamydia trachomatis*. Symptoms include chronic unilateral hyperemia and mucopurulent discharge. Diagnosis is clinical. Treatment is with systemic antibiotics.

Adult inclusion conjunctivitis is caused by *Chlamydia trachomatis* serotypes D through K. In most instances, adult inclusion conjunctivitis results from sexual contact with a person who has a genital infection. Usually, patients have acquired a new sex partner in the preceding 2 mo. Rarely, adult inclusion conjunctivitis is acquired from contaminated, incompletely chlorinated swimming pool water.
Symptoms and Signs

Adult inclusion conjunctivitis has an incubation period of 2 to 19 days. Most patients have a unilateral mucopurulent discharge. The tarsal conjunctiva is often more hyperemic than the bulbar conjunctiva. Characteristically, there is a marked tarsal follicular response. Occasionally, superior corneal opacities and vascularization occur. Preauricular lymph nodes may be swollen on the side of the involved eye. Often, symptoms have been present for many weeks or months and have not responded to topical antibiotics.

Diagnosis

• Clinical evaluation

• Laboratory testing

Chronicity, mucopurulent discharge, marked tarsal follicular response, and failure of topical antibiotics differentiate adult inclusion conjunctivitis from other bacterial conjunctivitides. Smears, bacterial cultures, and chlamydial studies should be done. Immunofluorescent staining techniques, PCR, and special cultures are used to detect C. trachomatis. Smears and conjunctival scrapings should be examined microscopically and stained with Gram stain to identify bacteria and stained with Giemsa stain to identify the characteristic epithelial cell basophilic cytoplasmic inclusion bodies of chlamydial conjunctivitis.

Treatment

• Antibiotics

Azithromycin 1 g po once only or either doxycycline 100 mg po bid or erythromycin 500 mg po qid for 1 wk cures the conjunctivitis and concomitant genital infection. Sex partners also require treatment.

Trachoma

(Egyptian Ophthalmia; Granular Conjunctivitis)

Trachoma is a chronic conjunctivitis caused by Chlamydia trachomatis and is characterized by progressive exacerbations and remissions. It is the leading cause of preventable blindness worldwide. Initial symptoms are conjunctival hyperemia, eyelid edema, photophobia, and lacrimation. Later, corneal neovascularization and scarring of the conjunctiva, cornea, and eyelids occur. Diagnosis is usually clinical. Treatment is with topical or systemic antibiotics.

Trachoma is endemic in poverty-stricken parts of North Africa, the Middle East, the Indian subcontinent, Australia, and Southeast Asia. The causative organism is Chlamydia trachomatis (serotypes A, B, Ba, and C). In the US, trachoma is rare, occurring occasionally among Native Americans and immigrants. The disease occurs mainly in children, particularly those between the ages of 3 and 6. Older children and adults are much less susceptible because of increased immunity and better personal hygiene. Trachoma is highly contagious in its early stages and is transmitted by eye-to-eye contact, hand-to-eye contact, eye-seeking flies, or the sharing of contaminated articles (eg, towels, handkerchiefs, eye makeup).

Symptoms and Signs

Trachoma usually affects both eyes. After an incubation period of about 7 days, conjunctival hyperemia, eyelid edema, photophobia, and lacrimation gradually appear, usually bilaterally. Small follicles develop in the upper tarsal conjunctiva 7 to 10 days later and gradually increase in size and number for 3 or 4 wk (see Plate 20). Inflammatory papillae appear on the upper tarsal conjunctiva, and corneal neovascularization begins during this stage, with invasion of the upper half of the cornea by loops of vessels from the limbus (called pannus). The stage of follicular/papillary hypertrophy and corneal neovascularization may last from several months to > 1 yr, depending on response to therapy. The entire cornea may ultimately be involved, reducing vision.
Without treatment, a cicatricial (scarring) stage follows. The follicles and papillae gradually shrink and are replaced by scar tissue that often causes entropion and lacrimal duct obstruction. Entropion leads to further corneal scarring and neovascularization. Secondary bacterial infection is common, contributing to scarring and disease progression. The corneal epithelium becomes dull and thickened, and lacrimation is decreased. Small corneal ulcers may appear at the site of peripheral corneal infiltrates, stimulating further neovascularization.

With treatment and healing, the conjunctiva becomes smooth and grayish white. Rarely, corneal neovascularization regresses completely without treatment, and corneal transparency is restored. Impaired vision or blindness occurs in about 5% of people with trachoma.

**Diagnosis**

- Clinical findings (eg, tarsal lymphoid follicles, linear conjunctival scars, corneal pannus)

Diagnosis is usually clinical because testing is rarely available in endemic areas. Lymphoid follicles on the tarsal plate or along the corneal limbus, linear conjunctival scarring, and corneal pannus are considered diagnostic in the appropriate clinical setting. If diagnosis is uncertain, *C. trachomatis* can be isolated in culture or identified by PCR and immunofluorescence techniques. In the early stage, minute basophilic cytoplasmic inclusion bodies within conjunctival epithelial cells in Giemsa-stained conjunctival scrapings differentiate trachoma from nonchlamydial conjunctivitis. Inclusion bodies are also found in adult inclusion conjunctivitis (see p. 583), but the setting and developing clinical picture distinguish it from trachoma. Palpebral vernal conjunctivitis appears similar to trachoma in its follicular hypertrophic stage, but symptoms are different, milky flat-topped papillae are present, and eosinophils (not basophilic inclusion bodies) are found in the scrapings.

**Treatment**

- Oral azithromycin

For individual or sporadic cases, azithromycin 20 mg/kg (maximum 1 g) po as a single dose is 78% effective. Alternatives are doxycycline 100 mg bid or tetracycline 250 mg qid for 4 wk. In hyperendemic areas, tetracycline or erythromycin ophthalmic ointment applied bid for 5 consecutive days each month for 6 mo has been effective as treatment and prophylaxis. Endemic trachoma has been dramatically reduced by using community-wide oral azithromycin in a single dose or in repeated doses. Reinfection due to re-exposure is common among endemic areas. Better personal hygiene and environmental measures (eg, access to potable water) can reduce reinfection.

Eyelid deformities (eg, entropion) should be treated surgically.

**Allergic Conjunctivitis**

*(Atopic Conjunctivitis; Atopic Keratoconjunctivitis; Hay Fever Conjunctivitis; Perennial Allergic Conjunctivitis; Seasonal Allergic Conjunctivitis; Vernal Keratoconjunctivitis)*

Allergic conjunctivitis is an acute, intermittent, or chronic conjunctival inflammation usually caused by airborne allergens. Symptoms include itching, lacrimation, discharge, and conjunctival hyperemia. Diagnosis is clinical. Treatment is with topical antihistamines and mast cell stabilizers.

**Etiology**

Allergic conjunctivitis is due to a type I hypersensitivity reaction to a specific antigen.

**Seasonal allergic conjunctivitis** (hay fever conjunctivitis) is caused by airborne pollen of trees, grasses, or weeds. It tends to peak during the spring, late summer, or early fall and disappear during the winter months—corresponding to the life cycle of the causative plant.
Perennial allergic conjunctivitis (atopic conjunctivitis, atopic keratoconjunctivitis) is caused by dust mites, animal dander, and other nonseasonal allergens. These allergens, particularly those in the home, tend to cause symptoms year-round.

Vernal keratoconjunctivitis is a more severe type of conjunctivitis most likely allergic in origin. It is most common among males aged 5 to 20 who also have eczema, asthma, or seasonal allergies. Vernal conjunctivitis typically reappears each spring and subsides in the fall and winter. Many children outgrow the condition by early adulthood.

Symptoms and Signs

General: Patients report bilateral mild to intense ocular itching, conjunctival hyperemia, photosensitivity (photophobia in severe cases), eyelid edema, and watery or stringy discharge. Concomitant rhinitis is common. Many patients have other atopic diseases, such as eczema, allergic rhinitis, or asthma.

Findings characteristically include conjunctival edema and hyperemia and a discharge. The bulbar conjunctiva may appear translucent, bluish, and thickened. Chemosis and a characteristic boggy blepharedema of the lower eyelid are common. Chronic itching can lead to chronic eyelid rubbing, periocular hyperpigmentation, and dermatitis.

Seasonal and perennial conjunctivitis: Fine papillae on the upper tarsal conjunctiva give it a velvety appearance. In more severe forms, larger tarsal conjunctival papillae, conjunctival scarring, corneal neovascularization, and corneal scarring with variable loss of visual acuity can occur.

Vernal keratoconjunctivitis: Usually, the palpebral conjunctiva of the upper eyelid is involved, but the bulbar conjunctiva is sometimes affected. In the palpebral form, square, hard, flattened, closely packed, pale pink to grayish cobblestone papillae are present, chiefly in the upper tarsal conjunctiva (see Plate 8). The uninvolved tarsal conjunctiva is milky white. In the bulbar (limbal) form, the circumcorneal conjunctiva becomes hypertrophied and grayish. Discharge may be tenacious and mucoid, containing numerous eosinophils.

Occasionally, a small, circumscribed loss of corneal epithelium occurs, causing pain and increased photophobia. Other corneal changes (eg, central plaques) and white limbal deposits of eosinophils (Trantas’ dots) may be seen.

Diagnosis

The diagnosis is usually clinical. Eosinophils are present in conjunctival scrapings, which may be taken from the lower or upper tarsal conjunctiva; however, such testing is rarely indicated.

Treatment

• Symptomatic measures

• Topical antihistamines, vasoconstrictors, NSAIDs, mast cell stabilizers, or a combination

• Topical corticosteroids or cyclosporine for recalcitrant cases

Avoidance of known allergens and use of tear supplements can reduce symptoms; antigen desensitization is occasionally helpful. Topical OTC antihistamine/vasoconstrictors (eg, naphazoline/pheniramine) are useful for mild cases. If these drugs are insufficient, topical prescription antihistamines (eg, olopatadine, ketotifen), NSAIDs (eg, ketorolac), or mast cell stabilizers (eg, pemirolast, nedocromil, azelastine) can be used separately or in combination. Topical corticosteroids (eg, loteprednol, fluorometholone 0.1%, prednisolone acetate 0.12% to 1% drops tid) can be useful in recalcitrant cases. Because topical corticosteroids can exacerbate ocular herpes simplex virus infections, possibly leading to corneal ulceration and perforation and, with long-term use, to glaucoma and possibly cataracts, their use should be initiated and monitored by an ophthalmologist. Topical cyclosporine may be indicated when...
Corticosteroids are needed but cannot be used.

Seasonal allergic conjunctivitis is less likely to require multiple drugs or intermittent topical corticosteroids.

**Other Conjunctival Disorders**

**Pinguecula and pterygium:** These lesions are benign growths of the conjunctiva that can result from chronic actinic irritation. Both typically appear adjacent to the cornea at the 3-o'clock position, the 9-o'clock position, or both (see Fig. 63-1).

A pinguecula is a raised yellowish white mass on the bulbar conjunctiva, adjacent to the cornea. It does not tend to grow onto the cornea. However, it may cause irritation or cosmetic blemish and, although rarely necessary, can easily be removed.

A pterygium is a fleshy triangular growth of bulbar conjunctiva that may spread across and distort the cornea, induce astigmatism, and change the refractive power of the eye. Symptoms may include decreased vision and foreign body sensation. It is more common in hot, dry climates. Removal is often indicated for cosmesis, to reduce irritation, and to improve or preserve vision.

**Subconjunctival hemorrhages:** These extravasations of blood beneath the conjunctiva usually result from minor trauma, straining, sneezing, or coughing; rarely, they occur spontaneously. The extent and location of hyperemia can help determine etiology. Diffuse hyperemia of the bulbar and tarsal conjunctivae is typical of conjunctivitis. Subconjunctival hemorrhages alarm the patient but are of no pathologic significance except when associated with blood dyscrasias, which is rare, or other facial or ocular injuries. They are absorbed spontaneously, usually within 2 wk. Topical corticosteroids, antibiotics, vasoconstrictors, and compresses do not speed reabsorption; reassurance is adequate therapy.

**Episcleritis**

Episcleritis is self-limiting, recurring, idiopathic inflammation of the episcleral tissue that does not threaten vision. Symptoms are a localized area of hyperemia of the globe, irritation, and lacrimation. Diagnosis is clinical. Treatment is symptomatic.

Episcleritis occurs in young adults, more commonly among women. It is usually idiopathic; it can be associated with connective tissue diseases and rarely with serious systemic diseases.

Mild irritation occurs. Additionally, a bright red patch is present just under the bulbar conjunctiva (simple episcleritis). A hyperemic, edematous, raised nodule (nodular episcleritis) may also be present. The palpebral conjunctiva is normal.

Episcleritis is distinguished from conjunctivitis because hyperemia is localized to a limited area of the globe and lacrimation is much less. It is distinguished from scleritis by lack of photophobia and lack of severe pain.

The condition is self-limited, and a diagnostic assessment for systemic disorders is not routinely warranted. A topical corticosteroid (eg, prednisolone acetate, 1% drops qid for 5 days, gradually reduced over 3 wk) or an oral NSAID usually shortens the attack; corticosteroids are usually prescribed by an ophthalmologist. Topical vasoconstrictors (eg, tetrahydrozoline) to improve appearance are optional.

[Fig. 63-1. Pinguecula and pterygium.]

**Scleritis**

Scleritis is a severe, destructive, vision-threatening inflammation involving the deep episclera and sclera. Symptoms are moderate to marked pain, hyperemia of the globe, lacrimation, and photophobia. Diagnosis is clinical. Treatment is with systemic corticosteroids and possibly immunosuppressants.
Scleritis is most common among women aged 30 to 50 yr, and many have connective tissue diseases, such as RA, SLE, polyarteritis nodosa, Wegener's granulomatosis, or relapsing polychondritis. A few cases are infectious in origin. About half of the cases of scleritis have no known cause. Scleritis most commonly involves the anterior segment and occurs in 3 types—diffuse, nodular, and necrotizing (scleromalacia perforans).

**Symptoms and Signs**

Pain (often characterized as a deep, boring ache) is severe enough to interfere with sleep and appetite. Photophobia and lacrimation may occur. Hyperemic patches develop deep beneath the bulbar conjunctiva and are more violaceous than those of episcleritis or conjunctivitis. The palpebral conjunctiva is normal. The involved area may be focal (usually one quadrant of the globe) or involve the entire globe and may contain a hyperemic, edematous, raised nodule (nodular scleritis) or an avascular area (necrotizing scleritis). Posterior scleritis is less common and is less likely to cause red eye but more likely to cause blurred or decreased vision.

In severe cases of necrotizing scleritis, perforation of the globe and loss of the eye may result. Connective tissue disease occurs in 20% of patients with diffuse or nodular scleritis and in 50% of patients with necrotizing scleritis. Necrotizing scleritis in patients with connective tissue disease signals underlying systemic vasculitis.

**Diagnosis**

Diagnosis is made clinically and by slit-lamp examination. Smears or rarely biopsies are necessary to confirm infectious scleritis. CT or ultrasonography may be needed for posterior scleritis.

**Prognosis**

Of patients with scleritis, 14% lose significant visual acuity within 1 yr, and 30% lose significant visual acuity within 3 yr. Patients with necrotizing scleritis and underlying systemic vasculitis have a mortality rate of up to 50% in 10 yr (mostly due to MI).

**Treatment**

- **Systemic corticosteroids**

Occasionally, NSAIDs are sufficient for mild cases. However, usually a systemic corticosteroid (eg, prednisone 1 mg/kg po once/day) is the initial therapy. If patients are unresponsive to or intolerant of systemic corticosteroids or have necrotizing scleritis and connective tissue disease, systemic immunosuppression with cyclophosphamide or azathioprine is indicated, but only in consultation with a rheumatologist. Scleral grafts may be indicated for threatened perforation.
Chapter 64. Corneal Disorders

Introduction

The cornea is subject to infection, noninfectious inflammation, ulceration, mechanical damage, and environmental injury. Infection (keratitis), frequently with secondary conjunctivitis, can be due to viruses, bacteria, *Acanthamoeba*, or fungi. Ulceration usually represents progression of keratitis. Symptoms that suggest corneal involvement rather than simple conjunctivitis include pain, particularly with exposure to light, and slight impairment of vision. Evaluation of the cornea requires slit-lamp examination and sometimes microbial studies.

Bullous Keratopathy

**Bullous keratopathy is the presence of corneal epithelial bullae, resulting from corneal endothelial disease.**

Bullous keratopathy is caused by edema of the cornea, resulting from failure of the corneal endothelium to maintain the normally dehydrated state of the cornea. Most frequently, it is due to Fuchs' corneal endothelial dystrophy or corneal endothelial trauma. Fuchs' dystrophy causes bilateral, progressive corneal endothelial cell loss, sometimes leading to symptomatic bullous keratopathy by age 50 to 60. Corneal endothelial trauma can occur during intraocular surgery (eg, cataract removal) or after placement of a poorly designed or malpositioned intraocular lens implant, leading to bullous keratopathy. Bullous keratopathy after cataract removal is called pseudophakic (if an intraocular lens implant is present) or aphakic (if no intraocular lens implant is present) bullous keratopathy.

Subepithelial fluid-filled bullae form on the corneal surface as the corneal stroma swells, leading to eye discomfort, decreased visual acuity, loss of contrast, glare, and photophobia. Sometimes bullae rupture, causing pain and foreign body sensation. Bacteria can invade a ruptured bulla, leading to a corneal ulcer.

The bullae and swelling of the corneal stroma can be seen on slit-lamp examination.

Treatment requires an ophthalmologist and includes topical dehydrating agents (eg, hypertonic saline), intraocular pressure-lowering agents, soft contact lenses for some mild to moderate cases, and treatment of any secondary microbial infection. Corneal transplantation is usually curative.

Corneal Ulcer

**A corneal ulcer is a corneal epithelial defect with underlying inflammation (which soon results in necrosis of corneal tissue) due to invasion by bacteria, fungi, viruses, or *Acanthamoeba*. It can be initiated by mechanical trauma or nutritional deficiencies. Symptoms are progressive redness, foreign body sensation, ache, photophobia, and lacrimation. Diagnosis is by slit-lamp examination, fluorescein staining, and microbial studies. Treatment with topical antimicrobials and often dilating drops is urgent and requires an ophthalmologist.**

Etiology

Corneal ulcers have many causes (see Table 64-1). Bacterial ulcers (most commonly due to contact lens wear) may complicate herpes simplex keratitis and be particularly refractory to treatment. Ulcers caused by *Acanthamoeba* (also most commonly due to contact lens wear) and fungi (most commonly due to trauma with vegetable material) are indolent but progressive; those caused by *Pseudomonas aeruginosa* (seen almost exclusively in contact lens wearers) develop rapidly, causing deep and extensive corneal necrosis. Wearing contact lenses while sleeping or wearing inadequately disinfected contact lenses can cause corneal ulcers (see p. 572).

Pathophysiology

Ulcers are characterized by corneal epithelial defects with underlying inflammation, and soon necrosis of
the corneal stroma develops. Corneal ulcers tend to heal with scar tissue, resulting in opacification of the cornea and decreased visual acuity. Uveitis, corneal perforation with iris prolapse, pus in the anterior chamber (hypopyon), panophthalmitis, and destruction of the eye may occur with or without treatment. More severe symptoms and complications tend to occur with deeper ulcers.

**Symptoms and Signs**

 Conjunctival redness, eye ache, foreign body sensation, photophobia, and lacrimation may be minimal initially.

 A corneal ulcer begins as a corneal epithelial defect that stains with fluorescein and an underlying dull, grayish, circumscribed superficial opacity. Subsequently, the ulcer suppurates and necroses to form an excavated ulcer. Considerable circumcorneal conjunctival hyperemia is usual (see Plate 9). In long-standing cases, blood vessels may grow in from the limbus (corneal neovascularization). The ulcer may spread to involve the width of the cornea, may penetrate deeply, or both. Hypopyon (layered WBCs in the anterior chamber) may occur.

 Corneal ulcers due to *Acanthamoeba* are often intensely painful and may show transient corneal epithelial defects, multiple corneal stromal infiltrates, and, later, a large ringshaped infiltrate. Fungal ulcers, which are more chronic than bacterial ulcers, are densely infiltrated and show occasional discrete islands of infiltrate (satellite lesions) at the periphery.

**Diagnosis**

 - Slit-lamp examination
  
  Diagnosis is made by slit-lamp examination; a corneal infiltrate with an epithelial defect that stains with fluorescein is diagnostic. All but small ulcers should be cultured by scraping with a sterile platinum spatula (typically by an ophthalmologist). Microscopic examination of scrapings can identify *Acanthamoeba*.

**Treatment**

 - Empiric topical broad-spectrum antibiotic therapy
  
  Treatment for corneal ulcers, regardless of cause, begins with moxifloxacin 0.5% or gatifloxacin 0.3% for small ulcers and fortified (higher than stock concentration) antibiotic drops, such as tobramycin 15 mg/mL and cefazolin 50 mg/mL, for more significant ulcers, particularly those that are near the center of the cornea. Frequent dosing (eg, q 15 min for 4 doses, followed by q 1 h around the clock) is necessary initially. Patching is contraindicated because it creates a stagnant, warm environment that favors bacterial growth and prevents the administration of topical drugs.

  Herpes simplex (see below) is treated with trifluridine 1% drops q 2 h while the patient is awake or acyclovir 400 mg po 5 times/day for about 14 days.

  Fungal infections are treated with one of many topical antifungal drops (eg, natamycin 5%, amphotericin B 0.15%), initially q 1 h during the day and q 2 h overnight. Deep infections may require addition of oral ketoconazole, fluconazole, or itraconazole.

 If *Acanthamoeba* is identified, traditional therapy is propamidine and neomycin supplemented with miconazole, clotrimazole, or oral ketoconazole. Additional treatments include polyhexamethylene biguanide 0.02% or chlorhexidine 0.02% q 1 to 2 h until clinical improvement is evident, then gradually reduced to 4 times/day and continued for a number of months until all inflammation has resolved.
Polyhexamethylene biguanide and chlorhexidine are not commercially available as ocular agents but can be prepared by a compounding pharmacy. Topical propamidine 0.1% q 1 to 2 h is often added for 3 days. For all ulcers, treatment may also include a cycloplegic, such as atropine 1% or scopolamine 0.25% 1 drop tid, to decrease the ache of a corneal ulcer and to reduce the formation of posterior synechiae. In severe cases, debridement of the infected epithelium or even penetrating keratoplasty may be required. Patients who are poorly compliant or who have large, central, or refractory ulcers may need to be hospitalized.

**Herpes Simplex Keratitis**

(Herpes Simplex Keratoconjunctivitis)

Herpes simplex keratitis is corneal infection with herpes simplex virus (see also p. 1417). It may involve the iris. Symptoms and signs include foreign body sensation, lacrimation, photophobia, and conjunctival hyperemia. Recurrences are common and may lead to corneal hypoesthesia, ulceration, and permanent scarring. Diagnosis is based on the characteristic dendritic corneal ulcer and sometimes viral culture. Treatment is with topical and occasionally systemic antiviral drugs.

Herpes simplex usually affects the corneal surface but sometimes involves the deeper layers of the cornea (corneal stroma). Stromal involvement is probably an immunologic response to the virus.

As with all herpes simplex virus infections, there is a primary infection, followed by a latent phase, in which the virus goes into the nerve roots. Latent virus may reactivate, causing recurrent symptoms.

**Symptoms and Signs**

**Primary infection:** The initial (primary) infection is usually nonspecific self-limiting conjunctivitis, often in early childhood and sometimes without corneal involvement. If the cornea is involved, early symptoms include foreign body sensation, lacrimation, photophobia, and conjunctival hyperemia. Sometimes vesicular blepharitis (blisters on the eyelid) follows, symptoms worsen, vision blurs, and blisters break down and ulcerate, then resolve without scarring in about a week.

**Recurrent infection:** Recurrences usually take the form of epithelial keratitis (also called dendritic keratitis) with tearing, foreign body sensation, and a characteristic branching (dendritic or serpentine) lesion of the corneal epithelium with knoblike terminals that stain with fluorescein (see Plate 14). Multiple recurrences may result in corneal hypoesthesia or anesthesia, ulceration, and permanent scarring.

**Stromal involvement:** Most patients with disciform keratitis, which involves the corneal stroma, have a history of epithelial keratitis. Disciform keratitis is a deeper, disk-shaped, localized area of corneal edema and haze accompanied by anterior uveitis. This form may cause pain and vision loss.

Stromal keratitis can cause necrosis of the stroma and severe ache, photophobia, foreign body sensation, and decreased vision.

**Diagnosis**

Slit-lamp examination is mandatory. Finding a dendrite is enough to confirm the diagnosis in most cases. When the appearance is not conclusive, viral culture of the lesion can confirm the diagnosis.

**Treatment**

- Topical trifluridine
- Sometimes oral or IV acyclovir
For stromal involvement or uveitis, topical corticosteroids in addition to antiviral drugs

Most patients are managed by an ophthalmologist. If stromal or uveal involvement occurs, treatment is more involved and referral to an ophthalmologist is mandatory.

Topical therapy (eg, trifluridine 1% drops 9 times/day) is usually effective. Occasionally, acyclovir 400 mg po 5 times/day is indicated. Immunocompromised patients may require IV antivirals (eg, acyclovir 5 mg/kg IV q 8 h for 7 days). If the epithelium surrounding the dendrite is loose and edematous, debridement by gentle swabbing with a cotton-tipped applicator before beginning drug therapy may speed healing.

Topical corticosteroids are contraindicated in epithelial keratitis but may be effective when used with an antiviral drug to manage later-stage stromal involvement (disciform or stromal keratitis) or uveitis. In such cases, patients may be given prednisolone acetate 1% instilled q 2 h initially, lengthening the interval to q 4 to 8 h as symptoms improve. Topical drugs to relieve photophobia include atropine 1% or scopolamine 0.25% tid.

**Herpes Zoster Ophthalmicus**

(Herpes Zoster Virus Ophthalmicus; Ophthalmic Herpes Zoster; Varicella-Zoster Virus Ophthalmicus)

Herpes zoster ophthalmicus is reactivation of a varicella-zoster virus infection (shingles) (see also p. 1420) involving the eye. Symptoms and signs, which may be intense, include dermatomal forehead rash and painful inflammation of all the tissues of the anterior and, rarely, posterior structures of the eye. Diagnosis is based on the characteristic appearance of the anterior structures of the eye plus zoster dermatitis of the first branch of the trigeminal nerve. Treatment is with oral antiviral drugs, mydriatics, and topical corticosteroids.

Herpes zoster of the forehead involves the globe in three fourths of cases when the nasociliary nerve is affected (as indicated by a lesion on the tip of the nose) and in one third of cases not involving the tip of the nose. Overall, the globe is involved in half of patients.

**Symptoms and Signs**

A prodrome of tingling of the forehead may occur. During acute disease, in addition to the forehead rash, symptoms and signs may include severe pain; marked eyelid edema; conjunctival, episcleral, and circumcorneal conjunctival hyperemia; corneal edema; and photophobia (see Plate 15).

**Complications:** Keratitis accompanied by uveitis may be severe and followed by scarring. Late sequelae—glaucoma, cataract, chronic or recurrent uveitis, corneal scarring, corneal neovascularization, and hypesthesia—are common and may threaten vision. Postherpetic neuralgia may develop late.

**Diagnosis**

- Zoster rash on the forehead or eyelid plus eye findings

Diagnosis is based on a typical acute herpes zoster rash on the forehead, eyelid, or both or on a characteristic history plus signs of previous zoster rash. Vesicular or bullous lesions in this distribution that do not yet involve the eye suggest significant risk and should prompt an ophthalmologic consultation to determine whether the eye is involved. Culture and immunologic or PCR studies of skin at initial evaluation or serial serologic tests are done only when lesions are atypical and the diagnosis uncertain.

**Treatment**

- Oral antivirals (eg, acyclovir, famciclovir, valacyclovir)

- Sometimes topical corticosteroids
Early treatment with acyclovir 800 mg po 5 times/day or famciclovir 500 mg or valacyclovir 1 g po tid for 7 days reduces ocular complications. Patients with keratitis or uveitis require topical corticosteroids (eg, prednisolone acetate 1% instilled qid initially, lengthening the interval as symptoms lessen). The pupil should be dilated with atropine 1% or scopolamine 0.25% 1 drop tid. Intraocular pressure must be monitored and treated if it rises significantly above normal values.

Use of a brief course of high-dose oral corticosteroids to prevent postherpetic neuralgia in patients > 60 yr who are in good general health remains controversial.

**Interstitial Keratitis**

(Parenchymatous Keratitis)

Interstitial keratitis is chronic, nonulcerative inflammation of the middle layers of the cornea (ie, mid-stroma) that is sometimes associated with uveitis. The cause is usually infectious. Symptoms are photophobia, pain, lacrimation, and vision blurring. Diagnosis is by slit-lamp examination and serologic tests to determine the cause. Treatment is directed at the cause and may require topical corticosteroids.

Interstitial keratitis, a manifestation of certain corneal infections, is rare in the US. Most cases occur in children or adolescents as a late complication of congenital syphilis (see p. 2821). Ultimately, both eyes may be involved. A similar but less dramatic bilateral keratitis occurs in Cogan's syndrome, Lyme disease, and Epstein-Barr virus infection. Rarely, acquired syphilis, herpes simplex, herpes zoster, or TB may cause a unilateral form in adults.

**Symptoms and Signs**

Photophobia, pain, lacrimation, and vision blurring are common. The lesion begins as patches of inflammation in the middle corneal layers (ie, mid-stroma) that cause opacification. Typically with syphilis and occasionally with other causes, the entire cornea develops a ground-glass appearance, obscuring the iris. New blood vessels grow in from the limbus (neovascularization) and produce orange-red areas (salmon patches). Anterior uveitis and choroiditis are common in syphilitic interstitial keratitis. Inflammation and neovascularization usually begin to subside after 1 to 2 mo. Some corneal opacity usually remains, causing mild to moderate vision impairment.

**Diagnosis**

- Corneal opacification and other typical findings on slit-lamp examination
- Serologic testing to determine etiology

The specific etiology must be determined. The stigmas of congenital syphilis, vestibuloauditory symptoms, history of an expanding rash, and tick exposure support a specific etiology. However, all patients should have serologic testing, including all of the following:

- Fluorescent treponemal antibody absorption test or the microhemagglutination assay for *Treponema pallidum*
- Lyme titer
- Epstein-Barr virus panel

Patients with negative serologic test results may have Cogan's syndrome, an idiopathic syndrome consisting of interstitial keratitis and vestibular and auditory deficits. To prevent permanent vestibuloauditory damage, symptoms of hearing loss, tinnitus, or vertigo require referral to an otolaryngologist.

**Treatment**
• Sometimes topical corticosteroids

Keratitis may resolve with treatment of the underlying condition. Additional topical treatment with a corticosteroid, such as prednisolone 1% qid, is often advisable. An ophthalmologist should be consulted.

**Cogan's Syndrome**

**Cogan's syndrome is a rare autoimmune disease involving the eye and the inner ear.**

Cogan's syndrome affects young adults, with 80% of patients between 14 and 47 yr. The disease appears to result from an autoimmune reaction directed against an unknown common autoantigen in the cornea and inner ear. About 10 to 30% of patients also have severe systemic vasculitis, which may include life-threatening aortitis.

**Symptoms and Signs**

The presenting symptoms involve the ocular system in 38% of patients, the vestibuloauditory system in 46%, and both in 15%. By 5 mo, 75% of patients have both ocular and vestibuloauditory symptoms. Nonspecific systemic complaints include fever, headache, joint pain, and myalgia.

**Ocular:** Ocular involvement includes any combination of the following:

• Bilateral interstitial keratitis or other corneal stromal keratitis

• Episcleritis or scleritis

• Uveitis

• Papillitis

• Other orbital inflammation (eg, vitritis, choroiditis)

Ocular symptoms include irritation, pain, photophobia, and decreased vision. Ocular examination shows a patchy corneal stromal infiltrate typical of interstitial keratitis (see p. 591), ocular redness, optic nerve edema, proptosis, or a combination of these symptoms.

**Vestibuloauditory:** Vestibuloauditory symptoms include sensorineural hearing loss, tinnitus, and vertigo.

**Vascular:** A diastolic heart murmur may be present when aortitis is significant. Claudication may be present if limb vessels are affected.

**Diagnosis**

Diagnosis is based on clinical findings and exclusion of other causes (eg, syphilis, Lyme disease, Epstein-Barr virus infection) by appropriate serologic tests. Evaluation by an ophthalmologist and otolaryngologist is important.

**Treatment**

• Initially topical and sometimes systemic corticosteroids

Untreated disease may lead to corneal scarring and visual loss and, in 60 to 80% of patients, permanent hearing loss. Keratitis, episcleritis, and anterior uveitis can usually be treated with topical prednisolone acetate 1% q 1 h to qid. To treat deeper ocular inflammation and especially to treat vestibuloauditory symptoms before they become permanent, prednisone 1 mg/kg po once/day is begun as soon as possible and continued for 2 to 6 mo. Some clinicians add cyclophosphamide, methotrexate, or cyclosporine for recalcitrant cases.
Keratoconjunctivitis Sicca

(Dry Eyes; Keratitis Sicca)

Keratoconjunctivitis sicca is chronic, bilateral desiccation of the conjunctiva and cornea due to an inadequate tear film. Symptoms include itching, burning, irritation, and photophobia. Diagnosis is clinical; the Schirmer test may be helpful. Treatment is with topical tear supplements and sometimes blockage of the nasolacrimal openings.

Etiology

There are 2 main types:

• Aqueous tear-deficient keratoconjunctivitis sicca is caused by inadequate tear volume.

• Evaporative keratoconjunctivitis sicca (more common) is caused by accelerated tear evaporation due to poor tear quality.

Aqueous tear-deficient keratoconjunctivitis sicca is most commonly an isolated idiopathic condition in postmenopausal women. It is also commonly part of Sjogren’s syndrome (see p. 303), RA, or SLE. Less commonly, it is secondary to other conditions that scar the lacrimal ducts (eg, cicatricial pemphigoid, Stevens-Johnson syndrome, trachoma). It may result from a damaged or malfunctioning lacrimal gland due to graft-vs-host disease, HIV (diffuse infiltrative lymphocytosis syndrome), local radiation therapy, or familial dysautonomia.

Evaporative keratoconjunctivitis sicca is caused by loss of the tear film due to abnormally rapid evaporation caused by an inadequate oil layer on the surface of the aqueous layer of tears. Symptoms may result from abnormal oil quality (ie, meibomian gland dysfunction) or a degraded normal oil layer (ie, seborrheic blepharitis). Patients frequently have acne rosacea.

Drying can also result from exposure due to inadequate eye closure at night (nocturnal lagophthalmos) or, rarely, from inadequate tear volume due to an insufficient blink rate.

Symptoms and Signs

Patients report itching; burning; a gritty, pulling, or foreign body sensation; or photophobia. A sharp stabbing pain, eye strain or fatigue, and blurred vision may also occur. Some patients note a flood of tears after severe irritation. Typically, symptoms fluctuate in intensity and may be intermittent. Certain factors can worsen symptoms:

• Prolonged visual efforts (eg, reading, working on the computer, driving, watching television)

• Local environments that are dry, windy, dusty, or smoky

• Certain systemic drugs, including isotretinoin, sedatives, diuretics, antihypertensives, oral contraceptives, and all anticholinergics (including antihistamines and many GI drugs)

Symptoms lessen on cool, rainy, or foggy days or in other high-humidity environments, such as in the shower. Recurrent and prolonged blurring and frequent intense irritation can impair daily function. However, permanent impairment of vision is rare.

With both forms, the conjunctiva is hyperemic, and there is often scattered, fine, punctate loss of corneal epithelium (superficial punctate keratitis), conjunctival epithelium, or both. When the condition is severe, the involved areas, mainly between the eyelids (the intrapalpebral or exposure zone), stain with fluorescein. Patients often blink at an accelerated rate because of irritation.

With the aqueous tear-deficient form, the conjunctiva can appear dry and lusterless with redundant folds.
With the evaporative form, abundant tears may be present as well as foam at the eyelid margin. Very rarely, severe, advanced, chronic drying leads to significant vision loss due to keratinization of the ocular surface or loss of corneal epithelium, leading to sequelae such as scarring, neovascularization, infections, ulceration, and perforation.

**Diagnosis**

- Schirmer test and tear breakup tests

Diagnosis is based on characteristic symptoms and clinical appearance. The Schirmer test and tear breakup test may differentiate type.

The Schirmer test determines whether tear production is normal. After blotting the closed eye to remove excess tears, a strip of filter paper is placed, without topical anesthesia, at the junction of the middle and lateral third of the lower eyelid. If < 5.5 mm of wetting occurs after 5 min on 2 successive occasions, the patient has aqueous tear-deficient keratoconjunctivitis sicca.

With evaporative keratoconjunctivitis sicca, the Schirmer test is usually normal. The tear film can be made visible under cobalt blue light at the slit lamp by instillation of a small volume of highly concentrated fluorescein (made by wetting a fluorescein strip with saline and shaking the strip to remove any excess moisture). Blinking several times reapply’s a complete tear film. The patient then stares, and the length of time until the first dry spot develops is determined (tear breakup test, or TBUT). An accelerated rate of intact tear film breakup (< 10 sec) is characteristic of evaporative keratoconjunctivitis sicca.

If aqueous tear-deficient keratoconjunctivitis sicca is diagnosed, Sjogren's syndrome (see p. 303) should be suspected, especially if xerostomia is also present. Serologic tests and labial salivary gland biopsy are used for diagnosis. Patients with primary or secondary Sjogren's syndrome are at increased risk of several serious diseases (eg, primary biliary cirrhosis, non-Hodgkin lymphoma). Therefore, proper evaluation and monitoring are essential.

**Treatment**

- Artificial tears

- Sometimes occlusion of nasolacrimal punctum or tarsorrhaphy

Frequent use of artificial tears can be effective for both forms. More viscous artificial tears coat the ocular surface longer, and artificial tears that contain polar lipids such as glycerin reduce evaporation; both types are particularly useful in evaporative keratoconjunctivitis sicca. Artificial tear ointments applied before sleep are particularly useful when patients have nocturnal lagophthalmos or irritation on waking. Most cases are treated adequately throughout the patient's life with such supplementation. Staying hydrated, using humidifiers, and avoiding dry, drafty environments can often help. Not smoking and avoiding secondary smoke are important. In recalcitrant cases, occlusion of the nasolacrimal punctum may be indicated. In severe cases, a partial tarsorrhaphy can reduce tear loss through evaporation. Topical cyclosporine and ω-3 fatty acid dietary supplements may be a useful adjunct in some patients.

Patients with evaporative keratoconjunctivitis sicca often benefit from treatment of concomitant blepharitis and associated rosacea with measures such as warm compresses, eyelid margin scrubs, and intermittent topical eyelid antibiotic ointments (eg, bacitracin at bedtime), systemic doxycycline 50 to 100 mg po once or twice/day (contraindicated in pregnant or nursing patients), or both.

Cyclosporine drops that decrease the inflammation associated with dryness of the eye are available. They lead to meaningful improvement but only in a fraction of patients. These drops sting and take months before an effect is noticed.

**Keratoconus**

Keratoconus is a bulging distortion of the cornea, leading to loss of visual acuity.
Keratoconus is a slowly progressive thinning and bulging of the cornea, usually bilateral, beginning between ages 10 and 25. Its cause is unknown.

The distorted cone shape of the cornea causes major changes in the refractive characteristics of the cornea (irregular astigmatism) that cannot be fully corrected with glasses. Progressing keratoconus necessitates frequent change of eyeglasses. Contact lenses may provide better vision correction and should be tried when eyeglasses are not satisfactory. Corneal transplant surgery may be necessary if visual acuity with contact lenses is inadequate, contact lenses are not tolerated, or a visually significant corneal scar (caused by tearing of stromal fibers) is present.

Newer treatments seem promising. Implantation of corneal ring segments appears to have the potential to save selected patients from transplantation. Corneal cross-linking, an ultraviolet light treatment that strengthens the cornea, has had positive results in European studies and may become more common.

**Keratomalacia**

(Xerotic Keratitis; Xerophthalmia)

*Keratomalacia is degeneration of the cornea caused by nutritional deficiency.*

Keratomalacia is caused by vitamin A deficiency typically in patients with protein-calorie undernutrition. It is characterized by a hazy, dry cornea. Corneal ulceration with secondary infection is common. The lacrimal glands and conjunctiva are also affected. Lack of tears causes extreme dryness of the eyes, and foamy spots appear on the temporal and often nasal bulbar conjunctiva (Bitot's spots). Night blindness may occur. For further details, including specific therapy, see Vitamin A Deficiency on p. 34.

**Peripheral Ulcerative Keratitis**

(Marginal Keratolysis; Peripheral Rheumatoid Ulceration)

*Peripheral ulcerative keratitis is inflammation and ulceration of the cornea that often occurs with chronic connective tissue diseases. Irritation and decreased vision result.*

Peripheral ulcerative keratitis is a serious corneal ulceration; it often occurs with autoimmune diseases that are active, long-standing, or both, such as RA, Wegener's granulomatosis, and relapsing polychondritis.

Patients often have decreased visual acuity, photophobia, and foreign body sensation. A crescentic area of opacification in the periphery of the cornea, due to infiltration by WBCs and ulceration, stains with fluorescein. Infectious causes, such as bacteria, fungi, and herpes simplex virus, must be ruled out by culturing the ulcer and eyelid margins.

Among patients with rheumatic disease and peripheral ulcerative keratitis, the 10-yr mortality rate is about 40% (usually due to MI) without treatment and about 8% with systemic cytotoxic therapy.

Any patient with peripheral ulcerative keratitis should be promptly referred to an ophthalmologist. Systemic cyclophosphamide or other immunosuppressants treat the keratitis, life-threatening vasculitis, and underlying autoimmune disease. Treatment also includes local approaches to control inflammation (eg, tissue adhesive and bandage contact lenses) and repair damage (eg, patch grafts). Other possibly helpful drugs include collagenase inhibitors, such as systemic tetracycline or topical 20% N-acetylcysteine.

**Phlyctenular Keratoconjunctivitis**

(Phlyctenular Conjunctivitis; Phlyctenulosis)

*Phlyctenular keratoconjunctivitis, a hypersensitivity reaction of the cornea and conjunctiva to*
**bacterial antigens, is characterized by discrete nodular areas of corneal or conjunctival inflammation.**

Phlyctenular keratoconjunctivitis results from a hypersensitivity reaction to bacterial antigens, primarily staphylococcal, but TB, *Chlamydia*, and other agents have been implicated. It is more common in children. Many patients also have blepharitis.

Patients have multiple lesions, consisting of small yellow-gray nodules (phlyctenules) that appear at the limbus, on the cornea, or on the bulbar conjunctiva and persist from several days to 2 wk. On the conjunctiva, these nodules ulcerate but heal without a scar. When the cornea is affected, severe lacrimation, photophobia, blurred vision, aching, and foreign body sensation may be prominent. Frequent recurrence, especially with secondary infection, may lead to corneal opacity and neovascularization with loss of visual acuity.

Diagnosis is by characteristic clinical appearance. Testing for TB may be indicated (eg, for patients at risk).

Treatment for nontuberculous cases is with a topical corticosteroid-antibiotic combination. If patients have seborrheic blepharitis, eyelid scrubs may help prevent recurrence.

**Superficial Punctate Keratitis**

Superficial punctate keratitis is corneal inflammation of diverse causes characterized by scattered, fine, punctate corneal epithelial loss or damage. Symptoms are redness, lacrimation, photophobia, and slightly decreased vision. Diagnosis is by slit-lamp examination. Treatment depends on the cause.

Superficial punctate keratitis is a nonspecific finding. Causes may include any of the following:

- Viral conjunctivitis (most commonly adenovirus)
- Blepharitis
- Keratoconjunctivitis sicca
- Trachoma
- Chemical burns
- Ultraviolet (UV) light exposure (eg, welding arcs, sunlamps, snow glare)
- Contact lens overwear
- Systemic drugs (eg, adenine arabinoside)
- Topical drug or preservative toxicity.

Symptoms include photophobia, foreign body sensation, lacrimation, redness, and slightly decreased vision. Slit-lamp or ophthalmoscope examination of the cornea reveals a characteristic hazy appearance with multiple punctate speckles that stain with fluorescein. With viral conjunctivitis, preauricular adenopathy is common and chemosis may occur.

Keratitis that accompanies adenovirus conjunctivitis resolves spontaneously in about 3 wk. Blepharitis (see p. 575), keratoconjunctivitis sicca (see p. 592), and trachoma (see p. 583) require specific therapy. When caused by overwearing contact lenses, keratitis is treated with discontinuation of the contact lens and an antibiotic ointment (eg, ciprofloxacin 0.3% qid), but the eye is not patched because serious infection may result. Contact lens wearers with superficial punctate keratitis should be examined the next day. Suspected causative topical drugs (active ingredient or preservative) should be stopped.
**Ultraviolet keratitis:** UVB light (wavelength < 300 nm) can burn the cornea, causing keratitis or keratoconjunctivitis. Arc welding is a common cause; even a brief, unprotected glance at a welding arc may result in a burn. Other causes include high-voltage electric sparks, artificial sun lamps, and sunlight reflected off snow at high altitudes. UV radiation increases 4 to 6% for every 1000-ft (305-m) increase in altitude above sea level, and snow reflects 85% of UVB.

Symptoms are usually not apparent for 8 to 12 h after exposure and last 24 to 48 h. Patients have lacrimation, pain, redness, swollen eyelids, photophobia, headache, foreign body sensation, and decreased vision. Permanent vision loss is rare.

Diagnosis is by history, presence of superficial punctate keratitis, and absence of a foreign body or infection.

Treatment consists of an antibiotic ointment (eg, bacitracin or gentamicin 0.3% ointment q 8 h) and occasionally a short-acting cycloplegic drug (eg, cyclopentolate 1% drop q 4 h). Severe pain may require systemic analgesics. The corneal surface regenerates spontaneously in 24 to 48 h. The eye must be rechecked in 24 h. Dark glasses or welder's helmets that block UV light are preventive.

**Corneal Transplantation**

*(Corneal Graft; Penetrating Keratoplasty)*

**Indications:** Corneal transplantations are done for several reasons:

- To reconstruct the cornea (eg, replacing a perforated cornea)
- To relieve intractable pain (eg, severe foreign body sensation due to recurrent ruptured bullae in bullous keratopathy)
- To treat a disorder unresponsive to medical management (eg, severe, uncontrolled fungal corneal ulcer)
- To improve the optical qualities of the cornea and thus improve vision (eg, replacing a cornea that is scarred after a corneal ulcer, is clouded because of edema as occurs in Fuchs' dystrophy or after cataract surgery, is opaque because of deposits of nontransparent abnormal corneal stromal proteins as occurs in hereditary corneal stromal dystrophy, or has irregular astigmatism as occurs with keratoconus)

The most common indications are the following:

- Bullous keratopathy (pseudophakic or aphakic, Fuchs' endothelial dystrophy)
- Keratoconus
- Repeat graft
- Keratitis or postkeratitis (caused by viral, bacterial, fungal, or *Acanthamoeba* infection or perforation)
- Corneal stromal dystrophies

**Procedure:** Tissue matching is not routinely done. Cadaveric donor tissue cannot be used from anyone suspected of having a communicable disease.

Corneal transplantation can be done using general anesthesia or local anesthesia plus IV sedation.

Topical antibiotics are used for several weeks postoperatively and topical corticosteroids for several months. To protect the eye from inadvertent trauma after transplantation, the patient wears shields, glasses, or sunglasses. If transplantation involves the full thickness of the cornea (as in penetrating
keratoplasty, or PKP), achievement of full visual potential may take up to 18 mo because of changing refraction with wound healing and after suture removal. If only the endothelium is replaced (as in Descemet's stripping endothelial keratoplasty), achievement of full visual potential usually occurs by 6 mo. In many patients, earlier and better vision is attained by wearing a rigid contact lens over the corneal transplant.

**Complications:** Complications include the following:

- Graft rejection
- Infection (intraocular and corneal)
- Wound leak
- Glaucoma
- Graft failure
- High refractive error (especially astigmatism, myopia, or both)
- Recurrence of disease (with herpes simplex or hereditary corneal stromal dystrophy)

Graft rejection rates are usually < 10% but may be up to 68% in higher-risk patients. Rejection symptoms include decreased vision, photosensitivity, ocular ache, and ocular redness. Graft rejection is treated with topical corticosteroids (eg, prednisolone 1% hourly), sometimes with a supplemental periocular injection (eg, triamcinolone acetonide 40 mg). If graft rejection is severe or if graft function is marginal, additional corticosteroids are given orally (eg, prednisone 1 mg/kg once/day) and occasionally IV (eg, methylprednisolone 3 to 5 mg/kg once). Typically, the rejection episode reverses, and graft function returns fully. The graft may fail if the rejection episode is unusually severe or long-standing or if multiple episodes of graft rejection occur. Replant is possible, but the long-term prognosis is worse than for the original graft.

**Prognosis**

The chance of long-term transplant success is

- > 90% for keratoconus, corneal scars, early bullous keratopathy, or hereditary corneal stromal dystrophies
- 80 to 90% for more advanced bullous keratopathy or inactive viral keratitis
- 50% for active corneal infection
- 0 to 50% for chemical or radiation injury

The generally high rate of success of corneal transplantation is attributable to many factors, including the avascularity of the cornea and the fact that the anterior chamber has venous drainage but no lymphatic drainage. These conditions promote low-zone tolerance (an immunologic tolerance that results from constant exposure to low doses of an antigen) and a process termed anterior chamber-associated immune deviation, in which there is active suppression of intraocular lymphocytes and delayed-type hypersensitivity to transplanted intraocular antigens. Another important factor is the effectiveness of the corticosteroids used topically, locally, and systemically to treat graft rejection.

**Corneal Limbal Stem Cell Transplantation**

Corneal limbal stem cell transplantation surgically replaces critical stem cells at the limbus (the area where the conjunctiva meets the cornea). Host stem cells normally reside in this area. Transplantation is done when the host stem cells have been too severely damaged to recover from disease or injury.
Conditions such as severe chemical burns, Stevens-Johnson syndrome, and severe contact lens overwear may cause persistent nonhealing corneal epithelial defects. These defects result from failure of corneal epithelial stem cells to produce sufficient epithelial cells to repopulate the cornea. If untreated, persistent nonhealing corneal epithelial defects are vulnerable to infection, which can lead to scarring, perforation, or both. Under these circumstances, a corneal transplant, which replaces only the central cornea and not the limbus, is insufficient; stem cells are needed to produce new cells that repopulate the cornea, restoring the regenerative capacity of the ocular surface.

Corneal limbal stem cells can be transplanted from the patient's healthy eye or from a cadaveric donor eye. The patient's damaged corneal epithelial stem cells are removed by a partial-thickness dissection of the limbus (ie, all the epithelium and the superficial stroma of the limbus). Donor limbal tissue, which is prepared by a similar dissection, is sutured into the prepared bed.
Chapter 65. Glaucoma

Introduction

Glaucomas are a group of eye disorders characterized by progressive optic nerve damage at least partly due to increased intraocular pressure (IOP). Glaucoma is the 3rd most common cause of blindness worldwide and the 2nd most common cause of blindness in the US, where it is the leading cause of blindness for blacks and Hispanics. About 3 million Americans and 14 million people worldwide have glaucoma, but only half are aware of it. Glaucoma can occur at any age but is 6 times more common among people > 60 yr.

Glaucomas are categorized as open-angle or closed-angle (angle-closure)—see Tables 65-1, 65-2, and 65-3. The "angle" refers to the angle formed by the junction of the iris and cornea at the periphery of the anterior chamber (see Fig. 65-1). The angle is where > 98% of the aqueous humor exits the eye via either the trabecular meshwork and Schlemm's canal (the major pathway, particularly in the elderly) or the ciliary body face and choroidal vasculature. These outflow pathways are not simply a mechanical filter and drain but instead involve active physiologic processes.

Glaucomas are further subdivided into primary (cause of outflow resistance or angle closure is unknown) and secondary (outflow resistance results from another disorder), accounting for > 20 adult types.

Pathophysiology

Axons of retinal ganglion cells travel through the optic nerve carrying images from the eye to the brain. Damage to these axons causes ganglion cell death with resultant optic nerve atrophy and patchy vision loss. Elevated IOP (in unaffected eyes, the average range is 11 to 21 mm Hg) plays a role in axonal damage, either by direct nerve compression or diminution of blood flow. However, the relationship between pressure and nerve damage is variable. Of people with IOP > 21 mm Hg (ie, ocular hypertension), only about 1 to 2%/yr (about 10% over 5 yr) develop glaucoma. Additionally, about one third of patients with glaucoma do not have IOPs > 21 mm Hg (known as lowtension glaucoma or normal-tension glaucoma).

IOP is determined by the balance of aqueous secretion and drainage. Elevated IOP is caused by inhibited or obstructed outflow, not oversecretion. In open-angle glaucoma, IOP is elevated because outflow is inadequate despite an angle that appears unobstructed. In angle-closure glaucoma, IOP is elevated when a physical distortion of the peripheral iris mechanically blocks outflow.

Symptoms and Signs

Symptoms and signs vary with the type of glaucoma, but the defining characteristic is optic nerve damage as evidenced by an abnormal optic disk (see p. 601 and Plate 13) and certain types of visual field deficits (see p. 601).

IOP may be elevated or within the average range. (For techniques of measurement, see p. 540)

Diagnosis

- Characteristic visual field defects
- Exclusion of other causes
- IOP usually > 21 mm Hg (but not required for the diagnosis)

Glaucoma should be suspected in a patient with any of the following:
• Typical visual field defects

• Abnormal optic nerve on ophthalmoscopy

• Elevated IOP

Such patients (and those with any risk factors) should be referred to an ophthalmologist for a comprehensive examination that includes a thorough history, family history, examination of the optic disks (preferably using a binocular examination technique), formal visual field examination, IOP measurement, and gonioscopy (visualization of the anterior chamber angle with a special mirrored contact lens prism). Glaucoma is diagnosed when characteristic findings of optic nerve damage are present and other causes (eg, multiple sclerosis)

[Table 65-1. Open-Angle Glaucoma: Classification Based on Mechanisms of Outflow Obstruction*] have been excluded. Elevated IOP makes the diagnosis more likely but is not essential.

Screening: Screening can be done by primary physicians by checking visual fields with frequency-doubling technology (FDT) perimetry and ophthalmoscopic evaluation of the optic nerve. FDT perimetry involves use of a desktop device that can screen for visual field abnormalities suggestive of glaucoma in 2 to 3 min per eye. Although IOP should be measured, screening based only on IOP has low sensitivity, low specificity, and low positive predictive value. Patients > 40 yr and those who have risk factors for open-angle or angle-closure glaucoma should receive a comprehensive eye examination every 1 to 2 yr.

Treatment

• Decreasing IOP by using drugs or laser or incisional surgery

[Table 65-3. Developmental Abnormalities of the Anterior Chamber Angle Causing Glaucoma: Classification Based on Mechanisms of Outflow Obstruction*]

Patients with characteristic optic nerve and corresponding visual field changes are treated regardless of IOP. Lowering the IOP is the only clinically proven treatment. For chronic adult and juvenile glaucomas, the initial target IOP is at least 20% below pretreatment readings.

Three methods are available: drugs, laser surgery, and incisional surgery. The type of glaucoma determines the appropriate method. Drugs and most laser surgeries (trabeculoplasty) modify the existing aqueous secretion and drainage system. Most incisional surgeries (eg, guarded filtration procedures [trabeculectomy], glaucoma drainage implant devices [tube shunts]) create a new drainage system.

Prophylactic IOP lowering in patients with ocular hypertension delays the onset of glaucoma. However, because the rate of conversion from ocular hypertension to glaucoma in untreated people is low, the decision to treat prophylactically should be individualized based on the presence of risk factors, magnitude of IOP elevation, and patient factors (ie, preference for drugs vs surgery, drug adverse effects). Generally, treatment is recommended for patients with IOP > 30 mm Hg even if the visual field is full and the optic nerve disk appears healthy because the likelihood of damage is significant at that IOP level.

[Fig. 65-1. Aqueous humor production and flow.]

Primary Open-Angle Glaucoma

Primary open-angle glaucoma is a syndrome of optic nerve damage associated with an open
anterior chamber angle and an elevated or sometimes average intraocular pressure (IOP). Symptoms occur late and involve visual field loss. Diagnosis is by ophthalmoscopy, gonioscopy, visual field examination, and measurement of IOP. Treatment includes topical drugs (eg, prostaglandin analogs, β-blockers) and often requires laser or incisional surgery to increase aqueous drainage.

Etiology

Although open-angle glaucomas can have numerous causes (see Table 65-1), 60 to 70% of cases have no identifiable cause and are termed primary open-angle glaucoma. Both eyes usually are affected, but typically not equally.

Risk factors include older age, positive family history, black race, thinner central corneal thickness, systemic hypertension, diabetes, and myopia. In blacks, glaucoma is more severe and develops at an earlier age, and blindness is 6 to 8 times more likely.

Pathophysiology

IOP can be elevated or within the average range.

**Elevated-pressure glaucoma:** Two thirds of patients with glaucoma have elevated (> 21 mm Hg) IOP. Aqueous humor drainage is inadequate, whereas production by the ciliary body is normal. Identifiable mechanisms (ie, secondary open-angle glaucomas) are not present. These mechanisms include developmental anomalies, scarring caused by trauma or infection, and plugging of channels by detached iris pigment (ie, pigment dispersion syndrome) or abnormal protein deposits (eg, pseudoexfoliation syndrome).

**Normal- or low-pressure glaucoma:** In at least one third of patients with glaucoma, IOP is within the average range, but optic nerve damage and visual field loss typical of glaucoma are present. These patients have a higher incidence of vasospastic diseases (eg, migraines, Raynaud’s syndrome) than the general population, suggesting that a vascular disorder compromising blood flow to the optic nerve may play a role.

Symptoms and Signs

Early symptoms are uncommon. Usually, the patient becomes aware of visual field loss only when optic nerve atrophy is marked; the typically asymmetric deficits contribute to delay in recognition. However, some patients have complaints, such as missing stairs if their inferior visual field has been lost, noticing portions of words missing when reading, or having difficulty with driving.

Examination findings include an unobstructed open angle on gonioscopy and characteristic optic nerve appearance and visual field defects. IOP may be normal or high but is almost always higher in the eye with more optic nerve damage.

**Optic nerve appearance:** The optic nerve head (ie, disk) is normally a slightly vertically elongated circle with a centrally located depression called the cup. The neurosensory rim is the tissue between the margin of the cup and the edge of the disk and is composed of the ganglion cell axons from the retina.

Characteristic optic nerve changes include

1. Increased cup:disk ratio
2. Thinning of the neurosensory rim
3. Pitting or notching of the rim
4. Nerve fiber layer hemorrhage that crosses the disk margin (ie, Drance hemorrhage or splinter hemorrhages)
• Vertical elongation of the cup

• Quick angulations in the course of the exiting blood vessels

Thinning of the neurosensory rim over time alone can be diagnostic of glaucoma regardless of the IOP or visual field. However, most initial diagnoses of glaucoma involve some visual field change.

**Visual field defects:** Visual field changes caused by lesions of the optic nerve include

• Nasal step defects (which do not cross the horizontal meridian—an imaginary horizontal line between the upper and lower parts of the visual field)

• Arcuate (arc-shaped) scotomata extending nasally from the blind spot

• Temporal wedge defects

• Paracentral scotomata

In contrast, deficits of the more proximal visual pathways (ie, from the lateral geniculate nucleus to the occipital lobe) involve quadrants or hemispheres of the visual field; thus, deficits do not cross the vertical meridian.

**Diagnosis**

• Visual field testing

• Ophthalmoscopy

• Measurement of IOP

• Exclusion of other optic neuropathies

Diagnosis is suggested by the examination, but similar findings can result from other optic neuropathies (eg, caused by ischemia, cytomegalovirus infection, or vitamin B\textsubscript{12} deficiency).

Before a diagnosis of normal-pressure glaucoma can be established, the following factors may need to be ruled out: inaccurate IOP readings, large diurnal fluctuations (causing intermittent normal readings), optic nerve damage caused by previously resolved glaucoma (eg, a previously elevated IOP due to corticosteroid use or uveitis), intermittent angle-closure glaucoma, and other ocular or neurologic disorders that cause similar visual field defects.

Optic disk photography or a detailed optic disk drawing is helpful for future comparison. The frequency of follow-up examinations varies from weeks to years, depending on the patient’s reliability, severity of the glaucoma, and response to treatment.

**Treatment**

• Decreasing IOP 20 to 40%

• Initially, drugs (eg, prostaglandin analogs, β-blockers such as timolol)

• Sometimes surgery, such as laser trabeculoplasty or guarded filtration procedure

Vision lost by glaucoma cannot be recovered. The goal is to prevent further optic nerve and visual field damage by lowering IOP. The target level is 20 to 40% below pretreatment readings. In general, the greater the damage caused by glaucoma, the lower the IOP must be to prevent further damage. If damage progresses, the IOP goal is lowered further and additional therapy is initiated.
Initial treatment is usually drug therapy, proceeding to laser therapy and then incisional surgery if the target IOP is not met. Surgery may be the initial treatment if IOP is extremely high.

**Drug therapy:** Multiple drugs are available (see Table 65-4). Topical agents are preferred. The most popular are prostaglandin analogs, followed by β-blockers (particularly timolol). Other drugs include α2-selective adrenergic agonists, cholinergic agonists, and carbonic anhydrase inhibitors. Oral carbonic anhydrase inhibitors are effective, but adverse effects limit their use.

Patients taking topical glaucoma drugs should be taught passive lid closure with punctal occlusion to help reduce systemic absorption and associated adverse effects, although the effectiveness of these maneuvers is controversial. Patients who have difficulty instilling drops directly onto the conjunctiva may place the drop on the nose just medial to the medial canthus, then roll the head slightly toward the eye so that the liquid flows into the eye.

Typically, to gauge effectiveness, clinicians start drugs in only one eye (one-eye trial); once improvement in the treated eye has been confirmed at a subsequent visit (typically 1 to 4 wk later), both eyes are treated.

**Surgery:** Surgery for primary open-angle and normal-pressure glaucoma includes laser trabeculoplasty, a guarded filtration procedure, and possibly tube shunts or ciliodestructive procedures.

**Argon laser trabeculoplasty** (ALT) may be the initial treatment for patients who do not respond to or who cannot tolerate drug therapy. Laser energy is applied to either 180° or 360° of the trabecular meshwork to improve the drainage of aqueous humor. Within 2 to 5 yr, about 50% of patients require additional drug therapy or surgery because of insufficient IOP control.

**Selective laser trabeculoplasty** (SLT) uses a pulsed double-frequency neodymium:yttrium-aluminum-garnet laser. SLT and ALT are equally effective initially, but SLT may have greater effectiveness in subsequent treatments.

**A guarded filtration procedure** is the most commonly used filtration procedure. A hole is made in the limbal sclera (trabeculectomy), which is covered by a partial-thickness scleral flap that controls egress of aqueous from the eye to the subconjunctival space, forming a filtration bleb. Adverse effects of glaucoma filtration surgery include acceleration of cataract growth, pressures that are too low, and transient swelling during the perioperative period. Patients with trabeculectomies are at increased risk of bacterial endophthalmitis and should be instructed to report any symptoms or signs of bleb infection (blebitis) or endophthalmitis immediately.

Viscocanalostomy, canaloplasty, and Trabectome® surgery are newer filtration procedures that do not involve creating a fistula between the anterior chamber and subconjunctival space. Viscocanalostomy and canaloplasty involve dilating Schlemm's canal. Trabectome® surgery uses a proprietary device to remove a portion of the inner aspect of one of the drains of the eye (trabecular meshwork). More long-term studies with these procedures are needed and are on-going. Currently, these new procedures do not appear as effective as trabeculectomy but seem to offer greater safety.

**Angle-Closure Glaucoma**

Angle-closure glaucoma is glaucoma associated with a physically obstructed anterior chamber angle, which may be chronic or, rarely, acute. Symptoms of acute angle closure are severe ocular pain and redness, decreased vision, colored halos around lights, headache, nausea, and vomiting. Intraocular pressure (IOP) is elevated. Immediate treatment of the acute condition with multiple topical and systemic drugs is required to prevent permanent vision loss, followed by the definitive treatment, iridotomy.

Angle-closure glaucoma accounts for about 10% of all glaucomas in the US.
Etiology

Angle-closure glaucoma is caused by factors that either pull or push the iris up into the angle (i.e., junction of the iris and cornea at the periphery of the anterior chamber), physically blocking drainage of aqueous and raising IOP (see Table 65-2). Elevated IOP damages the optic nerve.

Pathophysiology

Angle closure may be primary (cause is unknown) or secondary to another condition (see Table 65-2) and can be acute, subacute (intermittent), or chronic.

[Table 65-4. Drugs Used to Treat Glaucoma]

Primary angle-closure glaucoma: Narrow angles are not present in young people. As people age, the lens of the eye continues to grow. In some but not all people, this growth pushes the iris forward, narrowing the angle. Risk factors for developing narrow angles include Asian ethnicity, hyperopia, family history, and advanced age.

In people with narrow angles, the distance between the pupillary iris and the lens is also very narrow. When the iris dilates, forces pull it centripetally and posteriorly causing iris-lens contact, which prevents aqueous from passing between the lens and iris into the anterior chamber (this mechanism is termed pupillary block). Pressure from the continued secretion of aqueous into the posterior chamber by the ciliary body pushes the peripheral iris anteriorly (causing a forward-bowing iris called iris bombe), closing the angle. This closure blocks aqueous outflow, resulting in rapid (within hours) and severe (> 40 mm Hg) elevation of IOP. Because of the rapid onset, this condition is called primary acute angle-closure glaucoma and is an ophthalmic emergency requiring immediate treatment.

Intermittent angle-closure glaucoma occurs if the episode of pupillary block resolves spontaneously after several hours, usually after sleeping supine.

Chronic angle-closure glaucoma occurs if the angle narrows slowly, allowing scarring between the peripheral iris and trabecular meshwork; IOP elevation is slow.

Pupillary dilation (mydriasis) can push the iris into the angle and precipitate acute angle-closure glaucoma in any person with narrow angles. This development is of particular concern when applying topical agents to dilate the eye for examination (e.g., cyclopentolate, phenylephrine) or for treatment (e.g., homatropine) or when giving systemic drugs that have the potential to dilate the pupils (e.g., scopolamine, α-adrenergic agonists commonly used to treat urinary incontinence, drugs with anticholinergic effects).

Secondary angle-closure glaucomas: The mechanical obstruction of the angle is due to a coexisting condition, such as proliferative diabetic retinopathy (PDR), ischemic central vein occlusion, uveitis, or epithelial down-growth. Contraction of a neovascular membrane (e.g., in PDR) or inflammatory scarring associated with uveitis can pull the iris into the angle.

Symptoms and Signs

Acute angle-closure glaucoma: Patients have severe ocular pain and redness, decreased vision, colored halos around lights, headache, nausea, and vomiting. The systemic complaints may be so severe that patients are misdiagnosed as having a neurologic or GI problem. Examination typically reveals conjunctival hyperemia, a hazy cornea, a fixed mid-dilated pupil, and anterior chamber inflammation. Vision is decreased. IOP is usually 40 to 80 mm Hg. The optic nerve is difficult to visualize because of corneal edema, and visual field testing is not done because of discomfort.

Chronic angle-closure glaucoma: This type of glaucoma manifests similarly to open-angle glaucoma (see p. 600). Some patients have ocular redness, discomfort, blurred vision, or headache that lessens with sleep (perhaps because of sleep-induced miosis and posterior displacement of the lens by gravity). On gonioscopy, the angle is narrow, and peripheral anterior synechiae (PAS) may be seen. IOP may be normal but is usually higher in the affected eye.
Diagnosis

- **Acute**: Measurement of IOP and clinical findings

- **Chronic**: Gonioscopy showing peripheral anterior synechiae and characteristic optic nerve and visual field abnormalities

Diagnosis of acute angle-closure glaucoma is clinical and by measurement of IOP. Gonioscopy may be difficult to perform in the involved eye because of a clouded cornea with friable corneal epithelium. However, examination of the other eye reveals a narrow or occludable angle. If the other eye has a wide angle, a diagnosis other than primary angle-closure glaucoma should be considered.

Diagnosis of chronic angle-closure glaucoma is based on the presence of PAS on gonioscopy and characteristic optic nerve and visual field changes (see p. 601).

Treatment

- **Acute**: Timolol, pilocarpine, and apraclonidine drops and a systemic osmotic drug followed promptly by laser peripheral iridotomy

- **Chronic**: Similar to primary open-angle glaucoma except that laser peripheral iridotomy may be done if the clinician feels that the procedure may slow the mechanical closing of the angle

**Acute angle-closure glaucoma**: Treatment must be initiated immediately because vision can be lost quickly and permanently. The patient should receive several drugs at once. A suggested regimen is timolol 0.5% one drop q 30 min for 2 doses; pilocarpine 2 to 4% one drop q 15 min for the first 1 to 2 h; apraclonidine 0.5 to 1% one drop q 30 min for 2 doses; acetazolamide 500 mg po initially followed by 250 mg q 6 h; and an osmotic agent, such as oral glycerol 1 mL/kg diluted with an equal amount of cold water, mannitol 1.0 to 1.5 mg/kg IV, or isosorbide 100 g po (220 mL of a 45% solution [NOTE: This form of isosorbide is not isosorbide dinitrate.]). Response is evaluated by measuring IOP. Miotics are generally not effective when IOP is > 40 or 50 mm Hg because of an anoxic pupillary sphincter.

Definitive treatment is with laser peripheral iridotomy (LPI), which opens another pathway for fluid to pass from the posterior to the anterior chamber, breaking the pupillary block. It is done as soon as the cornea is clear and inflammation has subsided. In some cases the cornea clears within hours of lowering the IOP; in other cases, it can take 1 to 2 days. Because the chance of having an acute attack in the other eye is 80%, LPI is done on both eyes.

The risk of complications with LPI is extremely low compared with its benefits. Glare, which can be bothersome, may occur if the iridotomy is not placed superiorly enough for the upper lid to cover it.

**Chronic angle-closure glaucoma**: Patients with chronic, subacute, or intermittent angle-closure glaucoma should also have LPI. Additionally, patients with a narrow angle, even in the absence of symptoms, should undergo prompt LPI to prevent angle-closure glaucoma.

The drug and surgical treatments are the same as with open-angle glaucoma. Laser trabeculoplasty is relatively contraindicated if the angle is so narrow that additional PAS may form after the laser procedure.
Chapter 66. Cataract

(For developmental or congenital cataracts, see p. 2920.)

A cataract is a congenital or degenerative opacity of the lens. The main symptom is gradual, painless vision blurring. Diagnosis is by ophthalmoscopy and slit-lamp examination. Treatment is surgical removal and placement of an intraocular lens.

Lens opacity can develop in several locations:

• Central lens nucleus (nuclear cataract)
• Beneath the posterior lens capsule (posterior subcapsular cataract)

Etiology

Cataracts occur with aging. Other risk factors may include the following:

• Trauma (sometimes causing cataracts years later)
• Smoking
• Alcohol use
• Exposure to x-rays
• Heat from infrared exposure
• Systemic disease (eg, diabetes)
• Uveitis
• Systemic drugs (eg, corticosteroids)
• Undernutrition
• Dark eyes
• Possibly chronic ultraviolet exposure

Many people have no risk factors other than age. Some cataracts are congenital, associated with numerous syndromes and diseases.

Symptoms and Signs

Cataracts generally develop slowly over years. Early symptoms may be loss of contrast, glare (halos and starbursts around lights), needing more light to see well, and problems distinguishing dark blue from black. Painless blurring eventually occurs. The degree of blurring depends on the location and extent of the opacity. Double vision occurs rarely.

With a nuclear cataract (see Plate 4), distance vision worsens. Near vision may improve in the early stages because of changes in the refractive index of the lens; presbyopic patients may be temporarily able to read without glasses (second sight).

A posterior subcapsular cataract disproportionately affects vision because the opacity is located at the crossing point of incoming light rays. Such cataracts reduce visual acuity more when the pupil constricts (eg, in bright light, during reading). They are also the type most likely to cause loss of contrast as well as
glare, especially from bright lights or from car headlights while driving at night.

Rarely, the cataract swells, occluding the trabecular drainage meshwork and causing secondary closed-angle glaucoma and pain.

**Diagnosis**

- Ophthalmoscopy followed by slit-lamp examination

Diagnosis is best made with the pupil dilated. Well-developed cataracts appear as gray, white, or yellow-brown opacities in the lens. Examination of the red reflex through the dilated pupil with the ophthalmoscope held about 30 cm away usually discloses subtle opacities. Small cataracts stand out as dark defects in the red reflex. A large cataract may obliterate the red reflex. Slit-lamp examination provides more details about the character, location, and extent of the opacity.

**Treatment**

- Surgical removal of the cataract
- Placement of an intraocular lens

Frequent refractions and corrective lens prescription changes may help maintain useful vision during cataract development. Occasionally, long-term pupillary dilation (with phenylephrine 2.5% q 4 to 8 h) is helpful for small centrally located cataracts. Indirect lighting while reading minimizes pupillary constriction and may optimize vision for close tasks. Polarized lenses reduce glare.

Usual indications for surgery include the following:

- Best vision obtained with glasses is worse than 20/40 (< 6/12), or vision is significantly decreased under glare conditions (eg, oblique lighting while trying to read a chart) in a patient with bothersome halos or starbursts.
- Patients sense that vision is limiting (eg, by preventing activities of daily living such as driving, reading, hobbies, and occupational activities).
- Vision could potentially be meaningfully improved if the cataract is removed (ie, a significant portion of the vision loss must be caused by the cataract).

Far less common indications include cataracts that cause glaucoma or that obscure the fundus in patients who need periodic fundus examinations for management of diseases such as diabetic retinopathy and glaucoma. There is no advantage to removing a cataract early.

Cataract extraction is usually done using a topical or local anesthetic and IV sedation. There are 3 extraction techniques. In **intracapsular cataract extraction**, the cataract and lens capsule are removed in one piece; this technique is rarely used. In **extracapsular cataract extraction**, the hard central nucleus is removed in one piece and then the soft cortex is removed in multiple small pieces. In **phacoemulsification**, the hard central nucleus is dissolved by ultrasound and then the soft cortex is removed in multiple small pieces. Phacoemulsification requires the smallest incision, thus enabling the fastest healing, and is usually the preferred procedure. In extracapsular extraction and phacoemulsification, the lens capsule is not removed.

A plastic or silicone lens is almost always implanted intraocularly to replace the optical focusing power lost by removal of the crystalline lens. The lens implant is usually placed on or within the lens capsule (posterior chamber lens). The lens can also be placed in front of the iris (anterior chamber lens) or attached to the iris and within the pupil (iris plane lens). Iris plane lenses are rarely used in the US because many designs led to a high frequency of postoperative complications. Multifocal intraocular lenses are newer and have different focusing zones that may reduce dependence on glasses after surgery. Patients occasionally experience glare or halos with these lenses, especially under low-light
In most cases, a tapering schedule of topical antibiotics (eg, moxifloxacin 0.5% 1 drop qid) and topical corticosteroids (eg, prednisolone acetate 1% 1 drop qid) is used for up to 4 wk postsurgery. Patients often wear an eye shield while sleeping and should avoid the Valsalva maneuver, heavy lifting, excessive forward bending, and eye rubbing for several weeks.

Major complications of cataract surgery are rare. Complications include the following:

- **Intraoperative:** Bleeding beneath the retina, causing the intraocular contents to extrude through the incision (choroidal hemorrhage), vitreous prolapsing out of the incision (vitreous loss), fragments of the cataract dislocating into the vitreous, incisional burn, and detachment of corneal endothelium and its basement membrane (Descemet's membrane)

- **Within the first week:** Endophthalmitis (infection within the eye) and glaucoma

- **Within the first month:** Cystoid macular edema

- **Months later:** Bullous keratopathy (ie, swelling of the cornea due to damage to the corneal pump cells during cataract surgery), retinal detachment, and posterior capsular opacification (common, but treatable with laser)

After surgery, vision returns to 20/40 (6/12) or better in 95% of eyes if there are no preexisting disorders such as amblyopia, retinopathy, macular degeneration, and glaucoma. If an intraocular lens is not implanted, contact lenses or thick glasses are needed to correct the resulting hyperopia.

**Prevention**

Many ophthalmologists recommend ultraviolet-coated eyeglasses or sunglasses as a preventive measure. Reducing risk factors such as alcohol, tobacco, and corticosteroids and controlling blood glucose in diabetes delay onset. A diet high in vitamin C, vitamin A, and carotenoids (contained in vegetables such as spinach and kale) may protect against cataracts.
Chapter 67. Uveitis

Introduction

Uveitis is inflammation of the uveal tract—the iris, ciliary body, and choroid. Most cases are idiopathic, but identifiable causes include various infections and systemic diseases, many of which are autoimmune. Symptoms include decreased vision, ocular ache, redness, photophobia, and floaters. Although intraocular inflammation is identified clinically, identifying the cause of the inflammation typically requires testing. Treatment depends on cause but typically includes topical, locally injected, or systemic corticosteroids with a topical cycloplegic-mydriatic drug. Noncorticosteroid immunosuppressive drugs may be used in severe and refractory cases. Infectious causes require antimicrobial therapy.

Inflammation of the uvea (uveitis) may occur with or without vitreitis, retinitis, papillitis, or optic neuritis. Uveitis is classified anatomically as anterior, intermediate, or posterior uveitis or panuveitis.

**Anterior uveitis** is localized primarily to the anterior segment of the eye and includes iritis (inflammation in the anterior chamber alone) and iridocyclitis (inflammation in the anterior chamber and anterior vitreous).

**Intermediate uveitis** (peripheral uveitis or chronic cyclitis) occurs in the vitreous.

**Posterior uveitis** refers to any form of retinitis, choroiditis, or inflammation of the optic disk.

**Panuveitis** (also called diffuse uveitis) implies inflammation in both the anterior and posterior chambers.

Etiology

Most cases are idiopathic and presumed to be autoimmune in origin. Identifiable causes include

- Trauma
- Ocular and systemic infections
- Systemic autoimmune disorders

The most common cause of anterior uveitis is trauma (traumatic iridocyclitis). Other causes are spondyloarthropathies (20 to 25%), juvenile idiopathic arthritis, and herpesvirus (herpes simplex and varicella-zoster) infection. Half of all cases of anterior uveitis are idiopathic.

Most intermediate uveitis is idiopathic. Uncommon identifiable causes include multiple sclerosis, sarcoidosis, TB, syphilis, and, in endemic regions, Lyme disease.

Most posterior uveitis (retinitis) is idiopathic. The most commonly recognized cause of posterior uveitis in immunocompetent patients is toxoplasmosis; the most commonly recognized cause in patients with HIV/AIDS is cytomegalovirus (CMV).

The most commonly identified cause of panuveitis is sarcoidosis, but most cases remain idiopathic despite appropriate testing.

Infrequently, systemic drugs cause uveitis (usually anterior). Examples are sulfonamides, pamidronate (an inhibitor of bone resorption), rifabutin, and cidofovir.

Systemic diseases causing uveitis and their treatment are discussed elsewhere in THE MANUAL.

Symptoms and Signs

Symptoms and signs may be subtle and vary depending on the site and severity of inflammation.
**Anterior uveitis** tends to be the most symptomatic, usually manifesting with pain (ocular ache), redness, photophobia, and, to a variable degree, decreased vision. Signs include hyperemia of the conjunctiva adjacent to the cornea (ciliary flush or limbal injection). Slit-lamp findings include cells and flare (a haze) in the anterior chamber (aqueous humor), keratic precipitates (WBC clumps on the inner corneal surface), and posterior synechiae. With severe anterior uveitis, WBCs may layer in the anterior chamber (hypopyon).

**Intermediate uveitis** is typically painless and manifests with floaters and decreased vision. The primary sign is cells in the vitreous humor. Aggregates and condensations of inflammatory cells often occur over the pars plana (near the junction of the iris and sclera), forming snowballs. Vision may be decreased because of floaters or cystoid macular edema, which results from fluid leakage from blood vessels in the macula. Confluent and condensed vitreous cells and snowballs over the pars plana may cause a classic snowbank appearance, which can be associated with neovascularization of the retinal periphery.

**Posterior uveitis** may give rise to diverse symptoms but most commonly causes floaters and decreased vision as occurs in intermediate uveitis. Signs include cells in the vitreous humor; white or yellow-white lesions in the retina (retinitis), underlying choroid (choroiditis), or both; exudative retinal detachments; retinal vasculitis; and optic disk edema.

**Panuveitis** may cause any combination of the previously mentioned symptoms and signs.

**Consequences:** Consequences of uveitis include profound and irreversible vision loss, especially when uveitis is unrecognized, inadequately treated, or both. The most frequent complications include cataract; glaucoma; retinal detachment; neovascularization of the retina, optic nerve, or iris; and cystoid macular edema (the most common cause of decreased vision in patients with uveitis).

**Diagnosis**

- Slit-lamp examination
- Ophthalmoscopy after pupil dilation

Uveitis should be suspected in any patient who has ocular ache, redness, photophobia, floaters, or decreased vision. Patients with anterior uveitis have ocular ache in the affected eye if light is shined in the unaffected eye (true photophobia), which is uncommon in conjunctivitis. Diagnosis of anterior uveitis is by recognizing cells and flare in the anterior chamber. Cells and flare are seen with a slit lamp and are most evident when using a narrow, intensely bright light focused on the anterior chamber in a dark room. Findings of intermediate and posterior uveitis are most easily seen after dilating the pupil (see p. 538). Indirect ophthalmoscopy (usually done by an ophthalmologist) is more sensitive than direct ophthalmoscopy. (NOTE: If uveitis is suspected, patients should be referred immediately for complete ophthalmologic evaluation.)

Many conditions that cause intraocular inflammation can mimic uveitis and should be considered in the appropriate clinical settings. Such conditions include intraocular cancers in the very young (typically retinoblastoma and leukemia) and in the elderly (intraocular lymphoma). Less commonly, retinitis pigmentosa (see p. 618) can manifest with mild inflammation, which may be confused with uveitis.

**Treatment**

- Corticosteroids (usually topical)
- Cycloplegic-mydriatic drugs

Treatment of active inflammation usually involves corticosteroids given topically or by periocular or intraocular injection along with a cycloplegic-mydriatic drug (eg, homatropine 2% or 5% drops bid to qid depending on severity). Antimicrobial drugs are used to treat infectious uveitis. Particularly severe or chronic cases may require systemic corticosteroids, systemic noncorticosteroid immunosuppressive
drugs, laser phototherapy, cryotherapy applied transsclerally to the retinal periphery, or surgical removal of the vitreous (vitrectomy).

**Uveitis Caused by Connective Tissue Disease**

A number of connective tissue diseases cause inflammation of the uveal tract.

**Spondyloarthropathies:** The seronegative spondyloarthropathies (see p. 341) are a common cause of anterior uveitis. RA, in contrast, is not associated with uveitis. Ocular inflammation is most common with ankylosing spondylitis but also occurs with reactive arthritis, inflammatory bowel disease (ulcerative colitis and Crohn's disease), and psoriatic arthritis. Uveitis is classically unilateral, but recurrences are common and active inflammation may alternate between eyes. Men are affected more commonly than women. Most patients, regardless of sex, are HLA-B27 positive.

Treatment requires a topical corticosteroid and a cycloplegic-mydriatic drug. Occasionally, periocular corticosteroids are required.

**Juvenile idiopathic arthritis (JIA, also known as juvenile RA):** JIA characteristically causes chronic bilateral iridocyclitis in children, particularly those with the pauciarticular variety (see p. 339). Unlike most forms of anterior uveitis, however, JIA tends not to cause pain, photophobia, and conjunctival injection but only blurring and meiosis and is, therefore, often referred to as white iritis. JIA-associated uveitis is more common among girls.

Recurrent bouts of inflammation are best treated with a topical corticosteroid and a cycloplegic-mydriatic drug. Long-term control often requires use of a noncorticosteroid immunosuppressive drug (eg, methotrexate, mycophenolate mofetil).

**Sarcoidosis:** Sarcoidosis (see also p. 1965) accounts for 10 to 20% of cases of uveitis, and about 25% of patients with sarcoidosis develop uveitis. Sarcoid uveitis is more common among blacks and the elderly.

Virtually any symptoms and signs of anterior, intermediate, posterior, or panuveitis can occur. Suggestive findings include conjunctival granulomas, large keratic precipitates on the corneal endothelium (so-called granulomatous or mutton fat precipitates), iris granulomas, and retinal vasculitis. Biopsy of suggestive lesions, which provides the most secure diagnosis, is usually done on the conjunctiva; it is rarely done on intraocular tissues because of the risk associated with the procedure.

Treatment usually involves topical, periocular, intraocular, or systemic corticosteroids, or a combination, along with a topical cycloplegic-mydriatic drug. Patients with moderate to severe inflammation may require a noncorticosteroid immunosuppressive drug (eg, methotrexate, mycophenolate mofetil, azathioprine).

**Behçet's syndrome:** This condition is rare in North America but is a fairly common cause of uveitis in the Middle East and Far East (see also p. 315).

Typical findings include severe anterior uveitis with hypopyon, retinal vasculitis, and optic disk inflammation. The clinical course is usually severe with multiple recurrences.

Diagnosis requires the presence of associated systemic manifestations, such as oral aphthous or genital ulcers; dermatitis, including erythema nodosum; thrombophlebitis; or epididymitis. Oral aphthae may be biopsied to show an occlusive vasculitis. There are no laboratory tests for Behçet's syndrome.

Treatment with local and systemic corticosteroids and a cycloplegic-mydriatic drug may alleviate acute exacerbations, but most patients eventually require systemic corticosteroids and a noncorticosteroid immunosuppressive drug (eg, cyclosporine, chlorambucil) to control the inflammation and avoid the serious complications of long-term corticosteroid treatment. Biologic agents such as interferons and tumor necrosis factor inhibitors have been effective in selected patients unresponsive to other therapies.

**Vogt-Koyanagi-Harada (VKH) syndrome:** VKH syndrome is an uncommon systemic disorder...
characterized by uveitis accompanied by cutaneous and neurologic abnormalities. VKH syndrome is particularly common among people of Asian, Asian Indian, and American Indian descent. Women in their 20s and 30s are affected more often than men. The etiology is unknown, although an autoimmune reaction directed against melanin-containing cells in the uveal tract, skin, inner ear, and meninges is strongly suspected.

Neurologic symptoms tend to occur early and include tinnitus, dysacusis (auditory agnosia), vertigo, headache, and meningismus. Cutaneous findings frequently occur later and include patchy vitiligo (especially common on the eyelids, low back, and buttocks), poliosis (a localized patch of white hair), and alopecia, often involving the head and neck. Common findings include serous retinal detachment, optic disk edema, and choroiditis. Long-term complications include cataracts, glaucoma, subretinal fibrosis, and choroidal neovascularization.

Early treatment includes local and systemic corticosteroids and a cycloplegic-mydriatic drug. Many patients also require a noncorticosteroid immunosuppressive drug (eg, methotrexate, azathioprine, mycophenolate mofetil).

**Endophthalmitis**

**Endophthalmitis is an acute panuveitis resulting most often from bacterial infection.**

Most cases of endophthalmitis are caused by gram-positive bacteria, such as *Staphylococcus epidermidis* or *S. aureus*. Gram-negative organisms can also cause endophthalmitis, tend to be more virulent, and predict a poorer prognosis. Fungal and protozoan causes of endophthalmitis are rare. Most cases occur after penetrating ocular trauma or intraocular surgery (exogenous). Less commonly, infection reaches the eye via the bloodstream after systemic surgery or dental procedures or when IV lines or IV drugs are used (endogenous).

Endophthalmitis is a medical emergency because vision prognosis is directly related to the time from onset to treatment. Rarely, untreated intraocular infections extend beyond the confines of the eye to involve the orbit and CNS.

Exogenous endophthalmitis typically causes severe ocular ache and decreased vision. Signs include intense conjunctival hyperemia and intraocular inflammation within the anterior chamber and vitreous, occasionally with eyelid edema.

Diagnosis requires a high index of suspicion in at-risk patients, especially those with recent eye surgery or trauma. Gram stain and culture of aspirates from the anterior chamber and vitreous are standard. Patients with suspected endogenous endophthalmitis should also have blood and urine cultures.

Initial treatment includes broad-spectrum intravitreal antibiotics, most commonly vancomycin and ceftazidime. Patients with endogenous endophthalmitis should receive both intravitreal and IV antibiotics. Therapy is modified based on culture and sensitivity results.

Vision prognosis is often poor, even with early and appropriate treatment. Patients with count-fingers or worse vision at presentation should be considered for vitrectomy and use of intraocular corticosteroids. Corticosteroids are, however, contraindicated in fungal endophthalmitis.

**Infectious Uveitis**

A number of infectious diseases cause uveitis (see Table 67-1). The most common are

**Table 67-1. Infectious Causes of Uveitis**

herpes simplex virus, varicella-zoster virus, and CMV infection and toxoplasmosis. Different organisms affect different parts of the uveal tract.
Herpesvirus: Herpes simplex virus (see also p. 1417) causes anterior uveitis. Varicellazoster virus does so less commonly, although the prevalence of zoster-associated anterior uveitis increases with age. Symptoms include ocular ache, photophobia, and decreased vision. Signs include redness; conjunctival injection and anterior chamber inflammation (cells and flare), often accompanied by corneal inflammation (keratitis); decreased corneal sensation; and patchy or sectorial iris atrophy. Intraocular pressure may be elevated as well; elevation can be detected by using applination tonometry with a Schiotz tonometer, a Goldmann tonometer, or a pneumotonometer.

Treatment should generally be initiated by an ophthalmologist and should include a topical corticosteroid and a cycloplegic-mydriatic drug. Acyclovir (400 mg po 5 times/day for herpes simplex virus and 800 mg po 5 times/day for herpes zoster virus) may also be given. Drops to lower intraocular pressure may be required in patients with ocular hypertension.

Much less commonly, varicella-zoster and herpes simplex viruses cause a rapidly progressing form of retinitis called acute retinal necrosis (ARN), which typically manifests as confluent retinitis, occlusive retinal vasculitis, and moderate to severe vitreous inflammation. One third of ARN cases become bilateral, and in three fourths of eyes, retinal detachment occurs. ARN may also occur in patients with HIV/AIDS, but severely immunocompromised patients can have less prominent vitreous inflammation. Vitreous biopsy for culture and PCR analysis may be useful in diagnosing ARN. Treatment options include IV acyclovir, IV ganciclovir or fosfomycin, intravitreal ganciclovir or fosfomycin, and oral valacyclovir or valganciclovir.

Toxoplasmosis: Toxoplasmosis (see also p. 1390) is the most common cause of retinitis in immunocompetent patients. Most cases are transmitted congenitally, although acquired cases occur. Symptoms of floaters and decreased vision may be due to cells in the vitreous humor or to retinal lesions or scars. Concurrent anterior segment involvement can occur and may cause ocular ache, redness, and photophobia. Laboratory testing should include serum anti-Toxoplasma antibody titers.

Treatment is recommended for patients with posterior lesions that threaten vital visual structures, such as the optic disk or macula, and for immunocompromised patients. Multidrug therapy is commonly prescribed; it includes pyrimethamine, sulfonamides, clindamycin, and, in select cases, systemic corticosteroids. Corticosteroids should not, however, be used without concurrent antimicrobial coverage. Long-acting periocular and intraocular corticosteroids (eg, triamcinolone acetonide) should be avoided. Patients with small peripheral lesions that do not directly threaten vital visual structures may be observed without treatment and should begin to show slow improvement in 1 to 2 mo.

Cytomegalovirus: CMV (see also p. 1416) is the most common cause of retinitis in immunocompromised patients, affecting ≤ 5% of patients with HIV/AIDS receiving highly active antiretroviral therapy (HAART). Most affected patients have a CD4+ count < 100 cells/μL. CMV retinitis may also occur in neonates and in pharmacologically immunosuppressed patients but is uncommon.

The diagnosis is largely clinical based on direct or indirect ophthalmoscopic examination; serologic tests are of limited use. Treatment in patients with HIV/AIDS is with systemic or local (implant) ganciclovir, systemic fosfomycin, or valganciclovir. Therapy is typically continued indefinitely, unless immune reconstitution is achieved with combination antiretroviral therapy (typically a CD4+ count > 100 cells/μL for at least 3 mo).

Sympathetic Ophthalmia

Sympathetic ophthalmia is inflammation of the uveal tract after trauma or surgery to the other eye.

Sympathetic ophthalmia is a rare granulomatous uveitis that occurs after penetrating trauma or surgery to the other eye. Sympathetic ophthalmia has been estimated to occur in up to 0.5% of nonsurgical and in < 0.1% of surgical penetrating eye wounds. The underlying mechanism is thought to be an autoimmune reaction directed against melanin-containing cells in the uvea. Uveitis appears within 2 to 12 wk after injury in about 80% of cases. Isolated cases of sympathetic ophthalmia have occurred as early as 1 wk or as late as 30 yr after the initial injury or surgery.
Symptoms typically include floaters and decreased vision. Choroiditis, often with overlying exudative retinal detachment, is common.

Treatment typically requires oral corticosteroids plus a long-term noncorticosteroid immunosuppressive drug. Prophylactic enucleation of a severely injured eye should be considered within 2 wk of vision loss to minimize the risk of sympathetic ophthalmia developing in the other eye, but only when the injured eye has no vision potential.
Chapter 68. Retinal Disorders

Introduction

(For Retinopathy of Prematurity, see p. 2781.)

The retina is the light-sensing layer of tissue at the back of the eye; it contains the rods, cones, and nerve endings that transform light into neural impulses. Retinal disorders may be inherited or caused by vascular disease, inflammation, infection, cancer, or trauma. Visual rehabilitation is indicated for all patients who have severe vision loss.

Age-Related Macular Degeneration

(Senile Macular Degeneration)

Age-related macular degeneration (AMD) is the most common cause of irreversible central vision loss in elderly patients. Funduscopic findings are diagnostic; fluorescein angiography and optical coherence tomography assist in directing treatment. Treatment is with dietary supplements, intravitreal injection of anti-vascular endothelial growth factor, laser photocoagulation, photodynamic therapy, and low-vision devices.

AMD is a leading cause of permanent, irreversible vision loss in the elderly. It is more common among whites.

Etiology

Risk factors include the following:

• Genetic variants (eg, abnormal complement factor H)
• Smoking
• Cardiovascular disease
• Hypertension
• A diet low in ω-3 fatty acids and dark green leafy vegetables
• Age

Pathophysiology

Two different forms occur:

• Dry (atrophic), in about 90% of cases
• Wet (exudative or neovascular), in about 10% of cases

Ninety percent of the blindness caused by AMD occurs in patients who have the wet form.

Dry AMD causes retinal pigmentation changes, yellow spots (drusen—see Plate 3), and areas of chorioretinal atrophy (referred to as geographic atrophy). There is no elevated macular scar, edema, hemorrhage, or exudation.

Wet AMD begins as dry AMD. Choroidal neovascularization (abnormal new vessel formation) occurs under the retina. Localized macular edema or hemorrhage may elevate an area of the macula or cause a localized retinal pigment epithelial detachment. Eventually, neovascularization causes an elevated scar under the macula.
Symptoms and Signs

**Dry AMD:** The loss of central vision is slow, painless, and usually mild. Central blind spots (scotomas) usually occur late and can sometimes become severe. Symptoms are usually bilateral.

Funduscopic changes include the following:

- Pigment changes
- Drusen
- Areas of chorioretinal atrophy

**Wet AMD:** Rapid vision loss is more typical of wet AMD. The first symptom is usually visual distortion, such as a central blind spot (scotoma) or curving of straight lines (metamorphopsia). Peripheral vision and color vision are generally unaffected; however, the patient may become legally blind (< 20/200 vision) in the affected eye or eyes, particularly if AMD is not treated. Wet macular degeneration usually affects one eye at a time; thus, symptoms of wet AMD are often unilateral.

Funduscopic changes include the following:

- Subretinal hemorrhage in or around the macula
- Localized retinal elevation
- Retinal edema
- Gray discoloration of the subretinal space
- Exudates in or around the macula
- Detachment of retinal pigment epithelium

**Diagnosis**

- Funduscopic examination
- Fluorescein angiography
- Optical coherence tomography

Both forms of AMD are diagnosed by funduscopic examination. Visual changes can often be detected with an Amsler grid (see p. 539). Fluorescein angiography is done when findings suggest wet AMD. Angiography demonstrates and characterizes subretinal choroidal neovascular membranes and can delineate areas of geographic atrophy. Optical coherence tomography (OCT) aids in identifying intraretinal and subretinal fluid and can help assess response to treatment.

**Treatment**

- Dietary supplements for dry or unilateral wet AMD
- Intravitreal anti-vascular endothelial growth factor drugs or laser treatments for wet AMD
- Supportive measures

**Dry AMD:** There is no way to reverse damage caused by dry AMD, but patients with extensive drusen, pigment changes, or geographic atrophy benefit from daily supplements of the following:
• Zinc oxide 80 mg
• Copper 2 mg
• Vitamin C 500 mg
• Vitamin E 400 IU
• β-Carotene 15 mg (or vitamin A 28,000 IU)

Vitamin A is sometimes substituted for β-carotene. In smokers, β-carotene and vitamin A can increase the risk of lung cancer. For this reason, they are contraindicated in patients who have smoked in the previous 7 yr. Reducing cardiovascular risk factors, including eating foods high in ω-3 fatty acids and dark green leafy vegetables may help.

Wet AMD: Patients with wet AMD in one eye may benefit from daily supplements that are recommended for dry AMD. The choice of other treatment depends on the size, location, and type of neovascularization. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs (usually ranibizumab or bevacizumab or, occasionally, pegaptanib) can substantially reduce the risk of vision loss and can help restore reading vision in up to one third of patients. Thermal laser photocoagulation of neovascularization outside the fovea may prevent severe vision loss. Photodynamic therapy, a type of laser treatment, helps under specific circumstances. Corticosteroids (eg, triamcinolone) are sometimes injected intraocularly along with an anti-VEGF drug. Other treatments, including transpupillary thermotherapy, subretinal surgery, and macular translocation surgery, are seldom used.

Supportive measures: For patients who have lost central vision, low-vision devices such as magnifiers, high-power reading glasses, computer monitors, and telescopic lenses, are available. Also, certain types of software can display computer data in large print or read information aloud in a synthetic voice. Low-vision counseling is advised.

Central Retinal Artery Occlusion

(Retinal Artery Occlusion)

Central retinal artery occlusion is blockage of the central retinal artery, usually due to an embolism. Its symptom is sudden, painless, unilateral blindness. Diagnosis is by history and characteristic retinal findings on funduscopy. Decreasing intraocular pressure can be attempted within the first 24 h of occlusion. If patients present within the first few hours of occlusion, some centers catheterize the carotid artery and selectively inject thrombolytic drugs.

Etiology

Retinal artery occlusion may be due to embolism or thrombosis.

Emboli may come from any of the following:

• Atherosclerotic plaques
• Endocarditis
• Fat
• Atrial myxoma

Giant cell arteritis (see p. 319) is another important cause of arterial occlusion.

Occlusion can affect a branch of the retinal artery as well as the central retinal artery.
Neovascularization (abnormal new vessel formation) of the retina or iris (rubeosis iridis) with secondary (neovascular) glaucoma can occur weeks to months after occlusion. Vitreous hemorrhage may result from retinal neovascularization.

**Symptoms and Signs**

Retinal artery occlusion causes sudden, painless blindness or visual field defect, usually unilaterally.

The pupil may respond poorly to direct light but constricts briskly when the other eye is illuminated (relative afferent pupillary defect). In acute cases, funduscopy discloses a pale, opaque fundus with a red fovea (cherry-red spot—see Plate 5). Typically, the arteries are attenuated and may even appear bloodless. An embolic obstruction is sometimes visible. If a major branch is occluded rather than the entire artery, fundus abnormalities and vision loss are limited to that sector of the retina.

Patients who have giant cell arteritis often have headache, a tender and palpable temporal artery, jaw claudication, fatigue, or a combination.

**Diagnosis**

- Clinical evaluation
- Sometimes fluorescein angiography

The diagnosis is suspected when a patient has acute, painless vision loss. Funduscopy is usually confirmatory. Fluorescein angiography is often done and shows obstruction clearly.

Once the diagnosis is made, carotid Doppler ultrasonography and echocardiography should be done to locate any embolic source so that further embolization can be prevented.

If giant cell arteritis is suspected, ESR, C-reactive protein, and platelet count are done.

**Prognosis**

Patients with a branch artery occlusion often maintain good to fair vision, but vision loss is often profound with central artery occlusion, even with treatment. Once retinal infarction occurs (possibly in < 2 h, almost always by 24 h), vision loss is permanent.

**Treatment**

- Sometimes reduction of intraocular pressure

Immediate treatment is indicated if occlusion occurred within 24 h of presentation. Reduction of intraocular pressure by ocular hypotensive drugs (eg, topical timolol 0.5%, acetazolamide 500 mg IV or po), intermittent digital massage over the closed eyelid, or anterior chamber paracentesis may dislodge an embolus and allow it to enter a smaller branch of the artery, thus reducing the area of retinal ischemia. Some centers have tried infusing thrombolytics into the carotid artery to dissolve the obstructing clot. Nonetheless, treatments for retinal artery occlusions rarely improve visual acuity. Surgical or laser-mediated embolectomy is available but not commonly done.

Patients with occlusion secondary to temporal arteritis should receive high-dose systemic corticosteroids.

**Central Retinal Vein Occlusion**

(Retinal Vein Occlusion)

Central retinal vein occlusion is a blockage of the central retinal vein by a thrombus. It causes
painless vision loss, usually suddenly. Diagnosis is by funduscopy. Most treatments are ineffective.

Etiology

Major risk factors include

• Hypertension

• Age

Other risk factors include

• Glaucoma

• Diabetes

• Increased blood viscosity

Occlusion may also be idiopathic. The condition is uncommon among young people. Occlusion may affect a branch of the retinal vein or the central retinal vein.

Neovascularization of the retina or iris (rubeosis iridis) with secondary (neovascular) glaucoma can occur weeks to months after occlusion. Vitreous hemorrhage may result from retinal neovascularization.

Symptoms and Signs

Painless visual loss is usually sudden, but it can also occur gradually over a period of days to weeks. Funduscopy reveals hemorrhages throughout the retina, engorgement and tortuosity of the retinal veins, and, usually, significant retinal edema (see Plate 6). These changes are limited to one quadrant if obstruction involves only a branch of the central retinal vein.

Diagnosis

• Funduscopy

The diagnosis is suspected in patients with painless visual loss, particularly those at risk. Funduscopy confirms the diagnosis. Patients with a central retinal vein occlusion are evaluated for hypertension and glaucoma and tested for diabetes. Young patients are tested for increased blood viscosity (with a CBC and other coagulable factors as deemed necessary).

Prognosis

Most patients have some visual deficit. In mild cases, there can be spontaneous improvement to near-normal vision over a variable period of time. Visual acuity at presentation is a good indicator of final vision. If visual acuity is at least 20/40, visual acuity will likely remain good, occasionally near normal. If visual acuity is worse than 20/200, it will remain at that level or worsen in 80% of patients.

Treatment

• Panretinal photocoagulation if neovascularization develops

There is no generally accepted medical therapy for occlusion itself. However, if neovascularization develops, panretinal photocoagulation should be initiated because it may decrease vitreous hemorrhages and prevent neovascular glaucoma.

Clinical trials are investigating intravitreal injection of corticosteroids and anti-vascular endothelial growth factor.
Diabetic Retinopathy

Diabetic retinopathy includes microaneurysms, intraretinal hemorrhage, exudates, macular edema, macular ischemia, neovascularization, vitreous hemorrhage, and traction retinal detachment. Symptoms may not develop until late in the disease. Diagnosis is by funduscopy; further details are elucidated by fluorescein angiography and optical coherence tomography. Treatment includes control of diabetes and BP and ocular laser photocoagulation, intravitreal injection of drugs, vitrectomy, or a combination.

Pathophysiology

Diabetic retinopathy is a major cause of blindness. The degree of retinopathy is highly correlated with

- Duration of diabetes
- Blood glucose levels
- BP levels

Pregnancy can impair blood glucose control and thus worsen retinopathy.

Nonproliferative retinopathy: (also called background retinopathy) develops first and causes increased capillary permeability, microaneurysms, hemorrhages, exudates, macular ischemia, and macular edema (thickening of the retina caused by fluid leakage from capillaries).

Proliferative retinopathy: develops after nonproliferative retinopathy and is more severe; it may lead to vitreous hemorrhage and traction retinal detachment. Proliferative retinopathy is characterized by abnormal new vessel formation (neovascularization), which occurs on the inner (vitreous) surface of the retina and may extend into the vitreous cavity and cause vitreous hemorrhage. The neovascularization is often accompanied by preretinal fibrous tissue, which, along with the vitreous humor, can contract, resulting in traction retinal detachment. Neovascularization may also occur in the anterior segment of the eye on the iris; neovascular membrane growth in the angle of the eye at the peripheral margin of the iris can result, leading to neovascular glaucoma. Vision loss with proliferative retinopathy may be severe.

Clinically significant macular edema can occur with nonproliferative or proliferative retinopathy and is the most common cause of vision loss due to diabetic retinopathy.

Symptoms and Signs

Nonproliferative retinopathy: Vision symptoms accompany macular edema or macular ischemia. However, patients may be unaware of vision loss. The first signs of nonproliferative retinopathy are

- Capillary microaneurysms
- Dot and blot retinal hemorrhages
- Hard exudates
- Cotton-wool spots (soft exudates)

Hard exudates are discrete, yellow, and generally deeper than retinal vessels and suggest retinal edema. Cotton-wool spots are areas of microinfarction that lead to retinal opacification; they are fuzzy-edged and white and obscure underlying vessels (see Plate 10).

Signs in later stages are
Macular edema (seen on slit-lamp biomicroscopy as elevation and blurring of retinal layers)

Venous dilation and intraretinal microvascular abnormalities

**Proliferative retinopathy:** Symptoms may include blurred vision, black spots or flashing lights in the field of vision, and sudden, severe painless vision loss. Some of these symptoms may be caused by vitreous hemorrhage or traction retinal detachment.

Proliferative retinopathy, unlike nonproliferative retinopathy, causes fine preretinal capillaries (newly developed capillaries) to appear on the optic nerve or retinal surface (see Plates 11 and 23). Macular edema or retinal hemorrhage may be visible on funduscopy.

**Diagnosis**

- Funduscopy
- Fluorescein angiography
- Sometimes optical coherence tomography

Diagnosis is by funduscopy. Fluorescein angiography is used to determine the extent of damage, to develop a treatment plan, and to monitor the results of treatment. Optical coherence tomography is also useful to assess severity of macular edema and treatment response.

**Screening:** Because early detection is important, all patients with diabetes should have an annual dilated ophthalmologic examination. Pregnant patients with diabetes should be examined every trimester. Vision symptoms are indications for ophthalmologic referral.

**Treatment**

- Control of blood glucose and BP
- For macular edema, focal laser and possibly vitrectomy or intravitreal drugs
- For high-risk or complicated proliferative retinopathy, panretinal laser photocoagulation and sometimes vitrectomy

Control of blood glucose and BP are critical; intensive control of blood glucose slows progression of retinopathy. Clinically significant diabetic macular edema is treated with focal laser. Intravitreal injection of triamcinolone, as well as anti-vascular endothelial growth factor (VEGF) drugs, may help in more severe cases. Vitrectomy can help in recalcitrant diabetic macular edema. In select cases of severe nonproliferative retinopathy, panretinal laser photocoagulation may be used; however, most patients can be followed closely until proliferative retinopathy develops.

Proliferative diabetic retinopathy with high-risk characteristics of vitreous hemorrhage, extensive preretinal neovascularization, or anterior segment neovascularization/neovascular glaucoma, should be treated with panretinal laser photocoagulation. This treatment reduces the risk of severe vision loss significantly.

Vitrectomy can help preserve and often restore lost vision in patients with any of the following:

- Vitreous hemorrhage that persists for 3 mo
- Extensive preretinal membrane formation
- Traction retinal detachment
Prevention

Control of blood glucose and BP is critical; intensive control of blood glucose delays onset of retinopathy.

Hypertensive Retinopathy

Hypertensive retinopathy is retinal vascular damage caused by hypertension. Symptoms develop late. Funduscopic examination shows arteriolar constriction, arteriovenous nicking, vascular wall changes, flame-shaped hemorrhages, cotton-wool spots, yellow hard exudates, and papilledema. Treatment is directed at controlling BP and, when vision loss occurs, treating the retina.

Pathophysiology

Acute BP elevation typically causes reversible vasoconstriction in retinal blood vessels, and hypertensive crisis may cause papilledema. More prolonged or severe hypertension leads to exudative vascular changes, a consequence of endothelial damage and necrosis. Other changes (eg, arteriole wall thickening) typically require years of elevated BP to develop. Smoking compounds the adverse effects of hypertension on the retina.

Hypertension is a major risk factor for other retinal disorders (eg, retinal artery or vein occlusion, diabetic retinopathy). Also, hypertension combined with diabetes greatly increases risk of vision loss. Patients with hypertensive retinopathy are at high risk of hypertensive damage to other end organs.

Symptoms and Signs

Symptoms usually do not develop until late in the disease.

In the early stages, funduscopy identifies arteriolar constriction, with a decrease in the ratio of the width of the retinal arterioles to the retinal venules.

Chronic, poorly controlled hypertension causes the following:

• Permanent arterial narrowing

• Arteriovenous crossing abnormalities (arteriovenous nicking)

• Arteriosclerosis with moderate vascular wall changes (copper wiring) to more severe vascular wall hyperplasia and thickening (silver wiring)

Sometimes total vascular occlusion occurs. Arteriovenous nicking is a major predisposing factor to the development of a branch retinal vein occlusion.

If acute disease is severe, the following can develop:

• Superficial flame-shaped hemorrhages

• Small white superficial foci of retinal ischemia (cotton-wool spots—see Plate 18)

• Yellow hard exudates

• Optic disk edema (papilledema)

Yellow hard exudates represent intraretinal lipid deposition from leaking retinal vessels. These exudates can form a star-shaped lesion in the macula, particularly when hypertension is severe (see Plate 17). In severe hypertension, the optic disk becomes congested and edematous (papilledema).
indicating hypertensive crisis).

Diagnosis

Diagnosis is by history (duration and severity of hypertension) and funduscopy.

Treatment

Hypertensive retinopathy is managed primarily by controlling hypertension. Other vision-threatening conditions should also be aggressively controlled. If vision loss occurs, treatment of the retinal edema with laser or with intravitreal injection of corticosteroids or anti-vascular endothelial growth factor (VEGF) drugs may be useful.

Retinal Detachment

Retinal detachment is separation of the neural retina from the underlying retinal pigment epithelium. The most common cause is a retinal tear. Symptoms are decreased peripheral or central vision, often described as a curtain or dark cloud coming across the field of vision. Associated symptoms can include painless vision disturbances, including flashing lights and excessive floaters. Traction and serous retinal detachments cause either central or peripheral vision loss. Diagnosis is by funduscopy; ultrasonography may help determine the presence and type of retinal detachment if it cannot be seen with funduscopy. Immediate treatment is imperative if rhegmatogenous retinal detachment is acute and threatens central vision. Treatment of rhegmatogenous detachment may include sealing retinal holes (by laser, diathermy, or cryotherapy), supporting the holes with scleral buckling, pneumatic retinopexy, and vitrectomy.

Etiology

There are 3 types of detachment: rhegmatogenous, which involves a retinal tear, and traction and serous (exudative) detachment, which do not involve a tear (nonrhegmatogenous).

Rhegmatogenous detachment is the most common. Risk factors include the following:

- Myopia
- Previous cataract surgery
- Ocular trauma

Traction retinal detachment can be caused by vitreoretinal traction due to preretinal fibrous membranes as may occur in proliferative diabetic or sickle cell retinopathy.

Serous detachment results from transudation of fluid into the subretinal space. Causes include severe uveitis, especially in Vogt-Koyanagi-Harada syndrome, choroidal hemangiomas, and primary or metastatic choroidal cancers (see p. 619).

Symptoms and Signs

Retinal detachment is painless. Early symptoms of rhegmatogenous detachment may include dark or irregular vitreous floaters (particularly in large numbers), flashes of light (photopsias), and blurred vision. As detachment progresses, the patient notices a curtain, veil, or grayness in the field of vision. If the macula is involved, central vision becomes poor. Patients may have simultaneous vitreous hemorrhage. Traction and exudative (serous) retinal detachments can cause blurriness of vision, but they may not cause any symptoms in the early stages.

Diagnosis
• Indirect funduscopy with pupillary dilation

Retinal detachment should be suspected in patients, particularly those at risk, who have any of the following:

• Sudden increase or change in floaters
• Photopsias
• Curtain or veil across the visual field
• Any sudden, unexplained loss of vision
• Vitreous hemorrhage that obscures the retina

Funduscopy shows the retinal detachment and can differentiate the subtypes of retinal detachment in nearly all cases. Direct funduscopy using a handheld ophthalmoscope can miss some retinal detachments, which may be peripheral. Peripheral fundus examination, using either indirect ophthalmoscopy with scleral depression or using a 3-mirror lens, should be done.

If vitreous hemorrhage (which may be due to a retinal tear), cataract, corneal opacification, or traumatic injury obscures the retina, retinal detachment should be suspected and B-scan ultrasonography should be done.

**Treatment**

• Sealing retinal holes
• Scleral buckling
• Pneumatic retinopexy
• Vitrectomy

Although often localized, retinal detachments due to retinal tears can expand to involve the entire retina if they are not treated promptly. *Any patient with a suspected or established retinal detachment should be examined urgently by an ophthalmologist.*

**Rhegmatogenous detachment** is treated with one or more methods, depending on the cause and location of the lesion. One method involves sealing the retinal holes by laser, diathermy, or cryotherapy. The eye may be treated by scleral buckling (which indents the sclera, pushing the retina inward and thereby relieving vitreous traction on the retina); during this procedure, fluid may be drained from the subretinal space. Pneumatic retinopexy (intravitreal injection of gas) and vitrectomy are other treatments. Retinal tears without detachment can be sealed by laser photocoagulation or transconjunctival cryopexy. Nearly all rhegmatogenous detachments can be reattached surgically.

**Nonrhegmatogenous detachments** due to vitreoretinal traction may be treated by surgical vitrectomy; transudative detachments due to uveitis may respond to systemic corticosteroids, systemic corticosteroid-sparing drugs (eg, methotrexate, azathioprine, anti-tumor necrosis factor drugs), or a slow-release corticosteroid implant, which is surgically implanted into the eye. Primary and metastatic choroidal cancers also require treatment. Choroidal hemangiomas may respond to localized photocoagulation.

**Retinitis Pigmentosa**

Retinitis pigmentosa is a slowly progressive, bilateral degeneration of the retina and retinal pigment epithelium caused by various genetic mutations. Symptoms include night blindness and loss of peripheral vision. Diagnosis is by funduscopy, which demonstrates pigmentation in a bone-spicule configuration in the equatorial retina, narrowing of the retinal arterioles, a waxy
pallor of the optic disk, posterior subcapsular cataracts, and cells in the vitreous. Electroretinography helps confirm the diagnosis.

Abnormal gene coding for retinal proteins appears to be the cause of retinitis pigmentosa; several genes have been identified. Transmission may be autosomal recessive, autosomal dominant, or, infrequently, X-linked. It may occur as part of a syndrome (eg, Bassen-Kornzweig, Laurence-Moon). Some of these syndromes include congenital hearing loss as well.

**Symptoms and Signs**

Retinal rods are affected, causing defective night vision that becomes symptomatic at varying ages, sometimes in early childhood. Night vision may eventually be lost. A peripheral ring scotoma (detectable by visual field testing) widens gradually, so that central vision may also be affected in advanced cases.

The most conspicuous funduscopic finding is hyperpigmentation in a bone-spicule configuration in the midperipheral retina. Other findings include the following:

- Narrowing of the retinal arterioles
- Cystoid macular edema
- Waxy yellow appearance of the disk
- Posterior subcapsular cataracts
- Cells in the vitreous (less commonly)
- Myopia

**Diagnosis**

- Funduscopy
- Electroretinography

The diagnosis is suspected in patients with poor night vision or a family history. Diagnosis is by funduscopy, usually supplemented with electroretinography. Other retinopathies that can simulate retinitis pigmentosa should be excluded; they include retinopathies associated with syphilis, rubella, phenothiazine or chloroquine toxicity, and nonocular cancer. Family members should be examined and tested as necessary or desired to establish the hereditary pattern. Patients with a hereditary syndrome may wish to seek genetic counseling before having children.

**Treatment**

- Vitamin A

There is no way to reverse damage caused by retinitis pigmentosa, but vitamin A palmitate 20,000 units po once/day may help slow disease progression in some patients. Patients taking vitamin A palmitate should have regular liver function tests. Vision decreases as the macula becomes increasingly involved and can evolve to legal blindness.

**Epiretinal Membrane**

(Macular Pucker; Cellophane Maculopathy; Premacular Fibrosis)

Epiretinal membrane is formation of a thin membrane over the retina, which interferes with vision.
Epiretinal membrane typically occurs after age 50 and is most common among people > 75. An epiretinal membrane is a thin fibrotic membrane that forms over the retina and contracts, wrinkling the retina underneath.

Risk factors for epiretinal membrane are the following:

- Diabetic retinopathy
- Uveitis
- Retinal detachment
- Ocular injury

Most cases are idiopathic.

Symptoms may include blurred vision or distorted vision (eg, straight lines may appear wavy). Many patients say that it seems like they are looking through plastic wrap or cellophane. Diagnosis is by funduscopy. Fluorescein angiography and optical coherence tomography may also be helpful.

Most people need no treatment. If problems with vision are significant, the membrane can be removed surgically (membrane peel).

Cancers Affecting the Retina

Cancers affecting the retina usually begin in the choroid. Because the retina depends on the choroid for its support and half of its blood supply, damage to the choroid by a cancer is likely to affect vision.

Choroidal melanoma: Choroidal melanoma originates in the choroidal melanocytes. Choroidal melanoma is the most common cancer originating in the eye, with an incidence of about 1 in 2500 whites. It is less common among darker-skinned people. It occurs most frequently at age 55 to 60. It may spread locally or metastasize and be fatal.

Symptoms tend to develop late and include loss of vision and symptoms of retinal detachment (see p. 617).

Diagnosis is by funduscopy, supplemented, when indicated, by other tests, such as ultrasonography, CT, fluorescein angiography, and serial photographs.

Small cancers are treated with laser, radiation, or radioactive implants, which may preserve vision and save the eye. Rarely, local resection is used. Large cancers require enucleation.

Choroidal metastases: Choroidal metastases are common because the choroid is highly vascular. The most common primary cancers are those of the breast in women and of the lung and prostate in men.

Symptoms tend to develop late and include loss of vision and symptoms of retinal detachment.

Diagnosis is often incidental during routine ophthalmoscopy. Ultrasonography is usually done, and the diagnosis is confirmed using fine-needle biopsy.

Treatment is usually with chemotherapy, radiation therapy, or both.
Chapter 69. Optic Nerve Disorders

Introduction

The optic pathway includes the retina, optic nerve, optic chiasm, optic radiations, and occipital cortex (see Fig. 69-1). Damage along the optic pathway causes a variety of visual field changes (see Table 60-1 on p. 540).

Hereditary Optic Neuropathies

Hereditary optic neuropathies are genetic defects that cause vision loss, occasionally with cardiac or neurologic abnormalities. There is no effective treatment.

Hereditary optic neuropathies typically manifest in childhood or adolescence with bilateral, symmetric central vision loss. Optic nerve damage is usually permanent and in some cases progressive. By the time optic atrophy is detected, substantial optic nerve injury has already occurred.

Dominant optic atrophy: This disorder is inherited in an autosomal dominant fashion. It is believed to be the most common of the hereditary optic neuropathies, with prevalence in the range of 1:10,000 to 1:50,000. It is thought to be optic abiotrophy, premature degeneration of the optic nerve leading to progressive vision loss. Onset is in the 1st decade of life.

Leber's hereditary optic neuropathy: This disorder involves a mitochondrial DNA abnormality that affects cellular respiration. Although mitochondrial DNA throughout the body is affected, vision loss is the primary manifestation. Most cases (80 to 90%) occur in males. The disease is inherited with a maternal inheritance pattern, meaning that all offspring of a woman with the abnormality inherit the abnormality, but only females can pass on the abnormality because the zygote receives mitochondria only from the mother.

Symptoms and Signs

Dominant optic atrophy: Most patients have no associated neurologic abnormalities, although nystagmus and hearing loss have been reported. The only symptom is slowly progressive bilateral vision loss, usually mild until late in life. The entire optic disk or, at times, only the temporal part is pale without visible vessels. A blue-yellow color vision deficit is characteristic.

Leber's hereditary optic neuropathy: Vision loss typically begins between 15 and 35 yr (range, 1 to 80 yr). Painless central vision loss in one eye is usually followed weeks to months later by loss in the other eye. Simultaneous vision loss has been reported. Most patients lose vision to worse than 20/200 acuity. Ophthalmoscopic examination may show telangiectatic microangiopathy, swelling of the nerve fiber layer around the optic disk, and an absence of leakage on fluorescein angiography. Eventually, optic atrophy supervenes.

Some patients with Leber's hereditary optic neuropathy have cardiac conduction defects. Other patients have minor neurologic abnormalities, such as a postural tremor, loss of ankle reflexes, dystonia, spasticity, or a multiple sclerosis-like illness.

Diagnosis

Molecular genetic testing is available to confirm the diagnosis of dominant optic atrophy.

Molecular genetic testing is available to confirm the diagnosis of dominant optic atrophy. Diagnosis of Leber's hereditary optic atrophy is mainly clinical. ECG should be done to diagnose occult cardiac conduction defects.

Treatment
• Symptomatic treatment

There is no effective treatment for the hereditary optic neuropathies. Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful. Genetic counseling is suggested.

Leber's hereditary optic neuropathy: Corticosteroids, vitamin supplements, and antioxidants have been tried without success. A small study found benefits from quinone analogs (ubiquinone and idebenone) during the early phase. Suggestions to avoid agents that might stress mitochondrial energy production (eg, alcohol) have no proven benefit but are theoretically reasonable. Patients should avoid tobacco products and excessive alcohol intake. Cardiac and neurologic abnormalities should be referred to a specialist.

Ischemic Optic Neuropathy

Ischemic optic neuropathy is infarction of the optic disk. The only constant symptom is painless vision loss. Diagnosis is clinical. Treatment is ineffective.

Two varieties of optic nerve infarction exist: nonarteritic and arteritic. The nonarteritic variant occurs more frequently, typically affecting people about 50 yr and older. Vision loss tends not to be as severe as in the arteritic variant, which typically affects an older group, typically about 70 yr and older.

Most ischemic optic neuropathy is unilateral. Bilateral, sequential cases occur in about 20%, but bilateral simultaneous involvement is uncommon. Atherosclerotic narrowing of the posterior ciliary arteries may predispose to nonarteritic optic nerve infarction, particularly after a hypotensive episode. Any of the inflammatory arteritides, especially giant cell arteritis (see p. 319), can precipitate the arteritic form.

Acute ischemia causes nerve edema, which further worsens ischemia. A small optic cup to optic disk ratio is a risk factor for nonarteritic ischemic optic neuropathy but not for the arteritic variety. Usually, no medical condition is apparent to cause the nonarteritic variety, although diabetes and hypertension are present in some patients and are thought to be risk factors. Vision loss on awakening leads investigators to suspect nocturnal hypotension as a potential cause of the nonarteritic variety.

Symptoms and Signs

Vision loss with both varieties is typically rapid (over minutes, hours, or days) and painless. Some patients notice the loss on awakening. Symptoms such as general malaise, muscle aches and pains, headaches over the temple, pain when combing hair, jaw claudication, and tenderness over the temporal artery may be present with temporal arteritis; however, such symptoms may not occur until after vision is lost. Visual acuity is reduced, and an afferent pupillary defect is present. The optic disk is swollen with surrounding hemorrhages. Visual field examination often shows a defect in the inferior and central visual fields.

Diagnosis

• ESR

• CT or MRI if vision loss is progressive

Diagnosis is based mainly on a clinical evaluation, but ancillary testing may be needed. Most important is to exclude the arteritic variety because the other eye is at risk if treatment is not started quickly. ESR is usually dramatically elevated in the arteritic variety and is normal in the nonarteritic variety. C-reactive protein is also a useful monitoring test. If temporal arteritis is suspected, temporal artery biopsy should be done. For isolated cases of progressive vision loss, CT or MRI should be done to rule out compressive lesions.

Prognosis

There is no effective treatment, and most lost vision is not recovered; however, in the nonarteritic variety,
up to 40% of patients spontaneously recover some useful vision.

**Treatment**

• Corticosteroids for the arteritic variety

The arteritic variety is treated with oral corticosteroids (prednisone 80 mg po once/day and tapered based on ESR) to protect the other eye. Treatment should not be delayed while awaiting biopsy results. Treatment of the nonarteritic variety with aspirin or corticosteroids has not been helpful. Risk factors are controlled. Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful in both types.

**Optic Neuritis**

Optic neuritis is inflammation of the optic nerve. Symptoms are usually unilateral, with eye pain and partial or complete vision loss. Diagnosis is primarily clinical. Treatment is directed at the underlying condition; most cases resolve spontaneously.

**Etiology**

Optic neuritis is most common among adults 20 to 40 yr. Most cases result from demyelinating disease, particularly multiple sclerosis (see p. 1779), in which case there may be recurrences. Optic neuritis is often the presenting manifestation of multiple sclerosis. Other causes include the following:

• Infectious diseases (eg, viral encephalitis [particularly in children], sinusitis, meningitis, TB, syphilis, HIV)

• Tumor metastasis to the optic nerve

• Chemicals and drugs (eg, lead, methanol, quinine, arsenic, antibiotics)

Rare causes include diabetes, pernicious anemia, Graves’ disease, bee stings, and trauma. Often, the cause remains obscure despite thorough evaluation.

**Symptoms and Signs**

The main symptom is vision loss, frequently maximal within 1 or 2 days and varying from a small central or paracentral scotoma to complete blindness. Most patients have mild eye pain, which often feels worse with eye movement.

If the optic disk is swollen, the condition is called papillitis. Otherwise, it is called retrobulbar neuritis. The most characteristic findings include reduced visual acuity, a visual field deficit, and disturbed color vision (often out of proportion to loss of visual acuity). An afferent pupillary defect is usually detectable if the contralateral eye is unaffected or involved to a lesser degree. Testing of color vision is a useful adjunct. In about two thirds of patients, inflammation is entirely retrobulbar, causing no visible changes in the optic fundus. In the rest, disk hyperemia, edema in or around the disk, vessel engorgement, or a combination is present. A few exudates and hemorrhages may be present near or on the optic disk.

**Diagnosis**

• Clinical evaluation

• MRI

Optic neuritis is suspected in patients with characteristic pain and vision loss. Neuroimaging, preferably with gadolinium-enhanced MRI, is usually done and may show an enlarged, enhancing optic nerve. MRI may also help diagnose multiple sclerosis. Fluid attenuating inversion recovery (FLAIR) MRI sequences may show typical demyelinating lesions in a periventricular location if optic neuritis is related to demyelination.
**Prognosis**

Prognosis depends on the underlying condition. Most episodes resolve spontaneously, with return of vision in 2 to 3 mo. Most patients with a typical history of optic neuritis and no underlying systemic disease, such as a connective tissue disease, recover vision, but > 25% have a recurrence in the same eye or in the other eye. MRI is used to determine future risk of demyelinating disease.

**Treatment**

- Corticosteroids

Corticosteroids are an option, especially if multiple sclerosis is suspected. Treatment with methylprednisolone (500 mg to 1000 mg IV once/day) for 3 days followed by prednisone (1 mg/kg po once/day) for 11 days may speed recovery, but ultimate vision results are no different from those with observation alone. IV corticosteroids have been reported to delay onset of multiple sclerosis for at least 2 yr. Treatment with oral prednisone alone does not improve vision outcome and may increase the rate of recurrent episodes. Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful.

**Papilledema**

Papilledema is swelling of the optic disk due to increased intracranial pressure. All other causes of optic disk swelling, such as that caused by malignant hypertension or thrombosis of the central retinal vein, do not involve increased intracranial pressure and therefore are not causes of papilledema. There are no early symptoms, although vision may be disturbed for a few seconds. Papilledema requires an immediate search for the cause. Diagnosis is by ophthalmoscopy with further tests, usually brain imaging, to determine cause. Treatment is directed at the underlying condition.

Papilledema is a sign of elevated intracranial pressure and is almost always bilateral. Causes include the following:

- Brain tumor or abscess
- Cerebral trauma or hemorrhage
- Meningitis
- Arachnoidal adhesions
- Cavernous or dural sinus thrombosis
- Encephalitis
- Idiopathic intracranial hypertension (pseudotumor cerebri), a condition with elevated CSF pressure and no mass lesion

**Symptoms and Signs**

Vision is usually not affected initially, but seconds-long graying out of vision, flickering, or blurred or double vision may occur. Patients may have symptoms of increased intracranial pressure, such as headache or nausea and vomiting.

Ophthalmoscopic examination reveals engorged and tortuous retinal veins, a hyperemic and swollen optic disk (optic nerve head), and retinal hemorrhages around the disk but not into the retinal periphery (see Plate 19). Isolated disk edema (eg, caused by optic neuritis or ischemic optic neuropathy) without elevated CSF pressure is not considered papilledema.
In the early stages, visual acuity and pupillary response to light are usually normal and become abnormal only after the condition is well advanced. Visual field testing may detect an enlarged blind spot. Later, nerve fiber bundle defects may be apparent.

**Diagnosis**

- Clinical evaluation
- Immediate neuroimaging

The degree of disk swelling can be quantified by comparing the plus lens numbers needed to focus an ophthalmoscope on the most elevated portion of the disk and on the unaffected portion of the retina.

Differentiating papilledema from other causes of a swollen optic disk, such as optic neuritis, ischemic optic neuropathy, hypotony, central retinal vein occlusion, uveitis, or pseudo swollen disks (eg, optic nerve drusen), requires a thorough ophthalmologic evaluation. If papilledema is suspected clinically, MRI with gadolinium contrast or CT with contrast is done immediately to exclude causes such as an intracranial mass. Lumbar puncture and measurement of CSF pressure should be done if a mass lesion has been ruled out. Lumbar puncture in patients with intracranial mass lesions can result in brain stem herniation. B-scan ultrasonography is the best diagnostic tool for the pseudo disk edema of optic nerve drusen.

**Treatment**

- Treatment of underlying disorder

Urgent treatment of the underlying disorder is indicated to decrease intracranial pressure. If intracranial pressure is not reduced, secondary optic nerve atrophy and vision loss eventually occur, along with other serious neurologic sequelae.

**Toxic Amblyopia**

(Nutritional Amblyopia)

Toxic amblyopia is reduction in visual acuity believed to be the result of a toxic reaction in the orbital portion (papillomacular bundle) of the optic nerve. It can be caused by various toxic and nutritional factors and probably unknown factors. The main symptom is painless vision loss. Diagnosis is by history and visual field examination. Treatment is avoiding suspected toxic agents and improving nutrition.

**Etiology**

Toxic amblyopia is usually bilateral and symmetric. In alcoholics, undernutrition may be the cause. True tobacco-induced amblyopia is rare. Lead, methanol, chloramphenicol, digoxin, ethambutol, and many other chemicals can damage the optic nerve. Deficiencies of protein and antioxidants are likely risk factors. Toxic amblyopia may occur with other nutritional disorders, such as Strachan's syndrome (polyneuropathy and orogenital dermatitis).

**Symptoms and Signs**

Vision blurring and dimness typically develop over days to weeks. An initially small central or pericentral scotoma slowly enlarges, typically involving both the fixation and the blind spot (centrocecal scotoma), and progressively interferes with vision. Total blindness may occur in methanol ingestion, but other nutritional causes typically do not cause profound vision loss. Retinal abnormalities do not usually occur, but temporal disk pallor may develop late.

**Diagnosis**

- Mainly clinical evaluation
A history of undernutrition or toxic or chemical exposure combined with typical bilateral scotomata on visual field testing justifies treatment. Laboratory testing for lead, methanol, and other suspected toxins is done.

**Prognosis**

Vision may improve if the cause is treated or removed quickly. Once the optic nerve has atrophied, vision usually does not recover.

**Treatment**

The cause is treated. Exposure to toxic substances should stop immediately. Chelation therapy is indicated in lead poisoning. Dialysis, fomepizole, ethanol, or a combination is used for methanol poisoning. Treatment with oral or parenteral B vitamins before vision loss becomes severe may reverse the condition when undernutrition is the presumed cause.

Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful.

The role of antioxidants has not been fully characterized. Their use could be justified on a theoretic basis; however, there is no proof of efficacy, and the at-risk population that should receive such supplements has not been defined.
Chapter 70. Orbital Diseases

Introduction

Orbital diseases may be vascular, thyroid-related (Graves' disease), infectious, inflammatory, or neoplastic. Cavernous sinus thrombosis causes many of the same symptoms and signs as orbital diseases. Infiltrative ophthalmopathy due to Graves' disease, the most frequent cause of orbital disease, is discussed on p. 780. Orbital fractures are discussed on p. 3232. (See Fig. 60-1 on p. 537 for anatomy of the orbit.)

Cavernous Sinus Thrombosis

Cavernous sinus thrombosis (CST) is a very rare, typically septic thrombosis of the cavernous sinus, usually caused by bacterial sinusitis. Symptoms and signs include pain, proptosis, ophthalmoplegia, vision loss, papilledema, and fever. Diagnosis is confirmed by CT or MRI. Treatment is with IV antibiotics. Complications are common, and prognosis is poor.

Etiology

The cavernous sinuses are trabeculated sinuses located at the base of the skull that drain venous blood from facial veins. CST is an extremely rare complication of common facial infections, most notably nasal furuncles (50%), sphenoidal or ethmoidal sinusitis (30%), and dental infections (10%). Most common pathogens are Staphylococcus aureus (70%), followed by Streptococcus sp; anaerobes are more common when the underlying condition is dental or sinus infection.

Thrombosis of the lateral sinus (related to mastoiditis) and thrombosis of the superior sagittal sinus (related to bacterial meningitis) occur but are rarer than CST.

Pathophysiology

The 3rd, 4th, and 6th cranial nerves and the ophthalmic and maxillary branches of the 5th cranial nerve are adjacent to the cavernous sinus and are commonly affected. Complications include meningoencephalitis, brain abscess, stroke, blindness, and pituitary insufficiency.

Symptoms and Signs

Initial symptoms are progressively severe headache or facial pain, usually unilateral and localized to retro-orbital and frontal regions. High fever is common. Later, ophthalmoplegia (initially the 6th cranial nerve, lateral gaze), proptosis, and lid edema develop and often become bilateral. Facial sensation may be diminished or absent. Decreased level of consciousness, confusion, seizures, and focal neurologic deficits are signs of CNS spread. Patients may also have anisocoria or mydriasis (3rd cranial nerve dysfunction), papilledema, and vision loss.

Diagnosis

• MRI or CT

CST is often misdiagnosed because it is rare. It should be considered in patients who have signs consistent with orbital cellulitis. Features that distinguish CST from orbital cellulitis include cranial nerve dysfunction, bilateral eye involvement, and mental status changes.

Diagnosis is based on neuroimaging. MRI is the better study, but CT is also helpful. Useful adjunct testing may include blood cultures and lumbar puncture. Lumbar puncture may show inflammatory cells (PMNs, lymphocytes, monocytes); other possible abnormalities include low glucose, high protein, and positive CSF cultures. Cultures of any suspected source infections are also done.

Prognosis
Mortality is 30% in all patients and 50% in those with underlying sphenoid sinusitis. An additional 30% develop serious sequelae (eg, ophthalmoplegia, blindness, disability due to stroke, pituitary insufficiency), which may be permanent.

**Treatment**

- IV high-dose antibiotics

- Sometimes corticosteroids

Initial antibiotics can include nafcillin or oxacillin 1 to 2 g q 4 to 6 h combined with a 3rd-generation cephalosporin (eg, ceftriaxone 1 g q 12 h). In areas where methicillin-resistant *S. aureus* is prevalent, vancomycin 1 g IV q 12 h should be substituted for nafcillin or oxacillin. A drug for anaerobes (eg, metronidazole 500 mg q 8 h) should be added if an underlying sinusitis or dental infection is present.

In cases with underlying sphenoid sinusitis, surgical sinus drainage is indicated, especially if there is no clinical response to antibiotics within 24 h.

Secondary treatment may include corticosteroids (eg, dexamethasone 10 mg po q 6 h) for cranial nerve dysfunction; anticoagulation is controversial because most patients respond to antibiotics, and adverse effects may exceed benefits.

**Inflammatory Orbital Disease**

Orbital inflammation (inflammatory orbital pseudotumor) can affect any or all structures within the orbit. The inflammatory response can be nonspecific, granulomatous, or vasculitic. The inflammation can be part of an underlying medical disorder or can exist in isolation. Patients of all ages can be affected. The process can be acute or chronic and can recur.

**Symptoms and Signs**

Symptoms and signs typically include a sudden onset of pain along with swelling and erythema of the eyelids. Proptosis, diplopia, and vision loss are also possible.

**Diagnosis**

- CT or MRI

Similar findings occur with orbital infection, but there is no history of trauma or adjacent focus of infection (eg, sinusitis). Neuroimaging with CT or MRI is required. For chronic or recurrent disease, biopsy may be used to find evidence of an underlying medical condition.

**Treatment**

Treatment depends on the type of inflammatory response and may include oral corticosteroids, radiation therapy, and one of several immunomodulating drugs. In difficult cases, some initial success has occurred with monoclonal antibodies against tumor necrosis factor α or with another monoclonal antibody that causes lymphocyte depletion.

**Preseptal and Orbital Cellulitis**

Preseptal cellulitis (periorbital cellulitis) is infection of the eyelid and surrounding skin anterior to the orbital septum. Orbital cellulitis (postseptal cellulitis) is infection of the orbital tissues posterior to the orbital septum. Either can be caused by an external focus of infection (eg, a wound), infection that extends from the nasal sinuses or teeth, or metastatic spread from infection elsewhere. Symptoms include eyelid pain, discoloration, and swelling; orbital cellulitis also causes fever, malaise, proptosis, impaired ocular movement, and impaired vision. Diagnosis is based on history, examination, and CT or MRI. Treatment is with antibiotics and
Preseptal cellulitis and orbital cellulitis are 2 distinct diseases that share a few clinical symptoms and signs. Preseptal cellulitis usually begins superficial to the orbital septum. Orbital cellulitis usually begins deep to the orbital septum. Both are more common among children; preseptal cellulitis is far more common than orbital cellulitis.

**Etiology**

Preseptal cellulitis is caused by contiguous spread of infection from local facial or eyelid injuries, insect or animal bites, conjunctivitis, chalazion, or sinusitis.

Orbital cellulitis is most often caused by extension of infection from adjacent sinuses, especially the ethmoid sinus (75 to 90%); it is less commonly caused by direct infection accompanying local trauma (eg, insect or animal bite, penetrating eyelid injuries) or contiguous spread of infection from the face or teeth or by hematogenous spread.

Pathogens vary by etiology and patient age. *Streptococcus pneumoniae* is the most frequent pathogen associated with sinus infection, whereas *Staphylococcus aureus* and *Streptococcus pyogenes* predominate when infection arises from local trauma. *Haemophilus influenzae* type b, once a common cause, is now less common because of widespread vaccination. Fungi are uncommon pathogens, causing orbital cellulitis in diabetic or immunosuppressed patients. Infection in children < 9 yr is typically with a single aerobic organism; patients > 15 yr typically have polymicrobial mixed aerobic and anaerobic (*Bacteroides, Peptostreptococcus*) infections.

**Pathophysiology**

Because orbital cellulitis originates from large adjacent foci of fulminant infection (eg, sinusitis) separated by only a thin bone barrier, orbital infection can be extensive and severe. Subperiosteal fluid collections, some quite large, can accumulate; they are called subperiosteal abscesses, but many are sterile initially.

Complications include vision loss (3 to 11%) due to ischemic retinopathy and optic neuropathy caused by increased intraorbital pressure; restricted ocular movements (ophthalmoplegia) caused by soft-tissue inflammation; and intracranial sequelae from central spread of infection, including cavernous sinus thrombosis, meningitis, and cerebral abscess.

**Symptoms and Signs**

Symptoms and signs of preseptal cellulitis include tenderness, swelling, warmth, and redness or discoloration (violaceous in the case of *H. influenzae*) of the eyelid. Patients may be unable to open their eyes because of swelling, but visual acuity is not affected.

Symptoms and signs of orbital cellulitis include swelling and redness of the eyelid and surrounding soft tissues, conjunctival hyperemia and chemosis, decreased ocular motility, pain with eye movements, decreased visual acuity, and proptosis caused by orbital swelling. Signs of the primary infection are also often present (eg, nasal discharge and bleeding with sinusitis, periodontal pain and swelling with abscess). Fever, malaise, and headache should raise suspicion of associated meningitis. Some or all of these findings may be absent early in the course of the infection.

Subperiosteal abscesses, if large enough, can contribute to symptoms of orbital cellulitis such as swelling and redness of the eyelid, decreased ocular motility, proptosis, and decreased visual acuity.

**Diagnosis**

• Mainly clinical evaluation

• CT or MRI if orbital cellulitis is possible
Diagnosis is suspected clinically. Other disorders to consider include trauma, insect or animal bites without cellulitis, retained foreign bodies, allergic reactions, tumors, and inflammatory orbital pseudotumor.

Eyelid swelling may require the use of lid retractors for evaluation of the globe, and initial signs of complicated infection may be subtle. An ophthalmologist should be consulted when orbital cellulitis is suspected.

Preseptal cellulitis and orbital cellulitis are often distinguishable clinically. Preseptal cellulitis is likely if eye findings are normal except for eyelid swelling. The presence of a local nidus of infection on the skin makes preseptal cellulitis even more likely.

If findings are equivocal, if the examination is difficult (as in young children), or if nasal discharge is present (suggesting sinusitis), CT or MRI should be done to confirm orbital cellulitis, to exclude tumor and pseudotumor, and to diagnose sinusitis if present. MRI is better than CT if cavernous sinus thrombosis is being considered.

The direction of proptosis may be a clue to the site of infection; eg, extension from the frontal sinus pushes the globe down and out, and extension from the ethmoid sinus pushes the globe laterally and out.

Blood cultures are often done (ideally before beginning antibiotics) in patients with orbital cellulitis but are positive in less than one third. Lumbar puncture is done if meningitis is suspected. Cultures of the paranasal sinus fluid are done if sinusitis is the suspected source. Other laboratory tests are not particularly helpful.

Treatment

• Antibiotics

Preseptal cellulitis: Initial therapy should be directed against sinusitis pathogens (S. pneumoniae, nontypable H. influenzae, S. aureus, Moraxella catarrhalis); however, in areas where methicillin-resistant S. aureus is prevalent, clinicians should add appropriate antibiotics (eg, clindamycin, trimethoprim/sulfamethoxazole, or doxycycline for oral treatment and vancomycin for inpatient treatment). In patients with dirty wounds, gram-negative infection must be considered.

Outpatient treatment is an option if orbital cellulitis has been definitively excluded; children should have no signs of systemic infection and should be in the care of responsible parents or guardians. Patients should be closely followed by an ophthalmologist. Outpatient treatment options include amoxicillin/clavulanate 30 mg/kg po q 8 h (for children < 12 yr) or 500 mg po tid or 875 mg po bid (for adults) for 10 days.

For inpatients, ampicillin/sulbactam 50 mg/kg IV q 6 h (for children) or 1.5 to 3 g (for adults) IV q 6 h (maximum 8 g ampicillin/day) for 7 days is an option.

Orbital cellulitis: Patients with orbital cellulitis should be hospitalized and treated with meningitis-dose antibiotics. A 2nd- or 3rd-generation cephalosporin, such as cefotaxime 50 mg/kg IV q 6 h (for children < 12 yr) or 1 to 2 g IV q 6 h (for adults) for 14 days, is an option when sinusitis is present; imipenem, ceftriaxone, and piperacillin/tazobactam are other options. If cellulitis is related to trauma or foreign body, treatment should cover gram-positive (vancomycin 1 g IV q 12 h) and gram-negative (eg, ertapenem 100 mg IV once/day) pathogens and be taken for 7 to 10 days or until clinical improvement.

Surgery to decompress the orbit, drain an abscess, open infected sinuses, or a combination is indicated in any of the following circumstances:

• Vision is compromised.

• Suppuration or foreign body is suspected.
• Imaging shows orbital or large subperiosteal abscess.

• The infection does not resolve with antibiotics.

**Tumors of the Orbit**

Orbital tumors can be benign or malignant and arise primarily within the orbit or secondarily from an adjacent source, such as the eyelid, paranasal sinus, or intracranial compartment.

Causes differ by age group. The more common benign pediatric tumors include dermoid tumors and vascular lesions such as capillary hemangioma and lymphangioma. In adults, cavernous hemangiomas predominate.

Some orbital tumors usually cause proptosis and displacement of the globe in a direction opposite the tumor. Pain, diplopia, and vision loss may also be present. Diagnosis, in most cases, is based on the history, examination, and neuroimaging (CT, MRI, or both).

**Treatment**

Treatment varies by tumor type. Treatment of dermoid tumors is excision. Capillary hemangiomas tend to spontaneously involute and therefore do not need any treatment; however, especially when located on the upper eyelid, they may affect vision and require treatment with interlesional injection of corticosteroids or surgical debulking.

**Children:** The common pediatric malignant tumors include rhabdomyosarcoma and metastatic lesions related to leukemia or neuroblastoma. If rhabdomyosarcoma is resectable, surgery is done, followed by chemotherapy and orbital radiation therapy. Leukemic disease is usually managed by orbital radiation therapy, chemotherapy, or both.

**Adults:** The most common benign tumors are meningiomas, mucoceles, and cavernous hemangiomas. When symptomatic, sphenoid wing meningiomas are treated with debulking via craniotomy, sometimes followed by a course of radiation therapy. Because meningioma cells infiltrate bone of the skull base, complete resection usually is not possible. Mucoceles are treated by draining them into the nose because they most commonly arise from the ethmoid or frontal sinus. Cavernous hemangiomas are excised.

Common malignant tumors include lymphoma, squamous cell carcinoma, and metastatic disease. Lymphomas involving the orbit are typically B-cell and characteristically low grade. Lymphomas can be bilateral and simultaneous and can be part of a systemic process or exist in the orbit in isolation.

Radiation therapy effectively treats orbital lymphomas with few adverse effects, although the addition of monoclonal antibodies against a surface receptor (CD20) on the lymphocyte is also effective. Most squamous cell carcinomas arise from the adjacent paranasal sinuses. Surgery, radiation therapy, or both form the backbone of therapy. Metastatic disease is usually treated with radiation therapy. Metastatic disease involving the orbit is usually an unfavorable prognostic sign; carcinoid tumors are a notable exception.
### Introduction

History and physical examination are adequate for diagnosing many skin lesions. Some require biopsy or other testing.

Important information to obtain from history includes:

- Personal or family history of atopy (suggesting atopic dermatitis)
- Occupational exposures (contact dermatitis)
- Long-term exposure to sunlight or other forms of radiation (benign and malignant skin tumors)
- Systemic disease (diabetes and Candida or tinea, hepatitis C and cryoglobulinemia)
- Sexual history (syphilis and gonorrhea)
- Use of drugs (Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Travel history (Lyme disease, skin infections)

A negative history is as important as a positive history. The history of the particular skin lesions is also important, including time and site of initial appearance, spread, change in appearance, and triggering factors.

Visual inspection is the central evaluation tool; many skin disorders are diagnosed by the characteristic appearance or morphology of the lesions.

### Description of Skin Lesions

An extensive language has been developed to standardize the description of skin lesions, including:

- Primary morphology (lesion type)
- Secondary morphology (configuration)
- Texture
- Distribution
- Color

Rash is a general term for a temporary skin eruption.

### Primary Morphology

**Macules** are flat, nonpalpable lesions usually < 10 mm in diameter. Macules represent a change in color and are not raised or depressed compared to the skin surface. A patch is a large macule. Examples include freckles, flat moles, tattoos, port-wine stains, and the rashes of rickettsial infections, rubella, measles, and some allergic drug eruptions.

**Papules** are elevated lesions usually < 10 mm in diameter that can be felt or palpated. Examples include nevi, warts, lichen planus, insect bites, seborrheic and actinic keratoses, some lesions of acne, and skin cancers. The term maculopapular is often loosely and improperly used to describe many red skin rashes.
Plaques are palpable lesions > 10 mm in diameter that are elevated or depressed compared to the skin surface. Plaques may be flat topped or rounded. Lesions of psoriasis and granuloma annulare commonly form plaques.

Nodules are firm papules or lesions that extend into the dermis or subcutaneous tissue. Examples include cysts, lipomas, and fibromas.

Vesicles are small, clear, fluid-filled blisters < 10 mm in diameter. Vesicles are characteristic of herpes infections, acute allergic contact dermatitis, and some autoimmune blistering disorders (eg, dermatitis herpetiformis).

Bullae are clear fluid-filled blisters > 10 mm in diameter. These may be caused by burns, bites, irritant or allergic contact dermatitis, and drug reactions. Classic autoimmune bullous diseases include pemphigus vulgaris and bullous pemphigoid. Bullae also may occur in inherited disorders of skin fragility.

Pustules are vesicles that contain pus. Pustules are common in bacterial infections and folliculitis and may arise in some inflammatory disorders including pustular psoriasis.

Urticaria (wheals or hives—see Plate 53) is characterized by elevated lesions caused by localized edema. Wheals are a common manifestation of hypersensitivity to drugs, stings or bites, autoimmunity, and, less commonly, physical stimuli including temperature, pressure, and sunlight. The typical wheal lasts < 24 h.

Scales are heaped-up accumulations of horny epithelium that occur in disorders such as psoriasis, seborrheic dermatitis, and fungal infections. Pityriasis rosea and chronic dermatitis of any type may be scaly.

Crusts (scabs) consist of dried serum, blood, or pus. Crusting can occur in inflammatory or infectious skin diseases (eg, impetigo).

Erosions are open areas of skin that result from loss of part or all of the epidermis. Erosions can be traumatic or can occur with various inflammatory or infectious skin diseases. An excoriation is a linear erosion caused by scratching, rubbing, or picking.

Ulcers result from loss of the epidermis and at least part of the dermis. Causes include venous stasis dermatitis, physical trauma with or without vascular compromise (eg, from decubitus ulcers, peripheral arterial disease), infections, and vasculitis.

Petechiae are nonblanchable punctate foci of hemorrhage. Causes include platelet abnormalities (eg, thrombocytopenia, platelet dysfunction), vasculitis, and infections (eg, meningococcemia, Rocky Mountain spotted fever, other rickettsioses).

Purpura is a larger area of hemorrhage that may be palpable. Palpable purpura is considered the hallmark of leukocytoclastic vasculitis. Purpura may indicate a coagulopathy. Large areas of purpura may be called ecchymoses or, colloquially, bruises.

Atrophy is thinning of the skin, which may appear dry and wrinkled, resembling cigarette paper. Atrophy may be caused by chronic sun exposure, aging, and some inflammatory and neoplastic skin diseases, including cutaneous T-cell lymphoma and lupus erythematosus. Atrophy also may result from long-term use of potent topical corticosteroids.

Scars are areas of fibrosis that replace normal skin after injury. Some scars become hypertrophic or thickened and raised. Keloids are hypertrophic scars that extend beyond the original wound margin.

Telangiectases are foci of small, permanently dilated blood vessels that are most often idiopathic but may occur in rosacea, systemic diseases (especially systemic sclerosis), or inherited diseases (eg,
ataxia-telangiectasia, hereditary hemorrhagic telangiectasia) or after long-term therapy with topical fluoroinated corticosteroids.

**Secondary Morphology (Configuration)**

Configuration is the shape of single lesions and the arrangement of clusters of lesions.

**Linear lesions** take on the shape of a straight line and are suggestive of some forms of contact dermatitis, linear epidermal nevi, and lichen striatus.

**Annular lesions** are rings with central clearing. Examples include granuloma annulare, some drug eruptions, some dermatophyte infections (eg, ringworm), and secondary syphilis.

**Nummular lesions** are circular or coin-shaped; an example is nummular eczema.

**Target (bull's-eye or iris) lesions** appear as rings with central duskeness and are classic for erythema multiforme.

**Serpiginous lesions** have linear, branched, and curving elements. Examples include some fungal and parasitic infections (eg, cutaneous larva migrans).

**Reticulated lesions** have a lacy or networked pattern. Examples include cutis marmorata and livedo reticularis.

**Herpetiform** describes grouped papules or vesicles arranged like those of a herpes simplex infection.

**Zosteriform** describes lesions clustered in a dermatomal distribution similar to herpes zoster.

**Texture**

Some skin lesions have visible or palpable texture that suggests a diagnosis.

**Verrucous lesions** have an irregular, pebbly, or rough surface. Examples include warts and seborrheic keratoses.

**Lichenification** is thickening of the skin with accentuation of normal skin markings; it results from repeated rubbing.

**Induration**, or deep thickening of the skin, can result from edema, inflammation, or infiltration, including by cancer. Indurated skin has a hard, resistant feeling. Induration is characteristic of panniculitis, some skin infections, and cutaneous metastatic cancers.

**Umbilicated lesions** have a central indentation and are usually viral. Examples include molluscum contagiosum and herpes simplex.

**Xanthomas**, which are yellowish, waxy lesions, may occur in lipid disorders.

**Location and Distribution**

It is important to note whether

- Lesions are single or multiple
- Particular body parts are affected (eg, palms or soles, scalp, mucosal membranes)
- Distribution is random or patterned, symmetric or asymmetric
- Lesions are on sun-exposed or protected skin
Although few patterns are pathognomonic, some are consistent with certain diseases.

**Psoriasis** frequently affects the scalp, extensor surfaces of the elbows and knees, umbilicus, and the gluteal cleft.

**Lichen planus** frequently arises on the wrists, forearms, genitals, and lower legs.

**Vitiligo** may be patchy and isolated or may group around the distal extremities and face.

**Chronic cutaneous lupus erythematosus** has characteristic lesions on sun-exposed skin of the face, especially the forehead, nose, and the conchal bowl of the ear.

**Hidradenitis suppurativa** involves skin containing a high density of apocrine glands, including the axillae, groin, and under the breasts.

### Color

**Red skin** (erythema) can result from many different inflammatory or infectious diseases. Cutaneous tumors are often pink or red. Superficial vascular lesions such as port-wine stains may appear red.

**Orange skin** is most often seen in hypercarotenemia, a usually benign condition of carotene deposition after excess dietary ingestion of β-carotene.

**Yellow skin** is typical of jaundice, xanthelasmas and xanthomas, and pseudoxanthoma elasticum.

**Green fingernails** suggest *Pseudomonas aeruginosa* infection.

**Violet skin** may result from cutaneous hemorrhage or vasculitis. Vascular lesions or tumors, such as Kaposi's sarcoma and hemangiomas, can appear purple. A lilac color of the eyelids or heliotrope eruption is characteristic of dermatomyositis.

**Shades of blue, silver, and gray** can result from deposition of drugs or metals in the skin, including minocycline, amiodarone, and silver (argyria). Ischemic skin appears purple to gray in color. Deep dermal nevi appear blue.

**Black skin** lesions may be melanocytic, including nevi and melanoma. Black eschars are collections of dead skin that can arise from vascular infarction, which may be caused by infection (eg, anthrax, angioinvasive fungi including *Rhizopus*, meningococcemia), calciphylaxis, arterial insufficiency, or vasculitis.

### Other Clinical Signs

**Dermatographism** is the appearance of an urticarial wheal after focal pressure (eg, stroking or scratching the skin) in the distribution of the pressure. Up to 5% of normal patients may exhibit this sign, which is a form of physical urticaria.

**Darier’s sign** refers to rapid swelling of a lesion when stroked. It occurs in patients with urticaria pigmentosa or mastocytosis.

**Nikolsky’s sign** is epidermal shearing that occurs with gentle lateral pressure on seemingly uninvolved skin in patients with toxic epidermal necrolysis and some autoimmune bullous diseases.

**Auspitz sign** is the appearance of pinpoint bleeding after scale is removed from plaques in psoriasis.

**Koebner phenomenon** describes the development of lesions within areas of trauma (eg, caused by scratching, rubbing, injury). Psoriasis frequently exhibits this phenomenon, as may lichen planus.
Diagnostic Tests

Diagnostic tests are indicated when the cause of a skin lesion or disease is not obvious from history and physical examination alone (for patch testing, see p. 667).

**Biopsy:** A skin biopsy can be done by a primary care physician. One procedure is a punch biopsy, in which a tubular punch (diameter usually 4 mm) is inserted into deep dermal or subcutaneous tissue to obtain a specimen, which is snipped off at its base. More superficial lesions may be biopsied by shaving with a scalpel or razor blade. Bleeding is controlled by aluminum chloride solution or electrodesiccation; large incisions are closed by sutures. Larger or deeper biopsies can be done by excising a wedge of skin with a scalpel. All pigmented lesions should be excised deeply for histologic evaluation of depth; superficial biopsies are often inadequate. Diagnosis and cure are achieved simultaneously for most small tumors by complete excision that includes a small border of normal skin.

**Scrapings:** Skin scrapings help diagnose fungal infections and scabies. For fungal infection, scales are taken from the border of the lesion and placed onto a microscope slide. Then a drop of 10 to 20% potassium hydroxide (KOH) is added. Hyphae, budding yeast, or both confirm the diagnosis of tinea or candidiasis. For scabies, scrapings are taken from suspected burrows and placed directly under a coverslip with mineral oil; findings of mites, feces, or eggs confirm the diagnosis.

**Wood's light:** Wood's light (black light) can help distinguish hypopigmentation from depigmentation (depigmentation of vitiligo fluoresces ivory-white and hypopigmented lesions do not). Erythrasma fluoresces bright orangered. Tinea capitis caused by *Microsporum canis* and *Microsporum audouinii* fluoresces a light, bright green. (NOTE: Most tinea capitis in the US is caused by *Trichophyton* species, which do not fluoresce.) The earliest clue to cutaneous *Pseudomonas* infection (eg, in burns) may be green fluorescence.

**Tzanck testing:** Tzanck testing can be used to diagnose viral disease, such as herpes simplex and herpes zoster, and is done when active intact vesicles are present. Tzanck testing cannot distinguish between herpes simplex and herpes zoster infections. An intact blister is the preferred lesion for examination. The blister roof is removed with a sharp blade, and the base of the unroofed vesicle is scraped with a #15 scalpel blade. The scrapings are transferred to a slide and stained with Wright's stain or Giemsa stain. Multinucleated giant cells are a sign of herpes infection.

**Diascopy:** Diascopy is used to determine whether a lesion is vascular (inflammatory) or nonvascular (nevus) or hemorrhagic (petechia or purpura). A microscope slide is pressed against a lesion to see whether it blanches. Hemorrhagic lesions and nonvascular lesions do not blanch; inflammatory lesions do. Diascopy is sometimes used to identify sarcoid skin lesions, which, when tested, turn an apple jelly color.

**Itching**

(Pruritus)

Itching is a symptom that can cause significant discomfort and is one of the most common reasons for consultation with a dermatologist. Itching leads to scratching, which can cause inflammation, skin degradation, and possible secondary infection. The skin can become lichenified, scaly, and excoriated.

**Pathophysiology**

Itch can be prompted by diverse stimuli, including light touch, vibration, and wool fibers. There are a number of chemical mediators as well as different mechanisms by which the sensation of itch occurs.

**Mediators:** Histamine is one of the most significant mediators. It is synthesized and stored in mast cells in the skin and is released in response to various stimuli. Other mediators (eg, neuropeptides) can either cause the release of histamine or act as pruritogens themselves, thus explaining why antihistamines ameliorate some cases of itching and not others. Opioids have a central pruritic action as well as...
stimulating the peripherally mediated histamine itch.

**Mechanisms:** There are 4 mechanisms of itch:

- Dermatologic—typically caused by inflammatory or pathologic processes (eg, urticaria, eczema)
- Systemic—related to diseases of organs other than skin (eg, cholestasis)
- Neuropathic—related to disorders of the CNS or peripheral nervous system (eg, multiple sclerosis)
- Psychogenic—related to psychiatric conditions

Intense itching stimulates vigorous scratching, which in turn can cause secondary skin conditions (eg, inflammation, excoriation, infection), which can lead to more itching. However, scratch can temporarily reduce the sensation of itch by activating inhibitory neuronal circuits.

**Etiology**

Itching can be a symptom of a primary skin disease or, less commonly, a systemic disease (see Table 71-1).

**Table 71-1. Some Causes of Itching**

**Skin disorders:** Many skin disorders cause itching. The most common include

- Dry skin
- Atopic dermatitis (eczema)
- Contact dermatitis
- Fungal skin infections

**Systemic disorders:** In systemic disorders, itching may occur with or without skin lesions. However, when itching is prominent without any identifiable skin lesions, systemic disorders and drugs should be considered more strongly. Systemic disorders are less often a cause of itching than skin disorders, but some of the more common causes include

- Allergic reaction (eg, to foods, drugs, bites and stings)
- Cholestasis
- Chronic renal failure

Less common systemic causes of itching include hyperthyroidism, hypothyroidism, diabetes, iron deficiency, dermatitis herpetiformis, and polycythemia vera.

**Drugs:** Drugs can cause itching as an allergic reaction or by directly triggering histamine release (most commonly morphine, some IV contrast agents).

**Evaluation**

**History:** History of present illness should determine onset of itching, initial location, course, duration, patterns of itching (eg, nocturnal or diurnal, intermittent or persistent, seasonal variation), and whether any rash is present. A careful drug history should be obtained; both oral (eg, opioids, cocaine, aspirin, prescription and OTC) and topical (eg, hydrocortisone, benadryl, moisturizers) drugs are included. History also should include any factors that make the itching better or worse.
Review of systems should seek symptoms of causative disorders, including steatorrhea and right upper quadrant pain (cholestasis); constitutional symptoms of fever, weight loss, and night sweats (cancer); intermittent weakness, numbness, tingling, and visual disturbances or loss (multiple sclerosis); irritability, sweating, weight loss, and palpitations (hyperthyroidism) or depression, dry skin, and weight gain (hypothyroidism); urinary frequency, excessive thirst, and weight loss (diabetes); and headache, pica, hair thinning, and exercise intolerance (iron deficiency anemia).

Past medical history should identify known causative disorders (eg, renal disease, cholestatic disorder, cancer being treated with chemotherapy) and the patient's emotional state. Social history should focus on family members with similar itching and skin symptoms (eg, scabies, pediculosis); relationship of itching to occupation or exposures to plants, animals, or chemicals; and history of recent travel.

Physical examination: Physical examination begins with a review of clinical appearance for signs of jaundice, weight loss or gain, and fatigue. Close examination of the skin should be done, taking note of presence, morphology, extent, and distribution of lesions. Cutaneous examination also should make note of signs of secondary infection (eg, erythema, swelling, warmth, yellow or honey-colored crusting).

The examination should make note of significant adenopathy suggestive of cancer. Abdominal examination should focus on organomegaly, masses, and tenderness (cholestatic disorder or cancer). Neurologic examination focuses on weakness, spasticity, or numbness (multiple sclerosis).

Red flags: The following findings are of particular concern:

- Constitutional symptoms of weight loss, fatigue, and night sweats
- Extremity weakness, numbness, or tingling
- Abdominal pain and jaundice
- Urinary frequency, excessive thirst, and weight loss

Interpretation of findings: Generalized itching that begins shortly after use of a drug is likely caused by that drug. Localized itching (often with rash) that occurs in the area of contact with a substance is likely caused by that substance. However, many systemic allergies can be difficult to identify because patients typically have consumed multiple different foods and have been in contact with many substances before developing itching. Similarly, identifying a drug cause in a patient taking several drugs may be difficult. Sometimes the patient has been taking the offending drug for months or even years before developing a reaction.

If an etiology is not immediately obvious, the appearance and location of skin lesions can suggest a diagnosis (see Table 71-1).

In the minority of patients in whom no skin lesions are evident, a systemic disorder should be considered. Some disorders that cause itching are readily apparent on evaluation (eg, chronic renal failure, cholestatic jaundice). Other systemic disorders that cause itching are suggested by findings (see Table 71-1). Rarely, itching is the first manifestation of significant systemic disorders (eg, polycythemia vera, certain cancers, hyperthyroidism).

Testing: Many dermatologic disorders are diagnosed clinically. However, when itching is accompanied by discrete skin lesions of uncertain etiology, biopsy can be appropriate. When an allergic reaction is suspected but the substance is unknown, skin testing (either prick or patch testing depending on suspected etiology) is often done. When a systemic disorder is suspected, testing is directed by the suspected cause and usually involves CBC; liver, renal, and thyroid function measurements; and appropriate evaluation for underlying cancer.

Treatment

Any underlying disorder is treated. Supportive treatment involves the following (see also
Skin care: Itching due to any cause benefits from use of cool or lukewarm (but not hot) water when bathing, mild or moisturizing soap, limited bathing duration and frequency, frequent lubrication, humidification of dry air, and avoidance of irritating or tight clothing. Avoidance of contact irritants (eg, wool clothing) also may be helpful.

Topical drugs: Topical drugs may help localized itching. Options include lotions or creams that contain camphor and/or menthol, pramoxine, or corticosteroids. Corticosteroids are effective in relieving itch caused by inflammation but should be avoided for conditions that have no evidence of inflammation. Topical diphenhydramine and doxepin should be avoided because they may sensitize the skin.

Systemic drugs: Systemic drugs are indicated for generalized itching or local itching resistant to topical agents. Antihistamines, most notably hydroxyzine, are effective, especially for nocturnal itch, and are most commonly used. Sedating antihistamines must be used cautiously in elderly patients during the day because they can lead to falls; newer nonsedating antihistamines such as loratadine, fexofenadine, and cetirizine can be useful for daytime itching. Other drugs include doxepin (typically taken at night due to high level of sedation), cholestyramine (for renal failure, cholestasis, polycythemia vera), opioid antagonists such as naltrexone (for biliary pruritus), and possibly gabapentin (for uremic pruritus).

Physical agents that may be effective for itching include ultraviolet phototherapy.

Geriatrics Essentials

Xerotic eczema is very common among elderly patients. It is especially likely if itching is primarily on the lower extremities.

Severe, diffuse itching in the elderly should raise concern for cancer, especially if another etiology is not immediately apparent.

When treating the elderly, sedation can be a significant problem with antihistamines. Use of nonsedating antihistamines during the day and sedating antihistamines at night, liberal use of topical ointments and corticosteroids (when appropriate), and consideration of ultraviolet phototherapy can help avoid the complications of sedation.

Key Points

• Itching is usually a symptom of a skin disorder or systemic allergic reaction but can result from a systemic disorder.

• If skin lesions are not evident, systemic causes should be investigated.

• Skin care (eg, limiting bathing, avoiding irritants, moisturizing regularly, humidifying environment) should be observed.

• Symptoms can be relieved by topical or systemic drugs.

Urticaria

(Hives; Wheals)

Urticaria is migratory, well-circumscribed, erythematous, pruritic plaques on the skin (see Plate 53).
Urticaria also may be accompanied by angioedema, which results from mast cell and basophil activation in the deeper dermis and subcutaneous tissues and manifests as edema of the face and lips, extremities, or genitals. Angioedema can be life-threatening if airway obstruction occurs because of laryngeal edema or tongue swelling.

Pathophysiology

Urticaria results from the release of histamine, bradykinin, kallikrein, and other vasoactive substances from mast cells and basophils in the superficial dermis, resulting in intradermal edema caused by capillary and venous vasodilation and occasionally caused by leukocyte infiltration.

The process can be immune mediated or nonimmune mediated.

Immune-mediated mast cell activation includes

• Type I hypersensitivity reactions, in which allergen-bound IgE antibodies bind to high-affinity cell surface receptors on mast cells and basophils

• Autoimmune disorders, in which antibodies to an IgE receptor functionally cross-link IgE receptors and cause mast cell degranulation

Nonimmune-mediated mast cell activation includes

• Direct nonallergic activation of mast cells by certain drugs

• Drug-induced cycloxygenase inhibition that activates mast cells by poorly understood mechanisms

[Table 71-2. Some Therapeutic Approaches to Itching]

• Activation by physical or emotional stimuli; mechanism is poorly understood but possibly involves the release of neuropeptides that interact with mast cells

Etiology

Urticaria is classified as acute (< 6 wk) or chronic (> 6 wk); acute cases (70%) are more common than chronic (30%).

Acute urticaria (see Table 71-3) most often results from

• Type I hypersensitivity reactions

A presumptive trigger (eg, drug, food ingestion, insect sting, infection) occasionally can be identified.

Chronic urticaria most often results from

• Idiopathic causes

• Autoimmune disorders

Chronic urticaria often lasts months to years, eventually resolving without a cause being found.

Evaluation

Because there are no definitive diagnostic tests for urticaria, evaluation largely relies on history and physical examination.
History: **History of present illness** should include a detailed account of the individual episodes of urticaria, including distribution, size, and appearance of lesions; frequency of occurrence; duration of individual lesions; and any prior episodes. Activities and exposures during, immediately before, and within the past 24 h of the appearance of urticaria should be noted. Clinicians specifically should ask about recent exercise; exposure to potential allergens (see Table 71-3), insects, or animals; new laundry detergent or soaps; new foods; recent infections; or recent stressful life events. The patient should be asked about the duration between any suspected trigger and the appearance of urticaria and which particular triggers are suspected. Important associated symptoms include pruritus, rhinorrhea, swelling of the face and tongue, and dyspnea.

**Review of systems** should seek symptoms of causative disorders, including fever, fatigue, abdominal pain, and diarrhea (infection); heat or cold intolerance, tremor, or weight change (autoimmune thyroiditis); joint pain (cryoglobulinemia, SLE); malar rash (SLE); dry eyes and dry mouth (Sjogren's syndrome); cutaneous ulcers and hypopigmented lesions after resolution of urticaria (urticarial vasculitis); small pigmented papules (mastocytosis); lymphadenopathy (viral illness, cancer, serum sickness); acute or chronic diarrhea (viral or parasitic enterocolitis); and fevers, night sweats, or weight loss (cancer).

**Past medical history** should include a detailed allergy history, including known atopic conditions (eg, allergies, asthma, eczema) and known possible causes (eg, autoimmune disorders, cancer). All drug use should be reviewed, including OTC drugs and herbal products, specifically any agents particularly associated with urticaria (see Table 71-3). Family history should elicit any history of rheumatoid disease, autoimmune disorders, or cancer. Social history should cover any recent travel and any risk factors for transmission of infectious disease (eg, hepatitis, HIV).

**Physical examination:** Vital signs should note the presence of bradycardia or tachycardia and tachypnea. General examination should immediately seek any signs of respiratory distress and also note cachexia, jaundice, or agitation.

Examination of the head should note any swelling of the face, lips, or tongue; scleral icterus; malar rash; tender and enlarged thyroid; lymphadenopathy; or dry eyes and dry mouth. The oropharynx should be inspected and the sinuses should be palpated and transilluminated for signs of occult infection (eg, sinus infection, tooth abscess).

Abdominal examination should note any masses, hepatomegaly, splenomegaly, or tenderness. Neurologic examination should note any tremor or hyperreflexia or hyporeflexia. Musculoskeletal examination should note the presence of any inflamed or deformed joints.

Skin examination should note the presence and distribution of urticarial lesions as well as any cutaneous ulceration, hyperpigmentation, small papules, or jaundice. Urticarial lesions usually appear as well-demarcated transient swellings involving the dermis. These swellings are typically red and vary in size from pinprick to covering wide areas. Some lesions can be very large. In other cases, smaller urticarial lesions may become confluent. However, skin lesions also may be absent at the time of the visit. Maneuvers to evoke physical urticaria can be done during the examination, including exposure to vibration (tuning fork), warmth (tuning fork held under warm water), cold (stethoscope or chilled tuning fork), water, or pressure (lightly scratching an unaffected area with a fingernail).

**Red flags:** The following findings are of particular concern:

- Angioedema (swelling of the face, lips, or tongue)

  [Table 71-3, Some Causes of Urticaria]

- Stridor, wheezing, or other respiratory distress

- Hyperpigmented lesions, ulcers, or urticaria that persist > 48 h

- Signs of systemic illness (eg, fever, lymphadenopathy, jaundice, cachexia)
Interpretation of findings: Acute urticaria is nearly always due to some defined exposure to a drug or physical stimulus or an acute infectious illness. However, the trigger is not always clear from the history, particularly because allergy may develop without warning to a previously tolerated substance.

Most chronic urticaria is idiopathic. The next most common cause is an autoimmune disorder. The causative autoimmune disorder is sometimes clinically apparent. Urticarial vasculitis sometimes is associated with connective tissue disorders (particularly SLE or Sjogren's syndrome). In urticarial vasculitis, urticaria is accompanied by findings of cutaneous vasculitis; it should be considered when the urticaria are painful rather than pruritic, last > 48 h, do not blanch, or are accompanied by vesicles or purpura.

Testing: Usually, no testing is needed for an isolated episode of urticaria unless symptoms and signs suggest a specific disorder (eg, infection).

Unusual, recurrent, or persistent cases warrant further evaluation. Referral for allergy skin testing should be done, and routine laboratory tests should consist of CBC, blood chemistries, liver function tests, and thyroid-stimulating hormone (TSH). Further testing should be guided by symptoms and signs (eg, of autoimmune disorders) and any abnormalities on the screening tests (eg, hepatitis serologies and ultrasonography for abnormal liver function tests; ova and parasites for eosinophilia; cryoglobulin titer for elevated liver function tests or elevated creatinine; thyroid autoantibodies for abnormal TSH).

Skin biopsy should be done if there is any uncertainty as to the diagnosis or if wheals persist > 48 h (to rule out urticarial vasculitis).

Clinicians should not recommend the patient do an empiric challenge (eg, "Try such and such again and see whether you get a reaction") because subsequent reactions may be more severe.

Treatment

Any identified causes are treated or remedied. Implicated drugs or foods should be stopped.

Nonspecific symptomatic treatment (eg, taking cool baths, avoiding hot water and scratching, and wearing loose clothing) may be helpful.

Drugs: Antihistamines remain the mainstay of treatment. They must be taken on a regular basis, rather than as needed. Newer oral antihistamines often are preferred because of once-daily dosing and because some are less sedating. Appropriate choices include

• Cetirizine 10 mg once/day
• Fexofenadine 180 mg once/day
• Desloratadine 5 mg once/day
• Levocetirizine 5 mg once/day

Older oral antihistamines (eg, hydroxyzine 10 to 25 mg q 4 to 6 h; diphenhydramine 25 to 50 mg q 6 h) are sedating but inexpensive and also quite effective.

Systemic corticosteroids (eg, prednisone 30 to 40 mg po once/day) are given for severe symptoms but should not be used long term. Topical corticosteroids or antihistamines are not beneficial.

Angioedema: Patients who have angioedema involving the oropharynx or any involvement of the airway should receive epinephrine 0.3 mL of 1:1000 solution sc and be admitted to the hospital. On discharge, patients should be supplied with and trained in the use of an auto-injectable epinephrine pen.

Geriatrics Essentials
The older oral antihistamines (eg, hydroxyzine, diphenhydramine) are sedating and can cause confusion, urinary retention, and delirium. They should be used cautiously to treat urticaria in elderly patients.

**Key Points**

- Urticaria can be caused by allergic or nonallergic mechanisms.
- Most acute cases are caused by an allergic reaction to a specific substance.
- Most chronic cases are idiopathic or result from autoimmune disease.
- Treatment is based on severity; nonsedating antihistamines and avoidance of triggers are first-line options.
- Topical corticosteroids and antihistamines are not beneficial.
- Concomitant systemic symptoms require a thorough evaluation for the etiology.

**Skin Manifestations of Internal Disease**

The skin frequently serves as a marker for underlying internal disease. The type of lesion typically relates to a specific disease or type of disease.

**Internal cancer:** Of patients with dermatomyositis, about 50% have associated breast, lung, ovarian, and GI cancers.

Acute onset of multiple seborrheic keratoses (Leser-Trelat sign) may indicate underlying internal cancer, particularly adenocarcinoma. However, because of the high prevalence of seborrheic keratoses in healthy adults, this sign may be overdiagnosed.

Acute febrile neutrophilic dermatosis is associated with hematologic cancer.

Acanthosis nigricans (see Plate 24) that is associated with cancer can be of rapid onset and particularly widespread. Pruritus without a clearly associated dermatitis may indicate occult cancer, often lymphoma.

Paraneoplastic pemphigus is a relatively rare autoimmune blistering disease that has been associated with various cancers, including leukemias.

The carcinoid syndrome (flushing and erythema of the neck) is associated with carcinoid tumor.

Erythema gyratum repens is a rare eruption consisting of concentric erythematous lesions, resembling wood grain, which has been associated with various cancers.

**Endocrinopathies:** Many skin findings are associated with endocrinopathies but are not specific.

Patients with diabetes mellitus may have acanthosis nigricans, necrobiosis lipoidica, perforating disorders, and sclerodema adultorum.

Thyroid disease, both hypothyroidism and hyperthyroidism, can affect hair, nails, and skin.

Cushing's disease causes striae distensae, moon facies, and skin fragility.

Addison's disease is characterized by hyperpigmentation that is accentuated in skin creases and areas of trauma.

**GI disorders:** Skin conditions commonly associated with GI disorders include
• Pyoderma gangrenosum: Inflammatory bowel disease

• Lichen planus and porphyria cutanea tarda: Hepatitis C infection

• Diffuse hyperpigmentation, or bronze diabetes: Hemochromatosis

• Erythema nodosum: Inflammatory bowel disease, sarcoidosis, and various infections

• Eruptive xanthomas: Elevated serum triglycerides
Chapter 72. Principles of Topical Dermatologic Therapy

Introduction

Topical dermatologic treatments include

- Cleansing agents
- Absorbents
- Anti-infective agents
- Anti-inflammatory agents
- Astringents (drying agents that precipitate protein and shrink and contract the skin)
- Emollients (skin hydrators and softeners)
- Keratolytics (agents that soften, loosen, and facilitate exfoliation of the squamous cells of the epidermis)

Vehicles

Topical therapies can be delivered in various vehicles, which include

- Powders
- Liquids
- Combinations of liquid and oil

The vehicle influences a therapy's effectiveness and may itself cause adverse effects (eg, contact or irritant dermatitis). Generally, aqueous preparations are drying (because the liquid evaporates) and are used in acute inflammatory conditions. Oil-based preparations are moisturizing and are preferred for chronic inflammation.

Powders: Inert powders may be mixed with active agents (eg, antifungals) to deliver therapy. They are prescribed for lesions in moist or intertriginous areas.

Liquids: Liquid vehicles include

- Baths and soaks
- Solutions
- Lotions
- Gels

Baths and soaks are used when therapy must be applied to large areas, such as with extensive contact dermatitis or atopic dermatitis.

Solutions are ingredients dissolved in a solvent, usually ethyl alcohol, propylene glycol, polyethylene glycol, or water. Solutions are convenient to apply (especially to the scalp for disorders such as psoriasis or seborrhea) but tend to be drying. Two common solutions are Burow's solution and Domeboro's solution.

Lotions are water-based emulsions. They are easily applied to hairy skin. Lotions cool and dry acute inflammatory and exudative lesions, such as contact dermatitis, tinea pedis, and tinea cruris.
Gels are ingredients suspended in a solvent thickened with polymers. Gels are often more effective for controlled release of topical agents. They are often used in acne, rosacea, and psoriasis of the scalp.

**Combination vehicles:** Combinations include

- Creams
- Ointments

Combination vehicles usually contain oil and water but may also contain propylene or polyethylene glycol.

Creams are semi-solid emulsions of oil and water. They are used for moisturizing and cooling and when exudation is present. They vanish when rubbed into skin.

Ointments are oil based (eg, petrolatum) with little if any water. Ointments are optimal lubricants and increase drug penetration because of their occlusive nature; a given concentration of drug is generally more potent in an ointment. They are preferred for lichenified lesions and lesions with thick crusts or heaped-up scales, including psoriasis and lichen simplex chronicus. Ointments are less irritating than creams for erosions or ulcers.

**Dressings**

Dressings protect open lesions, facilitate healing, increase drug absorption, and protect the patient’s clothing.

**Nonocclusive dressings:** The most common are gauze dressings. They maximally allow air to reach the wound, which is often preferred in healing, and allow the lesion to dry. Nonocclusive dressings wetted with solution, usually saline, are used to help cleanse and debride thickened or crusted lesions. The dressings are applied wet and removed after the solution has evaporated (wet-to-dry dressings); materials from the skin then adhere to the dressing.

**Occlusive dressings:** Occlusive dressings increase the absorption and effectiveness of topical therapy. Most common are transparent films such as polyethylene (plastic household wrap) or flexible, transparent, semi-permeable dressings. Hydrocolloid dressings can be applied with a gauze cover in patients with cutaneous ulceration. Zinc oxide gelatin (Unna’s paste boot) is an effective occlusive dressing for patients with stasis dermatitis and ulcers. Plastic tape impregnated with flurandrenolide, a corticosteroid, can be used for isolated or recalcitrant lesions.

Occlusive dressings applied over topical corticosteroids to increase absorption are sometimes used to treat psoriasis, atopic dermatitis, skin lesions of lupus erythematosus, and chronic hand dermatitis, among other conditions. Systemic absorption of topical corticosteroids may occur and cause

- Development of miliaria
- Skin atrophy
- Striae
- Bacterial or fungal infections
- Adrenal suppression
- Acneiform eruptions

Other occlusive dressings are used to protect and help heal open wounds, such as burns (see p. 3242).

**Categories and Indications**
Major categories of topical agents include

- Cleansing
- Moisturizing
- Drying
- Anti-inflammatory
- Antimicrobial
- Keratolytic
- Astringent
- Antipruritic

**Cleansing agents:** The principal cleansing agents are soaps, detergents, and solvents. Soap is the most popular cleanser, but synthetic detergents are also used. Baby shampoos are usually well tolerated around the eyes and for cleansing wounds and abrasions; they are useful for removing crusts and scales in psoriasis, eczema, and other forms of dermatitis. However, acutely irritated, weeping, or oozing lesions are most comfortably cleansed with water or isotonic saline.

Water is the principal solvent for cleansing. Organic solvents (e.g., acetone, petroleum products, propylene glycol) are very drying, can be irritating, and cause irritant or, less commonly, allergic contact dermatitis. Removal of hardened tar and dried paint from the skin may require a petrolatum-based ointment or commercial waterless cleanser.

**Moisturizing agents:** Moisturizers (emollients) restore water and oils to the skin and help to maintain skin hydration. They typically contain glycerin, mineral oil, or petrolatum and are available as lotions, creams, ointments, and bath oils. Stronger moisturizers contain urea 2%, lactic acid 5 to 12%, and glycolic acid 10% (higher concentrations are used as keratinolytics, e.g., for ichthyosis). They are most effective when applied to already moistened skin (i.e., after a bath or shower).

**Drying agents:** Excessive moisture in intertriginous areas (e.g., between the toes; in the intergluteal cleft, axillae, groin, and inframammary areas) can cause irritation and maceration. Powders dry macerated skin and reduce friction by absorbing moisture. However, some powders tend to clump and can be irritating if they become moist. Cornstarch and talc are most often used. Although talc is more effective, talc may cause granulomas if inhaled and is no longer used in baby powders. Cornstarch may promote fungal growth. Aluminum chloride solutions are another type of drying agent (often useful in hyperhidrosis).

**Anti-inflammatory agents:** Topical anti-inflammatory agents are either corticosteroids or noncorticosteroids.

**Corticosteroids** are the mainstay of treatment for most noninfectious inflammatory dermatoses. Lotions are useful on intertriginous areas and the face. Gels are useful on the scalp and in management of contact dermatitis. Creams are useful on the face and in intertriginous areas and for management of inflammatory dermatoses. Ointments are useful for dry scaly areas and when increased potency is required. Corticosteroid-impregnated tape is useful to protect an area from excoriation. It also increases corticosteroid absorption and therefore potency.

Topical corticosteroids range in potency from mild (class VII) to superpotent (class I—see Table 72-1). Intrinsic differences in potency are attributable to fluorination or chlorination (halogenation) of the compound.

Topical corticosteroids are generally applied 2 to 3 times daily, but high-potency formulations may require
application only once/day or even less frequently. Most dermatoses are treated with mid-potency to high-potency formulations; mild formulations are better for mild inflammation and for use on the face or intertriginous areas, where systemic absorption is more likely. All agents can cause skin atrophy, striae, and acneiform eruptions when used for > 1 mo. This effect is particularly problematic on the thinner skin of the face or genitals. Corticosteroids also promote fungal growth. Contact dermatitis in reaction to preservatives and additives is also common with prolonged use. Contact dermatitis to the corticosteroid itself may also occur. Perioral dermatitis occurs with mid-potency or high-potency formulations used on the face but is uncommon with mild formulations. High-potency formulations may cause adrenal suppression when used in children, over extensive skin surfaces, or for long periods. Relative contraindications include conditions in which infection plays an underlying role and acneiform disorders.

**Noncorticosteroid anti-inflammatory agents** include tar preparations. Tar comes in the form of crude coal tar and is indicated for psoriasis. Adverse effects include irritation, folliculitis, staining of clothes and furniture, and photosensitization. Contraindications include infected skin. Several herbal products are commonly used in commercial products, although their effectiveness has not been well established. Among the most popular are chamomile and calendula.

**Antimicrobials:** Topical antimicrobials include

- **Antibiotics**
  - Topical clindamycin and erythromycin are used as primary or adjunctive treatment for acne vulgaris in patients who do not warrant or tolerate oral antibiotics. Mupirocin has excellent gram-positive (Staphylococcus aureus, streptococci) coverage and can be used to treat impetigo when deep tissues are not affected. OTC antibiotics such as bacitracin and polymyxin are often used in postoperative care of a skin biopsy site and to prevent infection in scrapes, minor burns, and excoriations. Topical neomycin causes contact dermatitis more frequently than other antibiotics. The use of topical antibiotics and washing with antiseptic soaps in healing wounds may, however, actually slow healing.

- **Antifungals** are used to treat candidiasis, a wide variety of dermatophytoses, and other fungal infections (see Table 82-1 on p. 704).

- **Insecticides** (eg, permethrin, malathion) are used treat lice infestation and scabies (see Table 83-1 on p. 712).

- **Nonspecific antiseptic agents** include iodine solutions (eg, povidone iodine, clioquinol), gentian violet, silver preparations (eg, silver nitrate, silver sulfadiazine), and zinc pyrithione. Iodine is indicated for presurgical skin preparation. Gentian violet is used when an inexpensive chemically and physically stable antiseptic/antimicrobial is needed. Silver preparations are effective in treating burns and ulcers and have strong antimicrobial properties; several wound dressings are impregnated with silver. Zinc pyrithione is an antifungal and a common ingredient in shampoos used to treat dandruff due to psoriasis or seborrheic dermatitis. Healing wounds should generally not be treated with topical antiseptics other than silver because they are irritating and tend to kill fragile granulation tissue.

**Keratolytics:** Keratolytics soften and facilitate exfoliation of epidermal cells. Examples include 3 to 6% salicylic acid and urea. Salicylic acid is used to treat psoriasis, seborrhea, acne, and warts. Adverse
effects are burning and systemic toxicity if large areas are covered. It should rarely be used in children and infants. Urea is used to treat plantar keratodermas and ichthyosis. Adverse effects are irritation and intractable burning. It should not be applied to large areas.

**Astringents**: Astringents are drying agents that precipitate protein and shrink and contract the skin. The most commonly used astringents are aluminum acetate (Burow’s solution) and aluminum sulfate plus Ca acetate (Domeboro’s solution). Usually applied with dressings or as soaks, astringents are used to treat infectious eczema, exudative skin lesions, and pressure ulcers. Witch hazel is a popular OTC astringent.

**Antipruritics**: Doxepin is a topical antihistamine that is effective in treating itching of atopic dermatitis, lichen simplex chronic dermatitis, and nummular dermatitis. Topical benzocaine and diphenhydramine (present in certain OTC lotions) are sensitizing and not recommended. Other antipruritics include camphor 0.5 to 3%, menthol 0.1 to 0.2%, pramoxine hydrochloride, and eutectic mixture of local anesthetics (EMLA), which contain equal parts lidocaine and prilocaine in an oil-in-water vehicle. Topical antipruritics are preferred over systemic drugs (eg, oral antihistamines) when smaller surface areas of skin are affected and pruritus is not intractable. Calamine lotion is soothing but not specifically antipruritic.
Chapter 73. Acne and Related Disorders

Introduction

Acne vulgaris is a common skin problem, affecting most adolescents and many adults. Perioral dermatitis and rosacea can produce similar lesions.

Acne Vulgaris

Acne vulgaris (acne) is the formation of comedones, papules, pustules, nodules, and/or cysts as a result of obstruction and inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous gland). It most often affects adolescents. Diagnosis is by examination. Treatment is a variety of topical and systemic agents intended to reduce sebum production, infection, and inflammation and to normalize keratinization.

Pathophysiology

Acne occurs when pilosebaceous units become obstructed with plugs of sebum and desquamated keratinocytes, then colonized and sometimes infected with the normal skin anaerobe Propionibacterium acnes. Manifestations differ depending on whether P. acnes stimulates inflammation in the follicle; acne can be noninflammatory or inflammatory.

Comedones, uninfected sebaceous plugs impacted within follicles, are the signature of noninflammatory acne. Comedones are termed open or closed depending on whether the follicle is dilated or closed at the skin surface. Inflammatory acne comprises papules, pustules, nodules, and cysts.

Papules appear when lipases from P. acnes metabolize triglycerides into free fatty acids (FFA), which irritate the follicular wall. Pustules occur when active P. acnes infection causes inflammation within the follicle. Nodules and cysts occur when rupture of follicles due to inflammation, physical manipulation, or harsh scrubbing releases FFAs, bacteria, and keratin into tissues, triggering soft-tissue inflammation.

Etiology

The most common trigger is puberty, when surges in androgen stimulate sebum production and hyperproliferation of keratinocytes. Other triggers include hormonal changes that occur with pregnancy or throughout the menstrual cycle; occlusive cosmetics, cleansing agents, and clothing; and humidity and sweating. Associations between acne exacerbation and diet (eg, chocolate), inadequate face washing, masturbation, and sex are unfounded. Some studies question an association with milk products. Acne may improve in summer months because of sunlight's anti-inflammatory effects. Proposed associations between acne and hyperinsulinism require further investigation.

Symptoms and Signs

Cystic acne can be painful; other types cause no physical symptoms but can be a source of significant emotional distress. Lesion types frequently coexist at different stages.

Comedones appear as whiteheads or blackheads. Whiteheads (closed comedones) are flesh-colored or whitish palpable lesions 1 to 3 mm in diameter; blackheads (open comedones) are similar in appearance but with a dark center.

Papules and pustules are red lesions 2 to 5 mm in diameter. In both, the follicular epithelium becomes damaged with accumulation of neutrophils and then lymphocytes. When the epithelium ruptures, the comedo contents elicit an intense inflammatory reaction in the dermis. Relatively deep inflammation produces papules. Pustules are more superficial.

Nodules are larger, deeper, and more solid than papules. Such lesions resemble inflamed epidermoid cysts, although they lack true cystic structure.
Cysts are suppurative nodules. Rarely cysts become infected and form abscesses. Long-term cystic acne can cause scarring that manifests as tiny, deep pits (icepick scars), larger pits, shallow depressions, or areas of hypertrophic scar.

Acne conglobata is the most severe form of acne vulgaris, affecting men more than women. Patients have abscesses, draining sinuses, fistulated comedones, and keloidal and atrophic scars. The back and chest are severely involved. The arms, abdomen, buttocks, and even the scalp may be affected.

Acne fulminans is acute, febrile, ulcerative acne, characterized by the sudden appearance of confluent abscesses leading to hemorrhagic necrosis. Leukocytosis and joint pain and swelling may also be present.

Pyoderma faciale (also called rosacea fulminans) occurs suddenly on the midface of young women. It may be analogous to acne fulminans. The eruption consists of erythematous plaques and pustules, involving the chin, cheeks, and forehead.

Diagnosis

- Assessment for contributing factors (eg, hormonal, mechanical, or drug-related)
- Determination of severity (mild, moderate, severe)
- Assessment of psychosocial impact

Diagnosis is by examination. Differential diagnosis includes rosacea (in which no comedones are seen), corticosteroid-induced acne (which lacks comedones and in which pustules are usually in the same stage of development), perioral dermatitis (usually with a more perioral and periorbital distribution), and acneiform drug eruptions. Acne severity is graded mild, moderate, or severe based on the number and type of lesions; a standardized system is outlined in Table 73-1.

Prognosis

Acne of any severity usually remits spontaneously by the early to mid-20s, but a substantial minority of patients, usually women, may have acne into their 40s; options for treatment may be limited because of child-bearing. Many adults occasionally develop mild, isolated acne lesions. Noninflammatory and mild inflammatory acne usually heals without scars. Moderate to severe inflammatory acne heals but often leaves scarring. Scarring is not only physical; acne may be a huge emotional stressor for adolescents who may withdraw, using the acne as an excuse to avoid difficult personal adjustments. Supportive counseling for patients and parents may be indicated in severe cases.

Treatment

- Comedones: Topical tretinoin
- Mild inflammatory acne: Topical antibiotics, benzoyl peroxide, or both
- Moderate acne: Oral antibiotics
- Severe acne: Oral isotretinoin
- Cystic acne: Intraleosinal triamcinolone

Treatments are directed at reducing sebum production, comedone formation, inflammation, and infection (see Fig. 73-1). Selection of
treatment is generally based on severity; options are summarized in Table 73-2. Affected areas should be cleansed daily, but extra washing, use of antibacterial soaps, and scrubbing confer no added benefit. Changes in diet are also unnecessary and ineffective, although moderation of milk intake might be considered for treatment-resistant adolescent acne. Peeling agents such as sulfur, salicylic acid, and resorcinol are minor therapeutic adjuncts.

Treatment should involve educating the patient and tailoring the plan to one that is realistic for the patient. Treatment failure can frequently be attributed to lack of adherence to the plan and also to lack of follow-up. Consultation with a specialist may be necessary.

Mild acne: Single-agent therapy is generally sufficient for comedonal acne; papulopustular acne generally requires dual therapy (eg, the combination of tretinoin with benzoyl peroxide or topical antibiotics). Treatment should be continued for 6 wk or until lesions respond. Maintenance treatment may be necessary to maintain control.

A mainstay of treatment for comedones is daily topical tretinoin as tolerated. Daily adapalene gel, tazarotene cream or gel, azelaic acid cream, and glycolic or salicylic acid in propylene glycol are alternatives for patients who cannot tolerate topical tretinoin. Adverse effects include erythema, burning, stinging, and peeling. Adapalene and tazarotene are retinoids; like tretinoin, they tend to be somewhat irritating and photosensitizing. Azelaic acid has comedolytic and antibacterial properties by an unrelated mechanism and may be synergistic with retinoids.

Mild inflammatory acne should be treated with topical benzoyl peroxide, topical antibiotics (eg, erythromycin, clindamycin), glycolic acid, or a combination. Combination preparations of these agents may help limit development of resistance. None have significant adverse effects other than drying and irritation (and rare allergic reactions to benzoyl peroxide). Topical retinoids are often used concomitantly.

Physical extraction of comedones using a comedo extractor is an option for patients unresponsive to topical treatment. Comedo extraction may be done by a physician, nurse, or physician assistant. One end of the comedo extractor is like a blade or bayonet that punctures the closed comedo. The other end exerts pressure to extract the comedo. Oral antibiotics (eg, tetracycline, minocycline, doxycycline, erythromycin) can be used when wide distribution of lesions makes topical therapy impractical.

Moderate acne: Moderate acne responds best to oral systemic therapy with antibiotics. Antibiotics effective for acne include tetracycline, minocycline, erythromycin, and doxycycline. Full benefit takes ≥ 12 wk. Topical therapy as for mild acne is usually used concomitantly with oral antibiotics.

Tetracycline is usually a good first choice: 250 or 500 mg bid (between meals and at bedtime) for 4 wk or until lesions respond, after which it may be reduced to the lowest effective dose. Rarely, dosage must be increased to 500 mg qid. After control is achieved, it is reasonable to attempt to taper and discontinue the oral antibiotic and continue topical therapy for control. Because relapse often follows short-term treatment, therapy may need to be continued for months to years, although for maintenance tetracycline 250 or 500 mg once/day is often sufficient. Minocycline 50 or 100 mg bid causes fewer GI adverse effects, is easier to take, and is less likely to cause photosensitization, but it is the most costly option. Erythromycin and doxycycline are considered 2nd-line drugs because both can cause GI adverse effects, and doxycycline is a frequent photosensitizer. Subantimicrobial doses of doxycycline have also been proven effective for acne and rosacea.
Long-term use of antibiotics may cause a gram-negative pustular folliculitis around the nose and in the center of the face. This uncommon superinfection may be difficult to clear and is best treated with oral isotretinoin after discontinuing the oral antibiotic. Ampicillin is an alternative treatment for gram-negative folliculitis. In women, prolonged antibiotic use can cause candidal vaginitis; if local and systemic therapy does not eradicate this problem, antibiotic therapy for acne must be stopped.

**Severe acne:** Oral isotretinoin is the best treatment for patients with moderate acne in whom antibiotics are unsuccessful and for those with severe inflammatory acne. Dosage of isotretinoin is usually 1 mg/kg once/day for 16 to 20 wk, but the dosage may be increased to 2 mg/kg once/day. If adverse effects make this dosage intolerable, it may be reduced to 0.5 mg/kg once/day. After therapy, acne may continue to improve. Most patients do not require a 2nd course of treatment; when needed, it should be resumed only after the drug has been stopped for 4 mo. Retreatment is required more often if the initial dosage is low (0.5 mg/kg). With this dosage (which is very popular in Europe), fewer adverse effects occur, but prolonged therapy is usually required.

Isotretinoin is nearly always effective, but use is limited by adverse effects, including dryness of conjunctivae and mucosae of the genitals, chapped lips, arthralgias, depression, elevated lipid levels, and the risk of birth defects if treatment occurs during pregnancy. Hydration with water followed by petrolatum application usually alleviates mucosal and cutaneous dryness. Arthralgias (mostly of large joints or the lower back) occur in about 15% of patients. Increased risk for depression and suicide is much publicized but probably rare. CBC; liver function; and fasting glucose, triglyceride, and cholesterol levels should be determined before treatment. Each should be reassessed at 4 wk and, unless abnormalities are noted, need not be repeated until the end of treatment. Triglycerides rarely increase to a level at which the drug should be stopped. Liver function is seldom affected. Because isotretinoin is teratogenic, women of childbearing age are urged to use 2 methods of contraception for 1 mo before treatment, during treatment, and for at least 1 mo after stopping treatment. Pregnancy tests should be done before beginning therapy and monthly until 1 mo after therapy stops.

Intralesional injection of 0.1 mL triamcinolone acetonide suspension 2.5 mg/mL (the 10 mg/mL suspension must be diluted) is indicated for patients with firm (cystic) acne who seek quick clinical improvement and to reduce scarring. Local atrophy may occur but is usually transient. For isolated, very boggy lesions, incision and drainage are often beneficial but may result in residual scarring.

**Other forms of acne:** Pyoderma faciale is treated with oral corticosteroids and isotretinoin. Acne fulminans is treated with oral corticosteroids and systemic antibiotics. Acne conglobata is treated with oral isotretinoin if systemic antibiotics fail. For acne with endocrine abnormalities, antiandrogens are indicated. Spironolactone, which has some antiandrogen effects, is sometimes prescribed to treat acne at a dose of 50 to 100 mg po once/day. Cyproterone acetate is used in Europe. When other measures fail, an estrogen-progesterone-containing contraceptive may be tried; therapy ≥ 6 mo is needed to evaluate effect.

**Scarring:** Small scars can be treated with chemical peels, laser resurfacing, or dermabrasion. Deeper, discrete scars can be excised. Wide, shallow depressions can be treated with subcision or collagen injection. Collagen implants are temporary and must be repeated every few years.

**Perioral Dermatitis**

Perioral dermatitis is an erythematous, papulopustular facial eruption that resembles acne and/or rosacea but typically starts around the mouth.

A variety of causes have been proposed, including exposure to topical corticosteroids and/or fluoride in water and toothpaste, but the etiology is unknown. Despite its name, perioral dermatitis is not a true dermatitis. It primarily affects women of childbearing age and children. The eruption classically starts at the nasolabial folds and spreads periorally sparing a zone around the vermilion border of the lips. But the eruption can also spread periorbitally and to the forehead.

Diagnosis is by appearance; perioral dermatitis is distinguished from acne by the absence of comedones and from rosacea by the latter's lack of lesions around the mouth and eyes. Seborrheic dermatitis and...
contact dermatitis must be excluded. Biopsy, which is generally not clinically necessary, shows spongiosis and a lymphohistiocytic infiltrate affecting vellus hair follicles. In the lupoid variant, granulomas may be present.

Treatment is to stop fluorinated dental products and topical corticosteroids (if being used) and then either use topical antibiotics (eg, erythromycin 2% or metronidazole 0.75% gel or cream bid), or oral tetracycline 250 to 500 mg po bid (between meals) for 4 wk, tapered to the lowest effective dose. Alternative oral antibiotics include doxycycline 50 to 100 mg bid and minocycline 50 to 100 mg bid. In contrast to acne, antibiotics can usually be stopped. Reasons for efficacy of antibiotics are unclear given the absence of evidence of infection. Isotretinoin has been successfully used to treat granulomatous perioral dermatitis.

**Rosacea**

Rosacea (acne rosacea) is a chronic inflammatory disorder characterized by facial flushing, telangiectasias, erythema, papules, pustules, and in severe cases, rhinophyma (see Plate 43). Diagnosis is based on the characteristic appearance and history. Treatment depends on severity and includes topical metronidazole, topical and oral antibiotics, rarely isotretinoin, and, for severe rhinophyma, surgery.

Rosacea most commonly affects patients aged 30 to 50 with fair complexions, most notably those of Irish and Northern European descent, but it affects and is probably under-recognized in darker-skinned patients.

**Etiology**

The etiology is unknown, although associations with abnormal vasomotor control, impaired facial venous drainage, an increase in follicle mites (*Demodex folliculorum*), and *Helicobacter pylori* infection have been proposed. People with rosacea may have elevated levels of small antimicrobial peptides that are part of the body's natural defense system. People with rosacea may also have higher than normal levels of cathelicidin as well as another group of enzymes called stratum corneum tryptic enzymes.

**Symptoms and Signs**

Rosacea is limited to the face and scalp and manifests in 4 phases:

- Prerosacea phase
- Vascular phase
- Inflammatory phase
- Late stage

In the prerosacea phase, patients describe embarrassing flushing and blushing, often accompanied by uncomfortable stinging. Common reported triggers for these flares include sun exposure, emotional stress, cold or hot weather, alcohol, spicy foods, exercise, wind, cosmetics, and hot baths or hot drinks. These symptoms persist throughout other phases of the disorder.

In the vascular phase, patients develop facial erythema and edema with multiple telangiectases, possibly as a result of persistent vasomotor instability.

An inflammatory phase often follows, in which sterile papules and pustules (leading to the designation of rosacea as adult acne) develop.

Some patients go on to develop late-stage rosacea, characterized by coarse tissue hyperplasia of the cheeks and nose (rhinophyma) caused by tissue inflammation, collagen deposition, and sebaceous gland hyperplasia.
The phases of rosacea are usually sequential. Some patients go directly into the inflammatory stage, bypassing the earlier stages. Treatment may cause rosacea to return to an earlier stage. Progression to the late stage is not inevitable.

Ocular rosacea often accompanies facial rosacea and manifests as some combination of blepharoconjunctivitis, iritis, scleritis, and keratitis, causing itching, foreign body sensation, erythema, and edema of the eye.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on the characteristic appearance; there are no specific diagnostic tests. The age of onset and absence of comedones help distinguish rosacea from acne. Differential diagnosis includes acne vulgaris, SLE, sarcoidosis, photodermatitis, drug eruptions (particularly from iodides and bromides), granulomas of the skin, and perioral dermatitis.

**Treatment**

- Avoidance of triggers
- Consideration of topical or oral antibiotics
- Consideration of isotretinoin if antibiotics are unsuccessful
- Consideration of dermabrasion and tissue excision for rhinophyma

Primary initial treatment of rosacea involves avoidance of triggers (including use of sunscreen). Antibiotics may be used for inflammatory disease. The objective of treatment is control of symptoms, not cure.

Metronidazole cream 1%, lotion (0.75%), or gel (0.75%) and azelaic acid 20% cream, applied bid, are equally effective; 2.5% benzoyl peroxide, applied once/day or bid, can be added for improved control. Less effective alternatives include sodium sulfacetamide 10%/sulfur 5% lotion; clindamycin 1% solution, gel, or lotion; and erythromycin 2% solution, all applied bid. Many patients require indefinite treatment for chronic control.

Oral antibiotics are indicated for patients with multiple papules or pustules and for those with ocular rosacea; options include tetracycline 250 to 500 mg bid, doxycycline 50 to 100 mg bid, minocycline 50 to 100 mg bid, and erythromycin 250 to 500 mg bid. Dose should be reduced to the lowest one that controls symptoms once a beneficial response is achieved. Recalcitrant cases may respond to oral isotretinoin. Subantimicrobial doses of doxycycline are also effective for acne and rosacea.

Techniques for treatment of rhinophyma include dermabrasion and tissue excision; cosmetic results are good.
Chapter 74. Bullous Diseases

Introduction

Bullae are elevated, fluid-filled blisters ≥ 5 mm in diameter. Bullous diseases include bullous pemphigoid, dermatitis herpetiformis, epidermolysis bullosa acquista, herpes gestationis (pemphigoid gestationis—see p. 2666), linear IgA disease, pemphigus vulgaris, and pemphigus foliaceus. Staphylococcal scalded skin syndrome (see p. 701) and toxic epidermal necrolysis (see p. 689) also cause bullae.

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune skin disorder causing chronic, pruritic bullous eruptions in elderly patients. Diagnosis is by skin biopsy. Corticosteroids are used initially. Most patients require long-term maintenance therapy, for which a variety of drugs can be used.

In bullous pemphigoid, antibodies are directed against the basement membrane zone of the epidermis, causing separation between the epidermis and dermis. Bullous pemphigoid must be distinguished from pemphigus vulgaris (see p. 658), a much more serious disease.

Symptoms and Signs

Characteristic tense bullae develop on normal-appearing or erythematous skin, most often in flexural areas. Nikolsky's sign, in which lateral pressure on skin adjacent to a blister causes epidermal detachment, is negative. Bullous pemphigoid can manifest initially as hives with annular, dusky-red, edematous lesions, with or without peripheral vesicles. Itching is common, usually without other symptoms. Oral lesions occur in about one third of patients but heal rapidly.

Diagnosis

- Skin biopsy and antibody titers

Patients should have a skin biopsy and serum antibody titers for hemidesmosomal BP antigens BP230 (BPAg1) and BP180 (BPAg2).

Bullous pemphigoid must be differentiated from pemphigus vulgaris (see Table 74-1), linear IgA disease, erythema multiforme, drug-induced eruptions, benign mucous membrane pemphigoid, paraneoplastic pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa acquisita.

Prognosis

Prognosis is good, and the disorder usually subsides within months to years; however, the disorder is potentially fatal, especially in the elderly and debilitated patients, with death being caused by infection and sepsis or the effects of the drugs.

Treatment

- Corticosteroids, topical or oral
- Anti-inflammatory drugs

Mild bullous pemphigoid sometimes resolves without treatment, but resolution usually takes months or years. Patients with more severe disease receive prednisone 60 to 80 mg po once/day, which can be tapered to a maintenance level of ≤ 10 to 20 mg/day after several weeks. Most patients achieve remission after 2 to 10 mo. Occasional new lesions in elderly patients do not require increasing the prednisone dosage.

[Table 74-1, Distinguishing Pemphigoid from Pemphigus Vulgaris]
The disorder occasionally responds to a combination of tetracycline or minocycline and nicotinamide. Other treatment options include dapsone, sulfapyridine, erythromycin, and tetracycline used alone for their anti-inflammatory rather than their antibiotic properties. IV immune globulin has been used occasionally. For patients with generalized and recalcitrant disease, immunosuppressants such as azathioprine, cyclophosphamide, rituximab, and cyclosporine may be used. However, use of immunosuppressants for bullous pemphigoid is controversial.

**Dermatitis Herpetiformis**

Dermatitis herpetiformis is a cutaneous manifestation associated with gluten sensitivity. It produces a chronic eruption characterized by clusters of intensely pruritic vesicles, papules, and urticaria-like lesions. The cause is autoimmune. Diagnosis is by skin biopsy with direct immunofluorescence testing. Treatment is usually with dapsone or sulfapyridine and a gluten-free diet.

This disease usually manifests in patients 30 to 40 yr old (but may occur from age 2 to 90 yr) and is rare in blacks and Asians.

More than 90% of affected patients have a gluten-sensitive enteropathy, which is often asymptomatic. Dermatitis herpetiformis develops in 15 to 25% of patients with celiac sprue. Patients have a slightly higher incidence of other autoimmune disorders, including type 1 diabetes mellitus, sarcoidosis, SLE, and thyroid abnormalities. The incidence of enteropathy-associated T-cell lymphoma is also increased.

The term herpetiformis refers to the clustered appearance of the lesions rather than a relationship to herpesvirus.

**Symptoms and Signs**

Onset is usually gradual. Vesicles, papules, and urticaria-like lesions are usually distributed symmetrically on extensor aspects (elbows, knees, sacrum, buttocks, occiput). Vesicles and papules occur in about one third of patients. Itching and burning are severe, and scratching often obscures the primary lesions with eczematization of nearby skin, leading to an erroneous diagnosis of eczema. NSAIDs and iodides may worsen the rash.

**Diagnosis**

- Skin biopsy

Diagnosis is based on skin biopsy and direct immunofluorescence testing of a lesion and adjacent normal-appearing skin. Granular IgA deposition in the dermal papillary tips is invariably present and important for diagnosis. Patients should be evaluated for celiac sprue (see p. 158).

**Treatment**

- Gluten-free diet
- Dapsone

Strict adherence to a gluten-free diet for a prolonged time (eg, 6 to 12 mo) controls the disease in some patients, obviating or reducing the need for drug therapy. When drugs are needed, dapsone generally results in remarkable improvement. Initial dosages of dapsone are 25 to 50 mg po once/day in adults and 0.5 mg/kg in children. Usually, this dose dramatically relieves symptoms, including itching, within 1 to 3 days; if it does, the dose is continued. If no improvement occurs, the dose can be increased every week, up to 300 mg/day. Most patients can be maintained on 50 to 150 mg/day, and some require as little as 25 mg/wk. After initial therapy and stabilization of the disease, the majority of patients can be maintained on a strict gluten-free diet. Although less effective, sulfapyridine may be used as an alternative for patients who cannot tolerate dapsone. Initial oral dosage is 500 mg bid, increasing by 1 g/day q 1 to 2 wk until...
Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita is a chronic autoimmune mucocutaneous disease causing blistering and skin fragility.

Epidermolysis bullosa acquisita usually appears in adults. Bullous lesions may develop on normal-appearing skin spontaneously or may be caused by minor trauma. The trauma-prone areas of the skin, such as the extensor surfaces of elbows, knees, ankles, and buttocks, are most commonly affected. Pain and scarring are common. Because the hands and feet are often involved, disability can be significant. Occasionally, mucosa of eyes, mouth, or genitals is involved. Laryngeal and esophageal involvement also occurs. Diagnosis is by skin biopsy. Lesions respond poorly to corticosteroids. Mild disease may be treated with colchicine, but more severe disease may require cyclosporine or immune globulin.

Linear Immunoglobulin A Disease

Linear immunoglobulin A (IgA) disease is an uncommon bullous disease distinguished from bullous pemphigoid and dermatitis herpetiformis by the linear deposits of IgA in the basement membrane zone.

Linear IgA disease occurs in adults and children. The childhood form is most frequently termed chronic bullous disease of childhood.

In linear IgA disease, vesicular or bullous skin lesions occur frequently in a clustered (herpetiform) arrangement. There is a predilection for flexural areas (eg, inguinal crease). As in dermatitis herpetiformis, severe burning and pruritus of cutaneous lesions are prominent features. It was previously considered a form of dermatitis herpetiformis but has no concomitant gluten-sensitive enteropathy and immunopathology. Also, genetic studies indicate that linear IgA disease is a separate disorder. Drug-induced linear IgA disease, most commonly associated with vancomycin, has been reported.

Diagnosis is by skin biopsy. Dapsone is the treatment of choice. Doses should be similar to those used for dermatitis herpetiformis (see p. 657), and CBC monitoring should follow the same parameters. Other treatment options include glucocorticoids (systemic, topical, and intralesional), cyclophosphamide, azathioprine, colchicine, tetracycline and nicotinamide, and cyclosporine.

Pemphigus Vulgaris

Pemphigus vulgaris is an uncommon, potentially fatal, autoimmune disorder characterized by intraepidermal blisters and extensive erosions on apparently healthy skin and mucous membranes. Diagnosis is by skin biopsy with direct immunofluorescence testing. Treatment is with corticosteroids and sometimes immunosuppressants.

Pemphigus vulgaris usually occurs in middle-aged or elderly patients and is rare in children. One variant, paraneoplastic pemphigus, occurs in older patients with cancer (primarily lymphoreticular); outcome is poor.

The disorder is characterized by the presence of autoantibodies directed against intercellular adhesion molecules desmoglein-1 and desmoglein-3 in the epidermis. They are Ca-dependent cadherins, involved in adhesion and cell signaling between epidermal cells. Acantholysis results from either direct inhibition of
function of the desmogleins by autoantibody binding or from autoantibody-induced cell signaling that results in down-regulation of cell-cell adhesion and formation of blisters. These autoantibodies are present in both serum and skin during active disease. Any area of stratified squamous epithelium may be affected, including mucosal surfaces.

**Symptoms and Signs**

The primary lesions are flaccid bullae of various sizes (see Plate 41), but often skin or mucosa just shears off, leaving painful erosions. Lesions typically occur first in the mouth, where they rupture and remain as chronic, often painful, erosions for variable periods before the skin is affected; dysphagia and poor oral intake are common. Lesions also may occur in the upper esophagus. Cutaneous bullae typically arise from normal-appearing skin, rupture, and leave a raw area and crusting. Itching is usually absent. Open skin lesions often become infected. If large portions of the body are affected, fluid and electrolyte loss may be significant.

**Diagnosis**

- Clinical evaluation
- Biopsy with direct immunofluorescence testing
- Sometimes titers of antibodies against desmoglein-3 or desmoglein-1

Pemphigus vulgaris should be suspected in patients with any bullous disorder or chronic mucosal ulceration. It must be differentiated from other chronic oral ulcers and from other bullous dermatoses (eg, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, drug eruptions, toxic epidermal necrolysis, erythema multiforme, dermatitis herpetiformis, bullous contact dermatitis). Two physical signs in pemphigus vulgaris are helpful:

- Lateral pressure on skin adjacent to a blister causes epidermal detachment (Nikolsky's sign).
- Pressure on a blister can cause the blister to extend to adjacent skin (Asboe-Hansen sign).

Biopsy of the edge of a fresh lesion and of a nearby area of normal skin is required; light microscopy and direct immunofluorescence testing are usually diagnostic. Serum antibodies (eg, to desmoglein-3) can be used for diagnosis and for differentiating from pemphigus foliaceus; serial titers can help follow disease activity.

**Prognosis**

Before systemic corticosteroids were used, pemphigus vulgaris was usually fatal; most patients died within 5 yr of disease onset. Even with treatment, pemphigus vulgaris is a serious disorder with an inconsistent and unpredictable response to treatment, a prolonged course, and virtually inevitable adverse drug effects.

**Treatment**

- Corticosteroids, oral or IV
- Sometimes immunosuppressants
- Sometimes plasmapheresis and IV immune globulin (IVIG)

Referral to a dermatologist with expertise in treating this disorder is recommended. Hospitalization is required initially for all but the most minor cases. Cleansing and dressing of open skin lesions is similar to that done for partial-thickness burns (eg, reverse isolation, hydrocolloid or silver sulfadiazine dressings—see p. 3246).
Drug treatment aims to decrease the production of autoantibodies and stop the eruption of new lesions. The mainstay is systemic corticosteroids. Some patients with few lesions may respond to oral prednisone 20 to 30 mg once/day, but most require 1.0 mg/kg once/day as an initial dose. Some clinicians begin with even higher doses, which may slightly hasten initial response but does not appear to improve outcome. If new lesions continue to appear after 5 to 7 days, IV pulse therapy with methylprednisolone 1 g once/day can be tried.

Immunosuppressants such as methotrexate, cyclophosphamide, azathioprine, gold, mycophenolate mofetil, cyclosporine, or rituximab can reduce the need for corticosteroids and thus minimize the undesirable effects of long-term corticosteroid use. Plasmapheresis and high-dose IVIG to reduce antibody titers have also been effective.

Once no new lesions have appeared for 7 to 10 days, corticosteroid dose should be tapered monthly by about 10 mg/day (tapering continues more slowly once 20 mg/day is reached). A relapse requires a return to the starting dose. If the patient has been stable after a year, a trial without treatment can be attempted but must be closely monitored.

**Pemphigus Foliaceus**

**Pemphigus foliaceus is a generally benign blistering disorder. It is characterized by splitting high in the epidermis, causing erosions to form on the skin.**

Pemphigus foliaceus usually occurs in middle-aged patients. Foci of high incidence occur in South America, especially Brazil.

The primary lesion is a flaccid bulla. However, because splitting occurs high in the epidermis, bullae are rarely seen; the blisters are so fragile that they rupture. Clinically, scaly, crusted cutaneous erosions, often on an erythematous base, can be seen. Mucosal surfaces are not usually involved. In one variant, pemphigus erythematosus, lesions occur on light-exposed skin and are often similar to those of cutaneous lupus erythematosus.

Diagnosis is by biopsy of a lesion and neighboring normal skin and by serum antibody titers against the cell adhesion molecule desmoglein 1 (160 kd). Because the disorder is much more benign than pemphigus vulgaris, treatment is generally less aggressive. Superpotent topical corticosteroids may be sufficient in some patients. Others require oral prednisone and additional immunosuppressants. A combination of tetracycline 500 mg qid and nicotinamide 1.5 g/day has been effective in some patients. Plasmapheresis is an option for severe disease.
Chapter 75. Cornification Disorders

Introduction

Cornification disorders include calluses, corns, ichthyosis, and keratosis pilaris.

Calluses and Corns

(Tylomas; Helomas; Clavi)

Calluses and corns are circumscribed areas of hyperkeratosis at a site of intermittent pressure or friction. Calluses are more superficial, cover broader areas of skin, and usually asymptomatic. Corns are deeper, more focal, and frequently painful. Diagnosis is by appearance. Treatment is with manual abrasion with or without keratolytics. Prevention involves altering biomechanics, such as changing footwear. Rarely, surgery is required.

Calluses and corns are caused by intermittent pressure or friction, usually over a bony prominence (eg, heel, metatarsal heads).

Corns consist of a sharply circumscribed keratinous plug, pea-sized or slightly larger, which extends through most of the underlying dermis. An underlying adventitial bursitis may develop. Hard corns occur over prominent bony protuberances, especially on the toes and plantar surface. Soft corns occur between the toes. Most corns result from poorly fitting footwear, but small seed-sized corns on non-weight-bearing aspects of the soles and palms may represent inherited keratosis punctata.

Calluses lack a central plug and have a more even appearance. They usually occur on the hands or feet but may occur elsewhere, especially in a person whose occupation entails repeated trauma to a particular area (eg, the mandible and clavicle of a violinist).

Symptoms and Signs

Calluses are usually asymptomatic but, if friction is extreme, may become irritated, causing mild burning discomfort. At times, the discomfort may mimic that of interdigital neuralgia.

Corns may be painful or tender when pressure is applied. A bursa or fluid-filled pocket sometimes forms beneath a corn.

Diagnosis

• Clinical evaluation

A corn may be differentiated from a plantar wart or callus by paring away the horny skin. After paring, a callus shows smooth translucent skin, whereas a wart (see p. 715) appears sharply circumscribed, sometimes with soft macerated tissue or with central black dots (bleeding points) representing thrombosed capillaries. A corn, when pared, shows a sharply outlined yellowish to tan translucent core that interrupts the normal architecture of the papillary dermis. Interdigital neuralgia can be ruled out by the absence of interspace pain on palpation.

Treatment

• Manual removal
• Keratolytics
• Cushioning
• Altering foot biomechanics
A nail file, emery board, or pumice stone used immediately after bathing is often a practical way to manually remove hyperkeratotic tissue. Keratolytics (eg, 17% salicylic acid in collodion, 40% salicylic acid plasters, 40% urea) can also be used, taking care to avoid applying the agents to normal skin. Normal skin may be protected by covering it with petrolatum before application of the keratolytic.

Cushioning and altering foot biomechanics can help prevent corns and help treat existing corns. Although difficult to eliminate, pressure on the affected surface should be reduced and redistributed. For foot lesions, soft, well-fitting shoes are important; they should have a roomy toe box so that toes can move freely in the shoe. Stylish shoes often prevent this freedom of motion. Shoes that increase discomfort of a lesion should be eliminated from the wardrobe. Pads or rings of suitable shapes and sizes, moleskin or foam-rubber protective bandages, arch inserts (orthotics), or metatarsal plates or bars may help redistribute the pressure. For corns and calluses on the ball of the foot, an orthotic should not be full length but should extend only to the ball or part of the shoe immediately behind the corn or callus. Surgical off-loading or removal of the offending bone is rarely necessary.

Patients who have a tendency to develop calluses and corns may need the regular services of a podiatrist. Patients with impaired peripheral circulation, especially if associated with diabetes, require expert care.

**Ichthyosis**

**Ichthyosis is scaling and flaking of skin ranging from mild but annoying dryness (xeroderma) to severe disfiguring disease (inherited ichthyosis). Ichthyosis can also be a sign of systemic disease. Diagnosis is clinical. Treatment involves emollients and sometimes oral retinoids.**

**Xeroderma:** Xeroderma (xerosis), or dry skin, is neither inherited nor associated with systemic abnormalities. Dry skin results from loss of the water content of the skin, resulting in fine white scales. Risk factors for xerosis include the following:

- Residence in a dry, cold climate
- Older age
- Atopic dermatitis
- Frequent bathing, particularly if using harsh soaps

**Inherited ichthyoses:** Inherited ichthyoses, which are characterized by excessive accumulation of scale on the skin surface, are classified according to clinical and genetic criteria (see Table 75-1). Some occur in isolation without associated abnormalities (eg, ichthyosis vulgaris, X-linked ichthyosis, lamellar ichthyosis, epidermolytic hyperkeratosis [bullous congenital ichthyosiform erythroderma]). Other ichthyoses are part of a syndrome that involves multiple organs. For instance, Refsum's disease (see p. 3024) and Sjogren-Larsson syndrome (hereditary intellectual disability and spastic paralysis caused by a defect in fatty aldehyde dehydrogenase) are autosomal recessive conditions with skin and extracutaneous organ involvement. A dermatologist should assist in diagnosis and management, and a medical geneticist should be consulted for genetic counseling.

**Table 75-1. Clinical and Genetic Features of Some Inherited Ichthyoses**

Acquired ichthyosis: Ichthyosis may be an early manifestation of some systemic disorders (eg, leprosy, hypothyroidism, lymphoma, AIDS). Some drugs cause ichthyosis (eg, nicotinic acid, triparanol, butyrophenones). The dry scaling may be fine and localized to the trunk and legs, or it may be thick and widespread. Biopsy of ichthyotic skin is usually not diagnostic of the systemic disorder; however, there are exceptions, most notably sarcoidosis, in which a thick scaling may appear on the legs, and biopsy usually shows the typical granulomas.
Treatment

- Minimization of exacerbating factors
- Moisturization and keratolytics
- Sometimes infection prophylaxis

When ichthyosis is caused by a systemic disorder, abatement is greatest if the primary disorder can be corrected. Otherwise, treatment is symptomatic, including using emollients and keratolytics and avoiding drying.

**Moisturization and keratolytics:** In any ichthyosis, there is impaired epidermal barrier function, and moisturizers should be applied immediately after bathing. Substances that are applied to the skin may have increased absorption. For example, hexachlorophene products should not be used because of increased absorption and toxicity.

An emollient, preferably plain petrolatum, mineral oil, or lotions containing urea or α-hydroxy acids (eg, lactic, glycolic, and pyruvic acids), should be applied twice daily, especially after bathing while the skin is still wet. Blotting with a towel removes excess applied material.

Ichthyosis typically responds well to propylene glycol. To remove scale (eg, if ichthyosis is severe), patients can apply a preparation containing 40 to 60% propylene glycol in water under occlusion (eg, a thin plastic film or bag), every night after hydrating the skin (eg, by bathing or showering); in children, the preparation should be applied twice daily without occlusion. Occlusion should be maintained overnight. After scaling has decreased, less frequent application is required. Other useful keratolytics include ceramide-based creams, 6% salicylic acid gel, hydrophilic petrolatum and water (in equal parts), and the α-hydroxy acids in various bases. Topical calcipotriol cream has been used with success; however, this vitamin D derivative can result in hypercalcemia when used over broad areas, especially in small children.

**Retinoids** are effective in treating ichthyosis. Oral synthetic retinoids are effective for most ichthyoses. Acitretin (see p. 679) is effective in treating most forms of inherited ichthyosis. In lamellar ichthyosis, 0.1% tretinoin cream or oral isotretinoin may be effective. The lowest effective dose should be used. Long-term (1 yr) treatment with oral isotretinoin has resulted in bony exostoses in some patients, and other long-term adverse effects may arise. (CAUTION: Oral retinoids are contraindicated in pregnancy because of their teratogenicity, and acitretin should be avoided in women of childbearing potential because of its teratogenicity and long half-life.)

**Infection prophylaxis:** Patients with epidermolytic hyperkeratosis may need long-term treatment with cloxacillin 250 mg po tid or qid or erythromycin 250 mg po tid or qid, as long as thick intertriginous scaling is present, to prevent bacterial superinfection from causing painful, foul-smelling pustules. Regularly using soaps containing chlorhexidine may also reduce the bacteria, but these soaps tend to dry the skin.

**Keratosis Pilaris**

**Keratosis pilaris is a disorder of keratinization in which horny plugs fill the openings of hair follicles.**

Keratosis pilaris is common. The cause is unknown, but there is often an autosomal dominant inheritance. Multiple small, pointed, keratotic follicular papules appear mainly on the lateral aspects of the upper arms, thighs, and buttocks. Facial lesions may also occur, particularly in children. Lesions are most prominent in cold weather and sometimes abate in the summer. Skin may appear red. The problem is mainly cosmetic, but the disorder may cause itching or, rarely, follicular pustules.

Treatment is usually unnecessary and often unsatisfactory. Hydrophilic petrolatum and water (in equal parts), cold cream, or petrolatum with 3% salicylic acid may help flatten the lesions. Buffered lactic acid (ammonium lactate) lotions or creams, urea creams, 6% salicylic acid gel, or 0.1% tretinoin cream may also be effective. Acid creams should be avoided in young children because of burning and stinging.
Pulse-dye laser has been used successfully to treat facial redness.
Chapter 76. Dermatitis

Introduction

Dermatitis is superficial inflammation of the skin characterized by redness, edema, oozing, crusting, scaling, and sometimes vesicles. Pruritus is common. Eczema is a term often used interchangeably with dermatitis.

Atopic Dermatitis

Atopic dermatitis (AD) is an immune-mediated inflammation of the skin arising from an interaction between genetic and environmental factors. Recent research suggests that a heritable epidermal barrier defect is a primary cause, and defects in the filaggrin gene have been specifically implicated. Pruritus is the primary symptom; skin lesions range from mild erythema to severe lichenification. Diagnosis is by history and examination. Treatment is moisturizers, avoidance of allergic and irritant triggers, and often topical corticosteroids. Atopic dermatitis frequently resolves completely by age 30.

Etiology

AD primarily affects children in urban areas or developed countries; at least 5% of children in the US are affected. Like asthma, it may be linked to proallergic/proinflammatory T-cell immune responses. Such responses are becoming more common in developed countries because trends toward smaller families, cleaner indoor environments, and early use of vaccinations and antibiotics deprive children of the early exposure to infections and allergens that otherwise suppress proallergic T cells and thereby induce tolerance to various antigens.

Pathophysiology

AD can be divided into 2 forms:

• Extrinsic: IgE-mediated (70 to 80% of cases)
• Intrinsic: Non-IgE-mediated (20 to 30% of cases)

Extrinsic AD: This form occurs when environmental exposures trigger immunologic, usually allergic (ie, IgE-mediated), reactions in genetically susceptible people. Common environmental triggers include

• Foods (eg, milk, eggs, soy, wheat, peanuts, fish)
• Airborne allergens (eg, dust mites, molds, dander)
• Staphylococcus aureus colonization on skin due to deficiencies in endogenous antimicrobial peptides
• Topical products (eg, cosmetics)

AD is common within families, suggesting a genetic component. Many patients with AD have a mutation in the gene encoding for the filaggrin protein, which is a component of the cornified cell envelope produced by differentiating keratinocytes. Also, research has shown that skin affected by AD is deficient in ceramides, which increases transepidermal water loss.

Intrinsic AD: This form is not mediated by IgE. Intrinsic AD is nonfamilial and idiopathic, and its pathophysiology is generally not well understood.

Symptoms and Signs

Manifestations of intrinsic and extrinsic AD are similar. AD usually appears in infancy, typically by 3 mo. In the acute phase, lasting 1 to 2 mo (see
in the acute phase, lasting 1 to 2 mo (see Plate 27), red, weeping, crusted lesions appear on the face and spread to the neck, scalp, extremities, and abdomen. In the chronic phase (see Plate 28), scratching and rubbing create skin lesions (typically erythematous macules and papules that lichenify with continued scratching). Lesions typically appear in antecubital and popliteal fossae and on the eyelids, neck, and wrists and may occasionally become generalized. Lesions slowly resolve to dry, scaly macules (xerosis) that can fissure and facilitate exposure to irritants and allergens. In older children and adults, intense pruritus is the key feature. Patients have a reduced threshold for perceiving itch, and itch worsens with allergen exposures, dry air, sweating, local irritation, wool garments, and emotional stress.

Complications: Secondary bacterial infections, especially staphylococcal and streptococcal, and regional lymphadenitis are common.

Eczema herpeticum (Kaposi's varicelliform eruption) is a diffuse herpes simplex infection occurring in patients with AD. It manifests as grouped vesicles in areas of active or recent dermatitis, although normal skin can be involved. High fever and adenopathy may develop after several days. Occasionally, this infection can become systemic, which may be fatal. Sometimes the eye is involved, causing a painful corneal lesion.

Fungal and nonherpetic viral skin infections (eg, common warts, molluscum contagiosum) can also occur.

Patients with long-standing AD may develop cataracts in their 20s or 30s.

Frequent use of topical products exposes the patient to many potential allergens, and contact dermatitis may aggravate and complicate AD, as may the generally dry skin that is common among these patients.

Diagnosis

- Clinical evaluation
- Sometimes testing for allergic triggers with skin prick testing or radioallergosorbent testing levels

Diagnosis is clinical (see Table 76-1). AD is often hard to differentiate from other dermatoses (eg, seborrheic dermatitis, contact dermatitis, nummular dermatitis, psoriasis), although a family history of atopy and the distribution of lesions are helpful. For example, psoriasis is usually extensor rather than flexurally distributed, may involve the fingernails, and has a shinier (micaceous) scale. Seborrheic dermatitis affects the face (eg, nasolabial folds, eyebrows, glabellar region, scalp) most commonly. Nummular dermatitis is not flexural, and lichenification is rare. Because patients can still develop other skin disorders, not all subsequent skin problems should be attributed to AD.

There is no definitive laboratory test for AD. However, allergic precipitants of AD can be identified with skin testing, measurement of allergen-specific IgE levels, or both.

Prognosis

AD in children often abates by age 5 yr, although exacerbations are common throughout adolescence and into adulthood. Girls and patients with severe disease, early age of onset, family history, and associated rhinitis or asthma are more likely to have prolonged disease. Even in these patients, AD frequently resolves completely by age 30. AD may have long-term psychologic sequelae as children confront many challenges of living with a visible, sometimes disabling, skin disease during formative years.

[Table 76-1, Clinical Findings in Atopic Dermatitis*]

Treatment

- Supportive care (eg, moisturizers, symptomatic treatment for pruritus)
• Avoidance of precipitating factors

• Topical corticosteroids

• Sometimes immune modulators (most often topical but sometimes oral)

• Sometimes ultraviolet (UV) therapy

Treatment can usually be given at home, but patients who have exfoliative dermatitis (see p. 668), cellulitis, or eczema herpeticum may need to be hospitalized.

Supportive care: Skin care involves moisturizing. Bathing and hand washing should be infrequent, and lukewarm (not hot) water should be used; soap use should be minimized on dermatitic areas because it may be drying and irritating. Colloidal oatmeal baths can be helpful. When toweling dry, the skin should be blotted or patted dry rather than rubbed.

Body oils or emollients such as white petrolatum, vegetable oil, or hydrophilic petrolatum (unless the patient is allergic to lanolin) applied immediately after bathing may help retain skin moisture and reduce itching. Continuously wet dressings (not wet-to-dry) are an alternative for severe lesions. Coal tar cream or oil can be an effective topical anti-pruritic but also can be inconvenient because it stains clothing.

Antihistamines can help relieve pruritus. Options include hydroxyzine 25 mg po tid or qid (for children, 0.5 mg/kg q 6 h or 2 mg/kg in a single bedtime dose) and diphenhydramine 25 to 50 mg po at bedtime. Low-sedating H1 receptor blockers, such as loratadine 10 mg po once/day, fexofenadine 60 mg po bid or 180 mg po once/day, and cetirizine 5 to 10 mg po once/day, may be useful, although their efficacy has not been defined. Doxepin (a tricyclic antidepressant also with H1 and H2 receptor blocking activity) 25 to 50 mg po at bedtime may also help, but its use is not recommended for children < 12 yr. Fingernails should be cut short to minimize excoriations and secondary infections.

Avoidance of precipitating factors: Household antigens can be controlled by using synthetic fiber pillows and impermeable mattress covers; washing bedding in hot water; removing upholstered furniture, soft toys, carpets, and pets (to reduce dust mites and animal dander); using air circulators equipped with high-efficiency particulate air (HEPA) filters in bedrooms and other frequently occupied living areas; and using dehumidifiers in basements and other poorly aerated damp rooms (to reduce molds). Reduction of emotional stress is useful but often difficult. Antistaphylococcal antibiotics, both topical (eg, mupirocin, fusidic acid) and oral (eg, dicloxacillin, cephalaxin, erythromycin [all 250 mg qid]), can control S. aureus nasal colonization and are indicated in patients with severe disease unresponsive to specific therapies and positive nasal cultures. Extensive dietary changes intended to eliminate exposure to allergenic foods are unnecessary and probably ineffective; food hypersensitivities rarely persist beyond childhood.

Corticosteroids: Corticosteroids are the mainstay of therapy. Creams or ointments applied twice daily are effective for most patients with mild or moderate disease. Emollients are applied between corticosteroid applications and can be mixed with them to decrease the corticosteroid amount required to cover an area. Systemic corticosteroids (prednisone 60 mg or, for children 1 mg/kg, po once/day for short courses of 7 to 14 days) are indicated for extensive or refractory disease but should be avoided whenever possible, because disease often recurs and topical therapy is safer. Prolonged, widespread use of high-potency corticosteroid creams or ointments should be avoided in infants because adrenal suppression may ensue.

Other therapies: Tacrolimus and pimecrolimus are T-cell inhibitors effective for AD. They should be used when patients do not respond to corticosteroids and tar or when corticosteroid adverse effects such as skin atrophy, striae formation, or adrenal suppression is a concern. Tacrolimus or pimecrolimus cream is applied twice daily. Burning or stinging after application is usually transient and abates after a few days. Flushing is less common.

Repair of the stratum corneum and barrier function may help alleviate AD. Research has shown that skin affected by AD is particularly deficient in ceramides and that a deficiency in ceramides increases transepidermal water loss. Several ceramide-containing emollient products are considered helpful for AD...
control.

Phototherapy is helpful for extensive AD. Natural sun exposure ameliorates disease in many patients, including children. Alternatively, therapy with ultraviolet A (UVA) or B (UVB) may be used. Narrowband UVB therapy is proving more effective than traditional broadband UVB therapy and is also effective in children. Psoralen plus UVA (PUVA—see p. 679) therapy is reserved for extensive, refractory AD. Adverse effects include sun damage (eg, PUVA lentigines, nonmelanoma skin cancer). Because of these adverse effects, PUVA is rarely indicated for children or young adults.

Systemic immune modulators effective in at least some patients include cyclosporine, interferon gamma, mycophenolate, methotrexate, and azathioprine. All downregulate or inhibit T-cell function and have anti-inflammatory properties. These agents are indicated for widespread, recalcitrant, or disabling AD that fails to abate with topical therapy and phototherapy.

Eczema herpeticum is treated with acyclovir. Infants receive 10 to 20 mg/kg IV q 8 h; older children and adults with mild illness may receive 200 mg po 5 times/day. Involvement of the eye is considered an ophthalmic emergency, and if eye involvement is suspected, an ophthalmology consult should be obtained.

**Contact Dermatitis**

**Contact dermatitis (CD)** is acute inflammation of the skin caused by irritants or allergens. The primary symptom is pruritus. Skin changes range from erythema to blistering and ulceration, often on or near the hands but occurring on any exposed skin surface. Diagnosis is by exposure history, examination, and sometimes skin patch testing. Treatment entails antipruritics, topical corticosteroids, and avoidance of causes.

**Pathophysiology**

CD is caused by irritants or allergens.

**Irritant contact dermatitis (ICD):** ICD accounts for 80% of all cases of CD. It is a nonspecific inflammatory reaction to substances contacting the skin; the immune system is not activated. Numerous substances are involved, including

- Chemicals (eg, acids, alkalis, solvents, metal salts)
- Soaps (eg, abrasives, detergents)
- Plants (eg, poinsettias, peppers)
- Body fluids (eg, urine, saliva)

Properties of the irritant (eg, extreme pH, solubility in the lipid film on skin), environment (eg, low humidity, high temperature, high friction), and patient (eg, very young or old) influence the likelihood of developing ICD. ICD is more common among patients with atopic disorders, in whom ICD also may initiate immunologic sensitization and hence allergic CD.

**Phototoxic dermatitis** (see p. 675) is a variant in which topical (eg, perfumes, coal tar) or ingested (eg, psoralens) agents generate damaging free radicals and inflammatory mediators only after absorption of ultraviolet light.

**Allergic contact dermatitis (ACD):** ACD is a type IV cell-mediated hypersensitivity reaction that has 2 phases:

- Sensitization to an antigen
- Allergic response after reexposure
In the sensitization phase, allergens are captured by Langerhans' cells (dendritic epidermal cells), which migrate to regional lymph nodes where they process and present the antigen to T cells. The process may be brief (6 to 10 days for strong sensitizers such as poison ivy) or prolonged (years for weak sensitizers such as sunscreens, fragrances, and glucocorticoids). Sensitized T cells then migrate back to the epidermis and activate on any reexposure to the allergen, releasing cytokines, recruiting inflammatory cells, and leading to the characteristic symptoms and signs of ACD.

In autoeczematization, epidermal T cells activated by an allergen migrate locally or through the circulation to cause dermatitis at sites remote from the initial trigger. However, contact with fluid from vesicles or blisters cannot trigger a reaction elsewhere on the patient or on another person.

Multiple allergens cause ACD (see Table 76-2), and cross-sensitization among agents is common (eg, between benzocaine and paraphenylenediamine). Cross-sensitization means that exposure to one substance can result in an allergic response after exposure to a different but related substance.

ACD variants include photoallergic CD and systemically induced ACD. In photoallergic CD (see p. 675), a substance becomes sensitizing only after it undergoes structural change triggered by ultraviolet light. Typical causes include aftershave lotions, sunscreens, and topical sulfonamides. Reactions may extend to non-sun-exposed skin. In systemically induced ACD, ingestion of an allergen after topical sensitization causes diffuse dermatitis (eg, oral diphenhydramine after sensitization with topical diphenhydramine).

Symptoms and Signs

ICD: ICD is more painful than pruritic. Signs range from mild erythema to hemorrhage, crusting, erosion, pustules, bullae, and edema.

ACD: In ACD, the primary symptom is intense pruritus; pain is usually the result of excoriation or infection. Skin changes range from transient erythema through vesiculation to severe swelling with bullae, ulceration, or both. Changes often occur in a pattern, distribution, or combination that suggests a specific exposure, such as linear streaking on an arm or leg (eg, from brushing against poison ivy) or circumferential erythema (under a wristwatch or waistband). Any surface may be involved, but hands are the most common surface due to handling and touching potential allergens. With airborne exposure (eg, perfume aerosols), areas not covered by clothing are predominantly affected. The dermatitis is typically limited to the site of contact but may later spread due to scratching and autoeczematization. In systemically induced ACD, skin changes may be distributed over the entire body.

Diagnosis

• Clinical evaluation
• Sometimes patch testing

CD can often be diagnosed by skin changes and exposure history. The patient's occupation, hobbies, household duties, vacations, clothing, topical drug use, cosmetics, and spouse's activities must be considered. The "use" test, in which a suspected agent is applied far from the original area of dermatitis, usually on the flexor forearm, is useful when perfumes, shampoos, or other home agents are suspected.

Patch testing is indicated when ACD is suspected and does not respond to treatment. In patch testing, standard contact allergens are applied to the upper back using adhesive-mounted patches containing minute amounts of allergen or plastic (Finn) chambers containing allergen held in place with porous tape. Thin-layer rapid use epicutaneous (TRUE) patch testing involves 2 adhesive strips that can be applied and interpreted by any provider. Skin under the patches is evaluated 48 and 96 h after application. False-positive results occur when concentrations provoke an irritant rather than an allergic reaction, when...
reaction to one antigen triggers a nonspecific reaction to others, or with cross-reacting antigens. False-negative results occur when patch allergens do not include the offending antigen. Definitive diagnosis requires a history of exposure to the test agent in the original area of dermatitis.

**Prognosis**

Resolution may take up to 3 wk. Reactivity is usually lifelong. Patients with photoallergic CD can have flares for years when exposed to sun (persistent light reaction).

**Treatment**

- Avoidance of offending agents
- Supportive care (eg, cool compresses, dressings, antihistamines)
- Corticosteroids (most often topical but sometimes oral)

CD is prevented by avoiding the trigger; patients with photosensitive CD should avoid exposure to sun.

Topical treatment includes cool compresses (saline or Burow's solution) and corticosteroids; patients with mild to moderate ACD are given mid-potency topical corticosteroids (eg, triamcinolone 0.1% ointment or betamethasone valerate cream 0.1%). Oral corticosteroids (eg, prednisone 60 mg once/day for 7 to 14 days) can be used for severe blistering or extensive disease. Systemic antihistamines (eg, hydroxyzine, diphenhydramine) help pruritus; antihistamines with low anticholinergic potency, such as low-sedating H₁ blockers, are not as effective. Wet-to-dry dressings can soothe oozing blisters, dry the skin, and promote healing.

**Exfoliative Dermatitis**

(Erythroderma)

Exfoliative dermatitis is widespread erythema and scaling of the skin caused by preexisting skin disorders, drugs, cancer, or unknown causes. Symptoms and signs are pruritus, diffuse erythema, and epidermal sloughing. Diagnosis is clinical. Treatment involves corticosteroids and correction of the cause.

Exfoliative dermatitis is a manifestation of rapid epidermal cell turnover. Its cause is unknown, but it most often occurs in the context of preexisting skin disorders (eg, atopic dermatitis, contact dermatitis, seborrheic dermatitis, psoriasis, pityriasis rubra pilaris), use of drugs (eg, penicillin, sulfonamides, isoniazid, phenytoin, barbiturates), and cancer (eg, mycosis fungoides, leukemia, and, rarely, adenocarcinomas). Up to 25% of patients have no identifiable underlying disease.

**Symptoms and Signs**

Symptoms include pruritus, malaise, and chills. Diffuse erythema initially occurs in patches but spreads and involves all or nearly all of the body. Extensive epidermal sloughing leads to abnormal thermoregulation, nutritional deficiencies because of extensive protein losses, increased metabolic rate with a hypercatabolic state, and hypovolemia due to transdermal fluid losses.

**Diagnosis**

- Clinical evaluation

Diagnosis is by history and examination. Preexisting skin disease may underlie the extensive erythema and suggest a cause. Biopsy is often nonspecific but is indicated when mycosis fungoides is suspected. Blood tests may reveal hypoproteinemia, hypocalcemia, and iron deficiency, each a consequence of extensive protein, electrolyte, and RBC loss; however, these findings are not diagnostic.
Treatment

• Supportive care (eg, rehydration)

• Topical care (eg, emollients, colloidal oatmeal baths)

• Systemic corticosteroids for severe disease

The disease may be life threatening; hospitalization is often necessary. Any known cause is treated. Supportive care consists of correction of dehydration, correction of electrolyte abnormalities and nutritional deficiencies, and comprehensive wound care and dressings to prevent bacterial superinfection. Because drug eruptions and contact dermatitis cannot be ruled out by history alone, all drugs should be stopped if possible or changed. Skin care is with emollients and colloidal oatmeal baths. Weak topical corticosteroids (eg, 1 to 2.5% hydrocortisone ointment) may be used. Corticosteroids (prednisone 40 to 60 mg po once/day for 10 days, then tapered) are used for severe disease.

Prognosis depends on the cause. Cases related to drug reactions have the shortest duration, lasting 2 to 6 wk after the drug is withdrawn.

Hand and Foot Dermatitis

Hand and foot dermatitis is not a single disorder. Rather, it is a categorization of dermatitis that affects the hands and feet selectively due to one of several causes.

Patients often present with isolated dermatitis of the hands or feet. Causes include

• Contact dermatitis

• Fungal infection

• Psoriasis

• Scabies

Other causes include systemic viral infection in children (hand-foot-and-mouth disease—see p. 1426) or certain chemotherapies (hand-foot syndrome). Some cases are idiopathic.

Diagnosis can sometimes be inferred from location and appearance of the skin lesions (see Table 76-3).

Treatment of all forms of hand and foot dermatitis should be directed at the cause when possible. Topical corticosteroids or antifungals may be tried empirically. Patients should also avoid prolonged contact with water that would otherwise remove protective oils and lead to paradoxical drying of the skin.

Dyshidrotic dermatitis: Pruritic vesicles or bullae on the palms, sides of the fingers, or soles are characteristic of this disorder. Scaling, redness, and oozing often follow vesiculation. Pompholyx is a severe form with bullae. The cause is unknown, but fungal infection, contact dermatitis, and id reactions to tinea pedis can cause a similar clinical appearance and should be ruled out. Treatment includes topical corticosteroids, tacrolimus or pimecrolimus, oral antibiotics, and ultraviolet light.

Keratolysis exfoliativa: Painless patchy peeling of the palms, soles, or both is characteristic of this disorder. The cause is unknown; treatment is unnecessary because the condition is self-resolving.

Hyperkeratotic eczema: Thick yellow-brown plaques on the palms and sometimes soles are characteristic of this disorder. The cause is unknown. Treatment is with topical corticosteroids and keratolytics, oral psoralen plus ultraviolet A (PUVA), and retinoids.

Id reaction: The appearance of vesicles usually on the sides of the fingers in response to active
dermatitis elsewhere is characteristic of this disorder. The cause may be an allergic reaction.

**Housewives' eczema:** This irritant contact dermatitis affects people whose hands are frequently immersed in water. It is worsened by washing dishes, clothes, and babies because repeated exposure to even mild detergents and water or prolonged sweating under rubber gloves may irritate dermatitic skin or cause an irritant contact dermatitis.

**Hand-foot syndrome:** This disorder (also called acral erythema or palmar-plantar erythrodynesthesia) represents cutaneous toxicity caused by certain systemic chemotherapies (eg, capecitabine, cytarabine, fluorouracil, idarubicin, doxorubicin, taxanes, methotrexate, cisplatin, tegafur). Manifestations include pain, swelling, numbness, tingling, redness, and sometimes flaking or blistering of the palms or soles. Treatment is with oral or topical corticosteroids, topical dimethylsulfoxide, oral vitamin B₆ (pyridoxine), OTC analgesics (eg, acetaminophen, ibuprofen), and supportive measures (eg, cool compresses, minimizing manual tasks).

**Lichen Simplex Chronicus**

*Neurodermatitis*

Lichen simplex chronicus is eczema caused by repeated scratching; by several mechanisms, chronic scratching causes further itching, creating a vicious circle. Diagnosis is by examination.

[Table 76-3. Differential Diagnosis of Hand Dermatitis]

Treatment is through education and behavioral techniques to prevent scratching and corticosteroids and antihistamines.

**Etiology**

Lichen simplex chronicus is thickening of the skin with variable scaling that arises secondary to repetitive scratching or rubbing. Lichen simplex chronicus is not a primary process. Perceived pruritus in a specific area of skin (with or without underlying pathology) provokes rubbing and mechanical trauma, resulting in secondary lichenification and further pruritus. Lichen simplex chronicus frequently occurs in people with anxiety disorders and nonspecific emotional stress as well as in patients with any type of underlying chronic dermatitis.

**Pathophysiology**

The underlying pathophysiology is unknown but may involve alterations in the way the nervous system perceives and processes itchy sensations. Skin that tends toward eczematous conditions (eg, atopic dermatitis) is more prone to lichenification.

**Symptoms and Signs**

Lichen simplex chronicus is characterized by pruritic, dry, scaling, hyperpigmented, lichenified plaques in irregular, oval, or angular shapes. It involves easily reached sites, most commonly the legs, arms, neck, and upper trunk.

**Diagnosis**

- Clinical evaluation

Diagnosis is by examination. A fully developed plaque has an outer zone of discrete, brownish papules and a central zone of confluent papules covered with scales. Look-alike conditions include tinea corporis, lichen planus, and psoriasis; lichen simplex chronicus can be distinguished from these by potassium hydroxide wet mount and biopsy.

**Treatment**
• Education and behavioral techniques

• Corticosteroids (most often topical but sometimes intralesional)

• Antihistamines

Primary treatment is patient education about the effects of scratching and rubbing. Secondary treatment is topical corticosteroids (eg, triamcinolone acetonide, fluocinonide); surgical tape impregnated with flurandrenolide (applied in the morning and replaced in the evening) may be preferred because occlusion prevents scratching. Small areas may be locally infiltrated (intralesional injections) with a long-acting corticosteroid such as triamcinolone acetonide 2.5 mg/mL (diluted with saline), 0.3 mL/cm² of lesion; treatment can be repeated every 3 to 4 wk. Oral H₁-blocking antihistamines may be useful. Emollients may also be helpful.

**Nummular Dermatitis**

Nummular (discoid) dermatitis is inflammation of the skin characterized by coin-shaped or disc-shaped lesions. Diagnosis is clinical. Treatment may include antibiotics, corticosteroids, and ultraviolet light therapy.

Nummular dermatitis is most common among middle-aged patients and is often associated with dry skin, especially during the winter. The cause is unknown.

**Symptoms and Signs**

Discoid lesions often start as patches of confluent vesicles and papules that later ooze serum and form crusts. Lesions are eruptive, widespread, and pruritic. They are often more prominent on the extensor aspects of the extremities and on the buttocks but also appear on the trunk. Exacerbations and remissions may occur, and when they do, new lesions tend to reappear at the sites of healed lesions.

**Diagnosis**

Diagnosis is clinical based on the characteristic appearance and distribution of the skin lesions.

**Treatment**

• Supportive care

• Antibiotics

• Corticosteroids (most often topical, but sometimes intralesional or oral)

• Ultraviolet light therapy

No treatment is uniformly effective. Oral antibiotics (eg, dicloxacillin or cephalaxin 250 mg qid) may be given, along with use of tap water compresses, especially when weeping and pus are present. Less inflamed lesions may respond to tetracycline 250 mg po qid, which has a beneficial (although not necessarily antibacterial) effect. Corticosteroid cream or ointment should be rubbed in 3 times daily. An occlusive dressing with a corticosteroid cream under polyethylene film or with flurandrenolide-impregnated tape can be applied at bedtime. Intralesional corticosteroid injections may be beneficial for the few lesions that do not respond to therapy. In more widespread, resistant, and recurrent cases, ultraviolet B radiation alone or oral psoralen plus ultraviolet A (PUVA) radiation may be helpful. Occasionally, oral corticosteroids are required, but long-term use should be avoided; a reasonable starting dose is prednisone 40 mg every other day.

**Seborrheic Dermatitis**
Seborrheic dermatitis (SD) is inflammation of skin that has a high density of sebaceous glands (eg, face, scalp, upper trunk). The cause is unknown, but Pityrosporum ovale, a normal skin organism, plays some role. SD occurs with increased frequency in patients with HIV and in those with certain neurologic disorders. SD causes occasional pruritus, dandruff, and yellow, greasy scaling along the hairline and on the face. Diagnosis is made by examination. Treatment is tar or other medicated shampoo and topical corticosteroids and antifungals.

Despite the name, the composition and flow of sebum are usually normal. The pathogenesis of SD is unclear, but its activity has been linked to the number of Pityrosporum yeasts present on the skin. The incidence and severity of disease seem to be affected by genetic factors, emotional or physical stress, and climate (usually worse in cold weather). SD may precede or be associated with psoriasis (called seborrhiasis). SD may be more common and more severe among patients with neurologic disorders (especially Parkinson's disease) or HIV/AIDS. Very rarely, the dermatitis becomes generalized.

Symptoms and Signs

Symptoms develop gradually, and the dermatitis is usually apparent only as dry or greasy diffuse scaling of the scalp (dandruff) with variable pruritus. In severe disease, yellow-red scaling papules appear along the hairline, behind the ears, in the external auditory canals, on the eyebrows, in the axillae, on the bridge of the nose, in the nasolabial folds, and over the sternum. Marginal blepharitis with dry yellow crusts and conjunctival irritation may develop. SD does not cause hair loss.

Neonates may develop SD with a thick, yellow, crusted scalp lesion (cradle cap); fissuring and yellow scaling behind the ears; red facial papules; and stubborn diaper rash. Older children may develop thick, tenacious, scaly plaques on the scalp that may measure 1 to 2 cm in diameter.

Diagnosis

• Clinical evaluation

Diagnosis is made by physical examination. SD may occasionally be difficult to distinguish from other disorders, including psoriasis, atopic dermatitis or contact dermatitis, tinea, and rosacea.

Treatment

• Topical therapy

**Adults:** In adults, zinc pyrithione, selenium sulfide, sulfur and salicylic acid, or tar shampoo should be used daily or every other day until dandruff is controlled and twice/wk thereafter. A corticosteroid lotion (eg, 0.01% fluocinolone acetonide solution, 0.025% triamcinolone acetonide lotion) can be rubbed into the scalp or other hairy areas twice daily until scaling and redness are controlled. For SD of the postauricular areas, nasolabial folds, eyelid margins, and bridge of the nose, 1% hydrocortisone cream is rubbed in 2 or 3 times daily, decreasing to once/day when SD is controlled; hydrocortisone cream is the safest corticosteroid for the face because fluorinated corticosteroids may cause adverse effects (eg, telangiectasia, atrophy, perioral dermatitis). In some patients, 2% ketoconazole cream or other topical imidazoles applied twice daily for 1 to 2 wk induce a remission that lasts for months. For eyelid margin seborrhea, a dilution of 1 part baby shampoo to 9 parts water is applied with a cotton swab.

**Infants and children:** In infants, a baby shampoo is used daily, and 1% hydrocortisone cream is rubbed in twice daily. For thick lesions on the scalp of a young child, 2% salicylic acid in olive oil or a corticosteroid gel is applied at bedtime to affected areas and rubbed in with a toothbrush. The scalp is shampooed daily until the thick scale is gone.

**Stasis Dermatitis**

Stasis dermatitis is inflammation of the skin of the lower legs caused by chronic venous insufficiency. Symptoms are itching, scaling, hyperpigmentation, and sometimes ulceration.
Diagnosis is clinical. Treatment is directed at the chronic venous insufficiency and preventing occurrence or progression of associated ulcers.

Stasis dermatitis occurs in patients with chronic venous insufficiency (see p. 2231) because pooled venous blood in the legs compromises the endothelial integrity in the microvasculature, resulting in fibrin leakage, local inflammation, and local cell necrosis.

Symptoms and Signs

Initially, hyperpigmentation and red-brown discoloration from RBC extravasation appear. Later, eczematous changes develop and manifest as erythema, scaling, weeping, and crusting (see Plate 46), all of which can be made worse by bacterial superinfection or by contact dermatitis caused by the many topical treatments often applied. When chronic venous insufficiency and stasis dermatitis are both inadequately treated, stasis dermatitis progresses to frank skin ulceration (see Plate 47), chronic edema, thickened fibrotic skin, or lipodermatosclerosis (a painful induration resulting from panniculitis, which, if severe, gives the lower leg an inverted bowling pin shape with enlargement of the calf and narrowing at the ankle).

Diagnosis

Diagnosis is clinical based on the characteristic appearance of the skin lesions and other signs of chronic venous insufficiency.

Treatment

- Elevation, compression, and dressings
- Sometimes topical or oral antibiotics

Chronic venous insufficiency must be adequately treated with leg elevation and compression stockings (see p. 2232). For acute stasis dermatitis (characterized by crusts, exudation, and superficial ulceration), continuous and then intermittent tap water compresses should be applied. For a weeping lesion, a hydrocolloid dressing may be best. For less acute dermatitis, a corticosteroid cream or ointment should be applied 3 times/day or incorporated into zinc oxide paste.

Ulcers are best treated with compresses and bland dressings (eg, zinc oxide paste); other dressings (eg, hydrocolloids) are also effective (see also p. 740). Ulcers in ambulatory patients may be healed with Unna's paste boot (zinc gelatin), the less messy zinc gelatin bandage, or a colloid dressing (all are available commercially). Colloid-type dressings used under elastic support are more effective than Unna's paste boot. It may be necessary to change the dressing every 2 or 3 days, but as edema recedes and the ulcer heals, once or twice/wk is sufficient. After the ulcer heals, an elastic support should be applied before the patient rises in the morning. Regardless of the dressing used, reduction of edema (usually with compression) is paramount for healing.

Oral antibiotics (eg, cephalosporins, dicloxacillin) are used to treat superimposed cellulitis. Topical antibiotics (eg, mupirocin, silver sulfadiazine) are useful for treating erosions and ulcers. When edema and inflammation subside, split-thickness skin grafts may be needed for large ulcers.

Complex or multiple topical drugs or OTC remedies should not be used. The skin in stasis dermatitis is more vulnerable to direct irritants and to potentially sensitizing topical agents (eg, antibiotics; anesthetics; vehicles of topical drugs, especially lanolin or wool alcohols).
Chapter 77. Reactions to Sunlight

Introduction

The skin may respond to excessive sunlight in several ways: various chronic changes (eg, dermatoheliosis, actinic keratoses), photosensitivity, or sunburn.

Ultraviolet (UV) radiation: Although the sun emits a wide range of UV electromagnetic radiation (ie, UVA, 320 to 400 nm; UVB, 280 to 320 nm; UVC, 100 to 280 nm), only UVA and UVB reach the earth's surface. The character and amount of such radiation vary greatly with the seasons and with changing atmospheric conditions. Exposure of skin to sunlight depends on multiple lifestyle factors, (eg, clothing, occupation), geographic factors (eg, altitude, latitude), and time of year (UV intensity is higher in summer).

Sunburn-producing rays (primarily wavelengths < 320 nm) are filtered out by glass and to a great extent by smoke and smog. Sunburn-producing rays may pass through light clouds, fog, or 30 cm of clear water, causing severe burns in unsuspecting people. Snow, sand, and water enhance exposure by reflecting the rays. Stratospheric ozone, which filters out shorter wavelengths of UV, is depleted by man-made chlorofluorocarbons (eg, in refrigerants and aerosols). A decreased ozone layer increases inadvertent exposure to UVA and UVB.

Sun-tanning lamps use artificial light that is more UVA than UVB. This UVA use is often advertised as a "safer" way to tan; however, many of the same long-term deleterious effects may occur as with UVB exposure, including photoaging and skin cancer. Quite simply, there is no "safe tan."

Pathophysiology

After exposure to sunlight, the epidermis thickens, and melanocytes produce the pigment melanin at an increased rate, causing tanning. Tanning provides some natural protection against future exposure. Exposure leads to both inactivation and loss of epidermal Langerhans' cells, which are immunologically important.

People differ greatly in their sensitivity and response to sunlight based on the amount of melanin in their skin. Skin is classified into 6 types (I to VI) in decreasing order of susceptibility to sun injury. Classification is based on skin color, UV sensitivity, and response to sun exposure. Skin type I is white to lightly pigmented, very sensitive to UV light, has no immediate pigment darkening, always burns easily, and never tans. Skin type VI is dark brown or black, least sensitive to UV light, has significant immediate pigment darkening, and tans profusely (deep black). Dark-skinned people are not immune to the effects of the sun and can become sunburned with strong or prolonged exposure. Long-term effects of UV exposure in dark-skinned people are the same as those in light-skinned people but are often delayed and less severe. People with blonde or red hair are especially susceptible to the acute and chronic effects of UV radiation. Uneven melanocyte activation occurs in many fair-haired people and results in freckling. There is no skin pigmentation in people with albinism (see p. 719) because of a defect in melanin metabolism. Patchy areas of depigmentation are present in patients with vitiligo (see p. 720) because of immunologic destruction of melanocytes.

Prevention

Avoidance: Simple precautions help prevent sunburn and the chronic effects of sunlight. These precautions are recommended for people of all skin types, particularly those who are fair skinned and burn easily. Exposure to bright midday sun should not be > 30 min, even for people with dark skin. In temperate zones, exposure is less hazardous before 10 AM and after 3 PM because more sunburn-producing wavelengths are filtered out. Fog and clouds do not reduce risk, and risk is increased at high altitude.

Clothing: Skin should be covered. Fabrics with a tight weave block the sun better than do those with a loose weave. Special clothing that provides high sun protection is commercially available. Broad-brimmed hats protect the face, ears, and neck. Regular use of UV-protective, wrap-around sunglasses helps shield
**Sunscreens:** Although sunscreens help protect the skin from sunburn and chronic sun damage, they do not always prevent damage. Older sunscreens tended to filter only UVB light, but many newer sunscreens are now "full spectrum" and effectively filter UVA light as well. In the US, the FDA rates sunscreens by sun protection factor (SPF): the higher the number, the greater the protection. Agents with SPF ≥ 15 are recommended. The SPF, however, only quantifies the protection against UVB exposure; there is no scale for UVA protection.

Sunscreens are available in a wide variety of formulations, including creams, gels, foams, sprays, and sticks. Self-tanning products do not provide significant protection from UV exposure.

Most sunscreens contain several agents that function as chemical screens, absorbing light or providing a physical screen that reflects or scatters light. Common chemical sunscreen agents mostly absorb UVB rays and include the aminobenzoates, which include p-aminobenzoic acid (PABA), salicylates, cinnamates, benzophenones (eg, avobenzone), and the anthrilates (an aminobenzoate derivative). Of these, the benzophenones are particularly effective at screening UVA rays.

Other sunscreens, called sunblocks, contain zinc oxide and titanium dioxide, which physically block both UVB and UVA rays. Micronized formulations of these products have significantly improved their cosmetic acceptability.

Sunscreen failure is common and usually results from insufficient application of the product, application too late (sunscreens should optimally be applied 30 min before exposure), or failure to reapply after swimming or exercise.

Allergic or photoallergic reactions to sunscreens must be distinguished from other photosensitive skin eruptions. Patch or photopatch testing with sunscreen components may be necessary to make the diagnosis. This testing is usually done by dermatologists with a particular expertise in allergic contact dermatitis.

**Chronic Effects of Sunlight**

**Aging:** Chronic exposure to sunlight ages the skin (dermatoheliosis, extrinsic aging), producing both fine and coarse wrinkles, rough leathery texture, mottled pigmentation, and telangiectasia. The atrophic effects in some people may resemble those seen after x-ray therapy (chronic radiation dermatitis).

**Actinic keratoses:** Actinic keratoses are precancerous changes in skin cells (keratinocytes) that are a frequent, disturbing consequence of many years of sun exposure. People with blonde or red hair, blue eyes, and skin type I or II are particularly susceptible.

The keratoses are usually pink or red, poorly marginated, and scaly on palpation, although some are light gray or pigmented, giving them a brown appearance. They should be differentiated from seborrheic keratoses (see p. 746), which increase in number and size with aging. Seborrheic keratoses tend to appear waxy and stuck-on but can often take on an appearance similar to actinic keratoses. Close inspection usually reveals distinguishing characteristics of the lesion. Unlike actinic keratoses, seborrheic keratoses also occur on non-sun-exposed areas of the body and are not premalignant.

**Skin cancers** (see p. 748): The incidence of squamous cell carcinoma and basal cell carcinoma in fair, light-skinned people is directly proportional to the total annual sunlight in the area. Such lesions are especially common among people who were extensively exposed to sunlight as children and adolescents and among those who are chronically exposed to the sun as part of their profession or recreational activities (eg, athletes, farmers, ranchers, sailors, frequent sunbathers). Sun exposure also substantially increases the risk of malignant melanomas.

**Treatment**

Various combination therapies, including chemical peels, 5-fluorouracil (5-FU), topical α-hydroxy acids,
Imiquimod, photodynamic therapy, and tretinoin, have been used to reduce carcinogenic changes and improve the cosmetic appearance of chronically sun-damaged skin. These therapies are often effective in ameliorating superficial skin changes (eg, coarse and fine wrinkles, irregular pigmentation, sallowness, roughness, minor laxity) but have a much less pronounced effect on deeper changes (eg, telangiectasias). Lasers are capable of treating both superficial and deep changes in the dermis and are used to treat cosmetic and precancerous skin changes. Many chemicals are used in OTC cosmetic products without significant evidence that they improve chronic changes of the skin caused by sunlight.

**Actinic keratoses:** There are several options, depending on the number and location of lesions.

- Liquid nitrogen
- Topical 5-FU
- Topical imiquimod

If only a few actinic keratoses are present, cryotherapy (freezing with liquid nitrogen) is the most rapid and satisfactory treatment.

If there are too many lesions to freeze, topical 5-FU applied to the affected area nightly or twice daily for 2 to 6 wk often clears the majority of lesions. Several strengths and formulations of 5-FU are commercially available. Many patients tolerate 0.5% 5-FU cream applied once/day for 4 wk on the face better than stronger concentrations. Actinic keratoses on the arms may require stronger concentrations, such as 5% cream. Topical 5-FU produces a brisk reaction, with redness, scaling, and burning, often affecting areas with no visible actinic keratoses. If the reaction is too brisk, application may be suspended for 1 to 3 days. Topical 5-FU has few significant adverse effects except for this unsightly and uncomfortable reaction, which can be masked by cosmetics and, when necessary, suppressed with topical corticosteroids. 5-FU should not be used to treat basal cell carcinomas, except those shown by biopsy to be of the superficial type.

A relatively new drug, imiquimod, is often used for treatment of actinic keratoses and superficial basal cell carcinomas. It stimulates the immune system to recognize and destroy cancerous skin lesions. For treatment of skin cancers, see Ch. 90.

**Photosensitivity**

Photosensitivity is a poorly understood cutaneous reaction to sunlight probably involving the immune system. It may be idiopathic or occur after exposure to certain drugs or chemicals, and it is sometimes a feature of systemic disorders (eg, SLE, porphyria, pellagra, xeroderma pigmentosum). Diagnosis is clinical. Treatment varies by type.

In addition to the acute and chronic effects of sunlight, a variety of unusual reactions may occur soon after only a brief sun exposure. Unless the cause is obvious, patients with pronounced photosensitivity should be evaluated for systemic or cutaneous disorders associated with light sensitivity such as SLE (see p. 305) and porphyria (see p. 807). Treatment for chemical photosensitivity is topical corticosteroids and avoidance of the causative substance.

**Solar urticaria:** In certain patients, urticaria develops at a site of sun exposure within a few minutes. Rarely, if large areas are involved, syncope, dizziness, wheezing, and other systemic symptoms may develop. Etiology is unclear but may involve endogenous skin constituents functioning as photoallergens, leading to mast cell degranulation as in other types of urticaria. Solar urticaria can be distinguished from other types of urticaria in that wheals in solar urticaria occur only on exposed skin after ultraviolet (UV) light exposure. Solar urticaria can be classified based on the component of the UV spectrum (UVA, UVB, and visible light) that produces them. Treatment can be difficult and may include H1 blockers, antimalarial drugs, topical corticosteroids, sunscreens, and psoralen UV light (PUVA). The wheals of solar urticaria usually last just minutes to hours, but the disorder is chronic and can wax and wane over years.

**Chemical photosensitivity:** Over 100 substances, ingested or applied topically, are known to
predispose to cutaneous reactions following sun exposure. A limited number are responsible for most reactions (see Table 77-1). Reactions are divided into phototoxicity and photoallergy.

In **phototoxicity**, light-absorbing compounds directly generate free radicals and inflammatory mediators, causing tissue damage manifesting as pain and erythema (like sunburn). This reaction does not require prior sun exposure and can appear in any person, although reaction is highly variable. Typical causes of phototoxic reactions include topical (eg, perfumes, coal tar) or ingested (eg, tetracyclines, psoralen-containing plants) agents. Phototoxic reactions do not generalize to non-sun-exposed skin.

**Photoallergy** is a type IV (cell-mediated) immune response; light absorption causes structural changes in the drug or substance, allowing it to bind to tissue protein and function as a hapten. Prior exposure is required. Typical causes of photoallergic reactions include aftershave lotions, sunscreens, and sulfonamides. Reaction may extend to non-sun-exposed skin. Symptoms include erythema, pruritus, and sometimes vesicles.

**Table 77-1.** Some Substances that Sensitize the Skin to Sunlight

<table>
<thead>
<tr>
<th>Substance</th>
<th>Sensitization Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphous light eruption</td>
<td>These eruptions are unusual reactions to light that do not seem to be associated with systemic disease or drugs. Eruptions appear on sun-exposed areas, usually 30 min to several hours after exposure. Lesions are pruritic, erythematous, and often papular but may be papulovesicular or plaquelike. They are most common among women and people from northern climates when first exposed to spring or summer sun than among those exposed to sun year-round. Lesions subside within several days to 1 wk or so. Actinic purigo is a similar (perhaps related) phenomenon with more nodular-appearing lesions that may persist year-round, worsening with sun exposure.</td>
</tr>
<tr>
<td>Sunburn</td>
<td>Sunburn is characterized by erythema and sometimes pain and blisters caused by exposure to solar ultraviolet radiation. Treatment is similar to that for thermal burns, including cool compresses, NSAIDs, and, for severe cases, sterile dressings and topical antimicrobials. Prevention by sun avoidance and use of sunscreens is crucial.</td>
</tr>
<tr>
<td>Sunburn</td>
<td>Sunburn results from overexposure of the skin to ultraviolet (UV) radiation; wavelengths in the UVB spectrum (280 to 320 nm) cause the most pronounced effects.</td>
</tr>
</tbody>
</table>

**Symptoms and Signs**

Symptoms and signs appear in 1 to 24 h and, except in severe reactions, peak within 72 h. Skin changes range from mild erythema, with subsequent superficial scaling, to pain, swelling, skin tenderness, and blisters. Constitutional symptoms (eg, fever, chills, weakness, shock), similar to a thermal burn, may develop if a large portion of the body surface is affected; these symptoms may be caused by the release of inflammatory cytokines such as IL-1.

Secondary infection, blotchy pigmentation, and miliaria-like eruptions are the most common late complications. Exfoliated skin may be extremely vulnerable to sunlight for several weeks.

**Treatment**
• Supportive measures

Further exposure should be avoided until sunburn has completely subsided. Cold tap water compresses and oral NSAIDs help relieve symptoms, as may topical aloe vera. Topical corticosteroids are no more effective than cool compresses. Blistered areas should be managed similarly to other partial-thickness burns (see p. 3246), with sterile dressings and topical bacitracin or silver sulfadiazine. Ointments or lotions containing local anesthetics (eg, benzocaine) should be avoided because of the risk of allergic contact dermatitis.

Early treatment of extensive, severe sunburn with a systemic corticosteroid (eg, prednisone 20 to 30 mg po bid for 4 days for adults or teenagers) may decrease the discomfort, but this use is controversial.

Prevention

Simple precautions (eg, avoiding the sun especially during midday, wearing tightly woven clothing, using sunscreens) usually prevent most cases of sunburn (see p. 673).
Chapter 78. Psoriasis and Scaling Diseases

Introduction

Psoriasis, parapsoriasis, pityriasis rosea, pityriasis rubra pilaris, pityriasis lichenoides, lichen planus, and lichen sclerosus are dissimilar disorders grouped together because their primary lesions have similar characteristics: sharply margined, scaling papules or plaques without wetness, crusts, fissures, and excoriations. Lesion appearance and distribution distinguish these diseases from each other.

Psoriasis

Psoriasis is an inflammatory disease that manifests most commonly as well-circumscribed, erythematous papules and plaques covered with silvery scales. Cause is unclear but seems to involve the immune system. Common triggers include trauma, infection, and certain drugs. Symptoms are usually minimal with occasional mild itching, but cosmetic implications may be major. Some people develop severe disease with painful arthritis. Diagnosis is based on appearance and distribution of lesions. Treatment is with emollients, vitamin D analogs, retinoids, tar, anthralin, corticosteroids, phototherapy, and, when severe, methotrexate, retinoids, immunomodulatory agents (biologics), or immunosuppressants.

Psoriasis is hyperproliferation of epidermal keratinocytes combined with inflammation of the epidermis and dermis. It affects about 1 to 5% of the population worldwide; light-skinned people are at greater risk. Peak onset is roughly bimodal, most often at ages 16 to 22 and at ages 57 to 60, but the disorder can occur at any age.

Etiology

The cause is unclear but involves immune stimulation of epidermal keratinocytes; T cells seem to play a central role. Family history is common, and certain genes and HLA antigens (Cw6, B13, B17) are associated with psoriasis. An environmental trigger is thought to evoke an inflammatory response and subsequent hyperproliferation of keratinocytes.

Well-identified triggers include

- Injury (Koebner phenomenon)
- Sunburn
- HIV
- β-Hemolytic streptococcal infection
- Drugs (especially β-blockers, chloroquine, lithium, ACE inhibitors, indomethacin, terbinafine, and interferon alfa)
- Emotional stress
- Alcohol consumption

Symptoms and Signs

Lesions are either asymptomatic or pruritic and are most often localized on the scalp, extensor surfaces of the elbows and knees, sacrum, buttocks, and penis. The nails, eyebrows, axillae, umbilicus, and perianal region may also be affected. The disease can be widespread, involving confluent areas of skin extending between these regions. Lesions differ in appearance depending on type.

Among the various subtypes (see Table 78-1), plaque psoriasis (psoriasis vulgaris or chronic plaque psoriasis) is the most common pattern;
lesions are discrete, erythematous papules or plaques covered with thick, silvery, shiny scales. Lesions appear gradually and remit and recur either spontaneously or with appearance and resolution of triggers.

Arthritis develops in 5 to 30% of patients and can be disabling (see p. 344); joint destruction may ultimately occur.

Psoriasis is rarely life-threatening but can affect a patient's self-image. Besides image, the sheer amount of time required to treat extensive skin or scalp lesions and to maintain clothing and bedding may adversely affect quality of life.

**Diagnosis**

- Clinical evaluation
- Rarely biopsy

Diagnosis is most often by clinical appearance and distribution of lesions. Differential diagnosis includes seborrheic dermatitis, dermatophytoses, cutaneous lupus erythematosus, eczema, lichen planus, pityriasis rosea, squamous cell carcinoma in situ (Bowen's disease, especially when on the trunk), lichen simplex chronicus, and secondary syphilis. Biopsy is rarely necessary and may not be diagnostic.

Disease is graded as mild, moderate, or severe based on the body surface area affected and how the lesions affect patients' quality of life. There are many more complex scoring systems for disease severity (eg, the Psoriasis Area and Severity Index), but these systems are useful mainly in research protocols.

**Treatment**

- Topical treatments
- Systemic treatments
- Ultraviolet (UV) light therapy

Treatment options are extensive and include emollients, salicylic acid, coal tar, anthralin, corticosteroids, vitamin D3 analogs, methotrexate, topical and oral retinoids, topical and oral calcineurin inhibitors, immunosuppressants, immunomodulatory agents (biologics), and ultraviolet light therapy.

**Topical treatments: Emollients** include emollient creams, ointments, petrolatum, paraffin, and even hydrogenated vegetable (cooking) oils. They reduce scaling and are most effective when applied twice daily and immediately after bathing. Lesions may appear redder as scaling decreases or becomes more transparent. Emollients are safe and should probably always be used for mild to moderate plaque psoriasis.

**Salicylic acid** is a keratolytic that softens scales, facilitates their removal, and increases absorption of other topical agents. It is especially useful as a component of scalp treatments; scalp scale can be quite thick.

**Coal tar** ointments, solutions, or shampoos are anti-inflammatory and decrease keratinocyte hyperproliferation via an unknown mechanism. They are typically applied at night and washed off in the morning. They can be used in combination with topical corticosteroids or with exposure to natural or artificial broad-band UVB light (280 to 320 nm) in slowly increasing increments (Goeckerman regimen).

**Anthralin** is a topical antiproliferative, anti-inflammatory agent. Its mechanism is unknown. Effective dose is 0.1% cream or ointment increased to 1% as tolerated. Anthralin may be irritating and should be used with caution in intertriginous areas; it also stains. Irritation and staining can be avoided

[Table 78-1. Subtypes of Psoriasis]
by washing off the anthralin 20 to 30 min after application. Using a liposome-encapsulated preparation may also avoid some disadvantages of anthralin.

**Corticosteroids** are usually used topically but may be injected into small or recalcitrant lesions. (CAUTION: Systemic corticosteroids may precipitate exacerbations or development of pustular psoriasis and should not be used to treat psoriasis.) Topical corticosteroids are used twice daily, sometimes with anthralin or coal tar applied at bedtime. Corticosteroids are most effective when used overnight under occlusive polyethylene coverings or incorporated into tape; a corticosteroid cream is applied without occlusion during the day. Corticosteroid potency (see p. 647) is selected according to the extent of involvement. As lesions abate, the corticosteroid should be applied less frequently or at a lower potency to minimize local atrophy, striae formation, and telangiectases. Ideally, after about 3 wk, an emollient should be substituted for the corticosteroid for 1 to 2 wk (as a rest period); this substitution limits corticosteroid dosage and prevents tachyphylaxis. Topical corticosteroid use can be expensive because large quantities (about 1 oz or 30 g) are needed for each application when a large body surface area is affected. Topical corticosteroids applied for long duration to large areas of the body may cause systemic effects and exacerbate psoriasis. For small, thick, localized, or recalcitrant lesions, high-potency corticosteroids are used with an occlusive dressing or flurandrenolide tape; these dressings are left on overnight and changed in the morning. Relapse after topical corticosteroids are stopped is often faster than with other agents.

**Vitamin D₃ analogs** (eg, calcipotriol, calcitriol) are topical vitamin D analogs that induce normal keratinocyte proliferation and differentiation; they can be used alone or in combination with topical corticosteroids. Some clinicians have patients apply calcipotriol on weekdays and corticosteroids on weekends.

**Calcineurin inhibitors** (eg, tacrolimus, pimecrolimus) are available in topical form and are generally well-tolerated. They are not as effective as corticosteroids but may avoid the complications of corticosteroids when treating facial and intertriginous psoriasis. They may be associated with an increased risk of lymphoma and skin cancer.

**Tazarotene** is a topical retinoid. It is less effective than corticosteroids as monotherapy but is a useful adjunct.

**Systemic treatments:** **Methotrexate** taken orally is the most effective treatment for severe disabling psoriasis, especially severe psoriatic arthritis or widespread erythrodermic or pustular psoriasis unresponsive to topical agents or psoralen plus ultraviolet A (PUVA) light therapy. Methotrexate seems to interfere with the rapid proliferation of epidermal cells. Hematologic, renal, and hepatic function should be monitored. Dosage regimens vary, so only physicians experienced in its use for psoriasis should undertake methotrexate therapy.

**Systemic retinoids** (eg, acitretin, isotretinoin) may be effective for severe and recalcitrant cases of psoriasis vulgaris, pustular psoriasis (in which isotretinoin may be preferred), and hyperkeratotic palmoplantar psoriasis. Because of the teratogenic potential and long-term retention of acitretin in the body, women who use it must not be pregnant and should be warned against becoming pregnant for at least 2 yr after treatment ends. Pregnancy restrictions also apply to isotretinoin, but the agent is not retained in the body beyond 1 mo. Long-term treatment may cause diffuse idiopathic skeletal hyperostosis (DISH—see p. 342).

**Immunosuppressants** can be used for severe psoriasis. Cyclosporine is a commonly used immunosuppressant. It should be limited to courses of several months (rarely, up to 1 yr) and alternated with other therapies. Its effect on the kidneys and potential long-term effects on the immune system preclude more liberal use. Other immunosuppressants (eg, hydroxyurea, 6-thioguanine, mycophenolate mofetil) have narrow safety margins and are reserved for severe, recalcitrant psoriasis.

**Immunomodulatory agents** (biologics—see p. 1086) include tumor necrosis factor (TNF)-α inhibitors (etanercept, adalimumab, infliximab) and the T-cell modulator alefacept. TNF-α inhibitors lead to clearing of psoriasis, but their safety profile is still under study. Efalizumab is no longer available in the US due to increased risk of progressive multifocal
leukoencephalopathy.

**Phototherapy:** UV light therapy is typically used in patients with extensive psoriasis. The mechanism of action is unknown, although UVB light reduces DNA synthesis and can induce mild systemic immunosuppression. In PUVA, oral methoxypsoralen, a photosensitizer, is followed by exposure to long-wave UVA light (330 to 360 nm). PUVA has an antiproliferative effect and also helps to normalize keratinocyte differentiation. Doses of light are started low and increased as tolerated. Severe burns can result if the dose of drug or UVA is too high. Although the treatment is less messy than topical treatment and may produce remissions lasting several months, repeated treatments may increase the incidence of UV-induced skin cancer and melanoma. Less UV light is required when used with oral retinoids (the so-called re-PUVA regimen). Narrow-band UVB light (311 to 312 nm) used without psoralens is similar in effectiveness to PUVA. Excimer laser therapy is a type of phototherapy using extremely pure wavelengths.

**Choice of therapy:** Choice of specific agents and combinations requires close cooperation with the patient, always keeping in mind the untoward effects of the treatments. There is no single ideal combination or sequence of agents, but treatment should be kept as simple as possible. Monotherapy is preferred, but combination therapy is the norm. Rotational therapy refers to the substitution of one therapy for another after 1 to 2 yr to reduce the adverse effects caused by chronic use and to circumvent disease resistance. Sequential therapy refers to initial use of potent agents (eg, cyclosporine) to quickly gain control followed by use of agents with a better safety profile.

**Mild plaque psoriasis** can be treated with emollients, keratolytics, tar, topical corticosteroids, vitamin D₃ analogs, or anthralin alone or in combination. Exposure to sunlight is beneficial, but sunburn can induce exacerbations.

**Moderate to severe plaque psoriasis** should be treated with topical agents and either phototherapy or systemic agents. Immunosuppressants are used for quick, short-term control (eg, in allowing a break from other modalities) and for the most severe disease. Immunomodulatory agents (biologics) are used for moderate to severe disease unresponsive to other agents.

**Scalp plaques** are notoriously difficult to treat because they resist systemic therapy, and because hair blocks application of topical agents and scale removal and shields skin from UV light. A suspension of 10% salicylic acid in mineral oil may be rubbed into the scalp at bedtime manually or with a toothbrush, covered with a shower cap (to enhance penetration and avoid messiness), and washed out the next morning with a tar (or other) shampoo. More cosmetically acceptable corticosteroid solutions can be applied to the scalp during the day. These treatments are continued until the desired clinical response is achieved. Resistant skin or scalp patches may respond to local superficial intralesional injection of triamcinolone acetonide suspension diluted with saline to 2.5 or 5 mg/mL, depending on the size and severity of the lesion. Injections may cause local atrophy, which is usually reversible.

Special treatment needs for subtypes are described in Table 78-1.

For psoriatic arthritis, treatment with systemic therapy is important to prevent joint destruction; methotrexate or a TNF-α inhibitor may be effective.

**Parapsoriasis**

Parapsoriasis describes a poorly understood and poorly distinguished group of diseases that share clinical features. There are 2 general forms: a small-plaque type, which is usually benign, and a large-plaque type, which is a precursor of cutaneous T-cell lymphoma (CTCL). It is extremely rare for small-plaque parapsoriasis to transform into CTCL.

The plaques are usually asymptomatic; their typical appearance is thin, scaling, dull pink patches and plaques with a slightly atrophic or wrinkled appearance. Small-plaque parapsoriasis is defined by lesions <5 cm in diameter, whereas large-plaque parapsoriasis has lesions >6 cm in diameter. Sometimes digitate plaques develop along the dermatomes, especially on the flanks and abdomen, in small-plaque parapsoriasis.
Treatment of small-plaque parapsoriasis is unnecessary but can include emollients, topical tar preparations or corticosteroids, phototherapy, or a combination. Treatment of large-plaque parapsoriasis is phototherapy or topical corticosteroids.

Course for both types is unpredictable; periodic clinical follow-up and biopsies give the best indication of risk of developing CTCL.

**Pityriasis Rosea**

Pityriasis rosea (PR) is an inflammatory disease characterized by diffuse, scaling papules or plaques. Treatment is usually unnecessary.

PR most commonly occurs between ages 10 and 35. It affects women more often and peaks in incidence in cooler months in temperate climates. The cause may be viral infection (some research has implicated human herpesviruses 6 and 7). Drugs may cause a PR-like reaction.

**Symptoms and Signs**

The condition classically begins with a single, primary, 2- to 10-cm herald patch that appears on the trunk or proximal limbs (see Plate 42). A general centrifugal eruption of 0.5- to 2-cm rose- or fawn-colored oval papules and plaques follows within 7 to 14 days. The lesions have a scaly, slightly raised border (collarette) and resemble ringworm (tinea corporis). Most patients itch, occasionally severely. Papules may dominate with little or no scaling in blacks, children, and pregnant women. The rose or fawn color is not as evident in blacks; blacks also more commonly have inverse PR (lesions in the axillae or groin that spread centrifugally). Classically, lesions orient along skin lines, giving PR a Christmas tree-like distribution when multiple lesions appear on the back. A prodrome of malaise and headache precedes the lesions in a minority of patients.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on clinical appearance and distribution. Differential diagnosis includes tinea corporis, tinea versicolor, drug eruptions, psoriasis, parapsoriasis, pityriasis lichenoides chronica, lichen planus, and secondary syphilis. Serologic testing for syphilis is indicated when the palms or soles are affected, when a herald patch is not seen, or when lesions occur in an unusual sequence or distribution.

**Treatment**

- Antipruritic therapy

No specific treatment is necessary because the eruption usually remits within 5 wk and recurrence is rare. Artificial or natural sunlight may hasten resolution. Antipruritic therapy such as topical corticosteroids, oral antihistamines, or topical measures may be used as needed.

**Pityriasis Rubra Pilaris**

Pityriasis rubra pilaris is a rare chronic disorder that causes hyperkeratotic yellowing of the palms and soles and red follicular papules that merge to form red-orange scaling plaques and confluent areas of erythema with islands of normal skin between lesions.

The cause of pityriasis rubra pilaris is unknown.

The 2 most common forms of the disorder are

- Juvenile classic (characterized by autosomal dominant inheritance and childhood onset)
**Pityriasis Lichenoides**

Pityriasis lichenoides is a clonal T-cell disorder that may develop in response to foreign antigens (e.g., infections or drugs) and may be associated with cutaneous T-cell lymphoma.

Pityriasis lichenoides has acute and chronic forms existing in a clinical continuum. The acute form typically appears in children and young adults, with crops of asymptomatic chickenpox-like lesions that typically resolve within weeks to months. Antibiotics (e.g., tetracycline, erythromycin) or phototherapy may help.

The chronic form initially manifests as flatter, reddish brown, scaling papules that may take months or longer to resolve. No treatment has proved effective.

**Lichen Planus**

Lichen planus (LP) is a recurrent, pruritic, inflammatory eruption characterized by small, discrete, polygonal, flat-topped, violaceous papules that may coalesce into rough scaly patches, often accompanied by oral lesions. Diagnosis is usually clinical and supported by skin biopsy. Treatment generally requires topical or intralesional corticosteroids. Severe cases may require phototherapy or systemic immunosuppressants.

**Etiology**

LP is thought to be caused by a T cell-mediated autoimmune reaction against basal epithelial keratinocytes in people with genetic predisposition. Drugs (especially β-blockers, NSAIDs, ACE inhibitors, sulfonyleureas, gold, antimalarial drugs, penicillamine, and thiazides) can cause LP; drug-induced LP (sometimes called lichenoid drug eruption) may be indistinguishable from nondrug-induced LP or may have a pattern that is more eczematous. Associations with hepatitis C-induced liver insufficiency, primary biliary cirrhosis, and other forms of hepatitis have been reported.

**Symptoms and Signs**

Typical lesions are pruritic, purple, polygonal, flat-topped papules and plaques (see Plate 39). Lesions initially are 2 to 4 mm in diameter, with angular borders, a violaceous color, and a distinct sheen in cross-lighting. They are usually symmetrically distributed, most commonly on the flexor surfaces of the wrists, legs, trunk, glans penis, and oral and vaginal mucosae but can be widespread. The face is rarely involved. Onset may be abrupt or gradual. Children are affected infrequently. During the acute phase, new papules may appear at sites of minor skin injury (Koebner phenomenon), such as a superficial scratch. Lesions may coalesce or change over time, becoming hyperpigmented, atrophic, hyperkeratotic (hypertrophic LP), or vesiculobullous. Although pruritic, lesions are rarely excoriated or crusted. If the scalp is affected, patchy scarring alopecia (lichen planopilaris) may occur.

The oral mucosa is involved in about 50% of cases; oral lesions may occur without cutaneous lesions and usually persist for life. Reticulated, lacy, bluish-white, linear lesions (Wickham's striae) are a hallmark
of oral LP, especially on the buccal mucosae. Tongue margins and gingival mucosae in edentulous areas may also be affected. An erosive form of LP may occur in which the patient develops shallow, often painful, recurrent oral ulcers, which, if long-standing, rarely become cancerous. Chronic exacerbations and remissions are common. Vulvar and vaginal mucosae are often involved. Up to 50% of women with oral mucosal findings have undiagnosed vulvar LP. In men, genital involvement is common, especially of the glans penis.

Nails are involved in up to 10% of cases. Findings vary in intensity with nail bed discoloration, longitudinal ridging and lateral thinning, and complete loss of the nail matrix and nail, with scarring of the proximal nail fold onto the nail bed (pterygium formation).

**Diagnosis**

- Clinical evaluation
- Biopsy

Although diagnosis is suggested by appearance of the lesions, similar lesions may result from any of the papulosquamous disorders, lupus erythematosus, and secondary syphilis, among others. Oral or vaginal LP may resemble leukoplakia, and the oral lesions must also be distinguished from candidiasis, carcinoma, aphthous ulcers, pemphigus, cicatricial pemphigoid, and chronic erythema multiforme. Typically, biopsy is done.

If LP is diagnosed, some clinicians do laboratory testing for liver dysfunction, including hepatitis B and C infections.

**Prognosis**

Many cases resolve without intervention, presumably because the inciting agent is no longer present. Recurrence after years may be due to reexposure to the trigger or some change in the triggering mechanism. Sometimes treatment of a previously occult infection, such as a dental abscess, results in resolution.

Vulvovaginal LP may be chronic and refractory to therapy, causing decreased quality of life.

**Treatment**

- Topical treatments
- Systemic treatments
- Sometimes light therapy

Asymptomatic LP does not require treatment. Drugs suspected of triggering LP should be stopped.

Few controlled studies have evaluated treatments. Options differ by location and extent of disease. Most cases of LP on the trunk or extremities can be treated with local drugs. Topical corticosteroids are first-line treatment for most cases of localized disease. High-potency ointments or creams (eg, clobetasol, fluocinonide) may be used on the thicker lesions on the extremities; lower-potency drugs (eg, triamcinolone, desonide) may be used on the face, groin, and axillae. As always, courses should be limited to reduce risk of corticosteroid atrophy. Potency may be enhanced with use of polyethylene wrapping or flurandrenolide tape. Intralesional corticosteroids (triamcinolone acetonide solution diluted with saline to 5 to 10 mg/mL) can be used every 4 wk for hyperkeratotic plaques and those resistant to other therapies.

Topical therapy is impractical for generalized LP; oral drugs or phototherapy is used. Oral corticosteroids (eg, prednisone 20 mg once/day for 2 to 6 wk followed by a taper) may be used for severe cases. The disease may rebound when therapy ceases; however, long-term systemic corticosteroids should not be
Oral retinoids (eg, acitretin 30 mg once/day for 8 wk) are indicated for otherwise recalcitrant cases. Griseofulvin 250 mg po bid given for 3 to 6 mo may be effective. Cyclosporine (1.25 to 2.5 mg/kg bid) can be used when corticosteroids or retinoids fail. Light therapy using psoralen plus ultraviolet A (PUVA) or narrow-band UVB is an alternative to oral therapies, especially if they have failed or are contraindicated for medical reasons.

Treatment of oral LP differs slightly. Viscous lidocaine may help relieve symptoms of erosive ulcers. Tacrolimus 0.1% ointment applied twice daily may induce lasting remission, although it has not been fully evaluated. Other treatment options include topical (in an adhesive base), intralesional, and systemic corticosteroids. Erosive oral LP may respond to oral dapsone or cyclosporine. Cyclosporine rinses also may be helpful.

Dapsone, hydroxychloroquine, azathioprine, systemic cyclosporine, and topical tretinoin may also be useful. As with any disease with so many therapies, individual drugs have not been uniformly successful.

**Lichen Sclerosus**

*Lichen sclerosus is an inflammatory dermatosis of unknown cause, possibly autoimmune, that usually affects the anogenital area.*

The earliest signs are skin fragility, bruising, and sometimes blistering. Lesions typically cause mild to severe itching. When lichen sclerosus manifests in children, the appearance may be confused with sexual abuse. With time, the involved tissue becomes atrophic, thinned, hypopigmented (there may be flecks of postinflammatory hyperpigmentation), fissured, and scaly. Hyperkeratotic and fibrotic forms exist. Severe and longstanding cases cause scarring and distortion of normal anogenital architecture. In women, this distortion can even lead to total absorption of the labia minora and fusion over the clitoris. In men, phimosis or fusion of the foreskin to the coronal sulcus can occur.

Diagnosis can usually be based on appearance, especially in advanced cases; however, biopsy should be done on any anogenital dermatosis that does not resolve with mild conventional therapy (eg, topical hydrocortisone, antifungal drug). It is especially important to biopsy any area that becomes thickened or ulcerated, because lichen sclerosus is a precursor of squamous cell carcinoma.

**Treatment**

- **Topical corticosteroids**

Treatment consists of potent topical corticosteroids (drugs that otherwise should be used with extreme caution in this area). The disease is generally intractable, so long-term follow-up, especially to monitor for squamous cell carcinoma and sexual function and for psychologic support, is indicated.
Chapter 79. Hypersensitivity and Inflammatory Disorders

Introduction

The immune system plays a significant role in a large number of skin disorders, including dermatitis, sunlight reactions, and bullous diseases. Although all of these disorders involve some level of inflammation, certain skin disorders are primarily characterized by their inflammatory component or as a hypersensitivity reaction, be it to a drug, infection, or cancer.

Acute Febrile Neutrophilic Dermatosis

(Sweet's Syndrome)

Acute febrile neutrophilic dermatosis is characterized by tender, indurated, dark-red papules and plaques with prominent edema in the upper dermis and dense infiltrate of neutrophils. Cause is not known. It frequently occurs with underlying cancer, especially hematologic cancers.

Etiology

Acute febrile neutrophilic dermatosis may occur with various disorders, including

- Acute respiratory illness
- GI infection
- Cancer
- Drug exposure
- Inflammatory or autoimmune disorders
- Pregnancy

About 25% of patients have an underlying cancer, 75% of which are hematologic cancers, especially myelodysplastic syndromes and acute myeloid leukemia. When not due to cancer, acute febrile neutrophilic dermatosis affects mostly women ages 30 to 50, with a female: male ratio of 3:1. In contrast, men who develop the condition tend to be older (60 to 90).

The cause is unknown; however, type 1 helper T-cell cytokines, including IL-2 and interferon-γ, are predominant and may play a role in lesion formation.

Symptoms and Signs

Patients are febrile, with an elevated neutrophil count, and have tender, dark-red plaques or papules, most often on the face, neck, and upper extremities, especially the dorsum of hands. Oral lesions can also occur. Rarely, bullous and pustular lesions are present. The lesions often develop in crops. Each crop is preceded by fever and persists for days to weeks.

Extracutaneous manifestations can involve the eyes (eg, conjunctivitis, episcleritis, iridocyclitis), joints (eg, arthralgia, myalgia, arthritis), and internal organs (eg, neutrophilic alveolitis; sterile osteomyelitis; psychiatric or neurologic changes; transient kidney, liver, and pancreatic insufficiency).

Diagnosis

- Clinical evaluation
- Skin biopsy
Diagnosis is suggested by the appearance of the lesions and is supported by the presence of associated conditions. Differential diagnosis includes erythema multiforme, erythema elevation diutinum, acute cutaneous lupus erythematosus, pyoderma gangrenosum, and erythema nodosum. If diagnosis is unclear, skin biopsy should be done. The histopathologic pattern is that of edema in the upper dermis with a dense infiltrate of neutrophils in the dermis. Vasculitis may be present but is secondary.

**Treatment**

- Corticosteroids

Treatment involves systemic corticosteroids, chiefly prednisone 0.5 to 1.5 mg/kg po once/day tapered over 3 wk. Antipyretics are also recommended. In difficult cases, dapsone 100 to 200 mg po once/day, indomethacin 150 mg po once/day for 1 wk and 100 mg po once/day for 2 additional wk, or K iodide 900 mg po once/day or 300 mg po tid can be given.

**Drug Eruptions and Reactions**

Drugs can cause multiple skin eruptions and reactions. The most serious of these are discussed elsewhere in THE MANUAL and include Stevens-Johnson syndrome and toxic epidermal necrolysis, hypersensitivity syndrome, serum sickness, exfoliative dermatitis, angioedema and anaphylaxis, and drug-induced vasculitis. Drugs can also be implicated in hair loss, lichen planus, erythema nodosum, pigmentation changes, SLE, photosensitivity reactions, pemphigus, and pemphigoid. Other drug reactions are classified by lesion type (see Table 79-1).

[Table 79-1, Types of Drug Reactions and Typical Causative Agents]

**Symptoms and Signs**

Symptoms and signs vary based on the cause and the specific reaction (see Table 79-1).

**Diagnosis**

- Clinical evaluation and drug exposure history
- Sometimes skin biopsy

A detailed history is often required for diagnosis, including recent use of OTC drugs. Because the reaction may not occur until several days or even weeks after first exposure to the drug, it is important to consider all new drugs and not only the one that has been most recently started. No laboratory tests reliably aid diagnosis, although biopsy of affected skin is often suggestive. Sensitivity can be definitively established only by rechallenge with the drug, which may be hazardous and unethical in patients who have had severe reactions.

**Treatment**

- Discontinuation of offending drug
- Sometimes antihistamines and corticosteroids

Most drug reactions resolve when drugs are stopped and require no further therapy. Whenever possible, chemically unrelated compounds should be substituted for suspect drugs. If no substitute drug is available and if the reaction is a mild one, it might be necessary to continue the treatment under careful watch despite the reaction. Pruritus can be controlled with antihistamines and topical corticosteroids. For IgE-mediated reactions (eg, urticaria), desensitization (see p. 1124) can be considered when there is critical need for a drug.
When progression from urticaria to anaphylaxis is a concern, treatment is with aqueous epinephrine (1:1000) 0.2 mL sc or IM and with the slower-acting but more persistent soluble hydrocortisone 100 mg IV, which may be followed by an oral corticosteroid for a short period (see also p. 1121).

**Erythema Multiforme**

Erythema multiforme (EM) is an inflammatory reaction, characterized by target or iris skin lesions. Oral mucosa may be involved. Diagnosis is clinical. Lesions spontaneously resolve but frequently recur. Erythema multiforme can occur as reaction to a drug or an infectious agent such as herpes simplex virus or mycoplasma.Suppressive antiviral therapy may be indicated for patients with frequent or symptomatic recurrence due to herpes simplex virus.

For years, EM was thought to represent the milder end of a spectrum of drug hypersensitivity disorders that included Stevens-Johnson syndrome and toxic epidermal necrolysis. Recent evidence suggests that EM is different from these other disorders.

**Etiology**

The majority of cases are caused by herpes simplex virus (HSV) infection (HSV-1 more so than HSV-2), although it is unclear whether EM lesions represent a specific or nonspecific reaction to the virus. Current thinking holds that EM is caused by a T-cell-mediated cytolytic reaction to HSV DNA fragments present in keratinocytes. A genetic disposition is presumed given that EM is such a rare clinical manifestation of HSV infection, and several HLA subtypes have been linked with the predisposition to develop lesions. Less commonly, cases are caused by drugs, vaccines, other viral diseases (especially hepatitis C), or possibly SLE. EM that occurs in patients with SLE is sometimes referred to as Rowell's syndrome.

**Symptoms and Signs**

EM manifests as the sudden onset of asymptomatic, erythematous macules, papules, wheals, vesicles, bullae, or a combination on the distal extremities (including palms and soles) and face. The classic lesion is annular, with a violaceous center and pink halo separated by a pale ring (target or iris lesion). Distribution is symmetric and centripetal; spread to the trunk is common. Some patients have itching. Oral lesions include target lesions on the lips and vesicles and erosions on the palate and gingivae.

**Diagnosis**

- Clinical evaluation

Diagnosis is by clinical appearance; biopsy is rarely necessary. Differential diagnosis includes essential urticaria, vasculitis, bullous pemphigoid, pemphigus, linear IgA dermatosis, acute febrile neutrophilic dermatosis, and dermatitis herpetiformis; oral lesions must be distinguished from aphthous stomatitis, pemphigus, herpetic stomatitis, and hand-foot-and-mouth disease. Patients with widely disseminated purpuric macules and blisters and prominent involvement of the trunk and face are likely to have Stevens-Johnson syndrome rather than EM.

**Treatment**

- Supportive care
- Sometimes prophylactic antivirals

EM spontaneously resolves, so treatment is usually unnecessary. Topical corticosteroids and anesthetics may ameliorate symptoms and reassure patients. Recurrences are common, and empiric oral maintenance therapy with acyclovir 400 mg po q 12 h, famciclovir 250 mg po q 12 h, or valacyclovir 1000 mg po q 24 h can be attempted if symptoms recur more than 5 times/yr and HSV association is suspected or if recurrent EM is consistently preceded by herpes flares.

**Panniculitis**
Panniculitis describes inflammation of the subcutaneous fat that can result from multiple causes. Diagnosis is by clinical evaluation and biopsy. Treatment depends on the cause.

Etiology

There are multiple causes of panniculitis, including

- Infections (the most common)
- Physical factors (eg, cold, trauma)
- Proliferative disorders
- Connective tissue disorders (eg, SLE, systemic sclerosis)

Idiopathic panniculitis is sometimes referred to as Weber-Christian disease.

Symptoms and Signs

Panniculitis is characterized by tender and erythematous subcutaneous nodules located over the extremities and sometimes over the posterior thorax, abdominal area, breasts, face, or buttocks. Rarely, nodules can involve the mesentery, lungs, scrotum, and cranium. Signs of systemic inflammation can accompany panniculitis. In Weber-Christian disease, systemic involvement can result in fever as well as signs of organ dysfunction, including hepatic, pancreatic, and bone marrow insufficiency, which is potentially fatal.

Diagnosis

- Clinical evaluation
- Excisional biopsy

Diagnosis is by usually by clinical appearance and can be confirmed by excisional biopsy.

Treatment

- Supportive care
- Anti-inflammatory drugs
- Immunosuppressants

There is no specific definitive treatment for panniculitis. A variety of strategies have been used with modest results, including NSAIDs, antimalarials, dapsone, and thalidomide. Corticosteroids (1 to 2 mg/kg po or IV once/day) and other immunosuppressive or chemotherapeutic drugs have been used to treat patients with progressive symptoms or signs of systemic involvement. Surgical abdominal panniculectomy has been used with varying levels of success in morbidly obese patients but should be reserved for patients with serious disease that does not respond to other measures.

Erythema Nodosum

Erythema nodosum (EN) is a specific form of panniculitis (see p. 687) characterized by tender, red or violet, palpable, subcutaneous nodules on the shins and occasionally other locations. It often occurs with an underlying systemic disease, notably streptococcal infections, sarcoidosis, inflammatory bowel disease, and TB. Diagnosis is by clinical evaluation and biopsy. Treatment depends on the cause.
Etiology

EN primarily affects people in their 20s and 30s but can occur at any age; women are more often affected. Etiology is unknown, but an immunologic reaction is suspected because EN is frequently accompanied by other disorders; the most common are

- Streptococcal infection (especially in children)
- Sarcoidosis
- Inflammatory bowel disease
- TB

Other possible triggers include

- Other bacterial infections (eg, *Yersinia*, *Salmonella*, mycoplasma, chlamydia, leprosy, lymphogranuloma venereum)
- Fungal infections (eg, coccidioidomycosis, blastomycosis, histoplasmosis)
- Rickettsial infections
- Viral infections (eg, Epstein-Barr, hepatitis B)
- Use of drugs (eg, sulfonamides, iodides, bromides, oral contraceptives)
- Hematologic and solid cancers
- Pregnancy

Up to one third of cases of EN are idiopathic.

Symptoms and Signs

EN is a subset of panniculitis that manifests as erythematous, tender plaques or nodules, primarily in the pretibial region (see Plate 34), accompanied by fever, malaise, and arthralgia.

Diagnosis

- Clinical evaluation
- Excisional biopsy

Diagnosis is usually by clinical appearance and can be confirmed by excisional biopsy of a nodule when necessary. A diagnosis of EN should prompt evaluation for causes. Evaluation might include biopsy, skin testing (PPD or anergy panel), antinuclear antibodies, CBC, chest x-ray, and antistreptolysin O titer or pharyngeal culture. ESR is often high.

Treatment

- Supportive care
- Anti-inflammatory drugs
- Corticosteroids
EN almost always resolves spontaneously. Treatment includes bed rest, elevation, cool compresses, and NSAIDs. K iodide 300 to 500 mg po tid can be given to decrease inflammation. Systemic corticosteroids are effective but are an intervention of last resort as they can worsen an occult infection. If an underlying disorder is identified, it should be treated.

**Granuloma Annulare**

Granuloma annulare is a benign, chronic, idiopathic condition characterized by papules or nodules that spread peripherally to form a ring around normal or slightly depressed skin.

**Etiology**

Etiology is unclear but proposed mechanisms include cell-mediated immunity (type IV), immune complex vasculitis, and an abnormality of tissue monocytes. Granuloma annulare is not associated with systemic disorders, except that the incidence of abnormal glucose metabolism is increased among adults with many lesions. In some cases, exposure to sunlight, insect bites, TB skin testing, BCG vaccination, trauma, *Borrelia* infection, and viral infections have induced disease flares. The condition is twice as prevalent among women.

**Symptoms and Signs**

Lesions are erythematous, yellowish tan, bluish, or the color of the surrounding skin; one or more lesions may occur, most often on dorsal feet, legs, hands, or fingers. They are usually asymptomatic but may occasionally be tender. The lesions often expand or join to form rings. The center of each ring may be a slightly depressed, pale or light brown. In some cases, lesions may become generalized and widespread.

**Diagnosis**

Diagnosis is usually clinical but can be confirmed by skin biopsy.

**Treatment**

- Sometimes corticosteroids, anti-inflammatory drugs, or psoralen plus ultraviolet A (PUVA) therapy

Usually no treatment is necessary; spontaneous resolution is common. For patients with more widespread or bothersome lesions, quicker resolution may be promoted by the use of high-strength topical corticosteroids under occlusive dressings every night, flurandrenolide-impregnated tape, and intralesional corticosteroids. PUVA therapy is also effective and practical for patients with widespread disease. Recent reports have suggested that tumor necrosis factor-α inhibitors (eg, infliximab, adalimumab), 595-nm pulsed dye laser, and fractional photothermolysis are useful in managing disseminated and recalcitrant lesions.

**Pyoderma Gangrenosum**

Pyoderma gangrenosum is a chronic progressive skin necrosis of unknown etiology often associated with systemic illness.

**Etiology**

Etiology is unknown, but pyoderma gangrenosum can be associated with vasculitis, gammopathies, RA, leukemia, lymphoma, hepatitis C virus infection, SLE, sarcoidosis, polyarthritis, and especially inflammatory bowel disease and is thought to be caused by an abnormal immune response.

**Pathophysiology**

Pathophysiology is poorly understood but may involve problems with neutrophil chemotaxis. Ulcerations of pyoderma gangrenosum may occur after trauma or injury to the skin in 30% of patients; this process is termed pathergy.
Symptoms and Signs

Pyoderma gangrenosum begins as an inflamed erythematous papule, pustule, or nodule. The lesion, which may resemble a furuncle or an arthropod bite at this stage, then ulcerates and expands rapidly, developing a swollen necrotic base and a raised dusky to violaceous border. An undermined border is common, if not pathognomonic. Systemic symptoms such as fever, malaise, and arthralgias are common. The ulcers coalesce to form larger ulcers, often with cribriform or sieve-like scarring.

Diagnosis

Diagnosis is clinical. Biopsies of lesions are not often diagnostic but may be supportive; 40% of biopsies from a leading edge show vasculitis with neutrophils and fibrin in superficial vessels.

Treatment

- Corticosteroids
- Sometimes other anti-inflammatory drugs or immunosuppressants
- Avoidance of surgical debridement

Prednisone 60 to 80 mg po once/day is still the mainstay of treatment, although cyclosporine 3 mg/kg po once/day is also quite effective. Dapsone, clofazimine, thalidomide, tumor necrosis factor-α inhibitors (eg, infliximab), and mycophenolate mofetil have also been used successfully. Surgical treatments are avoided because of the risk of wound extension.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous hypersensitivity reactions. Drugs, especially sulfa drugs, antiepileptics, and antibiotics, are the most common causes. Macules rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing. Diagnosis is usually obvious by appearance of initial lesions and clinical syndrome. Treatment is supportive care; corticosteroids, cyclophosphamide, and other drugs may be tried. Prognosis depends on how early the disorders are diagnosed and treated. Mortality can be as high as 7.5% in children and 20 to 25% in adults.

SJS and TEN are clinically similar except for their distribution. By one commonly accepted definition, changes affect < 10% of body surface area in SJS and > 30% of body surface area in TEN; involvement of 15 to 30% of body surface area is considered SJS-TEN overlap.

The disorders affect between 1 and 5 people/million. Incidence, severity, or both of these disorders may be higher in bone-marrow transplant recipients, in Pneumocystis jirovecii-infected HIV patients, in patients with SLE, and in patients with other chronic rheumatologic diseases.

Etiology

Drugs precipitate over 50% of SJS cases and up to 95% of TEN cases. The most common drug causes include

- Sulfa drugs (eg, cotrimoxazole, sulfasalazine)
- Other antibiotics (eg, aminopenicillins, fluoroquinolones, cephalosporins)
- Antiepileptics (eg, phenytoin, carbamazepine, phenobarbital, valproate, lamotrigine)
- Miscellaneous individual drugs (eg, piroxicam, allopurinol, chloromezanone)
Cases that are not caused by drugs are attributed to

• Infection (mostly with *Mycoplasma pneumoniae*)
• Vaccination
• Graft-vs-host disease

Rarely, a cause cannot be identified.

**Pathophysiology**

Exact mechanism is unknown; however, one theory holds that altered drug metabolism in some patients causes formation of reactive metabolites that bind to and alter cell proteins, triggering a T-cell-mediated cytotoxic reaction to drug antigens in keratinocytes.

Another possible mechanism involves interactions between Fas (a cell-surface receptor that induces apoptosis) and its ligand, particularly a soluble form of Fas ligand released from mononuclear cells. Recent findings suggest that granulysin released from cytotoxic T cells and natural killer cells might play a role in keratinocyte death.

**Symptoms and Signs**

Within 1 to 3 wk after the start of the offending drug, patients develop a prodrome of malaise, fever, headache, cough, and conjunctivitis. Macules, often in a target configuration, then appear suddenly, usually on the face, neck, and upper trunk. These macules simultaneously appear elsewhere on the body, coalesce into large flaccid bullae, and slough over a period of 1 to 3 days. Nails and eyebrows may be lost along with epithelium.

In severe cases of TEN, large sheets of epithelium slide off the entire body at pressure points (Nikolsky's sign), exposing weepy, painful, and erythematous skin. Painful oral crusts and erosions, keratoconjunctivitis, and genital problems (eg, phimosis, vaginal synechiae) accompany skin sloughing in up to 90% of cases. Bronchial epithelium may also slough, causing cough, dyspnea, pneumonia, pulmonary edema, and hypoxemia. Glomerulonephritis and hepatitis may develop.

**Diagnosis**

• Clinical evaluation
• Often skin biopsy

Diagnosis is often obvious from appearance of lesions and rapid progression of symptoms. Histologic examination of sloughed skin shows necrotic epithelium, a distinguishing feature.

Differential diagnosis in SJS and early TEN includes erythema multiforme, viral exanthems, and drug rash; and, in later stages of TEN, paraneoplastic pemphigus, toxic shock syndrome, exfoliative erythroderma, and thermal burn. In children, TEN is less common and must be distinguished from staphylococcal scalded skin syndrome.

**Prognosis**

Severe TEN is similar to extensive burns; patients are acutely ill, may be unable to eat or open their eyes, and suffer massive fluid and electrolyte losses. They are at high risk of infection, multiorgan failure, and death. With early therapy, survival rates approach 90%. The severity-of-illness score for TEN (see Table 79-2) systematically scores 7 independent risk factors within the first 24 h of presentation to the hospital to determine the mortality rate for a particular patient.

**Treatment**
• Supportive care

• Possibly immune modulator treatment

• Possibly plasmapheresis

Treatment is most successful when SJS or TEN is recognized early and treated in an inpatient dermatologic or ICU setting; treatment in a burn unit may be needed for severe disease. Ophthalmology consultation is mandatory for patients with ocular involvement. Drugs should be stopped immediately. Patients

[Table 79-2. Severity-of-Illness Score for Toxic Epidermal Necrolysis (Scorten)]

are isolated to minimize exposure to infection and are given fluids, electrolytes, blood products, and nutritional supplements as needed. Skin care includes prompt treatment of secondary bacterial infections. Prophylactic antibiotics are controversial.

Drug treatment of STS and TEN is controversial. High-dose systemic corticosteroids (e.g., methylprednisolone 80 to 200 mg IV or prednisone 80 mg po once/day for 7 to 10 days or until progression stops) or cyclophosphamide (300 mg IV q 24 h for 7 days or until significant improvement) can be given to inhibit T-cell-mediated cytolysis. Cyclosporine (3 to 5 mg/kg po once/day) inhibits CD8 cells and has been shown to decrease the duration of active disease by 2 to 3 days in some instances. However, corticosteroids are controversial and are thought by some to increase mortality. Plasmapheresis can remove reactive drug metabolites or antibodies. Early high-dose IV immune globulin (IVIG) 2.7 g/kg over 3 days blocks antibodies and Fas ligand. Despite some remarkable results using high-dose IVIG for TEN, clinical trials involving small cohorts have reported conflicting results.
Chapter 80. Sweating Disorders

Introduction

There are two types of sweat glands: apocrine and eccrine.

Apocrine glands are clustered in the axillae, areolae, genitals, and anus; modified apocrine glands are found in the external auditory meatus. Apocrine glands become active at puberty; their excretions are oily and viscid and are presumed to play a role in sexual olfactory messages. The most common disorders of apocrine glands are bromhidrosis and hidradenitis suppurativa (see p. 698).

Eccrine glands are sympathetically innervated, distributed over the entire body, and active from birth. Their secretions are watery and serve to cool the body in hot environments or during activity. Disorders of eccrine glands include hyperhidrosis, hypohidrosis, and miliaria.

Bromhidrosis

Bromhidrosis is excessive or abnormal body odor caused by decomposition by bacteria and yeasts of apocrine secretions and cellular debris.

Apocrine secretions are lipid-rich, sterile, and odorless but become odoriferous when decomposed. Eccrine bromhidrosis is not as fragrant because eccrine sweat is nearly 100% water. The cause of apocrine bromhidrosis is poor hygiene of skin and clothing.

In some people, a few days of washing with an antiseptic soap, which may be combined with use of antibacterial creams containing clindamycin or erythromycin, may be necessary. Shaving the hair in the armpits may also help control odor.

Hyperhidrosis

Hyperhidrosis is excessive sweating, which can be focal or diffuse and has multiple causes. Sweating of the axillae, palms, and soles is most often due to stress; diffuse sweating is usually idiopathic but should raise suspicions for cancer, infection, and endocrine disease. Diagnosis is obvious, but tests for underlying causes may be indicated. Treatment is topical aluminum chloride, tap water iontophoresis, botulinum toxin, and, in extreme cases, surgery.

Etiology

Hyperhidrosis can be focal or generalized.

Focal sweating: Emotional causes are common, causing sweating on the palms, soles, axillae, and forehead at times of anxiety, excitement, anger, or fear. It may be due to a generalized stress-increased sympathetic outflow. Although such sweating is a normal response, patients with hyperhidrosis sweat excessively and under conditions that do not cause sweating in most people.

Gustatory sweating occurs around the lips and mouth when ingesting foods and beverages that are spicy or hot in temperature. There is no known cause in most cases, but gustatory sweating can be increased in diabetic neuropathy, facial herpes zoster, cervical sympathetic ganglion invasion, CNS injury or disease, or parotid gland injury. In the case of parotid gland injury, surgery, infection, or trauma may disrupt parotid gland innervation and lead to regrowth of parotid parasympathetic fibers into sympathetic fibers innervating local sweat glands in skin where the injury took place, usually over the parotid gland. This condition is called Frey's syndrome.

Other causes of focal sweating include pretibial myxedema (shins), hypertrophic osteoarthropathy (palms), and blue rubber bleb nevus syndrome and glomus tumor (over lesions). Compensatory sweating is intense sweating after sympathectomy.

Generalized sweating: Generalized sweating involves most of the body. Although most cases are
idiopathic, numerous conditions can be involved (see Table 80-1).

Symptoms and Signs

Sweating is often present during examination and sometimes is extreme. Clothing can be soaked, and palms or soles may become macerated and fissured. Hyperhidrosis can cause emotional distress to patients and may lead to social withdrawal. Palmar or plantar skin may appear pale.

Diagnosis

• History and examination
• Iodine and starch test
• Tests to identify a cause

Hyperhidrosis is diagnosed by history and examination but can be confirmed with the iodine and starch test (apply iodine solution to the affected area, let dry, dust on corn starch: areas of sweating appear dark). Testing is necessary only to confirm foci of sweating (as in Frey's syndrome or to locate the [Table 80-1. Some Causes of Generalized Sweating]

area needing surgical or botulinum toxin treatment) or in a semiquantitative way when following the course of treatment.

Tests to identify a cause of hyperhidrosis are guided by a review of symptoms and might include CBC to detect leukemia, serum glucose to detect diabetes, and thyroid-stimulating hormone to screen for thyroid dysfunction.

Treatment

• Aluminum chloride hexahydrate solution
• Tap water iontophoresis
• Botulinum toxin type A
• Surgery

Initial treatment of focal and generalized sweating is similar.

Aluminum chloride hexahydrate 6 to 20% solution in absolute ethyl alcohol is indicated for topical treatment of axillary, palmar, and plantar sweating; these preparations require a prescription. The solution blocks sweat ducts and is most effective when applied nightly and covered tightly with a thin polyvinylidene or polyethylene film; it should be washed off in the morning. Sometimes an anticholinergic drug is taken before applying to prevent sweat from washing the aluminum chloride away. Initially, several applications weekly are needed to achieve control, then a maintenance schedule of once or twice weekly is followed. If treatment under occlusion is irritating, it should be tried without occlusion. This solution should not be applied to inflamed, broken, wet, or recently shaved skin. High-concentration, water-based aluminum chloride solutions may provide adequate relief in milder cases. Topical alternatives to aluminum chloride, including glutaraldehyde, formaldehyde, and tannic acid, are effective but can cause contact dermatitis and skin discoloration. A solution of methenamine also may help.

Tap water iontophoresis, in which salt ions are introduced into the skin using electric current, is an option for patients unresponsive to topical treatments. The affected areas (typically palms or soles) are placed in 2 tap water basins each containing an electrode across which a 15- to 25-mA current is applied for 10 to 20 min. This routine is done daily for 1 wk and then repeated weekly or bimonthly. Treatments may be
made more effective with topical or oral anticholinergic drugs. Although the treatments are usually effective, the technique is time-consuming and somewhat cumbersome, and some patients tire of the routine.

Botulinum toxin type A is a neurotoxin that decreases the release of acetylcholine from sympathetic nerves serving eccrine glands. Injected directly into the axillae, palms, or forehead, botulinum toxin inhibits sweating for about 5 mo depending on dose. Complications include local muscle weakness and headache. Injections are effective but painful and expensive.

Surgery is indicated if more conservative treatments fail. Patients with axillary sweating can be treated with surgical excision of axillary sweat glands either through open dissection or by liposuction (the latter seems to have lower morbidity). Patients with palmar sweating can be treated with endoscopic transthoracic sympathectomy. The potential morbidity of surgery must be considered, especially in sympathectomy. Potential complications include phantom sweating, compensatory sweating, gustatory sweating, neuralgia, and Horner's syndrome.

Hypohidrosis

Hypohidrosis is inadequate sweating.

Hypohidrosis due to skin abnormalities is rarely clinically significant. It is most commonly focal and caused by local skin injury (eg, from trauma, radiation, infection [eg, leprosy], or inflammation) or by atrophy of glands from connective tissue disease (eg, systemic sclerosis, SLE, Sjogren's syndrome). Hypohidrosis may be caused by drugs, especially those with anticholinergic properties. It is also caused by diabetic neuropathy and a variety of congenital syndromes. Heatstroke causes inadequate sweating but is a CNS rather than a skin disorder (see p. 3265). A rare presentation is fever of unknown origin.

Diagnosis is by clinical observation of decreased sweating or by heat intolerance. Treatment is by cooling measures (eg, air-conditioning, wet garments).

Miliaria

In miliaria, sweat flow is obstructed and trapped within the skin, causing papular lesions.

Miliaria most often occurs in warm humid weather but may occur in cool weather in an overdressed patient. Lesions vary depending on the depth of tissue at which the sweat duct is obstructed.

• **Miliaria crystallina** is ductal obstruction in the uppermost epidermis, with retention of sweat subcorneally. It causes clear droplike vesicles that rupture with light pressure.

• **Miliaria rubra** (prickly heat) is ductal obstruction in the mid-epidermis with retention of sweat in the epidermis and dermis. It causes irritated, pruritic papules (prickling).

• **Miliaria pustulosa** is similar to miliaria rubra but manifests as pustules rather than papules.

• **Miliaria profunda** is ductal obstruction at the entrance of the duct into the dermal papillae at the dermo-epidermal junction, with retention of sweat in the dermis. It causes papules that are larger and more deeply seated than those of miliaria pustulosa. Papules are frequently painful.

Diagnosis is by clinical appearance in the context of hot environment.

Treatment is cooling and drying of the involved areas and avoidance of conditions that may induce sweating; an air-conditioned environment is ideal. Once the rash develops, corticosteroid creams or lotions are used, sometimes with a bit of menthol added.
Chapter 81. Bacterial Skin Infections

Introduction

Bacterial skin infections may be uncomplicated or complicated. Uncomplicated infections usually respond promptly to systemic antibiotics and local wound care. A skin infection is considered complicated when it meets 2 of the following 5 criteria:

- Involves a preexisting wound or ulceration of the skin
- Involves the deeper soft tissues
- Requires surgical intervention
- Is caused or exacerbated by underlying comorbid disease states (eg diabetes, systemic immunosuppression)
- Is unresponsive to conventional antibiotic therapy or is recurrent

All uncomplicated skin infections have the potential to become complicated. Complicated skin and soft-tissue infections may require multidrug therapy and the assistance of other consultants (eg, surgeons, infectious disease specialists), particularly in light of resistance in many strains of bacteria and the rapid loss of efficacy among more potent antibiotics. Recurrent skin infections should raise suspicion of colonization (eg, staphylococcal nasal carriage), resistant strains of bacteria (eg, methicillin-resistant Staphylococcus aureus [MRSA]), cancer, poorly controlled diabetes, or other reasons for immunocompromise (eg, HIV, hepatitis, advanced age, congenital susceptibility). Bacteria are involved in the pathophysiology of acne, but acne is not primarily considered a bacterial skin infection.

Cellulitis

Cellulitis is acute bacterial infection of the skin and subcutaneous tissue most often caused by streptococci or staphylococci. Symptoms and signs are pain, rapidly spreading erythema, and edema; fever may occur, and regional lymph nodes may enlarge. Diagnosis is by appearance; cultures are sometimes helpful but awaiting culture results should not delay empiric therapy. Treatment is with antibiotics. Prognosis is excellent with timely treatment.

Etiology

- *Streptococcus pyogenes*
- *Staphylococcus aureus*

Cellulitis is most often caused by group A β-hemolytic streptococci (eg, *Streptococcus pyogenes*) or *Staphylococcus aureus*. Streptococci cause diffuse, rapidly spreading infection because enzymes produced by the organism (streptokinase, DNase, hyaluronidase) break down cellular components that would otherwise contain and localize the inflammation. Staphylococcal cellulitis is typically more localized and usually occurs in open wounds or cutaneous abscesses.

Recently, methicillin-resistant *S. aureus* (MRSA) has become more common in the community (community-associated MRSA [CA-MRSA]). Historically, MRSA was typically confined to patients who were exposed to the organism in a hospital or nursing facility. MRSA infection should now be considered in patients with community-acquired cellulitis, particularly in those with cellulitis that is recurrent or unresponsive to monotherapy.

Less common causes are group B streptococci (eg, *Streptococcus agalactiae*) in older patients with diabetes; gram-negative bacilli (eg, *Haemophilus influenzae*) in children; and *Pseudomonas aeruginosa* in patients with diabetes or neutropenia, hot tub or spa users, and hospitalized patients. Animal bites may
result in cellulitis; Pasteurella multocida is the cause in cat bites, and Capnocytophaga sp is responsible in dog bites. Immersion injuries in fresh water may result in cellulitis caused by Aeromonas hydrophila; in warm salt water, by Vibrio vulnificus.

Risk factors include skin abnormalities (eg, trauma, ulceration, fungal infection, other skin barrier compromise due to preexisting skin disease), which are common in patients with chronic venous insufficiency or lymphedema. Scars from saphenous vein removal for cardiac or vascular surgery are common sites for recurrent cellulitis, especially if tinea pedis is present. Frequently, no predisposing condition or site of entry is evident.

Symptoms and Signs

Infection is most common in the lower extremities. Cellulitis is typically unilateral; stasis dermatitis closely mimics cellulitis but is usually bilateral. The major findings are local erythema and tenderness, frequently with lymphangitis and regional lymphadenopathy. The skin is hot, red, and edematous (see Plate 31), often with surface appearance resembling the skin of an orange (peau d'orange). The borders are usually indistinct, except in erysipelas (a type of cellulitis with sharply demarcated margins—see p. 696). Petechiae are common; large areas of ecchymosis are rare. Vesicles and bullae may develop and rupture, occasionally with necrosis of the involved skin. Cellulitis may mimic deep venous thrombosis but can often be differentiated by one or more features (see Table 81-1). Fever, chills, tachycardia, headache, hypotension, and delirium may precede cutaneous findings by several hours, but many patients do not appear ill. Leukocytosis is common.

[Table 81-1. Differentiating Cellulitis and Deep Venous Thrombosis]

Diagnosis

• Examination

• Blood and sometimes tissue cultures for immunocompromised patients

Diagnosis is by examination. Skin and (when present) wound cultures are generally not indicated because they rarely identify the infecting organism. Blood cultures are useful in immunocompromised patients to detect or rule out bacteremia. Culture of involved tissue may be required in immunocompromised patients if they are not responding to empiric therapy or if blood cultures do not isolate an organism.

Prognosis

Most cellulitis resolves quickly with antibiotic therapy. Local abscesses occasionally form, requiring incision and drainage. Serious but rare complications include severe necrotizing subcutaneous infection (see p. 700) and bacteremia with metastatic foci of infection.

Recurrences in the same area are common, sometimes causing serious damage to the lymphatics, chronic lymphatic obstruction, and lymphedema.

Treatment

• Antibiotics

Treatment is with antibiotics. For most patients, empiric treatment effective against both group A streptococci and S. aureus is used. Oral therapy is usually adequate with dicloxacillin 250 mg or cephalaxin 500 mg qid for mild infections. Levofloxacin 500 mg po once/day or moxifloxacin 400 mg once/day works well for patients who are unlikely to adhere to multiple daily dosing schedules. For more serious infections, oxacillin or nafcillin 1 g IV q 6 h is given. Use of initial empiric therapy against MRSA is not typically advised unless there is compelling clinical evidence (eg, contact with a documented case or outbreak; culture-documented prevalence of > 10% or 15% in a practice area). For penicillin-allergic patients or those with suspected or confirmed MRSA infection, vancomycin 1 g IV q 12 h is the drug of
choice (see also p. 1230). Linezolid is another option for the treatment of MRSA at a dose of 600 mg IV or po q 12 h for 10 to 14 days. Teicoplanin has a mechanism of action similar to vancomycin. It is commonly used outside the US to treat MRSA; the usual dose is 6 mg/kg IV q 12 h for 2 doses, followed by 6 mg/kg (or 3 mg/kg) IV or IM once/day. Immobilization and elevation of the affected area help reduce edema; cool, wet dressings relieve local discomfort.

Cellulitis in a patient with neutropenia requires empiric antipseudomonal antibiotics (eg, tobramycin 1.5 mg/kg IV q 8 h and piperacillin 3 g IV q 4 h) until blood culture results are available. Penicillin is the drug of choice for cellulitis caused by *P. multocida*; an aminoglycoside (eg, gentamicin) is effective against *A. hydrophila*, and tetracycline is preferred for *V. vulnificus* infections.

Recurrent leg cellulitis is prevented by treating concomitant tinea pedis, which often eliminates the source of bacteria residing in the inflamed, macerated tissue. If such therapy is unsuccessful or not indicated, recurrent cellulitis can sometimes be prevented by benzathine penicillin 1.2 million units IM monthly or penicillin V or erythromycin 250 mg po qid for 1 wk/mo. If these regimens prove unsuccessful, tissue culture may be required.

**Erysipelas**

Erysipelas is a type of superficial cellulitis (see p. 694) with dermal lymphatic involvement.

Erysipelas should not be confused with erysipeloid, a skin infection caused by *Erysipelothrix* (see p. 1241). Erysipelas is characterized clinically by shiny, raised, indurated, and tender plaque-like lesions with distinct margins (see Plate 33). There is also a bullous form of erysipelas. Erysipelas is most often caused by group A (or rarely group C or G) β-hemolytic streptococci and occurs most frequently on the legs and face. However, other causes have been reported, including *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *S. warneri*, *Streptococcus pneumoniae*, *S. pyogenes*, and *Moraxella* sp. Erysipelas of the face must be differentiated from herpes zoster, angioedema, and contact dermatitis. It is commonly accompanied by high fever, chills, and malaise; MRSA is more common in facial erysipelas than in lower-extremity erysipelas. Erysipelas may be recurrent and may result in chronic lymphedema.

**Diagnosis**

Diagnosis is by characteristic appearance; blood culture is done in toxic-appearing patients. Diffuse inflammatory carcinoma of the breast may also be mistaken for erysipelas.

**Treatment**

- Usually penicillin for lower-extremity erysipelas
- Initially vancomycin for facial erysipelas

Treatment of choice for lower-extremity erysipelas is penicillin V 500 mg po qid for ≥ 2 wk. In severe cases, penicillin G 1.2 million units IV q 6 h is indicated, which can be replaced by oral therapy after 36 to 48 h. Dicloxacillin 500 mg po qid for 10 days can be used for infections with staphylococci. Erythromycin 500 mg po qid for 10 days may be used in penicillin-allergic patients; however, there is growing macrolide resistance in streptococci. In infections resistant to these antibiotics, cloxacillin or nafcillin can be used. In Europe, pristinamycin and roxithromycin have been shown to be good choices for erysipelas. If facial erysipelas is present or if MRSA is otherwise suspected, empiric therapy should be initiated with vancomycin 1 g IV q 12 h (which is active against MRSA). Cold packs and analgesics may relieve local discomfort. Fungal foot infections may be an entry site for infection and may require antifungal treatment to prevent recurrence.

**Cutaneous Abscess**

A cutaneous abscess is a localized collection of pus in the skin and may occur on any skin...
Symptoms and signs are pain and a tender, firm or fluctuant swelling. Diagnosis is usually obvious by examination. Treatment is incision and drainage.

Bacteria causing cutaneous abscesses are typically indigenous to the skin of the involved area. For abscesses on the trunk, extremities, axillae, or head and neck, the most common organisms are *Staphylococcus aureus* and streptococci. In recent years, methicillin-resistant *S. aureus* (MRSA) has become a more common cause.

Abscesses in the perineal (ie, inguinal, vaginal, buttock, perirectal) region contain organisms found in the stool, commonly anaerobes or a combination of aerobes and anaerobes. Carbuncles and furuncles are follicle-based cutaneous abscesses with characteristic features (see p. 697).

Cutaneous abscesses tend to form in patients with bacterial overgrowth, antecedent trauma (particularly when a foreign body is present), or immunologic or circulatory compromise.

**Symptoms and Signs**

Cutaneous abscesses are painful, tender, indurated, and sometimes erythematous. They vary in size, typically 1 to 3 cm in length, but sometimes much larger. Initially the swelling is firm; later, as the abscess "points," the overlying skin becomes thin and feels fluctuant. The abscess may then spontaneously drain. Local cellulitis, lymphangitis, regional lymphadenopathy, fever, and leukocytosis are variable accompanying features.

**Diagnosis**

- Examination
- Gram stain and culture to identify MRSA

Diagnosis is usually obvious by examination. Gram stain and culture are recommended, primarily to identify MRSA.

Conditions resembling simple cutaneous abscesses include hidradenitis suppurativa (see p. 698) and ruptured epidermal cysts. Epidermal cysts (often incorrectly referred to as sebaceous cysts) rarely become infected; however, rupture releases keratin into the dermis, causing an exuberant inflammatory reaction sometimes clinically resembling infection. Culture of these ruptured cysts seldom reveals any bacteria. Perineal abscesses may represent cutaneous emergence of a deeper perirectal abscess or drainage from Crohn's disease via a fistulous tract. These other conditions are usually recognizable by history and rectal examination.

**Treatment**

- Incision and drainage
- Sometimes antibiotics

Some small abscesses resolve without treatment, coming to a point and draining. Warm compresses help accelerate the process. Incision and drainage are indicated when significant pain, tenderness, and swelling are present; it is unnecessary to await fluctuance. Under sterile conditions, local anesthesia is administered as either a lidocaine injection or a freezing spray.

Patients with large, extremely painful abscesses may benefit from IV sedation and analgesia during drainage. A single puncture with the tip of a scalpel is often sufficient to open the abscess. After the pus drains, the cavity should be bluntly probed with a gloved finger or curette to clear loculations, and then irrigated with 0.9% saline solution. Some clinicians pack the cavity loosely with a gauze wick that is removed 24 to 48 h later. Local heat and elevation may hasten resolution of inflammation.

Antibiotics are unnecessary unless the patient has signs of systemic infection, cellulitis, multiple
abscesses, immunocompromise, or a facial abscess in the area drained by the cavernous sinus. In these cases, empiric therapy should be started with a drug active against MRSA (eg, trimethoprim/sulfamethoxazole, clindamycin; for severe infection, vancomycin) pending results of bacterial culture.

**Folliculitis**

**Folliculitis is a bacterial infection of hair follicles.**

Folliculitis is usually caused by *Staphylococcus aureus* but occasionally *Pseudomonas aeruginosa* (hot tub folliculitis) or other organisms. Hot tub folliculitis occurs because of inadequate treatment of water with chlorine or bromine.

Symptoms of folliculitis are mild pain, pruritus, or irritation. Signs of folliculitis are a superficial pustule or inflammatory nodule surrounding a hair follicle. Infected hairs easily fall out or are removed, but new papules tend to develop. Growth of stiff hairs into the skin may cause chronic low-grade irritation or inflammation that may mimic infectious folliculitis (pseudofolliculitis barbae—see p. 731).

**Treatment**

Because most folliculitis is caused by *S. aureus*, clindamycin 1% lotion or gel may be applied topically bid for 7 to 10 days. Alternatively, benzoyl peroxide 5% wash may be used when showering for 5 to 7 days. Extensive cutaneous involvement may warrant systemic therapy (eg, cephalexin 250 to 500 mg po tid to qid for 10 days). If these measures do not result in a cure, or folliculitis recurs, pusules are Gram stained and cultured to rule out gram-negative or methicillin-resistant *S. aureus* (MRSA) etiology, and nares are cultured to rule out nasal staphylococcal carriage. Potassium hydroxide wet mount should be done on a plucked hair to rule out fungal folliculitis.

Treatment for MRSA usually requires 2 oral antibiotics, and the choice of therapeutic drugs should be based on culture and sensitivity reports.

Hot tub folliculitis usually resolves without treatment. However, adequate chlorination of the hot tub is necessary to prevent recurrences and to protect others from infection.

**Furuncles and Carbuncles**

**Furuncles are skin abscesses caused by staphylococcal infection, which involve a hair follicle and surrounding tissue.** Carbuncles are clusters of furuncles connected subcutaneously, causing deeper suppuration and scarring. They are smaller and more superficial than subcutaneous abscesses (see p. 696). Diagnosis is by appearance. Treatment is warm compresses and often oral antistaphylococcal antibiotics.

Both furuncles and carbuncles may affect healthy young people but are more common in the obese, the immunocompromised (including those with neutrophil defects), the elderly, and possibly those with diabetes. Clustered cases may occur among those living in crowded quarters with relatively poor hygiene or among contacts of patients infected with virulent strains. Predisposing factors include bacterial colonization of skin or nares, hot and humid climates, and occlusion or abnormal follicular anatomy (eg, comedones in acne). Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause.

Furuncles are common on the neck, breasts, face, and buttocks. They are uncomfortable and may be painful when closely attached to underlying structures (eg, on the nose, ear, or fingers). Appearance is a nodule or pustule that discharges necrotic tissue and sanguineous pus. Carbuncles may be accompanied by fever and prostration.

**Diagnosis**

Diagnosis is by examination. Material for culture should be obtained.
Treatment

- Drainage

- Often antibiotics effective against MRSA

Abscesses are incised and drained. Intermittent hot compresses are used to facilitate drainage. Antibiotics, when used, should be effective against MRSA, pending culture and sensitivity test results. In afebrile patients, treatment of a single lesion < 5 mm requires no antibiotics. If a single lesion is ≥ 5 mm, an oral antibiotic is given for 5 to 10 days; choices include trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg to 320/1600 mg bid, clindamycin 300 to 600 mg q 6 to 8 h, and doxycycline or minocycline 100 mg q 12 h. Patients with fever, multiple abscesses, or carbuncles are given 10 days of TMP/SMX 160/800 mg to 320/1600 mg bid plus rifampin 300 mg bid. Systemic antibiotics are also needed for

- Lesions < 5 mm that do not resolve with drainage

- Evidence of expanding cellulitis

- Immunocompromised patients

- Patients at risk of endocarditis

Furuncles frequently recur and can be prevented by applying liquid soap containing either chlorhexidine gluconate with isopropyl alcohol or 2 to 3% chloroxylenol and by giving maintenance antibiotics over 1 to 2 mo. Patients with recurrent furunculosis should be treated for predisposing factors such as obesity, diabetes, occupational or industrial exposure to inciting factors, and nasal carriage of S. aureus or MRSA colonization.

Erythrasma

Erythrasma is an intertriginous infection with Corynebacterium minutissimum that is most common among patients with diabetes and among people living in the tropics.

Erythrasma resembles tinea or intertrigo. It is most common in the foot, where it manifests as superficial scaling, fissuring, and maceration most commonly confined to the 3rd and 4th web spaces. Erythrasma is also common in the groin, where it manifests as irregular but sharply margined pink or brown patches with fine scaling. Erythrasma may also involve the axillae, submammary or abdominal folds, and perineum, particularly in obese middle-aged women and in patients with diabetes.

Erythrasma fluoresces a characteristic coral-red color under Wood's light. Absence of hyphae in skin scrapings also distinguishes erythrasma from tinea.

Treatment is erythromycin or tetracycline 250 mg po qid for 14 days. Topical erythromycin or clindamycin is also effective. Recurrence is common.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic, scarring inflammation of apocrine glands of the axillae, groin, and around the nipples and anus.

Blockage of apocrine ducts has been suggested as the cause, leading to subsequent inflammation, bacterial overgrowth, and scarring. Staphylococcus aureus is almost always implicated in acute cases, but gram-negative organisms such as Proteus may predominate in chronic cases.

Swollen, tender masses resembling cutaneous abscesses develop. Pain, fluctuance, discharge, and sinus tract formation are characteristic in chronic cases. In chronic axillary cases, coalescence of inflamed nodules causes palpable cordlike fibrotic bands. The condition may become disabling because of pain and foul odor.
Diagnosis

Diagnosis is by examination. Bacterial cultures may be helpful if there appears to be a concomitant cellulitis or loculated abscess.

Treatment

Treatment of acute cases consists of high-dose oral tetracycline (500 mg bid), doxycycline (100 to 200 mg once/day), minocycline (100 mg once/day), or erythromycin (250 to 500 mg qid) until the lesions resolve. Topical clindamycin applied bid may be equally effective. Incision and drainage are necessary for an abscess or fluctuance of the affected area but alone do not resolve the problem (unlike in cutaneous abscesses). Isotretinoin 1 mg/kg po bid has also been effective in some patients, but recurrences are common. Intralesional corticosteroid injections (eg, triamcinolone 1 to 10% suspension intradermally) may help with inflammation and pain. Surgical excision and repair or grafting of the affected areas is often necessary if the disease persists. Ablative laser therapy (CO$_2$ or erbium:YAG) is an alternate surgical treatment. Several studies report success in treating hidradenitis suppurativa with etanercept or infliximab, injectable tumor necrosis factor-α inhibitors. Although not the gold standard, this option may be useful when all other treatment modalities have failed.

Impetigo and Ecthyma

Impetigo is a superficial skin infection with crusting or bullae caused by streptococci, staphylococci, or both. Ecthyma is an ulcerative form of impetigo.

No predisposing lesion is identified in most patients, but impetigo may follow any type of break in the skin. General risk factors seem to be moist environment, poor hygiene, and chronic nasal carriage of staphylococci. Impetigo may be bullous or nonbullous. Staphylococcus aureus is the predominant cause of nonbullous impetigo and the cause of all bullous impetigo. Bullae are caused by exfoliative toxin produced by staphylococci. Methicillin-resistant S. aureus (MRSA) has been isolated in about 20% of recent cases of impetigo.

Symptoms and Signs

Nonbullous impetigo typically manifests as clusters of vesicles or pustules that rupture and develop a honey-colored crust (exudate from the lesion base) over the lesions (see Plate 35). Bullous impetigo is similar except that vesicles typically enlarge rapidly to form bullae. The bullae burst and expose larger bases, which become covered with honey-colored varnish or crust. Ecthyma is characterized by small, purulent, shallow, punched-out ulcers with thick, brown-black crusts and surrounding erythema.

Impetigo and ecthyma cause mild pain or discomfort. Pruritus is common; scratching may spread infection, inoculating adjacent and nonadjacent skin.

Diagnosis

• Clinical evaluation

Diagnosis is by characteristic appearance. Cultures of lesions are indicated only when the patient does not respond to empiric therapy. Patients with recurrent impetigo should have nasal culture. Persistent infections should be cultured to identify MRSA.

Treatment

• Topical mupirocin or retapamulin

• Sometimes oral antibiotics
The affected area should be washed gently with soap and water several times a day to remove any crusts. Treatment for localized disease is topical mupirocin antibiotic ointment tid for 7 days or retapamulin ointment bid for 5 days. Oral antibiotics (eg, dicloxacillin or cephalaxin 250 to 500 mg qid, 12.5 mg/kg qid for children, for 10 days) may be needed in patients with extensive or resistant lesions. Use of initial empiric therapy against MRSA is not typically advised unless there is compelling clinical evidence (eg, contact with a documented case or outbreak; high culture-documented prevalence in a practice area). Treatment of MRSA should be directed by culture and sensitivity test results; typically, clindamycin, rifampin, and trimethoprim/sulfamethoxazole are effective against most strains of community-associated MRSA.

Other therapy includes restoring a normal cutaneous barrier in patients with underlying atopic dermatitis or extensive xerosis using topical emollients and corticosteroids if warranted. Chronic staphylococcal nasal carriers are given topical antibiotics (mupirocin) for 1 wk each of 3 consecutive months.

Prompt recovery usually follows timely treatment. Delay can cause cellulitis, lymphangitis, furunculosis, and hyperpigmentation or hypopigmentation with or without scarring. Children aged 2 to 4 yr are at risk of acute glomerulonephritis if nephritogenic strains of group A streptococci are involved; nephritis seems to be more common in the southern US than in other regions.

**Lymphadenitis**

(See also **Lymphangitis**, below.)

**Lymphadenitis is an acute infection of one or more lymph nodes.**

Lymphadenitis is a feature of many bacterial, viral, fungal, and protozoal infections. Focal lymphadenitis is prominent in streptococcal infection, TB or nontuberculous mycobacterial infection, tularemia, plague, cat-scratch disease, primary syphilis, lymphogranuloma venereum, chancroid, and genital herpes simplex. Multifocal lymphadenitis is common in infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, brucellosis, secondary syphilis, and disseminated histoplasmosis.

**Symptoms and Signs**

Lymphadenitis typically causes pain, tenderness, and lymph node enlargement. Pain and tenderness typically distinguish lymphadenitis from lymphadenopathy. With some infections, the overlying skin is inflamed, occasionally with cellulitis. Abscesses may form, and penetration to the skin produces draining sinuses. Fever is common.

**Diagnosis**

The underlying disorder is usually suggested by history and examination. If not, aspiration and culture or excisional biopsy is indicated.

**Treatment**

- Treatment of cause

Treatment is directed at the cause and is usually empiric. Options include IV antibiotics, antifungals, and antiparasitics depending upon etiology or clinical suspicion. Many patients with lymphadenitis may respond to outpatient therapy with oral antibiotics. However, many also go on to form abscesses, which require surgical drainage; an extensive procedure is done with accompanying IV antibiotics. In children, IV antibiotics are commonly needed. Hot, wet compresses may relieve some pain. Lymphadenitis usually resolves with timely treatment, although residual, persistent, nontender lymphadenopathy is common.

**Lymphangitis**

(See also **Lymphadenitis**, above.)
Lymphangitis is acute bacterial infection (usually streptococcal) of peripheral lymphatic channels.

Bacteria enter the lymphatic channels from an abrasion, wound, or coexisting infection (usually cellulitis). Patients with underlying lymphedema are at particular risk. Red, irregular, warm, tender streaks develop on an extremity and extend proximally from a peripheral lesion toward regional lymph nodes, which are typically enlarged and tender. Systemic manifestations (eg, fever, shaking chills, tachycardia, headache) may occur and may be more severe than cutaneous findings suggest. Leukocytosis is common. Bacteremia may occur. Rarely, cellulitis with suppurative, necrosis, and ulceration develops along the involved lymph channels as a consequence of primary lymphangitis.

Diagnosis is clinical. Isolation of the responsible organism is usually unnecessary. Most cases respond rapidly to antistreptococcal antibiotics (see Cellulitis on p. 694).

**Necrotizing Subcutaneous Infection**

(Necrotizing Fasciitis)

Necrotizing subcutaneous infection (NSI) is typically caused by a mixture of aerobic and anaerobic organisms that cause necrosis of subcutaneous tissue, usually including the fascia. This infection most commonly affects the extremities and perineum. Affected tissues become red, hot, and swollen, resembling severe cellulitis (see p. 694). Without timely treatment, the area becomes gangrenous. Patients are acutely ill. Diagnosis is by history and examination and is supported by evidence of overwhelming infection. Treatment involves antibiotics and surgical debridement. Prognosis is poor without early, aggressive treatment.

**Etiology**

NSI typically results from infection with group A streptococci (eg, *Streptococcus pyogenes*) or a mixture of aerobic and anaerobic bacteria (eg, *Bacteroides* sp). These organisms typically extend to subcutaneous tissue from a contiguous ulcer, an infection, or after trauma. Streptococci can arrive from a remote site of infection via the bloodstream. Perineal involvement (also called Fournier's gangrene) is usually a complication of recent surgery, perirectal abscess, periurethral gland infection, or retroperitoneal infection from perforated abdominal viscera. Patients with diabetes are at particular risk of NSI.

**Pathophysiology**

NSI causes tissue ischemia by widespread occlusion of small subcutaneous vessels. Vessel occlusion results in skin infarction and necrosis, which facilitates the growth of obligate anaerobes (eg, *Bacteroides*) while promoting anaerobic metabolism by facultative organisms (eg, *Escherichia coli*), resulting in gangrene. Anaerobic metabolism produces hydrogen and nitrogen, relatively insoluble gases that may accumulate in subcutaneous tissues.

**Symptoms and Signs**

The primary symptom is intense pain. However, in areas denervated by peripheral neuropathy, pain may be minimal or absent. Affected tissue is red, hot, and swollen and rapidly becomes discolored. Bullae, crepitis (from soft-tissue gas), and gangrene may develop. Subcutaneous tissues (including adjacent fascia) necrose, with widespread undermining of surrounding tissue. Muscles are spared initially. Patients are acutely ill, with high fever, tachycardia, altered mental status ranging from confusion to obtundation, and hypotension. Patients may be bacteremic or septic and may require aggressive hemodynamic support.

**Diagnosis**

- Clinical examination
- Blood and wound cultures
Diagnosis, made by history and examination, is supported by leukocytosis, soft-tissue gas on x-ray, positive blood cultures, and deteriorating metabolic and hemodynamic status.

NSI must be differentiated from clostridial soft-tissue infections, in which cellulitis, myositis, and myonecrosis often occur (see p. 1295). Such infections are anaerobic. Anaerobic cellulitis produces lots of gas but little pain, edema, or change in skin; it very seldom travels into the muscle. Anaerobic myonecrosis has pronounced skin changes, pain, and edema and usually penetrates into muscle.

**Prognosis**

Mortality rate is about 30%. Old age, underlying medical problems, delayed diagnosis and therapy, and insufficient surgical debridement worsen prognosis.

**Treatment**

- Surgical debridement
- Antibiotics
- Amputation if necessary

Treatment of early NSI is primarily surgical. IV antibiotics are adjuncts, usually including 2 or more drugs, but regimens vary depending on results of Gram stain and culture (eg, penicillin G 4 million units q 4 h combined with clindamycin 600 to 900 mg q 8 h or ceftriaxone 2 g q 12 h). Evidence of bullae, ecchymosis, fluctuance, crepitus, and systemic spread of infection requires immediate surgical exploration and debridement. The initial incision should be extended until an instrument or finger can no longer separate the skin and subcutaneous tissue from the deep fascia. The most common error is insufficient surgical intervention; repeat operation every 1 to 2 days, with further incision and debridement as needed, should be carried out routinely. Amputation of an extremity may be necessary.

IV fluids may be needed in large volumes before and after surgery. Antibiotic choices should be reviewed based on Gram stain and culture of tissues obtained during surgery. Hyperbaric O$_2$ therapy as adjuvant therapy may also be of benefit; however, the evidence is inconclusive.

**Staphylococcal Scalded Skin Syndrome**

Staphylococcal scalded skin syndrome (SSSS) is an acute epidermolysis caused by a staphylococcal toxin. Infants and children are most susceptible. Symptoms are widespread bullae with epidermal sloughing. Diagnosis is by examination and sometimes biopsy. Treatment is antistaphylococcal antibiotics and local care. Prognosis is excellent with timely treatment.

SSSS almost always affects children < 6 yr (especially infants); it rarely occurs in older patients unless they have renal failure or are immunocompromised. Epidemics may occur in nurseries, presumably transmitted by the hands of personnel who are in contact with an infected infant or who are nasal carriers of *Staphylococcus aureus*. Sporadic cases also occur.

SSSS is caused by group II coagulase-positive staphylococci, usually phage type 71, which elaborate exfoliatin (also called epidermolysin), a toxin that splits the upper part of the epidermis just beneath the granular cell layer (see also p. 1228). The primary infection often begins during the first few days of life in the umbilical stump or diaper area; in older children, the face is the typical site. Toxin produced in these areas enters the circulation and affects the entire skin.

[Table 81-2. Differentiating Staphylococcal Scalded Skin Syndrome (SSSS) and Toxic Epidermal Necrolysis (TEN)]

**Symptoms and Signs**
The initial lesion is usually superficial and crusted. Within 24 h, the surrounding skin becomes painful and scarlet, changes that quickly spread to other areas. The skin may be exquisitely tender and have a wrinkled tissue paper-like consistency. Large, flaccid blisters arise on the erythematous skin and quickly break to produce erosions. Intact blisters extend laterally with gentle pressure (Nikolsky's sign). The epidermis may peel easily, often in large sheets (see Plate 45). Widespread desquamation occurs within 36 to 72 h, and patients become very ill with systemic manifestations (eg, malaise, chills, fever). Desquamated areas appear scalded. Loss of the protective skin barrier can lead to sepsis and to fluid and electrolyte imbalance.

**Diagnosis**

- Biopsy

Diagnosis is suspected clinically, but confirmation usually requires biopsy (frozen section may give earlier results). Specimens show noninflammatory superficial splitting of the epidermis. In children, skin cultures are seldom positive; in adults, they are frequently positive. Cultures should be taken from the nose, conjunctiva, throat, and nasopharynx.

**Differential diagnosis:** Differential diagnosis includes drug hypersensitivity, viral exanthemas, scarlet fever, thermal burns, genetic bullous diseases (eg, some types of epidermolysis bullosa), acquired bullous diseases (eg, pemphigus vulgaris, bullous pemphigoid), and toxic epidermal necrolysis (see p. 689 and Table 81-2). Stevens-Johnson syndrome is characterized by mucosal involvement, which is absent in SSSS.

**Treatment**

- Antibiotics

Penicillinase-resistant antistaphylococcal antibiotics given IV must be started immediately. Nafcillin 12.5 to 25 mg/kg IV q 6 h for neonates > 2 kg and 25 to 50 mg/kg for older children is given until improvement is noted, followed by oral cloxacillin 12.5 mg/kg q 6 h (for infants and children weighing ≤ 20 kg) and 250 to 500 mg q 6 h (for older children). Corticosteroids are contraindicated. Topical therapy and patient handling must be minimized.

If disease is widespread and lesions are weeping, the skin should be treated as for burns (see p. 3245). Hydrolyzed polymer gel dressings may be very useful, and the number of dressing changes should be minimized.

Steps to detect carriers and prevent or treat nursery epidemics are discussed elsewhere (see p. 2828).
Chapter 82. Fungal Skin Infections

Introduction

Fungal skin infections are caused by yeasts (Candida sp) or dermatophytes (Epidermophyton, Microsporum, and Trichophyton spp).

Candidiasis

Candidiasis (moniliasis) is skin infection with Candida sp, most commonly Candida albicans. Infections can occur anywhere and are most common in skinfolds and web spaces and on the genitals, cuticles, and oral mucosa. Symptoms and signs vary by site. Diagnosis is by clinical appearance and potassium hydroxide wet mount of skin scrapings. Treatment is with drying agents and antifungals.

Most candidal infections are of the skin and mucous membranes, but invasive candidiasis is common in immunosuppressed patients and can be life threatening. Systemic candidiasis is discussed in Ch. 142.

Etiology

Candida is a group of about 150 yeast species. C. albicans is responsible for about 70 to 80% of all candidal infections. Other significant species include C. glabrata, C. tropicalis, C. krusei, and C. dubliniensis.

Candida is a ubiquitous yeast that resides harmlessly on skin and mucous membranes until dampness, heat, and impaired local and systemic defenses provide a fertile environment for it to grow. Risk factors for candidiasis include

• Hot weather
• Restrictive clothing
• Poor hygiene
• Infrequent diaper or undergarment changes in children and elderly patients
• Altered flora from antibiotic therapy
• Inflammatory diseases (eg, psoriasis) that occur in skinfolds
• Immunosuppression resulting from corticosteroids and immunosuppressive drugs, pregnancy, diabetes, other endocrinopathies (eg, Cushing's disease, hypoadrenalism, hypothyroidism), blood dyscrasias, or T-cell defects

Candidiasis occurs most commonly in intertriginous areas such as the axillae, groin, and gluteal folds (eg, diaper rash—see Plate 30), in digital web spaces, in the glans penis, and beneath the breasts. Vulvovaginal candidiasis is common in women (see p. 2544). Candidal nail infections and paronychia may develop after improperly done manicures and in kitchen workers and others whose hands are continually exposed to water (see p. 734). In obese people, candidal infections may occur beneath the pannus (abdominal fold). Oropharyngeal candidiasis (see Plate 32) is a common sign of local or systemic immunosuppression.

Chronic mucocutaneous candidiasis typically affects the nails, skin, and oropharynx. Patients have cutaneous anergy to Candida, absent proliferative responses to Candida antigen (but normal proliferative responses to mitogens), and an intact antibody response to Candida and other antigens. Chronic mucocutaneous candidiasis may occur as an autosomal recessive illness associated with
hypoparathyroidism and Addison's disease (Candida-endocrinopathy syndrome).

Symptoms and Signs

Intertriginous infections manifest as pruritic, well-demarcated, erythematous patches of varying size and shape; erythema may be difficult to detect in darker-skinned patients. Primary patches may have adjacent satellite papules and pustules. Perianal candidiasis produces white maceration and pruritus ani. Vulvovaginal candidiasis causes pruritus and discharge (see p. 2544).

Candidal infection is a frequent cause of chronic paronychia, which manifests as painful red periungual swelling. Subungual infections are characterized by distal separation of one or several fingernails (onycholysis), with white or yellow discoloration of the subungual area (see p. 735).

Oropharyngeal candidiasis causes white plaques on oral mucous membranes that may bleed when scraped.

Perleche is candidiasis at the corners of the mouth, which causes cracks and tiny fissures. It may stem from chronic lip licking, thumb sucking, ill-fitting dentures, or other conditions that make the corners of the mouth moist enough that yeast can grow.

Chronic mucocutaneous candidiasis is characterized by red, pustular, crusted, and thickened plaques resembling psoriasis, especially on the nose and forehead, and is invariably associated with chronic oral candidiasis.

Diagnosis

• Clinical appearance

• Potassium hydroxide wet mounts

Diagnosis is based on clinical appearance and identification of yeast and pseudohyphae in potassium hydroxide wet mounts of scrapings from a lesion. Positive culture is usually meaningless because Candida is omnipresent.

Treatment

• Sometimes drying agents

• Topical or oral antifungals

Intertriginous infection is treated with drying agents as needed (eg, Burow's solution for oozing lesions, gentian violet for toe web spaces) and topical antifungals (see Table 82-1). Powdered formulations are ideal for dry lesions (eg, miconazole powder bid for 2 to 3 wk). Fluconazole 150 mg po once/wk for 2 to 4 wk is indicated for extensive intertriginous candidiasis; topical antifungal agents may be used at the same time.

Candidal diaper rash is treated with more frequent change of diapers, avoidance of disposable diapers with plastic coverings, and an imidazole cream bid. Oral nystatin is an option for infants with coexisting oropharyngeal candidiasis; 1 mL of suspension (100,000 units/mL) is placed in each buccal pouch qid.

Candidal paronychia is treated by protecting the area from wetness and giving topical or oral antifungals. These infections are often resistant to treatment.

Oral candidiasis is treated with fluconazole 200 mg po on the first day, then 100 mg po once/day for 2 to 3 wk thereafter.

Chronic mucocutaneous candidiasis requires long-term oral antifungal treatment with ketoconazole 400 mg once/day or itraconazole 200 mg once/day.
Dermatophytoses

Dermatophytoses are fungal infections of keratin in the skin and nails (nail infection is called tinea unguium—see p. 734). Symptoms and signs vary by site of infection. Diagnosis is by clinical appearance and by examination of skin scrapings on potassium hydroxide wet mount. Treatment varies by site but always involves topical or oral antifungal drugs.

Dermatophytes are molds that require keratin for nutrition and must live on stratum corneum, hair, or nails to survive. Human infections are caused by *Epidermophyton*, *Microsporum*, and *Trichophyton* spp. These infections differ from candidiasis in that they are rarely if ever invasive. Transmission is person-to-person, animal-to-person, and rarely, soil-to-person. The organism may persist indefinitely. Most people do not develop clinical infection; those who do may have impaired T-cell responses from an alteration in local defenses (eg, from trauma with vascular compromise) or from primary (hereditary) or secondary (eg, diabetes, HIV) immunosuppression.

Symptoms and Signs

Symptoms and signs vary by site (skin, hair, nails). Organism virulence and host susceptibility and hypersensitivity determine severity. Most often, there is little or no inflammation; asymptomatic or mildly itching lesions with a scaling, slightly raised border remit and recur intermittently. Occasionally, inflammation is more severe and manifests as sudden vesicular or bullous disease (usually of the foot) or as an inflamed boggy lesion of the scalp (kerion).

Diagnosis

• Clinical appearance

• Potassium hydroxide wet mount

Diagnosis is based on clinical appearance and site of infection and confirmed by skin scrapings and demonstration of hyphae on potassium hydroxide (KOH) wet mount. Identification of specific organisms by culture is unnecessary except for scalp infection (where an animal source may be identified and treated) and nail infection (which may be caused by a nondermatophyte). Culture may also be useful when overlying inflammation and bacterial infection are severe and/or accompanied by alopecia.

Differential diagnosis includes

• Folliculitis decalvans

• Bacterial pyodermas

• Entities that cause scarring alopecia, such as discoid lupus, lichen planopilaris, and pseudopelade

Treatment

• Topical or oral antifungals

• Sometimes corticosteroids

Topical antifungals are generally adequate (see Table 82-1). In general, OTC terbinafine is best; econazole or ciclopirox may be better if candidal infection cannot be excluded. Oral antifungals are used for most nail and scalp infections, resistant skin infections, and patients unwilling or unable to adhere to prolonged topical regimens; doses and duration differ by site of infection.

Corticosteroid creams can be used to help relieve itching and pain for the first few days. Low-dose
hydrocortisone can be applied separately, or more potent corticosteroids may be added to the antifungal
cream. Oral corticosteroids are occasionally used for treatment of severe inflammatory lesions.

**Tinea Barbae**

(Barber's Itch)

*Tinea barbae* is a dermatophyte infection of the beard area most often caused by *Trichophyton mentagrophytes* or *T. verrucosum*.

*Tinea barbae* manifests as superficial annular lesions, but deeper infection similar to folliculitis may occur. It may also occur as an inflammatory kerion that can result in scarring hair loss. Diagnosis is by KOH wet mount, culture, or biopsy.

Treatment is micronized griseofulvin 500 mg to 1 g po once/day until 2 to 3 wk after clinical clearance. Terbinafine 250 mg po once/day and itraconazole 200 mg po once/day have also been used. If the lesions are severely inflamed, a short course of prednisone should be added (to lessen symptoms and perhaps reduce the chance of scarring), starting with 40 mg po once/day (for adults) and tapering the dose over 2 wk.

**Tinea Capitis**

(Scalp Ringworm)

*Tinea capitis* is a dermatophyte infection of the scalp.

*Tinea capitis* mainly affects children, is contagious, and can be epidemic. *T. tonsurans* is the most common cause in the US, followed by *Microsporum canis* and *M. audouini*; other *Trichophyton* sp (eg, *T. schoenleinii*, *T. violaceum*) are common elsewhere.

*Tinea capitis* causes the gradual appearance of round patches of dry scale, alopecia, or both. *T. tonsurans* infection causes "black dot ringworm," in which hair shafts break at the scalp surface; *M. audouinii* infection causes "gray patch ringworm," in which hair shafts break above the surface, leaving short stubs. *Tinea capitis* less commonly manifests as diffuse scaling, like dandruff, or in a diffuse pustular pattern.

**Kerion:** Dermatophyte infection occasionally leads to formation of a kerion, which is a large, boggy, inflammatory scalp mass (see Plate 48) caused by a severe inflammatory reaction to the dermatophyte. A kerion may have pustules and crusting and can be mistaken for an abscess. A kerion may result in scarring hair loss.

**Diagnosis**

- Clinical appearance
- KOH wet mount
- Sometimes Wood's light examination

*Tinea capitis* is diagnosed by clinical appearance and by KOH wet mount of plucked hairs or of hairs and scale obtained by scraping or brushing. Spore size and appearance inside (endothrix) or outside (ectothrix) the hair shaft distinguish organisms and can help guide treatment. Blue-green fluorescence during Wood's light examination is diagnostic for infection with *M. canis* and *M. audouini* and can distinguish tinea from erythrasma.

Differential diagnosis of *tinea capitis* includes

- Seborrheic dermatitis
Psoriasis

Treatment

• Oral antifungals
• Selenium sulfide shampoo
• Sometimes prednisone

Children are treated with micronized griseofulvin suspension 10 to 20 mg/kg po once/day (doses vary by several parameters, but maximum dose is generally 1 g/day) or, if > 2 yr, with ultramicronized griseofulvin 5 to 10 mg/kg (maximum 750 mg/day) po once/day or in 2 divided doses with meals or milk for 4 to 6 wk or until all signs of infection are gone. Terbinafine also may be used; children < 20 kg are given 62.5 mg once/day; those 20 to 40 kg, 125 mg once/day, and those > 40 kg, 250 mg once/day. An imidazole or ciclopirox cream should be applied to the scalp to prevent spread, especially to other children, until tinea capitis is cured; selenium sulfide 2.5% shampoo should also be used at least twice/wk. Children may attend school during treatment.

Adults are treated with terbinafine 250 mg po once/day for 2 to 4 wk, which is more effective for endothrix infections, or itraconazole 200 mg once/day for 2 to 4 wk or 200 mg bid given for 1 wk, followed by 3 wk without the drug (pulsed) for 2 to 3 mo.

For severely inflamed lesions and for kerion, a short course of prednisone should be added (to lessen symptoms and perhaps reduce the chance of scarring), starting with 40 mg po once/day (1 mg/kg for children) and tapering the dose over 2 wk.

Tinea Corporis

(Body Ringworm)

Tinea corporis is a dermatophyte infection of the face, trunk, and extremities.

Common causes are *T. mentagrophytes*, *T. rubrum*, and *M. canis*.

Tinea corporis causes pink-to-red annular patches and plaques with raised scaly borders that expand peripherally and tend to clear centrally (see Plate 49). A variant form appears as nummular scaling patches studded with small papules or pustules.

Diagnosis

• Clinical evaluation

Differential diagnosis includes

• Pityriasis rosea
• Drug eruptions
• Nummular dermatitis
• Erythema multiforme
• Tinea versicolor
• Erythrasma
Psoriasis

Secondary syphilis

Treatment

Topical or oral antifungals

Treatment of mild-to-moderate lesions is an imidazole, ciclopirox, naftifine, or terbinafine in cream, lotion, or gel. The drug should be rubbed in bid continuing at least 7 to 10 days after lesions disappear, typically at about 2 to 3 wk.

Extensive and resistant lesions occur in patients infected with *T. rubrum* and in people with debilitating systemic diseases. For such cases, the most effective therapy is oral itraconazole 200 mg once/day or terbinafine 250 mg once/day for 2 to 3 wk.

Tinea Cruris

(Jock Itch)

*Tinea cruris* is a dermatophyte infection of the groin.

Common organisms include *T. rubrum* or *T. mentagrophytes*. The primary risk factors are associated with a moist environment (ie, warm weather, wet and restrictive clothing, obesity causing constant apposition of skin folds). Men are affected more than women because of apposition of the scrotum and thigh.

Typically, a pruritic, ringed lesion extends from the crural fold over the adjacent upper inner thigh (see Plate 50). Infection may be bilateral. Lesions may be complicated by maceration, miliaria, secondary bacterial or candidal infection, and reactions to treatment. In addition, scratch dermatitis and lichenification can occur. Recurrence is common because fungi may repeatedly infect susceptible people. Flare-ups occur more often during summer.

Diagnosis

Clinical evaluation

Differential diagnosis includes

- Contact dermatitis
- Psoriasis
- Erythrasma
- Candidiasis

Scrotal involvement is usually absent or slight; by contrast, the scrotum is often inflamed in candidal intertrigo or lichen simplex chronicus.

Treatment

Topical antifungal cream or lotion

Antifungal choices include terbinafine, miconazole, clotrimazole, ketoconazole, econazole, naftifine, and ciclopirox applied bid for 10 to 14 days. Itraconazole 200 mg po once/day or terbinafine 250 mg po once/day for 3 to 6 wk may be needed in patients who have refractory, inflammatory, or widespread infections.
Tinea Pedis

(Athlete’s Foot)

Tinea pedis is a dermatophyte infection of the feet.

Tinea pedis is the most common dermatophytosis because moisture from foot sweating facilitates fungal growth. Tinea pedis may occur as any of 4 clinical forms or in combination:

• Chronic hyperkeratotic
• Chronic intertriginous
• Acute ulcerative
• Vesiculobullous

Chronic hyperkeratotic tinea pedis due to *T. rubrum* causes a distinctive pattern of lesion, manifesting as scaling and thickening of the soles, which often extends beyond the plantar surface in a moccasin distribution. Differential diagnosis is sterile maceration (due to hyperhidrosis and occlusive footgear), contact dermatitis (due to type IV delayed hypersensitivity to various materials in shoes, particularly adhesive cement, thiuram compounds in footwear that contains rubber, and chromate tanning agents used in leather footwear), irritant dermatitis, and psoriasis.

Chronic intertriginous tinea pedis is characterized by scaling, erythema, and erosion of the interdigital and subdigital skin of the feet, most commonly affecting the lateral 3 toes.

Acute ulcerative tinea pedis (most often caused by *T. mentagrophytes var. interdigitale*) typically begins in the 3rd and 4th interdigital spaces and extends to the lateral dorsum and/or the plantar surface of the arch. These toe web lesions are usually macerated and have scaling borders (see Plate 51). Secondary bacterial infection, cellulitis, and lymphangitis are common complications.

Vesiculobullous tinea pedis, in which vesicles develop on the soles and coalesce into bullae, is the less common result of a flare of interdigital tinea pedis; risk factors are occlusive shoes and environmental heat and humidity.

Diagnosis

Diagnosis is usually obvious based on clinical examination and review of risk factors.

Treatment

• Moisture reduction and drying agents
• Topical and oral antifungals

The safest treatment is topical antifungals, but recurrence is common and treatment must often be prolonged. Alternatives that provide a more durable response include itraconazole 200 mg po once/day for 1 mo (or pulse therapy with 200 mg bid 1 wk/mo for 1 to 2 mo) and terbinafine 250 mg po once/day for 2 to 6 wk. Concomitant topical antifungal use may reduce recurrences.

Moisture reduction on the feet and in footwear is necessary for preventing recurrence. Permeable or open-toe footwear and sock changes are important especially during warm weather. Interdigital spaces should be manually dried after bathing. Drying agents are also recommended; options include antifungal powders (eg, miconazole), gentian violet, Burow’s solution (5% aluminum sub-acetate) soaks bid, and 20 to 25% aluminum chloride hexahydrate powder once/day.

Dermatophytid Reaction
Dermatophytid is an inflammatory reaction to dermatophytosis at a cutaneous site distant from the primary infection.

Dermatophytid (identity or id) reactions are protean; they are not related to localized growth of the fungus but rather are an inflammatory reaction elsewhere on the body. Lesions are typically pruritic but may manifest as

- Vesicular eruptions on the hands and feet
- Follicular papules
- Erysipelas-like plaques
- Erythema nodosum
- Erythema annulare centrifugum
- Urticaria

Distribution may be extensive.

Diagnosis is by KOH wet mounts that are negative at the site of the id reaction and positive at the distant site of dermatophyte infection.

Treatment of the primary infection cures dermatophytid; pending cure, topical corticosteroids and/or antipruritics (eg, hydroxyzine 25 mg qid) can be used to relieve symptoms.

**Intertrigo**

Intertrigo is skinfold changes caused by moisture and infection.

Intertrigo develops when friction and trapped moisture in intertriginous areas cause skin maceration with formation of patches or plaques; bacterial, yeast, and dermatophyte infection is common. Typical locations are the inframammary, infrapannicular, interdigital, axillary, infragluteal, and genitocrural folds.

Diagnosis is based on clinical appearance; potassium hydroxide wet mounts and cultures can guide treatment.

If no bacteria or yeast are detected, drying agents (powders such as talc rather than cornstarch, which can support fungal growth, Burow's solution) to decrease moisture should be therapeutic. If bacteria or yeasts are present, topical antibacterial lotions or antifungal creams are given in addition to drying agents.

**Tinea Versicolor**

(Pityriasis Versicolor)

Tinea versicolor is skin infection with *Malassezia furfur* that manifests as multiple asymptomatic scaly patches varying in color from white to brown. Diagnosis is based on clinical appearance and skin scrapings. Treatment is topical antifungals.

*Malassezia furfur* is a dimorphic fungus that is normally a harmless component of normal skin flora but that in some people causes tinea versicolor. The high prevalence of tinea versi-color in young adults suggests a link to increased sebaceous secretions; other risk factors include heat and humidity and immunosuppression due to corticosteroids, pregnancy, undernutrition, diabetes, and other disorders.
Tinea versicolor usually is asymptomatic. Classically, it causes the appearance of multiple tan, brown, salmon, or white scaling lesions (see Plate 52) on the trunk, neck, abdomen, and occasionally face. The lesions coalesce. In whites, the condition is often diagnosed in summer months because the lesions, which do not tan, become more obvious against tanned skin.

Diagnosis

• Clinical appearance

• Potassium hydroxide wet mount

• Sometimes Wood's light examination

Diagnosis is based on clinical appearance and by identification of hyphae and budding cells ("spaghetti and meatballs") on potassium hydroxide wet mount. Wood's light examination reveals golden-white fluorescence.

Treatment

• Topical antifungals

• Sometimes oral antifungals

Treatment is any topical antifungal drug. Examples include selenium sulfide shampoo 2.5% (in 10-min applications daily for 1 wk or 24-h applications weekly for 1 mo); topical azoles (eg, ketoconazole 2% daily for 2 wk); and bathing with zinc pyrithione soap 2% or sulfur-salicylic shampoo 2% for 1 to 2 wk.

Oral treatment is indicated for patients with extensive disease and those with frequent recurrences. Two convenient regimens are a single 400-mg dose of fluconazole and ketoconazole 200 mg once/day for 1 to 5 days.

Hypopigmentation from tinea versicolor is reversible in months to years after the yeast has cleared. Recurrence is almost universal after treatment because the causative organism is a normal skin inhabitant. Fastidious hygiene, regular use of zinc pyrithione soap, or once-monthly use of topical antifungal therapy lowers the likelihood of recurrence.
Parasitic skin infections can cause severe itching and be distressing. Most skin parasites are insects or worms that burrow into the skin for part or all of their life cycle. Also, some systemic parasitic infections have cutaneous manifestations; these include certain nematodes (ancylostomiasis, dracunculosis, strongyloidiasis, toxocariasis—see p. 1342) and flukes (schistosomiasis—see p. 1358). Very rarely, patients have delusional parasitosis.

Cutaneous Larva Migrans (Creeping Eruption)

Cutaneous larva migrans (CLM) is the skin manifestation of hookworm infestation. CLM is caused by Ancylostoma sp, most commonly dog or cat hookworm Ancylostoma braziliense. Hookworm ova in dog or cat feces develop into infective larvae when left in warm moist ground or sand; transmission occurs when skin directly contacts contaminated soil or sand and larvae penetrate unprotected skin, usually of the feet, legs, buttocks, or back. CLM occurs worldwide but most commonly in tropical environments.

CLM causes intense pruritus; signs are erythema and papules at the site of entry, with a winding, threadlike subcutaneous trail of reddish-brown inflammation. Diagnosis is by history and clinical appearance.

Topical thiabendazole 15% liquid or cream (compounded) bid to tid for 5 days is extremely effective. Oral thiabendazole is not well tolerated and not usually used. Albendazole (400 mg po once/day for 7 days) and ivermectin can cure the infestation and are well tolerated.

CLM may be complicated by a self-limiting pulmonary reaction called Loffler's syndrome (patchy pulmonary infiltrates and peripheral blood eosinophilia).

Cutaneous Myiasis

Cutaneous myiasis is skin infestation by the larvae of certain fly species.

Myiasis involves the larvae of two-winged (dipterous) flies. Three types of cutaneous infestation exist, depending on the species involved:

- Furuncular
- Wound
- Migratory

Other organs sometimes are involved (eg, nasopharynx, GI tract, GU tract). Infestation usually occurs in tropical countries, so most cases in the US occur in people who have recently arrived from endemic areas.

Furuncular myiasis: Many of the common sources are known as bot flies. Dermatobia hominis, native to South and Central America, is the most common cause in travelers returning to the US. Other species include Cordylobia anthropophaga (in sub-Saharan Africa), and various Cuterebra sp (in tropical Africa). Many of the flies do not lay their eggs on humans but on other insects (eg, mosquitoes) or objects (eg, drying laundry) that may contact skin. Eggs on the skin hatch into larvae, which burrow into the skin and develop through successive stages (instars) into mature larvae; mature larvae may be 1 to 2 cm long, depending on the species. If the infestation is untreated, larvae eventually emerge from the skin and drop...
to the ground to continue their life cycle.

Typical symptoms include itching, a sensation of movement, and sometimes lancinating pain. The initial lesion may resemble an arthropod bite or bacterial furuncle but may be distinguished by the presence of a central punctum with serosanguineous drainage; sometimes a small portion of the end of the larva is visible.

Because larvae require atmospheric O$_2$, occlusion of the skin opening may cause them to depart or at least come closer to the surface, facilitating manual removal. The numerous occlusal methods include use of petrolatum, nail polish, bacon, or a paste of tobacco. However, larvae that die during occlusion are difficult to remove and often trigger an intense inflammatory reaction. Other options for removal include manual expression (ie, squeezing) and extraction through a small incision. Ivermectin, oral (200 μg/kg, one dose) or topical, may kill the larvae or induce migration.

**Wound myiasis:** Open wounds, typically in the homeless, alcoholics, and other people in poor social circumstances, may be infested by fly larvae, most often from green or black blowflies. Unlike larvae of common houseflies, most agents of wound myiasis invade healthy as well as necrotic tissue. Treatment is usually with irrigation and manual debridement.

**Migratory myiasis:** The most common agents are *Gasterophilus intestinalis* and *Hypoderma* sp. These flies typically infest horses and cattle; people acquire them via contact with infested animals or, less often, via direct egg-laying on their skin. Larvae of these agents burrow under the skin, causing pruritic, advancing lesions, which may be mistaken for cutaneous larva migrans; however, fly larvae are much larger than nematodes, and the lesions created by fly larvae last longer. Treatment is similar to that of furuncular myiasis.

**Delusional Parasitosis**

In delusional parasitosis, patients mistakenly believe that they are infested with parasites.

Patients have an unshakable belief that they are infested with insects, worms, mites, lice, or other organisms. They often provide vivid descriptions of how the organisms enter their skin and move around their bodies, and bring samples of hair, skin, and debris such as dried scabs, dust, and lint on slides or in containers (the matchbox sign) to prove that the infestation is real. The condition is considered a hypochondriacal psychosis, but the cause is unknown.

Diagnosis is suspected by history. Work-up requires ruling out true infestations and other physiologic disease by physical examination and judicious testing, such as skin scrapings and CBC.

Treatment is with antipsychotic drugs (see p. 1562). Typically, the patient seeks confirmation that the drug treats the infestation itself, and any suggestion that the treatment is for something else is met with resistance and/or rejection. Thus, effective treatment often requires diplomacy and a delicate balance between offering proper treatment and respecting the patient's right to know.

**Lice**

(Pediculosis)

Lice can infect the scalp, body, pubis, and eyelashes. Head lice are transmitted by close contact; body lice, in cramped, crowded conditions; and pubic lice, by sexual contact.

**Symptoms, signs, diagnosis, and treatment differ by location of infestation.**

Lice are wingless, blood-sucking insects that infest the head (*Pediculus humanus* var. *capitis*), body (*P. humanus* var. *corporis*), or pubis (*Phthirus pubis*). The 3 kinds of lice differ substantially in morphology and clinical features. Head lice and pubic lice live directly on the host; body lice live in garments. All types occur worldwide.

**Head lice:** Head lice are most common in girls aged 5 to 11 but can affect almost anyone; infestations
are rare in blacks. Head lice are easily transmitted from person to person with close contact (as occurs within households and classrooms) and may be ejected from hair by static electricity or wind; transmission by these routes (or by sharing of combs, brushes, and hats) is likely but unproven. There is no association between head lice and poor hygiene or low socioeconomic status.

Infestation typically involves the hair and scalp, but the eyebrows, eyelashes, and beard may be involved as well. Active infection usually involves ≤ 20 lice and causes severe pruritus. Examination is most often normal but may reveal scalp excoriations and posterior cervical adenopathy.

Diagnosis depends on demonstration of living lice. Lice are detected by a thorough combing-through of wet hair from the scalp with a fine-tooth detection comb; lice are usually found at the back of the head or behind the ears. Nits are ovoid, grayish white eggs fixed to the base of hair shafts (see Plate 38). Each adult female louse lays 3 to 5 eggs/day, so nits typically vastly outnumber lice and are not a measure of severity of infestation.

Treatment is outlined in Table 83-1. Drug resistance is common and should be managed with use of oral ivermectin and by attempting to rotate pediculicides. Termination of live (viable) nits is important in preventing reinfestation; live nits fluoresce on illumination with a Wood's lamp. Most pediculicides also kill nits. Dead nits remain after successful treatment and do not signify active infection; they do not have to be removed. Nits grow away from the scalp with time; the absence of nits less than one fourth of an inch from the scalp rules out current active infection. Hot air has been shown to kill > 88% of eggs but has been variably effective in killing hatched lice. Thirty minutes of hot air, slightly cooler than a blow drier, may be an effective adjunctive measure to treat head lice.

Controversy surrounds the need to clean the personal items of people with lice or nits and the need to exclude children with head lice or nits from school; there are no conclusive data supporting either approach.

**Body lice:** Body lice primarily live on bedding and clothing, not people, and are most frequently found in cramped, crowded conditions (eg, military barracks) and in people of low socioeconomic status. Transmission is by sharing of contaminated clothing and bedding. Body lice are important vectors of epidemic typhus, trench fever, and relapsing fever.

Body lice cause pruritus; signs are small red puncta caused by bites, usually associated with linear scratch marks, urticaria, or superficial bacterial infection. These findings are especially common on the shoulders, buttocks, and abdomen. Nits may be present on body hairs.

Diagnosis is by demonstration of lice and nits in clothing, especially at the seams.

Primary treatment is thorough cleaning or replacement of clothing and bedding, which is often difficult because affected people often have few resources and little control over their environment.

**Pubic lice:** Pubic lice ("crabs") are sexually transmitted in adolescents and adults and may be transmitted to children by close parental contact. They may also be transmitted by fomites (towels, bedding, clothing). They most commonly infest pubic and perianal hairs but may spread to thighs, trunk, and facial hair (beard, mustache, and, in children, eyelashes).

Pubic lice cause pruritus. Physical signs are few, but some patients have excoriations and regional lymphadenopathy and/or lymphadenitis. Pale, bluish gray skin macules (maculae caeruleae) on the trunk, buttocks, and thighs are caused by anticoagulant activity of louse saliva while feeding; they are unusual but characteristic of infestation. Eyelash infestation manifests as eye itching, burning, and irritation.

Diagnosis is by demonstration of nits and/or living lice by close inspection (Wood's light) or microscopic analysis. A supporting sign of infestation is scattering of dark brown specks (louse excreta) on skin or undergarments.
Treatment is outlined in Table 83-1. Treatment of eyelid and eyelash infestation is often difficult and involves use of petrolatum, physostigmine ointment, oral ivermectin, or physical removal of lice with forceps. Sex partners should also be treated.

Scabies

Scabies is an infestation of the skin with the mite *Sarcoptes scabiei*. Scabies causes intensely pruritic lesions with erythematous papules and burrows in web spaces, wrists, waistline, and genitals. Diagnosis is based on examination and scrapings. Treatment is with topical scabicides or, rarely, oral ivermectin.

Etiology

Scabies is caused by the mite *Sarcoptes scabiei var. hominis*, an obligate human parasite that lives in burrowed tunnels in the stratum corneum. Scabies is easily transmitted from person to person through physical contact; animal and fomite transmission probably also occurs. The primary risk factor is crowded conditions (as in schools, shelters, barracks, and some households); there is no clear association with poor hygiene. For unknown reasons, crusted scabies is more common in immunosuppressed patients (e.g., those with HIV infection, hematologic cancer, chronic corticosteroid or other immunosuppressant use), patients with severe physical disabilities or intellectual disability, and Australian Aborigines. Infestations occur worldwide. Patients in warm climates develop small erythematous papules with few burrows. Severity is related to the patient's immune status, not geography.

Symptoms and Signs

The primary symptom is intense pruritus, classically worse at night, although that timing is not specific to scabies.

**Classic scabies:** Erythematous papules initially appear in finger web spaces, flexor surfaces of the wrist and elbow, axillary folds, along the belt line, or on the lower buttocks. Papules can spread to any area of the body, including the breasts and penis. The face remains uninvolved in adults. Burrows are pathognomonic for disease, manifesting as fine, wavy, and slightly scaly lines several mm to 1 cm long. A tiny dark papule—the mite—is often visible at one end.

Signs of classic scabies may be atypical. In blacks and other people with dark skin, scabies can manifest as granulomatous nodules. In infants, the palms, soles, face, and scalp may be involved, especially in the posterior auricular folds. In elderly patients, scabies can cause intense pruritus with subtle skin findings, making it a challenge to diagnose. In immunocompromised patients, there may be widespread nonpruritic scaling (particularly on the palms and soles in adults and on the scalp in children).

**Other forms:** Crusted (Norwegian) scabies is due to an impaired host immune response, allowing mites to proliferate and number in the millions. Nodular scabies is more common in infants and young children and may be due to hypersensitivity to retained organisms. Bullous scabies occurs more commonly in children. When it occurs in the elderly, it can mimic bullous pemphigoid, resulting in a delay in diagnosis. Scalp scabies occurs in infants and immunocompromised people and can mimic dermatitis, particularly atopic or seborrheic dermatitis. Scabies incognito is a widespread atypical form resulting from application of topical corticosteroids.

**Diagnosis**

- Clinical evaluation
- Burrow scrapings

Diagnosis is suspected by physical findings, especially burrows, and confirmed by mites, ova, or fecal pellets on microscopic examination of burrow scrapings. Scrapings should be obtained by placing glycerol, mineral oil, or immersion oil over a burrow or papule (to prevent dispersion of mites and material...
during scraping), which is then unroofed with the edge of a scalpel. The material is then placed on a slide and covered with a coverslip; potassium hydroxide should be avoided because it dissolves fecal pellets.

**Treatment**

- Topical permethrin or lindane

- Sometimes oral ivermectin

Primary treatment is topical or oral scabicides (see Table 83-1). Permethrin is the 1st-line topical drug.

Older children and adults should apply permethrin or lindane to the entire body from the neck down and wash it off after 8 to 14 h. Treatments should be repeated in 7 days.

For infants and young children, permethrin should be applied to the head and neck, avoiding periorbital and perioral regions. Special attention should be given to intertriginous areas, fingernails, toenails, and the umbilicus. Mittens on infants can keep permethrin out of the mouth. Lindane is not recommended in children < 2 yr and in patients with a seizure disorder because of potential neurotoxicity.

Precipitated sulfur 6 to 10% in petrolatum, applied for 24 h for 3 consecutive days, is safe and effective.

Ivermectin is indicated for patients who do not respond to topical treatment, are unable to adhere to topical regimens, or are immunocompromised with Norwegian scabies. Ivermectin has been used with success in epidemics involving close contacts, such as nursing homes.

Close contacts should also be treated, and personal items (eg, towels, clothing, bedding) should be washed or isolated for at least 3 days.

Pruritus can be treated with corticosteroid ointments and/or oral antihistamines (eg, hydroxyzine 25 mg po qid). Secondary infection should be considered in patients with weeping, yellow-crusted lesions and treated with the appropriate systemic or topical antistaphylococcal or antistreptococcal antibiotic.

Symptoms and lesions take up to 3 wk to resolve despite killing of the mites, making failed treatment due to resistance, poor penetration, incompletely applied therapy, reinfection, or nodular scabies difficult to recognize. Skin scrapings can be done periodically to check for persistent scabies.
Chapter 84. Viral Skin Diseases

Introduction

Many systemic viral infections cause skin lesions. Molluscum contagiosum and warts are the 2 most common primary viral skin diseases without systemic manifestations. Herpes simplex virus infection is discussed on p. 1417.

Molluscum Contagiosum

Molluscum contagiosum is clusters of smooth, waxy, or pearly umbilicated papules 1 to 5 mm in diameter caused by molluscum contagiosum virus, a poxvirus.

Molluscum contagiosum virus commonly causes a localized chronic infection. Transmission is by direct contact; spread occurs by autoinoculation and via fomites (eg, towels, bath sponges).

Symptoms and Signs

Molluscum contagiosum can appear anywhere on the skin except the palms and soles. Lesions consist of clusters of flesh-colored papules, which occur most commonly on the face, trunk, and extremities in children and on the pubis, penis, or vulva in adults. Lesions may grow to 10 to 15 mm in diameter, especially among patients with HIV infection and other immunocompromised patients. Lesions are usually not pruritic or painful and may be discovered only coincidentally during a physical examination. However, the lesions can become inflamed and itchy as the body fights off the virus.

Diagnosis

• Clinical evaluation

Diagnosis is based on clinical appearance; hematoxylin and eosin staining of expressed fluid demonstrates inclusion bodies but is necessary only when diagnosis is uncertain. Differential diagnosis includes folliculitis, milia, and warts (for lesions < 2 mm) and juvenile xanthogranuloma and Spitz nevus (for lesions > 2 mm).

Treatment

• Curettage, cryosurgery, laser therapy, or electrocautery

• Topical irritants (eg, trichloroacetic acid, cantharidin, tretinoin, tazarotene), imiquimod, or both

• Sometimes combination therapies

Most lesions spontaneously regress in 1 to 2 yr, but they can remain for 2 to 3 yr. Treatment is indicated for cosmetic reasons or for prevention of sexual spread. Options include curettage, cryosurgery, laser therapy, electrocautery, trichloroacetic acid (25 to 40% solution), cantharidin, tretinoin, tazarotene and imiquimod 5% cream. Especially in children, treatments that cause minimal pain (eg, tretinoin, imiquimod, tazarotene, cantharidin) are used first. Curettage or liquid nitrogen can be used after application of a topical anesthetic such as EMLA (eutectic mixture of local anesthetics) or 4% lidocaine cream. EMLA cream must be applied judiciously because it can cause systemic toxicity, especially in children. In adults, curettage is very effective but painful. Dermatologists often use combination therapy such as liquid nitrogen or cantharidin in the office and imiquimod cream at home. This form of therapy is typically successful, but resolution often takes 1 to 2 mo in some patients.

Nondermatologists should feel comfortable using imiquimod cream. The cream is applied at night, 1 drop to each molluscum lesion and rubbed in well, until the cream turns clear. The area is washed with soap and water. The cream can be applied 3 to 7 times/wk. Molluscum lesions within the orbital rim should not be treated, and those in the genital region can easily become irritated. Lesions should be treated until they develop a scant amount of redness; treatment is then withheld to avoid weeping and crusting.
Cantharidin is safe and effective but can cause blistering. Cantharidin is applied in 1 small drop directly to the molluscum lesion. Areas that patients (especially children) may rub are covered with a bandage because contact with the fingers should be avoided. Cantharidin should not be applied to the face or near the eyes because blistering is unpredictable. If cantharidin comes into contact with the cornea, it can scar the cornea. Cantharidin should be washed off with soap and water in 6 h. Parents should be warned about blistering if their children are prescribed this drug.

**Warts**

*(Verrucae Vulgaris)*

**Warts are common, benign epidermal lesions caused by human papillomavirus infection. They can appear anywhere on the body in a variety of morphologies. Diagnosis is by examination. Warts are usually self limited but may be treated by excision, cautery, cryotherapy, liquid nitrogen, and topical or injected agents.**

Warts are almost universal in the population; they affect all ages but are most common among children and are uncommon among the elderly.

**Etiology**

Warts are caused by human papillomavirus (HPV) infection; there are over 100 HPV subtypes. Trauma and maceration facilitate initial epidermal inoculation. Spread may then occur by autoinoculation. Local and systemic immune factors appear to influence spread; immunosuppressed patients (especially those with HIV infection or a renal transplant) are at particular risk of developing generalized lesions that are difficult to treat. Humoral immunity provides resistance to HPV infection; cellular immunity helps established infection to regress.

**Symptoms and Signs**

Warts are named by their clinical appearance and location; different forms are linked to different HPV types (for unusual manifestations, see Table 84-1).

**Common warts:** Common warts (verrucae vulgaris) are caused by HPV 1, 2, 4, 27, and 29. They are usually asymptomatic but sometimes cause mild pain, especially when they are located on a weight-bearing surface (eg, bottom of the feet). They are sharply demarcated, rough, round or irregular, firm, and light gray, yellow, brown, or gray-black nodules 2 to 10 mm in diameter. They appear most often on sites subject to trauma (eg, fingers, elbows, knees, face) but may spread elsewhere. Variants of unusual shape (eg, pedunculated or resembling a cauliflower) appear most frequently on the head and neck, especially the scalp and beard area.

**Filiform warts:** These warts are long, narrow, frondlike growths, usually located on the eyelids, face, neck, or lips. They are usually asymptomatic. This morphologically distinct variant of the common wart is benign and easy to treat.

**Flat warts:** Flat warts, caused by HPV 3, 10, 28, and 49, are smooth, flat-topped, yellow-brown papules, most often located on the face and along scratch marks; they are more common among children and young adults and develop by autoinoculation. They generally cause no symptoms but can be difficult to treat.

**Palmar and plantar warts:** These warts, caused by HPV 1, occur on the palms and soles; they are flattened by pressure and surrounded by cornified epithelium (see Plate 55). They are

[Table 84-1. Wart Variants]
often tender and can make walking and standing uncomfortable. They can be distinguished from corns and calluses by their tendency to pinpoint bleeding when the surface is pared away. Classically, warts hurt with side-to-side pressure, and calluses hurt with direct pressure; in reality, this is not a reliable sign.

**Mosaic warts:** Mosaic warts are plaques formed by the coalescence of myriad smaller, closely set plantar warts. As with other plantar warts, they are often tender.

**Periungual warts:** These warts appear as thickened, fissured cauliflower-like skin around the nail plate. Patients frequently lose the cuticle and are susceptible to paronychia. Periungual warts are more common among patients who bite their nails.

**Genital warts:** Genital warts (see p. 1470) manifest as discrete flat to broad-based smooth to velvety papules on the perineal, perirectal, labial, and penile areas. Infection with high-risk HPV types (most notably types 16 and 18) is the main cause of cervical cancer. These warts are usually asymptomatic.

### Diagnosis

- **Clinical evaluation**
- **Rarely biopsy**

Diagnosis is based on clinical appearance; biopsy is rarely needed. A cardinal sign of warts is the absence of skin lines crossing their surface and the presence of pinpoint black dots (thrombosed capillaries) or bleeding when warts are shaved. Differential diagnosis includes corns (clavi), lichen planus, seborrheic keratosis, skin tags, and squamous cell carcinomas. DNA typing is available in some medical centers but is generally not needed.

### Prognosis

Many warts regress spontaneously; others persist for years and recur at the same or different sites, even with treatment. Factors influencing recurrence appear to be related to the patient's overall immune status as well as local factors. Patients who subject themselves to local trauma (eg, athletes, mechanics, butchers) may have recalcitrant and recurrent HPV infection. Genital HPV infection has malignant potential, but malignant transformation is rare in HPV-induced skin warts, except among immunosuppressed patients.

### Treatment

- **Topical irritants (eg, salicylic acid, cantharidin, podophyllum resin)**
- **Destructive methods (eg, cryosurgery, electrocautery, curettage, excision, laser)**

Treatment is aimed at eliciting an immune response to HPV. In most instances, this response is achieved by applying an irritant (eg, salicylic acid [SCA], trichloroacetic acid, 5-fluorouracil, podophyllum resin, tretinoin, cantharidin).

These compounds can be used in combination or with a destructive method (eg, cryosurgery, electrocautery, curettage, excision, laser). Direct antiviral effects can be achieved with bleomycin and interferon alfa-2b, but these treatments are reserved for the most recalcitrant warts. Topical imiquimod 5% cream induces skin cells to locally produce antiviral cytokines. Topical cidofovir, HPV vaccines, and contact immunotherapy (eg, squaric acid dibutyl ester and *Candida* allergen) have been used to treat warts. Oral treatments include cimetidine, isotretinoin, and oral zinc. In most instances, modalities should be combined to increase the likelihood of success.

**Common warts:** In immunocompetent patients, common warts usually spontaneously regress within 2 to 4 yr, but some linger for many years. Numerous treatments are available. Destructive methods include

- **Electrocautery**
• Cryosurgery with liquid nitrogen

• SCA preparations

Which method is used depends on the location and severity of involvement. For example, 17% liquid SCA can be used on the fingers, and 40% plaster SCA can be used on the soles.

The most common topical agent to be used is SCA. SCA is available in a liquid, plaster, or impregnated within tape. Patients apply SCA to their warts at night and leave on for 8 to 48 h depending on the site.

Cantharidin can be used alone or in combination (1%) with SCA (30%) and podophyllum (5%) in a collodion base. Cantharidin alone is removed with soap and water after 6 h; cantharidin with SCA or podophyllum is removed in 2 h. The longer these agents are left in contact with the skin, the more brisk the blistering response.

Cryosurgery is painful but extremely effective. Electrodesiccation with curettage, laser surgery, or both is effective and indicated for isolated lesions but may cause scarring. Recurrent or new warts occur in about 35% of patients within 1 yr, so methods that scar should be avoided as much as possible.

Filiform warts: Treatment is removal with scalpel, scissors, curettage, or liquid nitrogen. Liquid nitrogen should be applied so that up to 2 mm of skin surrounding the wart turns white. Damage to the skin occurs when the skin thaws, which usually takes 10 to 20 sec. Blisters can occur 24 to 48 h after treatment with liquid nitrogen. Care must be taken when treating cosmetically sensitive sites, such as the face and neck, because hypopigmentation frequently occurs after treatment with liquid nitrogen. Patients with darkly pigmented skin can develop permanent depigmentation.

Flat warts: Treatment is daily tretinoin (retinoic acid 0.05% cream). If peeling is not sufficient for wart removal, another irritant (eg, 5% benzoyl peroxide) or 5% SCA cream can be applied sequentially with tretinoin. Imiquimod 5% cream can be used alone or in combination with topical drugs or destructive measures. Topical 5-fluorouracil (1% or 5% cream) can also be used. Spontaneous resolution may follow unprovoked inflammation of the lesions; however, flat warts are frequently recalcitrant to treatment.

Plantar warts: Treatment is vigorous maceration with 40% SCA plaster kept in place for several days. The wart is debrided while damp and soft, then destroyed by freezing or using caustics (eg, 30 to 70% trichloroacetic acid). Other destructive treatments (eg, CO₂ laser, pulsed-dye laser, various acids) are often effective. Duct tape is effective when applied for 6-day intervals, followed by debridement of macerated tissue.

Periungual warts: Combination therapy with liquid nitrogen and imiquimod 5% cream, tretinoin, or SCA is effective.

Recalcitrant warts: Several methods whose long-term value and risks are not fully known are available for recalcitrant warts. Intralesional injection of small amounts of a 0.1% solution of bleomycin in saline often cures stubborn plantar and periungual warts. However, Raynaud's syndrome or vascular damage may develop in injected digits, especially when the drug is injected at the base of the digit, so caution is warranted. Interferon, especially interferon alfa, administered intralesionally (3 times/wk for 3 to 5 wk) or IM, has also cleared recalcitrant skin and genital warts. Extensive warts sometimes improve or clear with oral isotretinoin or acitretin. Cimetidine at doses up to 800 mg po tid has been used with success but is more effective when combined with another therapy.

Zoonotic Diseases

Two viral skin diseases are rarely transmitted from animals to humans.

Contagious ecthyma: Contagious ecthyma (contagious pustular dermatitis) is caused by orf virus, a poxvirus that infects ruminants (most often sheep and goats). Farmers, veterinarians, zoo caretakers, and others with direct animal contact are at risk. The cutaneous findings pass through 6 stages that together
last about 1 wk:

- Stage 1 (papular): A single red edematous papule on a finger (most commonly right index finder)
- Stage 2 (target): A larger nodule with a red center surrounded by a white ring with a red periphery
- Stage 3 (acute): A rapidly growing infected-looking tumor
- Stage 4 (regenerative): A nodule with black dots covered with a thin transparent crust
- Stage 5 (papillomatous): A nodule with a surface studded with small projections
- Stage 6 (regressive): A flattened nodule with a thick crust

Patients can develop regional adenopathy, lymphangitis, and fever.

Diagnosis is by history of contact; differential diagnosis is extensive depending upon the stage of the lesion. Acute lesions must be differentiated from milker's nodules, *Mycobacterium marinum* infection, and other bacterial infections; regressed lesions must be differentiated from cutaneous tumors, such as Bowen's disease or squamous cell carcinoma. Lesions spontaneously heal; no treatment is necessary.

**Milker's nodules**: These nodules are caused by paravaccinia virus, a parapoxvirus that causes udder lesions in cows. Infection requires direct contact and produces macules that progress to papules, vesicles, and nodules. This infection has 6 stages, which are similar to those of contagious ecthyma. Fever and lymphadenopathy are uncommon. Diagnosis is by history of contact and cutaneous findings. Differential diagnosis varies depending upon morphology but includes primary inoculation TB, sporotrichosis, anthrax, and tularemia. Lesions heal spontaneously; no treatment is necessary.
Chapter 85. Pigmentation Disorders

Introduction

Pigmentation disorders involve hypopigmentation, depigmentation, or hyperpigmentation. Areas may be focal or diffuse.

Focal hypopigmentation is most commonly a consequence of

- Injury
- Inflammatory dermatoses (eg, atopic dermatitis, psoriasis)
- Burns
- Chemical exposure

Focal hypopigmentation or depigmentation is also a feature of vitiligo (which may involve large areas of skin), leprosy, nutritional deficiencies (kwashiorkor), and genetic conditions (tuberosus sclerosis, piebaldism, Waardenburg’s syndrome).

Diffuse hypopigmentation is most often caused by

- Albinism
- Vitiligo

Focal hyperpigmentation typically occurs after inflammation of various causes, but it also may occur in patients with a systemic disorder or cancer.

Albinism

Albinism (officially called oculocutaneous albinism) is an inherited defect in melanin formation that causes diffuse hypopigmentation of the skin, hair, and eyes; deficiency of melanin (and hence pigmentary dilution) may be total or partial, but all areas of the skin are involved. Ocular involvement causes strabismus, nystagmus, and decreased vision. Diagnosis is usually obvious from the skin, but ocular evaluation is necessary. No treatment for the skin involvement is available other than protection from sunlight.

Pathophysiology

Oculocutaneous albinism (OCA) is a group of rare inherited disorders in which a normal number of melanocytes are present but melanin production is absent or greatly decreased. Cutaneous and ocular pathologies (ocular albinism) are both present. Ocular albinism involves abnormal optic tract CNS development manifested by foveal hypoplasia with decreased photoreceptors and misrouting of optic chiasmal fibers. Ocular albinism may occur without cutaneous abnormalities.

Most cases are autosomal recessive; autosomal dominant inheritance is rare. There are 4 main genetic forms:

- Type I is caused by absent (OCA1A; 40% of all OCA) or reduced (OCA1B) tyrosinase activity; tyrosinase catalyzes several steps in melanin synthesis.
- Type II (50% of all OCA) is caused by mutations in the P (pink-eyed) gene. The function of the P protein is not yet known. Tyrosinase activity is present.
- Type III occurs only in people with dark skin (skin types III to V). It is caused by mutations in a tyrosinase-related protein 1 gene whose product is important in eumelanin synthesis.
Type IV is an extremely rare form in which the genetic defect is in a gene that codes a membrane transporter protein. Type IV is the most common form of OCA in Japan.

In a group of inherited diseases, a clinical phenotype of OCA occurs in conjunction with bleeding disorders. In the Hermansky-Pudlak syndrome, OCA-like findings occur with platelet abnormalities and a ceroid-lipofuscin lysosomal storage disease. This syndrome is rare except in people with family origin in Puerto Rico, where its incidence is 1 in 1800. In the Chediak-Higashi syndrome, OCA-like findings occur (hair is silvery gray), and a decrease in platelet-dense granules results in a bleeding diathesis. Patients have severe immunodeficiency due to abnormal lymphocyte lytic granules. Progressive neurologic degeneration occurs.

**Symptoms and Signs**

The different genetic forms have a variety of phenotypes.

Type I (OCA1A) is classic tyrosinase-negative albinism; skin and hair are milky white, and eyes are blue-gray. Pigmentary dilution in OCA1B ranges from obvious to subtle.

Type II has phenotypes with pigmentary dilution that ranges from minimal to moderate. Pigmented nevi and lentigines may develop if skin is exposed to the sun; some lentigines become large and dark. Eye color varies greatly.

In type III, skin is brown, hair is rufous (reddish), and eye color can be blue or brown.

In type IV, the phenotype is similar to that for type II.

Patients with ocular involvement may have decreased retinal pigmentation (see Plate 25), leading to photophobia. In addition, nystagmus, strabismus, reduced visual acuity, and loss of binocular vision likely result from defective routing of the optic fibers.

**Diagnosis**

- Clinical evaluation

Diagnosis of all types of OCA is based on examination of the skin. Early ocular examination may detect iris translucency, reduced retinal pigmentation, foveal hypoplasia, reduced visual acuity, and ocular movement disorders (strabismus and nystagmus).

**Treatment**

- Sun protection
- Sometimes surgical intervention for ocular movement disorders

There is no treatment for albinism. Patients are at high risk of sunburn and skin cancers (especially squamous cell carcinoma) and should avoid direct sunlight, use sunglasses with UV filtration, wear protective clothing, and use sunscreen with an SPF of ≥ 30 that protects against UVA and UVB wavelengths (see p. 673). Some surgical interventions may lessen ocular movement disorders.

**Vitiligo**

Vitiligo is a loss of skin melanocytes that causes areas of skin depigmentation of varying sizes. Cause is unknown, but the condition may be autoimmune; up to one third of patients have evidence of other autoimmune disease. Diagnosis is often obvious on examination. First-line treatment is topical corticosteroids. Calcineurin inhibitors (tacrolimus and pimecrolimus) and psoralens plus ultraviolet A are commonly used. For severe widespread pigment loss, depigmentation (bleaching) of residual patches of normal skin may be done with hydroquinone.
Vitiligo affects 0.5 to 2% of the population.

**Etiology**

Etiology is unclear, but melanocytes are lacking in affected areas. It is both familial (autosomal dominant, with incomplete penetrance and variable expression) and acquired. Proposed mechanisms include autoimmune destruction of melanocytes, reduced survival of melanocytes, and primary melanocyte defects. Occasionally, vitiligo occurs after a direct physical injury to the skin (eg, as a response to sunburn). This form of vitiligo is called the Koebner phenomenon. Patients may associate the onset of vitiligo with emotional stress.

Some patients have antibodies to melanin. Up to 30% have other autoimmune antibodies (to thyroglobulin, adrenal cells, and parietal cells) or clinical autoimmune endocrinopathies (Addison's disease, diabetes mellitus, pernicious anemia, and thyroid dysfunction), leading to speculation that vitiligo is an autoimmune disease. However, the relationship is unclear and may be coincidental. The strongest association is with hyperthyroidism (Graves' disease) and hypothyroidism (Hashimoto's thyroiditis).

**Symptoms and Signs**

Vitiligo is characterized by depigmented areas (see Plate 54), usually sharply demarcated and often symmetric. Depigmentation may be localized, involving 1 or 2 spots or entire body segments (segmental vitiligo); rarely, it may be generalized, involving most of the skin surface (universal vitiligo). However, vitiligo most commonly involves the face (especially around the orifices), digits, dorsal hands, flexor wrists, elbows, knees, shins, dorsal ankles, armpits, inguinal area, anogenital area, umbilicus, and nipples. Cosmetic disfigurement can be especially devastating in dark-skinned patients. Hair in vitiliginous areas is usually white.

**Diagnosis**

- Clinical evaluation

Depigmented skin is typically obvious on examination. Skin lesions are accentuated under Wood's light. Differential diagnosis includes postinflammatory hypopigmentation, morphea, leprosy, chemical leukoderma, and leukoderma due to melanoma. Additional testing for autoimmune endocrine disease is probably unnecessary unless symptoms or signs suggest a particular disorder.

**Treatment**

- Protection of affected areas from sunlight
- Topical corticosteroids
- Topical calcineurin inhibitors when face or groin involved
- Sometimes psoralen plus ultraviolet A (PUVA) therapy

Treatment is supportive and cosmetic. Physicians must be aware of individual and ethnic sensibilities regarding uniform skin coloring; the disease can be psychologically devastating. All depigmented areas are prone to severe sunburn and must be protected with clothing or sunscreen.

Small, scattered lesions may be camouflaged with makeup. First-line therapy for more extensive involvement is potent topical corticosteroids, which may cause hypopigmentation or atrophy in normal surrounding skin. Calcineurin inhibitors (tacrolimus and pimecrolimus) may be particularly useful for treating areas of the skin (such as the face and groin) where adverse effects of topical corticosteroid therapy most commonly occur. Oral and topical PUVA is often successful, although hundreds of treatment sessions may be necessary. Narrowband UVB is as effective as topical PUVA and has few adverse effects. Lasers may be useful, particularly for localized disease that does not respond to initial topical
therapy.

Surgery is reasonable only for patients with stable, limited disease when medical therapy has failed. Therapies include autologous micrografting, suction blister grafting, and tattooing; tattooing is especially useful for difficult-to-repigment areas such as the nipples, lips, and fingertips.

Depigmentation of unaffected skin to achieve homogeneous skin tone is possible with 20% monobenzyl ether of hydroquinone applied twice daily and is indicated only when most of the skin is involved and the patient is prepared for permanent pigment loss. This treatment can be extremely irritating, so a smaller test area should be treated before widespread use. Treatment for ≥ 1 yr may be required.

**Hyperpigmentation**

Hyperpigmentation has multiple causes and may be focal or diffuse. Most cases are due to an increase in melanin production and deposition.

Focal hyperpigmentation is most often postinflammatory in nature, occurring after injury (eg, cuts and burns) or other causes of inflammation (eg, acne, lupus). Focal linear hyperpigmentation is commonly due to phytophotodermatitis, which results from ultraviolet light combined with furocoumarins in limes, celery, and other plants.

Hyperpigmentation also has systemic and neoplastic causes.

**Melasma (chloasma):** Melasma consists of dark brown, sharply marginated, roughly symmetric patches of hyperpigmentation on the face (usually on the forehead, temples, and cheeks). It occurs primarily in pregnant women (melasma gravidarum, or the mask of pregnancy) and in women taking oral contraceptives. Ten percent of cases occur in nonpregnant women and dark-skinned men. Melasma is more prevalent and lasts longer in people with dark skin.

Because all cases are associated with sun exposure, the mechanism probably involves overproduction of melanin by hyperfunctional melanocytes. Other than sun exposure, aggravating factors include

- Autoimmune thyroid disorders
- Photosensitizing drugs

In women, melasma fades slowly and incompletely after childbirth or cessation of hormone use. In men, melasma rarely fades.

Treatment depends on whether the pigmentation is epidermal or dermal; epidermal pigmentation becomes accentuated with Wood's light or can be diagnosed with biopsy. Only epidermal pigmentation responds to treatment. First-line therapy includes a combination of hydroquinone 2 to 4%, tretinoin 0.05 to 1%, and a class V to VII topical corticosteroid. Hydroquinone 3 to 4% applied twice daily is often effective, but long courses are usually required; 2% hydroquinone is useful as maintenance. Hydroquinone should be tested behind one ear or on a small patch on the forearm for 1 wk before use on the face because it may cause irritation. Bleaching agents, such as 0.1% tretinoin and azelaic acid 15 to 20% cream, can be used in place of or with hydroquinone. Chemical peeling with glycolic acid or 30 to 50% trichloroacetic acid is an option for patients with severe melasma unresponsive to topical bleaching agents.

**Lentigines:** Lentigines (singular: lentigo) are flat, tan to brown oval spots. They are commonly due to chronic sun exposure (solar lentigines; sometimes called liver spots) and occur most frequently on the face and back of the hands. They typically first appear during middle age and increase in number with age. Although progression from lentigines to melanoma has not been established, lentigines are an independent risk factor for melanoma. They are treated with cryotherapy or laser; hydroquinone is not effective.

Nonsolar lentigines are sometimes associated with systemic disorders, such as Peutz-Jeghers syndrome (in which profuse lentigines of the lips occur), multiple lentigines syndrome (Leopard syndrome), or
Diffuse hyperpigmentation due to systemic disorders: Common systemic causes include Addison’s disease (see p. 792), hemochromatosis (see p. 1032), and primary biliary cirrhosis (see p. 244). Skin findings are nondiagnostic as to cause.

Drug-induced hyperpigmentation: Changes are usually diffuse but sometimes have drug-specific distribution patterns or hues (see Table 85-1). Mechanisms include

- Increased melanin in the epidermis (tends to be more brown)
- Melanin in the epidermis and high dermis (mostly brown with hints of gray or blue)
- Increased melanin in the dermis (tends to be more grayish or blue)
- Dermal deposition of the drug or metabolite (usually slate or bluish gray)

Focal hyperpigmentation frequently follows drug-induced lichen planus (also known as lichenoid drug reactions).

In fixed drug eruptions, red plaques or blisters form at the same site each time a drug is taken; residual postinflammatory hyperpigmentation usually persists. Typical lesions occur on the face (especially the lips), hands, feet, and genitals. Typical inciting drugs include sulfonamides, tetracycline, NSAIDs (especially phenazone derivatives), barbiturates, and carbamazepine.
Chapter 86. Hair Disorders

Introduction

Hair growth in both men and women is regulated by androgens. Testosterone stimulates hair growth in the pubic area and underarms. Dihydrotestosterone stimulates beard hair growth and scalp hair loss.

Hair disorders include alopecia, hypertrichosis, hirsutism, and pseudofolliculitis barbae. Although most hair disorders are not serious, they are often perceived as major cosmetic issues that demand treatment. Dandruff is not a hair disorder but rather a skin disorder (seborrheic dermatitis) of the scalp (see p. 671).

Alopecia

(Baldness)

Alopecia is defined as loss of hair. Hair loss is often a cause of great concern to the patient for cosmetic and psychologic reasons, but it can also be an important sign of systemic disease.

Pathophysiology

Growth cycle: Hair grows in cycles. Each cycle consists of a long growing phase (anagen), a brief transitional apoptotic phase (catagen), and a short resting phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle, beginning the cycle again. Normally, about 100 scalp hairs reach the end of resting phase each day and fall out. When significantly more than 100 hairs/day go into resting phase, clinical hair loss (telogen effluvium) may occur. A disruption of the growing phase causing abnormal loss of anagen hairs is an anagen effluvium.

Classification: Alopecia can be classified as focal or diffuse and by the presence or absence of scarring.

Scarring alopecia is the result of active destruction of the hair follicle. The follicle is irreparably damaged and replaced by fibrotic tissue. Several hair disorders show a biphasic pattern in which nonscarring alopecia occurs early in the course of the disease, and then permanent hair loss occurs as the disease progresses. Scarring alopecias can be subdivided further into primary forms, where the target of inflammation is the follicle itself, and secondary forms, where the follicle is destroyed as a result of nonspecific inflammation (see Table 86-1).

Nonscarring alopecia results from processes that reduce or slow hair growth without irreparably damaging the hair follicle. Disorders that primarily affect the hair shaft also are considered nonscarring alopecia.

Etiology

The alopecias comprise a large group of disorders with multiple and varying etiologies (see Table 86-1).

The most common cause of alopecia is

• Androgenetic alopecia (male-pattern or female-pattern hair loss)

Androgenetic alopecia is an androgen-dependent hereditary disorder in which dihydrotestosterone plays a major role.

Other common causes of hair loss are

• Drugs (including chemotherapeutic agents)

• Infection
Less common causes are primary hair shaft abnormalities, autoimmune disease, heavy metal poisoning, and rare dermatologic conditions.

Evaluation

History: History of present illness should cover the onset and duration of hair loss, whether hair shedding is increased, and whether hair loss is generalized or localized. Associated symptoms such as pruritus and scaling should be noted. Patients should be asked about typical hair care practices, including use of braids, rollers, and hair dryers, and whether they routinely pull or twist their hair.

Review of systems should include recent exposures to noxious stimuli (eg, drugs, toxins, radiation) and stressors (eg, surgery, chronic illness, fever, psychologic stressors). Symptoms of possible causes should be sought, including fatigue and cold intolerance (hypothyroidism) and, in women, hirsutism, deepening of the voice, and increased libido (virilizing syndrome). Other features, including dramatic weight loss, dietary practices (including vegetarianism), and obsessive-compulsive behavior, should be noted. In women, a hormonal/gynecologic/obstetric history should be obtained.

Past medical history should note known possible causes of hair loss, including endocrine and skin disorders. Current and recent drug use should be reviewed for offending agents (see Table 86-1). A family history of hair loss should be recorded.

Physical examination: Examination of the scalp should note the distribution of hair loss, the presence and characteristics of any skin lesions, and whether there is scarring. Part widths should be measured. Abnormalities of the hair shafts should be noted.

A full skin examination should be done to evaluate hair loss elsewhere on the body (eg, eyebrows, eyelashes, arms, legs), rashes that may be associated with certain types of alopecia (eg, lichen planus, atopy, psoriasis, discoid lupus lesions, hidradenitis, signs of secondary syphilis or of other bacterial or fungal infections), and signs of virilization in women (eg, hirsutism, acne, deepening voice, clitoromegaly). Signs of potential underlying systemic disorders should be sought, and a thyroid examination should be done.

Red flags: The following findings are of particular concern:

- Virilization in women
- Signs of systemic illness or constellations of nonspecific findings possibly indicating poisoning

Interpretation of findings: Hair loss that begins at the temples or vertex and spreads to diffuse thinning or nearly complete hair loss is typical of male-pattern hair loss. Hair thinning in the frontal, parietal, and crown regions is typical of female-pattern hair loss (see Fig. 86-1).

Hair loss that occurs 2 to 4 wk after chemotherapy or radiation therapy (anagen effluvium) can typically be ascribed to those causes. Hair loss that occurs 3 to 4 mo after a major stressor (pregnancy, febrile illness, surgery, medication change, or severe psychologic stressor) suggests a diagnosis of telogen effluvium.

Other findings help suggest alternative diagnoses (see Table 86-2).
Other than hair loss, scalp symptoms (eg, itching, burning, tingling) are often absent and, when present, are not specific to any cause.

Signs of hair loss in patterns other than those described above are nondiagnostic and may require microscopic hair examination or scalp biopsy for definitive diagnosis.

**Testing:** Evaluation for causative disorders (eg, endocrinologic, autoimmune, toxic) should be done based on clinical suspicion.

Male-pattern or female-pattern hair loss generally requires no testing. When it occurs in young men with no family history, the physician should question the patient about use of anabolic steroids and other drugs. In addition to questions regarding drug and illicit drug use, women with significant hair loss and evidence of virilization should have testosterone and dehydroepiandrosterone sulfate (DHEAS) levels measured (see p. 730).

The **pull test** helps evaluate diffuse scalp hair loss. Gentle traction is exerted on a bunch of hairs (40 to 60) on at least 3 different areas of the scalp, and the number of extracted hairs is counted and examined microscopically. Normally, < 3 telogen-phase hairs should come out with each pull. If at least 3 hairs are obtained with each pull or if > 10 hairs total are obtained, the pull test is positive and suggestive of telogen effluvium.

The **pluck test** pulls individual hairs out abruptly ("by the roots"). The roots of the plucked hairs are examined microscopically to determine the phase of growth and thus help diagnose a defect of telogen or anagen or an occult systemic disease. Anagen hairs have sheaths attached to their roots; telogen hairs have tiny bulbs without sheaths at their roots. Normally, 85 to 90% of hairs are in the anagen phase; about 10 to 15% are in telogen phase; and < 1% are in catagen phase. Telogen effluvium shows an increased percentage of telogen-phase hairs on microscopic examination, whereas anagen effluvium shows a decrease in telogen-phase hairs and an increased number of broken hairs. Primary hair shaft abnormalities are usually obvious on microscopic examination of the hair shaft.

**Scalp biopsy** is indicated when alopecia persists and diagnosis is in doubt. Biopsy may differentiate scarring from nonscarring forms. Specimens should be taken from areas of active inflammation, ideally at the border of a bald patch. Fungal and bacterial cultures may be useful; immunofluorescence studies may help identify lupus erythematosus, lichen planopilaris, and systemic sclerosis.

**Daily hair counts** can be done by the patient to quantify hair loss when the pull test is negative. Hairs lost in the first morning combing or during washing are collected in clear plastic bags daily for 14 days. The number of hairs in each bag is then recorded. Scalp hair counts of > 100/day are abnormal except after shampooing, when hair counts of up to 250 may be normal. Hairs may be brought in by the patient for microscopic examination.

**Treatment**

**Androgenetic alopecia:** **Minoxidil** (2% for women, 2% or 5% for men) prolongs the anagen growth phase and gradually enlarges miniaturized follicles (vellus hairs) into mature terminal hairs. Topical minoxidil 1 mL bid applied to the scalp is most effective for vertex alopecia in male-pattern or female-pattern hair loss. However, usually only 30 to 40% of patients experience significant hair growth, and minoxidil is generally not effective or indicated for other causes of hair loss except possibly alopecia areata. Hair regrowth can take 8 to 12 mo. Treatment is continued indefinitely because, once treatment is stopped, hair loss resumes. The most frequent adverse effects are mild scalp irritation, allergic contact dermatitis, and increased facial hair.

**Finasteride** inhibits the 5α-reductase enzyme, blocking conversion of testosterone to dihydrotestosterone, and is useful for male-pattern hair loss. Finasteride 1 mg po once/day can stop hair
loss and can stimulate hair growth. Efficacy is usually evident within 6 to 8 mo of treatment. Adverse effects include decreased libido, erectile and ejaculatory dysfunction, hypersensitivity reactions, gynecomastia, and myopathy. There may be a decrease in prostate-specific antigen levels in older men, which should be taken into account when that test is used for cancer screening. Common practice is to continue treatment for as long as positive results persist. Once treatment is stopped, hair loss returns to previous levels. Finasteride is not indicated for women and is contraindicated in pregnant women because it has teratogenic effects in animals.

**Hormonal modulators** such as oral contraceptives or spironolactone may be useful for female-pattern hair loss associated with hyperandrogenemia.

**Surgical options** include follicle transplant, scalp flaps, and alopecia reduction. Few procedures have been subjected to scientific scrutiny, but patients who are self-conscious about their hair loss may consider them.

**Hair loss due to other causes:** Underlying disorders are treated.

Multiple treatment options for alopecia areata exist and include topical, intralocular, or, in severe cases, systemic corticosteroids, topical minoxidil, topical anthralin, topical immunotherapy (diphencyprone or squaric acid dibutylester), or psoralen plus ultraviolet A (PUVA).

Treatment for traction alopecia is elimination of physical traction or stress to the scalp.

Treatment for tinea capitis is topical or oral antifungals (see p. 707).

Trichotillomania is difficult to treat, but behavior modification, clomipramine, or an SSRI (eg, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) may be of benefit.

Scarring alopecia as seen in central centrifugal scarring alopecia, dissecting cellulitis of the scalp, and acne keloidalis nuchae is best treated by a long-acting oral tetracycline in combination with a potent topical corticosteroid.

Lichen planopilaris and chronic cutaneous lupus lesions may be treated with oral antimalarials, corticosteroids, retinoids, or immunosuppressants.

Hair loss due to chemotherapy is temporary and is best treated with a wig; when hair regrows, it may be different in color and texture from the original hair. Hair loss due to telogen effluvium or anagen effluvium is usually temporary as well and abates after the precipitating agent is eliminated.

**Key Points**

- **Androgenetic alopecia** (male-pattern and female-pattern hair loss) is the most common type of hair loss.

- Concomitant virilization in women or scarring hair loss should prompt a thorough evaluation for the underlying disorder.

- Microscopic hair examination or scalp biopsy may be required for definitive diagnosis.

**Alopecia Areata**

**Alopecia areata is sudden patchy hair loss in people with no obvious skin or systemic disorder.**

The scalp and beard are most frequently affected, but any hairy area may be involved. Hair loss may affect most or all of the body (alopecia universalis). Alopecia areata is thought to be an autoimmune disorder affecting genetically susceptible people exposed to unclear environmental triggers, such as
infection or emotional stress. It occasionally coexists with autoimmune vitiligo or thyroiditis.

**Diagnosis**

- **Examination**

Diagnosis is by inspection. Alopecia areata typically manifests as discrete circular patches of hair loss characterized by short broken hairs at the margins, which resemble exclamation points. Nails are sometimes pitted or display trachyonychia, a roughness of the nail also seen in lichen planus. Differential diagnosis includes tinea capitis, trichotillomania, discoid lupus, and secondary syphilis. Measures of thyroid-stimulating hormone, vitamin B<sub>12</sub>, and autoantibodies are indicated only when coexisting disease is suspected.

**Treatment**

- **Corticosteroids**
- **Sometimes topical anthralin, minoxidil or both**

Treatment is with corticosteroids. Triamcinolone acetonide suspension (in doses not to exceed 0.1 mL per injection site, eg, 10 mg/mL concentration to deliver 1 mg) can be injected intradermally if the lesions are small. Potent topical corticosteroids (such as betamethasone 0.05% bid) can be used; however, they often do not penetrate to the depth of the hair bulb where the inflammatory process is located. Oral corticosteroids are effective, but hair loss recurs after cessation of therapy and adverse effects limit use. Topical anthralin (0.5 to 1% for 10 to 20 min daily, then washed off, frequency titrated as tolerated up to 30 min bid) and/or minoxidil may be used. Induction of allergic contact dermatitis using diphencyprone or squaric acid dibutylerster leads to hair growth due to unknown mechanisms, but this treatment is best reserved for patients with diffuse involvement who have not responded to other therapies.

Alopecia areata may spontaneously regress, become chronic, or spread diffusely. Risk factors for chronicity include extensive involvement, onset before adolescence, atopy, and involvement of the peripheral scalp (ophiasis).

**Hirsutism**

**Hirsutism** is the excessive growth of thick or dark hair in women in locations that are more typical of male hair patterns (eg, mustache, beard, central chest, shoulders, lower abdomen, back, inner thigh). The amount of hair growth that is considered excessive may differ depending on ethnic background and cultural interpretation. Men vary significantly in amount of body hair, some being quite hairy, but rarely present for medical evaluation.

**Hypertrichosis** is a separate condition. It is simply an increase in the amount of hair growth anywhere on the body. Hypertrichosis may be generalized or localized.

**Pathophysiology**

Hair growth depends on the balance between androgens (eg, testosterone, dehydroepiandrosterone sulfate [DHEAS], dihydrotestosterone [DHT]) and estrogens. Androgens promote thick, dark hair growth, whereas estrogens slow hair growth or modulate it toward finer, lighter hairs.

When caused by increased androgen activity, hirsutism is often accompanied by virilization, which may manifest as loss of menses, increased muscle mass, voice deepening, and clitoral hypertrophy.

**Etiology**

There are a number of causes of hirsutism (see Table 86-3). Overall, the most common causes are the following:
Polycystic ovary syndrome

- Familial hirsutism

**Androgen excess:** Hirsutism typically results from abnormally high androgen activity as a result of increased central production of androgens (e.g., from ovarian or adrenal disorders) or increased peripheral conversion of testosterone to DHT by 5α-reductase. Free androgen levels also can increase as a result of decreased production of sex hormone-binding globulin, which can occur in a variety of conditions, including hyperinsulinemia and liver disease. However, the severity of hirsutism does not correlate with the level of circulating androgens because of individual differences in androgen sensitivity of the hair follicle.

[Table 86-3. Some Causes of Hirsutism]

**No androgen excess:** Hirsutism not associated with androgen excess may be physiologic (e.g., postmenopausal, during pregnancy), the result of systemic nonandrogenic endocrine conditions, or a familial phenomenon, especially in people of Mediterranean or Middle Eastern ancestry.

**Hypertrichosis** involves nonandrogenic hair growth and is usually caused by a drug, systemic illness (see **Table 86-4**), or paraneoplastic syndrome. It also occurs as part of a rare familial disorder.

**Evaluation**

**History:** **History of present illness** should cover the extent and acuity of hair growth as well as the age of onset.

**Review of systems** should seek signs of virilization (e.g., deepening of the voice, increased libido) and review menstrual and fertility history. Symptoms of causative disorders should be sought, including cold intolerance, fatigue, and weight gain (hypothyroidism); polyuria (diabetes); bingeing and purging (eating disorders); and weight loss and fevers (cancer).

**Past medical history** should specifically seek known causative disorders such as endocrine disorders, adrenal or ovarian pathology, and cancer.

**Family history** should inquire about excess hair growth in family members. Drug history should review all prescribed drugs and specifically query for the surreptitious use of anabolic steroids.

**Physical examination:** The presence of excess coarse and dark hair growth should be assessed at multiple sites, including the face, chest, lower abdomen, back, buttocks, and inner thigh. Signs of virilization should be sought, including clitoromegaly, acne, male-pattern hair loss, breast atrophy, and increased muscle mass.

General physical examination should note signs of potentially causative disorders.

The eyes should be examined for extraocular movements, and the visual fields should be assessed.

The breasts should be examined for galactorrhea.

The abdomen (including pelvic examination) should be examined for masses.

The skin should be examined for velvety, black pigmentation on the axillae and neck and under the breasts (acanthosis nigricans); acne; and striae.

The general habitus should be examined for fat distribution (particularly a round face and accumulation of fat at the base of the neck posteriorly).

[Table 86-4. Causes of Hypertrichosis]
Red flags: The following findings are of particular concern:

- Virilization
- Abrupt appearance of hirsutism
- Pelvic or abdominal mass

Interpretation of findings: Excess hair growth beginning after use of an anabolic steroid or other causative drug (see Tables 86-3 and 86-4) in an otherwise healthy female is likely due to that drug. Symptoms and signs sometimes point to a diagnosis (see Table 86-5).

Testing: Diagnostic testing in men with no other signs of illness is unnecessary. Women should have laboratory measurement of serum hormone levels, including the following:

- Free and total testosterone
- DHEAS
- Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- Androstenedione
- Thyroid-stimulating hormone
- Prolactin

High levels of testosterone accompanied by a normal level of DHEAS indicate that the ovaries, and not the adrenal glands, are producing the excess androgen. High levels of testosterone accompanied by moderate elevations in DHEAS suggest an adrenal origin for the hirsutism.

Often, in women with polycystic ovary syndrome, LH levels are elevated and FSH levels are depressed, which results in elevated LH/FSH ratios (> 3 is common).

Imaging: Pelvic ultrasonography, CT, or both should be done to rule out pelvic or adrenal cancer, particularly when a pelvic mass is appreciated, when the total testosterone level is > 200 ng/dL (> 100 ng/dL in postmenopausal women), or when the DHEAS level is > 7000 ng/dL (> 4000 ng/dL in postmenopausal women). However, the majority of patients with elevated DHEAS have adrenal hyperplasia rather than adrenal carcinoma.

Patients with signs of Cushing's syndrome or an adrenal mass on imaging studies should have 24-h urine cortisol levels measured.

Treatment

The underlying disorder should be treated, including stopping or changing causative drugs. Treatment for hirsutism itself is unnecessary if the patient does not find the excess hair cosmetically objectionable.

Nonandrogen-dependent excess hair growth, such as hypertrichosis, is treated primarily with physical hair removal methods. Patients with androgen-dependent hirsutism require a combination of hair removal and medical antiandrogen therapy.

Hair removal: There are several techniques. Depilatory techniques remove hair from the surface of the skin and include shaving and OTC depilatory creams, such as those containing barium sulfate and Ca thioglycolate.
Epilation involves removing intact hairs and the roots and can be achieved via mechanical means (eg, tweezing, plucking, waxing) or home epilating devices. Permanent epilation techniques, including electrolysis, thermolysis, and laser epilation, can result in more long-term hair removal but often require multiple treatments.

As an alternative to hair removal, hair bleaching is inexpensive and works well when hirsutism is not excessive. Bleaches lighten the color of the hair, rendering it less noticeable. There are several types of commercial hair-bleaching products, most of which use hydrogen peroxide as the active ingredient.

Topical eflornithine, applied twice daily, decreases hair growth and, with long-term use, may decrease the need to manually remove hair.

**Hormonal treatment:** Hirsutism resulting from androgen excess usually requires long-term therapy because the source of excess androgen rarely can be eliminated permanently. Hormonal treatments include

- Oral contraceptives
- Antiandrogenic drugs
- Sometimes other drugs

Oral contraceptives in standard doses often are the initial treatment for hirsutism caused by ovarian hyperandrogenism. Oral contraceptives reduce ovarian androgen secretion and increase sex hormone-binding globulin, thereby decreasing free testosterone levels.

Antiandrogenic therapy is also used and can include finasteride (5 mg po once/day), spironolactone (25 to 100 mg po bid), or flutamide (125 mg po once/day or bid). These drugs are contraindicated during pregnancy as they may cause feminization of a male fetus.

Insulin sensitizers such as metformin decrease insulin resistance, causing a decline in testosterone levels. However, they are less effective than other antiandrogenic drugs. Corticosteroids are used for adrenal suppression. Gonadotropin-releasing hormone agonists (eg, leuprolide acetate, nafarelin, triptorelin) can be used for severe forms of ovarian hyperandrogenism under the direction of a gynecologist or endocrinologist.

**Key Points**

- Hirsutism may be familial, and the degree of hair growth may vary with ethnicity.
- Polycystic ovary syndrome is the most frequent cause of hirsutism.
- Virilization suggests an androgenic disorder that requires further evaluation.
- Abrupt onset of hirsutism may indicate cancer.

**Pseudofolliculitis Barbae**

Pseudofolliculitis barbae (PFB) is irritation of the skin due to beard hairs that penetrate the skin before leaving the hair follicle or that leave the follicle and curve back into the skin, causing a foreign-body reaction.

PFB predominantly affects black men. It is most noticeable around the beard and neck. It causes small
papules and pustules that can be confused with bacterial folliculitis.

Diagnosis is by physical examination.

**Treatment**

Acute PFB can be treated with warm compresses and manual removal of ingrown hairs with a needle or tweezers. Topical hydrocortisone 1% or topical antibiotics can be used for mild inflammation. Oral tetracycline (250 to 500 mg qid) or oral erythromycin (250 to 500 mg qid, 333 mg tid, 500 mg bid) can be used for moderate to severe inflammation. Tretinoin (retinoic acid) liquid or cream or benzoyl peroxide cream may also be effective in mild or moderate cases but may irritate the skin. Topical eflornithine hydrochloride cream may help by slowing hair growth. Hairs should be allowed to grow out; grown hairs can then be cut to about 0.5 cm length. Depilatories are an alternative but may irritate the skin. Hair follicles can be permanently removed by electrolysis or laser treatment.
Chapter 87. Nail Disorders

Introduction

A variety of disorders can affect nails, including deformities, infections of the nail, paronychia, and ingrown toenails. Nail changes may occur in many systemic conditions and genetic syndromes.

Nails may also undergo changes due to local infection or trauma. For example, trauma to the finger may cause changes in the nail. The nail may develop a white coloration that starts at the nail bed and grows up with the nail. Sometimes, if a nail becomes separated from the nail bed, a new nail grows below the existing nail and replaces it when fully grown in.

Most nail infections are fungal (onychomycosis—see p. 734), but bacterial and viral infections can occur (eg, green-nail syndrome [Pseudomonas], herpetic whitlow [herpes simplex virus-1]). Paronychia is not actually an infection of the nail but rather of periungual tissues.

Common warts (verrucae vulgaris) result from papillomavirus infection and frequently infect the proximal nail fold and sometimes the subungual area. Onychophagia (nail-biting) can help to spread this infection. Warts involving these areas are especially difficult to treat. Freezing with liquid nitrogen may be effective.

Toenails require special attention in the elderly and in people with diabetes or peripheral vascular disease; a podiatrist can help avoid local breakdown and secondary infections.

Deformities

About 50% of nail deformities result from fungal infection. The remainder result from various causes, including trauma, psoriasis, lichen planus, and occasionally cancer. Diagnosis may be obvious on examination, but sometimes fungal scrapings and culture may be done. Deformities may resolve with treatment of the cause, but if not, manicurists may be able to hide nail deformities with appropriate trimming and polishes. Dystrophies are often considered together with deformities, but the two are slightly different; deformities are generally considered to be gross changes in nail shape, whereas dystrophies are changes in nail texture or composition (eg, onychomycosis).

Congenital deformities: In some congenital ectodermal dysplasias, patients have no nails (anonychia). In pachyonychia congenita, the nail beds are thickened, discolored, and hypercurved with a pincer nail deformity. Nail-patella syndrome (see p. 2910) causes triangular lunulae and partially absent thumb nails. Patients with Darier's disease can have nails with red and white streaks and a distal V-shaped nick.

Deformities associated with systemic problems: In Plummer-Vinson syndrome, 50% of patients have koilonychia (concave, spoon-shaped nails). Yellow nail syndrome (characterized by hard, hypercurved, transversely thickened, yellow nails with loss of the cuticle) occurs in patients with lymphedema of limbs, pleural effusion, and ascites. Half-and-half nails occur with renal failure; the proximal half of the nail is white, and the distal half is pink or pigmented. White nails occur with cirrhosis, although the distal third may remain pinker.

Deformities associated with dermatologic conditions: In psoriasis, nails may have a number of changes, including irregular pits, oil spots (localized areas of tan-brown discoloration), onycholysis, and thickening and crumbling of the nail plate. Lichen planus of the nail matrix causes scarring with early longitudinal ridging and splitting of the nail and later leads to pterygium formation. Pterygium of the nail is characterized by scarring from the proximal nail outward in a V formation, which leads ultimately to loss of the nail. Alopecia areata can be accompanied by regular pits that form a pattern.

Discoloration: Cancer chemotherapy drugs (especially the taxanes) can cause melanonychia (nail plate pigmentation), which can be diffuse or may occur in transverse bands. Some drugs cause characteristic changes in nail coloration. For example, quinacrine can cause nails to appear greenish yellow or white under ultraviolet light. Cyclophosphamide can cause the onychodermal bands (seal formed at the junction of the nail plate and distal nail bed at the free edge of the nail plate) to become slate-gray or bluish. With arsenic intoxication, the nails may turn diffusely brown. Tetracyclines, ketoconazole, phenothiazines,
sulfonamides, and phenindione can all cause brownish or blue discoloration. Gold therapy can turn nails light or dark brown. Tobacco use can result in yellow or brownish discoloration. In argyria, the nails may be diffusely blue-gray.

White transverse lines of the nails (Mees' lines) may occur with chemotherapy, acute arsenic intoxication, malignant tumors, MI, thallium and antimony intoxication, fluorosis, and even during etretinate therapy. They also develop with trauma to the finger, although traumatic white lines usually do not span the entire nail. The fungus *Trichophyton mentagrophytes* causes a chalky white discoloration of the nail plate.

Green-nail syndrome is caused by infection with *Pseudomonas*. It is generally a harmless infection, usually of 1 or 2 nails, and is noteworthy for its striking blue-green color. It often occurs in patients with onycholysis or chronic paronychia whose nails have been immersed in fresh water for a long period. Treatment is most effective with soaks of 1% acetic acid solution or alcohol diluted 1:4 with water. Patients should soak their affected nails twice a day for 10 min and should avoid trauma and excess moisture. Frequent clipping of the nail increases the response to treatment.

**Melanonychia striata:** Melanonychia striata are hyperpigmented bands that are longitudinal and extend from the proximal nail fold and cuticle to the free distal end of the nail plate. In dark-skinned people, these bands may be a normal physiologic variant requiring no treatment. Other causes include trauma; pregnancy; Addison's disease; post-inflammatory hyperpigmentation; and the use of certain drugs, including doxorubicin, 5-fluorouracil, zidovudine (AZT), and psorales. Melanonychia striata can also occur in benign melanocytic nevi and malignant melanoma. Hutchinson's sign of the nail (melanin extending through the lunula, cuticle, and proximal nail fold) may signal a melanoma in the nail matrix. Rapid biopsy and treatment are essential.

**Onychogryphosis:** Onychogryphosis is a nail dystrophy in which the nail, most often on the big toe, becomes thickened and curved. It may be caused by ill-fitting shoes. It is common among the elderly. Treatment consists of trimming the deformed nails.

**Onycholysis:** Onycholysis is separation of the nail plate from the nail bed or complete nail plate loss. It can occur as a drug reaction in patients treated with tetracyclines (photo-onycholysis), doxorubicin, 5-fluorouracil, cardiovascular drugs (particularly practolol and captopril), cloxacillin and cephaloridine (rarely), trimethoprim/sulfamethoxazole, diflunisal, etretinate, indomethacin, isoniazid, and isotretinoin. Partial onycholysis may also result from infection with *Candida albicans* as a component of onychomycosis or from trauma. Partial onycholysis may occur in patients with psoriasis or thyrotoxicosis.

**Onychotillomania:** In this disorder, patients pick at and self-mutilate their nails, which can lead to parallel transverse grooves and ridges (washboard deformity or habit-tic nails). It most commonly manifests in patients who habitually push back the cuticle on one finger, causing dystrophy of the nail plate as it grows. Subungual hemorrhages can also develop in onychotillomania.

**Pincer nail deformity:** Pincer nail deformity is a transverse over-curvature of the nail plate. It can occur in patients with psoriasis, SLE, Kawasaki disease, cancer, end-stage renal disease, and some genetic syndromes. Patients often have pain at the borders of the nail where the nail plate curves into the tips of the fingers.

**Subungual hematoma and nail bed trauma:** Subungual hematoma occurs when blood becomes trapped between the nail plate and nail bed, usually as a result of trauma. Subungual hematoma causes significant pain and eventual separation of and temporary loss of the nail plate. When the cause is a crush injury, underlying fracture and nail bed damage are common. Nail bed damage may result in permanent nail deformity.

If the injury is acute, nail trephination (eg, creating a hole in the nail plate using a cautery device, 18-gauge needle, or red-hot paperclip) can help relieve pain by draining accumulated blood. It is not clear whether removing the nail and repairing any nail bed damage reduces risk of permanent nail deformity.

**Trachyonychia:** Trachyonychia (rough, opaque nails) may occur with alopecia areata, lichen planus, atopic dermatitis, and psoriasis. It is most common among children.
**Tumors**: Benign and malignant tumors can affect the nail unit, causing deformity. These tumors include benign myxoid cysts, pyogenic granulomas, glomus tumors, Bowen's disease, squamous cell carcinoma, and malignant melanoma. When cancer is suspected, expeditious biopsy followed by referral to a surgeon is strongly advised.

**Onychomycosis**

Onychomycosis is fungal infection of the nail plate, nail bed, or both. The nails typically are deformed and discolored white or yellow. Diagnosis is by appearance, wet mount, culture, PCR, or a combination. Treatment, when indicated, is with selective use of oral terbinafine or itraconazole.

About 10% (range 2 to 14%) of the population has onychomycosis. Risk factors include

- Tinea pedis
- Preexisting nail dystrophy (eg, in patients with psoriasis)
- Older age
- Male sex
- Exposure to someone with tinea pedis or onychomycosis (eg, a family member or through public bathing)
- Peripheral vascular disease or diabetes
- Immunocompromise

Toenails are 10 times more commonly infected than fingernails. About 60 to 80% of cases are caused by dermatophytes (eg, *Trichophyton rubrum*); dermatophyte infection of the nails is called tinea unguium. Many of the remaining cases are caused by nondermatophyte molds (eg, *Aspergillus*, *Scopulariopsis*, *Fusarium*). Immunocompromised patients and those with chronic mucocutaneous candidiasis may have candidal onychomycosis (which is more common on the fingers). Subclinical onychomycosis can also occur in patients with recurrent tinea pedis. Onychomycosis may predispose patients to lower extremity cellulitis.

**Symptoms and Signs**

Nails have asymptomatic patches of white or yellow discoloration and deformity. There are 3 characteristic manifestations:

- Distal subungual, in which the nails thicken and yellow, keratin and debris accumulate distally and underneath, and the nail separates from the nail bed (onycholysis)
- Proximal subungual, a form that starts proximally and is a marker of immunosuppression
- White superficial, in which a chalky white scale slowly spreads beneath the nail surface

**Diagnosis**

- Clinical evaluation
- Potassium hydroxide wet mount examination
- Culture
Onychomycosis is suspected by appearance; predictive clinical features include involvement of the 3rd or 5th toenail, involvement of the 1st and 5th toenails on the same foot, and unilateral nail deformity. Subclinical onychomycosis should be considered in patients with recurrent tinea pedis. Differentiation from psoriasis or lichen planus is important, because the therapies differ, so diagnosis is typically confirmed by microscopic examination and culture of scrapings. Scrapings are taken from the most proximal position that can be accessed on the affected nail and are examined for hyphae on potassium hydroxide wet mount and cultured. Obtaining an adequate sample of nail can be difficult because the distal subungual debris, which is easy to sample, often does not contain living fungus. Therefore, removing the distal portion of the nail with clippers before sampling or using a small curette to reach more proximally beneath the nail increases the yield. PCR can also be done on nail clippings if cultures are negative and the cost of finding a definitive diagnosis is warranted.

**Treatment**

- Sometimes oral terbinafine or itraconazole

Onychomycosis is not always treated because many cases are asymptomatic or mild and unlikely to cause complications, and the oral drugs that are the most effective treatments can potentially cause hepatotoxicity and serious drug interactions. Some proposed indications for treatment include the following:

- Previous ipsilateral cellulitis
- Diabetes or other risk factors for cellulitis
- Presence of bothersome symptoms
- Psychosocial impact
- Desire for cosmetic improvement (controversial)

Treatment is oral terbinafine or itraconazole. Terbinafine 250 mg once/day for 12 wk (6 wk for fingernail) or itraconazole 200 mg bid 1 wk/mo for 3 mo is used and achieves a cure rate of 60 to 75%, but the recurrence rate is estimated to be as high as 10 to 50%. It is not necessary to treat until all abnormal nail is gone because these drugs remain bound to the nail plate and continue to be effective after oral administration has ceased. The affected nail will not revert to normal; however, newly growing nail will appear normal. Topical antifungal nail lacquer containing ciclopirox 8% or amorolfine 5% (not available in the US) is rarely effective as primary treatment but can improve cure rate when used as an adjunct with oral drugs, particularly in resistant infections.

To limit relapse, the patient should trim nails short, dry feet after bathing, wear absorbent socks, and use antifungal foot powder. Old shoes may harbor a high density of spores and, if possible, should not be worn.

**Paronychia**

Paronychia is infection of the periungual tissues. Acute paronychia causes redness, warmth, and pain along the nail margin. Diagnosis is by inspection. Treatment is with antistaphylococcal antibiotics and drainage of any pus.

Paronychia is usually acute, but chronic cases occur. In acute paronychia, the causative organisms are usually *Staphylococcus aureus* or streptococci and, less commonly, *Pseudomonas* or *Proteus* spp. Organisms enter through a break in the epidermis resulting from a hangnail, trauma to a nail fold, loss of the cuticle, or chronic irritation (eg, resulting from water and detergents). Biting or sucking the fingers can also predispose people to developing the infection. In toes, infection often begins at an ingrown toenail (see p. 736).

In patients with diabetes and those with peripheral vascular disease, toe paronychia can threaten the
Symptoms and Signs

Paronychia develops along the nail margin (lateral and proximal nail folds), manifesting over hours to days with pain, warmth, redness, and swelling. Pus usually develops along the nail margin and sometimes beneath the nail. Infection can spread to the fingertip pulp, causing a felon. Rarely, infection penetrates deep into the finger, sometimes causing infectious flexor tenosynovitis.

Diagnosis

Diagnosis is by inspection. Several skin conditions can cause changes that mimic paronychia and should be considered, particularly when treatment is not effective initially. These conditions include squamous cell carcinoma, proximal onychomycosis, pyogenic granuloma, pyoderma gangrenosum, and herpetic whitlow.

Treatment

- Antistaphylococcal antibiotics
- Drainage of pus

Early treatment is warm compresses or soaks and an antistaphylococcal antibiotic (eg, dicloxacillin or cephalexin 250 mg po qid, clindamycin 300 mg po qid). In areas where methicillin-resistant *S. aureus* is common, antibiotics that are effective against this organism (eg, trimethoprim/sulfamethoxazole) should be chosen based on results of local sensitivity testing. In patients with diabetes and others with peripheral vascular disease, toe paronychia should be monitored for signs of cellulitis or more severe infection (eg, extension of edema or erythema, lymphadenopathy, fever).

Fluctuant swelling or visible pus should be drained with a Freer elevator, small hemostat, or #11 scalpel blade inserted between the nail and nail fold. Skin incision is unnecessary. A thin gauze wick should be inserted for 24 to 48 h to allow drainage.

Chronic Paronychia

**Chronic paronychia is recurrent or persistent nail fold inflammation, typically of the fingers.**

Chronic paronychia occurs almost always in people whose hands are chronically wet (eg, dishwashers, bartenders, housekeepers), particularly if they are diabetic or immunocompromised. *Candida* is often present, but its role in etiology is unclear; fungal eradication does not always resolve the condition. The condition may be an irritant dermatitis with secondary fungal colonization.

The nail fold is painful and red as in acute paronychia, but there is almost never pus accumulation. Eventually, there is loss of the cuticle and separation of the nail fold from the nail plate. This forms a space that allows entry of irritants and microorganisms. The nail becomes distorted.

Diagnosis is clinical.

**Treatment**

- Keeping hands dry
- Topical corticosteroid or tacrolimus

Primary treatment is to keep the hands dry and to assist the cuticle in reforming to close the space between the nail fold and nail plate. Gloves or barrier creams are used if water contact is necessary. Topical drugs that may help include corticosteroids and, for their corticosteroid-sparing effects, immunosuppressants (eg, tacrolimus). Antifungal treatments are helpful only in reducing colonizing fungal...
organisms. Thymol 3% in ethanol applied several times a day to the space left by loss of cuticle aids in keeping this space dry and free of microorganisms. If there is no response to therapy, squamous cell carcinoma should be considered and a biopsy should be done.

**Ingrown Toenail**

(Onychocryptosis)

**An ingrown toenail is incurvation or impingement of a nail border into its adjacent nail fold, causing pain.**

Causes include tight shoes, abnormal gait (eg, toe-walking), bulbous toe shape, excessive trimming of the nail plate, or congenital variations in nail contour (congenital pincer nail deformity). Sometimes an underlying osteochondroma is responsible, especially in the young. In the elderly, peripheral edema is a risk factor. Eventually, infection can occur along the nail margin (paronychia—see p. 735).

**Symptoms and Signs**

Pain occurs at the corner of the nail fold or, less commonly, along its entire lateral margin. Initially only mild discomfort may be present, especially when wearing certain shoes. In chronic cases, granulation tissue becomes visible, more often in the young.

**Diagnosis**

• Clinical evaluation

Redness, swelling, and pain suggest paronychia. In young patients (eg, < 20 yr) with ingrown toenails, x-rays should be considered to exclude underlying osteochondroma. In the elderly, apparent granulation tissue around the toe suggests the possibility of amelanotic melanoma, which is often overlooked; biopsy is necessary.

**Treatment**

• Usually nail excision and destruction of adjacent nail matrix

In mild cases, inserting cotton between the ingrown nail plate and painful fold (using a thin toothpick) may provide immediate relief and, if continued, correct the problem. If the shoes are too tight, a larger toe box is indicated. In most cases, however, particularly with paronychia, excision of the ingrown toenail after injecting a local anesthetic is the only effective treatment. If ingrown toenails recur, permanent destruction of the nearby lateral nail matrix by applying phenol or trichloroacetic acetic acid or by surgical excision is indicated. Phenol should not be used if there is arterial insufficiency.
Chapter 88. Pressure Ulcers

Introduction

(Pressure Sores; Bedsores; Decubitus Ulcers; Decubiti)

Pressure ulcers (PUs) are areas of necrosis and ulceration where tissues are compressed between bony prominences and hard surfaces; they result from pressure alone or pressure in combination with friction, shearing forces, or both. Risk factors include old age, impaired circulation, immobilization, undernutrition, and incontinence. Severity ranges from nonblanchable skin erythema to full-thickness skin loss with extensive soft-tissue necrosis. Diagnosis is clinical. Prognosis is excellent for early-stage ulcers; neglected and late-stage ulcers pose risk of serious infection and nutritional stress and are difficult to heal. Treatment includes pressure reduction, avoidance of friction and shearing forces, local care, and sometimes skin grafts or myocutaneous flaps.

Etiology

An estimated 1.3 to 3 million patients in the US have PUs; incidence is highest in older patients, especially those who are hospitalized or in long-term care facilities. Aging increases risk, in part because of reduced subcutaneous fat and decreased capillary blood flow. Immobility and comorbidities increase risk further.

Patients who are cognitively impaired, immobile, or both are at increased risk. Immobility—because of decreased spontaneous movement (eg, due to stroke, sedation, or severe illness) or inability to change position frequently because of weakness—is the most important factor. Other risk factors include urinary and fecal incontinence; poor nutritional status, including dehydration; diabetes; and cardiovascular disease. Clinical assessment is sufficient to identify patients at risk; several scales (eg, Norton, Braden—see Fig. 88-1) are useful for predicting risk. The National Pressure Ulcer Advisory Panel has also issued guidelines for the prediction and prevention of PUs.

Pathophysiology

PUs develop when soft tissues are compressed between bony prominences and contact surfaces or when friction (eg, rubbing against clothing or bedding) or shearing forces (which develop when skin clings to surfaces) cause erosion, tissue ischemia, and infarction. PUs most frequently develop over the sacrum, ischial tuberosities, trochanters, malleoli, and heels, but they can develop elsewhere, including behind the ears when nasal cannulae are used for prolonged periods. Also, poorly fitting prosthetic devices can cause PUs to develop over bony prominences. Increased force and duration of pressure directly influence risk and severity, but PUs can develop in as little as 3 to 4 h in some settings (eg, trauma patients who are immobilized on rigid spine-immobilization boards). Ulcers worsen when skin is overly moist and macerated (eg, from perspiration or incontinence).

Other causes of skin ulcers: Chronic arterial and venous insufficiency can result in skin ulcers, particularly on the lower extremities. Although the underlying mechanism is vascular, the same forces that cause PUs can worsen these ulcers, and principles of treatment are similar.

Symptoms and Signs

Several staging systems exist; the most common classifies ulcers according to the depth of soft-tissue damage (see Table 88-1). PUs do not always present as Stage I and then progress to higher stages.
Sometimes the first sign of a PU is a deep, necrotic stage III or IV ulcer. In a rapidly developing PU, subcutaneous tissue can become necrotic before the epidermis erodes. A small ulcer might, like an iceberg, be quite large under the surface.

**Stage I** PUs manifest as nonblanchable erythema, usually over a bony prominence. Color changes may not be as visible in darkly pigmented skin. The lesion may also be warmer, cooler, firmer, softer, or more tender than adjacent or contralateral tissue. This stage is a misnomer in the sense that an actual ulcer (a defect of skin into the dermis) is not yet present. However, ulceration will occur if the course is not arrested and reversed.

**Stage II** PUs involve loss of epidermis with or without erosion (defect of epidermis) or true ulceration (partial-thickness loss of dermis); subcutaneous tissue is not exposed. The ulcers are shallow with a reddish base. Intact or partially ruptured blisters due to pressure are also stage II PUs. (NOTE: Non-pressure-related causes of erosion, ulceration, or blistering—eg, skin tears, tape burns, perineal dermatitis, maceration, excoriation—are excluded from stage II description.)

**Stages III and IV** PUs have deeper involvement of underlying tissue with more extensive destruction.

Ulcers covered with debris or eschar are by definition unstageable. However, stable, nonfluctuant heel lesions with dry eschar should not be debrided for the sake of staging. Bruising of an apparent stage II ulcer should raise the suspicion of a deeper-stage PU. PUs at any stage may be painful or pruritic but may not be noticed by patients with blunted awareness or sensation. Tenderness, erythema of surrounding skin, exudate, or foul odor suggests infection. Fever should raise suspicion of bacteremia or underlying osteomyelitis.

**Complications**

Nonhealing ulcers may be due to inadequate treatment but should raise suspicion of osteomyelitis or, rarely, squamous cell carcinoma within the ulcer (Marjolin's ulcer). Other complications of nonhealing PUs include sinus tracts, which can be superficial or connect the ulcer to deep adjacent structures (eg, to the bowel in sacral ulcers), and tissue calcification. In addition, PUs are a reservoir for hospital-acquired antibiotic-resistant organisms, which can slow healing and cause bacteremia and sepsis.

**Diagnosis**

- Clinical evaluation with continuous assessment
- Sometimes bone scan or MRI

Diagnosis is usually apparent clinically, but depth and extent can be difficult to determine. PUs are always colonized by bacteria, so wound surface cultures are uninterpretable. Underlying osteomyelitis is diagnosed with radionuclide bone scanning or gadolinium-enhanced MRI, but both techniques have poor sensitivity and specificity. Diagnosis may require bone biopsy and culture.

Continuous assessment is mandatory for effective management. Serial photographs can also document healing.

**Prognosis**

Prognosis for early-stage PUs is excellent with timely, appropriate treatment, but healing typically requires weeks. PUs often develop in patients with suboptimal care. If care cannot be improved, long-term outcome is poor, even if short-term wound healing is accomplished.

**Treatment**

- Pressure reduction
- Direct ulcer care
• Management of pain, infection, and undernutrition

• Sometimes adjunctive therapy or surgery

Treatment requires multiple simultaneous elements.

Reducing pressure: Reducing tissue pressure is accomplished through careful positioning of the patient, protective devices, and variation of support surfaces.

Frequent repositioning (and selection of the proper position) is most important. A written schedule should be used to direct and document repositioning. Bedbound patients should be turned a minimum of every 2 h, should be placed at a 30° angle to the mattress when on their side (ie, lateral decubitus) to avoid direct trochanteric pressure, and should be elevated as minimally as possible to avoid the shear forces on tissues that result from sliding down the bed. For repositioning patients, lifting devices (eg, a Stryker frame) or bed linen should be used instead of dragging the patient (which causes friction and shear forces). Patients placed in chairs should be repositioned every hour, and they should be encouraged to change position on their own every 15 min.

Protective padding includes pillows or foam wedges placed between knees, ankles, and heels when patients are on their side and pillows, foam, or heel protectors when patients are supine. Windows should be cut out of plaster casts at pressure sites in patients immobilized by fractures. Soft seat cushions should be provided for patients able to sit in a chair. Donut-shaped devices and sheepskins should be avoided as a treatment for PUs.

Support surfaces under bedbound patients can be changed to reduce pressure. A change from standard mattresses is indicated when patients are unable to reposition themselves and periodic repositioning care is unavailable.

Support surfaces are static or dynamic.

Static surfaces, which do not require electricity, include air, foam, gel, and water overlays and mattresses. Old-fashioned “egg crate” mattresses offer no advantage. In general, static surfaces increase surface support areas and decrease pressure and shear forces; they are indicated for high-risk patients without PUs and for patients with stage I PUs.

Dynamic surfaces require electricity. Alternating-air mattresses have air cells that are alternately inflated and deflated by a pump, thus shifting supportive pressure from site to site. Low-air-loss mattresses are giant air-permeable pillows that are continuously inflated with air; the air flow has a drying effect on tissues. These specialized mattresses are indicated for patients with stage I ulcers who develop hyperemia on static surfaces and for patients with stage III or IV ulcers. Air-fluidized (high-air-loss) mattresses contain silicone-coated beads that liquefy when air is pumped through the bed. Advantages include reduction of moisture on surfaces and cooling. They are indicated for patients with nonhealing stage III and IV ulcers or numerous truncal ulcers (see Table 88-2). Although specialized mattresses are designed to shift pressure and reduce forces that lead to PUs, they are best thought of as an adjunct to comprehensive care.

Ulcer care: Appropriate ulcer care involves cleaning, debridement, and dressings.

Cleaning should be done initially and with each dressing change; ordinary soap and water (not hot) is usually best. Cleaning often involves irrigation with saline solution at pressures sufficient to remove bacteria without traumatizing tissue; commercial syringes, squeeze bottles, or electrically pressurized systems can be used. Alternatively, a 35-mL syringe and an 18-gauge IV catheter can be used. Irrigation should continue until no further debris can be loosened. Antiseptics (eg, iodine, hydrogen peroxide) and
antiseptic washes interfere with tissue healing and should be avoided. Rubbing of skin should be minimized, and moisturizer should be applied gently after each cleansing.

**Debridement** is necessary to remove dead tissue. Methods include

- **Autolytic debridement**: Synthetic occlusive dressings are used to facilitate digestion of dead tissues by enzymes normally present in wound fluids. Autolytic debridement may be used for small wounds with simple accumulation of tissue proteins and wounds that need to be sealed off anyway (eg, for protection from feces or urine). DuoDERM or Contreet (which is impregnated with silver and thus offers antimicrobial effects) are commonly applied. Infected wounds, however, should not be occluded.

- **Mechanical debridement**: Hydrotherapy (whirlpool baths), ultrasound, medical maggots, wound irrigation, or dextranomers (small carbohydrate-based beads that help absorb exudate and liquid debris) should be used to remove thick exudate or loose necrotic tissue. A scalpel or scissors can be used to remove eschar (except in heel ulcers, in which dry eschar in the absence of edema, erythema, fluctuance, or drainage can be safely left alone) or extensive areas of dead tissue. Modest amounts of eschar or tissue can be debrided at the patient's bedside, but extensive or deep areas should be debrided in the operating room. Urgent debridement is indicated in advancing cellulitis or sepsis. Debridement with wet-to-dry dressings should be done only for wounds with very loose exudate and only with great care because it is often painful and it may remove healthy tissue or overdry the wound.

- **Enzymatic debridement** (using collagenase, papain, fibrinolysin, or streptokinase/streptodornase): This method can be used for patients whose caretakers are not trained to do mechanical debridement or for patients unable to tolerate surgery. It is most effective after careful and judicious cross-hatching of the wound with a scalpel to improve penetration. Collagenase is especially effective as collagen comprises 75% of the dry weight of skin.

**Dressings** should be used for stage I ulcers that are subject to friction or incontinence and for all other ulcers (see Table 88-3). Objectives are to keep the ulcer bed moist to retain tissue growth factors while allowing some evaporation and inflow of O₂, to keep surrounding skin dry, to facilitate autolytic debridement, and to establish a barrier to infection. Transparent films (eg, OpSite, Tegaderm, Bioclusive) are sufficient for ulcers with limited exudate; they should not be used over cavities and must be changed every 3 to 7 days. Some experts recommend a small amount of triple antibiotic ointment under the dressing. Hydrogels (Clear-Site, Vigilon, FlexiGel), which are cross-linked polymer dressings that come in sheets or gels, are indicated for very shallow wounds, such as re-epithelializing wounds with minimal exudate.

Hydrocolloids (eg, RepliCare, DuoDERM, Restore, Tegasorb), which combine gelatin, pectin, and carboxymethylcellulose in the form of wafers, powders, and pastes, are indicated for light-to-moderate exudate; some have adhesive backings and others are typically covered with transparent films to ensure adherence to the ulcer and must be changed every 3 days. Alginites (polysaccharide seaweed derivatives containing alginic acid), which come as pads, ropes, and ribbons (AlgiSite, Sorbsan, Curasorb), are indicated for absorbing extensive exudate and for controlling bleeding after surgical debridement. Foam dressings (Allevyn, LYOfoam, Hydrosorb, Mepilex, Curafoam, Contreet) are useful as they can handle various levels of exudate and provide a moist environment for wound healing. Waterproof versions protect the skin from incontinence. Dressings with adhesive backings stay in place longer and need less frequent changing.

**Pain management**: Primary treatment of pain is treatment of the PU itself, but NSAIDs or acetaminophen is used for mild-to-moderate pain. Opioids should be avoided if possible because sedation promotes immobility. Opioids may be necessary during dressing changes and debridement. In cognitively impaired patients, changes in vital signs can be used as an indication of pain.

**Infection management**: PUs should be continually reassessed for bacterial infection using clinical signs...
of erythema, warmth, increased drainage, fever, and elevated WBC count. Options for topical treatment include silver sulfadiazine, triple antibiotic, and metronidazole (the latter for anaerobic bacteria, which are often foul smelling). Systemic antibiotics should be administered for cellulitis, bacteremia, or osteomyelitis; usage should be guided by tissue culture or clinical suspicion and not by surface culture.

**Nutrition:** Undernutrition is common among patients with PUs and is a risk factor for nonhealing. Markers of undernutrition include albumin < 3.5 mg/dL or weight < 80% of ideal. Protein intake of 1.25 to 1.5 g/kg/day, sometimes requiring oral or parenteral supplementation (see p. 20), is desirable for optimal healing. Zinc supplementation supports wound healing, and replacement at a dose of 50 mg tid may be useful. Supplemental vitamin C 1 g/day may be provided. Providing a drink of water to patients at each repositioning may be useful to aid hydration.

**Adjuncts:** Multiple adjunctive treatments have been tried or are under investigation. Negative pressure therapy (for clean wounds) and the use of various topical recombinant growth factors (eg, nerve growth factor, platelet-derived growth factor-BB) and skin equivalents are showing promise in wound management; however, they do not ameliorate mechanical forces and tissue ischemia. Electrical stimulation, heat therapy, massage therapy, and hyperbaric O₂ therapy have not proven effective.

**Surgery:** Surgical debridement is necessary for any ulcer with devitalized tissue, except for stable, dry, nonfluctuant heel ulcers. Large defects, especially with exposure of musculoskeletal structures, require surgical closure. Skin grafts are useful for large, shallow defects. However, because grafts do not add to blood supply, measures must be taken to prevent pressure from developing to the point of ischemia and further breakdown. Myocutaneous flaps, because of their pressure-sharing bulk and rich vasculature, are the closures of choice over large bony prominences (eg, sacrum, ischia, trochanters).

**Ischemic and venous ulcers:** Wound care treatments also are useful for ischemic ulcers, but the underlying pathophysiology must be addressed (eg, better control of the inflammatory process in a rheumatoid ulcer or surgical stenting or bypass surgery to improve circulation in atherosclerosis). Pentoxifylline has been tried with minimal success. Some evidence supports the use of dalteparin for diabetic foot ulcers (5000 units sc once/day until healed); however, this finding has not been corroborated. Ischemic ulcers can become infected, often with anaerobic organisms, and the infection may spread, causing septicemia or osteomyelitis.

Venous ulcers are typically sterile at first but tend to lead to cellulitis. The same local care as for PUs can be used. In addition, treatment includes measures to reduce venous hypertension, such as using compression stockings or Unna boot bandages (applied at a pressure of 35 to 40 mm Hg) and elevating the leg above the heart. Pentoxifylline 800 mg po tid for up to 24 wk may be useful.

**Prevention**

Prevention requires

- Identification of high-risk patients
- Repositioning
- Conscientious skin care and hygiene
- Avoidance of oversedation

The mainstay of prevention is frequent repositioning. Pressure should not continue over any bony surface for > 2 h. Patients who cannot move themselves must be repositioned using pillows. Even when on low-pressure mattresses, patients must be turned. Pressure points should be checked for erythema or trauma at least once/day under adequate lighting. Patients and family members must be taught a routine of daily visual inspection and palpation of sites for potential ulcer formation.

Daily attention to hygiene and dryness is necessary to prevent maceration and secondary infection. Although sheepskin should not be used to redistribute pressure after ulceration has occurred, lying on a...
sheepskin as a preventive measure helps keep the skin in good condition. Protective padding, pillows, or a sheepskin can be used to separate body surfaces. Bedding and clothing should be changed frequently; sheets should be soft, clean, and free from wrinkles and particulate matter. In hot weather, the skin should be sponge-bathed and thoroughly dried afterward. In incontinent patients, ulcers should be protected from contamination; synthetic dressings can help. Skin breakdown can be prevented with careful cleansing and drying (patting and not rubbing the skin) and using anticandidal creams and moisture barrier creams or skin protective wipes (eg, Skin-Prep). Use of adhesive tape should be minimized because it can irritate and even tear fragile skin.

Areas subject to friction may be powdered with plain talc. Use of cornstarch is discouraged because it may allow microbial growth.

Oversedation should be avoided, and activity should be encouraged. Adequate nutrition is important.
Chapter 89. Benign Tumors

Introduction

(See also Warts on p. 715 and Genital Warts on p. 1470)

Most skin tumors are benign. However, because skin cancers must be treated early, proper diagnosis of unusual skin growths should always be made definitively and without undue delay.

Dermatofibroma

(Fibrous Histiocytoma)

Dermatofibroma is a firm, red-to-brown, small papule or nodule composed of fibroblastic tissue. It usually occurs on the thighs or legs.

Dermatofibromas are common, more so in women, and typically appear when people are in their 20s. Their cause is unknown. Lesions are usually 0.5 to 1 cm in diameter and feel like a lentil embedded in the skin. Most are asymptomatic, but some itch or ulcerate following minor trauma. Diagnosis is clinical; lesions typically dimple when grasped between the fingers. They may regress spontaneously, but they can be excised if troublesome.

Epidermal Cysts

(Keratinous Cyst; Epidermal Inclusion Cyst; Sebaceous Cyst; Milia; Pilar Cyst [Wen]; Steatocystoma)

Epidermal cysts are slow-growing benign cysts containing material that is keratinous (keratinous or epidermal inclusion cyst, sebaceous cyst, milia), follicular (pilar cyst, or wen), or sebaceous (steatocystoma). They frequently occur on the scalp, ears, face, back, or scrotum.

On palpation, the cystic mass is firm, globular, movable, and nontender; cysts range from about 1 to 5 cm in diameter. This kind of cyst seldom causes discomfort unless it has ruptured internally, causing a rapidly enlarging, painful foreign body reaction and abscess. Keratinous cysts, the most common, often are surmounted with a punctum or pore; their contents are cheesy and often fetid (due to secondary bacterial colonization). Milia are minute superficial keratinous cysts noted on the face.

Treatment

Cysts may be left or removed. A small incision may be made to evacuate the contents, then the cyst wall itself should be removed with a curet or hemostat; otherwise, the lesion will recur. Surgical excision with complete removal of the cyst wall is also effective. Internally ruptured cysts should be incised and drained; a gauze drain is inserted and removed after 2 to 3 days. Antibiotics are not needed unless cellulitis is present. Milia may be evacuated with a #11 blade.

Keloids

Keloids are smooth overgrowths of fibroblastic tissue that arise in an area of injury (eg, lacerations, surgical scars, truncal acne) or, occasionally, spontaneously.

Keloids are more frequent in blacks. They tend to appear on the upper trunk, especially the upper back and mid chest, and on deltoid areas. Unlike hyperplastic scars, keloidal scar tissue always extends beyond the area of original injury.

Keloids are shiny, firm, smooth, usually ovoid but sometimes contracted or webbed, and slightly pink or hyperpigmented (see Plate 37). Diagnosis is clinical.

Treatment
Treatment is often ineffective. Monthly corticosteroid injections (eg, triamcinolone acetonide 5 to 40 mg/mL) into the lesion sometimes flatten the keloid. Surgical or laser excision may debulk lesions, but they usually recur larger than before. Excision is more successful if preceded and followed by a series of intralesional corticosteroid injections. Gel sheeting (applying a soft, semiocclusive dressing made of cross-linked polymethylsiloxane polymer, or silicone) or pressure garments are other adjuncts to prevent recurrence.

**Keratoacanthoma**

Keratoacanthoma is a round, firm, usually flesh-colored nodule with sharply sloping borders and a characteristic central crater containing keratinous material; it usually resolves spontaneously.

Etiology is unknown. Most consider these lesions to be well-differentiated squamous cell carcinomas with a tendency to involute.

Development is rapid. Usually the lesion reaches its full size, typically 1 to 3 cm but may be > 5 cm, within 1 or 2 mo. Common sites are sun-exposed areas, the face, the forearm, and the dorsum of the hand. Spontaneous involution may start within a few months. However, because this lesion cannot be relied upon to involute, biopsy or excision is recommended. Spontaneous involution may leave substantial scarring; surgery or intralesional injections with methotrexate or 5-fluorouracil usually yield better cosmetic results, and excision allows histologic confirmation of the diagnosis.

**Lipomas**

Lipomas are soft, movable, subcutaneous nodules of adipocytes (fat cells); overlying skin is normal.

A patient may have one or many lipomas. They occur more often in women than men, rarely grow to be > 7 to 8 cm in diameter, and appear most commonly on the trunk, nape, and forearms. They are rarely symptomatic, but they may be painful, especially in patients with familial variants presenting with multiple lesions.

**Diagnosis**

- Usually clinical

A lipoma is usually easily movable within the subcutis. Lipomas are generally soft, but some become firmer. Some superficial dimpling may occur, but frank inflammation is not normal.

A rapidly growing lesion should be biopsied, although lipomas rarely become malignant.

**Treatment**

Treatment is not usually required, but bothersome lipomas may be removed by excision or liposuction.

**Moles**

(Pigmented, Melanocytic, or Nevus Cell Nevi)

Moles are pigmented macules, papules, or nodules composed of clusters of melanocytes or nevus cells. Their main significance (other than cosmetic) is their potential for being or becoming malignant. Lesions with characteristics of concern (changing or highly irregular borders, color changes, pain, bleeding, ulceration, or itching) are biopsied.

Almost everyone has a few moles, which usually appear in childhood or adolescence. There are different types of moles (see Table 89-1). During adolescence and pregnancy, more moles often appear, and existing ones may
enlarge or darken. Moles typically become more raised and less pigmented over the decades.

An individual mole is unlikely to become malignant (lifetime risk is about 1 in 3,000 to 10,000), but the single best predictor for risk of development of melanoma is the total number of moles. The presence of > 20 moles indicates a higher than average risk for melanoma; patients should be taught to self-monitor for warning signs and have skin surveillance as part of their primary care.

**Diagnosis**

• **Biopsy**

Because moles are extremely common and melanomas are uncommon, prophylactic removal is not justifiable. However, a mole should be biopsied and examined histologically if it has certain characteristics of concern:

• Changing or highly irregular borders
• Color changes
• Pain
• Bleeding
• Ulceration
• Itching

The biopsy specimen must be deep enough for accurate microscopic diagnosis and should contain the entire lesion if possible, especially if the concern for cancer is strong. However, wide primary excision should not be the initial procedure, even for highly abnormal-appearing lesions, because many such lesions are not melanomas. Incisional biopsy does not increase the likelihood of metastasis if the lesion is malignant, and it avoids extensive surgery for a benign lesion.

**Treatment**

• Sometimes excision

Moles can be removed by shaving or excision for cosmetic purposes, and all moles removed should be examined histologically. If hair growth is a concern for the patient, a hairy mole should be adequately excised rather than removed by shaving. Otherwise, hair regrowth will occur.

**Atypical Moles**

(Dysplastic Nevi)

Atypical moles (AM) are melanocytic nevi with irregular and ill-defined borders, variegated colors usually of brown and tan tones, and macular or papular components. Management is by monitoring and biopsy of highly atypical or changed lesions. Patients should reduce sun exposure and conduct regular self-examinations for new moles or changes in existing ones.

AM are nevi with a slightly different clinical and histologic appearance (disordered architecture and atypia of melanocytes). Patients with AM are at increased risk of melanoma; risk increases as the number of AM and as sun exposure increase. Some patients have only one or a few AM; others have many.

The propensity to develop AM may be inherited (autosomal dominant) or sporadic without apparent
familial association. Familial atypical mole-melanoma syndrome refers to the presence of multiple AM and melanoma in ≥ 2 1st-degree relatives. These patients are at markedly increased risk (25 times) for melanoma.

**Symptoms and Signs**

AM are often larger than other nevi (> 6 mm diameter) and primarily round (unlike many melanomas) but with indistinct borders and mild asymmetry. In contrast, melanomas have greater irregularity of color, not just tan and brown, but dark brown, black, red, and blue or whitish areas of depigmentation.

**Diagnosis**

- Regular physical examinations
- Biopsy

Although clinical findings suggest the diagnosis of AM (see Table 89-2), biopsy of the worst-appearing lesions should be done to establish the diagnosis and to determine the degree of atypia.

One or more atypical-appearing lesions should be biopsied. Patients with multiple AM and a personal or family history of melanoma should be examined regularly (eg, yearly for family history, more often for personal history, of melanoma).

**Treatment**

Atypical moles can be removed by excision or shaving.

**Prevention**

Patients with AM should avoid excessive sun exposure and use sunscreens. Also, they should be taught self-examination to detect changes in existing moles and to recognize features of melanomas. Some experts recommend yearly photographs of the skin surface. Regular follow-up examinations may be combined with baseline and follow-up color photographs of most of the patient's body; this method is most useful in patients with many AM.

If patients have a family history of melanoma (whether developing from AM or de novo) or other skin cancers, 1st-degree relatives should be examined. Patients who are from melanoma-prone families (ie, ≥ 2 1st-degree relatives with cutaneous melanomas) have a high lifetime risk of developing melanomas. The entire skin (including the scalp) of members of an at-risk family should be examined.

**Seborrheic Keratoses**

Seborrheic keratoses are pigmented superficial epithelial lesions that are usually warty but may occur as smooth papules.

The cause is unknown. The lesions commonly occur in middle or old age and most often appear on the trunk or temples; in blacks and Asians, especially women, lesions that are 1 to 3 mm often occur on the cheekbones; this condition is termed dermatosis papulosa nigra.

Seborrheic keratoses vary in size and grow slowly. They may be round or oval and flesh-colored, brown, or black. They usually appear stuck on and may have a verrucous, velvety, waxy, scaling, or crusted surface (see Plate 44).
Diagnosis is clinical.

They are not premalignant and need no treatment unless they are irritated, itchy, or cosmetically bothersome. Lesions may be removed with little or no scarring by cryotherapy (which can cause hypopigmentation) or by electro-desiccation and curettage after local injection of lidocaine.

**Skin Tags**

Skin tags (acrochordons, soft fibromas) are common soft, small, flesh-colored or hyperpigmented, pedunculated lesions; there are usually multiple lesions, typically on the neck, axilla, and groin.

Skin tags are usually asymptomatic but may be irritating. Irritating or unsightly skin tags can be removed by freezing with liquid nitrogen, light electrodessication, or excision with a scalpel or scissors. The standard of care is to submit all skin tags individually for histologic examination, especially if there is any question of the diagnosis. However, for a patient with dozens of identical lesions, an individual lesion is unlikely to be anything other than a skin tag.

**Vascular Lesions**

Vascular lesions include acquired lesions (eg, pyogenic granuloma) and those that are present at birth or arise shortly after birth (vascular birthmarks). Vascular birthmarks include vascular tumors (eg, infantile hemangioma) and vascular malformations. Vascular malformations are congenital, life-long, localized defects in vascular morphogenesis and include capillary (eg, nevus flammeus), venous, arteriovenous (eg, cirrroid aneurysm), and lymphatic malformations. Vascular birthmarks usually involve only the skin and subcutaneous tissues and rarely affect the CNS.

**Infantile Hemangioma**

Infantile hemangiomas (IH) are raised, red or purplish, hyperplastic vascular lesions appearing in the first year of life. Most spontaneously involute; those obstructing vision, the airway, or other structures require treatment, usually with oral corticosteroids. Surgery is rarely recommended.

IH is the most common tumor of infancy, affecting 10 to 12% of infants by age 1 yr. IH is present at birth in 10 to 20% of those affected and almost always within the first several weeks of life; occasionally, deeper lesions may not be apparent until a few months after birth. Size and vascularity increase rapidly, usually peaking at about age 1 yr.

IH can be classified by general appearance (superficial, deep, or cavernous) or by other descriptive terms (eg, strawberry hemangioma). However, because all of these lesions share a common pathophysiology and natural history, the inclusive term infantile hemangioma is preferred.

**Symptoms and Signs**

Superficial lesions have a bright red appearance; deeper lesions have a bluish color. Lesions can bleed or ulcerate from minor trauma; ulcers may be painful. IH in certain locations can interfere with function. Lesions on the face or oropharynx may interfere with vision or obstruct the airway; those near the urethral meatus or anus may interfere with elimination. A periocular hemangioma in an infant is an emergency because even a few days of disrupted vision can result in permanent visual defects. Lumbosacral hemangiomas may be a sign of neurologic or GU anomalies.

Lesions slowly involute starting at 12 to 18 mo, decreasing in size and vascularity. Generally, IH involute by 10%/year of age (eg, 50% by age 5, 60% by age 6), with maximal involution by age 10. Involuting lesions commonly have a yellowish or telangiectatic color and a wrinkled or lax fibrofatty texture. Residual changes are almost always proportional to the lesion's maximal size and vascularity.

**Diagnosis**
Diagnosis is clinical; the extent can be evaluated by MRI if lesions appear to encroach on vital structures.

**Treatment**

- Sometimes laser therapy
- Sometimes intralesional or systemic corticosteroid therapy
- General wound care for ulcerated lesions

Treatment is controversial. Many physicians treat lesions early to prevent subsequent enlargement or to make them less noticeable; others do not treat unless a lesion causes (or risks) functional problems by its location. When treatment is elected, laser therapy or intralesional or systemic corticosteroids are chosen based on the location, extent, and rate of growth of the lesion. For systemic corticosteroid therapy, prednisone 1 to 3 mg/kg po bid or tid is given for ≥ 2 wk. If resolution starts, the prednisone should be decreased slowly; if not, the drug should be stopped.

Topical treatments and wound care are useful for ulcerated lesions and help prevent scarring, bleeding, and pain. Compresses, topical mupirocin or metronidazole, barrier dressings (polyurethane film dressing or petrolatum-impregnated gauze), or barrier creams may be used.

Unless complications are life threatening or vital organs are compromised, surgical excision or other destructive procedures should be avoided because they frequently cause more scarring than occurs with spontaneous involution. To help parents accept nonintervention, the physician can review the natural history (photographic examples are helpful), provide serial photography of the lesion to document involution, and listen sympathetically to parents' concerns.

**Nevus Flammeus and Port-Wine Stain**

**Nevus flammeus and port-wine stains are capillary vascular malformations that are present at birth and appear as flat, pink, red, or purplish lesions.**

**Nevi flammei** are flat pink marks that are very common on the nape, glabella, and eyelids. Lesions around the eyes disappear in a few months. Nape lesions may disappear in early childhood, only to recur in middle age.

**Port-wine stains** are flat, reddish to purple lesions appearing anywhere on the body. Lesions become darker and more palpable with time (often becoming quite hyperplastic by late middle age), but the lateral extent increases only in proportion to the growth of the patient. Port-wine stains of the trigeminal area may be a component of the Sturge-Weber syndrome (in which a similar vascular lesion appears on the underlying meninges and cerebral cortex and is associated with epilepsy).

Diagnosis is clinical.

Treatment with vascular lasers produces excellent results in many cases, especially if the lesion is treated as early in life as possible. The lesion can also be hidden with an opaque cosmetic cream prepared to match the patient's skin color.

**Nevus Araneus**

(Spider Nevus; Spider Angioma; Vascular Spider)

**Nevus araneus is a bright red, faintly pulsatile vascular lesion consisting of a central arteriole with slender projections resembling spider legs (see Plate 26).**

These lesions are acquired. One lesion or small numbers of lesions unrelated to internal disease may
occur in children or adults. Patients with cirrhosis develop many spider angiomas that may become quite prominent. Many women develop lesions during pregnancy or while taking oral contraceptives.

The lesions are asymptomatic and usually resolve spontaneously about 6 to 9 mo postpartum or after oral contraceptives are stopped. Lesions are not uncommon on the faces of children. Compression of the central vessel temporarily obliterates the lesion.

Diagnosis is clinical.

Treatment is not usually required. If resolution is not spontaneous or treatment is desired for cosmetic purposes, the central arteriole can be destroyed with fine-needle electrodesiccation; vascular laser treatment may also be done.

**Pyogenic Granuloma**

Pyogenic granuloma is a fleshy, moist or crusty, usually scarlet vascular nodule composed of proliferating capillaries in an edematous stroma.

The lesion, composed of vascular tissue, is neither of bacterial origin nor a true granuloma. It develops rapidly, often at the site of recent injury (although injury may not be recalled), typically grows no larger than 2 cm in diameter, and probably represents a vascular and fibrous response to injury. There is no sex or age predilection. The overlying epidermis is thin, and the lesion tends to be friable, bleeds easily, and does not blanch on pressure. The base may be pedunculated and surrounded by a collarette of epidermis.

During pregnancy, pyogenic granulomas may become large and exuberant (eg, gingival pregnancy tumors, or telangiectatic epulis).

Diagnosis involves biopsy and histologic examination. Histologic analysis is required for all removed tissue because these lesions occasionally resemble and must be differentiated from melanomas or other malignant tumors.

Treatment consists of removal by excision or curettage and electrodesiccation, but the lesions may recur.

**Lymphatic Malformations**

(Lymphangioma; Lymphangioma Circumscriptum; Cystic Hygroma; Cavernous Lymphangioma)

Lymphatic vascular malformations are elevated lesions composed of dilated lymphatic vessels.

Most lymphatic malformations are present at birth or develop within the first 2 yr. Lesions are usually yellowish tan but occasionally reddish or purple if small blood vessels are intermingled. Puncture of the lesion yields a colorless or blood-tinged fluid.

Diagnosis is made clinically and by MRI.

Treatment is usually not needed. If the lesion is excised, recurrence is common, even when removal of dermal and subcutaneous tissues is extensive.
Chapter 90. Cancers of the Skin

Introduction

Skin cancer is the most common type of cancer and usually develops in sun-exposed areas of skin. The incidence is highest among outdoor workers, sportsmen, and sunbathers and is inversely related to the amount of melanin skin pigmentation; fair-skinned people are most susceptible. Skin cancers may also develop years after therapeutic x-rays or exposure to carcinogens (eg, arsenic ingestion).

Over one million new cases of skin cancer are diagnosed in the US yearly. About 80% are basal cell carcinoma, 16% are squamous cell carcinoma, and 4% are melanoma. Paget's disease of the nipple or extramammary Paget's (usually near the anus), Kaposi's sarcoma, tumors of adnexa, and cutaneous T-cell lymphoma (mycosis fungoides—see p. 1024) make up the remaining, less common, forms of skin cancer.

Initially, skin cancers are often asymptomatic. The most frequent presentation is a papule or blind pimple that does not go away. Any lesion that appears to be enlarging should be biopsied—whether tenderness, mild inflammation, crusting, or occasional bleeding is present or not. If treated early, most skin cancers are curable.

Screening: Routine screening for skin cancer is by patient self-examination, physician examination, or both.

Prevention: Because many skin cancers seem to be related to ultraviolet (UV) exposure, a number of measures are recommended to limit exposure.

• Sun avoidance: Seeking shade, minimizing outdoor activities between 10 AM and 4 PM (when sun's rays are strongest), and avoiding sunbathing and the use of tanning beds

• Use of protective clothing: Long-sleeved shirt, pants, and broad-brimmed hat

• Use of sunscreen: At least sun protection factor (SPF) 30 with UVA protection, used as directed; should not be used to prolong sun exposure

Current evidence is inadequate to determine whether these measures reduce incidence or mortality of melanoma; in nonmelanoma skin cancers (basal cell and squamous cell carcinoma), sun protection does decrease the incidence of new cancers.

Basal Cell Carcinoma

(Rodent Ulcer)

Basal cell carcinoma is a superficial, slowly growing papule or nodule (see Plate 29) that derives from certain epidermal cells. Basal cell carcinomas arise from keratinocytes near the basal layer and can be referred to as basaloid keratinocytes. Metastasis is rare, but local growth can be highly destructive. Diagnosis is by biopsy. Treatment depends on the tumor's characteristics and may involve curettage and electrodesiccation, surgical excision, cryosurgery, topical chemotherapy, or, occasionally, radiation therapy.

Basal cell carcinoma is the most common type of skin cancer, with > 800,000 new cases yearly in the US. It is more common in fair-skinned people with a history of sun exposure and is very rare in blacks.

Symptoms and Signs

The clinical manifestations and biologic behavior of basal cell carcinomas are highly variable. They may appear as

• Small, shiny, firm, almost translucent nodules
• Ulcerated, crusted papules or nodules

• Flat, scarlike, indurated plaques

• Red, margined, thin papules or plaques that are difficult to differentiate from psoriasis or localized dermatitis

Most commonly, the carcinoma begins as a shiny papule, enlarges slowly, and, after a few months or years, shows a shiny, pearly border with prominent engorged vessels (telangiectases) on the surface and a central dell or ulcer. Recurrent crusting or bleeding is not unusual. Commonly, the carcinomas may alternate between crust and heal, which may unjustifiably decrease patients' and physicians' concern about the importance of the lesion.

Basal cell carcinomas rarely metastasize but may invade healthy tissues. Rarely, patients die because the carcinoma invades or impinges on underlying vital structures or orifices (eyes, ears, mouth, bone, dura mater).

Diagnosis

• Biopsy and histologic examination

Treatment

Treatment should be done by a specialist. The clinical appearance, size, site, and histologic subtype determine the choice of treatment—curettage and electrodesiccation, surgical excision, cryosurgery, topical chemotherapy (imiquimod, 5-fluorouracil, and photodynamic therapy), or, occasionally, radiation therapy. Recurrent or incompletely treated cancers, large cancers, cancers at recurrence-prone sites, and morphea-like cancers with vague borders are often treated with Mohs microscopically controlled surgery, in which tissue borders are progressively excised until specimens are tumor-free (as determined by microscopic examination during surgery). Almost 25% of patients with a history of basal cell carcinoma develop a new basal cell cancer within 5 yr of the original carcinoma. Consequently, patients with a history of basal cell carcinoma should be seen annually for a skin examination.

Bowen's Disease

(Intraepidermal Squamous Cell Carcinoma)

Bowen's disease is a superficial squamous cell carcinoma in situ.

Bowen's disease is most common in sun-exposed areas but may arise at any location. Lesions can be solitary or multiple. They are red-brown and scaly or crusted, with little induration; they frequently resemble a localized thin plaque of psoriasis, dermatitis, or a dermatophyte infection. Diagnosis is by biopsy.

Treatment depends on the tumor's characteristics and may involve topical chemotherapy, curettage and electrodesiccation, surgical excision, or cryosurgery.

Squamous Cell Carcinoma

Squamous cell carcinoma is a malignant tumor of epidermal keratinocytes that invades the dermis; this cancer usually occurs in sun-exposed areas. Local destruction may be extensive, and metastases occur in advanced stages. Diagnosis is by biopsy. Treatment depends on the tumor's characteristics and may involve curettage and electrodesiccation, surgical excision, cryosurgery, or, occasionally, radiation therapy.

Squamous cell carcinoma, the 2nd most common type of skin cancer, may develop in normal tissue, in a preexisting actinic keratosis (see p. 674), in a patch of leukoplakia, or in a burn scar. The incidence in the
US is 200,000 to 300,000 cases annually, with 2000 deaths.

The clinical appearance is highly variable, but any nonhealing lesion on sun-exposed surfaces should be suspect. The tumor may begin as a red papule or plaque with a scaly or crusted surface and may become nodular, sometimes with a warty surface. In some cases, the bulk of the lesion may lie below the level of the surrounding skin. Eventually the tumor ulcerates and invades the underlying tissue.

**Diagnosis**

Biopsy is essential. Differential diagnosis includes many types of benign and malignant lesions, such as basal cell carcinoma, keratoacanthoma, actinic keratosis, verruca vulgaris, and seborrheic keratosis.

**Prognosis**

In general, the prognosis for small lesions removed early and adequately is excellent. Regional and distant metastases of squamous cell carcinomas on sun-exposed skin are uncommon but do occur, particularly with poorly differentiated tumors. However, about one third of lingual or mucosal cancers have metastasized before diagnosis (see p. 491).

Late-stage disease, which may require extensive surgery, is far more likely to metastasize. It spreads initially regionally to surrounding skin and lymph nodes and eventually to nearby organs. Cancers that occur near the ears, the vermilion, and in scars are more likely to metastasize. The overall 5-yr survival rate for metastatic disease is 34% despite therapy.

**Treatment**

Treatment is similar to that for basal cell carcinoma and includes curettage and electrodesiccation, surgical excision, cryosurgery, topical chemotherapy (imiquimod, 5-fluorouracil), and photodynamic therapy, or, occasionally, radiation therapy (see p. 749). Treatment and follow-up must be monitored closely because of the greater risk of metastasis. Squamous cell carcinoma on the lip or other mucocutaneous junction should be excised; at times, cure is difficult. Recurrences and large tumors should be treated aggressively with Mohs microscopically controlled surgery, or by a team approach with surgery and radiation therapy.

Metastatic disease is responsive to radiation therapy if metastases can be identified and are isolated. Widespread metastases do not respond well to chemotherapeutic regimens.

**Melanoma**

(Malignant Melanoma)

Malignant melanoma arises from melanocytes in a pigmented area (eg, skin, mucous membranes, eyes, or CNS). Metastasis is correlated with depth of dermal invasion. With spread, prognosis is poor. Diagnosis is by biopsy. Wide surgical excision is the rule for operable tumors. Metastatic disease requires chemotherapy but is difficult to cure.

About 60,000 new cases of melanoma occur yearly in the US, causing about 8400 deaths. Incidence has remained steady over the last 8 yr (it had previously been increasing at a faster rate than any other malignant tumor).

Melanomas occur mainly on the skin but also on the mucosa of the oral and genital regions and conjunctiva. Melanomas vary in size, shape, and color (usually pigmented) and in their propensity to invade and metastasize. Metastasis occurs via lymphatics and blood vessels. Local metastasis results in the formation of nearby satellite papules or nodules that may or may not be pigmented. Direct metastasis to skin or internal organs may occur, and occasionally, metastatic nodules or enlarged lymph nodes are discovered before the primary lesion is identified.

**Etiology**
Risk factors include

• Sun exposure
• Family and personal history
• Fair skin
• Increased numbers of melanocytic nevi
• Immunosuppression
• Occurrence of lentigo maligna
• Large congenital melanocytic nevus
• Dysplastic nevus syndrome

Patients with a personal history of melanoma have an increased risk of additional melanomas. People who have one or more 1st-degree relatives with a history of melanoma have an increased risk (up to 6 or 8 times) over those without a family history. Melanoma is rare in blacks.

About 40 to 50% of melanomas develop from pigmented moles (see also p. 744); almost all the rest arise from melanocytes in normal skin. Atypical moles (dysplastic nevi) may be precursors to melanoma (see p. 744). The very rare melanomas of childhood almost always arise from large pigmented moles (giant congenital nevi) present at birth. Although melanomas occur during pregnancy, pregnancy does not increase the likelihood that a mole will become a melanoma; moles frequently change in size and darken uniformly during pregnancy. However, the following signs of malignant transformation should be carefully sought:

• Change in size
• Irregular change in color, especially spread of red, white, and blue pigmentation to surrounding normal skin
• Change in surface characteristics, consistency, or shape
• Signs of inflammation in surrounding skin, with possible bleeding, ulceration, itching, or tenderness

Classification

There are 4 main types of melanoma.

**Lentigo maligna melanoma:** This type accounts for 5 to 15% of melanomas. It tends to arise in older patients. It arises from lentigo maligna (Hutchinson's freckle or malignant melanoma in situ). It appears on the face or other sun-exposed areas as an asymptomatic, flat, tan or brown, irregularly shaped macule or patch with darker brown or black spots scattered irregularly on its surface. In lentigo maligna, both normal and malignant melanocytes are confined to the epidermis. When malignant melanocytes invade the dermis, the lesion is called lentigo maligna melanoma, and the cancer may metastasize.

**Superficial spreading melanoma:** This type accounts for two thirds of melanomas. Typically asymptomatic, it occurs most commonly on women's legs and men's torsos. The lesion is usually a plaque with irregular, raised, indurated, tan or brown areas, which often have red, white, black, and blue spots or small, sometimes protuberant blue-black nodules (see Plate 40). Small notchlike indentations of the margins may be noted, along with enlargement or color change. Histologically, atypical melanocytes characteristically invade the dermis and epidermis.
Nodular melanoma: This type accounts for 10 to 15% of melanomas. It may occur anywhere on the body as a dark, protuberant papule or a plaque that varies from pearl to gray to black. Occasionally, a lesion contains little if any pigment or may look like a vascular tumor. Unless it ulcerates, nodular melanoma is asymptomatic, but patients usually seek advice because the lesion enlarges rapidly.

Acral-lentiginous melanoma: This type accounts for only 5 to 10% of melanomas, but it is the most common form of melanoma in blacks. It arises on palmar, plantar, and subungual skin and has a characteristic histologic picture similar to that of lentigo maligna melanoma.

Diagnosis

• Biopsy

The differential diagnosis includes basal cell and squamous cell carcinomas, seborrheic keratoses, atypical moles, blue nevi, dermatofibromas, moles, hematomas (especially on the hands or feet), venous lakes, pyogenic granulomas, and warts with focal thromboses. If doubt exists, biopsy should include the full depth of the dermis and extend slightly beyond the edges of the lesion. Biopsy should be excisional for small lesions and incisional for larger lesions. By doing step sections, the pathologist can determine the maximal thickness of the melanoma. Definitive radical surgery should not precede histologic diagnosis.

Pigmented lesions with the following features should be excised or biopsied:

• Recent enlargement

• Darkening

• Bleeding

• Ulceration

However, these features usually indicate that the melanoma has already invaded the skin deeply. Earlier diagnosis is possible if biopsy specimens can be obtained from lesions having variegated colors (eg, brown or black with shades of red, white, or blue), irregular elevations that are visible or palpable, and borders with angular indentations or notches. Polarized light and immersion contact dermoscopy, which is used to examine pigmented lesions, may be useful for distinguishing melanomas from benign lesions.

Staging: The staging of melanoma is based on clinical and pathologic criteria and closely corresponds to the traditional tumor-node-metastasis (TNM) classification system. The staging system classifies melanomas based on local, regional, or distant disease.

• Stage I and II: Localized primary melanoma

• Stage III: Metastasis to regional lymph nodes

• Stage IV: Distant metastatic disease

Stage strongly correlates with survival. A minimally invasive microstaging technique, the so-called sentinel lymph node biopsy (SLNB), is a major advance in the ability to stage cancers more accurately. Recommended staging studies depend on the Breslow depth (how deeply tumor cells have invaded) and histologic characteristics of the melanoma. Staging studies may include SLNB, laboratory tests (CBC, LDH, liver function tests), chest x-ray, CT, and PET and are done by a coordinated team that includes dermatologists, oncologists, general surgeons, plastic surgeons, and dermatopathologists.

Prognosis

Melanoma may spread rapidly, causing death within months of its recognition, yet the 5-yr cure rate of early, very superficial lesions is nearly 100%. Thus, cure depends on early diagnosis and early treatment.
For tumors of cutaneous origin (not CNS and subungual melanomas) that have not metastasized, the survival rate varies depending on the thickness of the tumor at the time of diagnosis (see Table 90-1). Mucosal melanomas (especially anorectal melanomas), which are more common in nonwhites, have a poor prognosis, although they often seem quite limited when discovered. Once melanoma has metastasized to the lymph nodes, 5-yr survival ranges from 25 to 70% depending on the degree of ulceration and number of nodes involved. Once melanoma has metastasized to distant sites, 5-yr survival is about 10%.

Degree of lymphocytic infiltration, which represents reaction by the patient's immunologic defense system, may correlate with the level of invasion and prognosis. Chances of cure are maximal when lymphocytic infiltration is limited to the most superficial lesions and decrease with deeper levels of tumor cell invasion, ulceration, and vascular or lymphatic invasion.

[Table 90-1. 5-yr Survival* for Malignant Melanoma Relative to Thickness and Ulceration]

**Treatment**

- Surgical excision
- Possibly adjuvant radiation therapy
- Possibly adjuvant interferon alfa
- Sometimes excision, imiquimod, and cryotherapy

Treatment is primarily by surgical excision. Although the width of margins is debated, most experts agree that a 1-cm lateral tumor-free margin is adequate for lesions < 1 mm thick. Thicker lesions may deserve larger margins, more radical surgery, and SLNB.

Lentigo maligna melanoma and lentigo maligna are usually treated with wide local excision and, if necessary, skin grafting. Intensive radiation therapy is much less effective. Treatment of lentigo maligna includes early excision (before the lesion is very large), imiquimod, and controlled cryotherapy. Most other treatment methods usually do not penetrate deeply enough into involved follicles, which must be removed.

Spreading or nodular melanomas are usually treated with wide local excision extending down to the fascia. Lymph node dissection may be recommended when nodes are involved. (See also the American Academy of Dermatology Association's Guidelines of Care for Primary Cutaneous Melanoma.)

**Metastatic disease:** Metastatic disease is generally inoperable, but in certain cases, localized and regional metastases can be excised. Chemotherapy with dacarbazine or temozolamide (oral dacarbazine analog) and aldesleukin can be used for the treatment of metastatic melanoma. Adjuvant therapy with recombinant biologic response modifiers (particularly interferon alfa) to suppress clinically inapparent micrometastases may also be used for inoperable metastatic melanoma. Brain metastases may be treated with palliative radiation, but the response is poor.

The following are under study:

- Infusion of lymphokine-activated killer cells or antibodies (for advanced-stage disease)
- Vaccine therapy

**Kaposi's Sarcoma**

(Multiple Idiopathic Hemorrhagic Sarcoma)

Kaposi's sarcoma (KS) is a multicentric vascular tumor caused by herpesvirus type 8. It can occur in classic, AIDS-associated, endemic, and iatrogenic forms. Diagnosis is by biopsy.
Treatment for indolent superficial lesions involves cryotherapy, electrocoagulation, excision, or electron beam radiation therapy. Radiation therapy is used for more extensive disease. In the AIDS-associated form, antiretrovirals provide the most improvement.

KS originates from endothelial cells in response to infection by human herpesvirus 8 (HHV-8). Immunosuppression (particularly by AIDS and drugs for organ transplant recipients) markedly increases the likelihood of KS in HHV-8-infected patients. The tumor cells have a spindle shape, resembling smooth muscle cells, fibroblasts, and myofibroblasts.

Classification

Classic KS: This form occurs most often in older (> 60 yr) men of Italian, Jewish, or Eastern European ancestry. The course is indolent, and the disease is usually confined to a small number of lesions on the skin of the lower extremities (see Plate 36); visceral involvement occurs in < 10%. This form is usually not fatal.

AIDS-associated (epidemic) KS: This form is the most common AIDS-associated cancer and is more aggressive than classic KS. Multiple cutaneous lesions are typically present, often involving the face and trunk. Mucosal, lymph node, and GI involvement is common. Sometimes KS is the first manifestation of AIDS.

Endemic KS: This form occurs in Africa independent of HIV infection. There are 2 main types:

- Prepubertal lymphadenopathic form: It predominantly affects children; primary tumors involve lymph nodes, with or without skin lesions. The course is usually fulminant and fatal.

- Adult form: This form resembles classic KS.

Iatrogenic (immunosuppressive) KS: This form typically develops several years after organ transplantation. The course is more or less fulminant, depending on the degree of immunosuppression.

Symptoms and Signs

Cutaneous lesions are asymptomatic purple, pink, or red macules that may coalesce into blue-violet to black plaques and nodules. Some edema may be present. Occasionally, nodules fungate or penetrate soft tissue and invade bone. Mucosal lesions appear as bluish to violaceous macules, plaques, and tumors. GI lesions can bleed, sometimes extensively, but usually are asymptomatic.

Diagnosis

- Biopsy

Diagnosis is confirmed by punch biopsy. Patients with AIDS or immunosuppression require evaluation for visceral spread by CT of the chest and abdomen. If CT is negative but pulmonary or GI symptoms are present, bronchoscopy or GI endoscopy should be considered.

Treatment

- Surgical excision, cryotherapy, or electrocoagulation for superficial lesions

- Local radiation therapy for multiple lesions or lymph node disease

- Antiretroviral therapy or sometimes IV interferon alfa for AIDS-associated KS

- Reduction of immunosuppressants for iatrogenic KS

Indolent lesions often require no treatment. One or a few superficial lesions can be removed by excision, cryotherapy, or electrocoagulation. Intralesional vinblastine or interferon alfa is also useful. Multiple
lesions and lymph node disease are treated locally with 10 to 20 Gy of radiation therapy.

AIDS-associated KS responds markedly to highly active antiretroviral therapy (HAART), probably because CD4+ count improves and HIV viral load decreases; however, there is some evidence that protease inhibitors in this regimen may block angiogenesis. AIDS patients with indolent disease and CD4+ counts > 150/μL and HIV RNA < 500 copies/mL can be treated with IV interferon alfa. Patients with more extensive or visceral disease can be given liposomal doxorubicin 20 mg/m^2 IV q 2 to 3 wk. If this regimen fails, patients may receive paclitaxel. Other agents being investigated as adjuncts include IL-12, desferrioxamine, and oral retinoids. Treatment of KS does not prolong life in most AIDS patients because infections dominate the clinical course.

Iatrogenic KS responds best to stopping immunosuppressants. In organ transplant patients, reduction of immunosuppressant dosage often results in reduction of KS lesions. If dosage reduction is not possible, conventional local and systemic therapies used in other forms of KS should be instituted. Sirolimus may also improve iatrogenic KS.

Treatment of endemic KS is challenging and typically palliative.

Paget's Disease of the Nipple

Paget's disease is a rare type of carcinoma that appears as a unilateral eczematosus to psoriasiform plaque surrounding the nipple. It involves extension to the epidermis of an underlying ductal adenocarcinoma of the breast.

Paget's disease of the nipple should not be confused with the metabolic bone disease that is also called Paget's disease. In Paget's disease of the nipple, metastatic disease is often present at the time of the diagnosis.

Paget's disease of the nipple also occurs at other sites, most often in the groin or perianal area (extramammary Paget's disease). The bladder, anus, and rectum are the most common sites. Extramammary Paget's disease is a rare intraepithelial adenocarcinoma of apocrine gland-bearing sites.

Diagnosis

• Biopsy

The redness, oozing, and crusting closely resemble dermatitis; but physicians should suspect carcinoma because the lesion is sharply margined, unilateral, and unresponsive to topical therapy. Biopsy shows typical histologic changes. Because this tumor is associated with underlying cancer, systemic evaluation is required.

Treatment

Treatment involves surgical removal of discovered tumors, including possible mastectomy for disease involving the nipple. Treatment may also involve ablation of overlying cutaneous involvement, either surgically or by CO_2 laser ablation.
Introduction

The endocrine system coordinates functioning between different organs through hormones, which are released into the bloodstream from specific types of cells within endocrine (ductless) glands. Once in circulation, hormones affect function of the target tissue. Some hormones exert an effect on cells of the organ from which they were released (paracrine effect), some even on the same cell type (autocrine effect). Hormones can be peptides of various sizes, steroids (derived from cholesterol), or amino acid derivatives.

Hormones bind selectively to receptors located inside or on the surface of target cells. Receptors inside cells interact with hormones that regulate gene function (eg, corticosteroids, vitamin D, thyroid hormone). Receptors on the cell surface bind with hormones that regulate enzyme activity or affect ion channels (eg, growth hormone, thyrotropin-releasing hormone).

Hypothalamic-Pituitary Relationships

Peripheral endocrine organ functions are controlled to varying degrees by pituitary hormones (see also Ch. 92). Some functions (eg, secretion of insulin by the pancreas, primarily controlled by the blood glucose level) are controlled to a minimal extent, whereas many (eg, secretion of thyroid or gonadal hormones) are controlled to a great extent. Secretion of pituitary hormones is controlled by the hypothalamus.

The interaction between the hypothalamus and pituitary (hypothalamic-pituitary axis) is a feedback control system. The hypothalamus receives input from virtually all other areas of the CNS and uses it to provide input to the pituitary. In response, the pituitary releases various hormones that stimulate certain endocrine glands throughout the body. Changes in circulating levels of hormones produced by these endocrine glands are detected by the hypothalamus, which then increases or decreases its stimulation of the pituitary to maintain homeostasis.

The hypothalamus modulates the activities of the anterior and posterior lobes of the pituitary in different ways. Neurohormones synthesized in the hypothalamus reach the anterior pituitary (adenohypophysis) through a specialized portal vascular system and regulate synthesis and release of the 6 major peptide hormones of the anterior pituitary. These anterior pituitary hormones regulate peripheral endocrine glands (the thyroid, adrenals, and gonads) as well as growth and lactation. No direct neural connection exists between the hypothalamus and the anterior pituitary. In contrast, the posterior pituitary (neurohypophysis) comprises axons originating from neuronal cell bodies located in the hypothalamus. These axons serve as storage sites for 2 peptide hormones synthesized in the hypothalamus; these hormones act in the periphery to regulate water balance, milk ejection, and uterine contraction.

Virtually all hormones produced by the hypothalamus and the pituitary are released in a pulsatile fashion; periods of such release are interspersed with periods of inactivity. Some hormones (eg, adrenocorticotropic hormone [ACTH], growth hormone, prolactin) have definite circadian rhythms; others (eg, luteinizing hormone and follicle-stimulating hormone during the menstrual cycle) have month-long rhythms with superimposed circadian rhythms.

Hypothalamic Controls

Thus far, 7 physiologically important hypothalamic neurohormones have been identified (see Table 91-1). Except for the biogenic amine dopamine, all are small peptides. Several are produced in the periphery as well as in the hypothalamus and function in local paracrine systems, especially in the GI tract. Vasoactive intestinal peptide, which also stimulates the release of prolactin, is one. Neurohormones may control the release of multiple pituitary hormones. Regulation of most anterior pituitary hormones depends on stimulatory signals from the hypothalamus; the exception is prolactin, which is regulated by inhibitory stimuli. If the pituitary stalk (which connects the pituitary to the hypothalamus) is severed,
prolactin release increases, whereas release of all other anterior pituitary hormones decreases.

Many hypothalamic abnormalities (including tumors and encephalitis and other inflammatory lesions) can alter the release of hypothalamic neurohormones. Because neurohormones are synthesized in different centers within the hypothalamus, some disorders affect only one neuropeptide, whereas others affect several. The result can be undersecretion or oversecretion of neurohormones. Clinical syndromes that result from the ensuing pituitary hormone dysfunction (eg, diabetes insipidus, acromegaly, hypopituitarism) are discussed in Ch. 92.

**Anterior Pituitary Function**

The cells of the anterior lobe (which constitutes 80% of the pituitary by weight) synthesize and release several hormones necessary for normal growth and development and also stimulate the activity of several target glands.

**Adrenocorticotropic hormone (ACTH):** ACTH is also known as corticotropin. Corticotropin-releasing hormone (CRH) is the primary stimulator of ACTH release, but antidiuretic hormone plays a role during stress. ACTH induces the adrenal cortex to release cortisol and several weak androgens, such as dehydroepiandrosterone (DHEA). Circulating cortisol and other corticosteroids (including exogenous corticosteroids) inhibit the release of CRH and ACTH. The CRH-ACTH-cortisol axis is a central component of the response to stress. Without ACTH, the adrenal cortex atrophies and cortisol release virtually ceases.

**Thyroid-stimulating hormone (TSH):** TSH regulates the structure and function of the thyroid gland and stimulates synthesis and release of thyroid hormones. TSH synthesis and release are stimulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH) and suppressed (by negative feedback) by circulating thyroid hormones.

**Luteinizing hormone (LH) and follicle-stimulating hormone (FSH):** LH and FSH control the production of the sex hormones. Synthesis and release of LH and FSH are stimulated by gonadotropin-releasing hormone (GnRH) and suppressed by estrogen and testosterone. In women, LH and FSH stimulate ovarian follicular development and ovulation (see p. 2497). In men, FSH acts on Sertoli cells and is essential for spermatogenesis; LH acts on Leydig cells of the testes to stimulate testosterone biosynthesis (see p. 2339).

**Growth hormone (GH):** GH stimulates somatic growth and regulates metabolism. Growth hormone-releasing hormone (GHRH) is the major stimulator and somatostatin is the major inhibitor of the synthesis and release of GH. GH controls synthesis of insulin-like growth factor 1 (IGF-1, also called somatomedin-C), which largely controls growth. Although IGF-1 is produced by many tissues, the liver is the major source. A variant of IGF-1 occurs in muscle, where it plays a role in enhancing muscle strength. It is less under control of GH than is the liver variant.

The metabolic effects of GH are biphasic. GH initially exerts insulin-like effects, increasing glucose uptake in muscle and fat, stimulating amino acid uptake and protein synthesis in liver and muscle, and inhibiting lipolysis in adipose tissue. Several hours later, more profound anti-insulin-like metabolic effects occur. They include inhibition of glucose uptake and use, causing blood glucose and lipolysis to increase, which increases plasma free fatty acids. GH levels increase during fasting, maintaining blood glucose levels and mobilizing fat as an alternative metabolic fuel. Production of GH decreases with aging. Ghrelin, a hormone produced in the fundus of the stomach, promotes GH release from the pituitary, increases food intake, and improves memory.

**Prolactin:** Prolactin is produced in cells called lactotrophs that constitute about 30% of the cells of the anterior pituitary. The pituitary doubles in size during pregnancy, largely because of hyperplasia and hypertrophy of lactotrophs. In humans, the major function of prolactin is stimulating milk production. Also, prolactin release occurs during sexual activity and stress. Prolactin may be a sensitive indicator of pituitary dysfunction; prolactin is the hormone most frequently produced in excess by pituitary tumors, and...
it may be one of the hormones to become deficient from infiltrative disease or tumor compression of the pituitary.

**Other hormones**: Several other hormones are produced by the anterior pituitary. These include pro-opiomelanocortin (POMC, which gives rise to ACTH), α- and β-melanocyte-stimulating hormone (MSH), β-lipotropin (β-LPH), the enkephalins, and the endorphins. POMC and MSH can cause hyperpigmentation of the skin and are only significant clinically in disorders in which ACTH levels are markedly elevated (eg, Addison's disease, Nelson syndrome). The function of β-LPH is unknown. Enkephalins and endorphins are endogenous opioids that bind to and activate opioid receptors throughout the CNS.

**Posterior Pituitary Function**

The posterior pituitary releases antidiuretic hormone (also called vasopressin or arginine vasopressin) and oxytocin. Both hormones are released in response to neural impulses and have half-lives of about 10 min.

**Antidiuretic hormone (ADH)**: ADH acts primarily to promote water conservation by the kidney by increasing the permeability of the distal tubular epithelium to water. At high concentrations, ADH also causes vasoconstriction. Like aldosterone, ADH plays an important role in maintaining fluid homeostasis and vascular and cellular hydration. The main stimulus for ADH release is increased osmotic pressure of water in the body, which is sensed by osmoreceptors in the hypothalamus. The other major stimulus is volume depletion, which is sensed by baroreceptors in the left atrium, pulmonary veins, carotid sinus, and aortic arch, and then transmitted to the CNS through the vagus and glossopharyngeal nerves. Other stimulants for ADH release include pain, stress, emesis, hypoxia, exercise, hypoglycemia, cholinergic agonists, β-blockers, angiotensin, and prostaglandins. Inhibitors of ADH release include alcohol, α-blockers, and glucocorticoids. A lack of ADH causes central diabetes insipidus (see p. 772); an inability of the kidneys to respond normally to ADH causes nephrogenic diabetes insipidus (see p. 2424). Removal of the pituitary gland usually does not result in permanent diabetes insipidus because some of the remaining hypothalamic neurons produce small amounts of ADH. Copeptin is coproduced with ADH in the posterior pituitary. Measuring it may be useful in distinguishing the cause of hyponatremia.

**Oxytocin**: Oxytocin has 2 major targets: the myoepithelial cells of the breast, which surround the alveoli of the mammary gland, and the smooth muscle cells of the uterus. Suckling stimulates the production of oxytocin, which causes the myoepithelial cells to contract. This contraction causes milk to move from the alveoli to large sinuses for ejection (ie, the milk letdown reflex of nursing mothers). Oxytocin stimulates contraction of uterine smooth muscle cells, and uterine sensitivity to oxytocin increases throughout pregnancy. However, plasma levels do not increase sharply during parturition, and the role of oxytocin in the initiation of labor is unclear. There is no recognized stimulus for oxytocin release in men, although men have extremely low levels.

**Endocrine Disorders**

Endocrine disorders can result from dysfunction originating in the peripheral endocrine gland itself (primary disorders) or from understimulation or overstimulation by the pituitary (secondary disorders). The disorders can result in hormone overproduction (hyperfunction) or underproduction (hypofunction). Rarely, endocrine disorders (usually hypofunction) occur because of abnormal tissue responses to hormones. Clinical manifestations of hypofunction disorders are often insidious and nonspecific.

**Hyperfunction**: Hyperfunction of endocrine glands may result from overstimulation by the pituitary but is most commonly due to hyperplasia or neoplasia of the gland itself. In some cases, cancers from other tissues can produce hormones (ectopic hormone production). Hormone excess also can result from exogenous hormone administration. In some cases, patients take hormones without telling the physician (factitious disease). Tissue hypersensitivity to hormones can occur. Antibodies can stimulate peripheral endocrine glands, as occurs in hyperthyroidism of Graves' disease. Destruction of a peripheral endocrine gland can rapidly release stored hormone (eg, thyroid hormones in thyroiditis). Enzyme defects in the synthesis of a peripheral endocrine hormone can result in overproduction of hormones proximal to the...
Finally, overproduction of a hormone can occur as an appropriate response to a disease state.

**Hypofunction**: Hypofunction of an endocrine gland can result from understimulation by the pituitary. Hypofunction originating within the peripheral gland itself can result from congenital or acquired disorders (including autoimmune disorders, tumors, infections, vascular disorders, and toxins). Genetic disorders causing hypofunction can result from deletion of a gene or by production of an abnormal hormone. A decrease in hormone production by the peripheral endocrine gland with a resulting increase in production of pituitary regulating hormone can lead to peripheral endocrine gland hyperplasia. For example, if synthesis of thyroid hormone is defective, thyroid-stimulating hormone (TSH) is produced in excessive amounts, causing goiter.

Several hormones require conversion to an active form after secretion from the peripheral endocrine gland. Certain disorders can block this step (eg, renal disease can inhibit production of the active form of vitamin D). Antibodies to the circulating hormone or its receptor can block the ability of the hormone to bind to its receptor. Disease or drugs can cause increased rate of clearance of hormones. Circulating substances may also block the function of hormones. Abnormalities of the receptor or elsewhere in the peripheral endocrine tissue can also cause hypofunction.

**Laboratory Testing**

Because symptoms of endocrine disorders can begin insidiously and may be nonspecific, clinical recognition is often delayed for months or years. For this reason, biochemical diagnosis is usually essential; it typically requires measuring levels of the peripheral endocrine hormone, the pituitary hormone, or both in the blood.

Free or bioavailable hormone (ie, hormone not bound to a specific binding hormone) is generally believed to be the active form. Free or bioavailable hormones are measured using equilibrium dialysis, ultrafiltration, or a solvent-extraction method to separate the free and albumin-bound hormone from the binding globulin. These methods can be expensive and time-consuming. Analog and competitive free hormone assays, although often used commercially, are not always accurate and should not be used.

Free hormone levels can also be estimated indirectly by assessing levels of the binding protein and using them to adjust levels of the total serum hormone. However, indirect methods are inaccurate if the binding capacity of the hormone-binding protein has been altered (eg, by a disorder).

Because most hormones have circadian rhythms, measurements need to be made at a prescribed time of day. Hormones that vary over short periods (eg, luteinizing hormone) necessitate obtaining 3 or 4 values over 1 or 2 h or using a pooled blood sample. Hormones with week-to-week variation (eg, testosterone) necessitate obtaining separate values a week apart.

In some cases, indirect estimates are used. For example, because growth hormone (GH) has a short serum half-life and is difficult to detect in serum, serum insulin-like growth factor 1 (IGF-1), which is produced in response to GH, is often measured as an index of GH activity. Sometimes, urine (eg, free cortisol when testing for Cushing's disease) or salivary hormone levels may be used. Whether measurement of circulating hormone metabolites indicates the amount of bioavailable hormone is under investigation.

In many cases, a dynamic test is necessary. Thus, in the case of hypofunctioning organs, a stimulating test can be used. In hyperfunction, a suppressive test can be used.

**Treatment**

Hypofunction disorders are usually treated by replacement of the peripheral endocrine hormone regardless of whether the defect is primary or secondary (an exception is GH replacement for pituitary dwarfism). If resistance to the hormone exists, drugs that reduce resistance can be used (eg, metformin or thiazolidinediones for type 2 diabetes mellitus). Occasionally, a hormone-stimulating drug is used.

Radiation therapy, surgery, and drugs that suppress hormone production are used to treat hyperfunction
disorders. In some cases, a receptor antagonist is used.

**Aging and Endocrinology**

Hormones undergo many changes as a person ages. Most hormone levels decrease. Some remain normal, including TSH, ACTH (basal), thyroxine, cortisol (basal), 1,25-dihydroxycholecalciferol, insulin (sometimes increases), and estradiol (in men). Hormones that increase, including ACTH (increased response to corticotropin-releasing hormone), follicle-stimulating hormone, sex-hormone binding globulin, and activin (in men), gonadotropins (in women), epinephrine (in the oldest old), parathyroid hormone, norepinephrine, cholecystokinin, vasoactive intestinal peptide and ADH (also loss of circadian rhythm), and atrial natriuretic factor, are associated with either receptor defects or postreceptor defects, resulting in hypofunction. Many age-related changes are similar to those in patients with hormone deficiency, leading to the hypothesis of a hormonal fountain of youth (ie, speculation that some changes associated with aging can be reversed by the replacement of one or more deficient hormones). Some evidence suggests that replacing certain hormones in the elderly can improve functional outcomes (eg, muscle strength, bone mineral density), but little evidence exists regarding effects on mortality. In some cases, replacing hormones may be harmful, as in estrogen replacement in most older women.

A competing theory is that the age-related decline in hormone levels represents a protective slowing down of cellular metabolism. This concept is based on the rate of living theory of aging (ie, the faster the metabolic rate of an organism, the quicker it dies). This concept is seemingly supported by studies on the effects of dietary restriction. Restriction decreases levels of hormones that stimulate metabolism, thereby slowing metabolic rate; this prolongs life in rodents.

Dehydroepiandrosterone (DHEA) and its sulfate levels decline dramatically with age. Despite optimism for the role of DHEA supplementation in older people, most controlled trials failed to show any major benefits.

Pregnenolone is the precursor of all known steroid hormones. As with DHEA, its levels decline with age. Studies in the 1940s showed its safety and benefits in people with arthritis, but additional studies failed to show any beneficial effects on memory and muscle strength.

Levels of GH and its peripheral endocrine hormone (IGF-1) decline with age. GH replacement in older people sometimes increases muscle mass but does not increase muscle strength (although it may in malnourished people). Adverse effects (eg, carpal tunnel syndrome, arthralgias, water retention) are very common. GH may have a role in the short-term treatment of some undernourished older patients, but in critically ill undernourished patients GH increases mortality. Secretagogues that stimulate GH production in a more physiologic pattern may improve benefit and decrease risk.

Levels of melatonin, a hormone produced by the pineal gland, also decline with aging. This decline may play an important role in the loss of circadian rhythms with aging. Estrogen replacement in older women is discussed in Ch. 247. Testosterone replacement in older men is discussed in Ch. 229.
Chapter 92. Pituitary Disorders

Introduction

The pituitary gland controls the functions of peripheral endocrine glands. Pituitary structure and function and relationships between the hypothalamus and the pituitary gland are discussed in Ch. 91.

Pituitary Lesions

Patients with hypothalamic-pituitary lesions generally present with some combination of symptoms and signs of a mass lesion (eg, headaches, visual field defects—particularly bitemporal hemianopia or the hemifield slide phenomenon [images drifting apart]—altered appetite, thirst); imaging evidence of a mass lesion as an incidental finding; or hypersecretion or hyposecretion of one or more pituitary hormones.

The most common cause of hypopituitary or hyperpituitary secretion is a pituitary or hypothalamic tumor. A pituitary tumor tends to produce an enlarged sella (sella turcica). Alternatively, an enlarged sella may represent empty sella syndrome.

Empty sella syndrome: In this disorder, the sella appears empty because it is filled with CSF, which flattens the pituitary gland against the wall of the sella. The syndrome may be congenital, primary, or secondary to injury (eg, ischemia after childbirth, surgery, head trauma, or radiation therapy). The typical patient is female (> 80%), obese (about 75%), and hypertensive (30%) and may have idiopathic intracranial hypertension (10%) or spinal fluid rhinorrhea (10%). Pituitary function in patients with empty sella syndrome is frequently normal. However, hypopituitarism may occur, as may headaches and visual field defects. Occasionally, patients have small coexisting pituitary tumors that secrete growth hormone (GH), prolactin, or ACTH. Diagnosis can be confirmed by CT or MRI. No specific therapy is needed for an empty sella alone.

Anterior lobe lesions: Hypersecretion of anterior lobe hormones (hyperpituitarism) is almost always selective. The anterior pituitary hormones most commonly secreted in excess are GH (as in acromegaly, gigantism), prolactin (as in galactorrhea), and ACTH (as in the pituitary type of Cushing's syndrome). Hyposcerection of anterior lobe hormones (hypopituitarism) may be generalized, usually due to a pituitary tumor, or is idiopathic, or may involve the selective loss of one or a few pituitary hormones.

Posterior lobe lesions: The 2 posterior lobe hormones are oxytocin and ADH. In women, oxytocin causes myoepithelial cells of the breast and myometrial cells of the uterus to contract. Oxytocin is present in men but has no proven function. Deficiency of ADH results in central diabetes insipidus (see p. 772). Excess ADH secretion results in the syndrome of inappropriate ADH secretion (see Sidebar 97-1 on p. 826).

Generalized Hypopituitarism

Generalized hypopituitarism refers to endocrine deficiency syndromes due to partial or complete loss of anterior lobe pituitary function. Various clinical features occur depending on the specific hormones that are deficient. Diagnosis involves imaging tests and measurement of pituitary hormone levels basally and after various provocative stimuli. Treatment depends on cause but generally includes removal of any tumor and administration of replacement hormones.

The many causes of hypopituitarism are listed in Table 92-1.

Symptoms and Signs

Symptoms and signs relate to the underlying disorder and to the specific pituitary hormones that are deficient or absent. Onset is usually insidious and may not be recognized by the patient; occasionally, onset is sudden or dramatic.
Most commonly, growth hormone (GH) is lost first, then gonadotropins, and finally thyroid-stimulating hormone (TSH) and ACTH. ADH deficiency is rare in primary pituitary disease but is common with stalk and hypothalamic lesions. Function of all target glands decreases when all hormones are deficient (panhypopituitarism).

Lack of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in children leads to delayed puberty (see Hypopituitarism in Children Resulting in Short Stature on p. 767). Premenopausal women develop amenorrhea, reduced libido, regression of secondary sexual characteristics, and infertility. Men develop erectile dysfunction, testicular atrophy, reduced libido, regression of secondary sexual characteristics, and decreased spermatogenesis with consequent infertility.

GH deficiency may contribute to decreased energy but is usually asymptomatic and clinically undetectable in adults (see p. 767 for effects in children). Suggestions that GH deficiency accelerates atherosclerosis are unproved. TSH deficiency leads to hypothyroidism, with such symptoms as facial puffiness, hoarse voice, bradycardia, and cold intolerance. ACTH deficiency results in hypoadrenalism with attendant fatigue, hypotension, and intolerance to stress and infection. ACTH deficiency does not result in the hyperpigmentation characteristic of primary adrenal failure.

Hypothalamic lesions, which can result in hypopituitarism, can also disturb the centers that control appetite, causing a syndrome resembling anorexia nervosa, or sometimes hyperphagia with massive obesity.

Sheehan's syndrome, which affects postpartum women, is pituitary necrosis due to hypovolemia and shock occurring in the immediate peripartum period. Lactation does not start after childbirth, and the patient may complain of fatigue and loss of pubic and axillary hair.

Pituitary apoplexy is a symptom complex caused by hemorrhagic infarction of either a normal pituitary gland or, more commonly, a pituitary tumor. Acute symptoms include severe headache, stiff neck, fever, visual field defects, and oculomotor palsies. The resulting edema may compress the hypothalamus, resulting in somnolence or coma. Varying degrees of hypopituitarism may develop suddenly, and the patient may present with vascular collapse because of deficient ACTH and cortisol. The CSF often contains blood, and MRI documents hemorrhage.

**Diagnosis**

- MRI or CT
- Free thyroxine (T₄), TSH, and prolactin levels
- Cortisol levels plus provocative testing of pituitary-adrenal axis
- Sometimes other provocative testing

Clinical features are often nonspecific, and the diagnosis must be established with certainty before committing the patient to a lifetime of hormone replacement therapy. Pituitary dysfunction must be distinguished from anorexia nervosa, chronic liver disease, myotonia dystrophica, polyglandular autoimmune disease (see Table 92-2), and disorders of the other endocrine glands. The clinical picture may be particularly confusing when the function of more than one gland decreases at the same time. Evidence of structural pituitary abnormalities and of hormonal deficiencies should be sought with imaging and laboratory tests.
**Imaging tests:** Patients should undergo high-resolution CT or MRI, with contrast media as required (to rule out structural abnormalities, such as pituitary adenomas). PET is a research tool used in a few specialized centers and therefore is rarely done. When no modern neuroradiologic facilities are available, a simple cone-down lateral x-ray of the sella turcica can identify pituitary macroadenomas with a diameter > 10 mm. Cerebral angiography is indicated only when other imaging tests suggest perisellar vascular anomalies or aneurysms.

**Laboratory testing:** Initial evaluation should include testing for TSH and ACTH deficiencies, because both conditions are potentially life threatening. Testing for deficiencies of other hormones is also discussed elsewhere (see p. 766).

Free T₄ and TSH levels should be determined. Levels of both are usually low in generalized hypopituitarism; a pattern of normal TSH level with low free T₄ may also occur. In contrast, elevated TSH levels with low free T₄ indicate a primary abnormality of the thyroid gland.

Synthetic thyrotropin-releasing hormone (TRH), 200 to 500 μg IV given over 15 to 30 sec, may help identify patients with hypothalamic as opposed to pituitary dysfunction, although this test is not often done. Serum TSH levels are generally measured at 0, 20, and 60 min after injection. If pituitary function is intact, TSH should rise by > 5 mU/L, peaking by 30 min after injection. A delayed rise in serum TSH levels may occur in patients with hypothalamic disease. However, some patients with primary pituitary disease also show a delayed rise.

Serum cortisol levels alone are not reliable indicators of ACTH-adrenal axis function. One of several provocative tests should be done. The short ACTH stimulation test is a safer and less labor-intensive test for cortisol deficiency than the insulin tolerance test. In the short ACTH stimulation test, synthetic ACTH 250 μg IV or IM (standard test) or 1 μg IV (low-dose test) is given, and the blood cortisol response is measured 30 and 60 min later. Cortisol should rise significantly; a peak of < 20 μg/dL is abnormal. However, the short ACTH stimulation test is abnormal in secondary cortisol deficiency only when done at least 2 to 4 wk after onset of the deficiency; before this time, the adrenal glands have not atrophied and remain responsive to exogenous ACTH.

The insulin tolerance test is considered the most accurate way of evaluating ACTH (as well as GH and prolactin) reserve, but because of its demands, it is probably best reserved for patients who fail the short synacthen test (if confirmation is needed) or when a test must be done within 2 to 4 wk of a possible pituitary injury. Regular insulin at a dosage of 0.1 units/kg body weight IV is given over 15 to 30 sec, and venous blood samples are obtained to determine GH, cortisol, and glucose levels at baseline (before insulin administration) and 20, 30, 45, 60, and 90 min later. If glucose drops to < 40 mg/dL (< 2.22 mmol/L) or symptoms of hypoglycemia develop, cortisol should increase by > 7 μg/dL or to > 20 μg/dL. (CAUTION: This test is hazardous in patients with severe documented panhypopituitarism or diabetes mellitus and in the elderly and is contraindicated in patients with coronary artery disease or epilepsy. A health care practitioner should be present during the test.) Usually, only transient perspiration, tachycardia, and nervousness occur. If the patient complains of palpitations, loses consciousness, or has a seizure, the test should be stopped promptly by giving 50 mL of 50% glucose solution IV.

Neither the short ACTH stimulation test nor the insulin tolerance test alone will differentiate between primary (Addison's disease) and secondary (hypopituitary) adrenal insufficiency. Tests to make this distinction and to evaluate the hypothalamic-pituitary-adrenal axis are described under Addison's disease (see p. 792). An alternative provocative test that is done much less often is the corticotropin-releasing hormone (CRH) test. CRH 1 μg/kg IV is given by rapid injection. Serum ACTH and cortisol levels are measured 15 min before, then at baseline, and 15, 30, 60, 90, and 120 min after the injection. Adverse effects include temporary flushing, a metallic taste in the mouth, and slight and transient hypotension.

Prolactin levels are routinely measured. These levels are often elevated up to 5 times normal values when a large pituitary tumor is present, even if it does not produce prolactin. The tumor compresses the pituitary stalk, preventing dopamine, which inhibits pituitary prolactin production and release, from reaching the pituitary. Patients with such hyperprolactinemia often have hypogonadotropism and
secondary hypogonadism.

Measurement of basal levels of LH and FSH is most helpful in evaluating hypopituitarism in postmenopausal women not taking exogenous estrogens in whom circulating gonadotropin concentrations are normally high (> 30 mIU/mL). Although gonadotropin levels tend to be low in other patients with panhypopituitarism, overlap exists with the normal range. Levels of both hormones should increase in response to synthetic gonadotropin-releasing hormone (GnRH) at a dose of 100 μg IV, with LH peaking about 30 min and FSH peaking 40 min after GnRH administration. However, normal, diminished, or absent responses to GnRH may occur in hypothalamic-pituitary dysfunction. Normal increases in LH and FSH in response to GnRH vary. Administration of exogenous GnRH is not helpful in distinguishing primary hypothalamic disorders from primary pituitary disorders.

Screening for GH deficiency in adults is not recommended unless GH treatment is contemplated (eg, for unexplained reduced energy and quality of life in patients with hypopituitarism in which other hormones have been fully replaced). GH deficiency is suspected if ≥ 2 other pituitary hormones are deficient. Because GH levels vary by time of day and other factors and are difficult to interpret, levels of insulin-like growth factor 1 (IGF-1), which reflect GH, are used; low levels suggest GH deficiency, but normal levels do not rule it out. A provocative test of GH release (see p. 767) may be necessary.

Although the usefulness of provocative testing of pituitary function using releasing hormones remains to be established, if such testing is elected, it is most efficient to evaluate multiple hormones simultaneously. Growth hormone-releasing hormone (1 μg/kg), CRH (1 μg/kg), TRH (200 μg), and GnRH (100 μg) are given together IV over 15 to 30 sec. Glucose, cortisol, GH, TSH, prolactin, LH, FSH, and ACTH are measured at frequent intervals for the ensuing 180 min. The normal responses are the same as those delineated earlier for individual testing.

**Treatment**

- Hormone replacement
- Treatment of cause (eg, tumor)

Treatment is replacement of the hormones of the hypofunctioning target glands, as discussed in the pertinent chapters in this section and elsewhere in THE MANUAL. Adults ≤ 50 yr deficient in GH are now sometimes treated with GH doses of 0.002 to 0.012 mg/kg sc once/day. Benefits of treatment include improved energy and quality of life, increased body muscle mass, and decreased body fat mass. Suggestions that GH replacement can prevent an acceleration of atherosclerosis induced by GH deficiency are unproved.

When hypopituitarism is due to a pituitary tumor, specific treatment must be directed at the tumor as well as replacing hormones. The appropriate management of such tumors is controversial. If the tumor is small and does not secrete prolactin, most endocrinologists favor transsphenoidal removal. Most endocrinologists consider dopamine agonists, such as bromocriptine or the longer-acting cabergoline, the initial treatment of prolactinomas, regardless of size, if there is amenorrhea in a woman or erectile dysfunction in a man (see Galactorrhea on p. 770). Patients with macroadenomas > 2 cm with extremely high circulating levels of prolactin may require surgery or irradiation in addition to dopamine agonist treatment. Supervoltage irradiation of the pituitary may be added or used alone. With larger tumors and suprasellar extension, resection of the entire tumor, either transsphenoidally or transfrontally, may not be possible, and adjunctive supervoltage irradiation may be warranted.

In pituitary apoplexy, immediate surgery is warranted if visual field disturbances or oculomotor palsies develop suddenly or if somnolence progresses to coma because of hypothalamic compression. Although management with high-dose corticosteroids and general support may suffice in a few cases, transsphenoidal decompression of the tumor should generally be undertaken promptly.

Surgery and irradiation may be followed by the loss of other pituitary hormone functions. Irradiated patients may lose endocrine function slowly over years. Therefore, posttreatment hormonal status should be evaluated frequently, preferably at 3 and 6 mo and yearly thereafter. Such evaluation should include at
least assessment of thyroid and adrenal function. Patients may also develop visual difficulties related to fibrosis of the optic chiasm. Sellar imaging and visual field assessment should be done at least every 2 yr initially for about 10 yr, particularly if residual tumor tissue is present.

**Selective Pituitary Hormone Deficiencies**

Selective deficiencies of pituitary hormones may represent an early stage in the development of more generalized hypopituitarism. Patients must be observed for signs of other pituitary hormone deficiencies, and sellar imaging should be done at intervals to check for signs of a pituitary tumor.

**Isolated growth hormone (GH) deficiency** is responsible for many cases of pituitary dwarfism (see p. 767). Although one autosomal dominant form of complete GH deficiency is associated with a deletion of the GH structural gene, such gene defects probably account for a minority of cases. Treatment of GH deficiency in adults < 50 yr is discussed on p. 765.

**Isolated gonadotropin deficiency** occurs in both sexes and must be distinguished from primary hypogonadism; men have low serum testosterone levels and infertility, and women have amenorrhea, low serum estrogen levels, and infertility. A eunuchoid habitus is generally present. However, patients with primary hypogonadism (see p. 2341) have elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), whereas those with gonadotropin deficiency, either secondary (pituitary) or tertiary (hypothalamic), have low-normal, low, or unmeasurable levels of LH and FSH. Although most cases of hypogonadotropic hypogonadism involve deficiencies of both LH and FSH, in rare cases the secretion of only one is impaired. Isolated gonadotropin deficiency must also be distinguished from hypogonadotropic amenorrhea secondary to exercise, diet, or mental stress (see p. 2501). Although the history may be helpful, differential diagnosis may be impossible.

In Kallmann syndrome, the specific lack of gonadotropin-releasing hormone (GnRH) is associated with midline facial defects, including anosmia and cleft lip or palate, and with color blindness. Embryologic studies have shown that GnRH neurons originally develop in the epithelium of the olfactory placode and migrate into the septal-preoptic region of the hypothalamus early in development. In at least some cases, gene defects, localized to the X chromosome in the X-linked form of the disorder and termed the KALIG-1 (Kallmann syndrome interval gene 1) gene, have been found in the adhesion proteins facilitating this neuronal migration. Administration of GnRH may be indicated (see p. 2894).

**Isolated ACTH deficiency** is rare. Weakness, hypoglycemia, weight loss, and decreased axillary and pubic hair suggest the diagnosis. Blood and urinary steroid levels are low and rise to normal after ACTH replacement. Clinical and laboratory evidence of other hormonal deficiencies is absent. Treatment is with cortisol replacement, as for Addison's disease (see p. 794).

**Isolated thyroid-stimulating hormone (TSH) deficiency** is likely when clinical features of hypothyroidism exist, serum TSH levels are not elevated, and no other pituitary hormone deficiencies exist. Serum TSH levels, as measured by immunoassay, are not always lower than normal, suggesting that the TSH secreted is biologically inactive. Administration of recombinant human TSH increases thyroid hormone levels (see also Hypothyroidism on p. 785).

**Isolated prolactin deficiency** has been noted rarely in women who fail to lactate after delivery. Basal prolactin levels are low and do not increase in response to provocative stimuli, such as thyroid-releasing hormone. Administration of prolactin is not indicated.

**Hypopituitarism in Children Resulting in Short Stature**

(Pituitary Dwarfism)

Hypopituitarism in children typically results in abnormally slow growth and short stature with normal proportions. It is usually due to a pituitary tumor but may be idiopathic. Diagnosis involves measurement of growth hormone (GH) levels at baseline and in response to pharmacologic stimuli. Treatment usually involves removal of the causative tumor and GH replacement.
Hypopituitarism in children may be generalized, involving deficiency of several pituitary hormones, but it is usually first expressed clinically as short stature resulting from deficiency of GH. Isolated deficiency of GH may also occur.

Hypopituitarism in children is usually due to a pituitary tumor (most commonly a craniopharyngioma) or is idiopathic. The combination of lytic lesions of the bone or skull and diabetes insipidus suggests Langerhans' cell histiocytosis (see p. 993). Hypothalamic or pituitary hormone deficiency as well as isolated GH deficiency may occur in patients with midline defects, such as cleft palate or septo-optic dysplasia, which involves absence of the septum pellucidum, optic nerve atrophy, and hypopituitarism. GH deficiency, either alone or in patients with other abnormalities, is hereditary in about 5% of cases.

Therapeutic radiation of the CNS for various cancers causes slowing of linear growth, which can often be linked to resulting GH deficiency. Radiation of the spine, either prophylactic or therapeutic, may further impair the growth potential of the vertebrae and further jeopardize height gain.

**Symptoms and Signs**

In a child with hypopituitarism, height is below the 3rd percentile, and growth velocity is < 6 cm/yr before age 4 yr, < 5 cm/yr from age 4 to 8 yr, and < 4 cm/yr before puberty. Skeletal maturation, assessed by bone age determination, is > 2 yr behind chronologic age.

Although of small stature, a child with hypopituitarism retains normal proportionality between upper and lower body segments. The child fails to begin pubertal development. However, a child with isolated GH deficiency secondary to hypopituitarism may undergo delayed pubertal development.

Growth data for height and weight should be plotted on a growth chart (auxologic assessment) for all children. When growth is abnormal, bone age should be determined from an x-ray of the left hand (by convention). In GH deficiency, skeletal maturation is usually delayed to the same extent as height. Evaluating the pituitary gland and sella turcica with CT or MRI is indicated to rule out calcifications and tumors; the sella turcica is abnormally small in 10 to 20% of patients.

**Diagnosis**

- Insulin-like growth factor 1 (IGF-1) levels and sometimes IGF binding protein type 3 (IGFBP-3) levels
- Usually confirmation by provocative testing

In mid to late childhood, IGF-1 levels, which reflect GH activity, are measured because GH levels are highly variable and difficult to interpret. Normal IGF-1 levels help exclude GH deficiency. However, IGF-1 levels are low in conditions other than GH deficiency, such as psychosocial deprivation, undernutrition, and hypothyroidism. Because IGF-1 levels are normally low in infancy and early childhood, they do not allow reliable discrimination between normal and subnormal in these age groups. In these children, levels of IGFBP-3 (the major carrier of IGF peptides) are measured. IGFBP-3 is less affected by undernutrition than is IGF-1.

In children with low levels of IGF-1 and IGFBP-3, GH deficiency is usually confirmed by measuring GH levels. Because basal GH levels are typically low or undetectable (except after the onset of sleep), assessment of GH levels requires provocative testing. However, provocative testing is nonphysiologic, subject to laboratory error, and poorly reproducible, and interpretation of data relies on arbitrary definitions of "normal" that vary by age and sex.

The insulin tolerance test may be the most effective provocative test for stimulating GH release. Less dangerous, but also less reliable, are tests using arginine infusion (500 mg/kg IV given over 30 min), levodopa (10 mg/kg to children; 500 mg po to adults), sleep, or 20 min of vigorous exercise. Generally, any GH level > 10 ng/mL or any response of > 5 ng/mL after a stimulus is sufficient to rule out GH deficiency. Increases in GH of < 5 ng/mL or to levels < 10 ng/mL are difficult to interpret. What constitutes a normal response, however, is arbitrary, and all provocative tests of GH secretion occasionally produce
misleading results. Because no single test is 100% effective in eliciting GH release, a 2nd provocative test should be done if the first is abnormal. GH levels generally peak 30 to 90 min after administration of insulin or the onset of arginine infusion, 30 to 120 min after levodopa, 60 to 120 min after the onset of sleep, and after 20 min of vigorous exercise. Because GH responses are generally abnormal in patients with diminished thyroid or adrenal function, testing should be conducted in these patients only after adequate hormone replacement therapy.

The value of exogenous growth hormone-releasing hormone (GHRH) alone in evaluating GH secretion is not established. In normal people, a dose of 1 μg/kg GHRH IV administered over 15 to 30 sec results in maximal but variable release of GH, typically reaching a peak about 60 min after GHRH injection. The variability in pituitary responsiveness to GHRH is consistent with the hypothesis that intermittent secretion of somatostatin, which opposes GHRH, is responsible for modulating pituitary GH output. Presumably, absent or diminished increases in GH in response to GHRH identify patients with GH deficiency, but whether the pattern of response distinguishes primary hypothalamic disease from pituitary disease is unclear. In children with GH deficiency presumably secondary to GHRH deficiency, highly variable GH responses to GHRH occur. The combination of arginine and GHRH improves the sensitivity for diagnosing GH deficiency.

Provocative testing may not detect subtle defects in the regulation of GH release. For example, in children with short stature secondary to GH secretory dysfunction, results of provocative testing for GH release are usually normal. However, serial measurements of GH levels over 12 to 24 h indicate abnormally low 12- or 24-h integrated GH secretion.

If diminished GH release is confirmed, secretion of other pituitary hormones and (if abnormal) hormones of their target peripheral endocrine glands also must be evaluated.

**Treatment**

• Recombinant GH supplements

Recombinant GH is indicated for all children with short stature who have documented GH deficiency. Dosing is usually from 0.03 to 0.05 mg/kg sc once/day. With therapy, height velocity often increases to 10 to 12 cm/yr in the first year and, although it increases more slowly thereafter, remains above pretreatment rates. Therapy is continued until an acceptable height is reached or growth rate falls below 2.5 cm/yr.

Adverse effects of GH therapy are few but include idiopathic intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis, and transient mild peripheral edema. Before the advent of recombinant GH, GH extracted from pituitary glands was used. This preparation rarely led to Creutzfeldt-Jakob disease 20 to 40 yr after treatment (see p. 1729). Pituitary-extracted GH was last used in the 1980s.

It is controversial whether short children with clinical features of GH deficiency but with normal GH secretion and normal IGF-1 levels should be treated with GH. Many experts recommend a trial of GH therapy for 6 to 12 mo, continuing GH only if there is a doubling of or an increase of 3 cm/yr over the pretreatment height velocity. Others object to this approach because it is expensive, is experimental, may lead to adverse effects, labels otherwise healthy children as abnormal, and raises ethical and psychosocial concerns that feed into the bias of "heightism."

Cortisol and thyroid hormone should be replaced throughout childhood, adolescence, and adulthood in patients with short stature due to pituitary dwarfism when circulating levels of these hormones are low (see pp. 786 and 794). When puberty fails to occur normally, treatment with gonadal sex steroids is indicated (see p. 2894).

GH therapy in children with short stature due to therapeutic radiation of the pituitary gland for cancer carries a theoretic risk of causing cancer recurrence. However, studies have not shown a greater-than-expected incidence of new cancers or a greater recurrence rate. GH replacement can probably be safely instituted at least 1 yr after the successful completion of anticancer therapy.
**Gigantism and Acromegaly**

Gigantism and acromegaly are syndromes of excessive secretion of growth hormone (hypersomatotropism) that are nearly always due to a pituitary adenoma. Before closure of the epiphyses, the result is gigantism. Later, the result is acromegaly, which causes distinctive facial and other features. Diagnosis is clinical and by skull and hand x-rays and measurement of growth hormone levels. Treatment involves removal or destruction of the responsible adenoma.

Many growth hormone (GH)-secreting adenomas contain a mutant form of the Gs protein, which is a stimulatory regulator of adenylate cyclase. Cells with the mutant form of Gs protein secrete GH even in the absence of growth hormone-releasing hormone (GHRH). A few cases of ectopic GHRH-producing tumors, especially of the pancreas and lung, also have been described.

**Symptoms and Signs**

**Pituitary gigantism:** This rare condition occurs if GH hypersecretion begins in childhood, before closure of the epiphyses. Skeletal growth velocity and ultimate stature are increased, but little bony deformity occurs. However, soft-tissue swelling occurs, and the peripheral nerves are enlarged. Delayed puberty or hypogonadotropic hypogonadism is also frequently present, resulting in a eunuchoid habitus.

**Acromegaly:** In acromegaly, GH hypersecretion usually starts between the 20s and 40s. When GH hypersecretion begins after epiphyseal closure, the earliest clinical manifestations are coarsening of the facial features (see Plate 21) and soft-tissue swelling of the hands and feet. Appearance changes, and larger rings, gloves, and shoes are needed. Photographs of the patient are important in delineating the course of the disease.

In adults with acromegaly, coarse body hair increases and the skin thickens and frequently darkens. The size and function of sebaceous and sweat glands increase, such that patients frequently complain of excessive perspiration and offensive body odor. Overgrowth of the mandible leads to protrusion of the jaw (prognathism) and malocclusion of teeth. Cartilaginous proliferation of the larynx leads to a deep, husky voice. The tongue is frequently enlarged and furrowed. In longstanding acromegaly, costal cartilage growth leads to a barrel chest. Articular cartilaginous proliferation occurs early in response to GH excess, with the articular cartilage possibly undergoing necrosis and erosion. Joint symptoms are common, and crippling degenerative arthritis may occur.

Peripheral neuropathies occur commonly because of compression of nerves by adjacent fibrous tissue and endoneural fibrous proliferation. Headaches are common because of the pituitary tumor. Bitemporal hemianopia may develop if suprasellar extension compresses the optic chiasm. The heart, liver, kidneys, spleen, thyroid, parathyroid glands, and pancreas are larger than normal. Cardiac disease occurs in perhaps one third of patients, with a doubling in the risk of death from cardiac disease. Hypertension occurs in up to one third of patients. The risk of cancer, particularly of the GI tract, increases 2-fold to 3-fold. GH increases tubular reabsorption of phosphate and leads to mild hyperphosphatemia. Impaired glucose tolerance occurs in nearly one half the patients with acromegaly and in gigantism, but clinically significant diabetes mellitus occurs in only about 10% of patients.

Galactorrhea occurs in some women with acromegaly, usually in association with hyperprolactinemia (see p. 770). However, galactorrhea may occur with GH excess alone, because GH itself stimulates lactation. Decreased gonadotropin secretion often occurs with GH-secreting tumors. About one third of men with acromegaly develop erectile dysfunction, and nearly all women develop menstrual irregularities or amenorrhea.

**Diagnosis**

- CT or MRI
- Insulin-like growth factor 1 (IGF-1) levels
• Usually GH levels

Diagnosis can be made from the characteristic clinical findings. CT, MRI, or skull x-rays disclose cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica. X-rays of the hands show tufting of the terminal phalanges and soft-tissue thickening. Generally, glucose tolerance is abnormal and serum phosphate levels are mildly elevated.

Serum IGF-1 should be measured in patients with suspected acromegaly; IGF-1 levels are typically substantially elevated (3-fold to 10-fold), and because IGF-1 levels do not fluctuate like GH levels do, they are the simplest way to assess GH hypersecretion. IGF-1 levels also can be used to monitor response to therapy.

Plasma GH levels measured by radioimmunoassay are typically elevated. Blood should be taken before the patient eats breakfast (basal state); in normal people, basal GH levels are < 5 ng/mL. Transient elevations of GH are normal and must be distinguished from pathologic hypersecretion. The degree of GH suppression after a glucose load remains the standard and thus should be measured in patients with elevated plasma GH; however, the results are assay-dependent, and the cutoff for normal suppression is controversial. Secretion in normal people is suppressed to < 2 ng/mL (a cutoff of < 1 ng/mL is often used) within 90 min of administration of glucose 75 g po. Most patients with acromegaly have substantially higher values. Basal plasma GH levels are also important in monitoring response to therapy.

CT or MRI of the head should be done to look for a tumor. If a tumor is not visible, excessive secretion of pituitary GH may be due to a non-CNS tumor producing excessive amounts of ectopic GHRH. Demonstration of elevated levels of plasma GHRH can confirm the diagnosis. Lungs and pancreas may be first evaluated in searching for the sites of ectopic production.

Treatment

• Surgery or radiation therapy

Ablative therapy with surgery or radiation is generally indicated. Transsphenoidal resection is preferred, but choices vary at different institutions. Stereotactic supervoltage radiation, delivering about 5000 cGy to the pituitary, is used, but GH levels may not fall to normal for several years. Treatment with accelerated protons (heavy particle radiation) permits delivery of larger doses of radiation (equivalent to 10,000 cGy) to the pituitary; such therapy poses higher risk of cranial nerve and hypothalamic damage and is available only in a few centers. Development of hypopituitarism several years after irradiation is common. Because radiation damage is cumulative, proton beam therapy should not be used after conventional γ-irradiation. A combined approach with both surgery and radiation therapy is indicated for patients with progressive extrasellar involvement by a pituitary tumor and for patients whose entire tumor cannot be resected, which is often the case.

Surgical removal of the tumor is likely to have been curative if GH levels after the glucose tolerance test and IGF-1 levels reach normal values. If one or both values are abnormal, further therapy is usually needed. If GH excess is poorly controlled, hypertension, heart failure, and a doubling in the death rate occur. If GH levels are < 5 ng/mL, however, mortality does not increase.

In general, drug therapy is indicated if surgery and radiation therapy are contraindicated, if they have not been curative, or if radiation therapy is being given time to work. In such instances, a somatostatin analog, octreotide, is given at 0.05 to 0.15 mg sc q 8 to 12 h; it suppresses GH secretion effectively in patients refractory to bromocriptine, surgery, or irradiation. Longer-acting somatostatin analogs, such as mannitol-modified release octreotide (octreotide LAR) given 10 to 30 mg IM q 4 to 6 wk and lanreotide given 30 mg IM q 10 to 14 days, are more convenient. Bromocriptine mesylate (1.25 to 5 mg po bid) may effectively lower GH levels in a small percentage of patients but is less effective than somatostatin analogs.

Pegvisomant, a GH receptor blocker, has been shown to reduce the effects of GH and lower IGF-1 levels in people with acromegaly, without apparent increase in pituitary tumor size. This drug may find a place in treating patients who are partially or totally unresponsive to somatostatin analogs.
Galactorrhea

Galactorrhea is lactation in men or in women who are not breastfeeding. It is generally due to a prolactin-secreting pituitary adenoma. Diagnosis is by measurement of prolactin levels and imaging tests. Treatment involves tumor inhibition with dopamine agonist drugs and sometimes removal or destruction of the adenoma.

Etiology

Galactorrhea is generally due to a prolactin-secreting pituitary adenoma (prolactinoma). Most tumors in women are microadenomas (<10 mm in diameter), but a small percentage are macroadenomas (>10 mm) when diagnosed. The frequency of microadenomas is much lower in men, perhaps because of later recognition.

Hyperprolactinemia and galactorrhea also may be caused by ingestion of certain drugs, including phenothiazines, other antipsychotics, certain antihypertensives (especially α-methyldopa), and opioids. Primary hypothyroidism can cause hyperprolactinemia and galactorrhea, because increased levels of thyroid-releasing hormone increase secretion of prolactin as well as thyroid-stimulating hormone (TSH). It is unclear why hyperprolactinemia is associated with hypogonadotropism and hypogonadism. Causes of hyperprolactinemia are listed in Table 92-3.

Symptoms and Signs

Abnormal lactation is not defined quantitatively; it is milk release that is inappropriate, persistent, or worrisome to the patient. Spontaneous lactation is more unusual than milk released in response to manual expression. The milk is white. Women with galactorrhea commonly also have amenorrhea or oligomenorrhea. Women with galactorrhea and amenorrhea may also have symptoms and signs of estrogen deficiency, including dyspareunia, due to inhibition of pulsatile luteinizing hormone and follicle-stimulating hormone release.

[Table 92-3, Causes of Hyperprolactinemia]

by high prolactin levels. However, estrogen production may be normal, and signs of androgen excess have been observed in some women with hyperprolactinemia. Hyperprolactinemia may occur with other menstrual cycle disturbances besides amenorrhea, including infrequent ovulation and corpus luteum dysfunction.

Men with prolactin-secreting pituitary tumors typically have headaches or visual difficulties. About two thirds of affected men have loss of libido and erectile dysfunction.

Diagnosis

• Prolactin levels

• Thyroxine (T₄) and TSH levels

• CT or MRI

Diagnosis of galactorrhea due to a prolactin-secreting pituitary adenoma is based on elevated prolactin levels. In general, prolactin levels correlate with the size of a pituitary tumor and can be used to follow patients over time. Serum gonadotropin and estradiol levels are either low or in the normal range in women with hyperprolactinemia. Primary hypothyroidism is easily ruled out by absence of elevated TSH.

High-resolution CT or MRI is the method of choice in identifying microadenomas. Visual field examination is indicated in all patients with macroadenomas and in any patient who elects drug therapy or surveillance only.
Treatment

• Depends on cause, symptoms, and other factors

The treatment of microprolactinomas is controversial. Asymptomatic patients who have prolactin levels < 100 ng/mL and normal CT or MRI results or who have only microadenomas can probably be observed; serum prolactin often normalizes within years. Patients with hyperprolactinemia should be monitored with quarterly measurement of prolactin levels and undergo sellar CT or MRI annually for at least an additional 2 yr. The frequency of sellar imaging can then be reduced if prolactin levels do not increase. Indications for treatment in women include the desire for pregnancy, amenorrhea or significant oligomenorrhea (because of the risk of osteoporosis), hirsutism, low libido, and troublesome galactorrhea. Indications in men include hypogonadism (because of the risk of osteoporosis), erectile dysfunction, low libido, and troublesome infertility.

The initial treatment is usually a dopamine agonist such as bromocriptine (1.25 to 5 mg po bid) or the longer-acting cabergoline (0.25 to 1.0 mg po once/wk or twice/wk). Cabergoline is the treatment of choice because it seems to be more easily tolerated and more potent than bromocriptine. Women trying to become pregnant should switch to bromocriptine at least 1 mo before planned conception and stop bromocriptine use at the time of a positive pregnancy test; long-term safety data are better established for bromocriptine than for cabergoline. Exogenous estrogen can be given to women with a microadenoma who are clinically hypoestrogenic or have low estradiol levels. Exogenous estrogen is unlikely to cause tumor expansion.

Patients with macroadenomas generally should be treated with dopamine agonists or surgically but only after thorough testing of pituitary function and evaluation for radiation therapy. Dopamine agonists are usually the initial treatment of choice and usually shrink the tumor. If prolactin levels fall and signs of compression by the tumor abate, no other therapy may be necessary. Surgery or radiation therapy may be easier to do or yield better results after tumor shrinkage induced by a dopamine agonist. Although dopamine agonist treatment usually needs to be continued long-term, prolactin-secreting tumors sometimes remit, either spontaneously or perhaps aided by the drug therapy. Sometimes, therefore, dopamine agonists can be stopped without a recurrence of the tumor or a rise in prolactin levels; remission is more likely with microadenomas than macroadenomas. Remission is also more likely after pregnancy.

High doses of dopamine agonists, particularly cabergoline and pergolide, are thought to have caused valvular heart disease in some patients with Parkinson’s disease. It is not clear whether the lower doses of dopamine agonists used for hyperprolactinemia similarly increase the risk of valvular heart disease, but the possibility should be discussed with patients, and echocardiographic surveillance should be considered. The risk may be less with bromocriptine or a nonergot-derived dopamine agonist (eg, quinagolide).

Radiation therapy should be used only in patients with progressive disease who do not respond to other forms of therapy. With irradiation, hypopituitarism often develops several years after therapy. Monitoring endocrine function and sellar imaging are indicated yearly for life.

Central Diabetes Insipidus

(Vasopressin-Sensitive Diabetes Insipidus)

(See also Sidebar 97-1 on p. 826 and Nephrogenic Diabetes Insipidus on p. 2424.)

Diabetes insipidus (DI) results from a deficiency of ADH due to a hypothalamic-pituitary disorder (central DI [CDI]) or from resistance of the kidney to ADH (nephrogenic DI [NDI]). Polyuria and polydipsia develop. Diagnosis is by water deprivation test showing failure to maximally concentrate urine; ADH levels and response to exogenous ADH help distinguish CDI from NDI. Treatment is with intranasal desmopressin or lypressin. Nonhormonal treatment includes use of diuretics (mainly thiazides) and ADH-releasing drugs, such as chlorpropamide. 
Pathophysiology

Polyuria may result from CDI, a deficiency of ADH, NDI, or compulsive or habitual water drinking (psychogenic polydipsia). The posterior lobe of the pituitary is the major site of ADH storage and release, but ADH is synthesized within the hypothalamus. Newly synthesized hormone can still be released into the circulation as long as the hypothalamic nuclei and part of the neurohypophyseal tract are intact. Only about 10% of neurosecretory neurons must remain intact to avoid CDI. The pathology of CDI thus always involves the supraoptic and paraventricular nuclei of the hypothalamus or a major portion of the pituitary stalk.

CDI may be complete (absence of ADH) or partial (insufficient amounts of ADH). CDI may be primary, in which there is a marked decrease in the hypothalamic nuclei of the neurohypophyseal system.

Etiology

Primary CDI: Genetic abnormalities of the ADH gene on chromosome 20 are responsible for autosomal dominant forms of primary CDI, but many cases are idiopathic.

Secondary CDI: CDI may also be secondary (acquired), caused by various lesions, including hypophysectomy, cranial injuries (particularly basal skull fractures), suprasellar and intrasellar tumors (primary or metastatic), Langerhans’ cell histiocytosis (Hand-Schuller-Christian disease), granulomas (sarcoidosis or TB), vascular lesions (aneurysm and thrombosis), and infections (encephalitis or meningitis).

Symptoms and Signs

Onset may be insidious or abrupt, occurring at any age. The only symptoms in primary CDI are polydipsia and polyuria. In secondary CDI, symptoms and signs of the associated lesions are also present. Enormous quantities of fluid may be ingested, and large volumes (3 to 30 L/day) of very dilute urine (sp gr usually < 1.005 and osmolality < 200 mOsm/L) are excreted. Nocturia almost always occurs. Dehydration and hypovolemia may develop rapidly if urinary losses are not continuously replaced.

Diagnosis

• Water deprivation test
• Sometimes ADH levels

CDI must be differentiated from other causes of polyuria (see Table 92-4), particularly psychogenic polydipsia and NDI. All tests for CDI (and for NDI) are based on the principle that increasing the plasma osmolality in normal people will lead to decreased excretion of urine with increased osmolality.

The water deprivation test is the simplest and most reliable method for diagnosing CDI but should be done only while the patient is under constant supervision. Serious dehydration may result. Additionally, if psychogenic polydipsia is suspected, the patient must be observed to prevent surreptitious drinking. The test is started in the morning by weighing the patient, obtaining venous blood to determine electrolyte concentrations and osmolality, and measuring urinary osmolality. Voided urine is collected hourly, and its sp gr or, preferably, osmolality is measured. Dehydration is continued until orthostatic hypotension and postural tachycardia appear, ≥ 5% of the initial body weight has been lost, or the urinary concentration does not increase > 0.001 sp gr or > 30 mOsm/L in sequentially voided specimens. Serum electrolytes and osmolality are again determined, and 5 units of aqueous vasopressin are injected sc. Urine for sp gr or osmolality measurement is collected one final time 60 min postinjection, and the test is terminated.
A normal response produces maximum urine osmolality after dehydration (often > 1.020 sp gr or > 700 mOsm/L), exceeding the plasma osmolality; osmolality does not increase more than an additional 5% after injection of vasopressin. Patients with CDI are generally unable to concentrate urine to greater than the plasma osmolality but are able to increase their urine osmolality by > 50% after vasopressin administration. Patients with partial CDI are often able to concentrate urine to above the plasma osmolality but show a rise in urine osmolality of > 9% after vasopressin administration. Patients with NDI are unable to concentrate urine to greater than the plasma osmolality and show no additional response to vasopressin administration.

Measurement of circulating ADH is the most direct method of diagnosing CDI; levels at the end of the water deprivation test (before the vasopressin injection) are low in CDI and appropriately elevated in NDI. However, ADH levels are difficult to measure, and the test is not routinely available. In addition, water deprivation is so accurate that direct measurement of ADH is unnecessary. Plasma ADH levels are diagnostic after either dehydration or infusion of hypertonic saline.

**Psychogenic polydipsia:** Psychogenic polydipsia may present a difficult problem in differential diagnosis. Patients may ingest and excrete up to 6 L of fluid/day and are often emotionally disturbed. Unlike patients with CDI and NDI, they usually do not have nocturia, nor does their thirst wake them at night. Continued ingestion of large volumes of water in this situation can lead to life-threatening hyponatremia (see p. 823).

Patients with acute psychogenic water drinking are able to concentrate their urine during water deprivation. However, because chronic water intake diminishes medullary tonicity in the kidney, patients with longstanding polydipsia are not able to concentrate their urine to maximal levels during water deprivation, a response similar to that of patients with partial CDI. However, unlike CDI, patients with psychogenic polydipsia show no response to exogenous ADH after water deprivation. This response resembles NDI, except that basal ADH levels are low compared with the elevated levels present in NDI. After prolonged restriction of fluid intake to ≤ 2 L/day, normal concentrating ability returns within several weeks.

**Treatment**

- Desmopressin

CDI can be treated with hormone replacement and treatment of any correctable cause. In the absence of appropriate management, permanent renal damage can result.

Desmopressin, a synthetic analog of ADH with minimal vasoconstrictive properties, has prolonged antidiuretic activity lasting for 12 to 24 h in most patients and may be administered intranasally, sc, iv, or orally. Desmopressin is the preparation of choice for both adults and children and is available as an intranasal solution in 2 forms. A dropper bottle with a calibrated nasal catheter has the advantage of delivering incremental doses from 5 to 20 μg but is awkward to use. A spray bottle that delivers 10 μg of desmopressin in 0.1 mL of fluid is easier to use but delivers a fixed quantity. For each patient, the duration of action of a given dose must be established, because variation among individuals is great. The duration of action can be established by following timed urine volumes and osmolality. The nightly dose is the lowest dose required to prevent nocturia. The morning and evening doses should be adjusted separately. The usual dosage range in adults is 10 to 40 μg, with most adults requiring 10 μg bid. For children age 3 mo to 12 yr, the usual dosage range is 2.5 to 10 μg bid. Overdosage can lead to fluid retention and decreased plasma osmolality, possibly resulting in seizures in small children. In such instances, furosemide can be given to induce diuresis. Headache may be a troublesome adverse effect but generally disappears if the dosage is reduced. Infrequently, desmopressin causes a slight increase in BP. Absorption from the nasal mucosa may be erratic, especially when URI or allergic rhinitis occurs. When intranasal delivery of desmopressin is inappropriate, it may be administered sc using about one tenth the intranasal dose. Desmopressin may be used IV if a rapid effect is necessary (eg, for hypovolemia). With oral desmopressin, dose equivalence with the intranasal formulation is unpredictable, so individual dose titration is needed. The initial dose is 0.1 mg po tid, and the maintenance dose is usually 0.1 to 0.2 mg tid.
Lypressin (lysine-8-vasopressin), a synthetic agent, is given by nasal spray at doses of 2 to 4 units (7.5 to 15 μg) q 3 to 8 h but, because of its short duration of action, has been largely replaced by desmopressin.

Aqueous vasopressin 5 to 10 units sc or IM can be given to provide an antidiuretic response that usually lasts ≤ 6 h. Thus, this drug has little use in long-term treatment but can be used in the initial therapy of unconscious patients and in patients with CDI who are undergoing surgery. Synthetic vasopressin can also be administered bid to qid as a nasal spray, with the dosage and interval tailored to each patient. Vasopressin tannate in oil 0.3 to 1 mL (1.5 to 5 units) IM may control symptoms for up to 96 h.

At least 3 groups of nonhormonal drugs are useful in reducing polyuria: various diuretics, primarily thiazides; ADH-releasing drugs, such as chlorpropamide, carbamazepine, and clofibrate; and prostaglandin inhibitors, which are modestly effective. These drugs have been particularly useful in partial CDI and do not cause the adverse effects of exogenous ADH.

The thiazides paradoxically reduce urine volume in partial and complete CDI (and NDI), primarily as a consequence of reducing ECF volume and increasing proximal tubular resorption. Urine volumes may fall by 25 to 50% with 15 to 25 mg/kg of chlorothiazide. Restricting salt intake may also help because it reduces urine output by reducing solute load.

Chlorpropamide, carbamazepine, and clofibrate can reduce or eliminate the need for vasopressin in some patients with partial CDI. None are effective in NDI. Chlorpropamide (3 to 5 mg/kg po once/day or bid) causes some release of ADH and also potentiates the action of ADH on the kidney. Clofibrate (500 to 1000 mg po bid) or carbamazepine (100 to 400 mg po bid) is recommended for adults only. These drugs may be used synergistically with a diuretic. However, significant hypoglycemia may result from chlorpropamide.

Prostaglandin inhibitors (such as indomethacin 0.5 to 1.0 mg/kg po tid, although most NSAIDs are effective) may reduce urine volume, but generally by no more than 10 to 25%, perhaps by decreasing renal blood flow and GFR. Together with indomethacin, restriction of Na intake and a thiazide diuretic help further reduce urine volume in NDI.
Chapter 93. Thyroid Disorders

Introduction

The thyroid gland, located in the anterior neck just below the cricoid cartilage, consists of 2 lobes connected by an isthmus. Follicular cells in the gland produce the 2 main thyroid hormones, tetraiodothyronine (thyroxine, T4) and triiodothyronine (T3). These hormones act on cells in virtually every body tissue by combining with nuclear receptors and altering expression of a wide range of gene products. Thyroid hormone is required for normal brain and somatic tissue development in the fetus and neonate, and, in people of all ages, regulates protein, carbohydrate, and fat metabolism.

T3 is the most active form; T4 has only minimal hormonal activity. However, T4 is much longer lasting and can be converted to T3 (in most tissues) and thus serves as a reservoir for T3. A 3rd form of thyroid hormone, reverse T3 (rT3), has no metabolic activity; levels of rT3 increase in certain diseases.

Additionally, parafollicular cells (C cells) secrete the hormone calcitonin, which is released in response to hypercalcemia and lowers serum Ca levels (see p. 838).

Synthesis and Release of Thyroid Hormones

Synthesis of thyroid hormones requires iodine (see Fig. 93-1). Iodine, ingested in food and water as iodide, is actively concentrated by the thyroid and converted to organic iodine (organification) within follicular cells by thyroid peroxidase. The follicular cells surround a space filled with colloid, which consists of thyroglobulin, a glycoprotein containing tyrosine within its matrix. Tyrosine in contact with the membrane of the follicular cells is iodinated at 1 (monoiodotyrosine) or 2 (diiodotyrosine) sites and then coupled to produce the 2 forms of thyroid hormone (diiodotyrosine + diiodotyrosine → T4; diiodotyrose + moniodotyrosine → T3).

[Fig. 93-1. Synthesis of thyroid hormones.]

T3 and T4 remain incorporated in thyroglobulin within the follicle until the follicular cells take up thyroglobulin as colloid droplets. Once inside the thyroid follicular cells, T3 and T4 are cleaved from thyroglobulin. Free T3 and T4 are then released into the bloodstream, where they are bound to serum proteins for transport, the major one being thyroxine-binding globulin (TBG), which has high affinity but low capacity for T3 and T4. TBG normally carries about 75% of bound thyroid hormones. The other binding proteins are thyroxine-binding prealbumin (transthyretin), which has high affinity but low capacity for T4, and albumin, which has low affinity but high capacity for T3 and T4. About 0.3% of total serum T3 and 0.03% of total serum T4 are free and in equilibrium with bound hormones. Only free T3 and free T4 are available to act on the peripheral tissues.

All reactions necessary for the formation and release of T3 and T4 are controlled by thyroid-stimulating hormone (TSH), which is secreted by pituitary thyrotropic cells. TSH secretion is controlled by a negative feedback mechanism in the pituitary: Increased levels of free T4 and T3 inhibit TSH synthesis and secretion, whereas decreased levels increase TSH secretion. TSH secretion is also influenced by thyrotropin-releasing hormone (TRH), which is synthesized in the hypothalamus. The precise mechanisms regulating TRH synthesis and release are unclear, although negative feedback from thyroid hormones inhibits TRH synthesis.

Most circulating T3 is produced outside the thyroid by monodeiodination of T4. Only one fifth of circulating T3 is secreted directly by the thyroid.

Laboratory Testing of Thyroid Function

TSH measurement is the best means of determining thyroid dysfunction (see Table 93-1). Normal results essentially rule out hyperthyroidism or hypothyroidism, except in rare patients.
with pituitary resistance to thyroid hormone or with central hypothyroidism due to disease in the hypothalamus, pituitary gland, or both. Serum TSH can be falsely low in very sick people. The serum TSH level also defines the syndromes of subclinical hyperthyroidism (low serum TSH) and subclinical hypothyroidism (elevated serum TSH), both

Table 93-1. Results of Thyroid Function Tests in Various Clinical Situations

of which are characterized by normal serum T₄, free T₄, serum T₃, and free T₃ levels.

Total serum T₄ is a measure of bound and free hormone. Changes in levels of thyroid hormone-binding serum proteins produce corresponding changes in total T₄, even though levels of physiologically active free T₄ are unchanged. Thus, a patient may be physiologically normal but have an abnormal total serum T₄ level. Free T₄ in the serum can be measured directly, avoiding the pitfalls of interpreting total T₄ levels.

Free T₄ index is a calculated value that corrects total T₄ for the effects of varying amounts of thyroid hormone-binding serum proteins and thus gives an estimate of free T₄ when total T₄ is measured. The thyroid hormone-binding ratio or T₃ resin uptake is used to estimate protein binding. Free T₄ index is readily available and compares well with direct measurement of free T₄.

Total serum T₃ and free T₃ can also be measured. Because T₃ is tightly bound to TBG (although 10 times less than T₄), total serum T₃ levels are influenced by alterations in serum TBG level and by drugs that affect binding to TBG. Free T₃ levels in the serum are measured by the same direct and indirect methods (free T₃ index) described for T₄ and are used mainly for evaluating thyrotoxicosis.

TBG can be measured; it is increased in pregnancy, by estrogen therapy or oral contraceptive use, and in the acute phase of infectious hepatitis. TBG may also be increased by an X-linked abnormality. It is most commonly decreased by illnesses that reduce hepatic protein synthesis, use of anabolic steroids, and excessive corticosteroid use. Large doses of certain drugs, such as phenytoin and aspirin and their derivatives, displace T₄ from its binding sites on TBG, which spuriously lowers total serum T₄ levels.

Autoantibodies to thyroid peroxidase are present in almost all patients with Hashimoto's thyroiditis (some of whom also have autoantibodies to thyroglobulin) and in most patients with Graves' disease. These autoantibodies are markers of autoimmune disease but probably do not cause disease. However, an autoantibody directed against the TSH receptor on the thyroid follicular cell is responsible for the hyperthyroidism in Graves' disease. Antibodies against T₄ and T₃ may be found in patients with autoimmune thyroid disease and may affect T₄ and T₃ measurements but are rarely clinically significant.

The thyroid is the only source of thyroglobulin, which is readily detectable in the serum of healthy people and is usually elevated in patients with nontoxic or toxic goiter. The principal use of serum thyroglobulin measurement is in evaluating patients after near-total or total thyroidectomy (with or without ¹³¹I ablation) for differentiated thyroid cancer. Normal or elevated serum thyroglobulin values indicate the presence of residual normal or cancerous thyroid tissue in patients receiving TSH-suppressive doses of L-thyroxine or after withdrawal of L-thyroxine. However, thyroglobulin antibodies can interfere with thyroglobulin measurement.

Radioactive iodine uptake can be measured. A trace amount of radioiodine is given orally or IV; a scanner then detects the amount of radioiodine taken up by the thyroid. The preferred radioiodine isotope is ¹²³I, which exposes the patient to minimal radiation (much less than ¹³¹I). Thyroid ¹²³I uptake varies widely with iodine ingestion and is low in patients exposed to excess iodine.

The test is valuable in the differential diagnosis of hyperthyroidism (high uptake in Graves' disease, low uptake in thyroiditis—see p. 782). It may also help in the calculation of the dose of ¹³¹I needed for treatment of hyperthyroidism.
Imaging by a scintillation camera can be done after radioisotope administration (radioiodine or technetium 99m pertechnetate) to produce a graphic representation of isotope uptake. Focal areas of increased (hot) or decreased (cold) uptake help distinguish areas of possible cancer (thyroid cancers exist in < 1% of hot nodules compared with 10 to 20% of cold nodules).

**Screening:** Screening every 5 yr by measuring serum TSH is recommended for all men ≥ 65 and for all women ≥ 35. For those with risk factors for thyroid disease, the serum TSH should be checked more often. Screening for hypothyroidism is as cost effective as screening for hypertension, hypercholesterolemia, and breast cancer. This single test is highly sensitive and specific in diagnosing or excluding two prevalent and serious disorders (hypothyroidism and hyperthyroidism), both of which can be treated effectively. Because of the high incidence of hypothyroidism in older people, screening on an annual basis is reasonable for those > age 70.

**Approach to the Patient With a Thyroid Nodule**

Thyroid nodules are common, increasingly so with increasing age. The reported incidence varies with the method of assessment. In middle-aged and elderly patients, palpation reveals nodules in about 5%. Results of ultrasonography and autopsy studies suggest that nodules are present in about 50% of adults. Many nodules are found incidentally on thyroid imaging studies done for other disorders.

**Etiology**

Most nodules are benign. Benign causes include hyperplastic colloid goiter, thyroid cysts, thyroiditis, and thyroid adenomas. Malignant causes include thyroid cancers (see p. 789).

**Evaluation**

**History:** Pain suggests thyroiditis or hemorrhage into a cyst. An asymptomatic nodule may be malignant but is usually benign. Symptoms of hyperthyroidism suggest a hyperfunctioning adenoma or thyroiditis, whereas symptoms of hypothyroidism suggest Hashimoto’s thyroiditis. Risk factors for thyroid cancer include

- History of thyroid irradiation, especially in infancy or childhood
- Age < 20 yr
- Male sex
- Family history of thyroid cancer or multiple endocrine neoplasia
- A solitary nodule
- Dysphagia
- Dysphonia
- Increasing size (particularly rapid growth or growth while receiving thyroid suppression treatment)

**Physical examination:** Signs that suggest thyroid cancer include stony hard consistency or fixation to surrounding structures, cervical lymphadenopathy, and hoarseness due to recurrent laryngeal nerve paralysis.

**Testing:** Initial evaluation of a thyroid nodule consists of measurement of levels of

- Thyroid-stimulating hormone (TSH)
- Free thyroxine (T4)
Antithyroid peroxidase antibodies

If TSH is suppressed, radioiodine scanning is done. Nodules with increased radionuclide uptake (hot) are seldom malignant. If thyroid function tests do not indicate hyperthyroidism or Hashimoto's thyroiditis, or if nodules are indeterminate or cold, fine-needle aspiration biopsy is done to distinguish benign from malignant nodules. Early use of fine-needle aspiration biopsy is a more economic approach than routine use of radioiodine scans. Ultrasonography is useful in determining the size of the nodule but is rarely diagnostic of cancer, although cancer is suggested by ultrasonographic or x-ray evidence of fine, stipped, psammomatous calcification (papillary carcinoma) or dense, homogeneous calcification (medullary carcinoma). Fine-needle aspiration biopsy is not routinely indicated for nodules < 1 cm on ultrasonography.

Treatment

Treatment is directed at the underlying disorder. Thyroxine suppression of TSH to shrink smaller benign nodules is effective in no more than half the cases.

Euthyroid Sick Syndrome

Euthyroid sick syndrome is low serum levels of thyroid hormones in clinically euthyroid patients with nonthyroidal systemic illness. Diagnosis is based on excluding hypothyroidism. Treatment is of the underlying illness; thyroid hormone replacement is not indicated.

Patients with various acute or chronic nonthyroid disorders may have abnormal thyroid function tests. Such disorders include acute and chronic illness, particularly fasting, starvation, protein-energy undernutrition, major trauma, MI, chronic renal failure, diabetic ketoacidosis, anorexia nervosa, cirrhosis, thermal injury, and sepsis.

Decreased triiodothyronine (T₃) levels are most common. Patients with more severe or prolonged illness also have decreased thyroxine (T₄) levels. Serum reverse T₃ (rT₃) is increased. Patients are clinically euthyroid and do not have elevated thyroid-stimulating hormone (TSH) levels.

Pathogenesis is unknown but may include decreased peripheral conversion of T₄ to T₃, decreased clearance of rT₃ generated from T₄, and decreased binding of thyroid hormones to thyroxine-binding globulin (TBG). Proinflammatory cytokines (eg, tumor necrosis factor-α, IL-1) may be responsible for some changes.

Interpretation of abnormal thyroid function test results in ill patients is complicated by the effects of various drugs, including the iodine-rich contrast agents and amiodarone, which impairs the peripheral conversion of T₄ to T₃, and by drugs such as dopamine and corticosteroids, which decrease pituitary secretion of TSH, resulting in low serum TSH levels and subsequent decreased T₄ secretion.

Diagnosis

- TSH
- Serum cortisol
- Clinical judgment

The diagnostic dilemma is whether the patient has hypothyroidism or euthyroid sick syndrome. The best test is measurement of TSH, which in euthyroid sick syndrome is low, normal, or slightly elevated but not as high as it would be in hypothyroidism. Serum rT₃ is elevated, although this measurement is rarely done. Serum cortisol is often elevated in euthyroid sick syndrome and low or low-normal in hypothyroidism due to pituitary-hypothalamic disease. Because tests are nonspecific, clinical judgment is required to interpret abnormal thyroid function tests in the acutely or chronically ill patient. Unless thyroid
dysfunction is highly suspected, thyroid function tests should not be ordered for patients in the ICU.

**Treatment**

Treatment with thyroid hormone replacement is not appropriate. When the underlying disorder is treated, results of thyroid tests normalize.

**Hashimoto's Thyroiditis**

(Autoimmune Thyroiditis; Chronic Lymphocytic Thyroiditis; Hashimoto's Struma)

**Hashimoto's thyroiditis** is chronic autoimmune inflammation of the thyroid with lymphocytic infiltration. Findings include painless thyroid enlargement and symptoms of hypothyroidism. Diagnosis involves demonstration of high titers of thyroid peroxidase antibodies. Lifelong L-thyroxine replacement is typically required.

Hashimoto's thyroiditis is believed to be the most common cause of primary hypothyroidism in North America. It is twice as prevalent among women. Incidence increases with age and in patients with chromosomal disorders, including Down, Turner's, and Klinefelter's syndromes. A family history of thyroid disorders is common.

Hashimoto's thyroiditis, like Graves' disease, is sometimes associated with other autoimmune disorders, including Addison's disease (adrenal insufficiency), type 1 diabetes mellitus, hypoparathyroidism, vitiligo, premature graying of hair, pernicious anemia, connective tissue diseases (eg, RA, SLE, Sjogren's syndrome), and Schmidt's syndrome (Addison's disease, diabetes, and hypothyroidism secondary to Hashimoto's thyroiditis). There may be an increased incidence of thyroid tumors, rarely thyroid lymphoma. Pathologically, there is extensive infiltration of lymphocytes with lymphoid follicles and scarring.

**Symptoms and Signs**

Patients complain of painless enlargement of the thyroid or fullness in the throat. Examination reveals a nontender goiter that is smooth or nodular, firm, and more rubbery than the normal thyroid. Many patients present with symptoms of hypothyroidism, but some present with hyperthyroidism.

**Diagnosis**

- Thyroxine (T₄)
- Thyroid-stimulating hormone (TSH)
- Thyroid autoantibodies

Testing consists of measuring T₄, TSH, and thyroid autoantibodies; early in the disease T₄ and TSH levels are normal and there are high levels of thyroid peroxidase antibodies and less commonly of antithyroglobulin antibodies. Thyroid radioactive iodine uptake may be increased, perhaps because of defective iodide organization together with a gland that continues to trap iodine. Patients later develop hypothyroidism with decreased T₄, decreased thyroid radioactive iodine uptake, and increased TSH. Testing for other autoimmune disorders is warranted only when clinical manifestations are present.

**Treatment**

Occasionally, the hypothyroidism is transient, but most patients require lifelong thyroid hormone replacement, typically L-thyroxine 75 to 150 μg po once/day.

**Hyperthyroidism**

(Thyrotoxicosis)
Hyperthyroidism is characterized by hypermetabolism and elevated serum levels of free thyroid hormones. Symptoms are many but include tachycardia, fatigue, weight loss, nervousness, and tremor. Diagnosis is clinical and with thyroid function tests. Treatment depends on cause.

Hyperthyroidism can be classified on the basis of thyroid radioactive iodine uptake and the presence or absence of circulating thyroid stimulators (see Table 93-1).

**Etiology**

Hyperthyroidism may result from increased synthesis and secretion of thyroid hormones (thyroxine \([T_4]\) and triiodothyronine \([T_3]\)) from the thyroid, caused by thyroid stimulators in the blood or by autonomous thyroid hyperfunction. It can also result from excessive release of thyroid hormone from the thyroid without increased synthesis. Such release is commonly caused by the destructive changes of various types of thyroiditis. Various clinical syndromes also cause hyperthyroidism.

**Graves' disease (toxic diffuse goiter)**, the most common cause of hyperthyroidism, is characterized by hyperthyroidism and one or more of the following:

- Goiter
- Exophthalmos
- Infiltrative dermopathy

Graves' disease is caused by an autoantibody against the thyroid receptor for thyroid-stimulating hormone (TSH); unlike most autoantibodies, which are inhibitory, this autoantibody is stimulatory, thus causing continuous synthesis and secretion of excess \(T_4\) and \(T_3\). Graves' disease (like Hashimoto's thyroiditis) sometimes occurs with other autoimmune disorders, including type 1 diabetes mellitus, vitiligo, premature graying of hair, pernicious anemia, connective tissue diseases, and polyglandular deficiency syndrome. The pathogenesis of infiltrative ophthalmopathy (responsible for the exophthalmos in Graves' disease) is poorly understood but may result from immunoglobulins directed to specific receptors in the orbital fibroblasts and fat that result in release of proinflammatory cytokines, inflammation, and accumulation of glycosaminoglycans. Ophthalmopathy may also occur before the onset of hyperthyroidism or as late as 20 yr afterward and frequently worsens or abates independently of the clinical course of hyperthyroidism. Typical ophthalmopathy in the presence of normal thyroid function is called euthyroid Graves' disease.

**Inappropriate TSH secretion** is a rare cause. Patients with hyperthyroidism have essentially undetectable TSH except for those with a TSH-secreting anterior pituitary adenoma or pituitary resistance to thyroid hormone. TSH levels are high, and the TSH produced in both disorders is biologically more active than normal TSH. An increase in the \(\alpha\)-subunit of TSH in the blood (helpful in differential diagnosis) occurs in patients with a TSH-secreting pituitary adenoma.

**Molar pregnancy, choriocarcinoma, and hyperemesis gravidarum** produce high levels of serum human chorionic gonadotropin (hCG), a weak thyroid stimulator. Levels of hCG are highest during the 1st trimester of pregnancy and result in the decrease in serum TSH and mild increase in serum free \(T_4\) sometimes observed at that time. The increased thyroid stimulation may be caused by increased levels of partially desialated hCG, an hCG variant that seems to be a more potent thyroid stimulator than more sialated hCG. Hyperthyroidism in molar pregnancy, choriocarcinoma, and hyperemesis gravidarum is transient; normal thyroid function resumes when the molar pregnancy is evacuated, the choriocarcinoma is appropriately treated, or the hyperemesis gravidarum abates.

**Nonautoimmune autosomal dominant hyperthyroidism** manifests during infancy. It results from mutations in the TSH receptor gene that produce continuous thyroid stimulation.
Toxic solitary or multinodular goiter (Plummer's disease) sometimes results from TSH receptor gene mutations producing continuous thyroid stimulation. Patients with toxic nodular goiter have none of the autoimmune manifestations or circulating antibodies observed in patients with Graves' disease. Also, in contrast to Graves' disease, toxic solitary and multinodular goiters usually do not remit.

Inflammatory thyroid disease (thyroiditis) includes subacute granulomatous thyroiditis, Hashimoto's thyroiditis, and silent lymphocytic thyroiditis, a variant of Hashimoto's thyroiditis (see p. 787). Hyperthyroidism results from destructive changes in the gland and release of stored hormone, not from increased synthesis. Hypothyroidism may follow.

Drug-induced hyperthyroidism can result from amiodarone and interferon alfa, which may induce thyroiditis with hyperthyroidism and other thyroid disorders. Although more commonly causing hypothyroidism, lithium can rarely cause hyperthyroidism. Patients receiving these drugs should be closely monitored.

Thyrotoxicosis factitia is hyperthyroidism resulting from conscious or accidental overingestion of thyroid hormone.

Excess iodine ingestion causes hyperthyroidism with a low thyroid radioactive iodine uptake. It most often occurs in patients with underlying nontoxic nodular goiter (especially elderly patients) who are given drugs that contain iodine (eg, amiodarone, iodine-containing expectorants) or who undergo radiologic studies using iodine-rich contrast agents. The etiology may be that the excess iodine provides substrate for functionally autonomous (ie, not under TSH regulation) areas of the thyroid to produce hormone. Hyperthyroidism usually persists as long as excess iodine remains in the circulation.

Metastatic thyroid cancer is a possible cause. Overproduction of thyroid hormone occurs rarely from functioning metastatic follicular carcinoma, especially in pulmonary metastases.

Struma ovarii develops when ovarian teratomas contain enough thyroid tissue to cause true hyperthyroidism. Radioactive iodine uptake occurs in the pelvis, and uptake by the thyroid is usually suppressed.

Pathophysiology

In hyperthyroidism, serum T₃ usually increases more than does T₄, probably because of increased secretion of T₃ as well as conversion of T₄ to T₃ in peripheral tissues. In some patients, only T₃ is elevated (T₃ toxicosis). T₃ toxicosis may occur in any of the usual disorders that cause hyperthyroidism, including Graves' disease, multinodular goiter, and the autonomously functioning solitary thyroid nodule. If T₃ toxicosis is untreated, the patient usually also develops laboratory abnormalities typical of hyperthyroidism (ie, elevated T₄ and ¹²³I uptake). The various forms of thyroiditis commonly have a hyperthyroid phase followed by a hypothyroid phase.

Symptoms and Signs

Most symptoms and signs are the same regardless of the cause. Exceptions include infiltrative ophthamopathy and dermopathy, which occur only in Graves' disease.

The clinical presentation may be dramatic or subtle. A goiter or nodule may be present. Many common symptoms and signs of hyperthyroidism are similar to those of adrenergic excess, such as nervousness, palpitations, hyperactivity, increased sweating, heat hypersensitivity, fatigue, increased appetite, weight loss, insomnia, weakness, and frequent bowel movements (occasionally diarrhea). Hypomenorrhea may be present. Signs may include warm, moist skin; tremor; tachycardia; widened pulse pressure; atrial fibrillation; and palpitations.

Elderly patients, particularly those with toxic nodular goiter, may present atypically (apathetic or masked hyperthyroidism) with symptoms more akin to depression or dementia. Most do not have exophthalmos or tremor. Atrial fibrillation, syncope, altered sensorium, heart failure, and weakness are more likely.
Symptoms and signs may involve only a single organ system.

Eye signs include stare, eyelid lag, eyelid retraction, and mild conjunctival injection and are largely due to excessive adrenergic stimulation. They usually remit with successful treatment. Infiltrative ophthalmopathy, a more serious development, is specific to Graves' disease and can occur years before or after hyperthyroidism. It is characterized by orbital pain, lacrimation, irritation, photophobia, increased retro-orbital tissue, exophthalmos, and lymphocytic infiltration of the extraocular muscles, causing ocular muscle weakness that frequently leads to double vision.

Infiltrative dermopathy, also called pretibial myxedema (a confusing term, because myxedema suggests hypothyroidism), is characterized by nonpitting infiltration by proteinaceous ground substance, usually in the pretibial area. It rarely occurs in the absence of Graves' ophthalmopathy. The lesion is often pruritic and erythematous in its early stages and subsequently becomes brawny. Infiltrative dermopathy may appear years before or after hyperthyroidism.

**Thyroid storm**: Thyroid storm is an acute form of hyperthyroidism that results from untreated or inadequately treated severe hyperthyroidism. It is rare, occurring in patients with Graves' disease or toxic multinodular goiter (a solitary toxic nodule is less common and generally less severe). It may be precipitated by infection, trauma, surgery, embolism, diabetic ketoacidosis, or preeclampsia. Thyroid storm causes abrupt florid symptoms of hyperthyroidism with one or more of the following: fever, marked weakness and muscle wasting, extreme restlessness with wide emotional swings, confusion, psychosis, coma, nausea, vomiting, diarrhea, and hepatomegaly with mild jaundice. The patient may present with cardiovascular collapse and shock. *Thyroid storm is a life-threatening emergency requiring prompt treatment.*

**Diagnosis**

- **TSH**
- **Free T4**
- Sometimes radioactive iodine uptake

Diagnosis is based on history, physical examination, and thyroid function tests. Serum TSH measurement is the best test, because TSH is suppressed in hyperthyroid patients except in the rare instance when the etiology is a TSH-secreting pituitary adenoma or pituitary resistance to thyroid hormone. Screening selected populations for TSH level is warranted (see p. 776). Free T4 is increased in hyperthyroidism. However, T4 can be falsely normal in true hyperthyroidism in patients with a severe systemic illness (similar to the falsely low levels that occur in euthyroid sick syndrome) and in T3 toxicosis. If free T4 level is normal and TSH is low in a patient with subtle symptoms and signs of hyperthyroidism, then serum T3 should be measured to detect T3 toxicosis; an elevated level confirms that diagnosis.

The cause can often be diagnosed clinically (eg, exposure to a drug, the presence of signs specific to Graves' disease). If not, thyroid radioactive iodine uptake may be obtained by using $^{123}$I. When hyperthyroidism is due to hormone overproduction, thyroid radioactive iodine uptake is usually elevated.

TSH receptor antibodies can be measured to detect Graves' disease, but measurement is rarely necessary except during the 3rd trimester of pregnancy to assess the risk of neonatal Graves' disease; TSH receptor antibodies readily cross the placenta to stimulate the fetal thyroid. Most patients with Graves' disease have circulating antithyroid peroxidase antibodies, and fewer have antithyroglobulin antibodies.

Inappropriate TSH secretion is uncommon. The diagnosis is confirmed when hyperthyroidism occurs with elevated circulating free T4 and T3 concentrations and normal or elevated serum TSH.

If thyrotoxicosis factitia is suspected, serum thyroglobulin can be measured; it is usually low or low-normal.
—unlike in all other causes of hyperthyroidism.

In hyperthyroidism caused by excess iodine ingestion, low radioactive iodine uptake is typical because thyroid radioactive iodine uptake is inversely proportional to iodine intake.

**Treatment**

Treatment depends on cause but may include

- Propylthiouracil or methimazole
- β-Blockers
- Iodine
- Radioactive iodine
- Surgery

**Iodine:** Iodine in pharmacologic doses inhibits the release of T₃ and T₄ within hours and inhibits the organification of iodine, a transitory effect lasting from a few days to a week, after which inhibition usually ceases. Iodine is used for emergency management of thyroid storm, for hyperthyroid patients undergoing emergency nonthyroid surgery, and (because it also decreases the vascularity of the thyroid) for preoperative preparation of hyperthyroid patients undergoing subtotal thyroidectomy. Iodine generally is not used for routine treatment of hyperthyroidism. The usual dosage is 2 to 3 drops (100 to 150 mg) of a saturated K iodide solution po tid or qid or 0.5 to 1 g Na iodide in 1 L 0.9% saline solution given IV slowly q 12 h.

Complications of iodine therapy include inflammation of the salivary glands, conjunctivitis, and rash.

**Propylthiouracil and methimazole:** These antithyroid drugs block thyroid peroxidase, decreasing the organification of iodide, and impair the coupling reaction. Propylthiouracil in high doses also inhibits the peripheral conversion of T₄ to T₃. About 20 to 50% of patients with Graves' disease remain in remission after a 1- to 2-yr course of either drug. The return to normal or a marked decrease in gland size, the restoration of a normal serum TSH level, and less severe hyperthyroidism before therapy are good prognostic signs of long-term remission. The concomitant use of antithyroid drug therapy and L-thyroxine does not improve the remission rate in patients with Graves' disease. Because toxic nodular goiter rarely goes into remission, antithyroid drug therapy is given only in preparation for surgical treatment or ¹³¹I therapy.

The usual starting dosage of propylthiouracil is 100 to 150 mg po q 8 h and of methimazole 5 to 20 mg po tid. When T₄ and T₃ levels normalize, the dosage is decreased to the lowest effective amount, usually propylthiouracil 50 mg tid or methimazole 5 to 15 mg once/day. Usually, control is achieved in 2 to 3 mo. More rapid control can be achieved by increasing the dosage of propylthiouracil to 150 to 200 mg q 8 h. Such dosages or higher ones (up to 400 mg q 8 h) are generally reserved for severely ill patients, including those with thyroid storm. Maintenance doses can be continued for one or many years depending on the clinical circumstances. Carbimazole, which is used widely in Europe, is rapidly converted to methimazole. The usual starting dose is similar to that of methimazole; maintenance dosage is 5 to 20 mg po once/day, 2.5 to 10 mg bid, or 1.7 to 6.7 mg tid.

Adverse effects include rash, allergic reactions, abnormal liver function, and, in about 0.1% of patients, reversible agranulocytosis. Patients allergic to one drug can be switched to the other, but cross-sensitivity may occur. If agranulocytosis occurs, the patient cannot be switched to the other drug; other therapy (eg, radioiodine, surgery) should be used.

Each drug has advantages and disadvantages. Methimazole need only be given once/day, which improves adherence. Furthermore, when methimazole is used in dosages of < 40 mg/day, agranulocytosis
is less common; with propylthiouracil, agranulocytosis may occur at any dosage. Propylthiouracil may be preferred if antithyroid drugs must be used during pregnancy or breastfeeding because it is less likely to cross the placenta or enter breast milk. Methimazole has been used successfully in pregnant and nursing women without fetal or infant complications, but rarely methimazole has been associated with scalp and GI defects in the neonate. Propylthiouracil is also preferred for the treatment of thyroid storm, because the dosages used (800 to 1200 mg/day) partially block the peripheral conversion of T\textsubscript{4} to T\textsubscript{3}.

The combination of high-dose propylthiouracil and dexamethasone, also a potent inhibitor of T\textsubscript{4} to T\textsubscript{3} conversion, can relieve symptoms of hyperthyroidism and restore the serum T\textsubscript{3} level to normal within a week.

\textbf{β-Blockers:} Symptoms and signs of hyperthyroidism due to adrenergic stimulation may respond to β-blockers; propranolol has had the greatest use, but atenolol or metoprolol may be preferable.

Other manifestations typically do not respond.

- Manifestations typically responding to β-blockers: Tachycardia, tremor, mental symptoms, eyelid lag; occasionally heat intolerance and sweating, diarrhea, proximal myopathy
- Manifestations typically not responding to β-blockers: \textit{O}_{2} consumption, exophthalmos, goiter, bruit, circulating thyroxine levels, weight loss

Propranolol is indicated in thyroid storm (see Table 93-2). It rapidly decreases heart rate, usually within 2 to 3 h when given orally and within minutes when given IV. Esmolol may be used in the ICU because it requires careful titration and monitoring. Propranolol is also indicated for tachycardia with hyperthyroidism, especially in elderly patients, because antithyroid drugs usually take several weeks to become fully effective. Ca channel blockers may control tachyarrhythmias in patients in whom β-blockers are contraindicated.

\textbf{Radioactive sodium iodine (\textit{131}I, radioiodine):} In the US, \textit{131}I is the most common treatment for hyperthyroidism. Radioiodine is often recommended as the treatment of choice for Graves' disease and toxic nodular goiter in all patients, including children. Dosage of \textit{131}I is difficult to adjust because the response of the gland cannot be predicted; some physicians give a standard dose of 8 to 10 mCi. Others adjust the dose based on estimated thyroid size and the 24-h uptake to provide a dose of 80 to 120 \textmu Ci/g thyroid tissue.

When sufficient \textit{131}I is given to cause euthyroidism, about 25% of patients become hypothyroid 1 yr later, and the incidence continues to increase yearly. Thus, most patients eventually become hypothyroid. However, if smaller doses are used, incidence of recurrence is higher. Larger doses, such as 10 to 15 mCi, often cause hypothyroidism within 6 mo.

Radioactive iodine is not used during pregnancy. There is no proof that radioiodine increases the incidence of tumors, leukemia, thyroid cancer, or birth defects in children born to women who become pregnant later in life.

\textbf{Surgery:} Surgery is indicated for patients with Graves' disease whose hyperthyroidism has recurred after courses of antithyroid drugs and who refuse \textit{131}I therapy, patients who cannot tolerate antithyroid drugs, patients with very large goiters, and in some younger patients with toxic adenoma and multinodular goiter. Surgery may be done in elderly patients with giant nodular goiters.

Surgery usually restores normal function. Postoperative recurrences vary between 2 and 16%; risk of hypothyroidism is directly related to the extent of surgery and occurs in about one half of patients. Vocal cord paralysis and hypoparathyroidism are uncommon complications. Saturated solution of K iodide 3
drops (about 100 to 150 mg) po tid should be given for 10 days before surgery to reduce the vascularity of the gland. Propylthiouracil or methimazole must also be given, because the patient should be euthyroid before iodide is given. Dexamethasone can be added to rapidly restore euthyroidism. Surgical procedures are more difficult in patients who previously underwent thyroidectomy or radioiodine therapy.

**Treatment of thyroid storm:** A treatment regimen for thyroid storm is shown in Table 93-2.

**Treatment of infiltrative dermopathy and ophthalmopathy:** In infiltrative dermopathy (in Graves’ disease), topical corticosteroids sometimes relieve the pruritus. Dermopathy usually remits spontaneously after months or years. Ophthalmopathy should be treated jointly by the endocrinologist and ophthalmologist and may require corticosteroids, orbital radiation, and surgery.

**Subclinical Hyperthyroidism**

Subclinical hyperthyroidism is low serum TSH in patients with normal serum free T\(_4\) and T\(_3\) and absent or minimal symptoms of hyperthyroidism.

Subclinical hyperthyroidism is far less common than subclinical hypothyroidism (see p. 787). Patients with serum TSH < 0.1 mU/L have an increased incidence of atrial fibrillation (particularly elderly patients), reduced bone mineral density, increased fractures, and increased mortality. Patients with serum TSH that is only slightly below normal are less likely to have these features. Many patients with subclinical hyperthyroidism are taking L-thyroxine; in these patients, reduction of the dose is the most appropriate management unless therapy is aimed at maintaining a suppressed TSH in patients with thyroid cancer or nodules. The other causes of subclinical hyperthyroidism are the same as those for clinically apparent hyperthyroidism.

Therapy is indicated for patients with endogenous subclinical hyperthyroidism (serum TSH < 0.1 mU/L), especially those with atrial fibrillation or reduced bone mineral density. The usual treatment is \(^{131}\)I. In patients with milder symptoms (eg, nervousness), a trial of antithyroid drug therapy is worthwhile.

**Hypothyroidism**

(Myxedema)

Hypothyroidism is thyroid hormone deficiency. It is diagnosed by clinical features such as a typical facies, hoarse slow speech, and dry skin and by low levels of thyroid hormones. Management includes treatment of the cause and administration of thyroxine.

Hypothyroidism occurs at any age but is particularly common among the elderly. It occurs in close to 10% of women and 6% of men > 65. Although typically easy to diagnose in younger adults, it may be subtle and manifest atypically in the elderly.

**Primary hypothyroidism:** Primary hypothyroidism is due to disease in the thyroid; thyroid-stimulating hormone (TSH) is increased. The most common cause is probably autoimmune. It usually results from Hashimoto's thyroiditis and is often associated with a firm goiter or, later in the disease process, with a shrunken fibrotic thyroid with little or no function. The 2nd most common cause is post-therapeutic hypothyroidism, especially after radioactive iodine therapy or surgery for hyperthyroidism or goiter. Hypothyroidism during overtreatment with propylthiouracil, methimazole, and iodide abates after therapy is stopped.

Most patients with non-Hashimoto's goiters are euthyroid or have hyperthyroidism, but goitrous hypothyroidism may occur in endemic goiter. Iodine deficiency decreases thyroid hormonogenesis. In response, TSH is released, which causes the thyroid to enlarge and trap iodine avidly; thus, goiter results. If iodine deficiency is severe, the patient becomes hypothyroid, a rare occurrence in the US since the advent of iodized salt.

Iodine deficiency can cause endemic cretinism in children; endemic cretinism is the most common cause...
of congenital hypothyroidism in severely iodine-deficient regions and a major cause of mental deficiency worldwide.

Rare inherited enzymatic defects can alter the synthesis of thyroid hormone and cause goitrous hypothyroidism (see p. 2887).

Hypothyroidism may occur in patients taking lithium, perhaps because lithium inhibits hormone release by the thyroid. Hypothyroidism may also occur in patients taking amiodarone or other iodine-containing drugs, and in patients taking interferon alfa. Hypothyroidism can result from radiation therapy for cancer of the larynx or Hodgkin lymphoma (Hodgkin's disease). The incidence of permanent hypothyroidism after radiation therapy is high, and thyroid function (through measurement of serum TSH) should be evaluated at 6- to 12-mo intervals.

**Secondary hypothyroidism:** Secondary hypothyroidism occurs when the hypothalamus produces insufficient thyrotropin-releasing hormone (TRH) or the pituitary produces insufficient TSH. Sometimes, deficient TSH secretion due to deficient TRH secretion is termed tertiary hypothyroidism.

**Symptoms and Signs**

Symptoms and signs of primary hypothyroidism are often subtle and insidious. Symptoms may include cold intolerance, constipation, forgetfulness, and personality changes. Modest weight gain is largely the result of fluid retention and decreased metabolism. Paresthesias of the hands and feet are common, often due to carpal-tarsal tunnel syndrome caused by deposition of proteinaceous ground substance in the ligaments around the wrist and ankle. Women with hypothyroidism may develop menorrhagia or secondary amenorrhea.

The facial expression is dull; the voice is hoarse and speech is slow; facial puffiness and periorbital swelling occur due to infiltration with the mucopolysaccharides hyaluronic acid and chondroitin sulfate; eyelids droop because of decreased adrenergic drive; hair is sparse, coarse, and dry; and the skin is coarse, dry, scaly, and thick. The relaxation phase of deep tendon reflexes is slowed. Hypothermia is common. Dementia or frank psychosis (myxedema madness) may occur.

Carotenemia is common, particularly notable on the palms and soles, caused by deposition of carotene in the lipid-rich epidermal layers. Deposition of proteinaceous ground substance in the tongue may cause macroglossia. A decrease in both thyroid hormone and adrenergic stimulation causes bradycardia. The heart may be enlarged, partly because of dilation but chiefly because of pericardial effusion. Pleural or abdominal effusions also may be noted. The pericardial and pleural effusions develop slowly and only rarely cause respiratory or hemodynamic distress.

Elderly patients have significantly fewer symptoms than do younger adults, and complaints are often subtle and vague. Many elderly patients with hypothyroidism present with nonspecific geriatric syndromes—confusion, anorexia, weight loss, falling, incontinence, and decreased mobility. Musculoskeletal symptoms (especially arthralgias) occur often, but arthritis is rare. Muscular aches and weakness, often mimicking polymyalgia rheumatica or polymyositis, and an elevated CK level may occur. In the elderly, hypothyroidism may mimic dementia or parkinsonism.

Although secondary hypothyroidism is uncommon, its causes often affect other endocrine organs controlled by the hypothalamic-pituitary axis. In a woman with hypothyroidism, indications of secondary hypothyroidism are a history of amenorrhea rather than menorrhagia and some suggestive differences on physical examination. Secondary hypothyroidism is characterized by skin and hair that are dry but not very coarse, skin depigmentation, only minimal macroglossia, atrophic breasts, and low BP. Also, the heart is small, and serous pericardial effusions do not occur. Hypoglycemia is common because of concomitant adrenal insufficiency or growth hormone deficiency.

**Myxedema coma:** Myxedema coma is a life-threatening complication of hypothyroidism, usually occurring in patients with a long history of hypothyroidism. Its characteristics include coma with extreme hypothermia (temperature 24° to 32.2° C), areflexia, seizures, and respiratory depression with CO2 retention. Severe hypothermia may be missed unless low-reading thermometers are used. Rapid
diagnosis based on clinical judgment, history, and physical examination is imperative, because death is likely without rapid treatment. Precipitating factors include illness, infection, trauma, drugs that suppress the CNS, and exposure to cold.

Diagnosis

• TSH

• Free thyroxine (T₄)

Serum TSH is the most sensitive test, and screening of selected populations is warranted (see p. 776). In primary hypothyroidism, there is no feedback inhibition of the intact pituitary, and serum TSH is always elevated, whereas serum free T₄ is low. In secondary hypothyroidism, free T₄ and serum TSH are low (sometimes TSH is normal but with decreased bioactivity).

Many patients with primary hypothyroidism have normal circulating levels of triiodothyronine (T₃), probably caused by sustained TSH stimulation of the failing thyroid, resulting in preferential synthesis and secretion of biologically active T₃. Therefore, serum T₃ is not sensitive for hypothyroidism.

Anemia is often present, usually normocytic-normochromic and of unknown etiology, but it may be hypochromic because of menorrhagia and sometimes macrocytic because of associated pernicious anemia or decreased absorption of folate. Anemia is rarely severe (Hb > 9 g/dL). As the hypometabolic state is corrected, anemia subsides, sometimes requiring 6 to 9 mo.

Serum cholesterol is usually high in primary hypothyroidism but less so in secondary hypothyroidism.

In addition to primary and secondary hypothyroidism, other conditions may cause decreased levels of total T₄, such as serum thyroxine-binding globulin (TBG) deficiency, some drugs (see p. 785), and euthyroid sick syndrome (see p. 779).

Treatment

• L-Thyroxine, adjusted until TSH levels are in midnormal range

Various thyroid hormone preparations are available for replacement therapy, including synthetic preparations of T₄ (L-thyroxine), T₃ (liothyronine), combinations of the 2 synthetic hormones, and desiccated animal thyroid extract. L-Thyroxine is preferred; the usual maintenance dose is 75 to 150 μg po once/day, depending on age, body mass index, and absorption (for pediatric doses, see p. 2888). Therapy is begun with low doses, especially in the elderly, usually 25 μg once/day. The dose is adjusted every 6 wk until maintenance dose is achieved. The maintenance dose may need to be decreased in elderly patients and increased in pregnant women. Dose may also need to be increased if drugs that decrease T₄ absorption or increase its biliary excretion are administered concomitantly. The dose used should be the lowest that restores serum TSH levels to the midnormal range (though this criterion cannot be used in patients with secondary hypothyroidism).

Liothyronine should not be used alone for long-term replacement because of its short half-life and the large peaks in serum T₃ levels it produces. The administration of standard replacement amounts (25 to 37.5 μg bid) results in rapidly increasing serum T₃ to between 300 and 1000 ng/dL (4.62 to 15.4 nmol/L) within 4 h due to its almost complete absorption; these levels return to normal by 24 h. Additionally, patients receiving liothyronine are chemically hyperthyroid for at least several hours a day, potentially increasing cardiac risks.

Similar patterns of serum T₃ occur when mixtures of T₃ and T₄ are taken po, although peak T₃ is lower because less T₃ is given. Replacement regimens with synthetic T₄ preparations reflect a different pattern in serum T₃ response. Increases in serum T₃ occur gradually, and normal levels are maintained when adequate doses of T₄ are given. Desiccated animal thyroid preparations contain variable amounts of T₃.
and $T_4$ and should not be prescribed unless the patient is already taking the preparation and has normal serum TSH.

In patients with secondary hypothyroidism, L-thyroxine should not be given until there is evidence of adequate cortisol secretion (or cortisol therapy is given), because L-thyroxine could precipitate adrenal crisis.

**Myxedema coma:** Myxedema coma is treated as follows:

- $T_4$ given IV
- Corticosteroids
- Supportive care as needed
- Conversion to oral $T_4$ when patient is stable

Patients require a large initial dose of $T_4$ (300 to 500 $\mu$g IV) or $T_3$ (25 to 50 $\mu$g IV). The IV maintenance dose of $T_4$ is 75 to 100 $\mu$g once/day and of $T_3$, 10 to 20 $\mu$g bid until $T_4$ can be given orally. Corticosteroids are also given, because the possibility of central hypothyroidism usually cannot be initially ruled out. The patient should not be rewarmed rapidly, which may precipitate hypotension or arrhythmias. Hypoxemia is common, so $PaO_2$ should be monitored. If ventilation is compromised, immediate mechanical ventilatory assistance is required. The precipitating factor should be rapidly and appropriately treated and fluid replacement given carefully, because hypothyroid patients do not excrete water appropriately. Finally, all drugs should be given cautiously because they are metabolized more slowly than in healthy people.

**Subclinical Hypothyroidism**

Subclinical hypothyroidism is elevated serum TSH in patients with absent or minimal symptoms of hypothyroidism and normal serum levels of free $T_4$.

Subclinical thyroid dysfunction is relatively common; it occurs in more than 15% of elderly women and 10% of elderly men, particularly in those with underlying Hashimoto's thyroiditis.

In patients with serum TSH > 10 mU/L, there is a high likelihood of progression to overt hypothyroidism with low serum levels of free $T_4$ in the next 10 yr. These patients are also more likely to have hypercholesterolemia and atherosclerosis. They should be treated with L-thyroxine, even if they are asymptomatic. For patients with TSH levels between 4.5 and 10 mU/L, a trial of L-thyroxine is reasonable if symptoms of early hypothyroidism (eg, fatigue, depression) are present. L-Thyroxine therapy is also indicated in pregnant women and in women who plan to become pregnant to avoid deleterious effects of hypothyroidism on the pregnancy and fetal development. Patients should have annual measurement of serum TSH and free $T_4$ to assess progress of the condition if untreated or to adjust the L-thyroxine dosage.

**Silent Lymphocytic Thyroiditis**

Silent lymphocytic thyroiditis is a self-limited, subacute disorder occurring most commonly in women during the postpartum period. Symptoms are initially of hyperthyroidism, then hypothyroidism, and then generally recovery to the euthyroid state. Treatment of the hyperthyroid phase is with a $\beta$-blocker. If hypothyroidism is permanent, lifelong thyroxine supplementation is needed.

The term "silent" refers to the absence of thyroid tenderness in contrast with subacute thyroiditis, which usually causes thyroid tenderness. Silent lymphocytic thyroiditis causes most cases of postpartum thyroid dysfunction. It occurs in about 5 to 10% of postpartum women.
Thyroid biopsy reveals lymphocytic infiltration as in Hashimoto's thyroiditis but without lymphoid follicles and scarring. Thyroid peroxidase autoantibodies and, less commonly, antithyroglobulin antibodies are almost always positive during pregnancy and the postpartum period. Thus, this disorder would seem to be a variant of Hashimoto's thyroiditis (see p. 779).

**Symptoms and Signs**

The condition begins in the postpartum period, usually within 12 to 16 wk. Silent lymphocytic thyroiditis is characterized by a variable degree of painless thyroid enlargement with a hyperthyroid phase of several weeks, often followed by transient hypothyroidism due to depleted thyroid hormone stores but usually eventual recovery to the euthyroid state (as noted for painful subacute thyroiditis). The hyperthyroid phase is self-limited and may be brief or overlooked. Many women with this disorder are diagnosed when they become hypothyroid, which occasionally is permanent.

**Diagnosis**

- Clinical evaluation
- Serum thyroxine (T$_4$), triiodothyronine (T$_3$), and thyroid-stimulating hormone (TSH) levels

Silent lymphocytic thyroiditis is frequently undiagnosed. Suspicion of the diagnosis generally depends on clinical findings, typically once hypothyroidism has occurred. Eye signs and pretibial myxedema do not occur.

Thyroid function test results vary depending on the phase of illness. Initially, serum T$_4$ and T$_3$ are elevated and TSH is suppressed. In the hypothyroid phase, these findings are reversed. WBC count and ESR are normal. Needle biopsy provides definitive diagnosis but is usually unnecessary.

**Treatment**

- Usually a β-blocker
- Sometimes thyroid hormone replacement

Because silent lymphocytic thyroiditis lasts only a few months, treatment is conservative, usually requiring only a β-blocker (eg, propranolol) during the hyperthyroid phase (see p. 783). Antithyroid drugs, surgery, and radiiodine therapy are contraindicated. Thyroid hormone replacement may be required during the hypothyroid phase. Most patients recover normal thyroid function, although some remain permanently hypothyroid. Therefore, thyroid function should be reevaluated after 9 to 12 mo of thyroxine therapy; replacement is stopped for 5 wk, and TSH is remeasured. This disorder usually recurs after subsequent pregnancies.

**Subacute Thyroiditis**

(de Quervain's Thyroiditis; Giant Cell Thyroiditis; Granulomatous Thyroiditis)

Subacute thyroiditis is an acute inflammatory disease of the thyroid probably caused by a virus. Symptoms include fever and thyroid tenderness. Initial hyperthyroidism is common, sometimes followed by a transient period of hypothyroidism. Diagnosis is clinical and with thyroid function tests. Treatment is with high doses of NSAIDs or with corticosteroids. The disease usually resolves spontaneously within months.

History of an antecedent viral URI is common. Histologic studies show less lymphocytic infiltration of the thyroid than in Hashimoto's thyroiditis or silent thyroiditis, but there is characteristic giant cell infiltration, PMNs, and follicular disruption.

**Symptoms and Signs**
There is pain in the anterior neck and fever of 37.8° to 38.3° C. Neck pain characteristically shifts from side to side and may settle in one area, frequently radiating to the jaw and ears. It is often confused with dental pain, pharyngitis, or otitis and is aggravated by swallowing or turning of the head. Symptoms of hyperthyroidism are common early in the disease because of hormone release from the disrupted follicles. There is more lassitude and prostration than in other thyroid disorders. On physical examination, the thyroid is asymmetrically enlarged, firm, and tender.

**Diagnosis**

- Clinical findings
- Free thyroxine (T₄) and thyroid-stimulating hormone (TSH) levels
- ESR
- Radioactive iodine uptake

Diagnosis is primarily clinical, based on finding an enlarged, tender thyroid in patients with the appropriate clinical history. Thyroid testing with TSH and at least a free T₄ measurement is usually also done. Radioactive iodine uptake should be measured to confirm the diagnosis. When the diagnosis is uncertain, finer needle aspiration biopsy is useful. Thyroid ultrasonography with color Doppler shows reduced blood flow in contrast with the increased flow of Graves' disease. Laboratory findings early in the disease include an increase in free T₄ and triiodothyronine (T₃), a marked decrease in TSH and thyroid radioactive iodine uptake (often 0), and a high ESR. After several weeks, the thyroid is depleted of T₄ and T₃ stores, and transient hypothyroidism develops accompanied by a decrease in free T₄ and T₃, a rise in TSH, and recovery of thyroid radioactive iodine uptake. Weakly positive thyroid antibodies may be present. Measurement of free T₄, T₃, and TSH at 2- to 4-wk intervals identifies the stages of the disease.

**Prognosis**

Subacute thyroiditis is self-limited, generally subsiding in a few months; occasionally, it recurs and may result in permanent hypothyroidism when follicular destruction is extensive.

**Treatment**

- NSAIDs
- Sometimes corticosteroids, a β-blocker, or both

Discomfort is treated with high doses of aspirin or NSAIDs. In severe and protracted cases, corticosteroids (eg, prednisone 30 to 40 mg po once/day, gradually decreasing the dose over 3 to 4 wk) eradicate all symptoms within 48 h.

Bothersome hyperthyroid symptoms may be treated with a short course of a β-blocker. If hypothyroidism is pronounced or persists, thyroid hormone replacement therapy may be required, rarely permanently.

**Simple Nontoxic Goiter**

(Euthyroid Goiter)

Simple nontoxic goiter, which may be diffuse or nodular, is noncancerous hypertrophy of the thyroid without hyperthyroidism, hypothyroidism, or inflammation. Except in severe iodine deficiency, thyroid function is normal and patients are asymptomatic except for an obviously enlarged, nontender thyroid. Diagnosis is clinical and with determination of normal thyroid function. Treatment is directed at the underlying cause, but partial surgical removal may be
Simple nontoxic goiter, the most common type of thyroid enlargement, is frequently noted at puberty, during pregnancy, and at menopause. The cause at these times is usually unclear. Known causes include intrinsic thyroid hormone production defects and, in iodine-deficient countries, ingestion of foods that contain substances that inhibit thyroid hormone synthesis (goitrogens, eg, cassava, broccoli, cauliflower, cabbage). Other causes include the use of drugs that can decrease the synthesis of thyroid hormone (eg, amiodarone or other iodine-containing compounds, lithium).

Iodine deficiency is rare in North America but remains the most common cause of goiter worldwide (termed endemic goiter). Compensatory small elevations in thyroid-stimulating hormone (TSH) occur, preventing hypothyroidism, but the TSH stimulation results in goiter formation. Recurrent cycles of stimulation and involution may result in nontoxic nodular goiters. However, the true etiology of most nontoxic goiters in iodine-sufficient areas is unknown.

### Symptoms and Signs

The patient may have a history of low iodine intake or overingestion of food goitrogens, but these phenomena are rare in North America. In the early stages, the goiter is typically soft, symmetric, and smooth. Later, multiple nodules and cysts may develop.

### Diagnosis

- Thyroidal radioactive iodine uptake
- Thyroid scan
- Thyroxine (T₄), triiodothyronine (T₃), and TSH levels

In the early stages, thyroidal radioactive iodine uptake may be normal or high with normal thyroid scans. Thyroid function tests are usually normal. Thyroid antibodies are measured to rule out Hashimoto’s thyroiditis.

In endemic goiter, serum TSH may be slightly elevated, and serum T₄ may be low-normal or slightly low, but serum T₃ is usually normal or slightly elevated.

### Treatment

- Depends on cause

In iodine-deficient areas, iodine supplementation of salt; oral or IM administration of iodized oil yearly; and iodination of water, crops, or animal fodder eliminates iodine-deficiency goiter. Goitrogens being ingested should be stopped.

In other instances, suppression of the hypothalamic-pituitary axis with thyroid hormone blocks TSH production (and hence stimulation of the thyroid). Full TSH-suppressive doses of L-thyroxine (100 to 150 μg/day po depending on the serum TSH) are useful in younger patients. L-Thyroxine is contraindicated in older patients with nontoxic nodular goiter, because these goiters rarely shrink and may harbor areas of autonomy so that L-thyroxine therapy can result in hyperthyroidism. Large goiters occasionally require surgery or ¹³¹I to shrink the gland enough to prevent interference with respiration or swallowing or to correct cosmetic problems.

### Thyroid Cancers

The 4 general types of thyroid cancer are papillary, follicular, medullary, and anaplastic. Papillary and follicular carcinoma together are called differentiated thyroid cancer because of their histologic resemblance to normal thyroid tissue and because differentiated function (eg,
thyroglobulin secretion) is preserved. Most thyroid cancers manifest as asymptomatic nodules. Rarely, lymph node, lung, or bone metastases cause the presenting symptoms of small thyroid cancers. Diagnosis is often by fine-needle aspiration biopsy but may involve other tests. Except for anaplastic and metastatic medullary carcinoma, most thyroid cancers are not highly malignant and are seldom fatal. Treatment is surgical removal, usually followed by ablation of residual tissue with radioactive iodine.

Papillary Carcinoma

Papillary carcinoma accounts for 70 to 80% of all thyroid cancers. The female: male ratio is 3:1. It may be familial in up to 5% of patients. Most patients present between ages 30 and 60. The tumor is often more aggressive in elderly patients. Many papillary carcinomas contain follicular elements.

The tumor spreads via lymphatics to regional lymph nodes in one third of patients and may metastasize to the lungs. Patients < 45 yr with small tumors confined to the thyroid have an excellent prognosis.

Treatment

- Surgical resection
- Sometimes radioactive iodine

Treatment for encapsulated tumors < 1.5 cm localized to one lobe is usually near-total thyroidectomy, although some experts recommend only lobectomy and isthmectomy; surgery is almost always curative. Thyroid hormone in thyroid-stimulating hormone (TSH)-suppressive doses is given to minimize chances of regrowth and cause regression of any microscopic remnants of papillary carcinoma.

Tumors > 4 cm or that are diffusely spreading require total or near-total thyroidectomy with postoperative radiiodine ablation of residual thyroid tissue with appropriately large doses of $^{131}\text{I}$ administered when the patient is hypothyroid or after recombinant TSH injections. Treatment may be repeated every 6 to 12 mo to ablate any remaining thyroid tissue. TSH-suppressive doses of L-thyroxine are given after treatment, and serum thyroglobulin levels help detect recurrent or persistent disease. About 20 to 30% of patients, mainly older patients, have recurrent or persistent disease.

Follicular Carcinoma

Follicular carcinoma, including the Hurthle cell variant, accounts for about 15% of thyroid cancers. It is more common among older patients and in regions of iodine deficiency. It is more malignant than papillary carcinoma, spreading hematogenously with distant metastases.

Treatment requires near-total thyroidectomy with postoperative radiiodine ablation of residual thyroid tissue as in treatment for papillary carcinoma. Metastases are more responsive to radiiodine therapy than are those of papillary carcinoma. TSH-suppressive doses of L-thyroxine are given after treatment. Serum thyroglobulin should be monitored to detect recurrent or persistent disease.

Medullary Carcinoma

Medullary (solid) carcinoma constitutes about 3% of thyroid cancers and is composed of parafollicular cells (C cells) that produce calcitonin. It may be sporadic (usually unilateral); however, it is often familial, caused by a mutation of the $ret$ proto-oncogene. The familial form may occur in isolation or as a component of multiple endocrine neoplasia (MEN) syndromes types 2A and 2B (see pp. 912 and 913). Although calcitonin can lower serum Ca and phosphate, serum Ca is normal because the high level of calcitonin ultimately down-regulates its receptors. Characteristic amyloid deposits that stain with Congo red are also present.

Metastases spread via the lymphatic system to cervical and mediastinal nodes and sometimes to liver, lungs, and bone.
Symptoms and Signs

Patients typically present with an asymptomatic thyroid nodule, although many cases are now diagnosed during routine screening of affected kindreds with MEN-2A or MEN-2B before a palpable tumor develops.

Medullary carcinoma may have a dramatic biochemical presentation when associated with ectopic production of other hormones or peptides (eg, ACTH, vasoactive intestinal polypeptide, prostaglandins, kallikreins, serotonin).

Diagnosis

• Serum calcitonin levels

The best test is measurement of serum calcitonin, which is greatly elevated. A challenge with Ca (15 mg/kg IV over 4 h) provokes excessive secretion of calcitonin. X-rays may show a dense, homogenous, conglomerate calcification.

All patients with medullary carcinoma should have genetic testing; relatives of those with mutations should have genetic testing and measurement of basal and stimulated calcitonin levels.

Treatment

• Surgical resection

Total thyroidectomy is indicated even if bilateral involvement is not obvious. Lymph nodes are also dissected. If hyperparathyroidism is present, removal of hyperplastic or adenomatous parathyroids is required. Pheochromocytoma, if present, is usually bilateral. Pheochromocytomas should be identified and removed before thyroidectomy because of the danger of provoking hypertensive crisis during the operation. Long-term survival is common in patients with medullary carcinoma and MEN-IIA; more than two thirds of affected patients are alive at 10 yr. Medullary carcinoma of the sporadic type has a worse prognosis.

Relatives with an elevated calcitonin level without a palpable thyroid abnormality should undergo thyroidectomy, because there is a greater chance of cure at this stage. Some experts recommend surgery in relatives who have normal basal and stimulated serum calcitonin levels but who have the ret proto-oncogene mutation.

Anaplastic Carcinoma

Anaplastic carcinoma is an undifferentiated cancer that accounts for about 2% of thyroid cancers. It occurs mostly in elderly patients and slightly more often in women. The tumor is characterized by rapid, painful enlargement. Rapid enlargement of the thyroid may also suggest thyroid lymphoma, particularly if found in association with Hashimoto's thyroiditis.

No effective therapy exists, and the disease is generally fatal. About 80% of patients die within 1 yr of diagnosis. In a few patients with smaller tumors, thyroidectomy followed by external radiation has been curative. Chemotherapy is mainly experimental.

Radiation-Induced Thyroid Cancer

Thyroid tumors develop in people exposed to large amounts of environmental thyroid radiation, as occurs from atomic bomb blasts, nuclear reactor accidents, or incidental thyroid irradiation due to radiation therapy. Tumors may be detected 10 yr after exposure, but risk remains increased for 30 to 40 yr. Such tumors are usually benign; however, about 10% are papillary thyroid carcinoma. The tumors are frequently multicentric or diffuse.

Patients who had thyroid irradiation should undergo yearly thyroid palpation, ultrasonography, and measurement of thyroid autoantibodies (to exclude Hashimoto's thyroiditis). A thyroid scan does not
always reflect areas of involvement.

If ultrasonography reveals a nodule, fine-needle aspiration biopsy should be done. In the absence of suspicious or malignant lesions, many physicians recommend lifelong TSH-lowering doses of thyroid hormone to suppress thyroid function and thyrotropin secretion and possibly decrease the chance of developing a thyroid tumor.

Surgery is required if fine-needle aspiration biopsy suggests cancer. Near-total or total thyroidectomy is the treatment of choice, to be followed by radioiodine ablation of any residual thyroid tissue if a cancer is found (depending on the size, histology, and invasiveness).
Chapter 94. Adrenal Disorders

Introduction

The adrenal glands, located on the cephalad portion of each kidney, consist of a cortex and medulla, each with separate endocrine functions.

Cortex: The adrenal cortex produces glucocorticoids (primarily cortisol), mineralocorticoids (primarily aldosterone), and androgens (primarily dehydroepiandrosterone and androstenedione). Physiology of the hypothalamic-pituitary-adrenocortical system is further discussed in Ch. 91.

Glucocorticoids promote and inhibit gene transcription in many cells and organ systems. Prominent effects include anti-inflammatory actions and increased hepatic gluconeogenesis.

Mineralocorticoids regulate electrolyte transport across epithelial surfaces, particularly renal conservation of Na in exchange for K.

Adrenal androgens' chief physiologic activity occurs after conversion to testosterone and dihydrotestosterone.

Medulla: The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines (mainly epinephrine and lesser amounts of norepinephrine). Chromaffin cells also produce bioactive amines and peptides (eg, histamine, serotonin, chromogranins, neuropeptide hormones). Epinephrine and norepinephrine, the major effector amines of the sympathetic nervous system, are responsible for the "flight or fight" response (ie, chronotropic and inotropic effects on the heart; bronchodilation; peripheral and splanchnic vasoconstriction with skeletal muscular vasodilation; metabolic effects including glycogenolysis, lipolysis, and renin release).

Clinical syndromes: Most deficiency syndromes affect output of all adrenocortical hormones. Hypofunction may be primary (malfunction of the adrenal gland itself, as in Addison's disease) or secondary (due to lack of adrenal stimulation by the pituitary or hypothalamus, although some experts refer to hypothalamic malfunction as tertiary).

Hyperfunction causes distinct clinical syndromes. Hypersecretion of androgens results in adrenal virilism; of glucocorticoids, Cushing's syndrome; and of aldosterone, hyperaldosteronism (aldosteronism). These syndromes frequently have overlapping features. Hyperfunction may be compensatory, as in congenital adrenal hyperplasia (see p. 2889), or due to acquired hyperplasia, adenomas, or adenocarcinomas. Excess quantities of epinephrine and norepinephrine are produced in pheochromocytoma.

Addison's Disease

(Primary or Chronic Adrenocortical Insufficiency)

Addison's disease is an insidious, usually progressive hypofunctioning of the adrenal cortex. It causes various symptoms, including hypotension and hyperpigmentation, and can lead to adrenal crisis with cardiovascular collapse. Diagnosis is clinical and by finding elevated plasma ACTH with low plasma cortisol. Treatment depends on the cause but generally includes hydrocortisone and sometimes other hormones.

Addison's disease develops in about 4/100,000 annually. It occurs in all age groups, about equally in each sex, and tends to become clinically apparent during metabolic stress or trauma. Onset of severe symptoms (adrenal crisis) may be precipitated by acute infection (a common cause, especially with septicemia). Other causes include trauma, surgery, and Na loss from excessive sweating. With treatment, Addison's disease should not typically reduce life expectancy.

Etiology

About 70% of cases in the US are due to idiopathic atrophy of the adrenal cortex, probably caused by
autoimmune processes. The remainder result from destruction of the adrenal gland by granuloma (eg, TB), tumor, amyloidosis, hemorrhage, or inflammatory necrosis. Hypoadrenocorticism can also result from administration of drugs that block corticosteroid synthesis (eg, ketoconazole, the anesthetic etomidate). Addison's disease may coexist with diabetes mellitus or hypothyroidism in polyglandular deficiency syndrome (see p. 804). In children, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia (CAH—see also Congenital Adrenal Hyperplasia on p. 2889).

Pathophysiology

Both mineralocorticoids and glucocorticoids are deficient.

**Mineralocorticoid deficiency:** Because mineralocorticoids stimulate Na reabsorption and K excretion, deficiency results in increased excretion of Na and decreased excretion of K, chiefly in urine but also in sweat, saliva, and the GI tract. A low serum concentration of Na and a high concentration of K result. Inability to concentrate the urine, combined with changes in electrolyte balance, cause severe dehydration, plasma hypertonicity, acidosis, decreased circulatory volume, hypotension, and, eventually, circulatory collapse. However, when adrenal insufficiency is caused by inadequate ACTH production (secondary adrenal insufficiency—see p. 795), electrolyte levels are often normal or only mildly deranged.

**Glucocorticoid deficiency:** Glucocorticoid deficiency contributes to hypotension and causes severe insulin sensitivity and disturbances in carbohydrate, fat, and protein metabolism. In the absence of cortisol, insufficient carbohydrate is formed from protein; hypoglycemia and diminished liver glycogen result. Weakness follows, due in part to deficient neuromuscular function. Resistance to infection, trauma, and other stress is diminished. Myocardial weakness and dehydration reduce cardiac output, and circulatory failure can occur. Decreased blood cortisol results in increased pituitary ACTH production and increased blood β-lipotropin, which has melanocyte-stimulating activity and, together with ACTH, causes the hyperpigmentation of skin and mucous membranes characteristic of Addison's disease. Thus, adrenal insufficiency secondary to pituitary failure (see p. 795) does not cause hyperpigmentation.

Symptoms and Signs

Weakness, fatigue, and orthostatic hypotension are early symptoms and signs. Hyperpigmentation is characterized by diffuse tanning of exposed and, to a lesser extent, unexposed portions of the body, especially on pressure points (bony prominences), skin folds, scars, and extensor surfaces. Black freckles are common on the forehead, face, neck, and shoulders. Areas of vitiligo develop, as do bluish black discolorations of the areolae and mucous membranes of the lips, mouth, rectum, and vagina. Anorexia, nausea, vomiting, and diarrhea often occur. Decreased tolerance to cold, with hypometabolism, may be noted. Dizziness and syncope may occur. The gradual onset and nonspecific nature of early symptoms often lead to an incorrect initial diagnosis of neurosis. Weight loss, dehydration, and hypotension are characteristic of the later stages of Addison's disease.

**Adrenal crisis:** Adrenal crisis is characterized by profound asthenia; severe pain in the abdomen, lower back, or legs; peripheral vascular collapse; and, finally, renal shutdown with azotemia. Body temperature may be low, although severe fever often occurs, particularly when crisis is precipitated by acute infection. A significant number of patients with partial loss of adrenal function (limited adrenocortical reserve) appear well but experience adrenal crisis when under physiologic stress (eg, surgery, infection, burns, critical illness). Shock and fever may be the only signs.

Diagnosis

- Electrolytes
- Serum cortisol
- Serum ACTH
- Sometimes ACTH stimulation testing
Clinical symptoms and signs suggest adrenal insufficiency. Sometimes the diagnosis is considered only on discovery of characteristic abnormalities of serum electrolytes, including low Na (< 135 mEq/L), high K (> 5 mEq/L), low HCO₃ (15 to 20 mEq/L), and high BUN (see Table 94-1).

**Differential diagnosis:** Hyperpigmentation can result from bronchogenic carcinoma, ingestion of heavy metals (eg, iron, silver), chronic skin conditions, or hemochromatosis. Peutz-Jeghers syndrome is characterized by pigmentation of the buccal and rectal mucosa. Frequently, hyperpigmentation occurs with vitiligo, which may indicate Addison's disease, although other diseases can cause this association.

Weakness resulting from Addison's disease subsides with rest, unlike neuropsychiatric weakness, which is often worse in the morning than after activity. Most myopathies that cause weakness can be differentiated by their distribution, lack of abnormal pigmentation, and characteristic laboratory findings.

**Table 94-1. Test Results that Suggest Addison's Disease**

Patients with adrenal insufficiency develop hypoglycemia after fasting because of decreased gluconeogenesis. In contrast, patients with hypoglycemia due to oversecretion of insulin can have attacks at any time, usually have increased appetite with weight gain, and have normal adrenal function. Low serum Na due to Addison's disease must be differentiated from that of edematous patients with cardiac or liver disease (particularly those taking diuretics), the dilutional hyponatremia of the syndrome of inappropriate ADH secretion, and salt-losing nephritis. These patients are not likely to have hyperpigmentation, hyperkalemia, and increased BUN.

**Testing:** Laboratory tests, beginning with serum cortisol and ACTH levels, confirm adrenal insufficiency. Elevated ACTH (≥ 50 pg/mL) with low cortisol (< 5 μg/dL [< 138 nmol/L]) is diagnostic, particularly in patients who are severely stressed or in shock. Low ACTH (< 5 pg/mL) and cortisol suggest secondary adrenal insufficiency (see p. 795); it is important to note that ACTH levels within the normal range are inappropriate for very low cortisol levels.

If ACTH and cortisol levels are borderline and adrenal insufficiency is clinically suspected—particularly in a patient who is about to undergo major surgery—provocative testing must be done. If time is too short (eg, emergency surgery), the patient is given hydrocortisone empirically (eg, 100 mg IV or IM), and provocative testing is done subsequently.

Addison's disease is diagnosed by showing failure of exogenous ACTH to increase serum cortisol. Secondary adrenal insufficiency is diagnosed by a prolonged ACTH stimulation test, insulin tolerance test, or glucagon test.

ACTH stimulation testing is done by injecting cosyntropin (synthetic ACTH) 250 μg IV or IM. Some authorities believe that in patients with suspected secondary adrenal insufficiency, a low-dose ACTH stimulation test using 1 μg IV instead of the standard 250 μg should be done, because such patients may react normally to the higher dose. Patients taking glucocorticoid supplements or spironolactone should not take them on the day of the test. Normal preinjection serum cortisol ranges from 5 to 25 μg/dL (138 to 690 nmol/L) and doubles in 30 to 90 min, reaching at least 20 μg/dL (552 nmol/L). Patients with Addison's disease have low or low-normal values that do not rise above 20 μg/dL at 30 min. A normal response to cosyntropin may occur in secondary adrenal insufficiency. However, because pituitary failure may cause adrenal atrophy (and hence failure to respond to ACTH), the patient may need to be primed with long-acting ACTH 1 mg IM once/day for 3 days before the cosyntropin test if pituitary disease is suspected.

A prolonged ACTH stimulation test (sampling for 24 h) may be used to diagnose secondary (or tertiary—hypothalamic) adrenal insufficiency. Cosyntropin 1 mg IM is given and cortisol measured at intervals for 24 h. Results for the first hour are similar for both the short (sampling stopped after 1 h) and prolonged tests, but in Addison's disease there is no further rise beyond 60 min. In secondary and tertiary adrenal insufficiency, cortisol levels continue to rise for ≥ 24 h. Only in cases of prolonged adrenal atrophy is adrenal priming (with long-acting ACTH) necessary. The simple short test is usually done initially, because a normal response obviates the need for further investigation.
If adrenal crisis is suspected, confirmation of Addison's disease by ACTH stimulation testing is deferred until the patient has recovered. If ACTH stimulation testing is done, elevated ACTH levels together with low cortisol levels confirm the diagnosis.

In Western societies, the cause is usually assumed to be autoimmune, unless there is evidence otherwise. Adrenal autoantibodies can be assessed. A chest x-ray should be done for TB; if doubt exists, CT of the adrenals is helpful. In patients with autoimmune disease, the adrenals are atrophied, whereas in patients with TB or other granulomas, the adrenals are enlarged (initially) with frequent calcification. Bilateral adrenal hyperplasia suggests an enzyme defect.

**Treatment**

- Hydrocortisone or prednisone
- Fludrocortisone
- Dose increase during intercurrent illness

Normally, cortisol is secreted maximally in the early morning and minimally at night. Thus, hydrocortisone (identical to cortisol) is given in 2 or 3 divided doses with a typical total daily dose of 15 to 30 mg. One regimen gives half the total in the morning, and the remaining half split between lunchtime and early evening (eg, 10 mg, 5 mg, 5 mg). Others give two thirds in the morning and one third in the evening. Doses immediately before retiring should generally be avoided because they may cause insomnia. Alternatively, prednisone 5 mg po in the morning and 2.5 mg po in the evening may be used. Additionally, fludrocortisone 0.1 to 0.2 mg po once/day is recommended to replace aldosterone. The easiest way to adjust the dosage is to ensure that the renin level is within the normal range. Normal hydration and absence of orthostatic hypotension are evidence of adequate replacement therapy. In some patients, fludrocortisone causes hypertension, which is treated by reducing the dosage or starting a nondiuretic antihypertensive. Some clinicians tend to give too little fludrocortisone in an effort to avoid use of antihypertensives.

Intercurrent illnesses (eg, infections) are potentially serious and should be vigorously treated; the patient's hydrocortisone dose should be doubled during the illness. If nausea and vomiting preclude oral therapy, parenteral therapy is necessary. Patients should be instructed when to take supplemental prednisone and taught to self-administer parenteral hydrocortisone for urgent situations. A preloaded syringe with 100 mg hydrocortisone should be available to the patient. A bracelet or wallet card giving the diagnosis and corticosteroid dose may help in case of adrenal crisis that renders the patient unable to communicate. When salt loss is severe, as in very hot climates, the dose of fludrocortisone may need to be increased.

In coexisting diabetes mellitus and Addison's disease, the hydrocortisone dose usually should not be > 30 mg/day; otherwise, insulin requirements are increased.

**Adrenal crisis:** Therapy should be instituted immediately upon suspicion. (CAUTION: In adrenal crisis, a delay in instituting corticosteroid therapy, particularly if there is hypoglycemia and hypotension, may be fatal.) If the patient is acutely ill, confirmation by an ACTH stimulation test should be postponed until the patient has recovered.

Hydrocortisone 100 mg is injected IV over 30 sec and repeated q 6 to 8 h for the first 24 h. Immediate intravenous volume expansion is done by giving 1 L of a 5% dextrose in 0.9% saline solution over 1 to 2 h. Additional 0.9% saline is given IV until hypotension, dehydration, and hyponatremia have been corrected. Serum K may fall during rehydration, requiring replacement. Mineralocorticoids are not required when high-dose hydrocortisone is given. When illness is less acute, hydrocortisone 50 or 100 mg can be given IM q 6 h. Restoration of BP and general improvement should occur within 1 h after the initial dose of hydrocortisone. Inotropic agents may be needed until the effects of hydrocortisone are achieved.

A total dose of 150 mg hydrocortisone is usually given over the 2nd 24-h period if the patient has improved markedly, and 75 mg is given on the 3rd day. Maintenance oral doses of hydrocortisone (15 to
30 mg) and fludrocortisone (0.1 mg) are given daily thereafter, as described above. Recovery depends on treatment of the underlying cause (eg, infection, trauma, metabolic stress) and adequate hydrocortisone therapy.

For patients with some residual adrenal function who develop adrenal crisis when under stress, hydrocortisone treatment is the same, but fluid requirements may be much lower.

**Treatment of complications:** Fever > 40.6°C occasionally accompanies the rehydration process. Except in the presence of falling BP, antipyretics (eg, aspirin 650 mg) may be given po with caution. Complications of corticosteroid therapy may include psychotic reactions. If psychotic reactions occur after the first 12 h of therapy, the hydrocortisone dose should be reduced to the lowest level consistent with maintaining BP and good cardiovascular function. Antipsychotics may be temporarily required, but use should not be prolonged.

### Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is adrenal hypofunction due to a lack of ACTH. Symptoms are the same as for Addison's disease, but there is usually less hypovolemia (see p. 792). Diagnosis is clinical and by laboratory findings, including low plasma ACTH with low plasma cortisol.

Treatment depends on the cause but generally includes hydrocortisone.

Secondary adrenal insufficiency may occur in panhypopituitarism, in isolated failure of ACTH production, in patients receiving corticosteroids, or after corticosteroids are stopped. Inadequate ACTH can also result from failure of the hypothalamus to stimulate pituitary ACTH production, which is sometimes called tertiary adrenal insufficiency.

Panhypopituitarism (see p. 762) may occur secondary to pituitary tumors; craniopharyngioma in younger people; and various tumors, granulomas, and, rarely, infection or trauma that destroys pituitary tissue. Patients receiving corticosteroids for > 4 wk may have insufficient ACTH secretion during metabolic stress to stimulate the adrenals to produce adequate quantities of corticosteroids, or they may have atrophic adrenals that are unresponsive to ACTH. These problems may persist for up to 1 yr after corticosteroid treatment is stopped.

### Symptoms and Signs

Symptoms and signs are similar to those of Addison's disease (see p. 792). Differentiating clinical or general laboratory features include the absence of hyperpigmentation and relatively normal electrolyte and BUN levels; hyponatremia, if it occurs, is usually dilutional.

Patients with panhypopituitarism have depressed thyroid and gonadal function and hypoglycemia, and coma may supervene when symptomatic secondary adrenal insufficiency occurs. Adrenal crisis is especially likely if a patient is treated for a single endocrine gland problem, particularly with thyroxine, without hydrocortisone replacement.

### Diagnosis

- Serum cortisol
- Serum ACTH
- ACTH stimulation testing
- CNS imaging

Tests to differentiate primary and secondary adrenal insufficiency are discussed under Addison's disease (see p. 793). Patients with confirmed secondary adrenal insufficiency should have CT or MRI of the brain to rule out pituitary tumor or atrophy. Adequacy of the hypothalamic-pituitary-adrenal axis during tapering or after stopping long-term corticosteroid treatment can be determined by injecting cosyntropin 250 μg IV
After 30 min, serum cortisol should be > 20 μg/dL (> 552 nmol/L). An insulin stress test to induce hypoglycemia and a rise in cortisol is the gold standard for testing integrity of the hypothalamic-pituitary-adrenal axis.

The corticotropin-releasing hormone (CRH) test can be used to distinguish between hypothalamic and pituitary causes but is rarely used in clinical practice. After administration of CRH 100 μg (or 1 μg/kg) IV, the normal response is a rise of serum ACTH of 30 to 40 pg/mL; patients with pituitary failure do not respond, whereas those with hypothalamic disease usually do.

**Treatment**

- Hydrocortisone or prednisone
- Fludrocortisone not indicated
- Dose increase during intercurrent illness

Glucocorticoid replacement is similar to that described for Addison's disease. Each case varies regarding the type and degree of specific hormone deficiencies. Fludrocortisone is not required because the intact adrenals produce aldosterone. During acute febrile illness or after trauma, patients receiving corticosteroids for nonendocrine disorders may require supplemental doses to augment their endogenous hydrocortisone production. In panhypopituitarism, other pituitary deficiencies should be treated appropriately (see p. 766).

**Adrenal Virilism**

*(Adrenogenital Syndrome)*

Adrenal virilism is a syndrome in which excessive adrenal androgens cause virilization. Diagnosis is clinical and confirmed by elevated androgen levels with and without dexamethasone suppression; determining the cause may involve adrenal imaging. Treatment depends on the cause.

Adrenal virilism is caused by an androgen-secreting adrenal tumor or by adrenal hyperplasia. Malignant adrenal tumors may secrete excess androgens, cortisol, or mineralocorticoids (or all three), resulting in Cushing's syndrome (see p. 797) with suppression of ACTH secretion and atrophy of the contralateral adrenal as well as hypertension. Adrenal hyperplasia is usually congenital; delayed virilizing adrenal hyperplasia is a variant of congenital adrenal hyperplasia (see p. 2889). Both are caused by a defect in hydroxylation of cortisol precursors; cortisol precursors accumulate and are shunted into the production of androgens. The defect is only partial in delayed virilizing adrenal hyperplasia, so clinical disease may not develop until adulthood.

**Symptoms and Signs**

Effects depend on the patient's sex and age at onset and are more noticeable in women than in men. Symptoms and signs include hirsutism (sometimes the only sign in mild cases), baldness, acne, and deepening of the voice. Libido may increase. In prepubertal children, growth may accelerate. If untreated, premature epiphyseal closure and short stature occur. Affected prepubertal males may experience premature sexual maturation. Females may have amenorrhea, atrophy of the uterus, clitoral hypertrophy, decreased breast size, and increased muscularity. In adult men, the excess adrenal androgens may suppress gonadal function and cause infertility. Ectopic adrenal tissue in the testes may enlarge and simulate tumors.

**Diagnosis**

- Testosterone
- Other adrenal androgens (dehydroepiandrosterone sulfate [DHEAS], androstenedione)
• Dexamethasone suppression test

• Adrenal imaging

• 17-hydroxyprogesterone

Adrenal virilism is suspected clinically, although mild hirsutism and virilization with hypomenorrhea and elevated plasma testosterone may also occur in polycystic ovary (Stein-Leventhal) syndrome (see p. 2514). Adrenal virilism is confirmed by showing elevated levels of adrenal androgens. In adrenal hyperplasia, urinary dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are elevated, pregnanetriol excretion is often increased, and urinary free cortisol is normal or diminished. Plasma DHEA, DHEAS, 17-hydroxyprogesterone, testosterone, and androstenedione may be elevated. A level of > 30 nmol/L of 17-hydroxyprogesterone 30 min after administration of cosyntropin 0.25 mg IM strongly suggests the most common form of adrenal hyperplasia.

Virilizing tumors are excluded if dexamethasone 0.5 mg po q 6 h for 48 h suppresses production of excess androgens. If excessive androgen excretion is not suppressed, CT or MRI of the adrenals and ultrasonography of the ovaries are done to search for a tumor.

Treatment

• Oral corticosteroids for hyperplasia

• Removal of tumors

Recommended treatment for adrenal hyperplasia is dexamethasone 0.5 to 1 mg po at bedtime, but even these small doses may cause signs of Cushing's syndrome. Cortisol 25 mg po once/day or prednisone 5 to 10 mg po once/day can be used instead. Although most symptoms and signs of virilism disappear, hirsutism and baldness disappear slowly, the voice may remain deep, and fertility may be impaired.

Tumors require adrenalectomy. For patients with cortisol-secreting tumors, hydrocortisone should be given preoperatively and postoperatively because their nontumorous adrenal cortex will be atrophic and suppressed.

Cushing's Syndrome

Cushing's syndrome is a constellation of clinical abnormalities caused by chronic high blood levels of cortisol or related corticosteroids. Cushing's disease is Cushing's syndrome that results from excess pituitary production of ACTH, usually secondary to a pituitary adenoma. Typical symptoms include moon facies and truncal obesity with thin arms and legs. Diagnosis is by history of receiving corticosteroids or by finding elevated serum cortisol. Treatment depends on the cause.

Etiology

Hyperfunction of the adrenal cortex can be ACTH dependent or ACTH independent. ACTH-dependent hyperfunction may result from

• Hypersecretion of ACTH by the pituitary gland

• Secretion of ACTH by a nonpituitary tumor, such as small cell carcinoma of the lung or a carcinoid tumor (ectopic ACTH syndrome)

• Administration of exogenous ACTH

ACTH-independent hyperfunction usually results from therapeutic administration of corticosteroids or from adrenal adenomas or carcinomas. Rare causes include primary pigmented nodular adrenal dysplasia
(usually in adolescents) and macronodular dysplasia (in older patients).

Whereas the term Cushing's syndrome denotes the clinical picture resulting from cortisol excess from any cause, Cushing's disease refers to hyperfunction of the adrenal cortex from pituitary ACTH excess. Patients with Cushing's disease usually have a small adenoma of the pituitary gland.

**Symptoms and Signs**

Clinical manifestations include moon facies with a plethoric appearance (see Plate 22), truncal obesity with prominent supraclavicular and dorsal cervical fat pads (buffalo hump), and, usually, very slender distal extremities and fingers. Muscle wasting and weakness are present. The skin is thin and atrophic, with poor wound healing and easy bruising. Purple striae may appear on the abdomen. Hypertension, renal calculi, osteoporosis, glucose intolerance, reduced resistance to infection, and mental disturbances are common. Cessation of linear growth is characteristic in children. Females usually have menstrual irregularities. In females with adrenal tumors, increased production of androgens may lead to hypertrichosis, temporal balding, and other signs of virilism.

**Diagnosis**

- Dexamethasone suppression test
- Urinary free cortisol (UFC) level
- ACTH levels; if detectable, provocative testing

Diagnosis is usually suspected based on the characteristic symptoms and signs. Confirmation (and identification of the cause) generally requires hormonal and imaging tests.

In some centers, testing begins with measurement of UFC, the best assay for urinary excretion (normal, 20 to 100 μg/24 h [55.2 to 276 nmol/24 h]). UFC is elevated > 120 μg/24 h (> 331 nmol/24 h) in almost all patients with Cushing's syndrome. However, many patients with UFC elevations between 100 and 150 μg/24 h (276 and 414 nmol/24 h) have obesity, depression, or polycystic ovaries but not Cushing's syndrome. A patient with suspected Cushing's syndrome with grossly elevated UFC (> 4 times the upper limit of normal) almost certainly has Cushing's syndrome. Two to 3 normal collections virtually exclude the diagnosis. Slightly elevated levels generally necessitate further investigation.

An alternative approach to investigation uses the dexamethasone suppression test, in which 1, 1.5, or 2 mg of dexamethasone is given po at 11 to 12 PM and serum cortisol is measured at 8 to 9 AM the next morning. In most normal patients, this drug suppresses morning serum cortisol to ≤ 1.8 μg/mL (≤ 50 nmol/L), whereas patients with Cushing's syndrome virtually always have a higher level. A more specific but equally sensitive test is to give dexamethasone 0.5 mg po q 6 h for 2 days (low dose). In general, a clear failure to suppress levels in response to low-dose dexamethasone establishes the diagnosis.

If results of these tests are indeterminate, the patient is hospitalized for measurement of serum cortisol at midnight, which is more likely to be conclusive. Cortisol normally ranges from 5 to 25 μg/dL (138 to 690 nmol/L) in the early morning (6 to 8 AM) and declines gradually to < 1.8 μg/dL (≤ 50 nmol/L) at midnight. Patients with Cushing's syndrome occasionally have a normal morning cortisol level but lack normal diurnal decline in cortisol production, such that the midnight serum cortisol levels are above normal and the total 24-h cortisol production is elevated. Alternatively, salivary cortisol samples may be collected and stored in the refrigerator at home. Serum cortisol may be spuriously elevated in patients with congenital increases of corticosteroid-binding globulin or in those receiving estrogen therapy, but diurnal variation is normal in these patients.

ACTH levels are measured to determine the cause of Cushing's syndrome. Undetectable levels, both basally and particularly in response to corticotropin-releasing hormone (CRH), suggest a primary adrenal cause. High levels suggest a pituitary cause. If ACTH is detectable (ACTH-dependent Cushing's syndrome), provocative tests help differentiate Cushing's disease from ectopic ACTH syndrome, which is rarer. In response to high-dose dexamethasone (2 mg po q 6 h for 48 h), the 9 AM serum cortisol falls by...
> 50% in most patients with Cushing's disease but infrequently in those with ectopic ACTH syndrome. Conversely, ACTH rises by > 50% and cortisol rises by > 20% in response to human or ovine-sequence CRH (100 μg IV or 1 μg/kg IV) in most patients with Cushing's disease but very rarely in those with ectopic ACTH syndrome (see Table 94-2). An alternative approach to localization, which is more accurate but more invasive, is to catheterize both petrosal veins (which drain the pituitary) and measure ACTH from these veins 5 min after a bolus of CRH 100 μg or 1 μg/kg. A central-to-peripheral ACTH ratio > 3 virtually excludes ectopic ACTH syndrome, whereas a ratio < 3 suggests a need to seek such a source.

Pituitary imaging is done if ACTH levels and provocative tests suggest a pituitary cause; gadolinium-enhanced MRI is most accurate, but some microadenomas are visible on CT. If testing suggests a nonpituitary cause, imaging includes high-resolution CT of the chest, pancreas, and adrenals; scintiscanning with radiolabeled octreotide; and PET scanning.

In children with Cushing's disease, pituitary tumors are very small and usually cannot be detected with MRI. Petrosal sinus sampling is particularly useful in this situation. MRI is preferred to CT in pregnant women to avoid fetal exposure to radiation.

**Treatment**

- Metyrapone or ketoconazole
- Surgery or radiation to remove tumors

[Table 94-2. Diagnostic Tests in Cushing's Syndrome]

Initially, the patient's general condition should be supported by high protein intake and appropriate administration of K. If clinical manifestations are severe, it may be reasonable to block corticosteroid secretion with metyrapone 250 mg to 1 g po tid or ketoconazole 400 mg po once/day, increasing to a maximum of 400 mg tid. Ketoconazole is more readily available but slower in onset and sometimes hepatotoxic.

Pituitary tumors that produce excessive ACTH are removed surgically or extirpated with radiation. If no tumor is shown on imaging but a pituitary source is likely, total hypophysectomy may be attempted, particularly in older patients. Younger patients usually receive supervoltage irradiation of the pituitary, delivering 45 Gy. Improvement usually occurs in < 1 yr. However, in children, irradiation may reduce secretion of growth hormone and occasionally cause precocious puberty. In special centers, heavy particle beam irradiation, providing about 100 Gy, is often successful, as is a single focused beam of radiation therapy given as a single dose—radiosurgery. Response to irradiation occasionally requires several years, but response is more rapid in children.

Bilateral adrenalectomy is reserved for patients with pituitary hyperadrenocorticism who do not respond to both pituitary exploration (with possible adenomectomy) and irradiation. Adrenalectomy requires life-long corticosteroid replacement.

Nelson syndrome occurs when the pituitary gland continues to expand after adrenalectomy, causing a marked increase in the secretion of ACTH and its precursors, resulting in severe hyperpigmentation. It occurs in ≤ 50% of patients who undergo adrenalectomy. The risk is probably reduced if the patient undergoes pituitary radiation. Although irradiation may arrest continued pituitary growth, many patients also require hypophysectomy. The indications for hypophysectomy are the same as for any pituitary tumor: an increase in size such that the tumor encroaches on surrounding structures, causing visual field defects, pressure on the hypothalamus, or other complications. Routine irradiation is often done after hypophysectomy if it was not done previously, especially when a tumor is clearly present. Radiosurgery, or focused radiation therapy, can be given in a single fraction when standard external beam radiation therapy has already been done, as long as the lesion is at a reasonable distance from the optic nerve and chiasm.

Adrenocortical tumors are removed surgically. Patients must receive cortisol during the surgical and
postoperative periods because their nontumorous adrenal cortex will be atrophic and suppressed. Benign adenomas can be removed laparoscopically. With multinodular adrenal hyperplasia, bilateral adrenalectomy may be necessary. Even after a presumed total adrenalectomy, functional regrowth occurs in a few patients.

Ectopic ACTH syndrome is treated by removing the nonpituitary tumor that is producing the ACTH. However, in some cases, the tumor is disseminated and cannot be excised. Adrenal inhibitors, such as metyrapone 500 mg po tid (and up to a total of 6 g/day) or mitotane 0.5 g po once/day, increasing to a maximum of 3 to 4 g/day, usually control severe metabolic disturbances (eg, hypokalemia). When mitotane is used, large doses of hydrocortisone or dexamethasone may be needed. Measures of cortisol production may be unreliable, and severe hypercholesterolemia may develop. Ketoconazole 400 to 1200 mg po once/day also blocks corticosteroid synthesis, although it may cause liver toxicity and can cause addisonian symptoms. Alternatively, the corticosteroid receptors can be blocked with mifepristone (RU 486). Mifepristone increases serum cortisol but blocks effects of the corticosteroid. Sometimes ACTH-secreting tumors respond to long-acting somatostatin analogs, although administration for > 2 yr requires close follow-up, because mild gastritis, gallstones, cholangitis, and malabsorption may develop.

Primary Aldosteronism

(Conn's Syndrome)

Primary aldosteronism is aldosteronism caused by autonomous production of aldosterone by the adrenal cortex (due to hyperplasia, adenoma, or carcinoma). Symptoms and signs include episodic weakness, elevated BP, and hypokalemia. Diagnosis includes measurement of plasma aldosterone levels and plasma renin activity. Treatment depends on cause. A tumor is removed if possible; in hyperplasia, spironolactone or related drugs may normalize BP and eliminate other clinical features.

Aldosterone is the most potent mineralocorticoid produced by the adrenals. It causes Na retention and K loss. In the kidney, aldosterone causes transfer of Na from the lumen of the distal tubule into the tubular cells in exchange for K and hydrogen. The same effect occurs in salivary glands, sweat glands, cells of the intestinal mucosa, and in exchanges between ICFs and ECFs.

Aldosterone secretion is regulated by the renin-angiotensin system and, to a lesser extent, by ACTH. Renin, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidneys. Reduction in blood volume and flow in the afferent renal arterioles induces secretion of renin. Renin transforms angiotensinogen from the liver to angiotensin I, which is transformed by ACE to angiotensin II. Angiotensin II causes secretion of aldosterone and, to a much lesser extent, secretion of cortisol and deoxycorticosterone; it also has pressor activity. Na and water retention resulting from increased aldosterone secretion increases the blood volume and reduces renin secretion.

Primary aldosteronism is caused by an adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex or, more rarely, by adrenal carcinoma or hyperplasia. Adenomas are extremely rare in children, but the syndrome sometimes occurs in childhood adrenal carcinoma or hyperplasia. In adrenal hyperplasia, which is more common among older men, both adrenals are overactive, and no adenoma is present. The clinical picture can also occur with congenital adrenal hyperplasia from deficiency of 11 β-hydroxylase and the dominantly inherited dexamethasone-suppressible hyperaldosteronism. Hyperplasia as a cause of hyperaldosteronism may be more common than previously recognized but remains an infrequent cause in the presence of hypokalemia.

Symptoms and Signs

Hypernatremia, hypervolemia, and a hypokalemic alkalosis may occur, causing episodic weakness, paresthesias, transient paralysis, and tetany. Diastolic hypertension and hypokalemic nephropathy with polyuria and polydipsia are common. In many cases, the only manifestation is mild to moderate hypertension. Edema is uncommon.

Diagnosis
• Electrolytes
• Plasma aldosterone
• Plasma renin activity (PRA)
• Adrenal imaging
• Bilateral adrenal vein catheterization (for cortisol and aldosterone levels)

Diagnosis is suspected in patients with hypertension and hypokalemia. Initial laboratory testing consists of plasma aldosterone levels and PRA. Ideally, tests are done after the patient has not taken any drugs that affect the renin-angiotensin system (eg, thiazide diuretics, ACE inhibitors, angiotensin antagonists, β-blockers) for 4 to 6 wk. PRA is usually measured in the morning with the patient recumbent. Patients with primary aldosteronism typically have plasma aldosterone > 15 ng/dL (> 0.42 nmol/L) and low levels of PRA, with a ratio of plasma aldosterone (in ng/dL) to PRA (in ng/mL/h) > 20.

Low levels of both PRA and aldosterone suggest nonaldosterone mineralocorticoid excess (eg, due to licorice ingestion, Cushing's syndrome, or Liddle syndrome). High levels of both PRA and aldosterone suggest secondary hyperaldosteronism (see p. 801). The principal differences between primary and secondary aldosteronism are shown in Table 94-3. In children, Bartter syndrome (Table 94-3. Differential Diagnosis of Aldosteronism) is distinguished from primary hyperaldosteronism by the absence of hypertension and marked elevation of renin.

Patients with findings suggesting primary hyperaldosteronism should undergo CT or MRI to determine whether the cause is a tumor or hyperplasia. Aldosterone levels measured on awakening and 2 to 4 h later while standing also may help make this distinction; in adenoma, levels decline and in hyperplasia, levels increase. In most cases, bilateral catheterization of the adrenal veins to measure cortisol and aldosterone should be used to confirm whether the aldosterone excess is unilateral (tumor) or bilateral (hyperplasia).

Treatment

• Surgical removal of tumors
• Spironolactone or eplerenone for hyperplasia

Tumors should be removed laparoscopically. After removal of an adenoma, BP decreases in all patients; complete remission occurs in 50 to 70%.

With adrenal hyperplasia, 70% remain hypertensive after bilateral adrenalectomy; thus, surgery is not recommended. Hyperaldosteronism in these patients can usually be controlled by spironolactone, starting with 300 mg po once/day and decreasing over 1 mo to a maintenance dose, usually around 100 mg once/day; or by amiloride 5 to 10 mg po once/day or another K-sparing diuretic. The newer more specific drug eplerenone may be used because, unlike spironolactone, it does not block the androgen receptor. About half of patients with hyperplasia need additional antihypertensive treatment (see p. 2069).

Secondary Aldosteronism

Secondary aldosteronism is increased adrenal production of aldosterone in response to nonpituitary, extra-adrenal stimuli, including renal artery stenosis and hypovolemia. Symptoms are those of primary aldosteronism. Treatment involves correcting the cause.
Secondary aldosteronism is caused by reduced renal blood flow, which stimulates the renin-angiotensin mechanism with resultant hypersecretion of aldosterone. Causes of reduced renal blood flow include obstructive renal artery disease (eg, atheroma, stenosis), renal vasoconstriction (as occurs in accelerated hypertension), and edematous disorders (eg, heart failure, cirrhosis with ascites, nephrotic syndrome). Secretion may be normal in heart failure, but hepatic blood flow and aldosterone metabolism are reduced, so circulating levels of the hormone are high.

**Pheochromocytoma**

A pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells typically located in the adrenals. It causes persistent or paroxysmal hypertension. Diagnosis is by measuring catecholamine products in blood or urine. Imaging tests, especially CT or MRI, help localize tumors. Treatment involves removal of the tumor when possible. Drug therapy for control of BP includes α-blockade, usually combined with β-blockade.

The catecholamines secreted include norepinephrine, epinephrine, dopamine, and dopa in varying proportions. About 90% of pheochromocytomas are in the adrenal medulla, but they may also be located in other tissues derived from neural crest cells. Possible sites include the following:

- Paraganglia of the sympathetic chain
- Retroperitoneally along the course of the aorta
- Carotid body
- Organ of Zuckerkandl (at the aortic bifurcation)
- GU system
- Brain
- Pericardial sac
- Dermoid cysts

Pheochromocytomas in the adrenal medulla occur equally in both sexes, are bilateral in 10% of cases (20% in children), and are malignant in < 10%. Of extra-adrenal tumors, 30% are malignant. Although pheochromocytomas occur at any age, peak incidence is between the 20s and 40s. About 25% are now thought to be due to germline mutations.

Pheochromocytomas vary in size but average 5 to 6 cm in diameter. They weigh 50 to 200 g, but tumors weighing several kilograms have been reported. Rarely, they are large enough to be palpated or cause symptoms due to pressure or obstruction. Regardless of the histologic appearance, the tumor is considered benign if it has not invaded the capsule and no metastases are found, although exceptions occur.

Pheochromocytomas may be part of the syndrome of familial multiple endocrine neoplasia (MEN), types 2A and 2B, in which other endocrine tumors (parathyroid or medullary carcinoma of the thyroid) coexist or develop subsequently (see p. 909). Pheochromocytoma develops in 1% of patients with neurofibromatosis (von Recklinghausen's disease) and may occur with hemangiomas and renal cell carcinoma, as in von Hippel-Lindau disease. Familial pheochromocytomas and carotid body tumors may be due to mutations of the enzyme succinate dehydrogenase.

**Symptoms and Signs**

Hypertension, which is paroxysmal in 45% of patients, is prominent. About 1/1000 hypertensive patients has a pheochromocytoma. Common symptoms and signs are tachycardia, diaphoresis, postural hypotension, tachypnea, cold and clammy skin, severe headache, angina, palpitations, nausea, vomiting,
epigastric pain, visual disturbances, dyspnea, paresthesias, constipation, and a sense of impending doom. Paroxysmal attacks may be provoked by palpation of the tumor, postural changes, abdominal compression or massage, induction of anesthesia, emotional trauma, unopposed β-blockade (which paradoxically increases BP by blocking β-mediated vasodilation), or micturition (if the tumor is in the bladder). In elderly patients, severe weight loss with persistent hypertension is suggestive of pheochromocytoma.

Physical examination, except for the presence of hypertension, is usually normal unless done during a paroxysmal attack. Retinopathy and cardiomegaly are often less severe than might be expected for the degree of hypertension, but a specific catecholamine cardiomyopathy can occur.

**Diagnosis**

- Plasma free metanephrines or urinary metanephrines
- Chest and abdomen imaging (CT or MRI) if catecholamine screen positive
- Possibly nuclear imaging with $^{123}$I-meta-iodobenzylguanidine (MIBG)

Pheochromocytoma is suspected in patients with typical symptoms or particularly sudden, severe, or intermittent unexplained hypertension. Diagnosis involves demonstrating high levels of catecholamine products in the serum or urine.

**Blood tests:** Plasma free metanephrine is up to 99% sensitive. This test has superior sensitivity to measurement of circulating epinephrine and norepinephrine because plasma metanephrines are elevated continuously, unlike epinephrine and norepinephrine, which are secreted intermittently; however, grossly elevated plasma norepinephrine renders the diagnosis highly probable.

**Urine tests:** Urinary metanephrine is less specific than plasma free metanephrine, but sensitivity is about 95%. Two or 3 normal results while the patient is hypertensive render the diagnosis extremely unlikely. Measurement of urinary norepinephrine and epinephrine is nearly as accurate. The principal urinary metabolic products of epinephrine and norepinephrine are the metanephrines vanillylmandelic acid (VMA) and homovanillic acid (HVA). Healthy people excrete only very small amounts of these substances. Normal values for 24 h are as follows: free epinephrine and norepinephrine < 100 μg (< 582 nmol), total metanephrine < 1.3 mg (< 7.1 μmol), VMA < 10 mg (< 50 μmol), HVA < 15 mg (< 82.4 μmol). In pheochromocytoma, increased urinary excretion of epinephrine and norepinephrine and their metabolic products is intermittent. Elevated excretion of these compounds may also occur in other disorders (eg, neuroblastoma, coma, dehydration, sleep apnea) or extreme stress; in patients being treated with rauwolfia alkaloids, methyldopa, or catecholamines; or after ingestion of foods containing large quantities of vanilla (especially if renal insufficiency is present).

**Other tests:** Blood volume is constricted and may falsely elevate Hb and Hct levels. Hyperglycemia, glycosuria, or overt diabetes mellitus may be present, with elevated fasting levels of plasma free fatty acid and glycerol. Plasma insulin level is inappropriately low for the plasma glucose. After removal of the pheochromocytoma, hypoglycemia may occur, especially in patients treated with oral antihyperglycemics.

**Provocative tests** with histamine or tyramine are hazardous and should not be used. Glucagon 0.5 to 1 mg injected rapidly IV provokes a rise in BP of > 35/25 mm Hg within 2 min in normotensive patients with pheochromocytoma but is now generally unnecessary. Phentolamine mesylate must be available to terminate any hypertensive crisis.

**Screening tests** are preferred to provocative tests. The general approach is to measure plasma metanephrines, 24-h urinary catecholamines, or their metabolites as a screening test and to avoid provocative tests. In patients with elevated plasma catecholamines, a suppression test using oral clonidine or IV pentolinium can be used but is rarely necessary.

**Imaging tests to localize tumors** are usually done in patients with abnormal screening results. Tests should include CT and MRI of the chest and abdomen with and without contrast. With isotonic contrast
media, no adrenoceptor blockade is necessary. PET has also been used successfully. Repeated sampling of plasma catecholamine concentrations during catheterization of the vena cava with sampling at different locations, including the adrenal veins, can help localize the tumor: there will be a step up in norepinephrine level in a vein draining the tumor. Adrenal vein norepinephrine:epinephrine ratios may help in the hunt for a small adrenal source. Radiopharmaceuticals with nuclear imaging techniques can also help localize pheochromocytomas. $^{123}$I-MIBG is the most used compound outside the US; 0.5 mCi is injected IV, and the patient is scanned on days 1, 2, and 3. Normal adrenal tissue rarely picks up this isotope, but 85% of pheochromocytomas do. The imaging is usually positive only when the lesion is large enough to be obvious on CT or MRI, but it can help confirm that a mass is likely to be the source of the catecholamines. $^{131}$I-MIBG is a less sensitive alternative.

**Signs of an associated genetic disorder** (eg, cafe-au-lait patches in neurofibromatosis) should be sought. Patients should be screened for MEN with a serum Ca (and possibly calcitonin) and any other tests as directed by clinical findings.

**Treatment**

- Hypertension control with combination of α-blockers and β-blockers
- Surgical removal of tumor

Surgical removal is the treatment of choice. The operation is usually delayed until hypertension is controlled by a combination of α-blockers and β-blockers (usually phenoxybenzamine 20 to 40 mg po tid and propranolol 20 to 40 mg po tid). β-Blockers should not be used until adequate α-blockade has been achieved. Some α-blockers, such as doxazosin, may be equally effective but better tolerated.

The most effective and safest preoperative α-blockade is phenoxybenzamine 0.5 mg/kg IV in 0.9% saline over 2 h on each of the 3 days before the operation. Na nitroprusside can be infused for hypertensive crises preoperatively or intraoperatively. When bilateral tumors are documented or suspected (as in a patient with MEN), sufficient hydrocortisone (100 mg IV bid) given before and during surgery avoids acute glucocorticoid insufficiency due to bilateral adrenalectomy.

Most pheochromocytomas can be removed laparoscopically. BP must be continuously monitored via an intra-arterial catheter, and volume status is closely monitored. Anesthesia should be induced with a nonarrhythmogenic drug (eg, a thiobarbiturate) and continued with enflurane. During surgery, paroxysms of hypertension should be controlled with injections of phentolamine 1 to 5 mg IV or nitroprusside infusion (2 to 4 μg/kg/min), and tachyarrhythmias should be controlled with propranolol 0.5 to 2 mg IV. If a muscle relaxant is needed, drugs that do not release histamine are preferred. *Atropine should not be used preoperatively.* Preoperative blood transfusion (1 to 2 units) may be given before the tumor is removed in anticipation of blood loss. If BP has been well controlled before surgery, a diet high in salt is recommended to increase blood volume. An infusion of norepinephrine 4 to 12 mg/L in a dextrose-containing solution should be started if hypotension develops. Some patients whose hypotension responds poorly to levarterenol may benefit from hydrocortisone 100 mg IV, but adequate fluid replacement is usually all that is required.

**Malignant metastatic pheochromocytoma** should be treated with α- and β-blockers. The tumor may be indolent and survival long-lasting. However, even with rapid tumor growth, BP can be controlled. $^{131}$I-MIBG prolongs life when used to treat residual disease. Radiation therapy may reduce bone pain; chemotherapy is rarely effective but can be attempted if all else fails.

**Nonfunctional Adrenal Masses**

Nonfunctional adrenal masses are spaceoccupying lesions of the adrenal glands that have no hormonal activity. Symptoms, signs, and treatment depend on the nature and size of the mass.

The most common nonfunctioning adrenal mass in adults is an adenoma (50%), followed by carcinomas and metastatic tumors. Cysts and lipomas make up most of the remainder. However, the precise
proportions depend on the clinical presentation. Masses discovered on incidental screening are usually adenomas. Less commonly, in neonates, spontaneous adrenal hemorrhage may cause large adrenal masses, simulating neuroblastoma or Wilms' tumor. In adults, bilateral massive adrenal hemorrhage may result from thromboembolic disease or coagulopathy. Benign cysts are observed in elderly patients and may be due to cystic degeneration, vascular accidents, lymphomas, bacterial infections, fungal infections (eg, histoplasmosis), or parasitic infestations (eg, due to *Echinococcus*). Hematogenous spread of TB organisms may cause adrenal masses. A nonfunctional adrenal carcinoma produces a diffuse and infiltrating retroperitoneal process. Hemorrhage can occur, causing adrenal hematomas.

**Symptoms and Signs**

Most patients are asymptomatic. With any adrenal mass, adrenal insufficiency is rare unless both glands are involved.

The major signs of bilateral massive adrenal hemorrhage are abdominal pain, falling Hct, signs of acute adrenal failure, and suprarenal masses on CT or MRI. TB of the adrenals may cause calcification and Addison's disease. Nonfunctional adrenal carcinoma usually manifests as metastatic disease and may therefore not be amenable to surgery, though mitotane may afford chemotherapeutic control when used with supportive exogenous corticosteroids.

**Diagnosis**

- Adrenal hormone measurements
- Fine-needle biopsy

Nonfunctional adrenal masses are usually found incidentally during tests such as CT or MRI conducted for other reasons. Nonfunctionality is established clinically and confirmed by adrenal hormonal measurements (see p. 797). If metastatic disease is possible, fine-needle biopsy can be diagnostic but is contraindicated if adrenal carcinoma is strongly suspected.

**Treatment**

- Excision
- Periodic monitoring

If the tumor is solid, of adrenal origin, and > 4 cm, it should be excised, because biopsy cannot always distinguish benign from malignant tumors.

Tumors 2 to 4 cm in diameter are a particularly difficult clinical problem. If scanning does not suggest cancer and hormonal function does not seem altered (eg, normal electrolytes and catecholamines, no evidence of Cushing's syndrome), it is reasonable to reevaluate periodically, usually for up to 4 yr. If no progression is seen by then, further follow-up is unnecessary. However, many of these tumors secrete cortisol in quantities too small to cause symptoms, and whether they would eventually cause symptoms and morbidity if untreated is unclear. Most clinicians merely observe patients with these tumors.

Adrenal adenomas < 2 cm require no special treatment but should be observed for growth or development of secretory function (such as by looking for clinical signs and periodically measuring electrolytes).
Chapter 95. Polyglandular Deficiency Syndromes

Introduction

(Autoimmune Polyglandular Syndromes; Polyendocrine Deficiency Syndromes)

Polyglandular deficiency syndromes (PDS) are characterized by sequential or simultaneous deficiencies in the function of several endocrine glands that have a common cause. Etiology is most often autoimmune. Symptoms depend on the combination of deficiencies, which fall within 1 of 3 types. Diagnosis requires measurement of hormone levels and autoantibodies against affected endocrine glands. Treatment includes replacement of missing or deficient hormones and sometimes immunosuppressants.

Etiology

Although individual endocrine glands can be damaged by numerous causes, including infection, infarction, and tumors, these syndromes usually result from an autoimmune reaction, probably triggered by a virus or other environmental antigen.

Genetic factors increase susceptibility to these syndromes, as shown by the increased presence of certain HLA subtypes in affected people and the recognition of several inheritance patterns (see Table 95-1).

Pathophysiology

The underlying autoimmune reaction involves autoantibodies against endocrine tissues, cell-mediated autoimmunity, or both and leads to inflammation, lymphocytic infiltration, and partial or complete gland destruction. More than one endocrine gland is involved, although clinical manifestations are not always simultaneous. The autoimmune reaction and associated immune system dysfunction can also damage nonendocrine tissues.

Classification

Three patterns of autoimmune failure have been described (see Table 95-1), which likely reflect different autoimmune abnormalities.

Type I: Type I usually begins in childhood. The 3 primary components are

- Chronic mucocutaneous candidiasis
- Hypoparathyroidism
- Adrenal insufficiency (Addison's disease)

Candidiasis is usually the initial clinical manifestation, most often occurring in patients < 5 yr. Hypoparathyroidism occurs next, usually in patients < 10 yr. Lastly, adrenal insufficiency occurs in patients < 15 yr. Accompanying endocrine and nonendocrine disorders (see Table 95-1) continue to appear at least until patients are about age 40.

Type II (Schmidt's syndrome): Type II usually occurs in adults; peak incidence is age 30. It occurs 3 times more often in women. It typically manifests with

- Adrenal insufficiency
- Hypothyroidism or hyperthyroidism
• Type 1 diabetes (autoimmune etiology)

More rare features may also be present (see Table 95-1).

**Type III**: Type III is characterized by

• Glandular failure occurring in adults, particularly middle-aged women

• Hypothyroidism

• At least one of a variety of other disorders (see Table 95-1)

Type III does not involve the adrenal cortex.

**Symptoms and Signs**

The clinical appearance of patients with PDS is the sum of the individual endocrine deficiencies and associated nonendocrine disorders; their symptoms and signs are discussed elsewhere in THE MANUAL. The deficiencies do not always appear at the same time and may require a period of years to manifest; in such cases they do not follow a particular sequence.

**Diagnosis**

• Measurement of hormone levels

• Sometimes autoantibody titers

Diagnosis is suggested clinically and confirmed by detecting deficient hormone levels. Other causes of multiple endocrine deficiencies include hypothalamic-pituitary dysfunction and coincidental endocrine dysfunction due to separate causes (eg, tuberculous hypoadrenalism and nonautoimmune hypothyroidism in the same patient). Detecting autoantibodies to each affected glandular tissue can help differentiate PDS from the other causes, and elevated levels of pituitary tropic hormones (eg, thyroid-stimulating hormone) suggest the hypothalamic-pituitary axis is intact (although some patients with type II PDS have hypothalamic-pituitary insufficiency).

Because decades may pass before the appearance of all manifestations, lifelong follow-up is prudent; unrecognized hypoparathyroidism or adrenal insufficiency can be life threatening.

Relatives should be made aware of the diagnosis and screened when appropriate; measurement of glutamic acid decarboxylase antibodies may be useful in determining risk.

**Treatment**

• Hormone replacement

Treatment of the various individual glandular deficiencies is discussed elsewhere in THE MANUAL; the treatment of multiple deficiencies can be more complex than treatment of an isolated endocrine deficiency.

Chronic mucocutaneous candidiasis usually requires lifelong antifungal therapy (eg, oral fluconazole or ketoconazole—see p. 1103). If given early (within the first few weeks to months) in the course of endocrine failure, immunosuppressive doses of cyclosporine may benefit some patients.

**IPEX Syndrome**

**IPEX** (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) is a recessive syndrome involving aggressive autoimmunity.
This rare disorder results from mutation of the transcriptional activator, *FoxP3*, which causes regulatory T-cell dysfunction and a subsequent autoimmune disorder.

IPEX syndrome manifests as severe enlargement of the secondary lymphoid organs, type 1 diabetes mellitus, eczema, food allergies, and infections. Secondary enteropathy leads to persistent diarrhea.

Diagnosis is suggested by clinical features and confirmed by genetic analysis.

Untreated, IPEX syndrome is usually fatal in the first year of life. Immunosuppressants and bone marrow transplantation can prolong life but are rarely curative.

**POEMS Syndrome**

(Crow-Fukase Syndrome)

**POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) is a nonautoimmune polyglandular deficiency syndrome.**

POEMS syndrome is probably caused by circulating immunoglobulins caused by a plasma cell dyscrasia (see also p. 1025). Circulating cytokines (IL-1-β, IL-6), vascular endothelial growth factor, and tumor necrosis factor-α are also increased.

Patients may have the following:

- Hepatomegaly
- Lymphadenopathy
- Hypogonadism
- Diabetes mellitus type 2
- Primary hypothyroidism
- Hyperparathyroidism
- Adrenal insufficiency
- Excess production of monoclonal IgA and IgG due to plasmacytomas and skin abnormalities (eg, hyperpigmentation, dermal thickening, hirsutism, angiomas, hypertrichosis)

Other symptoms and signs may include edema, ascites, pleural effusion, papilledema, and fever.

Like other syndromes of undefined pathophysiology, POEMS syndrome is diagnosed based on the constellation of symptoms and signs. Criteria include the presence of polyneuropathy and monoclonal paraproteinemia plus any 2 of the other manifestations of the disorder.

Treatment consists of chemotherapy and radiation therapy followed by autologous hematopoietic or stem cell transplantation. Five-year survival is about 60%.
Chapter 96. Porphyrias

Introduction

Porphyrias result from genetic deficiencies of enzymes of the heme biosynthetic pathway. These deficiencies allow heme precursors to accumulate, causing toxicity. Porphyrias are defined by the specific enzyme deficiency. Two major clinical manifestations occur: neurovisceral abnormalities (the acute porphyrias) and cutaneous photosensitivity (the cutaneous porphyrias).

Heme, an iron-containing pigment, is synthesized mostly in the bone marrow (by erythroblasts and reticulocytes) and is incorporated into hemoglobin. Heme is also synthesized in the liver and incorporated into certain enzymes (eg, cytochromes). Heme synthesis requires 8 enzymes (see Table 96-1). These enzymes produce and transform molecular species called porphyrins (and their precursors), which are toxic if they accumulate.

Etiology

Most porphyrias are autosomal dominant. Homozygous or double heterozygous states may be incompatible with life, generally causing fetal death; the exceptions are \( \delta \)-aminolevulinic acid (ALA) dehydratase (ALAD)-deficiency porphyria and uroporphyrinogen III cosynthase deficiency, in which only homozygous or double heterozygous conditions (ie, 2 separate heterozygous mutations in the same gene in the same patient) cause disease. Disease penetrance in heterozygotes varies. In terms of genetic prevalence, the 2 most common porphyrias are acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT). The prevalence of each is about 1/10,000.

Pathophysiology

Porphyrias result from a deficiency of any of the last 7 enzymes of the heme biosynthetic pathway (deficiency of the first enzyme in the pathway, ALA synthase, causes sideroblastic anemia). Single genes encode each enzyme; any of numerous possible mutations can incapacitate the enzyme encoded by that gene. When an enzyme of heme synthesis is deficient or defective, its substrate and any other heme precursors normally modified by that enzyme may accumulate in bone marrow, liver, skin, or other tissues and have toxic effects. These precursors may appear in excess in the blood and be excreted in urine, bile, or stool.

Although porphyrias are most precisely defined according to the deficient enzyme, classification by major clinical features (phenotype) is often useful. Thus, porphyrias are usually divided into 2 classes:

* Acute
  * Cutaneous

Acute porphyrias manifest as intermittent attacks of abdominal, mental, and neurologic symptoms. They are typically triggered by drugs and other exogenous factors. Cutaneous porphyrias tend to cause continuous or undulating symptoms involving cutaneous photosensitivity. Some acute porphyrias also have cutaneous manifestations. Because of variable penetrance in heterozygous porphyrias, clinically expressed disease is less common than genetic prevalence (see Table 96-2).

Urine discoloration (red or reddish brown) may occur in the symptomatic phase of all porphyrias except erythropoietic protoporphyria (EPP) and ALAD-deficiency porphyria. Discoloration results from oxidized porphyrins, the porphyrin.
precursor porphobilinogen (PBG), or both. Sometimes the color develops after the urine has stood in light for about 30 min, allowing time for oxidation. In the acute porphyrias, except in ALAD-deficiency porphyria, about 1 in 3 heterozygotes (more frequently in females than males) also have increased urinary excretion of PBG (and urine discoloration) in the latent phase.

**Diagnosis**

Patients with symptoms suggesting porphyria are screened by blood or urine tests for porphyrins or the porphyrin precursors PBG and ALA (see Table 96-3). Abnormal results on screening are confirmed by further testing.

Asymptomatic patients, including suspected carriers and people who are between attacks, are evaluated similarly. However, the tests are less sensitive in these circumstances; measurement of RBC or WBC enzyme activity is considerably more sensitive. Genetic analysis is highly accurate and preferentially used within families when the mutation is known. Prenatal testing (involving amniocentesis or chorionic villus sampling) is possible but rarely indicated.

**Acute Porphyrias**

**Acute porphyrias** cause intermittent attacks of abdominal pain and neurologic symptoms. Attacks are precipitated by certain drugs and other factors. Patients with variegate porphyria and hereditary coproporphyria may develop

[Table 96-3. Screening for Porphyrias]

bullous eruptions due to sunlight exposure. Diagnosis is based on elevated levels of δ-aminolevulinic acid and porphyrin precursor porphobilinogen in the urine during attacks. Attacks are treated with glucose or, if more severe, IV heme. Symptomatic treatment, including analgesia, is given as necessary.

Acute porphyrias include, in order of prevalence, acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and the exceedingly rare δ-aminolevulinic acid dehydratase (ALAD)-deficiency porphyria.

Among heterozygotes, acute porphyrias are rarely expressed clinically before puberty and, after puberty, in only about 20 to 30%. Among homozygotes and double heterozygotes, onset generally is in childhood, and symptoms are often severe.

**Precipitating Factors**

Many precipitating factors exist, typically accelerating heme biosynthesis above the catalytic capacity of the defective enzyme. Accumulation of porphyrin precursor porphobilinogen (PBG) and δ-aminolevulinic acid (ALA), or in the case of ALAD-deficiency porphyria, ALA alone, results.

Hormonal factors are important. Women are more prone to attacks than men, particularly during periods of hormonal change (eg, just before menstruation, during use of oral contraceptives, during the early weeks of gestation, just after delivery). Nevertheless, pregnancy is not contraindicated.

Other factors include drugs (including barbiturates, other antiepileptic drugs, and sulfonamide antibiotics —see Table 96-4) and reproductive hormones (progesterone and related steroids), particularly those that induce hepatic ALA synthase and cytochrome P-450 enzymes. Attacks usually occur within 24 h after exposure to a precipitating drug. Low-calorie and low-carbohydrate diets, alcohol ingestion, and exposure to organic solvents can also precipitate symptoms. Infection or other illness, surgery, and mental problems are sometimes implicated. Attacks usually result from several, sometimes unidentifiable, factors.

Sunlight precipitates cutaneous symptoms in VP and HCP.
Symptoms and Signs

Symptoms and signs involve the nervous system, abdomen, or both (neurovisceral). Attacks develop over hours or days and can last up to several weeks. Most gene carriers experience no, or only a few, attacks in their lifetime. Others experience recurrent symptoms. In women, attacks often coincide with phases of the menstrual cycle.

The acute porphyric attack: Constipation, fatigue, irritability, and insomnia typically precede an acute attack. The most common symptoms with an attack are abdominal pain and vomiting. The pain may be excruciating and is disproportionate to abdominal tenderness. Abdominal manifestations may result from effects on visceral nerves or from local vasoconstrictive ischemia. Because there is no inflammation, the abdomen is not tender and there are no peritoneal signs. Temperature and WBC count are normal or slightly increased. Bowel distention may develop as a result of paralytic ileus. The urine is red or reddish brown and positive for PBG during an attack.

All components of the peripheral and central nervous systems may be involved. Motor neuropathy is common with severe and prolonged attacks. Muscle weakness usually begins in the extremities but can involve any motor neuron or cranial nerve and proceed to tetraplegia. Bulbar involvement can cause ventilatory failure.

CNS involvement may cause seizures or mental disturbances (eg, apathy, depression, agitation, frank psychosis, hallucinations). Seizures, psychotic behavior, and hallucinations may be due to hyponatremia or hypomagnesemia, which can also contribute to cardiac arrhythmias.

Excess catecholamines generally cause restlessness and tachycardia. Rarely, catecholamine-induced arrhythmias cause sudden death. Labile hypertension with transiently high BP may cause vascular changes progressing to irreversible hypertension if untreated. Renal failure in acute porphyria is multifactorial; acute hypertension (possibly leading to chronic hypertension) is likely a main precipitating factor.

Subacute or subchronic symptoms: Some patients have prolonged symptoms of lesser intensity (eg, obstipation, fatigue, headache, back or thigh pain, paresthesia, tachycardia, dyspnea, insomnia, mental disturbance, seizures).

Skin symptoms in VP and HCP: Fragile skin and bullous eruptions may develop on sun-exposed areas, even in the absence of neurovisceral symptoms. Often patients are not aware of the connection to sun exposure. Cutaneous manifestations are identical to those of porphyria cutanea tarda.

Late manifestations: Motor involvement during acute attacks may cause persistent weakness between attacks. Hepatocellular cancer, hypertension, and renal impairment become more common after middle age in AIP and possibly also in VP and HCP, especially in patients with previous porphyric attacks.

Diagnosis

• Urine screen for PBG
• If urine results are positive, quantitative ALA and PBG determination
• Genetic analysis if type must be identified

Acute attack: Misdiagnosis is common because the acute attack is confused with other causes of acute abdomen (sometimes leading to unnecessary surgery) or with a primary neurologic or mental disorder. However, in patients previously diagnosed as gene carriers or who have a positive family history, porphyria should be suspected. Still, even in known gene carriers, other causes must be considered.
Red or reddish brown urine, not present before onset of symptoms, is a cardinal sign and is present during full-blown attacks. A urine specimen should be examined in patients with abdominal pain of unknown cause, especially if severe constipation, vomiting, tachycardia, muscle weakness, bulbar involvement, or mental symptoms occur.

If porphyria is suspected, the urine is analyzed for PBG using a rapid qualitative or semiquantitative determination. A positive result or high clinical suspicion necessitates quantitative ALA and PBG measurements preferentially obtained from the same specimen. PBG and ALA levels > 5 times normal indicate an acute porphyrin attack unless patients are gene carriers in whom porphyrin precursor excretion occurs at similar levels even during the latent phase of the disorder.

If urinary PBG and ALA levels are normal, an alternative diagnosis must be considered. Elevated ALA with normal or slightly increased PBG suggests lead poisoning or ALAD-deficiency porphyria. Analysis of a 24-h urine specimen is not useful. Instead, a random urine specimen is used, and PBG and ALA levels are corrected for dilution by relating to the creatinine level of the sample. Electrolytes and Mg should be measured. Hyponatremia may be present because of excessive vomiting or diarrhea after hypotonic fluid replacement or because of the syndrome of inappropriate ADH secretion (SIADH).

**Determination of type:** Because treatment does not depend on the type of acute porphyria, identification of the specific type is valuable mainly for finding gene carriers among relatives. When the type and mutation are already known from previous testing of relatives, the diagnosis is clear but may be confirmed by gene analysis. Enzymatic diagnosis is not necessary. If there is no family history to guide the diagnosis, the different forms of acute porphyria are distinguished by characteristic patterns of porphyrin (and precursor) accumulation and excretion in plasma, urine, and stool. When urine analysis reveals increased levels of ALA and PBG, fecal porphyrins may be measured. Fecal porphyrins are usually normal or minimally increased in AIP but elevated in HCP and VP. Often, these markers are not present in the quiescent phase of the disorder. In HCP and VP, plasma porphyrins with characteristic fluorescence are sought. RBC PBG deaminase levels that are about 50% of normal suggest AIP. Diminished WBC protoporphyrinogen oxidase levels suggest VP, and diminished coproporphyrinogen oxidase levels suggest HCP.

**Family studies:** Children of a gene carrier have a 50% risk of inheriting the disorder. Because diagnosis followed by counseling reduces the risk of morbidity, children in affected families should be tested before the onset of puberty. Genetic testing is used if the mutation has been identified in the index case. If not, pertinent RBC or WBC enzyme levels are measured. Gene analysis can be used for in utero diagnosis (using amniocentesis or chorionic villus sampling) but is seldom indicated because of the favorable outlook for most gene carriers.

**Prognosis**

Advances in medical care and self-care have improved the prognosis for symptomatic patients. Still, some patients develop recurrent crises or progressive disease with permanent paralysis or renal failure. Also, frequent need for potent analgesics may give rise to drug addiction.

**Treatment**

- Triggers eliminated if possible
- Dextrose (oral or IV)
- IV heme

Treatment of the acute attack is identical for all the acute porphyrrias. Possible triggers (eg, drugs) are identified and eliminated. Unless the attack is mild, patients are hospitalized in a darkened, quiet, private room. Heart rate, BP, and fluid and electrolyte balance are monitored. Neurologic status, bladder function, muscle and tendon function, respiratory function, and pulse oximetry are continuously monitored. Symptoms (eg, pain, vomiting) are treated with nonporphyrinogenic drugs as needed (see Table 96-4).
Dextrose 300 to 500 g daily inhibits ALA synthase and relieves symptoms. It can be given by mouth if patients are not vomiting; otherwise, it is given IV. To avoid overhydration with consequent hyponatremia, 1 L of a 50% dextrose solution can be given by central venous catheter over 24 h.

IV heme is more effective than dextrose and should be given immediately in severe attacks, electrolyte imbalance, or muscle weakness. Heme usually resolves symptoms in 3 to 4 days. If heme therapy is delayed, nerve damage is more severe and recovery is slower and possibly incomplete. Heme is available in the US as lyophilized hematin to be reconstituted in a glass vial with sterile water. The dose is 3 mg/kg IV once/day for 4 days. In this form, heme degradation products form rapidly and may cause phlebitis at the infusion site; they also have a transient anticoagulant effect. Adverse effects can be reduced by reconstitution with, eg, 20% human albumin. Heme arginate is a more stable, generally toxicity-free alternative.

In patients with severe recurrent attacks, who are at risk of renal damage or permanent neurologic damage, liver transplantation is an option. Renal transplantation, with or without simultaneous liver exchange, should be considered in patients with active disease and terminal renal failure, because there is considerable risk that nerve damage will progress at the start of dialysis.

**Prevention**

Carriers of acute porphyria should avoid the following:

- Potentially harmful drugs (see Table 96-4)
- Alcohol
- Emotional stress
- Exposure to organic solvents (eg, in painting or dry cleaning)
- Crash diets
- Periods of starvation

Diets for obesity should provide gradual weight loss and be adopted only during periods of remission. Carriers of VP or HCP should minimize sun exposure; sunscreens that block only ultraviolet B light are ineffective, but opaque titanium dioxide preparations are beneficial. Support associations for porphyria patients can provide written information and direct counseling.

Patients should be identified prominently in the medical record as carriers and should carry a card verifying the carrier state and precautions to be observed.

A high-carbohydrate diet may decrease the risk of acute attacks. A high-carbohydrate diet or a lump of sugar every hour may help relieve symptoms of an acute attack. Prolonged use should be avoided in order to decrease risk of obesity and dental caries.

Patients who experience recurrent and predictable attacks (typically women with attacks related to the menstrual cycle) may benefit from prophylactic heme therapy given shortly before the expected onset. There is no standardized regimen; a specialist should be consulted. Frequent premenstrual attacks in some women are aborted by administration of a gonadotropin-releasing hormone analog plus low-dose estrogen. Oral contraceptives are sometimes used successfully, but the progestin component is likely to exacerbate the porphyria.

To prevent renal damage, chronic hypertension is treated (using safe drugs). Patients with evidence of impaired renal function are referred to a nephrologist.

The incidence of hepatocellular cancer is high among carriers of acute porphyria, especially in patients
with active disease. Patients who are > 50 should undergo yearly or twice yearly surveillance, including liver screening with contrast-enhanced ultrasonography. Early intervention can be curative and increases life expectancy.

**Cutaneous Porphyrias**

Cutaneous porphyrias tend to manifest as undulating or unremitting disease with a relatively steady production of phototoxic porphyrins in the liver or bone marrow. These porphyrins accumulate in the skin and, on sunlight exposure (visible light, including near-ultraviolet [UV]), generate cytotoxic radicals that cause cutaneous manifestations.

Cutaneous porphyrias include porphyria cutanea tarda, erythropoietic protoporphyria (EPP), and the extremely rare hepatoerythropoietic porphyria and congenital erythropoietic porphyria (see Table 96-5). The acute porphyrias variegate porphyria and hereditary coproporphyria also have cutaneous manifestations.

In all cutaneous porphyrias except EPP, cutaneous photosensitivity manifests as fragile skin and bullous eruptions. Skin changes generally occur on sun-exposed areas (eg, face, neck, dorsal sides of fingers and hands) or traumatized skin. The cutaneous reaction is insidious, and often patients are unaware of the connection to sun exposure. In contrast, the photosensitivity in EPP occurs within minutes or hours after sun exposure, manifesting as a burning pain that persists for hours, often without any objective signs on the skin.

**Porphyria Cutanea Tarda**

Porphyria cutanea tarda (PCT) is a comparatively common porphyria affecting mainly the skin. Liver disease is common. Symptoms include fragile skin and blisters affecting sun-exposed areas. Iron plays a key role in pathogenesis. Several environmental factors lower the threshold for the phototoxic skin reaction, including alcohol ingestion, estrogens, hepatitis C infection, and possibly HIV infection. Drugs, with the exceptions of iron and estrogens, are not triggers. Diagnosis is by porphyrin analysis of urine and stool. Differentiation from the acute cutaneous porphyrias hereditary coproporphyria and variegate porphyria is important. Treatment includes iron depletion by phlebotomy and forced porphyrin excretion by treatment with chloroquine. Prevention is by avoidance of sunlight, alcohol, estrogens, and iron-containing drugs.

**Pathophysiology**

PCT results from hepatic deficiency of uroporphyrinogen decarboxylase (UPGD—see Table 96-1). In about 80% of patients, the responsible mutation is sporadic; the remaining 20% are hereditary.

Porphyrins accumulate in the liver and are transported to the skin, where they cause photosensitivity. The 50% decrease in UPGD activity in heterozygous patients is insufficient to cause clinical PCT. Other factors must further impair enzyme activity. Iron plays a central role, probably by generating oxygen radicals that inhibit UPGD by oxidizing its substrate; thus, hemochromatosis is a significant risk factor. Alcohol, estrogens, and chronic viral infection probably contribute in different ways by increasing iron activity in hepatic tissue. The drugs that commonly trigger acute porphyria (see Table 96-4) do not trigger PCT.

Liver disease is common in PCT and may be due partly to porphyrin accumulation, chronic hepatitis C infection, concomitant hemosiderosis, or excess alcohol ingestion. Cirrhosis occurs in ≤ 35% of patients, and hepatocellular carcinoma occurs in 7 to 24% (more common among middle-aged men).

The 2 major forms of the disease, types 1 and 2, have the same precipitants, symptoms, and treatment. Overall prevalence may be on the order of 1/10,000.
In type 1 PCT (sporadic), decarboxylase deficiency is restricted to the liver and no genetic background is recognized. It usually manifests in middle age or later.

In type 2 PCT (familial), decarboxylase deficiency is inherited in an autosomal dominant fashion with limited penetrance. Prevalence is lower than in sporadic PCT. Deficiency occurs in all cells, including RBCs. It may develop earlier than type 1, occasionally in childhood.

Secondary PCT-like conditions (pseudoporphyria) may occur with certain photosensitizing drugs (eg, furosemide, tetracyclines, sulfonamides, some NSAIDs). Because porphyrins are poorly dialyzed, some patients receiving long-term hemodialysis develop a skin condition that resembles PCT; this condition is termed pseudoporphyria of end-stage renal disease.

**Symptoms and Signs**

Patients present with fragile skin, mainly on sun-exposed areas. Phototoxicity is delayed: patients do not always connect sun exposure with symptoms.

Spontaneously or after minor trauma, tense bullae develop. Accompanying erosions and ulcers may develop secondary infection; they heal slowly, leaving atrophic scars. Sun exposure occasionally leads to erythema, edema, or itching. Hyperemic conjunctivitis may develop, but other mucosal sites are not affected. Areas of hypopigmentation or hyperpigmentation may develop, as may facial hypertrichosis and pseudosclerodermoid changes.

**Diagnosis**

- Levels of plasma porphyrins, urinary uroporphyrin and heptacarboxyl porphyrin, and fecal isocoproporphyrin

In otherwise healthy patients, fragile skin and blister formation suggest PCT. Differentiation from acute porphyrias with cutaneous symptoms (variegate porphyria [VP] and hereditary coproporphyria [HCP]) is important because in patients with VP and HCP, the erroneous prescription of porphyrigenic drugs may trigger the severe neurovisceral symptoms of the acute porphyrias. Previous unexplained neurologic symptoms or abdominal pain may suggest an acute porphyria. A history of exposure to chemicals that can cause pseudoporphyria should be sought.

Although all porphyrias that cause skin lesions are accompanied by elevated plasma porphyrins, elevated urinary uroporphyrin and heptacarboxyl porphyrin and fecal isocoproporphyrin indicate PCT. Urine levels of porphyrin precursor porphobilinogen (PBG) and, usually, δ-aminolevulinic acid (ALA) are normal in PCT. RBC activity of UPGD is normal in type 1 PCT but decreased in type 2.

Because concurrent hepatitis C infection is common and may be asymptomatic, serum markers for hepatitis C (see p. 253) should be investigated.

**Treatment**

Two different therapeutic strategies are available:

- Reduction of body iron stores
- Increase in porphyrin excretion

These strategies can be combined for more rapid remission. The treatment is monitored by determinations of urinary porphyrin excretion every other or every 3rd month until full remission.

Iron removal by phlebotomy is usually effective. A pint of blood is removed every 2nd or every 3rd week; shorter intervals unnecessarily risk causing anemia. When serum ferritin falls slightly below normal, phlebotomy is stopped. Usually, only 5 to 6 sessions are needed. Urine and plasma porphyrins fall
gradually with treatment, lagging behind but paralleling the fall in ferritin. The skin eventually becomes normal. After remission, further phlebotomy is needed only if there is a recurrence.

Low-dose chloroquine or hydroxychloroquine (100 to 125 mg po twice/wk) removes excess porphyrins from the liver by increasing the excretion rate. Higher doses can cause transient liver damage and worsening of porphyria. When remission is achieved, the regimen is stopped.

Chloroquine and hydroxychloroquine are not effective in advanced renal disease, and phlebotomy is usually contraindicated because of underlying anemia. However, recombinant erythropoietin mobilizes excess iron and resolves the anemia enough to permit phlebotomy. In end-stage renal disease, deferoxamine is an adjunct to phlebotomy for reduction of hepatic iron, the complexed iron being removed during dialysis. Dialyzers with ultrapermeable membranes and extra high blood flow rates are needed.

Patients with overt PCT and hepatitis C infection are preferentially treated with pegylated interferon alfa-2a and ribavirin. Previous iron depletion augments the response to antiviral therapy.

Children with symptomatic PCT are treated with small-volume phlebotomies or oral chloroquine; dosage is determined by body weight.

Skin symptoms occurring during pregnancy are treated with phlebotomy. In refractory cases, low-dose chloroquine can be added; no teratogenic effects have been recognized. Depending on degree of hemodilution and iron depletion, the skin symptoms usually abate as pregnancy advances.

Postmenopausal estrogen supplementation is interrupted during treatment for PCT. Stopping estrogens often induces remission. After remission, estrogens can be reintroduced, preferentially in transdermal administration to reduce hepatic porphyrrogenic exposure.

Prevention

Patients should avoid sun exposure; hats and clothing protect best, as do zinc or titanium oxide sunscreens. Typical sunscreens that block UV light are ineffective, but UVA-absorbing sunscreens, such as those containing dibenzylmethanes, may help somewhat. Alcohol ingestion should be avoided permanently, but estrogen supplementation can usually be resumed safely after a disease remission.

Erythropoietic Protoporphyria

Erythropoietic protoporphyria (EPP) typically manifests in infancy with burning skin pain after even short exposure to sunlight. Gallstones are common later in life, and acute liver failure occurs in about 10%. Diagnosis is based on symptoms and increased levels of protoporphyrin in RBCs and plasma. Treatment is with β-carotene or dihydroxyacetone and avoidance of sunlight. In patients with liver failure, combined liver and bone marrow transplantation may be life saving as well as curative.

Etiology

EPP results from deficiency of the enzyme ferrochelatase in erythroid tissue. Clinical prevalence is about 1/75,000. Phototoxic protoporphyrins accumulate in bone marrow and RBCs, enter the plasma, and are deposited in the skin or excreted by the liver into bile and stool. Heavy biliary protoporphyrin excretion can cause gallstones. These cytotoxic molecules sometimes damage the hepatobiliary tract, resulting in hepatic protoporphyrin accumulation that leads to acute liver failure; liver failure may become clinically acute within days.

Inheritance pattern is basically autosomal dominant but complex. Clinical manifestations occur only in people who have both the defective EPP gene and an unusual low-output (but otherwise normal) allele from the healthy parent.

Symptoms and Signs
Severity varies greatly, even among patients within a single family. Usually, an infant or young child with EPP cries for hours after even short exposure to sun. However, because cutaneous signs are usually absent and young children cannot describe their symptoms, EPP often goes undiagnosed.

If unrecognized, EPP causes psychosocial problems because children inexplicably refuse to go outdoors. The pain may be so distressing that it causes nervousness, tenseness, aggressiveness, or even feelings of detachment from the surroundings or suicidal thoughts.

During childhood, crusting may develop around the lips and on the back of the hands after prolonged sun exposure. Blistering and scarring do not occur. If skin protection is chronically neglected, rough, thickened, and leathery skin may develop, especially over the knuckles. Linear perioral furrows (carp mouth) may develop.

Biliary excretion of large amounts of protoporphyrin can cause cholestasis that progresses to nodular cirrhosis and acute liver failure in ≤ 10% of patients; symptoms include jaundice, malaise, upper abdominal pain, and tender hepatic enlargement.

**Diagnosis**

- RBC and plasma protoporphyrin measurement

EPP should be suspected in children and adults with painful cutaneous photosensitivity who experience no blisters or scarring. Family history is usually negative. The diagnosis is confirmed by finding increased RBC and plasma protoporphyrin levels. A genetic marker for susceptibility to cholestatic complications has been identified.

Screening of potential carriers among relatives is by showing increased RBC protoporphyrin contents and decreased ferrochelatase activity (assayed in lymphocytes) or by genetic testing if the mutation has been identified in the index case. Susceptibility for cutaneous disease in carriers is indicated by finding the low-output ferrochelatase allele.

**Treatment**

- Avoidance of triggers (eg, sun exposure, alcohol, fasting)
- Symptomatic treatment
- Sometimes oral β-carotene

Acute skin symptoms are alleviated by cold baths or wet towels, analgesics, and antihistamines. Regular physician-patient consultations that provide information, discussion, and opportunities for genetic counseling together with physical checkups are important.

Patients should avoid sun exposure; opaque titanium dioxide or zinc oxide sunscreens are beneficial, and UVA-absorbing sunscreens, such as those containing dibenzylmethanes, may help somewhat. Protection against the operating light is strictly required in liver transplantation to avoid serious phototoxic injury to inner organs. Covering of light sources with filters that block wavelengths < 470 nm is required.

Endoscopy, laparoscopy, and nontransplant abdominal surgery are not connected with risk of phototoxic damage.

[Table 96-6. Doses of β-Carotene in Erythropoietic Protoporphyria]

Patients should avoid alcohol and fasting, both of which increase the rate of RBC production and thus the protoporphyrin load. Drugs that trigger acute porphyrias (see Table 96-4) need not be avoided.

Systemic β-carotene causes slight yellow protective skin coloration and neutralizes the toxic radicals in the skin that cause symptoms. Dose depends on patient age (see Table 96-6).
Another antioxidant, cysteine, may also lessen photosensitivity. The brown protective skin color obtained with topically applied dihydroxyacetone is generally cosmetically preferable to the yellowish tint caused by β-carotene.

If the above-mentioned measures are ineffective (eg, patients have increasing photosensitivity, rising porphyrin levels, or progressive jaundice), RBC hypertransfusion (ie, to abovenormal Hb levels) can reduce the production rate of porphyrin-loaded RBCs. Administration of bile acids facilitates biliary excretion of protoporphyrin. Oral cholestyramine or charcoal interrupts the enterohepatic circulation. Liver failure may require immediate liver transplantation. Bone marrow exchange corrects the basic metabolic defect.

Patients with EPP should undergo annual surveillance for risks of cholestasis. Tests include RBC porphyrin levels, porphyrin excretion patterns, and liver function. Abnormal findings should be evaluated by a porphyria specialist and a hepatologist. If the liver appears involved, biopsy is done to identify progressive disease. Patients should be vaccinated against hepatitis A and B and advised to avoid alcohol.
Chapter 97. Fluid and Electrolyte Metabolism

Introduction

Body fluid volume and electrolyte concentration are normally maintained within very narrow limits despite wide variations in dietary intake, metabolic activity, and environmental stresses. Homeostasis of body fluids is preserved primarily by the kidneys.

Water and Sodium Balance

Water and Na balance are closely interdependent. Total body water (TBW) is about 60% of body weight (ranging from about 50% in obese people to 70% in lean people). Almost two thirds of TBW is in the intracellular compartment (intracellular fluid, or ICF); the other one third is extracellular (extracellular fluid, or ECF). Normally, about 25% of the ECF is in the intravascular compartment; the other 75% is interstitial fluid (see Fig. 97-1).

The major intracellular cation is K, with an average concentration of 140 mEq/L. The extracellular K concentration is 3.5 to 5 mEq/L. The major extracellular cation is Na, with an average concentration of 140 mEq/L and an intracellular Na concentration of 12 mEq/L.

Osmotic forces: The concentration of combined solutes in water is osmolarity (amount of solute per L of solution), which, in body fluids, is similar to osmolality (amount of solute per kg of solution). Plasma osmolality can be measured in the laboratory or estimated according to the formula

\[
\text{Plasma osmolality (mOsm/kg)} = \frac{2[\text{serum Na}]}{18} + \frac{[\text{Glucose}]}{18} + \frac{[\text{BUN}]}{2.8}
\]

where serum Na is expressed in mEq/L and glucose and BUN are expressed in mg/dL. Osmolality of body fluids is normally between 275 and 290 mOsm/kg. Na is the major determinant of serum osmolality. Apparent changes in osmolality may result from errors in the measurement of Na with electrodes that are not ion selective (see under Diagnosis on p. 826). An osmolar gap is present when measured osmolality exceeds estimated osmolality by ≥ 10 mOsm/kg. It is caused by unmeasured osmotically active substances present in the plasma. The most common are alcohols (ethanol, methanol, isopropanol, ethylene glycol), mannitol, and glycine.

Water crosses cell membranes freely from areas of low solute concentration to areas of high solute concentration. Thus, osmolality tends to equalize across the various body fluid compartments, resulting primarily from movement of water, not solutes. Solutes such as urea that freely diffuse across cell membranes have little or no effect on water shifts (little or no osmotic activity), whereas solutes that are restricted primarily to one fluid compartment, such as Na and K, have the greatest osmotic activity. Tonicity, or effective osmolality, reflects osmotic activity and determines the force drawing water across fluid compartments (the osmotic force). Osmotic force can be opposed by other forces. For example, plasma proteins have a small osmotic effect that tends to draw water into the plasma; this osmotic effect is normally counteracted by vascular hydrostatic forces that drive water out of the plasma.

Water intake and excretion: The average daily fluid intake is about 2.5 L. The amount needed to replace losses from the urine and other sources is about 1 to 1.5 L/day in healthy adults. However, on a short-term basis, an average young adult with normal kidney function may ingest as little as 200 mL of water each day to excrete the nitrogenous and other wastes generated by cellular metabolism. More is needed in people with any loss of renal concentrating capacity. Renal concentrating capacity is lost in
• The elderly

• People with diabetes insipidus, certain renal disorders, hypercalcemia, severe salt restriction, chronic overhydration, or hyperkalemia

• People who ingest ethanol, phenytoin, lithium, demeclocycline, or amphotericin B

• People with osmotic diuresis (eg, due to high-protein diets or hyperglycemia)

Other obligatory water losses are mostly insensible losses from the lungs and skin, averaging about 0.4 to 0.5 mL/kg/h or about 650 to 850 mL/day in a 70-kg adult. With fever, another 50 to 75 mL/day may be lost for each degree C of temperature elevation above normal. GI losses are usually negligible, except when marked vomiting, diarrhea, or both occur. Sweat losses can be significant during environmental heat exposure or excessive exercise.

Water intake is regulated by thirst. Thirst is triggered by receptors in the anterolateral hypothalamus that respond to increased serum osmolality (as little as 2%) or decreased body fluid volume. Rarely hypothalamic dysfunction decreases the capacity for thirst.

Water excretion by the kidneys is regulated primarily by ADH (vasopressin). ADH is released by the posterior pituitary and results in increased water reabsorption in the distal nephron. ADH release is stimulated by any of the following:

• Increased serum osmolality

• Decreased blood volume

• Decreased BP

• Stress

ADH release may be impaired by certain substances (eg, ethanol, phenytoin) and central diabetes insipidus (see p. 772).

Water intake decreases serum osmolality. Low serum osmolality inhibits ADH secretion, allowing the kidneys to produce dilute urine. The diluting capacity of healthy kidneys in young adults is such that maximum daily fluid intake can be as much as 25 L; greater amounts quickly lower serum osmolality.

**Disorders of Fluid Volume**

Because Na is the major osmotically active ion in the ECF, total body Na content determines ECF volume. Deficiency or excess of total body Na content causes ECF volume depletion or overload. Plasma Na concentration does not necessarily reflect total body Na.

Dietary intake and renal excretion regulate total body Na content. When total Na content and ECF volume are low, the kidneys increase Na conservation. When total Na content and ECF volume are high, Na excretion (natriuresis) increases so that volume decreases.

Renal Na excretion can be adjusted widely to match Na intake. Renal Na excretion requires delivery of Na to the kidneys and so depends on renal blood flow and GFR. Thus, inadequate Na excretion may be secondary to decreased renal blood flow, as in chronic kidney disease or heart failure.

**Renin-angiotensin-aldosterone axis:** The renin-angiotensin-aldosterone axis is the main regulatory mechanism of renal Na excretion. In volume-depleted states, GFR and Na delivery to the distal nephrons decreases, causing release of renin. Renin cleaves angiotensinogen (renin substrate) to form angiotensin I. ACE then cleaves angiotensin I to angiotensin II. Angiotensin II does the following:

• Increases Na retention by decreasing the filtered load of Na and enhancing proximal tubular Na...
reabsorption.

• Increases BP (has pressor activity)

• Increases thirst

• Directly impairs water excretion

• Stimulates the adrenal cortex to secrete aldosterone, which increases Na reabsorption via multiple renal mechanisms

Angiotensin I can also be transformed to angiotensin III, which stimulates aldosterone release as much as angiotensin II but has much less pressor activity. Aldosterone release is also stimulated by hyperkalemia.

Other natriuretic factors: Several other natriuretic factors have been identified, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and a C-type natriuretic peptide (CNP).

ANP is secreted by cardiac atrial tissue. Concentration increases in response to ECF volume overload (eg, heart failure, chronic kidney disease, cirrhosis with ascites) and primary aldosteronism and in some patients with primary hypertension. Decreases have occurred in the subset of patients with nephrotic syndrome who have presumed ECF volume contraction. High concentrations increase Na excretion and increase GFR even when BP is low.

BNP is synthesized mainly in the atria and left ventricle and has similar triggers and effects to ANP. BNP assays are readily available. High BNP concentration is used to diagnose volume overload.

CNP, in contrast to ANP and BNP, is primarily vasodilatory.

Na depletion and excess: Na depletion requires inadequate Na intake plus abnormal losses from the skin, GI tract, or kidneys (defective renal Na conservation). Defective renal Na conservation may be caused by primary renal disease, adrenal insufficiency, or diuretic therapy.

Na overload requires higher Na intake than excretion; however, because normal kidneys can excrete large amounts of Na, Na overload generally reflects defective regulation of renal blood flow and Na excretion (eg, as occurs in heart failure, cirrhosis, or chronic kidney disease).

Volume Depletion

Volume depletion, or ECF volume contraction, occurs as a result of loss of total body Na. Causes include vomiting, excessive sweating, diarrhea, burns, diuretic use, and kidney failure. Clinical features include diminished skin turgor, dry mucous membranes, tachycardia, and orthostatic hypotension. Diagnosis is clinical. Treatment involves administration of Na and water.

Because water crosses plasma membranes in the body through passive osmosis, loss of the major extracellular cation (Na) quickly results in water loss from the ECF space as well. In this way, Na loss always causes water loss. However, depending on many factors, serum Na concentration can be high, low, or normal in volume-depleted patients (despite the decreased total body Na content). ECF volume is related to effective circulating volume. A decrease in ECF (hypovolemia) generally causes a decrease in effective circulating volume, which in turn causes decreased organ perfusion and leads to clinical sequelae. Common causes of volume depletion are listed in Table 97-1.

Symptoms and Signs

In mild volume depletion (< 5% of ECF), the only sign may be diminished skin turgor (best assessed at the upper torso). Skin turgor may be low in elderly patients regardless of volume status. Patients may complain of thirst. Dry mucous membranes do not always correlate with volume depletion, especially in
the elderly and in mouth-breathe. Oliguria is typical.

When ECF volume has diminished by 5 to 10%, orthostatic tachycardia, hypotension, or both are usually, but not always, present. Also, orthostatic changes can occur in patients without ECF volume depletion, particularly patients deconditioned or bedridden. Skin turgor may decrease further.

[Table 97-1. Common Causes of Volume Depletion]

When fluid loss exceeds 10% of ECF volume, signs of shock can occur (eg, tachypnea, tachycardia, hypotension, confusion, poor capillary refill).

**Diagnosis**

- Clinical findings
- Sometimes serum electrolytes, BUN, and creatinine
- Rarely serum osmolality and urine chemistries

Volume depletion is suspected in patients at risk, most often in patients with a history of inadequate fluid intake (especially in comatose or disoriented patients), increased fluid losses, diuretic therapy, and renal or adrenal disorders.

Diagnosis is usually clinical. When the cause is obvious and easily correctable (eg, acute gastroenteritis in otherwise healthy patients), laboratory testing is unnecessary; otherwise, serum electrolytes, BUN, and creatinine are measured. Serum osmolality and urine Na, creatinine, and osmolality are measured when there is suspicion of clinically meaningful electrolyte abnormality that is not clear from serum tests and for patients with cardiac or renal disease. When metabolic alkalosis is present, urine Cl is also measured.

Central venous pressure and pulmonary artery occlusion pressure are decreased in volume depletion, but measurement is rarely required. Measurement, which requires an invasive procedure, is occasionally necessary for patients for whom even small amounts of added volume may be detrimental, such as those with unstable heart failure or advanced chronic kidney disease.

The following concepts are helpful when interpreting urine electrolyte and osmolality values:

- During volume depletion, normally functioning kidneys conserve Na. Thus, the urine Na concentration is usually <15 mEq/L; the fractional excretion of Na (urine Na/serum Na divided by urine creatinine/serum creatinine) is usually <1%; also, urine osmolality is often >450 mOsm/kg.

- When metabolic alkalosis is combined with volume depletion, urine Na concentration may be high because large amounts of HCO₃ are spilled in the urine, obligating the excretion of Na to maintain electrical neutrality. In this instance, a urine Cl concentration of <10 mEq/L more reliably indicates volume depletion.

- Misleadingly high urinary Na (generally >20 mEq/L) or low urine osmolality can also occur due to renal Na losses resulting from renal disease, diuretics, or adrenal insufficiency.

Volume depletion frequently increases the BUN and serum creatinine concentrations with the ratio of BUN to creatinine often >20:1. Values such as Hct often increase in volume depletion but are difficult to interpret unless baseline values are known.

**Treatment**

- Replacement of Na and water

The cause of volume depletion is corrected and fluids are given to replace existing volume deficits as well as any ongoing fluid losses and to provide daily fluid requirements. Mild-to-moderate volume deficits may
be replaced by increased oral intake of Na and water when patients are conscious and not vomiting. When volume deficits are severe or when oral fluid replacement is impractical, IV 0.9% saline is given. Typical IV regimens are discussed on p. 2297; oral regimens are discussed on p. 2809.

Volume Overload

Volume overload generally refers to expansion of the ECF volume. ECF volume expansion typically occurs in heart failure, nephrotic syndrome, and cirrhosis. Renal Na retention leads to increased total body Na content. This increase results in varying degrees of volume overload. In heart failure, the increased ECF volume results in decreased effective circulating volume, which in turn causes decreased organ perfusion leading to clinical sequelae. Serum Na concentration can be high, low, or normal in volume-overloaded patients (despite the increased total body Na content).

An increase in total body Na is the key pathophysiologic event. It increases osmolality, which triggers compensatory mechanisms that cause water retention. When sufficient fluid accumulates in the ECF (usually > 2.5 L), edema (see p. 2031) develops.

Among the most common causes of ECF volume overload are the following:

- Heart failure
- Cirrhosis
- Renal failure
- Nephrotic syndrome
- Premenstrual edema
- Pregnancy

Clinical features include weight gain and edema. Diagnosis is clinical. Treatment aims to correct the cause.

Hyponatremia

Hyponatremia is decrease in serum Na concentration < 136 mEq/L caused by an excess of water relative to solute. Common causes include diuretic use, diarrhea, heart failure, and renal disease. Clinical manifestations are primarily neurologic (due to an osmotic shift of water into brain cells causing edema), especially in acute hyponatremia, and include headache, confusion, and stupor; seizures and coma may occur. Diagnosis is by measuring serum Na. Serum and urine electrolytes and osmolality help determine the cause. Treatment involves restricting water intake and promoting its loss, replacing any Na deficit, and treating the cause.

Etiology

Hyponatremia reflects an excess of total body water (TBW) relative to total body Na content. Because total body Na content is reflected by ECF volume status, hyponatremia must be considered along with status of the ECF volume: hypovolemia, euvoelma, and hypervolemia (see Table 97-2). Note that the ECF volume is not the same as effective plasma volume. For example, decreased effective plasma volume may occur with decreased ECF volume, but it may also occur with an increased ECF volume (eg, in heart failure, hypoalbuminemia, or capillary leak syndrome).

Hypovolemic hyponatremia: Deficiencies in both TBW and total body Na exist, although proportionally more Na than water has been lost; the Na deficit causes hypovolemia. In hypovolemic hyponatremia, both serum osmolality and blood volume decrease. ADH secretion increases despite a decrease in osmolality.
to maintain blood volume. The resulting water retention increases plasma dilution and hyponatremia.

Table 97-2. Principal Causes of Hyponatremia

**Extrarenal fluid losses**, such as those that occur with the losses of Na-containing fluids as in protracted vomiting, severe diarrhea, or sequestration of fluids in a 3rd space (see Table 97-3), can cause hyponatremia typically when losses are replaced by ingesting plain water or liquids low in Na (see Table 97-4) or by hypotonic IV fluid. Significant ECF fluid losses also cause release of ADH, causing water retention by the kidneys, which can maintain or worsen hyponatremia. In extrarenal causes of hypovolemia, because the normal renal response to volume loss is Na conservation, urine Na concentration is typically < 10 mEq/L.

**Renal fluid losses** resulting in hypovolemic hyponatremia may occur with mineralocorticoid deficiency, diuretic therapy, osmotic diuresis, or salt-losing nephropathy. Salt-losing nephropathy encompasses a loosely defined group of intrinsic renal disorders with primarily renal tubular dysfunction. This group includes interstitial nephritis, medullary cystic disease, partial urinary tract obstruction, and, occasionally, polycystic kidney disease. Renal causes of hypovolemic hyponatremia can usually be differentiated from extrarenal causes by the history. Patients with ongoing renal fluid losses can also be distinguished from patients with extrarenal fluid losses because the urine Na concentration because the urine Na concentration is inappropriately high (> 20 mEq/L). Urine Na concentration may not help in differentiation when metabolic alkalosis (as occurs with protracted vomiting) is present and large amounts of HCO₃ are spilled in the urine, obligating the excretion of Na to maintain electrical neutrality. In metabolic alkalosis, urine Cl concentration frequently differentiates renal from extrarenal sources of volume depletion (see p. 862).

Table 97-3. Composition of Body Fluids

Table 97-4. Approximate Na Content of Common Beverages

**Diuretics** may also cause hypovolemic hyponatremia. Thiazide diuretics, in particular, decrease the kidneys’ diluting capacity and increase Na excretion. Once volume depletion occurs, the nonosmotic release of ADH causes water retention and worsens hyponatremia. Concomitant hypokalemia shifts Na intracellularly and enhances ADH release, thereby worsening hyponatremia. This effect of thiazides may last for up to 2 wk after cessation of therapy; however, hyponatremia usually responds to replacement of K and volume deficits along with judicious monitoring of water intake until the drug effect dissipates. Elderly patients may have increased Na diuresis and are especially susceptible to thiazide-induced hyponatremia, particularly when they have a preexisting defect in renal capacity to excrete free water. Rarely, such patients develop severe, life-threatening hyponatremia within a few weeks after the initiation of a thiazide diuretic. Loop diuretics much less commonly cause hyponatremia.

**Euvolemic hyponatremia**: In euvolemic (dilutional) hyponatremia, total body Na and thus ECF volume are normal or near-normal; however, TBW is increased.

Primary polydipsia can cause hyponatremia only when water intake overwhelms the kidneys' ability to excrete water. Because normal kidneys can excrete up to 25 L urine/day, hyponatremia due solely to polydipsia results only from the ingestion of large amounts of water or from defects in renal capacity to excrete free water. Patients affected include those with psychosis or more modest degrees of polydipsia plus renal insufficiency.

Euvolemic hyponatremia may also result from excessive water intake in the presence of Addison’s disease, hypothyroidism, or nonosmotic ADH release (eg, due to stress; postoperative states; use of drugs such as chlorpropamide, tolbutamide, opioids, barbiturates, vincristine, clofibrate, or carbamazepine). Postoperative hyponatremia most commonly occurs because of a combination of nonosmotic ADH release and excessive administration of hypotonic fluids after surgery. Certain drugs (eg, cyclophosphamide, NSAIDs, chlorpropamide) potentiate the renal effect of endogenous ADH, whereas others (eg, oxytocin) have a direct ADH-like effect on the kidneys. A deficiency in water excretion is common in all these conditions. Diuretics can cause or contribute to euvolemic hyponatremia if another factor causes water retention or excessive water intake. The syndrome of inappropriate ADH secretion
Hypervolemic hyponatremia: Hypervolemic hyponatremia is characterized by an increase in both total body Na (and thus ECF volume) and TBW with a relatively greater increase in TBW. Various edematous disorders, including heart failure and cirrhosis, cause hypervolemic hyponatremia. Rarely, hyponatremia occurs in nephrotic syndrome, although pseudohyponatremia may be due to interference with Na measurement by elevated lipids. In each of these disorders, a decrease in effective circulating volume results in the release of ADH and angiotensin II. The following factors contribute to hyponatremia:

- The antidiuretic effect of ADH on the kidneys
- Direct impairment of renal water excretion by angiotensin II
- Decreased GFR
- Stimulation of thirst by angiotensin II

Urine Na excretion is usually < 10 mEq/L, and urine osmolality is high relative to serum osmolality.

Hyponatremia in AIDS: Hyponatremia has been reported in > 50% of hospitalized patients with AIDS. Among the many potential contributing factors are

- Administration of hypotonic fluids
- Impaired renal function
- Nonosmotic ADH release due to intravascular volume depletion
- Administration of drugs that impair renal water excretion

In addition, adrenal insufficiency has become increasingly common among AIDS patients as the result of cytomegalovirus adrenalitis, mycobacterial infection, or interference with adrenal glucocorticoid and mineralocorticoid synthesis by ketoconazole. SIADH may be present because of coexistent pulmonary or CNS infections.

**Sidebar 97-1 Syndrome of Inappropriate ADH Secretion**

The syndrome of inappropriate ADH secretion (SIADH) is attributed to excessive ADH release. It is defined as less-than-maximally-dilute urine in the presence of plasma hypo-osmolality (hyponatremia) without volume depletion or overload, emotional stress, pain, diuretics, or other drugs that stimulate ADH secretion in patients with normal cardiac, hepatic, renal, adrenal, and thyroid function. SIADH is associated with myriad disorders (see Table 97-5).

**Symptoms and Signs**

Symptoms mainly involve CNS dysfunction. However, when hyponatremia is accompanied by disturbances in total body Na content, signs of ECF volume depletion or overload also occur (see p. 823). In general, older chronically ill patients with hyponatremia develop more symptoms than younger otherwise healthy patients. Symptoms are also more severe with faster-onset hyponatremia. Symptoms generally occur when the effective plasma osmolality falls to < 240 mOsm/kg. Symptoms can be subtle and consist mainly of changes in mental status, including altered personality, lethargy, and confusion. As the serum Na falls to < 115 mEq/L, stupor, neuromuscular hyperexcitability, hyperreflexia, seizures, coma, and death can result.

Severe cerebral edema may occur in premenopausal women with acute hyponatremia, perhaps because...
estrogen and progesterone inhibit brain Na\(^+\), K\(^+\)-ATPase and decrease solute extrusion from brain cells. Sequelae include hypothalamic and posterior pituitary infarction and occasionally brain stem herniation.

**Diagnosis**

- Serum and urine electrolytes and osmolality
- Clinical assessment of volume status

Hyponatremia is occasionally suspected in patients who have neurologic abnormalities and are at risk. However, because findings are nonspecific, hyponatremia is often recognized only after serum electrolyte measurement.

[Table 97-5, Disorders Associated with Syndrome of Inappropriate ADH Secretion]

Serum Na may be low when severe hyperglycemia increases osmolality and water moves out of cells into the ECF. Serum Na concentration falls about 1.6 mEq/L for every 100-mg/dL (5.55-mmol/L) rise in the serum glucose concentration above normal. This condition is often called translocational hyponatremia because it is caused by translocation of Na across cell membranes. Pseudohyponatremia with normal serum osmolality may occur in hyperlipidemia or extreme hyperproteinemia, because the lipid or protein occupies space in the volume of serum taken for analysis; the concentration of Na in serum itself is not affected. Newer methods of measuring serum electrolytes with ion-selective electrodes circumvent this problem.

**Identification of the cause:** Identifying the cause can be complex. The history sometimes suggests a cause (eg, significant fluid loss due to vomiting or diarrhea, renal disease, compulsive fluid ingestion, intake of drugs that stimulate ADH release or enhance ADH action).

The volume status, particularly the presence of obvious volume depletion or overload, suggests certain causes (see [Table 97-1]). Overtly hypovolemic patients usually have an obvious source of fluid loss (typically treated with hypotonic fluid replacement). Overtly hypervolemic patients usually have a readily recognizable condition, such as heart failure or hepatic or renal disease. Euvolemic patients and patients with equivocal volume status require more laboratory testing to identify a cause.

Laboratory tests should include serum and urine osmolality and electrolytes. Euvolemic patients should also have thyroid and adrenal function tested. Hypo-osmolality in euvoletic patients should cause excretion of a large volume of dilute urine (eg, osmolality < 100 mOsm/kg and sp gr < 1.003). Serum Na concentration and serum osmolality that are low and urine osmolality that is inappropriately high (120 to 150 mmol/L) with respect to the low serum osmolality suggest volume overload, volume contraction, or SIADH. Volume overload and volume contraction are differentiated clinically (see pp. 822 and 823). When neither volume overload nor volume contraction appears likely, SIADH is considered. Patients with SIADH are usually euvoletic or slightly hypervolemic. BUN and creatinine values are normal, and serum uric acid is generally low. Urine Na concentration is usually > 30 mmol/L, and fractional excretion of Na is > 1% (for calculation, see p. 2310).

In patients with hypovolemia and normal renal function, Na reabsorption results in a urine Na of < 20 mmol/L. Urine Na > 20 mmol/L in hypovolemic patients suggests mineralocorticoid deficiency or salt-losing nephropathy. Hyperkalemia suggests adrenal insufficiency.

**Treatment**

- When hypovolemic, 0.9% saline
- When hypervolemic, fluid restriction and sometimes a diuretic
- When euvoletic, treatment of cause
• Rarely cautious correction with hypertonic (3%) saline

Rapid correction of hyponatremia, even mild hyponatremia, risks neurologic complications (see p. 828). Except possibly in the first few hours of treatment of severe hyponatremia, Na should be corrected no faster than 0.5 mEq/L/h. Even with severe hyponatremia, increase in serum Na concentration should not exceed 10 mEq/L over the first 24 h. Any identified cause of hyponatremia is treated concurrently.

**Mild hyponatremia:** Mild, asymptomatic hyponatremia (ie, serum Na > 120 mEq/L) requires restraint because small adjustments are generally sufficient. In diuretic-induced hyponatremia, elimination of the diuretic may be enough; some patients need some Na or K replacement. Similarly, when mild hyponatremia results from inappropriate hypotonic parenteral fluid administration in patients with impaired water excretion, merely altering fluid therapy may suffice.

With hypovolemia and normal adrenal function, administration of 0.9% saline usually corrects both hyponatremia and hypovolemia. When the serum Na is < 120 mEq/L, hyponatremia may not completely correct upon restoration of intravascular volume; restriction of free water ingestion to ≤ 500 to 1000 mL/24 h may be needed.

In hypervolemic patients, in whom hyponatremia is due to renal Na retention (eg, heart failure, cirrhosis, nephrotic syndrome) and diuretic, water restriction combined with treatment of the underlying disorder is required. In patients with heart failure, an ACE inhibitor, in conjunction with a loop diuretic, can correct refractory hyponatremia. In other patients in whom simple fluid restriction is ineffective, a loop diuretic in escalating doses can be used, sometimes in conjunction with IV 0.9% normal saline. K and other electrolytes lost in the urine must be replaced. When hyponatremia is more severe and unresponsive to diuretics, intermittent or continuous hemofiltration may be needed to control ECF volume while hyponatremia is corrected with IV 0.9% normal saline.

In euvolemia, treatment is directed at the cause (eg, hypothyroidism, adrenal insufficiency, diuretic use). When SIADH is present, severe water restriction (eg, 250 to 500 mL/24 h) is generally required. Additionally, a loop diuretic may be combined with IV 0.9% saline as in hypervolemic hyponatremia. Lasting correction depends on successful treatment of the underlying disorder. When the underlying disorder is not correctable, as in metastatic cancer, and patients find severe water restriction unacceptable, demeclocycline (300 to 600 mg q 12 h) may be helpful by inducing a concentrating defect in the kidneys. However, demeclocycline may cause acute renal failure. Renal failure is usually reversible when the drug is stopped. IV conivaptan, an ADH receptor antagonist, causes effective water diuresis without significant loss of electrolytes in the urine and can be used in hospitalized patients for treatment of resistant hyponatremia.

**Severe hyponatremia:** Severe hyponatremia (serum Na < 109 mEq/L; effective osmolality < 238 mOsm/kg) in asymptomatic patients can be treated safely with stringent restriction of water intake. Treatment is more controversial when neurologic symptoms (eg, confusion, lethargy, seizures, coma) are present. The debate primarily concerns the pace and degree of hyponatremia correction. Many experts recommend that serum Na be raised no faster than 1 mEq/L/h, but replacement rates of up to 2 mEq/L/h for the first 2 to 3 h have been suggested for patients with seizures. Regardless, the rise should be ≤ 10 mEq/L over the first 24 h. More vigorous correction risks precipitation of osmotic demyelination syndrome.

Hypertonic (3%) saline (containing 513 mEq Na/L) may be used, but only with frequent (q 2 to 4 h) electrolyte determinations. For patients with seizures or coma, ≤ 100 mL/h may be administered over 4 to 6 h in amounts sufficient to raise the serum Na 4 to 6 mEq/L. This amount (in mEq) may be calculated using the Na deficit formula as

\[
\text{(Desired change in Na)} \times \text{TBW}
\]

where TBW is 0.6 × body weight in kg in men and 0.5 × body weight in kg in women.

For example, the amount of Na needed to raise the Na from 106 to 112 in a 70-kg man can be calculated as follows:

\[
(112 \text{ mEq/L} - 106 \text{ mEq/L}) \times (0.6 \text{ L/kg} \times 70 \text{ kg}) = 252 \text{ mEq}
\]
Because there is 513 mEq Na/L in hypertonic saline, roughly 0.5 L of hypertonic saline is needed to raise the Na from 106 to 112 mEq/L.

Adjustments may be needed based on serum Na concentrations, which are monitored closely for the first few hours of treatment. Patients with seizures, coma, or altered mental status need supportive treatment, which may involve endotracheal intubation, mechanical ventilation, and benzodiazepines (eg, lorazepam 1 to 2 mg IV q 5 to 10 min prn) for seizures.

**Osmotic demyelination syndrome:** Osmotic demyelination syndrome (previously called central pontine myelinolysis) may follow too-rapid correction of hyponatremia. Demyelination may affect the pons and other areas of the brain. Lesions are more common among patients with alcoholism, undernutrition, or other chronic debilitating illness. Flaccid paralysis, dysarthria, and dysphagia can evolve over a few days or weeks. The lesion may extend dorsally to involve sensory tracts and leave patients with a locked-in syndrome (an awake and sentient state in which patients, because of generalized motor paralysis, cannot communicate, except possibly by coded eye movements). Damage often is permanent. When Na is replaced too rapidly (eg, > 14 mEq/L/8 h) and neurologic symptoms start to develop, it is critical to prevent further serum Na increases by stopping hypertonic fluids. In such cases, inducing hyponatremia with hypotonic fluid may mitigate the development of permanent neurologic damage.

**Hypernatremia**

(For hypernatremia in neonates, see p. 2797.)

Hypernatremia is serum Na concentration > 145 mEq/L. It implies a deficit of total body water relative to total body Na, caused by water intake being less than water losses. A major symptom is thirst; other clinical manifestations are primarily neurologic (due to an osmotic shift of water out of brain cells), including confusion, neuromuscular excitability, seizures, and coma. Diagnosis requires measurement of serum Na and sometimes other tests. Treatment is usually controlled water replacement. When the response is poor, testing (eg, monitored water deprivation or administration of vasopressin) is directed at detecting causes other than decreased water intake.

**Etiology**

Hypernatremia reflects a deficit of total body water (TBW) relative to total body Na content. Because total body Na content is reflected by ECF volume status, hypernatremia must be considered along with status of the ECF volume: hypovolemia, euvolemia, and hypervolemia. Note that the ECF volume is not the same as effective plasma volume. For example, decreased effective plasma volume may occur with decreased ECF volume, but it may also occur with an increased ECF volume (eg, in heart failure, hypoalbuminemia, or capillary leak syndrome).

Hypernatremia usually implies either an impaired thirst mechanism or limited access to water. The severity of the underlying disorder that results in an inability to drink in response to thirst and the effects of brain hyperosmolality are thought to be responsible for a high mortality rate in hospitalized adults with hypernatremia. There are several common causes of hypernatremia (see Table 97-6).

**Hypovolemic hypernatremia:** Hypernatremia associated with hypovolemia occurs with Na loss accompanied by a relatively greater loss of water from the body. Common extrarenal causes include most of those that cause hyponatremia and volume depletion (see p. 823). Either hypernatremia or hyponatremia can occur with severe volume loss, depending on the relative amounts of Na and water lost and the amount of water ingested before presentation.

Renal causes of hypernatremia and volume depletion include therapy with diuretics. Loop diuretics inhibit Na reabsorption in the concentrating portion of the nephrons and can increase water clearance. Osmotic diuresis can also impair renal concentrating capacity because of a hypertonic substance present in the tubular lumen of the distal nephron. Glycerol, mannitol, and occasionally urea can cause osmotic diuresis.
resulting in hypernatremia. The most common cause of hypernatremia due to osmotic diuresis is hyperglycemia in patients with diabetes. Because glucose does not penetrate cells in the absence of insulin, hyperglycemia further dehydrates the ICF compartment. The degree of hyperosmolality in hyperglycemia may be obscured by the lowering of serum Na resulting from movement of water out of cells into the ECF (translational hyponatremia—see Hyponatremia on p. 823). Patients with renal disease can also be predisposed to hypernatremia when their kidneys are unable to maximally concentrate urine.

**Euvolemic hypernatremia:** Hypernatremia with euvolemia is a decrease in TBW with nearnormal total body Na (pure water deficit). Extrarenal causes of water loss, such as excessive sweating, result in some Na loss, but because sweat is hypotonic, hypernatremia can result before significant hypovolemia. A deficit of almost purely water also occurs in central and nephrogenic diabetes insipidus.

Essential hypernatremia (primary hypodipsia) occasionally occurs in children with brain damage and in chronically ill elderly adults. It is characterized by an impaired thirst mechanism (eg, caused by lesions of the brain's thirst center). Altered osmotic trigger for ADH release is another possible cause of euvolemic hypernatremia; some lesions cause both an impaired thirst mechanism and an altered osmotic trigger. The nonosmotic release of ADH seems intact, and these patients are generally euvolemic.

**Hypervolemic hypernatremia:** Hypernatremia in rare cases is associated with volume overload. In this case, hypernatremia results from a grossly elevated Na intake associated with limited access to water. One example is the excessive administration of hypertonic NaHCO₃ during treatment of lactic acidosis. Hypernatremia can also be caused by the administration of hypertonic saline or incorrectly formulated hyperalimentation.

**Hypernatremia in the elderly:** Hypernatremia is common among the elderly, particularly postoperative patients and those receiving tube feedings or parenteral nutrition. Other contributing factors may include the following:

[Table 97-6. Principal Causes of Hypernatremia]

- Dependence on others to obtain water
- Impaired thirst mechanism
- Impaired renal concentrating capacity (due to diuretics, impaired ADH release, or nephron loss accompanying aging or other renal disease)
- Impaired angiotensin II production (which may contribute directly to the impaired thirst mechanism)

**Symptoms and Signs**

The major symptom of hypernatremia is thirst. The absence of thirst in conscious patients with hypernatremia suggests an impaired thirst mechanism. Patients with difficulty communicating may be unable to express thirst or obtain access to water.

The major signs of hypernatremia result from CNS dysfunction due to brain cell shrinkage. Confusion, neuromuscular excitability, hyperreflexia, seizures, or coma may result; cerebrovascular damage with subcortical or subarachnoid hemorrhage and venous thromboses are common among patients who died from severe hypernatremia.

In chronic hypernatremia, osmotically active substances occur in CNS cells (idiogenic osmoles) and increase intracellular osmolality. Therefore, the degree of brain cell dehydration and resultant CNS symptoms are less severe in chronic than in acute hypernatremia.

When hypernatremia occurs with abnormal total body Na, the typical symptoms of volume depletion or overload are present (see Volume Depletion on p. 822 and Volume Overload on p. 823). A large volume of hypotonic urine is characteristically excreted in patients with renal concentrating defects. When losses are extrarenal, the route of water loss is often evident (eg, vomiting, diarrhea, excessive sweating), and
the urinary Na concentration is low.

**Diagnosis**

- Serum Na

The diagnosis is clinical and by measuring serum Na. In patients who do not respond to simple rehydration or in whom hypernatremia recurs despite adequate access to water, further diagnostic testing is warranted. Determination of the underlying disorder requires assessment of urine volume and osmolality, particularly after water deprivation.

In patients with increased urine output, a water deprivation test (see p. 773) is occasionally used to differentiate among several polyuric states, such as central and nephrogenic diabetes insipidus.

**Treatment**

- Replacement of intravascular volume and of free water

Replacement of intravascular volume and of free water is the main goal of treatment. Oral hydration is effective in conscious patients without significant GI dysfunction. In severe hypernatremia or in patients unable to drink because of continued vomiting or mental status changes, IV hydration is preferred. Hypernatremia that lasts < 24 h should be corrected within 24 h. However, hypernatremia that is chronic or of unknown duration should be corrected over 48 h, and the serum osmolality should be lowered at a rate of no faster than 2 mOsm/L/h to avoid cerebral edema caused by excess brain solute. The amount of water (in liters) necessary to replace existing deficits may be estimated by the following formula:

\[
\text{Free water deficit} = \text{TBW} \times \frac{\text{serum Na}}{140} - 1
\]

where TBW is in liters and is estimated by multiplying weight in kilograms by 0.6; serum Na is in mEq/L. This formula assumes constant total body Na content. In patients with hypernatremia and depletion of total body Na content (ie, who have volume depletion), the free water deficit is greater than that estimated by the formula.

In patients with hypernatremia and ECF volume overload (excess total body Na content), the free water deficit can be replaced with 5% D/W, which can be supplemented with a loop diuretic. However, too-rapid infusion of 5% D/W may cause glycosuria, thereby increasing salt-free water excretion and hypertonicity, especially in patients with diabetes mellitus. Other electrolytes, including serum K, should be monitored and should be replaced as needed.

In patients with hypernatremia and euvolemia, free water can be replaced using either 5% D/W or 0.45% saline.

Treatment of patients with central diabetes insipidus is discussed on p. 774. Acquired nephrogenic diabetes insipidus is discussed on p. 2424.

In patients with hypernatremia and hypovolemia, particularly in patients with diabetes with nonketotic hyperglycemic coma, 0.45% saline can be given as an alternative to a combination of 0.9% normal saline and 5% D/W to replenish Na and free water. Alternatively, ECF volume and free water can be replaced separately, using the formula given previously to estimate the free water deficit. When severe acidosis (pH < 7.10) is present, NaHCO₃ solution can be added to 5% D/W or 0.45% saline, as long as the final solution remains hypotonic.

**Disorders of Potassium Concentration**

K is the most abundant intracellular cation, but only about 2% of total body K is extracellular. Because most intracellular K is contained within muscle cells, total body K is roughly proportional to lean body mass. An average 70-kg adult has about 3500 mEq of K.

K is a major determinant of intracellular osmolality. The ratio between ICF and ECF K concentrations
K is a major determinant of intracellular osmolality. The ratio between ICF and ECF K concentrations strongly influences cell membrane polarization, which in turn influences important cell processes, such as the conduction of nerve impulses and muscle (including myocardial) cell contraction. Thus, relatively small alterations in serum K concentration can have significant clinical manifestations.

In the absence of factors that shift K in or out of cells (see p. 832), the serum K concentration correlates closely with total body K content. Once intracellular and extracellular concentrations are stable, a decrease in serum K concentration of about 1 mEq/L indicates a total K deficit of about 200 to 400 mEq. Patients with K < 3 mEq/L typically have a significant K deficit.

K shifts: Factors that shift K in or out of cells include the following:

• Insulin concentrations
• β-Adrenergic activity
• Acid-base status

Insulin moves K into cells; high concentrations of insulin thus lower serum K concentration. Low insulin concentrations, as in diabetic ketoacidosis, cause K to move out of cells, thus raising serum K, sometimes even in the presence of total body K deficiency.

β-Adrenergic agonists, especially selective β2-agonists, move K into cells, whereas β-blockade and α-agonists promote movement of K out of cells.

Acute metabolic acidosis causes K to move out of cells, whereas acute metabolic alkalosis causes K to move into cells. However, changes in serum HCO₃⁻ concentration may be more important than changes in pH; acidosis caused by accumulation of mineral acids (nonanion gap, hyperchloremic acidosis) is more likely to elevate serum K. In contrast, metabolic acidosis due to accumulation of organic acids (increased anion gap acidosis) is not associated with hyperkalemia. Thus, the hyperkalemia common in diabetic ketoacidosis results more from insulin deficiency than from acidosis. Acute respiratory acidosis and alkalosis affect serum K concentration less than metabolic acidosis and alkalosis. Nonetheless, serum K concentration should always be interpreted in the context of the serum pH (and HCO₃⁻ concentration).

K metabolism: Dietary K intake normally varies between 40 and 150 mEq/day. In the steady state, fecal losses are usually close to 10% of intake. Urinary excretion contributes to K balance.

When K intake is > 150 mEq/day, about 50% of the excess K appears in the urine over the next several hours. Most of the remainder is transferred into the intracellular compartment, thus minimizing the rise in serum K. When elevated K intake continues, aldosterone secretion is stimulated and thus renal K excretion rises. In addition, K absorption from stool appears to be under some regulation and may fall by 50% in chronic K excess.

When K intake falls, intracellular K again serves to buffer wide swings in serum K concentration. Renal K conservation develops relatively slowly in response to decreases in dietary K and is far less efficient than the kidneys' ability to conserve Na. Thus, K depletion is a frequent clinical problem. Urinary K excretion of 10 mEq/day represents near-maximal renal K conservation and implies significant K depletion.

Acute acidosis impairs K excretion, whereas chronic acidosis and acute alkalosis can promote K excretion. Increased delivery of Na to the distal nephrons, as occurs with high Na intake or loop diuretic therapy, promotes K excretion.

False K concentrations: Pseudohypokalemia, or falsely low serum K, occasionally occurs in patients with chronic myelocytic leukemia with a WBC count > 10⁵/μL when the specimen remains at room temperature before being processed because of uptake of serum K by abnormal leukocytes in the sample. It is prevented by prompt separation of plasma or serum in blood samples.

Pseudohyperkalemia, or falsely elevated serum K, is more common, typically occurring due to hemolysis.
and release of intracellular K. To prevent false results, phlebotomy personnel should not rapidly aspirate blood through a narrow-gauge needle or excessively agitate blood samples. Pseudohyperkalemia can also result from platelet count > 400,000/μL due to release of K from platelets during clotting. In cases of pseudohyperkalemia, the plasma K (unclotted blood), as opposed to serum K, is normal.

Hypokalemia

Hypokalemia is serum K concentration < 3.5 mEq/L caused by a deficit in total body K stores or abnormal movement of K into cells. The most common causes are excess losses from the kidneys or GI tract. Clinical features include muscle weakness and polyuria; cardiac hyperexcitability may occur with severe hypokalemia. Diagnosis is by serum measurement. Treatment is giving K and managing the cause.

Etiology

Hypokalemia can be caused by decreased intake of K but is usually caused by excessive losses of K in the urine or from the GI tract.

GI tract losses: Abnormal GI K losses occur in all of the following:

- Chronic diarrhea, including chronic laxative abuse and bowel diversion
- Clay (bentonite) ingestion, which binds K and greatly decreases absorption
- Vomiting
- Protracted gastric suction (which removes volume and HCl, causing the kidneys to excrete HCO₃⁻ and, to electrically balance lost HCO₃⁻, K)
- Rarely, villous adenoma of the colon, which causes massive K secretion

GI K losses may be compounded by concomitant renal K losses due to metabolic alkalosis and stimulation of aldosterone due to volume depletion.

Intracellular shift: The transcellular shift of K into cells may also cause hypokalemia. This shift can occur in any of the following:

- Glycogenesis during TPN or enteral hyperalimentation (stimulating insulin release)
- After administration of insulin
- Stimulation of the sympathetic nervous system, particularly with β₂-agonists (eg, albuterol, terbutaline), which may increase cellular K uptake
- Thyrotoxicosis (occasionally) due to excessive β-sympathetic stimulation (hypokalemic thyrotoxic periodic paralysis)
- Familial periodic paralysis (see p. 3008), a rare autosomal dominant disorder characterized by transient episodes of profound hypokalemia thought to be due to sudden abnormal shifts of K into cells. Episodes frequently involve varying degrees of paralysis. They are typically precipitated by a large carbohydrate meal or strenuous exercise.

Renal losses: Various disorders can increase renal K excretion. Excess mineralocorticoid effect can directly increase K secretion by the distal nephrons and occurs in any of the following:

- Adrenal steroid excess that is due to Cushing's syndrome, primary hyperaldosteronism, rare renin-secreting tumors, glucocorticoid-remediable aldosteronism (a rare inherited disorder involving abnormal
aldosterone metabolism), and congenital adrenal hyperplasia.

• Ingestion of substances such as glycyrrhizin (present in natural licorice and used in the manufacture of chewing tobacco), which inhibits the enzyme 11\(\beta\)-hydroxysteroid dehydrogenase (11\(\beta\)-HSDH), preventing the conversion of cortisol, which has some mineralocorticoid activity, to cortisone, which does not, resulting in high circulating concentrations of cortisol and renal K wasting.

• Bartter and Gitelman's syndromes, uncommon genetic disorders characterized by renal K and Na wasting, excessive production of renin and aldosterone, and normotension. Bartter syndrome (see also p. 2988) is caused by mutations in a loop diuretic-sensitive ion transport mechanism in the loop of Henle. Gitelman's syndrome is caused by loss of function mutations in a thiazide-sensitive ion transport mechanism in the distal nephron.

Liddle syndrome (see also p. 2423) is a rare autosomal dominant disorder characterized by severe hypertension and hypokalemia. Liddle syndrome is caused by unrestrained Na reabsorption in the distal nephron due to one of several mutations found in genes encoding for epithelial Na channel subunits. Inappropriately high reabsorption of Na results in both hypertension and renal K wasting.

Renal K wasting can also be caused by numerous congenital and acquired renal tubular diseases, such as the renal tubular acidoses and Fanconi syndrome, an unusual syndrome resulting in renal wasting of K, glucose, phosphate, uric acid, and amino acids.

Hypomagnesemia is a common correlate of hypokalemia. Much of this is attributable to common underlying causes (ie, diuretics, diarrhea), but hypomagnesemia itself may also result in increased renal K losses.

**Drugs:** Diuretics are by far the most commonly used drugs that cause hypokalemia. K-wasting diuretics that block Na reabsorption proximal to the distal nephron include

• Thiazides
• Loop diuretics
• Osmotic diuretics

By inducing diarrhea, laxatives, especially when abused, can cause hypokalemia. Surreptitious diuretic or laxative abuse or both is a frequent cause of persistent hypokalemia, particularly among patients preoccupied with weight loss and among health care practitioners with access to prescription drugs.

Other drugs that can cause hypokalemia include

• Amphotericin B
• Antipseudomonal penicillins (eg, carbenicillin)
• Penicillin in high doses
• Theophylline intoxication (both acute and chronic)

**Symptoms and Signs**

Mild hypokalemia (serum K 3 to 3.5 mEq/L) rarely causes symptoms. Serum K < 3 mEq/L generally causes muscle weakness and may lead to paralysis and respiratory failure. Other muscular dysfunction includes cramping, fasciculations, paralytic ileus, hypoventilation, hypotension, tetany, and rhabdomyolysis. Persistent hypokalemia can impair renal concentrating ability, causing polyuria with secondary polydipsia.

**Diagnosis**
• Serum K measurement

• ECG

• When the mechanism not evident clinically, 24-h urinary K excretion and serum Mg concentration

Hypokalemia (serum K < 3.5 mEq/L) may be found on routine serum electrolyte measurement. It should be suspected in patients with typical changes on an ECG or who have muscular symptoms and risk factors and confirmed by blood testing.

**ECG:** ECG should be done on patients with hypokalemia. Cardiac effects of hypokalemia are usually minimal until serum K concentrations are < 3 mEq/L. Hypokalemia causes sagging of the ST segment, depression of the T wave, and elevation of the U wave. With marked hypokalemia, the T wave becomes progressively smaller and the U wave becomes increasingly larger. Sometimes, a flat or positive T wave may be confused with QT prolongation (see Fig. 97-2). Hypokalemia may cause premature ventricular and atrial contractions, ventricular and atrial tachyarrhythmias, and 2nd- or 3rd-degree atrioventricular block. Such arrhythmias become more severe with increasingly severe hypokalemia; eventually, ventricular fibrillation may occur. Patients with significant preexisting heart disease and patients receiving digoxin are at risk of cardiac conduction abnormalities even from mild hypokalemia.

**Diagnosis of cause:** The cause is usually apparent by history (particularly the drug history); when it is not, further investigation is warranted. After acidosis and other causes of intracellular K shift (increased β-adrenergic effect, hyperinsulinemia) have been eliminated, 24-h urinary K and serum Mg concentrations are measured. In hypokalemia, K secretion is normally < 15 mEq/L. Extrarenal (GI) K loss or decreased K ingestion is suspected in chronic unexplained hypokalemia when renal K secretion is < 15 mEq/L. Secretion of > 15 mEq/L suggests a renal cause for K loss. Unexplained hypokalemia with increased renal K secretion and hypertension suggests an aldosterone-secreting tumor or Liddle syndrome. Unexplained hypokalemia with increased renal K loss and normal BP suggests Bartter or Gitelman’s syndrome, but hypomagnesemia, surreptitious vomiting, and diuretic abuse are more common and should also be considered.

**Treatment**

• Oral K supplements

• IV K supplements for severe hyperkalemia or ongoing K losses

Many oral K supplements are available. Because high single doses can cause GI irritation and occasional bleeding, deficits are usually replaced in divided doses. Liquid KCl given orally elevates concentrations within 1 to 2 h but has a bitter taste and is tolerated particularly poorly in doses > 25 to 50 mEq. Wax-impregnated KCl preparations are safe and better tolerated. GI bleeding may be even less common with microencapsulated KCl preparations. Several of these preparations contain 8 or 10 mEq/capsule. Because a decrease in serum K of 1 mEq/L correlates with about a 200- to 400-mEq deficit in total body K stores, total deficit can be estimated and replaced over a number of days at 20 to 80 mEq/day.

When hypokalemia is severe (eg, with ECG changes or severe symptoms), is unresponsive to oral therapy, or occurs in hospitalized patients who are taking digitalis or who have significant heart disease or ongoing losses, K must be replaced IV. Because K solutions can irritate peripheral veins, the concentration should not exceed 40 mEq/L. The rate of correction of hypokalemia is limited because of the lag in K movement into cells. **Routine infusion rates should not exceed 10 mEq/h.** In hypokalemic-induced arrhythmia, IV KCl must be given more rapidly, usually through a central vein or using multiple peripheral veins simultaneously. Infusion of 40 mEq KCl/h can be undertaken but only with continuous cardiac monitoring and hourly serum K determinations. Glucose solutions are avoided because elevation...
in the serum insulin concentrations could result in transient worsening of hypokalemia.

Even when K deficits are severe, it is rarely necessary to give > 100 to 120 mEq of K in a 24-h period unless K loss continues. In K deficit with high serum K concentration, as in diabetic ketoacidosis, IV K is deferred until the serum K starts to fall. When hypokalemia occurs with hypomagnesemia, both the K and Mg deficiencies must be corrected to stop ongoing renal K wasting (see Hypomagnesemia on p. 852).

**Prevention**

Routine K replacement is not necessary in most patients receiving diuretics. However, serum K should be monitored during diuretic use when risk of hyperkalemia or of its complications is high. Risk is high in:

- Patients with decreased left ventricular function
- Patients taking digoxin
- Patients with diabetes (in whom insulin concentrations can fluctuate)
- Patients with asthma who are taking β2-agonists

Triamterene 100 mg po once/day or spironolactone 25 mg po qid does not increase K excretion and may be useful in patients who become hypokalemic but must use diuretics. When hypokalemia develops, K supplementation, usually with oral KCl, is indicated.

**Hyperkalemia**

Hyperkalemia is serum K concentration > 5.5 mEq/L resulting from excess total body K stores or abnormal movement of K out of cells. There are usually several simultaneous contributing factors, including increased K intake, drugs that impair renal K excretion, and acute or chronic kidney disease. It can also occur in metabolic acidosis as in diabetic ketoacidosis. Clinical manifestations are generally neuromuscular, resulting in muscle weakness and cardiac toxicity that, when severe, can degenerate to ventricular fibrillation or asystole. Diagnosis is by measuring serum K. Treatment may involve decreasing K intake, adjusting drugs, giving a cation exchange resin and, in emergencies, Ca gluconate, insulin, and dialysis.

**Etiology**

The most common cause of increased serum K concentration is probably pseudohyperkalemia caused by hemolysis of RBCs in the blood sample. Normal kidneys eventually excrete K loads, so sustained, nonartifactual hyperkalemia usually implies diminished renal K excretion. However, other factors usually contribute. They can include increased K intake, increased K release from cells, or both (see Table 97-7). When sufficient KCl is ingested or given parenterally, severe hyperkalemia may result even with normal renal function but is usually temporary.

Hyperkalemia due to total body K excess is particularly common in oliguric states (especially acute renal failure) and with rhabdomyolysis, burns, bleeding into soft tissue or the GI tract, and adrenal insufficiency. In chronic renal failure, hyperkalemia is uncommon until the GFR falls to < 10 to 15 mL/min unless dietary or IV K intake is excessive.

**Symptoms and Signs**

Although flaccid paralysis occasionally occurs, hyperkalemia is usually asymptomatic until cardiac toxicity develops.

In the rare disorder hyperkalemic familial periodic paralysis, weakness frequently develops during attacks and can progress to frank paralysis.

**Diagnosis**
Hyperkalemia (serum K > 5.5 mEq/L) may be found on routine serum electrolyte measurement. It should be suspected in patients with typical changes on an ECG or patients at high risk, such as those with renal failure, advanced heart failure treated with ACE inhibitors and K-sparing diuretics, or urinary obstruction.

**ECG:** ECG should be done on patients with hyperkalemia. ECG changes (see Fig. 97-2) are frequently visible when serum K is > 5.5 mEq/L. Slowing of conduction characterized by an increased PR interval and shortening of the QT interval as well as tall, symmetric, peaked T waves are visible initially. K > 6.5 mEq/L causes further slowing of conduction with widening of the QRS interval, disappearance of the P wave, and nodal and escape ventricular arrhythmias. Finally, the QRS complex degenerates into a sine wave pattern, and ventricular fibrillation or asystole ensues.

**Diagnosis of the cause:** Pseudohyperkalemia should be considered in patients without risk factors or ECG abnormalities. Hemolysis may be reported by the laboratory. When pseudohyperkalemia is suspected, K concentration should be repeated, taking measures to avoid hemolysis of the sample.

Diagnosis of the cause of hyperkalemia requires a detailed history, including a review of drugs, a physical examination with emphasis on volume status, and measurement of electrolytes, BUN, and creatinine. In cases in which renal failure is present, additional tests, including renal ultrasonography to exclude obstruction, are needed (see p. 2438).

**Treatment**

- Treatment of the cause
- For mild hyperkalemia, Na polystyrene sulfonate

For moderate or severe hyperkalemia, IV insulin and glucose, an IV Ca solution, possibly an inhaled β2-agonist, and usually hemodialysis

**Mild hyperkalemia:** Patients with serum K < 6 mEq/L and no ECG abnormalities may respond to diminished K intake or stopping K-elevating drugs. The addition of a loop diuretic enhances renal K excretion as long as volume depletion is not present.

Na polystyrene sulfonate in sorbitol can be given (15 to 30 g in 30 to 70 mL of 70% sorbitol po q 4 to 6 h). It acts as a cation exchange resin and removes K through the GI mucosa. Sorbitol is administered with the resin to ensure passage through the GI tract. Patients unable to take drugs orally because of nausea or other reasons may be given similar doses by enema. Enemas are not as effective at lowering K in patients with ileus. Enemas should not be used if acute abdomen is suspected. About 1 mEq of K is removed per gram of resin given. Resin therapy is slow and often fails to lower serum K significantly in hypercatabolic states. Because Na is exchanged for K when Na polystyrene sulfonate is used, Na overload may occur, particularly in oliguric patients with preexisting volume overload.

**Moderate to severe hyperkalemia:** Serum K between 6 and 6.5 mEq/L needs prompt attention, but the actual treatment depends on the clinical situation. If no ECG changes are present and renal function is intact, maneuvers described previously are usually effective. Follow-up serum K levels are needed to ensure that the hyperkalemia has been successfully treated. If serum K is > 6.5 mEq/L, more aggressive
therapy is required. Administration of regular insulin 5 to 10 units IV is followed immediately by or
administered simultaneously with rapid infusion of 50 mL 50% glucose. Infusion of 10% D/W should
follow at 50 mL/h to prevent hypoglycemia. The effect on serum K peaks in 1 h and lasts for several
hours.

If ECG changes include the loss of P-wave or widening of the QRS complex, treatment with IV Ca as well
as insulin and glucose is indicated; 10 to 20 mL 10% Ca gluconate (or 5 to 10 mL 22% Ca gluceptate) is
given IV over 5 to 10 min. Ca antagonizes the effect of hyperkalemia on cardiac muscle. Ca should be
given with caution to patients taking digoxin because of the risk of precipitating hypokalemia-related
arrhythmias. If the ECG shows a sine wave pattern or asystole, Ca gluconate may be given more rapidly
(5 to 10 mL IV over 2 min). CaCl can also be used but can be irritating to peripheral veins and cause
tissue necrosis if extravasated. CaCl should be given only through a correctly positioned central venous
catheter. The benefits of Ca occur within minutes but last only 20 to 30 min. Ca infusion is a temporizing
measure while awaiting the effects of other treatments or initiation of hemodialysis and may need to be
repeated.

A high-dose $\beta_2$-agonist, such as albuterol 10 to 20 mg inhaled over 10 min (5 mg/mL concentration), can
lower serum K by 0.5 to 1.5 mEq/L and may be a helpful adjunct. The peak effect occurs in 90 min.
However, $\beta_2$-agonists are contraindicated in patients with unstable angina and acute MI.

Administration of IV NaHCO$_3$ is controversial. It may lower serum K over several hours. Reduction may
result from alkalinization or the hypertonicity due to the concentrated Na in the preparation. The
hypertonic Na that it contains may be harmful for dialysis patients who also may have volume overload.
When given, the usual dose is 45 mEq (1 ampule of 7.5% NaHCO$_3$) infused over 5 min and repeated in
30 min. HCO$_3$ therapy has little effect when used by itself in patients with severe renal insufficiency
unless acidemia is also present.

In addition to strategies for lowering K by shifting it into cells, maneuvers to remove K from the body
should also be done early in the treatment of severe or symptomatic hyperkalemia. K can be removed via
the GI tract by administration of Na polystyrene sulfonate (see p. 836) or by hemodialysis. Hemodialysis
should be instituted promptly after emergency measures in patients with renal failure or when emergency
treatment is ineffective. Dialysis should be considered early in patients with end-stage renal disease and
hyperkalemia because they are at increased risk of progression to more severe hyperkalemia and serious
cardiac arrhythmias. Peritoneal dialysis is relatively inefficient at removing K.

Disorders of Calcium Concentration

Ca is required for the proper functioning of muscle contraction, nerve conduction, hormone release, and
blood coagulation. In addition, proper Ca concentration is required for various other metabolic processes.

Maintenance of body Ca stores depends on

- Dietary Ca intake
- Absorption of Ca from the GI tract
- Renal Ca excretion

In a balanced diet, roughly 1000 mg of Ca is ingested each day and about another 200 mg/day is
secreted into the GI tract in the bile and other GI secretions. Depending on the concentration of
circulating vitamin D, particularly 1,25(OH)$_2$D (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D,
which is converted in the kidney from 25(OH)D, the inactive form), roughly 200 to 400 mg of Ca is
absorbed from the intestine each day. The remaining 800 to 1000 mg appears in the stool. Ca balance is
maintained through renal Ca excretion averaging 200 mg/day.

Both extracellular and intracellular Ca concentrations are tightly regulated by bidirectional Ca transport
across the plasma membrane of cells and intracellular organelles, such as the endoplasmic reticulum, the
sarcoplasmic reticulum of muscle cells, and the mitochondria. Cytosolic ionized Ca is maintained within the micromolar range (< 1/1000 of the serum concentration). Ionized Ca acts as an intracellular 2nd messenger; it is involved in skeletal muscle contraction, excitation-contraction coupling in cardiac and smooth muscle, and activation of protein kinases and enzyme phosphorylation. Ca is also involved in the action of other intracellular messengers, such as cAMP and inositol 1,4,5-triphosphate, and thus mediates the cellular response to numerous hormones, including epinephrine, glucagon, ADH (vasopressin), secretin, and cholecystokinin. Parathyroid hormone (PTH) increases urinary cAMP.

Despite its important intracellular roles, about 99% of body Ca is in bone, mainly as hydroxyapatite crystals. About 1% of bone Ca is freely exchangeable with the ECF and, therefore, is available for buffering changes in Ca balance.

Normal total serum Ca concentration ranges from 8.8 to 10.4 mg/dL (2.20 to 2.60 mmol/L). About 40% of the total blood Ca is bound to plasma proteins, primarily albumin. The remaining 60% includes ionized Ca plus Ca complexed with phosphate (PO$_4$) and citrate. Total Ca (ie, protein-bound, complexed, and ionized Ca) is usually what is determined by clinical laboratory measurement. Ideally, ionized or free Ca should be determined because it is the physiologically active form of Ca in plasma; this determination, because of its technical difficulty, is usually restricted to patients in whom significant alteration of protein binding of serum Ca is suspected. Ionized Ca is generally assumed to be about 50% of the total serum Ca.

**Regulation of Calcium Metabolism**

The metabolism of Ca and of PO$_4$ (see p. 850) is intimately related. The regulation of both Ca and PO$_4$ balance is greatly influenced by concentrations of circulating PTH, vitamin D, and, to a lesser extent, calcitonin. Ca and inorganic PO$_4$ concentrations are also linked by their ability to chemically react to form CaPO$_4$. The product of concentrations of Ca and PO$_4$ (in mEq/L) is estimated to be 60 normally; when the product exceeds 70, precipitation of CaPO$_4$ crystals in soft tissue is much more likely. Calcification of vascular tissue accelerates arteriosclerotic vascular disease and may occur when the Ca × PO$_4$ product is even lower (> 55), especially in patients with chronic kidney disease.

PTH is secreted by the parathyroid glands. It has several actions, but perhaps the most important is to defend against hypocalcemia. Parathyroid cells sense decreases in serum Ca and, in response, release preformed PTH into the circulation. PTH increases serum Ca within minutes by increasing renal and intestinal absorption of Ca and by rapidly mobilizing Ca and PO$_4$ from bone (bone resorption). Renal Ca excretion generally parallels Na excretion and is influenced by many of the same factors that govern Na transport in the proximal tubule. However, PTH enhances distal tubular Ca reabsorption independently of Na. PTH also decreases renal PO$_4$ reabsorption and thus increases renal PO$_4$ losses. Renal PO$_4$ loss prevents the solubility product of Ca and PO$_4$ from being exceeded in plasma as Ca concentrations rise in response to PTH. PTH also increases serum Ca by stimulating conversion of vitamin D (see p. 41) to its most active form, calcitriol. This form of vitamin D increases the percentage of dietary Ca absorbed by the intestine. Despite increased Ca absorption, long-term increases in PTH secretion generally result in further bone resorption by inhibiting osteoblastic function and promoting osteoclastic activity. PTH and vitamin D both function as important regulators of bone growth and bone remodeling (see p. 41).

Radioimmunoassays for the intact PTH molecule are still the recommended way to test for PTH. Second-generation assays for intact PTH are available. These tests measure bioavailable PTH or complete PTH. They give values equal to 50 to 60% of those obtained with the older assay. Usefulness of the newer assays is under investigation. Sometimes total or nephrogenous cAMP excretion is measured in diagnosis of pseudohypoparathyroidism.

Calcitonin is secreted by the thyroid parafollicular cells (C cells). Calcitonin tends to lower serum Ca concentration by enhancing cellular uptake, renal excretion, and bone formation. The effects of calcitonin on bone metabolism are much weaker than those of either PTH or vitamin D.

**Hypocalcemia**
Hypocalcemia in neonates is discussed on p. 2794.

Hypocalcemia is total serum Ca concentration < 8.8 mg/dL (< 2.20 mmol/L) in the presence of normal plasma protein concentrations or a serum ionized Ca concentration < 4.7 mg/dL (< 1.17 mmol/L). Causes include hypoparathyroidism, vitamin D deficiency, and renal disease. Manifestations include paresthesias, tetany, and, when severe, seizures, encephalopathy, and heart failure. Diagnosis involves measurement of serum Ca with adjustment for serum albumin concentration. Treatment is administration of Ca, sometimes with vitamin D.

Etiology

Hypocalcemia has a number of causes, including

• Hypoparathyroidism
• Pseudohypoparathyroidism
• Vitamin D deficiency and dependency
• Renal disease

Hypoparathyroidism: Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia and often causes chronic tetany. Hypoparathyroidism results from deficient parathyroid hormone (PTH), which can occur in autoimmune disorders or after the accidental removal of or damage to several parathyroid glands during thyroidectomy. Transient hypoparathyroidism is common after subtotal thyroidectomy, but permanent hypoparathyroidism occurs after < 3% of such thyroidectomies done by experienced surgeons. Manifestations of hypocalcemia usually begin about 24 to 48 h postoperatively but may occur after months or years. PTH deficiency is more common after radical thyroidectomy for cancer or as the result of surgery on the parathyroid glands (subtotal or total parathyroidectomy). Risk factors for severe hypocalcemia after subtotal parathyroidectomy include

• Severe preoperative hypercalcemia
• Removal of a large adenoma
• Elevated alkaline phosphatase
• Chronic kidney disease

Idiopathic hypoparathyroidism is an uncommon sporadic or inherited condition in which the parathyroid glands are absent or atrophied. It manifests in childhood. The parathyroid glands are occasionally absent and thymic aplasia and abnormalities of the arteries arising from the brachial arches (DiGeorge syndrome) are present. Other inherited forms include Addison's disease, autoimmune hypoparathyroidism associated with mucocutaneous candidiasis, and X-linked recessive idiopathic hypoparathyroidism.

Pseudohypoparathyroidism: Pseudohypoparathyroidism is an uncommon group of disorders characterized not by hormone deficiency but by target organ resistance to PTH. Complex genetic transmission of these disorders occurs.

Patients with type 1a pseudohypoparathyroidism (Albright's hereditary osteodystrophy) have a mutation in the stimulatory Gs-α1 protein of the adenylyl cyclase complex (GNAS1). The result is failure of normal renal phosphaturic response or increase in urinary cAMP to PTH. Patients are usually hypocalcemic as a result of hyperphosphatemia. Secondary hyperparathyroidism and hyperparathyroid bone disease can occur. Associated abnormalities include short stature, round facies, intellectual disability with calcification of the basal ganglia, shortened metacarpal and metatarsal bones, mild hypothyroidism, and other subtle endocrine abnormalities. Because only the maternal allele for GNAS1 is expressed in the kidneys, patients whose abnormal gene is paternal, although they have many of the somatic features of the disease, do not have hypocalcemia, hyperphosphatemia, or secondary hyperparathyroidism; this
condition is sometimes described as pseudopseudohypoparathyroidism.

Less is known about type Ib pseudohypoparathyroidism. Affected patients have hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism but do not have the other associated abnormalities.

Type II pseudohypoparathyroidism is even less common than type I. In affected patients, exogenous PTH raises the urinary cAMP normally but does not raise serum Ca or urinary phosphate (PO$_4$). An intracellular resistance to cAMP has been proposed.

**Vitamin D deficiency and dependency:** Vitamin D deficiency and dependency are discussed in full elsewhere (see p. 41). Vitamin D is ingested in foods naturally high in vitamin D or fortified with it. It is also formed in the skin in response to sunlight. Vitamin D deficiency may result from inadequate dietary intake or decreased absorption due to hepatobiliary disease or intestinal malabsorption. It can also result from alterations in vitamin D metabolism as occur with certain drugs (eg, phenytoin, phenobarbital, rifampin) or decreased formation in the skin due to lack of exposure to sunlight. Aging also decreases skin synthetic capacity. Decreased skin synthesis is an important cause of acquired vitamin D deficiency among people who spend a great deal of time indoors, who live in high northern or southern latitudes, and who wear clothing that covers them completely. Accordingly, subclinical vitamin D deficiency is fairly common, especially during winter months in temperate climates among the elderly. The institutionalized elderly are at particular risk because of decreased skin synthetic capacity, undernutrition, and lack of sun exposure. In fact, most people with deficiency have both decreased skin synthesis and dietary deficiency (see also p. 41).

Type I vitamin D-dependent rickets (pseudovitamin D-deficiency rickets) is an autosomal recessive disorder involving a mutation in the gene encoding the 1-α-hydroxylase enzyme. Normally expressed in the kidney, 1-α-hydroxylase is needed to convert inactive vitamin D to the active form calcitriol.

In type II vitamin D-dependent rickets, target organs cannot respond to calcitriol. Vitamin D deficiency, hypocalcemia, and severe hypophosphatemia occur. Muscle weakness, pain, and typical bone deformities can occur.

**Renal disease:** Renal tubular disease, including acquired proximal renal tubular acidosis due to nephrotoxins (eg, heavy metals) and distal renal tubular acidosis, can cause severe hypocalcemia due to abnormal renal loss of Ca and decreased renal conversion to 1,25(OH)$_2$D. Cadmium, in particular, causes hypocalcemia by injuring proximal tubular cells and interfering with vitamin D conversion.

Renal failure can result in hypocalcemia due to diminished formation of 1,25(OH)$_2$D from direct renal cell damage as well as suppression of 1-α-hydroxylase by hyperphosphatemia.

**Other causes:** Other causes of hypocalcemia include

- Mg depletion (can cause relative PTH deficiency and end-organ resistance to PTH action, usually when serum Mg concentrations are < 1.0 mg/dL [< 0.5 mmol/L]; Mg repletion increases PTH concentrations and improves renal Ca conservation)

- Acute pancreatitis (when lipolytic products released from the inflamed pancreas chelate Ca)

- Hypoproteinemia (reduces the protein-bound fraction of serum Ca; hypocalcemia due to diminished protein binding is asymptomatic—because ionized Ca is unchanged, this entity has been termed factitious hypocalcemia)

- Hungry bone syndrome (persistent hypocalcemia and hypophosphatemia occurring after surgical or medical correction of moderate to severe hyperparathyroidism in patients in whom serum Ca levels had been supported by high bone turnover induced by greatly elevated PTH—hungry bone syndrome has been described after parathyroidectomy, after renal transplantation, and rarely in patients with end-stage renal disease treated with calcimimetics)
Septic shock (due to suppression of PTH release and decreased conversion of 25(OH)D to 1,25(OH)₂D)

Hyperphosphatemia (causes hypocalcemia by poorly understood mechanisms; patients with renal failure and subsequent PO₄ retention are particularly prone)

Drugs including anticonvulsants (eg, phenytoin, phenobarbital) and rifampin, which alter vitamin D metabolism, and drugs generally used to treat hypercalcemia (see p. 847)

Transfusion of > 10 units of citrate-anticoagulated blood and use of radiocontrast agents containing the divalent ion-chelating agent ethylenediaminetetraacetate (can decrease the concentration of bioavailable ionized Ca while total serum Ca concentrations remain unchanged)

Infusion of gadolinium (may spuriously lower Ca concentration)

Although excessive secretion of calcitonin might be expected to cause hypocalcemia, low serum Ca concentrations rarely occur in patients with large amounts of circulating calcitonin due to medullary carcinoma of the thyroid.

Symptoms and Signs

Hypocalcemia is frequently asymptomatic. The presence of hypoparathyroidism is often suggested by the clinical manifestations of the underlying disorder (eg, short stature, round facies, intellectual disability, basal ganglia calcification in type Ia pseudohypoparathyroidism).

Major clinical manifestations of hypocalcemia are due to disturbances in cellular membrane potential, resulting in neuromuscular irritability.

Neurologic manifestations: Muscle cramps involving the back and legs are common. Insidious hypocalcemia may cause mild, diffuse encephalopathy and should be suspected in patients with unexplained dementia, depression, or psychosis. Papilledema occasionally occurs. Severe hypocalcemia with serum Ca < 7 mg/dL (< 1.75 mmol/L) may cause hyperreflexia, tetany, laryngospasm, or generalized seizures.

Tetany characteristically results from severe hypocalcemia but can result from reduction in the ionized fraction of serum Ca without marked hypocalcemia, as occurs in severe alkalosis. Tetany is characterized by the following:

- Sensory symptoms consisting of paresthesias of the lips, tongue, fingers, and feet
- Carpopedal spasm, which may be prolonged and painful
- Generalized muscle aching
- Spasm of facial musculature

Tetany may be overt with spontaneous symptoms or latent and requiring provocative tests to elicit. Latent tetany generally occurs at less severely decreased serum Ca concentrations: 7 to 8 mg/dL (1.75 to 2.20 mmol/L).

Chvostek's and Trousseau's signs are easily elicited at the bedside to identify latent tetany. Chvostek's sign is an involuntary twitching of the facial muscles elicited by a light tapping of the facial nerve just anterior to the exterior auditory meatus. It is present in ≤ 10% of healthy people and in most people with acute hypocalcemia but is often absent in chronic hypocalcemia. Trousseau's sign is the precipitation of carpopedal spasm by reduction of the blood supply to the hand with a tourniquet or BP cuff inflated to 20 mm Hg above systolic BP applied to the forearm for 3 min. Trousseau's sign also occurs in alkalosis, hypomagnesemia, hypokalemia, and hyperkalemia and in about 6% of people with no identifiable
electrolyte disturbance.

Other manifestations: Many other abnormalities may occur with chronic hypocalcemia, such as dry and scaly skin, brittle nails, and coarse hair. *Candida* infections occasionally occur in hypocalcemia but most commonly occur in patients with idiopathic hypoparathyroidism. Cataracts occasionally occur with long-standing hypocalcemia and are not reversible by correction of serum Ca.

Diagnosis

- Estimation or measurement of ionized Ca

- Sometimes further testing with Mg, PTH, PO₄, alkaline phosphatase, and vitamin D concentrations in blood and cAMP and PO₄ concentrations in urine

Hypocalcemia may be suspected in patients with characteristic neurologic manifestations or cardiac arrhythmias but is often found incidentally. Hypocalcemia is diagnosed by a total serum Ca concentration < 8.8 mg/dL (< 2.20 mmol/L). However, because low plasma protein can lower total, but not ionized, serum Ca, ionized Ca should be estimated based on albumin concentration (see Sidebar 97-2). Suspicion of low ionized Ca mandates its direct measurement, despite normal total serum Ca. Hypocalcemic patients should undergo measurement of renal function (eg, BUN, creatinine), serum PO₄, Mg, and alkaline phosphatase.

When no etiology (eg, alkalosis, renal failure, drugs, or massive blood transfusion) is obvious, further testing is needed (see Table 97-8). Additional testing begins with serum concentrations of Mg, PO₄, PTH, alkaline phosphatase, and occasionally vitamin D levels (25(OH)D, and 1,25(OH)₂D). Urinary PO₄ and cAMP concentrations are measured when pseudohypoparathyroidism is suspected.

PTH concentration should be measured as an assay of the intact molecule. Because hypocalcemia is the major stimulus for PTH secretion, PTH should be elevated in hypocalcemia. Thus,

- Low or even low-normal PTH concentrations are inappropriate and suggest hypoparathyroidism.

- An undetectable PTH concentration suggests idiopathic hypoparathyroidism.

- A high PTH concentration suggests pseudohypoparathyroidism or an abnormality of vitamin D metabolism.

Sidebar 97-2 Estimation of Ionized Calcium Concentration

Ionized Ca concentration can be estimated from routine laboratory tests, usually with reasonable accuracy. In hypoalbuminemia, measured serum Ca is often low, mainly reflecting a low concentration of protein-bound Ca, while ionized Ca can be normal. Measured total serum Ca decreases or increases by about 0.8 mg/dL (0.20 mmol/L) for every 1-g/dL decrease or increase in albumin. Thus, an albumin concentration of 2.0 g/dL (normal, 4.0 g/dL) should itself reduce measured serum Ca by 1.6 mg/dL. Similarly, increases in serum proteins, as occur in multiple myeloma, can raise total serum Ca. Acidosis increases ionized Ca by decreasing protein binding, whereas alkalosis decreases ionized Ca.

Hypoparathyroidism is further characterized by high serum PO₄ and normal alkaline phosphatase.

In type I pseudohypoparathyroidism, despite the presence of a high concentration of circulating PTH, urinary cAMP and urinary PO₄ are absent. Provocative testing by injection of parathyroid extract or recombinant human PTH fails to raise serum or urinary cAMP. Patients with type Ia pseudohypoparathyroidism frequently also have skeletal abnormalities, including short stature and shortened 1st, 4th, and 5th metacarpals. Patients with type Ib disease have renal manifestations without
skeletal abnormalities.

In vitamin D deficiency, osteomalacia or rickets may be present, usually with typical skeletal abnormalities on x-ray. Diagnosis of vitamin D deficiency and dependency and measurement of vitamin D concentrations are discussed on p. 42.

Severe hypocalcemia can affect the ECG. It typically shows prolongation of the QTc and ST intervals. Changes in repolarization, such as T-wave peaking or inversion, also occur. ECG may show arrhythmia or heart block occasionally in patients with severe hypocalcemia. However, evaluation of hypocalcemia does not mandate ECG testing.

Treatment

• IV Ca gluconate for tetany

• Oral Ca for postoperative hypoparathyroidism

• Oral Ca and vitamin D for chronic hypocalcemia

[Table 97-8. Typical Laboratory Test Results in Some Disorders Causing Hypocalcemia]

For tetany, Ca gluconate 10 mL of 10% solution IV over 10 min is given. Response can be dramatic but may last for only a few hours. Repeated boluses or a continuous infusion with 20 to 30 mL of 10% Ca gluconate in 1 L of 5% D/W over the next 12 to 24 h may be needed. Infusions of Ca are hazardous in patients receiving digoxin and should be given slowly and with continuous ECG monitoring. When tetany is associated with hypomagnesemia, it may respond transiently to Ca or K administration but is permanently relieved only by repletion of Mg, typically given as a 10% Mg sulfate (MgSO$_4$) solution (1 g/10 mL) IV, followed by oral Mg salts (eg, Mg gluconate 500 to 1000 mg po tid).

In transient hypoparathyroidism after thyroidectomy or partial parathyroidectomy, supplemental oral Ca may be sufficient; 1 to 2 g of elemental Ca/day may be given as Ca gluconate (90 mg elemental Ca/1 g) or Ca carbonate (400 mg elemental Ca/1 g). However, hypocalcemia may be particularly severe and prolonged after subtotal parathyroidectomy, particularly in patients with chronic kidney disease or in patients from whom a large tumor was removed. Prolonged parenteral administration of Ca may be necessary postoperatively; supplementation with as much as 1 g/day of elemental Ca (eg, 111 mL of Ca gluconate, which contains 90 mg elemental Ca/10 mL) may be required for 5 to 10 days before oral Ca and vitamin D are sufficient. Elevated serum alkaline phosphatase in such patients may be a sign of rapid uptake of Ca into bone. The need for large amounts of parenteral Ca usually does not fall until the alkaline phosphatase concentration begins to decrease.

In chronic hypocalcemia, oral Ca and occasionally vitamin D supplements are usually sufficient: 1 to 2 g of elemental Ca/day may be given as Ca gluconate or Ca carbonate. In patients without renal failure, vitamin D is given as a standard oral supplement (eg, cholecalciferol 800 IU once/day). Vitamin D therapy is not effective unless adequate dietary or supplemental Ca and PO$_4$ (see p. 851) are supplied.

For patients with renal failure, calcitriol or another 1,25(OH)$_2$D analog is used because these drugs require no renal metabolic alteration. Patients with hypoparathyroidism have difficulty converting cholecalciferol to its active form and also usually require calcitriol, usually 0.5 to 2 μg po once/day. Pseudohypoparathyroidism can occasionally be managed with oral Ca supplementation alone. When used, calcitriol requires 1 to 3 μg/day.

Vitamin D analogs include dihydrotachysterol (usually given orally at 0.8 to 2.4 once/day for a few days, followed by 0.2 to 1.0 mg once/day) and calcidiol (eg, 4000 to 6000 IU po once/wk). Use of vitamin D analogs, particularly the longer-acting calcidiol, can be complicated by vitamin D toxicity, with severe symptomatic hypercalcemia. Serum Ca concentration should be monitored weekly at first and then at 1- to 3-mo intervals after Ca concentrations have stabilized. The maintenance dose of calcitriol or its analog, dihydrotachysterol, usually decreases with time.
Hypercalcemia

Hypercalcemia is total serum Ca concentration > 10.4 mg/dL (> 2.60 mmol/L) or ionized serum Ca > 5.2 mg/dL (> 1.30 mmol/L). Principal causes include hyperparathyroidism, vitamin D toxicity, and cancer. Clinical features include polyuria, constipation, muscle weakness, confusion, and coma. Diagnosis is by serum ionized Ca and parathyroid hormone concentrations. Treatment to increase Ca excretion and reduce bone resorption of Ca involves saline, Na diuresis, and drugs such as pamidronate.

Etiology

Hypercalcemia usually results from excessive bone resorption. There are many causes of hypercalcemia (see Table 97-9), but the most common are hyperparathyroidism and cancer.

Pathophysiology

**Primary hyperparathyroidism** is a generalized disorder resulting from excessive secretion of parathyroid hormone (PTH) by one or more parathyroid glands. It probably is the most common cause of hypercalcemia, particularly among patients who are not hospitalized. Incidence increases with age and is higher in postmenopausal women. It also occurs in high frequency ≥ 3 decades after neck irradiation. Familial and sporadic forms exist. Familial forms due to parathyroid adenoma occur in patients with other endocrine tumors (see p. 909). Primary hyperparathyroidism causes hypophosphatemia and excessive bone resorption. Although asymptomatic hypercalcemia is the most frequent presentation, nephrolithiasis is also common, particularly when hypercalciuria occurs due to long-standing hypercalcemia. Histologic examination shows a parathyroid adenoma in about 85% of patients with primary hyperparathyroidism, although it is sometimes difficult to distinguish an adenoma from a normal gland. About 15% of cases are due to hyperplasia of ≥ 2 glands. Parathyroid cancer occurs in < 1% of cases.

The syndrome of **familial hypocalciuric hypercalcemia (FHH)** is transmitted as an autosomal dominant trait. Most cases involve an inactivating mutation of the Ca-sensing receptor gene, resulting in higher concentrations of serum Ca being needed to inhibit PTH secretion. Subsequent PTH secretion induces renal phosphate (PO₄) excretion. Persistent hypercalcemia (usually asymptomatic), often from an early age; normal to slightly elevated concentrations of PTH; hypocalciuria; and hypermagnesemia occur. Renal function is normal, and nephrolithiasis is unusual. However, severe pancreatitis occasionally occurs. This syndrome, which is associated with parathyroid hyperplasia, is not relieved by subtotal parathyroidectomy.

**Secondary hyperparathyroidism** occurs most commonly in advanced chronic kidney disease when decreased formation of active vitamin D in the kidneys and other factors lead to hypocalcemia and chronic stimulation of PTH secretion. Hyperphosphatemia that develops in response to chronic kidney disease also contributes. Once established, hypercalcemia or normocalcemia may occur. The sensitivity of the parathyroid to Ca may be diminished because of pronounced glandular hyperplasia and elevation of the Ca set point (ie, the amount of Ca necessary to reduce secretion of PTH).

**Tertiary hyperparathyroidism** results in autonomous hypersecretion of PTH regardless of serum Ca concentration. Tertiary hyperparathyroidism generally occurs in patients with long-standing secondary hyperparathyroidism, as in patients with end-stage renal disease of several years' duration.

**Cancer** is a common cause of hypercalcemia, usually in hospitalized patients. Although there are several mechanisms, elevated serum Ca ultimately occurs as a result of bone resorption. Humoral hypercalcemia of cancer (ie, hypercalcemia with no or minimal bone metastases) occurs most commonly with squamous cell carcinoma, renal cell carcinoma, breast cancer, prostate cancer, and ovarian cancer. Many cases of humoral hypercalcemia of cancer were formerly attributed to ectopic production of PTH. However, some
of these tumors secrete a PTH-related peptide that binds to PTH receptors in both bone and kidney and mimics many of the effects of the hormone, including osteoclastic bone resorption. Hematologic cancers, most often multiple myeloma, but also certain lymphomas and lymphosarcomas, cause hypercalcemia by elaborating a group of cytokines that stimulate osteoclasts to resorb bone, resulting in osteolytic lesions, diffuse osteopenia, or both. Hypercalcemia may result from local elaboration of osteoclast-activating cytokines or prostaglandins, direct bone resorption by the metastatic tumor cells, or both.

**Vitamin D toxicity** can be caused by high concentrations of endogenous 1,25(OH)₂D. Although serum concentrations are low in most patients with solid tumors, patients with lymphoma and T-cell leukemia sometimes have elevated concentrations due to dysregulation of the 1-α-hydroxylase enzyme present in tumor cells. Exogenous vitamin D in pharmacologic doses causes excessive bone resorption as well as increased intestinal Ca absorption, resulting in hypercalcemia and hypercalciuria (see p. 44).

**Granulomatous disorders**, such as sarcoidosis, TB, leprosy, berylliosis, histoplasmosis, and coccidioidomycosis, lead to hypercalcemia and hypercalciuria. In sarcoidosis, hypercalcemia and hypercalciuria seem to be due to unregulated conversion of 25(OH)D to 1,25(OH)₂D, presumably due to expression of the 1-α-hydroxylase enzyme in mononuclear cells within sarcoid granulomas. Similarly, elevated serum concentrations of 1,25(OH)₂D have been reported in hypercalcemic patients with TB and silicosis. Other mechanisms must account for hypercalcemia in some instances, because depressed 1,25(OH)₂D concentrations occur in some patients with hypercalcemia and leprosy.

**Immobilization**, particularly complete prolonged bed rest in patients at risk (see Table 97-9), can result in hypercalcemia due to accelerated bone resorption. Hypercalcemia develops within days to weeks of onset of bed rest. Reversal of hypercalcemia occurs promptly on resumption of weight bearing. Young adults with several bone fractures and people with Paget's disease of bone are particularly prone to hypercalcemia when at bed rest.

**Idiopathic infantile hypercalcemia** (Williams syndrome—see Table 299-2 on p. 3003) is an extremely rare sporadic disorder with dysmorphic facial features, cardiovascular abnormalities, renovascular hypertension, and hypercalcemia. PTH and vitamin D metabolism are normal, but the response of calcitonin to Ca infusion may be abnormal.

In **milk-alkali syndrome**, excessive amounts of Ca and absorbable alkali are ingested, usually during self-treatment with Ca carbonate antacids for dyspepsia or to prevent osteoporosis, resulting in hypercalcemia, metabolic alkalosis, and renal insufficiency. The availability of effective drugs for peptic ulcer disease and osteoporosis has greatly reduced the incidence of this syndrome.

**Symptoms and Signs**

In mild hypercalcemia, many patients are asymptomatic. Clinical manifestations of hypercalcemia include constipation, anorexia, nausea and vomiting, abdominal pain, and ileus. Impairment of the renal concentrating mechanism leads to polyuria, nocturia, and polydipsia. Elevation of serum Ca > 12 mg/dL (> 3.00 mmol/L) can cause emotional lability, confusion, delirium, psychosis, stupor, and coma. Hypercalcemia may cause neuromuscular symptoms, including skeletal muscle weakness. Hypercalciuria with nephrolithiasis is common. Less often, prolonged or severe hypercalcemia causes reversible acute renal failure or irreversible renal damage due to nephrocalcinosis (precipitation of Ca salts within the kidney parenchyma). Peptic ulcers and pancreatitis may occur in patients with hyperparathyroidism for reasons that are not related to hypercalcemia.

Severe hypercalcemia causes a shortened QTc interval on ECG, and arrhythmias may occur, particularly in patients taking digoxin. Hypercalcemia > 18 mg/dL (> 4.50 mmol/L) may cause shock, renal failure, and death.

**Diagnosis**

- Total serum Ca concentration
• Chest x-ray; measurement of electrolytes, BUN, creatinine, ionized Ca, PO4, and alkaline phosphatase; and serum protein immunoelectrophoresis to determine the cause

• Sometimes PTH and urinary excretion of Ca with or without PO4

Hypercalcemia is diagnosed by a serum Ca concentration > 10.4 mg/dL (> 2.60 mmol/L) or ionized serum Ca > 5.2 mg/dL (> 1.30 mmol/L). The condition is frequently discovered during routine laboratory screening. Serum Ca can be artfactually elevated (see Table 97-10). Hypercalcemia can also be masked by low serum protein. When protein and albumin are abnormal and when ionized hypercalcemia is suspected because of clinical findings (eg, because of symptoms of hypercalcemia), ionized serum Ca should be measured.

Initial evaluation: Initial evaluation should include a review of the history, particularly of past serum Ca concentration; physical examination; a chest x-ray; and laboratory studies, including electrolytes, BUN, creatinine, ionized Ca, PO4, alkaline phosphatase, and serum protein immunoelectrophoresis. The cause is apparent from clinical data and results of these tests in ≥ 95% of patients. Patients without an obvious cause of hypercalcemia after this evaluation should undergo measurement of intact PTH and 24-h urinary Ca. When hyperparathyroidism is suspected, PO4 renal excretion is often measured.

Asymptomatic hypercalcemia that has been present for years or is present in several family members raises the possibility of FHH. Primary hyperparathyroidism generally manifests late in life but can be present for several years before symptoms occur. When no cause is obvious, concentrations of serum Ca < 11 mg/dL (< 2.75 mmol/L) suggest hyperparathyroidism or other nonmalignant causes, whereas concentration > 13 mg/dL (> 3.25 mmol/L) suggest cancer.

Measurement of intact PTH levels help differentiate PTH-mediated hypercalcemia (eg, caused by hyperparathyroidism or FHH), in which PTH levels are high or high-normal, from most other (PTH-independent) causes. In PTH-independent causes, levels are usually < 20 pg/mL.

The chest x-ray is particularly helpful, revealing most granulomatous disorders, such as TB, sarcoidosis, and silicosis, as well as primary lung cancer and lytic and Paget's lesions in bones of the shoulder, ribs, and thoracic spine.

Chest and bone (eg, skull, extremity) x-rays can also show the bony effects of secondary hyperparathyroidism, most commonly in long-term dialysis patients. In osteitis fibrosa cystica (often due to primary hyperparathyroidism), increased osteoclastic activity from over-stimulation by PTH causes rarefaction of bone with fibrous degeneration and cyst and fibrous nodule formation. Because characteristic bone lesions occur only with relatively advanced disease, bone x-rays are recommended only for symptomatic patients. X-rays typically show bone cysts, a heterogeneous appearance of the skull, and subperiosteal resorption of bone in the phalanges and distal clavicles.

Hyperparathyroidism: In hyperparathyroidism, the serum Ca is rarely > 12 mg/dL (> 3.00 mmol/L), but the ionized serum Ca is almost always elevated. Low serum PO4 concentration suggests hyperparathyroidism, especially when coupled with elevated PO4 renal excretion. When hyperparathyroidism results in increased bone turnover, serum alkaline phosphatase is frequently increased. Increased intact PTH, particularly inappropriate elevation (ie, a high concentration in the absence of hypocalcemia) or an inappropriate high-normal concentration (ie, despite hypercalcemia), is diagnostic. Urinary Ca excretion is usually normal or high in hyperparathyroidism. Primary hyperparathyroidism is suggested by an absence of a family history of endocrine neoplasia, childhood neck irradiation, or other obvious cause. Chronic kidney disease suggests the presence of secondary hyperparathyroidism, but primary hyperparathyroidism can also be present. In patients with chronic kidney disease, high serum Ca and normal serum PO4 suggest primary hyperparathyroidism, whereas elevated PO4 suggests secondary hyperparathyroidism.
The need for localization of parathyroid tissue before surgery on the parathyroid(s) is controversial. High-resolution CT with or without CT-guided biopsy and immunoassay of thyroid venous drainage, MRI, high-resolution ultrasonography, digital subtraction angiography, and thallium-201-technetium-99 scanning all have been used and are highly accurate, but they have not improved the usually high cure rate of parathyroidectomy done by experienced surgeons. Technetium-99 sestamibi, a newer radionuclide agent for parathyroid imaging, is more sensitive and specific than older agents and may be useful for identifying solitary adenomas.

For residual or recurrent hyperparathyroidism after initial parathyroid surgery, imaging is necessary and may reveal abnormally functioning parathyroid glands in unusual locations throughout the neck and mediastinum. Technetium-99 sestamibi is probably the most sensitive imaging test. Use of several imaging studies (MRI, CT, or high-resolution ultrasonography in addition to technetium-99 sestamibi) before repeat parathyroidectomy is sometimes necessary.

Cancer: A serum Ca > 13 mg/dL (> 3.00 mmol/L) suggests some cause of hypercalcemia other than hyperparathyroidism. Urinary Ca excretion is usually normal or high in cancer. In humoral hypercalcemia of cancer, PTH is often decreased or undetectable; PO₄ is often decreased; and metabolic alkalosis, hypochloremia, and hypoalbuminemia are often present. Suppressed PTH differentiates humoral hypercalcemia of cancer from primary hyperparathyroidism. Humoral hypercalcemia of cancer can also be diagnosed by detection of PTH-related peptide in serum.

Multiple myeloma is suggested by simultaneous anemia, azotemia, and hypercalcemia or by the presence of a monoclonal gammopathy. Myeloma is confirmed by bone marrow examination.

FHH: FHH should be considered in patients with hypercalcemia and elevated or high-normal intact PTH levels. FHH is distinguished from primary hyperparathyroidism by the early age of onset, frequent occurrence of hypermagnesemia, and presence of hypercalcemia without hypercalciuria in other family members. The fractional excretion of Ca (ratio of Ca clearance to creatinine clearance) is low (< 1%) in FHH; it is almost always elevated (1 to 4%) in primary hyperparathyroidism. Intact PTH can be elevated or normal, perhaps reflecting altered feedback regulation of the parathyroid glands.

Milk-alkali syndrome: In addition to a history of increased intake of Ca antacids, milk-alkali syndrome is recognized by the combination of hypercalcemia, metabolic alkalosis, and, occasionally, azotemia with hypocalciuria. The diagnosis can be confirmed when the serum Ca concentration rapidly returns to normal when Ca and alkali ingestion stops, although renal insufficiency can persist when nephrocalcinosis is present. Circulating PTH usually is suppressed.

Other causes: In hypercalcemia due to sarcoidosis, other granulomatous disorders, and some lymphomas, serum concentration of 1,25(OH)₂D may be elevated. Vitamin D toxicity is also characterized by elevated 1,25(OH)₂D concentration. In other endocrine causes of hypercalcemia, such as thyrotoxicosis and Addison's disease, typical laboratory findings of the underlying disorder help establish the diagnosis. When Paget's disease is suspected, plain x-rays (see p. 361) are done first and may show characteristic abnormalities.

Treatment

• Oral PO₄ for serum Ca < 11.5 mg/dL with mild symptoms and no kidney disease

• IV saline and furosemide for more rapid correction for serum Ca < 18 mg/dL

• Bisphosphonates or other Ca-lowering drugs for serum Ca < 18 mg/dL and > 11.5 mg/dL or moderate symptoms

• Hemodialysis for serum Ca > 18 mg/dL

• Surgical removal for moderate, progressive primary hyperparathyroidism and sometimes for mild disease
• PO₄ restriction and binders and sometimes calcitriol for secondary hyperparathyroidism

There are 4 main strategies for lowering serum Ca: • Decrease intestinal Ca absorption
• Increase urinary Ca excretion
• Decrease bone resorption
• Remove excess Ca through dialysis

The treatment used depends on both the degree and the cause of hypercalcemia.

**Mild hypercalcemia:** In mild hypercalcemia (serum Ca < 11.5 mg/dL [< 2.88 mmol/L]), in which symptoms are mild, treatment is deferred pending definitive diagnosis. After diagnosis, the underlying disorder is treated. When symptoms are significant, treatment aimed at lowering serum Ca is necessary. Oral PO₄ can be used. When taken with meals, it binds some Ca, preventing its absorption. A starting dose is 250 mg of elemental PO₄ (as Na or K salt) qid. The dose can be increased to 500 mg qid prn unless diarrhea develops. Another treatment is increasing urinary Ca excretion by giving isotonic saline plus a loop diuretic. Initially, 1 to 2 L of saline is given over 2 to 4 h unless significant heart failure is present, because nearly all patients with significant hypercalcemia are hypovolemic. Furosemide 20 to 40 mg IV q 2 to 4 h is given as needed to maintain a urine output of roughly 250 mL/h (monitored hourly). Care must be taken to avoid volume depletion. K and Mg are monitored as often as every 4 h during treatment and replaced IV as needed to avoid hypokalemia and hypomagnesemia. Serum Ca begins to decrease in 2 to 4 h and falls to nearnormal within 24 h.

**Moderate hypercalcemia:** Moderate hypercalcemia (serum Ca > 11.5 mg/dL [< 2.88 mmol/L] and < 18 mg/dL [< 4.51 mmol/L]) can be treated with isotonic saline and a loop diuretic as is done for mild hypercalcemia or, depending on its cause, agents that decrease bone resorption (usually bisphosphonates, calcitonin, or infrequently plicamycin or gallium nitrate), corticosteroids, or chloroquine.

**Bisphosphonates** inhibit osteoclasts. They are usually the drugs of choice for cancer-associated hypercalcemia. Pamidronate can be given for cancer-associated hypercalcemia as a one-time dose of 30 to 90 mg IV, repeated only after 7 days. It lowers serum Ca for ≤ 2 wk. Zoledronate can also be given in doses of 4 to 8 mg IV and lowers serum Ca very effectively for an average of > 40 days. Ibandronate 4 to 6 mg IV can be given for cancer-associated hypercalcemia; it is effective for about 14 days. Etidronate 7.5 mg/kg IV once/day for 3 to 5 days is used to treat Paget’s disease and cancer-associated hypercalcemia. Maintenance dosage is 20 mg/kg po once/day, but the dose must be reduced when GFR is low. Repetitive use of IV bisphosphonates to treat hypercalcemia associated with metastatic bone disease or myeloma has been associated with osteonecrosis of the jaw. Some reports suggest this finding may be more common with zoledronate. Renal toxicity has been reported in patients receiving zoledronate. Oral bisphosphonates (eg, alendronate or risedronate) can be given to maintain Ca in the normal range but are not generally used for treating hypercalcemia acutely.

**Calcitonin** (thyrocalcitonin) is a rapidly acting peptide hormone normally secreted in response to hypercalcemia by the C cells of the thyroid. Calcitonin seems to lower serum Ca by inhibiting osteoclastic activity. A dosage of 4 to 8 IU/kg sc q 12 h of salmon calcitonin is safe. Its usefulness in the treatment of cancer-associated hypercalcemia is limited by its short duration of action with the development of tachyphylaxis (often after about 48 h) and by the lack of response in ≥ 40% of patients. However, the combination of salmon calcitonin and prednisone may control serum Ca for several months in some patients with cancer. If calcitonin stops working, it can be stopped for 2 days (while prednisone is continued) and then resumed.

**Corticosteroids** (eg, prednisone 20 to 40 mg po once/day) can help control hypercalcemia as adjunctive therapy by decreasing calcitriol production and thus intestinal Ca absorption in most patients with vitamin D toxicity, idiopathic hypercalcemia of infancy, and sarcoidosis. Some patients with myeloma, lymphoma, leukemia, or metastatic cancer require 40 to 60 mg of prednisone once/day. However, > 50% of such patients fail to respond to corticosteroids, and response, when it occurs, takes several days; thus, other
treatment usually is necessary.

**Chloroquine PO₄** 500 mg po once/day inhibits 1,25(OH)₂D synthesis and reduces serum Ca concentration in patients with sarcoidosis. Routine ophthalmologic surveillance (eg, retinal examinations every 6 to 12 mo) is mandatory to detect dose-related retinal damage.

**Plicamycin** 25 μg/kg IV once/day in 50 mL of 5% D/W over 4 to 6 h is effective in patients with hypercalcemia due to cancer but is rarely used because other treatments are safer.

**Gallium nitrate** is also effective in hypercalcemia due to cancer but is used infrequently because of renal toxicity and limited clinical experience.

**Severe hypercalcemia:** In severe hypercalcemia (serum Ca > 18 mg/dL [> 4.50 mmol/L] or with severe symptoms), hemodialysis with low-Ca dialysate may be needed in addition to other treatments. Although there is no completely satisfactory way to correct severe hypercalcemia in patients with renal failure, hemodialysis is probably the safest and most reliable short-term treatment.

**IV PO₄** (disodium PO₄ or monopotassium PO₄) should be used only when hypercalcemia is life threatening and unresponsive to other methods and when short-term hemodialysis is not possible. No more than 1 g should be given IV in 24 h; usually 1 or 2 doses over 2 days lower serum Ca for 10 to 15 days. Soft-tissue calcification and acute renal failure may result. (NOTE: IV infusion of Na sulfate is even more hazardous and less effective than PO₄ infusion and should not be used.)

**Hyperparathyroidism:** Treatment for hyperparathyroidism depends on severity.

Patients with **asymptomatic primary hyperparathyroidism** with no indications for surgery may be treated conservatively with methods to ensure that serum Ca concentrations remain low. Patients should remain active (ie, avoid immobilization that could exacerbate hypercalcemia), follow a low-Ca diet, drink plenty of fluids to minimize the chance of nephrolithiasis, and avoid drugs that can raise serum Ca, such as thiazide diuretics. Serum Ca and renal function are monitored every 6 mo. Bone density is monitored every 12 mo. However, subclinical bone disease, hypertension, and longevity are concerns. Osteoporosis is treated with bisphosphonates.

**Surgery** is indicated for patients with symptomatic or progressive hypoparathyroidism. The indications for surgery in patients with asymptomatic, primary hyperparathyroidism are controversial. Surgical parathyroidectomy increases bone density and may have modest effects on some quality of life symptoms, but most patients do not have progressive deterioration in biochemical abnormalities or bone density. Still, concerns about hypertension and longevity remain. Many experts recommend surgery in the following circumstances:

- Serum Ca 1 mg/dL (0.25 mmol/L) greater than the upper limits of normal Calciuria > 400 mg/day (> 10 mmol/day)
- Creatinine clearance 30% less than that of age-matched controls
- Peak bone density at the hip, lumbar spine, or radius 2.5 standard deviations below controls (T score = -2.5)
- Age < 50 yr
- The possibility of poor adherence with follow-up

Surgery consists of removal of adenomatous glands. PTH concentration can be measured before and after removal of the presumed abnormal gland using rapid assays. A fall of 50% or more 10 min after removal of the adenoma indicates successful treatment. In patients with disease of > 1 gland, several glands are removed, and often a small portion of a normalappearing parathyroid gland is reimplanted in the belly of the sternocleidomastoid muscle or subcutaneously in the forearm to prevent
hypoparathyroidism. Parathyroid tissue is also occasionally preserved using cryopreservation to allow for later autologous transplantation in case persistent hypoparathyroidism develops.

When hyperparathyroidism is mild, the serum Ca concentration drops to just below normal within 24 to 48 h after surgery; serum Ca must be monitored. In patients with severe osteitis fibrosa cystica, prolonged, symptomatic hypocalcemia may occur postoperatively unless 10 to 20 g elemental Ca is given in the days before surgery. Even with preoperative Ca administration, large doses of Ca and vitamin D may be required (see p. 841) while bone Ca is repleted.

**Hyperparathyroidism in renal failure** is usually secondary. Measures used for treatment can also be used for prevention. One aim is to prevent hyperphosphatemia. Treatment combines dietary PO₄ restriction and PO₄-binding agents, such as Ca carbonate or sevelamer. Despite the use of PO₄ binders, dietary restriction of PO₄ is needed. Aluminum-containing compounds have been used to limit PO₄ concentration, but they should be avoided, especially in patients receiving long-term dialysis, to prevent aluminum accumulation in bone resulting in severe osteomalacia. Vitamin D administration is potentially hazardous in renal failure because it can increase PO₄ absorption and contribute to hypercalcemia; administration requires frequent monitoring of Ca and PO₄. Treatment should be limited to patients with any of the following:

- Symptomatic osteomalacia (unrelated to aluminum)
- Secondary hyperparathyroidism
- Postparathyroidectomy hypocalcemia

Although oral calcitriol is often given along with oral Ca to suppress secondary hyperparathyroidism, the results are variable in patients with end-stage renal disease. The parenteral form of calcitriol, or vitamin D analogs such as paricalcitol, may better prevent secondary hyperparathyroidism in such patients, because the higher attained serum concentration of 1,25(OH)₂D directly suppresses PTH release. Simple osteomalacia may respond to 0.25 to 0.5 μg once/day of oral calcitriol, whereas correction of postparathyroidectomy hypocalcemia may require prolonged administration of as much as 2 μg of calcitriol once/day and ≥ 2 g of elemental Ca/day. The calcimimetic, cinacalcet, modulates the set point of the Ca-sensing receptor on parathyroid cells and decreases PTH concentration in dialysis patients without increasing serum Ca. In patients with osteomalacia caused by having taken large amounts of aluminum-containing PO₄ binders, removal of aluminum with deferoxamine is necessary before calcitrol administration reduces bone lesions.

**FHH:** Although FHH results from histologically abnormal parathyroid tissue, the response to subtotal parathyroidectomy is unsatisfactory. Because overt clinical manifestations are rare, drug therapy is not routinely indicated.

**Disorders of Phosphate Concentration**

Phosphorus is one of the most abundant elements in the human body. Most phosphorus in the body is complexed with O₂ as phosphate (PO₄). About 85% of the about 500 to 700 g of PO₄ in the body is contained in bone, where it is an important constituent of crystalline hydroxyapatite. In soft tissues, PO₄ is mainly found in the intracellular compartment as an integral component of several organic compounds, including nucleic acids and cell membrane phospholipids. PO₄ is also involved in aerobic and anaerobic energy metabolism. RBC 2,3-diphosphoglycerate (2,3-DPG) plays a crucial role in O₂ delivery to tissue. Adenosine diphosphate (ADP) and ATP contain PO₄ and use chemical bonds between PO₄ groups to store energy. Inorganic PO₄ is a major intracellular anion but is also present in plasma. The normal serum inorganic PO₄ concentration in adults ranges from 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L). PO₄ concentration is 50% higher in infants and 30% higher in children, possibly because of the important roles these PO₄-dependent processes play in growth.
The typical American diet contains about 800 to 1500 mg of PO₄. The amount in the stool varies depending on the amount of PO₄ binding compounds (mainly Ca) in the diet. Also, like Ca, GI PO₄ absorption is enhanced by vitamin D. Renal PO₄ excretion roughly equals GI absorption to maintain PO₄ balance. PO₄ depletion can occur in various disorders and normally results in conservation of PO₄ by the kidneys. Bone PO₄ serves as a reservoir, which can buffer changes in plasma and intracellular PO₄.

**Hypophosphatemia**

Hypophosphatemia is serum phosphate (PO₄) concentration < 2.5 mg/dL (0.81 mmol/L). Causes include alcoholism, burns, starvation, and diuretic use. Clinical features include muscle weakness, respiratory failure, and heart failure; seizures and coma can occur. Diagnosis is by serum PO₄ concentration. Treatment consists of PO₄ supplementation.

**Etiology**

Hypophosphatemia occurs in 2% of hospitalized patients but is more prevalent in certain populations (eg, it occurs in up to 10% of hospitalized patients with alcoholism).

Hypophosphatemia has numerous causes, but clinically significant acute hypophosphatemia occurs in relatively few clinical settings, including the following:

- The recovery phase of diabetic ketoacidosis
- Acute alcoholism
- Severe burns
- When receiving TPN
- Refeeding after prolonged undernutrition
- Severe respiratory alkalosis

Acute severe hypophosphatemia with serum PO₄ < 1 mg/dL (< 0.32 mmol/L) is most often caused by transcellular shifts of PO₄, often superimposed on chronic PO₄ depletion.

Chronic hypophosphatemia usually is the result of decreased renal PO₄ reabsorption. Causes include the following:

- Hyperparathyroidism
- Other hormonal disturbances, such as Cushing's syndrome and hypothyroidism
- Electrolyte disorders, such as hypomagnesemia and hypokalemia
- Theophylline intoxication
- Long-term diuretic use

Severe chronic hypophosphatemia usually results from a prolonged negative PO₄ balance. Causes include

- Chronic starvation or malabsorption, especially when combined with vomiting or copious diarrhea
- Long-term ingestion of large amounts of PO₄-binding aluminum, usually in the form of antacids
Ingestion of aluminum is particularly prone to cause PO₄ depletion when combined with decreased dietary intake and dialysis losses of PO₄ in patients with end-stage renal disease.

**Symptoms and Signs**

Although hypophosphatemia usually is asymptomatic, anorexia, muscle weakness, and osteomalacia can occur in severe chronic depletion. Serious neuromuscular disturbances may occur, including progressive encephalopathy, seizures, coma, and death. The muscle weakness of profound hypophosphatemia may be accompanied by rhabdomyolysis, especially in acute alcoholism. Hematologic disturbances of profound hypophosphatemia include hemolytic anemia, decreased release of O₂ from Hb, and impaired leukocyte and platelet function.

**Diagnosis**

• Serum PO₄ levels

Hypophosphatemia is diagnosed by a serum PO₄ concentration < 2.5 mg/dL (< 0.81 mmol/L). Most causes of hypophosphatemia (eg, diabetic ketoacidosis, burns, refeeding) are readily apparent. Testing to diagnose the cause is done when clinically indicated (eg, suggestive liver function test results or signs of cirrhosis in patients with suspected alcoholism).

**Treatment**

• Oral PO₄ replacement

• IV PO₄ when serum PO₄ is < 0.5 mEq/L or symptoms are severe

**Oral treatment:** Treatment of the underlying disorder and oral PO₄ replacement are usually adequate in asymptomatic patients, even when the serum concentration is very low. PO₄ can be given in doses up to about 1 g po tid in tablets containing Na or K PO₄. Oral Na or K PO₄ may be poorly tolerated because of diarrhea. Ingestion of 1 L of low-fat or skim milk provides 1 g of PO₄ and may be more acceptable. Removal of the cause of hypophosphatemia may include stopping PO₄-binding antacids or diuretics or correcting hypomagnesemia.

**Parenteral treatment:** Parenteral PO₄ is usually given IV. It should be administered in any of the following circumstances:

• When serum PO₄ is < 0.5 mEq/L (< 0.16 mmol/L)

• Rhabdomyolysis, hemolysis, or CNS symptoms are present

• Oral replacement is not feasible due to underlying disorder

IV administration of KPO₄ (as buffered mix of K₂HPO₄ and KH₂PO₄) is relatively safe when renal function is well preserved. NaPO₄ (rather than KPO₄) preparations generally should be used in patients with impaired renal function. The usual parenteral dose of KPO₄ is 2.5 mg (0.08 mmol)/kg IV over 6 h. Patients with alcoholism may require ≥ 1 g/day during TPN; supplemental PO₄ is stopped when oral intake is resumed. Serum Ca and PO₄ concentrations should be monitored during therapy, particularly when PO₄ is given IV or to patients with impaired renal function. In most cases, no more than 7 mg/kg (about 500 mg for a 70-kg adult) of PO₄ should be given over 6 h. Close monitoring is done and more rapid rates of PO₄ administration should be avoided to prevent hypocalcemia, hyperphosphatemia, and metastatic calcification due to excessive Ca × PO₄ product.

**Hyperphosphatemia**
Hyperphosphatemia is serum phosphate (PO₄) concentration > 4.5 mg/dL (> 1.46 mmol/L). Causes include chronic renal failure, hypoparathyroidism, and metabolic or respiratory acidosis. Clinical features may be due to accompanying hypocalcemia and include tetany. Diagnosis is by serum PO₄. Treatment includes restriction of PO₄ intake and administration of PO₄-binding antacids, such as Ca carbonate.

The usual cause of hyperphosphatemia is a decrease in renal excretion of PO₄. Advanced renal insufficiency (GFR < 30 mL/min) reduces excretion sufficiently to increase serum PO₄. Defects in renal excretion of PO₄ in the absence of renal failure also occur in pseudohypoparathyroidism and hypoparathyroidism. Hyperphosphatemia can also occur with excessive oral PO₄ administration and occasionally with overzealous use of enemas containing PO₄.

Hyperphosphatemia occasionally results from a transcellular shift of PO₄ into the extracellular space that is so large that the renal excretory capacity is overwhelmed. This transcellular shift occurs most frequently in diabetic ketoacidosis (despite total body PO₄ depletion), crush injuries, and nontraumatic rhabdomyolysis as well as in overwhelming systemic infections and tumor lysis syndrome.

Major causes of hyperphosphatemia include

- GFR < 30 mL/min
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Excessive oral PO₄ administration
- Overzealous use of enemas containing PO₄
- Shifts of PO₄ into the extracellular space (eg, in diabetic ketoacidosis, rhabdomyolysis, overwhelming systemic infections, and tumor lysis syndrome)

Hyperphosphatemia plays a critical role in the development of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced chronic kidney disease as well as in patients on dialysis. Lastly, hyperphosphatemia can be spurious in cases of hyperproteinemia (multiple myeloma or Waldenstrom's macroglobulinemia), hyperlipidemia, hemolysis, or hyperbilirubinemia.

Hyperphosphatemia can lead to hypocalcemia by causing Ca and PO₄ precipitation into soft tissues, especially when the serum Ca × PO₄ product is chronically > 55 in patients with chronic kidney disease.

**Symptoms and Signs**

Most patients with hyperphosphatemia are asymptomatic, although symptoms of hypocalcemia, including tetany, can occur when concomitant hypocalcemia is present. Soft-tissue calcifications are common among patients with chronic kidney disease.

**Diagnosis**

- PO₄ concentration > 4.5 mg/dL (> 1.46 mmol/L)

Hyperphosphatemia is diagnosed by PO₄ concentration. When the etiology is not obvious (eg, rhabdomyolysis, tumor lysis syndrome, renal failure, overingestion of PO₄-containing laxatives), additional evaluation is warranted to exclude hypoparathyroidism or pseudohypoparathyroidism, which is end-organ resistance to parathyroid hormone (PTH—see p. 839). False elevation of serum PO₄ also
should be excluded by measuring serum protein, lipid, and bilirubin concentrations.

**Treatment**

- PO$_4$ restriction
- PO$_4$ binders

The mainstay of treatment in patients with renal failure is reduction of PO$_4$ intake, which is usually accomplished with avoidance of foods containing high amounts of PO$_4$ and with use of PO$_4$-binding drugs taken with meals. Because of the possibility of aluminum-related osteomalacia, Ca carbonate and Ca acetate replace aluminum-containing antacids in patients with end-stage renal disease. Because of the possibility of excessive Ca × PO$_4$ product causing vascular calcification in dialysis patients taking Ca-containing binders, a PO$_4$-binding resin without Ca, sevelamer, is widely used in dialysis patients in doses of 800 to 2400 mg tid with meals. Lanthanum carbonate, another PO$_4$ binder that lacks Ca, can also be used in dialysis patients. It is given in doses of 500 to 1000 mg tid with meals.

**Disorders of Magnesium Concentration**

Mg is the 4th most plentiful cation in the body. A 70-kg adult has about 2000 mEq of Mg. About 50% is sequestered in bone and is not readily exchangeable with Mg in other compartments. The ECF contains only about 1% of total body Mg. The remainder resides in the intracellular compartment. Normal serum Mg concentration ranges from 1.4 to 2.1 mEq/L (0.70 to 1.05 mmol/L).

The maintenance of serum Mg concentration is largely a function of dietary intake and effective renal and intestinal conservation. Within 7 days of initiation of a Mg-deficient diet, renal and stool Mg excretion each fall to about 1 mEq/day (0.5 mmol/day).

About 70% of serum Mg is ultrafiltered (filtered through minute pores) by the kidney; the remainder is bound to protein. Protein binding of Mg is pH dependent. Serum Mg concentration is not closely related to either total body Mg or intracellular Mg content. However, severe serum hypomagnesemia may reflect diminished total body Mg.

Many enzymes are activated by or are dependent on Mg. Mg is required by all enzymatic processes involving ATP and by many of the enzymes involved in nucleic acid metabolism. Mg is required for thiamine pyrophosphate cofactor activity and seems to stabilize the structure of macromolecules such as DNA and RNA. Mg is also related to Ca and K metabolism in an intimate but poorly understood way.

**Hypomagnesemia**

Hypomagnesemia is serum Mg concentration < 1.4 mEq/L (< 0.70 mmol/L). Causes include inadequate Mg intake and absorption or increased excretion due to hypercalcemia or drugs such as furosemide. Clinical features are often due to accompanying hypokalemia and hypocalcemia and include lethargy, tremor, tetany, seizures, and arrhythmias. Treatment is with Mg replacement.

Serum Mg concentration, even when free Mg ion is measured, may be normal even with decreased intracellular or bone Mg stores. Mg depletion usually results from inadequate intake plus impairment of renal conservation or GI absorption. There are numerous causes of clinically significant Mg deficiency (see Table 97-11).

**Symptoms and Signs**

Clinical manifestations are anorexia, nausea, vomiting, lethargy, weakness, personality change, tetany (eg, positive Trousseau's or Chvostek's sign or spontaneous carpopedal spasm, hyperreflexia), and tremor and muscle fasciculations. The neurologic signs, particularly tetany, correlate with development of
concomitant hypocalcemia, hypokalemia, or both. Myopathic potentials are found on electromyography but are also compatible with hypocalcemia or hypokalemia. Severe hypomagnesemia may cause generalized tonic-clonic seizures, especially in children.

**Diagnosis**

- Considered in patients with risk factors and with unexplained hypocalcemia or hypokalemia
- Serum Mg concentration < 1.4 mEq/L (< 0.70 mmol/L)

Hypomagnesemia is diagnosed by a serum Mg concentration. Severe hypomagnesemia usually results in concentrations of < 1.0 mEq/L (< 0.50 mmol/L). Associated hypocalcemia and hypocalciuria are common. Hypokalemia with increased urinary K excretion and metabolic alkalosis may be present. Mg deficiency should be suspected even when serum Mg concentration is normal in patients with unexplained hypocalcemia or refractory hypokalemia. Mg deficiency should also be suspected in patients with unexplained neurologic symptoms and alcoholism, with chronic diarrhea, or after cyclosporine, cisplatinum-based chemotherapy or prolonged therapy with amphotericin B or aminoglycosides.

**[Table 97-11. Causes of Hypomagnesemia]**

**Treatment**

- Oral Mg salts
- IV or IM Mg sulfate for severe hypomagnesemia or inability to tolerate or adhere to oral therapy

Treatment with Mg salts is indicated when Mg deficiency is symptomatic or persistently < 1 mEq/L (< 0.50 mmol/L). Patients with alcoholism are treated empirically. In such cases, deficits approaching 12 to 24 mg/kg are possible. About twice the amount of the estimated deficit should be given in patients with intact renal function, because about 50% of the administered Mg is excreted in urine. Oral Mg salts (eg, Mg gluconate 500 to 1000 mg po tid) are given for 3 to 4 days. Oral treatment is limited by the onset of diarrhea. Parenteral administration is reserved for patients with severe, symptomatic hypomagnesemia who cannot tolerate oral drugs. Sometimes a single injection is given in patients with alcoholism who are unlikely to adhere to ongoing oral therapy. When Mg must be replaced parenterally, a 10% Mg sulfate (MgSO$_4$) solution (1 g/10 mL) is available for IV use and a 50% solution (1 g/2 mL) is available for IM use. The serum Mg concentration should be monitored frequently during Mg therapy, particularly when Mg is given to patients with renal insufficiency or in repeated parenteral doses. In these patients, treatment is continued until a normal serum Mg concentration is achieved.

In severe, symptomatic hypomagnesemia (eg, Mg < 1 mEq/L [< 0.5 mmol/L] with seizures or other severe symptoms), 2 to 4 g of MgSO$_4$ IV is given over 5 to 10 min. When seizures persist, the dose may be repeated up to a total of 10 g over the next 6 h. In patients in whom seizures stop, 10 g in 1 L of 5% D/W can be infused over 24 h, followed by up to 2.5 g q 12 h to replace the deficit in total Mg stores and prevent further drops in serum Mg. When serum Mg is ≤ 1 mEq/L (< 0.5 mmol/L) but symptoms are less severe, MgSO$_4$ may be given IV in 5% D/W at a rate of 1 g/h as slow infusion for up to 10 h. In less severe cases of hypomagnesemia, gradual repletion may be achieved by administration of smaller parenteral doses over 3 to 5 days until the serum Mg concentration is normal.

**Hypermagnesemia**

**Hypermagnesemia is a serum Mg concentration > 2.1 mEq/L (> 1.05 mmol/L).** The major cause is renal failure. Symptoms include hypotension, respiratory depression, and cardiac arrest. Diagnosis is by serum Mg concentration. Treatment includes IV administration of Ca gluconate and possibly furosemide; hemodialysis can be helpful in severe cases.

Symptomatic hypermagnesemia is fairly uncommon. It occurs most commonly in patients with renal failure after ingestion of Mg-containing drugs, such as antacids or purgatives.
Symptoms and signs include hyporeflexia, hypotension, respiratory depression, and cardiac arrest.

**Diagnosis**

Serum Mg concentrations > 2.1 mEq/L (> 1.05 mmol/L)

At serum Mg concentrations of 5 to 10 mEq/L (2.5 to 5 mmol/L), the ECG shows prolongation of the PR interval, widening of the QRS complex, and increased T-wave amplitude. Deep tendon reflexes disappear as the serum Mg concentration approaches 10 mEq/L (5.0 mmol/L); hypotension, respiratory depression, and narcosis develop with increasing hypermagnesemia. Cardiac arrest may occur when blood Mg concentration is > 12 to 15 mEq/L (6.0 to 7.5 mmol/L).

**Treatment**

- Ca gluconate
- Diuresis or dialysis

Treatment of severe Mg toxicity consists of circulatory and respiratory support with administration of 10% Ca gluconate 10 to 20 mL IV. Ca gluconate may reverse many of the Mg-induced changes, including respiratory depression. Administration of IV furosemide can increase Mg excretion when renal function is adequate; volume status should be maintained. Hemodialysis may be valuable in severe hypermagnesemia, because a relatively large fraction (about 70%) of blood Mg is not protein bound and thus removable with hemodialysis. When hemodynamic compromise occurs and hemodialysis is impractical, peritoneal dialysis is an option.
Chapter 98. Acid-Base Regulation and Disorders

Introduction

Metabolic processes continually produce acid and, to a lesser degree, base. Hydrogen ion (H\(^+\)) is especially reactive; it can attach to negatively charged proteins and, in high concentrations, alter their overall charge, configuration, and function. To maintain cellular function, the body has elaborate mechanisms that maintain blood H\(^+\) concentration within a narrow range—typically 37 to 43 nmol/L (pH 7.43 to 7.37, where pH = -log [H\(^+\)]) and ideally 40 nmol/L (pH = 7.40). Disturbances of these mechanisms can have serious clinical consequences.

Acid-base equilibrium is closely tied to fluid and electrolyte balance, and disturbances in one of these systems often affect another. Fluid and electrolytes are discussed in Ch. 97.

Acid-Base Physiology

Most acid comes from carbohydrate and fat metabolism, which generates 15,000 to 20,000 mmol of CO\(_2\) daily. CO\(_2\) is not an acid itself but combines with water (H\(_2\)O) in the blood to create carbonic acid (H\(_2\)CO\(_3\)), which in the presence of the enzyme carbonic anhydrase dissociates into H\(^+\) and HCO\(_3^-\). The H\(^+\) binds with Hb in RBCs and is released with oxygenation in the alveoli, at which time the reaction is reversed, creating H\(_2\)O and CO\(_2\), which is exhaled in each breath.

Lesser amounts of organic acid derive from the following:

- Incomplete metabolism of glucose and fatty acids into lactic acid and ketoacids
- Metabolism of sulfur-containing amino acids (cysteine, methionine) into sulfuric acid
- Metabolism of cationic amino acids (arginine, lysine)
- Hydrolysis of dietary phosphate

This "fixed" or "metabolic" acid load cannot be exhaled and therefore must be neutralized or excreted.

Most base comes from metabolism of anionic amino acids (glutamate and aspartate) and from oxidation and consumption of organic anions such as lactate and citrate, which produce HCO\(_3^-\).

Acid-Base Balance

Acid-base balance is maintained by chemical buffering and by pulmonary and renal elimination.

Chemical buffering: Chemical buffers are solutions that resist changes in pH. Intracellular and extracellular buffers provide an immediate response to acid-base disturbances. Bone also plays an important buffering role. A buffer is made up of a weak acid and its conjugate base. The conjugate base can accept H\(^+\) and the weak acid can relinquish it thereby minimizing changes in free H\(^+\) concentration.

The most important extracellular buffer is the HCO\(_3^-\)/CO\(_2\) system, described by the equation:

\[ \text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{CO}_2 + \text{H}_2\text{O} \]

An increase in H\(^+\) drives the equation to the right and generates CO\(_2\). This important buffer system is highly regulated; CO\(_2\) concentrations can be finely controlled by alveolar ventilation, and H\(^+\) and HCO\(_3^-\)
concentrations can be finely regulated by renal excretion.

The relationship between $\text{HCO}_3^-$ and $\text{CO}_2$ in the system can be described by the Kassirer-Bleich equation, derived from the Henderson-Hasselbalch equation:

$$\text{H}^+ = 24 \times \frac{\text{PCO}_2}{\text{HCO}_3^-}$$

This equation illustrates that acid-base balance depends on the ratio of $\text{PCO}_2$ and $\text{HCO}_3^-$, not on the absolute value of either one alone. With this formula, any 2 values (usually $\text{H}^+$ and $\text{PCO}_2$) can be used to calculate the other (usually $\text{HCO}_3^-$).

Other important physiologic buffers include intracellular organic and inorganic phosphates and proteins, including Hb in RBCs. Less important are extracellular phosphate and plasma proteins. Bone becomes an important buffer after consumption of extracellular $\text{HCO}_3^-$. Bone initially releases sodium carbonate ($\text{NaHCO}_3$) and potassium carbonate ($\text{KHCO}_3$) in exchange for $\text{H}^+$. With prolonged acid loads, bone releases calcium carbonate ($\text{CaCO}_3$) and calcium phosphate ($\text{CaPO}_4$). Long-standing acidemia therefore contributes to bone demineralization and osteoporosis.

**Pulmonary regulation:** $\text{CO}_2$ concentration is finely regulated by changes in tidal volume and respiratory rate (minute ventilation). A decrease in pH is sensed by arterial chemoreceptors and leads to increases in tidal volume or respiratory rate; $\text{CO}_2$ is exhaled and blood pH increases. In contrast to chemical buffering, which is immediate, pulmonary regulation occurs over minutes to hours. It is about 50 to 75% effective; it does not completely normalize pH.

**Renal regulation:** The kidneys control pH by adjusting the amount of $\text{HCO}_3^-$ that is reabsorbed and the amount of $\text{H}^+$ that is excreted; increase in $\text{HCO}_3^-$ is equivalent to removing free $\text{H}^+$. Changes in renal acid-base handling occur hours to days after changes in acid-base status.

$\text{HCO}_3^-$ reabsorption occurs mostly in the proximal tubule and, to a lesser degree, in the collecting tubule. $\text{H}_2\text{O}$ within the tubular cell dissociates into $\text{H}^+$ and hydroxide ($\text{OH}^-$); in the presence of carbonic anhydrase, the $\text{OH}^-$ combines with $\text{CO}_2$ to form $\text{HCO}_3^-$, which is transported back into the peritubular capillary, while the $\text{H}^+$ is secreted into the tubular lumen and joins with freely filtered $\text{HCO}_3^-$ to form $\text{CO}_2$ and $\text{H}_2\text{O}$, which are also reabsorbed. Thus, reabsorbed $\text{HCO}_3^-$ ions are newly generated and not the same as those that were filtered. Decreases in effective circulating volume (such as occur with diuretic therapy) increase $\text{HCO}_3^-$ reabsorption, while increases in parathyroid hormone in response to an acid load decrease $\text{HCO}_3^-$ reabsorption. Also, increased $\text{PCO}_2$ leads to increased $\text{HCO}_3^-$ reabsorption, while $\text{Cl}^-$ depletion (typically from volume depletion) leads to increased $\text{Na}^+$ reabsorption and $\text{HCO}_3^-$ generation by the proximal tubule.

Acid is actively excreted into the proximal and distal tubules where it combines with urinary buffers—primarily freely filtered $\text{HPO}_4^{2-}$, creatinine, uric acid, and ammonia—to be transported outside the body. The ammonia buffering system is especially important because other buffers are filtered in fixed concentrations and can be depleted by high acid loads; by contrast, tubular cells actively regulate ammonia production in response to changes in acid load. Arterial pH is the main determinant of acid secretion, but excretion is also influenced by $\text{K}^+$, $\text{Cl}^-$, and aldosterone levels. Intracellular $\text{K}^+$ concentration and $\text{H}^+$ secretion are reciprocally related; $\text{K}^+$ depletion causes increased $\text{H}^+$ secretion and hence metabolic alkalosis.
Acid-Base Disorders

Acid-base disorders are changes in arterial PCO$_2$, serum HCO$_3^-$, and serum pH.

- Acidemia is serum pH < 7.35.
- Alkalemia is serum pH > 7.45.
- Acidosis refers to physiologic processes that cause acid accumulation or alkali loss.
- Alkalosis refers to physiologic processes that cause alkali accumulation or acid loss.

Actual changes in pH depend on the degree of physiologic compensation and whether multiple processes are present.

Classification

Primary acid-base disturbances are defined as metabolic or respiratory based on clinical context and whether the primary change in pH is due to an alteration in serum HCO$_3^-$ or in PCO$_2$.

Metabolic acidosis is serum HCO$_3^-$ < 24 mEq/L. Causes are

- Increased acid production
- Acid ingestion
- Decreased renal acid excretion
- GI or renal HCO$_3^-$ loss

Metabolic alkalosis is serum HCO$_3^-$ > 24 mEq/L. Causes are

- Acid loss
- HCO$_3^-$ retention

Respiratory acidosis is PCO$_2$ > 40 mm Hg (hypercapnia). Cause is

- Decrease in minute ventilation (hypoventilation)

Respiratory alkalosis is PCO$_2$ < 40 mm Hg (hypocapnia). Cause is

- Increase in minute ventilation (hyperventilation)

Whenever an acid-base disorder is present, compensatory mechanisms begin to correct the pH (see Table 98-1). Compensation cannot return pH completely to normal and never overshoots.

[Table 98-1, Primary Changes and Compensations in Simple Acid-Base Disorders]

[Table 98-2, Clinical Consequences of Acid-Base Disorders]

A simple acid-base disorder is a single acid-base disturbance with its accompanying compensatory response.
Mixed acid-base disorders comprise 2 or more primary disturbances.

**Symptoms and Signs**

Compensated or mild acid-base disorders cause few symptoms or signs. Severe, uncompensated disorders have multiple cardiovascular, respiratory, neurologic, and metabolic consequences (see Table 98-2 and Fig. 189-4 on p. 1857).

**Diagnosis**

- ABG
- Serum electrolytes
- Anion gap calculated
- If metabolic acidosis is present, delta gap calculated and Winter's formula applied
- Search for compensatory changes

Evaluation is with ABG and serum electrolytes. The ABG directly measures arterial pH and PCO$_2$. HCO$_3^-$ levels on ABG are calculated using the Henderson-Hasselbalch equation; levels on serum chemistry panels are directly measured and are more accurate. Acid-base balance is generally most accurately assessed with measurement of pH and pCO$_2$ on arterial blood. In cases of circulatory failure or during cardiopulmonary resuscitation, measurements on venous blood may more accurately reflect conditions at the tissue level and may be a more useful guide to bicarbonate administration and adequacy of ventilation.

The pH establishes the primary process (acidosis or alkalosis), although it moves toward the normal range with compensation. Changes in PCO$_2$ reflect the respiratory component, and changes in HCO$_3^-$ reflect the metabolic component. However, several calculations may be required to determine whether changes in PCO$_2$ and HCO$_3^-$ are primary or compensatory and whether a mixed disorder is present; in mixed disorders, values may be deceptively normal. Interpretation must also consider clinical conditions (eg, chronic lung disease, renal failure, drug overdose).

**Sidebar 98-1 The Anion Gap**

The anion gap is defined as plasma Na concentration minus the sum of Cl$^-$ and HCO$_3^-$ concentrations; Na$^+$ - (Cl$^-$ + HCO$_3^-$). The term "gap" is misleading, because the law of electroneutrality requires the same number of positive and negative charges in an open system; the gap appears on laboratory testing because certain cations (+) and anions (-) are not measured on routine laboratory chemistry panels. Thus

$$\text{Na}^+ + \text{unmeasured cations (UC)} = \text{Cl}^- + \text{HCO}_3^- + \text{unmeasured anions (UA)}$$

and

$$\text{the anion gap, Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) = \text{UA} - \text{UC}$$

The predominant unmeasured anions are PO$_4^{3-}$, sulfate (SO$_4^{2-}$), various negatively charged proteins, and some organic acids, accounting for 20 to 24 mEq/L. The predominant unmeasured extracellular cations are K$^+$, Ca$^{++}$, and Mg$^{++}$ and account for about 11 mEq/L. Thus the typical anion gap is 23 - 11 = 12 mEq/L. The anion gap can be affected by increases or decreases in the UC or UA.
**Increased anion gap** is most commonly caused by metabolic acidosis in which negatively charged acids—mostly ketones, lactate, sulfates, or metabolites of methanol, ethylene glycol, and salicylate—consume (are buffered by) HCO$_3^-$; Other causes of increased anion gap include hyperalbuminemia and uremia (increased anions) and hypocalcemia or hypomagnesemia (decreased cations).

**Decreased anion gap** is unrelated to metabolic acidosis but is caused by hypoalbuminemia (decreased anions); hypercalcemia, hypermagnesemia, lithium intoxication, and hypergammaglobulinemia (increased cations); or hyperviscosity or halide (bromide or iodide) intoxication. The effect of low albumin can be accounted for by adjusting the normal range for the anion gap 2.5 mEq/L upward for every 1-g/dL fall in albumin.

**Negative anion gap** occurs rarely as a laboratory artifact in severe cases of hypernatremia, hyperlipidemia, and bromide intoxication.

**The delta gap:** The difference between the patient's anion gap and the normal anion gap is termed the delta gap. This amount is considered an HCO$_3^-$ equivalent, because for every unit rise in the anion gap, the HCO$_3^-$ should lower by 1 (by buffering). Thus, if the delta gap is added to the measured HCO$_3^-$, the result should be in the normal range for HCO$_3^-$; elevation indicates the additional presence of a metabolic alkalosis.

**Example:** A vomiting, ill-appearing alcoholic patient has laboratory results showing

Na, 137; K, 3.8; Cl, 90; HCO$_3^-$, 22; pH, 7.40; PCO$_2$, 41; PO$_2$, 85

At first glance, results appear unremarkable. However, calculations show elevation of the anion gap:

137 - (90 + 22) = 25 (normal, 10)

indicating a metabolic acidosis. Respiratory compensation is evaluated by Winter's formula:

Predicted PCO$_2$ = 1.5 (22) + 8 ± 2
   = 41 ± 2

Predicted = measured, so respiratory compensation is appropriate.

Because there is metabolic acidosis, the delta gap is calculated, and the result is added to measured HCO$_3^-$_:

25 - 10 = 15
15 + 22 = 37

The resulting corrected HCO$_3^-$ is above the normal range for HCO$_3^-$, indicating a primary metabolic alkalosis is also present. Thus, the patient has a mixed acid-base disorder. Using clinical information, one could theorize a metabolic acidosis arising from alcoholic ketoacidosis combined with a metabolic alkalosis from recurrent vomiting with loss of Cl$^-$ and volume.

The anion gap (see Sidebar 98-1) should always be calculated; elevation almost always indicates a metabolic acidosis. A normal anion gap with a low HCO$_3^-$ (eg, < 24 mEq/L) and high serum Cl$^-$ indicates a non-anion gap (hyperchloremic) metabolic acidosis. If metabolic acidosis is present, a delta gap is calculated (see Sidebar 98-1) to identify concomitant metabolic alkalosis, and Winter's formula is applied.
to see whether respiratory compensation is appropriate or reflects a 2nd acid-base disorder (predicted \( \text{PCO}_2 = 1.5 \text{[HCO}_3^-] + 8 \pm 2 \); if \( \text{PCO}_2 \) is higher, there is also a primary respiratory acidosis—if lower, respiratory alkalosis).

Respiratory acidosis is suggested by \( \text{PCO}_2 > 40 \text{ mm Hg} \); \( \text{HCO}_3^- \) should compensate acutely by increasing 3 to 4 mEq/L for each 10-mm Hg rise in \( \text{PCO}_2 \) sustained for 4 to 12 h (there may be no increase or only 1 to 2 mEq/L, which slowly increases to 3 to 4 mEq/L over days). Greater increase in \( \text{HCO}_3^- \) implies a primary metabolic alkalosis; lesser increase suggests no time for compensation or coexisting primary metabolic acidosis.

Metabolic alkalosis is suggested by \( \text{HCO}_3^- > 28 \text{ mEq/L} \). The \( \text{PCO}_2 \) should compensate by increasing about 0.6 to 0.75 mm Hg for each 1 mEq/L increase in \( \text{HCO}_3^- \) (up to about 55 mm Hg). Greater increase implies concomitant respiratory acidosis; lesser increase, respiratory alkalosis.

Respiratory alkalosis is suggested by \( \text{PCO}_2 < 38 \text{ mm Hg} \). The \( \text{HCO}_3^- \) should compensate over 4 to 12 h by decreasing 5 mEq/L for every 10-mm Hg decrease in \( \text{PCO}_2 \). Lesser decrease means there has been no time for compensation or existence of a primary metabolic alkalosis. Greater decrease implies a primary metabolic acidosis.

Nomograms (acid-base maps) are an alternative way to diagnose mixed disorders, allowing for simultaneous plotting of pH, \( \text{HCO}_3^- \), and \( \text{PCO}_2 \).

**Metabolic Acidosis**

Metabolic acidosis is primary reduction in \( \text{HCO}_3^- \), typically with compensatory reduction in \( \text{PCO}_2 \); pH may be markedly low or slightly subnormal. Metabolic acidoses are categorized as high or normal anion gap based on the presence or absence of unmeasured anions in serum. Causes include accumulation of ketones and lactic acid, renal failure, and drug or toxin ingestion (high anion gap) and GI or renal \( \text{HCO}_3^- \) loss (normal anion gap). Symptoms and signs in severe cases include nausea and vomiting, lethargy, and hyperpnea. Diagnosis is clinical and with ABG and serum electrolyte measurement. The cause is treated; IV Na\( \text{HCO}_3 \) may be indicated when pH is very low.

**Etiology**

Metabolic acidosis is acid accumulation due to increased acid production or acid ingestion; decreased acid excretion; or GI or renal \( \text{HCO}_3^- \) loss. Acidemia (arterial pH < 7.35) results when acid load overwhelsms respiratory compensation. Causes are classified by their effect on the anion gap (see Sidebar 98-1 and Table 98-3).

**High anion gap acidosis:** The most common causes of a high anion gap metabolic acidosis are

- Ketoacidosis,
- Lactic acidosis
- Renal failure
- Toxic ingestions

Ketoacidosis is a common complication of type 1 diabetes mellitus, but it also occurs with chronic
alcoholism, undernutrition, and, to a lesser degree, fasting. In these conditions, the body converts from glucose to free fatty acid (FFA) metabolism; FFAs are converted by the liver into ketoacids, acetoacetic acid, and \( \beta \)-hydroxybutyrate (all unmeasured anions). Ketoacidosis is also a rare manifestation of congenital isovaleric and methylmalonic acidemia.

Lactic acidosis (see p. 861) is the most common cause of metabolic acidosis in hospitalized patients. Lactate accumulation results from a combination of excess formation and decreased utilization of lactate. Excess lactate production occurs during states of anaerobic metabolism. The most serious form occurs during the various types of shock. Decreased utilization generally occurs with hepatocellular dysfunction from decreased liver perfusion or as a part of generalized shock.

Renal failure causes anion gap acidosis by decreased acid excretion and decreased \( \text{HCO}_3^- \) reabsorption. Accumulation of sulfates, phosphates, urate, and hippurate accounts for the high anion gap.

Toxins may have acidic metabolites or trigger lactic acidosis. Rhabdomyolysis is a rare cause of metabolic acidosis thought to be due to release of protons and anions directly from muscle.

**Normal anion gap acidosis:** The most common causes of normal anion gap acidosis are

- GI or renal \( \text{HCO}_3^- \) loss
- Impaired renal acid excretion

Normal anion gap metabolic acidosis is also called hyperchloremic acidosis because the kidneys resorb \( \text{Cl}^- \) with Na instead of reabsorbing \( \text{HCO}_3^- \).

Many GI secretions are rich in \( \text{HCO}_3^- \) (eg, biliary, pancreatic, and intestinal fluids); loss due to diarrhea, tube drainage, or fistulas can cause acidosis. In ureterosigmoidostomy (insertion of ureters into the sigmoid colon after obstruction or cystectomy), the colon secretes and loses \( \text{HCO}_3^- \) in exchange for urinary \( \text{Cl}^- \)

**[Table 98-3. Causes of Metabolic Acidosis]**

and absorbs urinary ammonium, which dissociates into ammonia (\( \text{NH}_3^+ \)) and hydrogen ion (\( \text{H}^+ \)). Ion-exchange resin uncommonly causes \( \text{HCO}_3^- \) loss by binding \( \text{HCO}_3^- \).

The renal tubular acidoses (see p. 2426) either impair \( \text{H}^+ \) secretion (types 1 and 4) or \( \text{HCO}_3^- \) absorption (type 2). Impaired acid excretion and a normal anion gap also occur in early renal failure, tubulointerstitial renal disease, and when carbonic anhydrase inhibitors (eg, acetazolamide) are taken.

**Symptoms and Signs**

Symptoms and signs (see Table 98-2) are primarily those of the cause. Mild acidemia is itself asymptomatic. More severe acidemia (pH < 7.10) may cause nausea, vomiting, and malaise. Symptoms may appear at higher pH if acidosis develops rapidly. The most characteristic sign is hyperpnea (long, deep breaths at a normal rate), reflecting a compensatory increase in alveolar ventilation.

Severe, acute acidemia predisposes to cardiac dysfunction with hypotension and shock, ventricular arrhythmias, and coma. Chronic acidemia causes bone demineralization disorders (eg, rickets, osteomalacia, osteopenia).

**Diagnosis**

- ABG and serum electrolytes
Anion gap and delta gap calculated

Winter's formula for calculating compensatory changes

Testing for cause

Recognition of metabolic acidosis and appropriate respiratory compensation are discussed on p. 857. Determining the cause of metabolic acidosis begins with the anion gap.

The cause of an elevated anion gap may be clinically obvious (eg, hypovolemic shock, missed hemodialysis), but if not, blood testing should include glucose, BUN, creatinine, lactate, and tests for possible toxins. Salicylate levels can be measured in most laboratories, but methanol and ethylene glycol frequently cannot; their presence may be suggested by presence of an osmolar gap. Calculated serum osmolarity \(2 [Na] + [glucose]/18 + BUN/2.8 + \text{blood alcohol}/5\) is subtracted from measured osmolarity. A difference > 10 implies the presence of an osmotically active substance, which in the case of a high anion gap acidosis is methanol or ethylene glycol. Although ingestion of ethanol may cause an osmolar gap and a mild acidosis, it should never be considered the cause of a significant metabolic acidosis.

If the anion gap is normal and no cause is obvious (eg, marked diarrhea), urinary electrolytes are measured and the urinary anion gap is calculated as \([Na] + [K] - [Cl]\). A normal urinary anion gap (including in patients with GI losses) is 30 to 50 mEq/L; an elevation suggests renal HCO\(_3\)- loss (for evaluation of renal tubular acidosis, see p. 2427). In addition, when metabolic acidosis is present, a delta gap is calculated (see Sidebar 98-1) to identify concomitant metabolic alkalosis, and Winter's formula (see p. 858) is applied to see whether respiratory compensation is appropriate or reflects a 2nd acid-base disorder.

**Treatment**

• Cause treated

• NaHCO\(_3\) rarely indicated

Treatment is directed at the underlying cause. Hemodialysis is required for renal failure and sometimes for ethylene glycol, methanol, and salicylate poisoning.

Treatment of acidemia with NaHCO\(_3\) is clearly indicated only in certain circumstances and is probably deleterious in others. When metabolic acidosis results from loss of HCO\(_3\)- or accumulation of inorganic acids (ie, normal anion gap acidosis), HCO\(_3\)- therapy is generally safe and appropriate. However, when acidosis results from organic acid accumulation (ie, high anion gap acidosis), HCO\(_3\)- therapy is controversial; it does not clearly decrease mortality in these conditions, and there are several possible risks. With treatment of the underlying condition, lactate and ketoacids are metabolized back to HCO\(_3\)-; exogenous HCO\(_3\)- loading may therefore cause an "overshoot" metabolic alkalosis. In any condition, HCO\(_3\)- may also cause Na and volume overload, hypokalemia, and, by inhibiting respiratory drive, hypercapnia. Furthermore, because HCO\(_3\)- does not diffuse across cell membranes, intracellular acidosis is not corrected and may paradoxically worsen because some of the added HCO\(_3\)- is converted to CO\(_2\), which does cross into the cell and is hydrolyzed to H\(^+\) and HCO\(_3\)-.

Despite these and other controversies, most experts still recommend HCO\(_3\)- IV for severe metabolic acidosis (pH < 7.00), with a target pH of 7.20.

Treatment requires 2 calculations. The first is the level to which HCO\(_3\)- must be raised, calculated by the
Kassirer-Bleich equation, using a value for $[H^+]$ of 63 nmol/L at a pH of 7.2:

$$63 = 24 \times \text{PCO}_2/\text{HCO}_3^-$$

or

desired $\text{HCO}_3^-$ = $0.38 \times \text{PCO}_2$

The amount of $\text{HCO}_3^-$ needed to achieve that level is

$$\text{NaHCO}_3 \text{ required (mEq)} = (\text{desired } [\text{HCO}_3^-] - \text{observed } [\text{HCO}_3^-]) \times 0.4 \times \text{body weight (kg)}$$

This amount of NaHCO$_3$ is given over several hours. Serum pH and HCO$_3^-$ levels can be checked 30 min to 1 h after administration, which allows for equilibration with extravascular HCO$_3^-$.  

Alternatives to NaHCO$_3$ include  

- Tromethamine, an amino alcohol that buffers both metabolic ($H^+$) and respiratory (carbonic acid $[H_2CO_3]$) acid
- Carbicarb, an equimolar mixture of NaHCO$_3$ and carbonate (the latter consumes CO$_2$ and generates HCO$_3^-$)
- Dichloroacetate, which enhances oxidation of lactate

These alternatives are all of unproven benefit and cause complications of their own.

$K^+$ depletion, common in metabolic acidosis, should be identified through frequent serum $K^+$ monitoring and treated as needed with oral or parenteral KCl.

**Lactic Acidosis**

Lactic acidosis results from overproduction of lactate, decreased metabolism of lactate, or both.

Lactate is a normal byproduct of glucose and amino acid metabolism. The most serious form of lactic acidosis, type A, occurs when lactic acid is overproduced in ischemic tissue to generate ATP during O$_2$ deficit. Overproduction typically occurs during tissue hypoperfusion in hypovolemic, cardiac, or septic shock and is worsened by decreased lactate metabolism in the poorly perfused liver. It may also occur with primary hypoxia due to lung disease and with various hemoglobinopathies.

Type B lactic acidosis occurs in states of normal global tissue perfusion (and hence ATP production) and is less ominous. Lactate production may be increased from local relative hypoxia as with vigorous muscle use (eg, exertion, seizures, hypothermic shivering) and with cancer and ingestion of certain drugs or toxins (see Table 98-3). Drugs include the nucleoside reverse transcriptase inhibitors and the biguanides phenformin and, less so, metformin; although phenformin has been removed from the market in most of the world, it is still available from China (including as a component of some Chinese proprietary medicines). Metabolism may be decreased due to hepatic insufficiency or thiamin deficiency.

D-Lactic acidosis is an unusual form of lactic acidosis in which D-lactic acid, the product of bacterial carbohydrate metabolism in the colon of patients with jejunoleal bypass or intestinal resection, is systemically absorbed. It persists in circulation because human lactate dehydrogenase can metabolize only L-lactate.
Findings in and treatment of types A and B lactic acidosis are as for other metabolic acidoses. In D-lactic acidosis, the anion gap is lower than expected for the decrease in HCO$_3^-$, and there may be a urinary osmolar gap (difference between calculated and measured urine osmolarity). Treatment is IV fluids, restriction of carbohydrates, and sometimes antibiotics (eg, metronidazole).

**Metabolic Alkalosis**

Metabolic alkalosis is primary increase in HCO$_3^-$ with or without compensatory increase in PCO$_2$; pH may be high or nearly normal. Common causes include prolonged vomiting, hypovolemia, diuretic use, and hypokalemia. Renal impairment of HCO$_3^-$ excretion must be present to sustain alkalosis. Symptoms and signs in severe cases include headache, lethargy, and tetany. Diagnosis is clinical and with ABG and serum electrolyte measurement. The underlying cause is treated; oral or IV acetazolamide or HCl is sometimes indicated.

**Etiology**

Metabolic alkalosis is HCO$_3^-$ accumulation due to acid loss, alkali administration, intracellular shift of hydrogen ion (H$^+$—as occurs in hypokalemia), or HCO$_3^-$ retention. Regardless of initial cause, persistence of metabolic alkalosis indicates that the kidneys have increased their HCO$_3^-$ reabsorption, because HCO$_3^-$ is normally freely filtered by the kidneys and hence excreted. Volume depletion and hypokalemia are the most common stimuli for increased HCO$_3^-$ reabsorption, but any condition that elevates aldosterone or mineralocorticoids (which enhance Na reabsorption and K and H$^+$ excretion) can elevate HCO$_3^-$. Thus, hypokalemia is both a cause and a frequent consequence of metabolic alkalosis. Causes are listed; the most common are volume depletion (particularly when involving loss of gastric acid and Cl from recurrent vomiting or nasogastric suction) and diuretic use (see Table 98-4).

Metabolic alkalosis involving loss or excess secretion of Cl is termed Cl-responsive, because it typically corrects with IV administration of NaCl-containing fluid. Cl-unresponsive metabolic alkalosis does not, and it typically involves severe Mg or K deficiency or mineralocorticoid excess. The 2 forms can coexist, eg, in patients with volume overload made hypokalemic from high-dose diuretics.

**Symptoms and Signs**

Symptoms and signs of mild alkalemia are usually related to the underlying disorder. More severe alkalemia increases protein binding of ionized Ca$^{++}$, leading to hypocalcemia and subsequent headache, lethargy, and neuromuscular excitability, sometimes with delirium, tetany, and seizures. Alkalemia also lowers threshold for anginal symptoms and arrhythmias. Concomitant hypokalemia may cause weakness.

**Diagnosis**

- ABG and sercum electrolytes
- Diagnosis of cause usually clinical
- Sometimes measurement of urinary Cl$^-$ and K$^+$

Recognition of metabolic alkalosis and appropriate respiratory compensation is discussed on p. 857 and requires ABG and measurement of serum electrolytes (including Ca and Mg).

Common causes can often be determined by history and physical examination. If history is unrevealing and renal function is normal, urinary Cl$^-$ and K$^+$ concentrations are measured (values are not diagnostic
in renal insufficiency). Urinary Cl < 20 mEq/L indicates significant renal Cl⁻ reabsorption and hence a Cl-
responsive cause (see Table 98-4). Urinary Cl > 20 mEq/L suggests a Cl-unresponsive form.

Urinary K and presence or absence of hypertension help differentiate Cl-unresponsive alkaloses. Urinary
K < 30 mEq/day signifies hypokalemia or laxative misuse. Urinary K > 30 mEq/day without hypertension
suggests diuretic abuse or Bartter or Gitelman's syndrome. Urinary K > 30 mEq/day with hypertension
requires evaluation for hyperaldosteronism, mineralocorticoid excess, and

[Table 98-4. Causes of Metabolic Alkalosis]

renovascular disease. Tests typically include plasma renin activity and aldosterone and cortisol levels
(see pp. 797 and 800).

Treatment

• Cause treated

• IV 0.9% saline solution for Cl-responsive metabolic alkalosis

Underlying conditions are treated, with particular attention paid to correction of hypovolemia and
hypokalemia.

Patients with Cl-responsive metabolic alkalosis are given 0.9% saline solution IV; infusion rate is typically
50 to 100 mL/h greater than urinary and other sensible and insensible fluid losses until urinary Cl rises to
> 25 mEq/L and urinary pH normalizes after an initial rise from bicarbonaturia. Patients with Cl-
unresponsive metabolic alkalosis rarely benefit from rehydration alone.

Patients with severe metabolic alkalosis (eg, pH > 7.6) sometimes require more urgent correction of
serum pH. Hemofiltration or hemodialysis is an option, particularly if volume overload and renal
dysfunction are present. Acetazolamide 250 to 375 mg po or IV once/day or bid increases HCO₃⁻
excretion but may also accelerate urinary losses of K⁺ and phosphate (PO₄³⁻); volume-overloaded
patients with diuretic-induced metabolic alkalosis and those with posthypercarnic metabolic alkalosis may
especially benefit.

Hydrochloric acid in a 0.1 to 0.2 normal solution IV is safe and effective but must be given through a
central catheter because it is hyperosmotic and scleroses peripheral veins. Dosage is 0.1 to 0.2
mmol/kg/h. Frequent monitoring of ABG and electrolytes is needed.

Respiratory Acidosis

Respiratory acidosis is primary increase in PCO₂ with or without compensatory increase in
HCO₃⁻; pH is usually low but may be near normal. Cause is a decrease in respiratory rate,
volume (hypoventilation), or both due to CNS, pulmonary, or iatrogenic conditions. Respiratory
acidosis can be acute or chronic; the chronic form is asymptomatic, but the acute, or
worsening, form causes headache, confusion, and drowsiness. Signs include tremor, myoclonic
jerks, and asterixis. Diagnosis is clinical and with ABG and serum electrolyte measurements.
The cause is treated; O₂ and mechanical ventilation are often required.

Respiratory acidosis is CO₂ accumulation (hypercapnia) due to a decrease in respiratory rate, respiratory
volume (hypoventilation), or both. Causes of hypoventilation (discussed under Ventilatory Failure on p.
2288) include

• Conditions that impair CNS respiratory drive

• Conditions that impair neuromuscular transmission and other conditions that cause muscular weakness
• Obstructive, restrictive, and parenchymal pulmonary disorders

Hypoxia typically accompanies hypoventilation.

Respiratory acidosis may be acute or chronic. Distinction is based on the degree of metabolic compensation; CO₂ is initially buffered inefficiently, but over 3 to 5 days the kidneys increase HCO₃⁻ reabsorption significantly.

**Symptoms and Signs**

Symptoms and signs depend on the rate and degree of PCO₂ increase. CO₂ rapidly diffuses across the blood-brain barrier. Symptoms and signs are a result of high CNS CO₂ concentrations (low CNS pH) and any accompanying hypoxemia.

Acute (or acutely worsening chronic) respiratory acidosis causes headache, confusion, anxiety, drowsiness, and stupor (CO₂ narcosis). Slowly developing, stable respiratory acidosis (as in COPD) may be well tolerated, but patients may have memory loss, sleep disturbances, excessive daytime sleepiness, and personality changes. Signs include gait disturbance, tremor, blunted deep tendon reflexes, myoclonic jerks, asterixis, and papilledema.

**Diagnosis**

• ABG and serum electrolytes

• Diagnosis of cause usually clinical

Recognition of respiratory acidosis and appropriate renal compensation (see p. 857) requires ABG and measurement of serum electrolytes. Causes are usually obvious from history and examination. Calculation of the alveolar-arterial (A-a) O₂ gradient (inspired PO₂ - [arterial PO₂ + 5/4 arterial PCO₂]) can help distinguish pulmonary from extrapulmonary disease; a normal gradient essentially excludes pulmonary disorders.

**Treatment**

• Adequate ventilation

• NaHCO₃ almost always contraindicated

Treatment is provision of adequate ventilation by either endotracheal intubation or noninvasive positive pressure ventilation (for specific indications and procedures, see Ch. 225). Adequate ventilation is all that is needed to correct respiratory acidosis, although chronic hypercapnia generally must be corrected slowly (eg, over several hours or more), because too-rapid PCO₂ lowering can cause a posthypercapnic "overshoot" alkalosis when the underlying compensatory hyperbicarbonatemia becomes unmasked; the abrupt rise in CNS pH that results can lead to seizures and death. Any K⁺ and Cl⁻ deficits are corrected.

NaHCO₃ is almost always contraindicated, because HCO₃⁻ can be converted to PCO₂ in serum but crosses the blood-brain barrier slowly, thus increasing serum pH without affecting CNS pH. One exception may be in cases of severe bronchospasm, in which HCO₃⁻ may improve responsiveness of bronchial smooth muscle to β-agonists.

**Respiratory Alkalosis**

(See also Hyperventilation Syndrome on p. 1836.)

Respiratory alkalosis is a primary decrease in Pco₂ with or without compensatory decrease in
HCO$_3^-$; pH may be high or near normal. Cause is an increase in respiratory rate or volume (hyperventilation) or both. Respiratory alkalosis can be acute or chronic. The chronic form is asymptomatic, but the acute form causes light-headedness, confusion, paresthesias, cramps, and syncope. Signs include hyperpnea or tachypnea and carpopedal spasms. Diagnosis is clinical and with ABG and serum electrolyte measurements. Treatment is directed at the cause.

**Etiology**

Respiratory alkalosis is a primary decrease in PCO$_2$ ( hypocapnia) due to an increase in respiratory rate or volume (hyperventilation) or both. Ventilation increase occurs most often as a physiologic response to hypoxia, metabolic acidosis, and increased metabolic demands (eg, fever) and, as such, is present in many serious conditions. In addition, pain and anxiety and some CNS disorders can increase respirations without a physiologic need.

**Pathophysiology**

Respiratory alkalosis can be acute or chronic. Distinction is based on the degree of metabolic compensation. Excess HCO$_3^-$ is buffered by extracellular hydrogen ion (H$^+$) within minutes, but more significant compensation occurs over 2 to 3 days as the kidneys decrease H$^+$ excretion.

**Pseudorespiratory alkalosis:** Pseudorespiratory alkalosis is low arterial PCO$_2$ and high pH in mechanically ventilated patients with severe metabolic acidosis due to poor systemic perfusion (eg, cardiogenic shock, during CPR). Pseudorespiratory alkalosis occurs when mechanical ventilation (often hyperventilation) eliminates larger-than-normal amounts of alveolar CO$_2$. Exhalation of large amounts of CO$_2$ causes respiratory alkalosis in arterial blood (hence on ABG measurements), but poor systemic perfusion and cellular ischemia cause cellular acidosis, leading to acidosis of venous blood. Diagnosis is by demonstration of marked arteriovenous differences in PCO$_2$ and pH and by elevated lactate levels; treatment is improvement of systemic hemodynamics.

**Symptoms and Signs**

Symptoms and signs depend on the rate and degree of fall in PCO$_2$. Acute respiratory alkalosis causes light-headedness, confusion, peripheral and circumoral paresthesias, cramps, and syncope. Mechanism is thought to be change in cerebral blood flow and pH. Tachypnea or hyperpnea is often the only sign; carpopedal spasm may occur in severe cases. Chronic respiratory alkalosis is usually asymptomatic and has no distinctive signs.

**Diagnosis**

- ABG and serum electrolytes
- If hypoxia present, cause vigorously pursued

Recognition of respiratory alkalosis and appropriate renal compensation (discussed on p. 857) requires ABG and serum electrolyte measurements. Minor hypophosphatemia and hypokalemia due to intracellular shifts and decreased ionized Ca$^{++}$ due to an increase in protein binding may be present.

Presence of hypoxia or an increased alveolar-arterial (A-a) O$_2$ gradient (inspired PO$_2$ - [arterial PO$_2$ + 5/4 arterial PCO$_2$]) requires search for a cause. Other causes are often apparent on history and examination. However, because pulmonary embolism often manifests without hypoxia (see p. 1908), embolism must be strongly considered in a hyperventilating patient before ascribing the cause to anxiety.

**Treatment**

Treatment is directed at the underlying cause. Respiratory alkalosis is not life threatening, so no
interventions to lower pH are necessary. Increasing inspired CO2 through rebreathing (such as from a paper bag) is common practice but may be dangerous in at least some patients with CNS disorders in whom CSF pH may already be below normal.
Introduction

Diabetes mellitus and its complications (diabetic ketoacidosis, nonketotic hyperosmolar syndrome) are the most common disorders of carbohydrate metabolism, but alcoholic ketoacidosis and hypoglycemia are also important.

Diabetes Mellitus

Diabetes mellitus (DM) is impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia. Early symptoms are related to hyperglycemia and include polydipsia, polyphagia, and polyuria. Later complications include vascular disease, peripheral neuropathy, and predisposition to infection. Diagnosis is by measuring plasma glucose.

Treatment is diet, exercise, and drugs that reduce glucose levels, including insulin and oral antihyperglycemic drugs. Prognosis varies with degree of glucose control.

There are 2 main categories of DM—type 1 and type 2, which can be distinguished by a combination of features (see Table 99-1). Terms that describe the age of onset (juvenile or adult) or type of treatment (insulin- or non-insulin-dependent) are no longer accurate because of overlap in age groups and treatments between disease types.

Impaired glucose regulation (impaired glucose tolerance, or impaired fasting glucose—see Table 99-2) is an intermediate, possibly transitional, state between normal glucose metabolism and DM that becomes common with age. It is a significant risk factor for DM and may be present for many years before onset of DM. It is associated with an increased risk of cardiovascular disease, but typical diabetic microvascular complications generally do not develop.

Etiology

Type 1: In Type 1 DM (previously called juvenile-onset or insulin-dependent), insulin production is absent because of autoimmune pancreatic β-cell destruction possibly triggered by an environmental exposure in genetically susceptible people. Destruction progresses subclinically over months or years until β-cell mass decreases to the point that insulin concentrations are no longer adequate to control plasma glucose levels. Type 1 DM generally develops in childhood or adolescence and until recently was the most common form diagnosed before age 30; however, it can also develop in adults (latent autoimmune diabetes of adulthood, which often initially seems to be type 2 DM). Some cases of type 1 DM, particularly in nonwhite populations, do not seem to be autoimmune in nature and are considered idiopathic. Type 1 accounts for < 10% of all cases of DM.

The pathogenesis of the autoimmune β-cell destruction involves incompletely understood interactions between susceptibility genes, autoantigens, and environmental factors. Susceptibility genes include those within the major histocompatibility complex (MHC)—especially HLA-DR3, DQB1*0201 and HLA-DR4, DQB1*0302, which are present in > 90% of patients with type 1 DM—and those outside the MHC, which seem to regulate insulin production and processing and confer risk of DM in concert with MHC genes. Susceptibility genes are more common among some populations than among others and explain the higher prevalence of type 1 DM among some ethnic groups (Scandinavians, Sardinians).

Autoantigens include glutamic acid decarboxylase, insulin, insulinoma-associated protein, and other proteins in β cells. It is thought that these proteins are exposed or released during normal β-cell turnover or β-cell injury (eg, due to infection), activating a cell-mediated immune response resulting in β-cell destruction (insulitis). Glucagon-secreting α cells remain unharmed. Antibodies to autoantigens, which
can be detected in serum, seem to be a response to (not a cause of) β-cell destruction.

Several viruses (including coxsackievirus, rubella virus, cytomegalovirus, Epstein-Barr virus, and retroviruses) have been linked to the onset of type 1 DM. Viruses may directly infect and destroy β cells, or they may cause β-cell destruction indirectly by exposing autoantigens, activating autoreactive lymphocytes, mimicking molecular sequences of autoantigens that stimulate an immune response (molecular mimicry), or other mechanisms.

Diet may also be a factor. Exposure of infants to dairy products (especially cow's milk and the milk protein β casein), high nitrates in drinking water, and low vitamin D consumption have been linked to increased risk of type 1 DM. Early (< 4 mo) or late (> 7 mo) exposure to gluten and cereals increases islet cell autoantibody production. Mechanisms for these associations are unclear.

Type 2: In type 2 DM (previously called adult-onset or non-insulin-dependent), insulin secretion is inadequate. Often insulin levels are very high, especially early in the disease, but peripheral insulin resistance and increased hepatic production of glucose make insulin levels inadequate to normalize plasma glucose levels. Insulin production then falls, further exacerbating hyperglycemia. The disease generally develops in adults and becomes more common with age. Plasma glucose levels reach higher levels after eating in older than in younger adults, especially after high carbohydrate loads, and take longer to return to normal, in part because of increased accumulation of visceral and abdominal fat and decreased muscle mass.

Type 2 DM is becoming increasingly common among children as childhood obesity has become epidemic: 40 to 50% of new-onset DM in children is now type 2. Over 90% of adults with DM have type 2 disease. There are clear genetic determinants, as evidenced by the high prevalence of the disease within ethnic groups (especially American Indians, Hispanics, and Asians) and in relatives of people with the disease. Although several genetic polymorphisms have been identified, no gene responsible for the most common forms of type 2 DM has been identified.

Pathogenesis is complex and incompletely understood. Hyperglycemia develops when insulin secretion can no longer compensate for insulin resistance. Although insulin resistance is characteristic in people with type 2 DM and those at risk for it, evidence also exists for β-cell dysfunction and impaired insulin secretion, including impaired first-phase insulin secretion in response to IV glucose infusion, a loss of normally pulsatile insulin secretion, an increase in proinsulin secretion signaling impaired insulin processing, and an accumulation of islet amyloid polypeptide (a protein normally secreted with insulin). Hyperglycemia itself may impair insulin secretion, because high glucose levels desensitize β cells, cause β-cell dysfunction (glucose toxicity), or both. These changes typically take years to develop in the presence of insulin resistance.

Obesity and weight gain are important determinants of insulin resistance in type 2 DM. They have some genetic determinants but also reflect diet, exercise, and lifestyle. Adipose tissue increases plasma levels of free fatty acids that may impair insulin-stimulated glucose transport and muscle glycogen synthase activity. Adipose tissue also seems to function as an endocrine organ, releasing multiple factors (adipocytokines) that favorably (adiponectin) and adversely (tumor necrosis factor-α, IL-6, leptin, resistin) influence glucose metabolism. Intrauterine growth restriction and low birth weight have also been associated with insulin resistance in later life and may reflect prenatal environmental influences on glucose metabolism.

Miscellaneous types: Miscellaneous causes of DM that account for a small proportion of cases include genetic defects affecting β-cell function, insulin action, and mitochondrial DNA (eg, maturity-onset diabetes of youth); pancreatic diseases (eg, cystic fibrosis, pancreatitis, hemochromatosis); endocrinopathies (eg, Cushing's syndrome, acromegaly); toxins (eg, the rodenticide pyriminyl [Vacor]); and drug-induced diabetes, most notably from glucocorticoids, β-blockers, protease inhibitors, and therapeutic doses of niacin. Pregnancy causes some insulin resistance in all women, but only a few develop gestational DM (see p. 2638).

Symptoms and Signs
The most common symptoms of DM are those of hyperglycemia: an osmotic diuresis caused by glycosuria leading to urinary frequency, polyuria, and polydipsia that may progress to orthostatic hypotension and dehydration. Severe dehydration causes weakness, fatigue, and mental status changes. Symptoms may come and go as plasma glucose levels fluctuate. Polyphagia may accompany symptoms of hyperglycemia but is not typically a primary patient concern. Hyperglycemia can also cause weight loss, nausea and vomiting, and blurred vision, and it may predispose to bacterial or fungal infections.

Patients with type 1 DM typically present with symptomatic hyperglycemia and sometimes with diabetic ketoacidosis (DKA—see p. 883). Some patients experience a long but transient phase of near-normal glucose levels after acute onset of the disease (honeymoon phase) due to partial recovery of insulin secretion.

Patients with type 2 DM may present with symptomatic hyperglycemia but are often asymptomatic, and their condition is detected only on routine testing. In some patients, initial symptoms are those of diabetic complications, suggesting that the disease has been present for some time. In some patients, hyperosmotic coma occurs initially, especially during a period of stress or when glucose metabolism is further impaired by drugs, such as corticosteroids.

Complications

Years of poorly controlled hyperglycemia lead to multiple, primarily vascular complications that affect small (microvascular) vessels, large (macrovascular) vessels, or both. The mechanisms by which vascular disease develops include glycosylation of serum and tissue proteins with formation of advanced glycation end products; superoxide production; activation of protein kinase C, a signaling molecule that increases vascular permeability and causes endothelial dysfunction; accelerated hexosamine biosynthetic and polyol pathways leading to sorbitol accumulation within tissues; hypertension and dyslipidemias that commonly accompany DM; arterial microthromboses; and proinflammatory and prothrombotic effects of hyperglycemia and hyperinsulinemia that impair vascular autoregulation. Immune dysfunction is another major complication and develops from the direct effects of hyperglycemia on cellular immunity.

Microvascular disease underlies the 3 most common and devastating manifestations of DM:

- Retinopathy
- Nephropathy
- Neuropathy

Microvascular disease may also impair skin healing, so that even minor breaks in skin integrity can develop into deeper ulcers and easily become infected, particularly in the lower extremities. Intensive control of plasma glucose can prevent many of these complications but may not reverse them once established.

Diabetic retinopathy: Diabetic retinopathy is the most common cause of adult blindness in the US (see also p. 615). It is characterized initially by retinal capillary microaneurysms and later by macular edema and neovascularization (see Plate 23). There are no early symptoms or signs, but focal blurring, vitreous or retinal detachment, and partial or total vision loss eventually develop; rate of progression is highly variable. Diagnosis is by retinal examination. Treatment is argon laser photocoagulation or vitrectomy. Strict glycemic control and early detection and treatment are critical to preventing vision loss.

Diabetic nephropathy: Diabetic nephropathy (see also p. 2401) is a leading cause of chronic renal failure in the US. It is characterized by thickening of the glomerular basement membrane, mesangial expansion, and glomerular sclerosis. These changes cause glomerular hypertension and progressive decline in GFR. Systemic hypertension may accelerate progression. The disease is usually asymptomatic until nephrotic syndrome or renal failure develops.

Diagnosis is by detection of urinary albumin. A urine dipstick positive for protein signifies albumin
excretion > 300 mg/day and advanced diabetic nephropathy (or an improperly collected or stored specimen). If the dipstick is negative for protein, the albumin:creatinine ratio on a spot urine specimen or urinary albumin in a 24-h collection should be measured. A ratio > 30 mg/g or an albumin concentration 30 to 300 mg/24 h signifies microalbuminuria and early diabetic nephropathy.

Treatment is rigorous glycemic control combined with BP control. An ACE inhibitor, an angiotensin II receptor blocker, or both should be used to treat hypertension at the earliest sign of microalbuminuria or even before, because these drugs lower intraglomerular BP and thus have renoprotective effects.

**Diabetic neuropathy:** Diabetic neuropathy is the result of nerve ischemia due to microvascular disease, direct effects of hyperglycemia on neurons, and intracellular metabolic changes that impair nerve function. There are multiple types, including

- Symmetric polyneuropathy (with small- and large-fiber variants)
- Autonomic neuropathy
- Radiculopathy
- Cranial neuropathy
- Mononeuropathy

Symmetric polyneuropathy is most common and affects the distal feet and hands (stocking-glove distribution); it manifests as paresthesias, dysesthesias, or a painless loss of sense of touch, vibration, proprioception, or temperature. In the lower extremities, these symptoms can lead to blunted perception of foot trauma due to ill-fitting shoes and abnormal weight bearing, which can in turn lead to foot ulceration and infection or to fractures, subluxation, and dislocation or destruction of normal foot architecture (Charcot's joint).

Small-fiber neuropathy is characterized by pain, numbness, and loss of temperature sensation with preserved vibration and position sense. Patients are prone to foot ulceration and neuropathic joint degeneration and have a high incidence of autonomic neuropathy.

Predominant large-fiber neuropathy is characterized by muscle weakness, loss of vibration and position sense, and lack of deep tendon reflexes. Atrophy of intrinsic muscles of the feet and foot drop are common.

Autonomic neuropathy can cause orthostatic hypotension, exercise intolerance, resting tachycardia, dysphagia, nausea and vomiting (due to gastroparesis), constipation and diarrhea (including dumping syndrome), fecal incontinence, urinary retention and incontinence, erectile dysfunction and retrograde ejaculation, and decreased vaginal lubrication.

Radiculopathies most often affect the proximal L2 through L4 nerve roots, causing pain, weakness, and atrophy of the lower extremities (diabetic amyotrophy), or the proximal T4 through T12 nerve roots, causing abdominal pain (thoracic polyradiculopathy).

Cranial neuropathies cause diplopia, ptosis, and anisocoria when they affect the 3rd cranial nerve or motor palsies when they affect the 4th or 6th cranial nerve.

Mononeuropathies cause finger weakness and numbness (median nerve) or foot drop (peroneal nerve). Patients with DM are also prone to nerve compression disorders, such as carpal tunnel syndrome. Mononeuropathies can occur in several places simultaneously (mononeuritis multiplex). All tend to affect older patients predominantly and usually abate spontaneously over months; however, nerve compression disorders do not.

Diagnosis of symmetric polyneuropathy is by detection of sensory deficits and diminished ankle reflexes. Loss of ability to detect the light touch of a nylon monofilament identifies patients at highest risk of foot
ulceration (see Fig. 99-1). Electromyography and nerve conduction studies may be needed for all forms of neuropathy and are sometimes used to exclude other causes of neuropathic symptoms, such as nondiabetic radiculopathy and carpal tunnel syndrome. Strict glycemic control may lessen neuropathy. Treatments for relief of symptoms include topical capsaicin cream, tricyclic antidepressants (eg, imipramine), SNRIs (eg, duloxetine), anticonvulsants (eg, gabapentin, carbamazepine), and mexiletine. Patients with sensory loss should examine their feet daily to detect minor foot trauma and prevent it from progressing to limb-threatening infection.

**Macrovascular disease:** Large-vessel atherosclerosis is a result of the hyperinsulinemia, dyslipidemias, and hyperglycemia characteristic of DM. Manifestations are

- Angina pectoris and MI
- Transient ischemic attacks and strokes
- Peripheral arterial disease

[Fig. 99-1, Diabetic foot screening.]

Diagnosis is by history and examination; the role of screening tests is evolving. Treatment is rigorous control of atherosclerotic risk factors, including normalization of plasma glucose, lipids, and BP, combined with smoking cessation and daily intake of aspirin and ACE inhibitors. In contrast with microvascular disease, intensive control of plasma glucose alone is not an effective preventive measure.

**Cardiomyopathy:** Diabetic cardiomyopathy is thought to result from many factors, including epicardial atherosclerosis, hypertension and left ventricular hypertrophy, microvascular disease, endothelial and autonomic dysfunction, obesity, and metabolic disturbances. Patients develop heart failure due to impairment in left ventricular systolic and diastolic function and are more likely to develop heart failure after MI.

**Infection:** Patients with poorly controlled DM are prone to bacterial and fungal infections because of adverse effects of hyperglycemia on granulocyte and T-cell function. Most common are mucocutaneous fungal infections (eg, oral and vaginal candidiasis) and bacterial foot infections (including osteomyelitis), which are typically exacerbated by lower extremity vascular insufficiency and diabetic neuropathy.

**Other complications:** Diabetic foot complications (skin changes, ulceration, infection, gangrene) are common and are attributable to vascular disease, neuropathy, and relative immunosuppression.

Patients with DM have an increased risk of developing some rheumatologic diseases, including muscle infarction, carpal tunnel syndrome, Dupuytren's contracture, adhesive capsulitis, and sclerodactyly. They may also develop ophthalmologic disease unrelated to diabetic retinopathy (eg, cataracts, glaucoma, corneal abrasions, optic neuropathy); hepatobiliary diseases (eg, nonalcoholic fatty liver disease [steatosis and steatohepatitis], cirrhosis, gallstones); and dermatologic disease (eg, tinea infections, lower-extremity ulcers, diabetic dermopathy, necrobiosis lipoidica diabeticorum, diabetic systemic sclerosis, vitiligo, granuloma annulare, acanthosis nigricans [a sign of insulin resistance]). Depression and dementia are also common.

**Diagnosis**

- Fasting plasma glucose levels
- Sometimes oral glucose tolerance testing

DM is indicated by typical symptoms and signs and confirmed by measurement of plasma glucose. Measurement after an 8- to 12-h fast (fasting plasma glucose [FPG]) or 2 h after ingestion of a concentrated glucose solution (oral glucose tolerance testing [OGTT]) is best (see Table 99-2). OGTT is more sensitive for diagnosing DM and impaired glucose tolerance but is less convenient and reproducible.
than FPG. It is therefore rarely used routinely, except for diagnosing gestational DM (see p. 2638) and for research purposes.

In practice, DM or impaired fasting glucose regulation is often diagnosed using random measures of plasma glucose or of glycosylated Hg (HbA$_{1C}$). A random glucose value > 200 mg/dL (≥ 11.1 mmol/L) may be diagnostic, but values can be affected by recent meals and must be confirmed by repeat testing; testing twice may not be necessary in the presence of diabetic symptoms. HbA$_{1C}$ measurements reflect glucose levels over the preceding 2 to 3 mo. HbA$_{1C}$ measurements are now included in the diagnostic criteria for DM: • HbA$_{1C}$ ≥ 6.5% = DM

• HbA$_{1C}$ 5.7 to 6.4% = prediabetes or at risk of DM

However, values may be falsely high or low (see Monitoring on p. 873), and tests must be done in a certified clinical laboratory. HbA$_{1C}$ is also used for monitoring DM control.

Urine glucose measurement, once commonly used, is no longer used for diagnosis or monitoring because it is neither sensitive nor specific.

**Screening for disease:** Screening for DM should be conducted for people at risk of the disease. Patients with DM are screened for complications.

People at high risk of type 1 DM (eg, siblings and children of people with type 1 DM) can be tested for the presence of islet cell or antiglutamic acid decarboxylase antibodies, which precede onset of clinical disease. However, there are no proven preventive strategies for people at high risk, so such screening is usually reserved for research settings.

Risk factors for type 2 DM include age > 45; obesity; sedentary lifestyle; family history of DM; history of impaired glucose regulation; gestational DM or delivery of a baby > 4.1 kg; history of hypertension or dyslipidemia; polycystic ovary syndrome; and black, Hispanic, or American Indian ethnicity.

Risk of insulin resistance among overweight people (body mass index ≥ 25 kg/m$^2$) is increased with serum triglycerides ≥ 130 mg/dL (≥ 1.47 mmol/L); triglyceride/high-density lipoprotein (HDL) ratio ≥ 3.0 (≥ 1.8); and insulin ≥ 108 pmol/L. People with these characteristics are at particularly high risk and should be screened for DM with an FPG level at least once every 3 yr as long as plasma glucose measurements are normal and at least annually if results reveal impaired fasting glucose levels (see Table 99-2).

**Screening for complications:** All patients with type 1 DM should begin screening for diabetic complications 5 yr after diagnosis. For patients with type 2 DM, screening begins at diagnosis. Typical screening for complications includes

• Foot examination

• Funduscopic examination

• Urine testing for proteinuria and microalbuminuria

• Measurement of serum creatinine and lipid profile

Patients should have their feet examined at least annually for impaired sense of pressure, vibration, pain, or temperature, which is characteristic of peripheral neuropathy. Pressure sense is best tested with a monofilament esthesiometer (see Fig. 99-1). The entire foot, and especially skin beneath the metatarsal heads, should be examined for skin cracking and signs of ischemia, such as ulcerations, gangrene, fungal nail infections, deceased pulses, and hair loss.

Funduscopic examination should be done by an ophthalmologist; the screening interval is controversial but ranges from annually for patients with established retinopathy to every 3 yr for those without retinopathy on at least one examination.
Spot or 24-h urine testing is indicated annually to detect proteinuria or microalbuminuria, and serum creatinine should be measured to assess renal function.

Many physicians consider baseline electrocardiography important given the risk of heart disease. Lipid profile should be checked at least annually and more often when abnormalities are present. BP should be measured at every examination.

**Treatment**

- Diet and exercise
- For type 1 DM, insulin
- For type 2 DM, oral antihyperglycemics, insulin, or both
- Often ACE inhibitors, statins, and aspirin to prevent complications

**Goals and methods:** Treatment involves control of hyperglycemia to relieve symptoms and prevent complications while minimizing hypoglycemic episodes.

Goals for glycemic control are

- Blood glucose between 80 and 120 mg/dL (4.4 and 6.7 mmol/L) during the day
- Blood glucose between 100 and 140 mg/dL (5.6 and 7.8 mmol/L) at bedtime
- HbA<sub>1c</sub> levels < 7%

Glucose levels are typically determined by home monitoring (see Monitoring: on p. 873). These goals may be adjusted for patients in whom strict glucose control may be inadvisable, such as the frail elderly; patients with a short life expectancy; patients who experience repeated bouts of hypoglycemia, especially with hypoglycemic unawareness; and patients who cannot communicate the presence of hypoglycemia symptoms (eg, young children).

Key elements for all patients are patient education, dietary and exercise counseling, and monitoring of glucose control.

All patients with type 1 DM require insulin.

Patients with type 2 DM and mildly elevated plasma glucose should be prescribed a trial of diet and exercise, followed by a single oral antihyperglycemic drug if lifestyle changes are insufficient, additional oral drugs as needed (combination therapy), and insulin when ≥ 2 drugs are ineffective for meeting recommended goals.

Patients with type 2 DM and more significant glucose elevations at diagnosis are typically prescribed lifestyle changes and oral antihyperglycemic drugs simultaneously.

Insulin is indicated as initial therapy for women with type 2 DM who are pregnant and for patients who present with acute metabolic decompensation, such as nonketotic hyperosmolar syndrome (NKHS) or DKA. Patients with severe hyperglycemia (plasma glucose > 400 mg/dL) may respond better to oral therapy after glucose levels are normalized with a brief period of insulin treatment.

Patients with impaired glucose regulation should receive counseling addressing their risk of developing DM and the importance of lifestyle changes for preventing DM. They should be monitored closely for development of DM symptoms or elevated plasma glucose. Ideal follow-up intervals have not been determined, but annual or biannual checks are probably appropriate.
Patient education: Education about causes of DM, diet, exercise, drugs, self-monitoring with fingerstick testing, and the symptoms and signs of hypoglycemia, hyperglycemia, and diabetic complications is crucial to optimizing care. Most patients with type 1 DM can also be taught how to adjust their insulin doses. Education should be reinforced at every physician visit and hospitalization. Formal diabetes education programs, generally conducted by diabetes nurses and nutrition specialists, are often very effective.

Diet: Adjusting diet to individual circumstances can help patients control fluctuations in their glucose level and, for patients with type 2 DM, lose weight.

In general, all patients with DM need to be educated about a diet that is low in saturated fat and cholesterol and contains moderate amounts of carbohydrate, preferably from whole grain sources with higher fiber content. Although dietary protein and fat contribute to caloric intake (and thus, weight gain or loss), only carbohydrates have a direct effect on blood glucose levels. A low-carbohydrate, high-fat diet improves glucose control for some patients, but its long-term safety is uncertain.

Patients with type 1 DM should use carbohydrate counting or the carbohydrate exchange system to match insulin dose to carbohydrate intake and facilitate physiologic insulin replacement. "Counting" the amount of carbohydrate in the meal is used to calculate the preprandial insulin dose. In general, patients require 1 unit of rapid-acting insulin for each 15 g of carbohydrate in a meal. This approach requires detailed patient education and is most successful when guided by a dietitian experienced in working with diabetic patients. Some experts advise use of the glycemic index to delineate between rapid and slowly metabolized carbohydrates, although others believe the index adds little.

Patients with type 2 DM should restrict calories, eat regularly, increase fiber intake, and limit intake of refined carbohydrates and saturated fats. Some experts also recommend dietary protein restriction to ≤ 0.8 g/kg/day to prevent progression of early nephropathy (see p. 2401). Nutrition consultation should complement physician counseling; the patient and the person who prepares the patient's meals should both be present.

Exercise: Physical activity should increase incrementally to whatever level a patient can tolerate. Some experts believe that aerobic exercise is better than isometric exercise for weight loss and protection from vascular disease, but resistance training also can improve glucose control, and all forms of exercise are beneficial.

Patients who experience hypoglycemic symptoms during exercise should be advised to test their blood glucose and ingest carbohydrates or lower their insulin dose as needed to get their glucose slightly above normal just before exercise. Hypoglycemia during vigorous exercise may require carbohydrate ingestion during the workout period, typically 5 to 15 g of sucrose or another simple sugar.

Patients with known or suspected cardiovascular disease may benefit from exercise stress testing before beginning an exercise program, while activity goals may need to be modified for patients with diabetic complications such as neuropathy and retinopathy.

Monitoring: DM control can be monitored by measuring blood levels of

- Glucose
- HbA1c
- Fructosamine

Self-monitoring of whole blood glucose using fingertip blood, test strips, and a glucose meter is most important. It should be used to help patients adjust dietary intake and insulin and to help physicians recommend adjustments in the timing and doses of drugs.

Many different monitoring devices are available. Nearly all require test strips and a means for pricking the skin and obtaining a sample. Most come with control solutions, which should be used periodically to verify...
proper meter calibration. Choice among devices is usually based on patient preferences for features such as time to results (usually 5 to 30 sec), size of display panel (large screens may benefit patients with poor eyesight), and need for calibration. Meters that allow for testing at sites less painful than fingertips (palm, forearm, upper arm, abdomen, thigh) are also available.

Continuous glucose monitoring systems using a subcutaneous catheter can provide real-time results, including an alarm to warn of hypoglycemia, hyperglycemia, or rapidly changing glucose levels. Such devices are expensive and do not eliminate the need for fingerstick glucose testing, but they may be useful for selected patients.

Patients with poor glucose control and those given a new drug or a new dose of a currently used drug may be asked to self-monitor 1 (usually morning fasting) to ≥ 5 times/day, depending on the patient’s needs and abilities and the complexity of the treatment regimen. Most patients with type 1 DM benefit from testing at least 4 times/day.

**HbA1c levels** reflect glucose control over the preceding 2 to 3 mo and hence assess control between physician visits. HbA1c should be assessed quarterly in patients with type 1 DM and at least annually in patients with type 2 DM whose plasma glucose seems stable (more frequently when control is uncertain). Home testing kits are useful for patients who are able to follow the testing instructions rigorously.

Control suggested by HbA1c values sometimes seems to differ from that suggested by daily glucose readings because of falsely elevated or normal values. False elevations may occur with renal insufficiency (urea interferes with the assay), low RBC turnover (as occurs with iron, folate, or vitamin B₁₂ deficiency anemia), high-dose aspirin, and high blood alcohol concentrations. Falsely normal values occur with increased RBC turnover, as occurs with hemolytic anemias and hemoglobinopathies (eg, HbS, HbC) or during treatment of deficiency anemias.

**Fructosamine**, which is mostly glycosylated albumin but also comprises other glycosylated proteins, reflects glucose control in the previous 1 to 2 wk. Fructosamine monitoring may be used during intensive treatment of DM and for patients with Hb variants or high RBC turnover (which cause false HbA1c results), but it is mainly used in research settings.

**Urine glucose monitoring** provides a crude indication of hyperglycemia and can be recommended only when blood glucose monitoring is impossible. By contrast, self-measurement of urine ketones is recommended for patients with type 1 DM if they experience symptoms, signs, or triggers of ketoacidosis, such as nausea or vomiting, abdominal pain, fever, cold or flu-like symptoms, or unusual sustained hyperglycemia (> 250 to 300 mg/dL) during glucose self-monitoring.

**Insulin:** Insulin is required for all patients with type 1 DM if they become ketoacidotic without it; it is also helpful for management of many patients with type 2 DM. Insulin replacement should ideally mimic β-cell function using 2 insulin types to provide basal and prandial requirements (physiologic replacement); this approach requires close attention to diet and exercise as well as to insulin timing and dose. Most insulin preparations are now recombinant human, practically eliminating the once-common allergic reactions to the drug when it was extracted from animal sources. Except for use of regular insulin IV in hospitalized patients, insulin is administered subcutaneously. A number of analogs, created by modifications of the human insulin molecule that alter subcutaneous absorption rates, are available.

Insulin types are commonly categorized by their time to onset and duration of action (see Table 99-3). However, these parameters vary within and among patients depending on many factors (eg, site and technique of injection,

[Table 99-3, Onset, Peak, and Duration of Action of Human Insulin Preparations*]

amount of subcutaneous fat, blood flow at the injection site).

Rapid-acting insulins, including lispro and aspart, are rapidly absorbed because reversal of an amino acid pair prevents the insulin molecule from associating into dimers and polymers. They begin to reduce
plasma glucose often within 15 min but have short duration of action (< 4 h). These insulins are best used at mealtime to control postprandial spikes in plasma glucose.

Regular insulin is slightly slower in onset (30 to 60 min) than lispro and aspart but lasts longer (6 to 8 h). It is the only form for IV use.

Neutral protamine Hagedorn (NPH, or insulin isophane) is intermediate-acting; onset of action is about 2 h after injection, peak effect is 4 to 12 h after injection, and duration of action is 18 to 26 h. Unlike NPH, insulin glargine has no discernible peak of action and provides a steady basal effect over 24 h. Combinations of NPH and regular insulin and of insulin lispro and lispro protamine (a form of lispro modified to act like NPH) are commercially available in premixed preparations (see Table 99-3).

Different insulin types can be drawn into the same syringe for injection but should not be premixed in bottles except by a manufacturer. On occasion, mixing insulins may affect rates of insulin absorption, producing variability of effect and making glycemic control less predictable, especially if mixed > 1 h before use. Insulin glargine should never be mixed with any other insulin.

Many prefilled insulin pen devices are available as an alternative to the conventional vial and syringe method. Insulin pens may be more convenient for use away from home and may be preferable for patients with limited vision or manual dexterity. Spring-loaded self-injection devices (for use with a syringe) may be useful for the occasional patient who is fearful of injection, and syringe magnifiers are available for patients with low vision.

Lispro, aspart, or regular insulin can also be given continuously using an insulin pump. Continuous subcutaneous insulin infusion pumps can eliminate the need for multiple daily injections, provide maximal flexibility in the timing of meals, and substantially reduce variability in glucose levels. Disadvantages include cost, mechanical failures leading to interruptions in insulin supply, and the inconvenience of wearing an external device. Frequent and meticulous self-monitoring and close attention to pump function are necessary for safe and effective use of the insulin pump.

Oligomeric or liposomal oral forms and transmucosal (eg, intranasal, oral spray) or transdermal delivery systems show promise but require further study.

Complications of insulin treatment: Hypoglycemia is the most common complication of insulin treatment, occurring more often as patients try to achieve strict glucose control and approach near-normoglycemia. Symptoms of mild or moderate hypoglycemia include headache, diaphoresis, palpitations, light-headedness, blurred vision, agitation, and confusion. Symptoms of more severe hypoglycemia include seizures and loss of consciousness. In older patients, hypoglycemia may cause strokelike symptoms of aphasia or hemiparesis and is more likely to precipitate stroke, MI, and sudden death. Patients with type 1 DM with long duration of disease may be unaware of hypoglycemic episodes because they no longer experience autonomic symptoms (hypoglycemia unawareness).

Patients should be taught to recognize symptoms of hypoglycemia, which usually respond rapidly to the ingestion of sugar, including candy, juice, and glucose tablets. Typically, 15 g of glucose or sucrose should be ingested. Patients should check their glucose levels 15 min after glucose or sucrose ingestion and ingest an additional 15 g if their glucose level is not > 80 mg/dL. For patients who are unconscious or unable to swallow, hypoglycemia can be treated immediately with glucagon 1 mg sc or IM or a 50% dextrose solution 50 mL IV (25 g) followed, if necessary, by IV infusion of a 5% or 10% dextrose solution to maintain adequate plasma glucose levels.

Hyperglycemia may follow hypoglycemia either because too much sugar was ingested or because hypoglycemia caused a surge in counter-regulatory hormones (glucagon, epinephrine, cortisol, growth hormone). Too high a bedtime insulin dose can drive glucose down and stimulate a counter-regulatory response, leading to morning hyperglycemia (Somogyi phenomenon). A more common cause of unexplained morning hyperglycemia, however, is a rise in early morning growth hormone (dawn phenomenon). In this case, the evening insulin dose should be increased, changed to a longer-acting preparation, or injected later.
Hypokalemia may be caused by intracellular shifts of K due to insulin-induced stimulation of the Na-K pump, but it is uncommon. Hypokalemia more commonly occurs in acute care settings where IV insulin is used.

Local allergic reactions at the site of insulin injections are rare, especially with the use of human insulins, but they may still occur in patients with latex allergy because of the natural rubber latex contained in vial stoppers. They can cause immediate pain or burning followed by erythema, pruritus, and induration the latter sometimes persist for days. Most reactions spontaneously disappear after weeks of continued injection and require no specific treatment, although antihistamines may provide symptomatic relief.

Generalized allergic reaction is extremely rare with human insulins but can occur when insulin is restarted after a lapse in treatment. Symptoms develop 30 min to 2 h after injection and include urticaria, angioedema, pruritus, bronchospasm, and anaphylaxis. Treatment with antihistamines often suffices, but epinephrine and IV glucocorticoids may be needed. If insulin treatment is needed after a generalized allergic reaction, skin testing with a panel of purified insulin preparations and desensitization should be done.

Local fat atrophy or hypertrophy at injection sites is relatively rare and is thought to result from an immune reaction to a component of the insulin preparation. Either may resolve by rotation of injection sites.

Insulin resistance occurs mostly in patients with type 2 DM. The causes are usually obesity and genetic factors. Circulating anti-insulin antibodies are a rare cause. This type of insulin resistance can sometimes be treated by changing insulin preparations (eg, from animal to human insulin) and by administering corticosteroids if necessary.

Insulin regimens for type 1 DM: Regimens range from twice/day split-mixed (eg, split doses of rapid- and intermediate-acting insulins) to more physiologic basal-bolus regimens using multiple daily injections (eg, single fixed [basal] dose of long-acting and variable prandial [bolus] doses of rapid-acting insulin) or an insulin pump. Intensive treatment, defined as glucose monitoring ≥ 4 times/day and ≥ 3 injections/day or continuous insulin infusion, is more effective than conventional treatment (1 to 2 insulin injections daily with or without monitoring) for preventing diabetic retinopathy, nephropathy, and neuropathy. However, intensive therapy may result in more frequent episodes of hypoglycemia and weight gain and is generally effective only in patients who are able and willing to take an active role in their self-care.

In general, most patients with type 1 DM can start with a total dose of 0.2 to 0.8 units of insulin/kg/day. Obese patients may require higher doses. Physiologic replacement involves giving 40 to 60% of the daily insulin dose as an intermediate- or long-acting preparation to cover basal needs, with the remainder given as a rapid- or short-acting preparation to cover postprandial increases. This approach is most effective when the dose of rapid- or short-acting insulin is determined by a sliding scale that takes into account preprandial blood glucose and anticipated meal content. Dose can be adjusted 1 to 2 units for each 50 mg/dL (2.7 mmol/L) above or below target glucose level. This physiologic regimen allows greater freedom of lifestyle because patients can skip or time-shift meals and maintain normoglycemia. However, no specific insulin regimen has proved more effective than others, and these recommendations are for initiation of therapy; thereafter, choice of regimens generally rests on physiologic response and patient and physician preferences.

Insulin regimens for type 2 DM: Regimens for type 2 DM also vary. In many patients, glucose levels are adequately controlled with lifestyle changes or oral drugs, but insulin should be added when glucose remains inadequately controlled by ≥ 2 oral drugs. Although uncommon, adult-onset type 1 DM may be the cause. Insulin should replace oral drugs in women who become pregnant. The rationale for combination therapy is strongest for use of insulin with oral biguanides and insulin sensitizers. Regimens vary from a single daily injection of long- or intermediate-acting insulin (usually at bedtime) to the multiple-injection regimen used by patients with type 1 DM. In general, the simplest effective regimen is preferred. Because of insulin resistance, some patients with type 2 DM require very large doses (> 2 units/kg/day). A common complication is weight gain, which is mostly attributable to reduction in loss of glucose in urine and improved metabolic efficiency.

Oral antihyperglycemic drugs: Oral anti-hyperglycemic drugs (see
Tables 99-4 and 99-5) are the primary treatment for type 2 DM, although insulin is often added when ≥ 2 oral drugs fail to provide adequate glycemic control. Oral antihyperglycemic drugs may

- Enhance pancreatic insulin secretion (secretagogues)
- Sensitize peripheral tissues to insulin (sensitizers)
- Impair GI absorption of glucose

Drugs with different mechanisms of action may be synergistic.

**Sulfonylureas** (SUs) are insulin secretagogues. They lower plasma glucose by stimulating pancreatic β-cell insulin secretion and may secondarily improve peripheral and hepatic insulin sensitivity by reducing glucose toxicity. First-generation drugs (see Table 99-4) are more likely to cause adverse effects and are used infrequently. All SUs promote hyperinsulinemia and weight gain of 2 to 5 kg, which over time may potentiate insulin resistance and limit their usefulness. All also can cause hypoglycemia. Risk factors include age > 65, use of long-acting drugs (especially chlorpropamide, glyburide, or glipizide), erratic eating and exercise, and renal or hepatic insufficiency. Hypoglycemia caused by long-acting drugs may last for days after treatment cessation, occasionally causes permanent neurologic disability, and can be fatal. For these reasons, some physicians hospitalize hypoglycemic patients, especially older ones. Chlorpropamide also causes the syndrome of inappropriate ADH secretion. Most patients taking SUs alone eventually require additional drugs to achieve normoglycemia, suggesting that SUs may exhaust β-cell function. However, worsening of insulin secretion and insulin resistance is probably more a feature of DM itself than of drugs used to treat it.

**Short-acting insulin secretagogues** (repaglinide, nateglinide) stimulate insulin secretion in a manner similar to SUs. They are faster acting, however, and may stimulate insulin secretion more during meals than at other times. Thus, they may be especially effective for reducing postprandial hyperglycemia and seem to have lower risk of hypoglycemia. There may be some weight gain, although apparently less than with SUs. Repaglinide seems to be as effective as SUs or metformin in lowering glucose levels. Nateglinide may be somewhat less effective and therefore more appropriate for patients with mild hyperglycemia. Patients who have not responded to other oral drug classes (eg, SUs, metformin) are not likely to respond to these drugs.

**Biguanides** lower plasma glucose by decreasing hepatic glucose production (gluconeogenesis and glycogenolysis). They are considered peripheral insulin sensitizers, but their stimulation of peripheral glucose uptake may simply be a result of reductions in glucose from their hepatic effects. Biguanides also lower lipid levels and may also decrease GI nutrient absorption, increase β-cell sensitivity to circulating glucose, and decrease levels of plasminogen activator inhibitor 1, thereby exerting an antithrombotic effect. Metformin is the only biguanide commercially available in the US. It is at least as effective as SUs in reducing plasma glucose, rarely causes hypoglycemia, and can be safely used with other drugs and insulin. In addition, metformin does not cause weight gain and may even promote weight loss by suppressing appetite. However, the drug commonly causes GI adverse effects (eg, dyspepsia, diarrhea), which for most people recede with time. Less commonly, metformin causes vitamin B12 malabsorption, but clinically significant anemia is rare. Contribution of metformin to life-threatening lactic acidosis is controversial, but the drug is thought to be contraindicated in patients at risk of acidemia (including those with renal insufficiency [creatinine ≥ 1.4 mg/dL], heart failure, hypoxia or severe respiratory disease, alcoholism, other forms of metabolic acidosis, or dehydration). The drug should be withheld during surgery, administration of IV contrast, and any serious illness. Many people receiving metformin monotherapy eventually require an additional drug.

**Thiazolidinediones** (TZDs) decrease peripheral insulin resistance (insulin sensitizers), but their specific mechanisms of action are not well understood. The drugs bind a nuclear receptor primarily present in fat...
cells (peroxisome-proliferator-activated receptor-γ [PPAR-γ]) that is involved in the transcription of genes that regulate glucose and lipid metabolism. TZDs also increase HDL levels, lower triglycerides, and may have anti-inflammatory and anti-atherosclerotic effects. TZDs are as effective as SUs and metformin in reducing HbA1C. Because the drug class is relatively new, data on long-term safety and effectiveness are not available. Though one TZD (troglitazone) caused acute liver failure, currently available drugs have not proven hepatotoxic. Nevertheless, periodic monitoring of liver function is recommended. TZDs may cause peripheral edema, especially in patients taking insulin, and may worsen heart failure in susceptible patients. Weight gain, due to fluid retention and increased adipose tissue mass, is common and may be substantial (> 10 kg) in some patients. Rasaglitazone may increase risk of heart failure, angina, MI, stroke, and fracture.

\[\textit{α-Glucosidase inhibitors} (AGIs) competitively inhibit intestinal enzymes that hydrolyze dietary carbohydrates; carbohydrates are digested and absorbed more slowly, thereby lowering postprandial plasma glucose. AGIs are less effective than other oral drugs in reducing plasma glucose, and patients often stop the drugs because they may cause dyspepsia, flatulence, and diarrhea. But the drugs are otherwise safe and can be used in combination with all other oral drugs and with insulin.

\[\textit{Dipeptidyl peptidase-4 inhibitors} (eg, sitagliptin, saxagliptin) block glucagon-like peptide-1 (GLP-1) breakdown by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4). Vildagliptin, a similar drug, is being developed.

\[\textit{Injectable antihyperglycemic drugs}: Injectable antihyperglycemic drugs other than insulin are the GLP-1 agonists and the amylin analog, pramlintide (see Table 99-4). These drugs are used in combination with other antihyperglycemics.

\[\textit{GLP-1 agonists} (eg, exenatide [an incretin hormone], liraglutide) enhance glucose-dependent insulin secretion and slow gastric emptying. Exenatide may also reduce appetite and promote weight loss and stimulate β-cell proliferation. It is given by injection 5 or 10 μg bid before meals and may be used in combination with oral antihyperglycemics. Other GLP-1 agonists, including a long-acting form of exenatide, are being developed.

The \textit{amylin analog} pramlintide mimics amylin, a pancreatic β-cell hormone that helps regulate postprandial glucose levels. Pramlintide suppresses postprandial glucagon secretion, slows gastric emptying, and promotes satiety. It is given by injection and is used in combination with mealtime insulin. Patients with type 1 DM are given 30 to 60 μg sc before meals, and those with type 2 DM are given 120 μg.

\[\textit{Other antihyperglycemic treatments}]: Transplantation of pancreatic or islet cells is an alternative means of insulin delivery; both techniques effectively transplant insulin-producing β-cells into insulin-deficient (type 1) patients. Indications, tissue sources, procedures, and limitations of both procedures are discussed elsewhere (see p. 1138).

Other oral antihyperglycemic drugs are under investigation. These drugs include PPAR-α and PPAR-γ agonists (ragaglitazar, tesaglitazar); non-TZD insulin sensitizers, including recombinant human insulin-like growth factor-1 (IGF-1); and phosphodiesterase inhibitors, which augment pancreatic insulin secretion.

Adjunctive treatments: Measures to prevent or treat complications of DM are critical. ACE inhibitors, angiotensin II receptor blockers, or both are indicated for patients with evidence of early nephropathy (microalbuminuria or proteinuria), even in the absence of hypertension, and are a good choice for treating hypertension in patients who have DM and who have not yet shown renal impairment.

ACE inhibitors also help prevent cardiovascular events in patients with DM. Aspirin 81 to 325 mg once/day provides cardiovascular protection and should be used by most adults with DM in the absence of a specific contraindication. Patients with type 2 DM tend to have high levels of triglycerides and small, dense low-density lipoproteins (LDL) and low levels of HDL; they should receive aggressive treatment.
with the same treatment goals as those of patients with known coronary artery disease (LDL < 100 mg/dL [< 2.6 mmol/L], HDL > 40 mg/dL [> 1.1 mmol/L], and triglycerides < 150 mg/dL [< 1.7 mmol/L]—see Table 100-4 on p. 897).

Orlistat, an intestinal lipase inhibitor, reduces dietary fat absorption; it reduces serum lipids and helps promote weight loss. Sibutramine, a centrally acting anorectic drug, is for short-term use to promote weight loss. Both of these drugs may be useful in selected patients as part of a comprehensive weight loss program. Surgical treatment for obesity, such as gastric banding or bypass, also leads to weight loss and improved glucose control in patients who have DM and are unable to lose weight through other means.

Regular professional podiatric care, including trimming of toenails and calluses, is important for patients with sensory loss or circulatory impairment. Such patients should be advised to inspect their feet daily for cracks, fissures, calluses, corns, and ulcers. Feet should be washed daily in lukewarm water, using mild soap, and dried gently and thoroughly. A lubricant (eg, lanolin) should be applied to dry, scaly skin. Nonmedicated foot powders should be applied to moist feet. Toenails should be cut, preferably by a podiatrist, straight across and not too close to the skin. Adhesive plasters and tape, harsh chemicals, corn cures, water bottles, and electric pads should not be used on skin. Patients should change stockings daily and not wear constricting clothing (eg, garters, socks or stockings with tight elastic tops). Shoes should fit well, be wide-toed without open heels or toes, and be changed frequently. Special shoes should be prescribed to reduce trauma if the foot is deformed (eg, previous toe amputation, hammer toe, bunion). Walking barefoot should be avoided. Patients with neuropathic foot ulcers should avoid weight bearing until ulcers heal. If they cannot, they should wear appropriate orthotic protection. Because most patients with these ulcers have little or no macrovascular occlusive disease, debridement and antibiotics frequently result in good healing and may prevent major surgery (see p. 672). After the ulcer has healed, appropriate inserts or special shoes should be prescribed. In refractory cases, especially if osteomyelitis is present, surgical removal of the metatarsal head (the source of pressure) or amputation of the involved toe or transmetatarsal amputation may be required. A neuropathic joint can often be satisfactorily managed with orthopedic devices (eg, short leg braces, molded shoes, sponge-rubber arch supports, crutches, prostheses).

All patients with DM should be vaccinated against *Streptococcus pneumoniae* (once) and influenza virus (annually).

**Special Populations and Settings**

The term brittle diabetes has been used to refer to patients who have dramatic, recurrent swings in glucose levels, often for no apparent reason. However, this concept has no biologic basis and should not be used. Labile plasma glucose levels are more likely to occur in patients with type 1 DM because endogenous insulin production is completely absent and, in some patients, counterregulatory response to hypoglycemia is impaired. Other causes include occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (eg, Addison's disease).

Patients with chronic difficulty maintaining acceptable glucose levels should be evaluated for situational factors that affect glucose control. Such factors include inadequate patient education or understanding that leads to errors in insulin administration, inappropriate food choices, and psychosocial stress that expresses itself in erratic patterns of drug use and food intake.

The initial approach is to thoroughly review self-care techniques, including insulin preparation and injection and glucose testing. Increased frequency of self-testing may reveal previously unrecognized patterns and provides the patient with helpful feedback. A thorough dietary history, including timing of meals, should be taken to identify potential contributions to poor control. Underlying disorders should be ruled out by physical examination and appropriate laboratory tests. For some insulin-treated patients, changing to a more intensive regimen that allows for frequent dose adjustments (based on glucose testing) is helpful. In some cases, the frequency of hypoglycemic and hyperglycemic episodes diminishes over time even without specific treatment, suggesting life circumstances may contribute to causation.

**Children:** Children with type 1 DM require physiologic insulin replacement as do adults, and similar
treatment regimens, including insulin pumps, are used. However, the risk of hypoglycemia, because of unpredictable meal and activity patterns and limited ability to report hypoglycemic symptoms, may require modification of treatment goals. Most young children can be taught to actively participate in their own care, including glucose testing and insulin injections. School personnel and other caregivers must be informed about the disease and instructed about the detection and treatment of hypoglycemic episodes. Screening for microvascular complications can generally be deferred until after puberty.

Children with type 2 DM require the same attention to diet and weight control and recognition and management of dyslipidemia and hypertension as do adults. Most children with type 2 DM have severe obesity, so lifestyle modification is the cornerstone of therapy. Children with mild hyperglycemia generally begin treatment with metformin unless they have ketosis, renal insufficiency, or another contraindication to metformin use. Dosage is 500 to 1000 mg bid. If response is insufficient, an insulin secretagogue (such as a SU or repaglinide) or insulin may be added. TZDs are generally avoided because long-term safety is unknown.

**Adolescents:** Glucose control typically deteriorates as children with DM enter adolescence. Multiple factors contribute, including pubertal and insulin-induced weight gain; hormonal changes that decrease insulin sensitivity; psychosocial factors that lead to insulin nonadherence (eg, mood and anxiety disorders); family conflict, rebellion, and peer pressure; eating disorders that lead to insulin omission as a means of controlling weight; and experimentation with cigarettes, alcohol, and substance use. For these reasons, some adolescents experience recurrent episodes of hyperglycemia and DKA requiring emergency department visits and hospitalization.

Treatment often involves intensive medical supervision combined with psychosocial interventions (eg, mentoring or support groups), individual or family therapy, and psychopharmacology when indicated. Patient education is important so that adolescents can safely enjoy the freedoms of early adulthood. Rather than judging personal choices and behaviors, providers must continually reinforce the need for careful glycemic control, especially frequent blood sugar monitoring and use of frequent, low-dose, fast-acting insulins as needed.

**Hospitalization:** Diabetes can be a primary reason for hospitalization or can accompany other illnesses that require inpatient care. All diabetic patients with DKA, NKHS, or prolonged or severe hypoglycemia should be hospitalized. Others with SU-induced hypoglycemia, poorly controlled hyperglycemia, or acute worsening of diabetic complications may benefit from brief hospitalization, as do children and adolescents with new-onset disease. Control may worsen on discharge when insulin regimens developed in controlled inpatient settings prove inadequate to the uncontrolled conditions outside the hospital.

When other illnesses mandate hospitalization, many patients do well without any change in drugs. However, glucose control may prove difficult, and it is often neglected when other diseases are more acute. Restricted physical activity and acute illness worsen hyperglycemia in some patients, whereas dietary restrictions and symptoms that accompany illness (eg, nausea, vomiting, diarrhea, anorexia) precipitate hypoglycemia in others—especially when antihyperglycemic drug doses remain unchanged. In addition, it may be difficult to control glucose adequately in hospitalized patients because usual routines (eg, timing of meals, drugs, and procedures) are inflexibly timed relative to diabetes treatment regimens. Inpatients who are able to eat may continue usual outpatient regimens; others may be appropriately treated with basal insulin without or with supplemental short-acting insulin. Sliding-scale insulin should not be the only intervention to correct hyperglycemia; it is reactive rather than proactive, and no data suggest it leads to outcomes equivalent to or better than other approaches. Longer-acting insulins should be adjusted to prevent hyperglycemia rather than just using short-acting insulins to correct it.

Inpatient hyperglycemia worsens short-term prognosis for many acute conditions, most notably stroke and acute MI, and often prolongs hospital stay. Critical illness causes insulin resistance and hyperglycemia even in patients without known DM. Insulin infusion to maintain plasma glucose between 100 and 150 mg/dL (4.4 and 6.1 mmol/L) prevents adverse outcomes such as organ failure, may enhance recovery from stroke, and leads to improved survival in patients requiring prolonged (> 5 days) critical care. Severely ill patients, especially those receiving glucocorticoids or pressors, may need very high doses of insulin (> 5 to 10 units/h) because of insulin resistance. Insulin infusion should also be considered for patients receiving TPN and for patients with type 1 DM who cannot ingest anything orally.
Surgery: The physiologic stress of surgery can increase plasma glucose in patients with DM and induce DKA in those with type 1 DM. For type 1 patients, one half to two thirds of the usual morning dose of intermediate-acting insulin or 70 to 80% of the dose of long-acting insulin (glargine or detemir) can be given the morning before surgery with an IV infusion of a 5% dextrose solution at a rate of 100 to 150 mL/h. During and after surgery, plasma glucose (and ketones if hyperglycemia suggests the need) should be measured at least every 2 h. Glucose infusion is continued (monitoring is done at 2- to 4-h intervals), and regular or short-acting insulin is given sc q 4 to 6 h as needed to maintain the plasma glucose level between 100 and 200 mg/dL (5.55 and 11.01 mmol/L) until the patient can be switched to oral feedings and resume the usual insulin regimen. Additional doses of intermediate- or long-acting insulin should be given if there is a substantial delay (> 24 h) in resuming the usual regimen. This approach may also be used for insulin-treated patients with type 2 DM, but frequent measurement of ketones may be omitted.

Some physicians prefer to withhold sc insulin on the day of surgery and to give insulin by IV infusion. One approach is to add 6 to 10 units of regular insulin to 1 L of 5% dextrose in 0.9% saline solution or water infused initially at 100 to 150 mL/h on the morning of surgery based on the plasma glucose level. Alternatively, separate insulin (1 to 2 units/h) and dextrose (75 to 125 mL/h of 5% dextrose) infusions may be used and allow for easier titration. Insulin adsorption onto IV tubing can lead to inconsistent effects, which can be minimized by prefllushing the IV tubing with insulin solution. Insulin infusion is continued through recovery, with insulin adjusted based on the plasma glucose levels obtained in the recovery room and at 1- to 2-h intervals thereafter.

Most patients with type 2 DM who are treated with oral antihyperglycemic drugs maintain acceptable glucose levels when fasting and may not require insulin in the perioperative period. Most oral drugs, including SUs and metformin, should be withheld on the day of surgery, and plasma glucose levels should be measured preoperatively and postoperatively and every 6 h while patients receive IV fluids. Oral drugs may be resumed when patients are able to eat, but metformin should be withheld until normal renal function is confirmed 48 h after surgery.

Prevention

Type 1: No treatments definitely prevent the onset or progression of type 1 DM. Azathioprine, corticosteroids, and cyclosporine induce remission of early type 1 DM in some patients, presumably through suppression of autoimmune β-cell destruction. However, toxicity and the need for lifelong treatment limit their use. In a few patients, short-term treatment with anti-CD3 monoclonal antibodies reduces insulin requirements for at least the first year of recent-onset disease by suppressing autoimmune T-cell response.

Type 2: Type 2 DM usually can be prevented with lifestyle modification. Weight loss of as little as 7% of baseline body weight, combined with moderate-intensity physical activity (eg, walking 30 min/day), may reduce the incidence of DM in high-risk people by > 50%. Metformin and acarbose have also been shown to reduce the risk of DM in patients with impaired glucose regulation. TZDs may also be protective, perhaps by inducing PPAR-γ activity but require further study before they can be recommended for routine preventive use.

Complications: Risk of DM complications can be decreased by strict control of plasma glucose, defined as HbA1c < 7%, and by control of hypertension and lipid levels (see pp. 2069 and 896). Specific measures for prevention of progression of complications once detected are described under Complications (see p. 868) and Treatment (see p. 871).

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. DKA occurs mostly in type 1 diabetes mellitus (DM). It causes nausea, vomiting, and abdominal pain and can progress to cerebral edema, coma, and death. DKA is diagnosed by detection of hyperketonemia and anion gap metabolic acidosis in the presence of hyperglycemia. Treatment involves volume expansion, insulin replacement, and prevention of hypokalemia.
DKA is most common among patients with type 1 DM and develops when insulin levels are insufficient to meet the body's basic metabolic requirements. DKA is the first manifestation of type 1 DM in a minority of patients. Insulin deficiency can be absolute (eg, during lapses in the administration of exogenous insulin) or relative (eg, when usual insulin doses do not meet metabolic needs during physiologic stress). Common physiologic stresses that can trigger DKA include acute infection (particularly pneumonia and UTI), MI, stroke, pancreatitis, and trauma. Drugs implicated in causing DKA include corticosteroids, thiazide diuretics, and sympathomimetics. DKA is less common in type 2 DM, but it may occur in situations of unusual physiologic stress.

Pathophysiology

Insulin deficiency causes the body to metabolize triglycerides and muscle instead of glucose for energy. Serum levels of glycerol and free fatty acids (FFAs) rise because of unrestrained lipolysis, as does alanine because of muscle catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major ketoacids produced, acetoacetic acid and β-hydroxybutyric acid, are strong organic acids that create metabolic acidosis. Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration.

Hyperglycemia due to insulin deficiency causes an osmotic diuresis that leads to marked urinary losses of water and electrolytes. Urinary excretion of ketones obligates additional losses of Na and K. Serum Na may fall from natriuresis or rise due to excretion of large volumes of free water. K is also lost in large quantities, sometimes > 300 mEq/24 h. Despite a significant total body deficit of K, initial serum K is typically normal or elevated because of the extracellular migration of K in response to acidosis. K levels generally fall further during treatment as insulin therapy drives K into cells. If serum K is not monitored and replaced as needed, life-threatening hypokalemia may develop.

Symptoms and Signs

Symptoms and signs of DKA include those of hyperglycemia (see p. 868) with the addition of nausea, vomiting, and—particularly in children—abdominal pain. Lethargy and somnolence are symptoms of more severe decompensation. Patients may be hypotensive and tachycardic from dehydration and acidosis; they may breathe rapidly and deeply to compensate for acidemia (Kussmaul's respirations). They may also have fruity breath due to exhaled acetone. Fever is not a sign of DKA itself and, if present, signifies underlying infection. In the absence of timely treatment, DKA progresses to coma and death.

Acute cerebral edema, a complication in about 1% of DKA patients, occurs primarily in children and less often in adolescents and young adults. Headache and fluctuating level of consciousness herald this complication in some patients, but respiratory arrest is the initial manifestation in others. The cause is not well understood but may be related to too-rapid reductions in serum osmolality or to brain ischemia. It is most likely to occur in children < 5 yr when DKA is the initial manifestation of DM. Children with the highest BUN and lowest PaCO₂ at presentation seem to be at greatest risk. Delays in correction of hyponatremia and the use of HCO₃ during DKA treatment are additional risk factors.

Diagnosis

- Arterial pH
- Serum ketones
- Calculation of anion gap

In patients suspected of having DKA, serum electrolytes, BUN and creatinine, glucose, ketones, and osmolarity should be measured. Urine should be tested for ketones. Patients who appear significantly ill and those with positive ketones should have ABG measurement. DKA is diagnosed by an arterial pH <
7.30 with an anion gap > 12 (see Sidebar 98-1 on p. 858) and serum ketones in the presence of hyperglycemia. A presumptive diagnosis can be made when urine glucose and ketones are strongly positive. Urine test strips and some assays for serum ketones may underestimate the degree of ketosis because they detect acetoacetic and not β-hydroxybutyric acid, which is usually the predominant ketoacid.

Symptoms and signs of a triggering illness should be pursued with appropriate studies (eg, cultures, imaging studies). Adults should have an ECG to screen for acute MI and to help determine the significance of abnormalities in serum K.

Other laboratory abnormalities include hyponatremia, elevated serum creatinine, and elevated serum osmolarity. Hyperglycemia may cause dilutional hyponatremia, so measured serum Na is corrected by adding 1.6 mEq/L for each 100 mg/dL elevation of serum glucose over 100 mg/dL. To illustrate, for a patient with serum Na of 124 mEq/L and glucose of 600 mg/dL, add 1.6 ([(600-100)/100] = 8 mEq/L to 124 for a corrected serum Na of 132 mEq/L. As acidosis is corrected, serum K drops. An initial K level < 4.5 mEq/L indicates marked K depletion and requires immediate K supplementation. Serum amylase and lipase are often elevated, even in the absence of pancreatitis (which may be present in alcoholic DKA patients and in those with coexisting hypertriglyceridemia).

**Prognosis**

Mortality rates for DKA are between 1 and 10%. Shock or coma on admission indicates a worse prognosis. Main causes of death are circulatory collapse, hypokalemia, and infection. Among children with cerebral edema, 57% recover completely, 21% survive with neurologic sequelae, and 21% die.

**Treatment**

- IV 0.9% saline
- Correction of any hypokalemia
- IV insulin (as long as serum K is ≥ 3.3 mEq/L)
- Rarely IV NaHCO₃ (if pH < 7 after 1 h of treatment)

The most urgent goals are rapid intravascular volume repletion, correction of hyperglycemia and acidosis, and prevention of hypokalemia. Identification of precipitating factors is also important. Treatment should occur in intensive care settings because clinical and laboratory assessments are initially needed every hour or every other hour with appropriate adjustments in treatment.

Intravascular volume should be restored rapidly to raise BP and ensure glomerular perfusion; once intravascular volume is restored, remaining total body water deficits are corrected more slowly, typically over about 24 h. Initial volume repletion in adults is typically achieved with rapid IV infusion of 1 to 3 L of 0.9% saline solution, followed by saline infusions at 1 L/h or faster as needed to raise BP, correct hyperglycemia, and keep urine flow adequate. Adults with DKA typically need a minimum of 3 L of saline over the first 5 h. When BP is stable and urine flow adequate, normal saline is replaced by 0.45% saline. When plasma glucose falls to < 250 mg/dL, IV fluid should be changed to 5% dextrose in 0.45% saline.

For children, fluid deficits are estimated at 60 to 100 mL/kg body weight. Maintenance fluids (for ongoing losses) must also be provided (see p. 2808). Initial fluid therapy should be 0.9% saline (20 mL/kg) over 1 to 2 h, followed by 0.45% saline once BP is stable and urine output adequate. The remaining fluid deficit should be replaced over 36 h, typically requiring a rate (including maintenance fluids) of about 2 to 4 mL/kg/h, depending on the degree of dehydration.

Hyperglycemia is corrected by giving regular insulin 0.15 unit/kg IV bolus initially, followed by continuous IV infusion of 0.1 unit/kg/h in 0.9% saline solution. Insulin should be withheld until serum K is ≥ 3.3 mEq/L (see p. 886). Insulin adsorption onto IV tubing can lead to inconsistent effects, which can be minimized by preflushing the IV tubing with insulin solution. If plasma glucose does not fall by 50 to 75
mg/dL in the first hour, insulin doses should be doubled. Children should be given a continuous IV insulin infusion of 0.1 unit/kg/h or higher with or without a bolus.

Ketones should begin to clear within hours if insulin is given in sufficient doses. However, clearance of ketones may seem to lag because of conversion of β-hydroxybutyrate to acetoacetate (which is the "ketone" measured in most hospital laboratories) as acidosis resolves. Serum pH and HCO₃ levels should also quickly improve, but restoration of a normal serum HCO₃ level may take 24 h. Rapid correction of pH by HCO₃ administration may be considered if pH remains < 7 after about an hour of initial fluid resuscitation, but HCO₃ is associated with development of acute cerebral edema (primarily in children) and should not be used routinely. If used, only modest pH elevation should be attempted (target pH of about 7.1), with doses of 50 to 100 mEq over 30 to 60 min, followed by repeat measurement of arterial pH and serum K.

When plasma glucose becomes 250 to 300 mg/dL (13.88 to 16.65 mmol/L) in adults, 5% dextrose should be added to IV fluids to reduce the risk of hypoglycemia. Insulin dosage can then be reduced (minimum 1 to 2 units/h), but the continuous IV infusion of regular insulin should be maintained until the anion gap has narrowed and blood and urine are consistently negative for ketones. Insulin replacement may then be switched to regular insulin 5 to 10 units sc q 4 to 6 h. When the patient is stable and able to eat, a typical split-mixed or basal-bolus insulin regimen is begun. IV insulin should be continued for 1 to 4 h after the initial dose of sc insulin is given. Children should continue to receive 0.05 unit/kg/h insulin infusion until sc insulin is initiated and pH is > 7.3.

Hypokalemia prevention requires replacement of 20 to 30 mEq K in each liter of IV fluid to keep serum K between 4 and 5 mEq/L. If serum K is < 3.3 mEq/L, insulin should be withheld and K given at 40 mEq/h until serum K is ≥ 3.3 mEq/L; if serum K is > 5 mEq/L, K supplementation can be withheld. Initially normal or elevated serum K measurements may reflect shifts from intracellular stores in response to acidemia and belie the true K deficits that almost all DKA patients have. Insulin replacement rapidly shifts K into cells, so levels should be checked hourly or every other hour in the initial stages of treatment. Hypophosphatemia often develops during treatment of DKA, but phosphate repletion is of unclear benefit in most cases. If indicated (eg, if rhabdomyolysis, hemolysis, or neurologic deterioration occurs), K phosphate 1 to 2 mmol/kg of phosphate, can be infused over 6 to 12 h. If K phosphate is given, the serum Ca level usually decreases and should be monitored.

Treatment of suspected cerebral edema is hyperventilation, corticosteroids, and mannitol, but these measures are often ineffective after the onset of respiratory arrest.

**Nonketotic Hyperosmolar Syndrome** (Hyperosmolar Hyperglycemic State)

Nonketotic hyperosmolar syndrome (NKHS) is a metabolic complication of diabetes mellitus (DM) characterized by hyperglycemia, extreme dehydration, hyperosmolar plasma, and altered consciousness. It most often occurs in type 2 DM, often in the setting of physiologic stress. NKHS is diagnosed by severe hyperglycemia and serum hyperosmolarity and absence of significant ketosis. Treatment is IV saline solution and insulin. Complications include coma, seizures, and death.

NKHS is a complication of type 2 DM and has a mortality rate of up to 40%. It usually develops after a period of symptomatic hyperglycemia in which fluid intake is inadequate to prevent extreme dehydration due to hyperglycemia-induced osmotic diuresis. The precipitating factor may be a coexisting acute infection, drugs that impair glucose tolerance (glucocorticoids) or increase fluid loss (diuretics), medical nonadherence, or other medical conditions. Serum ketones are not present because the amounts of insulin present in most patients with type 2 DM are adequate to suppress ketogenesis. Because symptoms of acidosis are not present, most patients endure a significantly longer period of osmotic dehydration before presentation, and thus plasma glucose (> 600 mg/dL [> 33 mmol/L]) and osmolarity (> 320 mOsm/L) are typically much higher than in diabetic ketoacidosis (DKA).
Symptoms and Signs

The primary symptom of NKHS is altered consciousness varying from confusion or disorientation to coma, usually as a result of extreme dehydration with or without prerenal azotemia, hyperglycemia, and hyperosmolarity. In contrast to DKA, focal or generalized seizures and transient hemiplegia may occur.

Diagnosis

- Blood glucose level
- Serum osmolarity

Generally, NKHS is initially suspected when a markedly elevated glucose level is found in a fingerstick specimen obtained in the course of a workup of altered mental status. If measurements have not already been obtained, measurement of serum electrolytes, BUN and creatinine, glucose, ketones, and osmolarity should be done. Urine should be tested for ketones. Serum K levels are usually normal, but Na may be low or high depending on volume deficits. BUN and serum creatinine levels are markedly increased. Arterial pH is usually > 7.3, but occasionally mild metabolic acidosis develops due to lactate accumulation.

The average fluid deficit is 10 L, and acute circulatory collapse is a common cause of death. Widespread thrombosis is a frequent finding on autopsy, and in some cases bleeding may occur as a consequence of disseminated intravascular coagulation. Other complications include aspiration pneumonia, acute renal failure, and acute respiratory distress syndrome.

Treatment

- IV 0.9% saline
- Correction of any hypokalemia
- IV insulin (as long as serum K is ≥ 3.3 mEq/L)

Treatment is 0.9% saline solution 1 L IV over 30 min, then at 1 L/h to raise BP and improve circulation and urine output. It can be replaced by 0.45% saline when BP becomes normal and plasma glucose reaches 300 mg/dL. The rate of infusion of IV fluids should be adjusted depending on BP, cardiac status, and the balance between fluid input and output.

Insulin is given at 0.15 unit/kg IV bolus followed by a 0.1 unit/kg/h infusion after the first liter of saline has been infused. Hydration alone can sometimes precipitously decrease plasma glucose, so insulin dose may need to be reduced. A too-quick reduction in osmolality can lead to cerebral edema. Occasional patients with insulin-resistant type 2 DM with NKHS require larger insulin doses. Once plasma glucose reaches 200 to 250 mg/dL, insulin infusion should be reduced to basal levels (1 to 2 units/h) until rehydration is complete and the patient is able to eat. Addition of 5% dextrose infusion may occasionally be needed to avoid hypoglycemia. After recovery from the acute episode, patients are usually switched to adjusted doses of sc insulin. Most patients can resume using oral antihyperglycemic drugs once their condition is stable.

K replacement is similar to DKA: 40 mEq/h for serum K < 3.3 mEq/L; 20 to 30 mEq/h for serum K between 3.3 and 4.9 mEq/L; and none for serum K ≥ 5 mEq/L.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis is a metabolic complication of alcohol use and starvation characterized by hyperketonemia and anion gap metabolic acidosis without significant hyperglycemia. Alcoholic ketoacidosis causes nausea, vomiting, and abdominal pain. Diagnosis is by history and findings of ketoacidosis without hyperglycemia. Treatment is IV saline solution and dextrose infusion.
Alcoholic ketoacidosis is attributed to the combined effects of alcohol and starvation on glucose metabolism.

Pathophysiology

Alcohol diminishes hepatic gluconeogenesis and leads to decreased insulin secretion, increased lipolysis, impaired fatty acid oxidation, and subsequent ketogenesis. Counter-regulatory hormones are increased and may further inhibit insulin secretion. Plasma glucose levels are usually low or normal, but mild hyperglycemia sometimes occurs.

Symptoms and Signs

Typically, an alcohol binge leads to vomiting and the cessation of alcohol or food intake for ≥ 24 h. During this period of starvation, vomiting continues and abdominal pain develops, leading the patient to seek medical attention. Pancreatitis may occur.

Diagnosis

• Clinical evaluation
• Calculation of anion gap
• Exclusion of other disorders

Diagnosis requires a high index of suspicion; similar symptoms in an alcoholic patient may result from acute pancreatitis, methanol or ethylene glycol poisoning, or diabetic ketoacidosis (DKA). In patients suspected of having alcoholic ketoacidosis serum electrolytes (including Mg), BUN and creatinine, glucose, ketones, amylase, lipase, and osmolarity should be measured. Urine should be tested for ketones. Patients who appear significantly ill and those with positive ketones should probably have ABG and serum lactate measurement. The absence of hyperglycemia makes DKA improbable. Those with mild hyperglycemia may have underlying diabetes mellitus, which may be recognized by elevated levels of glycosylated Hb (HbA1c). Typical laboratory findings include a high anion gap metabolic acidosis, ketonemia, and low levels of K, Mg, and P. Detection of acidosis may be complicated by concurrent metabolic alkalosis due to vomiting, resulting in a relatively normal pH; the main clue is the elevated anion gap. If history does not rule out toxic alcohol ingestion as a cause of the elevated anion gap, serum methanol and ethylene glycol levels should be obtained. Ca oxalate crystals in the urine also suggests ethylene glycol poisoning. Lactic acid levels are often elevated because of hypoperfusion and the altered balance of reduction and oxidation reactions in the liver.

Treatment

• IV thiamin and other vitamins plus Mg
• IV 5% dextrose in 0.9% saline

Treatment begins with an IV infusion of 5% dextrose in 0.9% saline solution, preceded by thiamin 100 mg IV to prevent development of Wernicke's encephalopathy or Korsakoff's psychosis. Initial IV fluids should contain added water-soluble vitamins and Mg, with K replacement as required. Ketoacidosis and GI symptoms usually respond rapidly. Use of insulin is appropriate only if there is any question of atypical DKA or if hyperglycemia > 300 mg/dL develops.

Hypoglycemia

Hypoglycemia unrelated to exogenous insulin therapy is an uncommon clinical syndrome characterized by low plasma glucose level, symptomatic sympathetic nervous system stimulation, and CNS dysfunction. Many drugs and disorders cause it. Diagnosis requires blood tests done at the time of symptoms or during a 72-h fast. Treatment is provision of glucose
combined with treatment of the underlying disorder.

Most commonly, symptomatic hypoglycemia is a complication of drug treatment of diabetes mellitus (DM). Oral antihyperglycemics or insulin may be involved.

Symptomatic hypoglycemia unrelated to treatment of DM is relatively rare, in part because the body has extensive counter-regulatory mechanisms to compensate for low blood glucose levels. Glucagon and epinephrine levels surge in response to acute hypoglycemia and seem to be the first line of defense. Cortisol and growth hormone levels also increase acutely and are important in the recovery from prolonged hypoglycemia. The threshold for release of these hormones is usually above that for hypoglycemic symptoms.

Etiology

Causes of physiologic hypoglycemia can be classified as

- Reactive (postprandial) or fasting
- Insulin-mediated or non-insulin-mediated
- Drug-induced or nondrug-induced

Insulin-mediated causes include exogenous administration of insulin or an insulin secretagogue and insulin-secreting tumors (insulinomas). A helpful practical classification is based on clinical status: whether hypoglycemia occurs in patients who appear healthy or ill. Within these categories, causes of hypoglycemia can be divided into drug-induced and other causes. Pseudohypoglycemia occurs when processing of blood specimens in untreated test tubes is delayed and cells, such as RBCs and leukocytes (especially if increased, as in leukemia or polycythemia), consume glucose. Factitious hypoglycemia is true hypoglycemia induced by nontherapeutic administration of sulfonylureas or insulin.

Symptoms and Signs

The surge in autonomic activity in response to low plasma glucose causes sweating, nausea, warmth, anxiety, tremulousness, palpitations, and possibly hunger and paresthesias. Insufficient glucose supply to the brain causes headache, blurred or double vision, confusion, difficulty speaking, seizures, and coma. In controlled settings, autonomic symptoms begin at or beneath a plasma glucose level of about 60 mg/dL (3.33 mmol/L), whereas CNS symptoms occur at or below a glucose level of about 50 mg/dL (2.78 mmol/L). However, symptoms suggestive of hypoglycemia are far more common than the condition itself. Most people with glucose levels at these thresholds have no symptoms, and most people with symptoms suggestive of hypoglycemia have normal glucose concentrations.

Diagnosis

- Blood glucose level correlated with clinical findings
- Response to dextrose (or other sugar) administration
- Sometimes 72-h fast
- Sometimes insulin, C-peptide, and proinsulin levels

In principle, diagnosis requires verification that a low plasma glucose level (< 50 mg/dL [< 2.78 mmol/L]) exists at the time hypoglycemic symptoms occur and that the symptoms are responsive to dextrose administration. If a practitioner is present when symptoms occur, blood should be sent for glucose testing. If glucose is normal, hypoglycemia is ruled out and no further testing is needed. If glucose is abnormally low, serum insulin, C-peptide, and proinsulin measured from the same tube can distinguish insulin-mediated from non-insulin-mediated and factitious from physiologic hypoglycemia and can obviate the need for further testing. Insulin growth factor 2 (IGF-2) levels may help identify non-islet cell (IGF-2
secreting) tumors, which are an unusual cause of hypoglycemia.

In practice, however, it is unusual that practitioners are present when patients experience symptoms suggestive of hypoglycemia. Home glucose meters are unreliable for quantifying hypoglycemia, and there are no clear glycosylated Hb (HbA\textsubscript{1c}) thresholds that distinguish long-term hypoglycemia from normoglycemia. So the need for more extensive diagnostic testing is based on the probability that an underlying disorder that could cause hypoglycemia exists given a patient's clinical appearance and coexisting illnesses.

A 72-h fast done in a controlled setting is the standard for diagnosis. Patients drink only noncaloric, noncaffeinated beverages, and plasma glucose is measured at baseline, whenever symptoms occur, and q 4 to 6 h or q 1 to 2 h if glucose falls below 60 mg/dL (3.3 mmol/L). Serum insulin, C-peptide, and proinsulin should be measured at times of hypoglycemia to distinguish endogenous from exogenous (factitious) hypoglycemia. The fast is terminated at 72 h if the patient has experienced no symptoms and glucose remains normal, sooner if glucose decreases to ≤ 45 mg/dL (≤ 2.5 mmol/L) in the presence of hypoglycemic symptoms. End-of-fast measurements include β-hydroxybutyrate (which should be low in insulinoma), serum sulfonylurea to detect drug-induced hypoglycemia, and plasma glucose after IV glucagon injection to detect an increase characteristic of insulinoma. Sensitivity, specificity, and predictive values for detecting hypoglycemia by this protocol have not been reported. There is no definitive lower limit of glucose that unequivocally defines pathologic hypoglycemia during a 72-h fast. Normal women tend to have lower fasting glucose levels than men and may have glucose levels as low as 30 mg/dL without symptoms. If symptomatic hypoglycemia has not occurred by 72 h, the patient should exercise vigorously for about 30 min. If hypoglycemia still does not occur, insulinoma is essentially excluded and further testing is generally not indicated.

**Treatment**

- Oral sugar or IV dextrose
- Sometimes parenteral glucagon

Immediate treatment of hypoglycemia involves provision of glucose. Patients able to eat or drink can drink juices, sucrose water, or glucose solutions; eat candy or other foods; or chew on glucose tablets when symptoms occur. Infants and younger children may be given 10% dextrose solution 2 to 5 mL/kg IV bolus. Adults and older children unable to eat or drink can be given glucagon 0.5 (< 20 kg) or 1 mg (≥ 20 kg) sc or IM or 50% dextrose 50 to 100 mL IV bolus, with or without a continuous infusion of 5 to 10% dextrose solution sufficient to resolve symptoms. The efficacy of glucagon depends on the size of hepatic glycogen stores; glucagon has little effect on plasma glucose in patients who have been fasting or who are hypoglycemic for long periods.

Underlying disorders causing hypoglycemia must also be treated. Islet cell and non-islet cell tumors must first be localized, then removed by enucleation or partial pancreatectomy; about 6% recur within 10 yr. Diazoxide and octreotide can be used to control symptoms while the patient is awaiting surgery or when a patient refuses or is not a candidate for a procedure. Islet cell hypertrophy is most often a diagnosis of exclusion after an islet cell tumor is sought but not identified. Drugs that cause hypoglycemia, including alcohol, must be stopped. Treatment of hereditary and endocrine disorders; hepatic, renal, and heart failure; and sepsis and shock are described elsewhere.
**Chapter 100. Lipid Disorders**

**Introduction**

Lipids are fats that are either absorbed from food or synthesized by the liver. Triglycerides (TGs) and cholesterol contribute most to disease, although all lipids are physiologically important. The primary function of TGs is to store energy in adipocytes and muscle cells; cholesterol is a ubiquitous constituent of cell membranes, steroids, bile acids, and signaling molecules. All lipids are hydrophobic and mostly insoluble in blood, so they require transport within hydrophilic, spherical structures called lipoproteins, which possess surface proteins (apolipoproteins, or apolipoproteins) that are cofactors and ligands for lipid-processing enzymes (see Table 100-1). Lipoproteins are classified by size and density (defined as the ratio of lipid to protein) and are important because high levels of low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL) are major risk factors for atherosclerotic heart disease (see p. 2081).

**Physiology**

Pathway defects in lipoprotein synthesis, processing, and clearance can lead to accumulation of atherogenic lipids in plasma and endothelium.

**Exogenous (dietary) lipid metabolism:** Over 95% of dietary lipids are TGs; the rest are phospholipids, free fatty acids (FFAs), cholesterol (present in foods as esterified cholesterol), and fat-soluble vitamins. Dietary TGs are digested in the stomach and duodenum into monoglycerides (MGs) and FFAs by gastric lipase, emulsification from vigorous stomach peristalsis, and pancreatic lipase. Dietary cholesterol esters are de-esterified into free cholesterol by these same mechanisms. MGs, FFAs, and free cholesterol are then solubilized in the intestine by bile acid micelles, which shuttle them to intestinal villi for absorption. Once absorbed into the enterocyte, they are reassembled into TGs and packaged with cholesterol into chylomicrons, the largest lipoproteins.

**Chylomicrons** transport dietary TGs and cholesterol from within enterocytes through lymphatics into the circulation. In the capillaries of adipose and muscle tissue, apoprotein C-II (apo C-II) on the chylomicron activates endothelial lipoprotein lipase (LPL) to convert 90% of chylomicron TG to fatty acids and glycerol, which are taken up by adipocytes and muscle cells for energy use or storage. Cholesterol-rich chylomicron remnants then circulate back to the liver, where they are cleared in a process mediated by apoprotein E (apo E).

**Endogenous lipid metabolism:** Lipoproteins synthesized by the liver transport endogenous TGs and cholesterol. Lipoproteins circulate through the blood continuously until the TGs they contain are taken up by peripheral tissues or the lipoproteins themselves are cleared by the liver. Factors that stimulate hepatic lipoprotein synthesis generally lead to elevated plasma cholesterol and TG levels.

**Very-low-density lipoproteins (VLDL)** contain apoprotein B-100 (apo B), are synthesized in the liver, and transport TGs and cholesterol to peripheral tissues. VLDL is the way the liver exports excess TGs derived from plasma FFA and chylomicron remnants; VLDL synthesis increases with increases in intrahepatic FFA, such as occur with high-fat diets and when excess adipose tissue releases FFAs directly into the circulation (eg, in obesity, uncontrolled diabetes mellitus). APO C-II on the VLDL surface activates endothelial LPL to break down TGs into FFAs and glycerol, which are taken up by cells.

**Intermediate-density lipoproteins (IDL)** are the product of LPL processing of VLDL and chylomicrons. IDL are cholesterol-rich VLDL and chylomicron remnants that are either cleared by the liver or metabolized by hepatic lipase into LDL, which retains apo B.

**Low-density lipoproteins (LDL)**, the products of VLDL and IDL metabolism, are the most cholesterol-rich of all lipoproteins. About 40 to 60% of all LDL are cleared by the liver in a process mediated by apo B and hepatic LDL receptors. The rest are taken up by either hepatic LDL or nonhepatic non-LDL (scavenger) receptors. Hepatic LDL receptors are down-regulated by delivery of cholesterol to the liver.
by chylomicrons and by increased dietary saturated fat; they can be up-regulated by decreased dietary fat and cholesterol. Nonhepatic scavenger receptors, most notably on macrophages, take up excess oxidized circulating LDL not processed by hepatic receptors. Monocytes rich in oxidized LDL migrate into the subendothelial space and become macrophages; these macrophages then take up more oxidized LDL and form foam cells within atherosclerotic plaques (see p. 2081). There are 2 forms of LDL: large, buoyant and small, dense LDL. Small, dense LDL is especially rich in cholesterol esters, associated with metabolic disturbances such as hypertriglyceridemia and insulin resistance, and especially atherogenic. The increased atherogenicity of small, dense LDL derives from less efficient hepatic LDL receptor binding, leading to prolonged circulation and exposure to endothelium and increased oxidation.

High-density lipoproteins (HDL) are initially cholesterol-free lipoproteins that are synthesized in both enterocytes and the liver. HDL metabolism is complex, but HDL’s overall role is to obtain cholesterol from peripheral tissues and other lipoproteins and transport it to where it is needed most—other cells, other lipoproteins (using cholesteryl ester transfer protein [CETP]), and the liver (for clearance). Its overall effect is anti-atherogenic. Efflux of free cholesterol from cells is mediated by ATP-binding cassette transporter A1 (ABCA1), which combines with apoprotein A-I (apo A-I) to produce nascent HDL. Free cholesterol in nascent HDL is then esterified by the enzyme lecithin-cholesterol acyl transferase (LCAT), producing mature HDL. Blood HDL levels may not completely represent reverse cholesterol transport.

Lipoprotein (a) [Lp (a)] is LDL that contains apoprotein(a), characterized by 5 cysteine-rich regions called kringles. One of these regions is homologous with plasminogen and is thought to competitively inhibit fibrinolysis and thus predispose to thrombus. The Lp(a) may also directly promote atherosclerosis. The metabolic pathways of Lp(a) production and clearance are not well characterized, but levels increase in patients with diabetic nephropathy.

Dyslipidemia

(Hyperlipidemia)

Dyslipidemia is elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins. Treatment is dietary changes, exercise, and lipid-lowering drugs.

There is no natural cutoff between normal and abnormal lipid levels because lipid measurements are continuous. A linear relation probably exists between lipid levels and cardiovascular risk, so many people with “normal” cholesterol levels benefit from achieving still lower levels. Consequently, there are no numeric definitions of dyslipidemia; the term is applied to lipid levels for which treatment has proved beneficial. Proof of benefit is strongest for lowering elevated low-density lipoprotein (LDL) levels. In the overall population, evidence is less strong for a benefit from lowering elevated TG and increasing low high-density lipoprotein (HDL) levels, in part because elevated TG and low HDL levels are more predictive of cardiovascular risk in women than in men.

HDL levels do not always predict cardiovascular risk. For example, high HDL levels caused by some genetic disorders may not protect against cardiovascular disorders, and low HDL levels caused by some genetic disorders may not increase the risk of cardiovascular disorders. Although HDL levels predict cardiovascular risk in the overall population, the increased risk may be caused by other factors, such as accompanying lipid and metabolic abnormalities, rather than the HDL level itself.

Classification

Dyslipidemias were traditionally classified by patterns of elevation in lipids and lipoproteins (Fredrickson phenotype—see Table 100-2). A more practical system categorizes dyslipidemias as primary or secondary and characterizes them by increases in cholesterol only (pure or isolated hypercholesterolemia), increases in TGs only (pure or isolated hypertriglyceridemia), or increases in both cholesterol and TGs (mixed or combined hyperlipidemias). This system does not take into account specific lipoprotein abnormalities (eg,
low HDL or high LDL) that may contribute to disease despite normal cholesterol and TG levels.

Etiology

Primary (genetic) causes and secondary (lifestyle and other) causes contribute to dyslipidemias in varying degrees. For example, in familial combined hyperlipidemia, expression may occur only in the presence of significant secondary causes.

**Primary causes:** Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL (see Table 100-3). Primary disorders, the most common cause of dyslipidemia in children, do not cause a large percentage of cases in adults. The names of many reflect an old nomenclature in which lipoproteins were detected and distinguished by how they separated into \( \alpha \) (HDL) and \( \beta \) (LDL) bands on electrophoretic gels.

**Table 100-2. Lipoprotein Patterns (Fredrickson Phenotypes)**

**Secondary causes:** Secondary causes contribute to most cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats. Trans fats are polyunsaturated or monounsaturated fatty acids to which hydrogen atoms have been added; they are commonly used in many processed foods and are as atherogenic as saturated fat. Other common secondary causes include diabetes mellitus, alcohol overuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis and other cholestatic liver diseases, and drugs, such as thiazides, \( \beta \)-blockers, retinoids, highly active antiretroviral agents, estrogen and progestins, and glucocorticoids.

**Diabetes** is an especially significant secondary cause because patients tend to have an atherogenic combination of high TGs; high small, dense LDL fractions; and low HDL (diabetic dyslipidemia, hypertriglyceridemic hyperapo B). Patients with type 2 diabetes are especially at risk. The combination may be a consequence of obesity, poor control of diabetes, or both, which may increase circulating free fatty acids (FFAs), leading to increased hepatic very-low-density lipoprotein (VLDL) production. TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting formation of TG-rich, small, dense LDL and clearance of TG-rich HDL. Diabetic dyslipidemia is often exacerbated by the increased caloric intake and physical inactivity that characterize the lifestyles of some patients with type 2 diabetes. Women with diabetes may be at special risk of cardiac disease from this form.

**Table 100-3. Genetic (Primary) Dyslipidemias**

Symptoms and Signs

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease. High levels of TGs (> 1000 mg/dL [> 11.3 mmol/L]) can cause acute pancreatitis. High levels of LDL can cause eyelid xanthelmasmas; arcus corneae; and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints. Patients with the homozygous form of familial hypercholesterolemia may have the above findings plus planar or cutaneous xanthomas. Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet. Patients with the rare dysbetalipoproteinemia can have palmar and tuberous xanthomas.

Severe hypertriglyceridemia (> 2000 mg/dL [> 22.6 mmol/L]) can give retinal arteries and veins a creamy white appearance (lipemia retinalis). Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma. Symptoms can include paresthesias, dypsnea, and confusion.

Diagnosis

- Serum lipid profile (measured total cholesterol, TG, and HDL cholesterol and calculated LDL cholesterol and VLDL)
Dyslipidemia is suspected in patients with characteristic physical findings or complications of dyslipidemia (eg, atherosclerotic disease). Primary lipid disorders are suspected when patients have physical signs of dyslipidemia, onset of premature atherosclerotic disease (at < 60 yr), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dL (> 6.2 mmol/L). Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL cholesterol, and LDL cholesterol.

**Lipid profile measurement:** TC, TGs, and HDL cholesterol are measured directly; TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL. TC values vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL cholesterol can be measured in the non-fasting state, but most patients should have all lipids measured while fasting for maximum accuracy and consistency.

Testing should be postponed until after resolution of acute illness, because TGs increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an acute MI; however, results obtained within 24 h after MI are usually reliable enough to guide initial lipid-lowering therapy.

LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually one fifth of the total lipid in the particle. Thus, LDL cholesterol = TC - [HDL cholesterol + (TGs ÷ 5)] (Friedewald formula). This calculation is valid only when TGs are < 400 mg/dL and patients are fasting, because eating increases TGs. The calculated LDL cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and lipoprotein (a) [Lp(a)]. LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary. The role of apoprotein B testing is under study because values reflect all non-HDL cholesterol (in VLDL, VLDL remnants, IDL, and LDL) and may be more predictive of CAD risk than LDL alone.

**Other tests:** Patients with premature atherosclerotic cardiovascular disease, cardiovascular disease with normal or near-normal lipid levels, or high LDL levels refractory to drug therapy should probably have Lp(a) levels measured. Lp(a) levels may also be directly measured in patients with borderline high LDL cholesterol levels to determine whether drug therapy is warranted. C-reactive protein and homocysteine measurement may be considered in the same populations.

**Secondary causes:** Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, creatinine, thyroid-stimulating hormone (TSH), and urinary protein—should be done in most patients with newly diagnosed dyslipidemia and when a component of the lipid profile has inexplicably changed for the worse.

**Screening:** A fasting lipid profile (TC, TGs, HDL cholesterol, and calculated LDL cholesterol) should be obtained in all adults ≥ 20 yr and should be repeated every 5 yr. Lipid measurement should be accompanied by assessment of other cardiovascular risk factors, defined as

- Diabetes mellitus
- Cigarette use
- Hypertension
- Family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65

A definite age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80s, especially in the presence of atherosclerotic cardiovascular disease.
Indications for screening patients < 20 yr are atherosclerotic risk factors, such as diabetes, hypertension, cigarette smoking, and obesity; premature CAD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dL (> 6.2 mmol/L) or known dyslipidemia in a parent. If information on relatives is unavailable, as in the case of adopted children, screening is at the discretion of the health care practitioner.

Patients with an extensive family history of heart disease should also be screened by measuring Lp(a) levels.

**Treatment**

- Risk assessment by explicit criteria
- Lifestyle changes (eg, exercise, dietary modification)
- For high LDL cholesterol, statins, sometimes bile acid sequestrants, ezetimibe, and other measures
- For high TG or low HDL cholesterol, niacin, fibrates, and sometimes other measures

**General principles:** Treatment is indicated for all patients with cardiovascular disease (secondary prevention) and for some without (primary prevention). The National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines are the most common reference for deciding which adults should be treated (see Tables 100-4 and 100-5). The guidelines focus primarily on reducing elevated LDL cholesterol levels and secondarily on treating high TGs, low HDL, and metabolic syndrome (see p. 64). An alternate treatment guide (the Sheffield table) uses TC:HDL ratios combined with presence of CAD risk factors to predict cardiovascular risk, but this approach probably leads to undertreatment.

Treatment of children is controversial; dietary changes may be difficult to implement, and no data suggest that lowering lipid levels in childhood effectively prevents heart disease in adulthood. Moreover, the safety and effectiveness of long-term lipid-lowering treatment are questionable. Nevertheless, the American Academy of Pediatrics (AAP) recommends treatment for some children who have elevated LDL cholesterol levels.

Treatment options depend on the specific lipid abnormality, although different lipid abnormalities often coexist. In some patients, a single abnormality may require several therapies; in others, a single treatment may be adequate for several abnormalities. Treatment should always include treatment of hypertension and diabetes, smoking cessation, and in patients with a 10-yr risk of MI or death from CAD of ≥ 10% (as determined from the Framingham tables—see Tables 100-6 and 100-7), low-dose daily aspirin. In general, treatment options for men and women are the same.

**Elevated LDL cholesterol:** In adults, ATPIII guidelines recommend treatment for those with any of the following:

- Elevated LDL cholesterol levels and a history of CAD
- Conditions that confer a risk of future cardiac events similar to that of CAD itself (CAD equivalents, defined as diabetes mellitus, abdominal aortic aneurysm, peripheral arterial disease, and symptomatic carotid artery disease)
- ≥ 2 CAD risk factors
ATPIII guidelines recommend that these patients have LDL cholesterol levels lowered to < 100 mg/dL, but accumulating evidence

[Table 100-5, Ncep Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia]

suggests that this target may be too high and a target LDL cholesterol < 70 mg/dL is an option for patients at very high risk (eg, patients with known CAD and diabetes, other poorly controlled risk factors, metabolic syndrome, or acute coronary syndrome). When drugs are used, a dose providing at least a 30 to 40% decrease in LDL cholesterol is desirable (see Table 100-8).

For children, the AAP recommends dietary treatment for children with LDL cholesterol > 110 mg/dL. Drug therapy is recommended for children > 8 yr and with either of the following:

- Poor response to dietary therapy, LDL cholesterol ≥ 190 mg/dL, and no family history of premature cardiovascular disease
- LDL cholesterol ≥ 160 mg/dL and a family history of premature cardiovascular disease or ≥ 2 risk factors for premature cardiovascular disease

Childhood risk factors besides family history and diabetes include cigarette smoking, hypertension, low HDL cholesterol (< 35 mg/dL), obesity, and physical inactivity.

Treatment options to lower LDL cholesterol in all age groups include lifestyle changes (diet and exercise), drugs, dietary supplements, procedural interventions, and experimental therapies. Many of these options are also effective for treating other lipid abnormalities. Exercise lowers LDL cholesterol in some people; it is also essential to maintain ideal body weight. Dietary changes and exercise should be the initial approach whenever feasible.

**Lifestyle changes** can involve diet and exercise. Dietary changes include decreasing intake of saturated fats and cholesterol; increasing the proportion of dietary fiber, and complex carbohydrates; and maintaining ideal body weight. Referral to a dietitian is often useful, especially for older people. The length of time for which lifestyle changes should be attempted before beginning lipid-lowering drugs is controversial. In patients at average or low cardiovascular risk, 3 to 6 mo is reasonable. Generally, 2 to 3 visits with a patient over 2 to 3 mo are sufficient to assess motivation and adherence.

Drugs are the next step when lifestyle changes are not effective. However, for patients with extremely elevated LDL cholesterol (> 200 mg/dL [> 5.2 mmol/L]) and those at high cardiovascular risk, drug therapy should accompany diet and exercise from the start.

**Statins** are the drugs and possibly treatment of choice for LDL cholesterol reduction; they demonstrably reduce cardiovascular mortality. Statins inhibit hydroxymethylglutaryl CoA reductase, a key enzyme in cholesterol synthesis, leading to up-regulation of LDL receptors and increased LDL clearance. They reduce LDL cholesterol by up to 60% and produce small increases in HDL and modest decreases in TGs. Statins also seem to decrease intraarterial inflammation, systemic inflammation, or both by stimulating production of endothelial nitric oxide and may have other beneficial effects. Adverse effects are uncommon but include liver enzyme elevations and myositis or rhabdomyolysis. Muscle toxicity without enzyme elevation has also been reported. Adverse effects are more common among older patients, patients with several disorders, and patients taking several drugs. In some patients, changing from one statin to another or lowering the dose relieves the problem. Muscle toxicity seems to be most common when some of the statins are used with drugs that inhibit cytochrome P3A4 (eg, macrolide antibiotics, azole antifungals, cyclosporine) and with fibrates, especially gemfibrozil. Properties of statins differ

[Table 100-7, Framingham Risk Tables for Women]
slightly by drug, and the choice of drug should be based on patient characteristics, LDL cholesterol level, and provider discretion (see Table 100-8).

**Bile acid sequestrants** block intestinal bile acid reabsorption, forcing up-regulation of hepatic LDL receptors to recruit circulating cholesterol for bile synthesis. They are proved to reduce cardiovascular mortality. Bile acid sequestrants are usually used with statins or with nicotinic acid (see p. 903) to augment LDL cholesterol reduction and are the drugs of choice for children and women who are or are planning to become pregnant. Bile acid sequestrants are safe, but their use is limited by adverse effects of bloating, nausea, cramping, and constipation. They may also increase TGs, so their use is contraindicated in patients with hypertriglyceridemia. Cholestyramine and colestipol, but not colesevelam, interfere with absorption of other drugs—namely thiazides, β-blockers, warfarin, digoxin, and thyroxine—an effect that can be decreased by administration 4 h before or 1 h after other drugs.

**Cholesterol absorption inhibitors**, such as ezetimibe, inhibit intestinal absorption of cholesterol and phytosterol. Ezetimibe usually lowers LDL cholesterol by 15 to 20% and causes small increases in HDL and a mild decrease in TGs. Ezetimibe can be used as monotherapy in patients intolerant to statins or added to statins for patients on maximum doses with persistent LDL cholesterol elevation. Adverse effects are infrequent.

**Dietary supplements** that lower LDL cholesterol levels include fiber supplements and commercially available margarines and other products containing plant sterols (sitosterol and campesterol) or stanols. The latter reduce LDL cholesterol by up to 10% without affecting HDL or TGs by competitively displacing cholesterol from intestinal micelles.

**Procedural approaches** are reserved for patients with severe hyperlipidemia (LDL cholesterol > 300 mg/dL) that is refractory to conventional therapy, such as occurs with familial hypercholesterolemia. Options include LDL apheresis (in which LDL is removed by extracorporeal plasma exchange), ileal bypass (to block reabsorption of bile acids), liver transplantation (which transplants LDL receptors), and portocaval shunting (which decreases LDL production by unknown mechanisms). LDL apheresis is the procedure of choice in most instances when maximally tolerated therapy fails to lower LDL adequately. Apheresis is also the usual therapy in patients with the homozygous form of familial hypercholesterolemia who have limited or no response to drug therapy.

**Future therapies** to reduce LDL include peroxisome proliferator-activated receptor agonists that have thiazolidinedione-like and fibrate-like properties, LDL-receptor activators, LPL activators, and recombinant apo E. Cholesterol vaccination (to induce anti-LDL antibodies and hasten LDL clearance from serum) and gene transfer are conceptually appealing therapies that are under study but years away from being available for use.

**Elevated TGs**: Though it is unclear whether elevated TGs independently contribute to cardiovascular disease, they are associated with multiple metabolic abnormalities that contribute to CAD (eg, diabetes, metabolic syndrome). Consensus is emerging that lowering elevated TGs is beneficial (see Table 100-4). No target goals exist, but levels < 150 mg/dL (< 1.7 mmol/L) are generally considered desirable. No guidelines specifically address treatment of elevated TGs in children.

The overall treatment strategy is to first implement lifestyle changes, including exercise, weight loss, and avoidance of concentrated dietary sugar and alcohol. Intake of 2 to 4 servings/wk of marine fish high in ω-3 fatty acids may be effective, but the amount of ω-3 fatty acids is often lower than needed; supplements may be helpful. In patients with diabetes, glucose levels should be tightly controlled. If these measures are ineffective, lipid-lowering drugs should be considered. Patients with very high TGs should begin drug therapy at diagnosis to more quickly reduce the risk of acute pancreatitis.

**Fibrates** reduce TGs by about 50%. They seem to stimulate endothelial LPL, leading to increased fatty acid oxidation in the liver and muscle and decreased hepatic VLDL synthesis. They also increase HDL by up to 20%. Fibrates can cause GI adverse effects, including dyspepsia, abdominal pain, and elevated
liver enzymes. They uncommonly cause cholelithiasis. Fibrates may potentiate muscle toxicity when used with statins and potentiate the effects of warfarin.

**Nicotinic acid** may also be useful (see below).

**Statins** can be used in patients with TGs < 500 mg/dL if LDL cholesterol elevations are also present; statins may reduce both LDL cholesterol and TGs through reduction of VLDL. If only TGs are elevated, fibrates are the drug of choice.

**Omega-3 fatty acids** in high doses (1 to 6 g/day of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) can be effective in reducing TGs. The ω-3 fatty acids EPA and DHA are the active ingredients in marine fish oil or ω-3 capsules. Adverse effects include eructation and diarrhea. These may be decreased by giving the fish oil capsules with meals in divided doses (eg, bid or tid). Omega-3 fatty acids can be a useful adjunct to other therapies.

**Low HDL:** Treatment to increase HDL cholesterol levels may decrease risk of death, but data are limited. ATPIII guidelines define low HDL cholesterol as < 40 mg/dL [< 1.04 mmol/L]; the guidelines do not specify an HDL cholesterol target level and recommend interventions to raise HDL cholesterol only after LDL cholesterol targets have been reached. Treatments for LDL cholesterol and TG reduction often increase HDL cholesterol, and the 3 objectives can sometimes be achieved simultaneously. No guidelines specifically address treatment of low HDL cholesterol in children.

Treatment includes **lifestyle changes** such as an increase in exercise and weight loss. Alcohol raises HDL cholesterol but is not routinely recommended as a therapy because of its many other adverse effects. Drugs are useful when lifestyle changes alone are insufficient.

**Nicotinic acid (niacin)** is the most effective drug for increasing HDL. Its mechanism of action is unknown, but it seems to both increase HDL production and inhibit HDL clearance; it may also mobilize cholesterol from macrophages. Niacin also decreases TGs and, in doses of 1500 to 2000 mg/day, reduces LDL cholesterol. Niacin causes flushing, pruritus, and nausea; premedication with low-dose aspirin may prevent these adverse effects. Extended-release preparations cause flushing less often. However, most OTC slow-release preparations are not recommended; an exception is polygel controlled-release niacin. Niacin can cause liver enzyme elevations and occasionally liver failure, insulin resistance, and hyperuricemia and gout. It may also increase homocysteine levels. In patients with average LDL cholesterol and below-average HDL cholesterol levels, niacin combined with statin treatment may be effective in preventing cardiovascular disorders.

**Fibrates** increase HDL. Infusion of recombinant HDL (eg, apoprotein A-1 Milano, an HDL variant in which a cysteine is substituted for an arginine at position 173 allowing for dimer formation) seems promising as a treatment for atherosclerosis but requires further study.

**Elevated Lp(a):** The upper limit of normal for Lp(a) is about 30 mg/dL (0.8 mmol/L), but values in African Americans run higher. Few data exist to guide the treatment of elevated Lp(a) or to establish treatment efficacy. Niacin is the only drug that directly decreases Lp(a); it can lower Lp(a) by ≤ 20% at higher doses. The usual approach in patients with elevated Lp(a) is to lower LDL cholesterol aggressively.

**Secondary causes:** Treatment of diabetic dyslipidemia should always involve lifestyle changes, with statins to reduce LDL cholesterol, fibrates to decrease TGs, or both drugs. Metformin lowers TGs, which may be a reason to choose it over other oral antihyperglycemic drugs when treating diabetes. Some thiazolidinediones (TZDs) increase both HDL cholesterol and LDL cholesterol (probably the less atherogenic large, buoyant type of LDL). Some TZDs also decrease TGs. These antihyperglycemic drugs should not be chosen over lipid-lowering drugs to treat lipid abnormalities in diabetic patients but may be useful adjuncts. Patients with very high TG levels and less than optimally controlled diabetes may have better response to insulin than to oral antihyperglycemic drugs.

Treatment of dyslipidemia in patients with hypothyroidism, renal disease, liver disease, or a combination of these disorders involves treating the underlying disorders primarily and lipid abnormalities secondarily. Abnormal lipid levels in patients with low-normal thyroid function (high-normal TSH levels) improve with
hormone replacement. Reducing the dosage of or stopping drugs that cause lipid abnormalities should be considered.

**Monitoring treatment:** Lipid levels should be monitored periodically after starting treatment. No data support specific monitoring intervals, but measuring lipid levels 2 to 3 mo after starting or changing therapies and once or twice yearly after lipid levels are stabilized is common practice.

Despite the low incidence of liver and muscle toxicity with statin use (0.5 to 2% of all users), current recommendations are for baseline measurements of liver and muscle enzyme levels at the beginning of treatment. Many practitioners obtain at least one additional set of liver enzyme measurements 4 to 12 wk after beginning treatment and annually thereafter. Statin therapy can be continued unless liver enzymes increase to > 3 times the upper limit of normal. Muscle enzyme levels need not be checked regularly unless patients develop myalgias or other muscle symptoms. If statin-induced muscle damage is suspected, statin use is stopped and CK may be measured. When muscle symptoms subside, a lower dose or a different statin can be tried.

**Elevated High-Density Lipoprotein Levels**

**Elevated high-density lipoprotein (HDL) level is HDL cholesterol > 80 mg/dL (> 2.1 mmol/L).**

Elevated HDL cholesterol levels usually correlate with decreased cardiovascular risk; however, high HDL cholesterol levels caused by some genetic disorders may not protect against cardiovascular disease, probably because of accompanying lipid and metabolic abnormalities.

Primary causes are single or multiple genetic mutations that result in overproduction or decreased clearance of HDL. Secondary causes of high HDL cholesterol include all of the following:

- Chronic alcoholism without cirrhosis
- Primary biliary cirrhosis
- Hyperthyroidism
- Drugs (eg, corticosteroids, insulin, phenytoin)

The unexpected finding of high HDL cholesterol in patients not taking lipid-lowering drugs should prompt a diagnostic evaluation for a secondary cause with measurements of AST, ALT, and thyroid-stimulating hormone; a negative evaluation suggests a possible primary cause.

**Cholesteryl ester transfer protein (CETP) deficiency** is a rare autosomal recessive disorder caused by a CETP gene mutation. CETP facilitates transfer of cholesterol esters from HDL to other lipoproteins, and CETP deficiency affects low-density lipoprotein (LDL) cholesterol and slows HDL clearance. Affected patients display no symptoms or signs but have HDL cholesterol > 150 mg/dL. Protection from cardiovascular disorders has not been proved. No treatment is necessary.

**Familial hyperalphalipoproteinemia** is an autosomal dominant condition caused by various unidentified and known genetic mutations, including those that cause apoprotein A-I overproduction and apoprotein C-III variants. The disorder is usually diagnosed incidentally when plasma HDL cholesterol levels are > 80 mg/dL. Affected patients have no other symptoms or signs. No treatment is necessary.

**Hypolipidemia**

**Hypolipidemia is a decrease in plasma lipoprotein caused by primary (genetic) or secondary factors. It is usually asymptomatic and diagnosed incidentally on routine lipid screening. Treatment of secondary hypolipidemia involves treating underlying disorders. Treatment of primary hypolipidemia is often unnecessary, but patients with some genetic disorders require high-dose vitamin E and dietary supplementation of fats and other fat-soluble vitamins.**
Hypolipidemia is defined as a total cholesterol (TC) < 120 mg/dL (< 3.1 mmol/L) or low-density lipoprotein (LDL) cholesterol < 50 mg/dL (< 0.13 mmol/L). Secondary causes are far more common than primary causes and include all of the following:

- Hyperthyroidism
- Chronic infections and other inflammatory states
- Hematologic and other cancers
- Undernutrition (including that accompanying chronic alcohol use)
- Malabsorption

The unexpected finding of low cholesterol or low LDL cholesterol in a patient not taking a lipid-lowering drug should prompt a diagnostic evaluation, including measurements of AST, ALT, and thyroid-stimulating hormone; a negative evaluation suggests a possible primary cause.

There are 3 primary disorders in which single or multiple genetic mutations result in underproduction or increased clearance of LDL.

**Abetalipoproteinemia (Bassen-Kornzweig syndrome):** This autosomal recessive condition is caused by mutations in the gene for microsomal triglyceride (TG) transfer protein, a protein critical to chylomicron and very-low-density lipoprotein (VLDL) formation. Dietary fat cannot be absorbed, and lipoproteins in both metabolic pathways are virtually absent from serum; TC is typically < 45 mg/dL (< 1.16 mmol/L), TGs are < 20 mg/dL (< 0.23 mmol/L), and LDL is undetectable. The condition is often first noticed in infants with fat malabsorption, steatorrhea, and failure to thrive. Intellectual disability may result. Because vitamin E is distributed to peripheral tissues via VLDL and LDL, most affected people eventually develop severe vitamin E deficiency. Symptoms and signs include visual changes from slow retinal degeneration, sensory neuropathy, posterior column signs, and cerebellar signs of dysmetria, ataxia, and spasticity, which can eventually lead to death. RBC acanthocytosis is a distinguishing feature on blood smear. Diagnosis is made by the absence of apoprotein B (apo B) in plasma; intestinal biopsies show lack of microsomal transfer protein. Treatment is with high doses (100 to 300 mg/kg once/day) of vitamin E with supplementation of dietary fat and other fat-soluble vitamins. The prognosis is poor.

**Hypobetalipoproteinemia:** Hypobetalipoproteinemia is an autosomal dominant or codominant condition caused by mutations in the gene coding for apo B. Heterozygous patients have truncated apo B, leading to rapid LDL clearance. Heterozygous patients manifest no symptoms or signs except for TC < 120 mg/dL and LDL cholesterol < 80 mg/dL. TGs are normal. Homozygous patients have either shorter truncations, leading to lower lipid levels (TC < 80 mg/dL, LDL cholesterol < 20 mg/dL), or absent apo B synthesis, leading to symptoms and signs of abetalipoproteinemia. Diagnosis is by finding low levels of LDL cholesterol and apo B; hypobetalipoproteinemia and abetalipoproteinemia are distinguished from one another by family history. People who are heterozygous and people who are homozygous with low but detectable LDL cholesterol require no treatment. Treatment of people who are homozygous with no LDL is the same as for abetalipoproteinemia.

**Chylomicron retention disease:** Chylomicron retention disease is a very rare autosomal recessive condition caused by an unknown mutation leading to deficient apo B secretion from enterocytes. Chylomicron synthesis is absent, but VLDL synthesis remains intact. Affected infants have fat malabsorption, steatorrhea, and failure to thrive and may develop neurologic disorders similar to those in abetalipoproteinemia. Diagnosis is by intestinal biopsy of patients with low cholesterol levels and absence of postprandial chylomicrons. Treatment is supplementation of fat and fatsoluble vitamins.
Chapter 101. Amyloidosis

Amyloidosis is any of a group of disparate conditions characterized by extracellular deposition of various insoluble proteins. These proteins may accumulate locally, causing relatively few symptoms, or widely, involving multiple organs and causing severe multiorgan failure. Amyloidosis can be primary or be secondary to various infectious, inflammatory, or malignant conditions. Rarely, it results from any of several inherited metabolic defects. Diagnosis is by biopsy of affected tissue. Treatment varies with the type of amyloidosis.

Amyloid deposits may be formed from at least 18 different proteins, including immunoglobulin fragments. Amyloid deposits are metabolically inert but interfere physically with organ structure and function. All stain positive with Congo red dye, stain pink with hematoxylin and eosin, and have apple-green birefringence under polarized light after Congo red staining. Amyloid deposits have a fibrillar, usually rigid, and nonbranching ultrastructure. They form a β-pleated sheet that can be seen by x-ray diffraction. In addition to the fibrillar amyloid protein, the deposits also contain serum amyloid P component and glycosaminoglycans. On gross inspection, affected organs appear waxy and translucent.

Etiology

There are 3 major systemic forms of amyloidosis: primary, secondary, and familial. Also, there are 2 major localized forms, Aβ (associated with Alzheimer's disease) and AA amyloidosis (which occurs in the pancreas of patients with type 2 diabetes), as well as several miscellaneous forms (eg, Aβ2-microglobulin associated with chronic hemodialysis).

Primary amyloidosis (AL): AL is a monoclonal plasma cell disorder in which the abnormal protein is an immunoglobulin, usually a light chain fragment (Bence Jones protein) but occasionally a heavy chain fragment (AH amyloidosis). These chains either have an aberrant structure or are processed abnormally so that some form insoluble deposits. Common sites for deposition include the skin, nerves, heart, GI tract (including tongue), kidneys, liver, spleen, and blood vessels. A mild plasmacytosis occurs in the bone marrow, which is suggestive of multiple myeloma, but most patients do not have true multiple myeloma (with lytic bone lesions, renal tubular casts, and anemia). However, about 10 to 20% of patients with multiple myeloma also develop amyloidosis.

Secondary amyloidosis (AA): This form can occur secondary to several infectious, inflammatory, and malignant (eg, renal cell carcinomas and others) conditions and is caused by the degradation of the acute-phase reactant serum amyloid A (SAA). Common causative infections include TB, bronchiectasis, osteomyelitis, and leprosy. Inflammatory conditions include RA, juvenile idiopathic arthritis (formerly juvenile RA), Crohn's disease, and familial Mediterranean fever. Inflammatory cytokines (eg, IL-1, tumor necrosis factor, IL-6) that are produced in these disorders cause increased hepatic production of the precursor protein SAA, which circulates in the serum.

AA amyloidosis shows a predilection for the spleen, liver, kidneys, adrenals, and lymph nodes. The liver, spleen, and kidneys are often enlarged, firm, and rubbery. Involvement of the heart and peripheral or autonomic nerves is rare. However, no organ system is spared, and vascular involvement may be widespread.

Familial amyloidosis: The familial form results from accumulation of a mutated version of a plasma protein (most commonly transthyretin [TTR], hence ATTR). Nearly all of the abnormal protein is produced by the liver. Over 80 mutations of the gene for TTR have been identified, all inherited in an autosomal dominant pattern.

Age at onset of symptoms is highly variable, ranging from the teens to the 70s. ATTR amyloidosis causes peripheral sensory and motor neuropathy, often with an autonomic neuropathy. Carpal tunnel syndrome is common. Later in the illness, cardiovascular and renal involvement occurs. Vitreous abnormalities may also develop.

Other very rare hereditary amyloidoses result from mutations of other physiologic proteins, including
apolipoprotein A-1, lysozyme, fibrinogen, gelsolin, and cystatin C. These amyloidoses have various systemic and localized effects.

**A β₂-microglobulin (dialysis-related) amyloidosis:** This form occurs in patients with chronic renal failure who have been on hemodialysis or peritoneal dialysis for long periods, usually > 8 yr. The amyloid deposits consist of β₂-microglobulin, a component of the class I major histocompatibility complex, which is normally cleared by the kidneys but cannot be removed by dialysis membranes. Deposits preferentially occur in and around bones and joints and in the carpal tunnel and have been found in the GI tract and in other organs.

**A β-protein amyloidosis:** This form occurs in patients with Alzheimer's disease. Although the exact role of amyloid deposits is unclear, the neuritic plaques characteristic of Alzheimer's disease contain amyloid deposits consisting of a β-protein fragment of β-amyloid precursor protein (a transmembrane glycoprotein). The β-protein fragment is sometimes complexed with apolipoprotein E. Within the plaques, nonfibrillar forms of the β protein are intermixed with fibrillar amyloid forms.

β-Protein amyloid deposition may also occur around cerebral blood vessels, which is thought to be a cause of nonhypertensive cerebral hemorrhage (cerebral amyloid angiopathy). The angiopathy may occur sporadically or as a hereditary syndrome (Dutch hereditary cerebral hemorrhage).

**Symptoms and Signs**

Symptoms and signs are nonspecific and relate to the organ or system affected. Symptoms in AA amyloidosis are often obscured by the underlying disease.

When the kidneys are affected, nephrotic syndrome is the most striking early manifestation. Initially, only slight proteinuria may occur; later, the distinctive symptom complex develops with anasarca, hypoproteinemia, and massive proteinuria.

Hepatic involvement causes painless hepatomegaly, which may be massive (liver weight > 7 kg). Except for occasional elevation of alkaline phosphatase, liver function tests remain normal. Jaundice is rare. Occasionally, portal hypertension develops, with resulting esophageal varices and ascites.

Cardiac involvement causes a restrictive cardiomyopathy, eventually leading to heart failure. Cardiomegaly and various degrees of heart block or arrhythmia may occur.

Peripheral neuropathy, with paresthesias of the fingers and toes, is a common presenting manifestation in AL and ATTR amyloidoses. Autonomic neuropathy may cause orthostatic hypotension, erectile dysfunction, sweating abnormalities, and GI motility disturbances.

Rheumatologic symptoms in patients with Aβ₂-microglobulin amyloidosis include carpal tunnel syndrome and chronic pain in the shoulder, wrist, and fingers. Pathologic fractures, particularly of the humerus and femur, may occur.

GI amyloid may cause motility abnormalities of the esophagus and small and large intestines. Gastric atony, malabsorption, bleeding, or pseudo-obstruction may also occur. MacroGLOSSia is common in AL amyloidoses.

**Diagnosis**

- Biopsy
Amyloidosis is suspected clinically but can be diagnosed only by biopsy. Subcutaneous abdominal fat pad aspiration and biopsy of rectal mucosa are the best approaches. Other useful biopsy sites are the gingiva, skin, nerves, kidneys, and liver. Tissue sections are stained with Congo red dye and examined with a polarizing microscope for characteristic birefringence. Isotopically labeled serum AP (in which AP represents the pentagonal component of amyloid) can be used in a scintigraphic test to confirm the diagnosis.

**Prognosis**

Prognosis depends on the type of amyloidosis and the organ system involved. AL amyloidosis with multiple myeloma has the poorest prognosis: death within 1 yr is common. Untreated ATTR amyloidoses are fatal within 10 to 15 yr. Prognosis in other familial amyloidoses varies. In general, renal or cardiac involvement in patients with any type of amyloidosis is of particular concern.

Prognosis in AA amyloidosis depends on successful treatment of the underlying disorder, although rare patients undergo spontaneous regression of the amyloid deposits without such treatment.

**Treatment**

• Symptom relief

• Sometimes kidney transplantation

• Sometimes chemotherapy for AL amyloidosis

Management is generally symptomatic, although treatment of the underlying disorder can sometimes arrest amyloidosis. In patients with renal amyloid, kidney transplantation provides long-term survival comparable to that in other renal diseases, although mortality is higher in the early years. Amyloid ultimately recurs in a donor kidney, but several recipients have done very well and have survived up to 10 yr. Heart transplantation has been successful in carefully selected patients with AL amyloidosis and severe cardiac involvement.

Patients with AL amyloidosis are often treated with chemotherapy. A common protocol uses melphalan 0.075 mg/kg po bid and prednisone 0.2 mg/kg po qid. Melphalan with autologous stem cell transplantation achieves good short-term success and apparent cures in some cases.

In patients with ATTR amyloidosis, liver transplantation—which removes the site of synthesis of the mutant protein—is very effective.

For AA amyloidosis with familial Mediterranean fever, colchicine 0.6 mg po once/day or bid is effective. Underlying infections in patients with AA amyloidosis of infectious origin must be treated aggressively. Treatment of amyloid resulting from cancer (eg, renal cell carcinoma) is directed at the cancer.
Chapter 102. Carcinoid Tumors

Introduction

Carcinoid tumors develop from neuroendocrine cells in the GI tract (90%—see p. 191), pancreas, and pulmonary bronchi (see p. 2013). More than 95% of all GI carcinoids originate in only 3 sites: the appendix, ileum, and rectum. Although carcinoids are often benign or only locally invasive, those affecting the ileum and bronchus are frequently malignant.

Carcinoids can be endocrinologically inert or produce various hormones. The most common endocrinologic syndrome is carcinoid syndrome; however, most patients with carcinoids do not develop carcinoid syndrome. The likelihood that a tumor will be endocrinologically active varies with its site of origin, being highest for tumors originating in the ileum and proximal colon (40 to 50%). The likelihood is lower with bronchial carcinoids, lower still with appendiceal carcinoids, and essentially zero with rectal carcinoids.

Endocrinologically inert carcinoids are suspected because of their symptoms and signs (eg, pain, luminal bleeding, GI obstruction). They can be detected by angiography, CT, or MRI. Small-bowel carcinoids may exhibit filling defects or other abnormalities on barium x-rays. Definitive diagnosis is made histologically after biopsy or resection.

Endocrinologically active carcinoids are diagnosed and treated as described below.

Carcinoid Syndrome

Carcinoid syndrome develops in some people with carcinoid tumors and is characterized by cutaneous flushing, abdominal cramps, and diarrhea. Right-sided valvular heart disease may develop after several years. The syndrome results from vasoactive substances (including serotonin, bradykinin, histamine, prostaglandins, polypeptide hormones) secreted by the tumor, which is typically a metastatic intestinal carcinoid. Diagnosis is clinical and by demonstrating increased urinary 5-hydroxyindoleacetic acid. Tumor localization may require a radionuclide scan or laparotomy. Treatment of symptoms is with somatostatin or octreotide, but surgical removal is done where possible; chemotherapy may be used for malignant tumors.

Etiology

Endocrinologically active tumors of the diffuse peripheral endocrine or paracrine system produce various amines and polypeptides with corresponding symptoms and signs, including carcinoid syndrome. Carcinoid syndrome is usually due to endocrinologically active malignant tumors that develop from neuroendocrine cells (mostly in the ileum) and produce serotonin. It can, however, occur from tumors elsewhere in the GI tract (particularly the appendix and rectum), pancreas, bronchi, or, rarely, the gonads. Rarely, certain highly malignant tumors (eg, oat cell carcinoma of the lung, pancreatic islet cell carcinoma, medullary thyroid carcinoma) are responsible.

An intestinal carcinoid does not usually cause the syndrome unless hepatic metastases have occurred, because metabolic products released by the tumor are rapidly destroyed by blood and liver enzymes in the portal circulation (eg, serotonin by hepatic monoamine oxidase). Hepatic metastases, however, release metabolic products via the hepatic veins directly into the systemic circulation. Metabolic products released by primary pulmonary and ovarian carcinoids bypass the portal route and may similarly induce symptoms. Rare intestinal carcinoids with only intra-abdominal spread can drain directly into the systemic circulation or the lymphatics and cause symptoms.

Pathophysiology

Serotonin acts on smooth muscle to cause diarrhea, colic, and malabsorption. Histamine and bradykinin, through their vasodilator effects, cause flushing. The role of prostaglandins and various polypeptide hormones, which may be produced by paracrine cells, awaits further investigation; elevated human chorionic gonadotropin and pancreatic polypeptide levels are occasionally present with carcinoids.
Many patients develop right-sided endocardial fibrosis, leading to pulmonary stenosis and tricuspid regurgitation. Left heart lesions, which have been reported with bronchial carcinoids, are rare because serotonin is destroyed during passage through the lungs.

Symptoms and Signs

The most common (and often earliest) sign is an uncomfortable flushing, typically of the head and neck, often precipitated by emotional stress or the ingestion of food, hot beverages, or alcohol. Striking skin color changes may occur, ranging from pallor or erythema to a violaceous hue. Abdominal cramps with recurrent diarrhea occur and are often the patient's major complaint. Malabsorption syndrome may occur. Patients with valvular lesions may have a heart murmur. A few patients have asthmatic wheezing, and some have decreased libido and erectile dysfunction; pellagra develops rarely.

Diagnosis

• Urinary 5-hydroxyindoleacetic acid (5-HIAA)

Serotonin-secreting carcinoids are suspected based on their symptoms and signs. Diagnosis is confirmed by demonstrating increased urinary excretion of the serotonin metabolite 5-HIAA. To avoid false-positive results, clinicians do the test after the patient has abstained from serotonin-containing foods (eg, bananas, tomatoes, plums, avocados, pineapples, eggplant, walnuts) for 3 days. Certain drugs, including guaifenesin, methocarbamol, and phenothiazines, also interfere with the test and should be stopped temporarily before testing. On the 3rd day, a 24-h urine sample is collected for assay. Normal excretion of 5-HIAA is < 10 mg/day (< 52 μmol/day); in patients with carcinoid syndrome, excretion is usually > 50 mg/day (> 260 μmol/day).

Provocative tests with Ca gluconate, catecholamines, pentagastrin, or alcohol have been used to induce flushing. These tests may be helpful when the diagnosis is in doubt, but they must be done with care. Localization of the tumor involves the same techniques used to localize a nonfunctioning carcinoid (see p. 907) but may require extensive evaluation, sometimes including laparotomy. A scan with radionuclide-labeled somatostatin receptor ligand indium-111 pentetreotide or with iodine-123 metaiodobenzylguanidine may show metastases.

Other conditions that manifest with flushing and that could, therefore, be confused with carcinoid syndrome should be excluded. In patients in whom 5-HIAA excretion is not increased, disorders that involve systemic activation of mastocytes (eg, systemic mastocytosis with increased urinary levels of histamine metabolites and increased serum tryptase level) and idiopathic anaphylaxis may be responsible. Additional causes of flushing include menopause, ethanol ingestion, drugs such as niacin, and certain tumors (eg, vipomas, renal cell carcinoma, medullary thyroid carcinoma).

Prognosis

Despite metastatic disease, these tumors are slow growing, and survival of 10 to 15 yr is not unusual.

Treatment

• Surgical resection

• Octreotide for symptoms

Resection of primary lung carcinoids is often curative. For patients with hepatic metastases, surgery is only diagnostic or palliative, and radiation therapy is unsuccessful, in part because of the poor tolerance of normal hepatic tissue to radiation. No effective chemotherapeutic regimen has been established, but streptozocin with 5-fluorouracil is most widely used, sometimes with doxorubicin.

Certain symptoms, including flushing, have been relieved by somatostatin (which inhibits release of most hormones) without lowering urinary 5-HIAA or gastrin. Numerous studies have suggested good results
with octreotide, a long-acting analog of somatostatin. Octreotide is the drug of choice for controlling diarrhea and flushing. Case reports indicate that tamoxifen has been effective infrequently; leukocyte interferon (IFN-α) has temporarily relieved symptoms.

Flushing also can be treated with phenothiazines (eg, prochlorperazine 5 to 10 mg or chlorpromazine 25 to 50 mg po q 6 h). Histamine_2_ blockers may also be used. Phentolamine (an α-blocker) 5 to 15 mg IV has prevented experimentally induced flushes. Corticosteroids (eg, prednisone 5 mg po q 6 h) may be useful for severe flushing caused by bronchial carcinoids.

Diarrhea may be controlled by codeine phosphate 15 mg po q 4 to 6 h, tincture of opium 0.6 mL po q 6 h, loperamide 4 mg po as a loading dose and 2 mg after each loose bowel to a maximum of 16 mg/day, diphenoxylate 5 mg po qid, or peripheral serotonin antagonists such as cyproheptadine 4 to 8 mg po q 6 h or methysergide 1 to 2 mg po qid.

Niacin and adequate protein intake are needed to prevent pellagra, because dietary tryptophan is diverted to serotonin by the tumor. Enzyme inhibitors that prevent the conversion of 5-hydroxytryptophan to serotonin include methyldopa 250 to 500 mg po q 6 h and phenoxybenzamine 10 mg/day.
Chapter 103. Multiple Endocrine Neoplasia Syndromes

Introduction

(Familial Endocrine Adenomatosis; Multiple Endocrine Adenomatosis)

The multiple endocrine neoplasia (MEN) syndromes comprise 3 genetically distinct familial diseases involving adenomatous hyperplasia and malignant tumors in several endocrine glands. Clinical features depend on the glandular elements involved.

Each syndrome is inherited as an autosomal dominant trait with a high degree of penetrance, variable expressivity, and production of seemingly unrelated effects by a single mutant gene. The specific mutation is not always known.

Symptoms and signs develop at any age. Proper management includes early identification of affected individuals within a kindred and surgical removal of the tumors when possible. Although these syndromes are generally considered clinically distinct, significant overlap exists (see Table 103-1).

Multiple Endocrine Neoplasia, Type 1

(Multiple Endocrine Adenomatosis, Type I; Wermer's Syndrome)

Multiple endocrine neoplasia, type 1 (MEN 1) is a hereditary syndrome characterized by tumors of the parathyroid glands, pancreatic islet cells, and pituitary gland. Clinical features most commonly include hyperparathyroidism and asymptomatic hypercalcemia. Genetic screening is used to detect carriers. Diagnosis is by hormonal and imaging tests. Tumors are surgically removed when possible.

MEN 1 is probably caused by an inactivating mutation of the tumor suppressor gene that encodes the transcription factor menin; many mutations of this gene may be responsible.

About 40% of MEN 1 cases involve tumors of all 3 affected glands—the parathyroids, pancreas, and pituitary. Almost any combination of the tumors and symptom complexes outlined below is possible. A patient with a MEN 1 gene mutation and one of the MEN 1 tumors is at risk of developing any of the other tumors later on. Age at onset ranges from 4 to 81 yr, but peak incidence occurs in the 20s in women and 30s in men. Women are affected twice as often as men.

Symptoms and Signs

The clinical features depend on the glandular elements affected (see Table 103-1).

Parathyroid: Hyperparathyroidism is present in ≥ 90% of patients. Asymptomatic hypercalcemia is the most common manifestation: about 25% of patients have evidence of nephrolithiasis or nephrocalcinosis. In contrast to sporadic cases of hyperparathyroidism, diffuse hyperplasia or multiple adenomas are more common than solitary adenomas.

Pancreas: Pancreatic islet cell tumors occur in 60 to 70% of patients. Tumors are usually multicentric. Multiple adenomas or diffuse islet cell hyperplasia commonly occurs; such tumors may arise from the small bowel rather than the pancreas. About 30% of tumors are malignant and have local or distant metastases. Malignant islet cell tumors due to MEN 1 syndrome often have a more benign course than do sporadically occurring malignant islet cell tumors.

About 40% of islet cell tumors originate from a β cell, secrete insulin (insulinoma), and can cause fasting hypoglycemia. β-Cell tumors are more common among patients < 40. About 60% of islet cell tumors...
Most islet cell tumors secrete pancreatic polypeptide, the clinical significance of which is unknown. Gastrin is secreted by many non-β-cell tumors (increased gastrin secretion in MEN 1 also often originates from the duodenum). Increased gastrin secretion increases gastric acid, which may inactivate pancreatic lipase, leading to diarrhea and steatorrhea. Increased gastrin secretion also leads to peptic ulcers in > 50% of MEN 1 patients. Usually the ulcers are multiple or atypical in location, and often bleed, perforate, or become obstructed. Peptic ulcer disease may be intractable and complicated (Zollinger-Ellison syndrome—see p. 200). Among patients presenting with Zollinger-Ellison syndrome, 20 to 60% have MEN 1.

A severe secretory diarrhea can develop and cause fluid and electrolyte depletion with non-β-cell tumors. This complex, referred to as the watery diarrhea, hypokalemia, and achlorhydria syndrome (WDHA; pancreatic cholera—see p. 201), has been ascribed to vasoactive intestinal polypeptide, although other intestinal hormones or secretagogues (including prostaglandins) may contribute. Hypersecretion of glucagon, somatostatin, chromogranin, or calcitonin, ectopic secretion of ACTH (causing Cushing's syndrome), and hypersecretion of growth hormone-releasing hormone (causing acromegaly) sometimes occur in non-β-cell tumors. All of these are rare in MEN 1.

Nonfunctioning pancreatic tumors also occur in patients with MEN 1 and may be the most common type of pancreatoduodenal tumor in MEN 1. The size of the nonfunctioning tumor correlates with risk of metastasis and death.

**Diagnosis**

- Clinical evaluation for other tumors of the triad
- Serum Ca, parathyroid hormone (PTH), gastrin, and prolactin levels
- Tumor localization with MRI, CT, or scintigraphy
- Genetic testing

Patients with tumors of the parathyroids, pancreas, or pituitary, particularly those with a family history of endocrinopathy, should undergo clinical screening for other tumors of MEN 1. Such screening includes the following:

- Asking about symptoms of peptic ulcer disease, diarrhea, nephrolithiasis, hypoglycemia, and hypopituitarism
- Examining for visual field defects, galactorrhea in women, and features of acromegaly and subcutaneous lipomas
• Measuring levels of serum Ca, intact PTH, gastrin, and prolactin

Additional laboratory or radiologic tests should be done if these screening tests suggest an endocrine abnormality related to MEN 1. An insulin-secreting β-cell tumor of the pancreas is diagnosed by detecting fasting hypoglycemia with an elevated plasma insulin level.

A gastrin-secreting non-β-cell tumor of the pancreas or duodenum is diagnosed by elevated basal plasma gastrin levels, an exaggerated gastrin response to infused Ca, and a paradoxical rise in gastrin level after infusion of secretin. An elevated basal level of pancreatic polypeptide or gastrin or an exaggerated response of these hormones to a standard meal may be the earliest sign of pancreatic involvement. CT or MRI can help localize tumors. Because these tumors are often small and difficult to localize, other imaging tests (eg, somatostatin receptor scintigraphy, endoscopic ultrasonography, intraoperative ultrasonography) may be necessary.

Acromegaly is diagnosed by elevated growth hormone levels that are not suppressed by glucose administration and by elevated levels of serum insulin-like growth factor 1.

In patients with 2 or more endocrine abnormalities related to MEN 1 who are not from a known MEN 1 kindred (index case), direct DNA sequencing of the MEN 1 gene identifies a specific mutation in 80 to 90%. If an index case is identified, 1st-degree relatives should consider genetic screening. Early presymptomatic screening of family members of MEN 1 patients has not been shown to reduce morbidity or mortality; annual clinical and biochemical screening may thus be preferable in this group.

Treatment

• Surgical excision when possible

• Drug management of hormone excess

Treatment of parathyroid and pituitary lesions is primarily surgical, although prolactinoma is usually managed with dopamine agonists. Islet cell tumors are more difficult to manage because the lesions are often small and difficult to find and multiple lesions are common. If a single tumor cannot be found, total pancreatectomy may be required for adequate control of hyperinsulinism. Diazoxide may be a useful adjunct in treating hypoglycemia. Streptozocin and other cytotoxic drugs may ameliorate symptoms by reducing tumor burden.

The treatment of gastrin-secreting non-β-cell tumors is complex. Localization and removal of the tumor should be attempted. If localization is impossible, a proton pump inhibitor frequently produces symptomatic relief from peptic ulcer disease. With the availability of these drugs, gastrectomy is rarely required.

Octreotide, a somatostatin analog, can block hormone secretion from nongastrin-secreting pancreatic tumors and is well tolerated, particularly if given as a long-acting preparation administered every 4 wk. Palliative treatments for metastatic pancreatic tumors include hepatic artery embolization and interferon alfa (in combination with octreotide).

Multiple Endocrine Neoplasia, Type 2A

(MEN 2; Multiple Endocrine Adenomatosis, Type 2; Sipple's Syndrome)

Multiple endocrine neoplasia, type 2A (MEN 2A) is a hereditary syndrome characterized by medullary carcinoma of the thyroid, pheochromocytoma, hyperparathyroidism, and occasionally cutaneous lichen amyloidosis. Clinical features depend on the glandular elements affected. Familial medullary thyroid carcinoma is a distinct variant of MEN 2A. Diagnosis involves genetic testing. Hormonal and imaging tests help locate the tumors, which are removed surgically when possible.

Mutations in the RET proto-oncogene on chromosome 10 have been identified in MEN 2A, MEN 2B, and
familial medullary thyroid carcinoma (FMTC). The RET protein is a receptor tyrosine kinase; MEN 2A and FMTC mutations result in activation of certain intracellular pathways.

**Symptoms and Signs**

Clinical features depend on the type of tumor present. (Table 103-1).

**Thyroid:** Almost all patients have medullary thyroid carcinoma (MTC—see p. 790). The tumor usually develops during childhood and begins with thyroid parafollicular C-cell hyperplasia. Tumors are frequently multicentric.

**Adrenal:** Pheochromocytoma usually originates in the adrenal glands. Pheochromocytoma occurs in 40 to 50% of patients within a MEN 2A kindred, and in some kindreds pheochromocytoma accounts for 30% of deaths. In contrast to sporadic pheochromocytoma (see p. 801), the familial variety within MEN 2A begins with adrenal medullary hyperplasia and is multicentric and bilateral in > 50% of cases. Extra-adrenal pheochromocytomas are rare. Pheochromocytomas are almost always benign, but some tend to recur locally.

Pheochromocytomas that occur with MEN 2A (and 2B) usually produce epinephrine disproportionately to norepinephrine, in contrast to sporadic cases.

Hypertensive crisis secondary to pheochromocytoma is a common manifestation. Hypertension in MEN 2A patients with pheochromocytoma is more often paroxysmal than sustained, in contrast to the usual sporadic case. Patients with pheochromocytomas may have paroxysmal palpitations, anxiety, headaches, or sweating; many are asymptomatic.

**Parathyroid:** Ten to 20% of patients have evidence of hyperparathyroidism (which may be long-standing), with hypercalcemia, nephrolithiasis, nephrocalcinosis, or renal failure. Hyperparathyroidism frequently involves multiple glands as either diffuse hyperplasia or multiple adenomas, and mild abnormalities in parathyroid function may also be present in MEN 2A.

**Other manifestations:** Cutaneous lichen amyloidosis, a pruritic, scaly, papular skin lesion, located in the interscapular region or on extensor surfaces, occurs in some MEN 2A kindreds. Increased incidence of Hirschsprung's disease has been reported in children in at least one MEN 2A kindred.

**Diagnosis**

- Clinical suspicion
- Genetic testing
- Serum Ca, parathyroid hormone, and plasma free metanephrine or urinary catecholamine levels in affected patients
- Pheochromocytoma localization with MRI or CT

Many cases are identified during screening of family members of known cases. MEN 2A should also be suspected in patients with bilateral pheochromocytoma or at least 2 of its characteristic endocrine manifestations. The diagnosis can be confirmed with genetic testing. Although only 25% of MTC cases are familial, genetic testing of people with apparent sporadic MTC should be considered if patients are < 35 yr, tumors are bilateral or multicentric, or a family history is suspected.

Because pheochromocytoma may be asymptomatic, its exclusion may be difficult (see p. 802). The most sensitive tests are plasma free metanephrines and fractionated urinary catecholamines (particularly epinephrine). CT or MRI is useful in localizing the pheochromocytoma or establishing the presence of bilateral lesions.

Hyperparathyroidism is diagnosed by hypercalcemia, hypophosphatemia, and increased parathyroid
Screening: Genetic screening of family members of MEN 2A patients is now the diagnostic test of choice; the availability of such testing has made biochemical screening for early MTC largely obsolete. Among affected family members, annual screening for hyperparathyroidism and pheochromocytoma should begin in early childhood and continue indefinitely. Screening for hyperparathyroidism is with measurement of serum Ca. Screening for pheochromocytoma includes questions about symptoms, measurement of BP, and laboratory testing.

Treatment

- Surgical excision of identified tumors
- Prophylactic thyroidectomy

In patients presenting with pheochromocytoma and either MTC or hyperparathyroidism, the pheochromocytoma should be removed first; even if asymptomatic, it greatly increases risk of other surgeries. Once MTC has metastasized, chemotherapy and radiation therapy are largely ineffective in lengthening survival but may slow disease progression. Radioimmunotherapy has improved survival in initial studies.

Once genetic testing identifies a child as having a RET mutation, prophylactic thyroidectomy is recommended, generally when the child is between 4 and 6 yr; this potentially fatal condition can be cured or prevented by early thyroidectomy.

Multiple Endocrine Neoplasia, Type 2B

(MEN 3; Mucosal Neuroma Syndrome; Multiple Endocrine Adenomatosis, Type 2B)

Multiple endocrine neoplasia, type 2B (MEN 2B) is an autosomal dominant syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, multiple mucosal neuromas and intestinal ganglioneuromas, and often a marfanoid habitus. Symptoms depend on the glandular elements present. Diagnosis and treatment are the same as for MEN 2A.

Ninety-five percent of MEN 2B cases result from a single amino acid substitution in the RET protein. More than 50% are de novo mutations and thus seem to be sporadic rather than familial.

Symptoms and Signs

Symptoms and signs reflect the glandular abnormalities present (see Table 103-1). About 50% of patients have the complete syndrome with mucosal neuromas, pheochromocytomas, and medullary thyroid carcinoma (MTC). Fewer than 10% have neuromas and pheochromocytomas alone, whereas the remaining patients have neuromas and medullary carcinoma of the thyroid without pheochromocytoma.

Often, mucosal neuromas are the earliest sign, and they occur in most or all patients. Neuromas appear as small glistening bumps on the lips, tongue, and buccal mucosa. The eyelids, conjunctivae, and corneas also commonly develop neuromas. Thickened eyelids and diffusely hypertrophied lips are characteristic. GI abnormalities related to altered motility (constipation, diarrhea, and, occasionally, megacolon) are common and thought to result from diffuse intestinal ganglioneuromatosis. Patients may have a marfanoid habitus. Skeletal abnormalities of the spine (lordosis, kyphosis, scoliosis), pes cavus, and talipes equinovarus are common.

MTC and pheochromocytoma resemble the corresponding disorders in MEN 2A syndrome; both tend to be bilateral and multicentric. MTC, however, tends to be particularly aggressive in MEN 2B and may be present in very young children.

Although the neuromas, facial characteristics, and GI disorders are present at an early age, the syndrome may not be recognized until MTC or pheochromocytoma manifests in later life.
Diagnosis

• Clinical suspicion

• Genetic testing

• Plasma free metanephrine or urinary catecholamine levels

• Pheochromocytoma localization with MRI or CT

MEN 2B is suspected in patients with a family history of MEN 2B, pheochromocytoma, multiple mucosal neuromas, or MTC. Genetic testing is highly accurate and is done in 1st-degree relatives and any symptomatic family members of MEN 2B patients.

Pheochromocytoma may be suspected clinically and is confirmed by measuring plasma free metanephrines or urinary catecholamines (see p. 802). Laboratory testing for MTC may be done (see p. 790). MRI or CT is used to search for pheochromocytomas and MTC.

Treatment

• Surgical excision of identified tumors

• Prophylactic thyroidectomy

Affected patients should have total thyroidectomy as soon as the diagnosis is established. Pheochromocytoma, if present, should be removed before thyroidectomy is done. Gene carriers should undergo prophylactic thyroidectomy in infancy or early childhood.
9 - Hematology and Oncology

Chapter 104. Approach to the Patient With Anemia

Introduction

Red blood cell (RBC) production (erythropoiesis) takes place in the bone marrow under the control of the hormone erythropoietin (EPO). Juxtaglomerular cells in the kidney produce EPO in response to decreased O₂ delivery (as in anemia and hypoxia) and increased levels of androgens. In addition to EPO, RBC production requires adequate supplies of substrates, mainly iron, vitamin B₁₂, and folate. Vitamin B₁₂ and folate are discussed in Ch. 4; iron is discussed on pp. 53 and 924.

RBCs become senescent after about 120 days. They then lose their cell membranes and are largely cleared from the circulation by the phagocytic cells of the spleen, liver, and bone marrow. Hb is broken down in these cells and in hepatocytes primarily by the heme oxygenase system with conservation (and subsequent reutilization) of iron, degradation of heme to bilirubin through a series of enzymatic steps, and reutilization of protein. Maintenance of a steady number of RBCs requires daily renewal of 1/120 of the cells; immature RBCs (reticulocytes) are continually released and constitute 0.5 to 1.5% of the peripheral RBC population.

Low levels of androgens leading to decreased EPO levels in women and girls and in elderly patients can predispose to anemia, as does the decline in the capacity of bone marrow to produce RBCs. With aging, Hb and Hct decrease slightly, but not below normal values. In women, other factors that frequently contribute to lower levels of RBCs include cumulative menstrual blood loss and increased demand for iron due to multiple pregnancies.

Etiology of Anemia

Anemia is a decrease in the number of RBCs, Hct, or Hb content.

The RBC mass represents the balance between production and destruction or loss of RBCs. Thus, anemia can result from one or more of 3 basic mechanisms (see Table 104-1):

- Blood loss
- Deficient erythropoiesis
- Excessive hemolysis (RBC destruction)

Blood loss can be acute or chronic. Anemia does not develop until several hours after acute blood loss, when interstitial fluid diffuses into the intravascular space and dilutes the remaining RBC mass. During the first few hours, however, levels of polymorphonuclear granulocytes, platelets, and, in severe hemorrhage, immature WBCs and normoblasts may rise. Chronic blood loss results in anemia if loss is more rapid than can be replaced or, more commonly, if accelerated erythropoiesis depletes body iron stores (see p. 924).

Deficient erythropoiesis (see p. 924) has myriad causes. Complete cessation of erythropoiesis results in a decline in RBCs of about 7 to 10%/wk (1%/day). Impaired erythropoiesis, even if not sufficient to decrease the numbers of RBCs, often causes abnormal RBC size and shape.

Excessive hemolysis (see p. 934) can be caused by intrinsic abnormalities of RBCs or by extrinsic factors, such as the presence of antibodies on their surface, that lead to their early destruction. An enlarged spleen sequesters and destroys RBCs more rapidly than normal. Some causes of hemolysis deform as well as destroy RBCs. Excessive hemolysis does not normally decrease reticulocyte production.
unless iron or other essential nutrients are depleted.

**Evaluation of Anemia**

Anemia is not a diagnosis; it is a manifestation of an underlying disorder. Thus, even mild, asymptomatic anemia should be investigated so that the primary problem can be diagnosed and treated.

Acute or chronic blood loss is the first consideration. The diagnosis usually is based on history, examination, and a stool test for occult blood. Further testing for occult bleeding is sometimes necessary.

If blood loss is not detected, laboratory testing is usually done to determine whether anemia is due to deficient RBC production or excessive hemolysis.

**History**

The history should address risk factors for particular anemias, symptoms of anemia itself, and symptoms that reflect the underlying disorder.

Anemia has many risk factors. For example, a vegan diet predisposes to vitamin B₁₂ deficiency anemia, whereas alcoholism increases the risk of folate deficiency anemia. A number of hemoglobinopathies are inherited, and certain drugs predispose to hemolysis. Cancer, rheumatic disorders, and chronic inflammatory disorders can suppress bone marrow activity or enlarge the spleen.

The symptoms of anemia are neither sensitive nor specific and do not help differentiate between types of anemias. Symptoms reflect compensatory responses to tissue hypoxia and usually develop when Hb falls to < 7 g/dL. However, they may develop at higher Hb levels in patients with limited cardiopulmonary reserve or in whom the anemia developed very rapidly. Symptoms such as weakness, seeing spots, fatigue, drowsiness, angina, syncope, and dyspnea on exertion can indicate anemia. Vertigo, headache, pulsatile tinnitus, amenorrhea, loss of libido, and GI complaints may also occur. Heart failure or shock can develop in patients with severe tissue hypoxia or hypovolemia.

Certain symptoms may suggest the cause of the anemia. For example, melena, epistaxis, hematochezia, hematemesis, or menorrhagia indicates bleeding. Jaundice and dark urine, in the absence of liver disease, suggest hemolysis. Weight loss may suggest cancer. Diffuse severe bone or chest pain may suggest sickle cell disease, and stocking-glove paresthesias may suggest vitamin B₁₂ or folate deficiency.

**Physical Examination**

Complete physical examination is necessary. Signs of anemia itself are neither sensitive nor specific; however, pallor is common with severe anemia.

Signs of underlying disorders are often more diagnostically accurate than are signs of anemia. Heme-positive stool identifies GI bleeding. Hemorrhagic shock (eg, hypotension, tachycardia, pallor, tachypnea, diaphoresis, confusion—see p. 2292) may result from acute bleeding. Jaundice may suggest hemolysis. Splenomegaly may occur with hemolysis, hemoglobinopathy, connective tissue disease, myeloproliferative disorder, infection, or cancer. Peripheral neuropathy suggests vitamin B₁₂ deficiency. Abdominal distention in a patient with blunt trauma suggests acute hemorrhage. Petechiae develop in thrombocytopenia or platelet dysfunction. Fever and heart murmurs suggest infectious endocarditis, a possible cause of hemolysis. Rarely, high-output heart failure develops as a compensatory response to anemia-induced tissue hypoxia.

**Testing**

- CBC with WBC and platelets
- RBC indices and morphology
Laboratory evaluation begins with a CBC, including WBC and platelet counts, RBC indices and morphology (MCV, MCH, MCHC, RBC volume distribution width [RDW]), and examination of the peripheral smear. Reticulocyte count demonstrates how well the bone marrow compensates for the anemia. Subsequent tests are selected on the basis of these results and on the clinical presentation. Recognition of general diagnostic patterns can expedite the diagnosis (see Table 104-2).

The automated CBC directly measures Hb, RBC count, and MCV (a measure of RBC size). Hct (a measure of the percentage of blood made up of RBCs), MCH (a measure of the Hb content in individual RBCs), and MCHC (a measure of the Hb level in individual RBCs) are calculated values. The diagnostic criterion for anemia in men is Hb < 14 g/dL, Hct < 42%, or RBC < 4.5 million/L; for women, Hb < 12 g/dL, Hct < 37%, or RBC < 4 million/L. For infants, normal values vary with age, necessitating use of age-related tables. RBC populations are termed microcytic (small cells) if MCV is < 80 fl, and macrocytic (large cells) if MCV is > 100 fl. However, because reticulocytes are also larger than mature red cells, large numbers of reticulocytes can elevate the MCV and not represent an alteration of RBC production. Automated techniques can also determine the degree of variation in RBC size, expressed as the RDW. A high RDW may be the only indication of simultaneous microcytic and macrocytic disorders (or simultaneous microcytosis and reticulocytosis); such a pattern may result in a normal MCV, which measures only the mean value. The term hypochromia refers to RBC populations in which MCH is < 27 pg/RBC or MCHC is < 30%. RBC populations with normal MCH and MCHC values are normochromic.

The RBC indices can help indicate the mechanism of anemia and narrow the number of possible causes. Microcytic indices occur with altered heme or globin synthesis. The most common causes are iron deficiency, thalassemia, and related Hb-synthesis defects. In some patients with anemia of chronic disease, the MCV is microcytic or borderline microcytic. Macrocytic indices occur with impaired DNA synthesis (eg, due to vitamin B₁₂ or folate deficiencies or chemotherapeutic drugs such as hydroxyurea and antifolate agents) and in alcoholism because of abnormalities of the cell membrane. Acute bleeding may briefly produce macrocytic indices because of the release of large young reticulocytes. Normocytic indices occur in anemias resulting from deficient EPO or inadequate response to it (hypoproliferative anemias). Hemorrhage, before iron deficiency develops, usually results in normocytic and normochromic anemia unless the number of large reticulocytes is excessive.

The peripheral smear is highly sensitive for excessive RBC production and hemolysis. It is more accurate than automated technologies for recognition of altered RBC structure, thrombocytopenia, nucleated RBCs, or immature granulocytes and can detect other abnormalities (eg, malaria and other parasites, intracellular RBC or granulocyte inclusions) that can occur despite normal automated blood cell counts. RBC injury may be identified by finding RBC fragments, portions of disrupted cells (schistocytes), or evidence of significant membrane alterations from oval-shaped cells (ovalocytes) or spherocytic cells. Target cells (thin RBCs with a central dot of Hb) are RBCs with insufficient Hb or excess cell membrane (eg, due to hemoglobinopathies or liver disorders). The peripheral smear can also reveal variation in RBC shape (poikilocytosis) and size (anisocytosis).

The reticulocyte count is expressed as the percentage of reticulocytes (normal range, 0.5 to 1.5%) or as the absolute reticulocyte count (normal range, 50,000 to 150,000/μL). Higher values indicate excessive production, or reticulocytosis; in the presence of anemia, reticulocytosis suggests excessive RBC destruction. Low numbers in the presence of anemia indicate decreased RBC production. The reticulocyte response can usually be estimated based on the number of blue-stained cells found when the peripheral smear is stained with a supravital stain; this estimates makes a reticulocyte count, which requires flow cytometry or a large amount of time, unnecessary.

Bone marrow aspiration and biopsy provide direct observation and assessment of RBC precursors.
The presence of abnormal maturation (dyspoiesis) of blood cells and the amount, distribution, and cellular pattern of iron content can be assessed. Bone marrow aspiration and biopsy are done to diagnose the following conditions:

- Unexplained anemias
- Other cytopenias
- Unexplained leukocytosis

[Table 104-2, Characteristics of Common Anemias]

- Thrombocytosis
- Suspected leukemia, multiple myeloma, or myelophthisis

Cytogenetic and molecular analyses can be done on aspirate material in hematopoietic or other tumors or in suspected congenital lesions of RBC precursors (eg, Fanconi’s anemia). Flow cytometry can be done in suspected lymphoproliferative or myeloproliferative states to define the immunophenotype. Bone marrow aspiration and biopsy are not technically difficult and do not pose significant risk of morbidity. These procedures are safe and helpful when hematologic disease is suspected. Both usually can be done as a single procedure. Because biopsy requires adequate bone depth, the sample is usually taken from the posterior (or, less commonly, anterior) iliac crest. If only aspiration is necessary, the sternum may be used.

Serum bilirubin and LDH can sometimes help differentiate between hemolysis and blood loss; both are elevated in hemolysis and normal in blood loss. Other tests are discussed under specific anemias and bleeding disorders (see p. 921).

### Treatment of Anemia

When possible, the cause of the anemia is treated. When the Hb falls dangerously low (eg, < 7 g/dL for patients without cardiopulmonary insufficiency or higher for patients with it), RBC transfusion temporarily increases O$_2$-carrying capacity. RBC transfusion should be reserved for patients

- With or at high risk of cardiopulmonary symptoms
- With active, uncontrollable blood loss
- With some form of hypoxic or ischemic end-organ failure (eg, neurologic ischemic symptoms, angina, tachycardia in patients with underlying heart failure or severe COPD)

Transfusion procedures and blood components are discussed in Ch. 121.
Chapter 105. Anemias Caused by Deficient Erythropoiesis

Introduction

Anemia (a decrease in the number of RBCs, Hb content, or Hct) can result from decreased RBC production (erythropoiesis), increased RBC destruction, or blood loss. Anemias due to decreased erythropoiesis are recognized by reticulocytopenia, which is usually evident on the peripheral smear (see p. 921). The RBC indices, mainly the MCV, narrow the differential diagnosis of deficient erythropoiesis and determine what further testing is necessary.

Microcytic anemias result from deficient or defective heme or globin synthesis. Microcytic anemias include iron deficiency anemias, iron-transport deficiency anemias, iron-utilization anemias (including some sideroblastic anemias and lead poisoning), and thalassemias (which also cause hemolysis—see p. 946). Patients with microcytic anemias typically require testing of iron stores (see below).

Normocytic anemias result from primary bone marrow failure. They are usually characterized by a normal RBC distribution width (RDW) and normochromic indices. The mechanisms involved are hypoproliferation (deficiency of or inadequate response to erythropoietin [EPO]), hypoplasia (in aplastic anemia), myelophthisis, and myelodysplasia.

Macrocytic anemias result most often from impaired DNA synthesis, as occurs with deficiencies of vitamin B12 or folate.

Some anemias have variable findings on the peripheral smear. Anemia of chronic disease may be microcytic or normocytic. Anemias due to myelodysplastic syndromes may be microcytic, normocytic, or macrocytic. Treatment of deficient RBC production depends on the cause; however, stimulation of erythropoiesis with human recombinant EPO often is helpful in the anemia due to renal failure. Because erythropoiesis increases the iron requirement, supplemental iron is helpful when administering any treatment that aims to increase erythropoiesis.

Iron Deficiency Anemia

(Anemia of Chronic Blood Loss; Chlorosis)

Iron deficiency is the most common cause of anemia and usually results from blood loss. Symptoms are usually nonspecific. RBCs tend to be microcytic and hypochromic, and iron stores are low as shown by low serum ferritin and low serum iron levels with high serum total iron binding capacity. If the diagnosis is made, occult blood loss is suspected. Treatment involves iron replacement and treatment of the cause of blood loss.

Pathophysiology

Iron is distributed in active metabolic and storage pools. Total body iron is about 3.5 g in healthy men and 2.5 g in women; the difference relates to women's smaller body size, lower androgen levels, and dearth of stored iron because of iron loss due to menses and pregnancy. The distribution of body iron in an average man is Hb, 2100 mg; ferritin, 700 mg (in cells and plasma); hemosiderin, 300 mg (in cells); myoglobin, 200 mg; tissue (heme and nonheme) enzymes, 150 mg; and transport-iron compartment, 3 mg.

Iron absorption: Iron is absorbed in the duodenum and upper jejunum. Absorption of iron is determined by the type of iron molecule and by what other substances are ingested. Iron absorption is best when food contains heme iron (meat). Dietary nonheme iron must be reduced to the ferrous state and released from food binders by gastric secretions. Nonheme iron absorption is reduced by other food items (eg, vegetable fiber phytates and polyphenols; tea tannates, including phosphoproteins; bran) and certain antibiotics (eg, tetracycline). Ascorbic acid is the only common food element known to increase nonheme iron absorption.
The average American diet, which contains 6 mg of elemental iron/kcal of food, is adequate for iron homeostasis. Of about 15 mg/day of dietary iron, adults absorb only 1 mg, which is the approximate amount lost daily by cell desquamation from the skin and intestines. In iron depletion, absorption increases, although the exact signaling mechanism is not known; however, absorption rarely increases to > 6 mg/day unless supplemental iron is added. Children have a greater need for iron and appear to absorb more to meet this need.

**Iron transport and usage:** Iron from intestinal mucosal cells is transferred to transferrin, an iron-transport protein synthesized in the liver; transferrin can transport iron from cells (intestinal, macrophages) to specific receptors on erythroblasts, placental cells, and liver cells. For heme synthesis, transferrin transports iron to the erythroblast mitochondria, which insert the iron into protoporphyrin for it to become heme. Transferrin (plasma half-life, 8 days) is extruded for reutilization. Synthesis of transferrin increases with iron deficiency but decreases with any type of chronic disease.

**Iron storage and recycling:** Iron not used for erythropoiesis is transferred by transferrin, an iron-transporting protein, to the storage pool; iron is stored in 2 forms, ferritin and hemosiderin. The most important is ferritin (a heterogeneous group of proteins surrounding an iron core), which is a soluble and active storage fraction located in the liver (in hepatocytes), bone marrow, and spleen (in macrophages); in RBCs; and in serum. Iron stored in ferritin is readily available for any body requirement. Circulating (serum) ferritin level parallels the size of the body stores (1 ng/mL = 8 mg of iron in the storage pool). The 2nd storage pool of iron is in hemosiderin, which is relatively insoluble and is stored primarily in the liver (in Kupffer cells) and in bone marrow (in macrophages).

Because iron absorption is so limited, the body recycles and conserves iron. Transferrin grasps and recycles available iron from aging RBCs undergoing phagocytosis by mononuclear phagocytes. This mechanism provides about 97% of the daily iron needed (about 25 mg of iron). With aging, iron stores tend to increase because iron elimination is slow.

**Iron deficiency:** Deficiency develops in stages. In the first stage, iron requirement exceeds intake, causing progressive depletion of bone marrow iron stores. As stores decrease, absorption of dietary iron increases in compensation. During later stages, deficiency impairs RBC synthesis, ultimately causing anemia.

Severe and prolonged iron deficiency also may cause dysfunction of iron-containing cellular enzymes.

**Etiology**

Because iron is poorly absorbed, dietary iron barely meets the daily requirement for most people. Even so, people who eat a typical Western diet are unlikely to become iron deficient solely as a result of dietary deficiency. However, even modest losses, increased requirements, or decreased intake readily causes iron deficiency.

**Blood loss** is almost always the cause. In men, the most frequent cause is chronic occult bleeding, usually from the GI tract. In premenopausal women, cumulative menstrual blood loss (mean, 0.5 mg iron/day) is a common cause. Another possible cause of blood loss in men and women is chronic intravascular hemolysis (see p. 934) when the amount of iron released during hemolysis exceeds the haptoglobin-binding capacity. Vitamin C deficiency can contribute to iron deficiency anemia by causing capillary fragility, hemolysis, and bleeding.

**Increased iron requirement** may contribute to iron deficiency. From birth to age 2 and during adolescence, when rapid growth requires a large iron intake, dietary iron often is inadequate. During pregnancy, the fetal iron requirement increases the maternal iron requirement (mean, 0.5 to 0.8 mg/day —see Anemia in Pregnancy on p. 2634) despite the absence of menses. Lactation also increases the iron requirement (mean, 0.4 mg/day).

**Decreased iron absorption** can result from gastrectomy and upper small-bowel malabsorption syndromes. Rarely, absorption is decreased by dietary deprivation from undernutrition.
Symptoms and Signs

Most symptoms of iron deficiency are due to anemia. Such symptoms include fatigue, loss of stamina, shortness of breath, weakness, dizziness, and pallor. Fatigue also may result from dysfunction of iron-containing cellular enzymes.

In addition to the usual manifestations of anemia, some uncommon symptoms occur in severe iron deficiency. Patients may have pica, an abnormal craving to eat substances (eg, ice, dirt, paint). Other symptoms of severe deficiency include glossitis, cheilosis, concave nails (koilonychia), and, rarely, dysphagia caused by a postcricoid esophageal web (Plummer-Vinson syndrome).

Diagnosis

• CBC, serum iron, iron-binding capacity, and serum ferritin

• Rarely bone marrow examination

Iron deficiency anemia is suspected in patients with chronic blood loss or microcytic anemia, particularly if pica is present. In such patients, CBC, serum iron and iron-binding capacity, and serum ferritin are obtained.

Iron and iron-binding capacity (or transferrin) are usually both measured because their relationship is important. Various tests exist; the range of normal values relates to the test used. In general, normal serum iron is 75 to 150 μg/dL (13 to 27 μmol/L) for men and 60 to 140 μg/dL (11 to 25 μmol/L) for women; total iron-binding capacity is 250 to 450 μg/dL (45 to 81 μmol/L). Serum iron level is low in iron deficiency and in many chronic diseases and is elevated in hemolytic disorders and in iron-overload syndromes (see p. 1032). Patients taking oral iron may have normal serum iron despite a deficiency; in such circumstances, a valid test requires cessation of iron therapy for 24 to 48 h. The iron-binding capacity increases in iron deficiency. Serum transferrin receptor levels reflect the amount of RBC precursors available for active proliferation; levels are sensitive and specific. The range of normal is 3.0 to 8.5 μg/mL. Levels increase in early iron deficiency and with increased erythropoiesis.

Serum ferritin levels closely correlate with total body iron stores. The range of normal in most laboratories is 30 to 300 ng/mL, and the mean is 88 ng/mL in men and 49 ng/mL in women. Low levels (< 12 ng/mL) are specific for iron deficiency. However, ferritin is an acute-phase reactant, and levels increase in inflammatory and neoplastic disorders, so ferritin may also be elevated in cases of liver injury (eg, hepatitis) and in some tumors (especially acute leukemia, Hodgkin lymphoma, and GI tract tumors).

The most sensitive and specific criterion for iron-deficient erythropoiesis is absent bone marrow stores of iron, although a bone marrow examination is rarely needed.

Stages of iron deficiency: Laboratory test results help stage iron deficiency anemia.

Stage 1 is characterized by decreased bone marrow iron stores; Hb and serum iron remain normal, but serum ferritin level falls to < 20 ng/mL. The compensatory increase in iron absorption causes an increase in iron-binding capacity (transferrin level).

During stage 2, erythropoiesis is impaired. Although the transferrin level is increased, the serum iron level decreases; transferrin saturation decreases. Erythropoiesis is impaired when serum iron falls to < 50 μg/dL (< 9 μmol/L) and transferrin saturation to < 16%. The serum ferritin receptor level rises (> 8.5 mg/L).

During stage 3, anemia with normal-appearing RBCs and indices develops.

During stage 4, microcytosis and then hypochromia develop.

During stage 5, iron deficiency affects tissues, resulting in symptoms and signs.
Diagnosis of iron deficiency anemia prompts consideration of its cause, usually bleeding. Patients with obvious blood loss (eg, women with menorrhagia) may require no further testing. Men and postmenopausal women without obvious blood loss should undergo evaluation of the GI tract, because anemia may be the only indication of an occult GI cancer. Rarely, chronic epistaxis or GU bleeding is underestimated by the patient and requires evaluation in patients with normal GI study results.

**Other microcytic anemias:** Iron deficiency anemia must be differentiated from other microcytic anemias (see Table 105-1). If tests exclude iron deficiency in patients with microcytic anemia, then anemia of chronic disease, structural Hb abnormalities (eg, hemoglobinopathies), and congenital RBC membrane abnormalities are considered. Clinical features, Hb studies (eg, Hb electrophoresis and Hb A2), and genetic testing (eg, for α-thalassemia) may help distinguish these entities.

**[Table 105-1. Differential Diagnosis of Microcytic Anemia Due to Decreased RBC Production]**

**Treatment**

- Oral supplemental iron
- Rarely parenteral iron

Iron therapy without pursuit of the cause is poor practice; the bleeding site should be sought even in cases of mild anemia.

Iron can be provided by various iron salts (eg, ferrous sulfate, gluconate, fumarate) or saccharated iron po 30 min before meals (food or antacids may reduce absorption). A typical initial dose is 60 mg of elemental iron (eg, as 325 mg of ferrous sulfate) given once/day or bid. Larger doses are largely unabsorbed but increase adverse effects especially. Ascorbic acid either as a pill (500 mg) or as orange juice when taken with iron enhances iron absorption without increasing gastric distress. Parenteral iron causes the same therapeutic response as oral iron but can cause adverse effects, such as anaphylactoid reactions, serum sickness, thrombophlebitis, and pain. It is reserved for patients who do not tolerate or who will not take oral iron or for patients who steadily lose large amounts of blood because of capillary or vascular disorders (eg, hereditary hemorrhagic telangiectasia). The dose of parenteral iron is determined by a hematologist. Oral or parenteral iron therapy should continue for ≥ 6 mo after correction of Hb levels to replenish tissue stores.

The response to treatment is assessed by serial Hb measurements until normal RBC values are achieved. Hb rises little for 2 wk but then rises 0.7 to 1 g/wk until near normal, at which time rate of increase tapers. Anemia should be corrected within 2 mo. A subnormal response suggests continued hemorrhage, underlying infection or cancer, insufficient iron intake, or, very rarely, malabsorption of oral iron.

**Sideroblastic Anemias**

Sideroblastic anemias are iron-utilization anemias that are usually part of a myelodysplastic syndrome, causing a normocytic-normochromic anemia with high RBC distribution width or a microcytic-hypochromic anemia, particularly with increased serum iron and ferritin and transferrin saturation.

Sideroblastic anemias are among the anemias characterized by inadequate marrow utilization of iron for Hb synthesis despite the presence of adequate or increased amounts of iron (iron-utilization anemias). Other iron-utilization anemias include some hemoglobinopathies, primarily thalassemias (see p. 946). Sideroblastic anemias are characterized by the presence of polychromatophilic, stippled, targeted RBCs (siderocytes). Sideroblastic anemias are generally part of a myelodysplastic syndrome but may be hereditary or may occur secondary to drugs (eg, chloramphenicol, cycloserine, isoniazid, pyrazinamide) or toxins (including ethanol and lead). Pyridoxine deficiency can lead to sideroblastic anemia. Deficient reticulocyte production, intramedullary death of RBCs, and bone marrow erythroid hyperplasia (and dysplasia) occur. Although hypochromic RBCs are produced, other RBCs may be large, producing
normochromic indices; if so, variation in RBC size (dimorphism) usually produces a high RBC distribution width (RDW).

Sideroblastic anemia is suspected in patients with microcytic anemia or a high RDW anemia, particularly with increased serum iron, serum ferritin, and transferrin saturation (see Iron Deficiency Anemia on p. 924). The peripheral smear shows RBC dimorphism. RBCs may appear stippled. Bone marrow examination is necessary and reveals erythroid hyperplasia. Iron staining reveals the pathognomonic iron-engorged paranuclear mitochondria in developing RBCs (ringed sideroblasts). Other features of myelodysplasia, such as chromosomal abnormalities, are frequently evident. Serum lead is measured if sideroblastic anemia has an unknown cause.

Elimination of a toxin or drug (especially alcohol) can lead to recovery. Rarely, congenital cases respond to pyridoxine 50 mg po tid, but incompletely. Pyridoxine deficiency is corrected by vitamin B6 supplementation.

Anemia of Chronic Disease

(Iron-Reutilization Anemia)

Anemia of chronic disease is a multifactorial anemia often coexistent with iron deficiency. Diagnosis generally requires the presence of chronic infection, inflammation, or cancer; microcytic or marginal normocytic anemia; and values for serum transferrin receptor and serum ferritin that are between those typical for iron deficiency and sideroblastic anemia. Treatment is to reverse the underlying disorder or, if the disorder is irreversible, to give erythropoietin.

Worldwide, anemia of chronic disease is the 2nd most common anemia. Early on, the RBCs are normocytic; with time they become microcytic. The major issue is that the marrow erythroid mass fails to expand appropriately in response to anemia.

Etiology

This type of anemia was thought to occur as part of a chronic disorder, most often infection, inflammatory disease (especially RA), or cancer; however, the same process appears to begin acutely during virtually any infection or inflammation. Three pathophysiologic mechanisms have been identified:

• Slightly shortened RBC survival occurs via unknown mechanisms in patients with cancer or chronic granulomatous infections.

• Erythropoiesis is impaired because of decreases in both erythropoietin (EPO) production and marrow responsiveness to EPO.

• Intracellular iron metabolism is impaired.

Reticuloendothelial cells retain iron from senescent RBCs, making iron unavailable for Hb synthesis. There is thus a failure to compensate for the anemia with increased RBC production. Macrophage-derived cytokines (eg, IL-1β, tumor necrosis factor-α, interferon-β) in patients with infections, inflammatory states, and cancer cause or contribute to the decrease in EPO production and the impaired iron metabolism.

Diagnosis

• Symptoms and signs of underlying disorder

• CBC and serum iron, ferritin, transferrin, and transferrin receptor

Clinical findings are usually those of the underlying disorder (infection, inflammation, or cancer). Anemia of chronic disease is suspected in patients with microcytic or marginal normocytic anemia with chronic infection, inflammation, or cancer. If anemia of chronic disease is suspected, serum iron, transferrin,
transferrin receptor, and serum ferritin are measured. Hb usually is > 8 g/dL unless an additional mechanism contributes to anemia (see also Table 105-1). If iron deficiency is present in addition to anemia of chronic disease, serum ferritin generally remains < 100 ng/mL, and, if there is infection, inflammation, or cancer, a ferritin level of slightly < 100 ng/mL suggests that iron deficiency is superimposed on anemia of chronic disease. However, because serum ferritin may be falsely elevated as an acute-phase reactant, the serum transferrin receptor measurement may better differentiate iron deficiency from anemia of chronic disease when serum ferritin is > 100 ng/mL.

**Treatment**

- Treatment of underlying disorder
- Recombinant EPO and iron supplements

Treating the underlying disorder is most important. Because the anemia is generally mild, transfusions usually are not required, and recombinant EPO may be offered. Because both reduced production of and marrow resistance to EPO occur, the EPO dose may need to be 150 to 300 units/kg sc 3 times/wk. A good response is likely if after 2 wk of therapy Hb has increased > 0.5 g/dL and serum ferritin is < 400 ng/mL. Iron supplements (see p. 927) are required to ensure an adequate response to EPO. However, careful monitoring of Hb response is needed because adverse effects (eg, venous thromboembolism, MI, death) may occur when Hb rises to > 12 g/dL.

**Hypoproliferative Anemias**

Hypoproliferative anemias result from deficient erythropoietin (EPO) or a diminished response to it; they tend to be normocytic and normochromic. Renal, metabolic, and endocrine disorders are common causes. Treatment includes measures to correct the underlying disorder and sometimes EPO.

Hypoproliferation is a common mechanism in anemias of renal disease, hypometabolic or endocrine deficiency states (eg, hypothyroidism, hypopituitarism), and protein deprivation. The mechanism appears to be a relative or absolute decreased production of EPO. In hypometabolic states, the bone marrow may also fail to respond to EPO.

**Anemia of renal disease:** The deficiency in renal production of EPO and the severity of anemia correlate with the extent of renal dysfunction; anemia occurs when creatinine clearance is < 45 mL/min. Renal glomerular lesions (eg, from amyloidosis, diabetic nephropathy) generally result in the most severe anemia for their degree of excretory failure.

The term anemia of renal disease refers only to that caused by decreased EPO, but other mechanisms may increase its severity. In uremia, mild hemolysis is common; its basis is uncertain. Less common is RBC fragmentation (traumatic hemolytic anemia), which occurs when the renovascular endothelium is injured (eg, in malignant hypertension, membranoproliferative glomerulonephritis, polyarteritis nodosa, or acute cortical necrosis). Traumatic hemolysis in children can be an acute, sometimes fatal illness called hemolytic-uremic syndrome (see p. 961).

Diagnosis is based on demonstration of renal insufficiency and normocytic anemia, peripheral reticulocytopenia, and a paucity of erythroid hyperplasia for the degree of anemia. RBC fragmentation on the peripheral smear, particularly if there is thrombocytopenia, suggests simultaneous traumatic hemolysis.

Therapy is directed at improving renal function and increasing RBC production. If renal function returns to normal, anemia is slowly corrected. In patients receiving long-term dialysis, EPO, beginning with 50 to 100 units/kg IV or sc 3 times/wk with iron supplements, is the treatment of choice. In almost all cases, maximum increases in RBCs are reached by 8 to 12 wk. Reduced doses of EPO (about one half the induction dose) can then be given 1 to 3 times/wk. Transfusions are rarely necessary. Careful monitoring of the response is needed to avoid adverse effects when Hb increases to > 12 g/dL.
Other hypoproliferative anemias: Clinical and laboratory findings of other hypoproliferative normochromic-normocytic anemias are milder but otherwise mimic those of the anemia of renal disease. The mechanism of the anemia of protein depletion may be general hypometabolism. Hypometabolism may diminish the marrow response to EPO. Protein's role in hematopoiesis is unclear.

Aplastic Anemia

(Hypoplastic Anemia)

Aplastic anemia is a normocytic-normochromic anemia that results from a loss of blood cell precursors, causing hypoplasia of bone marrow, RBCs, WBCs, and platelets. Symptoms result from severe anemia, thrombocytopenia (petechiae, bleeding), or leukopenia (infections). Diagnosis requires demonstration of peripheral pancytopenia and the absence of cell precursors in bone marrow. Treatment is equine antithymocyte globulin and cyclosporine. Erythropoietin, granulocyte-macrophage colony-stimulating factor, and bone marrow transplantation may also be useful.

The term aplastic anemia commonly implies a panhypoplasia of the marrow with associated leukopenia and thrombocytopenia. In contrast, pure RBC aplasia is restricted to the erythroid cell line. Although both disorders are uncommon, aplastic anemia is more common.

Etiology

True aplastic anemia (most common in adolescents and young adults) is idiopathic in about one half of cases. Recognized causes are chemicals (eg, benzene, inorganic arsenic), radiation, and drugs (eg, antineoplastic drugs, antibiotics, NSAIDs, anticonvulsants, acetazolamide, gold salts, penicillamine, quinacrine). The mechanism is unknown, but selective (perhaps genetic) hypersensitivity appears to be the basis.

Fanconi's anemia is a very rare, familial form of aplastic anemia with bone abnormalities, microcephaly, hypogonadism, and brown pigmentation of skin. It occurs in children with abnormal chromosomes. Fanconi's anemia is often inapparent until some illness (especially an acute infection or inflammatory disorder) supervenes, causing peripheral cytopenias. With clearing of the supervening illness, peripheral values return to normal despite reduced marrow mass.

Pure RBC aplasia may be acute and reversible. Acute erythroblastopenia is a brief disappearance of RBC precursors from the bone marrow during various acute viral illnesses (particularly human parvovirus infection), especially in children. The anemia lasts longer than the acute infection. Chronic pure RBC aplasia has been associated with hemolytic disorders, thymomas, and autoimmune mechanisms and, less often, with drugs (eg, tranquilizers, anticonvulsants), toxins (organic phosphates), riboflavin deficiency, and chronic lymphocytic leukemia. A rare congenital form, Diamond-Blackfan anemia, usually occurs during infancy but has also been reported in adulthood. Diamond-Blackfan anemia is associated with bony abnormalities of the thumbs or digits and short stature.

Symptoms and Signs

Although onset of aplastic anemia usually is insidious, often occurring over weeks or months after exposure to a toxin, occasionally it is acute. Signs vary with the severity of the pancytopenia. Symptoms and signs of anemia (eg, pallor) usually are severe.

Severe thrombocytopenia may cause petechiae, ecchymosis, and bleeding from the gums, into the conjunctivae, or other tissues. Agranulocytosis commonly causes life-threatening infections. Splenomegaly is absent unless induced by transfusion hemosiderosis. Symptoms of pure RBC aplasia are generally milder and relate to the degree of the anemia or to the underlying disorder.

Diagnosis

• CBC
Bone marrow examination

Aplastic anemia is suspected in patients, particularly young patients, with pancytopenia (e.g., WBC < 1500/μL, platelets < 50,000/μL). Pure RBC aplasia (including Diamond-Blackfan anemia) is suspected in patients with bony abnormalities and normocytic anemia but normal WBC and platelet counts. If either diagnosis is suspected, bone marrow examination is done.

In aplastic anemia, RBCs are normochromic-normocytic (sometimes marginally macrocytic). The WBC count reduction occurs chiefly in the granulocytes. Platelets are often far below 50,000/μL. Reticulocytes are decreased or absent. Serum iron is elevated. The bone marrow is acellular. In pure RBC aplasia, normocytic anemia, reticulocytopenia, and elevated serum iron are present, but WBC and platelet counts are normal. Bone marrow cellularity and maturation may be normal except for absence of erythroid precursors.

Treatment

- Equine antithymocyte globulin, corticosteroids, and cyclosporine
- Sometimes hematopoietic cell transplantation
- Sometimes cytokines
- Sometimes surgery in thymoma-associated RBC aplasia

In aplastic anemia, treatment of choice is equine antithymocyte globulin (ATG) 10 to 20 mg/kg diluted in 500 mL saline and infused IV over 4 to 6 h once/day for 10 consecutive days. Shorter regimens are also used. About 60% of patients respond to ATG. Allergic reactions and serum sickness may occur; some experts advocate skin testing (to identify allergy to horse serum) and concomitant corticosteroids (prednisone 40 mg/m² po once/day beginning on day 7 for 10 days or until symptoms subside). Cyclosporine (5 to 10 mg/kg po once/day) is as effective as ATG and produces responses in about 50% of patients who do not respond to ATG, suggesting that its mechanism of action is different. Combined ATG and cyclosporine is also effective. If aplastic anemia is very severe or fails to respond to ATG and cyclosporine, bone marrow transplantation or treatment with cytokines (erythropoietin, granulocyte colony-stimulating factor, or granulocyte-macrophage colony-stimulating factor) may be effective.

Hematopoietic stem cell transplantation may help younger patients (particularly patients < 30) but requires an identical twin or an HLA-compatible sibling. At diagnosis, siblings are evaluated for HLA compatibility. Because transfusions pose a risk to subsequent transplantation, blood products are used only when essential.

Pure RBC aplasia has been successfully managed with immunosuppressants (prednisone, cyclosporine, or cyclophosphamide), especially when an autoimmune mechanism is suspected. Because patients with thymoma-associated pure RBC aplasia improve after thymectomy, CT is used to seek the presence of such a lesion, and surgery is considered.

Myelophthisic Anemia

Myelophthisic anemia is a normocytic-normochromic anemia that occurs when normal marrow space is infiltrated and replaced by nonhematopoietic or abnormal cells. Causes include tumors, granulomatous disorders, and lipid storage diseases. Marrow fibrosis often occurs. Splenomegaly may develop. Characteristic changes in peripheral blood include anisocytosis, poikilocytosis, and excessive numbers of RBC and WBC precursors. Diagnosis usually requires bone marrow biopsy. Treatment is supportive and includes measures directed at the underlying disorder.

Descriptive terms used in this anemia can be confusing. Myelofibrosis, which is replacement of marrow by fibrous tissue bands, may be idiopathic (primary) or secondary. True myelofibrosis is a stem cell defect.
in which the fibrosis is secondary to other hematopoietic intramedullary events. Myelosclerosis is new bone formation that sometimes accompanies myelofibrosis. Myeloid metaplasia refers to extramedullary hematopoiesis in the liver, spleen, or lymph nodes that may accompany myelophthisis due to any cause. An old term, agnogenic myeloid metaplasia, indicates primary myelofibrosis with or without myeloid metaplasia.

**Etiology**

The most common cause is replacement of bone marrow by metastatic cancer (most often, breast or prostate; less often, kidney, lung, adrenal, or thyroid); extramedullary hematopoiesis tends to be modest. Other causes include myeloproliferative disorders (especially late-stage or spent polycythemia vera), granulomatous diseases, and (lipid) storage diseases. Myelofibrosis can occur in all of these.

Factors that may contribute to decreased RBC production include a decreased amount of functioning hematopoietic tissue, disordered metabolism related to the underlying disorder, and, in some cases, erythrophagocytosis. Extramedullary hematopoiesis or disruption of the marrow sinusoids causes release of immature cells. Abnormally shaped RBCs often result in increased RBC destruction.

**Symptoms and Signs**

Myeloid metaplasia may result in splenomegaly, particularly in patients with storage diseases. In severe cases, symptoms of anemia and of the underlying disorder may be present. Massive splenomegaly can cause abdominal pressure, early satiety, and left upper quadrant abdominal pain; hepatomegaly may be present. Hepatosplenomegaly is rare with myelofibrosis from malignant tumors.

**Diagnosis**

- CBC, RBC indices, reticulocyte count, and peripheral smear
- Bone marrow examination

Myelophthisic anemia is suspected in patients with normocytic anemia, particularly when splenomegaly or a potential underlying disorder is present. If it is suspected, a peripheral smear should be obtained, because a leukoerythroblastic pattern (immature myeloid cells and nucleated RBCs, such as normoblasts in the smear) suggests myelophthisic anemia. Anemia, usually moderately severe, is characteristically normocytic but may be slightly macrocytic. RBC morphology may show extreme variation (anisocytosis and poikilocytosis) in size and shape. The WBC count may vary. The platelet count is often low, and platelets are often large and bizarre in shape. Reticulocytosis often occurs; it may be caused by premature release of reticulocytes from the marrow or extramedullary sites and thus does not always indicate increased blood regeneration.

Although examination of peripheral blood can be suggestive, diagnosis usually requires bone marrow examination. Indications include a leukoerythroblastic pattern and unexplained splenomegaly. The marrow may be difficult to aspirate; marrow trephine biopsy is usually required. Findings vary according to the underlying disorder. Erythropoiesis is normal or increased in some cases. However, the life span of RBCs is often reduced. Hematopoiesis may be present in the spleen and liver.

X-rays, if obtained incidentally, may disclose bony lesions (myelosclerosis) characteristic of long-standing myelofibrosis or other osseous changes (ie, osteoblastic or lytic lesions of a tumor), suggesting the cause of anemia.

**Treatment**

- Treatment of underlying disorder
- Transfusions and corticosteroids
- Hydroxyurea
Possibly thalidomide

The underlying disorder is treated. In idiopathic cases, management is supportive. Erythropoietin (20,000 to 40,000 units sc once/wk or twice/wk) and corticosteroids (eg, prednisone 10 to 30 mg po once/day) have been used, but only modest responses have been observed. Hydroxyurea (500 mg po once/day or once every other day) decreases spleen size and normalizes RBC values in many patients, but the response requires 6 to 12 mo of treatment. Thalidomide (50 to 100 mg po once/day in the evening) may provide modest responses, but it increases the risk of thrombosis and causes fatigue, which can be severe.

Megaloblastic Macrocytic Anemias

Megaloblastic anemias result most often from deficiencies of vitamin B₁₂ and folate. Ineffective hematopoiesis affects all cell lines but particularly RBCs. Diagnosis is usually based on a CBC and peripheral smear, which may show a macrocytic anemia with anisocytosis and poikilocytosis, large oval RBCs (macro-ovalocytes), hypersegmented neutrophils, and reticulocytopenia. Treatment is directed at the underlying disorder.

Macrocyes are enlarged RBCs (ie, MCV > 100 fL/cell). Macrocytic RBCs occur in a variety of clinical circumstances, many unrelated to the megaloblastosis and the resultant anemia. Macrocytosis may be due to megaloblasts or other enlarged RBCs (see Sidebar 105-1). Megaloblasts are large nucleated RBC precursors with noncondensed chromatin. Megaloblastosis precedes macrocytic anemia.

Etiology

The most common cause of megaloblastic states is deficiency or defective utilization of vitamin B₁₂ (see p. 37) or folate (see p. 29). Other causes include drugs (generally antineoplastics or immunosuppressants) that interfere with DNA synthesis and rare metabolic disorders (eg, hereditary orotic aciduria); some cases are of unknown etiology.

Pathophysiology

Megaloblastic states result from defective DNA synthesis. RNA synthesis continues, resulting in a large cell with a large nucleus. All cell lines have dyspoiesis, in which cytoplasmic maturity is greater than nuclear maturity; this dyspoiesis produces megaloblasts in the marrow before they appear in the peripheral blood. Dyspoiesis results in intramedullary cell death, making erythropoiesis ineffective and causing indirect hyperbilirubinemia and hyperuricemia. Because dyspoiesis affects all cell lines, reticulocytopenia and, during later stages, leukopenia and thrombocytopenia develop. Large, oval RBCs (macro-ovalocytes) enter the circulation. Hypersegmentation of polymorphonuclear neutrophils is common; the mechanism of their production is unknown.

Symptoms and Signs

Anemia develops insidiously and may not cause symptoms until it is severe. Deficiencies of vitamin B₁₂ may cause neurologic manifestations, including peripheral neuropathy, dementia, and subacute combined degeneration. Folate deficiency may also cause diarrhea and glossitis. Many patients with folate deficiency appear wasted, particularly with temporal wasting.

Diagnosis

• CBC, RBC indices, reticulocyte count, and peripheral smear

• Sometimes bone marrow examination

Megaloblastic anemia is suspected in anemic patients with macrocytic indices. Diagnosis is usually based on peripheral smear. When fully developed, the anemia is macrocytic, with MCV > 100 fL/cell. The smear

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shows macro-ovalocytosis, anisocytosis, and poikilocytosis. The RBC distribution width (RDW) is high. Howell-Jolly bodies (residual fragments of the nucleus) are common. Reticulocytopenia is present. Hypersegmentation of the granulocytes develops early; neutropenia develops later. Thrombocytopenia is often present in severe cases, and platelets may be bizarre in size and shape. If the diagnosis is questionable, a bone marrow examination may be needed.

**Treatment**

Before treatment, the cause must be identified. Deficiency of vitamin B$_{12}$ or folate is suspected if megaloblastic anemia is recognized; these disorders are indistinguishable on the basis of peripheral blood and bone marrow findings, so vitamin B$_{12}$ and folate levels are required (see pp. 30 and 39).

**Sidebar 105-1 Nonmegaloblastic Macrocytosis**

Most macrocytic (ie, MCV > 100 fl/cell) anemias are megaloblastic. Nonmegaloblastic macrocytosis occurs in various clinical states, not all of which are understood. Anemia commonly occurs in patients with macrocytosis but usually results from mechanisms independent of macrocytosis.

Macrocytosis due to excess RBC membrane occurs in patients with chronic liver disease when cholesterol esterification is defective. Macrocytosis with an MCV of about 100 to 105 fl/cell can occur with chronic alcohol use in the absence of folate deficiency. Mild macrocytosis can occur in aplastic anemia, especially as recovery occurs. Macrocytosis is also common in myelodysplasia. Because RBC membrane molding occurs in the spleen after cell release from the marrow, RBCs may be slightly macrocytic after splenectomy, although these changes are not associated with anemia.

Nonmegaloblastic macrocytosis is suspected in patients with macrocytic anemias when testing excludes vitamin B$_{12}$ and folate deficiencies. The macro-ovalocytes on peripheral smear and the increased RBC distribution width that are typical of classic megaloblastic anemia may be absent. If nonmegaloblastic macrocytosis is unexplained clinically (eg, by the presence of aplastic anemia, chronic liver disease, or alcohol use) or if myelodysplasia is suspected, bone marrow examination and cytogenetic analysis are done to exclude myelodysplasia. In nonmegaloblastic macrocytosis, the marrow is not megaloblastic, but in myelodysplasia and advanced liver disease there are megaloblastoid RBC precursors with dense nuclear chromatin that differ from the usual fine fibrillar pattern in megaloblastic anemias.

Treatment depends on the cause. For treatment of folate and vitamin B$_{12}$ deficiencies, see pp. 30 and 39. Drugs causing megaloblastic states may need to be eliminated or given in reduced doses.

**Myelodysplasia and Iron-Transport Deficiency Anemia**

In myelodysplastic syndrome (see p. 1014), anemia is commonly prominent. The anemia can be microcytic or normochromic-normocytic, usually with a dimorphic (large and small) population of circulating cells. Bone marrow examination shows decreased erythroid activity, megaloblastoid and dysplastic changes, and, sometimes, increased numbers of ringed sideroblasts. Treatment is the same as for sideroblastic anemias (see p. 928).

Iron-transport deficiency anemia (atransferrinemia) is exceedingly rare. It occurs when iron cannot move from storage sites (eg, mucosal cells, liver) to the erythopoietic precursors. The presumed mechanism is absence of transferrin or presence of a defective transferrin molecule. In addition to anemia, hemosiderosis of lymphoid tissue, especially along the GI tract, is prominent.
Chapter 106. Anemias Caused by Hemolysis

Introduction

At the end of their normal life span (about 120 days), RBCs are removed from the circulation. Hemolysis involves premature destruction and hence a shortened RBC life span (< 120 days). Anemia results when bone marrow production can no longer compensate for the shortened RBC survival; this condition is termed hemolytic anemia. If the marrow can compensate, the condition is termed compensated hemolytic anemia.

Etiology

Hemolysis can result from disorders extrinsic to the RBC or from intrinsic RBC abnormalities (see Table 106-1).

Disorders extrinsic to the RBC: Most extrinsic disorders are acquired; the RBCs are normal and transfused cells as well as autologous cells are destroyed. Disorders extrinsic to the RBC include reticuloendothelial hyperactivity (hypersplenism—see p. 985), immunologic abnormalities (eg, autoimmune hemolytic anemia, isoimmune hemolytic anemia), mechanical injury (traumatic hemolytic anemia), and certain infections. Infectious organisms may cause hemolytic anemia through the direct action of toxins (eg, from Clostridium perfringens, α- or β-hemolytic streptococci, meningococci) or by invasion and destruction of RBC by the organism (eg, Plasmodium sp, Bartonella sp).

Intrinsic RBC abnormalities: Defects intrinsic to the RBC that can cause hemolysis involve one or more components or functions of the RBC: the membrane, cell metabolism, and the Hb. Abnormalities include hereditary and acquired cell membrane disorders (eg, spherocytosis), disorders of RBC metabolism (eg, G6PD deficiency), and hemoglobinopathies (eg, sickle cell diseases, thalassemias). Quantitative and functional abnormalities of certain RBC membrane proteins (α- and β-spectrin, protein 4.1, F-actin, ankyrin) cause hemolytic anemias.

Pathophysiology

Hemolysis may be acute, chronic, or episodic. Chronic hemolysis may be complicated by aplastic crisis (temporary failure of erythropoiesis), usually caused by an infection, often parvovirus. Hemolysis can be extravascular, intravascular, or both.

[Table 106-1. Hemolytic Anemias]

Normal RBC processing: Senescent RBCs lose membrane and are cleared from the circulation largely by the phagocytic cells of the spleen, liver, bone marrow, and reticuloendothelial system. Hb is broken down in these cells primarily by the heme oxygenase system. The iron is conserved and reutilized, and heme is degraded to bilirubin, which is conjugated in the liver to bilirubin glucuronide and excreted in the bile.

Extravascular hemolysis: Most pathologic hemolysis is extravascular and occurs when damaged or abnormal RBCs are cleared from the circulation by cells of the spleen, liver, and bone marrow similar to the process by which senescent RBCs are removed. The spleen usually contributes to hemolysis by destroying mildly abnormal RBCs or cells coated with warm antibodies. An enlarged spleen may sequester even normal RBCs. Severely abnormal RBCs or RBCs coated with cold antibodies or complement (C3) are destroyed within the circulation and in the liver, which (because of its large blood flow) can remove damaged cells efficiently.

Intravascular hemolysis: Intravascular hemolysis is an important reason for premature RBC destruction and usually occurs when the cell membrane has been severely damaged by any of a number of different mechanisms, including autoimmune phenomena, direct trauma (eg, march hemoglobinuria), shear stress (eg, defective mechanical heart valves), and toxins (eg, clostridial toxins, venomous snake bite).
Intravascular hemolysis results in hemoglobinemia when the amount of Hb released into plasma exceeds the Hb-binding capacity of the plasma-binding protein haptoglobin, a globulin normally present in concentrations of about 1.0 g/L in plasma. With hemoglobinemia, unbound Hb dimers are filtered into the urine and reabsorbed by renal tubular cells; hemoglobinuria results when reabsorptive capacity is exceeded. Iron is embedded in hemosiderin within the tubular cells; some of the iron is assimilated for reutilization and some reaches the urine when the tubular cells slough.

**Consequences of hemolysis:** Unconjugated (indirect) hyperbilirubinemia and jaundice occur when the conversion of Hb to bilirubin exceeds the liver's capacity to conjugate and excrete bilirubin (see p. 270). Bilirubin catabolism causes increased stercobilin in the stool and urobilinogen in the urine and sometimes cholelithiasis.

The bone marrow responds to the excess loss of RBCs by accelerating production and release of RBCs, resulting in a reticulocytosis.

**Symptoms and Signs**

Systemic manifestations resemble those of other anemias and include pallor, fatigue, dizziness, and possible hypotension. Hemolytic crisis (acute, severe hemolysis) is uncommon; it may be accompanied by chills, fever, pain in the back and abdomen, prostration, and shock. Severe hemolysis can cause jaundice and splenomegaly. Hemoglobinuria causes red or reddish-brown urine.

**Diagnosis**

- Peripheral smear, reticulocyte count, serum bilirubin, LDH, and ALT
- Sometimes, measurement of urinary hemosiderin and serum haptoglobin
- Rarely, measurement of RBC survival using a radioactive label

Hemolysis is suspected in patients with anemia and reticulocytosis, particularly if splenomegaly or another possible cause is recognized. If hemolysis is suspected, peripheral smear is examined and serum bilirubin, LDH, and ALT are measured. If results of these tests are inconclusive, urinary hemosiderin and serum haptoglobin are measured.

Abnormalities of RBC morphology are seldom diagnostic but often suggest the presence and cause of hemolysis (see Table 106-2).

[Table 106-2, RBC Morphologic Changes in Hemolytic Anemias]

Other suggestive findings include increased levels of serum LDH and indirect bilirubin with a normal ALT, and the presence of urinary urobilinogen. Intravascular hemolysis is suggested by RBC fragments (schistocytes) on the peripheral smear and by decreased serum haptoglobin levels; however, haptoglobin levels can decrease because of hepatocellular dysfunction and can increase because of systemic inflammation. Intravascular hemolysis is also suggested by urinary hemosiderin. Urinary Hb, like hematuria and myoglobinuria, produces a positive benzidine reaction on dipstick testing; it can be differentiated from hematuria by the absence of RBCs on microscopic urine examination. Free Hb may make plasma reddish brown, noticeable often in centrifuged blood; myoglobin does not.

Although hemolysis can usually be identified by these simple criteria, the definitive diagnosis is demonstration of decreased RBC survival, preferably with a radioactive label, such as radiochromium ($^{51}$Cr). The measured survival of radiolabeled RBCs can establish hemolysis and also identify the sites of sequestration by using body surface counting. This procedure is rarely required, however.

Once hemolysis has been identified, the specific disorder is sought. One approach to narrowing the differential diagnosis in hemolytic anemias is to consider risk factors (eg, geographic location, genetics, underlying disorder), examine the patient for splenomegaly, and do a direct antiglobulin (Coombs') test.
and peripheral smear; most hemolytic anemias produce abnormalities in one of these variables that can
direct further testing. Other laboratory tests that can help discern the causes of hemolysis include the
following:

• Quantitative Hb electrophoresis
• RBC enzyme assays
• Flow cytometry
• Cold agglutinins
• Osmotic fragility

Although some tests can help differentiate intravascular from extravascular hemolysis, making the
distinction is sometimes difficult. During increased RBC destruction, both types are commonly involved,
although to differing degrees.

Treatment

Treatment depends on the specific mechanism of hemolysis.

Hemoglobinuria and hemosiderinuria may necessitate iron-replacement therapy. Corticosteroids are
helpful in the initial treatment of warm antibody autoimmune hemolysis. Long-term transfusion therapy
may cause excessive iron accumulation, necessitating chelation therapy. Splenectomy is beneficial in
some situations, particularly when splenic sequestration is the major cause of RBC destruction. If
possible, splenectomy is delayed until 2 wk after vaccination with pneumococcal, Haemophilus
influenzae, and meningococcal vaccines. In cold agglutinin disease, the patient is kept warm. Folate
replacement is needed for patients with ongoing long-term hemolysis.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia is caused by autoantibodies that react with RBCs at
temperatures ≥ 37° C (warm antibody hemolytic anemia) or < 37° C (cold agglutinin disease). Hemolysis is usually extravascular. The direct antiglobulin (Coombs') test establishes the
diagnosis and may suggest the cause. Treatment depends on the cause and may include
corticosteroids, splenectomy, IV immune globulin, immunosuppressants, avoidance of blood
transfusions, and withdrawal of drugs.

Etiology

Warm antibody hemolytic anemia: Warm antibody hemolytic anemia is the most common form of
autoimmune hemolytic anemia (AIHA); it is more common among women. Autoantibodies in warm antibody
hemolytic anemia generally react at temperatures ≥ 37° C. They may occur spontaneously or in
association with certain disorders (SLE, lymphoma, chronic lymphocytic leukemia). Some drugs (eg, α-
methylldopa, levodopa—see Table 106-3) stimulate production of autoantibodies against Rh antigens (α-methylldopa-type of AIHA).
Other drugs stimulate production of autoantibodies against the antibiotic-RBC-membrane complex as part of
a transient hapten mechanism; the hapten may be stable (eg, high-dose penicillin, cephalosporins) or
unstable (eg, quinidine, sulfonamides).

In warm antibody hemolytic anemia, hemolysis occurs primarily in the spleen. It is often severe and can be
fatal. Most of the autoantibodies in warm antibody hemolytic anemia are IgG. Most are panagglutinins and
have limited specificity.

Cold agglutinin disease: Cold agglutinin disease (cold antibody disease) is caused by autoantibodies
that react at temperatures < 37° C. It sometimes occurs with infections
(especially mycoplasmal pneumonias or infectious mononucleosis) and lymphoproliferative states; about one half of cases are idiopathic, which is the common form in older adults. Infections tend to cause acute disease, whereas idiopathic disease tends to be chronic. The hemolysis occurs largely in the extravascular mononuclear phagocyte system of the liver. The anemia is usually mild (Hb > 7.5 g/dL). Autoantibodies in cold agglutinin disease are usually IgM. The higher the temperature (ie, the closer to normal body temperature) at which these antibodies react with the RBC, the greater the hemolysis.

**Paroxysmal cold hemoglobinuria:** Paroxysmal cold hemoglobinuria (PCH; Donath-Landsteiner syndrome) is a rare type of cold agglutinin disease. Hemolysis results from exposure to cold, which may even be localized (eg, from drinking cold water, from washing hands in cold water). An IgG autohemolysin binds to RBCs at low temperatures and causes intravascular hemolysis after warming. It occurs most often after a nonspecific viral illness or in otherwise healthy patients, although it occurs in some patients with congenital or acquired syphilis. The severity and rapidity of development of the anemia varies and may be fulminant.

**Symptoms and Signs**

Symptoms of warm antibody hemolytic anemia tend to be due to the anemia. If the disorder is severe, fever, chest pain, syncope, or heart failure may occur. Mild splenomegaly is typical.

Cold agglutinin disease manifests as an acute or chronic hemolytic anemia. Other cryopathic symptoms or signs may be present (eg, acrocyanoses, Raynaud's syndrome, cold-associated occlusive changes). Symptoms of PCH may include severe pain in the back and legs, headache, vomiting, diarrhea, and passage of dark brown urine; hepatosplenomegaly may be present.

**Diagnosis**

- Assays for hemolytic anemia (eg, peripheral smear, reticulocyte count; sometimes urinary hemosiderin, serum haptoglobin)
- Direct antiglobulin test

AIHA is suspected in patients with hemolytic anemia, particularly if symptoms are severe or other suggestive symptoms are present. Routine laboratory tests generally suggest extravascular hemolysis (eg, hemosiderinuria is absent; haptoglobin levels are near normal) unless anemia is sudden and severe or PCH is the cause. Spherocytosis and a high MCHC are typical.

AIHA is diagnosed by detection of autoantibodies with the direct antiglobulin (direct Coombs’) test. Antiglobulin serum is added to washed RBCs from the patient; agglutination indicates the presence of immunoglobulin or complement (C) bound to the RBCs. Generally IgG is present in warm antibody hemolytic anemia, and C3 (C3b and C3d) in cold antibody disease. The test is ≤ 98% sensitive for AIHA; false-negative results can occur if antibody density is very low or if the autoantibodies are IgA or IgM. In general, the intensity of the direct antiglobulin test correlates with the number of molecules of IgG or C3 bound to the RBC and, roughly, with the rate of hemolysis. A complementary test consists of mixing the patient's plasma with normal RBCs to determine whether such antibodies are free in the plasma (the indirect antiglobulin [indirect Coombs'] test). A positive indirect antiglobulin test and a negative direct test generally indicate an alloantibody caused by pregnancy, prior transfusions, or lectin cross-reactivity rather than immune hemolysis. Even identification of a warm antibody does not define hemolysis, because 1/10,000 healthy blood donors has a positive test result.

Once AIHA has been identified by the Coombs’ test, testing should differentiate between warm antibody hemolytic anemia and cold agglutinin disease as well as the mechanism responsible for warm antibody hemolytic anemia. This determination can often be made by observing the pattern of the direct antiglobulin reaction. Three patterns are possible:

- The reaction is positive with anti-IgG and negative with anti-C3. This pattern is common in idiopathic...
AIHA and in the drug-associated or \( \alpha \)-methyldopa-type of AIHA, usually warm antibody hemolytic anemia.

• The reaction is positive with anti-IgG and anti-C3. This pattern is common in patients with SLE and idiopathic AIHA, usually warm antibody hemolytic anemia, and is rare in drug-associated cases.

• The reaction is positive with anti-C3 but negative with anti-IgG. This pattern occurs in cold agglutinin disease. It is uncommon in idiopathic AIHA, warm antibody hemolytic anemia, when the IgG antibody is of low affinity, in some drug-associated cases, and in PCH.

Other studies can suggest the cause of AIHA but are not definitive. In cold agglutinin disease, RBCs clump on the peripheral smear, and automated cell counts often reveal an increased MCV and spuriously low Hb due to such clumping; hand warming of the tube and recounting result in values significantly closer to normal. Warm antibody hemolytic anemia can often be differentiated from cold agglutinin disease by the temperature at which the direct antiglobulin test is positive; a test that is positive at temperatures \( \geq 37^\circ\text{C} \) indicates warm antibody hemolytic anemia, whereas a test that is positive at lower temperatures indicates cold agglutinin disease.

If PCH is suspected, the Donath-Landsteiner test, which is specific for PCH, should be done. Testing for syphilis is recommended.

Treatment

• For drug-induced warm antibody hemolytic anemia, drug withdrawal, sometimes IV immune globulin

• For idiopathic warm antibody hemolytic anemia, corticosteroids

• For cold agglutinin disease, avoidance of cold

Treatment depends on the specific mechanism of the hemolysis.

**Warm antibody hemolytic anemias:** In drug-induced warm antibody hemolytic anemias, drug withdrawal decreases the rate of hemolysis. With \( \alpha \)-methyldopa-type AIHA, hemolysis usually ceases within 3 wk; however, a positive Coombs’ test may persist for \( > 1 \text{ yr} \). With hapten-mediated AIHA, hemolysis ceases when the drug is cleared from the plasma. Corticosteroids have only little effect in drug-induced hemolysis; infusions of immune globulin may be more effective.

Corticosteroids (eg, prednisone 1 mg/kg po once/day or higher doses) are the treatment of choice in idiopathic warm antibody AIHA. In very severe hemolysis, an initial loading dose of 100 to 200 mg is recommended. Most patients have an excellent response, which in about one third is sustained after 12 to 20 wk of therapy. When stable RBC values are achieved, corticosteroids are tapered slowly. In patients who relapse after corticosteroid cessation or who are not helped by corticosteroids, splenectomy is done. About one third to one half of patients have a sustained response after splenectomy. In cases of fulminant hemolysis, plasma exchange has been used. For less severe but uncontrolled hemolysis, immune globulin infusions have provided temporary control. Long-term management with immunosuppressants (including cyclosporine) has been effective in patients in whom corticosteroids and splenectomy have been ineffective.

The presence of panagglutinating antibodies in warm antibody hemolytic anemia makes cross-matching of donor blood difficult. In addition, transfusions often superimpose an alloantibody on the autoantibody, accelerating hemolysis. Thus, transfusions should be avoided whenever possible. When necessary, they should be given only in small aliquots (100 to 200 mL over 1 to 2 h, with monitoring for hemolysis).

**Cold agglutinin disease:** Treatment is largely supportive in acute cases, because the anemia may be self-limited. In chronic cases, treatment of the underlying disorder often controls the anemia. However, in idiopathic chronic cases, mild anemia (Hb, 9 to 10 g/dL) may persist for life. Avoidance of cold exposure is often helpful. Splenectomy is of no value. Immunosuppressants have only modest effectiveness. Transfusions should be given sparingly, with the blood warmed through an on-line warmer. Because the
autologous RBCs have already survived the autoantibodies, autologous cell survival is better than that of transfused cells, limiting the efficacy of transfusion.

In PCH, therapy consists of strict avoidance of exposure to cold. Splenectomy is of no value. Immunosuppressants have been effective but should be restricted to patients with progressive or idiopathic cases. Treatment of concomitant syphilis may cure PCH.

**Paroxysmal Nocturnal Hemoglobinuria**

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder characterized by intravascular hemolysis and hemoglobinuria, the latter accentuated during sleep. Leukopenia, thrombocytopenia, and episodic crises are common. Diagnosis requires flow cytometry. Treatment is supportive.

PNH is most common among men in their 20s, but it occurs in both sexes and at any age.

**Etiology**

PNH is an acquired genetic mutation resulting in a membrane defect in stem cells and their progeny, including RBCs, WBCs, and platelets. It results in unusual sensitivity to normal (C3) in the plasma, leading to ongoing intravascular hemolysis of RBCs and diminished marrow production of WBCs and platelets. The defect is a missing glycosyl-phosphatidylinositol anchor for membrane proteins caused by an abnormality of the *PIG-A* gene, which is located on the X chromosome.

**Pathophysiology**

Protracted urinary Hb loss may result in iron deficiency. Patients are strongly predisposed to both venous and arterial thrombi, including the Budd-Chiari syndrome. Thrombi are commonly fatal. Some patients with PNH develop aplastic anemia, and some with aplastic anemia develop PNH.

Crises may be precipitated by infection, iron use, vaccination, or menstruation. Abdominal and lumbar pain and symptoms of severe anemia may occur; gross hemoglobinuria and splenomegaly are common.

**Diagnosis**

- Flow cytometry
- Possibly acid hemolysis test (Ham's test)

PNH is suspected in patients who have typical symptoms of anemia or unexplained normocytic anemia with intravascular hemolysis, particularly if leukopenia or thrombocytopenia is present. Historically, if PNH was suspected, the sugar-water test was usually the first test done; it relies on enhanced hemolysis of C3-dependent systems in isotonic solutions of low ionic strength, is simple to do, and is sensitive. However, the test is nonspecific; positive results require confirmation by further testing. The most sensitive and specific test is determination of the absence of specific RBC or WBC membrane proteins (CD59 and CD55) by flow cytometry. An alternative is the acid hemolysis test (Ham's test). Hemolysis usually occurs if blood is acidified with HCl, incubated for 1 h, and centrifuged. Bone marrow examination is not necessary but, if done to exclude other disorders, usually shows marrow hypoplasia. Gross hemoglobinuria is common during crises, and the urine may contain hemosiderin.

**Treatment**

- Supportive measures
- Possibly monoclonal antibody

Treatment is largely symptomatic. However, a new monoclonal antibody that is a terminal complement inhibitor, eculizumab, has reduced transfusion requirements, thromboembolism, and symptoms.
Supportive measures include corticosteroids, androgen hormones, iron and folate supplementation, and sometimes transfusions and stem cell transplantation. Empiric use of corticosteroids (eg, prednisone 20 to 40 mg po once/day) controls symptoms and stabilizes RBC values in > 50% of patients. Androgenic hormones and recombinant erythropoietin to stimulate hematopoiesis have been used in some patients. Generally, transfusions are reserved for crises. Transfusions containing plasma (and C3) should be avoided. Washing RBCs with saline before transfusion is no longer necessary. Heparin followed by warfarin may be required for thromboses but should be used cautiously. Oral iron and folate supplements may be necessary. Most cases can be managed by these supportive measures for years to decades. Allogenic stem cell transplantation has been successful in a small number of cases.

**Traumatic Hemolytic Anemia**

(Microangiopathic Hemolytic Anemia)

Traumatic hemolytic anemia is intravascular hemolysis caused by excessive shear or turbulence in the circulation.

Trauma may originate outside the vessel, as in skeletal impact, eg, repetitive foot striking (march hemoglobinuria) or from karate or bongo playing; within the heart across a pressure gradient, as in calcific aortic stenosis or with faulty aortic valve prostheses; in arterioles, as in severe (especially malignant) hypertension, some malignant tumors, or polyarteritis nodosa; or in end arterioles, often across fibrin deposits, as in thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. The trauma causes odd-shaped RBC fragments (eg, triangles, helmet shapes) called schistocytes in the peripheral blood; their appearance on the peripheral smear is diagnostic. The small schistocytes cause low MCV and high RBC distribution width (the latter reflecting the anisocytosis).

Treatment addresses the underlying process. Iron deficiency anemia occasionally is superimposed on the hemolysis as a result of chronic hemosiderinuria and, when present, responds to iron-replacement therapy.

**Hereditary Spherocytosis and Hereditary Elliptocytosis**

Hereditary spherocytosis and hereditary elliptocytosis are congenital RBC membrane disorders. Symptoms, generally milder in hereditary elliptocytosis, include variable degrees of anemia, jaundice, and splenomegaly. Diagnosis requires demonstration of increased RBC osmotic fragility and a negative direct antiglobulin test. Rarely, patients < 45 yr with symptomatic disease require splenectomy.

Hereditary spherocytosis (chronic familial icterus; congenital hemolytic jaundice; familial spherocytosis; spherocytic anemia) is an autosomal dominant disease with variable gene penetrance. It is characterized by hemolysis of spheroidal RBCs and anemia.

Hereditary elliptocytosis (ovalocytosis) is a rare autosomal dominant disorder in which RBCs are oval or elliptical. Hemolysis is usually absent or slight, with little or no anemia; splenomegaly is often present.

**Pathophysiology**

Alterations in membrane proteins cause the RBC abnormalities in both disorders. In hereditary spherocytosis, the cell membrane surface area is decreased disproportionately to the intracellular content. The decreased surface area of the cell impairs the flexibility needed for the cell to traverse the spleen's microcirculation, causing intrasplenic hemolysis. In hereditary elliptocytosis, genetic mutations result in weakness of the cytoskeleton of the cell, leading to deformation of the cell. The abnormally shaped RBCs are taken up and destroyed by the spleen.

**Symptoms and Signs**

Symptoms and signs of hereditary spherocytosis are usually mild, and the anemia may be so well compensated that it is not recognized until an intercurrent viral illness transiently decreases RBC
production, simulating an aplastic crisis. However, these episodes are self-limited, resolving with resolution of the infection. Moderate jaundice and symptoms of anemia are present in severe cases. Splenomegaly is almost invariable but only rarely causes abdominal discomfort. Hepatomegaly may be present. Cholelithiasis (pigment stones) is common and may be the presenting symptom. Congenital skeletal abnormalities (eg, tower-shaped skull, polydactylism) occasionally occur. Although usually one or more family members have had symptoms, several generations may be skipped because of variations in the degree of gene penetrance.

Clinical features of hereditary elliptocytosis are similar to those of hereditary spherocytosis but tend to be milder.

**Diagnosis**

- **RBC fragility assay, RBC autohemolysis assay, and direct antiglobulin test**

These disorders are suspected in patients with unexplained hemolysis, particularly if splenomegaly, a family history of similar manifestations, or suggestive RBC indices are present. Because RBCs are spheroidal and the MCV is normal, the mean corpuscular diameter is below normal, and RBCs resemble microspherocytes. MCHC is increased. Reticulocytosis of 15 to 30% and leukocytosis are common.

If these disorders are suspected, the RBC osmotic fragility test (which mixes RBCs with varying concentrations of saline), the RBC autohemolysis test (which measures the amount of spontaneous hemolysis occurring after 48 h of sterile incubation), and, to rule out spherocytosis due to autoimmune hemolytic anemia, the direct antiglobulin (Coombs') test are done. RBC fragility is characteristically increased, but in mild cases, it may be normal unless sterile defibrinated blood is first incubated at 37° C for 24 h. RBC autohemolysis is increased and can be corrected by the addition of glucose. The direct antiglobulin test results are negative.

**Treatment**

- **Sometimes splenectomy**

Splenectomy, after appropriate vaccination, is the only specific treatment for either disorder but is rarely needed. It is indicated in patients < 45 yr with Hb persistently < 10 g/dL, jaundice or biliary colic, or persistent aplastic crisis. If the gallbladder has stones or other evidence of cholestasis, it should be removed during splenectomy. Although spherocytosis persists after splenectomy, the cells survive longer in the circulation. Usually, symptoms resolve and anemia and reticulocytosis decrease. However, RBC fragility remains high.

**Stomatocytosis and Anemia Caused by Hypophosphatemia**

**Stomatocytosis (presence of cup- or bowl-shaped RBCs) and hypophosphatemia are RBC membrane abnormalities causing hemolytic anemia.**

**Stomatocytosis:** Stomatocytosis is a rare condition of RBCs in which a mouth-like or slitlike pattern replaces the normal central zone of pallor. These cells are associated with congenital and acquired hemolytic anemia. The symptoms result from the anemia.

The rare congenital stomatocytosis, which shows autosomal dominant inheritance, causes a severe hemolytic anemia presenting very early in life. The RBC membrane is hyperpermeable to monovalent cations (Na and K); movement of divalent cations and anions is normal. About 20 to 30% of circulating RBCs are stomatocytic; RBC fragility is increased, as is autohemolysis with inconstant correction with glucose. Splenectomy ameliorates anemia in some cases.

Acquired stomatocytosis with hemolytic anemia occurs primarily with recent excessive alcohol ingestion. Stomatocytes in the peripheral blood and hemolysis disappear within 2 wk of alcohol withdrawal.

**Anemia caused by hypophosphatemia:** RBC pliability varies according to intracellular ATP levels.
Because the serum phosphate concentration affects RBC ATP levels, serum phosphate level < 0.5 mg/dL (< 0.16 mmol/L) depletes RBC ATP; the complex metabolic sequelae of hypophosphatemia also include 2,3-diphosphoglyceric acid depletion, a shift to the left in the O₂ dissociation curve, decreased glucose utilization, and increased lactate production. The resultant rigid, nonyielding RBCs are susceptible to injury in the capillary circulatory bed, leading to hemolysis and small, sphere-shaped RBCs (microspherocytosis).

Severe hypophosphatemia may occur in alcohol withdrawal, diabetes mellitus, refeeding after starvation, the recovery (diuretic) phase after severe burns, hyperalimentation, severe respiratory alkalosis, and in uremic patients receiving dialysis who are taking antacids. Phosphate supplements prevent or reverse the anemia and are considered for patients at risk of or who have hypophosphatemia.

Embden-Meyerhof Pathway Defects

Embden-Meyerhof pathway defects are autosomal recessive RBC metabolic disorders that cause hemolytic anemia.

Pyruvate kinase deficiency is one such enzyme defect. In all of these pathway defects, hemolytic anemia occurs only in homozygotes, and the exact mechanism of hemolysis is unknown. Spherocytes are absent, but small numbers of irregularly shaped spheres may be present. In general, assays of ATP and diphosphoglycerate help identify any metabolic defect and localize the defective sites for further analysis. There is no specific therapy for these hemolytic anemias, although most patients require no treatment other than supplemental folate 1 mg po once/day during acute hemolysis. Hemolysis and anemia persist after splenectomy, although some improvement may occur, particularly in patients with pyruvate kinase deficiency.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked enzymatic defect common in blacks that can result in hemolysis after acute illnesses or intake of oxidant drugs (including salicylates and sulfonamides). Diagnosis is based on assay for G6PD, although tests are often falsely negative during acute hemolysis. Treatment is supportive.

The only important defect in the hexose monophosphate shunt pathway is caused by G6PD deficiency. Over 100 mutant forms of the enzyme have been identified. Clinically, the most common form is the drug-sensitive variety. This X-linked disorder is fully expressed in males and homozygous females and is variably expressed in heterozygous females. This defect occurs in about 10% of black males and in < 10% of black females in the US and in lower frequencies among people with ancestors from the Mediterranean basin (eg, Italians, Greeks, Arabs, Sephardic Jews).

Pathophysiology

G6PD deficiency reduces energy available to maintain the integrity of the red cell membrane, which shortens RBC survival.

Hemolysis selectively affects older RBCs among affected blacks and among most affected whites. Hemolysis occurs commonly after fever, acute viral and bacterial infections, and diabetic acidosis. Less commonly, hemolysis occurs after exposure to drugs or to other substances that produce peroxide and cause oxidation of Hb and RBC membranes. These drugs and substances include primaquine, salicylates, sulfonamides, nitrofurans, phenacetin, naphthalene, some vitamin K derivatives, dapsone, phenazopyridine, nalidixic acid, methylene blue, and, in some whites, fava beans. Whether continued use of the offending drug leads to a compensated hemolytic state or lethal hemolysis depends on the degree of G6PD deficiency and the oxidant potential of the drug. Chronic congenital hemolysis (without drug use) occurs in some whites. Because older cells are selectively destroyed in blacks, hemolysis is usually self-limited, affecting < 25% of RBC mass; in whites, the deficiency is more severe, and profound hemolysis may lead to hemoglobinuria and acute renal failure.

Diagnosis
• G6PD assay

The diagnosis is considered in patients with acute hemolysis, particularly black males. G6PD assay is done. Anemia, jaundice, and reticulocytosis develop during hemolysis. Heinz bodies, possibly particles of dead cytoplasm or denatured Hb, may be visible early during the hemolytic episode but do not persist in patients with an intact spleen because they are removed by it. A specific diagnostic clue is the presence in the peripheral blood of RBCs that appear to have had one or more bites (1-μm wide) taken from the cell periphery (bite cells), possibly as a result of Heinz body removal by the spleen. Many screening tests are available. However, during and immediately after a hemolytic episode, tests may yield false-negative results because of destruction of the older, more deficient RBCs and the presence of reticulocytes rich in G6PD. Specific enzyme assays are the best diagnostic tests.

Treatment

During acute hemolysis, treatment is supportive; transfusions are rarely needed. Patients are advised to avoid drugs or substances that initiate hemolysis.

Sickle Cell Disease

(Hb S Disease)

Sickle cell disease (a hemoglobinopathy—see Sidebar 106-1) causes a chronic hemolytic anemia occurring almost exclusively in blacks, caused by homozygous inheritance of Hb S. Sickle-shaped RBCs clog capillaries, causing organ ischemia. Acute exacerbations (crises) may develop frequently. Infection, bone marrow aplasia, or lung involvement (acute chest syndrome) can develop acutely and be fatal. Normocytic hemolytic anemia is characteristic. Diagnosis requires Hb electrophoresis. Crises are treated with analgesics and other supportive measures. Transfusions are occasionally required. Vaccines against bacterial infections, prophylactic antibiotics, and aggressive treatment of infections prolong survival. Hydroxyurea may decrease the frequency of crises.

Homozygotes (about 0.3% of blacks in the US) have sickle cell anemia; heterozygotes (8 to 13% of blacks) are typically not anemic.

Pathophysiology

In Hb S, valine is substituted for glutamic acid in the 6th amino acid of the β chain. Oxygenated Hb S is much less soluble than oxygenated Hb A; it forms a semisolid gel that causes RBCs to deform in a sickle shape at sites of low PO\(_2\). Distorted, inflexible RBCs adhere to vascular endothelium and plug small arterioles and capillaries, which leads to infarction. Venous plugging predisposes to thromboses. Because sickled RBCs are fragile, the mechanical trauma of circulation causes hemolysis. Chronic compensatory marrow hyperactivity deforms the bones.

Acute exacerbations: Acute exacerbations (crises) occur intermittently, often for no known reason. In some cases, fever, viral infection, or local trauma appears to precipitate a crisis.

Sidebar 106-1 Hemoglobinopathies

Hb molecules consist of polypeptide chains whose chemical structure is genetically controlled. The normal adult Hb molecule (Hb A) consists of 2 pairs of chains designated α and β. Normal blood also contains a ≤ 2.5% concentration of Hb A₂ (composed of α and δ chains). Fetal Hb (Hb F, which has γ chains in the place of β chains) gradually decreases, particularly in the first months of life, until it makes up < 2% of total Hb in adults (see Hemoglobinopathies on p. 2636). Hb F concentration increases in certain disorders of Hb synthesis and in aplastic and myeloproliferative states.

Some hemoglobinopathies result in anemias that are severe in patients who are homozygous but mild in
patients who are heterozygous. Some patients are heterozygous for 2 such abnormalities and have anemia with characteristics of both traits.

Different Hbs, as distinguished by electrophoretic mobility, are alphabetically designated in order of discovery (eg, A, B, C), although the first abnormal Hb, sickle cell Hb, was designated Hb S. Structurally different Hbs with the same electrophoretic mobility are named for the city or location in which they were discovered (eg, Hb S Memphis, Hb C Harlem). Standard description of a patient's Hb composition places the Hb of greatest concentration first (eg, AS in sickle cell trait).

In the US, important anemias are caused by defective synthesis of Hb S or Hb C and the thalassemias, and immigration of Southeast Asians has made Hb E disease common.

Painful crisis is the most common type; it is caused by ischemia and infarction, typically of the bones, but also of the spleen, lung, or kidney.

Aplastic crisis occurs when marrow erythropoiesis slows during acute infection (especially viral), during which an acute erythroblastopenia may occur.

Acute chest syndrome results from pulmonary microvascular occlusion and is a common cause of death, with mortality rates of up to 10%. It occurs in all age groups but is most common in childhood. Repeated episodes predispose to chronic pulmonary hypertension.

In children, acute sequestration of sickled cells in the spleen may occur, exacerbating anemia.

Priapism, a serious complication that can cause erectile dysfunction, is most common in young men.

**Complications:** Long-term consequences include impaired growth and development. Increased susceptibility to infection, particularly pneumococcal and *Salmonella* infections (including *Salmonella* osteomyelitis), also results. These infections are especially common in early childhood and can be rapidly fatal.

Other consequences include ischemic stroke, CNS vasculitis, avascular necrosis of the hips, renal concentrating defects, renal failure, heart failure, and pulmonary fibrosis.

**Symptoms and Signs**

Most symptoms occur only in patients who are homozygous and result from anemia and vaso-occlusive events resulting in tissue ischemia and infarction. Anemia is usually severe but varies highly among patients; mild jaundice and pallor are common.

Patients may be poorly developed and often have a relatively short trunk with long extremities and a tower-shaped skull. Hepatosplenomegaly is common in children, but because of repeated infarctions and subsequent fibrosis (autosplenectomy), the spleen in adults is commonly very small. Cardiomegaly and systolic ejection (flow) murmurs are common. Cholelithiasis and chronic punched-out ulcers around the ankles are common.

Painful crisis causes severe pain in long bones (eg, pretibial pain), the hands and feet (eg, hand-foot syndrome), and joints. Joint pain may result from hemarthrosis or avascular necrosis of the femoral head. Severe abdominal pain may develop with or without vomiting and, when due to sickling itself, is usually accompanied by back and joint pain.

Acute chest syndrome is characterized by sudden onset of fever, chest pain, and pulmonary infiltrates. The infiltrates begin in the lower lobes, are bilateral in one third of cases, and may be accompanied by pleural effusion. It may follow bacterial pneumonia. Hypoxemia may develop rapidly, causing dyspnea.

**Heterozygotes:** Patients who are heterozygous (Hb AS) do not experience hemolysis, painful crises, or thrombotic complications except possibly during hypoxic conditions (eg, at high altitudes, during sudden
decompression in airplanes). However, rhabdomyolysis and sudden death may occur during sustained, exhausting exercise. Impaired ability to concentrate urine (hyponothenuria) is common. Unilateral hematuria (by unknown mechanisms and usually from the left kidney) can occur but is self-limited. Typical renal papillary necrosis can occur but is less common than among homozygous patients.

**Diagnosis**

- DNA testing (prenatal diagnosis)
- Peripheral smear
- Solubility testing
- Hb electrophoresis (or thin-layer isoelectric focusing)

The type of testing done depends on the age of the patient. DNA testing can be used for prenatal diagnosis or to confirm a diagnosis of the sickle cell genotype. Screening of neonates is available in most US states and involves Hb electrophoresis. Screening and diagnosis in children and adults involve examination of the peripheral smear, Hb solubility testing, and Hb electrophoresis.

**Prenatal screening:** The sensitivity of prenatal diagnosis has been greatly improved with the availability of the PCR technique. It is recommended for families at risk for sickle cell (eg, couples with medical or family histories of anemia or of suggestive ethnic background). DNA samples can be obtained by chorionic villus sampling at 8 to 10 wk gestation. Amniotic fluid can also be tested at 14 to 16 wk. Diagnosis is important for genetic counseling.

**Newborn screening:** Universal testing is currently recommended and is frequently one of a battery of newborn screening tests. To distinguish between Hbs F, S, A, and C, the recommended tests are Hb electrophoresis using cellulose acetate or acid citrate agar, thin-layer isoelectric focusing, or Hb fractionation by high performance liquid chromatography (HPLC). Repeat testing at age 3 to 6 mo may be necessary for confirmation. Solubility testing for Hb S is unreliable during the first few months of life.

**Screening and diagnosis of children and adults:** Patients with a family history of sickle cell disease or trait should be screened with peripheral smear, Hb solubility testing, and Hb electrophoresis.

Patients with symptoms or signs suggesting the disorder or its complications (eg, poor growth, acute and unexplained bone pain, aseptic necrosis of the femoral head, unexplained hematuria), and black patients with normocytic anemia (particularly if hemolysis is present) require laboratory tests for hemolytic anemia (see p. 936), Hb electrophoresis, and examination of RBCs for sickling. If sickle cell disease is present, RBC count is usually between 2 and 3 million/μL with Hb reduced proportionately; cells are normocytic (microcytosis suggests a concomitant α-thalassemia). Nucleated RBCs frequently appear in the peripheral blood, and reticulocytosis ≥ 10% is common. Dry-stained smears may show sickled RBCs (crescent-shaped, often with elongated or pointed ends).

The homozygous state is differentiated from other sickle hemoglobinopathies by electrophoresis showing only Hb S with a variable amount of Hb F. The heterozygote is differentiated by the presence of more Hb A than Hb S on electrophoresis. Hb S must be distinguished from other Hb with a similar electrophoretic pattern by showing the pathognomonic RBC morphology.

Bone marrow examination is not used for diagnosis. If it is done to differentiate other anemias, it shows hyperplasia, with normoblasts predominating; bone marrow may become aplastic during sickling or severe infections. ESR, if done to exclude other disorders (eg, juvenile RA causing hand and foot pain), is low. Incidental findings on skeletal x-rays may include widening of the diploic spaces of the skull and a sun-ray appearance of the diploic trabeculations. The long bones often show cortical thinning, irregular densities, and new bone formation within the medullary canal. Unexplained hematuria, even among patients not suspected of having sickle cell disease, should prompt consideration of sickle cell trait.

**Evaluation of exacerbations:** If patients with known sickle cell disease have acute exacerbations,
including pain, fever, or other symptoms of infection, aplastic crisis is considered and CBC and reticulocyte count are done. Reticulocyte count < 1% suggests aplastic crisis, particularly when Hb decreases below the patient's usual level. In a painful crisis without aplasia, WBC count rises, often with a shift to the left, particularly during bacterial infection. Platelet count usually increases. If measured, serum bilirubin is usually elevated (eg, 2 to 4 mg/dL [34 to 68 μmol/L]), and urine may contain urobilinogen.

In patients with chest pain or difficulty breathing, acute chest syndrome and pulmonary embolism are considered; chest x-ray and pulse oximetry are necessary. Hypoxemia or pulmonary parenchymal infiltrates on chest x-ray suggest acute chest syndrome or pneumonia. Hypoxemia without pulmonary infiltrates suggests pulmonary embolism.

In patients with fever, infection and acute chest syndrome are considered; cultures, chest x-ray, and other appropriate diagnostic tests are done.

**Prognosis**

The life span of homozygous patients has steadily increased to > 50 yr. Common causes of death are acute chest syndrome, intercurrent infections, pulmonary emboli, infarction of a vital organ, and renal failure.

**Treatment**

- Broad-spectrum antibiotics (for infection)
- Analgesics and IV hydration (for vasoocclusive pain crisis)
- Sometimes transfusions
- Immunizations, folate supplementation, and hydroxyurea (for health maintenance)

Treatment includes regular health maintenance measures as well as specific treatment of the complications as they arise. Complications are treated supportively. No effective in vivo anti-sickling drug is available. Splenectomy is valueless. Stem cell transplantation has been curative in a small number of patients but has a 5 to 10% mortality rate and so is not commonly done. Gene therapy offers hope for a cure, but it is still under study.

Indications for hospitalization include suspected serious (including systemic) infection, aplastic crisis, acute chest syndrome, and, often, intractable pain or the need for transfusion. Fever alone may not be a reason to hospitalized. However, patients who appear acutely ill and have a temperature > 38°C should be admitted so that cultures can be obtained from multiple areas and IV antibiotics can be given.

**Antibiotics**: Patients with suspected serious bacterial infections or acute chest syndrome require broad-spectrum antibiotics immediately.

**Analgesics**: Painful crises are managed with liberal administration of analgesics, usually opioids. IV morphine (continuous or bolus) is effective and safe; meperidine is avoided. Although dehydration contributes to sickling and may precipitate crises, it is unclear whether vigorous hydration is helpful during crises. Nevertheless, maintaining normal intravascular volume has been a mainstay of therapy. During crises, pain and fever may persist for as long as 5 days.

**Transfusion**: Transfusion is given in many situations in which its efficacy has not been demonstrated. However, routine transfusion therapy is indicated for prevention of recurrent cerebral thrombosis, especially in children. Transfusion is usually done when Hb is < 5 g/dL. Specific indications include acute splenic sequestration, aplastic crises, cardiopulmonary symptoms or signs (eg, high-output heart failure, hypoxemia with PO₂ < 65 mm Hg), preoperative use, priapism, and life-threatening events that would benefit from improved O₂ delivery (eg, sepsis, severe infection, acute chest syndrome, stroke, acute organ ischemia). Transfusion is not helpful during an uncomplicated painful crisis; however, it may break
a cycle of closely spaced painful crises. Transfusion may be needed in pregnancy.

Partial exchange transfusion is usually preferred to simple transfusion if routine or multiple transfusions are necessary. It can be done with modern apheresis machines. If the initial Hb is low (< 7 g/dL), this process cannot be initiated before first transfusing red cells. Partial exchange transfusion minimizes iron accumulation and hyperviscosity.

Health maintenance: For long-term management the following interventions have reduced mortality, particularly during childhood:

- Pneumococcal, Haemophilus influenzae, and meningococcal vaccines
- Early identification and treatment of serious bacterial infections
- Prophylactic antibiotics, including continuous prophylaxis with oral penicillin from age 4 mo to 6 yr
- Use of hydroxyurea and folate supplementation

Supplemental folate, 1 mg po once/day, is usually prescribed.

Hydroxyurea, by increasing Hb F and thereby reducing sickling, decreases painful crises (by 50%) and decreases acute chest syndrome and transfusion requirements. The dose of hydroxyurea is variable and is adjusted to increase Hb F. Hydroxyurea may be more effective when combined with erythropoietin (eg, 40,000 to 60,000 units/wk). However, hydroxyurea is a leukemogen and causes neutropenia and thrombocytopenia. It is also a teratogen and should not be given to females of child-bearing age.

Erythropoietin use in patients with anemia unrelated to chemotherapy has been associated with increased frequency of venous thromboembolic events and cardiopulmonary complications (eg, MI); it is generally not helpful in patients with sickle cell disease.

Hemoglobin C Disease

Hemoglobin C disease is a hemoglobinopathy (see Sidebar 106-1) that causes symptoms similar to those of sickle cell disease, but milder.

Of blacks in the US, 2 to 3% have the trait, which is asymptomatic. Symptoms in homozygotes are usually similar to those of sickle cell disease, but milder. However, the abdominal crises of sickle cell disease do not occur, and the spleen is usually enlarged. Splenic sequestration is possible.

Hemoglobin C disease is suspected in all patients with a family history and in black patients with clinical features suggesting sickle cell disease, particularly in adults with splenomegaly. The anemia is usually mild but can be moderately severe. The smear is normocytic, with 30 to 100% target cells, spherocytes, and, rarely, crystal-containing RBCs. Nucleated RBCs may be present. The RBCs do not sickle. On electrophoresis, the Hb is type C. In heterozygotes, the only laboratory abnormality is centrally targeted RBCs.

No specific treatment is recommended. Anemia usually is not severe enough to require blood transfusion.

Hemoglobin S-C Disease

Hemoglobin S-C disease is a hemoglobinopathy (see Sidebar 106-1) that causes symptoms similar to those of sickle cell disease, but milder.

Because 10% of blacks carry the Hb S trait, the heterozygous S-C combination is more common than homozygous Hb C disease. The anemia in Hb S-C disease is milder than the anemia in sickle cell disease; some patients even have normal Hb levels. Most symptoms are those of sickle cell disease, but symptoms are usually less frequent and less severe. However, gross hematuria, retinal hemorrhages, and aseptic necrosis of the femoral head are common. Hb S-C disease is suspected in patients whose clinical
features suggest sickle cell disease or whose RBCs demonstrate sickling. Stained blood smears show target cells and a rare sickle cell. Sickling is identified in a sickling preparation, and Hb electrophoresis establishes the diagnosis. Treatment can be similar to that of sickle cell disease but is determined by severity of symptoms.

**Hemoglobin E Disease**

Homzygous Hb E disease (a hemoglobinopathy—see Sidebar 106-1) causes a mild hemolytic anemia, usually without splenomegaly.

Hb E is the 3rd most prevalent Hb worldwide (after Hb A and Hb S), primarily in black and Southeast Asian (> 15% incidence of homozygous disease) populations, although rarely in Chinese populations. Heterozygotes (Hb AE) are asymptomatic. Patients heterozygous for Hb E and β-thalassemia have a hemolytic disease more severe than S-thalassemia or homozygous Hb E disease and usually have splenomegaly.

In heterozygotes (Hb AE), routine laboratory test results of peripheral blood are normal. In homozygotes, a mild microcytic anemia with prominent target cells exists. Diagnosis of Hb E disorders is by Hb electrophoresis. Treatment in homozygous patients with severe disease usually involves chronic transfusions.

**Thalassemias**

(Mediterranean Anemia; Thalassemia Major and Minor)

Thalassemias are a group of inherited microcytic, hemolytic anemias characterized by defective Hb synthesis. They are particularly common in people of Mediterranean, African, and Southeast Asian ancestry. Symptoms and signs result from anemia, hemolysis, splenomegaly, bone marrow hyperplasia, and, if there have been multiple transfusions, iron overload. Diagnosis is based on genetic tests and quantitative Hb analysis. Treatment for severe forms may include transfusion, splenectomy, chelation, and stem cell transplantation.

**Pathophysiology**

Thalassemia (a hemoglobinopathy—see Sidebar 106-1) is among the most common inherited disorders of Hb production. It results from unbalanced Hb synthesis caused by decreased production of at least one globin polypeptide chain (β, α, γ, δ).

β-Thalassemia results from decreased production of β-polypeptide chains. Inheritance is autosomal: Heterozygotes are carriers and have asymptomatic mild to moderate microcytic anemia (thalassemia minor); homozygotes (β-thalassemia major, or Cooley's anemia) develop severe anemia and bone marrow hyperactivity. β-δ-Thalassemia is a less common form of β-thalassemia in which δ-chain as well as β-chain production is impaired and which also has heterozygous and homozygous states.

α-Thalassemia, which results from decreased production of α-polypeptide chains, has a more complex inheritance pattern, because genetic control of α-chain synthesis involves 2 pairs of genes (4 genes). Heterozygotes for a single gene defect (α-thalassemia-2 [silent]) are usually clinically normal. Heterozygotes with defects in 2 of the 4 genes (α-thalassemia-1 [trait]) tend to develop mild to moderate microcytic anemia but no symptoms. Defects in 3 of the 4 genes more severely impairs α-chain production, resulting in the formation of tetramers of excess β chains (Hb H) or, in infancy, γ chains (Bart's Hb). Defects in all 4 genes are a lethal condition in utero, because Hb that lacks α chains does not transport O2. In blacks, the gene frequency for α-thalassemia is about 25%; only 10% have defects in more than 2 genes.

**Symptoms and Signs**

Clinical features of thalassemias are similar but vary in severity. β-Thalassemia major manifests by age 1 to 2 yr with symptoms of severe anemia and transfusional and absorptive iron overload. Patients are
jaundiced, and leg ulcers and cholelithiasis occur (as in sickle cell anemia). Splenomegaly, often massive, is common. Splenic sequestration may develop, accelerating destruction of transfused normal RBCs. Bone marrow hyperactivity causes thickening of the cranial bones and malar eminences. Long bone involvement predisposes to pathologic fractures and impairs growth, possibly delaying or preventing puberty. Iron deposits in heart muscle may cause heart failure. Hepatic siderosis is typical, leading to functional impairment and cirrhosis. Patients with Hb H disease often have symptomatic hemolytic anemia and splenomegaly.

Diagnosis

- Evaluation for hemolytic anemia if suspected
- Peripheral smear
- Electrophoresis
- DNA testing (prenatal diagnosis)

Thalassemias are suspected in patients with a family history, suggestive symptoms or signs, or microcytic hemolytic anemia. If thalassemias are suspected, laboratory tests for microcytic and hemolytic anemias and quantitative Hb studies are done. Serum bilirubin, iron, and ferritin levels are increased.

In \( \beta \)-thalassemia major, anemia is severe, often with Hb \( \leq 6 \) g/dL. RBC count is elevated relative to Hb because the cells are very microcytic. The blood smear is virtually diagnostic, with many nucleated erythroblasts; target cells; small, pale RBCs; and punctate and diffuse basophilia.

In quantitative Hb studies, elevation of Hb A\(_2\) is diagnostic for \( \beta \)-thalassemia minor. In \( \beta \)-thalassemia major, Hb F is usually increased, sometimes to as much as 90%, and Hb A\(_2\) is usually elevated to > 3%. The percentages of Hb F and Hb A\(_2\) are generally normal in \( \alpha \)-thalassemias, and the diagnosis of single or double gene defect thalassemias may be carried out with newer genetic tests and often is one of exclusion of other causes of microcytic anemia. Hb H disease can be diagnosed by demonstrating the fast-migrating Hb H or Bart’s fractions on Hb electrophoresis. The specific molecular defect can be characterized but does not alter the clinical approach. Recombinant DNA approaches of gene mapping (particularly the PCR) have become standard for prenatal diagnosis and genetic counseling.

If bone marrow examination is done for anemia (eg, to exclude other causes), it shows marked erythroid hyperplasia. X-rays done for other reasons in patients with \( \beta \)-thalassemia major show changes due to chronic bone marrow hyperactivity. The skull may show cortical thinning, widened diploic space, a sun-ray appearance of the trabeculae, and a granular or ground-glass appearance. The long bones may show cortical thinning, marrow space widening, and areas of osteoporosis. The vertebral bodies may have a granular or ground-glass appearance. The phalanges may appear rectangular or biconvex.

Prognosis

Life expectancy is normal for people with \( \beta \)-thalassemia minor or \( \alpha \)-thalassemia minor. The outlook for people with Hb H disease varies. Life expectancy is decreased in people with \( \beta \)-thalassemia major; only some live to puberty or beyond.

Treatment

- Sometimes splenectomy
- Sometimes RBC transfusion and chelation therapy
- Rarely allogeneic stem cell transplantation

People with \( \alpha \)- and \( \beta \)-thalassemia minor require no treatment. Splenectomy may be helpful if Hb H
disease causes severe anemia or splenomegaly.

Children with β-thalassemia major should receive as few transfusions as possible to avoid iron overload. However, suppression of abnormal hematopoiesis by periodic RBC transfusion may be valuable in severely affected patients. To prevent or delay iron overload, excess (transfusional) iron must be removed (eg, via chronic iron-chelation therapy). Splenectomy may help decrease transfusion requirements for patients with splenomegaly. Allogeneic stem cell transplantation has been successful, but the requirement for a histocompatible match, mortality and morbidity of the procedure, and lifelong requirement for immunosuppression have limited its usefulness.

Hemoglobin S-β-Thalassemia Disease

Hemoglobin S-β-thalassemia disease is a hemoglobinopathy (see Sidebar 106-1) that causes symptoms similar to those of sickle cell disease, but milder.

Because of the increased frequency of both Hb S and β-thalassemia genes in similar population groups, inheritance of both defects is relatively common. Clinically, the disorder causes symptoms of moderate anemia and signs of sickle cell anemia, which are usually less frequent and less severe than those of sickle cell disease. Mild to moderate microcytic anemia is usually present along with some sickled RBCs on stained blood smears. Diagnosis requires quantitative Hb studies. The Hb A₂ is > 3%. Hb S predominates on electrophoresis, and Hb A is decreased or absent. Hb F increase is variable. Treatment, if necessary, is the same as for sickle cell disease.
Chapter 107. Neutropenia and Lymphocytopenia

Introduction

Leukopenia is a reduction in the circulating WBC count to < 4000/μL. It is usually characterized by a reduced number of circulating neutrophils, although a reduced number of lymphocytes, monocytes, eosinophils, or basophils may also contribute. Thus, immune function is generally greatly decreased.

Neutropenia is a reduction in blood neutrophil count to < 1500/μL in whites and < 1200/μL in blacks. It is more serious when accompanied by monocytopenia and lymphocytopenia. Lymphocytopenia, in which the total number of lymphocytes is < 1000/μL in adults, is not always reflected in the total WBC count, because lymphocytes account for only 20 to 40% of the count.

Neutropenia

(Agranulocytosis; Granulocytopenia)

Neutropenia is a reduction in the blood neutrophil count. If it is severe, the risk and severity of bacterial and fungal infections increase. Focal symptoms of infection may be muted, but fever is present during most serious infections. Diagnosis is by WBC count, but evaluation requires identification of the cause. If fever is present, infection is presumed, and immediate, empiric broad-spectrum antibiotics are necessary. Treatment with granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor is sometimes helpful.

Neutrophils (granulocytes) are the body's main defense against bacterial and fungal infections. When neutropenia is present, the inflammatory response to such infections is ineffective. Normal lower limit of the neutrophil count (total WBC × % neutrophils and bands) is 1500/μL in whites and is somewhat lower in blacks (about 1200/μL).

Severity of neutropenia relates to the relative risk of infection:

• Mild (1000 to 1500/μL)
• Moderate (500 to 1000/μL)
• Severe (< 500/μL)

When neutrophil counts fall to < 500/μL, endogenous microbial flora (eg, in the mouth or gut) can cause infections. If the count falls to < 200/μL, inflammatory response may be nonexistent. Acute, severe neutropenia, particularly if another factor (eg, cancer) also impairs the immune system, predisposing to rapidly fatal infections. The integrity of the skin and mucous membranes, the vascular supply to tissue, and the nutritional status of the patient also influence the risk of infections.

The most frequently occurring pyogenic infections in patients with profound neutropenia are

• Cellulitis
• Liver abscesses
• Furunculosis
• Pneumonia
• Septicemia

Vascular catheters and other puncture sites confer extra risk of skin infections; the most common bacterial causes are coagulase-negative staphylococci and Staphylococcus aureus. Stomatitis, gingivitis, perirectal inflammation, colitis, sinusitis, paronychia, and otitis media often occur. Patients with prolonged
perirectal inflammation, colitis, sinusitis, paronychia, and otitis media often occur. Patients with prolonged neutropenia after bone marrow transplantation or chemotherapy and patients receiving high doses of corticosteroids are predisposed to fungal infections.

**Etiology**

Acute neutropenia (occurring over hours to a few days) can develop from rapid neutrophil use or destruction or from impaired production. Chronic neutropenia (lasting months to years) usually arises from reduced production or excessive splenic sequestration.

Neutropenia also may be classified as due to an intrinsic defect in marrow myeloid cells or as secondary (due to factors extrinsic to marrow myeloid cells—see Table 107-1).

**Neutropenia caused by intrinsic defects in myeloid cells or their precursors:** This type of neutropenia is uncommon, but when present, the most common causes include

- Chronic idiopathic neutropenia
- Congenital neutropenia

Cyclic neutropenia is a rare congenital granulocytopenic disorder, usually transmitted in an autosomal dominant fashion. It is characterized by regular, periodic oscillations in the number of peripheral neutrophils. The mean oscillatory period is 21 ± 3 days.

Severe congenital neutropenia (Kostmann's syndrome) is a rare disorder that occurs sporadically in the US and is characterized by an arrest in myeloid maturation at the promyelocyte stage of the bone marrow, resulting in an absolute neutrophil count of < 200/μL.

Chronic idiopathic neutropenia is a group of uncommon, poorly understood disorders involving stem cells committed to the myeloid series; RBC and platelet precursors are unaffected. The spleen is not enlarged. Chronic benign neutropenia is a type of chronic idiopathic neutropenia in which the rest of the immune system appears to remain intact; even with neutrophil counts < 200/μL, serious infections usually do not occur, probably because neutrophils are sometimes produced in adequate quantities in response to infection.

Neutropenia can also result from bone marrow failure due to rare syndromes (eg, cartilage-hair hypoplasia, Chediak-Higashi syndrome, dyskeratosis congenita, glycogen storage disease type IB, Shwachman-Diamond syndrome). Neutropenia is also a prominent feature of myelodysplasia (see p. 1014), where it may be accompanied by megaloblastoid features in the bone marrow, and of aplastic anemia (see p. 929) and can occur in dysgammaglobulinemia and paroxysmal nocturnal hemoglobinemia.

**Secondary neutropenia:** Secondary neutropenia can result from use of certain drugs, bone marrow infiltration or replacement, certain infections, or immune reactions. The most common causes include

- Drugs
- Infections
- Marrow infiltrative processes

[Table 107-1, Classification of Neutropenias]

Drug-induced neutropenia is one of the most common causes of neutropenia. Drugs can decrease neutrophil production through toxic, idiosyncratic, or hypersensitivity mechanisms or increase peripheral neutrophil destruction through immune mechanisms. Only the toxic mechanism (eg, with phenothiazines) produces dose-related neutropenia. Idiosyncratic reactions are unpredictable and occur with a wide variety of drugs, including alternative medicine preparations or extracts, and toxins. Hypersensitivity reactions are rare and occasionally involve anticonvulsants (eg, phenytoin, phenobarbital). These
Neutropenia may last for only a few days or for months or years. Often, hepatitis, nephritis, pneumonitis, or aplastic anemia accompanies hypersensitivity-induced neutropenia. Immune-mediated drug-induced neutropenia, thought to arise from drugs that act as haptens to stimulate antibody formation, usually persists for about 1 wk after the drug is stopped. It may result from aminopyrine, propylthiouracil, penicillin, or other antibiotics. Severe dose-related neutropenia occurs predictably after cytotoxic cancer drugs or radiation therapy suppresses bone marrow production.

Neutropenia due to ineffective bone marrow production can occur in megaloblastic anemias caused by vitamin B\textsubscript{12} or folate deficiency. Usually, macrocytic anemia and sometimes mild thrombocytopenia develop simultaneously.

Bone marrow infiltration by leukemia, myeloma, lymphoma, or metastatic solid tumors (eg, breast, prostate) can impair neutrophil production. Tumor-induced myelofibrosis may further exacerbate neutropenia. Myelofibrosis can also occur from granulomatous infections, Gaucher's disease, and radiation therapy. Hypersplenism of any cause can lead to moderate neutropenia, thrombocytopenia, and anemia.

Infections can cause neutropenia by impairing neutrophil production or by inducing immune destruction or rapid use of neutrophils. Sepsis is a particularly serious cause. Neutropenia that occurs with common childhood viral diseases develops during the first 1 to 2 days of illness and may persist for 3 to 8 days. Transient neutropenia may also result from virus- or endotoxemia-induced redistribution of neutrophils from the circulating to the marginal pool. Alcohol may contribute to neutropenia by inhibiting the neutrophilic response of the marrow during some infections (eg, pneumococcal pneumonia).

Chronic secondary neutropenia often accompanies HIV infection because of impaired production of neutrophils and accelerated destruction of neutrophils by antibodies. Autoimmune neutropenias may be acute, chronic, or episodic. They may involve antibodies directed against circulating neutrophils or neutrophil precursor cells. Most patients with autoimmune neutropenia have an underlying autoimmune disorder or lymphoproliferative disorder (eg, SLE, Felty's syndrome).

**Symptoms and Signs**

Neutropenia is asymptomatic until infection develops. Fever is often the only indication of infection. Focal symptoms may develop but are often subtle. Patients with drug-induced neutropenia due to hypersensitivity may have a fever, rash, and lymphadenopathy from the hypersensitivity.

Some patients with chronic benign neutropenia and neutrophil counts \(<\) 200/μL do not experience many serious infections. Patients with cyclic neutropenia or severe congenital neutropenia tend to have episodes of oral ulcers, stomatitis, or pharyngitis and lymph node enlargement during severe chronic neutropenia. Pneumonias and septicemia often occur.

**Diagnosis**

- Clinical suspicion (repeated or unusual infections)
- Confirmatory CBC with differential
- Evaluation for infection with cultures and imaging
- Identification of mechanism and cause of neutropenia

Neutropenia is suspected in patients with frequent, severe, or unusual infections or in patients at risk (eg, those receiving cytotoxic drugs or radiation therapy). Confirmation is by CBC with differential.

**Evaluation for infection**: The first priority is to determine whether an infection is present. Because infection may be subtle, physical examination systematically assesses the most common primary sites of infection: mucosal surfaces, such as the alimentary tract (gums, pharynx, anus); lungs; abdomen; urinary tract; skin and fingernails; venipuncture sites; and vascular catheters.
If neutropenia is acute, laboratory evaluation must proceed rapidly.

Cultures are the mainstay of evaluation. At least 2 sets of bacterial and fungal blood cultures are obtained from all febrile patients; if an indwelling IV catheter is present, cultures are obtained from the lumen and from a separate peripheral vein. Persistent or chronic drainage material is also cultured for fungi and atypical mycobacteria. Skin lesions are aspirated or biopsied for cytology and culture. Samples for urinalysis and urine cultures are obtained from all patients. If diarrhea is present, stool is evaluated for enteric bacterial pathogens and *Clostridium difficile* toxins.

Imaging studies are helpful. Chest x-rays are done on all patients. CT scan of the para-nasal sinuses may be helpful if symptoms or signs of sinusitis (eg, positional headache, upper tooth or maxillary pain, facial swelling, nasal discharge) are present. CT scan of the abdomen is usually done if symptoms (eg, pain) or history (eg, recent surgery) suggests an intra-abdominal infection.

**Identification of cause:** Next, mechanism and cause of neutropenia are determined. The history addresses all drugs, other preparations, and possible toxin exposure or ingestion. Physical examination addresses the presence of splenomegaly and signs of other underlying disorder (eg, arthritis, lymphadenopathy).

The most important test is bone marrow examination, which determines whether neutropenia is due to decreased marrow production or is secondary to increased destruction or use of the cells (determined by normal or increased production of the cells). Bone marrow may also indicate the specific cause of the neutropenia (eg, aplastic anemia, myelofibrosis, leukemia). Additional marrow studies (eg, cytogenetic analysis; special stains and flow cytometry for detecting leukemia, other malignant disorders, and infections) are obtained.

Further testing for the cause of neutropenia may be necessary, depending on the diagnoses suspected. In patients at risk of deficiency, levels of folate and vitamin B₁₂ are determined. Testing for the presence of antineutrophil antibodies is done if immune neutropenia is suspected. Differentiation between neutropenia caused by certain antibiotics and infection can sometimes be difficult. The WBC count just before the start of antibiotic treatment usually reflects the change in blood count due to the infection.

Patients who have had chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis have WBC counts with differential done 3 times/wk for 6 wk, so that periodicity suggestive of cyclic neutropenia can be evaluated. Platelet and reticulocyte counts are done simultaneously. Eosinophils, reticulocytes, and platelets frequently cycle synchronously with the neutrophils, whereas monocytes and lymphocytes may cycle out of phase.

**Treatment**

- Treatment of associated conditions (eg, infections, stomatitis)
- Sometimes antibiotic prophylaxis
- Myeloid growth factors
- Discontinuation of suspected etiologic agent (eg, drug)
- Sometimes corticosteroids
- Rarely splenectomy

**Acute neutropenia:** Suspected infections are always treated immediately. If fever or hypotension is present, serious infection is assumed, and empiric, high-dose, broad-spectrum antibiotics are given IV. Regimen selection is based on the most likely infecting organisms, the antimicrobial susceptibility of pathogens at that particular institution, and the regimen's potential toxicity. Because of the risk of creating resistant organisms, vancomycin is used only if gram-positive organisms resistant to other drugs are
Indwelling vascular catheters can usually remain in place even if bacteremia is suspected or documented, but removal is considered if infections involve *S. aureus* or *Bacillus*; *Corynebacterium*; or *Candida* sp or if blood cultures are persistently positive despite appropriate antibiotics. Infections caused by coagulase-negative staphylococci generally resolve with antimicrobial therapy alone. Indwelling Foley catheters can also predispose to infections in these patients, and change or removal of the catheter should be considered for persistent urinary infections.

If cultures are positive, antibiotic therapy is adjusted to the results of sensitivity tests. If a patient defervesces within 72 h, antibiotics are continued for at least 7 days and until the patient has no symptoms or signs of infection. When neutropenia is transient (such as that following myelosuppressive chemotherapy), antibiotic therapy is usually continued until the neutrophil count is > 500/μL; however, stopping antimicrobials can be considered in selected patients with persistent neutropenia, especially those in whom symptoms and signs of inflammation have resolved, if cultures remain negative.

Fever that persists > 72 h despite antibiotic therapy suggests a nonbacterial cause, infection with a resistant species, a superinfection with a 2nd bacterial species, inadequate serum or tissue levels of the antibiotics, or localized infection, such as an abscess. Neutropenic patients with persistent fever are reassessed every 2 to 4 days with physical examination, cultures, and chest x-ray. If the patient is well except for the presence of fever, the initial antibiotic regimen can be continued. If the patient is deteriorating, alteration of the antimicrobial regimen is considered.

Fungal infections are the most likely cause of persistent fevers and deterioration. Antifungal therapy (eg, with azole, echinocandin, or polyene drug) is added empirically if unexplained fever persists after 4 days of broad-spectrum antibiotic therapy. If fever persists after 3 wk of empiric therapy (including 2 wk of antifungal therapy) and the neutropenia has resolved, then stopping all antimicrobials is considered and the cause of fever reevaluated.

**Antibiotic prophylaxis** in afebrile neutropenic patients remains controversial. Trimethoprim/sulfamethoxazole (TMP/SMX) prevents *Pneumocystis jirovecii* pneumonia in neutropenic and nonneutropenic patients with associated impaired cell-mediated immunity. Also, TMP/SMX may prevent bacterial infections in patients expected to be profoundly neutropenic for > 1 wk. The disadvantages of TMP/SMX prophylaxis include adverse effects, potential myelosuppression, and development of resistant bacteria and oral candidiasis. Antifungal prophylaxis is not routinely recommended for neutropenic patients, but patients at high risk of developing fungal infections (eg, after bone marrow transplantation and after receiving high doses of corticosteroids) may benefit.

**Myeloid growth factors** (granulocyte-macrophage colony-stimulating factor [GM-CSF] and granulocyte colony-stimulating factor [G-CSF]) are now widely used to increase the neutrophil count and to prevent infections in patients with severe neutropenia (eg, after bone marrow transplantation and intensive cancer chemotherapy). They are expensive. However, if the risk of febrile neutropenia is ≥ 30% (as assessed by neutrophil count < 500 μL, presence of infection during a previous cycle of chemotherapy, associated comorbid disease, or age > 75), growth factors are indicated. In general, most clinical benefit occurs when the growth factor is administered beginning about 24 h after completion of chemotherapy. Patients with neutropenia caused by an idiosyncratic drug reaction may also benefit from myeloid growth factors, particularly if a delayed recovery is anticipated. The dose for G-CSF is 5 μg/kg sc once/day; for GM-CSF, 250 μg/m² sc once/day.

Glucocorticoids, anabolic steroids, and vitamins do not stimulate neutrophil production but can affect distribution and destruction. If acute neutropenia is suspected to be drug or toxin induced, all potentially etiologic agents are stopped. If neutropenia develops during treatment with a drug known to induce low counts (eg, chloramphenicol), then switching to an alternative antibiotic may be helpful.

Saline or hydrogen peroxide gargles every few hours, anesthetic lozenges (benzocaine 15 mg q 3 or 4 h), or chlorhexidine mouth rinses (1% solution) bid or tid may relieve the discomfort of stomatitis with oropharyngeal ulcerations. Oral or esophageal candidiasis is treated with nystatin (400,000 to 600,000 units oral rinse qid; swallowed if esophagitis is present) or with systemic antifungal drugs (eg,
fluconazole). A semisolid or liquid diet may be necessary during acute stomatitis or esophagitis to minimize discomfort.

**Chronic neutropenia:** Neutrophil production in congenital, cyclic, and idiopathic neutropenia can be increased with administration of G-CSF 1 to 10 μg/kg sc once/day. Effectiveness can be maintained with daily or intermittent G-CSF for months or years. Long-term G-CSF has also been used in other patients with chronic neutropenia, including those with myelodysplasia, HIV, and autoimmune disorders. In general, neutrophil counts increase, although clinical benefits are less clear, especially for patients who do not have severe neutropenia. For patients with autoimmune disorders or who have had an organ transplant, cyclosporine can also be beneficial.

In some patients with accelerated neutrophil destruction caused by autoimmune disorders, corticosteroids (generally, prednisone 0.5 to 1.0 mg/kg po once/day) increase blood neutrophils. This increase often can be maintained with alternate-day G-CSF therapy.

Splenectomy increases the neutrophil count in some patients with splenomegaly and splenic sequestration of neutrophils (eg, Felty's syndrome, hairy cell leukemia). However, splenectomy should be reserved for patients with severe neutropenia (ie, < 500/μL) and serious problems with infections in whom other treatments have failed. Patients should be vaccinated against infections caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* before and after splenectomy because splenectomy predisposes patients to infection by encapsulated organisms.

**Lymphocytopenia**

Lymphocytopenia is a total lymphocyte count of < 1000/μL in adults or < 3000/μL in children < 2 yr. Sequelae include opportunistic infections and an increased risk of malignant and autoimmune disorders. If the CBC reveals lymphocytopenia, testing for immunodeficiency and analysis of lymphocyte subpopulations should follow. Treatment is directed at the underlying disorder.

The normal lymphocyte count in adults is 1000 to 4800/μL; in children < 2 yr, 3000 to 9500/μL. At age 6 yr, the lower limit of normal is 1500/μL. Both B and T cells are present in the peripheral blood; about 75% of the lymphocytes are T cells and 25% B cells. Because lymphocytes account for only 20 to 40% of the total WBC count, lymphocytopenia may go unnoticed when WBC count is checked without a differential.

Almost 65% of blood T cells are CD4+ (helper) T cells. Most patients with lymphocytopenia have a reduced absolute number of T cells, particularly in the number of CD4+ T cells. The average number of CD4+ T cells in adult blood is 1100/μL (range, 300 to 1300/μL), and the average number of cells of the other major T-cell subgroup, CD8+ (suppressor) T cells, is 600/μL (range, 100 to 900/μL).

**Etiology**

Lymphocytopenia can be acquired or inherited.

**Acquired lymphocytopenia** can occur with a number of other disorders (see Table 107-2). The most common causes include

- Protein-energy undernutrition
- AIDS

Protein-energy undernutrition is the most common cause worldwide. AIDS is the most common infectious disease causing lymphocytopenia, which arises from destruction of CD4+ T cells infected with HIV. Lymphocytopenia may also reflect impaired lymphocyte production arising from destruction of thymic or lymphoid architecture. In acute viremia due to HIV or other viruses, lymphocytes may undergo accelerated destruction from active infections with the virus, may be trapped in the spleen or lymph nodes, or may migrate to the respiratory tract.
Inherited lymphocytopenia (see Table 107-2) most commonly results from

- Severe combined immunodeficiency disorder
- Wiskott-Aldrich syndrome

It may occur with inherited immunodeficiency disorders (see Ch. 126) and disorders that involve impaired lymphocyte production. Other inherited disorders, such as Wiskott-Aldrich syndrome, adenosine deaminase deficiency, and purine nucleoside phosphorylase deficiency, may involve accelerated T-cell destruction. In many disorders, antibody production is also deficient.

Iatrogenic lymphocytopenia is caused by cytotoxic chemotherapy, radiation therapy, or the administration of antilymphocyte globulin (or other lymphocyte antibodies). Long-term treatment for psoriasis using psoralen and ultraviolet irradiation may destroy T cells. Glucocorticoids can induce lymphocyte destruction.

Lymphocytopenia may occur with autoimmune diseases such as SLE, RA, myasthenia gravis, and protein-losing enteropathy.

Symptoms and Signs

Lymphocytopenia per se generally causes no symptoms. However, findings of an associated disorder may include absent or diminished

Table 107-2. Causes of Lymphocytopenia

- Tonsils or lymph nodes, indicative of cellular immunodeficiency; skin abnormalities, such as alopecia, eczema, pyoderma, or telangiectasia; evidence of hematologic disease, such as pallor, petechiae, jaundice, or mouth ulcers; and generalized lymphadenopathy and splenomegaly, which may suggest HIV infection.

Lymphocytopenic patients experience recurrent infections or develop infections with unusual organisms. Pneumocystis jirovecii, cytomegalovirus, rubeola, and varicella pneumonias often are fatal. Lymphocytopenia is also a risk factor for cancer and for autoimmune disorders.

Diagnosis

- Clinical suspicion (repeated or unusual infections)
- CBC with differential
- Measurement of lymphocyte subpopulations and immunoglobulin levels

Lymphocytopenia is suspected in patients with recurrent viral, fungal, or parasitic infections but is usually detected incidentally on a CBC. P. jirovecii, cytomegalovirus, rubeola, or varicella pneumonias with lymphocytopenia suggest immunodeficiency. Lymphocyte subpopulations are measured in lymphocytopenic patients. Measurements of immunoglobulin levels should also be done to evaluate antibody production. Patients with a history of recurrent infections undergo complete laboratory evaluation for immunodeficiency (see p. 1095), even if initial screening tests are normal.

Treatment

- Treatment of underlying disorder
- Sometimes IV immune globulin
- Possibly stem cell transplantation
Lymphocytopenia usually remits with removal of the underlying factor or successful treatment of the underlying disorder in the acquired lymphocytopenias. Intravenous immune globulin is indicated if patients have chronic IgG deficiency, lymphocytopenia, and recurrent infections. Hematopoietic stem cell transplantation can be considered for all patients with congenital immunodeficiencies and may be curative (see p. 1132).
Chapter 108. Thrombocytopenia and Platelet Dysfunction

Introduction

Platelets are cell fragments that function in the clotting system. Thrombopoietin, primarily produced in the liver in response to decreased numbers of bone marrow megakaryocytes and circulating platelets, stimulates the bone marrow to synthesize platelets from megakaryocytes. Platelets circulate for 7 to 10 days. About one third are always transiently sequestered in the spleen. The platelet count is normally 140,000 to 440,000/μL. However, the count can vary slightly according to menstrual cycle phase, decrease during near-term pregnancy (gestational thrombocytopenia), and increase in response to inflammatory cytokines (secondary, or reactive, thrombocytosis). Platelets are eventually destroyed, primarily by the spleen.

Platelet disorders include

• An abnormal increase in platelets (thrombocythemia, a myeloproliferative disorder—see p. 997)
• A decrease in platelets (thrombocytopenia)
• Platelet dysfunction

Any of these conditions, even those in which platelets are increased, may cause defective formation of hemostatic plugs and bleeding.

The risk of bleeding is inversely proportional to the platelet count. When the platelet count is < 50,000/μL, minor bleeding occurs easily and the risk of major bleeding increases. Counts between 20,000 and 50,000/μL predispose to bleeding with trauma, even minor trauma; with counts < 20,000/μL, spontaneous bleeding may occur; with counts < 5000/μL, severe spontaneous bleeding is more likely. However, patients with counts < 10,000/μL may be asymptomatic for years.

Etiology

Thrombocytopenia: Causes of thrombocytopenia can be classified by mechanism (see Table 108-1) and include failed platelet production, increased splenic sequestration of platelets with normal platelet survival, increased platelet destruction or consumption (both immunologic and nonimmunologic causes), dilution of platelets, and a combination of these mechanisms.

[Table 108-1. Classification of Thrombocytopenia]

Increased splenic sequestration is suggested by splenomegaly.

A large number of drugs may cause thrombocytopenia (see p. 960), typically by triggering immunologic destruction.

Overall, the most common specific causes of thrombocytopenia include

• Gestational thrombocytopenia
• Drug-induced thrombocytopenia due to immune-mediated platelet destruction (commonly quinine, trimethoprim/sulfamethoxazole)
• Drug-induced thrombocytopenia due to dose-dependent bone marrow suppression (by chemotherapeutic agents)
• Thrombocytopenia accompanying systemic infection
• Immune thrombocytopenic purpura (ITP)
Platelet dysfunction: Platelet dysfunction may stem from an intrinsic platelet defect or from an extrinsic factor that alters the function of normal platelets. Dysfunction may be hereditary or acquired. Hereditary disorders of platelet function consist of von Willebrand's disease, the most common hereditary hemorrhagic disease, and hereditary intrinsic platelet disorders (see p. 957), which are much less common. Acquired disorders of platelet function (see p. 957) are commonly due to diseases as well as to aspirin and other drugs.

Symptoms and Signs

Platelet disorders result in a typical pattern of bleeding:

- Multiple petechiae in the skin (typically most evident on the lower legs)
- Scattered small ecchymoses at sites of minor trauma
- Mucosal bleeding (epistaxis, bleeding in the GI and GU tracts, vaginal bleeding)
- Excessive bleeding after surgery

Heavy GI bleeding and bleeding into the CNS may be life threatening. However, bleeding into tissues (eg, deep visceral hematomas or hemarthroses) does not occur with thrombocytopenia, which causes immediate, superficial bleeding; tissue bleeding (often delayed for up to a day after trauma) suggests a coagulation disorder (eg, hemophilia).

Diagnosis

- Clinical presentation of petechiae and mucosal bleeding
- CBC with platelets, coagulation studies, peripheral blood smear
- Sometimes bone marrow aspiration
- Sometimes von Willebrand's antigen and factor activity studies

Platelet disorders are suspected in patients with petechiae and mucosal bleeding. A CBC with platelet count, coagulation studies, and a peripheral blood smear are obtained. Excessive platelets and thrombocytopenia are diagnosed from the platelet count; coagulation studies are normal unless there is a simultaneous coagulopathy. In patients with a normal CBC, platelet count, and INR and normal or only slightly prolonged PTT, platelet dysfunction is suspected.

Thrombocytopenia: In patients with thrombocytopenia, the peripheral smear may suggest the cause (see Table 108-2). If the smear shows abnormalities other than thrombocytopenia, such as nucleated RBCs or abnormal or immature WBCs, bone marrow aspiration is indicated. Bone marrow aspiration reveals the number and appearance of megakaryocytes and is the definitive test for many disorders causing marrow failure. However, normal number and appearance of megakaryocytes does not always indicate normal platelet production. For example, in patients with immune thrombocytopenic purpura, platelet production is frequently decreased, or not appropriately increased, despite the normal appearance of megakaryocytes. If the bone marrow is normal but the spleen is enlarged, increased splenic sequestration is the likely cause of thrombocytopenia; if the bone marrow is normal and the spleen is not enlarged, excess platelet destruction is the likely cause. Measurement of antiplatelet antibodies is not clinically useful. HIV testing is done in patients at risk of HIV infection.

Suspected platelet dysfunction: In patients with platelet dysfunction, a drug cause is suspected if symptoms began only after patients started taking a potentially causative drug. A hereditary cause is suspected if there is a lifelong history of easy bruising and bleeding after tooth extractions or surgery. In the case of a suspected hereditary cause, von Willebrand's antigen and factor activity studies are obtained. Platelet dysfunction caused by systemic disorders is typically mild and of minor clinical
importance. In these patients, the causative systemic disorder is the clinical concern, and hematologic tests are unnecessary.

(Table 108-2: Peripheral Blood Findings in Thrombocytopenic Disorders)

**Treatment**

- Avoidance of drugs that impair platelet function
- Rarely platelet transfusions

In patients with thrombocytopenia or platelet dysfunction, drugs that further impair platelet function, particularly aspirin and other NSAIDs, should not be given. Patients who are already taking such drugs should consider alternative drugs, such as acetaminophen, or simply stop using them.

Patients may require platelet transfusion, but transfusions are given only in limited situations (see p. 1039). Prophylactic transfusions are used sparingly because they may lose their effectiveness with repeated use due to the development of platelet alloantibodies. In platelet dysfunction or thrombocytopenia caused by decreased production, transfusions are reserved for patients with active bleeding or severe thrombocytopenia (eg, platelet count < 10,000/μL). In thrombocytopenia caused by platelet destruction, transfusions are reserved for life-threatening or CNS bleeding.

**Acquired Platelet Dysfunction**

Acquired platelet dysfunction, which is common, may result from aspirin, other NSAIDs, or systemic disorders.

Acquired abnormalities of platelet function are very common. Causes include

- Drugs
- Systemic disorders
- Cardiopulmonary bypass

Acquired platelet dysfunction is suspected and diagnosed when an isolated prolongation of bleeding time is observed and other possible diagnoses have been eliminated. Platelet aggregation studies are unnecessary.

**Drugs:** Aspirin and other NSAIDs, which are very commonly used drugs, may induce platelet dysfunction. Sometimes this effect is incidental (eg, when the drugs are used to relieve pain and inflammation) and sometimes therapeutic (eg, when aspirin is used for prevention of stroke or coronary thrombosis). Other therapeutic antiplatelet drugs include clopidogrel, ticlopidine, and the glycoprotein IIb/IIIa inhibitors.

Aspirin and NSAIDs prevent cyclooxygenase-mediated production of thromboxane A2. This effect can last 5 to 7 days. Aspirin modestly prolongs bleeding time in healthy people but may markedly prolong bleeding time in patients with underlying platelet dysfunction or a severe coagulation disturbance (eg, patients receiving heparin, patients with severe hemophilia).

**Systemic disorders:** Many disorders (eg, myeloproliferative and myelodysplastic disorders, uremia, macroglobulinemia and multiple myeloma, cirrhosis, SLE) can impair platelet function.

Uremia may prolong bleeding via unknown mechanisms. If bleeding is observed clinically, bleeding time may be corrected transiently with vigorous dialysis, cryoprecipitate administration, or desmopressin infusion. If indicated for treatment of anemia, RBC count can be increased by transfusion or by giving erythropoietin; this process also shortens the bleeding time.

**Cardiopulmonary bypass:** Platelets may become dysfunctional, prolonging the bleeding time as blood
circulates through a pump oxygenator during cardiopulmonary bypass. The mechanism appears to be activation of fibrinolysis on the platelet surface with resultant loss of the glycoprotein Ib-IX binding site for von Willebrand's factor. Regardless of platelet count, patients who bleed excessively after cardiopulmonary bypass and who have a long bleeding time are transfused with platelets. Giving aprotinin (a protease inhibitor that neutralizes plasmin activity) during bypass may preserve platelet function, prevent prolongation of bleeding time, and reduce the need for transfusion.

**Hereditary Intrinsic Platelet Disorders**

Hereditary intrinsic platelet disorders are rare and produce lifelong bleeding tendencies. Diagnosis is confirmed by platelet aggregation tests. Platelet transfusion is necessary to control serious bleeding.

Normal hemostasis requires platelet adhesion and activation.

**Adhesion** (ie, of platelets to exposed vascular subendothelium) requires von Willebrand's factor (VWF) and the platelet glycoprotein Ib-IX complex.

**Activation** promotes platelet aggregation and fibrinogen binding and requires the platelet glycoprotein Ib-IIa complex. Activation involves release of adenosine diphosphate (ADP) from platelet storage granules and conversion of arachidonic acid to thromboxane A$_2$ via a cyclooxygenase-mediated reaction.

Hereditary intrinsic platelet disorders can involve defects in any of these substrates and steps. These disorders are suspected in patients with lifelong bleeding disorders who have normal platelet counts and coagulation study results. Diagnosis usually is based on platelet aggregation tests; however, platelet aggregation tests are not quantitative, and interpretation of results is often inconclusive (see Table 108-3).

**Disorders of adhesion:** Bernard-Soulier syndrome is a rare autosomal recessive disorder. It impairs platelet adhesion via a defect in the glycoprotein Ib-IX complex. Bleeding may be severe. Platelets are unusually large. They do not aggregate with ristocetin but aggregate normally with ADP, collagen, and epinephrine.

Large platelets associated with functional abnormalities also occur in the May-Hegglin anomaly, a thrombocytopenic disorder with abnormal WBCs, and in the Chediak-Higashi syndrome (see p. 1101). Platelet transfusion is necessary to control serious bleeding.

**Disorders of activation:** Disorders of amplification of platelet activation are the most common hereditary intrinsic platelet disorders and produce mild bleeding. They may result from decreased ADP in the platelet granules (storage pool deficiency), from an inability to generate thromboxane A$_2$ from arachidonic acid, or from an inability of platelets to aggregate in response to thromboxane A$_2$. Platelet aggregation tests reveal impaired aggregation after exposure to collagen, epinephrine, and low levels of ADP and normal aggregation after exposure to high levels of ADP. The same pattern can result from use of NSAIDs or aspirin, the effect of which can persist for several days. Therefore, platelet aggregation tests should not be done in patients who have recently taken these drugs.

Thrombasthenia (Glanzmann disease) is a rare autosomal recessive disorder causing a defect in the platelet glycoprotein Ib-IIa complex; platelets cannot aggregate. Patients may experience severe mucosal bleeding (eg, nosebleeds that stop only after nasal packing and transfusions of platelet concentrates). The diagnosis is suggested by a finding of single platelets without aggregates on a peripheral blood smear obtained from a finger stick. It is confirmed by the finding that platelets fail to aggregate with epinephrine, collagen, or even high levels of ADP but do aggregate transiently with ristocetin. Platelet transfusion is necessary to control serious bleeding.

**Immune Thrombocytopenic Purpura**
Immune thrombocytopenic purpura (ITP) is a bleeding disorder caused by thrombocytopenia not associated with a systemic disease. Typically, it is chronic in adults but is usually acute and self-limited in children. Spleen size is normal. Diagnosis requires that other disorders be excluded through selective tests. Treatment includes corticosteroids, splenectomy, and immunosuppressants and thrombopoietic-mimetic drugs. For life-threatening bleeding, platelet transfusions, IV corticosteroids, and IV immune globulin are required.

ITP usually results from development of an autoantibody directed against a structural platelet antigen. In childhood ITP, the autoantibody may be triggered by binding of viral antigen to megakaryocytes.

Symptoms and Signs

The symptoms and signs are petechiae, purpura, and mucosal bleeding. Gross GI bleeding and hematuria are uncommon. The spleen is of normal size unless it is enlarged by a coexisting childhood viral infection.

Diagnosis

- CBC with platelets, peripheral blood smear
- Sometimes bone marrow aspiration
- Exclusion of other thrombocytopenic disorders

ITP is suspected in patients with isolated thrombocytopenia (ie, otherwise normal CBC and peripheral blood smear). Because manifestations of ITP are nonspecific, other causes of isolated thrombocytopenia (eg, drugs, alcohol, lymphoproliferative disorders, systemic illness) need to be excluded by clinical evaluation and appropriate testing. Typically, patients have coagulation studies, liver function tests (including testing for hepatitis C), and, because HIV-associated thrombocytopenia may be otherwise indistinguishable from ITP, HIV testing. Testing for antiplatelet antibodies does not aid diagnosis or treatment.

Bone marrow examination is not required to make the diagnosis but is done if blood counts or blood smear reveals abnormalities in addition to thrombocytopenia, when clinical features are not typical, and in patients > 60 yr (because myelodysplasia is more common in older patients). In patients with ITP, bone marrow examination reveals normal or possibly increased numbers of megakaryocytes in an otherwise normal bone marrow sample.

Prognosis

Children typically recover spontaneously, even from severe thrombocytopenia, in several weeks to months.

In adults, spontaneous remission is rare. However, some have mild and stable disease (ie, platelet counts > 30,000/μL); such cases may be more common than previously thought, many being discovered by the automated platelet counting now routinely done with CBC. Others have significant, symptomatic thrombocytopenia, although life-threatening bleeding and death are rare.

Treatment

- Oral corticosteroids
- Splenectomy
• Rituximab

• Sometimes thrombopoietic-mimetic drugs

• Sometimes other immunosuppressants

• For severe bleeding, IV immune globulin, IV corticosteroids, or platelet transfusions

Adults usually are given an oral corticosteroid (eg, prednisone 1 mg/kg once/day) initially. In patients who respond, the platelet count rises to normal within 2 to 6 wk. The corticosteroid dosage is then tapered. An alternative corticosteroid regimen is dexamethasone 40 mg po once/day for 4 days. However, most patients do not respond adequately or relapse as the corticosteroid is tapered. Splenectomy can achieve a complete remission in about two thirds of these patients but is usually reserved for those with severe thrombocytopenia, bleeding, or both; it may not be appropriate for those with mild disease. Rituximab (375 mg/m\(^2\) IV once/wk for 4 wk) may be used in patients who do not respond to splenectomy or in patients who are not candidates for splenectomy.

Because other treatments may not be effective for patients with ITP refractory to corticosteroids and splenectomy and because ITP often has a benign natural history, additional treatments may not be indicated unless the platelet count is < 10,000 to 20,000/μL and active bleeding is present. In these patients, thrombopoietin-mimetic drugs, such as romiplostim 1 to 5 μg/kg sc once/wk and eltrombopag 50 to 75 mg po once/day, may be used.

About 75 to 80% of patients respond to thrombopoietin-mimetic drugs even after failure of multiple previous treatments. However, these drugs are used for maintenance therapy rather than induction of remission and need to be administered continuously to maintain the platelet count > 50,000/μL. More intensive immunosuppression may be required with drugs such as cyclophosphamide and azathioprine in patients unresponsive to other drugs who have severe, symptomatic thrombocytopenia.

Treatment of children is usually supportive, because most children spontaneously recover. Even after months or years of thrombocytopenia, most children have spontaneous remissions. If mucosal bleeding occurs, corticosteroids or IV immune globulin is given. Initial use of corticosteroids and IV immune globulin is controversial, because they increase platelet count but may not improve clinical outcome. Splenectomy is rarely done in children. However, if thrombocytopenia is severe and symptomatic for > 6 mo, then splenectomy is effective.

In children or adults with ITP and life-threatening bleeding, rapid phagocytic blockade is attempted by giving IV immune globulin 1 g/kg once/day for 1 to 2 days. This treatment usually causes the platelet count to rise within 2 to 4 days, but the count remains high only for 2 to 4 wk. High-dose methylprednisolone (1 g IV once/day for 3 days) is less expensive than IV immune globulin and is easier to administer but may not be as effective. Patients with ITP and life-threatening bleeding are also given platelet transfusions. Platelet transfusions are not used prophylactically.

Oral corticosteroids or IV immune globulin may also be given when a transient increase of the platelet count is required for tooth extractions, childbirth, surgery, or other invasive procedures.

**Thrombocytopenia Due to Splenic Sequestration**

Increased splenic platelet sequestration can occur in various disorders that cause splenomegaly. Sequestration is expected in patients with congestive splenomegaly caused by advanced cirrhosis. The platelet count usually is > 30,000/μL unless the disorder causing the splenomegaly also impairs platelet production (eg, in myelofibrosis with myeloid metaplasia). Platelets are released from the spleen by epinephrine and therefore may be available at a time of stress. Therefore, thrombocytopenia caused only by splenic sequestration does not cause bleeding. Splenectomy corrects the thrombocytopenia but is not indicated unless severe thrombocytopenia from simultaneous marrow failure is present.

**Thrombocytopenia: Other Causes**
Platelet destruction can develop because of immunologic causes (HIV infection, drugs, connective tissue or lymphoproliferative disorders, blood transfusions) or nonimmunologic causes (sepsis, acute respiratory distress syndrome). Manifestations are petechiae, purpura, and mucosal bleeding. Laboratory findings depend on the cause. The history may be the only suggestion of the diagnosis. Treatment is correction of the underlying disorder.

**Acute respiratory distress syndrome:** Patients with acute respiratory distress syndrome may develop nonimmunologic thrombocytopenia, possibly secondary to deposition of platelets in the pulmonary capillary bed.

**Blood transfusions:** Posttransfusion purpura causes immunologic platelet destruction indistinguishable from immune thrombocytopenic purpura (ITP), except for a history of a blood transfusion within the preceding 7 to 10 days. The patient, usually a woman, lacks a platelet antigen (PLA-1) present in most people. Transfusion with PLA-1-positive platelets stimulates formation of anti-PLA-1 antibodies, which (by an unknown mechanism) can react with the patient's PLA-1-negative platelets. Severe thrombocytopenia results, taking 2 to 6 wk to subside.

**Connective tissue and lymphoproliferative disorders:** Connective tissue (eg, SLE) or lymphoproliferative disorders can cause immunologic thrombocytopenia. Corticosteroids and splenectomy are often effective.

**Drug-induced immunologic destruction:** Commonly used drugs that occasionally induce thrombocytopenia include

- Quinine
- Trimethoprim/sulfamethoxazole
- Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)
- Hydrochlorothiazide
- Carbamazepine
- Acetaminophen
- Chlorpropamide
- Ranitidine
- Rifampin
- Vancomycin

Drug-induced thrombocytopenia occurs typically by causing an immune reaction in which drug bound to the platelet creates a new and "foreign" antigen. This disorder is indistinguishable from ITP except for the history of drug ingestion. When the drug is stopped, the platelet count typically begins to increase within 1 to 2 days and recovers to normal within 7 days.

Up to 5% of patients receiving unfractionated heparin develop thrombocytopenia, which may occur even with very-low-dose heparin (eg, used in flushes to keep IV or arterial lines open). The mechanism is usually immunologic. Bleeding can occur, but more commonly platelets clump excessively, causing vessel obstruction, leading to paradoxical arterial and venous thromboses, which may be life threatening (eg, thromboembolic occlusion of limb arteries, stroke, acute MI). Heparin should be stopped in any patient who becomes thrombocytopenic or whose platelet count decreases by more than 50%. Because 5 days of heparin is sufficient to treat venous thrombosis and because most patients begin oral anticoagulants simultaneously with heparin, stopping heparin is usually safe. Low mol wt heparin (LMWH) may be less...
immunogenic than unfractionated heparin. However, LMWH is not useful if heparin-induced thrombocytopenia has already developed, because most antibodies cross-react with LMWH.

**Infections:** HIV infection may cause immunologic thrombocytopenia indistinguishable from ITP except for the association with HIV. The platelet count may increase with glucocorticoids, which are often withheld unless the platelet count falls to < 20,000/μL, because these drugs may further depress immune function. The platelet count also usually increases after treatment with antiviral drugs.

**Other infections** such as systemic viral infections (eg, Epstein-Barr virus, cytomegalovirus), rickettsial infections (eg, Rocky Mountain spotted fever), and bacterial sepsis are typically associated with thrombocytopenia.

**Pregnancy:** Mild thrombocytopenia, typically asymptomatic, occurs late in gestation in about 5% of normal pregnancies (gestational thrombocytopenia); it is usually mild (platelet counts < 70,000/μL are rare), requires no treatment, and resolves after delivery. However, severe thrombocytopenia may develop in pregnant women with preeclampsia and the HELLP syndrome (hemolysis, elevated liver function tests, and low platelets—see p. 2670); such women typically require immediate delivery, and platelet transfusion is considered if platelet count is < 20,000/μL (or < 50,000/L if delivery is to be cesarean).

**Sepsis:** Sepsis often causes nonimmunologic thrombocytopenia that parallels the severity of the infection. The thrombocytopenia has multiple causes: disseminated intravascular coagulation, formation of immune complexes that can associate with platelets, activation of complement, and deposition of platelets on damaged endothelial surfaces.

**Thrombotic Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome**

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are acute, fulminant disorders characterized by thrombocytopenia and microangiopathic hemolytic anemia. Other manifestations may include alterations in level of consciousness and renal failure. Diagnosis requires demonstrating characteristic laboratory test abnormalities, including Coombs'-negative hemolytic anemia. Treatment is plasma exchange and corticosteroids in adults and supportive care (sometimes including hemodialysis) in children.

**Pathophysiology**

TTP and HUS involve nonimmunologic platelet destruction. Loose strands of von Willebrand's factor (VWF) or fibrin are deposited in multiple small vessels and damage passing platelets and RBCs, causing significant thrombocytopenia and anemia. Platelets are also destroyed within multiple small thrombi. Multiple organs develop bland platelet-VWF thrombi (without the vessel wall granulocytic infiltration characteristic of vasculitis) localized primarily to arteriocapillary junctions, described as thrombotic microangiopathy. The brain, heart, and kidneys are particularly likely to be affected.

TTP and HUS differ mainly in the relative degree of renal failure. Typically, disorders in adults are described as TTP and are less likely to involve renal failure. HUS is used to describe the disorder in children, which typically involves renal failure.

**Etiology**

**Children:** Most cases follow acute hemorrhagic colitis resulting from Shiga toxin-producing bacteria (eg, *Escherichia coli* O157:H7, some strains of *Shigella dysenteriae*).

**Adults:** Many cases are idiopathic. Known causes and associations include

- **Drugs:** Quinine (most common), immunosuppressants, and cancer chemotherapy drugs (eg, cyclosporine, mitomycin C)

- **Pregnancy:** (often indistinguishable from severe preeclampsia or eclampsia)
Rarely, hemorrhagic colitis due to *Escherichia coli* O157:H7

A predisposing factor in many patients is congenital or acquired deficiency of the plasma enzyme ADAMTS13, which cleaves VWF and thus eliminates abnormally large VWF multimers that can cause platelet thrombi.

**Symptoms and Signs**

Manifestations of ischemia develop with varying severity in multiple organs. These manifestations include weakness, confusion and coma, abdominal pain, nausea, vomiting, diarrhea, and arrhythmias caused by myocardial damage. Children usually have a prodrome of vomiting, abdominal pain, and diarrhea (frequently bloody). Fever may occur, but high fever with chills does not occur in TTP or HUS and suggests sepsis. The clinical syndromes of TTP and HUS are indistinguishable, except that neurologic symptoms are less common with HUS.

**Diagnosis**

- CBC with platelets, peripheral blood smear, Coombs’ test
- Exclusion of other thrombocytopenic disorders

TTP-HUS is suspected in patients with suggestive symptoms, thrombocytopenia, and anemia. If the disorder is suspected, urinalysis, peripheral blood smear, reticulocyte count, serum LDH, renal function tests, serum bilirubin (direct and indirect), and Coombs’ test are done. The diagnosis is suggested by:

- Thrombocytopenia and anemia
- Fragmented RBCs on the blood smear (helmet cells, triangular RBCs, distorted-appearing RBCs; these changes describe microangiopathic hemolysis)
- Evidence of hemolysis (falling Hb level, polychromasia, elevated reticulocyte count, elevated serum LDH)
- Negative direct antiglobulin (Coombs’) test

Otherwise unexplained thrombocytopenia and microangiopathic hemolytic anemia are sufficient evidence for a presumptive diagnosis.

**Causes:** Although causes (eg, quinine sensitivity) or associations (eg, pregnancy) are clear in some patients, in most patients TTP-HUS appears suddenly and spontaneously without apparent cause. TTP-HUS is often indistinguishable, even with renal biopsy, from syndromes that cause identical thrombotic microangiopathies (eg, preeclampsia, systemic sclerosis, accelerated hypertension, acute renal allograft rejection).

Testing for ADAMTS13 activity is appropriate in patients with suspected TTP-HUS, except in children who have typical diarrhea-associated HUS. Although the results of ADAMTS13 testing do not affect initial treatment, results are important prognostically.

Stool testing (specific culture for *E. coli* O157:H7 or Shiga toxin assay) is done in children with diarrhea and also adults who had a prodrome of bloody diarrhea; however, the organism and toxin may have cleared by the time of presentation.

**Treatment**

- Plasma exchange and corticosteroids in adults

Typical diarrhea-associated HUS in children caused by enterohemorrhagic infection usually spontaneously remits and is treated with supportive care and not plasma exchange; over half of patients
require renal dialysis. In other cases, untreated TTP-HUS is almost always fatal. With plasma exchange, however, > 85% of patients recover completely.

Plasma exchange is continued daily until evidence of disease activity has subsided, as indicated by a normal platelet count, which may be several days to many weeks. Adults with TTP are also given corticosteroids. In patients with recurrence when plasma exchange is stopped or in patients with relapses, more intensive immunosuppression with rituximab may be effective. Most patients experience only a single episode of TTP-HUS. However, relapses occur in about 40% of patients who have a severe deficiency of ADAMTS13 activity caused by an autoantibody inhibitor. Patients must be evaluated quickly if symptoms suggestive of a relapse develop.

Von Willebrand’s Disease

Von Willebrand’s disease (VWD) is a hereditary deficiency of von Willebrand’s factor (VWF), which causes platelet dysfunction. Bleeding tendency is usually mild. Screening tests show a normal platelet count and, possibly, a slightly prolonged PTT. Diagnosis is based on low levels of VWF antigen and abnormal ristocetin cofactor activity. Treatment involves control of bleeding with replacement therapy (cryoprecipitate or pasteurized intermediate-purity factor VIII concentrate) or desmopressin.

VWF is synthesized and secreted by vascular endothelium to form part of the perivascular matrix. VWF promotes the platelet adhesion phase of hemostasis by binding with a receptor on the platelet surface membrane (glycoprotein Ib/IX), which connects the platelets to the vessel wall. VWF is also required to maintain normal plasma factor VIII levels. Levels of VWF can temporarily increase in response to stress, exercise, pregnancy, inflammation, or infection.

VWD is classified into 3 types:

• Type 1: a quantitative deficiency of VWF, which is the most common form and is an autosomal dominant disorder

• Type 2: a qualitative impairment in synthesis of VWF that can result from various genetic abnormalities and is an autosomal dominant disorder

• Type 3: a rare autosomal recessive disorder in which homozygotes have no detectable VWF

Although VWD, like hemophilia A, is a hereditary disorder that may, when severe, cause factor VIII deficiency, the deficiency is usually only moderate.

Symptoms and Signs

Bleeding manifestations are mild to moderate and include easy bruising, mucosal bleeding, bleeding from small skin cuts that may stop and start over hours, sometimes increased menstrual bleeding, and abnormal bleeding after surgical procedures (eg, tooth extraction, tonsillectomy). Platelets function well enough that petechiae and purpura do not occur.

Diagnosis

• Total plasma VWF antigen, VWF function, and plasma factor VIII level

VWD is suspected in patients with bleeding disorders, particularly those with a family history of the disorder. Screening coagulation tests reveal a normal platelet count, normal INR, and sometimes a slightly prolonged PTT. Bleeding time may be prolonged, but this test has poor reproducibility and is of limited value. Diagnosis requires measuring total plasma VWF antigen, VWF function as determined by the ability of plasma to support agglutination of normal platelets by ristocetin (ristocetin cofactor activity), and plasma factor VIII level. Stimuli that temporarily increase VWF levels can cause false-negative results in mild VWD; tests may need to be repeated.
In the common (type 1) form of VWD, results are concordant; i.e., VWF antigen, VWF function, and plasma factor VIII level are equally depressed. The degree of depression varies from about 15 to 60% of normal and determines the severity of a patient's abnormal bleeding. Levels of VWF antigen can also be as low as 40% of normal in healthy people with type O blood.

Type 2 variants are suspected if tests are discordant, i.e., VWF antigen is higher than expected for the degree of abnormality in ristocetin cofactor activity. (VWF antigen is higher than expected because the VWF defect in type 2 is qualitative, not quantitative.) Diagnosis is confirmed by demonstrating a reduced concentration of large VWF multimers on agarose gel electrophoresis. Four different type 2 variants are recognized, distinguished by different functional abnormalities of the VWF molecule.

Patients with type 3 VWD have no detectable VWF and a marked deficiency of factor VIII.

Treatment

- VWF replacement when necessary

Patients are treated only if they are actively bleeding or are undergoing an invasive procedure (e.g., surgery, dental extraction). Treatment involves replacement of VWF by infusion of pasteurized intermediate-purity factor VIII concentrates, which contain components of VWF. These concentrates are virally inactivated and therefore do not transmit HIV infection or hepatitis. Because they do not cause transfusion-transmitted infections, these concentrates are preferred to the previously used cryoprecipitate. High-purity factor VIII concentrates are prepared by immunoaffinity chromatography and contain no VWF.

Desmopressin is an analog of antidiuretic hormone (vasopressin) that stimulates release of VWF into the plasma and may increase levels of factor VIII. Desmopressin can be helpful for type 1 VWD but is usually of no value in other types and may even be harmful in some. To ensure adequate response to the drug, physicians give patients a test dose and measure the response of VWF antigen. Desmopressin 0.3 μg/kg given in 50 mL of 0.9% saline solution IV over 15 to 30 min may enable patients to undergo minor procedures (e.g., tooth extraction, minor surgery) without needing replacement therapy. If a replacement product is needed, desmopressin may reduce the required dose. One dose of desmopressin is effective for about 8 to 10 h. About 48 h must elapse for new stores of VWF to accumulate, permitting a 2nd injection of desmopressin to be as effective as the initial dose.
Chapter 109. Hemostasis

**Introduction**

Hemostasis, the arrest of bleeding from an injured blood vessel, requires the combined activity of vascular, platelet, and plasma factors. Regulatory mechanisms counterbalance the tendency of clots to form. Hemostatic abnormalities can lead to excessive bleeding or thrombosis.

**Vascular Factors**

Vascular factors reduce blood loss from trauma through local vasoconstriction (an immediate reaction to injury) and compression of injured vessels by extravasation of blood into surrounding tissues. Vessel wall injury triggers the attachment and activation of platelets and production of fibrin; platelets and fibrin combine to form a clot.

**Platelet Factors**

Various mechanisms, including endothelial cell nitric oxide and prostacyclin, promote blood fluidity by preventing platelet stasis and dilating intact blood vessels. These mediators are no longer produced when the vascular endothelium is disrupted. Under these conditions, platelets adhere to the damaged intima and form aggregates. Initial platelet adhesion is to von Willebrand's factor (VWF), previously secreted by endothelial cells into the subendothelium. VWF binds to receptors on the platelet surface membrane (glycoprotein Ib/IX). Platelets anchored to the vessel wall undergo activation. During activation, platelets release mediators from storage granules, including adenosine diphosphate (ADP). Other biochemical changes resulting from activation include hydrolysis of membrane phospholipids, inhibition of adenylate cyclase, mobilization of intracellular Ca, and phosphorylation of intracellular proteins.

Arachidonic acid is converted to thromboxane A₂; this reaction requires cyclooxygenase and is inhibited irreversibly by aspirin and reversibly by many NSAIDs. ADP, thromboxane A₂, and other mediators induce activation and aggregation of additional platelets on the injured endothelium. Another receptor is assembled on the platelet surface membrane from glycoproteins IIb and IIIa. Fibrinogen binds to the glycoprotein IIb/IIIa complexes of adjacent platelets, connecting them into aggregates.

Platelets provide surfaces for the assembly and activation of coagulation complexes and the generation of thrombin. Thrombin converts fibrinogen to fibrin. Fibrin strands bind aggregated platelets to help secure the platelet-fibrin hemostatic plug.

**Plasma Factors**

Plasma coagulation factors interact to produce thrombin, which converts fibrinogen to fibrin. Radiating from and anchoring the hemostatic plug, fibrin strengthens the clot.

In the intrinsic pathway, factor XII, high mol wt kininogen, prekallikrein, and activated factor XI (factor Xla) interact to produce factor IXa from factor IX. Factor IXa then combines with factor VIIIa and procoagulant phospholipid (present on the surface of activated platelets and tissue cells) to form a complex that activates factor X. In the extrinsic pathway, factor VIIa and tissue factor directly activate factor X (the factor VIIa/tissue factor complex also activates factor IX—see Fig. 109-1 and Table 109-1).

[Fig. 109-1. Pathways in blood coagulation.]

[Table 109-1. Components of Blood Coagulation Reactions]

Activation of the intrinsic or extrinsic pathway activates the common pathway, resulting in formation of the fibrin clot. Three steps are involved in common pathway activation:

1. A prothrombin activator is produced on the surface of activated platelets and tissue cells. The activator
is a complex of an enzyme, factor Xa, and 2 cofactors, factor Va and procoagulant phospholipid.

2. The prothrombin activator cleaves prothrombin into thrombin and another fragment.

3. Thrombin induces the generation of fibrin polymers from fibrinogen. Thrombin also activates factor XIII, an enzyme that catalyzes formation of stronger bonds between adjacent fibrin monomers, as well as factor VIII and factor XI.

Ca\(^{2+}\) ions are needed in most thrombin-generating reactions (Ca\(^{2+}\)-chelating agents [eg, citrate, ethylenediaminetetraacetic acid] are used in vitro as anticoagulants). Vitamin K-dependent clotting factors (factors II, VII, IX, and X) cannot bind normally to phospholipid surfaces through Ca\(^{2+}\) bridges and function in blood coagulation when synthesized in the absence of vitamin K.

Although the coagulation pathways are helpful in understanding mechanisms and laboratory evaluation of coagulation disorders, in vivo coagulation is predominantly via the extrinsic pathway. People with hereditary deficiencies of factor XII, high mol wt kininogen, or prekallikrein have no bleeding abnormality. People with hereditary factor XI deficiency have a mild to moderate bleeding disorder. In vivo, factor XI (an intrinsic pathway factor) is activated when a small amount of thrombin is generated. Factor IX can be activated both by factor Xla and factor Vlla/tissue factor complexes.

In vivo, initiation of the extrinsic pathway occurs when injury to blood vessels brings blood into contact with the tissue factor on membranes of cells within and around the vessel walls. This contact with tissue factor generates factor Vlla/tissue factor complexes that activate factor X and factor IX. Factor Xa, combined with its cofactor, factor Vlla, on phospholipid membrane surfaces generates additional factor Xa. Factor X activation by both factor Vlla/tissue factor and factor Xa/Vlla complexes is required for normal hemostasis. This requirement for factors VIII and IX explains why hemophilia type A (deficiency of factor VIII) or type B (deficiency of factor IX) results in bleeding, despite an intact extrinsic coagulation pathway initiated by factor Vlla/tissue factor complexes.

**Regulatory Mechanisms**

Several inhibitory mechanisms prevent activated coagulation reactions from amplifying uncontrollably, causing extensive local thrombosis or disseminated intravascular coagulation. These mechanisms include inactivation of procoagulant enzymes, fibrinolysis, and hepatic clearance of activated clotting factors.

**Inactivation of coagulation factors:** Plasma protease inhibitors (antithrombin, tissue factor pathway inhibitor, \(\alpha_2\)-macroglobulin, heparin cofactor II) inactivate coagulation enzymes. Antithrombin inhibits thrombin, factor Xa, factor Xla, and factor IXa. Heparin enhances antithrombin activity.

Two vitamin K-dependent proteins, protein C and protein S, form a complex that inactivates factors Vlla and Vla by proteolysis. Thrombin, when bound to a receptor on endothelial cells (thrombomodulin), activates protein C. Activated protein C, in combination with protein S and phospholipid cofactors, proteolyzes and inactivates factors Vlla and Vla.

**Fibrinolysis:** Fibrin deposition and lysis must be balanced to maintain and remold the hemostatic seal during repair of an injured vessel wall. The fibrinolytic system dissolves fibrin by means of plasmin, a proteolytic enzyme. Fibrinolysis is activated by plasminogen activators released from vascular endothelial cells. Plasminogen activators and plasminogen (from plasma) bind to fibrin, and plasminogen activators cleave plasminogen into plasmin (see [Fig. 109-2](#)). Plasmin then proteolyzes fibrin into soluble fibrin degradation products that are swept away in the circulation.

There are several plasminogen activators:

- **Tissue plasminogen activator** (tPA), from endothelial cells, is a poor activator when

[Fig. 109-2. Fibrinolytic pathway.]
free in solution but an efficient activator when bound to fibrin in proximity to plasminogen.

- **Urokinase** exists in single-chain and double-chain forms with different functional properties. Single-chain urokinase cannot activate free plasminogen but, like tPA, can readily activate plasminogen bound to fibrin. A trace concentration of plasmin cleaves single-chain to double-chain urokinase, which activates plasminogen in solution as well as plasminogen bound to fibrin. Epithelial cells that line excretory passages (eg, renal tubules, mammary ducts) secrete urokinase, which is the physiologic activator of fibrinolysis in these channels.

- **Streptokinase**, a bacterial product not normally found in the body, is another potent plasminogen activator.

Streptokinase, urokinase, and recombinant tPA (alteplase) have all been used therapeutically to induce fibrinolysis in patients with acute thrombotic disorders.

**Regulation of fibrinolysis:** Fibrinolysis is regulated by plasminogen activator inhibitors (PAIs) and plasmin inhibitors that slow fibrinolysis. PAI-1, the most important PAI, inactivates tPA and urokinase and is released from vascular endothelial cells and activated platelets. The primary plasmin inhibitor is α2-antiplasmin, which quickly inactivates free plasmin escaping from clots. Some α2-antiplasmin is also cross-linked to fibrin by the action of factor XIIIa during clotting. This cross-linking may prevent excessive plasmin activity within clots. tPA and urokinase are rapidly cleared by the liver, which is another mechanism of preventing excessive fibrinolysis.

**Excessive Bleeding**

Unusual or excessive bleeding may be indicated by several different signs and symptoms. Patients may present with unexplained nosebleeds (epistaxis), excessive or prolonged menstrual blood flow (menorrhagia), or prolonged bleeding after minor cuts, tooth brushing or flossing, or trauma. Other patients may have unexplained skin lesions, including petechiae (small intradermal or mucosal hemorrhages), purpura (areas of mucosal or skin hemorrhage larger than petechiae), ecchymoses (bruises), or telangiectasias (dilated small vessels visible on skin or mucosa). Some critically ill patients may suddenly bleed from vascular punctures or skin lesions and have severe hemorrhage from these sites or from the GI or GU tract. In some patients, a laboratory test abnormality suggesting the susceptibility to excessive bleeding is found incidentally.

**Etiology**

Excessive bleeding can result from several mechanisms (see [Table 109-2](#)), including the following:

- **Platelet disorders**
- **Coagulation disorders**
- **Defects in blood vessels**

Platelet disorders may involve an abnormal number of platelets (typically too few platelets, although an extremely elevated platelet count may be associated either with thrombosis or with excessive bleeding), defective platelet function, or both. Coagulation disorders may be acquired or hereditary.

Overall, the most common causes of excessive bleeding include

- **Severe thrombocytopenia**
- **Excessive anticoagulation with warfarin or heparin**
- **Liver disease (inadequate production of coagulation factors)**
Evaluation

History: History of present illness should determine the bleeding sites, the amount and duration of bleeding, and the relationship of bleeding to any possible precipitating factors.

Review of systems should specifically query about bleeding from sites other than those volunteered (eg, patients complaining of easy bruising should be questioned about frequent nosebleeds, gum bleeding while tooth brushing, melena, hemoptysis, blood in stool or urine). Patients should be asked about symptoms of possible causes, including abdominal pain and diarrhea (GI illness); joint pain (connective tissue disorders); and amenorrhea and morning sickness (pregnancy).

Past medical history should seek known systemic conditions associated with defects in platelets or coagulation, particularly

- Severe infection, cancer, cirrhosis, HIV infection, pregnancy, SLE, or uremia
- Prior excessive or unusual bleeding or transfusions
- Family history of excessive bleeding

Drug history should be reviewed, particularly use of heparin, warfarin, aspirin, and NSAIDs.

Physical examination: Vital signs and general appearance can indicate hypovolemia

(Table 109-2, Some Causes of Excessive Bleeding)

(tachycardia, hypotension, pallor, diaphoresis) or infection (fever, tachycardia, hypotension with sepsis).

The skin and mucous membranes (nose, mouth, vagina) are examined for petechiae, purpura, and telangiectasias. GI bleeding can often be identified by digital rectal examination. Signs of bleeding in deeper tissues may include tenderness during movement and local swelling, muscle hematomas, and, for intracranial bleeding, confusion, stiff neck, focal neurologic abnormalities, or a combination of these findings.

Characteristic findings of alcohol abuse or liver disease are ascites, splenomegaly (secondary to portal hypertension), and jaundice.

Red flags: The following findings are of particular concern:

- Signs of hypovolemia or hemorrhagic shock
- Pregnancy or recent delivery
- Signs of infection or sepsis

Interpretation of findings: Bleeding in a patient taking warfarin, especially if there has been a recent increase in dose, is likely due to the drug. Telangiectasias on the face, lips, oral or nasal mucosa, and tips of the fingers and toes in a patient with a positive family history of excessive bleeding is likely hereditary hemorrhagic telangiectasia.

Bleeding from superficial sites, including skin and mucous membranes, suggests a quantitative or qualitative defect in platelets or a defect in blood vessels (eg, amyloidosis).

Bleeding into deep tissues (eg, hemarthroses, muscle hematomas, retroperitoneal hemorrhage) suggests a defect in coagulation (coagulopathy).

A family history of excessive bleeding suggests an inherited coagulopathy (eg, hemophilia), a qualitative
platelet disorder, a type of von Willebrand's disease (VWD), or hereditary hemorrhagic telangiectasia. Absence of a known family history does not, however, exclude an inherited disorder of hemostasis.

Bleeding in a patient who is pregnant or has recently delivered, who is in shock, or who has a serious infection suggests disseminated intravascular coagulation (DIC).

Bloody diarrhea and thrombocytopenia in a child with fever and GI symptoms suggest the hemolytic-uremic syndrome (HUS), which is often associated with infection by *Escherichia coli* O157:H7.

In a child, a palpable, purpuric rash on the extensor surfaces of the extremities suggests Henoch-Schönlein purpura, particularly if accompanied by fever, polyarthralgia, or GI symptoms.

Patients with known alcohol abuse or liver disease may have coagulopathy, splenomegaly, or thrombocytopenia.

In patients with a history of IV drug abuse, HIV infection should be considered.

**Testing:** Most patients require laboratory evaluation (see [Table 109-3](#)). The initial tests are

- CBC with platelet count
- Peripheral blood smear
- PT and PTT

Screening tests evaluate the components of hemostasis, including the number of circulating platelets and the plasma coagulation pathways. The most common screening tests for bleeding disorders are the platelet count, PT, and PTT. If results are abnormal, a specific test can usually pinpoint the defect.

Determination of the level of fibrin degradation products measures in vivo activation of fibrinolysis.

**Table 109-3.** Laboratory Tests of Hemostasis by Phase

**Prothrombin time (PT)** screens for abnormalities in the extrinsic and common pathways of coagulation (plasma factors VII, X, V, prothrombin, and fibrinogen). The PT is reported as the international normalized ratio (INR), which reflects the ratio of the patient's PT to the laboratory's control value; the INR controls for differences in reagents among different laboratories. Because commercial reagents and instrumentation vary widely, each laboratory determines its own normal range for PT and PTT; a typical normal range for the PT is between 10 and 13 sec. An INR > 1.5 or a PT ≥ 3 sec longer than a laboratory's normal control value is usually abnormal and requires further evaluation. The INR is valuable in screening for abnormal coagulation in various acquired conditions (eg, vitamin K deficiency, liver disease, DIC). It is also used to monitor therapy with the oral vitamin K antagonist, warfarin.

**Partial thromboplastin time (PTT)** screens plasma for abnormalities in factors of the intrinsic and common pathways (prekallikrein; high mol wt kininogen; factors XII, XI, IX, VIII, X, and V; prothrombin; fibrinogen). The PTT tests for deficiencies of all clotting factors except factor VII (measured by the PT) and factor XIII. A typical normal range is 28 to 34 sec. A normal result indicates that at least 30% of all coagulation factors in the pathway are present in the plasma. Heparin prolongs the PTT, and the PTT is often used to monitor heparin therapy. Inhibitors that prolong the PTT include an autoantibody against factor VIII (see pp. 977 and 979) and antibodies against protein-phospholipid complexes (lupus anticoagulant—see pp. 973 and 979).

**Prolongation of PT or PTT** may reflect

- Factor deficiency
- Presence of an inhibitor of a component of the coagulation pathway
The PT and PTT do not become prolonged until one or more of the clotting factors tested are about 70% deficient. For determining if prolongation reflects a deficiency of one or more clotting factor or the presence of an inhibitor, the test is repeated after mixing the patient's plasma with normal plasma in a 1:1 ratio. Because this mixture provides about 50% of normal levels of all coagulation factors, failure of the mixture to correct almost completely the prolongation suggests the presence of an inhibitor in patient plasma.

The previously used bleeding time test is of doubtful reliability.

**Normal results** on initial tests exclude many bleeding disorders. The main exceptions are VWD and hereditary hemorrhagic telangiectasia. VWD is a common entity in which the associated deficiency of factor VIII is frequently insufficient to prolong the PTT. Patients who have normal initial test results, along with symptoms or signs of bleeding and a positive family history, should be tested for VWD by measuring plasma von Willebrand's factor (VWF) antigen, ristocetin cofactor activity (an indirect test for large VWF multimers), and factor VIII levels.

If thrombocytopenia is present, the peripheral blood smear often suggests the cause (see Table 108-2). If the smear is normal, patients should be tested for HIV. If the result of the HIV test is negative and the patient is not pregnant and has not taken a drug known to cause platelet destruction, then idiopathic thrombocytopenic purpura is likely. If there are signs of hemolysis (fragmented RBCs on smear, decreasing Hb level), thrombotic thrombocytopenic purpura (TTP) or HUS is suspected, although sometimes other hemolytic disorders can cause these findings. HUS occurs in children with hemorrhagic colitis. The Coombs' test is negative in TTP and HUS. If the CBC and peripheral blood smear demonstrate other cytopenias or abnormal WBCs, a hematologic abnormality affecting multiple cell types is suspected, and a bone marrow aspiration or biopsy is necessary for diagnosis.

**Prolonged PTT with normal platelets and PT** suggests hemophilia A or B. Factor VIII and IX assays are indicated. Inhibitors that prolong the PTT include an autoantibody against factor VIII and antibodies against protein-phospholipid complexes (lupus anticoagulant). Such inhibitors are suspected when a prolonged PTT does not correct upon 1:1 mixing with normal plasma.

**Prolonged PT with normal platelets and PTT** suggests factor VII deficiency. Congenital factor VII deficiency is rare; however, the short half-life of factor VII in plasma causes factor VII to decrease to low levels more rapidly than other vitamin K-dependent coagulation factors (eg, in patients given warfarin anticoagulation or in patients with incipient liver disease).

**Prolonged PT and PTT with thrombocytopenia** suggest DIC, especially in association with obstetric complications, sepsis, cancer, or shock. Confirmation is by finding elevated levels of D-dimers (or fibrin degradation products) and decreasing plasma fibrinogen levels on serial testing. Prolonged PT or PTT with normal platelet count occurs with liver disease or vitamin K deficiency or during anticoagulation with warfarin or unfractionated heparin. Liver disease is suspected based on history and is confirmed by finding elevation of serum aminotransferases and bilirubin; hepatitis testing is recommended.

**Imaging tests** are often required to detect occult bleeding in patients with bleeding disorders. For example, head CT should be done in patients with severe headaches, head injuries, or impairment of consciousness; and abdominal CT in patients with abdominal pain or other findings compatible with intraperitoneal or retroperitoneal hemorrhage.

**Treatment**

Treatment is directed at the underlying disorder and at any hypovolemia. For immediate treatment of bleeding due to a coagulopathy that has not yet been diagnosed, fresh frozen plasma, which contains all coagulation factors, should be infused pending definitive evaluation.

**Key Points**

- DIC should be suspected in patients with sepsis, shock, or complications of pregnancy or delivery.
• Drug causes are common, particularly mild platelet dysfunction caused by aspirin or NSAIDs.

• Easy bruising with no other clinical manifestations and normal laboratory test results is probably benign.
Chapter 110. Thrombotic Disorders

Introduction

In healthy people, homeostatic balance exists between procoagulant (clotting) forces and anticoagulant and fibrinolytic forces (see Ch. 109). Numerous genetic, acquired, and environmental factors can tip the balance in favor of coagulation, leading to the pathologic formation of thrombi in veins (eg, deep venous thrombosis [DVT]), arteries (eg, MI, ischemic stroke), or cardiac chambers. Thrombi can obstruct blood flow at the site of formation or detach and embolize to block a distant blood vessel (eg, pulmonary embolism, embolic stroke).

Etiology

Genetic defects that increase the propensity for venous thromboembolism include

- Factor V Leiden mutation, which causes resistance to activated protein C (APC)
- Prothrombin 20210 gene mutation
- Deficiency of protein C, protein S, protein Z, or antithrombin

Acquired defects also predispose to venous and arterial thrombosis (see Table 110-1).

Other disorders and environmental factors can increase the risk of thrombosis, especially if a genetic abnormality is also present.

Diagnosis

Diagnoses are summarized elsewhere in THE MANUAL specific to the location of the thrombus.

Predisposing factors: Predisposing factors should always be considered. In some cases, the condition is clinically obvious (eg, recent surgery or trauma, prolonged immobilization, cancer, generalized atherosclerosis). If no predisposing factor is readily apparent, further evaluation should be conducted in patients with

- Family history of venous thrombosis
- More than one episode of venous thrombosis
- Venous or arterial thrombosis before age 50
- Unusual sites of venous thrombosis (eg, cavernous sinus, mesenteric veins)

As many as half of all patients with spontaneous DVT have a genetic predisposition.

[Table 110-1, Acquired Causes of Thromboembolism]

Testing for predisposing congenital factors includes measurements of the quantity of activity of natural anticoagulant molecules in plasma and tests for specific gene defects. Testing begins with a group of screening tests, followed (if necessary) by specific assays.

Treatment

Treatment is summarized elsewhere in THE MANUAL specific to the location of the thrombus.

Factor V Resistance to Activated Protein C
APC (in complex with protein S) degrades factors Va and VIIIa, thus inhibiting coagulation. Any of several mutations to factor V make it resistant to inactivation by APC, increasing the tendency for thrombosis. Factor V Leiden is the most common of these mutations. Homozygous mutations increase the risk of thrombosis more than do heterozygous mutations.

Factor V Leiden as a single gene defect in European populations is present in about 5%, but it rarely occurs in native Asian or African populations. It is present in 20 to 60% of patients with spontaneous venous thrombosis.

Diagnosis is based on a functional plasma coagulation assay (the failure of patient plasma PTT to become prolonged in the presence of snake venom-activated patient protein C) and on molecular analysis of the factor V gene.

Treatment, if necessary, involves anticoagulation with heparin followed by warfarin.

Protein C Deficiency

Protein C is a vitamin K-dependent protein, as are coagulation factors VII, IX, and X, prothrombin, and proteins S and Z. Because APC degrades factors Va and VIIIa, APC is a natural plasma anticoagulant. Decreased protein C from genetic or acquired causes promotes venous thrombosis. Heterozygous deficiency of plasma protein C has a prevalence of 0.2 to 0.5%; about 75% of people with this defect experience a venous thromboembolism (50% by age 50). Homozygous or doubly heterozygous deficiency causes neonatal purpura fulminans, i.e., severe neonatal disseminated intravascular coagulation (DIC). Acquired decreases occur in patients with liver disease or DIC, during cancer chemotherapy (including L-asparaginase administration), and during warfarin therapy.

Diagnosis is based on antigenic and functional plasma assays.

Patients with symptomatic thrombosis require anticoagulation with heparin or low mol wt heparin, followed by warfarin; use of the vitamin K antagonist, warfarin, as initial therapy occasionally causes thrombotic skin infarction by lowering vitamin K-dependent protein C levels before a therapeutic decrease has occurred in most vitamin K-dependent clotting factors. Neonatal purpura fulminans is fatal without replacement of protein C (using normal plasma or purified concentrate) and anticoagulation with heparin.

Protein S Deficiency

Protein S, a vitamin K-dependent protein, is a cofactor for APC-mediated cleavage of factors Va and VIIIa. Heterozygous deficiency of plasma protein S predisposes to venous thrombosis and is similar to protein C deficiency in genetic transmission, prevalence, laboratory testing, treatment, and precautions. Homozygous deficiency of protein S can cause neonatal purpura fulminans that is clinically indistinguishable from that caused by homozygous deficiency of protein C. Acquired deficiencies of protein S (and protein C) occur during DIC and warfarin therapy and after L-asparaginase administration.

Diagnosis is based on antigenic assays of total or free plasma protein S. (Free protein S is the form unbound to C4 binding protein.)

Protein Z Deficiency

Protein Z, another vitamin K-dependent protein, functions as a cofactor to down-regulate coagulation by forming a complex with the plasma protein, Z-dependent protease inhibitor (ZPI). The complex inactivates factors Xa, XI, and IX on phospholipids surfaces. The consequence of either protein Z or ZPI deficiency in the pathophysiology of thrombosis and fetal loss is unresolved; however, either defect may make thrombosis more likely if an affected patient also has another congenital coagulation abnormality (e.g., factor V Leiden). Quantification of protein Z and ZPI is done in research laboratories by plasma electrophoresis and immunoblotting. It is not yet known whether anticoagulant therapy or prophylaxis is indicated in protein Z or ZPI deficiency.

Antithrombin Deficiency
Antithrombin is a protein that inhibits thrombin and factors Xa, IXa, and XIa. Heterozygous deficiency of plasma antithrombin has a prevalence of about 0.2 to 0.4%; about half of those affected develop venous thromboses. Homozygous deficiencies are probably lethal to the fetus in utero. Acquired deficiencies occur in patients with DIC, liver disease, or nephrotic syndrome and during heparin or L-asparaginase therapy.

Laboratory testing involves quantification of plasma inhibition of thrombin in the presence of heparin.

Oral warfarin is used for prophylaxis against venous thromboembolism.

**Prothrombin 20210 Gene Mutation**

A mutation of the prothrombin 20210 gene results in increased plasma prothrombin levels and increases the risk of venous thromboembolism. Treatment, if necessary, involves anticoagulation with heparin followed by warfarin.

**Antiphospholipid Antibody Syndrome**

(Anti-Cardiolipin Antibodies; Lupus Anticoagulant)

The antiphospholipid antibody syndrome consists of thrombosis and (in pregnancy) fetal demise associated with various autoimmune antibodies directed against one or more phospholipid-binding proteins (eg, β2-glycoprotein I, prothrombin, annexin). These proteins normally bind to phospholipid membrane constituents and protect them from excessive coagulation activation. The autoantibodies displace the protective proteins and, thus, produce procoagulant endothelial cell surfaces and cause arterial or venous thromboses. In vitro clotting tests may paradoxically be prolonged because the antiprotein/phospholipid antibodies interfere with coagulation factor assembly and activation on the phospholipid components added to plasma to initiate the tests. The lupus anticoagulant is an antiphospholipid autoantibody that binds to protein-phospholipid complexes. It was initially recognized in patients with SLE, but these patients now account for a minority of patients with the autoantibody.

The lupus anticoagulant is suspected if the PTT is prolonged and does not correct immediately upon 1:1 mixing with normal plasma but does return to normal upon the addition of an excessive quantity of phospholipids (done by the hematology laboratory). Antiphospholipid antibodies in patient plasma are measured by immunoassays of IgG and IgM antibodies that bind to phospholipid-β2-glycoprotein I complexes on microtiter plates.

Heparin, warfarin, and aspirin have been used for prophylaxis and treatment.

**Hyperhomocysteinemia**

Hyperhomocysteinemia may predispose to arterial thrombosis and venous thromboembolism, possibly because of injury to vascular endothelial cells. Plasma homocysteine levels are elevated ≥ 10-fold in homozygous cystathionine β-synthase deficiency. Milder elevations occur in heterozygous deficiency and in other abnormalities of folate metabolism, including methylenetetrahydrofolate dehydrogenase deficiency. However, by far the most common causes of hyperhomocysteinemia are acquired deficiencies of folate, vitamin B12, or vitamin B6.

The diagnosis is established by measuring plasma homocysteine levels.

Plasma homocysteine levels may be normalized by dietary supplementation with folic acid, vitamin B12, or vitamin B6 (pyridoxine) alone or in combination; however, it is not clear that this therapy reduces the risk of arterial or venous thrombosis.
Chapter 111. Coagulation Disorders

Introduction

Abnormal bleeding can result from disorders of the coagulation system (see p. 963), of platelets, or of blood vessels. Disorders of coagulation can be acquired or hereditary. The major causes of acquired coagulation disorders are vitamin K deficiency (see p. 46), liver disease, disseminated intravascular coagulation, and development of circulating anticoagulants. Severe liver disease (eg, cirrhosis, fulminant hepatitis, acute fatty liver of pregnancy) may disturb hemostasis by impairing clotting factor synthesis. Because all coagulation factors are made in the liver, both the PT and PTT are elevated in severe liver disorders. (PT results are typically reported as INR.) Occasionally, decompensated liver disease also causes excessive fibrinolysis and bleeding due to decreased hepatic synthesis of α2-antiplasmin.

The most common hereditary disorder of hemostasis is von Willebrand's disease (see p. 962). The most common hereditary coagulation disorders are the hemophilias.

Disseminated Intravascular Coagulation

(Consumption Coagulopathy; Defibrination Syndrome)

Disseminated intravascular coagulation (DIC) involves abnormal, excessive generation of thrombin and fibrin in the circulating blood. During the process, increased platelet aggregation and coagulation factor consumption occur. DIC that evolves slowly (over weeks or months) causes primarily venous thrombotic and embolic manifestations; DIC that evolves rapidly (over hours or days) causes primarily bleeding. Severe, rapidly evolving DIC is diagnosed by demonstrating thrombocytopenia, an elevated PTT and PT, increased levels of plasma D-dimer (or serum fibrin degradation products), and a decreasing plasma fibrinogen level. Treatment includes correction of the cause and replacement of platelets, coagulation factors (in fresh frozen plasma), and fibrinogen (in cryoprecipitate) to control severe bleeding. Heparin is used as therapy (or prophylaxis) in patients with slowly evolving DIC who have (or are at risk of) venous thromboembolism.

Etiology

DIC usually results from exposure of tissue factor to blood, initiating the coagulation cascade (see Fig. 109-2). DIC occurs in the following clinical circumstances:

• Complications of obstetrics (eg, abruptio placentae, saline-induced therapeutic abortion, retained dead fetus or products of conception, amniotic fluid embolism): Placental tissue with tissue factor activity enters or is exposed to the maternal circulation.

• Infection, particularly with gram-negative organisms: Gram-negative endotoxin causes generation or exposure of tissue factor activity in phagocytic, endothelial, and tissue cells.

• Cancer, particularly mucin-secreting adenocarcinomas of the pancreas and prostate and acute promyelocytic leukemia: Tumor cells express or release tissue factor.

• Shock due to any condition that causes ischemic tissue injury and release of tissue factor

Less common causes of DIC include severe tissue damage from head trauma, burns, frostbite, or gunshot wounds; complications of prostate surgery that allow prostatic material with tissue factor activity (along with plasminogen activators) to enter the circulation; venomous snake bites in which enzymes enter the circulation, activate one or several coagulation factors, and either generate thrombin or directly convert fibrinogen to fibrin; profound intravascular hemolysis; and aortic aneurysms or cavernous hemangiomas (Kasabach-Merritt syndrome) associated with vessel wall damage and areas of blood stasis.

Pathophysiology
**Slowly evolving DIC** primarily causes venous thromboembolic manifestations (eg, deep venous thrombosis, pulmonary embolism), although occasionally cardiac valve vegetations occur; abnormal bleeding is uncommon.

**Severe, rapidly evolving DIC**, in contrast, causes thrombocytopenia and depletion of plasma clotting factors and fibrinogen, which cause bleeding. Bleeding into organs, along with microvascular thromboses, may cause dysfunction and failure in multiple organs. Delayed dissolution of fibrin polymers by fibrinolysis may result in the mechanical disruption of RBCs, producing schistocytes and mild intravascular hemolysis (see p. 961).

**Symptoms and Signs**

In slowly evolving DIC, symptoms of venous thrombosis (see p. 2224) and pulmonary embolism (see p. 1908) may be present.

In severe, rapidly evolving DIC, skin puncture sites (eg, IV or arterial punctures) bleed persistently, ecchymoses form at sites of parenteral injections, and serious GI bleeding may occur.

**Diagnosis**

- Platelet count, PT, PTT, plasma fibrinogen, plasma D-dimer

DIC is suspected in patients with unexplained bleeding or venous thromboembolism, especially if a predisposing condition exists. If DIC is suspected, platelet count, PT, PTT, plasma fibrinogen level, and plasma D-dimer level (an indication of in vivo fibrin deposition and degradation) are obtained.

Slowly evolving DIC produces mild thrombocytopenia, a normal to minimally prolonged PT (results are typically reported as INR) and PTT, a normal or moderately reduced fibrinogen level, and an increased plasma D-dimer level. Because various disorders stimulate increased synthesis of fibrinogen as an acute-phase reactant, a declining fibrinogen level on 2 consecutive measurements can help make the diagnosis of DIC. Initial PTT values in slowly evolving DIC may actually be shorter than normal, probably because of the presence of activated coagulation factors in the plasma.

Severe, rapidly evolving DIC results in more severe thrombocytopenia, more prolonged PT and PTT, a rapidly declining plasma fibrinogen level, and a high plasma D-dimer level.

A factor VIII level can sometimes be helpful if severe, acute DIC must be differentiated from massive hepatic necrosis, which can cause similar abnormalities in coagulation studies. The factor VIII level is elevated in hepatic necrosis, because factor VIII is made in hepatocytes and released as they are destroyed; factor VIII is reduced in DIC because of the thrombin-induced generation of activated protein C, which proteolyses factor VIII.

**Treatment**

- Treatment of cause

- Possibly replacement therapy (eg, platelets, cryoprecipitate, fresh frozen plasma, natural anticoagulants)

- Sometimes heparin

Immediate correction of the cause is the priority (eg, broad-spectrum antibiotic treatment of suspected gram-negative sepsis, evacuation of the uterus in abruptio placentae). If treatment is effective, DIC should subside quickly. If bleeding is severe, adjunctive replacement therapy is indicated, consisting of platelet concentrates to correct thrombocytopenia; cryoprecipitate to replace fibrinogen and factor VIII; and fresh frozen plasma to increase levels of other clotting factors and natural anticoagulants (antithrombin, proteins C, S, and Z). The effectiveness of infusion of concentrates of antithrombin or activated protein C in severe, rapidly evolving DIC is unresolved.
Heparin is useful in the treatment of slowly evolving DIC with venous thrombosis or pulmonary embolism. Heparin usually is not indicated in rapidly evolving DIC with bleeding or bleeding risk, except in women with a retained dead fetus and evolving DIC with a progressive decrease in platelets, fibrinogen, and coagulation factors. In these patients, heparin is administered for several days to control DIC, increase fibrinogen and platelet levels, and decrease excessive coagulation factor consumption. Heparin is then stopped and the uterus evacuated.

Hemophilia

Hemophilias are common hereditary bleeding disorders caused by deficiencies of either clotting factor VIII or IX. The extent of factor deficiency determines the probability and severity of bleeding. Bleeding into deep tissues or joints usually develops within hours of trauma. The diagnosis is suspected in a patient with an elevated PTT and normal PT and platelet count; it is confirmed by specific factor assays. Treatment includes replacement of the deficient factor if acute bleeding is suspected, confirmed, or likely to develop (eg, before surgery).

Hemophilia A (factor VIII deficiency), which affects about 80% of patients with hemophilia, and hemophilia B (factor IX deficiency) have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission. Specific factor assays are required to distinguish the two.

Etiology

Hemophilia is an inherited disorder that results from mutations, deletions, or inversions affecting a factor VIII or factor IX gene. Because these genes are located on the X chromosome, hemophilia affects males almost exclusively. Daughters of men with hemophilia are obligate carriers, but sons are normal. Each son of a carrier has a 50% chance of having hemophilia, and each daughter has a 50% chance of being a carrier.

Pathophysiology

Normal hemostasis requires > 30% of normal factor VIII and IX levels. Most patients with hemophilia have levels < 5%. Carriers usually have levels of about 50%; rarely, random inactivation of their normal X chromosome in early embryonic life results in a carrier having factor VIII or IX levels of < 30%.

Most patients with hemophilia who were treated with plasma concentrates in the early 1980s were infected with HIV due to contaminated factor concentrates. Occasional patients developed immune thrombocytopenia secondary to HIV infection, which exacerbated bleeding.

Symptoms and Signs

Patients with hemophilia bleed into tissues (eg, hemarthroses, muscle hematomas, retroperitoneal hemorrhage). The bleeding may be immediate or occur slowly, depending on the extent of trauma and plasma level of factor VIII or IX. Pain often occurs as bleeding commences, sometimes before other signs of bleeding develop. Chronic or recurrent hemarthroses can lead to synovitis and arthropathy. Even a trivial blow to the head can cause intracranial bleeding. Bleeding into the base of the tongue can cause life-threatening airway compression.

Severe hemophilia (factor VIII or IX level < 1% of normal) causes severe bleeding throughout life, usually beginning soon after birth (eg, scalp hematoma after delivery or excessive bleeding after circumcision). Moderate hemophilia (factor levels 1 to 5% of normal) usually causes bleeding after minimal trauma. In mild hemophilia (factor levels 5 to 25% of normal), excessive bleeding may occur after surgery or dental extraction.

Diagnosis

• Platelet count, PT, PTT, factor VIII and IX assays
Hemophilia is suspected in patients with recurrent bleeding, unexplained hemorrhages, or a prolongation of the PTT. If hemophilia is suspected, PTT, PT, platelet count, and factor VIII and IX assays are obtained. In hemophilia, the PTT is prolonged, but the PT and platelet count are normal. Factor VIII and IX assays determine the type and severity of the hemophilia. Because factor VIII levels may also be reduced in von Willebrand's disease (VWD), von Willebrand's factor (VWF) activity, antigen, and multimer composition are measured in patients with newly diagnosed hemophilia A, particularly if the disorder is mild and a family history indicates that both male and female family members are affected. Determining if a female is a true carrier of hemophilia A is sometimes possible by measuring the factor VIII level. Similarly, measuring the factor IX level often identifies a carrier of hemophilia B. PCR analysis of DNA that comprises the factor VIII gene, available at specialized centers, can be used for diagnosis of the hemophilia A carrier state and for prenatal diagnosis of hemophilia A by chorionic villus sampling at 12 wk or amniocentesis at 16 wk. These procedures carry a 0.5 to 1% risk of miscarriage.

After repeated exposure to factor VIII replacement, about 15 to 35% of patients with hemophilia A develop factor VIII isoantibodies (alloantibodies) that inhibit the coagulant activity of any additional factor VIII infused. Patients should be screened for isoantibodies (eg, by measuring the degree of PTT shortening immediately after mixing the patient's plasma with an equal volume of normal plasma, and then by repeating the measurement after incubation for 1 h), especially before an elective procedure that requires replacement therapy. If isoantibodies are present, their titers can be measured by determining the extent of factor VIII inhibition by serial dilutions of patient plasma.

Treatment

• Replacement of deficient factor

• Sometimes antifibrinolytics

If symptoms suggest bleeding, treatment should begin immediately, even before diagnostic tests are completed. For example, treatment for headache that might indicate intracranial hemorrhage should begin before a CT scan is completed.

Replacement of the deficient factor is the primary treatment. In hemophilia A, the factor VIII level should be raised transiently to

• About 30% of normal to prevent bleeding after dental extraction or to abort an incipient joint hemorrhage

• 50% of normal if severe joint or IM bleeding is already evident

• 100% of normal before major surgery or if bleeding is intracranial, intracardiac, or otherwise life threatening

Repeated infusions at 50% of the initial calculated dose should then be given every 8 to 12 h to keep trough levels above 50% for 7 to 10 days after major surgery or life-threatening hemorrhage. Each unit/kg of factor VIII increases the factor VIII level by about 2%. Thus, to increase the level from 0% to 50%, about 25 units/kg are required.

Factor VIII can be given as purified factor VIII concentrate, which is derived from multiple donors. It undergoes viral inactivation, but inactivation may not eliminate parvovirus or hepatitis A. Recombinant factor VIII is free of viruses and is usually preferred unless patients are already seropositive for HIV or for hepatitis B or C virus.

In hemophilia B, factor IX can be given as a purified or recombinant viral-inactivated product every 24 h. The target levels of factor correction are the same as in hemophilia A. However, to achieve these levels, the dose must be higher than in hemophilia A because factor IX is smaller than factor VIII and, in contrast to VIII, has an extensive extravascular distribution.
Fresh frozen plasma contains factors VIII and IX. However, unless plasma exchange is done, sufficient whole plasma usually cannot be given to patients with severe hemophilia to raise factor VIII or IX to levels that prevent or control bleeding. Fresh frozen plasma should, therefore, be used only if rapid replacement therapy is necessary and factor concentrate is unavailable or the patient has a coagulopathy that is not yet defined precisely.

In patients with hemophilia who develop a factor VIII inhibitor, treatment is best accomplished using recombinant factor VIIIa in repeated high doses (eg, 90 g/kg).

Adjunctive therapies may include desmopressin or an antifibrinolytic drug. As described for VWD (see p. 963), desmopressin may temporarily raise factor VIII levels. The patient's response should be tested before desmopressin is used therapeutically. Its use after minor trauma or before elective dental surgery may obviate replacement therapy. Desmopressin should be used only for patients with mild hemophilia A (basal factor VIII levels ≥ 5%) who have demonstrated responsiveness.

An antifibrinolytic agent (ε-aminocaproic acid 2.5 to 4 g po qid for 1 wk or tranexamic acid 1.0 to 1.5 g po tid or qid for 1 wk) should be given to prevent late bleeding after dental extraction or other oropharyngeal mucosal trauma (eg, tongue laceration).

**Prevention**

Patients should avoid aspirin and NSAIDs (both inhibit platelet function). Regular dental care is essential so that tooth extractions and other dental surgery can be avoided. Drugs should be given orally or IV; IM injections can cause hematomas. Patients with hemophilia should be vaccinated against hepatitis B.

**Coagulation Disorders Caused by Circulating Anticoagulants**

Circulating anticoagulants are usually autoantibodies that neutralize specific clotting factors in vivo (eg, an autoantibody against factor VIII or factor V) or inhibit protein-bound phospholipid in vitro. Occasionally, the latter type of autoantibody causes bleeding in vivo by binding prothrombin.

Circulating anticoagulants should be suspected in patients with excessive bleeding combined with either a prolonged PTT or PT that does not correct when the test is repeated with a 1:1 mixture of normal plasma and the patient's plasma.

Antiphospholipid antibodies (see p. 975) typically cause thrombosis. However, in a subset of patients, the antibodies bind to prothrombin-phospholipid complexes and induce hypoprothrombinemia and bleeding.

**Factor VIII Anticoagulants**

Isoantibodies to factor VIII develop in about 15 to 35% of patients with severe hemophilia A as a complication of repeated exposure to normal factor VIII molecules during replacement therapy (see p. 978). Factor VIII autoantibodies also arise occasionally in patients without hemophilia, eg, in postpartum women as a manifestation of an underlying systemic autoimmune disorder or of transiently disordered immune regulation, or in elderly patients without overt evidence of other underlying disorders. Patients with a factor VIII anticoagulant can develop life-threatening hemorrhage.

Plasma containing a factor VIII antibody has a prolonged PTT that does not correct when normal plasma or another source of factor VIII is added in a 1:1 mixture to the patient's plasma. Testing is done immediately after mixture and again after incubation.

Therapy with cyclophosphamide and corticosteroids may suppress autoantibody production in patients without hemophilia. In postpartum women, the autoantibodies may disappear spontaneously.

Management of acute hemorrhage in patients with hemophilia who have factor VIII isoantibodies or autoantibodies is by recombinant factor VIIIa (see above).

**Uncommon Hereditary Coagulation Disorders**
Most hereditary coagulation disorders other than hemophilia are rare autosomal recessive conditions that cause disease only in homozygous people (see Table 111-1). Factor XI deficiency is uncommon in the general population but common in descendants of European Jews (gene frequency about 5 to 9%). Bleeding typically occurs after significant injuries, including trauma or surgery, in people who are homozygotes or compound heterozygotes.

Severe deficiency of α2-antiplasmin (1 to 3% of normal), the major physiologic inhibitor of plasmin, can also cause bleeding. Diagnosis

(Table 111-1, Screening Laboratory Test Results in Inherited Defects in Blood Coagulation)

is based on a specific α2-antiplasmin assay. ε-Aminocaproic acid or tranexamic acid is used to control or prevent acute bleeding. Heterozygous people with α2-antiplasmin levels of 40 to 60% of normal can occasionally experience excessive surgical bleeding if secondary fibrinolysis is extensive (eg, in patients who have had open prostatectomy).
Chapter 112. Bleeding Due to Abnormal Blood Vessels

Introduction

Bleeding may result from abnormalities in platelets, coagulation factors, or blood vessels. Vascular bleeding disorders result from defects in blood vessels, typically causing petechiae, purpura, and bruising but seldom leading to serious blood loss. Bleeding may result from deficiencies of vascular and perivascular collagen in Ehlers-Danlos syndrome and in other rare hereditary connective tissue disorders (eg, pseudoxanthoma elasticum, osteogenesis imperfecta, Marfan syndrome—see p. 2908). Hemorrhage may be a prominent feature of scurvy (see p. 40) or of Henoch-Schönlein purpura, a hypersensitivity vasculitis common during childhood (see p. 321). In vascular bleeding disorders, tests of hemostasis are usually normal. Diagnosis is clinical.

Autoerythrocyte Sensitization

(Autoerythrocyte Sensitization Syndrome)

Autoerythrocyte sensitization is a rare disorder affecting women. It is characterized by local pain and burning preceding painful ecchymoses that occur primarily on the extremities.

Autoerythrocyte sensitization typically occurs in white women who are experiencing emotional stress or who have concomitant psychologic illness. Episodes of ecchymosis are painful and can occur spontaneously or after trauma or surgery. Bruising can occur on different sites of the body from where the trauma occurs. Tests of the coagulation system are normal.

In women with autoerythrocyte sensitization, intradermal injection of 0.1 mL of autologous RBCs or RBC stroma may result in pain, swelling, and induration at the injection site. This result suggests that escape of RBCs into the tissues is involved in the pathogenesis of the lesion. However, most patients also have associated severe psychoneurotic symptoms. In addition, psychogenic factors, such as self-induced purpura, seem related to the pathogenesis of the syndrome in some patients.

Diagnosis is based on examination of the site of intradermal injection of autologous RBCs and of a separate control injection site (without RBCs) 24 to 48 h after injection. Excoriation, which can complicate the test's interpretation, is prevented by making both sites difficult for the patient to reach. Treatment is psychiatric intervention and therapy.

Dysproteinemias Causing Vascular Purpura

Conditions that cause an abnormal protein content in the blood, typically in the form of immunoglobulins, can affect vascular fragility and lead to purpura.

Amyloidosis (see p. 905) causes amyloid deposition within vessels in the skin and subcutaneous tissues, which may increase vascular fragility, producing purpura. In some patients, coagulation factor X is adsorbed by amyloid and becomes deficient, but this deficiency is usually not the cause of bleeding. Periorbital purpura or a purpuric rash that develops in a nonthrombocytopenic patient after gentle stroking of the skin suggests amyloidosis.

Cryoglobulinemia produces immunoglobulins that precipitate when plasma is cooled (ie, cryoglobulins) while flowing through the skin and subcutaneous tissues of the extremities. Monoclonal immunoglobulins formed in Waldenstrom's macroglobulinemia or in multiple myeloma (see p. 1029) occasionally behave as cryoglobulins, as may mixed IgM-gG immune complexes formed in some chronic infectious diseases, most commonly hepatitis C. Cryoglobulinemia can lead to small-vessel vasculitis, which can cause purpura. Cryoglobulins can be detected by laboratory testing.

Hypergammaglobulinemic purpura is a vasculitic purpura that primarily affects women. Recurrent crops of small, palpable purpuric lesions develop on the lower legs. These lesions leave small residual brown spots. Many patients have manifestations of an underlying immunologic disorder (eg, Sjogren's syndrome, SLE). The diagnostic finding is a polyclonal increase in IgG (broad-based or diffuse...
Hyperviscosity syndrome (see p. 1027) resulting from a markedly elevated plasma IgM concentration may also result in purpura and other forms of abnormal bleeding (eg, profuse epistaxis) in patients with Waldenstrom's macroglobulinemia.

Hereditary Hemorrhagic Telangiectasia

(Rendu-Osler-Weber Syndrome)

Hereditary hemorrhagic telangiectasia is a hereditary disorder of vascular malformation transmitted as an autosomal dominant trait affecting men and women.

Symptoms and Signs

The most characteristic lesions are small red-to-violet telangiectatic lesions on the face, lips, oral and nasal mucosa, and tips of the fingers and toes (see Plate 56). Similar lesions may be present throughout the mucosa of the GI tract, resulting in recurrent GI bleeding. Patients may experience recurrent, profuse nosebleeds. Some patients have pulmonary arteriovenous fistulas. These fistulas may cause significant right-to-left shunts, which can result in dyspnea, fatigue, cyanosis, or polycythemia. However, the first sign of their presence may be a brain abscess, transient ischemic attack, or stroke as a result of infected or noninfected emboli. Cerebral or spinal arteriovenous malformations occur in some families and may cause subarachnoid hemorrhage, seizures, or paraplegia.

Diagnosis

• Clinical evaluation

• Sometimes endoscopy or angiography

Diagnosis is based on the finding of characteristic arteriovenous malformations on the face, mouth, nose, and digits. Endoscopy or angiography is sometimes needed, however. Laboratory findings are usually normal except for iron deficiency anemia in most patients.

Screening: If a family history of pulmonary or cerebral arteriovenous malformations exists, screening at puberty and at the end of adolescence with pulmonary CT or cerebral MRI is recommended.

Treatment

• Sometimes laser ablation, surgical resection, or embolotherapy

• Supplemental iron therapy

• Possibly blood transfusions

Treatment for most patients is supportive, but accessible telangiectases (eg, in the nose or GI tract via endoscopy) may be treated with laser ablation. Arteriovenous fistulas may be treated by surgical resection or embolotherapy. Repeated blood transfusions may be needed; therefore, immunization with hepatitis B vaccine is important. Most patients require continuous iron therapy to replace iron lost in repeated mucosal bleeding; some patients require parenteral iron (see Iron Deficiency Anemia on p. 924). Treatment with drugs that inhibit fibrinolysis, such as aminocaproic acid, may be beneficial.

Purpura Simplex

(Easy Bruising)

Purpura simplex is increased bruising that results from vascular fragility.
Purpura simplex is extremely common. The cause and mechanism are unknown; it may represent a heterogeneous group of disorders or merely a variation of normal.

The disorder usually affects women. Bruises develop on the thighs, buttocks, and upper arms in people without known trauma. The history usually reveals no other abnormal bleeding, but easy bruising may be present in family members. Serious bleeding does not occur. The platelet count and tests of platelet function, blood coagulation, and fibrinolysis are normal.

No drug prevents the bruising; patients are often advised to avoid aspirin and aspirin-containing drugs, but there is no evidence that bruising is related to or worsened by their use. Patients should be reassured that the condition is not serious.

**Senile Purpura**

Senile purpura causes ecchymoses and results from increased vessel fragility due to connective tissue damage to the dermis caused by chronic sun exposure and aging.

Senile purpura typically affects elderly patients as their dermal tissues atrophy and blood vessels become more fragile. Patients develop persistent dark purple ecchymoses, which are characteristically confined to the extensor surfaces of the hands and forearms. New lesions appear without known trauma and then resolve over several days, leaving a brownish discoloration caused by deposits of hemosiderin; this discoloration may clear over weeks to months or may be permanent. The skin and subcutaneous tissue of the involved area often appear thinned and atrophic. No treatment hastens lesion resolution or is needed. Although cosmetically displeasing, the disorder has no health consequences.
Chapter 113. Spleen Disorders

Introduction

By structure and function the spleen is like 2 organs. The white pulp, consisting of periarterial lymphatic sheaths and germinal centers, acts as an immune organ. The red pulp, consisting of macrophages and granulocytes lining vascular spaces (the cords and sinusoids), acts as a phagocytic organ.

The white pulp is a site of production and maturation of B and T cells. B cells in the spleen generate protective humoral antibodies; in certain autoimmune disorders (eg, immune thrombocytopenic purpura [ITP], Coombs'-positive immune hemolytic anemias), inappropriate autoantibodies to circulating blood elements also may be synthesized.

The red pulp removes antibody-coated bacteria, senescent or defective RBCs, and antibody-coated blood cells (as may occur in immune cytopenias such as ITP, Coombs'-positive hemolytic anemias, and some neutropenias). The red pulp also serves as a reservoir for blood elements, especially WBCs and platelets. During its culling and pitting of RBCs, the spleen removes inclusion bodies, such as Heinz bodies (precipitates of insoluble globin), Howell-Jolly bodies (nuclear fragments), and whole nuclei; thus, after splenectomy or in the functionally hyposplenic state, RBCs with these inclusions appear in the peripheral circulation. Hematopoiesis normally occurs in the red pulp only during fetal life. Beyond fetal life, hematopoiesis may occur if injury to bone marrow (eg, by fibrosis or tumors) allows hematopoietic stem cells to circulate and repopulate the adult spleen (see Primary Myelofibrosis on p. 999 and Myelodysplastic Syndrome on p. 1014).

Splenomegaly

Splenomegaly is almost always secondary to other disorders. Its causes are myriad, as are the many possible ways of classifying them (see Table 113-1). In temperate climates, the most common causes are

- Myeloproliferative disorders
- Lymphoproliferative disorders
- Storage diseases (eg, Gaucher's disease)
- Connective tissue disorders

In the tropics, the most common causes are

- Infectious diseases (eg, malaria, kala-azar)

If splenomegaly is massive (spleen palpable 8 cm below the costal margin), the cause is usually chronic lymphocytic leukemia, non-Hodgkin lymphoma, chronic myelocytic leukemia, polycythemia vera, myelofibrosis with myeloid metaplasia, or hairy cell leukemia.

Splenomegaly can lead to cytopenia (see Hypersplenism on p. 985).

Evaluation

History: At presentation, most of the symptoms result from the underlying disorder. However, splenomegaly itself may cause early satiety by encroachment of the enlarged spleen on the stomach. Fullness and left upper quadrant abdominal pain are also possible. Severe pain suggests splenic infarction. Recurrent infections, symptoms of anemia, or bleeding manifestations suggest cytopenia and possible hypersplenism.

Physical examination: The sensitivity for detection of ultrasound-documented splenic enlargement is 60 to 70% for palpation and 60 to 80% for percussion. Up to 3% of normal,
thin, people have a palpable spleen. Also, a palpable left upper quadrant mass may indicate a problem other than an enlarged spleen.

Other helpful signs include a splenic friction rub that suggests splenic infarction and epigastric and splenic bruits that suggest congestive splenomegaly. Generalized adenopathy may suggest a myeloproliferative, lymphoproliferative, infectious, or autoimmune disorder.

**Testing:** If confirmation of splenomegaly is necessary because the examination is equivocal, ultrasonography is the test of choice because of its accuracy and low cost. CT and MRI may provide more detail of the organ's consistency. MRI is especially useful in detecting portal or splenic vein thromboses. Nuclear scanning is accurate and can identify accessory splenic tissue but is expensive and cumbersome to do.

Specific causes suggested clinically should be confirmed by appropriate testing (see elsewhere in THE MANUAL). If no cause is suggested, the highest priority is exclusion of occult infection, because early treatment affects the outcome of infection more than it does most other causes of splenomegaly. Testing should be thorough in areas of high geographic prevalence of infection or if the patient appears to be ill. CBC, blood cultures, and bone marrow examination and culture should be considered. If the patient is not ill, has no symptoms besides those due to splenomegaly, and has no risk factors for infection, the extent of testing is controversial but probably includes CBC, peripheral blood smear, liver function tests, and abdominal CT. Flow cytometry of peripheral blood is indicated if lymphoma is suspected.

Specific peripheral blood findings may suggest underlying disorders (eg, lymphocytosis in chronic lymphocytic leukemia; leukocytosis and immature forms in other leukemias). Excessive basophils, eosinophils, or nucleated or teardrop RBCs suggest myeloproliferative disorders. Cytopenias suggest hypersplenism. Spherocytosis suggests hypersplenism or hereditary spherocytosis. Liver function test results are diffusely abnormal in congestive splenomegaly with cirrhosis; an isolated elevation of serum alkaline phosphatase suggests hepatic infiltration, as in myeloproliferative and lymphoproliferative disorders and miliary TB.

Some other tests may be useful, even in asymptomatic patients. Serum protein electrophoresis identifying a monoclonal gammopathy or decreased immunoglobulins suggest lymphoproliferative disorders or amyloidosis; diffuse hypergammaglobulinemia suggests chronic infection (eg, malaria, kala-azar, brucellosis, TB) or cirrhosis with congestive splenomegaly, sarcoidosis, or connective tissue disorders. Elevation of serum uric acid suggests a myeloproliferative or lymphoproliferative disorder. Elevation of WBC alkaline phosphatase suggests a myeloproliferative disorder, whereas decreased levels suggest chronic myelocytic leukemia.

If testing reveals no abnormalities other than splenomegaly, the patient should be reevaluated at intervals of 6 to 12 mo or when new symptoms develop.

**Treatment**

Treatment is directed at the underlying disorder. The enlarged spleen itself needs no treatment unless severe hypersplenism is present. Patients with palpable or very large spleens probably should avoid contact sports to decrease the risk of splenic rupture.

**Hypersplenism**

**Hypersplenism is cytopenia caused by splenomegaly.**

Hypersplenism is a secondary process that can arise from splenomegaly of almost any cause (see Table 113-1). Splenomegaly increases the spleen's mechanical filtering and destruction of RBCs and often of WBCs and platelets. Compensatory bone marrow hyperplasia occurs in those cell lines that are reduced in the circulation.
Symptoms and Signs

Splenomegaly is the hallmark; spleen size correlates with the degree of anemia. The spleen can be expected to extend about 2 cm beneath the costal margin for each 1-g decrease in Hb. Other clinical findings usually result from the underlying disorder.

Diagnosis

Hypersplenism is suspected in patients with splenomegaly and anemia or cytopenias. Evaluation is similar to that of splenomegaly (see p. 984).

Unless other mechanisms coexist to compound their severity, anemia and other cytopenias are modest and asymptomatic (eg, platelet counts, 50,000 to 100,000/μL; WBC counts, 2500 to 4000/μL with normal WBC differential count). RBC morphology is generally normal except for occasional spherocytosis. Reticulocytosis is usual.

Treatment

• Possibly splenic ablation (splenectomy or radiation therapy)

• Vaccination for splenectomized patients

Treatment is directed at the underlying disorder. However, if hypersplenism is the only serious manifestation of the disorder (eg, Gaucher's disease), splenic ablation by splenectomy or radiation therapy may be indicated (see Table 113-2). Because the intact spleen protects against serious infections with encapsulated bacteria, splenectomy should be avoided whenever possible, and patients undergoing splenectomy require vaccination against infections caused by Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae. After splenectomy, patients are particularly susceptible to severe sepsis. Patients who develop fever should receive empiric antibiotics.

Splenic Injury

Splenic injury usually results from blunt abdominal trauma.

Significant impact (eg, motor vehicle crash) can damage the spleen, as can penetrating trauma (eg, knife wound, gunshot wound). Splenic enlargement as a result of fulminant Epstein-Barr viral disease (infectious mononucleosis or posttransplant Epstein-Barr virus-mediated pseudolymphoma) predisposes to injury with minimal trauma or even spontaneously. Splenic injuries range from subcapsular hematomas and small capsular lacerations to deep parenchymal lacerations, crush injury, and avulsion from the pedicle.

[Table 113-2, Indications for Splenectomy or Radiation Therapy in Hypersplenism]

The main immediate consequence is hemorrhage into the peritoneal cavity. The amount of hemorrhage may be small or large, depending on the nature and degree of injury. Many small lacerations, particularly in children, cease bleeding spontaneously. Larger injuries hemorrhage extensively, often causing hemorrhagic shock. A splenic hematoma sometimes ruptures, usually in the first few days, although rupture can occur from hours to even months after injury.

Symptoms and Signs

The manifestations of major hemorrhage, including hemorrhagic shock, abdominal pain, and distention, are usually clinically obvious. Lesser hemorrhage causes left upper quadrant abdominal pain, which sometimes radiates to the shoulder. Patients with unexplained left upper quadrant pain, particularly if there is evidence of hypovolemia or shock, should be asked about recent trauma.
Diagnosis

The diagnosis is confirmed with CT in stable patients and with bedside (point of care) ultrasonography or exploratory laparotomy in unstable patients.

Treatment

Treatment has traditionally been splenectomy. However, splenectomy should be avoided if possible, particularly in children, to avoid the resulting permanent susceptibility to bacterial infections. Most small, and some moderate-sized lacerations in stable patients (particularly children) are managed with hospital observation and sometimes transfusion rather than surgery. When surgery is needed, the spleen can be surgically repaired in a few cases, but splenectomy is still the main surgical treatment.
Chapter 114. Eosinophilic Disorders

Introduction

Eosinophils are granulocytes derived from the same progenitor cells as monocytes/macrophages, neutrophils, and basophils. The precise functions of eosinophils are unknown. Although they are phagocytic, eosinophils are less efficient than neutrophils in killing intracellular bacteria. And although eosinophilia commonly accompanies helminthic infections and eosinophils are toxic to helminths in vitro, there is no direct evidence that they kill parasites in vivo. Eosinophils may modulate immediate hypersensitivity reactions by degrading or inactivating mediators released by mast cells, such as histamine, leukotrienes (which may cause vasoconstriction and bronchoconstriction), lysophospholipids, and heparin. Prolonged eosinophilia may result in tissue damage by mechanisms that are not fully understood.

Eosinophil granules contain major basic protein and eosinophil cationic protein that are toxic to several parasites and to mammalian cells. These proteins bind heparin and neutralize its anticoagulant activity. Eosinophil-derived neurotoxin can severely damage myelinated neurons. Eosinophil peroxidase, which differs significantly from peroxidase of other granulocytes, generates oxidizing radicals in the presence of hydrogen peroxide and a halide. Charcot-Leyden crystals are primarily composed of phospholipase B and are located in sputum, tissues, and stool in disorders in which there is eosinophilia (eg, asthma, eosinophilic pneumonia).

The normal peripheral blood eosinophil count is < 350/μL, with diurnal levels that vary inversely with plasma cortisol levels; the peak occurs at night and the trough in the morning. The eosinophil count can decrease with stress, with use of β-blockers or corticosteroids, and sometimes with bacterial or viral infections. The count can increase with allergic disorders, with certain infections (typically parasitic), and from numerous other causes (see below). The circulating half-life of eosinophils is 6 to 12 h, with most eosinophils residing in tissues (eg, the upper respiratory and GI tracts, skin, uterus).

Eosinophil production appears to be regulated by T cells through the secretion of the hematopoietic growth factors granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and interleukin-5 (IL-5). Although GM-CSF and IL-3 also increase the production of other myeloid cells, IL-5 increases eosinophil production exclusively.

Eosinophilia

Eosinophilia is defined as a peripheral blood eosinophil count > 450/μL. Causes and associated disorders are myriad but often represent an allergic reaction or parasitic infection. Diagnosis involves selective testing directed at clinically suspected causes. Treatment is directed at the cause.

Eosinophilia has features of an immune response: an agent such as Trichinella spiralis invokes a primary response with relatively low levels of eosinophils, whereas repeated exposures result in an augmented or secondary eosinophilic response. Several compounds released by mast cells and basophils induce IgE-mediated eosinophil production. Such substances include eosinophil chemotactic factor of anaphylaxis, leukotriene B4, complement complex (C5-C6-C7), and histamine (over a narrow range of concentration).

Eosinophilia itself does not cause symptoms. However, occasionally patients with very severe eosinophilia (eg, eosinophil counts of > 100,000/μL), usually with eosinophilic leukemia, develop complications of hyperleukocytosis (see p. 990).

Etiology

Eosinophilia may be primary (ie, clonal proliferation of eosinophils associated with hematologic disorders such as leukemias and myeloproliferative disorders), secondary to (or associated with) numerous nonhematologic disorders (see Table 114-1), or idiopathic (if other causes cannot be identified).
The most common cause in the US is

- Allergic or atopic disorders (typically respiratory or dermatologic)

Other common causes include

- Infections (typically parasitic)
- Certain tumors (hematologic or solid, benign or malignant)

Almost any parasitic invasion of tissues can elicit eosinophilia, but protozoa and noninvasive metazoa usually do not.

Of the tumors, Hodgkin lymphoma may elicit marked eosinophilia, whereas eosinophilia is less common in non-Hodgkin lymphoma, chronic myelocytic leukemia, and acute lymphoblastic leukemia. Ovarian cancer is the most commonly associated solid tumor.

The pulmonary infiltrates with eosinophilia syndrome comprises a spectrum of clinical manifestations characterized by peripheral eosinophilia and eosinophilic pulmonary infiltrates (see p. 1953) but is usually of unknown cause.

Patients with eosinophilic drug reactions may be asymptomatic or have various syndromes, including interstitial nephritis, serum sickness, cholestatic jaundice, hypersensitivity vasculitis, and immunoblastic lymphadenopathy. Several hundred patients were reported to have developed an eosinophilia-myalgia syndrome after taking L-tryptophan for sedation or psychotropic support. This syndrome was probably caused by a contaminant rather than by L-tryptophan. The symptoms (severe muscle pain, tenosynovitis, muscle edema, rash) lasted weeks to months, and several deaths occurred.

**Evaluation**

The number of possible causes and associated disorders is very large. Common causes (eg, allergic, infectious, neoplastic disorders) should be considered first, but even they are often difficult to identify; a thorough history and physical examination are always required.

**History:** The questions most likely to be helpful pertain to the following:

- Travel (suggesting possible parasite exposure)
- Allergies
- Drug use
- Use of herbal products and dietary supplements, including L-tryptophan
- Systemic symptoms (eg, fever, weight loss, myalgias, arthralgias, rashes, lymphadenopathy)

Systemic symptoms suggest that a minor allergic or drug cause is less likely, and a detailed evaluation for an infectious, neoplastic, connective tissue, or other systemic disorder should be done. Other important parts of the history include family history of blood dyscrasias (eg, plasma cell disorders) and a complete review of systems, including symptoms of allergic, pulmonary, cardiac, GI, and neurologic dysfunction.

**Physical examination:** General physical examination is done, including the heart, skin, and neurologic and pulmonary systems. Certain physical findings may suggest causes or associated disorders. Examples include rash (allergic, dermatologic, or vasculitic disorders), abnormal lung findings (asthma, lung infections, or syndromes of pulmonary infiltration with eosinophilia), and generalized lymphadenopathy or
spleenomegaly (myeloproliferative disorders or cancer).

**Testing:** Eosinophilia is typically recognized when CBC is done for other reasons. Additional testing often includes the following:

- Stool ova and parasite testing
- Other tests to detect organ damage or for specific causes based on clinical findings

When the CBC indicates eosinophilia, an absolute eosinophil count is rarely needed.

In general, if a drug or allergic cause is not clinically suspected, 3 stool specimens should be examined for ova and parasites; however, negative findings do not rule out a parasitic cause (eg, trichinosis requires a muscle biopsy; visceral larva migrans and filarial infections require other tissue biopsies; duodenal aspirates may be needed to exclude specific parasites, eg, *Strongyloides* sp—see p. 1350).

Other specific diagnostic tests are determined by the clinical findings (particularly travel history) and may include chest x-ray, urinalysis, liver and kidney function tests, and serologic tests for parasitic and connective tissue diseases. If patients have generalized lymphadenopathy, splenomegaly, or systemic symptoms, blood tests are done; an elevated serum vitamin B\(_{12}\) level, low WBC alkaline phosphatase level, or abnormalities on the peripheral blood smear suggest an underlying myeloproliferative disorder, in which case a bone marrow aspirate and biopsy with cytogenetic studies may be helpful. Also, if routine evaluation does not reveal a cause, tests are done to detect organ damage. Testing can include some of the tests previously mentioned as well as LDH and liver function tests (suggesting liver damage or possibly a myeloproliferative disorder), echocardiogram, and pulmonary function tests.

**Treatment**

- Sometimes corticosteroids

Corticosteroid treatment of hypereosinophilic syndrome is discussed on p. 992.

Drugs known to be associated with eosinophilia are stopped. Other identified causes are treated.

If no cause is detected, the patient is followed for complications. A brief trial with low-dose corticosteroids may lower the eosinophil count if eosinophilia is secondary (eg, to allergy, connective tissue disorders, or parasitic infection) rather than primary. Such a trial is indicated if eosinophilia is persistent and progressive in the absence of a treatable cause.

**Hypereosinophilic Syndrome**

*(Idiopathic Hypereosinophilic Syndrome)*

**Hypereosinophilic syndrome (HES)** is a condition characterized by peripheral blood eosinophilia with manifestations of organ system involvement or dysfunction directly related to eosinophilia in the absence of parasitic, allergic, or other causes of eosinophilia. Symptoms are myriad, depending on which organs are dysfunctional. Diagnosis involves excluding other causes of eosinophilia and bone marrow and genetic tests. Treatment usually begins with prednisone and, in one common subtype, includes imatinib.

HES is traditionally defined by peripheral blood eosinophilia > 1500/μL persisting ≥6 mo. HES was previously considered to be idiopathic but is now known to result from various disorders, some of which have known causes. One limitation of the traditional definition is that it does not include those patients with some of the same abnormalities (eg, genetic defects) that are known causes of HES and who do not fulfill the traditional HES diagnostic criteria for degree or duration of eosinophilia. Another limitation is that some patients with eosinophilia and organ damage that characterize HES require treatment earlier than the 6 mo necessary to confirm the traditional diagnostic criteria.
HES is rare, has an unknown prevalence, and most often affects people age 20 through 50. Only some patients with prolonged eosinophilia develop organ dysfunction that characterizes hypereosinophilic syndrome. Although any organ may be involved, the heart, lungs, spleen, skin, and nervous system are typically affected. Cardiac involvement often causes morbidity and mortality.

**Subtypes:** There are two broad subtypes (see Table 114-2):

- Myeloproliferative variant
- Lymphoproliferative variant

The **myeloproliferative variant** is often associated with a small interstitial deletion in chromosome 4 and the FIPIL1/PDGFRα-associated fusion gene (reflecting tyrosine kinase activity that can transform hematopoietic cells). Patients often have

- Splenomegaly
- Thrombocytopenia
- Anemia
- Elevated serum vitamin B₁₂ levels
- Hypogranular or vacuolated eosinophils
- Myelofibrosis

[Table 114-2. Subtypes of Hypereosinophilic Syndrome]

Patients with this subtype often develop endomyocardial fibrosis and may rarely develop acute myeloid or lymphoblastic leukemia. Patients with the FIPIL1/PDGFRα-associated fusion gene are more often males and may be responsive to imatinib.

The **lymphoproliferative variant** is associated with a clonal population of T cells with aberrant phenotype. Patients more often have

- Angioedema, skin abnormalities, or both
- Hypergammaglobulinemia (especially IgE)
- Circulating immune complexes (sometimes with serum sickness)

They also more often respond favorably to corticosteroids and occasionally develop T-cell lymphoma.

**Other HES variants** include chronic eosinophilic leukemia, Gleich's syndrome (cyclical eosinophilia and angioedema), familial hypereosinophilic syndrome mapped to 5q 31-33, and other organ-specific syndromes. Hyperleukocytosis may occur in patients with eosinophilic leukemia and very high eosinophil counts (eg, > 100,000 cells/μL). Eosinophils can form aggregates that occlude small blood vessels, causing tissue ischemia and microinfarctions. Common manifestations include brain or lung hypoxia (eg, encephalopathy, dyspnea or respiratory failure).

**Symptoms and Signs**

Symptoms are diverse and depend on which organs are dysfunctional (see Table 114-3).

Occasionally, patients with very severe eosinophilia (eg, eosinophil counts of > 100,000/μL) develop
complications of hyperleukocytosis, such as manifestations of brain or lung hypoxia (eg, encephalopathy, dyspnea or respiratory failure).

**Diagnosis**

- Exclusion of secondary eosinophilia
- Tests to identify organ damage
- Bone marrow examination with cytogenetics

Evaluation for HES should be considered in patients who have peripheral blood eosinophilia > 1500/μL present on more than one occasion that is unexplained, particularly when there are manifestations of organ damage. Testing to exclude disorders causing eosinophilia should be done (see p. 990). Further evaluation should include blood chemistries (including liver enzymes, creatine kinase, renal function, and troponin), ECG; echocardiography; pulmonary function tests; and CT of the chest, abdomen, and pelvis. Bone marrow aspirate and biopsy with flow cytometry, cytogenetics, and reverse transcriptase-PCR or fluorescence in situ hybridization (FISH) is done to identify the FIPIL1/PDGFRA-associated fusion gene and other possible causes of eosinophilia (eg, BCR-ABL abnormalities characteristic of chronic myelogenous leukemia).

**Prognosis**

Death usually results from organ, particularly heart, dysfunction. Cardiac involvement is not predicted by the degree or duration of eosinophilia. Prognosis varies depending on response to therapy. Response to imatinib improves the prognosis among patients with the FIPIL1/PDGFRA-associated fusion gene. Current therapy has improved prognosis.

**Treatment**

- Corticosteroids for hypereosinophilia and often for ongoing treatment of organ damage
- Imatinib for patients with the FIPIL1/PDGFRA-associated fusion gene
- Supportive therapy

Treatments include immediate therapy, definitive therapies (treatments directed at the disorder itself), and supportive therapies.

**Immediate therapy:** For patients with very severe eosinophilia, complications of hyperleukocytosis, or both (usually patients with eosinophilic leukemia), high-dose IV corticosteroids (eg, prednisone 1 mg/kg or equivalent) should be initiated as soon as possible. If the eosinophil count is much lower (eg, by ≥ 50%) after 24 h, corticosteroid dose can be repeated daily; if not, an alternative treatment (eg, vincristine, imatinib, leukapheresis) is begun.

**Definitive therapy:** Patients with the FIPIL1/PDGFRA-associated fusion gene are usually treated with imatinib and, particularly if heart damage is suspected, corticosteroids. If imatinib is ineffective or poorly tolerated, another tyrosine kinase inhibitor (eg, dasatinib, nilotinib, sorafenib) can be used, or allogenic hematopoietic stem cell transplantation can be tried.

Patients without the FIPIL1/PDGFRA-associated fusion gene, even if asymptomatic, are often given one dose of prednisone 60 mg (or 1 mg/kg) po to determine corticosteroid responsiveness (ie, a decrease in the eosinophil count). In patients with symptoms or organ damage, prednisone is continued at the same dose for 2 wk, then tapered. Patients without symptoms and organ damage are monitored for at least 6 mo for these complications. If corticosteroids cannot be easily tapered, a corticosteroid-sparing drug (eg,
hydroxyurea, interferon alfa) can be used.

**Supportive therapy:** Supportive drug therapy and surgery may be required for cardiac manifestations (eg, infiltrative cardiomyopathy, valvular lesions, heart failure). Thrombotic complications may require the use of antiplatelet drugs (eg, aspirin, clopidogrel, ticlopidine); anticoagulation is indicated if a left ventricular mural thrombus is present or if transient ischemic attacks persist despite use of aspirin.
Chapter 115. Histiocytic Syndromes

Introduction

The histiocytic syndromes are clinically heterogeneous disorders that result from an abnormal proliferation of histiocytes—either monocyte-macrophages (antigen-processing cells) or dendritic cells (antigen-presenting cells). Classifying these disorders is difficult (see Table 115-1) and has changed over time as an understanding of the biology of these cells has evolved.

Langerhans' Cell Histiocytosis

(See also p. 1963.)

Langerhans' cell histiocytosis (LCH) is a proliferation of dendritic mononuclear cells with infiltration into organs locally or diffusely. Most cases occur in children. Manifestations may include lung infiltrates; bone lesions; rashes; and hepatic, hematopoietic, and endocrine dysfunction. Diagnosis is based on biopsy. Factors predicting a poor prognosis include age < 2 yr and dissemination, particularly involving the hematopoietic system, liver, lungs, or a combination. Treatments include supportive measures and chemotherapy or local treatment with surgery or radiation therapy as indicated by the extent of disease.

LCH is a dendritic cell disorder. It can cause distinct clinical syndromes that have been historically described as eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease. Because these syndromes may be varied manifestations of the same underlying disorder and because most patients with LCH have manifestations of more than one of these syndromes, the designations of the separate syndromes are now mostly of historical significance. Estimates of the prevalence of LCH vary widely (eg, from about 1:50,000 to 1:200,000).

In LCH, abnormally proliferating dendritic cells infiltrate one or more organs. Bone, skin, teeth, gingival tissue, ears, endocrine organs, lungs, liver, spleen, lymph nodes, and bone marrow may be involved. Organs may be affected by infiltration, causing dysfunction, or by compression from adjacent enlarged structures. In about half of patients, more than one organ is involved.

Symptoms and Signs

Symptoms and signs vary considerably depending on which organs are infiltrated. The syndromes are described by their historical designations, but few patients present with classic manifestations.

Eosinophilic granuloma: Solitary or multifocal eosinophilic granuloma (60 to 80% of LCH cases) occurs predominantly in older children and young adults, usually by age 30; incidence peaks between ages 5 and 10 yr. Lesions most frequently involve bone, often with pain, the inability to bear weight, or both and with overlying tender (sometimes warm) swelling.

Hand-Schuller-Christian disease: This syndrome (15 to 40% of LCH cases) occurs in children aged 2 to 5 yr and in some older children and adults. This systemic disorder classically involves the flat bones of the skull, ribs, pelvis, scapula, or a combination. Long bones and lumbosacral vertebrae are less frequently involved; the wrists, hands, knees, feet, and cervical vertebrae are rarely involved. In classic cases, patients have exophthalmos caused by orbital tumor mass. Rarely, vision loss or strabismus is caused by optic nerve or orbital muscle involvement. Tooth loss caused by apical and gingival infiltration is common in older patients.

Chronic otitis media and otitis externa due to involvement of the mastoid and petrous portions of the temporal bone with partial obstruction of the auditory canal are fairly common. Diabetes insipidus, the last component of the classic triad that includes flat bone involvement and exophthalmos, affects 5 to 50% of
patients, with higher percentages in children who have systemic disease and involvement of the orbit and skull. Up to 40% of children with systemic disease have short stature. Hyperprolactinemia and hypogonadism can result from hypothalamic infiltration.

**Letterer-Siwe disease:** This syndrome (10% of LCH cases), a systemic disorder, is the most severe form of LCH. Typically, a child < 2 yr presents with a scaly seborrheic, eczematoid, sometimes purpuric rash involving the scalp, ear canals, abdomen, and inter-triginous areas of the neck and face. Denuded skin may facilitate microbial invasion, leading to sepsis. Frequently, there is ear drainage, lymphadenopathy, hepatosplenomegaly, and, in severe cases, hepatic dysfunction with hypoproteinemia and diminished synthesis of clotting factors. Anorexia, irritability, failure to thrive, and pulmonary manifestations (e.g., cough, tachypnea, pneumothorax) may also occur. Significant anemia and sometimes neutropenia occur; thrombocytopenia is of grave prognostic significance. Parents frequently report precocious eruption of teeth, when in fact the gums are receding to expose immature dentition. Patients may appear abused or neglected.

**Diagnosis**

- **Biopsy**

LCH is suspected in patients (particularly young patients) with unexplained pulmonary infiltrates, bone lesions, or ocular or craniofacial abnormalities; and in children < 2 yr with typical rashes or severe, unexplained multiorgan disease.

X-rays are often done because of presenting symptoms. Bone lesions are usually sharply marginated, and round or oval, with a beveled edge giving the appearance of depth. However, some lesions are radiographically indistinguishable from Ewing's sarcoma, osteogenic sarcoma, other benign and malignant conditions, or osteomyelitis.

Diagnosis is based on biopsy. Langerhans' cells are usually prominent, except in older lesions. These cells are identified by a pathologist experienced in the diagnosis of LCH according to their immunohistochemical characteristics, which include cell surface CD 1a and S-100. Once diagnosis is established, the extent of disease must be determined by appropriate imaging and laboratory studies.

**Prognosis**

Prognosis is good for patients with both of the following:

- Disease restricted to skin, lymph nodes, or bone
- Age > 2 yr

With treatment, almost all such patients survive.

Morbidity and mortality are increased in patients with multiorgan involvement, particularly those with

- Age < 2 yr
- Involvement of the hematopoietic system, liver, lungs, or spleen

With treatment, the overall survival rate for patients with multiorgan disease is about 80%. Death is more likely among at-risk patients who do not respond to initial therapy. Disease recurrence is common. A chronic remitting and exacerbating course may occur, particularly among adults.

**Treatment**

- Supportive care
- Sometimes hormone replacement therapy for hypopituitarism
• Chemotherapy for multiorgan involvement

• Sometimes surgery or radiation therapy (usually for single bone involvement)

Because these syndromes are rare and complex, patients are usually referred to institutions experienced in the treatment of LCH. General supportive care is essential and may include scrupulous hygiene to limit ear, cutaneous, and dental lesions. Debridement or resection of severely affected gingival tissue limits oral involvement. Seborrhea-like dermatitis of the scalp may diminish with use of a selenium-based shampoo twice/wk. If shampooing is ineffective, topical corticosteroids are used in small amounts and briefly in small areas.

Patients with systemic disease are monitored for potential chronic disabilities, such as cosmetic or functional orthopedic and cutaneous disorders and neurotoxicity as well as for psychologic problems that may require psychosocial support.

Many patients require hormone replacement for diabetes insipidus or other manifestations of hypopituitarism.

Chemotherapy is indicated for patients with multiorgan involvement. Protocols sponsored by the Histiocyte Society are used; treatment protocols vary according to the risk category. Almost all patients with a good response to therapy can stop treatment. Protocols for poor responders are under study.

Local surgery or radiation therapy is used for disease involving a single bone and, rarely, when multiple lesions or multiple bones are involved. Easily accessible lesions in noncritical locations undergo surgical curettage. Surgery should be avoided when it may result in significant cosmetic deformities, orthopedic deformities, or loss of function. Radiation therapy involving megavoltage equipment may be given to patients at risk of skeletal deformity, visual loss secondary to exophthalmos, pathologic fractures, vertebral collapse, and spinal cord injury or to patients with severe pain. Doses of radiation are considerably less than those used to treat cancer. Surgery and radiation therapy should be done by specialists experienced in treating LCH.

Patients with multiorgan disease that progresses despite standard therapy usually respond to more aggressive chemotherapy. Patients who do not respond to salvage chemotherapy may undergo bone marrow transplantation, experimental chemotherapy, or immunosuppressive or other immunomodulatory therapy.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon disorder causing immune dysfunction in infants and young children. Many patients have an underlying immune disorder, although in some patients the underlying disorder is not known. Manifestations may include lymphadenopathy, hepatosplenomegaly, fever, and neurologic abnormalities. Diagnosis is by specific clinical and testing (genetic) criteria. Treatment is usually with chemotherapy and, in refractory cases or in cases with a genetic cause, hematopoietic stem cell transplantation.

HLH is characterized by

• High levels of cytokines (eg, IL-1, IL-2; TNF-α; interferon [INF]-γ; soluble IL-6, IL-10, IL-12; granulocyte-macrophage colony stimulating factor [GM-CSF])

• Uncontrolled proliferation and activation of cytotoxic T cells, natural killer cells, and macrophages in multiple tissues

Certain aspects of immune function, such as natural killer cell and cytotoxic T-cell activity, are abnormal.

HLH is uncommon. It affects mostly infants < 18 mo. HLH can be
Familial (primary)

Acquired (secondary)

In both forms, genetic abnormalities, clinical manifestations, and outcomes tend to be similar. Acquired HLH can be associated with other immune disorders (eg, leukemias, lymphomas, SLE, RA, polyarteritis nodosa, sarcoidosis, progressive systemic sclerosis, Sjogren's syndrome, Kawasaki disease) and can occur in kidney or liver transplant recipients. Acquired HLH may be secondary to other disorders or to immunosuppressive regimens used to treat them or possibly to infections.

Symptoms and Signs

Common early manifestations include fever, hepatomegaly, splenomegaly, rash, lymphadenopathy, and neurologic abnormalities (eg, seizures, retinal hemorrhages, ataxia, altered consciousness or coma). Bone lesions may occur, and clinical manifestations may mimic child abuse.

Diagnosis

Specific clinical and testing criteria

HLH is suspected in children with unexplained recurrent infections and typical laboratory abnormalities (cytopenias, coagulopathy, abnormal liver function test results, high serum ferritin levels) or with typical symptoms and signs.

Diagnosis requires the presence of > 5 of the following criteria:

- Fever (peak temperature of > 38.5°C for > 7 days)
- Splenomegaly (spleen palpable > 3 cm below costal margin)
- Cytopenia involving > 2 cell lines (Hb < 9 g/dL, absolute neutrophil count < 100/μL, platelets < 100,000/μL)
- Hypertriglyceridemia (fasting triglycerides > 2.0 mmol/L or > 3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen < 1.5 g/L or > 3 SD less than normal value for age)
- Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes)
- Low or absent natural killer cell activity
- Serum ferritin > 500 μg/L plus elevated soluble IL-2 (CD25) levels (> 2400 U/mL or very high for age)

Because some of these tests may not be widely available and HLH is uncommon, patients are usually referred to specialized centers for evaluation.

Treatment

Hematopoietic stem cell transplantation and chemotherapy

Treatment should be started if the disorder is suspected, even if not all diagnostic criteria are fulfilled. Patients are usually treated by a pediatric hematologist and in a referral center experienced in treating patients with HLH. Depending on the presence of factors such as a family history of HLH, coexisting infections, and demonstrated immune system defects, treatment can involve combinations of hematopoietic stem cell transplantation, dexamethasone, cyclosporine, etoposide, and methotrexate.

Rosai-Dorfman Disease
Rosai-Dorfman disease is a rare disorder characterized by accumulation of histiocytes and massive lymphadenopathy, particularly in the neck and head.

Rosai-Dorfman disease is most common among patients < 20 yr, particularly blacks. Cause is unknown.

The most common presenting symptoms are fever and massive, painless cervical adenopathy. Other nodal sites, including the mediastinum, retroperitoneum, axillae, and inguinal region, may be involved, as may the nasal cavity, salivary gland tissue, other regions of the head and neck, and CNS. Other manifestations may include lytic bone lesions, pulmonary nodules, and rash. The bone marrow and spleen are typically spared.

Laboratory testing usually shows leukocytosis, polyclonal hypergammaglobulinemia, hypochromic or normocytic anemia, and elevated ESR.

The disorder commonly resolves without treatment. Treatment is uncertain; chemotherapy has been tried.
Chapter 116. Myeloproliferative Disorders

Introduction

The myeloproliferative disorders are characterized by abnormal proliferation of one or more hematopoietic cell lines or connective tissue elements. They include

• Essential thrombocythemia
• Primary myelofibrosis
• Polycythemia vera
• Chronic myelocytic leukemia (see p. 1012)

Essential thrombocythemia, primary myelofibrosis, and polycythemia vera are Philadelphia chromosome-negative myeloproliferative disorders. Myeloproliferative disorders, particularly chronic myelocytic leukemia, sometimes lead to acute leukemia; some hematologists also classify hypereosinophilic syndrome and mastocytosis as myeloproliferative disorders. However, most experts argue that these disorders are sufficiently different and omit them.

Each disorder is identified according to its predominant feature or site of proliferation (see Table 116-1). Despite overlap, each disorder has a somewhat typical constellation of clinical features, laboratory findings, and course. Although proliferation of one cell line may dominate the clinical picture, each disorder is typically caused by clonal proliferation of a pluripotent stem cell, causing varying degrees of abnormal proliferation of RBC, WBC, and platelet precursors in the bone marrow. This abnormal clone does not, however, produce bone marrow fibroblasts, which can proliferate in polyclonal reactive fashion.

An abnormality of a tyrosine kinase called JAK2, involved in the bone marrow response to erythropoietin, contributes to the cause of polycythemia vera and causes a high proportion of cases of essential thrombocytemia and myelofibrosis.

[Table 116-1. Classification of Myeloproliferative Disorders]

Essential Thrombocytemia

(Essential Thrombocytosis; Primary Thrombocytemia)

Essential thrombocytemia (ET) is characterized by an increased platelet count, megakaryocytic hyperplasia, and a hemorrhagic or thrombotic tendency. Symptoms and signs may include weakness, headaches, paresthesias, bleeding, splenomegaly, and erythromelalgia with digital ischemia. Diagnosis is based on a platelet count > 450,000/μL, normal RBC mass or normal Hct in the presence of adequate iron stores, absence of myelofibrosis, the Philadelphia chromosome (or BCR-ABL rearrangement), and any other disorder that could cause thrombocytosis. Treatment is controversial but may include aspirin. Patients > 60 yr and those with previous thromboses and transient ischemic attacks require cytotoxic drugs to decrease risk of thromboses. Data suggest that risk of thrombosis does not correlate with platelet count, although anecdotal experience suggests otherwise.

Pathophysiology

ET is a typically clonal abnormality of a multipotent hematopoietic stem cell. However, some women who fulfill diagnostic criteria for ET have polyclonal hematopoiesis. ET usually occurs with bimodal peaks of between ages 50 and 70 yr and a separate peak among young females.

Platelet production is increased. Platelet survival is usually normal, although it may decrease due to splenic sequestration and in patients with erythromelalgia with digital ischemia.
In elderly patients with atherosclerosis, increased platelets may lead to serious bleeding or, more commonly, thrombosis. Thrombosis is the major cause of morbidity and mortality. Recent studies indicate that an elevated leukocyte count is a major independent risk factor for thromboses. Although anatomically (and intuitively), elevated platelet count may increase the risk of thrombosis, one study found an inverse relationship between absolute platelet count and thrombotic risk. Bleeding is more likely with extreme thrombocytosis (ie, > 1.5 million platelets/μL) due to an acquired von Willebrand's factor deficiency.

Symptoms and Signs

Common symptoms are

- Weakness
- Hemorrhage
- Gout
- Ocular migraines
- Paresthesias of the hands and feet

Thrombosis may cause symptoms in the affected site (eg, neurologic deficits with stroke or transient ischemic attack, leg pain, swelling or both with lower extremity thrombosis, chest pain and dyspnea with pulmonary embolism). Bleeding is usually mild and manifests as epistaxis, easy bruisability, or GI bleeding. Digital ischemia may occur, and splenomegaly (usually not extending > 3 cm below the left costal margin) occurs in < 50% of patients. Hepatomegaly may rarely occur. In pregnant patients, thrombosis may cause recurrent spontaneous abortions.

Diagnosis

- CBC and peripheral blood smear
- Cytogenetic studies
- Possibly bone marrow examination

ET should be considered in patients in whom common reactive causes (see p. 999) are excluded. If ET is suspected, CBC, peripheral blood smear, and cytogenetic studies, including Philadelphia chromosome or \( BCR-ABL \) assay, should be done. Some authorities recommend bone marrow examination, but although classic ET morphologic abnormalities have been described, the diagnostic value of bone marrow examination is not established. The platelet count can be > 1,000,000/μL but may be as low as 450,000/μL. Platelet count may decrease spontaneously during pregnancy. The peripheral smear may show platelet aggregates, giant platelets, and megakaryocyte fragments. The bone marrow shows megakaryocytic hyperplasia, with an abundance of platelets being released. Bone marrow iron is present. To distinguish from other myeloproliferative disorders that produce thrombocytosis, the diagnosis of ET requires a normal Hct, MCV, and iron studies; absence of the Philadelphia chromosome and \( BCR-ABL \) translocation; and absence of teardrop-shaped RBCs; there may be significant increase in bone marrow fibrosis (present in idiopathic myelofibrosis). The \( JAK2V617F \) mutation occurs in about 50% of patients, and a small minority of ET patients has acquired somatic thrombopoietin receptor gene mutations (\( c-mpl \)).

Prognosis

Life expectancy is near normal. Although symptoms are common, the course of the disease is often benign. Serious arterial and venous thrombotic complications are rare but can be life-threatening. Leukemic transformation occurs in < 2% of patients but may increase after exposure to cytotoxic therapy, especially alkylating agents.

Treatment
• Aspirin

• Platelet-lowering drugs (eg, hydroxyurea, anagrelide)

• Rarely plateletpheresis

For mild vasomotor symptoms (eg, headache, mild digital ischemia, erythromelalgia) and to decrease the risk of thrombosis in low-risk patients, aspirin 81 mg po once/day may be sufficient. Also, most pregnant patients are given aspirin. Use in low-risk patients is acceptable but not data-proven.

Because prognosis is often good, potentially toxic drugs that lower the platelet count should be used sparingly. Generally agreed indications for such therapy are

• Previous thromboses or transient ischemic attack

• Age > 60 yr

Other indications are controversial. Patients with significant bleeding and extreme thrombocytosis (high-risk patients) may need therapy to lower the platelet count. It is unclear whether asymptomatic patients < 60 yr need platelet-lowering drugs. Myelosuppressive drugs to lower platelet count include anagrelide, interferon alfa-2b, and hydroxyurea (sometimes with low-dose aspirin). Hydroxyurea is generally considered the drug of choice, although some clinicians prefer anagrelide. Because anagrelide and hydroxyurea cross the placenta, they are not used during pregnancy; interferon alfa-2b can be used in pregnant women when necessary.

Dosage and monitoring are described in the treatment of polycythemia vera (see p. 1000). The conventional aim of therapy is a platelet count < 450,000/μL without significant clinical toxicity or suppression of other bone marrow elements; however, this goal needs to be reevaluated in view of recent data suggesting an inverse relationship between platelet count and thrombotic risk.

Plateletpheresis has been used in rare patients with serious hemorrhage and recurrent thrombosis or before emergency surgery to immediately reduce the platelet count; this procedure, however, is rarely necessary. Due to the long half-life of platelets (7 days), hydroxyurea and anagrelide do not provide an immediate effect.

Thrombocytosis

(Secondary Thrombocythemia)

Thrombocytosis can develop secondary to

• Chronic inflammatory disorders, eg, RA, inflammatory bowel disease, TB, sarcoidosis, Wegener's granulomatosis

• Acute infection

• Hemorrhage

• Iron deficiency

• Hemolysis

• Cancer (particularly Hodgkin lymphoma, non-Hodgkin lymphoma)

• Splenectomy

• Myeloproliferative and hematologic disorders (eg, polycythemia vera, chronic myelocytic leukemia,
sideroblastic anemia, myelodysplasia [5q- syndrome], idiopathic myelodysplasia)

There are also congenital familial thrombocytoses such as those due to thrombopoietin and thrombopoietin receptor gene mutations.

Platelet function is usually normal. Unlike ET, thrombocytosis does not increase the risk of thrombotic or hemorrhagic complications unless patients have severe arterial disease or prolonged immobility. With secondary thrombocytosis, the platelet count is usually < 1,000,000/μL, and the cause may be obvious from the history and physical examination (perhaps with confirmatory testing). CBC and peripheral blood smear should help suggest iron deficiency or hemolysis. If a cause is not obvious, evaluation for a myeloproliferative disorder should be considered.

Treatment of the underlying disorder usually returns the platelet count to normal.

**Primary Myelofibrosis**

(Agnogenic Myeloid Metaplasia; Myelofibrosis with Myeloid Metaplasia)

Primary myelofibrosis (PMF) is a chronic, usually idiopathic disorder characterized by bone marrow fibrosis, splenomegaly, and anemia with immature and teardrop-shaped RBCs. Diagnosis requires bone marrow examination and exclusion of other conditions that can cause myelofibrosis (secondary myelofibrosis). Treatment is usually supportive.

**Pathophysiology**

Myelofibrosis is excessive bone marrow fibrosis and loss of hematopoietic cells, with subsequent marked increase in extramedullary hematopoiesis (primarily in the liver and spleen, which enlarge significantly). Myelofibrosis may be primary or secondary to a number of hematologic, malignant, and nonmalignant conditions (see Table 116-2).

PMF is more common than secondary myelofibrosis and results from neoplastic transformation of a multipotent bone marrow stem cell. These PMF progeny cells stimulate bone marrow fibroblasts (which are not part of the neoplastic transformation) to secrete excessive collagen. The peak incidence of PMF is between 50 and 70 yr.

In PMF, large numbers of nucleated RBCs (normoblasts) and granulocytes are released into the circulation (leukoerythroblastosis). Serum LDH level is often elevated. Bone marrow failure eventually occurs, with consequent anemia and thrombocytopenia. Rapidly

progressive, chemotherapy-incurable acute leukemia develops in about 10% of patients.

Malignant or acute myelofibrosis, an unusual variant, has a more rapidly progressive downhill course; this variant may actually be a true megakaryocytic leukemia.

**Symptoms and Signs**

In many patients, myelofibrosis is asymptomatic. Other patients have symptoms of anemia, splenomegaly, or, in later stages, general malaise, weight loss, fever, or splenic infarction. Hepatomegaly occurs in a significant proportion of patients. Lymphadenopathy is rare.

**Diagnosis**

• CBC and peripheral blood smear

• Bone marrow examination
PMF should be suspected in patients with splenomegaly, splenic infarction, anemia, or unexplained elevations in LDH. If the disorder is suspected, CBC should be done and peripheral blood morphology and bone marrow should be examined, including cytogenetic testing. If myelofibrosis is detected on bone marrow examination (eg, by increased fibroblasts and collagen as detected by reticulin staining, osteosclerosis), other disorders associated with myelofibrosis (see Table 116-2) should be excluded by appropriate clinical and laboratory evaluation.

Anemia is typically present and usually increases over time. Blood cell morphology is variable. RBCs are poikilocytic. Reticulocytosis and polychromatophilia may be present; teardrop-shaped RBCs (dacryocytes) are characteristic morphologic features. Nucleated RBCs and neutrophil precursors are typically present in peripheral blood. WBC counts are usually increased but are highly variable; a low WBC count tends to indicate a poor prognosis. Neutrophils are usually immature, and myeloblasts may be present, even in the absence of acute leukemia. Platelet counts initially may be high, normal, or decreased; however, thrombocytopenia tends to supervene as the disorder progresses.

If diagnosis is difficult, CD34+ cell count on peripheral blood can be done. Levels are much higher in patients with PMF.

Bone marrow aspiration is usually dry. Because demonstration of bone marrow fibrosis is required and fibrosis may not be uniformly distributed, biopsy should be repeated at a different site if the first biopsy is nondiagnostic.

Prognosis

The median survival is 5 yr from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival and some have a delay in initial diagnosis. Unfavorable prognostic markers include Hb < 10 g/dL, history of transfusions, leukocytosis and leukopenia, and platelet count < 100,000/μL. Patients in the least favorable risk group usually survive < 1 yr. No treatment reverses or controls the underlying process except for allogeneic stem cell transplant.

Treatment

• Symptomatic therapy

• Sometimes allogeneic stem cell transplantation

Treatment is directed at symptoms and complications. Androgens, splenectomy, chemotherapy, and splenic embolization and radiation therapy have been used for palliation. For patients with low erythropoietin levels relative to the degree of anemia, erythropoietin may increase Hct sufficiently; otherwise, RBC transfusion may be necessary. For younger patients with advanced disease, allogeneic stem cell transplantation should be considered. Nonmyeloablative allogeneic stem cell transplantation has been successfully used even in older patients; however, it is usually limited to patients < 65 yr.

Inhibitors of the JAK pathway appear to have a significant effect on splenomegaly and abnormal peripheral hematologic abnormalities. These drugs are in early trials.

Polycythemia Vera

(Primary Polycythemia)

Polycythemia vera (PV) is an idiopathic chronic myeloproliferative disorder characterized by an increase in RBC mass, which often manifests as an increased Hct. There is an increased risk of thrombosis and, rarely, acute leukemia and myelofibrotic transformation. Hepatosplenomegaly may also occur. Diagnosis is made by CBC, testing for JAK2 mutations, and clinical criteria. Treatment involves low-dose aspirin for all patients and myelosuppressive drugs for high-risk patients; phlebotomy, once standard, is now controversial.
PV is the most common of the myeloproliferative disorders; incidence in the US is estimated to be
1.9/100,000, with incidence increasing with age. PV may be slightly more common in men. The mean age
at diagnosis is around 60 yr. PV is very rare in children.

Pathophysiology

PV involves increased production of all cell lines, including RBCs, WBCs, and platelets. Thus, PV is
sometimes called a panmyelosis because of elevations of all 3 peripheral blood components. Increased
production confined to the RBC line is termed erythrocytosis; erythrocytosis may occur with PV but is
more commonly due to other causes (secondary erythrocytosis—see p. 1003). In PV, RBC production
proceeds independently of erythropoietin levels.

Extramedullary hematopoiesis may occur in the spleen, liver, and other sites that have the potential for
blood cell formation. Peripheral blood cell turnover increases. Eventually, progression to a spent-phase
may occur, with a phenotype indistinguishable from primary myelofibrosis. Transformation to acute
leukemia is rare, although the risk is increased with exposure to alkylating agents and radioactive
phosphorus, which should only be used rarely, if ever.

Complications: In PV, blood volume expands and hyperviscosity develops. Patients are prone to
develop thrombosis. Thrombosis can occur in most blood vessels, resulting in stroke, transient ischemic
attacks, deep venous thrombosis, MI, retinal artery or vein occlusion, splenic infarction (often with a
friction rub), or Budd-Chiari syndrome (see p. 261). Previously, most experts believed hyperviscosity was
the predisposing factor for thrombosis. Newer studies suggest that risk of thrombosis may be primarily
related to the degree of leukocytosis. However, this hypothesis has yet to be confirmed in dedicated,
prospective trials.

Platelets may function abnormally, predisposing to increased bleeding. Increased cell turnover may cause
hyperuricemia, increasing the risk of gout and urate kidney stones.

Genetic basis: Clonal hematopoiesis is a hallmark of PV, suggesting that a mutation of hematopoietic
stem cells is the cause of proliferation. The JAK2 V617F mutation (or one of several other rarer JAK2
mutations) is present in virtually all patients with PV. However, one or more other disease-initiating
mutations almost certainly exist. These mutations lead to sustained activation of the JAK2 protein, which
causes excess cell production, independent of erythropoietin levels.

Symptoms and Signs

PV itself is often asymptomatic. Occasionally, increased red cell volume and viscosity produce weakness,
headache, light-headedness, visual disturbances, fatigue, and dyspnea. Pruritus often occurs, particularly
after a hot bath. The face may be red and the retinal veins engorged. The palms and feet may be red,
warm, and painful, sometimes with digital ischemia (erythromelalgia). Hepatomegaly is common, and >
75% of patients have splenomegaly (which may be massive).

Thrombosis may cause symptoms in the affected site (eg, neurologic deficits with stroke or transient
ischemic attack, leg pain, swelling or both with lower extremity thrombosis, unilateral vision loss with
retinal vascular occlusion).

Bleeding (typically GI) occurs in about 10% of patients.

Hypermetabolism can cause low-grade fevers and weight loss and suggests progression to spent-phase
carcinemia, which is clinically indistinguishable from primary myelofibrosis.

Diagnosis

• CBC

• Testing for JAK2 mutations
• Sometimes bone marrow examination and serum erythropoietin level

• Use of WHO criteria

PV is often first suspected because of an abnormal CBC (eg, Hb > 18.5 g/dL in men or > 16.5 g/dL in women), but it must be considered in patients with suggestive symptoms, particularly Budd-Chiari syndrome (however, some patients develop Budd-Chiari syndrome before the Hct increases). Neutrophils and platelets are often, but not invariably, increased; in patients with only elevated Hb, PV may be present, but secondary erythrocytosis, a more common cause of elevated Hb, must first be considered (see p. 1003). PV should also be considered in the rare patient with a normal Hb level but microcytosis and evidence of iron deficiency; this combination of findings can occur with iron-limited hematopoiesis, which is a hallmark of some cases of PV.

New WHO criteria for diagnosis have been established (see Table 116-3). Thus, patients suspected of having PV typically should have testing for JAK2 mutations; bone marrow examination is not always necessary.

When done, bone marrow typically shows panmyelosis, large and clumped megakaryocytes, and sometimes reticulin fibers. However, no bone marrow findings absolutely differentiate between PV and other disorders of excessive erythrocytosis, such as congenital familial polycythemia.

[Table 116-3. WHO Criteria for Diagnosis of Polycythemia Vera*]

Patients with PV typically have low or low-normal serum erythropoietin levels. Elevated levels suggest secondary erythrocytosis.

Sometimes in vitro testing for endogenous erythroid colony formation is done (erythroid progenitors from peripheral blood or bone marrow from patients with PV, unlike those from healthy people, can form erythroid cells in culture without the addition of erythropoietin).

RBC mass determination with chromium-labeled RBCs can help differentiate between true and relative polycythemia and can also help to differentiate between PV and other myeloproliferative disorders. However, this test is technically difficult and is usually not done due to its limited availability and the fact it has been standardized only at sea level.

Nonspecific laboratory abnormalities that may occur in PV include elevated vitamin B12 and B12-binding capacity, hyperuricemia and hyperuricosuria (present in ≥ 30% of patients), increased expression of PRV-1 gene in leukocytes, and decreased expression of C-mpl (the receptor for thrombopoietin) in megakaryocytes and platelets. These tests are not needed for diagnosis.

Prognosis

Generally, PV is associated with a shortened life span. Median survival for all patients is around 8 to 15 yr, although many patients live much longer. Thrombosis is the most common cause of death, followed by complications of myelofibrosis and development of leukemia.

Treatment

• Aspirin therapy

• Possibly phlebotomy

• Possibly myelosuppressive therapy

Because PV is the only form of erythrocytosis for which myelosuppressive therapy may be indicated, accurate diagnosis is critical. Therapy must be individualized according to age, sex, medical status, clinical manifestations, and hematologic findings. Patients are classified as high-risk or low-risk. High-risk patients are > 60 yr and have a history of thrombosis or transient ischemic attacks or both.
Aspirin: Aspirin (81 to 100 mg po once/day) reduces the incidence of thrombotic complications. Thus, patients undergoing phlebotomy alone or phlebotomy and myelosuppression should be given aspirin unless contraindicated. Higher doses of aspirin are associated with an unacceptably increased risk of bleeding.

Phlebotomy: Phlebotomy has been the mainstay of therapy for high- and low-risk patients because experts believed it decreased the risk of thrombosis. However, use of phlebotomy is now controversial because recent studies suggest that the Hct level may not correlate with risk of thrombosis, and some clinicians no longer adhere to the strict phlebotomy guidelines. However, this issue requires further study, and phlebotomy may still be considered for any patient. In a minority of patients with symptomatic rubor and hyperviscosity symptoms, phlebotomy can be therapeutic. Common thresholds for phlebotomy are Hct > 45% in men and > 42% in women. Initially, 300 to 500 mL of blood are removed every other day. Less blood is removed (ie, 200 to 300 mL twice/wk) from elderly patients and from patients with cardiac or cerebrovascular disorders. Once the Hct is below the threshold value, it is checked monthly and maintained at this level by additional phlebotomies as needed. If necessary, intravascular volume can be maintained with crystalloid or colloid solutions.

Myelosuppressive therapy: Myelosuppressive therapy is indicated for high-risk patients.

Radioactive phosphorus ($^{32}$P) has long been used as a treatment for PV. It has a success rate of 80 to 90%. Remission may last 6 mo to several years. Radioactive phosphorus is well tolerated and requires fewer follow-up visits once the disorder is controlled. However, radioactive phosphorus is associated with an increased incidence of acute leukemic transformation, and the leukemia that develops after this therapy is often resistant to induction chemotherapy and is never curable. Thus, use of radioactive phosphorus requires careful patient selection (eg, used only for patients who are expected to die of other disorders within 5 yr). It should be used rarely; many clinicians do not use it at all.

Hydroxyurea, which inhibits the enzyme ribonucleoside diphosphate reductase, is also used to achieve myelosuppression. It has not been clearly shown to be leukemogenic; however, the possibility of leukemic conversion, although small, does exist. Hydroxyurea is started at a dose of 500 to 1000 mg po once/day. Patients are monitored with a weekly CBC. When a steady state is achieved, the interval between CBCs is lengthened to 2 wk and then to 4 wk. If the WBC count falls to < 4000/μL or the platelet count to < 100,000/μL, hydroxyurea is withheld and reinstituted at 50% of the dose when those values normalize. It is reasonable to titrate the hydroxyurea dose to achieve a near-normal Hct, although there is no evidence that titration is beneficial. It is likely that normalization of the WBC count is more important, but this theory has not been demonstrated prospectively. There is no evidence that normalization of the platelet count is necessary, and some clinicians do not increase the hydroxyurea dose as long as the platelet count is < 1.5 million/μL. Acute toxicity is infrequent; occasionally patients develop a rash, GI symptoms, fever, nail changes, and skin ulcers, which may require stopping hydroxyurea.

Interferon alfa-2b has been used if hydroxyurea does not control blood counts or is not tolerated. However, pegylated interferon alfa-2b is usually well tolerated. This drug affects the disease at the molecular level with relatively low toxicity.

Alkylating agents are leukemogenic and should be avoided.

Several inhibitors of the JAK2 pathway are currently in clinical trials, primarily in patients with advanced myelofibrosis.

Treatment of complications: Hyperuricemia should be treated with allopurinol 300 mg po once/day if it causes symptoms or if patients are receiving simultaneous myelosuppressive therapy. Pruritus may be managed with antihistamines but is often difficult to control; myelosuppression often is most effective. Cholestyramine 4 g po tid, cyproheptadine 4 mg po tid to qid, cimetidine 300 mg po qid, or paroxetine 20 to 40 mg po once/day may be successful. After bathing, the skin should be dried gently. Aspirin relieves symptoms of erythromelalgia; higher doses may be required but clearly increase the risk of hemorrhage.

Secondary Erythrocytosis
Secondary erythrocytosis is erythrocytosis that develops secondary to circulating erythropoiesis-stimulating substances.

In secondary erythrocytosis, only the RBC line is increased.

Common causes of secondary erythrocytosis include

- Smoking
- Chronic arterial hypoxemia
- Tumors (tumor-associated erythrocytosis)

Less common causes include certain congenital disorders such as

- High O2-affinity hemoglobinopathies
- Erythropoietin receptor mutations
- Chuvash polycythemia (in which a mutation in the VHL gene affects the hypoxia-sensing pathway)
- Proline hydroxylase 2 and hypoxia-inducible factor 2 (HIF-2) α mutations

Spurious erythrocytosis may occur with hemoconcentration (eg, from burns, diarrhea, diuretics).

In patients who smoke, reversible erythrocytosis results mainly from tissue hypoxia due to elevation of blood carboxyhemoglobin concentration; levels often normalize with smoking cessation.

Patients with chronic hypoxemia (arterial Hb O2 concentration < 92%), typically due to lung disease, right-to-left intracardiac shunts, renal transplantation, prolonged exposure to high altitudes (see p. 3275), or hypoventilation syndromes, often develop erythrocytosis. The primary treatment is to alleviate the underlying condition, but O2 therapy may help, and some degree of phlebotomy may decrease viscosity and alleviate symptoms. Because in some cases the elevated Hct is physiologic, phlebotomy may cause harm because it decreases tissue oxygenation.

Tumor-associated erythrocytosis can occur when renal tumors, cysts, hepatomas, cerebellar hemangioblastomas, or uterine leiomyomas secrete erythropoietin. Removal of the lesion may be curative.

High O2-affinity hemoglobinopathies are very rare. This diagnosis is suggested by a family history of erythrocytosis; it is established by measuring the P50 (the partial pressure of O2 at which Hb becomes 50% saturated) and, if possible, determining the complete oxyhemoglobin dissociation curve. Standard Hb electrophoresis may be normal and cannot reliably exclude this cause of erythrocytosis.

Evaluation: Tests done when erythrocytosis is present include

- Arterial O2 saturation
- Serum erythropoietin levels
- P50

A low or low-normal serum erythropoietin level suggests PV. Patients with hypoxia-induced erythrocytosis have an elevated level or inappropriately normal level for their elevated Hct. Patients with tumor-
associated erythrocytosis typically have elevated erythropoietin levels. Patients with elevated erythropoietin levels or microscopic hematuria should undergo abdominal imaging, CNS imaging, or both to seek a renal lesion or other tumor source of erythropoietin.

\[ P_{50} \] measures the affinity of Hb for \( O_2 \); a normal result excludes a high-affinity Hb (a familial abnormality) as the cause of erythrocytosis.
Chapter 117. Leukemias

Introduction

The leukemias are cancers of the WBCs involving bone marrow, circulating WBCs, and organs such as the spleen and lymph nodes.

Etiology

Risk of developing most leukemias increases with

• History of exposure to ionizing radiation (eg, post-atom bomb in Nagasaki and Hiroshima) or to chemicals (eg, benzene)

• Prior treatment with certain antineoplastic drugs, particularly procarbazine, nitrosureas (cyclophosphamide, melphalan), and epipodophyllotoxins (etoposide, teniposide)

• Infection with a virus (eg, human T-lymphotrophic virus 1 and 2, Epstein-Barr virus)

• Chromosomal translocations

• Preexisting conditions, including immunodeficiency disorders, chronic myeloproliferative disorders, and chromosomal disorders (eg, Fanconi's anemia, Bloom syndrome, ataxia-telangiectasia, Down syndrome, infantile X-linked agammaglobulinemia)

Pathophysiology

Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for differentiation. Abnormal proliferation, clonal expansion, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.

Manifestations of leukemia are due to suppression of normal blood cell formation and organ infiltration by leukemic cells. Inhibitory factors produced by leukemic cells and replacement of marrow space may suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocytopenia. Organ infiltration results in enlargement of the liver, spleen, and lymph nodes, with occasional kidney and gonadal involvement. Meningeal infiltration results in clinical features associated with increasing intracranial pressure (eg, cranial nerve palsies).

Classification

Leukemias were originally termed acute or chronic based on life expectancy but now are classified according to cellular maturity.

Acute leukemias consist of predominantly immature, poorly differentiated cells (usually blast forms). Acute leukemias are divided into lymphocytic (ALL) and myelocytic (AML) types, which may be further subdivided by the French-American-British (FAB) classification (see Table 117-1).

Chronic leukemias have more mature cells than do acute leukemias. Chronic leukemias are described as lymphocytic (CLL) or myelocytic (CML—see Table 117-2).

Myelodysplastic syndromes involve progressive bone marrow failure but with an insufficient proportion of blast cells (< 30%) for making a definite diagnosis of AML; 40 to 60% of cases evolve into AML.

A leukemoid reaction is marked granulocytic leukocytosis (ie, WBC > 30,000/μL) produced by normal bone marrow in response to systemic infection or cancer. Although not a neoplastic disorder, a leukemoid
Acute Leukemia

Acute leukemia occurs when a hematopoietic stem cell undergoes malignant transformation into a primitive, undifferentiated cell with abnormal longevity. These lymphocytes (acute lymphocytic leukemia [ALL]) or myeloid cells (acute myelocytic leukemia [AML]) proliferate abnormally, replacing normal marrow tissue and hematopoietic cells and inducing anemia, thrombocytopenia, and granulocytopenia. Because they are blood-borne, they can infiltrate various organs and sites, including the liver, spleen, lymph nodes, CNS, kidneys, and gonads.

Symptoms and Signs

Symptoms have usually been present for only days to weeks before diagnosis. Disrupted hematopoiesis leads to the most common presenting symptoms (anemia, infection, easy bruising and bleeding). Other presenting symptoms and signs are usually nonspecific (eg, pallor, fatigue, fever, malaise, weight loss, tachycardia, chest pain) and are attributable to anemia and a hypermetabolic state. The cause of fever is often not found, although granulocytopenia may lead to a rapidly progressing and potentially life-threatening bacterial infection. Bleeding is usually manifested by petechiae, easy bruising, epistaxis, bleeding gums, or menstrual irregularity. Hematuria and GI bleeding are uncommon. Bone marrow and periosteal infiltration may cause bone and joint pain, especially in children with ALL. Initial CNS involvement or leukemic meningitis (manifesting as headaches, vomiting, irritability, cranial nerve palsies, seizures, and papilledema) is uncommon. Extramedullary infiltration by leukemic cells may cause lymphadenopathy, splenomegaly, hepatomegaly, and leukemia cutis (a raised, nonpruritic rash).

Diagnosis

• CBC and peripheral blood smear

• Bone marrow examination

• Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies

• Imaging

CBC and peripheral smear are the first tests done; pancytopenia and peripheral blasts suggest acute leukemia. Blast cells in the peripheral smear may approach 90%, unless the WBC count is markedly decreased. Although the diagnosis can usually be made from the peripheral smear, bone marrow examination (aspiration or needle biopsy) should always be done. Blast cells in the bone marrow are between 20 and 95%. Aplastic anemia, viral infections such as infectious mononucleosis, and vitamin B₁₂ and folate deficiency should be considered in the differential diagnosis of severe pancytopenia. Leukemoid reactions to infectious disease (such as TB) can manifest as high blast counts.

Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies help distinguish the blasts of ALL from those of AML or other disease processes. Specific B-cell, T-cell, and myeloid-antigen monoclonal antibodies, together with flow cytometry, are very helpful in classifying ALL vs AML, which is critical for treatment.

Other laboratory findings may include hyperuricemia, hyperphosphatemia, hyperkalemia or hypokalemia, elevated serum hepatic transaminases or LDH, hypoglycemia, and hypoxia. Lumbar puncture and head CT scan are done in patients with CNS symptoms, B-cell ALL, high WBC count, or high LDH. Chest x-ray is done; if a mediastinal mass is present, CT may be done. CT, MRI, or abdominal ultrasonography may help assess splenomegaly or leukemia infiltration of other organs.
Prognosis

Cure is a realistic goal for both ALL and AML, especially in younger patients. Prognosis is worse in infants and the elderly and in those with hepatic or renal dysfunction, CNS involvement, myelodysplasia, or a high WBC count (> 25,000/µL). Survival in untreated acute leukemia generally is 3 to 6 mo. Prognosis varies according to karyotype.

Treatment

- Chemotherapy
- Supportive care

The goal of treatment is complete remission, including resolution of abnormal clinical features, restoration of normal blood counts and normal hematopoiesis with < 5% blast cells, and elimination of the leukemic clone. Although basic principles in treating ALL and AML are similar, the drug regimens differ. The complex nature of patients' clinical situations and the available treatment protocols necessitate an experienced team. Whenever possible, patients should be treated at specialized medical centers, particularly during critical phases (eg, remission induction).

Supportive care: Supportive care is similar in the acute leukemias and may include

- Transfusions
- Antibiotics or antifungal drugs
- Hydration and urine alkalization
- Psychologic support

Transfusions of platelets, RBCs, and granulocytes are administered as needed to patients with bleeding, anemia, and neutropenia, respectively. Prophylactic platelet transfusion is done when platelets fall to < 10,000/µL; a higher threshold (20,000/µL) is used for patients with the triad of fever, disseminated intravascular coagulation, and mucositis secondary to chemotherapy. Anemia (Hb < 8 g/dL) is treated with packed RBC transfusions. Granulocyte transfusions may help neutropenic patients with gram-negative or other serious sepsis but have no proven benefit as prophylaxis.

Antimicrobials are often needed because infections are serious in neutropenic, immunosuppressed patients and can progress quickly without the usual clinical evidence. After appropriate studies and cultures have been done, both febrile and afebrile patients with neutrophil counts < 500/µL should begin broad-spectrum bactericidal antibiotic treatment that is effective against gram-positive and gram-negative organisms (eg, ceftazidime, impenem, cilastatin). Fungal infections, especially pneumonias, are becoming more common and are difficult to diagnose; empiric antifungal drugs should be given if antibacterial therapy is not effective within 72 h. In patients with refractory pneumonitis, *Pneumocystis jirovecii* infection or a viral infection should be suspected and confirmed by bronchoscopy and bronchoalveolar lavage and treated appropriately. Empiric therapy with trimethoprim/sulfamethoxazole (TMP/SMX), amphotericin B, and acyclovir or other analogs, often with granulocyte transfections, is often necessary. In patients with drug-induced immunosuppression at risk of opportunistic infections, TMP/SMX is given to prevent *P. jirovecii* pneumonia.

Hydration (twice the daily maintenance volume), urine alkalization (pH 7 to 8), and electrolyte monitoring can prevent the hyperuricemia, hyperphosphatemia, and hyperkalemia (tumor lysis syndrome —see p. 1075) caused by the rapid lysis of leukemic cells during initial therapy (particularly in ALL). Hyperuricemia can be minimized by giving allopurinol (a xanthine oxidase inhibitor) or rasburicase (a recombinant urate-oxidase enzyme) before starting chemotherapy to reduce the conversion of xanthine to uric acid.
Psychologic support may help patients and their families weather the shock of illness and the rigors of treatment for a potentially life-threatening condition.

**Acute Lymphocytic Leukemia**

(Acute Lymphoblastic Leukemia)

**ALL** is the most common pediatric cancer; it also strikes adults of all ages. Malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived hematopoietic progenitor cell results in a high circulating number of blasts, replacement of normal marrow by malignant cells, and the potential for leukemic infiltration of the CNS and abdominal organs. Symptoms include fatigue, pallor, infection, and easy bruising and bleeding. Examination of peripheral smear and bone marrow is usually diagnostic. Treatment typically includes combination chemotherapy to achieve remission, intrathecal chemotherapy for CNS prophylaxis and/or cerebral irradiation for intracerebral leukemic infiltration, consolidation chemotherapy with or without stem cell transplantation, and maintenance chemotherapy for 1 to 3 yr to avoid relapse.

Two thirds of all ALL cases occur in children, with a peak incidence at age 2 to 5 yr; ALL is the most common cancer in children and the 2nd most common cause of death in children < 15 yr. A 2nd rise in incidence occurs after age 45.

**Prognosis**

Prognostic factors help determine treatment protocol and intensity.

**Favorable prognostic factors** are

- Age 3 to 7 yr
- WBC count < 25,000/μL
- French-American-British (FAB) L1 morphology
- Leukemic cell karyotype with > 50 chromosomes and t(12;21)
- No CNS disease at diagnosis

**Unfavorable factors** are

- A leukemic cell karyotype with chromosomes that are normal in number but abnormal in morphology (pseudodiploid)
- Presence of the Philadelphia (Ph) chromosome t(9;22)
- Increased age in adults
- B-cell immunophenotype with surface or cytoplasmic immunoglobulin

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. About 75% of children and 30 to 40% of adults have continuous disease-free survival for 5 yr and appear cured. Imatinib improves outcome in patients with Ph chromosome-positive ALL. Most investigatory protocols select patients with poor prognostic factors for more intense therapy, because the increased risk of and toxicity from treatment are outweighed by the greater risk of treatment failure leading to death.

**Treatment**
• Chemotherapy

• Sometimes stem cell transplantation or radiation therapy

The 4 general phases of chemotherapy for ALL include

• Remission induction

• CNS prophylaxis

• Postremission consolidation or intensification

• Maintenance

**Induction therapy:** The goal is to induce remission. Several regimens emphasize early introduction of an intensive multidrug regimen. Remission can be induced with daily oral prednisone and weekly IV vincristine with the addition of an anthracycline or asparaginase. Other drugs and combinations that may be introduced early in treatment are cytarabine and etoposide as well as cyclophosphamide. In some regimens, intermediate-dose or high-dose IV methotrexate is given with leucovorin rescue. The combinations and their dosages are modified according to the presence of risk factors. Imatinib can be added to the drug regimen in patients with Ph chromosome-positive ALL.

**CNS prophylaxis:** An important site of leukemic infiltration is the meninges; prophylaxis and treatment may include high-dose intrathecal methotrexate, cytosine arabinoside, and corticosteroids. Cranial nerve or whole-brain irradiation may be necessary and is often used for patients at high risk of CNS disease (eg, high WBC count, high serum LDH, B-cell phenotype) but has been used less often in recent years.

**Consolidation therapy:** The goal of consolidation is to prevent leukemic regrowth. Consolidation therapy usually lasts a few months and combines drugs that have different mechanisms of action than drugs used in induction regimens. Allogeneic stem cell transplantation is recommended as consolidation of Ph chromosome-positive ALL or in 2nd or later relapses or remissions.

**Maintenance therapy:** Most regimens include maintenance therapy with methotrexate and mercaptopurine. Therapy duration is usually 2 1/2 to 3 yr but may be shorter with regimens that are more intensive in earlier phases and for B-cell (L3) cases. For patients in continuous complete remission for 2 1/2 yr, the risk of relapse after therapy cessation is about 20%, usually within 1 yr. Thus, when therapy can be stopped, most patients are cured.

**Relapse:** Leukemic cells may reappear in the bone marrow, the CNS, or the testes. Bone marrow relapse is particularly ominous. Although a new round of chemotherapy may induce a 2nd remission in 80 to 90% of children (30 to 40% of adults), subsequent remissions tend to be brief. Only a few patients with late bone marrow relapses achieve long disease-free 2nd remissions or cure.

If an HLA-matched sibling is available, stem cell transplantation offers the greatest hope of long-term remission or cure (see p. 1132). Cells from other relatives or matched, unrelated donors are sometimes used. Transplantation is rarely used for patients > 65 yr because it is much less likely to be successful and because adverse effects are much more likely to be fatal.

When relapse involves the CNS, treatment includes intrathecal methotrexate (with or without cytarabine or corticosteroids) twice weekly until all signs disappear. Most regimens include systemic reinduction chemotherapy because of the likelihood of systemic spread of blast cells. The role of continued intrathecal drug use or CNS irradiation is unclear.

Testicular relapse may be evidenced clinically by painless firm swelling of the testis or may be identified on biopsy. If unilateral testicular involvement is clinically evident, the apparently uninvolved testis should undergo biopsy. Treatment is by irradiation of the involved testis and administration of systemic reinduction therapy as for isolated CNS relapse.
Acute Myelocytic Leukemia

(Acute Myelogenous Leukemia; Acute Myeloid Leukemia)

In AML, malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived myeloid progenitor cell results in high circulating numbers of immature blood forms and replacement of normal marrow by malignant cells. Symptoms include fatigue, pallor, easy bruising and bleeding, fever, and infection; symptoms of leukemic infiltration are present in only about 5% of patients (often as skin manifestations). Examination of peripheral smear and bone marrow is diagnostic. Treatment includes induction chemotherapy to achieve remission and postremission chemotherapy (with or without stem cell transplantation) to avoid relapse.

The incidence of AML increases with age; it is the more common acute leukemia in adults, with a median age of onset of 50 yr. AML may occur as a secondary cancer after chemotherapy or irradiation for a different type of cancer.

AML has a number of subtypes that are distinguished from each other by morphology, immunophenotype, and cytology. Five classes are described, based on predominant cell type, including myeloid, myeloid-monocytic, monocytic, erythroid, and megakaryocytic.

Acute promyelocytic leukemia (APL) is a particularly important subtype, representing 10 to 15% of all cases of AML, striking a younger age group (median age 31 yr) and particular ethnicity (Hispanics), in which the patient commonly presents with a coagulation disorder.

Prognosis

Remission induction rates range from 50 to 85%. Long-term disease-free survival reportedly occurs in 20 to 40% of patients and increases to 40 to 50% in younger patients treated with stem cell transplantation.

Prognostic factors help determine treatment protocol and intensity; patients with strongly negative prognostic features are usually given more intense forms of therapy, because the potential benefits are thought to justify the increased treatment toxicity. The most important prognostic factor is the leukemia cell karyotype. The specific chromosomal rearrangements of the different forms of AML can affect the outcome. Three levels of outcome have been identified: favorable, intermediate, and poor. Patients who have the cytogenetics t(8;21), t(15;17), and inv(16) typically have a favorable response to therapy, remission duration, and survival. Patients with a normal karyotype have an intermediate prognosis, and patients with a poor prognosis are those with a deletion of chromosome 5 or 7, trisomy 8, or a karyotype with > 3 abnormalities. Other negative factors include increasing age, a preceding myelodysplastic phase, secondary leukemia, high WBC count, and absence of Auer rods. The FAB or WHO classification alone does not predict response.

Treatment

• Chemotherapy (induction and consolidation)
• Sometimes stem cell transplantation

Induction therapy: Initial therapy attempts to induce remission and differs most from ALL in that AML responds to fewer drugs. The basic induction regimen includes cytarabine by continuous IV infusion or high doses for 5 to 7 days; daunorubicin or idarubicin is given IV for 3 days during this time. Some regimens include 6-thioguanine, etoposide, vincristine, and prednisone, but their contribution is unclear. Treatment usually results in significant myelosuppression, with infection or bleeding; there is significant latency before marrow recovery. During this time, meticulous preventive and supportive care is vital (see p. 1007).

In APL and some other cases of AML, disseminated intravascular coagulation (DIC) may be present on diagnosis and may worsen as leukemic cell lysis releases procoagulant. In APL with the translocation t(15;17), all-trans-retinoic acid corrects the DIC in 2 to 5 days; combined with daunorubicin or idarubicin,
this regimen can induce remission in 80 to 90% of patients and bring about long-term survival in 65 to 70%. Arsenic trioxide is also very active in APL.

Consolidation therapy: After remission, many regimens involve a phase of intensification with the same drugs used for induction or with other drugs. High-dose cytarabine regimens may lengthen remission duration, particularly when given as consolidation in patients < 60 yr. CNS prophylaxis usually is not given, because with better systemic disease control, CNS leukemia is a less frequent complication. In AML patients who have had consolidation, maintenance therapy has no demonstrated role.

Relapse: Patients who have not responded to treatment and younger patients who are in remission but who are at high risk of relapse (generally identified by certain chromosomal abnormalities) may be given high-dose chemotherapy and stem cell transplantation. Extramedullary sites are infrequently involved in isolated relapse. When relapse occurs, additional chemotherapy for patients unable to undergo stem cell transplantation is less effective and often poorly tolerated. Another course of chemotherapy is most effective in younger patients and in patients whose initial remission lasted > 1 yr. Gemtuzumab ozogamicin, a recombinant monoclonal antibody combined with a cytotoxic drug, is effective in some patients after relapse has occurred, but long-term benefits have not been determined.

Chronic Leukemia

Chronic leukemia usually manifests as abnormal leukocytosis with or without cytopenia in an otherwise asymptomatic person. Findings and management differ significantly between chronic lymphocytic leukemia (CLL) and chronic myelocytic leukemia (CML).

Chronic Lymphocytic Leukemia

The most common type of leukemia in the Western world, CLL involves mature-appearing defective neoplastic lymphocytes (almost always B cells) with an abnormally long life span. The peripheral blood, bone marrow, spleen, and lymph nodes undergo leukemic infiltration. Symptoms may be absent or may include lymphadenopathy, splenomegaly, hepatomegaly, and nonspecific symptoms attributable to anemia (fatigue, malaise). Diagnosis is by examination of peripheral smear and bone marrow aspirate. Treatment, delayed until symptoms develop, is aimed at lengthening life and decreasing symptoms and may involve chlorambucil or fludarabine, prednisone, and cyclophosphamide or doxorubicin or both. Monoclonal antibodies, such as alemtuzumab and rituximab, are increasingly being used. Palliative radiation therapy is reserved for patients whose lymphadenopathy or splenomegaly interferes with other organs.

Incidence of CLL increases with age; 75% of cases are diagnosed in patients > 60 yr. CLL is twice as common in men. Although the cause is unknown, some cases appear to have a hereditary component. CLL is rare in Japan and China and does not seem to increase among Japanese expatriates in the US, suggesting a genetic factor. CLL is more common among Jews of Eastern European descent.

Pathophysiology

In about 98% of cases, CD5+ B cells undergo malignant transformation, with lymphocytes initially accumulating in the bone marrow and then spreading to lymph nodes and other lymphoid tissues, eventually inducing splenomegaly and hepatomegaly. As CLL progresses, abnormal hematopoiesis results in anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin production. Many patients develop hypogammaglobulinemia and impaired antibody response, perhaps related to increased T-suppressor cell activity. Patients have increased susceptibility to autoimmune disease characterized by immunohemolytic anemias (usually Coombs' test-positive) or thrombocytopenia and a modest increase in risk of developing other cancers.

In 2 to 3% of cases, the clonal expansion is T cell in type, and even this group has a subtype (eg, large granular lymphocytes with cytopenias).
In addition, other chronic leukemic patterns have been categorized under CLL:

- Prolymphocytic leukemia
- Leukemic phase of cutaneous T-cell lymphoma (ie, Sezary syndrome)
- Hairy cell leukemia
- Lymphoma leukemia (ie, leukemic changes that occur in advanced stages of malignant lymphoma)

Differentiation of these subtypes from typical CLL is usually straightforward.

**Symptoms and Signs**

Onset is usually insidious; CLL is often diagnosed incidentally during routine blood tests or through evaluation of asymptomatic lymphadenopathy. Symptomatic patients usually have nonspecific complaints of fatigue, anorexia, weight loss, dyspnea on exertion, or a sense of abdominal fullness (secondary to an enlarged spleen). Initial findings include generalized lymphadenopathy and minimal-to-moderate hepatomegaly and splenomegaly. With progressive disease, there may be pallor due to anemia. Skin infiltration, either maculopapular or diffuse, may be a feature of T-cell CLL. Hypogammaglobulinemia and granulocytopenia in late CLL may predispose to bacterial, viral, and fungal infection, especially pneumonia. Herpes zoster is common and usually dermatomitic.

**Diagnosis**

- CBC and peripheral smear
- Bone marrow examination
- Immunophenotyping

CLL is confirmed by examining the peripheral smear and bone marrow; the hallmark is sustained, absolute peripheral lymphocytosis (> 5000/μL) and increased lymphocytes (> 30%) in the bone marrow. Differential diagnosis is simplified by immunophenotyping. Other findings at diagnosis may include hypogammaglobulinemia (< 15% of cases) and, rarely, elevated LDH. Only 10% of patients present with moderate anemia (sometimes immunohemolytic), thrombocytopenia, or both. A monoclonal serum immunoglobulin spike of the same type may be found on the leukemic cell surface in 2 to 4% of cases.

Clinical staging is useful for prognosis and treatment. Two common approaches are Rai and Binet staging, primarily based on hematologic changes and extent of disease (see Table 117-3).

**Prognosis**

The median survival of patients with B-cell CLL or its complications is about 7 to 10 yr. Patients in Rai stage 0 to II at diagnosis may survive for 5 to 20 yr without treatment. Patients in Rai stage III or IV are more likely to die within 3 to 4 yr of diagnosis. Progression to bone marrow failure is usually associated with short survival. Patients with CLL are more likely to develop a secondary cancer, especially skin cancer.

**Treatment**

- Symptom amelioration
- Supportive care

Although CLL is progressive, some patients may be asymptomatic for years; therapy is not indicated until progression or symptoms occur. Cure usually is not possible, so treatment attempts to ameliorate
symptoms and prolong life. Supportive care includes transfusion of packed RBCs or erythropoietin injections for anemia; platelet transfusions for bleeding associated with thrombocytopenia; and antimicrobials for bacterial, fungal, or viral infections. Because neutropenia and agammaglobulinemia limit bacterial killing, antibiotic therapy should be bactericidal. Therapeutic infusions of γ-globulin should be considered in patients with hypogammaglobulinemia and repeated or refractory infections or, for prophylaxis, when ≥ 2 severe infections occur within 6 mo.

[Table 117-3. Clinical Staging of Chronic Lymphocytic Leukemia]

Specific therapy includes

• Chemotherapy
• Corticosteroids
• Monoclonal antibody therapy
• Radiation therapy

These modalities may alleviate symptoms but have not been proven to prolong survival. Over-treatment is more dangerous than under-treatment.

Chemotherapy: Chemotherapy may be instituted in response to the advent of symptomatic disease, including constitutional symptoms (fever, night sweats, extreme fatigue, weight loss); significant hepatomegaly, splenomegaly, or lymphadenopathy; lymphocytosis > 100,000/µL; and infections accompanied by anemia, neutropenia, or thrombocytopenia. Alkylating drugs, especially chlorambucil, alone or with corticosteroids, have long been the usual therapy for B-cell CLL. However, fludarabine is more effective. Combination chemotherapy with fludarabine, cyclophosphamide, and rituximab more often induces complete remissions. It also lengthens remission duration and prolongs survival. Interferon alfa, deoxycoformycin, and 2-chlorodeoxyadenosine are highly effective for hairy cell leukemia. Patients with prolymphocytic leukemia and lymphoma leukemia usually require multidrug chemotherapy and often respond only partially.

Corticosteroids: Immunohemolytic anemia and thrombocytopenia are indications for corticosteroids. Prednisone 1 mg/kg po once/day may occasionally result in striking, rapid improvement in patients with advanced CLL, although response is often brief. The metabolic complications and increasing rate and severity of infections warrant caution in its prolonged use. Prednisone used with fludarabine increases the risk of Pneumocystis jirovecii and Listeria infections.

Monoclonal antibody therapy: Rituximab is the first monoclonal antibody used in the successful treatment of lymphoid cancers. The partial response rate with conventional doses in CLL is 10 to 15%. In previously untreated patients, the response rate is 75%, with 20% of patients achieving complete remission. Alemtuzumab has a 33% response rate in previously treated patients refractory to fludarabine and a 75 to 80% response rate in previously untreated patients. More problems with immunosuppression occur with alemtuzumab than with rituximab. Rituximab has been combined with fludarabine and with fludarabine and cyclophosphamide; these combinations have markedly improved the complete remission rate in both previously treated and untreated patients. Alemtuzumab is now being combined with rituximab and with chemotherapy to treat minimal residual disease and has effectively cleared bone marrow infiltration. Reactivation of cytomegalovirus and other opportunistic infections has occurred with alemtuzumab.

Radiation therapy: Local irradiation may be given to areas of lymphadenopathy or liver and spleen involvement for transient symptomatic palliation. Total body irradiation in small doses is occasionally successful.

Chronic Myelocytic Leukemia

(Chronic Granulocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloid Leukemia)
**CML** occurs when a pluripotent stem cell undergoes malignant transformation and clonal myeloproliferation, leading to a striking overproduction of immature granulocytes. Initially asymptomatic, CML progression is insidious, with a nonspecific “benign” stage (malaise, anorexia, weight loss) eventually giving way to accelerated or blast phases with more ominous signs, such as splenomegaly, pallor, easy bruising and bleeding, fever, lymphadenopathy, and skin changes. Peripheral smear, bone marrow aspirate, and demonstration of Philadelphia chromosome are diagnostic. Treatment is with imatinib, which significantly improves response and probably prolongs survival. The curative potential of imatinib is undefined. Myelosuppressive drugs (eg, hydroxyurea), stem cell transplantation, and interferon alfa are also used.

CML accounts for about 15% of all adult leukemias. CML can strike at any age, although it is uncommon before age 10, and the median age at diagnosis is 45 to 55. CML may occur in either sex.

**Pathophysiology**

Most cases of CML appear to be induced by a translocation known as the Philadelphia (Ph) chromosome, which is demonstrable in 95% of patients. It is a reciprocal translocation t(9;22) in which a piece of chromosome 9 containing the oncogene c-abl is translocated to chromosome 22 and fused to the gene **BCR**. The fusion gene **BCR-ABL** is important in the pathogenesis and expression of CML and results in the production of a specific tyrosine kinase. CML ensues when an abnormal pluripotent hematopoietic progenitor cell initiates excessive production of granulocytes, primarily in the bone marrow but also in extramedullary sites (eg, spleen, liver). Although granulocyte production predominates, the neoplastic clone includes RBC, megakaryocyte, monocyte, and even some T and B cells. Normal stem cells are retained and can emerge after drug suppression of the CML clone.

CML has 3 phases:

• **Chronic phase**: An initial indolent period that may last months to years

• **Accelerated myeloproliferative phase**: Treatment failure, worsening anemia, and progressive thrombocytopenia

• **Terminal phase**: Blast crisis; blast cell tumors possibly developing in extramedullary sites (eg, bone, CNS, lymph nodes, skin)

The terminal phase leads to fulminant complications resembling those of acute leukemia, including sepsis and bleeding. Some patients progress directly from the chronic to the blast phase.

**Symptoms and Signs**

Patients are often asymptomatic early on, with insidious onset of nonspecific symptoms (eg, fatigue, weakness, anorexia, weight loss, fever, night sweats, a sense of abdominal fullness), which may prompt evaluation. Initially, pallor, bleeding, easy bruising, and lymphadenopathy are unusual, but moderate or occasionally extreme splenomegaly is common (60 to 70% of cases). With disease progression, splenomegaly may increase, and pallor and bleeding occur. Fever, marked lymphadenopathy, and maculopapular skin involvement are ominous developments.

**Diagnosis**

• CBC and peripheral smear

• Bone marrow examination

• Cytogenetic studies (Ph chromosome)

CML is most frequently diagnosed by a CBC obtained incidentally or during evaluation of splenomegaly.
Granulocyte count is elevated, usually < 50,000/μL in asymptomatic patients and 200,000/μL to 1,000,000/μL in symptomatic patients, and platelet count is normal or moderately increased. Hb level is usually > 10 g/dL.

Peripheral smear may help differentiate CML from leukocytosis of other etiology. In CML, peripheral smear shows predominantly immature granulocytes and absolute eosinophilia and basophilia, although in patients with WBC counts < 50,000/μL, immature granulocytes may be uncommon. Leukocytosis in patients with myelofibrosis is usually associated with nucleated RBCs, teardrop-shaped RBCs, anemia, and thrombocytopenia. Myeloid leukemoid reactions resulting from cancer or infection are not often associated with absolute eosinophilia and basophilia.

The leukocyte alkaline phosphatase score is usually low in CML and increased in leukemoid reactions. Bone marrow examination should be done to evaluate the karyotype as well as cellularity (usually increased) and extent of myelofibrosis.

Diagnosis is confirmed by presence of the Ph chromosome on cytogenetic or molecular studies, although it is absent in 5% of patients.

During the accelerated phase of disease, anemia and thrombocytopenia usually develop. Basophils may increase, and granulocyte maturation may be defective. The proportion of immature cells and the leukocyte alkaline phosphatase score may increase. In the bone marrow, myelofibrosis may develop and sideroblasts may be seen on microscopy. Evolution of the neoplastic clone may be associated with development of new abnormal karyotypes, often an extra chromosome 8 or isochromosome 17.

Further evolution may lead to a blast crisis with myeloblasts (60% of patients), lymphoblasts (30%), and megakaryoblasts (10%). In 80% of these patients, additional chromosomal abnormalities occur frequently.

Prognosis

With imatinib, survival is > 90% at 5 yr after diagnosis. Before imatinib was used, with treatment 5 to 10% of patients died within 2 yr of diagnosis; 10 to 15% died each year thereafter. Median survival was 4 to 7 yr. Most (90%) deaths follow a blast crisis or an accelerated phase of the disease. Median survival after blast crisis is about 3 to 6 mo but can be up to 12 mo with remission.

Ph chromosome-negative CML and chronic myelomonocytic leukemia have a worse prognosis than Ph chromosome-positive CML. Their clinical behaviors resemble a myelodysplastic syndrome (see p. 1014).

Treatment

• A tyrosine kinase inhibitor, sometimes with chemotherapy
• Sometimes stem cell transplantation

Except when stem cell transplantation is successful, treatment is not curative; however, survival can be prolonged by treatment with imatinib.

Imatinib and several newer drugs inhibit the specific tyrosine kinase that results from the BCR-ABL gene product. It is dramatically effective in achieving complete clinical and cytogenetic remissions of Ph chromosome-positive CML and is clearly superior to other regimens (eg, interferon with or without cytosine arabinoside). Imatinib also is superior to other treatments in the accelerated and blast phases. In blast crisis, combinations of chemotherapy with imatinib have a higher response rate than does therapy with either approach alone. Treatment tolerance is excellent. The high level of durable complete remissions associated with imatinib therapy has led to the prospect of cure of the disease.

Older chemotherapy regimens are reserved for BCR-ABL-negative patients, patients who relapse after receiving imatinib, and patients in blast crisis. The main agents are busulfan, hydroxyurea, and interferon. Hydroxyurea is easiest to manage and has the fewest adverse effects. The starting dosage is generally
To 1000 mg po bid. Blood counts should be done every 1 to 2 wk and the dosage adjusted accordingly. Busulfan often causes unexpected general myelosuppression, and interferon causes a flu-like syndrome that often is unacceptable to patients. The main benefit of these therapies is reduction in distressing splenomegaly and adenopathy and control of the tumor burden to reduce the incidence of tumor lysis and gout. None of these therapies prolongs median survival > 1 yr compared with untreated patients; thus, reduction in symptoms is the major goal, and therapy is not continued when patients have significant toxic symptoms.

Allogeneic stem cell transplantation can be useful for patients refractory to frontline therapy.

Although splenic radiation is rarely used, it may be helpful in refractory cases of CML or in patients with terminal disease and marked splenomegaly. Total dosage usually ranges from 6 to 10 Gy delivered in fractions of 0.25 to 2 Gy/day. Treatment should begin with very low doses and careful evaluation of the WBC count. Response is usually disappointing.

Splenectomy may alleviate abdominal discomfort, lessen thrombocytopenia, and relieve transfusion requirements when splenomegaly cannot be controlled with chemotherapy or irradiation. Splenectomy does not play a significant role during the chronic phase of CML.

**Myelodysplastic Syndrome**

Myelodysplastic syndrome (MDS) involves a group of disorders typified by peripheral cytopenia, dysplastic hematopoietic progenitors, a hypercellular bone marrow, and a high risk of conversion to acute myelocytic leukemia (AML). Symptoms are referable to the specific cell line most affected and may include fatigue, weakness, pallor (secondary to anemia), increased infections and fever (secondary to neutropenia), and increased bleeding and bruising (secondary to thrombocytopenia). Diagnosis is by blood count, peripheral smear, and bone marrow aspiration. Treatment with 5-azacytidine may help; if AML supervenes, it is treated per the usual protocols.

**Pathophysiology**

MDS is a group of disorders, often termed preleukemia, refractory anemias, Philadelphia chromosome-negative chronic myelocytic leukemia, chronic myelomonocytic leukemia, or agnogenic myeloid metaplasia, resulting from a somatic mutation of hematopoietic precursors. Etiology is often unknown, but risk is increased with exposure to benzene, radiation, and chemotherapeutic agents (particularly long or intense regimens and those involving alkylating agents and epipodophyllotoxins).

MDS is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms. The bone marrow is normal or hypercellular, and ineffective hematopoiesis can cause anemia (most common), neutropenia, thrombocytopenia, or a combination. The disordered cell production is also associated with morphologic cellular abnormalities in bone marrow and blood. Extramedullary hematopoiesis may occur, leading to hepatomegaly and splenomegaly. Myelofibrosis is occasionally present at diagnosis or may develop during the course of MDS. Classification is by blood and bone marrow findings (see Table 117-4). The MDS clone is unstable and tends to progress to AML.

**Symptoms and Signs**

Symptoms tend to reflect the most affected cell line and may include pallor, weakness, and fatigue (anemia); fever and infections (neutropenia); and increased bruising, petechiae, epistaxis, and mucosal bleeding (thrombocytopenia). Splenomegaly and hepatomegaly are common. Symptoms may also be referable to other underlying disorders; e.g., in elderly patients with preexisting cardiovascular disorders, anemia from MDS may exacerbate anginal pain.

**Diagnosis**

- CBC
• Peripheral smear

• Bone marrow examination

MDS is suspected in patients (especially the elderly) with refractory anemia, leukopenia, or thrombocytopenia. Cytopenias secondary to congenital disorders, vitamin deficiencies, or drug adverse effects must be ruled out. Diagnosis

[Table 117-4. Myelodysplastic Syndrome Bone Marrow Findings and Survival]

is by examining peripheral blood and bone marrow and identifying morphologic abnormalities in 10 to 20% of cells of a particular lineage.

Anemia is the most common feature, associated usually with macrocytosis and anisocytosis. With automatic cell counters, these changes are indicated by an increased MCV and RBC distribution width. Some degree of thrombocytopenia is usual; on peripheral smear, platelets vary in size, and some appear hypogranular. The WBC count may be normal, increased, or decreased. Neutrophil cytoplasmic granularity is abnormal, with anisocytosis and variable numbers of granules. Eosinophils also may have abnormal granularity. Pseudo Pelger-Huet cells (hyposegmented neutrophils) may be seen. Monocytosis is characteristic of the chronic myelomonocytic leukemia subgroup, and immature myeloid cells may occur in the less well differentiated subgroups. The cytogenetic pattern is usually abnormal, with one or more clonal cytogenetic abnormalities often involving chromosomes 5 or 7.

Prognosis

Prognosis depends greatly on classification and on any associated disorder. Patients with refractory anemia or refractory anemia with sideroblasts are less likely to progress to the more aggressive forms and may die of unrelated causes.

Treatment

• Symptom amelioration

• Supportive care

• Possibly stem cell transplantation

Azacitidine relieves symptoms, decreases the rate of transformation to leukemia and the need for transfusions, and probably improves survival. Other therapy is supportive, including RBC transfusions as indicated, platelet transfusions for bleeding, and antibiotic therapy for bacterial infection. Deoxyazacitidine, a hypomethylating agent, is sometimes effective, even in patients who do not respond to azacitidine. In some patients, erythropoietin to support RBC needs, granulocyte colony-stimulating factor to manage severe symptomatic granulocytopenia, and, when available, thrombopoietin for severe thrombocytopenia can serve as important hematopoietic support but have not increased survival. Allogeneic stem cell transplantation is useful, and nonablative allogeneic bone marrow transplantations are now being studied for patients > 50 yr. Response of MDS to chemotherapy used for AML is similar to that of AML, after age and karyotype are considered.
Chapter 118. Lymphomas

Introduction

Lymphomas are a heterogeneous group of tumors arising in the reticuloendothelial and lymphatic systems. The major types are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL—see Table 118-1).

Lymphomas were once thought to be absolutely distinct from leukemias. However, better understanding of cell markers and tools with which to evaluate those markers now show that the differentiation between these 2 cancers is often vague. The notion that lymphoma is relatively restricted to the lymphatic system and leukemias to the bone marrow, at least in early stages, is also not always true.

Hodgkin Lymphoma

(Hodgkin's Disease)

Hodgkin lymphoma is a localized or disseminated malignant proliferation of cells of the lymphoreticular system, primarily involving lymph node tissue, spleen, liver, and bone marrow. Symptoms include painless lymphadenopathy, sometimes with fever, night sweats, unintentional weight loss, pruritus, splenomegaly, and hepatomegaly. Diagnosis is based on lymph node biopsy. Treatment is curative in about 75% of cases and consists of chemotherapy with or without radiation therapy.

In the US, about 8000 new cases of Hodgkin lymphoma are diagnosed annually. The male:female ratio is 1.4:1. Hodgkin lymphoma is rare before age 10 and is most common between ages 15 and 40; a 2nd peak occurs in people > 50 to 60.

Pathophysiology

Hodgkin lymphoma results from the clonal transformation of cells of B-cell origin, giving rise to pathognomonic binucleated Reed-Sternberg cells. The cause is unknown, but genetic susceptibility and environmental associations (eg, occupation, such as woodworking; history of treatment with phenytoin, radiation therapy, or chemotherapy; infection with Epstein-Barr virus, Mycobacterium tuberculosis, herpesvirus type 6, HIV) play a role. Risk is slightly increased in people with certain types of immunosuppression (eg, posttransplant patients taking immunosuppressants); in people with congenital immunodeficiency states (eg, ataxia-telangiectasia, Klinefelter's syndrome, Chediak-Higashi syndrome, Wiskott-Aldrich syndrome); and in people with certain autoimmune disorders (RA, celiac sprue, Sjogren's syndrome, SLE).

[Table 118-1: Comparison of Hodgkin Lymphoma and Non-Hodgkin Lymphoma]

Most patients also develop a slowly progressive defect in cell-mediated immunity (T-cell function) that, in advanced disease, contributes to common bacterial and unusual fungal, viral, and protozoal infections. Humoral immunity (antibody production) is depressed in advanced disease. Death often results from sepsis.

Symptoms and Signs

Most patients present with painless cervical adenopathy. Although the mechanism is unclear, pain may occur in diseased areas immediately after drinking alcoholic beverages, thereby providing an early indication of the diagnosis.

Other manifestations develop as the disease spreads through the reticuloendothelial system, generally to contiguous sites. Intense pruritus may occur early. Constitutional symptoms include fever, night sweats, and unintentional weight loss (> 10% of body weight in previous 6 mo), which may signify involvement of internal lymph nodes (mediastinal or retroperitoneal), viscera (liver), or bone marrow. Splenomegaly is often present; hepatomegaly may be present. Pel-Ebstein fever (a few days of high fever regularly
often present; hepatomegaly may be present. Pel-Ebstein fever (a few days of high fever regularly alternating with a few days to several weeks of normal or below-normal temperature) occasionally occurs. Cachexia is common as disease advances.

Bone involvement is often asymptomatic but may produce vertebral osteoblastic lesions (ivory vertebrae) and, rarely, pain with osteolytic lesions and compression fracture. Intracranial, gastric, and cutaneous lesions are rare and when present suggest HIV-associated Hodgkin lymphoma.

Local compression by tumor masses often causes symptoms, including
- Jaundice secondary to intrahepatic or extrahepatic bile duct obstruction
- Leg edema secondary to lymphatic obstruction in the pelvis or groin
- Severe dyspnea and wheezing secondary to tracheobronchial compression
- Lung cavitation or abscess secondary to infiltration of lung parenchyma, which may simulate lobar consolidation or bronchopneumonia

Epidural invasion that compresses the spinal cord may result in paraplegia. Horner's syndrome and laryngeal paralysis may result when enlarged lymph nodes compress the cervical sympathetic and recurrent laryngeal nerves. Neuralgic pain follows nerve root compression.

Diagnosis
- Chest x-ray
- CT of chest, abdomen, and pelvis
- CBC, ESR, alkaline phosphatase, LDH, liver function tests, albumin, Ca, BUN, and creatinine
- Lymph node biopsy
- Bone marrow biopsy
- Possibly PET for staging, bone scanning if bone pain is present, or MRI if neurologic symptoms are present

Hodgkin lymphoma is usually suspected in patients with painless lymphadenopathy or mediastinal adenopathy detected on routine chest x-ray. Similar lymphadenopathy can result from infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, non-Hodgkin lymphoma, or leukemia. Similar chest x-ray findings can result from lung cancer, sarcoidosis, or TB (for evaluation of a mediastinal mass, see p. 1994).

A chest x-ray is obtained if not already done. X-ray is usually followed by lymph node biopsy if findings are confirmed on CT or PET scan of the chest. If only mediastinal nodes are enlarged, mediastinoscopy or Chamberlain procedure (a limited left anterior thoracostomy allowing biopsy of mediastinal lymph nodes inaccessible by cervical mediastinoscopy) may be indicated. CT-guided biopsy may also be considered, but results of fine-needle aspiration are often inaccurate, so lymph node biopsy is preferred. CBC, ESR, alkaline phosphatase, and renal and liver function tests are generally done. Other tests are done depending on findings (eg, MRI for symptoms of cord compression, bone scan for evaluation of bone pain).

Biopsy reveals Reed-Sternberg cells (large binucleated cells) in a characteristically heterogeneous cellular infiltrate consisting of histiocytes, lymphocytes, monocytes, plasma cells, and eosinophils. Classic Hodgkin lymphoma has 4 histopathologic subtypes (see Table 118-2); there is also a lymphocyte-predominant type. Certain antigens on Reed-Sternberg cells may help differentiate Hodgkin lymphoma from non-Hodgkin lymphoma, and classic Hodgkin lymphoma from...
the lymphocyte-predominant type.

Other test results may be abnormal but are nondiagnostic. CBC may show slight polymorphonuclear leukocytosis. Lymphocytopenia may occur early and become pronounced with advanced disease. Eosinophilia is present in about 20% of patients, and thrombocytosis may be present. Anemia, often microcytic, usually develops with advanced disease. In advanced anemia, defective iron reutilization is characterized by low serum iron, low iron-binding capacity, and increased bone marrow iron. Pancytopenia is occasionally caused by bone marrow invasion, usually by the lymphocyte-depleted type. Hypersplenism (see p. 985) may appear in patients with marked splenomegaly. Elevated serum alkaline phosphatase levels may be present, but elevations do not always indicate bone marrow or liver involvement. Increases in leukocyte alkaline phosphatase, serum haptoglobin, ESR, and other acute-phase reactants usually reflect active disease.

**Staging:** After diagnosis, stage is determined to guide therapy. The commonly used Ann Arbor staging system (see Table 118-3) incorporates symptoms; physical examination findings; results of imaging tests, including chest x-ray, CT of the chest, abdomen, and pelvis; and unilateral bone marrow biopsy. Laparotomy is not required for staging. Other staging tests may include PET scan and cardiac and pulmonary function tests in anticipation of therapy. The Cotswold modifications of the Ann Arbor staging system incorporate the prognostic implications of tumor bulkiness and numerous disease sites.

Designation of the letter A to any stage means that no systemic symptoms are being experienced. Designation of the letter B means that at least one systemic symptom is experienced. The presence of symptoms correlates with response to treatment.

**Prognosis**

In classic Hodgkin lymphoma, disease-free survival 5 yr after therapy is considered a cure. Relapse is very rare after 5 yr. Chemotherapy with or without radiation therapy achieves cure in 70 to 80% of patients. Increased potential for relapse depends on many factors, including male sex, age > 45 yr, involvement of multiple extranodal sites, and presence of constitutional symptoms at diagnosis. Patients who do not achieve complete remission or who relapse within 12 mo have a poor prognosis.

**Treatment**

- Chemotherapy
- Radiation therapy
- Surgery
- Sometimes hematopoietic stem cell transplantation

The choice of treatment modality is complex and depends on the precise stage of disease. Before treatment, men should be offered sperm banking, and women should discuss fertility options with their oncologists.

Stage IA, IIA, IB, or IIB disease is generally treated with an abbreviated chemotherapy regimen of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) plus radiation therapy or with longer-course chemotherapy alone. Such treatment cures about 80% of patients. In patients with bulky mediastinal disease, chemotherapy may be of longer duration or of a different type, and radiation therapy is used routinely.

Stage IIIA disease is usually treated with ABVD combination chemotherapy. Involved field irradiation is
also sometimes added. Cure rates of 75 to 80% have been achieved.

[Table 118-3. Cotswold Modification of Ann Arbor Staging of Hodgkin Lymphoma and Non-Hodgkin Lymphoma]

Stage IIIB disease requires ABVD combination chemotherapy typically alone but sometimes with involved field irradiation. Survival rates range from 70 to 80%.

For stage IVA and IVB disease, ABVD combination chemotherapy is the standard regimen, producing complete remission in 70 to 80% of patients; >50% remain disease-free at 5 yr. Other effective drugs include nitrosoureas, ifosfamide, cisplatin or carboplatin, and etoposide. A promising new drug combination, Stanford V, is a 12-wk regimen that incorporates involved field irradiation for consolidation.

Autologous transplantation using peripheral stem cell products should be considered for all physiologically eligible patients with relapsed or refractory Hodgkin lymphoma who respond to salvage chemotherapy.

Complications of treatment: Chemotherapy with mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone (MOPP) and MOPP-like regimens increases the risk of leukemia, which generally develops after >3 yr. Both chemotherapy and radiation therapy increase the risk of malignant solid tumors (eg, breast, GI, lung, soft tissue). Mediastinal radiation increases the risk of coronary atherosclerosis. Breast cancer risk is increased in women beginning about 7 yr after they have received radiation treatment to adjacent nodal regions.

Posttreatment surveillance: Routine testing is done to identify recurrence. For a schedule of posttreatment surveillance, see

[Table 118-4. Hodgkin Lymphoma Posttreatment Surveillance]

Non-Hodgkin Lymphomas

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, the spleen, the liver, and the GI tract. Presenting symptoms usually include peripheral lymphadenopathy. However, some patients present without lymphadenopathy but with abnormal lymphocytes in circulation. Compared with Hodgkin lymphoma, there is a greater likelihood of disseminated disease at the time of diagnosis. Diagnosis is usually based on lymph node or bone marrow biopsy or both. Treatment involves radiation therapy, chemotherapy, or both. Stem cell transplantation is usually reserved for salvage therapy after incomplete remission or relapse.

NHL is more common than Hodgkin lymphoma. It is the 6th most common cancer in the US; about 65,000 new cases are diagnosed annually in all age groups. However, NHL is not one disease but rather a category of lymphocyte cancers. Incidence increases with age (median age, 50 yr).

Etiology

The cause of NHL is unknown, although, as with the leukemias, substantial evidence suggests a viral cause (eg, human T-cell leukemia-lymphoma virus, Epstein-Barr virus, hepatitis C virus, HIV). Risk factors for NHL include immunodeficiency (secondary to posttransplant immunosuppression, AIDS, primary immune disorders, sicca syndrome, RA), Helicobacter pylori infection, certain chemical exposures, and previous treatment for Hodgkin lymphoma. NHL is the 2nd most common cancer in HIV-infected patients (see p. 1457), and some AIDS patients present with lymphoma. C-myc gene rearrangements are characteristic of some AIDS-associated lymphomas.

Pathophysiology
Most (80 to 85%) NHLs arise from B cells; the remainder arise from T cells or natural killer cells. Either precursor or mature cells may be involved. Overlap exists between leukemia and NHL because both involve proliferation of lymphocytes or their precursors. A leukemia-like picture with peripheral lymphocytosis and bone marrow involvement may be present in up to 50% of children and in about 20% of adults with some types of NHL. Differentiation can be difficult, but generally patients with more extensive nodal involvement (especially mediastinal), fewer circulating abnormal cells, and fewer blast forms in the marrow (< 25%) are considered to have lymphoma. A prominent leukemic phase is less common in aggressive lymphomas, except Burkitt's and lymphoblastic lymphomas.

Hypogammaglobulinemia caused by a progressive decrease in immunoglobulin production occurs in 15% of patients and may predispose to serious bacterial infection.

**Classification**

Pathologic classification of NHLs continues to evolve, reflecting new insights into the cells of origin and the biologic bases of these heterogeneous diseases. The WHO classification (see Table 118-5) is valuable because it incorporates immunophenotype, genotype, and cytogenetics, but numerous other systems exist (eg, Lyon classification). Among the most important new lymphomas recognized by the WHO system are mucosa-associated lymphoid tumors (MALT—see p. 133); mantle cell lymphoma (previously diffuse small cleaved cell lymphoma); and anaplastic large cell lymphoma, a heterogeneous disorder with 75% of cases of T-cell origin, 15% of B-cell origin, and 10% unclassified. However, despite the plethora of entities, treatment is often similar except in certain T-cell lymphomas.

Lymphomas are commonly also categorized as indolent or aggressive. Indolent lymphomas are slowly progressive and responsive to therapy but are not curable with standard approaches. Aggressive lymphomas are rapidly progressive but responsive to therapy and often curable.

In children, NHL is almost always aggressive. Follicular and other indolent lymphomas are very rare. The treatment of these aggressive lymphomas (Burkitt's, diffuse large B cell, and lymphoblastic lymphoma) presents special concerns, including GI tract involvement (particularly in the terminal ileum); meningeal spread (requiring CSF prophylaxis or treatment); and other sanctuary sites of involvement (eg, testes, brain). In addition, with these potentially curable lymphomas, treatment adverse effects as well as outcome must be considered, including late risks of secondary cancer, cardiorespiratory sequelae, fertility preservation, and developmental consequences. Current research is focused on these areas as well as on the molecular events and predictors of lymphoma in children.

**Symptoms and Signs**

Many patients present with asymptomatic peripheral lymphadenopathy. Enlarged lymph nodes are rubbery and discrete and later become matted. Disease is localized in some patients, but most patients have several areas of involvement. Mediastinal and retroperitoneal lymphadenopathy may cause pressure symptoms on various organs. Extranodal sites may dominate clinically (eg, gastric involvement can simulate GI carcinoma; intestinal lymphoma may cause a malabsorption syndrome; HIV patients who develop NHL often present with CNS involvement).

The skin and bones are initially involved in 15% of patients with aggressive lymphoma and in 7% of those with indolent lymphoma. Occasionally, patients with extensive abdominal or thoracic disease develop chylous ascites or pleural effusion because of lymphatic obstruction. Weight loss, fever, night sweats, and asthenia indicate disseminated disease. Patients may have hepatomegaly and splenomegaly as well.

Two problems are common in NHL but rare in Hodgkin lymphoma: Congestion and edema of the face and neck from pressure on the superior vena cava (superior vena cava or superior mediastinal syndrome) may occur. Also, ureters may be compressed by retroperitoneal or pelvic lymph nodes or both; this compression may interfere with urinary flow and cause secondary renal failure.
Anemia is initially present in about 33% of patients and eventually develops in most. It may be caused by bleeding from GI lymphoma, with or without low platelet levels; hemolysis from hypersplenism or Coombs'-positive hemolytic anemia; bone marrow infiltration from lymphoma; or marrow suppression from chemotherapy or radiation therapy.

The acute illness of adult T-cell leukemia-lymphoma (associated with human T-lymphotrophic virus 1 [HTLV-1]) has a fulminating clinical course with skin infiltrates, lymphadenopathy, hepatosplenomegaly, and leukemia. The leukemic cells are malignant T cells, many with convoluted nuclei. Hypercalcemia often develops, related to humoral factors rather than to direct bone invasion.

Patients with anaplastic large cell lymphoma have rapidly progressive skin lesions, adenopathy, and visceral lesions. This disease may be mistaken for Hodgkin lymphoma or metastatic undifferentiated carcinoma.

**Diagnosis**

- Chest x-ray
- CT of chest, abdomen, and pelvis (possibly integrated PET-CT)
- CBC, ESR, alkaline phosphatase, LDH, liver function tests, albumin, Ca, BUN, creatinine, electrolytes, and uric acid
- HIV, hepatitis B virus, and hepatitis C virus testing
- Lymph node and bone marrow biopsy
- MRI of spine if neurologic symptoms are present

As with Hodgkin lymphoma, NHL is usually suspected in patients with painless lymphadenopathy or when mediastinal adenopathy is detected on routine chest x-ray. Painless lymphadenopathy can also result from infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, primary HIV infection, or leukemia. Similar chest x-ray findings can result from lung carcinoma, sarcoidosis, or TB. Less commonly, patients present after a finding of peripheral lymphocytosis on CBC done for nonspecific symptoms. In such cases, the differential diagnosis includes leukemia, Epstein-Barr virus infection, and Duncan's syndrome (X-linked lymphoproliferative syndrome).

Chest x-ray is obtained if not done previously, and a lymph node biopsy is done if lymphadenopathy is confirmed on CT or PET scan. If only mediastinal nodes are enlarged, patients require CT-guided needle biopsy or mediastinoscopy. Usually, tests should include CBC, alkaline phosphatase, renal and liver function tests, LDH, and uric acid. Other tests are done depending on findings (eg, MRI for symptoms of spinal cord compression or CNS abnormalities).

Histologic criteria on biopsy include destruction of normal lymph node architecture and invasion of the capsule and adjacent fat by characteristic neoplastic cells. Immunophenotyping studies to determine the cell of origin are of great value in identifying specific subtypes and helping define prognosis and management; these studies also can be done on peripheral cells. Demonstration of the leukocyte common antigen CD45 by immunoperoxidase rules out metastatic cancer, which is often in the differential diagnosis of "undifferentiated" cancers. The test for leukocyte common antigen, most surface marker studies, and gene rearrangement (to document B-cell or T-cell clonality) can be done on fixed tissues. Cytogenetics and flow cytometry require fresh tissue.

**Staging:** Although localized NHL does occur, the disease is typically disseminated when first recognized. Staging procedures include CT of the chest, abdomen, and pelvis; PET; and bone marrow biopsy. The final staging of NHL (see Table 118-3) is similar to that of Hodgkin lymphoma and is based on clinical and pathologic findings.

**Prognosis**
Patients with T-cell lymphomas generally have a worse prognosis than do those with B-cell types, although newer intensive treatment regimens may lessen this difference. Prognosis for each NHL variant is related to differences in tumor cell biology.

Survival also varies with other factors. The International Prognostic Index (IPI) is frequently used in aggressive lymphomas. It considers 5 risk factors:

- Age > 60
- Poor performance status (can be measured using the Eastern Cooperative Oncology Group tool)
- Elevated LDH
- > 1 extranodal site
- Stage III or IV disease

Outcome is worse with an increasing number of risk factors. Survival, as determined by IPI factor, has improved with the addition of rituximab to the standard chemotherapeutic regimen. Patients in the highest risk groups (patients with 4 or 5 risk factors) now have a 50% 5-yr survival. Low-risk patients without any of the risk factors have a very high cure rate. A modified IPI (follicular lymphoma IPI [FLIPI]) is being used in follicular lymphomas and in diffuse large B-cell lymphoma (revised IPI [R-IPI]).

**Treatment**

- Chemotherapy, radiation therapy, or both
- Sometimes anti-CD20 monoclonal antibody
- Sometimes hematopoietic stem cell transplantation

Treatment varies considerably with cell type, which are too numerous to permit detailed discussion. Generalizations can be made regarding localized vs advanced disease and aggressive vs indolent forms. Burkitt's lymphoma (see below) and mycosis fungoides (see p. 1024) are discussed separately.

**Localized disease (stages I and II):** Patients with indolent lymphomas rarely present with localized disease, but when they do, regional radiation therapy may offer long-term control. However, relapses may occur > 10 yr after radiation therapy.

About one half of patients with aggressive lymphomas present with localized disease, for which combination chemotherapy, with or without regional radiation, is usually curative. Patients with lymphoblastic lymphomas or Burkitt's lymphoma, even if apparently localized, must receive intensive combination chemotherapy with meningeal prophylaxis. Treatment may require maintenance chemotherapy (lymphoblastic), but cure is expected.

**Advanced disease (stages III and IV):** For indolent lymphomas, treatment varies considerably. A watch-and-wait approach, treatment with a single alkylating drug, or 2- or 3-drug regimens may be used. Criteria considered in selecting management options include age, general health, distribution of disease, tumor bulk, histology, and anticipated benefits of therapy. The B-cell specific anti-CD20 antibody rituximab and other biologic response modifiers appear to be of benefit; one of these drugs can be combined with chemotherapy or administered as single therapy. Radiolabeled-antibody therapy is also valuable.

In patients with the aggressive B-cell lymphomas (eg, diffuse large B cell), the standard drug combination is rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, prednisone (R-CHOP). Complete disease regression is expected in ≥ 70% of patients, depending on the IPI category. More than 70% of complete responders are cured, and relapses > 2 yr after treatment ceases are rare.
As cure rates have improved with the use of R-CHOP, autologous transplantation is reserved for patients with relapsed or refractory aggressive B-cell lymphomas, some younger patients with mantle cell lymphoma, and some patients with aggressive T-cell lymphomas.

**Lymphoma relapse:** The first relapse after initial chemotherapy is almost always treated with autologous stem cell transplantation. Patients usually should be ≤ 70 yr or in equivalent health and have responsive disease, good performance status, a source of uncontaminated stem cells, and an adequate number of CD34+ stem cells (harvested from peripheral blood or bone marrow). Consolidation myeloablative therapy may include chemotherapy with or without irradiation. Posttreatment immunotherapy (eg, rituximab, vaccination, IL-2) is being studied.

An allogeneic transplant is the donation of stem cells from a compatible donor (brother, sister, or matched unrelated donor). The stem cells have a 2-fold effect: reconstituting normal blood counts and providing a possible graft-vs-tumor effect.

In aggressive lymphoma, a cure may be expected in 30 to 50% of eligible patients undergoing myeloablative therapy.

In indolent lymphomas, cure with autologous transplantation remains uncertain, although remission may be superior to that with secondary palliative therapy alone. Reduced intensity allotransplantation appears to offer a potentially curative option in some patients with indolent lymphoma.

The mortality rate of patients undergoing myeloablative transplantation has decreased dramatically to 2 to 5% for most autologous procedures and to < 15% for most allogeneic procedures.

**Complications of treatment:** A late sequela of standard and high-dose chemotherapy is the occurrence of 2nd tumors, especially myelodysplasias and acute myelogenous leukemia. Chemotherapy combined with radiation therapy increases this risk, although its incidence is still only about 3%.

### Burkitt's Lymphoma

**Burkitt's lymphoma is a B-cell lymphoma occurring primarily in children. Endemic (African), sporadic (non-African), and immunodeficiency-related forms exist.**

Burkitt's lymphoma is endemic in central Africa and constitutes 30% of childhood lymphomas in the US. The form endemic to Africa often manifests as enlargement of the jaw or facial bones. In non-African Burkitt's lymphoma, abdominal disease predominates, often arising in the region of the ileocecal valve or the mesentery. The kidneys, ovaries, or breasts may be involved as well, and in adults, disease may be bulky and generalized, often with massive involvement of liver, spleen, and bone marrow. CNS involvement is often present at diagnosis or with relapsing lymphoma.

Burkitt's lymphoma is the most rapidly growing human tumor, and pathology reveals a high mitotic rate, a monoclonal proliferation of B cells, and a "starry-sky" pattern of benign macrophages that have engulfed apoptotic malignant lymphocytes. There is a distinctive genetic translocation involving the C-myc gene on chromosome 8 and the immunoglobulin heavy chain of chromosome 14. The disease is closely associated with Epstein-Barr virus infection in endemic lymphoma; however, it is uncertain whether Epstein-Barr virus plays an etiologic role. Burkitt's lymphoma occurs frequently in patients with AIDS and may be an AIDS-defining disease.

**Diagnosis**

Diagnosis is based on biopsy of lymph node or tissue from another suspected disease site. Staging includes CT of the chest, abdomen, and pelvis, bone marrow biopsy, CSF cytology, and PET scan.

**Treatment**

- Intensive chemotherapy
Treatment must be initiated rapidly and staging studies must be expedited because of rapid tumor growth. An intensive alternating regimen—cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC)—results in a cure rate of > 90% for children and adults. Meningeal prophylaxis is essential. With treatment, tumor lysis syndrome (see p. 1075) is common, and patients must receive IV hydration, allopurinol or rasburicase, alkalinization, and close attention to electrolytes (particularly K and Ca).

If the patient presents with bowel obstruction secondary to tumor and the tumor is completely resected at initial diagnostic-therapeutic laparotomy, then aggressive therapy is still indicated. Salvage therapy for treatment failures is generally unsuccessful, underscoring the importance of very aggressive initial therapy.

**Mycosis Fungoides**

**Mycosis fungoides is an uncommon chronic T-cell lymphoma primarily affecting the skin and occasionally the internal organs.**

Mycosis fungoides is rare compared with Hodgkin lymphoma and NHL. Unlike most other lymphomas, it is insidious in onset, sometimes appearing as a chronic, pruritic rash that is difficult to diagnose. It begins focally but may spread to involve most of the skin. Lesions are plaquelike but may become nodular or ulcerated. Eventually, systemic involvement of lymph nodes, liver, spleen, and lungs occurs, resulting in the advent of symptoms, which include fever, night sweats, and unintentional weight loss.

**Diagnosis**

- Skin biopsy
- For staging, bone marrow biopsy and CT of chest, abdomen, and pelvis

Diagnosis is based on skin biopsy, but histology may be equivocal early in the course because of insufficient quantities of lymphoma cells. The malignant cells are mature T cells (T4+, T11+, T12+). Characteristic Pautrier's microabscesses are present in the epidermis. In some cases, a leukemic phase called Sezary syndrome is characterized by the appearance of malignant T cells with serpentine nuclei in the peripheral blood.

Once mycosis fungoides has been confirmed, the stage (see Table 118-3) is determined by CT scan of the chest, abdomen, and pelvis and by bone marrow biopsy for blood or lymph node involvement. PET scan may also be used for suspected visceral involvement.

**Prognosis**

Most patients are > 50 yr at diagnosis; average life expectancy is 7 to 10 yr after diagnosis, even without treatment. However, survival rates vary markedly depending on stage at diagnosis. Patients who receive treatment for stage IA disease have a life expectancy analogous to that of similar people without mycosis fungoides. Patients who receive treatment for stage IIB disease survive for about 3 yr. Patients treated for stage III disease survive an average of 4 to 6 yr. Patients treated for stage IVA or IVB disease (extra-cutaneous disease) survive < 1.5 yr.

**Treatment**

- Radiation therapy, topical chemotherapy, phototherapy, or topical corticosteroids
- Sometimes systemic chemotherapy

Electron beam radiation therapy, in which most of the energy is absorbed in the first 5 to 10 mm of tissue, and topical nitrogen mustard have proved highly effective. Plaques may also be treated with sunlight and topical corticosteroids. Systemic treatment with alkylating drugs and folic acid antagonists produces transient tumor regression, but systemic treatment is primarily used when other therapies have failed.
after relapse, or in patients with documented extranodal or extracutaneous disease. Extracorporeal phototherapy with a chemosensitive drug has shown modest success. The adenosine deaminase inhibitors fludarabine and 2-chlorodeoxyadenosine show promise.
Chapter 119. Plasma Cell Disorders

Introduction

(Dysproteinemias; Monoclonal Gammopathies; Paraproteinemias; Plasma Cell Dyscrasias)

Plasma cell disorders are a diverse group of disorders of unknown etiology characterized by the disproportionate proliferation of one clone of B cells and the presence of a structurally and electrophoretically homogeneous (monoclonal) immunoglobulin or polypeptide subunit in serum, urine, or both.

Pathology

(For structural features and classification of the immunoglobulins, see p. 1083.)

After developing in the bone marrow, undifferentiated B cells enter peripheral lymphoid tissues, such as lymph nodes, spleen, and Peyer's patches. Here, they begin to differentiate into cells, each of which can respond to a limited number of antigens. After encountering the appropriate antigen, some B cells undergo clonal proliferation into plasma cells. Each clonal plasma cell line is committed to synthesizing one specific immunoglobulin antibody that consists of 2 identical heavy chains (gamma [γ], mu [μ], alpha [α], delta [δ], or epsilon [ε]) and 2 identical light chains (kappa [κ] or lambda [λ]). A slight excess of light chains is normally produced, and urinary excretion of small amounts of free polyclonal light chains (≤ 40 mg/24 h) is normal.

Plasma cell disorders are of unknown etiology and are characterized by the disproportionate proliferation of one clone. The result is a corresponding increase in the serum level of its product, the monoclonal immunoglobulin protein (M-protein).

M-proteins may consist of both heavy and light chains or of only one type of chain. Some show antibody activity, which may cause autoimmune damage of organs, particularly the kidneys. When M-proteins are produced, production of other immunoglobulins is commonly reduced, and immunity may become impaired. M-protein may coat platelets, inactivate clotting factors, increase blood viscosity, and cause bleeding by other mechanisms. M-proteins may also produce secondary amyloidosis. The clonal cells can infiltrate bone matrix or marrow, with resultant osteoporosis, hypercalcemia, anemia, or pancytopenia.

Plasma cell disorders can vary from asymptomatic, stable conditions (in which only the protein is present) to progressive cancers (eg, multiple myeloma—for classification, see Table 119-1). Rarely, transient plasma cell disorders occur in patients with drug hypersensitivity (sulfonamide, phenytoin, and penicillin), with presumed viral infections, and after heart or transplant surgery.

Plasma cell disorders may be suspected because of clinical manifestations, findings during evaluation of anemia, or an incidental finding of elevated serum protein or proteinuria that leads to further evaluation with serum or urine protein electrophoresis. Electrophoresis detects M-protein, which is further evaluated with immunofixation electrophoresis for identification of heavy and light chain classes.

Heavy Chain Diseases

Heavy chain diseases are neoplastic plasma cell disorders characterized by overproduction of monoclonal immunoglobulin heavy chains. Symptoms, diagnosis, and treatment vary according to the specific disorder.

Heavy chain diseases are plasma cell disorders that are generally malignant. In most plasma cell disorders, M-proteins are structurally similar to normal antibody molecules. In contrast, in heavy chain diseases, incomplete monoclonal immunoglobulins (true paraproteins) are produced. They consist of only heavy chain components (either α, γ, μ, or δ) without light chains (ε heavy chain disease has not been described). Most heavy chain proteins are fragments of their normal counterparts with internal deletions of variable length; these deletions appear to result from structural mutations. The clinical picture is more...
like lymphoma than multiple myeloma. Heavy chain diseases are considered in patients with clinical
manifestations suggesting lymphoproliferative disorders.

**IgA Heavy Chain Disease**

*(α-Chain Disease)*

IgA heavy chain disease is the most common heavy chain disease and is similar to
Mediterranean lymphoma (immunoproliferative small intestinal disease).

IgA heavy chain disease usually appears between ages 10 and 30 and is geographically

[Table 119-1, Classification of Plasma Cell Disorders]

concentrated in the Middle East. The cause may be an aberrant immune response to a parasite or other
microorganism. Villous atrophy and plasma cell infiltration of the jejunal mucosa are usually present and,
sometimes, infiltration of the mesenteric lymph nodes. The peripheral lymph nodes, bone marrow, liver,
and spleen usually are not involved. A respiratory tract form of the disease has been reported rarely.
Osteolytic lesions do not occur.

Almost all patients present with diffuse abdominal lymphoma and malabsorption. Serum protein
electrophoresis is normal in half of cases; often, there is an increased α2 and β fraction or a decreased γ
fraction. Diagnosis requires the detection of a monoclonal α chain on immunofixation electrophoresis.
This chain is sometimes found in concentrated urine. If it cannot be found in serum or urine, biopsy is
required. The abnormal protein can sometimes be detected in intestinal secretions. The intestinal cellular
infiltrate may be pleomorphic and not overtly malignant. Bence Jones proteinuria is absent.

The course is highly variable: Some patients die in 1 to 2 yr, whereas others have remissions that last
many years, particularly after treatment with corticosteroids, cytotoxic drugs, and broad-spectrum
antibiotics.

**IgG Heavy Chain Disease**

*(γ-Chain Disease)*

IgG heavy chain disease is generally similar to an aggressive malignant lymphoma but is
occasionally asymptomatic and benign.

IgG heavy chain disease occurs primarily in elderly men but can occur in children. Associated chronic
disorders include RA, Sjogren's syndrome, SLE, TB, myasthenia gravis, hypereosinophilic syndrome,
autoimmune hemolytic anemia, and thyroiditis. Reductions in normal immunoglobulin levels occur. Lytic
bone lesions are uncommon. Amyloidosis sometimes develops.

Common manifestations include lymphadenopathy and hepatosplenomegaly, fever, and recurring
infections. Palatal edema occurs in about one fourth of patients.

The CBC may show anemia, leukopenia, thrombocytopenia, eosinophilia, and circulating atypical
lymphocytes or plasma cells. Diagnosis requires demonstration by immunofixation of free monoclonal
heavy chain fragments of IgG in serum and urine. Of affected patients, one half have monoclonal serum
components > 1 g/dL (often broad and heterogeneous), and one half have proteinuria > 1 g/24 h.
Although heavy chain proteins may involve any IgG subclass, the G3 subclass is especially common.
Bone marrow or lymph node biopsy, done if other tests are not diagnostic, reveals variable
histopathology.

The median survival with aggressive disease is about 1 yr. Death usually results from bacterial infection
or progressive malignancy. Alkylation drugs, vincristine, or corticosteroids, and radiation therapy may yield
transient remissions.
IgM Heavy Chain Disease

(μ-Chain Disease)

**IgM heavy chain disease, which is rare, produces a clinical picture similar to chronic lymphocytic leukemia or other lymphoproliferative disorders.**

IgM heavy chain disease most often affects adults > 50 yr. Visceral organ involvement (spleen, liver, abdominal lymph nodes) is common, but extensive peripheral lymphadenopathy is not. Pathologic fractures and amyloidosis may occur. Serum protein electrophoresis usually is normal or shows hypogammaglobulinemia. Bence Jones proteinuria (type κ) is present in 10 to 15% of patients.

Diagnosis usually requires bone marrow examination; vacuolated plasma cells are present in two thirds of patients and, when present, are virtually pathognomonic. Death can occur in a few months or in many years. The usual cause of death is uncontrollable proliferation of chronic lymphocytic leukemia cells.

Treatment depends on the patient's condition but may consist of alkylating agents plus corticosteroids or may be similar to treatment of the lymphoproliferative disorder that it most closely resembles.

**Macroglobulinemia**

(Primary Macroglobulinemia; Waldenstrom's Macroglobulinemia)

Macroglobulinemia is a malignant plasma cell disorder in which B cells produce excessive amounts of IgM M-proteins. Manifestations may include hyperviscosity, bleeding, recurring infections, and generalized adenopathy. Diagnosis requires bone marrow examination and demonstration of M-protein. Treatment includes plasmapheresis as needed for hyperviscosity, and systemic therapy with alkylating drugs, corticosteroids, nucleoside analogs, or monoclonal antibodies.

Macroglobulinemia, an uncommon B-cell cancer, is clinically more similar to a lymphomatous disease than to myeloma and other plasma cell disorders. Cause is unknown. Men are affected more often than women; median age is 65.

After myeloma, macroglobulinemia is the 2nd most common malignant disorder associated with a monoclonal gammopathy. Excessive amounts of IgM M-proteins can also accumulate in other disorders, causing manifestations similar to macroglobulinemia. Small monoclonal IgM components are present in the sera of about 5% of patients with B-cell non-Hodgkin lymphoma; this circumstance is termed macroglobulinemic lymphoma. Additionally, IgM M-proteins are occasionally present in patients with chronic lymphocytic leukemia or other lymphoproliferative disorders.

Clinical manifestations of macroglobulinemia may be due to the large amount of high mol wt monoclonal IgM proteins circulating in plasma, but most patients do not develop problems related to high IgM levels. Some of these proteins are antibodies directed toward autologous IgG (rheumatoid factors) or I antigens (cold agglutinins). About 10% are cryoglobulins. Secondary amyloidosis occurs in 5% of patients.

**Symptoms and Signs**

Most patients are asymptomatic, but many present with manifestations of hyperviscosity syndrome: fatigue, weakness, skin and mucosal bleeding, visual disturbances, headache, symptoms of peripheral neuropathy, and other changing neurologic manifestations. An increased plasma volume can precipitate heart failure. Cold sensitivity, Raynaud's syndrome, or recurring bacterial infections may occur.

Examination may disclose lymphadenopathy, hepatosplenomegaly, and purpura. Marked engorgement and localized narrowing of retinal veins, which resemble sausage links, suggests hyperviscosity syndrome. Retinal hemorrhages, exudates, microaneurysms, and papilledema occur in late stages.

**Diagnosis**
• CBC with platelets, RBC indices, and peripheral blood smear

• Serum protein electrophoresis followed by serum and urine immunofixation

• Serum viscosity assay

• Bone marrow examination

• Sometimes lymph node biopsy

Macroglobulinemia is suspected in patients with symptoms of hyperviscosity or other typical symptoms, particularly if anemia is present. However, it is often diagnosed incidentally when protein electrophoresis reveals an M-protein that proves to be IgM by immunofixation. Laboratory evaluation includes tests used to evaluate plasma cell disorders (see Multiple Myeloma on p. 1029) as well as measurement of cryoglobulins, rheumatoid factor, and cold agglutinins; coagulation studies; and direct Coombs' test.

Moderate normocytic, normochromic anemia, marked rouleau formation, and a very high ESR are typical. Leukopenia, relative lymphocytosis, and thrombocytopenia occasionally occur. Cryoglobulins, rheumatoid factor, or cold agglutinins may be present. If cold agglutinins are present, the direct Coombs' test usually is positive. Various coagulation and platelet function abnormalities may occur. Results of routine blood studies may be spurious if cryoglobulinemia or marked hyperviscosity is present. Normal immunoglobulins are decreased in one half of patients.

Immunofixation electrophoresis of concentrated urine frequently shows a monoclonal light chain (usually κ), but gross Bence Jones proteinuria is unusual. Bone marrow studies show a variable increase in plasma cells, lymphocytes, plasmacytoid lymphocytes, and mast cells. Periodic acid-Schiff-positive material may be present in lymphoid cells. Lymph node biopsy, done if bone marrow examination is normal, is frequently interpreted as diffuse well-differentiated or plasmacytic lymphocytic lymphoma. Serum viscosity is measured to confirm suspected hyperviscosity and when present is usually > 4.0 (normal, 1.4 to 1.8).

**Treatment**

• Plasmapheresis (when hyperviscosity is present)

• Alkylating drugs, nucleoside analogs, monoclonal antibodies (rituximab), or a combination

• Possibly bortezomib, thalidomide, or lenalidomide

The course is variable, with a median survival of 7 to 10 yr. Age > 60 yr, anemia, and cryoglobulinemia predict shorter survival.

Often, patients require no treatment for many years. If hyperviscosity is present, initial treatment is plasmapheresis, which rapidly reverses bleeding as well as neurologic abnormalities. Plasmapheresis often needs to be repeated.

Long-term treatment with oral alkylating drugs may be indicated for palliation, but bone marrow toxicity can occur. Nucleoside analogs (fludarabine and 2-chlorodeoxyadenosine) produce responses in large numbers of newly diagnosed patients. Rituximab can reduce tumor burden without suppressing normal hematopoiesis. However, during the first several months, IgM levels may increase, requiring plasmapheresis. The proteasome inhibitor bortezomib and the immunomodulating agents thalidomide and lenalidomide are also effective in this cancer.

**Monoclonal Gammopathy of Undetermined Significance**

Monoclonal gammopathy of undetermined significance (MGUS) is the production of M-protein by noncancerous plasma cells in the absence of other manifestations typical of multiple
myeloma.

The incidence of MGUS increases with age, from 1% of people aged 25 yr to > 5% of people > 70 yr. MGUS may occur in association with other disorders (see Table 119-1), in which case M-proteins may be antibodies produced in large amounts in response to protracted antigenic stimuli.

MGUS usually is asymptomatic, but peripheral neuropathy can occur. Although most cases are initially benign, up to 25% (1%/yr) progress to myeloma or a related B-cell disorder, such as macroglobulinemia, amyloidosis, or lymphoma.

Diagnosis is usually suspected when M-protein is incidentally detected in blood or urine during a routine examination. On laboratory evaluation, M-protein is present in low levels in serum (< 3 g/dL) or urine (< 300 mg/24 h). MGUS is differentiated from other plasma cell disorders because M-protein levels remain relatively stable over time and lytic bone lesions, anemia, and renal dysfunction are absent. However, patients show enhanced bone loss and a higher rate of fractures. Thus, baseline evaluation with a skeletal survey and bone densitometry should be done. Bone marrow shows only mild plasmacytosis (< 10% of nucleated cells).

No antineoplastic treatment is recommended. However, recent studies suggest that MGUS patients with associated bone loss (osteopenia or osteoporosis) may benefit from treatment with bisphosphonates. Patients should be evaluated for progression of disease every 6 to 12 mo with clinical examination and serum and urine protein electrophoresis.

Multiple Myeloma

(Myelomatosis; Plasma Cell Myeloma)

Multiple myeloma is a cancer of plasma cells that produce monoclonal immunoglobulin and invade and destroy adjacent bone tissue. Common manifestations include bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections. Diagnosis requires demonstration of M-protein (sometimes present in urine and not serum) and either lytic bone lesions, light-chain proteinuria, or excessive plasma cells in bone marrow. A bone marrow biopsy is usually needed. Specific treatment includes conventional chemotherapy with the addition of bortezomib, lenalidomide, thalidomide, corticosteroids, and high-dose melphalan followed by autologous peripheral blood stem cell transplantation.

The incidence of multiple myeloma is 2 to 4/100,000. Male:female ratio is 1.6:1, and the median age is about 65 yr. Prevalence in blacks is twice that in whites. Etiology is unknown, although chromosomal and genetic factors, radiation, and chemicals have been suggested.

Pathophysiology

The M-protein produced by the malignant plasma cells is IgG in about 55% of myeloma patients and IgA in about 20%; of patients producing either IgG or IgA, 40% also have Bence Jones proteinuria, which is free monoclonal κ or λ light chains in the urine. In 15 to 20% of patients, plasma cells secrete only Bence Jones protein. IgD myeloma accounts for about 1% of cases.

Diffuse osteoporosis or discrete osteolytic lesions develop, usually in the pelvis, spine, ribs, and skull. Lesions are caused by bone replacement by expanding plasmacytomas or by cytokines that are secreted by malignant plasma cells that activate osteoclasts and suppress osteoblasts. The osteolytic lesions are usually multiple; occasionally, they are solitary intramedullary masses. Enhanced bone loss may also lead to hypercalcemia. Extrasosseous solitary plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract.

Renal failure (myeloma kidney) occurs in many patients at diagnosis or during the course of the disorder due to many causes, most commonly from deposition of light chains in the distal tubules and hypercalcemia. Patients also often develop anemia usually from kidney disease or suppression of erythropoiesis by cancer cells.
Susceptibility to bacterial infection may occur in some patients. Viral infections, especially herpes infections, are increasingly occurring as a result of newer treatment modalities. Secondary amyloidosis (see p. 906) occurs in 10% of myeloma patients, most often in patients with Bence Jones proteinuria of λ-type.

Variant expressions of multiple myeloma occur (see Table 119-2).

**Table 119-2. Variant Expressions of Multiple Myeloma**

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent bone pain (especially in the back or thorax), renal failure, and recurring bacterial infections are the most common problems on presentation, but many patients are identified when routine laboratory tests show an elevated total protein level in the blood or show proteinuria. Pathologic fractures are common, and vertebral collapse may lead to spinal cord compression and paraplegia. Symptoms of anemia predominate or may be the sole reason for evaluation in some patients, and a few patients have manifestations of hyperviscosity syndrome (see p. 1027). Peripheral neuropathy, carpal tunnel syndrome, abnormal bleeding, and symptoms of hypercalcemia (eg, polydipsia) are common. Patients may also present with renal failure. Lymphadenopathy and hepatosplenomegaly are unusual.</td>
</tr>
</tbody>
</table>

**Diagnosis**

- CBC with platelets, peripheral blood smear, ESR, and chemistry panel (BUN, creatinine, Ca, uric acid, LDH)
- Serum and urine protein electrophoresis followed by immunofixation
- X-rays (skeletal survey)
- Bone marrow examination

Multiple myeloma is suspected in patients > 40 yr with persistent unexplained bone pain, particularly at night or at rest, other typical symptoms, or unexplained laboratory abnormalities, such as elevated blood protein or urinary protein, hypercalcemia, renal insufficiency, or anemia. Laboratory evaluation includes routine blood tests, protein electrophoresis, x-rays, and bone marrow examination.

Routine blood tests include CBC, ESR, and chemistry panel. Anemia is present in 80% of patients, usually normocytic-normochronic anemia with formation of rouleau, which are clusters of 3 to 12 RBCs that occur in stacks. WBC and platelet counts are usually normal. ESR usually is > 100 mm/h; BUN, serum creatinine, LDH, and serum uric acid are frequently elevated. Anion gap is sometimes low. Hypercalcemia is present at diagnosis in about 10% of patients.

Protein electrophoresis is done on a serum sample and on a urine sample concentrated from a 24-h collection to quantify the amount of urinary M-protein. Serum electrophoresis identifies M-protein in about 80 to 90% of patients. The remaining 10 to 20% are usually patients with only free monoclonal light chains (Bence Jones protein) or IgD. They almost always have M-protein detected by urine protein electrophoresis. Immunofixation electrophoresis can identify the immunoglobulin class of the M-protein and can often detect light-chain protein if serum immuno-electrophoresis is falsely negative; immunofixation electrophoresis is done even when the serum test is negative if multiple myeloma is strongly suspected. Light-chain analysis with delineation of κ and λ ratios helps confirm the diagnosis. Light-chain analysis can also be used to monitor efficacy of therapy and provide prognostic data. Serum level of β2-microglobulin is measured if diagnosis is confirmed or very likely; it frequently is elevated, and albumin may be decreased. A new international staging system uses the levels of serum albumin and β2-microglobulin to indicate severity of disease and subsequent prognosis.

X-rays include a skeletal survey. Punched-out lytic lesions or diffuse osteoporosis is present in 80% of
cases. Radionuclide bone scans usually are not helpful. MRI can provide more detail and is obtained if specific sites of pain or neurologic symptoms are present.

Bone marrow aspiration and biopsy are done and reveal sheets or clusters of plasma cells; myeloma is diagnosed when > 10% of the cells are of this type. However, bone marrow involvement is patchy; therefore, some samples from patients with myeloma may show < 10% plasma cells. Still, the number of plasma cells in bone marrow is rarely normal. Plasma cell morphology does not correlate with the class of immunoglobulin synthesized. Chromosomal studies on bone marrow may reveal specific karyotypic abnormalities in plasma cells associated with differences in survival.

In patients without serum M protein, myeloma is indicated by Bence Jones proteinuria > 300 mg/24 h, osteolytic lesions (without evidence of metastatic cancer or granulomatous disease), and sheets or clusters of plasma cells in the bone marrow.

**Prognosis**

The disease is progressive and incurable, but median survival has recently improved to > 5 yr as a result of advances in treatment. Unfavorable prognostic signs at diagnosis are lower serum albumin and higher β2-microglobulin levels. Patients presenting with renal failure also do poorly unless kidney function improves with therapy.

Because multiple myeloma is ultimately fatal, patients are likely to benefit from discussions of end-of-life care that involve their doctors and appropriate family and friends. Points for discussion may include advance directives, the use of feeding tubes, and pain relief.

**Treatment**

- Chemotherapy for symptomatic patients
- Thalidomide, bortezomib, or lenalidomide with corticosteroids and/or chemotherapy
- Possibly maintenance therapy
- Possibly stem cell transplantation
- Possibly radiation therapy
- Treatment of complications (anemia, hypercalcemia, renal insufficiency, infections, skeletal lesions)

Treatment of myeloma has improved in the past decade, and long-term survival is a reasonable therapeutic target. Therapy involves direct treatment of malignant cells in symptomatic patients and the treatment of the complications. Asymptomatic patients probably do not benefit from treatment, which is usually withheld until symptoms or complications develop. However, patients with evidence of lytic lesions or bone loss (osteopenia or osteoporosis) should be treated with monthly infusions of zoledronic acid or pamidronate to reduce the risk of skeletal complications.

**Treatment of malignant cells:** Until recently, conventional chemotherapy consisted only of oral melphalan and prednisone given in cycles of 4 to 6 wk with monthly evaluation of response. Recent studies show superior outcome with the addition of either bortezomib or thalidomide. Other chemotherapeutic drugs, including other alkylating drugs (eg, cyclophosphamide, doxorubicin and its newer analog liposomal pegylated doxorubicin) also are more effective when combined with thalidomide or bortezomib. Many other patients are effectively treated with bortezomib, thalidomide, or lenalidomide plus glucocorticoids and/or chemotherapy.

Chemotherapy response is indicated by decreases in serum or urine M-protein, increases in RBCs, and improvement in renal function among patients presenting with kidney failure.

Autologous peripheral blood stem cell transplantation may be considered for patients who have adequate
cardiac, hepatic, pulmonary, and renal function, particularly those whose disease is stable or responsive after several cycles of initial therapy. Allogeneic stem cell transplantation after nonmyeloablative chemotherapy (e.g., low-dose cyclophosphamide and fludarabine) or low-dose radiation therapy can produce myeloma-free survival of 5 to 10 yr in some patients. However, allogeneic stem cell transplantation remains experimental because of the high morbidity and mortality from graft vs. host disease.

In relapsed or refractory myeloma, combinations of bortezomib, thalidomide, or its newer analog lenalidomide with chemotherapy or corticosteroids may be used. These drugs are usually combined with other effective drugs that the patient has not yet been treated with, although patients with prolonged remissions may respond to retreatment with the same regimen that led to the remission.

Maintenance therapy has been tried with nonchemotherapeutic drugs, including interferon alfa, which prolongs remission but does not improve survival and is associated with significant adverse effects. Following a response to corticosteroid-based regimens, corticosteroids alone are effective as a maintenance treatment. Thalidomide may also be effective as a maintenance treatment, and studies are evaluating maintenance therapy with bortezomib and lenalidomide among patients who have responded to these drugs alone or in combination therapeutic regimens.

Treatment of complications: In addition to direct treatment of malignant cells, therapy must also be directed at complications, which include anemia, hypercalcemia, renal insufficiency, infections, and skeletal lesions.

Anemia can be treated with recombinant erythropoietin (40,000 units sc once/wk) in patients whose anemia is inadequately relieved by chemotherapy. If anemia causes cardiovascular or significant systemic symptoms, packed RBCs are transfused. Plasmapheresis is indicated if hyperviscosity develops (see p. 1027).

Hypercalcemia is treated with saluresis, IV bisphosphonates, and sometimes with prednisone. Most patients do not require allopurinol. However, allopurinol is indicated for patients with high levels of serum uric acid or high tumor burden and a high risk of tumor lysis syndrome with treatment.

Renal compromise can be ameliorated with adequate hydration. Even patients with prolonged, massive Bence Jones proteinuria (≥ 10 to 30 g/day) may have intact renal function if they maintain urine output > 2000 mL/day. Dehydration combined with high-osmolar IV contrast may precipitate acute oliguric renal failure in patients with Bence Jones proteinuria.

Infection is more likely during chemotherapy-induced neutropenia. In addition, infections with the herpes zoster virus are occurring more frequently in patients treated with newer antimyeloma drugs. Documented bacterial infections should be treated with antibiotics; however, prophylactic use of antibiotics is not routinely recommended. Prophylactic use of antiviral drugs may be indicated for patients receiving specific drugs. Prophylactic IV immune globulin may reduce the risk of infection but is generally reserved for patients with recurring infections. Pneumococcal and influenza vaccines are indicated to prevent infection.

Skeletal lesions require multiple supportive measures. Maintenance of ambulation and supplemental Ca and vitamin D help preserve bone density. Analgesics and palliative doses of radiation therapy (18 to 24 Gy) can relieve bone pain. However, radiation therapy may impair the patient's ability to receive cytotoxic doses of systemic chemotherapy. Most patients, especially those with lytic lesions and generalized osteoporosis or osteopenia, should receive a monthly IV bisphosphonate (either pamidronate or zoledronic acid). Bisphosphonates reduce skeletal complications and lessen bone pain and may have an antitumor effect.
Chapter 120. Iron Overload

Introduction

(Hemosiderosis; Hemochromatosis)

(For iron poisoning, see p. 3341.)

Iron (Fe) in excess of bodily needs is deposited in tissues:

• Hemosiderosis is focal deposition of iron that does not cause tissue damage.

• Hemochromatosis (iron overload) is a typically systemic process in which iron deposition can cause tissue damage.

Iron overload may result from primary hemochromatosis (a genetic disorder of iron metabolism), from excess oral intake or absorption of iron, or from repeated blood transfusions. Morbidity is mainly due to iron accumulation in the endocrine organs (especially the pancreas, gonads, and pituitary), liver, and heart.

Hemosiderosis

Hemosiderosis is focal deposition of iron that does not cause tissue damage.

Focal hemosiderosis can result from hemorrhage within an organ. Iron liberated from extravasated RBCs is deposited within that organ, and significant hemosiderin deposits may eventually develop. Occasionally, iron loss from tissue hemorrhage causes iron deficiency anemia, because iron in tissues cannot be reused.

Usually the lungs are affected, and the cause usually is recurrent pulmonary hemorrhage, either idiopathic (eg, Goodpasture's syndrome) or due to chronic pulmonary hypertension (eg, from primary pulmonary hypertension, pulmonary fibrosis, severe mitral stenosis).

Another common site of accumulation is the kidneys, where hemosiderosis can result from extensive intravascular hemolysis (see p. 934). Free Hb is filtered at the glomerulus, resulting in iron deposition in the kidneys. The renal parenchyma is not damaged, but severe hemosiderinuria may result in iron deficiency.

Primary Hemochromatosis

(Hereditary Hemochromatosis)

Primary hemochromatosis is a genetic disorder characterized by excessive iron accumulation that results in tissue damage. Manifestations can include constitutional symptoms, liver disorders, cardiomyopathy, diabetes, erectile dysfunction, and arthropathy. Diagnosis is by serum ferritin level and gene assay. Treatment is usually with serial phlebotomies.

Etiology

Until recently, the cause in virtually all patients with primary hemochromatosis was thought to be a mutation of the \textit{HFE} gene. Recently, other causes have been identified; different mutations causing primary hemochromatosis occur in ferroportin disease, juvenile hemochromatosis, neonatal hemochromatosis (neonatal iron storage disease), hypotransferrinemia, and aceruloplasminemia. Although these types vary markedly in age of onset, clinical consequences of iron overload are the same in all.

More than 80\% of \textit{HFE}-related hemochromatosis is caused by the homozygous \textit{C282Y} or \textit{C282Y/H63D}
compound heterozygote mutation. The disorder is autosomal recessive, with a homozygous frequency of 1:200 and a heterozygous frequency of 1:8 in people of northern European ancestry. It is uncommon among blacks and rare among people of Asian ancestry. Of patients with clinical hemochromatosis, 83% are homozygous. However, for unknown reasons, phenotypic (clinical) disease is much less common than predicted by the frequency of the gene (ie, many homozygous people do not manifest the disorder).

Pathophysiology

Normal total body iron content is about 2.5 g in women and 3.5 g in men. Because symptoms may be delayed until iron accumulation is excessive, hemochromatosis may not be recognized until total body iron content is > 10 g, or often several times greater. In women, clinical manifestations are uncommon before menopause because iron loss due to menses (and sometimes pregnancy and childbirth) tends to offset iron accumulation.

The mechanism for iron overload is increased iron absorption from the GI tract, leading to chronic deposition of iron in the tissues. Hepcidin, a liver-derived peptide, is the critical control mechanism for iron absorption. Hepcidin, along with the normal HFE gene, prevents excessive iron absorption and storage in normal people.

In general, tissue injury appears to result from reactive free hydroxyl radicals generated when iron deposition in tissues catalyzes their formation. Other mechanisms may affect particular organs (eg, skin hyperpigmentation can result from increased melanin as well as iron accumulation).

Symptoms and Signs

The clinical consequences of iron overload are the same regardless of the etiology and pathophysiology of the overload.

Historically, experts believed that symptoms did not develop until significant organ damage had occurred. However, organ damage is slow and subtle, and fatigue and nonspecific constitutional symptoms often occur early.

Other symptoms relate to the organs with the largest iron deposits (see Table 120-1). In men, the initial symptoms may be hypogonadism and erectile dysfunction caused by gonadal iron deposition. Glucose intolerance or diabetes mellitus is another common initial presentation. Some patients present with hypothyroidism.

Liver disease is the most common complication and may progress to cirrhosis; 20 to 30% of patients with cirrhosis develop hepatocellular carcinoma. Liver disease is the most common cause of death. Cardiomyopathy with heart failure is the 2nd most common fatal complication. Hyperpigmentation (bronze diabetes) is common, as is symptomatic arthropathy.

[Table 120-1, Common Manifestations of Primary Hemochromatosis]

Diagnosis

• Serum ferritin level

• Genetic testing

Symptoms and signs may be nonspecific, subtle, and of gradual onset, so that index of suspicion should be high. Primary hemochromatosis should be suspected when typical manifestations, particularly combinations of such manifestations, remain unexplained after routine evaluation. Although any family history is a more specific clue, it is not usually present.

Serum ferritin measurement is the simplest and most direct initial test. Elevated levels (> 200 ng/mL in women or > 300 ng/mL in men) are usually present in primary hemochromatosis but can result from other abnormalities, such as inflammatory liver disorders (eg, chronic viral hepatitis, nonalcoholic
steatohepatitis, alcoholic liver disease), cancer, certain systemic inflammatory disorders (eg, RA, hemophagocytic lymphohistiocytosis), or obesity. Further testing is done if ferritin level is abnormal; testing includes serum iron (usually > 300 mg/dL) and iron binding capacity (transferrin saturation; levels usually > 50%). Gene assay is diagnostic of primary hemochromatosis caused by \textit{HFE} gene mutations. Other types of primary hemochromatosis (eg, ferroportin disease, juvenile hemochromatosis, neonatal hemochromatosis, transferrin deficiency, ceruloplasmin deficiency) are suspected in very rare instances in which ferritin and iron blood tests indicate iron overload and genetic testing is negative for the \textit{HFE} gene mutation, particularly in younger patients. Confirmation of these diagnoses is evolving.

Because the presence of cirrhosis affects prognosis, a liver biopsy is commonly done and tissue iron content is measured (when available). High-intensity MRI is a noninvasive alternative for estimating hepatic iron content that is becoming increasingly accurate.

Screening is required for first-degree relatives of people with primary hemochromatosis by measuring serum ferritin levels and testing for the 282Y/H63D gene.

**Treatment**

- **Phlebotomy**

Treatment is indicated for patients with clinical manifestations, elevated serum ferritin levels (particularly levels > 1000 ng/mL), or elevated transferrin saturation. Asymptomatic patients need only periodic (eg, yearly) clinical evaluation and measurement of serum iron, ferritin, and transferrin saturation.

Phlebotomy is the simplest and most effective method to remove excess iron. It delays progression of fibrosis to cirrhosis, sometimes even reversing cirrhotic changes, and prolongs survival, but it does not prevent hepatocellular carcinoma. About 500 mL of blood (about 250 mg of iron) is removed weekly until serum iron levels are normal and transferrin saturation is < 50%. Weekly phlebotomy may be needed for many months (eg, if 250 mg Fe are removed per week, 40 wk will be required to remove 10 g Fe). When iron levels are normal, phlebotomies can be intermittent to maintain transferrin saturation at < 30%.

Diabetes, cardiomyopathy, erectile dysfunction, and other secondary manifestations are treated as indicated.

Patients should follow a balanced diet; it is not necessary to restrict consumption of iron-containing foods (eg, red meat, liver). Alcohol should be consumed only in moderation because it can increase iron absorption and, in high amounts, increases the risk of cirrhosis.

**Ferroportin Disease**

Ferroportin disease occurs largely in people of southern European ancestry. It results from an autosomal dominant mutation in the \textit{SLC 40 A1} gene. It manifests in the first decade of life as increased serum ferritin levels with low or normal transferrin saturation; progressive saturation of transferrin occurs when patients are in their 20s and 30s. Clinical manifestations are milder than in \textit{HFE} disease, with modest liver disease and mild anemia. Tolerance to vigorous phlebotomy is poor; serial monitoring of Hb level and transferrin saturation is required.

**Juvenile Hemochromatosis**

Juvenile hemochromatosis is a rare autosomal recessive disorder caused by mutations in the \textit{HJV} gene that affect the transcription protein hemojuvelin. It often manifests in adolescents. Symptoms and signs include progressive hepatomegaly and hypogonadotropic hypogonadism. Ferritin levels are > 1000 ng/mL, and transferrin saturation is > 90%.

**Transferrin and Ceruloplasmin Deficiency**

(Hypotransferrinemia/At transferrinemia; Aceruloplasminemia)
In transferrin deficiency, absorbed iron that enters the portal system not bound to transferrin is deposited in the liver. Subsequent iron transfer to sites of RBC production is reduced because of transferrin deficiency.

In ceruloplasmin deficiency, lack of ferroxidase causes defective conversion of Fe$^{2+}$ to Fe$^{3+}$; such conversion is necessary for binding to transferrin. Defective transferrin binding impairs the movement of iron from intracellular stores to plasma transport, resulting in accumulation of iron in tissues.

Diagnosis is based on measurement of serum transferrin (ie, iron-binding capacity) and ceruloplasmin levels (see Inherited Copper Toxicity on p. 51). Treatment is experimental; eg, iron chelators may be better tolerated than phlebotomy because patients typically have anemia.

**Transferrin Receptor 2 Mutation**

Mutations in transferrin receptor 2, a protein that appears to control saturation of transferrin, can cause a rare autosomal recessive form of hemochromatosis. Symptoms and signs are similar to HFE hemochromatosis.

**Secondary Iron Overload**

(Secondary Hemochromatosis)

Secondary iron overload results from excess absorption of iron, repeated blood transfusions, or excess oral intake, typically in patients with disorders of erythropoiesis. Diagnosis is with serum iron studies. Treatment is usually by iron chelation.

**Etiology**

Secondary iron overload typically occurs in patients who have

- Hemoglobinopathies (eg, sickle cell disease, thalassemia, sideroblastic anemias)
- Congenital hemolytic anemias
- Myelodysplasia

Iron overload results from the following mechanisms:

- Increased iron absorption (which occurs, for unknown reasons, with ineffective erythropoiesis)
- Exogenous iron given to treat the anemia
- Repeated blood transfusions (each unit of blood provides about 250 mg of iron; tissue deposition becomes significant when more than about 40 units of blood are transfused)

Patients with hemoglobinopathies and congenital hemolytic anemias now typically live into adulthood, so complications of iron overload are now common. In such patients, iron overload involving the heart, the liver, and endocrine organs has become a common cause of death, but survival can be prolonged by iron removal.

**Diagnosis**

Patients with ineffective erythropoiesis should be evaluated for secondary iron overload, which is diagnosed by measuring serum ferritin, serum iron, and transferrin saturation.

**Treatment**

- Usually iron chelation with deferasirox or deferoxamine
Some patients can be treated with phlebotomy and given erythropoietin to maintain erythropoiesis. However, because it worsens anemia, phlebotomy is not recommended for many patients (eg, those with Hb level < 10 g/dL, those who are transfusion dependent, and those who develop symptoms of anemia after phlebotomy). Treatment in these patients is iron chelation. The goal of treatment is a transferrin saturation of < 50%.

Deferoxamine is the drug traditionally used for iron chelation therapy. It is given by a slow subcutaneous infusion overnight through a portable pump for 5 to 7 nights/wk or via 24-h IV infusion. Dose is 1 to 2 g in adults and 20 to 40 mg/kg in children. However, this therapy is complex to administer and requires an unusual time commitment from patients, resulting in a high rate of nonadherence. Important adverse effects include hypotension, GI disturbances, and anaphylaxis (acutely) and vision and hearing loss (with chronic use).

Deferasirox, an oral chelating agent, is an effective and increasingly used alternative to deferoxamine. Deferasirox reduces iron levels and prevents or delays onset of complications of iron overload. Initial dose is 20 mg/kg po once/day. Patients are monitored monthly with dose increases of up to 30 mg/kg once/day. Treatment can be interrupted when serum ferritin is < 500 ng/mL. Adverse effects (which occur in about 10% of patients) can include nausea, abdominal pain, diarrhea, and rash. Liver and kidney function may become abnormal; liver and kidney function tests should be done periodically (eg, monthly, sometimes more frequently for high-risk patients).
Chapter 121. Transfusion Medicine

Introduction

More than 29 million units of blood components are transfused yearly in the US, from about 8 million volunteer donors. Although transfusion is probably safer than ever, risk (and the public's perception of risk) mandates informed consent whenever practical.

Blood Collection

In the US, the collection, storage, and transport of blood and its components are standardized and regulated by the FDA, the AABB, and sometimes state or local health authorities. Donor screening includes an extensive questionnaire and health interview; measurement of temperature, heart rate, and BP; and Hb determination. Some potential donors are deferred either temporarily or permanently (see Table 121-1). Criteria for deferral protect prospective donors from possible ill effects of donation and recipients from disease. Donations are limited to once every 56 days. With rare exceptions, blood donors are unpaid.

In standard blood donation, about 450 mL of whole blood is collected in a plastic bag containing an anticoagulant preservative. Whole blood or packed RBCs preserved with citrate-phosphate-dextrose-adrenaline may be stored for 35 days. Packed RBCs may be stored for 42 days if an adenine-dextrose-saline solution is added.

Table 121-1. Some Reasons for Blood Donation Deferral or Denial

Autologous donation, which is use of the patient's own blood, is the preferred method of transfusion when conditions permit. In the 2 to 3 wk preceding elective surgery, up to 3 or 4 units of whole blood or packed RBCs are collected, and the patient is given iron supplements. Special blood salvage procedures are also available for collecting and autotransfusing blood shed after trauma and during surgery.

Pretransfusion Testing

Donor blood testing includes ABO and Rh0(D) antigen typing, antibody screening, and testing for infectious disease markers (see Table 121-2).

Compatibility testing tests the recipient's RBCs for antigens A, B, and Rh0(D); screens the recipient's plasma for antibodies against other RBC antigens; and includes a cross-match to ensure that the recipient's plasma is compatible with antigens on donor RBCs. Compatibility testing is done before a transfusion; however, in an emergency, testing is done after releasing blood from the blood bank. It can also help in diagnosing transfusion reactions.

ABO typing of donor and recipient blood is done to prevent transfusion of incompatible RBCs (see Fig. 121-1). As a rule, blood for transfusion should be of the same ABO type as that of the recipient. In urgent situations or when the correct ABO type is in doubt or unknown, type O Rh-negative packed RBCs (not whole blood—see p. 1040 for Acute Hemolytic Transfusion Reaction), which contains neither A nor B antigens, may be used for patients of any ABO type.

Rh typing determines whether the Rh factor Rh0(D) is present on (Rh-positive) or absent from (Rh-negative) the RBCs. Rh-negative patients should always receive Rh-negative blood except in life-threatening emergencies when Rh-negative blood is unavailable. Rh-positive patients may receive Rh-positive or Rh-negative blood. Occasionally, RBCs from some Rh-positive people react weakly on standard Rh typing (weak D, or D\u208u, positive), but these people are still considered Rh-positive.

Antibody screening for unexpected anti-RBC antibodies is routinely done on blood from prospective recipients and prenatally on maternal specimens. Unexpected anti-RBC antibodies are specific for RBC blood group antigens other than A and B [eg, Rh0(D), Kell (K), Duffy (Fy)]. Early detection is important,
because such antibodies can cause serious

[Table 121-2. Infectious Disease Transmission Testing]

[Fig. 121-1. Compatible RBC types.]

hemolytic transfusion reactions or hemolytic disease of the newborn (see p. 2784), and they may greatly complicate compatibility testing and delay procurement of compatible blood.

Indirect antiglobulin testing (the indirect Coombs' test) is used to screen for unexpected anti-RBC antibodies. This test may be positive in the presence of an unexpected blood group antibody or when free (non-RBC-attached) antibody is present in autoimmune hemolytic anemias (see p. 936). Reagent RBCs are mixed with the patient's serum, incubated, washed, tested with antihuman globulin, and observed for agglutination. Once an antibody is detected, its specificity is determined. Knowing the specificity of the antibody is helpful for assessing its clinical significance, selecting compatible blood, and managing hemolytic disease of the newborn.

Direct antiglobulin testing (the direct Coombs' test) detects antibodies that have coated the patient's RBCs in vivo. It is used when immune-mediated hemolysis is suspected. Patients' RBCs are directly tested with antihuman globulin and observed for agglutination. A positive result, if correlated with clinical findings, suggests autoimmune hemolytic anemia, drug-induced hemolysis, a transfusion reaction, or hemolytic disease of the newborn.

Antibody titration is done when a clinically significant, unexpected anti-RBC antibody is identified in the serum of a pregnant woman or in a patient with cold autoimmune hemolytic anemia (see p. 936). The maternal antibody titer correlates fairly well with the severity of hemolytic disease in the incompatible fetus and is often used to guide treatment in hemolytic disease of the newborn along with ultrasonography and amniotic fluid study.

The addition of a cross-match to ABO/Rh typing and antibody screening increases detection of incompatibility by only 0.01%. If the recipient has a clinically significant anti-RBC antibody, donor blood is restricted to RBC units negative for the corresponding antigen; further testing for compatibility is done by combining recipient serum, donor RBCs, and antihuman globulin. In recipients without clinically significant anti-RBC antibodies, an immediate spin cross-match, which omits the antiglobulin phase, confirms ABO compatibility.

Emergency transfusion is done when not enough time (generally < 60 min) is available for thorough compatibility testing because the patient is in hemorrhagic shock. When time permits (about 10 min is needed), ABO/Rh type-specific blood may be given. In more urgent circumstances, type O RBCs are transfused if the ABO type is uncertain, and Rh-negative blood is given if the Rh type is uncertain.

"Type and screen" may be requested in circumstances not likely to require transfusion, as in elective surgery. The patient's blood is typed for ABO/Rh antigens and screened for antibodies. If antibodies are absent and the patient needs blood, ABO/Rh type specific or compatible RBCs may be released without the antiglobulin phase of the cross-match. If an unexpected antibody is present, full testing is required.

**Blood Products**

Whole blood can provide improved O₂-carrying capacity, volume expansion, and replacement of clotting factors and was previously recommended for rapid massive blood loss. However, because component therapy is equally effective and is a more efficient use of donated blood, whole blood is not generally available in the US.

**RBCs:** Packed RBCs are ordinarily the component of choice with which to increase Hb. Indications depend on the patient. O₂-carrying capacity may be adequate with Hb levels as low as 7 g/L in healthy patients, but transfusion may be indicated with higher Hb levels in patients with decreased cardiopulmonary reserve or ongoing bleeding. One unit of RBCs increases an average adult's Hb by
about 1 g/dL, and the Hct by about 3% above the pretransfusion Hct value. When only volume expansion is required, other fluids can be used concurrently or separately. In patients with multiple blood group antibodies or with antibodies to high-frequency RBC antigens, rare frozen RBCs are used.

Washed RBCs are free of almost all traces of plasma, most WBCs, and platelets. They are generally given to patients who have severe reactions to plasma (eg, severe allergies, paroxysmal nocturnal hemoglobinuria, or IgA immunization). In IgA-immunized patients, blood collected from IgA-deficient donors may be preferable for transfusion.

WBC-depleted RBCs are prepared with special filters that remove ≥ 99.99% of WBCs. They are indicated for patients who have experienced nonhemolytic febrile transfusion reactions, for exchange transfusions, for patients who require cytomegalovirus-negative blood that is unavailable, and possibly for the prevention of platelet alloimmunization.

**Fresh frozen plasma:** Fresh frozen plasma (FFP) is an unconcentrated source of all clotting factors without platelets. Indications include correction of bleeding secondary to factor deficiencies for which specific factor replacements are unavailable, multifactor deficiency states (eg, massive transfusion, disseminated intravascular coagulation [DIC], liver failure), and urgent warfarin reversal, although prothrombin complex concentrate (PCC) should be the first choice if available. FFP can supplement RBCs when whole blood is unavailable for exchange transfusion. FFP should not be used simply for volume expansion.

**Cryoprecipitate:** Cryoprecipitate is a concentrate prepared from FFP. Each concentrate usually contains about 80 units each of factor VIII and von Willebrand's factor and about 250 mg of fibrinogen. It also contains fibronectin and factor XIII. Although originally used for hemophilia and von Willebrand's disease, cryoprecipitate is currently used as a source of fibrinogen in acute DIC with bleeding, treatment of uremic bleeding, cardiothoracic surgery (fibrin glue), obstetric emergencies such as abruptio placenta and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and rare factor XIII deficiency. In general, it should not be used for other indications.

**WBCs:** Granulocytes may be transfused when sepsis occurs in a patient with profound persistent neutropenia (WBCs < 500/μL) who is unresponsive to antibiotics. Granulocytes must be given within 24 h of harvest; however, testing for HIV, hepatitis, human T-cell lymphotropic virus, and syphilis may not be completed before infusion. Because of improved antibiotic therapy and drugs that stimulate granulocyte production during chemotherapy, granulocytes are seldom used.

**Immune globulins:** Rh immune globulin (Rhlg), given IM or IV, prevents development of maternal Rh antibodies that can result from fetomaternal hemorrhage. The standard dose of intramuscular Rhlg (300 μg) must be given to an Rh-negative mother immediately after abortion or delivery (live or stillborn) unless the infant is Rh(D) and D<sup>+</sup> negative or the mother's serum already contains anti-Rh<sub>H</sub>(D). If fetomaternal hemorrhage is > 30 mL, a larger dose is needed. If hemorrhage of this amount is suspected, testing of the volume of fetomaternal hemorrhage begins with the screening rosette test, which, if positive, is followed by a quantitative test (eg, Kleihauer-Betke). Rhlg is given IV only when IM administration is contraindicated (eg, in patients with coagulopathy).

Other immune globulins are available for postexposure prophylaxis for patients exposed to a number of infectious diseases, including cytomegalovirus, hepatitis A and B, measles, rabies, respiratory syncytial virus, rubella, tetanus, smallpox, and varicella (for usage, see under specific disease).

**Platelets:** Platelet concentrates are used to prevent bleeding in asymptomatic severe thrombocytopenia (platelet count < 10,000/μL), for bleeding patients with less severe thrombocytopenia (platelet count < 50,000/μL), for bleeding patients with platelet dysfunction due to antiplatelet drugs but with normal platelet count, for patients receiving massive transfusion that causes dilutional thrombocytopenia, and sometimes before invasive surgery, particularly with extracorporeal circulation for > 2 h (which often makes platelets dysfunctional). One platelet concentrate unit increases the platelet count by about 10,000/μL, and adequate hemostasis is achieved with a platelet count of about 10,000/μL in a patient without complicating conditions and about 50,000/μL for those undergoing surgery. Therefore, 4 to 6 units
of random donor platelet concentrates are commonly used in adults.

Platelet concentrates are increasingly being prepared by automated devices that harvest the platelets (or other cells) and return unneeded components (eg, RBCs, plasma) to the donor. This procedure, called cytapheresis, provides enough platelets from a single donation (equivalent to 6 random platelet units) for transfusion to an adult, which, because it minimizes infectious and immunogenic risks, is preferred to multiple donor transfusions in certain conditions.

Certain patients may not respond to platelet transfusions, possibly because of splenic sequestration or platelet consumption due to HLA or platelet-specific antigen alloimmunization. These patients may respond to multiple random donor platelets (because of greater likelihood that some units are HLA compatible), platelets from family members, or ABO-or HLA-matched platelets. Alloimmunization may be mitigated by transfusing WBC-depleted RBCs and WBC-depleted platelet concentrates.

Other products: Irradiated blood products are used to prevent graft-vs-host disease in patients at risk (see p. 1042). Blood substitutes are being developed that use inert chemicals or Hb solutions to carry and deliver O₂ to tissues. Perfluorocarbons are chemically and biologically inactive and are capable of dissolving O₂ and CO₂ under pressure. Because perfluorocarbons are not water miscible, they are prepared as emulsions. They are undergoing phase II and III clinical trials. Hb-based O₂ carrier solutions are undergoing phase III clinical trials in the US. Hb, human or bovine, is chemically modified, producing a solution capable of O₂ transport. These solutions can be stored at room temperature for up to 2 yr, making them attractive for transport to the site of trauma or to the battlefield. However, both perfluorocarbons and Hb-based O₂ carriers are cleared from plasma within 24 h.

Hematopoietic progenitor cells (stem cells) from autologous or allogenic donors can be transfused as a way of reconstituting hematopoietic function (particularly immune function) in patients undergoing myeloablative or myelotoxic therapy (see p. 1132).

Technique of Transfusion

CAUTION: Before transfusion is started, the patient's wristband, blood unit label, and compatibility test report must be checked at the bedside to ensure that the blood component is the one intended for the recipient.

Use of an 18-gauge (or larger) needle prevents mechanical damage to and hemolysis of RBCs. A standard filter should always be used for infusion of any blood component. Only 0.9% saline IV should be allowed into the blood bag or in the same tubing with blood. Hypotonic solutions lyse RBCs, and the Ca in Ringer's lactate can cause clotting.

Transfusion of 1 unit of blood or blood component should be completed by 4 h; longer duration increases the risk of bacterial growth. If transfusion must be given slowly because of heart failure or hypervolemia, units may be divided into smaller aliquots in the blood bank. For children, 1 unit of blood can be provided in small sterile aliquots used over several days, thereby minimizing exposure to multiple donors.

Close observation is important, particularly during the first 15 min, and includes recording temperature, BP, pulse, and respiratory rate. Periodic observation continues throughout and after the transfusion, during which fluid status is assessed. The patient is kept covered and warm to prevent chills, which may be interpreted as a transfusion reaction. Elective transfusions at night are discouraged.

Complications of Transfusion

The most common complications of transfusion are febrile nonhemolytic and chill-rigor reactions. The most serious complications are transfusion-related acute lung injury and acute hemolytic reaction due to ABO incompatible transfusion, which have very high mortality rates.

Early recognition of symptoms suggestive of a transfusion reaction and prompt reporting to the blood bank are essential. The most common symptoms are chills, rigors, fever, dyspnea, light-headedness,
urticaria, itching, and flank pain. If any of these symptoms (other than localized urticaria and itching) occur, the transfusion should be stopped immediately and the IV line kept open with normal saline. The remainder of the blood product and clotted and anticoagulated samples of the patient's blood should be sent to the blood bank for investigation. NOTE: **The unit in question should not be restarted, and transfusion of any previously issued unit should not be initiated.** Further transfusion should be delayed until the cause of the reaction is known, unless the need is urgent, in which case type O Rh-negative RBCs should be used.

Hemolysis of donor or recipient RBCs (usually the former) during or after transfusion can result from ABO/Rh incompatibility, plasma antibodies, or hemolyzed or fragile RBCs (eg, by overwarming stored blood or contact with hypotonic IV solutions). Hemolysis is most common and most severe when incompatible donor RBCs are hemolyzed by antibody in the recipient's plasma. Hemolytic reactions may be acute (within 24 h) or delayed (from 1 to 14 days).

**Acute hemolytic transfusion reaction (AHTR):** About 20 people die yearly in the US from AHTR. AHTR usually results from recipient plasma antibodies to donor RBC antigens. ABO incompatibility is the most common cause of AHTR. Antibodies against blood group antigens other than ABO can also cause AHTR. Mislabling the recipient's pretransfusion sample at collection or failing to match the intended recipient with the blood product immediately before transfusion is the usual cause, not laboratory error.

Hemolysis is intravascular, causing hemoglobinuria with varying degrees of acute renal failure and possibly disseminated intravascular coagulation (DIC). The severity of AHTR depends on the degree of incompatibility, the amount of blood given, the rate of administration, and the integrity of the kidneys, liver, and heart. An acute phase usually develops within 1 h of initiation of transfusion, but it may occur later during the transfusion or immediately afterward. Onset is usually abrupt. The patient may complain of discomfort and anxiety. Dyspnea, fever, chills, facial flushing, and severe pain may occur, especially in the lumbar area. Shock may develop, causing a rapid, feeble pulse; cold, clammy skin; low BP; and nausea and vomiting. Jaundice may follow acute hemolysis.

If AHTR occurs while the patient is under general anesthesia, the only symptom may be hypotension, uncontrollable bleeding from incision sites and mucous membranes caused by an associated DIC, or dark urine that reflects hemoglobinuria.

If AHTR is suspected, one of the first steps is to recheck the sample and patient identifications. Diagnosis is confirmed by measuring urinary Hb, serum LDH, bilirubin, and haptoglobin. Intravascular hemolysis produces free Hb in the plasma and urine; haptoglobin levels are very low. Hyperbilirubinemia may follow.

After the acute phase, the degree of acute renal failure determines the prognosis. Diuresis and a decreasing BUN usually portend recovery. Permanent renal insufficiency is unusual. Prolonged oliguria and shock are poor prognostic signs.

If AHTR is suspected, the transfusion should be stopped and supportive treatment begun. The goal of initial therapy is to achieve and maintain adequate BP and renal blood flow with IV 0.9% saline and furosemide. IV saline is given to maintain urine output of 100 mL/h for 24 h. The initial furosemide dose is 40 to 80 mg (1 to 2 mg/kg in children), with later doses adjusted to maintain urinary flow > 100 mL/h during the first day.

Antihypertensive drugs must be administered with caution. Pressor drugs that decrease renal blood flow (eg, epinephrine, norepinephrine, high-dose dopamine) are contraindicated. If a pressor drug is necessary, dopamine 2 to 5 μg/kg/min is usually administered.

A nephrologist should be consulted as early as possible, particularly if no diuretic response occurs within about 2 to 3 h after initiating therapy, which may indicate acute tubular necrosis. Further fluid and diuretic therapy may be contraindicated, and early dialysis may be helpful.

**Delayed hemolytic transfusion reaction:** Occasionally, a patient who has been sensitized to an RBC antigen has very low antibody levels and negative pretransfusion tests. After transfusion with RBCs bearing this antigen, a primary or anamnestic response may result (usually in 1 to 4 wk) and cause a
delayed hemolytic transfusion reaction. Delayed hemolytic transfusion reaction usually does not manifest as dramatically as AHTR. Patients may be asymptomatic or have a slight fever. Rarely, severe symptoms occur. Usually, only destruction of the transfused RBCs (with the antigen) occurs, resulting in a falling Hct and a slight rise in LDH and bilirubin. Because delayed hemolytic transfusion reaction is usually mild and self-limited, it is often unidentified, and the clinical clue may be an unexplained drop in Hb to the pretransfusion level occurring 1 to 2 wk posttransfusion. Severe reactions are treated similarly to acute reactions.

**Febrile nonhemolytic transfusion reaction:** Febrile reaction may occur without hemolysis. Antibodies directed against WBC HLA from otherwise compatible donor blood are one possible cause. This cause is most common in multitransfused or multiparous patients. Cytokines released from WBCs during storage, particularly in platelet concentrates, are another possible cause.

Clinically, febrile reactions consist of a temperature increase of ≥ 1° C, chills, and sometimes headache and back pain. Simultaneous symptoms of allergic reaction are common. Because fever and chills also herald a severe hemolytic transfusion reaction, all febrile reactions must be investigated as for AHTR, as with any transfusion reaction.

Most febrile reactions are treated successfully with acetaminophen and, if necessary, diphenhydramine (see p. 1042). Patients should also be treated (eg, with acetaminophen) before future transfusions. If a recipient has experienced more than one febrile reaction, special leukoreduction filters are used during future transfusions; most hospitals use prestorage, leukoreduced blood components.

**Allergic reactions:** Allergic reactions to an unknown component in donor blood are common, usually due to allergens in donor plasma or, less often, to antibodies from an allergic donor. These reactions are usually mild, with urticaria, edema, occasional dizziness, and headache during or immediately after the transfusion. Simultaneous fever is common. Less frequently, dyspnea, wheezing, and incontinence may occur, indicating a generalized spasm of smooth muscle. Rarely, anaphylaxis occurs, particularly in IgA-deficient recipients.

In a patient with a history of allergies or an allergic transfusion reaction, an antihistamine may be given prophylactically just before or at the beginning of the transfusion (eg, diphenhydramine 50 mg po or IV). **NOTE:** *Drugs must never be mixed with the blood.* If an allergic reaction occurs, the transfusion is stopped. An antihistamine (eg, diphenhydramine 50 mg IV) usually controls mild urticaria and itching, and transfusion may be resumed. However, a moderate allergic reaction (generalized urticaria or mild bronchospasm) requires hydrocortisone (100 to 200 mg IV), and a severe anaphylactic reaction requires additional treatment with epinephrine 0.5 mL of 1:1000 solution sc and 0.9% saline IV (see p. 1121) along with investigation by the blood bank. Further transfusion should not occur until the investigation is completed. Patients with severe IgA deficiency require transfusion of washed RBCs, washed platelets, and plasma from an IgA-deficient donor.

**Volume overload:** The high osmotic load of blood products draws volume into the intravascular space over the course of hours, which can cause volume overload in susceptible patients (eg, those with cardiac or renal insufficiency). RBCs should be infused slowly. The patient should be observed and, if signs of heart failure (eg, dyspnea, crackles) occur, the transfusion should be stopped and treatment for heart failure begun.

Typical treatment is with a diuretic such as furosemide 20 to 40 mg IV. Occasionally, patients requiring a higher volume of plasma infusion to reverse a warfarin overdose may be given a low dose of furosemide simultaneously; however, prothrombin complex concentrate (PCC) should be the first choice for such patients. Patients at high risk of volume overload (eg, those with heart failure or severe renal insufficiency) are treated prophylactically with a diuretic (eg, furosemide 20 to 40 mg IV).

**Acute lung injury:** Transfusion-related acute lung injury is an infrequent complication caused by anti-HLA and/or antigranulocyte antibodies in donor plasma that agglutinate and degranulate recipient granulocytes within the lung. Acute respiratory symptoms develop, and chest x-ray has a characteristic pattern of noncardiogenic pulmonary edema. This complication is the 2nd most common cause of transfusion-related death. Incidence is one in 5,000 to one in 10,000, but many cases are mild. Mild to
moderate transfusion-related acute lung injury probably is commonly missed. General supportive therapy typically leads to recovery without long-lasting sequelae. Diuretics should be avoided. Cases should be reported.

**Altered oxygen affinity:** Blood stored for > 7 days has decreased RBC 2,3-diphosphoglycerate (DPG), and the 2,3-DPG is absent after > 10 days. This absence results in an increased affinity for \(O_2\) and slower \(O_2\) release to the tissues. There is little evidence that 2,3-DPG deficiency is clinically significant except in exchange transfusions in infants, in sickle cell patients with acute chest syndrome and stroke, and in some patients with severe heart failure. After transfusion of RBCs, 2,3-DPG regenerates within 12 to 24 h.

**Graft-vs-host disease (GVHD):** Transfusion-associated GVHD (see p. 1131) is usually caused by transfusion of products containing immunocompetent lymphocytes to an immunocompromised host. The donor lymphocytes attack host tissues. GVHD can occur occasionally in immunocompetent patients if they receive blood from a donor (usually a close relative) who is homozygous for an HLA haplotype for which they are heterozygous. Symptoms and signs include fever, rash (centrifugally spreading rash becoming erythroderma with bullae), vomiting, watery and bloody diarrhea, lymphadenopathy, and pancytopenia due to bone marrow aplasia. Jaundice and elevated liver enzymes are also common. GVHD occurs 4 to 30 days after transfusion and is diagnosed based on clinical suspicion and skin and bone marrow biopsies. GVHD has > 90% mortality because no specific treatment is available.

Prevention of GVHD is with irradiation (to damage DNA of the donor lymphocytes) of all transfused blood products. It is done if the recipient is immunocompromised (eg, patients with congenital immune deficiency syndromes, hematologic cancers, or hematopoietic stem cell transplants; neonates), if donor blood is obtained from a 1st-degree relative, or when HLA-matched components, excluding stem cells, are transfused. Treatment with corticosteroids and other immunosuppressants, including those used for solid organ transplantation, is not an indication for blood irradiation.

**Complications of massive transfusion:** Massive transfusion is transfusion of a volume of blood greater than or equal to one blood volume in 24 h (eg, 10 units in a 70-kg adult). When a patient receives stored blood in such large volume, the patient's own blood may be, in effect, "washed out." In circumstances uncomplicated by prolonged hypotension or DIC, dilutional thrombocytopenia is the most likely complication. Platelets in stored whole blood are not functional. Clotting factors (except factor VIII) usually remain sufficient. Microvascular bleeding (abnormal oozing and continued bleeding from raw and cut surfaces) may result. Five to 8 units (1 unit/10 kg) of platelet concentrates are usually enough to correct such bleeding in an adult. Fresh frozen plasma and cryoprecipitate may be needed.

Hypothermia due to rapid transfusion of large amounts of cold blood can cause arrhythmias or cardiac arrest. Hypothermia is avoided by using an IV set with a heat-exchange device that gently warms blood. Other means of warming blood (eg, microwave ovens) are contraindicated because of potential RBC damage and hemolysis.

Citrate and K toxicities generally are not of concern even in massive transfusion; however, toxicities of both may be amplified in the presence of hypothermia. Patients with liver failure may have difficulty metabolizing citrate. Hypocalcemia can result but rarely necessitates treatment (which is 10 mL of a 10% solution of Ca gluconate IV diluted in 100 mL \(D_5W\), given over 10 min). Patients with renal failure may have elevated K if transfused with blood stored for > 1 wk (K accumulation is usually insignificant in blood stored for < 1 wk). Mechanical hemolysis during transfusion may increase K. Hypokalemia may occur about 24 h after transfusion of older RBCs (> 3 wk), which take up K.

**Infectious complications:** Bacterial contamination of packed RBCs occurs rarely, possibly due to inadequate aseptic technique during collection or to transient asymptomatic donor bacteremia. Refrigeration of RBCs usually limits bacterial growth except for cryophilic organisms such as *Yersinia* sp, which may produce dangerous levels of endotoxin. All RBC units are inspected before issue for bacterial growth, which is indicated by a color change. Because platelet concentrates are stored at room temperature, they have greater potential for bacterial growth and endotoxin production if contaminated. To minimize growth, storage is limited to 5 days. The risk of bacterial contamination of platelets is 1:2500.
Therefore, platelets are routinely tested for bacteria. Rarely, syphilis is transmitted in fresh blood or platelets. Storing blood for ≥ 96 h at 4 to 10° C kills the spirochete. Although federal regulations require a serologic test for syphilis on donor blood, infective donors are seronegative early in the disease. Recipients of infected units may develop the characteristic secondary rash.

Hepatitis may occur after transfusion of any blood product. The risk has been reduced by viral inactivation through heat treatment of serum albumin and plasma proteins and by the use of recombinant factor concentrates. Tests for hepatitis are required for all donor blood (see Table 121-2). The estimated risk of hepatitis B is 1:200,000; of hepatitis C, 1:2.6 million. Because its transient viremic phase and concomitant clinical illness likely preclude blood donation, hepatitis A (infectious hepatitis) is not a significant cause of transfusion-associated hepatitis.

HIV infection in the US is almost entirely HIV-1, although HIV-2 is also of concern. Testing for antibodies to both strains is required. Nucleic acid testing for HIV-1 antigen and HIV-1 p24 antigen testing are also required. Additionally, blood donors are asked about behaviors that may put them at high risk of HIV infection. HIV-0 has not been identified among blood donors. The estimated risk of HIV transmission due to transfusion is 1:2.6 million.

Cytomegalovirus (CMV) can be transmitted by WBCs in transfused blood. It is not transmitted through fresh frozen plasma. Because CMV does not cause disease in immunocompetent recipients, routine antibody testing of donor blood is not required. However, CMV may cause serious or fatal disease in immunocompromised patients, who should probably receive CMV-negative blood products that have been provided by CMV antibody-negative donors or by blood depleted of WBCs by filtration.

Human T-cell lymphotropic virus 1 (HTLV-1), which can cause adult T-cell lymphoma/leukemia, HTLV-1-associated myelopathy, and tropical spastic paraparesis, causes posttransfusion seroconversion in some recipients. All donor blood is tested for HTLV-1 and HTLV-2 antibodies. The estimated risk of false-negative results on testing of donor blood is 1:641,000.

Creutzfeldt-Jakob disease has never been reported to be transmitted by transfusion, but current practice precludes donation from a person who has received human-derived growth hormone or a dura mater transplant or who has a family member with Creutzfeldt-Jakob disease. New variant Creutzfeldt-Jakob disease (mad cow disease) has not been transmitted by blood transfusion. However, donors who have spent significant time in the United Kingdom and some other parts of Europe may be permanently deferred from donation (see Table 121-1).

Malaria is transmitted easily through infected RBCs. Many donors are unaware that they have malaria, which may be latent and transmissible for 10 to 15 yr. Storage does not render blood safe. Prospective donors must be asked about malaria or whether they have been in a region where it is prevalent. Donors who have had a diagnosis of malaria or who are immigrants, refugees, or citizens from countries in which malaria is considered endemic are deferred for 3 yr; travelers to endemic countries are deferred for 1 yr.

Babesiosis has rarely been transmitted by transfusion.

**Therapeutic Apheresis**

Therapeutic apheresis includes plasma exchange and cytapheresis, which are generally tolerated by healthy donors. However, many minor and a few major risks exist. Insertion of the large IV catheters necessary for apheresis can cause complications (eg, bleeding, infection, pneumothorax). Citrate anticoagulant may decrease serum ionized Ca. Replacement of plasma with a noncolloidal solution (eg, saline) shifts fluid from the intravascular space. Colloidal replacement solutions do not replace IgG and coagulation factors.

Most complications can be managed with close attention to the patient and manipulation of the procedure, but some severe reactions and a few deaths have occurred.
Plasma exchange: Therapeutic plasma exchange removes plasma components from blood. A blood cell separator extracts the patient's plasma and returns RBCs and platelets in plasma or a plasma-replacing fluid; for this purpose, 5% albumin is preferred to fresh frozen plasma (except for patients with thrombotic thrombocytopenic purpura) because it causes fewer reactions and transmits no infections. Therapeutic plasma exchange resembles dialysis but, in addition, can remove protein-bound toxic substances. A one-volume exchange removes about 66% of such components.

To be of benefit, plasma exchange should be used for diseases in which the plasma contains a known pathogenic substance, and plasma exchange should remove this substance more rapidly than the body produces it. For example, in rapidly progressive autoimmune disorders, plasma exchange may be used to remove existing harmful plasma components (eg, cryoglobulins, antiglomerular basement membrane antibodies) while immunosuppressive or cytotoxic drugs suppress their future production.

There are numerous indications (see Table 121-3). The frequency of plasma exchange, the volume to be removed, the replacement fluid, and other variables are individualized.

Table 121-3. Indications for Plasma Exchange According to the American Society for Apheresis

Low density lipoprotein cholesterol can be removed by plasma exchange with a recently implemented filtration method. Complications of plasma exchange are similar to those of therapeutic cytapheresis.

Cytapheresis: Therapeutic cytapheresis removes cellular components from blood, returning plasma. It is most often used to remove defective RBCs and substitute normal ones in patients with sickle cell anemia who have the following conditions: acute chest syndrome, stroke, pregnancy, or frequent, severe sickle cell crises. Cytapheresis achieves Hb S levels of < 30% without the risk of increased viscosity that can occur because of increased Hct with simple transfusion.

Therapeutic cytapheresis may also be used to reduce severe thrombocytosis or leukocytosis (cytoreduction) in acute or chronic leukemia when there is risk of hemorrhage, thrombosis, or pulmonary or cerebral complications of extreme leukocytosis (leukostasis). Cytapheresis is effective in thrombocytosis because platelets are not replaced as rapidly as WBCs. One or 2 procedures may reduce platelet counts to safe levels. Therapeutic WBC removal (leukapheresis) can remove kilograms of buffy coat in a few procedures, and it often relieves leukostasis and splenomegaly. However, the reduction in WBC count itself may be mild and only temporary.

Other uses of cytapheresis include collection of peripheral blood stem cells for autologous or allogeneic bone marrow reconstitution (an alternative to bone marrow transplantation) and collection of lymphocytes for use in immune modulation cancer therapy (adoptive immunotherapy).
Chapter 122. Overview of Cancer

Introduction

Cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and, often, metastasis. Cancer can develop in any tissue or organ at any age. There is often evidence of an immune response to tumors, but the role of the immune system in preventing and treating cancer is still uncertain.

Many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than aggressive treatment, particularly in the elderly or in patients with underlying comorbid disorders.

Cellular and Molecular Basis of Cancer

Cellular Kinetics

Generation time is the time required for a quiescent cell to complete a cycle in cell division (see Fig. 122-1) and give rise to 2 daughter cells. Malignant cells usually have a shorter generation time than nonmalignant cells from the same tissue, and there usually are a smaller percentage of cells in G0 (resting phase). Initial exponential tumor growth is followed by a plateau phase when cell death nearly equals the rate of formation of daughter cells. The slowing in growth rate is likely related to exhaustion of the supply of nutrients and O2 for the rapidly expanding tumor. Small tumors have a greater percentage of actively dividing cells than do large tumors.

Cellular kinetics of particular tumors is an important consideration in the design of antineoplastic drug regimens and may influence the dosing schedules and timing intervals of treatment. Many antineoplastic drugs are effective only if cells are actively dividing, and some drugs work only during a specific phase of the cell cycle and thus require prolonged administration to catch dividing cells during the phase of maximal sensitivity.

Tumor Growth and Metastasis

As a tumor grows, nutrients are provided by direct diffusion from the circulation. Local growth is facilitated by enzymes (eg, proteases) that destroy adjacent tissues. As tumor volume increases, tumor angiogenesis factors are produced to promote formation of the vascular supply required for further tumor growth.

Almost from inception, a tumor may shed cells into the circulation. From animal models, it is estimated that a 1-cm tumor sheds > 1 million cells/24 h into the venous circulation. Although most circulating tumor cells die as a result of intravascular trauma, an occasional cell may adhere to the vascular endothelium and penetrate into surrounding tissues, generating independent tumors (metastases) at distant sites. Metastatic tumors grow in much the same manner as primary tumors and may subsequently give rise to other metastases.

Experiments suggest that through random mutation, a subset of cells in the primary tumor may acquire the ability to invade and migrate to distant sites, resulting in metastasis.

Molecular Abnormalities

Genetic mutations are responsible for the generation of cancer cells. These mutations alter the quantity or function of protein products that regulate cell growth and division and DNA repair. Two major categories of mutated genes are oncogenes and tumor suppressor genes.
Oncogenes: These are abnormal forms of normal genes (proto-oncogenes) that regulate various aspects of cell growth. Mutation of these genes may result in direct and continuous stimulation of the pathways (eg, intracellular signal transduction pathways, transcription factors, secreted growth factors) that control cellular growth and division, DNA repair, angiogenesis, and other physiologic processes. There are > 100 known oncogenes that may contribute to human neoplastic transformation. For example, the ras gene encodes the Ras protein, which regulates cell division. Mutations may result in the inappropriate activation of the Ras protein, leading to uncontrolled cell growth and division. In fact, the Ras protein is abnormal in about 25% of human cancers. Other oncogenes have been implicated in specific cancers. These include

- **Her2/neu** (breast cancer)
- **BCR-ABL** (chronic myelocytic leukemia, B-cell acute lymphocytic leukemia)
- **C-myc** (Burkett's lymphoma)
- **N-myc** (small cell lung cancer, neuroblastoma)

Specific oncogenes may have important implications for diagnosis, therapy, and prognosis (see individual discussions under the specific cancer type).

Oncogenes typically result from acquired somatic cell mutations secondary to point mutations (eg, from chemical carcinogens), gene amplification (eg, an increase in the number of copies of a normal gene), or translocations. Occasionally, mutation of genes results in inheritance of a cancer predisposition, as in the inheritance of **BRCA1** or **BRCA2** in families with a high incidence of breast or ovarian cancer.

Tumor suppressor genes: Genes such as the **p53** gene play a role in normal cell division and DNA repair and are critical for detecting inappropriate growth signals in cells. If these genes, as a result of inherited or acquired mutations, become unable to function, genetic mutations in other genes can proceed unchecked, leading to neoplastic transformation.

As with most genes, 2 alleles are present that encode for each tumor suppressor gene. A defective copy of one gene may be inherited, leaving only one functional allele for the individual tumor suppressor gene. If a mutation is acquired in the other allele, the normal protective mechanisms of the tumor suppressor gene are lost, and dysfunction of other protein products or DNA damage may escape unregulated, leading to cancer. For example, the retinoblastoma (**RB**) gene encodes for the protein Rb, which regulates the cell cycle by stopping DNA replication. Mutations in the **RB** gene family occur in many human cancers, allowing affected cells to divide continuously.

Another important regulatory protein, p53, prevents replication of damaged DNA in normal cells and promotes cell death (apoptosis) in cells with abnormal DNA. Inactive or altered p53 allows cells with abnormal DNA to survive and divide. Mutations are passed to daughter cells, conferring a high probability of neoplastic transformation. The **p53** gene is defective in many human cancers. As with oncogenes, mutation of tumor suppressor genes such as **p53** or **RB** in germ cell lines may result in vertical transmission and a higher incidence of cancer in offspring.

Chromosomal abnormalities: Gross chromosomal abnormalities (see p. 2997) can occur through deletion, translocation, or duplication. If these alterations activate or inactivate genes that result in a proliferative advantage over normal cells, then a tumor may develop. Chromosomal abnormalities occur in certain human cancers (see Table 122-1). In some congenital diseases (Bloom syndrome, Fanconii's anemia, Down syndrome), DNA repair processes are defective and chromosomes break easily, putting children at high risk of developing acute leukemia and lymphomas.

Other influences: Most cancers likely involve several of the mechanisms described above that lead to neoplastic conversion. For example, the development of tumor in familial polyposis takes place through a
sequence of genetic events: epithelium hyperproliferation (loss of a suppressor gene on chromosome 5),
early adenoma (change in DNA methylation), intermediate adenoma (overactivity of the ras oncogene),
late adenoma (loss of a suppressor gene on chromosome 18), and finally, cancer (loss of a gene on
chromosome 17). Further genetic changes may be required for metastasis.

Telomeres are nucleoprotein complexes that cap the ends of chromosomes and maintain their integrity.
In normal tissue, telomere shortening (which occurs with aging) results in a finite limit in cell division. The
enzyme telomerase provides for telomere synthesis and maintenance; thus telomerase may potentially
allow for cellular immortality. Activation of telomerase in tumors allows continuous proliferation of tumors.

Environmental Factors

Infections: Viruses contribute to the pathogenesis of human cancers (see Table 122-2). Pathogenesis may occur through the integration of viral genetic elements into the host DNA. These new genes are expressed by the host; they may affect cell growth or division or disrupt normal host genes required for control of cell growth and division. Alternatively, viral infection may result in immune dysfunction, leading to decreased immune surveillance for early tumors.

Bacteria may also cause cancer. Helicobacter pylori infection increases the risk of several kinds of cancer (gastric adenocarcinoma, gastric lymphoma, mucosa-associated lymphoid tissue [MALT] lymphoma).

Parasites of some types can lead to cancer. Schistosoma haematobium causes chronic inflammation and fibrosis of the bladder, which may lead to cancer. Opisthorchis sinensis has been linked to carcinoma of the pancreas and bile ducts.

Radiation: Ultraviolet radiation may induce skin cancer (eg, basal and squamous cell carcinoma, melanoma) by damaging DNA. This DNA damage consists of formation of thymidine dimers, which may escape repair because of inherent defects in DNA repair (eg, xeroderma pigmentosum) or through rare, random events.

Ionizing radiation is also carcinogenic. For example, survivors of the atomic bomb explosions in Hiroshima and Nagasaki have a higher-than-expected incidence of leukemia and other cancers. Similarly, the previous use of x-rays to treat nonmalignant disease (acne, thymic or adenoid enlargement, and ankylosing spondylitis) resulted in higher rates of acute and chronic leukemias, Hodgkin and non-Hodgkin lymphomas, multiple myeloma, aplastic anemia terminating in acute nonlymphocytic leukemia, myelofibrosis, melanoma, and thyroid cancer. Use of x-rays in diagnostic imaging studies is thought to increase risk of cancer (see p. 3402). Industrial exposure (eg, to uranium by mine workers) is linked to development of lung cancer after a 15- to 20-yr latency. Long-term exposure to occupational irradiation or to internally deposited thorium dioxide predisposes people to angiosarcomas and acute nonlymphocytic leukemia.

Exposure to the radioactive gas radon, which is released from soil, increases the risk of lung cancer. Normally, radon disperses rapidly into the atmosphere and causes no harm. However, when a building is placed on soil with high radon content, radon can accumulate within the building, sometimes producing sufficiently high levels in the air to cause harm. In exposed people who also smoke, the risk of lung cancer is further increased.

Drugs and chemicals: Estrogens in oral contraceptives may slightly increase the risk of breast cancer, but this risk decreases over time. Estrogen and progestin used for hormone replacement therapy also increase the risk of breast cancer. Diethylstilbestrol (DES) increases the risk of breast cancer in women who took the drug and increases the risk of vaginal carcinoma in daughters of these women who were exposed before birth. Long-term use of anabolic steroids may increase the risk of liver cancer. Treatment
of cancer with chemotherapy drugs and with radiation therapy increases the risk of developing a second cancer.

Chemical carcinogens can induce gene mutations and result in uncontrolled growth and tumor formation (see Table 122-3). Other substances, called co-carcinogens, have little or no inherent carcinogenic potency but enhance the carcinogenic effect of another agent when exposed simultaneously.

**Dietary substances:** Certain substances consumed in the diet can increase the risk of cancer. For instance, a diet high in fat has been linked to an increased risk of colon, breast, and possibly prostate cancer. People who drink large amounts of alcohol are at much higher risk of developing esophageal cancer. A diet high in smoked and pickled foods or in barbecued meats increases the risk of developing stomach cancer. People who are overweight or obese have a higher risk of cancer of the breast, endometrium, colon, kidneys, and esophagus.

**Physical factors:** Chronic skin irritation leads to chronic dermatitis and, in rare cases, to squamous cell carcinoma. This occurrence is presumably due to random mutations that occur more frequently because of the increased cell turnover.

**Immunologic Disorders**

Immune system dysfunction as a result of inherited genetic mutation, acquired disorders, aging, or immunosuppressants interferes with normal immune surveillance of early tumors and results in higher rates of cancer. Known cancer-associated immune disorders include

- Ataxia-telangiectasia (acute lymphocytic leukemia [ALL], brain tumors, gastric cancer)
- Wiskott-Aldrich syndrome (lymphoma, ALL)
- X-linked agammaglobulinemia (lymphoma, ALL)
- Immune deficiency secondary to immunosuppressants or HIV infection (large cell lymphoma, Kaposi's sarcoma)
- Rheumatologic conditions, such as SLE, RA, and Sjogren's syndrome (B-type lymphoma)
- General immune disorders (lymphoreticular neoplasia)

**Cancer Diagnosis**

A diagnosis of cancer may be suspected based on history and physical examination but requires confirmation by tumor biopsy and histopathologic examination.

A complete history and physical examination may reveal unexpected clues to early cancer.

**History**

Physicians must be aware of predisposing factors and must specifically ask about familial cancer, environmental exposure (including smoking history), and prior or present illnesses (eg, autoimmune disorders, previous immunosuppressive therapy, hepatitis B or hepatitis C, HIV infection, abnormal Papanicolaou test, human papillomavirus infection). Symptoms suggesting occult cancer can include

- Fatigue
• Weight loss
• Fevers
• Night sweats
• Cough
• Hemoptyisis
• Hematemesis
• Hematochezia
• Change in bowel habits
• Persistent pain

**Physical examination**

Particular attention should be paid to skin, lymph nodes, lungs, breasts, abdomen, and testes. Prostate, rectal, and vaginal examinations are also important. Findings help direct further testing, including x-rays and biopsies.

**Testing**

Tests include imaging tests, serum tumor markers, and biopsy.

**Imaging tests** often include plain x-rays, ultrasonography, CT, and MRI. These tests assist in identifying abnormalities, determining qualities of a mass (solid or cystic), providing dimensions, and establishing relationship to surrounding structures, which may be important if surgery or biopsy is being considered.

**Serum tumor markers** may offer corroborating evidence in patients with findings suggestive of a specific cancer (see p. 1058). With some exceptions (eg, prostate-specific antigen [PSA]), these markers do not have enough sensitivity and specificity to be used for screening. They are the most useful in detecting early relapse and monitoring response to therapy. Useful examples include

- α-Fetoprotein (hepatocellular carcinoma, testicular carcinoma)
- Carcinoembryonic antigen (colon cancer)
- β-human chorionic gonadotropin (choriocarcinoma, testicular carcinoma)
- Serum immunoglobulins (multiple myeloma)
- DNA probes (eg, *bcr* probe to identify a chromosome 22 alteration in chronic myelogenous leukemia)
- CA 125 (ovarian cancer)
- CA 27-29 (breast cancer)
- PSA (prostate cancer)

**Biopsy** to confirm the diagnosis and tissue of origin is almost always required when cancer is suspected or detected. The choice of biopsy site is usually determined by ease of access and degree of invasiveness. If lymphadenopathy is present, fine-needle or core biopsy may yield the tumor type; if nondiagnostic, open biopsy is done. Other biopsy routes include bronchoscopy for easily accessible mediastinal or central pulmonary tumors, percutaneous liver biopsy if liver lesions are present, and CT- or
ultrasound-guided biopsy. If these procedures are not suitable, open biopsy may be necessary.

**Grading** is a histologic measure of tumor aggressiveness and provides important prognostic information. It is determined by examining the biopsy specimen. Grade is based on the morphologic appearance of tumor cells, including the appearance of the nuclei, cytoplasm, and nucleoli; frequency of mitoses; and amount of necrosis. For many cancers, grading scales have been developed.

**Molecular tests** such as chromosomal analogs, fluorescent in situ hybridization (FISH), PCR, and cell surface antigens (eg, in lymphomas, leukemias) delineate the origin of metastatic cancers originating from an unknown primary cancer or assist in recognizing chemotherapy resistance (eg, in acute myelogenous leukemia).

**Staging**

Once a histologic diagnosis is made, staging (ie, determination of the extent of disease) helps determine treatment decisions and prognosis. Clinical staging uses data from the history, physical examination, imaging tests, laboratory tests, and biopsy of bone marrow, lymph nodes, or other sites of suspected disease. For staging of specific neoplasms, see details in the organ-relevant chapter.

**Imaging tests:** Imaging tests, especially CT and MRI, can detect metastases to brain, lungs, or abdominal viscera, including the adrenal glands, retroperitoneal lymph nodes, liver, and spleen. MRI (with gadolinium contrast) is the procedure of choice for recognition and evaluation of brain tumors, both primary and metastatic. PET scanning is increasingly being used to determine the metabolic activity of a suspect lymph node or mass. Integrated PET-CT can be valuable, especially in lung, head and neck, and breast cancer and in lymphoma.

Ultrasonography can be used to study orbital, thyroid, cardiac, pericardial, hepatic, pancreatic, renal, and retroperitoneal areas. It may guide percutaneous biopsies and differentiate renal cell carcinoma from a benign renal cyst.

Nuclear scans can identify several types of metastases. Bone scans identify abnormal bone growth (ie, osteoblastic activity) before it is visible on plain x-ray. Thus, this technique is useless in neoplasms that are purely lytic (eg, multiple myeloma); routine bone x-rays are the study of choice in such diseases.

**Laboratory tests:** Serum chemistries and enzymes may help staging. Elevated liver enzyme (alkaline phosphatase, LDH, ALT) levels suggest the presence of liver metastases. Elevated alkaline phosphatase and serum Ca may be the first evidence of bone metastases. Elevated BUN or creatinine levels may indicate an obstructive uropathy secondary to a pelvic mass, intrarenal obstruction from tubular precipitation of myeloma protein, or uric acid nephropathy from lymphoma or other cancers. Elevated uric acid levels often occur in myeloproliferative and lymphoproliferative disorders.

**Invasive tests:** Mediastinoscopy (see p. 1863) is especially valuable in the staging of non-small cell lung cancer. When mediastinal lymph node involvement is found, patients do not usually benefit from thoracotomy and lung resection but may benefit from chemoradiation and subsequent tumor resection.

Bone marrow aspiration and biopsy are especially useful in detecting metastases from malignant lymphoma and small cell lung cancer, and their role in breast and prostate cancer staging is expanding. Bone marrow biopsy is positive at diagnosis in 50 to 70% of patients with malignant lymphoma (low and intermediate grade) and in 15 to 18% of patients with small cell lung cancer. Bone marrow biopsy should be done in patients with hematologic abnormalities (ie, anemia, thrombocytopenia, pancytopenia) that cannot be explained by other mechanisms.

Biopsy of regional lymph nodes is part of the evaluation of most tumors, such as breast, lung, or colon cancers.

**Cancer Screening**

Cancer can sometimes be detected in asymptomatic patients via regular physical examinations and
screening tests.

Physical examinations for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, prostate, and ovaries should also be done during routine medical care.

Screening tests are done in asymptomatic patients at risk. The rationale is that early diagnosis may decrease cancer mortality by detecting cancer at an early and curable stage. Early detection may allow for less radical therapy and reduce costs. Risks, however, include false-positive results, which necessitate confirmatory tests (e.g., biopsy, endoscopy) that can lead to anxiety, significant morbidity, and significant costs; and false-negative results, which may give a mistaken sense of security, causing patients to ignore subsequent symptoms.

Screening for cancer should be done in the following circumstances:

• When distinct high-risk groups can be identified (e.g., people with certain infections, exposures, or behaviors)

• When the disorder has an asymptomatic period during which treatment would alter outcome

• When the morbidity of the disorder is significant

• When an intervention is available that is acceptable and effective at changing the natural history of the disorder

The screening tests themselves should satisfy the following criteria:

• Cost and convenience are reasonable.

• Results are reliable and reproducible.

• Sensitivity and specificity are adequate.

• The positive predictive value (probability that a person with a positive test result has or will develop a disorder or condition—see p. 3391) is high in the population screened, and few false-negative results occur.

• The test or procedure is acceptable to patients.

Recommended screening schedules are constantly evolving based on ongoing studies (see Table 122-4).

**Clinical Sequelae of Cancer**

Cancer may lead to pain, weight loss, neuropathy, nausea, fatigue, seizures, or obstruction of visceral organs. Death typically occurs as a result of failure of one or more organ systems.

**Pain** in patients with metastatic cancer frequently results from bone metastases, nerve or plexus involvement, or pressure exerted by a tumor mass or effusion. Aggressive pain management is essential in the treatment of cancer and for maintenance of quality of life (see p. 1623).

**Cardiac tamponade** can result from malignant pericardial effusion and often occurs precipitously. The most common causes are breast cancer, lung cancer, and lymphoma. The preceding effusion may cause ill-defined chest pain or pressure that is worse when patients are supine and better when they are sitting up (see p. 2203). Patients with tamponade may experience signs and symptoms of decreased cardiac output (e.g., dizziness or syncope). On physical examination, heart sounds may be muffled and a friction rub and pulsus paradoxus may be present. X-ray may show a globular cardiac silhouette. Pericardiocentesis should be done for diagnostic and therapeutic purposes, and a pleuropericardial window or pericardectomy should be considered.
Pleural effusions should be drained if symptomatic and monitored for reaccumulation. If the effusion reaccumulates rapidly, thoracostomy tube drainage (see p. 1866) and sclerosing agents or repeated catheter drainage should be considered. Palliative surgical pleurectomy can be used for refractory effusions in advanced malignant disease.

Spinal cord compression (see p. 1810) can result from cancer spread to the vertebrae and requires immediate surgery or radiation therapy. Symptoms may include back pain, lower extremity paresthesias, and bowel and bladder dysfunction. Diagnosis is confirmed by CT or MRI.

Clots in the veins of the lower extremities often cause complications in cancer patients. Tumors produce procoagulants, such as tissue factors, leading to excess clot formation, particularly in after surgery. Anticoagulants may be necessary to prevent pulmonary emboli.

Metabolic and immune consequences of cancer can include hypercalcemia, hyperuricemia, increased ACTH production, antibodies that produce neurologic dysfunction, hemolytic anemia, and many other complications.

Metastatic Carcinoma of Unknown Primary Origin

A patient is considered to have carcinoma of unknown primary origin when a tumor is detected at one or more metastatic sites and routine evaluation fails to identify a primary tumor. Metastatic carcinoma of unknown primary origin constitutes up to 7% of all cancers and poses a therapeutic dilemma, because cancer treatment is typically directed at the specific primary tissue type.

The most common causative primary tumors are those of the testes, lungs, colon and rectum, and pancreas. Examination of these areas should be thorough.

Types of testing used to help specify the primary site include

- Laboratory testing
- Imaging tests
- Immunocytochemical and immunoperoxidase staining
- Tissue analysis

Laboratory tests should include a CBC, urinalysis, stool examination for occult blood, and serum chemistries (including prostate-specific antigen assays in males).

Imaging should be limited to a chest x-ray, abdominal CT, and mammography. An upper GI series and barium enema should be done if blood is present in the stool.

Increasing numbers of immunocytochemical stains can be used to test available cancerous tissue to help determine the primary tissue site. In addition, immunoperoxidase staining for immunoglobulin, gene rearrangement studies, and electron microscopy help diagnose large cell lymphoma, whereas immunoperoxidase staining for α-fetoprotein or β-human chorionic gonadotropin may suggest germ cell tumors. Tissue analysis for estrogen and progesterone receptors helps identify breast cancer, and immunoperoxidase staining for prostate-specific antigen helps identify prostate cancer.

Even if a precise histologic diagnosis cannot be made, one constellation of findings may suggest an origin. Poorly differentiated carcinomas near or at midline regions of the mediastinum or retroperitoneum...
in young or middle-aged males should be considered germ cell neoplasms—even in the absence of a testicular mass. Patients with this type of carcinoma should be treated with a cisplatin-based regimen, because nearly 50% of such patients experience long disease-free intervals. For most other unknown primary cancers, the responses to this regimen and to other multidrug chemotherapy regimens are modest and of brief duration (eg, median survival < 1 yr).

Paraneoplastic Syndromes

Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastasis.

Although the pathogenesis remains unclear, these symptoms may be secondary to substances secreted by the tumor or may be a result of antibodies directed against tumors that cross-react with other tissue. Symptoms may occur in any organ or physiologic system. Up to 20% of cancer patients experience paraneoplastic syndromes, but often these syndromes are unrecognized.

The most common cancers associated with paraneoplastic syndromes include

- Lung carcinoma (most common)
- Renal carcinoma
- Hepatocellular carcinoma
- Leukemias
- Lymphomas
- Breast tumors
- Ovarian tumors
- Neural cancers
- Gastric cancers
- Pancreatic cancers

Successful treatment is best obtained by controlling the underlying cancer, but some symptoms can be palliated with specific drugs (eg, cyproheptadine for carcinoid syndrome, bisphosphonates and corticosteroids for hypercalcemia).

General paraneoplastic symptoms: Patients with cancer often experience fever, night sweats, anorexia, and cachexia. These symptoms may arise from release of cytokines involved in the inflammatory or immune response or from mediators involved in tumor cell death, such as tumor necrosis factor-α. Alterations in liver function and steroidogenesis may also contribute.

Cutaneous paraneoplastic syndromes: Patients may experience many skin symptoms.

Itching is the most common cutaneous symptom experienced by patients with cancer (eg, leukemia, lymphomas) and may result from hypereosinophilia.

Flushing may also occur and is likely related to tumor-generated circulating vasoactive substances (eg, prostaglandins).

Pigmented skin lesions, or keratoses, may appear, including acanthosis nigricans (GI cancer), generalized dermic melanosis (lymphoma, melanoma, hepatocellular carcinoma), Bowen's disease (lung, GI, GU cancer), and large multiple seborrheic keratoses, ie, Leser-Trelat signs (lymphoma, GI cancer).
Secretion of melanin precursors from tumors may promote formation of these lesions.

**Ichthyosis**, or desquamation of the extensor surface of the extremities, may also occur.

**Hypertrichosis** may manifest as sudden appearance of coarse hair on the face and ears that resolves after resection or treatment of the tumor. Alternatively, alopecia may occur with certain tumor types. The mechanism by which alopecia occurs is not clear.

**Necrotizing migrating erythema** may occur with glucagonomas.

**Subcutaneous adipose nodular necrosis** may result from release of proteolytic enzymes from various pancreatic tumors.

**Herpes zoster** may result from reactivation of latent virus in patients with immune system depression or dysfunction.

**Endocrine paraneoplastic syndromes:** The endocrine system is often affected by paraneoplastic syndromes.

**Cushing's syndrome** (cortisol excess, leading to hyperglycemia, hypokalemia, hypertension, central obesity, moon facies) may result from ectopic production of ACTH or ACTH-like molecules, most often with small cell cancer of the lung.

**Abnormalities in water and electrolyte balance**, including hyponatremia, may result from production of ADH and parathyroid hormone-like hormones from small cell and non-small cell lung cancer.

**Hypoglycemia** may result from production of insulin-like growth factors or insulin production by pancreatic islet cell tumors or hemangiopericytomas.

**Hypertension** may result from abnormal epinephrine and norepinephrine secretion (pheochromocytomas) or from cortisol excess (ACTH-secreting tumors).

**Other ectopically produced hormones** include parathyroid hormone-related peptide (PTHRP—from squamous cell lung cancer, head and neck cancer, bladder cancer), calcitonin (from breast cancer, small cell lung cancer, and medullary thyroid carcinoma), and thyroid-stimulating hormone (from gestational choriocarcinoma). PTHRP causes hypercalcemia and its associated symptoms (polyuria, dehydration, constipation, muscle weakness); calcitonin causes a fall in the serum Ca level, with contractions and cardiac arrhythmias.

**GI paraneoplastic syndromes:** Watery diarrhea with subsequent dehydration and electrolyte imbalances may result from tumor-related secretion of prostaglandins or vasoactive intestinal peptide. Implicated tumors include pancreatic islet cell tumors and others. Protein-losing enteropathies may result from tumor mass inflammation, particularly with lymphomas.

**Hematologic paraneoplastic syndromes:** Patients with cancer may develop pure RBC aplasia, anemia of chronic disease, leukocytosis (leukemoid reaction), thrombocytosis, eosinophilia, basophilia, and disseminated intravascular coagulation. In addition, idiopathic thrombocytopenic purpura and a Coombs'-positive hemolytic anemia can complicate the course of lymphoid cancers and Hodgkin lymphoma. Erythrocytosis may occur in various cancers, especially renal cancers and hepatomas, due to ectopic production of erythropoietin or erythropoietin-like substances, and monoclonal gammopathies may sometimes be present.

Demonstrated mechanisms of hematologic abnormalities include tumor-generated substances that mimic or block normal endocrine signals for hematologic line development and generation of antibodies that cross-react with receptors or cell lines.

**Neurologic paraneoplastic syndromes:** Several types of peripheral neuropathy are among the neurologic paraneoplastic syndromes. Cerebellar syndromes and other central neurologic paraneoplastic...
syndromes also occur.

Peripheral neuropathy is the most common neurologic paraneoplastic syndrome. It is usually a distal sensorimotor polyneuropathy that causes mild motor weakness, sensory loss, and absent distal reflexes. The syndrome is indistinguishable from that accompanying many chronic illnesses.

Subacute sensory neuropathy is a more specific but rare peripheral neuropathy. Dorsal root ganglia degeneration and progressive sensory loss with ataxia but little motor weakness develop; the disorder may be disabling. Anti-Hu, an autoantibody, is found in the serum of some patients with lung cancer. There is no treatment.

Guillain-Barre syndrome, another peripheral neuropathy, is more common in patients with Hodgkin lymphoma than in the general population.

Eaton-Lambert syndrome is an immune-mediated, myasthenia-like syndrome with weakness usually affecting the limbs and sparing ocular and bulbar muscles. It is pre-synaptic, resulting from impaired release of acetylcholine from nerve terminals. An IgG antibody is involved. The syndrome can precede, occur with, or develop after the diagnosis of cancer. It occurs most commonly in men with intrathoracic tumors (70% have small or oat cell lung carcinoma). Symptoms and signs include fatigability, weakness, pain in proximal limb muscles, peripheral paresthesias, dry mouth, erectile dysfunction, and ptosis. Deep tendon reflexes are reduced or lost. The diagnosis is confirmed by finding an incremental response to repetitive nerve stimulation: Amplitude of the compound muscle action potential increases > 200% at rates > 10 Hz. Treatment is first directed at the underlying cancer and sometimes induces remission. Guanidine (initially 125 mg po qid, gradually increased to a maximum of 35 mg/kg), which facilitates acetylcholine release, often lessens symptoms but may depress bone marrow and liver function. Corticosteroids and plasmapheresis benefit some patients.

Subacute cerebellar degeneration causes progressive bilateral leg and arm ataxia, dysarthria, and sometimes vertigo and diplopia. Neurologic signs may include dementia with or without brain stem signs, ophthalmoplegia, nystagmus, and extensor plantar signs, with prominent dysarthria and arm involvement. Cerebellar degeneration usually progresses over weeks to months, often causing profound disability. Cerebellar degeneration may precede the discovery of the cancer by weeks to years. Anti-Yo, a circulating autoantibody, is found in the serum or CSF of some patients, especially women with breast or ovarian cancer. MRI or CT may show cerebellar atrophy, especially late in the disease. Characteristic pathologic changes include widespread loss of Purkinje cells and lymphocytic cuffing of deep blood vessels. CSF occasionally has mild lymphocytic pleocytosis. Treatment is nonspecific, but some improvement may follow successful cancer therapy.

Opsoclonus (spontaneous chaotic eye movements) is a rare cerebellar syndrome that may accompany childhood neuroblastoma. It is associated with cerebellar ataxia and myoclonus of the trunk and extremities. Anti-Ri, a circulating autoantibody, may be present. The syndrome often responds to corticosteroids and treatment of the cancer.

Subacute motor neuronopathy is a rare disorder causing painless lower motor neuron weakness of upper and lower extremities, usually in patients with Hodgkin lymphoma or other lymphomas. Anterior horn cells degenerate. Spontaneous improvement usually occurs.

Subacute necrotizing myelopathy is a rare syndrome in which rapid ascending sensory and motor loss occurs in gray and white matter of the spinal cord, leading to paraplegia. MRI helps rule out epidural compression from metastatic tumor—a much more common cause of rapidly progressive spinal cord dysfunction in patients with cancer. MRI may show necrosis in the spinal cord.

Encephalitis may occur as a paraneoplastic syndrome, taking several different forms, depending on the area of the brain involved. Global encephalitis has been proposed to explain the encephalopathy that occurs most commonly in small cell lung cancer. Limbic encephalitis is characterized by anxiety and depression, leading to memory loss, agitation, confusion, hallucinations, and behavioral abnormalities. Anti-Hu antibodies, directed against RNA binding proteins, may be present in the serum and spinal fluid. MRI may disclose areas of increased contrast uptake and edema.
**Renal paraneoplastic syndrome:** Membranous glomerulonephritis may occur in patients with colon cancer, ovarian cancer, and lymphoma as a result of circulating immune complexes.

**Rheumatologic paraneoplastic syndromes:** Rheumatologic disorders mediated by autoimmune reactions can also be a manifestation of paraneoplastic syndromes.

**Arthropathies** (rheumatic polyarthritis, polymyalgia) or systemic sclerosis may develop in patients with hematologic cancers or with cancers of the colon, pancreas, or prostate. Systemic sclerosis or SLE may also develop in patients with lung and gynecologic cancers.

**Hypertrophic osteoarthropathy** is prominent with certain lung cancers and manifests as painful swelling of the joints (knees, ankles, wrists, elbows, metacarpophalangeal joints) with effusion and sometimes fingertip clubbing.

**Secondary amyloidosis** may occur with myeloma, lymphomas, or renal cell carcinomas.

**Dermatomyositis** and, to a lesser degree, **polymyositis** (see p. 299) are thought to be more common in patients with cancer, especially in those > 50 yr. Typically, proximal muscle weakness is progressive with pathologically demonstrable muscle inflammation and necrosis. A dusky, erythematous butterfly rash with a heliotrope hue may develop on the cheeks with periorbital edema. Corticosteroids may be helpful.
Chapter 123. Tumor Immunology

Introduction

Tumor recognition is a complex, challenging problem for the immune system, which must distinguish proper cellular growth and organization from neoplastic transformation. This process involves recognition of tumor antigens by effector cells and induction of immunity. The development of tumors despite the presence of antigens, the significance of immune recognition in the pathogenesis of tumors, and the potential for therapeutic augmentation of immune responses remain the subject of intense investigation.

Tumor Antigens

Many tumor cells produce antigens, which may be released in the bloodstream or remain on the cell surface. Antigens have been identified in most of the human cancers, including Burkitt's lymphoma, neuroblastoma, malignant melanoma, osteosarcoma, renal cell carcinoma, breast carcinoma, prostate cancer, lung carcinomas, and colon cancer. A key role of the immune system is detection of these antigens to permit subsequent targeting for eradication. However, despite their foreign structure, the immune response to tumor antigens varies and is often insufficient to prevent tumor growth.

Tumor-associated antigens (TAAs) are relatively restricted to tumor cells, whereas tumor-specific antigens (TSAs) are unique to tumor cells. TSAs and TAAs typically are portions of intracellular molecules expressed on the cell surface as part of the major histocompatibility complex.

Suggested mechanisms of origin for tumor antigens include

• Introduction of new genetic information from a virus (eg, human papillomavirus E6 and E7 proteins in cervical cancer)

• Alteration of oncogenes or tumor suppressor genes by carcinogens, which either generate a novel protein sequence directly or induce accumulation of proteins that are normally not expressed or are expressed at very low levels (eg, ras, p53)

• Abnormally high levels of proteins that normally are present at substantially lower levels (eg, prostate-specific antigens, melanoma-associated antigens) or that are expressed only during embryonic development (carcinoembryonic antigens)

• Uncovering of antigens normally buried in the cell membrane because of defective membrane homeostasis in tumor cells

• Release of antigens normally sequestered within the cell or its organelles when tumor cells die

Host Response to Tumors

The immune response to foreign antigens consists of humoral (eg, antibodies) and cellular mechanisms. Most humoral responses cannot prevent tumor growth. However, effector cells, such as T cells, macrophages, and natural killer cells, have relatively effective tumoricidal abilities. Effector cell activity is induced by cells that present tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs) on their surface (these cells are called antigen-presenting cells) and is supported by cytokines (eg, interleukins, interferons—see p. 1084). Despite the activity of effector cells, host immunoreactivity may fail to control tumor occurrence and growth.

Cellular Immunity

The T cell is the primary cell responsible for direct recognition and killing of tumor cells. T cells carry out immunologic surveillance, then proliferate and destroy newly transformed tumor cells after recognizing TAAs. The T-cell response to tumors is modulated by other cells of the immune system; some cells require the presence of humoral antibodies directed against the tumor cells (antibody-dependent cellular cytotoxicity) to initiate the interactions that lead to the death of tumor cells. In contrast, suppressor T cells
Cytotoxic T lymphocytes (CTLs) recognize antigens on target cells and lyse these cells. These antigens may be cell surface proteins or may be intracellular proteins (e.g., TAAs) that are expressed on the surface in combination with class I major histocompatibility complex (MHC) molecules. Tumor-specific CTLs have been found with neuroblastomas; malignant melanomas; sarcomas; and carcinomas of the colon, breast, cervix, endometrium, ovary, testis, nasopharynx, and kidney.

Natural killer (NK) cells are another population of effector cells with tumoricidal activity. In contrast to CTLs, NK cells lack the receptor for antigen detection but can still recognize normal cells infected with viruses or tumor cells. Their tumoricidal activity is termed natural because it is not induced by a specific antigen. The mechanism by which NK cells discriminate between normal and abnormal cells is under study. Evidence suggests that class I MHC molecules on the surface of normal cells inhibit NK cells and prevent lysis. Thus, the decreased level of class I molecule expression characteristic of many tumor cells may allow activation of NK cells and subsequent tumor lysis.

Macrophages can kill specific tumor cells when activated by a combination of factors, including lymphokines (soluble factors produced by T cells) and interferon. They are less effective than T-cell-mediated cytotoxic mechanisms. Under certain circumstances, macrophages may present TAAs to T cells and stimulate tumor-specific immune response.

Dendritic cells are dedicated antigen-presenting cells present in barrier tissues (e.g., skin, lymph nodes). They play a central role in initiation of tumor-specific immune response. These cells take up tumor-associated proteins, process them, and present TAAs to T cells to stimulate the CTL response against tumor. The presence of dendritic cells in tumor tissues correlates with improved prognosis.

Lymphokines produced by immune cells stimulate growth or induce activities of other immune cells. Such lymphokines include IL-2, also known as T-cell growth factor, and the interferons. IL-12 is produced by dendritic cells and specifically induces CTLs, thereby enhancing antitumor immune responses.

Regulatory T cells are normally present in the body and help prevent autoimmune reactions. They are produced during the active phase of immune responses to pathogens and limit the strong immune response that could damage the host. Accumulation of these cells in cancers inhibits antitumor immune responses.

Myeloid-derived suppressor cells consist of immature myeloid cells and their precursors. These cells accumulate in large numbers in cancers and potently suppress immune responses.

Humoral Immunity

In contrast to T-cell cytotoxic immunity, humoral antibodies do not appear to confer significant protection against tumor growth. Most antibodies cannot recognize TAAs. Regardless, humoral antibodies that react with tumor cells in vitro have been detected in the sera of patients with various tumors, including Burkitt's lymphoma; malignant melanoma; osteosarcoma; neuroblastoma; and carcinomas of the lung, breast, and GI tract.

Cytotoxic antibodies are directed against surface antigens of tumor cells. These antibodies can exert anti-tumor effects through complement fixation or by serving as a flag for destruction of tumor cells by T cells (antibody-dependent cell-mediated cytotoxicity). Another population of humoral antibodies, called enhancing antibodies (blocking antibodies), may actually favor rather than inhibit tumor growth. The mechanisms and relative importance of such immunologic enhancement are not well understood.

Failure of Host Defenses

Although many tumors are eliminated by the immune system (and thus are never detected), others continue to grow despite the presence of TAAs. Several mechanisms have been proposed to explain this deficient host response to the TAA, including the following:
Specific immunologic tolerance to TAAs in a process that involves antigen-presenting cells and suppressor T cells, possibly secondary to prenatal exposure to the antigen

- Suppression of immune response by chemical, physical, or viral agents (e.g., helper T-cell destruction by HIV)
- Suppression of the immune response by cytotoxic drugs or radiation
- Suppression of the immune response by the tumor itself through various complex and largely uncharacterized mechanisms that cause various problems including decreased T, B, and antigen-presenting cell function, decreased IL-2 production, and increased circulating soluble IL-2 receptors (which bind and hence inactivate IL-2)

**Tumor Immunodiagnosis**

Tumor-associated antigens (TAAs) can help diagnose various tumors and sometimes determine the response to therapy or recurrence. An ideal tumor marker would be released only from tumor tissue, be specific for a given tumor type, be detectable at low levels of tumor cell burden, have a direct relationship to the tumor cell burden, and be present in all patients with the tumor. However, although most tumors release detectable antigenic macromolecules into the circulation, no tumor marker has all the requisite characteristics to provide enough specificity or sensitivity to be used in early diagnosis or mass cancer screening programs.

**Carcinoembryonic antigen (CEA)** is a protein-polysaccharide complex present in colon carcinomas and in normal fetal intestine, pancreas, and liver. Blood levels are elevated in patients with colon carcinoma, but the specificity is relatively low because positive results also occur in heavy cigarette smokers and in patients with cirrhosis, ulcerative colitis, and other cancers (e.g., breast, pancreas, bladder, ovary, cervix). Monitoring CEA levels may be useful for detecting cancer recurrence after tumor excision if the patient initially had an elevated CEA and for refining estimates of prognosis by stage.

**α-Fetoprotein**, a normal product of fetal liver cells, is also present in the sera of patients with primary hepatoma, nonseminomatous germ cell tumors, and, frequently, ovarian or testicular embryonal carcinoma. Levels are sometimes useful for estimating prognosis or, less often, for diagnosis.

**β Subunit of human chorionic gonadotropin (β-hCG)**, measured by immunoassay, is the major clinical marker in women with gestational trophoblastic neoplasia (GTN)—a disease spectrum that includes hydatidiform mole, nonmetastatic GTN, and metastatic GTN (see also p. 2574)—and in about two thirds of men with testicular embryonal carcinoma or choriocarcinoma. The β subunit is measured because it is specific for hCG. This marker is present in low levels in healthy people. Levels are elevated during pregnancy.

**Prostate-specific antigen (PSA)**, a glycoprotein located in ductal epithelial cells of the prostate gland, can be detected in low concentrations in the sera of healthy men. Using an appropriate upper limit of normal, assays with monoclonal antibodies detect elevated serum levels of PSA in about 90% of patients with advanced prostate cancer, even in the absence of defined metastatic disease. It is more sensitive than prostatic acid phosphatase. However, because PSA is elevated in other conditions (e.g., benign prostatic hypertrophy, prostatitis, recent GU tract instrumentation), it is less specific. PSA can be used to monitor recurrence after prostatic carcinoma has been diagnosed and treated.

**CA 125** is clinically useful for screening, diagnosing, and monitoring therapy for ovarian cancer, although any peritoneal inflammatory process and some other cancers can increase levels.

**β2-Microglobulin** is often elevated in multiple myeloma and in some lymphomas. Its primary use is in prognosis.

**CA 19-9** was originally developed to detect colorectal cancer but proved more sensitive for pancreatic cancer. It is primarily used to judge the response to treatment in patients with advanced pancreatic cancers. CA 19-9 can also be elevated in other GI cancers, particularly cancer of the bile ducts, and...
some benign bile duct and cholestatic disorders.

**CA 15-3** and **CA 27-29** are elevated in most patients with metastatic breast cancer. Levels may also be elevated in other conditions. These markers are primarily used to monitor the response to therapy.

**Chromogranin A** is used as a marker for carcinoid and other neuroendocrine tumors. Sensitivity and specificity for neuroendocrine tumors can exceed 75%, and diagnostic accuracy is higher with diffuse than with localized tumors. Levels can be elevated in other cancers, such as lung and prostate, and some benign disorders (eg, primary hypertension, chronic kidney disease, chronic atrophic gastritis).

**Thyroglobulin** is produced by the thyroid and may be elevated with various thyroid disorders. It is primarily used after complete thyroidectomy to detect recurrent thyroid cancer and to monitor the response to treatment in metastatic thyroid cancer.

**TA-90** is a highly immunogenic subunit of a urinary tumor-associated antigen that is present in 70% of melanomas, soft-tissue sarcomas, and carcinomas of the breast, colon, and lung. Some studies have shown that TA-90 levels can accurately predict survival and the presence of subclinical disease after surgery for melanoma.

**Immunotherapy**

A number of immunologic interventions, both passive and active, can be directed against tumor cells.

**Passive Cellular Immunotherapy**

In passive cellular immunotherapy, specific effector cells are directly infused and are not induced or expanded within the patient.

**Lymphokine-activated killer (LAK) cells** are produced from the patient's endogenous T cells, which are extracted and grown in a cell culture system by exposing them to the lymphokine IL-2. The proliferated LAK cells are then returned to the patient's bloodstream. Animal studies have shown that LAK cells are more effective against cancer cells than are the original endogenous T cells, presumably because of their greater number. Clinical trials of LAK cells in humans are ongoing.

**Tumor-infiltrating lymphocytes (TILs)** may have greater tumoricidal activity than LAK cells. These cells are grown in culture in a manner similar to LAK cells. However, the progenitor cells consist of T cells that are isolated from resected tumor tissue. This process theoretically provides a line of T cells that has greater tumor specificity than those obtained from the bloodstream. Recent clinical studies have shown highly promising results.

Concomitant use of interferon enhances the expression of major histocompatibility complex (MHC) antigens and tumor-associated antigens (TAAs) on tumor cells, thereby augmenting the killing of tumor cells by the infused effector cells.

However, remissions using unmodified TILs have been infrequent. A new approach using T cells genetically modified to express receptors that recognize TAAs with high specificity to tumor cells is under study and may provide significant clinical benefit.

**Passive Humoral Immunotherapy**

Administration of exogenous antibodies constitutes passive humoral immunotherapy. Antilymphocyte serum has been used in the treatment of chronic lymphocytic leukemia and in T-cell and B-cell lymphomas, resulting in temporary decreases in lymphocyte counts or lymph node size.

Monoclonal antitumor antibodies may also be conjugated with toxins (eg, ricin, diphtheria) or with radioisotopes so that the antibodies deliver these toxic agents specifically to the tumor cells. Another technique involves bispecific antibodies, or linkage of one antibody that reacts with the tumor cell to a second antibody that reacts with a cytotoxic effector cell. This technique brings the effector cell in close proximity to the tumor cell via an antibody bridge.
opposition to the tumor cell, resulting in increased tumoricidal activity. However, these techniques are in early stages of testing; thus, potential clinical benefits are uncertain.

**Active Specific Immunotherapy**

Inducing cellular immunity (involving cytotoxic T cells) in a host that failed to spontaneously develop an effective response generally involves methods to enhance presentation of tumor antigens to host effector cells. Cellular immunity can be induced to specific, very well-defined antigens. Several techniques can be used to stimulate a host response; these techniques may involve giving peptides, DNA, or tumor cells (from the host or another patient). Peptides and DNA are often given using antigen-presenting cells (dendritic cells). These dendritic cells can also be genetically modified to secrete additional immune-response stimulants (eg, granulocyte-macrophage colony-stimulating factor [GM-CSF]).

**Peptide-based vaccines** use peptides from defined TAAs. An increasing number of TAAs have been identified as the target of T cells in cancer patients and are being tested in clinical trials. Recent data indicate that responses are most potent if TAAs are delivered using dendritic cells. These cells are obtained from the patient, loaded with the desired TAA, and then reintroduced intradermally; they stimulate endogenous T cells to respond to the TAA. The peptides also can be delivered by co-administration with immunogenic adjuvants.

**DNA vaccines** use recombinant DNA that encodes a specific (defined) antigenic protein. The DNA is incorporated into viruses that are injected directly into patients or, more often, introduced into dendritic cells obtained from the patients, which are then injected back into them. The DNA expresses the target antigen which triggers or enhances patients' immune response.

**Autochthonous tumor cells** (cells taken from the host) have been reintroduced to the host after use of ex vivo techniques (eg, irradiation, neuraminidase treatment, hapten conjugation, hybridization with other cell lines) to reduce their malignant potential and increase their antigenic activity. Sometimes the tumor cells are genetically modified to produce immunostimulatory molecules (including cytokines such as GM-CSF or IL-2, costimulatory molecules such as B7-1, and allogeneic class I MHC molecules); this modification helps attract effector molecules and enhances systemic tumor targeting. Clinical trials with GM-CSF-modified tumor cells have produced encouraging preliminary results.

**Allogeneic tumor cells** (cells taken from other patients) have been used in patients with acute lymphocytic leukemia and acute myeloblastic leukemia. Remission is induced by intensive chemotherapy and radiation therapy. Then, irradiated allogeneic tumor cells that have been modified either genetically or chemically to increase their immunogenic potential are injected into the patient. Sometimes patients are also given bacille Calmette-Guerin (BCG) vaccine or other adjuvants (see p. 1061) to enhance the immune response against the tumor. Prolonged remissions or improved reinduction rates have been reported in some series but not in most.

A novel approach to cancer treatment combining immunotherapy and conventional chemotherapy has shown some success (vs historic controls) in nonrandomized phase I and phase II clinical trials involving various cancers, types of vaccines, and chemotherapy.

**Nonspecific Immunotherapy**

**Interferons** (IFN-α, -β, -γ) are glycoproteins that have antitumor and antiviral activity. Depending on dose, interferons may either enhance or decrease cellular and humoral immune functions. Interferons also inhibit division and certain synthetic processes in a variety of cells. Clinical trials have indicated that interferons have antitumor activity in various cancers, including hairy cell leukemia, chronic myelocytic leukemia, AIDS-associated Kaposi's sarcoma, non-Hodgkin lymphoma, multiple myeloma, and ovarian carcinoma. However, interferons may have significant adverse effects, such as fever, malaise, leukopenia, alopecia, and myalgias.

Certain **bacterial adjuvants** (BCG and derivatives, killed suspensions of Corynebacterium parvum) have tumoricidal properties. They have been used with or without added tumor antigen to treat a variety of cancers, usually along with intensive chemotherapy or radiation therapy. For example, direct injection of
BCG into cancerous tissues has resulted in regression of melanoma and prolongation of disease-free intervals in superficial bladder carcinomas and may help prolong drug-induced remission in acute myeloblastic leukemia, ovarian carcinoma, and non-Hodgkin lymphoma.
**Chapter 124. Principles of Cancer Therapy**

**Introduction**

Curing cancer requires eliminating all cancer cells. The major modalities of therapy are

- Surgery and radiation therapy (for local and local-regional disease)
- Chemotherapy (for systemic disease) Other important methods include
- Hormonal therapy (for selected cancers, eg, prostate, breast, endometrium)
- Immunotherapy (monoclonal antibodies, interferons, and other biologic response modifiers and tumor vaccines—see p. 1059)
- Differentiating agents such as retinoids
- Targeted agents that exploit the growing knowledge of cellular and molecular biology

Overall treatment should be coordinated among a radiation oncologist, surgeon, and medical oncologist, where appropriate. Choice of modalities constantly evolves, and numerous controlled research trials continue. When available and appropriate, clinical trial participation should be considered and discussed with patients.

Various terms are used to describe the response to treatment (see Table 124-1). The disease-free interval often serves as an indicator of cure and varies with cancer type. For example, lung, colon, bladder, and testicular cancers are usually cured if a 5-yr disease-free interval occurs. However, breast cancer may recur even after 5 yr; thus a 10-yr disease-free interval is more indicative of cure.

Treatment decisions should weigh the likelihood of adverse effects against the likelihood of benefit; these decisions require frank communication and possibly the involvement of a multidisciplinary cancer team. Patient preferences for how to live out the end of life should be established early in the course of cancer treatment despite the difficulties of discussing death at such a sensitive time (see p. 3471).

**Modalities of Cancer Therapy**

Treatment of cancer can involve any of several modalities:

- Surgery
- Radiation therapy
- Chemotherapy

Often, modalities are combined to create a program that is appropriate for the patient and is based on patient and tumor characteristics as well as patient preferences.

Survival rates with the different modalities, alone and in combination, are listed for selected cancers (see Table 124-2).

**Surgery**

Surgery is the oldest form of effective cancer therapy. It may be used alone or in combination with other modalities.
Factors that increase operative risk in cancer patients include

- Age
- Comorbid conditions
- Debilitation due to cancer
- Paraneoplastic syndromes (less common—see p. 1054)

Cancer patients often have poor nutrition due to anorexia and the catabolic influences of tumor growth, and these factors may inhibit or slow recovery from surgery. Patients may be neutropenic or thrombocytopenic or may have clotting disorders; these conditions increase the risk of sepsis and hemorrhage. Therefore, preoperative assessment is paramount (see p. 3445).

Table 124-2. 5-yr Disease-Free Survival Rates by Cancer Therapy

**Primary tumor resection:** If a primary tumor has not metastasized, surgery may be curative. Establishing a complete margin of normal tissue around the primary tumor is critical for the success of primary tumor resection. Intraoperative examination of frozen tissue sections by a pathologist may be needed, with immediate resection of additional tissue if margins are positive for tumor cells. However, frozen tissue examination is inferior to examination of processed and stained tissue. Later review of margin tissue may prove the need for wider resection.

Surgical resection for primary tumor with local spread may also require removal of involved regional lymph nodes, resection of an involved adjacent organ, or en bloc resection. Survival rates with surgery alone are listed for selected cancers (see Table 124-2).

When the primary tumor has spread into adjacent normal tissues extensively, surgery may be delayed so that other modalities (eg, chemotherapy, radiation therapy) can be used to reduce the size of the required resection.

**Resection of metastases:** With regional lymph node metastases, nonsurgical modalities may be the best initial treatments, as in locally advanced lung cancer or head and neck cancer. Single metastases, especially those in the lung, can sometimes be resected with a reasonable rate of cure.

Patients with a limited number of metastases, particularly to the liver, brain, or lungs, may benefit from surgical resection of both the primary and metastatic tumor. For example, in colon cancer with liver metastases, resection produces 5-yr survival rates of 30 to 40% if < 4 hepatic lesions exist and if adequate tumor margins can be obtained.

**Cytoreduction:** Cytoreduction (surgical resection to reduce tumor burden) is often an option when removal of all tumor tissue is impossible, as in most cases of ovarian cancer. Cytoreduction may increase the sensitivity of the remaining tissue to other treatment modalities through mechanisms that are not entirely clear. Cytoreduction has yielded favorable results in pediatric solid tumors and in ovarian cancer.

**Palliative surgery:** Surgery to relieve symptoms and preserve quality of life may be a reasonable alternative when cure is unlikely or when an attempt at cure produces adverse effects that are unacceptable to the patient. Tumor resection may be indicated to control pain, to reduce the risk of hemorrhage, or to relieve obstruction of a vital organ (eg, intestine, urinary tract). Nutritional supplementation with a feeding gastrostomy or jejunostomy tube may be necessary if proximal obstruction exists.

**Reconstructive surgery:** Reconstructive surgery may improve a patient's comfort or quality of life after tumor resection (eg, breast reconstruction after mastectomy).

**Radiation Therapy**
Radiation therapy can cure many cancers (see Table 124-2), particularly those that are localized or that can be completely encompassed within the radiation field. Radiation therapy with surgery (for head and neck, laryngeal, or uterine cancer) or with chemotherapy and surgery (for sarcomas or breast, esophageal, lung, or rectal cancers) improves cure rates and allows for more limited surgery as compared with traditional surgical resection.

Radiation therapy can provide significant palliation when cure is not possible:

• For brain tumors: Prolongs patient functioning
• For cancers that compress the spinal cord: Prevents progression of neurologic deficits
• For superior vena cava syndromes: Relieves venous obstruction
• For painful bone lesions: Usually relieves symptoms

Radiation cannot destroy malignant cells without destroying some normal cells as well. Therefore, the risk to normal tissue must be weighed against the potential gain in treating the malignant cells. The final outcome of a dose of radiation depends on numerous factors, including:

• Nature of the delivered radiation (mode, timing, volume, dose)
• Properties of the tumor (cell cycle phase, oxygenation, molecular properties, overall sensitivity to radiation)

In general, cancer cells are selectively damaged because of their high metabolic rate. Normal tissue repairs itself more effectively, resulting in greater net destruction of tumor.

Important considerations in the use of radiation therapy include the following:

• Treatment timing (critical)
• Dose fractionation (critical)
• Normal tissue in or adjacent to the proposed radiation field
• Target volume
• Configuration of radiation beams
• Dose distribution
• Modality and energy most suited to the patient’s situation

Treatment is tailored to take advantage of the cellular kinetics of tumor growth, with the aim of maximizing damage to the tumor while minimizing damage to normal tissues.

Radiation therapy sessions begin with the precise positioning of the patient. Foam casts or plastic masks are often constructed to ensure exact repositioning for serial treatments. Laser-guided sensors are used. Typical courses consist of large daily doses given over 3 wk for palliative treatment or smaller doses given once/day 5 days/wk for 6 to 8 wk for curative treatment.

Types of radiation therapy: There are several different types of radiation therapy.

External beam radiation therapy can be done with photons (gamma radiation), electrons, or protons. Gamma radiation using a linear accelerator is the most common type of radiation therapy. The radiation dose to adjacent normal tissue can be limited by conformal technology, which reduces scatter at the field...
margins. Electron beam radiation therapy produces little tissue penetration and is best for skin or superficial cancers. Different energies of electrons are used based on the desired depth of penetration and type of tumor. Proton therapy, although limited in availability, can provide sharp margins and is particularly useful for tumors of the eye, the base of the brain, and the spine.

**Stereotactic radiation therapy** is radio-surgery with precise stereotactic localization of a tumor to deliver a single high dose or multiple, fractionated doses to a small intracranial or other target. Advantages include complete tumor ablation where conventional surgery would not be possible and minimal adverse effects. Disadvantages include limitations involving the size of the area that can be treated and the potential danger to adjacent tissues because of the high dose of radiation. In addition, it cannot be used in all areas of the body. Patients must be immobilized and the area kept completely still.

**Brachytherapy** involves placement of radioactive seeds into the tumor bed itself (e.g., in the prostate or cervix). Typically, placement is guided by CT or ultrasonography. Brachytherapy achieves higher effective radiation doses over a longer period than could be accomplished by use of fractionated, external irradiation.

**Systemic radioactive isotopes** can direct radiation to cancer in organs that have specific receptors for uptake of the isotope (i.e., radioactive iodine for thyroid cancer) or when the radionuclide is attached to a monoclonal antibody (e.g., tositumomab plus iodine-131 tositumomab for non-Hodgkin lymphoma). Isotopes can also accomplish palliation of generalized bony metastases (i.e., radiostrontium for prostate cancer).

Other agents or strategies, particularly chemotherapy, can sensitize tumor tissue to the delivered radiation and increase efficacy.

**Adverse effects:** Radiation can damage any intervening normal tissue.

**Acute adverse effects** depend on the area receiving radiation and may include

- Lethargy
- Fatigue
- Mucositis
- Dermatologic manifestations (erythema, pruritus, desquamation)
- Esophagitis
- Pneumonitis
- Hepatitis
- GI symptoms (nausea, vomiting, diarrhea, tenesmus)
- GU symptoms (frequency, urgency, dysuria)
- Cytopenias

Early detection and management of these adverse effects is important not only for the patient's comfort and quality of life but also to ensure continuous treatment; prolonged interruption can allow for tumor regrowth.

**Late complications** can include cataracts, keratitis, and retinal damage if the eye is in the treatment field; hypopituitarism; xerostomia; hypothyroidism; pneumonitis; pericarditis; esophageal stricture; hepatitis; ulcers; gastritis; nephritis; sterility; and muscular contractures. Radiation that reaches normal tissue can lead to poor healing of the tissues if further procedures or surgery is necessary. For example,
radiation to the head and neck impairs recovery from dental procedures (eg, restoration, extraction) and thus should be administered only after all necessary dental work has been done.

Radiation therapy can increase the risk of developing other cancers, particularly leukemias and cancers of the thyroid or breast. Peak incidence occurs 5 to 10 yr after exposure and depends on the patient's age at the time of treatment. For example, chest irradiation for Hodgkin lymphoma in adolescent girls leads to a higher risk of breast cancer than does the same treatment for postadolescent women.

**Chemotherapy**

The ideal chemotherapeutic drug would target and destroy only cancer cells. Only a few such drugs exist. Common chemotherapeutic drugs and their adverse effects are described (see [Table 124-3](#)).

The most common routes of administration are IV and oral. Frequent dosing for extended periods may necessitate subcutaneously implanted venous access devices (central or peripheral), multilumen external catheters, or peripherally inserted central catheters.

Drug resistance can occur to chemotherapy. Identified mechanisms include overexpression of target genes, mutation of target genes, drug inactivation by tumor cells, defective apoptosis in tumor cells, and loss of receptors for hormonal agents. One of the best characterized mechanisms is overexpression of the *MDR-1* gene, a cell membrane transporter that causes efflux of certain drugs (eg, vinca alkaloids, taxanes, anthracyclines). Attempts to alter *MDR-1* function and thus prevent drug resistance have been unsuccessful.

**Cytotoxic drugs:** Traditional cytotoxic chemotherapy, which damages cell DNA, kills many normal cells in addition to cancer cells. Antimetabolites, such as 5-fluorouracil and methotrexate, are cell cycle-specific and have no linear dose-response relationship. In contrast, other chemotherapeutic drugs (eg, DNA cross-linkers, also known as alkylating agents) have a linear dose-response relationship, producing more tumor killing as well as more toxicity at higher doses. At their highest doses, DNA cross-linkers may produce bone marrow aplasia, necessitating bone marrow transplantation to restore bone marrow function.

Single-drug chemotherapy may cure selected cancers (eg, choriocarcinoma, hairy cell leukemia). More commonly, multidrug regimens incorporating drugs with different mechanisms of action and different toxicities are used to increase the tumor cell kill, reduce dose-related toxicity, and decrease the probability of drug resistance. These regimens can provide significant cure rates (eg, in acute leukemia, testicular cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and, less commonly, solid tumors such as small cell lung cancer and nasopharyngeal cancer). Multidrug regimens typically are given as repetitive cycles of a fixed combination of drugs. The interval between cycles should be the shortest one that allows for recovery of normal tissue. Continuous infusion may increase cell kill with some cell cycle-specific drugs (eg, 5-fluorouracil).

For each patient, the probability of significant toxicities should be weighed against the likelihood of benefit. End-organ function should be assessed before chemotherapeutic drugs with organ-specific toxicities are used (eg, echocardiography before doxorubicin use). Dose modification or exclusion of certain drugs may be necessary in patients with chronic lung disease (eg, bleomycin), renal failure (eg, methotrexate), or hepatic dysfunction (eg, taxanes).

Despite these precautions, adverse effects commonly result from cytotoxic chemotherapy. The normal tissues most commonly affected are those with the highest intrinsic turnover rate: bone marrow, hair follicles, and the GI epithelium.

Imaging (eg, CT, MRI, PET) is frequently done after 2 to 3 cycles of therapy to evaluate response to treatment. Therapy continues if there is a clear response. If the tumor progresses despite therapy, the
regimen is often amended or stopped. If the disease remains stable with treatment and the patient can tolerate therapy, then a decision to continue is reasonable with the understanding that the disease will eventually progress.

**Hormonal therapy:** Hormonal therapy uses hormone agonists or antagonists to influence the course of cancer. It may be used alone or in combination with other treatment modalities.

Hormonal therapy is particularly useful in prostate cancer, which grows in response to androgens. Other cancers with hormone receptors on their cells (eg, breast, endometrium) can often be palliated by hormone antagonist therapy or hormone ablation.

Use of prednisone, a glucocorticosteroid, is also considered hormonal therapy. It is frequently used to treat tumors derived from the immune system (lymphomas, lymphocytic leukemias, multiple myeloma).

**Biologic response modifiers:** Interferons are proteins synthesized by cells of the immune system as a physiologic immune protective response to foreign antigens (viruses, bacteria, other foreign cells). In pharmacologic amounts, they can palliate some cancers, including hairy cell leukemia, chronic myelocytic leukemia, locally advanced melanoma, metastatic renal cell cancer, and Kaposi's sarcoma. Significant toxic effects of interferon include fatigue, depression, nausea, leukopenia, chills and fever, and myalgias.

Interleukins, primarily the lymphokine IL-2 produced by activated T cells, can be used in metastatic melanomas and can provide modest palliation in renal cell cancer.

**Differentiating drugs:** These drugs induce differentiation in cancer cells. All-trans-retinoic acid has been highly effective in treating acute promyelocytic leukemia. Other drugs in this class include arsenic compounds and the hypomethylating agents azacytidine and deoxyazacytidine. When used alone, these drugs have only transient effects, but their role in prevention and in combination with cytotoxic drugs is promising.

**Antiangiogenesis drugs:** Solid tumors produce growth factors that form new blood vessels necessary to support ongoing tumor growth. Several drugs that inhibit this process are available. Thalidomide is antiangiogenic, among its many effects. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), is effective against renal cancers and colon cancer. VEGF receptor inhibitors are also affective in renal cancer, hepatocellular cancers, and GI stromal tumors.

**Signal transduction inhibitors:** Many epithelial tumors possess mutations that activate signaling pathways that cause their continuous proliferation and failure to differentiate. These mutated pathways include growth factor receptors and the downstream proteins that transmit messages to the cell nucleus from growth factor receptors on the cell surface. Three such drugs, imatinib (an inhibitor of the BCR-ABL tyrosine kinase in chronic myelocytic leukemia) and erlotinib and gefitinib (inhibitors of the epidermal growth factor receptor), are now in routine clinical use. Other inhibitors of these signaling pathways are under study.

**Monoclonal antibodies:** Monoclonal antibodies directed against unique tumor antigens have some efficacy against neoplastic tissue (see also p. 1060). Trastuzumab, an antibody directed against a protein called Her-2 or Erb-B2, plus chemotherapy has shown benefit in metastatic breast cancer. Antibodies against CD antigens expressed on neoplastic cells, such as CD20 and CD33, are used to treat patients with non-Hodgkin lymphoma (rituximab, anti-CD20 antibody) and acute myelocytic leukemia (gemtuzumab, an antibody linked to a potent toxin).

The effectiveness of monoclonal antibodies may be increased by linking them to radioactive nuclide. One such drug, ibritumomab, is used to treat non-Hodgkin lymphoma.

**Multimodality and Adjuvant Chemotherapy**

In some tumors with a high likelihood of relapse despite optimal initial surgery or radiation therapy, relapse may be prevented by addition of adjuvant chemotherapy. Increasingly, combined-modality therapy (eg, radiation therapy, chemotherapy, surgery) is used. It may permit organ-sparing procedures and
preserve organ function.

**Adjuvant therapy:** Adjuvant therapy is systemic chemotherapy or radiation therapy given to eradicate residual occult tumor after initial surgery. Patients who have a high risk of recurrence may benefit from its use. General criteria are based on degree of local extension of the primary tumor, presence of positive lymph nodes, and certain morphologic or biologic characteristics of individual cancer cells. Adjuvant therapy has increased disease-free survival and cure rate in breast and in colorectal cancer.

**Neoadjuvant therapy:** Neoadjuvant therapy is chemotherapy, radiation therapy, or both given before surgical resection. This treatment may enhance resectability and preserve local organ function. For example, when this therapy is used in head and neck, esophageal, or rectal cancer, a smaller subsequent resection may be possible. Another advantage of neoadjuvant therapy is in assessing response to treatment; if the primary tumor does not respond, micrometastases are unlikely to be eradicated, and an alternate regimen should be considered. Neoadjuvant therapy may obscure the true pathologic stage of the cancer by altering tumor size and margins and converting histologically positive nodes to negative, complicating clinical staging. The use of neoadjuvant therapy has improved survival in inflammatory and locally advanced breast, stage IIIA lung, nasopharyngeal, and bladder cancers.

**Bone Marrow Transplantation**

Bone marrow or stem cell transplantation is an important component of the treatment of otherwise refractory lymphomas, leukemias, and multiple myeloma (for an in-depth discussion of this topic, see p. 1132).

**Gene Therapy**

Genetic modulation is under intense investigation. Strategies include the use of antisense therapy, systemic viral vector transfection, DNA injection into tumors, genetic modulation of resected tumor cells to increase their immunogenicity, and alteration of immune cells to enhance their antitumor response.

**Management of Adverse Effects**

Patients being treated for cancer frequently experience adverse effects. Managing these effects improves quality of life.

**Nausea and Vomiting**

Nausea and vomiting are commonly experienced by cancer patients and may result from the cancer itself (eg, paraneoplastic syndromes) or from its treatment (eg, chemotherapy, radiation therapy to the brain or abdomen). However, refractory nausea and vomiting should prompt further investigation, including basic laboratory testing (electrolytes, liver function tests, lipase) and x-rays to investigate possible bowel obstruction or intracranial metastases.

**Serotonin-receptor antagonists** are the most effective drugs but are also the most expensive. Virtually no toxicity occurs with granisetron and ondansetron aside from headache and orthostatic hypotension. A 0.15-mg/kg dose of ondansetron or a 10-μg/kg dose of granisetron is given IV 30 min before chemotherapy. Doses of ondansetron can be repeated 4 and 8 h after the first dose. The efficacy against highly emetogenic drugs, such as the platinum complexes, can be improved with co-administration of dexamethasone (8 mg IV given 30 min before chemotherapy with repeat doses of 4 mg IV q 8 h).

**A substance P/neurokinin-1 antagonist,** aprepitant, can limit nausea and vomiting resulting from highly emetogenic chemotherapy. Dosage is 125 mg po 1 h before chemotherapy on day 1, then 80 mg po 1 h before chemotherapy on days 2 and 3.

Other traditional antiemetics, including phenothiazines (eg, prochlorperazine 10 mg IV q 8 h, promethazine 12.5 to 25 mg po or IV q 8 h) and metoclopramide (10 mg po or IV given 30 min before chemotherapy with repeated doses q 6 to 8 h), are alternatives restricted to patients with mild to moderate nausea and vomiting.
Dronabinol (Δ-9-tetrahydrocannabinol [THC]) is an alternative treatment for nausea and vomiting caused by chemotherapy. THC is the principal psychoactive component of marijuana. Its mechanism of antiemetic action is unknown, but cannabinoids bind to opioid receptors in the forebrain and may indirectly inhibit the vomiting center. Dronabinol is administered in doses of 5 mg/m² po 1 to 3 h before chemotherapy, with repeated doses q 2 to 4 h after the start of chemotherapy (maximum of 4 to 6 doses/day). However, it has variable oral bioavailability, is not effective for inhibiting the nausea and vomiting of platinum-based chemotherapy regimens, and has significant adverse effects (eg, drowsiness, orthostatic hypotension, dry mouth, mood changes, visual and time sense alterations). Smoking marijuana may be more effective. Marijuana for this purpose can be obtained legally in some states. It is used less commonly because of barriers to availability and because many patients cannot tolerate smoking.

Benzodiazepines, such as lorazepam (1 to 2 mg po or IV given 10 to 20 min before chemotherapy with repeated doses q 4 to 6 h pm), are sometimes helpful for refractory or anticipatory nausea and vomiting.

Cytopenias

Anemia, leukopenia, and thrombocytopenia may develop during chemotherapy or radiation therapy.

**Anemia:** Clinical symptoms and decreased efficacy of radiation therapy usually occur at Hct levels of < 30% or Hb levels < 10 g/dL, sooner in patients with coronary artery disease or peripheral vascular disease. Recombinant erythropoietin therapy may be started when Hb falls to < 10 mg/dL, depending on symptoms. In general, 150 to 300 units/kg sc 3 times/wk (a convenient adult dose is 10,000 units) is effective and reduces the need for transfusions. Longer-acting formulations of erythropoietin require less frequent dosing (darbepoetin alfa 2.25 to 4.5 μg/kg sc q 1 to 2 wk). Unnecessary use of erythropoietin should be avoided. Packed RBC transfusions may be needed to relieve acute cardiorespiratory symptoms.

**Thrombocytopenia:** A platelet count < 10,000/mL, especially with bleeding, requires transfusion of platelet concentrates. Small molecules that mimic thrombopoietin are available but are not commonly used in cancer treatment.

Leukocyte depletion of transfused blood products may prevent alloimmunization to platelets and should be used in patients who are expected to need platelet transfusions during multiple courses of chemotherapy or for candidates for bone marrow or stem cell transplantation. Leukocyte depletion also lowers the probability of cytomegalovirus being transferred to the patient through WBCs. Gamma irradiation of blood products to inactivate lymphocytes and prevent transfusion-induced graft-vs-host disease is also indicated in patients undergoing severely immunosuppressive chemotherapy.

**Neutropenia:** Neutropenia (see also p. 948), usually defined by an absolute neutrophil count < 500/μL, predisposes to immediate life-threatening infection.

Afebrile patients with neutropenia require close outpatient follow-up for detection of fever and should be instructed to avoid contact with sick people or areas frequented by large numbers of people (eg, shopping malls, airports). Although most patients do not require antibiotics, patients with severe immunosuppression (ie, concomitant T-cell depletion or loss of function) and leukopenia are sometimes given trimethoprim/sulfamethoxazole (one double-strength tablet/day) as prophylaxis for *Pneumocystis jiroveci*. In transplant patients or others receiving high-dose chemotherapy, antiviral prophylaxis (acyclovir 800 mg po bid or 400 mg IV q 12 h) should be considered if serologic tests are positive for herpes simplex virus.

Fever > 38° C in a patient with neutropenia is an emergency. Evaluation should include immediate chest x-ray and cultures of blood, sputum, urine, stool, and any suspect skin lesions. Examination includes possible abscess sites (eg, skin, ears), skin and mucosa for presence of herpetic lesions, retina for vascular lesions suggestive of metastatic infection, and catheter sites. Rectal examination and use of a rectal thermometer are avoided if possible in neutropenic patients because of the risk of bacteremia.

Febrile neutropenic patients should receive broad-spectrum antibiotics chosen on the basis of the most
Febrile neutropenic patients should receive broad-spectrum antibiotics chosen on the basis of the most likely source. Typical regimens include cefepime or ceftazidime 2 g IV q 8 h immediately after samples for culture are obtained. If diffuse pulmonary infiltrates are present, sputum should be tested for \textit{P. jirovecii}, and if positive, appropriate therapy should be started. If fever resolves within 72 h after starting empiric antibiotics, then antibiotics are continued until the absolute neutrophil count is > 500/µL. If fever continues for 120 h, antifungal drugs should be added to treat possible fungal causes. Re-assessment for occult infection (often including CT of the chest and abdomen) should be undertaken at this time.

In selected patients with neutropenia related to chemotherapy, especially after high-dose chemotherapy, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) may be started to shorten the leukopenic period. GCSF 5 ŗg/kг sc once/day up to 14 days and longer-acting forms (eg, pegfilgrastim 6 mg sc single dose once per chemotherapy cycle) may be used to accelerate WBC recovery. These drugs should not be administered in the first 24 h after chemotherapy, and for pegfilgrastim, at least 14 days should elapse until the next planned chemotherapy dose. These drugs are begun at the onset of fever or sepsis or, in afebrile patients, when neutrophil counts fall to < 500/µL.

Many centers use outpatient treatment of selected low-risk patients with fever and neutropenia. Candidates must not have hypotension, altered mental status, respiratory distress, uncontrolled pain, or serious comorbid illnesses, such as diabetes, heart disease, or hypercalcemia. The regimen in such cases requires daily follow-up and often involves visiting nurse services and home antibiotic infusion. Some regimens involve oral antibiotics, such as ciprofloxacin 750 mg po bid plus amoxicillin/clavulanate 875 mg po bid or 500 mg po tid. If no defined institutional program for follow-up and treatment of neutropenic fever is available in an outpatient setting, then hospitalization is required.

**Gastrointestinal Effects**

**Oral lesions:** Oral lesions, such as ulcers, infections, and inflammation, are common.

Oral candidiasis can be treated with nystatin oral suspension 5 to 10 mL qid, clotrimazole troches 10 mg qid, or fluconazole 100 mg po once/day.

Mucositis from radiation therapy can cause pain and preclude sufficient oral intake, leading to undernutrition and weight loss. Rinses with analgesics and topical anesthetics (2% viscous lidocaine, 5 to 10 mL q 2 h or other commercially available mixtures) before meals, a bland diet without citrus food or juices, and avoidance of temperature extremes may allow patients to eat and maintain weight. If not, a feeding tube may be helpful if the small intestine is functional. For severe mucositis and diarrhea or an abnormally functioning intestine, parenteral alimentation may be needed.

**Diarrhea:** Diarrhea from pelvic radiation therapy or from chemotherapy can be alleviated with antidiarrheal drugs as needed (kaolin/pectin suspension 60 to 120 mL regular strength, or 30 to 60 mL concentrate, po at first sign of diarrhea and after each loose stool or prn; loperamide 2 to 4 mg po; or diphenoxylate/atropine 1 to 2 tablets po). Patients who underwent abdominal surgery or received broad-spectrum antibiotics within the preceding 3 mo should undergo stool testing for \textit{Clostridium difficile}.

**Constipation:** Constipation may result from opioid use. A stimulant laxative such as senna 2 to 6 tablets po at bedtime or bisacodyl 10 mg po at bedtime should be initiated when repeated opioid use is anticipated. Established constipation can be treated with various drugs (eg, bisacodyl 5 to 10 mg po q 12 to 24 h, milk of magnesia 15 to 30 mL po at bedtime, lactulose 15 to 30 mL q 12 to 24 h, Mg citrate 250 to 500 mL po once). Enemas and suppositories should be avoided in patients with neutropenia or thrombocytopenia.

**Anorexia:** Appetite may decrease secondary to cancer treatment or to a paraneoplastic syndrome. Corticosteroids (dexamethasone 4 mg po once/day, prednisone 5 to 10 mg po once/day) and megestrol acetate 400 to 800 mg once/day are most effective. However, the primary benefits are variably increased appetite and weight gain, not improved survival or quality of life.
Pain should be anticipated and aggressively treated (see also p. 1623). Use of multiple drug classes may provide better pain control with fewer or less severe adverse effects than single drug classes. NSAIDs should be avoided in patients with thrombocytopenia. Opioids are the mainstay of treatment, given around the clock in generally efficient doses, with supplemental doses given for occasional worse pain. If the oral route is unavailable, fentanyl is given transdermally. Antiemetics and prophylactic bowel regimens are often needed with opioids.

Neuropathic pain can be treated with gabapentin; the dose required is high (up to 3.6 g/day) but must be started low and then increased over a few weeks. Alternatively, a tricyclic antidepressant (eg, nortriptyline 25 to 75 mg po at bedtime) may be tried.

Useful nondrug treatments for pain include focal radiation therapy, nerve blockade, and surgery.

**Depression**

Depression is often overlooked. It may occur in response to the disease (its symptoms and feared consequences), adverse effects of the treatments, or both. Patients receiving interferon can develop depression as an adverse effect. Also, alopecia as an adverse effect of radiation therapy or chemotherapy can contribute to depression. Frank discussion of a patient's fears can often relieve anxiety; depression can often be treated effectively (see p. 1538).

**Tumor Lysis Syndrome**

Tumor lysis syndrome may occur secondary to release of intracellular components into the bloodstream as a result of tumor cell death after chemotherapy. It occurs mainly in acute leukemias and non-Hodgkin lymphomas but can also occur in other hematologic cancers and, uncommonly, after treatment of solid tumors. It should be suspected in patients with a large tumor burden who develop acute renal failure after initial treatment.

The diagnosis is confirmed by some combination of the following findings:

- Renal failure
- Hypocalcemia ( 8 mg/dL)
- Hyperuricemia (> 15 mg/dL)
- Hyperphosphatemia (> 8 mg/dL)

Allopurinol (200 to 400 mg/m$^2$ once/day, maximum 600 mg/day) and normal saline IV to achieve urine output > 2 L/day should be initiated with close laboratory and cardiac monitoring. Patients who have a cancer with rapid cell turnover should receive allopurinol for at least 2 days before and during chemotherapy; for patients with high cell burden, this regimen can be continued for 10 to 14 days after therapy. All such patients should receive vigorous IV hydration to establish a diuresis of at least 100 mL/h prior to treatment. Although some physicians advocate NaHCO$_3$ IV to alkalinize the urine and increase solubilization of uric acid, alkalinization may promote Ca phosphate deposition in patients with hyperphosphatemia, and a pH of about 7 should be avoided. Alternatively, rasburicase, an enzyme that oxidizes uric acid to allantoin (a more soluble molecule), may be used to prevent tumor lysis. The dose is 0.15 to 0.2 mg/kg IV over 30 min once/day for 5 to 7 days, typically initiated 4 to 24 h before the first chemotherapy treatment. Adverse effects may include anaphylaxis, hemolysis, hemoglobinuria, and methemoglobinemia.

**Cachexia**

Cachexia is wasting of both adipose and skeletal muscle. It occurs in many conditions and is common with many cancers when remission or control fails. Some cancers, especially pancreatic and gastric cancers, cause profound cachexia. Affected patients may lose 10 to 20% of body weight. Men tend to
experience worse cachexia with cancer than do women. Neither tumor size nor the extent of metastatic disease predicts the degree of cachexia. Cachexia is associated with reduced response to chemotherapy, poor functional performance, and increased mortality.

The primary cause of cachexia is not anorexia or decreased caloric intake. Rather, this complex metabolic condition involves increased tissue catabolism. Protein synthesis is decreased and degradation increased. Cachexia is mediated by certain cytokines, especially tumor necrosis factor-α, IL-1β, and IL-6, which are produced by tumor cells and host cells in the tissue mass. The ATP-ubiquitin-protease pathway plays a role as well.

Cachexia is easy to recognize, primarily by weight loss, which is most apparent with loss of temporalis muscle mass in the face. The loss of subcutaneous fat increases the risk of pressure ulcers over bony prominences.

**Treatment**

Treatment involves treatment of the cancer. If the cancer can be controlled or cured, regardless of modality, cachexia resolves.

Additional caloric supplementation does not relieve cachexia. Any weight gain is usually minimal and is likely to consist of adipose tissue rather than muscle. Neither function nor prognosis is improved. Thus, in most cachectic patients with cancer, high-calorie supplementation is not recommended, and parenteral nutritional support is not indicated, except in situations where oral intake of adequate nutrition is impossible.

However, other treatments can mitigate cachexia and improve function. Corticosteroids increase appetite and may improve a sense of well-being but do little to increase body weight. Likewise, cannabinoids (marijuana, dronabinol) increase appetite but not weight. Progestogens, such as megestrol acetate, 40 mg po bid or tid, may increase both appetite and body weight. Drugs to alter cytokine production and effects are being studied.

**Incurable Cancer**

Even in cases of incurable cancer, palliative or experimental therapy may improve quality and extent of life. But in many cases, physicians must resist the urge to administer a relatively ineffective chemotherapy drug. A better choice is to discuss the likely results of such treatments and to set realistic goals with the patient. A patient's decision to forgo cancer treatment must be respected. Another alternative is the clinical trial, the risks and benefits of which deserve discussion.

Regardless of prognosis, quality of life in cancer patients may improve with nutritional support, effective pain management, other symptomatic palliative care, and psychiatric and social support of the patient and family. Above all, patients must know that the clinical team will remain involved and accessible for supportive care, regardless of the prognosis. Hospice or other related end-of-life care programs are important parts of cancer treatment. For more information pertaining to patients with incurable disease, see Ch. 353.
Chapter 125. Biology of the Immune System

Introduction

The immune system distinguishes self from nonself and eliminates potentially harmful nonself molecules and cells from the body. The immune system also has the capacity to recognize and destroy abnormal cells that derive from host tissues (see p. 1057). Any molecule capable of being recognized by the immune system is considered an antigen (Ag).

The skin, cornea, and mucosa of the respiratory, GI, and GU tracts form a physical barrier that is the body's first line of defense. Some of these barriers also involve immune functions and other active defenses:

• Outer, keratinized epidermis: Keratinocytes in the skin secrete antimicrobial peptides (defensins), and sebaceous and sweat glands secrete microbe-inhibiting substances (eg, lactic acid, fatty acids). Also, many immune cells (eg, mast cells, intraepithelial lymphocytes, Ag-sampling Langerhans' cells) reside in the skin.

• Mucosa of the respiratory, GI, and GU tracts: The mucus contains antimicrobial substances, such as lysozyme, lactoferrin, and secretory IgA antibody (SIgA).

Breaching of anatomic barriers can trigger 2 types of immune response: innate and acquired. Many molecular components (eg, complement, cytokines, acute phase proteins) participate in both innate and acquired immunity.

Innate immunity: Innate (natural) immunity does not require prior exposure to an Ag (ie, memory) to be effective. Thus, it can respond immediately to an invader. However, it recognizes mainly Ag molecules that are broadly distributed rather than specific to one organism or cell. Components include

• Phagocytic cells

• Ag-presenting cells

• Natural killer (NK) cells

• Polymorphonuclear leukocytes

Phagocytic cells (neutrophils and monocytes in blood, macrophages and dendritic cells in tissues) ingest and destroy invading Ags. Attack by phagocytic cells can be facilitated when Ags are coated with antibody (Ab), which is produced as part of acquired immunity. Ag-presenting cells (macrophages, dendritic cells) present fragments of ingested Ags to T cells (which are part of acquired immunity). Natural killer cells kill virus-infected cells and some tumor cells. Certain polymorphonuclear leukocytes (eosinophils, basophils, mast cells) release inflammatory mediators.

Acquired immunity: Acquired (adaptive) immunity requires prior exposure to an Ag and thus takes time to develop after the initial encounter with a new invader. Thereafter, response is quick. The system remembers past exposures and is Ag-specific. Components include

• T cells

• B cells

Acquired immunity derived from certain T-cell responses is called cell-mediated immunity. Immunity derived from B-cell responses is called humoral immunity because B cells secrete soluble Ag-specific Ab. B cells and T cells work together to destroy invaders. Some of these cells do not directly destroy invaders but instead enable other WBCs to recognize and destroy invaders.
Immune Response

Successful immune defense requires activation, regulation, and resolution of the immune response.

Activation: The immune system is activated when a foreign Ag is recognized by circulating Abs or cell surface receptors. These receptors may be highly specific (Ab expressed on B cells or T-cell receptors) or broadly specific (eg, pattern-recognition receptors such as Toll-like, mannose, and scavenger receptors on dendritic and other cells). Broadly specific receptors recognize common microbial pathogen-associated molecular patterns in ligands, such as gram-negative lipopolysaccharide, gram-positive peptidoglycans, bacterial flagellin, unmethylated cytosine-guanosine dinucleotides (CpG motifs), and viral double-stranded RNA. Activation may also occur when Ab-Ag and complement-microorganism complexes bind to surface receptors for the crystallizable fragment (Fc) region of IgG (FcγR) and for C3b and iC3b.

Once recognized, an Ag, Ag-Ab complex, or complement-microorganism complex is phagocytosed. Most microorganisms are killed after they are phagocytosed, but others (eg, mycobacteria) inhibit the phagocyte's ability to kill them once they are engulfed. In such cases, T cell-derived cytokines, particularly interferon-γ (IFN-γ), stimulate the phagocyte to produce lytic enzymes and other microbicidal macrophage products, which kill the microorganism.

Unless Ag is rapidly phagocytosed and entirely degraded (an uncommon event), the acquired immune response is recruited. This response begins in the spleen for circulating Ag, in regional lymph nodes for tissue Ag, and in mucosa-associated lymphoid tissues (eg, tonsils, adenoids, Peyer's patches) for mucosal Ag. For example, Langerhans' dendritic cells in the skin phagocytose Ag and migrate to local lymph nodes; there, peptides derived from the Ag are expressed on the cell surface within class II major histocompatibility complex (MHC) molecules, which present the peptide to CD4 helper T (TH) cells. When the TH cell engages the MHC-peptide complex and receives various costimulatory signals, it is activated to express receptors for the cytokine IL-2 and secretes several cytokines. Each subset of TH cells secretes different substances, which effect different immune response (see p. 1081).

Class II MHC molecules present peptides derived from extracellular (exogenous) Ag to CD4 TH cells; in contrast, class I MHC molecules present peptides derived from intracellular (endogenous) Ag (eg, viruses) to CD8 cytotoxic T cells. The activated cytotoxic T cell then kills the infected cell.

Regulation: The immune response must be regulated to prevent overwhelming damage to the host (eg, anaphylaxis, widespread tissue destruction). Regulatory T cells (most of which express Foxp3 transcription factor) help control the immune response via secretion of immunosuppressive cytokines, such as IL-10 and transforming growth factor-β (TGF-β), or via a poorly defined cell contact mechanism. These regulatory cells help prevent autoimmune responses and probably help resolve ongoing responses to nonself Ag.

Resolution: The immune response resolves when Ag is sequestered and eliminated from the body. Without stimulation by Ag, cytokine secretion ceases, and activated cytotoxic T cells undergo apoptosis. Apoptosis tags a cell for immediate phagocytosis, which prevents spill-age of the cellular contents and development of subsequent inflammation. T and B cells that have differentiated into memory cells are spared this fate.

Geriatrics Essentials

With aging, the immune system becomes less effective in the following ways:

- The immune system becomes less able to distinguish self from nonself, making autoimmune disorders more common.

- Macrophages destroy bacteria, cancer cells, and other Ag more slowly, possibly contributing to the increased incidence of cancer among the elderly.
• T cells respond less quickly to Ag.
• There are fewer lymphocytes that can respond to new Ag.
• The aging body produces less complement in response to bacterial infections.
• Less Ab is produced in response to Ag, and Ab is less able to attach to Ag, possibly contributing to the increased incidence of pneumonia, influenza, infectious endocarditis, and tetanus and the increased risk of death due to these disorders among the elderly. These changes may also partly explain why vaccines are less effective in the elderly.

Components of the Immune System

The immune system consists of cellular and molecular components that work together to destroy antigens (Ags).

Antigen-Presenting Cells

Although some Ags can stimulate the immune response directly, T cell-dependent acquired immune responses typically require antigen-presenting cells (APCs) to present Ag-derived peptides within major histocompatibility complex (MHC) molecules. Intracellular Ag (eg, viruses) can be processed and presented to CD8 cytotoxic T cells by any nucleated cell because all nucleated cells express class I MHC molecules. However, extracellular Ag must be processed into peptides and complexed with surface class II MHC molecules on professional APCs to be recognized by CD4 helper T (T_H) cells. The following cells constitutively express class II MHC molecules and therefore act as professional APCs:

• B cells
• Monocytes
• Macrophages
• Dendritic cells

Monocytes in the circulation are precursors to tissue macrophages. Monocytes migrate into tissues, where over about 8 h, they develop into macrophages under the influence of macrophage colony-stimulating factor (M-CSF), secreted by various cell types (eg, endothelial cells, fibroblasts). At infection sites, activated T cells secrete cytokines (eg, interferon-γ [IFN-γ]) that induce production of macrophage migration inhibitory factor, preventing macrophages from leaving.

Macrophages are activated by IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF). Activated macrophages kill intracellular organisms and secrete IL-1 and tumor necrosis factor-α (TNF-α). These cytokines potentiate the secretion of IFN-γ and GM-CSF and increase the expression of adhesion molecules on endothelial cells, facilitating leukocyte influx and destruction of pathogens.

Dendritic cells are present in the skin (as Langerhans' cells), lymph nodes, and tissues throughout the body. Dendritic cells in the skin act as sentinel APCs, taking up Ag, then travel to local lymph nodes where they can activate T cells. Follicular dendritic cells are a distinct lineage, do not express class II MHC molecules, and therefore do not present Ag to T_H cells. However, they have receptors for the crystallizable fragment (Fc) region of IgG and for complement, which enable them to bind with immune complexes and present the complex to B cells in germinal centers of secondary lymphoid organs.

Polymorphonuclear Leukocytes

Polymorphonuclear (PMN) leukocytes, also called granulocytes because their cytoplasm contains granules, include

• Neutrophils
• Eosinophils

• Basophils

• Mast cells

All, except for mast cells, occur in the circulation, and all have multilobed nuclei. Mast cells are tissue-based and functionally similar to circulating blood basophils.

**Neutrophils** constitute 40 to 70% of total WBCs; they are a first line of defense against infection. Mature neutrophils have a half-life of about 2 to 3 days. During acute inflammatory responses (eg, to infection), neutrophils, drawn by chemotactic factors and alerted by the expression of adhesion molecules on blood vessel endothelium, leave the circulation and enter tissues. Their purpose is to phagocytose and digest pathogens. Microorganisms are killed when phagocytosis generates lytic enzymes and reactive O$_2$ compounds (eg, superoxide, hypochlorous acid) and triggers release of granule contents (eg, defensins, proteases, bactericidal permeability-increasing protein, lactoferrin, and lysozymes). DNA and histones are also released, and they, with granule contents such as elastase, generate fibers in the surrounding tissues; the fibers may facilitate killing by trapping bacteria and focusing enzyme activity.

**Eosinophils** constitute up to 5% of WBCs. They target organisms too large to be engulfed; they kill by secreting toxic substances (eg, reactive O$_2$ compounds similar to those produced in neutrophils), major basic protein (which is toxic to parasites), eosinophil cationic protein, and several enzymes. Eosinophils are also a major source of inflammatory mediators (eg, prostaglandins, leukotrienes, platelet-activating factor, many cytokines).

**Basophils** constitute < 5% of WBCs and share several characteristics with mast cells, although the 2 cell types have distinct lineages. Both have high-affinity receptors for IgE called FcεRI. When these cells encounter certain Ags, the bivalent IgE molecules bound to the receptors become cross-linked, triggering cell degranulation with release of preformed inflammatory mediators (eg, histamine, platelet-activating factor) and generation of newly synthesized mediators (eg, leukotrienes, prostaglandins, thromboxanes).

**Mast cells** occur in different tissues of the body. Mucosal mast cell granules contain tryptase and chondroitin sulfate; connective tissue mast cell granules contain tryptase, chymase, and heparin. By releasing these mediators, mast cells play a key role in generating protective acute inflammatory responses; basophils and mast cells are the source of type I hypersensitivity reactions associated with atopic allergy (see p. 1113). Degranulation can be triggered by cross-linking of IgE receptors or by the anaphylatoxin complement fragments C3a and C5a.

**Cytotoxic Leukocytes**

Cytotoxic leukocytes include

• Natural killer cells

• Lymphokine-activated killers

**Natural killer (NK) cells**: Typical NK cells constitute 5 to 15% of peripheral blood mononuclear cells. They have a round nucleus and granular cytoplasm and induce apoptosis in infected or abnormal cells by a number of pathways. As cells of the innate response, they lack antigen-specific receptors and immunologic memory. NK cells are best characterized by CD2$^+$, CD3$^-$, CD4$^-$, CD8$^+$, CD16$^+$ (a receptor for IgG-Fc), and CD56$^+$ surface markers.

Typical NK cells are thought to be important for tumor surveillance. NK cells express both activating and inhibitory receptors. The activating receptors on NK cells can recognize numerous ligands on target cells (eg, MHC class I-related chain A [MICA] and chain B [MICB]); the inhibitory receptors on NK cells recognize MHC class I molecules. NK cells can kill their target only when there is no strong signal from
inhibitory receptors. MHC class I molecules (normally expressed on nucleated cells) therefore prevent destruction of cells; their absence indicates that the cell is infected with certain viruses that inhibit MHC expression or has lost MHC expression because cancer has changed the cell.

NK cells can also secrete several cytokines (eg, IFN-γ, IL-1, TNF-α); they are a major source of IFN-γ. By secreting IFN-γ, NK cells can influence the acquired immune system by promoting differentiation of type 1 helper T (T H1) cells and inhibiting that of type 2 (T H2) cells.

**Lymphokine-activated killers (LAK):** Some leukocytes develop into potent lymphokine-activated killers, capable of killing a wide spectrum of tumor target cells and abnormal lymphocytes (eg, infected with certain viruses). These cells are a phenomenon rather than a unique subset of cells. LAK precursors are heterogeneous but can be classified primarily as NK-like (most common) or T-cell-like.

**Lymphocytes**

The 2 main types of lymphocytes are

- **B cells** (which mature in bone marrow)
- **T cells** (which mature in the thymus)

They are morphologically indistinguishable but have different immune functions. They can be distinguished by Ag-specific surface receptors and molecules called clusters of differentiation (CDs), whose presence and absence define some subsets. More than 300 CDs have been identified (for further information on CD Ags, see the Human Cell Differentiation Molecules web site at www.hlda8.org/). Each lymphocyte recognizes a specific Ag via surface receptors.

**B cells:** About 5 to 15% of lymphocytes in the blood are B cells; they are also present in the spleen, lymph nodes, and mucosa-associated lymphoid tissues. B cells can present Ag to T cells, but their primary function is to develop into plasma cells, which manufacture and secrete antibodies (Abs—see p. 1083).

After random rearrangement of the genes that encode immunoglobulin (Ig), B cells have the potential to recognize an almost limitless number of unique Ags. Gene rearrangement occurs in programmed steps in the bone marrow during B-cell development. The process starts with a committed stem cell, continues through pro-B and pre-B cell stages, and results in an immature B cell. If an immature B cell interacts with Ag, it may become inactivated (tolerant) or be eliminated (by apoptosis). Immature B cells that are not inactivated or eliminated may continue to develop into mature naive B cells, leave the marrow, and enter peripheral lymphoid organs, where they may encounter Ag. Their response to Ag has 2 stages:

- **Primary immune response:** When mature naive B cells first encounter Ag, they become lymphoblasts, undergo clonal proliferation, and differentiate into memory cells, which can respond to the same Ag in the future, or into mature Ab-secreting plasma cells. After first exposure, there is a latent period of days before Ab is produced. Then, only IgM is produced. After that, with the help of T cells, B cells can further rearrange their Ig genes and switch to production of IgG, IgA, or IgE. Thus, after first exposure, the response is slow and provides limited protective immunity.

- **Secondary (anamnestic or booster) immune response:** When memory B and T H cells are reexposed to the Ag, the memory B cells rapidly proliferate, differentiate into mature plasma cells, and promptly produce large amounts of Ab (chiefly IgG because of a T cell-induced isotype switch). The Ab is released into the blood and other tissues, where it can react with Ag. Thus, after reexposure, the immune response is faster and more effective.

**T cells:** T cells develop from bone marrow stem cells that travel to the thymus, where they go through rigorous selection. There are 3 main types of T cell:

- Helper
In selection, T cells that react to self Ag presented by self MHC molecules or to self MHC molecules (regardless of the Ag presented) are eliminated by apoptosis. Only T cells that can recognize nonself Ag complexed to self MHC molecules survive; they leave the thymus for peripheral blood and lymphoid tissues.

Most mature T cells express either CD4 or CD8 and have an Ag-binding, Ig-like surface receptor called the T-cell receptor (TCR). Genes that encode the TCR, like Ig genes, are rearranged, resulting in defined specificity and affinity for the Ag peptide displayed in the MHC molecule of an APC. As for B cells, the number of T-cell specificities is almost limitless.

For T cells to be activated, the TCR must engage with Ag-MHC. Costimulatory accessory molecules must also interact; otherwise, the T cell becomes anergic or dies by apoptosis. Some accessory molecules (eg, CTLA-4) inhibit previously activated T cells and thus dampen the immune response.

Helper T (T$_H$) cells are usually CD4 but may be CD8. They differentiate from T$_H$0 cells into one of the following:

- T$_H$1 cells: In general, T$_H$1 cells promote cell-mediated immunity via cytotoxic T cells and macrophages.
- T$_H$2 cells: T$_H$2 cells promote Ab production by B cells (humoral immunity).
- T$_H$17 cells: T$_H$17 cells promote tissue inflammation.

Each cell type secretes several cytokines (see Table 125-1). Different patterns of cytokine production identify other T$_H$-cell functional phenotypes.

The distinction between the different T$_H$ cells is clinically relevant. For example, a T$_H$1 response dominates in tuberculoid leprosy, and a T$_H$2 response dominates in lepromatous leprosy. A T$_H$1 response is characteristic of certain autoimmune disorders (eg, type 1 diabetes, multiple sclerosis), and a T$_H$2 response promotes IgE production and development of allergic disorders, as well as helps B cells produce autoantibodies in some autoimmune disorders (eg, Graves’ disease, myasthenia gravis). T$_H$17 cells, via their role in inflammation, may also contribute to autoimmune disorders.

Regulatory T cells mediate suppression of immune responses. The process involves functional subsets of CD4 T cells that either secrete cytokines with immunosuppressive properties or suppress the immune response by poorly defined mechanisms that require cell-to-cell contact. Some regulatory T cells express the CD8 T-cell phenotype.

Regulatory T cells mediate suppression of immune responses. The process involves functional subsets of CD4 T cells that either secrete cytokines with immunosuppressive properties or suppress the immune response by poorly defined mechanisms that require cell-to-cell contact. Some regulatory T cells express the CD8 T-cell phenotype.

Cytotoxic T (T$_C$) cells are usually CD8 but may be CD4; they are vital for eliminating intracellular pathogens, especially viruses. T$_C$ cells play a role in organ transplant rejection.

T$_C$-cell development involves 3 phases:

- A precursor cell that, when appropriately stimulated, can differentiate into a T$_C$ cell
- An effector cell that has differentiated and can kill its appropriate target
- A memory cell that is quiescent (no longer stimulated) but is ready to become an effector when restimulated by the original Ag-MHC combination
Fully activated TC cells, like NK cells, can kill an infected target cell by inducing apoptosis.

TC cells may be

- Syngeneic: Generated in response to self (autologous) cells modified by viral infection or other foreign proteins
- Allogeneic: Generated in response to cells that express foreign MHC products (eg, in organ transplantation when the donor's MHC molecules differ from the recipient's) Some TC cells can directly recognize foreign MHC (direct pathway); others may recognize fragments of foreign MHC presented by self MHC molecules of the transplant recipient (indirect pathway).

NK T cells are a distinct subset of T cells. Activated NK T cells secrete IL-4 and IFN-γ and may help regulate immune responses.

Antibodies

Abs act as the Ag receptor on the surface of B cells and, in response to Ag, are subsequently secreted by plasma cells. Abs recognize specific configurations (epitopes, or antigenic determinants) on the surfaces of Ags (eg, proteins, polysaccharides, nucleic acids). Abs and Ags fit tightly together because their shape and other surface properties (eg, charge) are complementary. The same Ab molecule can cross-react with related Ags if their epitopes are similar enough to those of the original Ag.

Structure: Abs consist of 4 polypeptide chains (2 identical heavy chains and 2 identical light chains) joined by disulfide bonds to produce a Y configuration (see Fig. 125-1). The heavy and light chains are divided into a variable (V) region and a constant (C) region.

V regions are located at the amino-terminal ends of the Y arms; they are called variable because the amino acids they contain are different in different Abs. The amino acids present determine the specificity of the Ig. Hypervariable regions within the V regions contain idiotypic determinants, to which certain natural (anti-idiotype) Abs can bind; this binding may help regulate B-cell responses. A B cell can switch the Ig heavy chain isotype it produces, but it retains its heavy chain V region and the entire light-chain, thereby retaining antigenic specificity.

The C region contains a relatively constant sequence of amino acids that is distinctive for each Ig isotype.

The amino-terminal (variable) end of the Ab binds to Ag to form an Ab-Ag complex. The Ag-binding (Fab) portion of Ig consists of a light chain and a fragment of a heavy chain and contains the V region of the Ig molecule (ie, the combining sites). The crystallizable fragment (Fc) contains most of the C region of the heavy chains; Fc is responsible for complement activation and binds to Fc receptors on cells.

Antibody classes: Antibodies are divided into 5 classes:

- IgM
- IgG
- IgA
- IgD
- IgE

The classes are defined by their type of heavy chain (μ for IgM, γ for IgG, α for IgA, ε for IgE, and δ for IgD); there are also 2 types of light chains (κ and λ). Each of the 5 Ig classes can bear either κ or λ light
IgM is the first Ab formed after exposure to new Ag. It has 5 Y-shaped molecules (10 heavy chains and 10 light chains), linked by a single joining (J) chain. IgM circulates primarily in the intravascular space; it complexes with and agglutinates Ag and can activate complement, thereby facilitating phagocytosis. Isohemagglutinins and many Abs to gram-negative bacteria are IgM. Monomeric IgM acts as a surface Ag receptor on B cells.

IgG is the most prevalent Ig isotype in serum and is present also in intravascular and extravascular spaces. It coats Ag to activate complement and facilitate phagocytosis by neutrophils and macrophages. IgG is the primary circulating Ig produced after reexposure to Ag (secondary immune response) and is the predominant isotype contained in commercial γ-globulin products. IgG protects against bacteria, viruses, and toxins; it is the only Ig isotype that crosses the placenta.

There are 4 subclasses of IgG: IgG1, IgG2, IgG3, and IgG4. They are numbered in descending order of serum concentration. IgG subclasses differ functionally mainly in their ability to activate complement; IgG1 and IgG3 are most efficient, IgG2 is less efficient, and IgG4 is inefficient. IgG1 and IgG3 are efficient mediators of Ab-dependent cellular cytotoxicity; IgG4 and IgG2 are less so.

IgA occurs at mucosal surfaces, in serum, and in secretions (saliva; tears; respiratory, GU, and GI tract secretions; colostrum), where it provides an early antibacterial and antiviral defense. J chain links IgA into a dimer to form secretory IgA. Secretory IgA is synthesized by plasma cells in the subepithelial regions of the GI and respiratory tracts.

IgD is coexpressed with IgM on the surface of naive B cells. Whether these 2 classes function differently on the surface of the B cell and, if so, how differently are unclear. They may simply be an example of molecular degeneracy. Serum IgD levels are very low, and the function of circulating IgD is unknown.

IgE is present in low levels in serum and in respiratory and GI mucous secretions. IgE binds with high affinity to receptors present in high levels on mast cells and basophils and to a lesser extent on several other hematopoietic cells, including dendritic cells. If Ag bridges 2 IgE molecules bound to the mast cell or basophil surface, the cells degranulate, releasing chemical mediators that cause an inflammatory response. IgE levels are elevated in atopic disorders (eg, allergic or extrinsic asthma, hay fever, atopic dermatitis) and parasitic infections.

Acute Phase Reactants

Acute phase reactants are plasma proteins whose levels dramatically increase if infection or tissue damage occurs. Most dramatically increased are C-reactive protein and mannose-binding lectin (which fix complement and act as opsonins), the transport protein α1-acid glycoprotein, and serum amyloid P component. Many acute phase reactants are made in the liver. Collectively, they may help limit tissue injury, enhance host resistance to infection, and promote tissue repair and resolution of inflammation.

Cytokines

Cytokines are polypeptides secreted by immune and other cells when the cell interacts with a specific Ag, endotoxin, or other cytokines. Main categories include

- IFNs (IFN-α, IFN-β, IFN-γ)
- TNFs (TNF-α, lymphotoxin-α, lymphotoxin-β)
- ILs
- Chemokines
- TGFs
Hematopoietic colony-stimulating factors (CSFs)

Although lymphocyte interaction with a specific Ag triggers cytokine secretion, cytokines themselves are not Ag-specific; thus, they bridge innate and acquired immunity and generally influence the magnitude of inflammatory or immune responses. They act sequentially, synergistically, or antagonistically. They may act in an autocrine or paracrine manner.

Cytokines deliver their signals via cell surface receptors. For example, the IL-2 receptor consists of 3 chains: α, β, and γ. The receptor's affinity for IL-2 is high if all 3 chains are expressed, intermediate if only the β and γ chains are expressed, or low if only the α chain is expressed. Mutations or deletion of the γ chain is the basis for X-linked severe combined immunodeficiency (see p. 1106).

Chemokines induce chemotaxis and migration of leukocytes. There are 4 subsets, defined by the number of intervening amino acids between the first 2 cysteine residues in the molecule. Chemokine receptors (CCR5 on memory T cells, monocytes/macrophages, and dendritic cells; CXCR4 on resting T cells) act as coreceptors for entry of HIV into cells.

Human Leukocyte Antigen System

The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, is controlled by genes located on chromosome 6. It encodes cell surface molecules specialized to present antigenic peptides to the T-cell receptor (TCR) on T cells. MHC molecules that present antigen (Ag) are divided into 2 main classes.

Class I MHC molecules are present on the surface of all nucleated cells and platelets. These polypeptides consist of a heavy chain bound to a β2-microglobulin molecule. The heavy chain consists of 2 peptide-binding domains, an Ig-like domain, and a transmembrane region with a cytoplasmic tail. The heavy chain of the class I molecule is encoded by genes at HLA-A, HLA-B, and HLA-C loci. Lymphocytes that express CD8 molecules react with class I MHC molecules. These lymphocytes often have a cytotoxic function, requiring them to be capable of recognizing any infected cell. All nucleated cells express class I MHC molecules and can thus act as antigen-presenting cells for CD8 T cells (CD8 binds to the nonpolymorphic part of the class I heavy chain). Some class I MHC genes encode nonclassical MHC molecules, such as HLA-G (which may play a role in protecting the fetus from the maternal immune response) and HLA-E (which presents peptides to certain receptors on natural killer cells).

Class II MHC molecules are usually present only on professional Ag-presenting cells (B cells, macrophages, dendritic cells, Langerhans' cells), thymic epithelium, and activated (but not resting) T cells; most nucleated cells can be induced to express class II MHC molecules by interferon (IFN)-γ. Class II MHC molecules consist of 2 polypeptide (α and β) chains; each chain has a peptide-binding domain, an Ig-like domain, and a transmembrane region with a cytoplasmic tail. Both polypeptide chains are encoded by genes in the HLA-DR, -DQ, or -DP region of chromosome 6. Lymphocytes reactive to class II molecules express CD4 and are often helper T cells.

The MHC class III region of the genome encodes several molecules important in inflammation; they include complement components C2, C4, and factor B; tumor necrosis factor (TNF)-α; lymphotoxin-α; lymphotoxin-β; and 3 heat shock proteins.

Individual alleles of the class I and II loci in the HLA system are given standard designations (eg, HLA-A1, -B5, -Cw1, -DR1). Alleles defined by DNA sequencing are named to identify the gene and to give each allele a unique number composed of the HLA locus, an asterisk, 2 numbers representing the serologic equivalent of the Ag, and 2 numbers representing the specific allele (eg, A*0201, DRB1*0103, DQA1*0102). Sometimes another number is added to identify a different subtype.

Some disorders are linked to specific HLA alleles (eg, psoriasis to HLA-Cw6, ankylosing spondylitis and reactive arthritis to HLA-B27, narcolepsy to HLA-DR2 and HLA-DQB1*0602, type 1 diabetes mellitus to HLA-DQ2 and HLA-DQ8, multiple sclerosis to HLA-DR2, RA to HLA-DRB1).

Complement System
The complement system is an enzyme cascade that helps defend against infection. Many complement proteins occur in serum as inactive enzyme precursors (zymogens); others reside on cell surfaces. The complement system bridges innate and acquired immunity by

- Augmenting antibody (Ab) responses and immunologic memory
- Lysing foreign cells
- Clearing immune complexes and apoptotic cells

Complement components have many biologic functions (eg, stimulation of chemotaxis, triggering of mast cell degranulation independent of IgE).

**Complement activation:** There are 3 pathways of complement activation (see Fig. 125-2):

- Classical
- Lectin
- Alternative

Classical pathway components are labeled with a C and a number (eg, C1, C3), based on the order in which they were identified. Alternative pathway components are often lettered (eg, factor B, factor D) or named (eg, properdin).

**Classical pathway** activation is Ab-dependent, occurring when C1 interacts with Ag-IgM or aggregated Ag-IgG complexes, or Ab-independent, occurring when polyanions (eg, heparin, protamine, DNA and RNA from apoptotic cells), gram-negative bacteria, or bound C-reactive protein reacts directly with C1. This pathway is regulated by C1 inhibitor (C1-INH). Hereditary angioedema is due to a genetic deficiency of C1-INH.

**Lectin pathway** activation is Ab-independent; it occurs when mannose-binding lectin (MBL), a serum protein, binds to mannose or fructose groups on bacterial cell walls, yeast walls, or viruses. This pathway otherwise resembles the classical pathway structurally and functionally.

**Alternate pathway** activation occurs when components of microbial cell surfaces (eg, yeast walls, bacterial cell wall lipopolysaccharide [endotoxin]) or Ig (eg, nephritic factor, aggregated IgA) cleave small amounts of C3. This pathway is regulated by properdin, factor H, and decay-accelerating factor.

The 3 activation pathways converge into a final common pathway when C3 convertase cleaves C3 into C3a and C3b (see Fig. 125-2). C3 cleavage may result in formation of the membrane attack complex (MAC), the cytotoxic component of the complement system. MAC causes lysis of foreign cells.

**Biologic activities:** Complement components have other immune functions that are mediated by complement receptors (CR) on various cells.

- CR1 (CD35) promotes phagocytosis and helps clear immune complexes.
- CR2 (CD21) regulates Ab production by B cells and is the Epstein-Barr virus receptor.
- CR3 (CD11b/CD18), CR4 (CD11c/CD18), and C1q receptors play a role in phagocytosis.
- C3a, C5a, and C4a (weakly) have anaphylatoxin activity: They cause mast cell degranulation, leading to increased vascular permeability and smooth muscle contraction.

[Fig. 125-2. Complement activation pathways.]
• C3b acts as an opsonin by coating microorganisms and thereby enhancing their phagocytosis.

• C3d enhances Ab production by B cells.

• C5a is a neutrophil chemoattractant; it regulates neutrophil and monocyte activities and may cause augmented adherence of cells, degranulation and release of intracellular enzymes from granulocytes, production of toxic oxygen metabolites, and initiation of other cellular metabolic events.

**Immunotherapeutics**

Immunotherapeutic agents use or modify immune mechanisms. Use of these agents is rapidly evolving; new classes, new agents, and new uses of current agents are certain to be developed. A number of different classes of immunotherapeutic agents have been developed (see Table 125-2):

- Monoclonal antibodies
- Fusion proteins
- Soluble cytokine receptors
- Recombinant cytokines
- Small-molecule mimetics

**Monoclonal antibodies:** Monoclonal antibodies (mAbs) are manufactured in vitro to recognize specific targeted Ags; they are used to treat solid and hematopoietic tumors and inflammatory disorders. The mAbs that are currently in clinical use include

- Murine
- Chimeric
- Humanized

**Murine mAbs** are produced by injecting a mouse with an Ag, harvesting its spleen to obtain plasma cells that are producing Ab specific to that Ag, fusing those cells with immortal mouse myeloma cells, growing these hybridoma cells (eg, in cell culture), and harvesting

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<th>Table 125-2. Some Immunotherapeutic Agents in Clinical Use*</th>
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| the Ab. Although mouse antibodies are similar to human antibodies, clinical use of murine mAbs is limited because they induce human anti-mouse Ab production, can cause immune complex serum sickness (a type III hypersensitivity reaction), and are rapidly cleared. An exception is muromonab-CD3 (OKT3), which effectively prevents acute rejection of solid organ transplants; it is typically given only once or twice to a patient receiving other immunosuppressants (see p. 1128).

To minimize the problems due to use of pure mouse Ab, researchers have used recombinant DNA techniques to create monoclonal Abs that are part human and part mouse. Depending on the proportion of the Ab molecule that is human, the resultant product is termed chimeric or humanized. In both cases, the process usually begins as above with production of mouse hybridoma cells that make Ab to the desired Ag. Then the DNA for some or all of the variable portion of the mouse Ab is merged with DNA for human immunoglobulin. The resultant DNA is placed in a mammalian cell culture, which then expresses the resultant gene, producing the desired Ab. If the mouse gene for the whole variable region is spliced next to the human constant region, the product is termed "chimeric"; if only parts of the mouse gene for the binding portion of the variable region are used, the product, termed "humanized," is even more human.
Chimeric mAbs activate Ag-presenting cells (APCs) and T cells more effectively than murine mAbs but can still induce production of human anti-chimeric Ab.

Humanized mAbs against various antigens (Ags) have been approved for the treatment of colorectal and breast cancer, leukemia, allergy, autoimmune disease, transplant rejection, and respiratory syncytial virus infection.

**Fusion proteins:** These hybrid proteins are created by linking together the gene sequences encoding all or part of 2 different proteins to generate a chimeric polypeptide that incorporates desirable attributes from the parent molecules (eg, a cell targeting component combined with a cell toxin). The circulating half-life of therapeutic proteins can also often be improved by fusing them to another protein that naturally has a longer serum half-life (eg, the Fc region of IgG).

**Soluble cytokine receptors:** Soluble versions of cytokine receptors are used as therapeutic reagents. They can block the action of cytokines by binding with them before they attach to their normal cell surface receptor.

Etanercept, a fusion protein, consists of 2 identical chains from the receptor for CD120b tumor necrosis factor (TNF)-α. This agent thus blocks TNF-α and is used to treat RA refractory to other treatments, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

Soluble IL receptors (eg, those for IL-1, IL-2, IL-4, IL-5, and IL-6) are being developed for treatment of inflammatory and allergic disorders and cancer.

**Recombinant cytokines:** Colony-stimulating factors (CSF), such as erythropoietin, granulocyte CSF (G-CSF), and granulocyte-macrophage CSF (GM-CSF), are used in patients undergoing chemotherapy or transplantation for hematologic disorders and cancers (see Table 125-2). Interferon-α (IFN-α) and IFN-γ are used to treat cancer, immunodeficiency disorders, and viral infections; IFN-β is used to treat relapsing multiple sclerosis. Many other cytokines are being studied.

Anakinra, used to treat RA, is a recombinant, slightly modified form of the naturally occurring IL-1R antagonist; this drug attaches to the IL-1 receptor and thus prevents binding of IL-1, but unlike IL-1, it does not activate the receptor.

Cells expressing cytokine receptors can be targeted by modified versions of the relevant cytokine (eg, denileukin diftitox, which is a fusion protein containing sequences from IL-2 and from diphtheria toxin). Denileukin is used in cutaneous T-cell lymphoma to target the toxin to cells expressing the CD25 component of the IL-2 receptor.

**Small-molecule mimetics:** Small linear peptides, cyclicized peptides, and small organic molecules have been developed as agonists or antagonists for various applications. Screening libraries of peptides and organic compounds can identify potential mimetics (eg, agonists for receptors for erythropoietin, thrombopoietin, and G-CSF).
Chapter 126. Immunodeficiency Disorders

Introduction

Immunodeficiency disorders increase susceptibility to infection. They may be secondary or primary; secondary is more common.

Secondary immunodeficiencies: Causes include systemic disorders (eg, diabetes, undernutrition, HIV infection) and immunosuppressive treatments (eg, chemotherapy, radiation therapy—see Table 126-1). Secondary immunodeficiency also occurs among critically ill, older, or hospitalized patients. Prolonged serious illness may impair immune responses; impairment is often reversible if the underlying illness resolves.

Immunodeficiency can result from loss of serum proteins (particularly IgG and albumin) through the kidneys in nephrotic syndrome, through skin in severe burns or dermatitis, or through the GI tract in enteropathy. Enteropathy may also lead to lymphocyte loss, resulting in lymphopenia. These disorders can mimic Band T-cell defects. Treatment focuses on the underlying disorder; a diet high in medium-chain triglycerides may decrease loss of lgs and lymphocytes from the GI tract and be remarkably beneficial.

Primary immunodeficiencies: These disorders are genetically determined; they may occur alone or as part of a syndrome. More than 200 have been described, and heterogeneity within each disorder may be considerable. The molecular basis for about 80% is known.

Table 126-1. Causes of Secondary Immunodeficiency

Table 126-2. Some Drugs that Cause Immunosuppression

Primary immunodeficiencies typically manifest during infancy and childhood as abnormally frequent (recurrent) or unusual infections. About 70% of patients are < 20 yr at onset; because transmission is often X-linked, 60% are male. Overall incidence of symptomatic disease is about 1/280 people.

Primary immunodeficiencies are classified by the main component of the immune system that is deficient, absent, or defective (see Table 126-3):

- B cells (or Ig)
- T cells
- Natural killer cells (very rare)
- Phagocytic cells
- Complement proteins

As more molecular defects are defined, classifying immunodeficiencies by their molecular defects will be more appropriate.

B-cell defects causing Ig and antibody deficiencies account for 50 to 60% of primary immunodeficiencies. Serum Ig and antibody titers decrease, predisposing to infections with encapsulated gram-positive bacteria. The most common B-cell disorder is selective IgA deficiency.

T-cell disorders account for about 5 to 10% of primary immunodeficiencies and predispose to infection by viruses, Pneumocystis jirovecii, fungi, other opportunistic organisms, and many common pathogens. T-cell disorders also cause Ig deficiencies because the B- and T-cell immune systems are interdependent. The most common T-cell disorders are DiGeorge syndrome, ZAP-70 deficiency, X-linked lymphoproliferative syndrome, and chronic mucocutaneous candidiasis (see p. 1102).
Combined B- and T-cell defects account for about 20% of primary immunodeficiencies. The most important form is severe combined immunodeficiency (SCID). In some forms of combined immunodeficiency (eg, purine nucleoside phosphorylase deficiency), Ig levels are normal or elevated, but because of inadequate T-cell function, antibody formation is impaired.

Natural killer cell defects are very rare and may predispose to viral infections and tumors.

Phagocytic cell defects account for 10 to 15% of primary immunodeficiencies; the ability of phagocytic cells (eg, monocytes, macrophages, granulocytes such as neutrophils and eosinophils) to kill pathogens is impaired. Cutaneous staphylococcal and gram-negative infections are characteristic. The most common phagocytic cell defects are chronic granulomatous disease, leukocyte adhesion deficiency, and Chediak-Higashi syndrome.

Complement deficiencies are rare (≤ 2%); they include isolated deficiencies of complement components or inhibitors and may be hereditary or acquired. Hereditary deficiencies are autosomal recessive except for deficiencies of C1 inhibitor, which is autosomal dominant, and properdin, which is X-linked. The deficiencies result in defective opsonization, phagocytosis, and lysis of pathogens and in defective clearance of antigen-antibody complexes. Recurrent infection, due to defective opsonization, and autoimmune disorders (eg, SLE, glomerulonephritis), due to defective clearance of antigen-antibody complexes (see Table 126-3), are the most serious consequences. One of these deficiencies causes hereditary angioedema.

Primary immunodeficiency syndromes are genetically determined immunodeficiencies with immune and nonimmune defects. Nonimmune manifestations are often more easily recognized than those of the immunodeficiency. Examples are ataxia-telangiectasia, cartilage-hair hypoplasia, DiGeorge syndrome, hyper-IgE syndrome, and Wiskott-Aldrich syndrome.

Geriatrics Essentials

Some decrease in immunity occurs with aging. For example, in the elderly, the thymus tends to produce fewer naive T cells; thus, fewer T cells are available to respond to new antigens. The number of T cells does not decrease (because of oligoclonality), but these cells can recognize only a limited number of antigens.

Signal transduction (transmission of antigen-binding signal across the cell membrane into the cell) is impaired, making T cells less likely to respond to antigens. Also, helper T cells may be less likely to signal B cells to produce antibodies.

The number of neutrophils does not decrease, but these cells become less effective in phagocytosis and microbicidal action.

Undernutrition, common among the elderly, impairs immune responses. Ca, zinc, and vitamin E are particularly important to immunity. Risk of Ca deficiency is increased in the elderly, partly because with aging, the intestine becomes less able to absorb Ca. Also, the elderly may not ingest enough Ca in their diet. Zinc deficiency is very common among the institutionalized elderly and homebound patients.

Approach to the Patient With Suspected Immunodeficiency

Immunodeficiency typically manifests as recurrent infections. However, more likely causes of recurrent infections in children are repeated exposures to infection at day care or school (infants and children may normally have up to 10 respiratory infections/yr), and more likely causes in children and adults are inadequate duration of antibiotic treatment, resistant organisms, and other disorders that predispose to infection (eg, congenital heart defects, allergic rhinitis, ureteral or urethral stenosis, immotile cilia syndrome, asthma, cystic fibrosis, severe dermatitis).
Immunodeficiency should be suspected when recurrent infections are the following:

- Severe
- Complicated
- In multiple locations
- Resistant to treatment
- Caused by unusual organisms

Initially, infections due to immunodeficiency are typically upper and lower respiratory tract infections (eg, sinusitis, bronchitis, pneumonia) and gastroenteritis, but they may be serious bacterial infections (eg, meningitis, sepsis).

Immunodeficiency should also be suspected in infants or young children with chronic diarrhea and failure to thrive, especially when the diarrhea is caused by unusual viruses (eg, adenovirus) or fungi (eg, Cryptosporidium sp). Other signs include skin lesions (eg, eczema, warts, abscesses, pyoderma, alopecia), oral or esophageal thrush, oral ulcers, and periodontitis.

Less common manifestations include severe viral infection with herpes simplex or varicella zoster virus and CNS problems (eg, chronic encephalitis, delayed development, seizure disorder). Frequent use of antibiotics may mask many of the common symptoms and signs. Immunodeficiency should be considered particularly in patients with infections and an autoimmune disorder (eg, hemolytic anemia, thrombocytopenia).

**Evaluation**

History and physical examination are helpful but must be supplemented by immune function testing. Prenatal testing is available for many disorders and is indicated if there is a family history of immunodeficiency and the mutation has been identified in family members.

**History:** Clinicians should determine whether patients have a history of risk factors for infection or of symptoms and risk factors for secondary immunodeficiency disorders. Family history is very important.

Age when recurrent infections began is important. Onset of infections before age 12 mo suggests combined B- and T-cell defects or a B-cell defect, which becomes evident when maternal antibodies are disappearing (at about age 6 mo). In general, the earlier the age at onset in children, the more severe the immunodeficiency. Often, certain other primary immunodeficiencies (eg, common variable immunodeficiency [CVID]) do not manifest until adulthood.

Certain infections suggest certain immunodeficiency disorders (see Table 126-4); however, no infection is specific to any one disorder, and certain common infections (eg, respiratory viral or bacterial infections) occur in many.

**Physical examination:** Patients with immunodeficiency may or may not appear chronically ill. Macular rashes, vesicles, pyoderma, eczema, petechiae, alopecia, or telangiectasia may be evident.

Cervical lymph nodes and adenoid and tonsillar tissue are typically very small or absent in X-linked agammaglobulinemia, X-linked hyper-IgM syndrome, severe combined immunodeficiency (SCID), and other T-cell immunodeficiencies despite a history of recurrent infections. In certain other immunodeficiencies (eg, chronic granulomatous disease), lymph nodes of the head and neck may be enlarged and suppurative.

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Typanic membranes may be scarred or perforated. The nostrils may be crusted, indicating purulent nasal discharge. Chronic cough is common, as are lung crackles, especially in adults with CVID. The liver
and spleen are often enlarged in patients with CVID or chronic granulomatous disease. Muscle mass and fat deposits of the buttocks are decreased. In infants, skin around the anus may break down because of chronic diarrhea. Neurologic examination may detect delayed developmental milestones or ataxia.

Other characteristic findings tentatively suggest a clinical diagnosis (see Table 126-5).

**Initial testing:** If a specific secondary immunodeficiency disorder is suspected clinically, testing should focus on that disorder (eg, diabetes, HIV infection, cystic fibrosis, primary ciliary dyskinesia).

Tests are needed to confirm a diagnosis of immunodeficiency (see Table 126-6). Initial screening tests should include

- CBC with manual differential
- Quantitative Ig measurements
- Antibody titers
- Skin testing for delayed hypersensitivity

[Table 126-4, Some Clues in Patient History to Type of Immunodeficiency]

If results are normal, immunodeficiency (especially Ig deficiency) can be excluded. If results are abnormal, further tests in specialized laboratories are needed to identify specific deficiencies. If chronic infections are objectively documented, initial and specific tests may be done simultaneously.

**CBC** can detect abnormalities in one or more cell types (eg, WBCs, platelets) characteristic of specific disorders. However, many abnormalities are transient manifestations of infection, drug use, or other factors; thus, abnormalities should be confirmed and followed.

- **Neutropenia** (absolute neutrophil count < 1200 cells/μL) may be congenital or cyclic or may occur in aplastic anemia.
- **Lymphopenia** (lymphocytes < 2000/μL at birth, < 4500/μL at age 9 mo, or < 1000/μL in older children or adults) suggests a T-cell disorder because 70% of circulating lymphocytes are T cells.
- **Leukocytosis** that persists between infections may occur in leukocyte adhesion deficiency.
- **Thrombocytopenia** in male infants suggests Wiskott-Aldrich syndrome.
- **Anemia** may suggest anemia of chronic disease or autoimmune hemolytic anemia, which may occur in CVID and other immunodeficiencies.

**Peripheral blood smear** should be examined for Howell-Jolly bodies and other unusual RBC forms, which suggest primary asplenia or impaired splenic function. Granulocytes may have morphologic abnormalities (eg, giant granules in Chediak-Higashi syndrome).

**Quantitative serum Ig levels** are measured. Low serum levels of IgG, IgM, or IgA suggest antibody deficiency, but results must be compared with those of age-matched controls. An IgG level < 200 mg/dL usually indicates significant antibody deficiency, although such levels may occur in protein-losing enteropathies or nephrotic syndrome.

- **IgM antibodies** can be assessed by measuring isohemagglutinin titers (anti-A, anti-B). All patients except infants < 6 mo and people with blood type AB have natural antibodies at
a titer of ≥ 1:8 (anti-A) or ≥ 1:4 (anti-B). Antibodies to blood groups A and B and to some bacterial polysaccharides are selectively deficient in certain disorders (eg, Wiskott-Aldrich syndrome, complete IgG2 deficiency).

- IgG antibody titers can be assessed in immunized patients by measuring antibody titers before and after administration of vaccine antigens (Haemophilus influenzae type B, tetanus, diphtheria, conjugated or nonconjugated pneumococcal, and meningococcal antigens); a less-than-twofold increase in titer at 2 to 3 wk suggests antibody deficiency regardless of Ig levels. Natural antibodies (eg, antistreptolysin O, heterophil antibodies) may also be measured.

**Table 126-6.** Initial and Additional Laboratory Tests for Immunodeficiency

With skin testing, most immunocompetent adults, infants, and children react to 0.1 mL of Candida albicans extract (1:100 for infants and 1:1000 for older children and adults) injected intradermally. Positive reactivity, defined as erythema and induration > 5 mm at 24, 48, and 72 h, excludes a T-cell disorder. Lack of response does not confirm immunodeficiency in patients with no previous exposure to Candida.

Chest x-ray may be useful in some infants; an absent thymic shadow suggests a T-cell disorder, especially if the x-ray is obtained before onset of infection or other stresses that may shrink the thymus. Lateral pharyngeal x-ray may show absence of adenoidal tissue.

**Additional testing:** If clinical findings or initial tests suggest a specific disorder of immune cell or complement function, other tests are indicated.

If patients have recurrent infections and lymphopenia, lymphocyte phenotyping using flow cytometry and monoclonal antibodies to T, B, and natural killer (NK) cells is indicated to check for lymphocyte deficiency. If T cells are low or absent, invitro mitogen stimulation studies are done to assess T-cell function. If MHC antigen deficiency is suspected, serologic (not molecular) HLA typing is indicated.

If phagocytic cell defects are suspected, a flow cytometric respiratory burst assay can detect whether O2 radicals are produced during phagocytosis; no production is characteristic of chronic granulomatous disease.

If the type or pattern of infections suggests complement deficiency, the serum dilution required to lyse 50% of antibody-coated RBCs (CH50) is measured. This test detects complement component deficiencies in the classical or alternative complement activation pathway but does not indicate which component is abnormal.

If examination or screening tests detect abnormalities suggesting lymphocyte or phagocytic cell defects, other tests can more precisely characterize specific disorders (see Table 126-7).

**Prenatal diagnosis:** An increasing number of primary immunodeficiency disorders can be diagnosed prenatally using chorionic villus sampling, cultured amniotic cells, or fetal blood sampling, but these tests are used only when a mutation in family members has already been identified (see p. 2602). X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, ataxia-telangiectasia, X-linked lymphoproliferative syndrome, all forms of SCID, and all forms of chronic granulomatous disease can be detected. Sex determination by ultrasonography can be used to exclude X-linked disorders.

**Prognosis**

Prognosis depends on the primary immunodeficiency disorder. Most patients with an Ig or a complement deficiency have a good prognosis with a near-normal life expectancy if they are diagnosed early, are treated appropriately, and have no coexisting chronic disorders (eg, pulmonary disorders such as bronchiectasis). Other immunodeficient patients (eg, those with a phagocytic cell defect or combined immunodeficiencies, such as Wiskott-Aldrich syndrome or ataxia-telangiectasia) have a guarded prognosis; most require intensive and frequent treatment. Some immunodeficient patients (eg, those with SCID) die during...
infancy unless immunity is provided through transplantation. All forms of SCID could be diagnosed at birth if a WBC count and manual differential of cord or peripheral blood were routinely done in neonates. Suspicion for SCID, a true pediatric emergency, must be high because prompt diagnosis is essential for survival. If done before patients reach age 3 mo, transplantation of bone marrow or stem cells from a matched or half-matched (haploidentical) relative is lifesaving in 95%.

**Treatment**

- Vaccines and avoidance of exposure to infection
- Antibiotics and sometimes surgery
- Replacement of missing immune components

Treatment generally involves preventing infection, managing acute infection, and replacing missing immune components when possible.

**Infection prevention:** Infection can be prevented by advising patients to avoid environmental exposures and giving live-virus vaccines (varicella, rotavirus, measles, mumps, rubella). Patients at risk of serious infections (eg, those with SCID, chronic granulomatous disease, Wiskott-Aldrich syndrome, or asplenia) or a specific infection (eg, with *Pneumocystis jirovecii* in patients with T-cell disorders) can be given prophylactic antibiotics (eg, 5 mg/kg trimethoprim/sulfamethoxazole po bid).

To prevent graft-vs-host disease after transfusions, clinicians should use blood products from cytomegalovirus-negative donors; the products should be filtered to remove WBCs and irradiated (15 to 30 Gy).

**Management of acute infection:** After appropriate cultures are obtained, antibiotics that target likely causes should be given promptly. Sometimes surgery (eg, to drain abscesses) is needed. Usually, self-limited viral infections cause severe persistent disease in immunocompromised patients. Antivirals (eg, amantadine, rimantadine, oseltamivir, or zanamivir for influenza; acyclovir for herpes simplex and varicella-zoster infections; ribavirin for respiratory syncytial virus or parainfluenza 3 infections) may be lifesaving.

**Replacement of missing immune components:** Such replacement helps prevent infection. Therapies used in more than one primary immunodeficiency disorder include the following:

- **IV immune globulin** (IVIG) is effective replacement therapy in most forms of antibody deficiency. The usual dose is 400 mg/kg once/mo; treatment is begun at a low infusion rate. Some patients need higher or more frequent doses. IVIG 800 mg/kg once/mo helps some antibody-deficient patients who do not respond well to conventional doses, particularly those with a chronic lung disorder. High-dose IVIG aims to keep IgG trough levels in the normal range (> 500 mg/dL). IVIG may also be given by slow sc infusions at weekly intervals.

- **Hematopoietic stem cell transplantation** using bone marrow, cord blood, or adult peripheral blood stem cells is effective for lethal T-cell and other immunodeficiencies. Pretransplantation chemotherapy is unnecessary in patients without T cells (eg, those with SCID). However, patients with intact T-cell function or partial T-cell deficiencies (eg, Wiskott-Aldrich syndrome, combined immunodeficiency with inadequate but not absent T-cell function) require pretransplantation chemotherapy to ensure graft acceptance. When a matched sibling donor is unavailable, haploidentical bone marrow from a parent can be used. In such cases, mature T cells that cause graft-vs-host disease must be rigorously depleted from parental marrow before it is given. Umbilical cord blood from an HLA-matched sibling can also be used as a source of stem cells. In some cases, bone marrow or umbilical cord blood from a matched unrelated donor can be used, but after transplantation, immunosuppressants are required to prevent graft-vs-host disease, and their use delays restoration of immunity.
Retroviral vector gene therapy has been successful in a few patients with X-linked and ADA-deficient SCID, but this treatment is not widely used because some patients with X-linked SCID developed leukemia.

**Ataxia-Telangiectasia**

Ataxia-telangiectasia results from a T-cell defect and causes progressive cerebellar ataxia, oculocutaneous telangiectasias, and recurrent sinopulmonary infections.

Inheritance is autosomal-recessive. Ataxia-telangiectasia is caused by mutations in the gene that encodes ataxia-telangiectasia-mutated (ATM) protein. ATM protein may be important in mitogenic signal transduction, meiotic recombination, and cell cycle control.

Age at onset of neurologic symptoms and evidence of immunodeficiency vary. Ataxia usually develops when children begin to walk. Progression of neurologic symptoms leads to severe disability. Speech becomes slurred, choreoathetoid movements and nystagmus develop, and muscle weakness usually progresses to muscle atrophy. Telangiectasias may not appear until age 4 to 6 yr; they are most prominent on the bulbar conjunctivae, ears, antecubital and popliteal fossae, and sides of the neck. Recurrent sinopulmonary infections lead to recurrent pneumonia, bronchiectasis, and chronic restrictive pulmonary disease. Patients often lack IgA and IgE and have a progressive T-cell defect. Certain endocrine abnormalities (eg, gonadal dysgenesis, testicular atrophy, diabetes mellitus) may occur.

Frequency of cancer (especially leukemia, brain tumors, and gastric cancer) is high, and frequency of chromosome breaks, consistent with a defect in DNA repair, is increased. Serum α₁-fetoprotein is usually elevated.

**Diagnosis**

Clinical findings of cerebellar ataxia (particularly when telangiectasias are present), low levels of IgA, and high levels of serum α₁-fetoprotein suggest the diagnosis. Diagnosis is confirmed by identifying mutations on both alleles of the gene for ATM protein.

**Treatment**

Treatment with antibiotics or IV immune globulin may help, but no treatment is effective for the CNS abnormalities. Thus, neurologic deterioration progresses, causing death, usually by age 30.

**Chediak-Higashi Syndrome**

Chediak-Higashi syndrome is characterized by impaired lysis of phagocytized bacteria, resulting in recurrent bacterial respiratory and other infections and oculocutaneous albinism.

Chediak-Higashi syndrome is rare. Inheritance is autosomal recessive. The syndrome is caused by a mutation in a gene that regulates intracellular protein trafficking. Giant lysosomal granules develop in neutrophils and other cells (eg, melanocytes, neural Schwann cells). The abnormal lysosomes cannot fuse with phagosomes, so ingested bacteria cannot be lysed normally.

Clinical findings include oculocutaneous albinism and susceptibility to recurrent respiratory and other infections. In about 85% of patients, an accelerated phase occurs, causing fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, bleeding diathesis, and neurologic changes. Once the accelerated phase occurs, the syndrome is usually fatal within 30 mo.

A peripheral blood smear is examined for giant granules in neutrophils and other cells; a bone marrow smear is examined for giant inclusion bodies in leukocyte precursor cells.

Transplantation of unfractionated HLA-identical bone marrow after pretransplantation cytoreductive chemotherapy may be curative.
Chronic Granulomatous Disease

Chronic granulomatous disease is characterized by WBCs that cannot produce activated O\textsubscript{2} compounds and by defects in phagocytic cell microbicidal function. Manifestations include recurrent infections; multiple granulomatous lesions of the lungs, liver, lymph nodes, and GI and GU tract; abscesses; lymphadenitis; hypergammaglobulinemia; elevated ESR; and anemia. Diagnosis is by assessing O\textsubscript{2} radical production in WBCs via a flow cytometric respiratory burst assay. Treatment is with antibiotics, antifungal drugs, and interferon-\gamma; granulocyte transfusions may be needed.

More than 50% of cases of chronic granulomatous disease (CGD) are inherited as an X-linked recessive trait and thus occur only in males; in the rest, inheritance is autosomal recessive. In CGD, WBCs do not produce hydrogen peroxide, superoxide, and other activated O\textsubscript{2} compounds because nicotinamide adenine dinucleotide phosphate oxidase activity is deficient. Phagocytic cell microbicidal function is defective; thus, bacteria and fungi are not killed despite normal phagocytosis.

Symptoms and Signs

CGD usually begins with recurrent abscesses during early childhood, but in a few patients, onset is delayed until the early teens. Typical pathogens are catalase-producing organisms (eg, *Staphylococcus aureus; Escherichia coli; Serratia, Klebsiella, and Pseudomonas* sp; fungi). *Aspergillus* infections are the leading cause of death.

Multiple granulomatous lesions occur in the lungs, liver, lymph nodes, and GI and GU tract (causing obstruction). Suppurative lymphadenitis, hepatosplenomegaly, pneumonia, and hematologic evidence of chronic infection are common. Skin, lymph node, lung, liver, and perianal abscesses; stomatitis; and osteomyelitis also occur. Growth may be delayed.

Diagnosis

Diagnosis is by a flow cytometric respiratory burst assay to detect O\textsubscript{2} radical production. The test can also identify female carriers of the X-linked form. Hypergammaglobulinemia and anemia can occur; ESR is elevated.

Treatment

- Prophylactic antibiotics, sometimes including antifungals
- Sometimes interferon (IFN)-\gamma
- For severe infections, granulocyte transfusions or bone marrow transplantation

Treatment is continuous prophylactic antibiotics, particularly trimethoprim/sulfamethoxazole 160/800 mg po bid alone or with cephalexin 500 mg po q 8 h. Oral antifungals are given as primary prophylaxis or are added if fungal infections occur even once; most useful are itraconazole po q 12 h (100 mg for patients < 13 yr; 200 mg for those ≥ 13 yr or weighing > 50 kg), voriconazole po q 12 h (100 mg for those weighing < 40 kg; 200 mg for those weighing ≥ 40 kg), or posaconazole (400 mg bid). IFN-\gamma may reduce severity and frequency of infections. Usual dose is 50 μg/m\textsuperscript{2} sc 3 times/wk.

Granulocyte transfusions can be lifesaving when infections are severe. When preceded by pretransplantation chemotherapy, HLA-identical sibling bone marrow transplantation may be successful.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is persistent or recurrent candidal infection due to T-cell defects.
Inheritance is autosomal dominant or recessive. Patients have cutaneous anergy to *Candida*, absent proliferative responses to *Candida* antigen (but normal proliferative responses to mitogens), and intact antibody response to *Candida* and other antigens. Candidiasis recurs or persists, usually beginning during infancy but sometimes during early adulthood. Life span is not affected.

Patients with the recessive form (autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy) develop endocrine disorders (eg, hypoparathyroidism, adrenal insufficiency, hypogonadism, thyroid disease, diabetes), and hepatitis.

Thrush is common, as are infections of the scalp, skin, nails, and GI and vaginal mucosa. Severity varies. Nails may be thickened, cracked, and discolored, with edema and erythema of the surrounding periungual tissue, resembling clubbing. Skin lesions are crusted, pustular, erythematous, and hyperkeratotic. Scalp lesions may result in scarring alopecia. Infants often present with refractory thrush, candidal diaper dermatitis, or both.

**Diagnosis**

Diagnosis is based on the presence of recurrent candidal skin or mucosal lesions when no other known causes of candidal infection (eg, diabetes, antibiotic use) are present. Candidal lesions are confirmed by other tests (eg, potassium hydroxide wet mount of scrapings).

**Treatment**

- Antifungal drugs

Usually, the infections can be controlled with a topical antifungal. However, long-term treatment with a systemic antifungal drug (eg, amphotericin B, fluconazole, ketoconazole) may be needed. Topical antifungals are usually ineffective. Sometimes an immunomodulator (eg, transfer factor) is also used.

**Common Variable Immunodeficiency**

Common variable immunodeficiency (acquired or adult-onset hypogammaglobulinemia) is characterized by low immunoglobulin (Ig) levels with phenotypically normal B cells that can proliferate but do not develop into Ig-producing cells.

Common variable immunodeficiency (CVID) includes several different molecular defects, but in most patients, the molecular defect is unknown. CVID is clinically similar to X-linked agammaglobulinemia in the types of infections that develop, but onset tends to be later, even in adulthood. T-cell immunity may be impaired in some patients. Autoimmune disorders (eg, SLE, Addison's disease, thyroiditis, RA, alopecia areata, autoimmune thrombocytopenia, autoimmune hemolytic or pernicious anemia) can occur, as can malabsorption, nodular lymphoid hyperplasia of the GI tract, lymphoid interstitial pneumonia, splenomegaly, and bronchiectasis. Gastric carcinoma and lymphoma occur in 10% of patients.

**Diagnosis**

- Measurement of serum Ig and antibody titers
- Flow cytometry
- Serum protein electrophoresis

Diagnosis is suggested by familial clustering of autoimmune disorders and is confirmed by measuring serum Ig and antibody titers to protein and polysaccharide vaccine antigens. If either measurement is low, B-cell quantification by flow cytometry is indicated to distinguish CVID from X-linked agammaglobulinemia, multiple myeloma, and chronic lymphocytic leukemia. Serum protein electrophoresis is indicated to screen for monoclonal gammopathies (eg, myeloma), which may be associated with reduced levels of other Ig isotypes. If patients are treated with IV immune globulin (IVIG) before testing, serologic tests have no...
value because the antibodies are from the IVIG.

**Treatment**

Treatment consists of IVIG 400 mg/kg once/mo and antibiotics as needed to treat infection. Rituximab or a corticosteroid may be required to treat autoimmune disorders.

**DiGeorge Syndrome**

**DiGeorge syndrome is thymic and parathyroid hypoplasia or aplasia leading to T-cell immunodeficiency and hypoparathyroidism.**

DiGeorge syndrome results from gene deletions in the DiGeorge chromosomal region at 22q11, mutations in genes at chromosome 10p13, and mutations in other unknown genes, which cause dysembryogenesis of structures that develop from pharyngeal pouches during the 8th wk of gestation. Most cases are sporadic; boys and girls are equally affected. Di-George syndrome may be partial (some T-cell function exists) or complete (T-cell function is absent).

Infants have low-set ears, midline facial clefts, a small receding mandible, hypertelorism, a shortened philtrum, and a congenital heart disorder. They also have thymic and parathyroid hypoplasia or aplasia, causing T-cell deficiency and hypoparathyroidism. Recurrent infections begin soon after birth, but the degree of immunodeficiency varies considerably, and T-cell function may improve spontaneously. Hypocalcemic tetany appears within 24 to 48 h of birth.

Prognosis often depends on severity of the heart disorder.

**Diagnosis**

- Immune function assessment
- Parathyroid function assessment
- Chromosome analysis

Diagnosis is based on clinical findings. An absolute lymphocyte count is done, followed by B- and T-cell counts if leukopenia is detected; blood tests to evaluate T-cell and parathyroid function are done. A lateral chest x-ray may help evaluate thymic shadow. Fluorescent in situ hybridization (FISH) testing can detect the chromosomal deletion in the 22q11 region; standard chromosomal tests to check for other abnormalities may also be done. Cardiac catheterization may be needed to identify heart defects.

**Treatment**

In partial DiGeorge syndrome, hypoparathyroidism is treated with Ca and vitamin D supplementation; long-term survival is not affected. Complete DiGeorge syndrome is fatal without treatment, which is transplantation of cultured thymus tissue.

**Hyper-IgE Syndrome**

**Hyper-IgE (Buckley) syndrome is combined Band T-cell immunodeficiency characterized by recurrent staphylococcal abscesses of the skin, lungs, joints, and viscera.**

Inheritance is autosomal dominant with incomplete penetrance; it is caused by mutations in the STAT3 (signal transducer and activator of transcription 3) gene.

Hyper-IgE syndrome starts during infancy. It typically causes recurrent staphylococcal abscesses of the skin, lungs, joints, and viscera with pulmonary pneumatoceles and a pruritic eosinophilic dermatitis. Patients have coarse facial features, delayed shedding of baby teeth, osteopenia, and recurrent fractures. All have tissue and blood eosinophilia and very high IgE levels (> 1000 IU/mL [> 2400 μg/L]).
Diagnosis is suspected based on symptoms and confirmed by measurement of serum IgE levels. Genetic testing can identify the abnormal gene.

Treatment consists of lifelong continuous antistaphylococcal antibiotics (eg, dicloxacillin, cephalexin).

**Hyper-IgM Syndrome**

Hyper-IgM syndrome is an Ig deficiency characterized by normal or elevated serum IgM levels and decreased levels or absence of other serum Igs, resulting in susceptibility to bacterial infections.

Hyper-IgM syndrome may be X-linked or autosomal. Most cases are caused by mutations in a gene that is located on the X chromosome; this gene encodes a protein (CD154, or CD40 ligand) on the surfaces of activated helper T cells. In the presence of cytokines, normal CD40 ligand interacts with B cells and thus signals them to switch from producing IgM to producing IgA, IgG, or IgE.

In X-linked hyper-IgM syndrome, T cells lack functional CD40 ligand and cannot signal B cells to switch. Thus, B cells produce only IgM; IgM levels may be normal or elevated. Patients with this form may have severe neutropenia and often present during infancy with *Pneumocystis jirovecii* pneumonia. Otherwise, clinical presentation is similar to that of X-linked agammaglobulinemia and includes recurrent pyogenic sinopulmonary infections during the first 2 yr of life. Susceptibility to *Cryptosporidium* infections may be increased. Lymphoid tissue is very small because germinal centers are missing. Many patients die before puberty, and those who live longer often develop cirrhosis or B-cell lymphomas.

At least 4 autosomal recessive forms involve a B-cell defect. In 2 of these forms (deficiency of activation-induced cytidine deaminase or uracil DNA glycosylase [UNG]), serum IgM levels are much higher than in the X-linked form; lymphoid hyperplasia (including lymphadenopathy, splenomegaly, and tonsillar hypertrophy) is present, and autoimmune disorders may be present.

**Diagnosis**

Diagnosis is clinical and by detecting normal or elevated serum IgM levels and low levels or absence of other Igs.

**Treatment**

Treatment is IV immune globulin 400 mg/kg once/mo. For the X-linked form, granulocyte colony-stimulating factor is also given as needed for neutropenia, and because prognosis is poor, bone marrow transplantation is preferred if an HLA-identical sibling donor is available.

**IgA Deficiency**

IgA deficiency is an IgA level < 10 mg/dL with normal IgG and IgM levels. It is the most common primary immunodeficiency. Many patients are asymptomatic, but some develop recurrent infections and autoimmune disorders. Some patients develop common variable immunodeficiency, and some remit spontaneously. Diagnosis is by measuring serum Igs. Treatment is avoidance of blood products that contain IgA; antibiotics are given as needed.

IgA deficiency affects up to 1/333 people. Transmission is autosomal dominant with incomplete penetrance. IgA deficiency is commonly associated with certain HLA haplotypes, and rare alleles or deletions of genes in the major histocompatibility complex (MHC) class III region (see p. 1085) are common. IgA deficiency also occurs in siblings of children with common variable immunodeficiency (CVID) and evolves into CVID in some patients. Use of drugs such as phenytoin, sulfasalazine, colloidal gold and D-penicillamine may lead to IgA deficiency in genetically susceptible patients.

**Symptoms and Signs**
Many patients are asymptomatic; others have recurrent sinopulmonary infections, diarrhea, allergies, or autoimmune disorders (eg, celiac or inflammatory bowel disease, SLE, chronic active hepatitis). Anti-IgA antibodies may develop after exposure to IgA in transfusions; anaphylactic reactions to IV immune globulin (IVIG) and other blood products that contain IgA may occur.

**Diagnosis**

- Clinical evaluation
- Measurement of serum Ig levels and antibody titers

Diagnosis is suspected in patients who have recurrent infections (including giardiasis); anaphylactic transfusion reactions; or a family history of CVID, IgA deficiency, or autoimmune disorders or who are taking drugs that lead to IgA deficiency. Diagnosis is confirmed by a serum IgA level < 10 mg/dL with normal IgG and IgM levels and normal antibody titers in response to vaccine antigens.

**Prognosis**

A few IgA-deficient patients develop CVID over time; others improve spontaneously. Prognosis is worse if an autoimmune disorder develops.

**Treatment**

- Avoidance of blood products that contain IgA
- Antibiotics as needed

Treatment is avoidance of blood products that contain IgA because even trace amounts can elicit an anti-IgA-mediated anaphylactic reaction. If RBC transfusion is needed, only washed RBCs or frozen blood can be used.

Antibiotics are given as needed for bacterial infections of the ears, sinuses, lungs, or GI or GU tract.

IVIG is contraindicated because many patients have antibodies to IgA and because IVIG is > 99% IgG, which patients do not need. Patients are advised to wear an identification bracelet to prevent inadvertent plasma or IVIG administration, which could lead to anaphylaxis.

**Leukocyte Adhesion Deficiency**

**Leukocyte adhesion deficiency results from an adhesion molecule defect that causes granulocyte and lymphocyte dysfunction and recurrent soft-tissue infections.**

Inheritance is autosomal recessive. Leukocyte adhesion deficiency is caused by deficiency of adhesive glycoproteins on the surfaces of WBCs; these glycoproteins facilitate cellular interactions, cell attachment to blood vessel walls, cell movement, and interaction with complement fragments. Deficiencies impair the ability of granulocytes (and lymphocytes) to migrate out of the intravascular compartment, to engage in cytotoxic reactions, and to phagocytose bacteria. Severity of disease correlates with degree of deficiency.

Severely affected infants have recurrent or progressive necrotic soft-tissue infections with staphylococcal and gram-negative bacteria, periodontitis, poor wound healing, leukocytosis, and delayed (> 3 wk) umbilical cord detachment. WBC counts remain high even between infections. Infections become increasingly difficult to control.

**Diagnosis**

Diagnosis is by detecting absence or severe deficiency of adhesive glycoproteins on the surface of WBCs using monoclonal antibodies (eg, anti-CD11, anti-CD18) and flow cytometry. Leukocytosis on CBC is common but nonspecific.
Treatment

Most patients die by age 5 unless treated successfully with bone marrow transplantation, but moderately affected patients survive into young adulthood.

Treatment is with antibiotics, often given continuously. Granulocyte transfusions can also help. Bone marrow transplantation is the only effective treatment and can be curative.

Severe Combined Immunodeficiency

Severe combined immunodeficiency is characterized by absent T cells and a low, high, or normal number of B cells and natural killer cells. Most infants develop opportunistic infections within the first 3 mo of life. Diagnosis is by detecting lymphopenia, absence or a very low number of T cells, and impaired lymphocyte proliferative responses to mitogens. Patients must be kept in a protected environment; definitive treatment is bone marrow stem cell transplantation.

Severe combined immunodeficiency (SCID) is caused by mutations in any one of at least 12 different genes. All but one type are autosomal recessive defects, so for the infant to be affected with SCID, the same gene must be mutated on both chromosomes. There are 4 different abnormal lymphocyte phenotypes. In all forms of SCID, T cells are absent (T-); the number of B cells and natural killer (NK) cells may be low or none (B-; NK-) or high or normal (B+; NK+), depending on the form of SCID. However, B cells, even when normal in number, cannot function because T cells are absent.

The most common form is X-linked. It affects the IL-2 receptor γ chain (a component of at least 6 cytokine receptors) and thus causes severe disease; phenotype is T- B+ NK-. The 2nd most common form results from adenosine deaminase (ADA) deficiency, which leads to apoptosis of precursors for B, T, and NK cells; phenotype is T- B- NK-. The next most common form results from IL-7 receptor α-chain deficiency; phenotype is T- B+ NK+.

Symptoms and Signs

By age 6 mo, most infants with SCID develop candidiasis, persistent viral infections, *Pneumocystis jirovecii* pneumonia, and diarrhea, leading to failure to thrive. Some have graft-vs-host disease due to maternal lymphocytes or blood transfusions. Other infants present at age 6 to 12 mo. Exfoliative dermatitis may develop as part of Omenn's syndrome, one form of SCID. ADA deficiency may cause bone abnormalities. The thymus is extremely small, and lymphoid tissue may be decreased or absent.

All forms of SCID are fatal during infancy unless they are diagnosed and treated early.

Diagnosis

- History of persistent infections
- CBC with differential
- Mitogen and vaccine antigen stimulation assays
- Tests to determine type of SCID

SCID is suspected in infants with a history of persistent infections. CBC, including absolute WBC count and differential, is done; Ig levels are measured. Responses to mitogens and to standard vaccine antigens are determined to evaluate WBC and antibody function. Chest x-rays to evaluate the thymus are not necessary for diagnosis.

The disorder is diagnosed in patients with the following:
• Lymphopenia

• A low number of or no T cells

• Absent lymphocyte proliferative responses to mitogens

Other tests are done to determine the type of SCID. ADA and purine nucleoside phosphorylase levels in WBCs, RBCs, and fibroblasts are measured. X-inactivation tests may be done to determine whether SCID is X-linked.

**Treatment**

• IV immune globulin (IVIG)

• Antibiotics

• Bone marrow stem cell transplantation

• Sometimes ADA injections or gene therapy

Patients must be kept in reverse isolation. Treatment with IVIG and antibiotics, including *P. jirovecii* prophylaxis, is helpful but not curative.

In 90 to 100% of infants with SCID or its variants, bone marrow stem cell transplantation from an HLA-identical, mixed leukocyte culture-matched sibling restores immunity. When an HLA-identical sibling is not available, haploidentical bone marrow from a parent that is rigorously depleted of T cells can be used. If SCID is diagnosed by age 3 mo, the survival rate after transplantation with either type of bone marrow is 96%. Pretransplantation chemotherapy is unnecessary because patients do not have T cells and therefore cannot reject a graft.

Patients with ADA deficiency who do not receive a bone marrow graft may be treated with injections of polyethylene glycol-modified bovine ADA once or twice/wk. Gene therapy has been successful in X-linked SCID but has caused T-cell leukemias, precluding its use. Gene therapy has also been successful in ADA-deficient SCID, and no posttreatment leukemias or lymphomas have been reported.

**Transient Hypogammaglobulinemia of Infancy**

Transient hypogammaglobulinemia of infancy is a temporary decrease in serum IgG and sometimes IgA and other Ig isotypes to levels below age-appropriate normal values.

In transient hypogammaglobulinemia of infancy, IgG levels continue to be low after the physiologic fall in maternal IgG at about age 3 to 6 mo. The condition rarely leads to significant infections and is not thought to be a true immunodeficiency.

Diagnosis is based on low serum Ig levels and tests showing that antibody production in response to vaccine antigens (eg, tetanus, diphtheria) is normal. Thus, this condition can be distinguished from permanent forms of hypogammaglobulinemia, in which specific antibodies to vaccine antigens are not produced.

IV immunoglobulin is unnecessary. This condition may persist for months to a few years but usually resolves.

**Wiskott-Aldrich Syndrome**

Wiskott-Aldrich syndrome results from a combined B- and T-cell defect and is characterized by recurrent infection, atopic dermatitis, and thrombocytopenia.

Inheritance is X-linked recessive. Wiskott-Aldrich syndrome is caused by mutations in the gene that
encodes the Wiskott-Aldrich syndrome protein (WASP), a cytoplasmic protein necessary for normal B- and T-cell signaling. Because B- and T-cell functions are impaired, infections with pyogenic bacteria and opportunistic organisms, particularly viruses and *Pneumocystis jiroveci*, develop.

The first manifestations are often hemorrhagic (usually bloody diarrhea), followed by recurrent respiratory infections, eczema, and thrombocytopenia. Cancers, especially Epstein-Barr virus lymphomas and acute lymphoblastic leukemia, develop in about 10% of patients > 10 yr.

**Diagnosis**

Diagnosis is based on tests showing impaired antibody responses to polysaccharide antigens, cutaneous anergy, partial T-cell immunodeficiency, elevated IgE and IgA levels, low IgM levels, and low or normal IgG levels. Antibodies to polysaccharide antigens (eg, blood group antigens A and B) may be selectively deficient. Platelets are small and defective, and splenic destruction of platelets is increased, causing thrombocytopenia. Mutation analysis may be used.

**Treatment**

Treatment is splenectomy, continuous antibiotics, IV immunoglobulin, and bone marrow transplantation. Without transplantation, most patients die by age 15; however, some patients survive into adulthood.

**X-linked Agammaglobulinemia**

*(Bruton’s Disease)*

**X-linked agammaglobulinemia is characterized by low levels or absence of lgs and absent B cells, leading to recurrent infections with encapsulated bacteria.**

X-linked agammaglobulinemia results from mutations in a gene on the X chromosome that encodes Bruton tyrosine kinase (Btk). Btk is essential for B-cell development and maturation; without it, there are no B cells and hence no antibodies. As a result, male infants have very small tonsils and do not develop lymph nodes; they have recurrent pyogenic lung, sinus, and skin infections with encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*). Patients are also susceptible to persistent CNS infections resulting from live-attenuated oral polio vaccine and from echoviruses and coxsackieviruses; these infections can also manifest as progressive dermatomyositis with or without encephalitis.

With early diagnosis and appropriate treatment, prognosis is good unless CNS viral infections develop.

**Diagnosis**

- Low Ig levels and absent B cells

Diagnosis is by detecting low IgG levels (< 100 mg/dL) and absent B cells (< 1% CD19+ cells via flow cytometry). Transient neutropenia may also be present. If the mutation has been identified in family members, mutational analysis of chorionic villus, amniocentesis, or percutaneous umbilical cord blood samples can provide prenatal diagnosis.

**Treatment**

Treatment is IV immune globulin 400 mg/kg once/mo. Prompt use of adequate antibiotics for each infection is crucial; bronchiectasis requires continuous rotation of antibiotics.

**X-linked Lymphoproliferative Syndrome**

*(Duncan’s Syndrome)*

**X-linked lymphoproliferative syndrome results from a T-cell and natural killer cell defect and is**
characterized by an abnormal response to Epstein-Barr virus infection, leading to liver failure, immunodeficiency, lymphoma, fatal lymphoproliferative disease, or bone marrow aplasia.

X-linked lymphoproliferative syndrome is caused by mutations in a gene on the X chromosome that encodes a T and natural killer (NK) cell-specific protein called SAP. Without SAP, lymphocytes proliferate unchecked in response to Epstein-Barr virus (EBV) infection, and NK cells do not function.

The syndrome is usually asymptomatic until EBV infection develops. Then, most patients develop fulminating or fatal infectious mononucleosis with liver failure (caused by cytotoxic T cells that react to EBV-infected B or other tissue cells); survivors of initial infection develop B-cell lymphomas, aplastic anemia, hypogammaglobulinemia (resembling that in common variable immunodeficiency), or a combination.

**Diagnosis**

Diagnostic findings in patients that survive initial EBV infection include hypogammaglobulinemia, decreased antibody responses to antigens (particularly to EBV nuclear antigen), impaired T-cell proliferative responses to mitogens, decreased NK-cell function, and an inverted CD4:CD8 ratio. Genetic diagnosis by mutation analysis is possible before EBV infection and symptoms develop.

**Treatment**

About 75% of patients die by age 10, and all die by age 40 unless bone marrow transplantation is done. Transplantation is curative if done before EBV infection or other disorders become irreversible, resulting in death.

**ZAP-70 Deficiency**

ZAP-70 (ζ-associated protein 70) deficiency is impaired T-cell activation caused by a signaling defect.

ZAP-70 is important in T-cell signaling and in T-cell selection in the thymus. ZAP-70 deficiency causes T-cell activation defects.

Patients who have ZAP-70 deficiency present during infancy or early childhood with recurrent infections similar to those in severe combined immunodeficiency (SCID); however, they live longer, and the deficiency may not be diagnosed until they are several years old. Patients have normal, low, or elevated serum Ig levels and normal or elevated numbers of circulating CD4 T cells but essentially no CD8 T cells. Their CD4 T cells do not respond to mitogens or allogeneic cells in vitro and do not produce cytotoxic T cells. In contrast, natural killer cell activity is normal.

Diagnosis is similar to that for SCID.

The disorder is fatal unless treated by bone marrow transplantation.
Chapter 127. Allergic and Other Hypersensitivity Disorders

**Introduction**

Allergic and other hypersensitivity disorders are exaggerated or inappropriate immune reactions.

**Classification**

The Gell and Coombs classification delineates 4 types of hypersensitivity reaction. Hypersensitivity disorders often involve more than 1 type.

**Type I:** Type I reactions (immediate hypersensitivity) are IgE-mediated. Antigen binds to IgE (which is bound to tissue mast cells and blood basophils), triggering release of preformed mediators (eg, histamine, proteases, chemotactic factors) and synthesis of other mediators (eg, prostaglandins, leukotrienes, platelet-activating factor, cytokines). These mediators cause vasodilation, increased capillary permeability, mucus hypersecretion, smooth muscle spasm, and tissue infiltration with eosinophils, type 2 helper T cells (T\(_{H2}\)), and other inflammatory cells. Type I reactions underlie atopic disorders (eg, allergic asthma, rhinitis, conjunctivitis) and latex and some food allergies.

**Type II:** Type II reactions result when antibody binds to cellular or tissue antigens or to a molecule coupled to a cell or tissue. The antigen-antibody complex activates cells that participate in antibody-dependent cell-mediated cytotoxicity (eg, NK cells, eosinophils, macrophages), complement, or both. The result is cell and tissue damage. Disorders involving type II reactions include hyperacute graft rejection of an organ transplant, Coombs'-positive hemolytic anemias, Hashimoto's thyroiditis, and antiglomerular basement membrane disease (eg, Goodpasture's syndrome).

**Type III:** Type III reactions cause acute inflammation in response to circulating antigen-antibody immune complexes deposited in vessels or tissue. These complexes can activate the complement system or bind to and activate certain immune cells, resulting in release of inflammatory mediators. Consequences of immune complex formation depend in part on the relative proportions of antigen and antibody in the immune complex. Early, there is excess antigen with small antigen-antibody complexes, which do not activate complement. Later, when antigen and antibody are more balanced, immune complexes are larger and tend to be deposited in various tissues (glomeruli, blood vessels), causing systemic reactions. The isotype of induced antibodies changes, and glycosylation of the complex's components contributes to the clinical response. Type III disorders include serum sickness, SLE, RA, leukocytoclastic vasculitis, cryoglobulinemia, hypersensitivity pneumonitis, bronchopulmonary aspergillosis, and several types of glomerulonephritis.

**Type IV:** Type IV reactions (delayed hypersensitivity) are T cell-mediated. There are 4 subtypes based on the T-cell subpopulation involved:

- IVa: Type 1 helper T cells
- IVb: Type 2 helper T cells
- IVc: Cytotoxic T cells
- IVd: IL-8-secreting T cells

These cells, sensitized after contact with a specific antigen, are activated by reexposure to the antigen; they damage tissue by direct toxic effects or through release of cytokines, which activate eosinophils, monocytes and macrophages, neutrophils, or killer cells depending on type. Disorders involving type IV reactions include contact dermatitis (eg, poison ivy), hypersensitivity pneumonitis, allograft rejection, TB, and many forms of drug hypersensitivity.

**Autoimmune disorders:** Immune system reactions directed against intrinsic body components can lead to autoimmune disease (see...
Angioedema

Angioedema is edema of the deep dermis and subcutaneous tissues. It is caused by exposure to drug, venom, dietary, or extracted allergens. The main symptom is diffuse, painful swelling that can be severe. Diagnosis is by examination. Treatment is elimination or avoidance of the allergen and H₁ blockers.

Acute angioedema is essentially anaphylaxis of the subcutaneous tissues. It is sometimes accompanied by urticaria (local wheals and erythema in the skin—see p. 639); the two have similar causes (eg, drug, venom, dietary, or extracted allergens). Also, angioedema is pathogenetically related to urticaria, which occurs at the epidermal-dermal junction.

Chronic (> 6 wk) angioedema is rarely IgE-mediated and is more difficult to explain. Cause is usually unknown (idiopathic), but chronic ingestion of an unsuspected drug or chemical (eg, penicillin in milk, a nonprescription drug, preservatives, other food additives) is sometimes the cause. A few cases are hereditary (see p. 1112).

Symptoms and Signs

Angioedema may be slightly pruritic or nonpruritic. It is characterized by locally diffuse and painful soft-tissue swelling that may be asymmetric, especially on the eyelids, lips (see Plate 57), face, and tongue but also on the back of hands or feet and on the genitals. Edema of the upper airways may cause respiratory distress, and the stridor may be mistaken for asthma. Complete airway obstruction may occur.

Diagnosis

• Clinical evaluation

The cause is often obvious, and diagnostic tests are seldom required because reactions are self-limited and nonrecurrent. No test is particularly useful. Erythropoietic protoporphyria may mimic allergic forms of angioedema and can be distinguished by measuring blood and fecal porphyrins (see p. 817).

Treatment

• Oral prednisone

• Sometimes sc epinephrine

• Sometimes IV antihistamines

[Table 127-1, Putative Autimmune Disorders]

For acute angioedema, treatment is removing or avoiding the allergen and relieving symptoms (eg, with H₁ blockers—see p. 1116 and Table 127-2). Prednisone 30 to 40 mg po once/day is indicated for more severe reactions. Topical corticosteroids are useless. If a cause is not obvious, all nonessential drugs should be stopped. Pharyngeal or laryngeal angioedema requires epinephrine 0.3 mL of a 1:1000 solution sc. It may be supplemented with an IV anti-histamine (eg, diphenhydramine 50 to 100 mg). Long-term treatment may involve H₁ and H₂ blockers and occasionally corticosteroids.

[Table 127-2, Oral H₁ Blockers]

Hereditary Angioedema
Hereditary angioedema is caused by deficiency or dysfunction of C1 inhibitor, a protein that regulates the classical complement activation pathway (see p. 1085).

Hereditary angioedema has 2 types:

• Type 1 (85%): C1 inhibitor is deficient.

• Type 2 (15%): C1 inhibitor malfunctions.

Inheritance is autosomal dominant. C1 inhibitor deficiency may also be acquired: when complement is consumed in neoplastic disorders (e.g., B-cell lymphoma), when C1 inhibitor autoantibody is produced in monoclonal gammopathy, or, rarely, when the autoantibody is produced in other disorders (e.g., SLE, dermatomyositis). Attacks can be precipitated by mild trauma (e.g., dental work, tongue piercing), viral illness, cold exposure, pregnancy, or ingestion of certain foods or may be aggravated by emotional stress.

Symptoms and signs are similar to those of angioedema except that edema progresses until complement components have been consumed; the GI tract is often involved, causing nausea, vomiting, colic, and signs of intestinal obstruction. Other common anatomic locations include the skin and the larynx. Episodes of swelling are self-limited; however, laryngeal involvement can lead to death.

**Diagnosis**

• Measurement of complement protein levels

Diagnosis is based on detection of low levels of C2 and C4, normal levels of C1q (a fragment of C1), and decreased C1 inhibitor function. In type 1, C1 inhibitor protein levels are low; in type 2, levels are normal or increased. In acquired C1 inhibitor deficiency, C1q levels are low.

**Treatment**

• Attenuated androgens

• Symptomatic treatments

Attenuated androgens (e.g., stanozolol 2 mg po tid, danazol 200 mg po tid) are used to stimulate hepatic C1 inhibitor synthesis. This treatment may be less effective for the acquired form. Some experts advocate giving fresh frozen plasma immediately before dental or medical procedures to prevent attacks, but this approach could theoretically provoke an attack by providing substrate for angioedema.

Purified C1 inhibitor and recombinant C1 inhibitor are being developed for acute treatment. Corticosteroids and antihistamines are not effective. Epinephrine can be of transient benefit in cases of airway involvement. Symptomatic relief can be provided by analgesics, antiemetics, and fluid replacement.

**Atopic and Allergic Disorders**

Type I hypersensitivity reactions underlie all atopic and many allergic disorders. The terms atopy and allergy are often used interchangeably but are different:

• **Atopy** is an exaggerated IgE-mediated immune response; all atopic disorders are type I hypersensitivity disorders.

• **Allergy** is any exaggerated immune response to a foreign antigen regardless of mechanism.

Thus, all atopic disorders are considered allergic, but many allergic disorders (e.g., hypersensitivity pneumonitis) are not atopic. Allergic disorders are the most common disorders among people.

Atopic disorders most commonly affect the nose, eyes, skin, and lungs. These disorders include atopic
dermatitis, contact dermatitis, urticaria (see p. 639), angioedema (which may be primary skin disorders or symptoms of systemic disorders), latex allergy (see Sidebar 127-1), allergic lung disorders (eg, asthma, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis), and allergic reactions to venomous stings.

Etiology

Complex genetic, environmental, and site-specific factors contribute to development of allergies.

Genetic factors may be involved, as suggested by familial inheritance of disease, association between atopy and specific HLA loci, and polymorphisms of several genes, including those for the high-affinity IgE receptor β-chain, IL-4 receptor α-chain, IL-4, IL-13, CD14, dipeptidyl-peptidase 10 (DPP10), and a disintegrin and metalloprotease domain 33 (ADAM33).

Environmental factors interact with genetic factors to maintain type 2 helper T (T\textsubscript{H2}) cell immune responses, which activate eosinophils and IgE production and are proallergic. Early childhood exposure to bacterial and viral infections and endotoxins (eg, lipopolysaccharide) may normally shift native T\textsubscript{H2}-cell responses to type 1 helper T (T\textsubscript{H1})-cell responses, which suppress T\textsubscript{H2} cells and therefore discourage allergic responses. Regulatory T (CD4+CD25+Foxp3+) cells (which are capable of suppressing T\textsubscript{H2}-cell responses) and IL-12-secreting dendritic cells (which drive T\textsubscript{H1}-cell responses) are perhaps also involved. But trends in developed countries toward smaller families with fewer children, cleaner indoor environments, and early use of vaccinations and antibiotics may deprive children of exposure to infectious agents that drive a predominantly T\textsubscript{H1}-cell response; such trends may explain the increased prevalence of some allergic disorders. Other factors thought to contribute to allergy development include chronic allergen exposure and sensitization, diet, and environmental pollutants.

Sidebar 127-1 Latex Sensitivity

Latex sensitivity is an exaggerated immune response to water-soluble proteins in latex products (eg, rubber gloves, dental dams, condoms, tubing for respiratory equipment, catheters, enema tips with inflatable latex cuffs), causing urticaria, angioedema, and anaphylaxis.

Reactions to latex may be acute (IgE-mediated) or delayed (cell-mediated). Acute reactions cause urticaria and anaphylaxis; delayed reactions cause dermatitis.

Diagnosis is based on history. Assays for detecting IgE anti-latex antibodies and patch tests for detecting anti-latex cellular immunity are being developed, but none is well-validated yet.

Treatment is avoidance of latex.

Site-specific factors include adhesion molecules in bronchial epithelium and in skin and molecules in the GI tract that direct T\textsubscript{H2} cells to target tissues.

Allergens: By definition, an allergen induces IgE-mediated and T\textsubscript{H2}-cell immune responses. Allergic triggers are almost always low molecular weight proteins; many of them can be constituted as airborne particles.

Allergens that most commonly cause acute and chronic allergic reactions include

- House dust
- Mite feces
- Animal dander
Pathophysiology

When allergen binds to IgE-sensitized mast cells and basophils, histamine is released from their intracellular granules. Mast cells are widely distributed but are most concentrated in skin, lungs, and GI mucosa; histamine facilitates inflammation and is the primary mediator of clinical atopy. Physical disruption of tissue and various substances (eg, tissue irritants, opioids, surface-active agents, complement components C3a and C5a) can trigger histamine release directly, independent of IgE.

Histamine causes the following:

- Local vasodilation (causing erythema)
- Increased capillary permeability and edema (producing a wheal)
- Surrounding arteriolar vasodilation mediated by neuronal reflex mechanisms (causing flare)
- Stimulation of sensory nerves (causing itching)
- Smooth muscle contraction in the airways (bronchoconstriction) and in the GI tract (increasing GI motility)
- Increased salivary and bronchial gland secretions

When released systemically, histamine is a potent arteriolar dilator and can cause extensive peripheral pooling of blood and hypotension; cerebral vasodilation may be a factor in vascular headache. Histamine increases capillary permeability; the resulting loss of plasma and plasma proteins from the vascular space can worsen circulatory shock. This loss triggers a compensatory catecholamine surge from adrenal chromaffin cells.

Symptoms and Signs

Common symptoms include rhinorrhea, sneezing, and nasal congestion (upper respiratory tract); wheezing and dyspnea (lower respiratory tract); and itching (eyes and skin).

Signs may include nasal turbinate edema, sinus pain during palpation, wheezing, conjunctival hyperemia and edema, and skin lichenification. Stridor, wheezing, and sometimes hypotension are life-threatening signs of anaphylaxis (see p. 1120). In some children, a narrow and high-arched palate, narrow chin, and elongated maxilla with overbite (allergic facies) are thought to be associated with chronic allergy.

Diagnosis

- Clinical evaluation
- CBC and serum IgE levels (nonspecific tests)
- Skin testing and radioallergosorbent testing (specific tests)
- Rarely, provocative testing

A thorough history is generally more reliable than testing or screening. History should include

- Questions about frequency and duration of attacks and changes over time
- Triggering factors if identifiable
• Relation to seasonal or situational settings (eg, predictably occurring during pollen seasons; after exposure to animals, hay, or dust; during exercise; or in particular places)

• Family history of similar symptoms or of atopic disorders

• Responses to attempted treatments

Age at onset may be important in asthma because childhood asthma is likely to be atopic and asthma beginning after age 30 is not.

**Nonspecific tests:** Certain tests can suggest but not confirm an allergic origin of symptoms.

CBC should be ordered to detect eosinophilia in all patients except those taking corticosteroids, which reduce the eosinophil count. An eosinophil differential of 5 to 15% of total WBCs suggests atopy but is nonspecific; 16 to 40% may reflect atopy or other conditions (eg, drug hypersensitivity, cancer, autoimmune disorders, parasitic infection); a differential of 50 to 90% almost never occurs in atopic disorders and is more characteristic of hypereosinophilic syndrome or visceral larva migrans. Total WBC is usually normal.

Conjunctival or nasal secretions or sputum can be examined for leukocytes; finding any eosinophils indicates that T\textsubscript{H}2-mediated allergic inflammation is likely.

Serum IgE levels are elevated in atopic disorders but are of little help in diagnosis because they may also be elevated in parasitic infections, infectious mononucleosis, autoimmune disorders, drug reactions, immunodeficiency disorders (hyper-IgE syndrome—see p. 1104—and Wiskott-Aldrich syndrome—see p. 1107), and in some forms of multiple myeloma. IgE levels are probably most helpful for following response to therapy in allergic bronchopulmonary aspergillosis (see p. 1887).

**Specific tests:** Skin testing uses standardized concentrations of antigen introduced directly into skin and is indicated when a detailed history and physical examination do not identify the cause and triggers for symptoms. Skin testing has higher positive predictive values for diagnosing allergic rhinosinusitis and conjunctivitis than for diagnosing allergic asthma or food allergy; negative predictive value for food allergy is high. The most commonly used antigens are pollens (tree, grass, weed), molds, house dust mites, animal danders and sera, insect venom, foods, and β-lactam antibiotics. Choice of antigens to include is based on patient history and geographic prevalence.

Two skin test techniques can be used

• Percutaneous (prick)

• Intradermal

The prick test can detect most allergies. The intradermal test is more sensitive but less specific; it can be used to evaluate sensitivity to allergens with negative or equivocal prick test results.

For the **prick test**, a drop of antigen extract is placed on the skin, which is then pricked or punctured through the extract by tenting up the skin with the tip of a 27-gauge needle held at a 20° angle or with a commercially available prick device.

For the **intradermal test**, just enough extract to produce a 1- or 2-mm bleb (typically 0.02 mL) is injected intradermally with a 0.5- or 1-mL syringe and a 27-gauge short-bevel needle.

Prick and intradermal skin testing should include the diluent alone as a negative control and histamine (10 mg/mL for prick tests, 0.01 mL of a 1:1000 solution for intradermal tests) as a positive control. For patients who have had a recent (< 1 yr) generalized reaction to the test antigen, testing begins with the standard reagent diluted 100-fold, then 10-fold, and then the standard concentration. A test is considered positive if a wheal and flare reaction occurs and wheal diameter is 3 to 5 mm greater than that of the
negative control after 15 to 20 min. False positives occur in dermatographism (a wheal and flare reaction provoked by stroking or scraping the skin). False negatives occur when allergen extracts have been stored incorrectly or are outdated. Certain drugs can also interfere with results and should be stopped a few days to a week before testing. These drugs include OTC and prescription antihistamines, tricyclic antidepressants, and monoamine oxidase inhibitors. Patients taking β-blockers should not be tested.

Radioallergosorbent testing (RAST) detects the presence of allergen-specific serum IgE and is indicated when skin testing is contraindicated because of generalized dermatitis, dermatographism, history of anaphylaxis to the allergen, or need to continue antihistamines. A known allergen in the form of an insoluble polymer-allergen conjugate is mixed with the serum to be tested and with $^{125}\text{I}$-labeled anti-IgE antibody. Any allergen-specific IgE in the serum binds the conjugate and can be quantified by measuring the $^{125}\text{I}$-labeled antibody.

Provocative testing involves direct exposure of the mucosae to allergen and is indicated for patients who must document their reaction (eg, for occupational or disability claims) and sometimes for diagnosis of food allergy.

Ophthalmic testing has no advantage over skin testing and is rarely used.

Nasal and bronchial challenge are primarily research tools, but bronchial challenge is sometimes used when the clinical significance of a positive skin test is unclear or when no antigen extracts are available (eg, for occupation-related asthma).

Treatment

• Removal or avoidance of allergic triggers

• Antihistamines

• Mast cell stabilizers

• Anti-inflammatory corticosteroids and leukotriene inhibitors

• Immunotherapy (desensitization)

Environmental control: Removal or avoidance of allergic triggers is the primary treatment for allergy, as well as the primary preventive strategy (see Prevention on p. 1117).

Antihistamines: Antihistamines block receptors; they do not affect histamine production or metabolism. $H_1$ blockers are a mainstay of treatment for allergic disorders. $H_2$ blockers are used primarily for gastric acid suppression and have limited usefulness for allergic reactions; they may be indicated for certain atopic disorders, especially chronic urticaria.

Oral $H_1$ blockers relieve symptoms in various atopic and allergic disorders (eg, seasonal hay fever, allergic rhinitis, conjunctivitis, urticaria, other dermatoses, minor reactions to blood transfusion incompatibilities and to x-ray radiopaque dyes); they are less effective for allergic bronchoconstriction and vasodilation. Onset of action is usually 15 to 30 min, with peak effects in 1 h; duration of action is usually 3 to 6 h.

Oral $H_1$ blockers are classified as sedating or nonsedating (better thought of as less sedating). Sedating antihistamines are widely available without prescription. All have significant sedative and anticholinergic properties; they pose particular problems for the elderly and for patients with glaucoma, benign prostatic hyperplasia, constipation, or dementia. Nonsedating (nonanticholinergic) antihistamines are preferred except when sedative effects may be therapeutic (eg, for nighttime relief of allergy, for short-term treatment of insomnia in adults or nausea in younger patients). Anticholinergic effects may also partially justify use of sedating antihistamines to relieve rhinorrhea in URIs.
Antihistamine solutions may be intranasal (azelastine to treat rhinitis) or ocular (azelastine, emedastine, ketotifen, levocabastine, or olopatadine to treat conjunctivitis). Topical diphenhydramine is available but should not be used; its efficacy is unproved, drug sensitization (ie, allergy) may occur, and anticholinergic toxicity can develop in young children who are simultaneously taking oral H₁ blockers.

**Mast cell stabilizers:** These drugs (eg, cromolyn) block the release of mediators from mast cells; they are used when other drugs (eg, antihistamines, topical corticosteroids) are ineffective or not well tolerated. Ocular forms (eg, lodoxamide, olopatadine, pemirolast) are also available.

**Anti-inflammatory drugs:** Corticosteroids can be given intranasally (see Table 127-3) or orally. Oral corticosteroids are indicated for systemic allergic disorders that are severe but self-limited (eg, seasonal asthma flares, severe widespread contact dermatitis) and for disorders refractory to other measures. NSAIDs are typically not useful, with the exception of topical ketorolac for allergic conjunctivitis.

Leukotriene modifiers are indicated for treatment of mild persistent asthma (see p. 1881) and seasonal allergic rhinitis.

Anti-IgE antibody (omalizumab) is indicated for moderately persistent or severe asthma refractory to standard treatment (see p. 1881).

**Immunotherapy:** Exposure to allergen in gradually increasing doses (hyposensitization or desensitization) via injection or in high doses sublingually can induce tolerance

and is indicated when allergen exposure cannot be avoided and drug treatment is inadequate. Mechanism is unknown but may involve induction of IgG antibodies, which compete with IgE for allergen or block IgE from binding with mast cell IgE receptors; induction of interferon-γ, IL-12, and cytokines secreted by TH₁ cells; or induction of regulatory T cells.

For full effect, injections must be given monthly. Dose typically starts at 0.1 to 1.0 biologically active units (BAU), depending on initial sensitivity, and is increased weekly or biweekly by ≤ 2 times with each injection until a maximum tolerated concentration is reached; patients should be observed for about 30 min postinjection during dose escalation because anaphylaxis may occur after injection. Maximum dose should be given q 4 to 6 wk year-round; year-round treatment is better than preseasonal or coseasonal treatment even for seasonal allergies. Allergens used are those that typically cannot be avoided: pollens, house dust mites, molds, and venom of stinging insects. Insect venoms are standardized by weight; a typical starting dose is 0.01 μg, and usual maintenance dose is 100 to 200 μg. Animal dander desensitization is ordinarily limited to patients who cannot avoid exposure (eg, veterinarians, laboratory workers), but there is little evidence that it is useful. Food desensitization is not indicated. Desensitization for penicillin and certain other antibiotics and for foreign (xenogeneic) serum can be done (see p. 1120).

Adverse effects are most commonly related to overdose, occasionally via an inadvertent IM or IV injection, and range from mild cough or sneezing to generalized urticaria, severe asthma, anaphylactic shock, and, rarely, death. They can be prevented by the following:

• Increasing the dose in small increments

• Repeating or decreasing the dose if local reaction to the previous injection is large (≥ 2.5 cm in diameter)

• Reducing the dose when a fresh extract is used

Reducing the dose of pollen extract during pollen season is recommended. Epinephrine, O₂, and resuscitation equipment should be immediately available for prompt treatment of anaphylaxis.
Prevention

Allergic triggers should be removed or avoided. Strategies include the following:

• Using synthetic fiber pillows and impermeable mattress covers
• Frequently washing bed sheets, pillowcases, and blankets in hot water
• Removing upholstered furniture, soft toys, carpets, and pets
• House cleaning and extermination to eliminate cockroach exposure
• Using dehumidifiers in basements and other poorly aerated, damp rooms
• Treating homes with heat-steam
• Using high-efficiency particulate air (HEPA) vacuums and filters
• Avoiding food triggers
• Limiting pets to certain rooms
• Frequently cleaning cloth furniture and carpets

Adjunctive nonallergenic triggers (eg, cigarette smoke, strong odors, irritating fumes, air pollution, cold temperatures, high humidity) should also be avoided or controlled when possible.

Allergic Rhinitis

Allergic rhinitis is seasonal or perennial itching, sneezing, rhinorrhea, nasal congestion, and sometimes conjunctivitis, caused by exposure to pollens or other allergens. Diagnosis is by history and skin testing. Treatment is with a combination of antihistamines, decongestants, nasal corticosteroids, and, for severe, refractory cases, desensitization.

Allergic rhinitis may occur seasonally (hay fever) or throughout the year (perennial rhinitis). At least 25% of perennial rhinitis is nonallergic.

Seasonal rhinitis is caused by

• Spring: Tree pollens (eg, oak, elm, maple, alder, birch, juniper, olive)
• Summer: Grass pollens (eg, Bermuda, timothy, sweet vernal, orchard, Johnson) and weed pollens (eg, Russian thistle, English plantain)
• Fall: Other weed pollens (eg, ragweed)

Causes also differ by region, and seasonal rhinitis is occasionally caused by airborne fungal spores. Perennial rhinitis is caused by year-round exposure to indoor inhaled allergens (eg, dust mites, cockroaches, animal dander, mold) or by strong reactivity to plant pollens in sequential seasons.

Allergic rhinitis and asthma frequently coexist; whether rhinitis and asthma result from the same allergic process (one-airway hypothesis) or rhinitis is a discrete asthma trigger is unclear.

Nonallergic forms of perennial rhinitis include infectious, vasomotor, atrophic, hormonal, drug-induced, and gustatory rhinitis (see p. 478).

Symptoms and Signs
Patients have itching (in the nose, eyes, or mouth), sneezing, rhinorrhea, and nasal and sinus obstruction. Sinus obstruction may cause frontal headaches; sinusitis is a frequent complication. Coughing and wheezing may also occur, especially if asthma is also present.

The most prominent feature of perennial rhinitis is chronic nasal obstruction, which, in children, can lead to chronic otitis media; symptoms vary in severity throughout the year. Itching is less prominent than in seasonal rhinitis.

Signs include edematous, bluish-red nasal turbinates, and, in some cases of seasonal rhinitis, conjunctival injection and eyelid edema.

**Diagnosis**

- Clinical evaluation
- Sometimes skin testing, RAST, or both

Allergic rhinitis can almost always be diagnosed based on history alone. Diagnostic testing is not routinely needed unless patients do not improve when treated empirically; for such patients, skin tests are done to identify a reaction to pollens (seasonal) or to dust mite, cockroach, animal dander, mold, or other antigens (perennial), which can be used to guide additional treatment. Occasionally, skin test results are ambivalent, or testing cannot be done (eg, because patients are taking drugs that interfere with results); then, RAST is done. Eosinophilia detected on nasal smear plus negative skin tests suggests aspirin sensitivity or nonallergic rhinitis with eosinophilia (NARES).

Diagnosis of infectious, vasomotor, atrophic, hormonal, drug-induced, and gustatory rhinitis is usually based on history or therapeutic trials.

**Treatment**

- Removal or avoidance of allergens for perennial rhinitis
- Antihistamines, decongestants, nasal corticosteroids, or a combination
- Sometimes immunotherapy for seasonal rhinitis
- Desensitization for severe, refractory rhinitis

Treatment of seasonal and perennial allergic rhinitis is generally the same, although attempts at environmental control (eg, eliminating dust mites and cockroaches) are recommended for perennial rhinitis.

The most effective first-line drug treatments are

- Oral antihistamines plus oral decongestants
- Nasal corticosteroids with or without oral antihistamines (see Table 127-3)

Less effective alternatives include nasal mast cell stabilizers (eg, cromolyn) given bid to qid, the nasal H₁ blocker azelastine 2 puffs once/day, and nasal ipratropium 0.03% 2 puffs q 4 to 6 h, which relieves rhinorrhea. Intranasal saline, often forgotten, helps mobilize thick nasal secretions and hydrate nasal mucous membranes.

Immunotherapy may be more effective for seasonal than for allergic perennial rhinitis; it is indicated when symptoms are severe, allergen cannot be avoided, and drug treatment is inadequate.

Desensitization may be needed for severe, refractory rhinitis. First attempts at desensitization should
begin soon after the pollen season ends to prepare for the next season; adverse reactions increase when desensitization is started during the pollen season because the person's allergic immunity is already maximally stimulated.

Montelukast relieves allergic rhinitis symptoms, but its role relative to other treatments is uncertain. Anti-IgE antibody is under study for treatment of allergic rhinitis but will probably have a limited role because less expensive, effective alternatives are available.

Treatment of NARES is nasal corticosteroids. Treatment of aspirin sensitivity is aspirin avoidance, with desensitization and leukotriene blockers as needed. Nasal polyps may respond to nasal corticosteroids.

**Food Allergy**

**Food allergy is an exaggerated immune response to dietary proteins.**

Food allergy should be distinguished from nonimmune reactions to food (eg, lactose intolerance, irritable bowel syndrome, infectious gastroenteritis) and reactions to additives (eg, monosodium glutamate, metabisulfite, tartrazine) or food contaminants (eg, latex dust in food handled by workers wearing latex gloves), which cause most food reactions. Prevalence of true food allergy ranges from < 1 to 3% and varies by geography and method of ascertainment; patients tend to confuse intolerance with allergy.

**Etiology**

Almost any food or food additive can cause an allergic reaction, but the most common triggers include

- **Infants and young children:** Milk, soy, eggs, peanuts, and wheat
- **Older children and adults:** Nuts and seafood

Cross-reactivity between food and nonfood allergens exists, and sensitization may occur nonenterally. For example, patients with oral allergies (typically, pruritus, erythema, and edema of the mouth when fruits and vegetables are eaten) may have been sensitized by pollen exposure; children with peanut allergy may have been sensitized by topical creams containing peanut oil used to treat rashes. Many patients who are allergic to latex are also allergic to bananas, kiwis, avocados, or a combination.

In general, food allergy is mediated by IgE, T cells, or both. IgE-mediated allergy (eg, urticaria, asthma, anaphylaxis) is acute in onset, usually develops during infancy, and occurs most often in people with a strong family history of atopy. T cell-mediated allergy (eg, dietary protein gastroenteropathies, celiac disease) manifests gradually and is chronic. Allergies mediated by both IgE and T cells (eg, atopic dermatitis, eosinophilic gastroenteropathy) tend to be delayed in onset or chronic.

**Eosinophilic gastroenteropathy:** This unusual disorder causes pain, cramps, and diarrhea with blood eosinophilia, eosinophilic infiltrates in the gut, protein-losing enteropathy, and a history of atopic disorders. Eosinophilic esophagitis sometimes accompanies eosinophilic gastroenteropathy. Initially, it may cause dysphagia and dysmotility or, in children, feeding intolerance and abdominal pain.

**Symptoms and Signs**

Symptoms and signs vary by allergen, mechanism, and patient age. The most common manifestation in infants is atopic dermatitis alone or with GI symptoms (nausea, vomiting, diarrhea). Children usually outgrow these manifestations and react increasingly to inhaled allergens, with symptoms of asthma and rhinitis; this progression is called atopic march. By age 10 yr, patients rarely have respiratory symptoms after the allergenic food is eaten, even though skin tests remain positive. If atopic dermatitis persists or appears in older children or adults, its activity seems largely independent of IgE-mediated allergy, even though atopic patients with extensive dermatitis have much higher serum IgE levels than those who are free of dermatitis.

When food allergy persists in older children and adults, reactions tend to be more severe (eg, explosive
urticaria, angioedema, even anaphylaxis). In a few patients, food (especially wheat and celery) triggers anaphylaxis only if they exercise soon afterward; mechanism is unknown. A few patients have food-induced or aggravated migraine, confirmed by blinded oral challenge. Occasionally, cheilitis, aphthae, pylorospasm, spastic constipation, pruritus ani, and perianal eczema are attributed to food allergy.

**Diagnosis**

- Skin testing or RAST
- Trial elimination diet (alone or after skin testing or RAST)

Severe food allergy is usually obvious in adults. When it is not and when it occurs in children (usually), diagnosis may be difficult, and the disorder must be differentiated from functional GI problems.

If a food reaction is suspected, the relationship of symptoms to foods is assessed by skin testing or IgE-specific RAST. A positive test does not confirm a clinically relevant allergy, but a negative test excludes it. If a skin test is positive, the tested food is eliminated from the diet; if symptoms are relieved, the patient is reexposed to the food (preferably in a double-blind test) to see whether symptoms recur.

Alternatives to skin testing include eliminating foods the patient suspects of causing symptoms and prescribing a diet that consists of relatively nonallergenic foods and that eliminates common food allergens (see Table 127-4). No foods or fluids may be consumed other than those specified. Pure products must always be used. Many commercially prepared products and meals contain an undesired food in large amounts (eg, commercial rye bread contains wheat flour) or in traces as flavoring or thickeners, and determining whether an undesired food is present may be difficult.

If no improvement occurs after 1 wk, another diet should be tried. If symptoms are relieved, one new food is added and eaten in large amounts for > 24 h or until symptoms recur. Alternatively, small amounts of the food to be tested are eaten in the clinician's presence, and the patient's reactions observed. Aggravation or recrudescence of symptoms after addition of a new food is the best evidence of allergy.

**Treatment**

- Food elimination diet
- Sometimes oral cromolyn
- Sometimes corticosteroids for eosinophilic enteropathy

[Table 127-4, Allowable Foods in Elimination Diets*]

Treatment consists of eliminating the food that triggers the allergic reaction. Thus, diagnosis and treatment overlap. When assessing an elimination diet's effect, clinicians must consider that food sensitivities may disappear spontaneously.

Oral desensitization (by first eliminating the allergenic food for a time, then giving small amounts and increasing them daily) is not effective nor is use of sublingual drops of food extracts. Antihistamines are of little value except in acute general reactions with urticaria and angioedema. Oral cromolyn has been used with apparent success. Prolonged corticosteroid treatment is helpful for symptomatic eosinophilic enteropathy.

**Anaphylaxis**

Anaphylaxis is an acute, life-threatening, IgE-mediated allergic reaction that occurs in previously sensitized people when they are reexposed to the sensitizing antigen. Symptoms include stridor, dyspnea, wheezing, and hypotension. Diagnosis is clinical. Bronchospasm and upper airway edema are treated with inhaled or injected β-agonists and sometimes...
endotracheal intubation. Hypotension requires IV fluids and vasopressors.

**Etiology**

Anaphylaxis is typically triggered by

- Drugs (eg, β-lactam antibiotics, insulin, streptokinase, allergen extracts)
- Foods (eg, nuts, eggs, seafood)
- Proteins (eg, tetanus antitoxin, blood transfusions)
- Animal venoms
- Latex

Peanut and latex allergens may be airborne. History of atopy does not increase risk of anaphylaxis but increases risk of death when anaphylaxis occurs.

**Pathophysiology**

Interaction of antigen with IgE on basophils and mast cells triggers release of histamine, leukotrienes, and other mediators that cause diffuse smooth muscle contraction (bronchoconstriction, vomiting, diarrhea) and vasodilation with plasma leakage.

**Anaphylactoid reactions:** These reactions are clinically indistinguishable from anaphylaxis but do not involve IgE and do not require prior sensitization. They occur via direct stimulation of mast cells or via immune complexes that activate complement. The most common triggers are iodinated radiographic radiopaque dye, aspirin, other NSAIDs, opioids, blood transfusions, Ig, and exercise.

**Symptoms and Signs**

Symptoms typically involve the skin, upper or lower airways, cardiovascular system, or GI tract. One or more areas may be affected, and symptoms do not necessarily progress, although each patient typically manifests the same reaction to subsequent exposure.

Symptoms range from mild to severe and include flushing, pruritus, sneezing, rhinorrhea, nausea, abdominal cramps, diarrhea, sense of choking or dyspnea, palpitations, and dizziness.

Signs include hypotension, tachycardia, urticaria, angioedema, wheezing, cyanosis, and syncope. Shock can develop within minutes, and patients may experience seizures, become unresponsive, and die. Cardiovascular collapse can occur without respiratory or other symptoms.

**Diagnosis**

Diagnosis is clinical. Risk of rapid progression to shock leaves no time for testing, although mild equivocal cases can be confirmed by measuring 24-h urinary levels of N-methylhistamine or serum levels of tryptase.

**Treatment**

- Epinephrine given immediately
- Sometimes intubation
- IV fluids and vasopressors for hypotension
- Antihistamines
• Inhaled \(\beta\)-agonists for bronchoconstriction

Epinephrine is the cornerstone of treatment and should be given immediately. It can be given sc or IM (usual dose is 0.3 to 0.5 mL of a 1:1000 solution in adults or 0.01 mL/kg in children, repeated every 10 to 30 min); maximal absorption occurs when the drug is given IM in the lateral thigh. Patients with cardiovascular collapse or severe airway obstruction may be given epinephrine IV in a single dose (3 to 5 mL of a 1:10,000 solution over 5 min) or by continuous drip (1 mg in 250 mL 5% D/W for a concentration of 4 \(\mu\)g/mL, starting at 1 \(\mu\)g/min up to 4 \(\mu\)g/min [15 to 60 mL/h]). Epinephrine may also be given by sublingual injection (0.5 mL of 1:1000 solution) or through an endotracheal tube (3 to 5 mL of a 1:10,000 solution diluted to 10 mL with saline). A 2nd injection of epinephrine sc may be needed. Glucagon 1-mg bolus followed by 1-mg/h infusion should be used in patients taking oral \(\beta\)-blockers, which attenuate the effect of epinephrine.

Patients who have stridor and wheezing unresponsive to epinephrine should be given \(O_2\) and be intubated. Early intubation is recommended because waiting for a response to epinephrine may allow upper airway edema to progress sufficiently to prevent endotracheal intubation and require cricothyrotomy.

Hypotension can usually be treated with 1 to 2 L (20 to 40 mL/kg in children) of isotonic IV fluids (eg, 0.9% saline). Hypotension refractory to fluids and IV epinephrine may require vasopressors (eg, dopamine 5 \(\mu\)g/kg/min).

Antihistamines—both \(H_1\) blockers (eg, diphenhydramine 50 to 100 mg IV) and \(H_2\) blockers (eg, cimetidine 300 mg IV)—should be given q 6 h until symptoms resolve. Inhaled \(\beta\)-agonists are useful for managing bronchoconstriction; albuterol 5 to 10 mg by continuous nebulization can be given.

Corticosteroids have no proven role but may help prevent late-phase reaction in 4 to 8 h; methylprednisolone 125 mg IV initially is adequate.

**Prevention**

Primary prevention is avoidance of known triggers. Desensitization is used for allergen triggers that cannot reliably be avoided (eg, insect stings). Patients with past reactions to radiopaque dye should not be reexposed; when exposure is absolutely necessary, patients are given 3 doses of prednisone 50 mg po q 6 h, starting 18 h before the procedure, and diphenhydramine 50 mg po 1 h before the procedure; however, no evidence supports the efficacy of this approach (see also p. 3404).

Patients with an anaphylactic reaction to insect stings, foods, or other known substances should wear an alert bracelet and carry a prefilled epinephrine syringe (containing 0.3 mg for adults and 0.15 mg for children) for prompt self-treatment after exposure.

**Autoimmune Disorders**

In autoimmune disorders, the immune system produces antibodies to an endogenous antigen. It may involve the following hypersensitivity reactions:

• **Type II**: Antibody-coated cells, like any similarly coated foreign particle, activate the complement system (see p. 1085), resulting in tissue injury.

• **Type III**: The mechanism of injury involves deposition of antibody-antigen complexes.

• **Type IV**: Injury is T-cell-mediated.

For specific autoimmune disorders, see elsewhere in THE MANUAL and also Table 127-1.

**Etiology**
Several mechanisms may account for the body's attack on itself.

Autoantigens may become immunogenic because they are altered chemically, physically, or biologically. Certain chemicals can couple with body proteins, making them immunogenic (as in contact dermatitis). Drugs can produce several autoimmune reactions by binding covalently to serum or tissue proteins (see below). Photosensitivity exemplifies physically induced autoimmunity: Ultraviolet light alters skin protein, to which the patient becomes allergic. In animal models, persistent infection with an RNA virus that combines with host tissues alters autoantigens biologically, resulting in an autoimmune disorder resembling SLE.

Antibodies produced in response to a foreign antigen may cross-react with normal autoantigens (eg, cross-reaction between streptococcal M protein and human heart muscle).

Normally, potentially pathologic autoimmune reactions are avoided because of the immunologic tolerance mechanisms of clonal deletion and clonal anergy. Any autoreactive lymphocytes not controlled by these mechanisms are usually restrained by Foxp3+ regulatory T cells. A regulatory T-cell defect may accompany any of these mechanisms for autoimmunity. Anti-idiotype antibodies (antibodies to the antigen-combining site of other antibodies) may interfere with regulation of antibody activity.

Genetic factors play a role. Relatives of patients with autoimmune disorders often have the same type of autoantibodies, and incidence of autoimmune disorders is higher in identical than in fraternal twins. Most autoimmune disorders have a polygenic etiology, and allelic variants within the HLA gene locus nearly always contribute. Women are affected more often than men. In genetically predisposed people, environmental factors may provoke disease (eg, certain drugs can trigger hemolytic anemia in patients with G6PD deficiency).

**Drug Hypersensitivity**

Drug hypersensitivity is an immune-mediated reaction to a drug. Symptoms range from mild to severe and include skin rash, anaphylaxis, and serum sickness. Diagnosis is clinical; skin testing is occasionally useful. Treatment is drug discontinuation, antihistamines (for symptoms), and sometimes desensitization.

Drug hypersensitivity must be distinguished from toxic and adverse effects that may be expected from the drug and from problems due to drug interactions (see p. 3167).

**Pathophysiology**

Some protein and large polypeptide drugs (eg, insulin, therapeutic antibodies) can directly stimulate antibody production. However, most drugs act as haptens, binding covalently to serum or cell-bound proteins, including peptides embedded in major histocompatibility complex (MHC) molecules. The binding makes the protein immunogenic, stimulating antidrug antibody production, T-cell responses against the drug, or both. Haptens may also bind directly to the MHC II molecule, directly activating T cells. When metabolized, prohaptens become haptens; eg, penicillin itself is not antigenic, but its main degradation product, benzylpenicilloic acid, can combine with tissue proteins to form benzylpenicilloyl (BPO), a major antigenic determinant. Some drugs bind and stimulate T-cell receptors (TCR) directly; the clinical significance of nonhapten TCR binding is being determined.

How primary sensitization occurs and how the immune system is initially involved is unclear, but once a drug stimulates an immune response, cross-reactions within and between drug classes can occur. For example, penicillin-sensitive patients are highly likely to react to semisynthetic penicillins (eg, amoxicillin, carbenicillin, ticarcillin), and about 10% react to cephalosporins, which have a similar β-lactam structure. However, some apparent cross-reactions (eg, between sulfonamide antibiotics and nonantibiotics) are due to a predisposition to allergic reactions rather than to specific immune cross-reactivity. Also, not every apparent reaction is allergic; for example, amoxicillin causes a rash that is not immune-mediated and does not preclude future use of the drug.

**Symptoms and Signs**
Symptoms and signs vary by patient and drug, and a single drug may cause different reactions in different patients. The most serious is anaphylaxis; exanthema (eg, morbilliform eruption), urticaria, and fever are common. Fixed drug reactions are uncommon.

Some distinct clinical syndromes exist.

• **Serum sickness:** This reaction typically occurs 7 to 10 days after exposure and causes fever, arthralgias, and rash. Mechanism involves drug-antibody complexes and complement activation. Some patients have frank arthritis, edema, or GI symptoms. Symptoms are self-limited, lasting 1 to 2 wk. β-Lactam and sulfonamide antibiotics, iron-dextran, and carbamazepine are most commonly implicated.

• **Hemolytic anemia:** This disorder may develop when an antibody-drug-RBC interaction occurs or when a drug (eg, methyldopa) alters the RBC membrane, uncovering an antigen that induces autoantibody production.

• **Pulmonary effects:** Some drugs induce respiratory symptoms, deterioration in pulmonary function, and other pulmonary changes (see p. 1952).

• **Renal effects:** Tubulointerstitial nephritis is the most common allergic renal reaction (see p. 2414); methicillin, antimicrobials, and cimetidine are commonly implicated.

• **Other autoimmune phenomena:** Hydralazine and procainamide can cause an SLE-like syndrome. The syndrome is relatively benign, sparing the kidneys and CNS; the antinuclear antibody test is positive. Penicillamine can cause SLE and other autoimmune disorders (eg, myasthenia gravis).

**Diagnosis**

• Patient's report of a reaction soon after taking a drug

• Skin testing

• Sometimes drug provocation testing

• Sometimes direct and indirect antiglobulin assays

Drug hypersensitivity is suggested when a reaction occurs within minutes to hours after drug administration. However, many patients report a past reaction of uncertain nature. In such cases, if there is no equivalent substitute (eg, when penicillin is needed to treat syphilis), testing should be considered.

**Skin testing:** Tests for immediate-type (IgE-mediated) hypersensitivity help identify reactions to β-lactam antibiotics, foreign (xenogeneic) serum, and some vaccines and polypeptide hormones. However, typically, only 10 to 20% of patients who report a penicillin allergy have a positive reaction on skin tests. Also, for most drugs (including cephalosporins), skin tests are unreliable and, because they detect only IgE-mediated reactions, do not predict the occurrence of morbilliform eruptions, hemolytic anemia, or nephritis.

Penicillin skin testing is needed if patients with a history of an immediate hypersensitivity reaction must take a penicillin. BPO-polylysine conjugate and penicillin G are used with histamine and saline as controls. The prick test (see p. 1115) is used first. If patients have a history of a severe explosive reaction, reagents should be diluted 100-fold for initial testing. If prick tests are negative, intradermal testing may follow. If skin tests are positive, treating patients with penicillin may induce an anaphylactic reaction. If tests are negative, a serious reaction is less likely but not excluded. Although the penicillin skin test has not induced de novo sensitivity in patients, patients should usually be tested only immediately before essential penicillin therapy is begun.

For xenogeneic serum skin testing, patients who are not atopic and who have not received xenogeneic (eg, horse) serum previously should first be given a prick test with a 1:10 dilution; if this test is negative,
0.02 mL of a 1:1000 dilution is injected intradermally. A wheal > 0.5 cm in diameter develops within 15 min in sensitive patients. All patients who may have received serum previously—whether or not they reacted—and those with a suspected allergic history should be tested first with a 1:1000 dilution. A negative result rules out the possibility of anaphylaxis but does not predict incidence of subsequent serum sickness.

Other testing: For drug provocation testing, a drug suspected of causing a hypersensitivity reaction is given in escalating doses to precipitate the reaction. This test is probably safe and effective if done in a controlled setting.

Tests for hematologic drug reactions include direct and indirect antiglobulin tests (see p. 937). Tests for other specific drug hypersensitivity (eg, radioallergosorbent testing [RAST], histamine release, basophil or mast cell degranulation, lymphocyte transformation) are unreliable or experimental.

Prognosis

Hypersensitivity decreases with time. IgE antibodies are present in 90% of patients 1 yr after an allergic reaction but in only about 20 to 30% after 10 yr. Patients who have anaphylactic reactions are more likely to retain antibodies to the causative drug longer. People with drug allergies should be taught about avoiding the drug and should carry identification or an alert bracelet. Charts should always be appropriately marked.

Treatment

• Drug discontinuation
• Supportive treatment (eg, antihistamines, corticosteroids, epinephrine)
• Sometimes desensitization

Treatment is stopping the implicated drug; most symptoms and signs clear within a few days after the drug is stopped.

Symptomatic and supportive treatment for acute reactions may include antihistamines for pruritus, NSAIDs for arthralgias, corticosteroids for severe reactions (eg, exfoliative dermatitis, bronchospasm), and epinephrine for anaphylaxis. Conditions such as drug fever, a nonpruritic skin rash, or mild organ system reactions require no treatment (for treatment of specific clinical reactions, see elsewhere in THE MANUAL).

Desensitization: Rapid desensitization may be necessary if sensitivity has been established and if treatment is essential and no alternative exists. If possible, desensitization should be done in collaboration with an allergist. The procedure should not be attempted in patients who have had Stevens-Johnson syndrome. Whenever desensitization is used, O₂, epinephrine, and resuscitation equipment must be available for prompt treatment of anaphylaxis.

Desensitization is based on incremental dosing of the antigen every 30 min, beginning with a minute dose to induce subclinical anaphylaxis before exposure to therapeutic doses. This procedure depends on constant presence of drug in the serum and so must not be interrupted; desensitization is immediately followed by full therapeutic doses. Hypersensitivity typically returns 24 to 48 h after treatment is stopped. Minor reactions (eg, itching, rash) are common during desensitization.

For penicillin, oral or IV regimens can be used; sc or IM regimens are not recommended. If only the intradermal skin test is positive, 100 units (or μg)/mL iv in a 50-mL bag (5000 units total) should be given very slowly at first. If no symptoms appear, flow rate can be increased gradually until the bag is empty, after 20 to 30 min. The procedure is then repeated with concentrations of 1,000 units/mL and 10,000 units/mL, followed by the full therapeutic dose. If any allergic symptoms develop, flow rate should be slowed, and patients are given appropriate drug treatment (see above). If the prick test for penicillin was positive or patients have had a severe anaphylactic reaction, the starting dose should be lower.
Oral penicillin desensitization begins with 100 units (or μg); doses are doubled every 15 min up to 400,000 units (dose 13). Then, the drug is given parenterally, and if symptoms occur, they are relieved with appropriate anti-anaphylactic drugs.

For allergies to trimethoprim-sulfamethoxazole and vancomycin, regimens similar to those for penicillin can be used.

If a skin test to xenogeneic serum is positive, risk of anaphylaxis is high. If serum treatment is essential, desensitization must precede it. Skin tests, using weak concentrations prepared by serial dilution, are used to determine the appropriate starting dose for desensitization (ie, the concentration that produces a negative or only a weak reaction). 0.1 mL of this solution is injected sc or slowly IV; the IV route, although not standard, gives the clinician control over concentration and rate of delivery. If no reaction occurs in 15 min, the dose is doubled every 15 min until 1 mL of undiluted serum is given. This dose is repeated IM, and if no reaction occurs in another 15 min, the full dose can be given. If a reaction occurs, treatment may still be possible; the dose is reduced, an antihistamine is given as for acute urticaria, and the dose is then increased by smaller increments.

**Mastocytosis**

Mastocytosis is mast cell infiltration of skin or other tissues and organs. Symptoms result mainly from mediator release and include pruritus, flushing, and dyspepsia due to gastric hypersecretion. Diagnosis is by skin or bone marrow biopsy or both. Treatment is with antihistamines and control of any underlying disorder.

Mastocytosis is a group of disorders characterized by proliferation of mast cells and infiltration of the skin, other organs, or both. Pathology results mainly from release of mast cell mediators, including histamine, heparin, leukotrienes, and various inflammatory cytokines. Histamine causes many symptoms, including gastric symptoms, but other mediators also contribute. Significant organ infiltration may cause organ dysfunction. Mediator release may be triggered by physical touch, exercise, alcohol, NSAIDs, opioids, insect stings, or foods.

Etiology in many patients involves an activating mutation (D816V) in the gene coding for the stem cell factor receptor c-kit, present on mast cells.

**Classification**

Mastocytosis may be cutaneous or systemic.

**Cutaneous mastocytosis:** This type typically occurs in children. Most patients present with urticaria pigmentosa, a local or diffusely distributed salmon or brown maculopapular skin rash caused by multiple small mast cell collections. Less common are diffuse cutaneous mastocytosis, which is skin infiltration without discrete lesions, and mastocytoma, which is a large (1 to 5 cm) solitary collection of mast cells.

**Systemic mastocytosis:** This type most commonly occurs in adults and is characterized by multifocal bone marrow lesions; it often involves other organs, most commonly the skin, lymph nodes, liver, spleen, or GI tract. Systemic mastocytosis is classified as

- Indolent mastocytosis, with no organ dysfunction and a good prognosis
- Mastocytosis associated with other hematologic disorders (eg, myeloproliferative disorders, myelodysplasia, lymphoma)
- Aggressive mastocytosis, characterized by impaired organ function
- Mast cell leukemia, with > 20% mast cells in bone marrow, no skin lesions, multiorgan failure, and a poor prognosis
Symptoms and Signs

Skin involvement is often pruritic. Stroking or rubbing skin lesions causes urticaria and erythema around the lesion (Darier's sign); this reaction differs from dermatographism, which involves normal skin.

Systemic symptoms can occur with any form. The most common is flushing; the most dramatic is an anaphylactoid reaction with syncope and shock. Other symptoms include epigastric pain due to peptic ulcer disease, nausea, vomiting, chronic diarrhea, arthralgias, bone pain, and neuropsychiatric changes (eg, irritability, depression, mood lability). Hepatic and splenic infiltration may cause portal hypertension with resultant ascites.

Diagnosis

• Clinical evaluation

• Skin lesion biopsy and sometimes bone marrow biopsy

Diagnosis is suggested by clinical presentation. Diagnosis is confirmed by biopsy of skin lesions and sometimes of bone marrow. Multifocal, dense infiltrates of mast cells are present.

Tests may be done to rule out disorders that cause similar symptoms (anaphylaxis, pheochromocytoma, carcinoid syndrome, and Zollinger-Ellison syndrome). Serum gastrin level is useful to rule out Zollinger-Ellison syndrome in patients with ulcer symptoms; urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) is measured to rule out carcinoid in patients with flushing.

If the diagnosis is uncertain, levels of mast cell mediators and their metabolites (eg, urinary N-methylhistamine and N-methylimidazole acetic acid) may be measured in plasma and urine; elevated levels support the diagnosis of mastocytosis. The level of tryptase (a marker of mast cell degranulation) is elevated in systemic mastocytosis but is typically normal in cutaneous mastocytosis. A bone scan, GI workup, and identification of the D816V c-kit mutation can also be helpful in cases where the diagnosis requires confirmation.

Treatment

• For cutaneous mastocytosis, H₁ blockers and possibly psoralen plus ultraviolet light or topical corticosteroids

• For systemic mastocytosis, H₁ and H₂ blockers and sometimes cromolyn

• For aggressive forms, interferon alfa-2b, corticosteroids, or splenectomy

Cutaneous mastocytosis: H₁ blockers are effective for symptoms. Children with cutaneous forms require no additional treatment because most cases resolve spontaneously. Adults with cutaneous forms may be treated with psoralen plus ultraviolet light or with topical corticosteroids once/day or bid. Mastocytoma usually involutes spontaneously and requires no treatment. Cutaneous forms rarely progress to systemic disease in children but may do so in adults.

Systemic mastocytosis: All patients should be treated with H₁ and H₂ blockers. Aspirin controls flushing but may enhance leukotriene production, thereby contributing to mast cell-related symptoms; it should not be given to children because Reye's syndrome is a risk. Cromolyn 200 mg po qid (100 mg qid for children 2 to 12 yr; not to exceed 40 mg/kg/day) may help by preventing mast cell degranulation. No treatment can reduce the number of tissue mast cells. Ketotifen 2 to 4 mg po bid is inconsistently effective.

In patients with an aggressive form, interferon alfa-2b 4 million units sc once/wk to a maximum of 3 million units/day induces regression of bone lesions. Corticosteroids (eg, prednisone 40 to 60 mg po once/day for 2 to 3 wk) may be required. Splenectomy may improve survival.
Cytotoxic drugs (eg, daunomycin, etoposide, 6-mercaptopurine) may be indicated for treatment of mast cell leukemia, but efficacy is unproved. Imatinib (a tyrosine kinase receptor inhibitor) may be useful in some patients but is ineffective in patients with the D816V c-kit mutation. Midostaurin (a 2nd-generation tyrosine kinase receptor inhibitor) is under study in such patients.
Chapter 128. Transplantation

Introduction

Transplants may be the patient's own tissue (autografts; eg, bone, bone marrow, and skin grafts), genetically identical (syngeneic) donor tissue (isografts), genetically dissimilar donor tissue (allografts, or homografts), or, rarely, grafts from a different species (xenografts, or heterografts). Transplanted tissue may be cells (as for hematopoietic stem cell [HSC], lymphocyte, and pancreatic islet cell transplants), parts or segments of an organ (as for hepatic or pulmonary lobar transplants and skin grafts), or entire organs (as for heart transplants).

Tissues may be grafted to an anatomically normal site (orthotopic; eg, heart transplants) or abnormal site (heterotopic; eg, a kidney transplanted into the iliac fossa). Almost always, transplantation is done to improve patient survival. However, some procedures (eg, hand, larynx, tongue, and facial transplantation) attempt to improve quality of life but jeopardize quantity of life and thus are controversial.

With rare exceptions, clinical transplantation uses allografts from living related, living unrelated, or deceased donors. Living donors are often used for kidney and HSC transplants and increasingly for segmental liver, pancreas, and lung transplants. Use of deceased-donor organs (from heart-beating or non-heart-beating donors) has helped reduce the disparity between organ demand and supply; however, demand still far exceeds supply, and the number of patients waiting for organ transplants continues to grow.

All allograft recipients are at risk of graft rejection; the recipient's immune system recognizes the graft as foreign and seeks to destroy it. Recipients of grafts containing immune cells are at risk of graft-vs-host disease. Risk of these complications is minimized by pretransplantation screening and immunosuppressive therapy during and after transplantation.

Organ distribution: Allocation depends on disease severity for some organs (liver, heart) and on disease severity, time on the waiting list, or both for others (kidney, lung, bowel). In the US and Puerto Rico, organs are allocated first among 12 geographic regions, then among local Organ Procurement Organizations. If no recipient in the first region is suitable, organs are reallocated to recipients in other regions.

Pretransplantation Screening

Before the risk and expense of transplantation are undertaken and scarce donor organs are committed, physicians screen potential recipients for medical and nonmedical factors that may affect the likelihood of success.

Tissue compatibility: In pretransplantation screening, recipients and donors are tested for human leukocyte antigen (HLA) and ABO antigens, and recipients are tested for presensitization to donor antigens. HLA tissue typing is most important for kidney and the most common types of HSC transplantation. Heart, liver, pancreas, and lung transplantation typically occurs quickly, often before HLA tissue typing can be completed, so the role of matching for these organs is less well established.

HLA tissue typing of peripheral blood or lymph node lymphocytes is used to match the most important known determinants of histocompatibility in the donor and recipient. More than 1250 alleles determine 6 HLA antigens (HLA-A, -B, -C, -DP, -DQ, -DR), so matching is a challenge; eg, in the US, only 2 of 6 antigens on average are matched in kidney donors and recipients. Matching of as many HLA antigens as possible significantly improves functional survival of grafts from living related kidney and HSC donors; HLA matching of grafts from unrelated donors also improves survival, although much less so because of multiple undetected histocompatibility differences. Better immunosuppressive therapy has expanded eligibility for transplantation; HLA mismatches no longer automatically disqualify patients for transplantation.

ABO compatibility and HLA compatibility are important for graft survival. ABO mismatches can precipitate hyperacute rejection of highly vascular grafts (eg, kidney, heart), which have ABO antigens on the
endothelial surfaces. Presensitization to HLA and ABO antigens results from prior blood transfusions, transplantations, or pregnancies and can be detected with serology tests or, more commonly, with a lymphocytotoxic test using the recipient's serum and donor's lymphocytes in the presence of complement. A positive cross-match indicates that the recipient's serum contains antibodies directed against ABO or class I HLA antigens in the donor; it is an absolute contraindication to transplantation, except possibly in infants (up to age 14 mo) who have not yet produced isoagglutinins. High-dose IV immune globulin has been used to suppress HLA antibodies and facilitate transplantation, but long-term outcomes are unknown. A negative cross-match does not guarantee safety; when ABO antigens are compatible but not identical (eg, donor O and recipient A, B, or AB), hemolysis is a potential complication due to antibody production by transplanted (passenger) donor lymphocytes.

Although matching for HLA and ABO antigens generally improves graft survival, nonwhite patients are disadvantaged because they may have different HLA polymorphisms from white donors, a higher rate of presensitization to HLA antigens, and a higher incidence of blood types O and B.

**Infection:** Donor and recipient exposure to common infectious pathogens and active infections must be detected before transplantation to minimize risk of transmitting infection from the donor and risk of worsening or reactivating existing infection in the recipient (due to use of immunosuppressants). This screening usually includes the history; serologic tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicellazoster virus (VZV), hepatitis B and C viruses, HIV, and West Nile virus (if exposure is suspected); and tuberculin skin testing. Positive findings may require post-transplantation antiviral treatment (eg, for CMV infection or hepatitis B) or contraindicate transplantation (eg, if HIV with AIDS is detected).

**Contraindications to transplantation:** Absolute contraindications to transplantation include active infection and cancer (except hepatocellular carcinoma confined to the liver and certain neuroendocrine tumors).

Relative contraindications include age > 65, poor functional or nutritional status (including severe obesity), HIV infection, and multiorgan insufficiency. Psychologic and social factors also play a role in success of transplantation. For example, people who abuse drugs or who are psychologically unstable are less likely to firmly adhere to the necessary lifelong regimen of treatments and follow-up visits. Eligibility decisions for patients with relative contraindications differ by medical center. Immunosuppressants are safe and effective for HIV-positive transplant recipients.

**Immunosuppression**

Immunosuppressants control graft rejection and are primarily responsible for the success of transplantation. However, they suppress all immune responses and contribute to many post-transplantation complications, including death due to overwhelming infection. Except when HLA-identical transplants are used, immunosuppressants must usually be continued long after transplantation, but initially high doses can be reduced a few weeks after the procedure, and low doses can be continued indefinitely unless rejection occurs.

**Corticosteroids:** A high dose is usually given at the time of transplantation, then is reduced gradually to a maintenance dose, which is given indefinitely. Several months after transplantation, corticosteroids can be given on alternate days; this regimen helps prevent growth restriction in children. If rejection occurs, high doses are reinstituted.

**Calcineurin inhibitors (CNIs):** These drugs (cyclosporine, tacrolimus) block T-cell transcription processes required for production of cytokines, thereby selectively inhibiting T-cell proliferation and activation.

**Cyclosporine** is the most commonly used drug in heart and lung transplantation. It can be given alone but is usually given with other drugs (eg, azathioprine, prednisone), so that lower, less toxic doses can be used. The initial dose is reduced to a maintenance dose soon after transplantation. The drug is metabolized by the cytochrome P-450 3A enzyme, and blood levels are affected by many other drugs. The most serious adverse effect is nephrotoxicity; cyclosporine causes vasoconstriction of afferent
(preglomerular) arterioles, leading to glomerular apparatus damage, refractory glomerular hypoperfusion, and, eventually, chronic renal failure. Also, B-cell lymphomas and polyclonal B-cell lymphoproliferation occur more often in patients receiving high doses of cyclosporine or combinations of cyclosporine and other immunosuppressants directed at T cells, possibly because of an association with EBV. Other adverse effects include diabetes, hepatotoxicity, refractory hypertension, increased incidence of other tumors, and less serious effects (eg, gum hypertrophy, hirsutism). Serum cyclosporine levels do not correlate with effectiveness or toxicity.

**Tacrolimus** is the most commonly used drug in kidney, liver, pancreas, and small-bowel transplantation. Tacrolimus may be started at the time of transplantation or days after the procedure. Dosing should be guided by blood levels, which are influenced by the same drug interactions as for cyclosporine. Tacrolimus may be useful when cyclosporine is ineffective or has intolerable adverse effects. Adverse effects of tacrolimus are similar to those of cyclosporine except tacrolimus is more prone to induce diabetes; gum hypertrophy and hirsutism are less common. Lymphoproliferative disorders seem to occur more often in patients taking tacrolimus, even weeks after transplantation. If they occur, tacrolimus should be stopped and cyclosporine or another immunosuppressive drug substituted.

**Purine metabolism inhibitors:** Examples are azathioprine and mycophenolate mofetil.

**Azathioprine,** an antimetabolite, is usually started at the time of transplantation. Most patients tolerate it indefinitely. The most serious adverse effects are bone marrow depression and, rarely, hepatitis. Azathioprine is often used with low doses of cyclosporine.

**Mycophenolate mofetil** (MMF), a prodrug metabolized to mycophenolic acid, reversibly inhibits inosine monophosphate dehydrogenase, an enzyme in the guanine nucleotide pathway that is rate-limiting in lymphocyte proliferation. MMF is given with cyclosporine (or tacrolimus) and corticosteroids to patients with a kidney, heart, or liver transplant. The most common adverse effects are leukopenia, nausea, vomiting, and diarrhea.

**Rapamycins:** These drugs (sirolimus, everolimus) block a key regulatory kinase in lymphocytes, resulting in arrest of the cell cycle and in inhibition of lymphocyte response to cytokine stimulation.

**Sirolimus** is typically given with cyclosporine and corticosteroids and may be useful for patients with renal insufficiency. Adverse effects include hyperlipidemia, impaired wound healing, and bone marrow depression with leukopenia, thrombocytopenia, and anemia.

**Everolimus** is typically used to prevent heart transplant rejection; adverse effects are similar to those of sirolimus.

**Immunosuppressive Igs:** Examples are antilymphocyte globulin (ALG) and antithymocyte globulin (ATG). Both are fractions of animal antisera directed against human cells: lymphocytes (ALG) or thymus cells (ATG). ALG and ATG suppress cellular immunity while preserving humoral immunity. They are used with other immunosuppressants to allow those drugs to be used in lower, less toxic doses. Use of ALG or ATG to control acute episodes of rejection improves graft survival rates; use at the time of transplantation may decrease rejection incidence and allow CNIs to be started later, thereby reducing toxicity. Use of highly purified serum fractions has greatly reduced incidence of adverse effects (eg, anaphylaxis, serum sickness, antigen-antibody-induced glomerulonephritis).

**Monoclonal antibodies (mAbs):** mAbs directed against T cells provide a higher concentration of anti-T-cell antibodies and fewer irrelevant serum proteins than do ALG and ATG. OKT3 inhibits T-cell receptor (TCR)-antigen binding, resulting in immunosuppression. OKT3 is used primarily to control episodes of acute rejection; it may also be used at the time of transplantation to reduce incidence or delay onset of rejection episodes. However, benefits of prophylactic use must be weighed against adverse effects, which include severe CMV infection and development of neutralizing antibodies; these effects preclude using OKT3 for an actual rejection episode. With first use, OKT3 binds to the TCR-CD3 complex, activating the cell and triggering release of cytokines, which cause a syndrome of fevers, rigors, myalgias, arthralgias, nausea, vomiting, and diarrhea. Pretreatment with corticosteroids, antipyretics, and antihistamines can ameliorate these symptoms. The first-dose reaction less commonly includes chest...
pain, dyspnea, and wheezing, possibly due to complement activation. Repeated use is associated with increased incidence of EBV-induced B-cell lymphoproliferative disorders. Rarely, aseptic meningitis and hemolytic uremic syndrome occur.

Anti-IL-2 receptor monoclonal antibodies inhibit T-cell proliferation by blocking the effect of IL-2, secreted by activated T cells. Basiliximab and daclizumab, 2 humanized anti-IL-2 receptor antibodies, are increasingly being used to treat acute rejection of kidney, liver, and small-bowel transplants; they are also used as adjunct immunosuppressive therapy at the time of transplantation. The only adverse effect reported is anaphylaxis. Also, experience with IL-2 receptor antibodies is limited, and an increased risk of lymphoproliferative disorders cannot be excluded.

**Irradiation:** Irradiation of a graft, local recipient tissues, or both can be used to treat kidney transplant rejection episodes when other treatment (eg, corticosteroids and ATG) is ineffective. Total lymphatic irradiation is experimental but appears to safely suppress cellular immunity, at first by stimulation of suppressor T cells and later possibly by clonal deletion of specific antigen-reactive cells.

**Future therapies:** Protocols and agents to induce graft antigen-specific tolerance without suppressing other immune responses are being sought. Two strategies are promising:

- Blockade of T-cell costimulatory pathways using a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)-IgG1 fusion protein
- Induction of chimerism (coexistence of donor and recipient immune cells in which graft tissue is recognized as self) using nonmyeloablative pretransplantation treatment (eg, with cyclophosphamide, thymic irradiation, ATG, and cyclosporine) to induce transient T-cell depletion, engraftment of donor HSCs, and subsequent tolerance of solid organ transplants from the same donor

**Post-transplantation Complications**

Complications include the following:

- Rejection
- Infection
- Renal insufficiency
- Cancer

**Rejection:** Rejection of solid organs may be hyperacute, accelerated, acute, or chronic (late). These categories overlap somewhat in timing but can be distinguished histopathologically. Symptoms vary by organ (see Table 128-1).

**Hyperacute rejection** occurs within 48 h of transplantation and is caused by preexisting complement-fixing antibodies to graft antigens (presensitization). It has become rare (1%) as pretransplantation screening has improved. Hyperacute rejection is characterized by small-vessel thrombosis and graft infarction. No treatment is effective except graft removal.

**Accelerated rejection** occurs 3 to 5 days after transplantation and is caused by preexisting noncomplement-fixing antibodies to graft antigens. Accelerated rejection is also rare. It is characterized histopathologically by cellular infiltrate with or without vascular changes. Treatment is with high-dose pulse corticosteroids or, if vascular changes occur, antilymphocyte preparations. Plasmapheresis, which may clear circulating antibodies more rapidly, has been used.

**Acute rejection** is graft destruction after transplantation and is caused by a T cell-mediated delayed hypersensitivity reaction to allograft histocompatibility antigens. It accounts for about one half of all rejection episodes that occur within 10 yr. Acute rejection is characterized by mononuclear cellular
infiltration, with varying degrees of hemorrhage, edema, and necrosis. Vascular integrity is usually maintained, although vascular endothelium appears to be a primary target. Acute rejection is often reversed by intensifying immunosuppressive therapy (eg, with pulse corticosteroids, ALG, or both). After rejection

| Table 128-1. Signs of Transplant Rejection by Category |

reversal, severely damaged parts of the graft heal by fibrosis, the remainder of the graft functions normally, immunosuppressant doses can be reduced to very low levels, and the allograft can survive for long periods.

**Chronic rejection** is graft dysfunction, often without fever, typically occurring months to years after transplantation but sometimes within weeks. Causes are multiple and include early antibody-mediated rejection, periprocedural ischemia and reperfusion injury, drug toxicity, infection, and vascular factors (eg, hypertension, hyperlipidemia). Chronic rejection accounts for most of the other one half of all rejection episodes. Proliferation of neointima consisting of smooth muscle cells and extracellular matrix (transplantation atherosclerosis) gradually and eventually occludes vessel lumina, resulting in patchy ischemia and fibrosis of the graft. Chronic rejection progresses insidiously despite immunosuppressive therapy; no established treatments exist.

**Infection:** Immunosuppressants, secondary immunodeficiencies that accompany organ failure, and surgery make transplant patients more vulnerable to infections. Rarely, a transplanted organ is the source of infection (eg, CMV).

The most common sign is fever, often without localizing signs. Fever can also be a symptom of acute rejection but is usually accompanied by signs of graft dysfunction. If these signs are absent, the approach is similar to that for other FUO (see p. 1157); timing of symptoms and signs after transplantation helps narrow the differential diagnosis.

In the first month after transplantation, most infections are caused by the same hospital-acquired bacteria and fungi that infect other surgical patients (eg, *Pseudomonas* sp causing pneumonia, gram-positive bacteria causing wound infections). The greatest concern with early infection is that organisms can infect a graft or its vascular supply at suture sites, causing mycotic aneurysms or dehiscence.

Opportunistic infections occur 1 to 6 mo after transplantation (for treatment, see elsewhere in The Manual). Infections may be bacterial (eg, listeriosis, nocardiosis), viral (eg, due to CMV, EBV, VZV, or hepatitis B or C virus), fungal (eg, aspergillosis, cryptococcosis, *Pneumocystis jirovecii* infection), or parasitic (eg, strongyloidiasis, toxoplasmosis, trypanosomiasis, leishmaniasis).

Risk of infection returns to baseline for about 80% of patients after 6 mo. About 10% develop complications of early infections, such as viral infection of the graft, metastatic infection (eg, CMV retinitis, colitis), or virus-induced cancers (eg, hepatitis and hepatocellular carcinoma, human papillomavirus and basal cell carcinoma). Others develop chronic rejection, require high doses of immunosuppressants (5 to 10%), and remain at high risk of opportunistic infections indefinitely.

After transplantation, most patients are given antimicrobials to reduce risk of infection. Choice of drug depends on individual risk and type of transplantation; regimens include trimethoprim/sulfamethoxazole 80/400 mg po once/day for 4 to 12 mo to prevent *P. jirovecii* infection or to prevent UTIs in kidney transplant patients. Neutropenic patients are sometimes given quinolone antibiotics (eg, levofloxacin 500 mg po or IV once/day) to prevent infection with gram-negative organisms. Inactivated vaccines can be safely given post-transplantation; risks due to live-attenuated vaccines must be balanced against their potential benefits, especially for patients taking low doses of immunosuppressants.

**Renal disorders:** GFR decreases 30 to 50% during the first 6 mo after solid organ transplantation in 15 to 20% of patients. They usually also develop hypertension. Incidence is greatest for recipients of small-bowel transplants (21%) and least for recipients of heart-lung transplants (7%). Nephrotoxic and diabetogenic effects of CNIs are the most important contributor, but periprocedural renal insults, pretransplantation renal insufficiency, hepatitis C infection, and use of other nephrotoxic drugs also
contribute. After the initial decrease, GFR typically stabilizes or decreases more slowly; nonetheless, mortality risk quadruples unless subsequent kidney transplantation is done. Renal insufficiency after transplantation may be prevented by early weaning from CNIs, but a safe minimum dose has not been determined.

**Cancer:** Long-term immunosuppression increases incidence of virus-induced cancer, especially squamous and basal cell carcinoma, lymphoproliferative disorders (mainly B-cell non-Hodgkin lymphoma), anogenital (including cervical) cancer, and Kaposi's sarcoma. Treatment is similar to that of cancer in nonimmunosuppressed patients; reduction or interruption of immunosuppression is not usually required for low-grade tumors but is recommended for more aggressive tumors and lymphomas.

Transfusion of partially HLA-matched cytotoxic T cells is under study as a possible treatment for some forms of lymphoproliferative disorders.

**Other complications:** Immunosuppressants (especially corticosteroids and CNIs) increase bone resorption and risk of osteoporosis for patients who are at risk before transplantation (eg, because of reduced physical activity, tobacco and alcohol use, or a preexisting renal disorder). Although not routine, use of vitamin D, bisphosphonates, or other antiresorptive drugs after transplantation may play a role in prevention.

Failure to grow, primarily as a consequence of chronic corticosteroid use, is a concern in children. Growth failure can be mitigated by tapering corticosteroids to the minimum dose that does not lead to graft rejection.

Systemic atherosclerosis can result from hyperlipidemia due to use of CNIs and corticosteroids; it typically occurs in kidney transplant recipients > 15 yr post-transplantation.

**Graft vs host disease (GVHD)** occurs when donor T cells react against recipient's self-antigens. GVHD primarily affects hematopoietic stem cell recipients (see p. 1132) but may also affect liver and small-bowel transplant recipients.

**Heart Transplantation**

Heart transplantation is an option for patients who have end-stage heart failure, coronary artery disease (CAD), arrhythmias, hypertrophic cardiomyopathy, or congenital heart disease and who remain at risk of death and have intolerable symptoms despite optimal use of drugs and medical devices. Transplantation may also be indicated for patients who cannot be weaned from temporary cardiac-assist devices after MI or nontransplant cardiac surgery and for patients with cardiac sequelae of a lung disorder requiring lung transplantation. The only absolute contraindication is pulmonary hypertension; relative contraindications include organ insufficiency (eg, pulmonary, renal, hepatic) and local or systemic infiltrative disorders (eg, cardiac sarcoma, amyloidosis).

All donated hearts come from brain-dead donors, who must be < 60 and have normal cardiac and pulmonary function and no history of CAD or other heart disorders. Donor and recipient must have compatible ABO blood type and heart size. About 25% of eligible recipients die before a donor organ becomes available. Left ventricular assist devices and artificial hearts provide interim hemodynamic support for patients waiting for a transplant. However, if left in place too long, these devices put the recipient at high risk of sepsis, device failure, and thromboembolism.

**Procedure**

Donor hearts are preserved by hypothermic storage. They must be transplanted within 4 to 6 h. The recipient is placed on a bypass pump, and the recipient heart is removed, preserving the posterior right atrial wall in situ. The donor heart is then transplanted orthotopically with aortic, pulmonary artery, and pulmonary vein anastomoses; a single anastomosis joins the retained posterior atrial wall to that of the donor organ.

Immunosuppressive regimens vary but are similar to those for kidney or liver transplantation (eg, anti-IL-2...
receptor monoclonal antibodies, a calcineurin inhibitor, corticosteroids). About 50 to 80% of patients have at least 1 episode of rejection (average 2 to 3); most patients are asymptomatic, but about 5% develop left ventricle dysfunction or atrial arrhythmias. Incidence of acute rejection peaks at 1 mo, decreases over the next 5 mo, and levels off by 1 yr. Risk factors for rejection include younger age, female recipient, or black donor, and HLA mismatching. Cytomegalovirus (CMV) infection may also influence risk.

Because graft damage can be irreversible and catastrophic, surveillance endomyocardial biopsy is usually done once/yr; degree and distribution of mononuclear cell infiltrate and presence of myocyte injury in specimens is determined. Differential diagnosis includes perioperative ischemia, CMV infection, and idiopathic B-cell infiltration (Quilty lesions). Mild rejection (grade 1) without detectable clinical sequelae requires no treatment; moderate or severe rejection (grades 2 to 4) or mild rejection with clinical sequelae is treated with corticosteroids and antithymocyte globulin or OKT3 as needed.

The main complication is cardiac allograft vasculopathy, a form of atherosclerosis that diffusely narrows or obliterates vessel lumina (in 25% of patients). Its cause is probably multifactorial and relates to donor age, cold and reperfusion ischemia, dyslipidemia, immunosuppressants, chronic rejection, and viral infection (adenovirus in children, CMV in adults). For early detection, surveillance stress testing or coronary angiography with or without intravascular ultrasonography is often done at the time of endomyocardial biopsy. Treatment is aggressive lipid lowering (see p. 896) and diltiazem; everolimus 1.5 mg po bid may be preventive.

Prognosis

Survival rates at 1 yr are 85%, and annual mortality thereafter is about 4%. Pretransplantation predictors of 1-yr mortality include need for preoperative ventilation or left ventricular assist devices, cachexia, female recipient or donor, and diagnoses other than heart failure or CAD. Post-transplantation predictors include elevated C-reactive protein and troponin levels.

Cause of death within 1 yr is most often acute rejection and infection; cause after 1 yr is most often cardiac allograft vasculopathy or a lymphoproliferative disorder. Prognosis of recipients alive at > 1 yr is excellent; exercise capacity remains below normal but is sufficient for daily activities and may increase over time with sympathetic reinnervation. More than 95% of patients reach New York Heart Association class I cardiac status, and > 70% return to full-time employment.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell (HSC) transplantation is a rapidly evolving technique that offers a potential cure for hematologic cancers (leukemias, lymphomas, myeloma) and other hematologic disorders (eg, primary immunodeficiency, aplastic anemia, myelodysplasia). HSC transplantation may be autologous or allogeneic; bone marrow, peripheral blood, or umbilical cord stem cells may be used. Peripheral blood has largely replaced bone marrow as a source of stem cells, especially in autologous HSC transplantation, because stem cell harvest is easier and neutrophil and platelet counts recover faster. Umbilical cord HSC transplantation has been restricted mainly to children because the number of stem cells is low.

There are no contraindications to autologous HSC transplantation. Contraindications to allogeneic HSC transplantation are relative and include age > 50, previous HSC transplantation, and significant comorbidities. Allogeneic HSC transplantation is limited mainly by lack of histocompatible donors. An HLA-identical sibling donor is ideal, followed by an HLA-matched sibling donor. Because only one fourth of patients have such a sibling donor, mismatched related or matched unrelated donors (identified through international registries) are often used. However, long-term disease-free survival rates may be lower than those with HLA-identical sibling donors. The technique for umbilical cord HSC transplantation is still being defined, but HLA-matching is probably unimportant.

Procedure

For bone marrow stem cell harvest, 700 to 1500 mL (maximum 15 mL/kg) of marrow is aspirated from the donor’s posterior iliac crests; local or general anesthesia is used. For peripheral blood harvest, the donor is treated with recombinant growth factors (granulocyte colony-stimulating factor or granulocyte-
macrophage colony-stimulating factor) to stimulate proliferation and mobilization of stem cells, with standard phlebotomy 4 to 6 days afterward. Fluorescence-activated cell sorting is used to identify and separate stem cells from other cells.

Stem cells are then infused over 1 to 2 h through a large-bore central venous catheter. In HSC transplantation for cancer, the recipient first is given a conditioning regimen (eg, cyclophosphamide 60 mg/kg IV once/day for 2 days with total body irradiation, busulfan 1 mg/kg po qid for 4 days plus cyclophosphamide without total body irradiation) to induce remission and suppress the immune system so that the graft can be accepted. Similar regimens are used for allogeneic HSC transplantation, even when cancer is not the indication, to reduce incidence of rejection and relapse, but not for autologous HSC transplantation. Nonmyeloablative conditioning regimens may reduce morbidity and mortality risks and may be useful for elderly patients, patients with comorbidities, and patients susceptible to a graft-vs-tumor effect (eg, those with multiple myeloma).

After transplantation, recipients are given colony-stimulating factors to shorten duration of post-transplantation leucopenia, prophylactic anti-infective drugs (see p. 1130), and, in allogeneic HSC transplantation, up to 6 mo of prophylactic immunosuppressants (typically methotrexate and cyclosporine) to prevent donor T cells from reacting against recipient major histocompatibility complex molecules (graft-vs-host disease [GVHD]). Broad-spectrum antibiotics are usually withheld unless fever develops. Engraftment typically occurs 10 to 20 days after HSC transplantation (earlier with peripheral blood stem cells) and is defined by an absolute neutrophil count > 500 × 10^6/L.

Major early complications (<100 days) include

- Failure to engraft
- Rejection
- Acute GVHD

Failure to engraft and rejection affect < 5% of patients and manifest as persistent pancytopenia or irreversible decline in blood counts. Treatment is corticosteroids for several weeks.

Acute GVHD occurs in recipients of allogeneic HSC transplants, 40% of HLA-matched sibling graft recipients, and 80% of unrelated donor graft recipients. It causes fever, rash, hepatitis with hyperbilirubinemia, vomiting, diarrhea, abdominal pain (which may progress to ileus), and weight loss. Risk factors include HLA and sex mismatching; unrelated donor; older age of recipient, donor, or both; donor presensitization; and inadequate GVHD prophylaxis. Diagnosis is obvious by history and physical examination; treatment is methylprednisolone 2 mg/kg IV once/day, increased to 10 mg/kg if there is no response within 5 days.

Major later complications include

- Chronic GVHD
- Disease relapse

Chronic GVHD may occur by itself, develop from acute GVHD, or occur after resolution of acute GVHD. It typically occurs 4 to 7 mo after HSC transplantation (range 2 mo to 2 yr). Chronic GVHD occurs in recipients of allogeneic HSC transplants, about 35 to 50% of HLA-matched sibling graft recipients, and 60 to 70% of unrelated donor graft recipients. It affects primarily the skin (eg, lichenoid rash, scleroderma) and mucous membranes (eg, keratoconjunctivitis sicca, periodontitis, orogenital lichenoid reactions), but it also affects the GI tract and liver. Immunodeficiency is a primary feature; bronchiolitis obliterans similar to that after lung transplantation can also develop. Ultimately, 20 to 40% die of GVHD; mortality rate is higher with more severe reactions. Treatment may not be necessary for skin and mucous membrane disease; treatment of more extensive disease is similar to that of acute GVHD. T-cell depletion of allogeneic donor grafts using monoclonal antibodies or mechanical separation reduces incidence and severity of GVHD but also eliminates a graft-vs-tumor effect that may enhance stem cell proliferation and
engraftment and reduce disease relapse rates. Relapse rates with autologous HSC transplantation are higher for this reason and because circulating tumor cells may be transplanted. Ex vivo tumor cell purging before autologous transplantation is under study.

In patients without chronic GVHD, all immunosuppression can be stopped 6 mo after HSC transplantation; thus, late complications are rare in these patients.

Prognosis

Prognosis varies by indication and procedure. Overall, disease relapse occurs in 40 to 75% of recipients of autologous HSC transplants and in 10 to 40% of recipients of allogeneic HSC transplants. Success (cancer-free bone marrow) rates are 30 to 40% for patients with relapsed, chemotherapy-sensitive lymphoma and 20 to 50% for patients with acute leukemia in remission; compared with chemotherapy alone, HSC transplantation improves survival of patients with multiple myeloma. Success rates are low for patients with more advanced disease or with responsive solid cancers (eg, breast cancer, germ cell tumors). Relapse rates are reduced in patients with GVHD, but overall mortality rates are increased if GVHD is severe. Intensive preparative regimens, effective GVHD prophylaxis, cyclosporine-based regimens, and improved supportive care (eg, antibiotics, herpesvirus and cytomegalovirus prophylaxis) have increased long-term disease-free survival after HSC transplantation.

Kidney Transplantation

Kidney transplantation is the most common type of solid organ transplantation; the primary indication is end-stage renal failure. Absolute contraindications include comorbidities that could compromise graft survival (eg, severe heart disorders, cancer), which can be detected via thorough screening. Relative contraindications include poorly controlled diabetes, which can lead to renal failure. Patients in their 60s may be transplant candidates if they are otherwise healthy and functionally independent with good social support, if they have a reasonably long life expectancy, and if transplantation is likely to substantially improve function and quality of life beyond simply freeing them from dialysis. Patients with type 1 diabetes may be candidates for simultaneous pancreas-kidney or pancreas-after-kidney transplantation.

More than one half of donated kidneys come from previously healthy, brain-dead people. About one third of these kidneys are marginal, with physiologic or procedure-related damage, but are used because demand is so great. The remaining donated kidneys come from living donors; because of limited supply, allografts from carefully selected living unrelated donors are being increasingly used. Living donors relinquish reserve renal capacity, may put themselves at risk of procedural and long-term morbidity, and may have psychologic conflicts about donation; therefore, they are evaluated for normal bilateral renal function, absence of systemic disease, histocompatibility, emotional stability, and ability to give informed consent. Hypertension, diabetes, and cancer (except possibly CNS tumors) usually preclude kidney donation from living donors.

Procedure

The donor kidney is removed during an open or laparoscopic procedure, perfused with cooling solutions containing relatively large concentrations of poorly permeating substances (eg, mannitol, hetastarch) and electrolyte concentrations approximating intracellular levels, then stored in an iced solution. Kidneys preserved this way usually function well if transplanted within 48 h. Although not commonly used, continuous pulsatile hypothermic perfusion with an oxygenated, plasma-based perfusate can extend ex vivo viability up to 72 h.

Dialysis may be required before transplantation to ensure a relatively normal metabolic state, but living-donor allografts appear to survive better in recipients who have not begun long-term dialysis before transplantation. Nephrectomy is usually not required unless native kidneys are infected. Whether transfusions are useful for anemic patients anticipating an allograft is unclear; transfusions can sensitize patients to alloantigens, but allografts may survive better in recipients who receive transfusions but do not become sensitized, possibly because transfusions induce some form of tolerance.

The transplanted kidney is usually placed in the iliac fossa. Renal vessels are anastomosed to the iliac
vessels, and the donor ureter is implanted into the bladder or anastomosed to the recipient ureter. Vesicoureteral reflux occurs in about 30% of recipients but is usually harmless.

Immunosuppressive regimens vary. Commonly, calcineurin inhibitors are begun immediately after transplantation in doses titrated to minimize toxicity and rejection while maintaining trough blood levels > 200 ng/mL. On the day of transplantation, IV or oral corticosteroids are also given; dose is tapered over the following 12 wk.

Despite use of immunosuppressants, about 20% of recipients have one or more rejection episodes within the first year after transplantation. Most episodes are probably insignificant, subclinical, and therefore never detected; however, they contribute to long-term insufficiency, graft failure, or both. Signs of rejection vary by type (see Table 128-1).

Rejection can be diagnosed by percutaneous needle biopsy if the diagnosis is unclear clinically. Biopsy may also help distinguish antibody-mediated from T-cell-mediated rejection and identify other common causes of graft insufficiency or failure (eg, calcineurin inhibitor toxicity, diabetic or hypertensive nephropathy, polyomavirus type 1 infection). Advanced tests that may improve accuracy of rejection diagnosis include measurement of urinary mRNA-encoding mediators of rejection and gene expression profiling of biopsy samples using DNA microarrays.

Chronic allograft nephropathy refers to graft insufficiency or failure ≥ 3 mo after transplantation. Most cases are attributable to one or more of the above causes. Some experts believe the term should be reserved to describe graft insufficiency or failure when biopsy shows chronic interstitial fibrosis and tubular atrophy not attributable to any other cause.

Intensified immunosuppressive therapy (eg, with high-dose pulse corticosteroids or antilymphocyte globulin) usually reverses accelerated or acute rejection. If immunosuppressants are ineffective, dose is tapered and hemodialysis is resumed until a subsequent transplant is available. Nephrectomy of the transplanted kidney is necessary if hematuria, graft tenderness, or fever develops after immunosuppressants are stopped.

Prognosis

Most rejection episodes and other complications occur within 3 to 4 mo after transplantation; most patients then return to more normal health and activity but must take maintenance doses of immunosuppressants indefinitely.

At 1 yr, survival rates with living-donor grafts are 98% for patients and 94% for grafts; rates with deceased-donor grafts are 94% and 88%, respectively. Subsequent annual graft loss rates are 3 to 5% with a living-donor graft and 5 to 8% with a deceased-donor graft.

Among patients whose graft survives the first year, one half die of other causes with the graft functioning normally; one half develop chronic allograft nephropathy with the graft malfunctioning in 1 to 5 yr. Rates of late failure are higher for blacks than for whites.

Doppler ultrasonographic measurement of peak systolic and minimal end-diastolic flow in renal segmental arteries ≥ 3 mo after transplantation may help assess prognosis, but the gold standard remains serial determination of serum creatinine.

Liver Transplantation

Liver transplantation is the 2nd most common type of solid organ transplantation. Indications include cirrhosis (70% of US transplants, 60 to 70% of which are attributed to hepatitis C); fulminant hepatic necrosis (about 8%); hepatocellular carcinoma (about 7%); biliary atresia and metabolic disorders, primarily in children (about 3% each); and other cholestatic (eg, primary sclerosing cholangitis) and noncholestatic (eg, autoimmune hepatitis) disorders (about 8%). For patients with hepatocellular carcinoma, transplantation is indicated for 1 tumor < 5 cm or up to 3 tumors < 3 cm (Milan criteria) and for some fibrolamellar types. For patients with liver metastases, transplantation is indicated only for
neuroendocrine tumors without extrahepatic growth after removal of the primary tumor.

Absolute contraindications are elevated intracranial pressure (> 40 mm Hg) or low cerebral perfusion pressure (< 60 mm Hg) in patients with fulminant hepatic necrosis, severe pulmonary hypertension (mean pulmonary arterial pressure > 50 mm Hg), sepsis, and advanced or metastatic hepatocellular carcinoma; all of these conditions lead to poor outcomes during or after transplantation.

Nearly all donated livers come from size- and ABO-matched deceased, heart-beating donors. Annually, about 500 come from living donors, who can live without their right lobe (in adult-to-adult transplantation) or the lateral segment of their left lobe (in adult-to-child transplantation). Advantages of living donation for the recipient include shorter waiting times, shorter cold ischemic times for explanted organs, and the ability to schedule transplantation to optimize the patient's condition. Disadvantages to the donor include mortality risk of 1/300 to 400 (compared with 1/3300 in living-donor kidney transplantation) and complications (especially bile leakage) in up to one fourth, usually when resection is lobar (not segmental). Living donors are also at risk of psychologic coercion. A few livers come from deceased, non-heart-beating donors.

Donor (deceased or living) risk factors for graft failure in the recipient include age > 50; hepatic steatosis; elevated liver enzymes, bilirubin, or both; prolonged stay in ICU; hypotension requiring vasopressors; and hypernatremia. Transplants from female donors to male recipients may also increase risk. But because imbalance between supply and demand is greatest for liver transplants (and is growing because prevalence of hepatitis-induced cirrhosis is increasing), livers from donors > 50 and with short cold ischemia times, those with fatty infiltration, and those with viral hepatitis (for transplantation into recipients with viral hepatitis-induced cirrhosis) are increasingly being used.

Additional techniques to increase supply include split liver transplantation, in which deceased-donor livers are divided into right and left lobes or right lobe and left lateral segment (done in or ex situ) and given to 2 recipients, and domino transplantation, rarely indicated, in which a deceased-donor liver is given to a recipient with an infiltrative disease (eg, amyloidosis), and the explanted diseased liver is given to an elderly recipient who can benefit from the diseased liver but is not expected to live long enough to experience adverse effects of transplant dysfunction.

Despite these innovations, many patients die waiting for transplants. Liver-assist devices (extracorporeal perfusion of cultured hepatocyte suspensions or immortalized hepatoma cell lines) are used in some centers to keep patients alive until a liver is available or acute dysfunction resolves. For distribution of available organs, patients on the national waitlist are given a prognostic score derived from creatinine, bilirubin, and INR measurements (for adults) or from age and serum albumin, bilirubin, INR, and growth failure measurements (for children). For patients with hepatocellular carcinoma, the score incorporates tumor size and waiting time (increasing with each). Patients with higher scores are more likely to die and are given higher priority for organs from ABO- and weight-matched donors.

Procedure

Deceased-donor livers are removed after exploratory laparotomy confirms absence of intra-abdominal disease that would preclude transplantation. Living donors undergo lobar or segmental resection. Explanted livers are perfused and stored in a cold preservation solution for up to 24 h before transplantation; incidence of graft nonfunction and ischemic-type biliary injury increases with prolonged storage.

Recipient hepatectomy is the most demanding part of the procedure because it is often done in patients with portal hypertension and coagulation defects. Intraoperative blood loss can total > 100 units in rare cases, but use of a cell saver machine and autotransfusion devices reduce allogeneic transfusion requirements to an average of 5 to 10 units. After hepatectomy, the suprahepatic vena cava of the donor graft is anastomosed to the recipient's vena cava in an end-to-side fashion ("piggy-back" technique). Donor and recipient portal veins, hepatic arteries, and bile ducts are then anastomosed. With this technique, a bypass pump is not needed to carry portal venous blood to the systemic venous circuit. Heterotopic placement of the liver provides an auxiliary liver and obviates several technical difficulties, but outcomes have been discouraging, and this technique is still experimental.
Immunosuppressive regimens vary. Commonly, anti-IL-2 receptor monoclonal antibodies are given on the day of transplantation, with a calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate mofetil, and corticosteroids. Except in patients with autoimmune hepatitis, corticosteroids can be tapered within weeks and often stopped after 3 to 4 mo. Compared with other solid organ transplantation, liver transplantation requires the lowest doses of immunosuppressants.

Liver allografts are less aggressively rejected than other organ allografts for unknown reasons; hyperacute rejection occurs less frequently than expected in patients presensitized to HLA or ABO antigens, and immunosuppressants can often be tapered relatively quickly and eventually stopped. Most episodes of acute rejection are mild and self-limited, occur in the first 3 to 6 mo, and do not affect graft survival. Risk factors include younger recipient age, older donor age, greater HLA mismatching, longer cold ischemia times, and autoimmune disorders; worse nutritional status (eg, in alcoholism) appears protective.

Symptoms and signs of rejection depend on the type of rejection (see Table 128-1). Symptoms of acute rejection occur in about 50% of patients; symptoms of chronic rejection occur in < 2%.

Differential diagnosis of acute rejection includes viral hepatitis (eg, cytomegalovirus or Epstein-Barr virus infection; recurrent hepatitis B, C, or both), calcineurin inhibitor toxicity, and cholestasis. Rejection can be diagnosed by percutaneous needle biopsy if the diagnosis is unclear clinically. Suspected rejection is treated with IV corticosteroids; antithymocyte globulin and OKT3 are options when corticosteroids are ineffective (in 10 to 20%). Retransplantation is tried when rejection is refractory to immunosuppressants.

Immunosuppression contributes to recurrence of viral hepatitis in patients who had viral hepatitis-induced cirrhosis before transplantation. Hepatitis C recurs in nearly all patients; usually, viremia and infection are clinically silent but may cause active hepatitis and cirrhosis. Risk factors for clinically significant reinfection may be related to the recipient (older age, HLA type, hepatocellular carcinoma), donor (older age, fatty infiltration, prolonged ischemic time, living donor), virus (high viral load, genotype 1B, failure to respond to interferon), or postprocedural events (immunosuppressant doses, acute rejection treated with corticosteroids or OKT3, cytomegalovirus infection). Standard treatment (see p. 258) is only marginally effective. Hepatitis B recurs in all but has been successfully managed with hepatitis B immune globulin and lamivudine; co-infection with hepatitis D appears protective against recurrence.

Early (within 2 mo) complications of liver transplantation include primary nonfunction in 1 to 5%, biliary dysfunction (eg, ischemic anastomotic strictures, bile leakage, ductal obstructions, leakage around T-tube site) in 15 to 20%, portal vein thrombosis in < 5%, hepatic artery thrombosis in 3 to 5% (especially in small children or patients taking sirolimus), hepatic artery mycotic or pseudoaneurysm, and hepatic artery rupture. Typical symptoms include fever, hypotension, and elevated liver function enzymes.

The most common late complications are intrahepatic or anastomotic bile duct strictures, which produce symptoms of cholestasis and cholangitis. Strictures can sometimes be treated endoscopically or through percutaneous transhepatic cholangiographic dilation, stenting, or both, but they often ultimately require retransplantation.

Prognosis

At 1 yr, survival rates with living-donor grafts are 90% for patients and 82% for grafts; rates with deceased-donor grafts are 86% and 82%, respectively. Overall rates for patients and grafts, respectively, are 79% and 72% at 3 yr and 73% and 65% at 5 yr. Survival is better for chronic than for acute liver failure. Death after 1 yr is rare and attributable to a recurrent disorder (eg, cancer, hepatitis) rather than to post-transplantation complications.

Recurrent hepatitis C infection leads to cirrhosis in 15 to 30% of patients by 5 yr. Hepatic disorders with an autoimmune component (eg, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis) recur in 20 to 30% by 5 yr.

Lung Transplantation
Lung transplantation is an option for patients who have respiratory insufficiency or failure and who remain at risk of death despite optimal medical treatment. The most common indications are COPD, idiopathic pulmonary fibrosis, cystic fibrosis, α₁-antitrypsin deficiency, and primary pulmonary hypertension. Less common indications include interstitial lung disorders (eg, sarcoidosis), bronchiectasis, and congenital heart disease. Single and double lung procedures are equally appropriate for most lung disorders without cardiac involvement; the exception is chronic diffuse infection (eg, bronchiectasis), for which double lung transplantation is best. Heart-lung transplantation is indicated for Eisenmenger’s syndrome and for any lung disorder with severe ventricular dysfunction likely to be irreversible; cor pulmonale is not an indication because it often reverses after lung transplantation. Single and double lung procedures are about equally common and are at least 8 times more common than heart-lung transplantation.

Relative contraindications include age (single lung recipients must be < 65; double lung recipients, < 60; and heart and lung recipients, < 55), active cigarette smoking, previous thoracic surgery, and, for some cystic fibrosis patients and at some medical centers, lung infection with resistant strains of *Burkholderia cepacia*, which greatly increases mortality risk.

Nearly all donated lungs are from brain-dead, heart-beating donors. Rarely, living adult (usually parent-to-child) lobar transplantation is done when deceased-donor organs are unavailable. Donors must be < 65 and never-smokers and have no active lung disorder as evidenced by

- Oxygenation: PaO₂/FIO₂ (fractional inspired O₂) > 250 to 300, with PaO₂ in mm Hg and FIO₂ in decimal fraction (eg, 0.5)
- Lung compliance: Peak inspiratory pressure < 30 cm H₂O at tidal volume (Vₜ) 15 mL/kg and positive end-expiratory pressure = 5 cm H₂O
- Gross appearance: Using bronchoscopy

Donor and recipients must be size-matched anatomically (by chest x-ray), physiologically (by total lung capacity), or both.

Timing of referral for transplantation should be determined by factors such as

- Degree of obstructive defect: Forced expiratory volume in 1 sec (FEV₁) < 25 to 30% predicted in patients with COPD, α₁-antitrypsin deficiency, or cystic fibrosis
- PaO₂ < 55 mm Hg
- PaCO₂ > 50 mm Hg
- Right atrial pressure > 10 mm Hg and peak systolic pressure > 50 mm Hg for patients with primary pulmonary hypertension
- Progression rate of clinical, radiographic, or physiologic disease

**Procedure**

The donor is anticoagulated, and a cold crystalloid preservation solution containing prostaglandins is flushed through the pulmonary arteries into the lungs. Donor organs are cooled with iced saline slush in situ or via cardiopulmonary bypass, then removed. Prophylactic antibiotics are often given.

**Single lung transplantation** requires posterolateral thoracotomy. The native lung is removed, and the bronchus, pulmonary artery, and pulmonary veins of the donor lung are anastomosed to their respective cuffs. The bronchial anastomosis requires intussusception or wrapping with omentum or pericardium to facilitate adequate healing. Advantages include a simpler operation, avoidance of cardiopulmonary
bypass and systemic anticoagulation (usually), more flexibility concerning size matching, and availability of the contralateral lung from the same donor for another recipient. Disadvantages include the possibility of ventilation/perfusion mismatch between the native and transplant lungs and the possibility of poor healing of the single bronchial anastomosis.

**Double lung transplantation** requires sternotomy or anterior transverse thoracotomy; the procedure is similar to 2 sequential single transplants. The primary advantage is definitive removal of all diseased tissue. The disadvantage is poor healing of the tracheal anastomosis.

**Heart-lung transplantation** requires median sternotomy with cardiopulmonary bypass. Aortic, right atrial, and tracheal anastomoses are required; the trachea is anastomosed immediately above the bifurcation. The primary advantages are improved graft function and more dependable healing of the tracheal anastomosis because of coronary-bronchial collaterals within the heart-lung block. Disadvantages include long operative time with the need for cardiopulmonary bypass, the need for close size matching, and use of 3 donor organs by one recipient.

Methylprednisolone IV is often given to recipients before reperfusion of the transplanted lung. A common immunosuppressive regimen combines a calcineurin inhibitor (cyclosporine or tacrolimus), a purine metabolism inhibitor (azathioprine or mycophenolate mofetil), and methylprednisolone. Prophylactic antithymocyte globulin (ATG) or OKT3 may also be given during the first 2 wk after transplantation. Corticosteroids may be omitted to facilitate healing of the bronchial anastomosis; higher doses of other drugs (eg, cyclosporine, azathioprine) are substituted. Immunosuppressants are continued indefinitely.

Rejection develops in most patients despite immunosuppressive therapy. Symptoms and signs are similar in hyperacute, acute, and chronic forms and include fever, dyspnea, cough, decreased SaO\textsubscript{2}, interstitial infiltrate on x-ray, and a decrease in FEV\textsubscript{1} by > 10 to 15%. Hyperacute rejection must be distinguished from early graft dysfunction caused by ischemic injury during the transplantation procedure. Diagnosis is confirmed if bronchoscopic transbronchial biopsy shows perivascular lymphocytic infiltration in small vessels. IV corticosteroids are usually effective. Treatment of recurrent or resistant cases varies and includes higher corticosteroid doses, aerosolized cyclosporine, ATG, and OKT3.

**Chronic rejection** (after > 1 yr) occurs in up to 50% of patients; it takes the form of obliterative bronchiolitis or, less commonly, atherosclerosis. Acute rejection may increase risk of chronic rejection. Patients with obliterative bronchiolitis present with cough, dyspnea, and decreased FEV\textsubscript{1} with or without physical and radiographic evidence of an airway process. Differential diagnosis includes pneumonia. Diagnosis is by bronchoscopy with biopsy. No treatment has proved effective, but options include corticosteroids, ATG or OKT3, inhaled cyclosporine, and retransplantation.

The most common surgical complication is poor healing of the bronchial or tracheal anastomosis. Up to 20% of single lung recipients develop bronchial stenosis that causes wheezing and airway obstruction; it can be treated with dilation or stent placement. Other surgical complications include hoarseness and diaphragmatic paralysis, caused by damage to the recurrent laryngeal or phrenic nerves; GI dysmotility, caused by damage to the thoracic vagus nerve; and pneumothorax. Supraventricular arrhythmias develop in some patients, probably because of conduction changes caused by pulmonary vein-atrial suturing.

**Prognosis**

At 1 yr, survival rates are 84% with living-donor grafts and 83% with deceased-donor grafts. At 5 yr, survival rates are 34% with living-donor grafts and 46% with deceased-donor grafts. Mortality rate is higher for patients with primary pulmonary hypertension, idiopathic pulmonary fibrosis, or sarcoidosis and lower for those with COPD or α\textsubscript{1}-antitrypsin deficiency. Mortality rate is higher for single lung transplantation than for double. Most common causes of death within 1 mo are primary graft failure, ischemia and reperfusion injury, and infection (eg, pneumonia) excluding cytomegalovirus; the most common cause between 1 mo and 1 yr is infection; and after 1 yr, it is obliterative bronchiolitis. Mortality risk factors include cytomegalovirus mismatching (donor positive, recipient negative), human leukocyte antigen (HLA-DR) mismatching, diabetes, and prior need for mechanical ventilation or inotropic support. Uncommonly, the disorder recurs, particularly in some patients with an interstitial lung disorder. Exercise
capacity is slightly limited because of a hyperventilatory response.

With heart-lung transplantation, overall survival rate at 1 yr is 60% for patients and grafts.

**Pancreas Transplantation**

Pancreas transplantation is a form of pancreatic β-cell replacement that can restore normoglycemia in diabetic patients. Because the recipient exchanges risks of insulin injection for risks of immunosuppression, eligibility is limited mostly to patients who have type 1 diabetes with renal failure and who are thus candidates for kidney transplantation; > 90% of pancreas transplantations include transplantation of a kidney. At many centers, failure of standard treatment and episodes of hypoglycemic unawareness are also eligibility criteria. Relative contraindications include age > 55 and significant atherosclerotic cardiovascular disease, defined as history of MI, coronary artery bypass graft surgery, percutaneous coronary intervention, or a positive stress test; these factors dramatically increase perioperative risk.

Options include simultaneous pancreas-kidney (SPK) transplantation; pancreas-after-kidney (PAK) transplantation; and pancreas-alone transplantation. The advantages of SPK are one-time exposure to induction immunosuppression, potential protection of the newly transplanted kidney from adverse effects of hyperglycemia, and the ability to monitor rejection in the kidney; the kidney is more prone to rejection than the pancreas, where rejection is difficult to detect. The advantage of PAK is the ability to optimize HLA matching and timing of kidney transplantation using a living donor. Pancreas-alone transplantation offers an advantage to patients who do not have end-stage renal disease but have other severe diabetes complications, including labile glucose control.

Donors are usually recently deceased patients who are aged 10 to 55 and have no history of glucose intolerance or alcohol abuse. For SPK, the pancreas and kidney come from the same donor, and the same restrictions for kidney donation apply (see p. 1133). A few (<1%) segmental transplantations from living donors have been done, but this procedure has substantial risks for the donor (eg, splenic infarction, abscess, pancreatitis, pancreatic leak and pseudocyst, secondary diabetes), which limit its widespread use.

**Procedure**

The donor is anticoagulated, and a cold preservation solution is flushed into the celiac artery. The pancreas is cooled in situ with iced saline slush, then removed en bloc with the liver (for transplantation into a different recipient) and the 2nd portion of the duodenum containing the ampulla of Vater.

The donor pancreas is positioned intraperitoneally and laterally in the lower abdomen. In SPK, the pancreas is placed into the right lower quadrant of the recipient's abdomen and the kidney into the left lower quadrant. The native pancreas is left in place. Anastomoses are made between the donor splenic or superior mesenteric artery and recipient iliac artery and between the donor portal vein and recipient iliac vein. Thus, endocrine secretions drain systemically, causing hyperinsulinemia; sometimes the pancreatic venous system is anastomosed to a portal vein tributary to re-create physiologic conditions, although this procedure is more demanding and its benefits are unclear. The duodenum is sewn to the bladder dome or to the jejunum for drainage of exocrine secretions.

Immunosuppression regimens vary but typically include immunosuppressive Igs, a calcineurin inhibitor, a purine synthesis inhibitor, and corticosteroids, which can be slowly tapered over 12 mo. Despite adequate immunosuppression, rejection develops in 60 to 80% of patients, primarily affecting exocrine, not endocrine, components. Compared with kidney transplantation alone, SPK has a greater risk of rejection, and rejection episodes tend to occur later, to recur more often, and to be corticosteroid-resistant. Symptoms and signs are nonspecific (see Table 128-1).

After SPK and PAK, pancreas rejection, indicated by an increase in serum creatinine, almost always accompanies kidney rejection. After pancreas-alone transplantation, a stable urinary amylase concentration in patients with urinary drainage excludes rejection; a decrease suggests some form of graft dysfunction but is not specific to rejection. Early detection is therefore difficult. Diagnosis is
confirmed by ultrasound-guided percutaneous or cystoscopic transduodenal biopsy. Treatment is with antithymocyte globulin.

Early complications affect 10 to 15% of patients and include wound infection and dehiscence, gross hematuria, intra-abdominal urinary leak, reflux pancreatitis, recurrent UTI, small-bowel obstruction, abdominal abscess, and graft thrombosis. Late complications relate to urinary loss of pancreatic NaHCO$_3$, causing volume depletion and non-anion gap metabolic acidosis. Hyperinsulinemia does not appear to adversely affect glucose or lipid metabolism.

**Prognosis**

At 1 yr, 78% of grafts survive, but > 90% of patients survive. Whether survival is higher than that of patients without transplantation is unclear; however, the primary benefits of the procedure are freedom from insulin therapy and stabilization or amelioration of many diabetic complications (eg, nephropathy, neuropathy). Graft survival is 95% for SPK, 74% for PAK, and 76% for pancreas-alone transplantation. The rate of immunologic graft loss for PAK and pancreas-alone transplants is higher, possibly because such a transplanted pancreas lacks a reliable monitor of rejection; in contrast, rejection after SPK can be monitored using established indicators of rejection for the transplanted kidney.

**Pancreatic Islet Cell Transplantation**

Islet cell transplantation has theoretical advantages over pancreas transplantation; the most important is that the procedure is less invasive. A secondary advantage is that islet cell transplantation appears to help maintain normoglycemia in patients who require total pancreatectomy for pain due to chronic pancreatitis. Nevertheless, the procedure remains experimental, although steady improvement appears to be occurring.

Its disadvantages are that transplanted glucagon-secreting α cells are nonfunctional (possibly complicating hypoglycemia) and several pancreata are usually required for a single islet cell recipient (exacerbating disparities between graft supply and demand and limiting use of the procedure).

Indications are the same as those for pancreas transplantation. Simultaneous islet cell-kidney transplantation may be desirable after the technique is improved.

**Procedure**

A pancreas is removed from a brain-dead donor; collagenase is infused into the pancreatic duct to separate islets from pancreatic tissue. A purified islet cell fraction is infused percutaneously into the portal vein. Islet cells travel into hepatic sinusoids, where they lodge and secrete insulin.

Results are best when 2 cadavers are used, with each supplying 2 or 3 infusions of islet cells, followed by an immunosuppressive regimen consisting of an anti-IL-2 receptor, monoclonal antibodies (daclizumab), tacrolimus, and sirolimus. Corticosteroids are not used. Immunosuppression must be continued lifelong or until islet cell function ceases.

Rejection is poorly defined but can be detected by deterioration in blood glucose control; treatment of rejection is not established. Procedural complications include percutaneous hepatic puncture with bleeding, portal vein thrombosis, and portal hypertension.

Successful islet cell transplantation maintains short-term normoglycemia, but long-term outcomes are unknown; additional injections of islet preparations may be necessary to obtain longer-lasting insulin independence.

**Small-Bowel Transplantation**

Small-bowel transplantation is indicated for patients who have malabsorption because of intestinal disorders (eg, gastroschisis, Hirschsprung’s disease, autoimmune enteritis) or intestinal resection (eg, for
mesenteric thromboembolism or extensive Crohn's disease) and who are at high risk of death (usually due to congenital enteropathies such as microvillus inclusion disease) or who develop complications of TPN (eg, liver failure, recurrent sepsis, total loss of venous access). Patients with locally invasive tumors that cause obstruction, abscesses, fistulas, ischemia, or hemorrhage (usually desmoid tumors associated with familial polyposis) are also candidates.

Procedure

Procurement from a brain-dead, beating-heart donor is complex, partly because the small bowel can be transplanted alone, with a liver, or with a stomach, liver, duodenum, and pancreas. The role of living-related donation for small-bowel allografts has yet to be defined. Procedures vary by medical center; immunosuppressive regimens also vary, but a typical regimen includes antilymphocyte globulin for induction, followed by high-dose tacrolimus and mycophenolate mofetil for maintenance.

Weekly endoscopy is indicated to check for rejection. Symptoms and signs of rejection include diarrhea, fever, and abdominal cramping. Endoscopic findings include mucosal erythema, friability, ulceration, and exfoliation; changes are distributed unevenly, may be difficult to detect, and can be differentiated from cytomegalovirus enteritis by viral inclusion bodies. Biopsy findings include blunted villi and inflammatory infiltrates in the lamina propria. Treatment of acute rejection is high-dose corticosteroids, antithymocyte globulin, or both.

Prognosis

Surgical complications affect 50% of patients and include anastomotic leaks, biliary leaks and strictures, hepatic artery thrombosis, and chylous ascites. Nonsurgical complications include graft ischemia and graft-vs-host disease caused by transplantation of gut-associated lymphoid tissue.

At 3 yr, > 50% of grafts with small-bowel transplantation alone survive, but patient survival is around 65%. With liver and small-bowel transplantation, survival rate is lower because the procedure is more extensive and the recipient's condition is more serious.

Tissue Transplantation

Skin allografts: Skin allografts are used for patients with extensive burns or other conditions causing massive skin loss. Allografts are used to cover broad denuded areas and thus reduce fluid and protein losses and discourage invasive infection. The allografts are ultimately rejected, but the resulting denuded areas develop well-vascularized granulations onto which autografts from the patient's healed sites take readily. Skin cells may be grown in culture, then returned to a burned patient to help cover extensive burns; artificial skin, composed of cultured cells on a synthetic underlayer, may also be used. Split-thickness skin grafts are used to accelerate healing of small wounds. A small piece of skin just a few millimeters thick is harvested, and the donor skin is then laid onto the graft site.

Cartilage transplantation: Cartilage transplantation is used for children with congenital nasal or ear defects and adults with severe injuries or joint destruction (eg, severe osteoarthritis). Chondrocytes are more resistant to rejection, possibly because the sparse population of cells in hyaline cartilage is protected from cellular attack by the cartilaginous matrix around them.

Bone transplantation: Bone transplantation is used for reconstruction of large bony defects (eg, after massive resection of bone cancer). No viable donor bone cells survive in the recipient, but dead matrix from allografts can stimulate recipient osteoblasts to recolonize the matrix and lay down new bone. This matrix acts as scaffolding for bridging and stabilizing defects until new bone is formed. Cadaveric allografts are preserved by freezing to decrease immunogenicity of the bone (which is dead at the time of implantation) and by glycerolization to maintain chondrocyte viability. No postimplantation immunosuppressive therapy is used. Although patients develop anti-HLA antibodies, early follow-up detects no evidence of cartilage degradation.

Corneal transplantation: Corneal transplantation is discussed on p. 595.
Adrenal autografting: Adrenal autografting by stereotactically placing medullary tissue within the CNS has been reported to alleviate symptoms in patients with Parkinson’s disease. Allografts of adrenal tissue, especially from fetal donors, have also been proposed. Fetal ventral mesencephalic tissue stereotactically implanted in the putamen of patients with Parkinson’s disease has been reported to reduce rigidity and bradykinesia. However, with the ethical and political debates about the propriety of using human fetal tissue, a controlled trial large enough to adequately assess fetal neural transplantation appears unlikely. Xenografts of endocrinologically active cells from porcine donors are being tested.

Fetal thymus implants: Fetal thymus implants obtained from stillborn infants may restore immunologic responsiveness in children with thymic aplasia and resulting abnormal development of the lymphoid system. Because the recipient is immunologically unresponsive, immunosuppression is not required; however, severe graft-vs-host disease may occur.
A healthy person lives in harmony with the microbial flora that helps protect its host from invasion by pathogens, usually defined as microorganisms that have the capacity to cause disease. The microbial flora is mostly bacteria and fungi and includes normal resident flora, which is present consistently and promptly reestablishes itself if disturbed, and transient flora, which may colonize the host for hours to weeks but does not permanently establish itself. Organisms that are normal flora can occasionally cause disease, especially when defenses are disrupted.

Tropisms (attractions to certain tissues) determine which body sites microorganisms colonize. Normal flora is influenced by tropisms and many other factors (eg, diet, hygiene, sanitary conditions, air pollution). For example, lactobacilli are common in the intestines of people with a high intake of dairy products; *Haemophilus influenzae* colonizes the tracheobronchial tree in patients with COPD.

**Host Defense Mechanisms**

Host defenses that protect against infection include natural barriers (eg, skin, mucous membranes), nonspecific immune responses (eg, phagocytic cells [neutrophils, macrophages] and their products), and specific immune responses (eg, antibodies, lymphocytes).

**Natural Barriers**

**Skin:** The skin usually bars invading microorganisms unless it is physically disrupted (eg, by injury, IV catheter, or surgical incision). Exceptions include human papillomavirus, which can invade normal skin, causing warts, and some parasites (eg, *Schistosoma mansoni*, *Strongyloides stercoralis*).

**Mucous membranes:** Many mucous membranes are bathed in secretions that have antimicrobial properties (eg, cervical mucus, prostatic fluid, and tears containing lysozyme, which splits the muramic acid linkage in bacterial cell walls, especially in gram-positive organisms). Local secretions also contain immunoglobulins, principally IgG and secretory IgA, which prevent microorganisms from attaching to host cells.

**Respiratory tract:** The respiratory tract has upper airway filters. If invading organisms reach the tracheobronchial tree, the mucociliary epithelium transports them away from the lung. Coughing also helps remove organisms. If the organisms reach the alveoli, alveolar macrophages and tissue histiocytes engulf them. However, these defenses can be overcome by large numbers of organisms or by compromised effectiveness resulting from air pollutants (eg, cigarette smoke) or interference with protective mechanisms (eg, endotracheal intubation, tracheostomy).

**GI tract:** GI tract barriers include the acid pH of the stomach and the antibacterial activity of pancreatic enzymes, bile, and intestinal secretions. Peristalsis and the normal loss of epithelial cells remove microorganisms. If peristalsis is slowed (eg, because of drugs such as belladonna or opium alkaloids), this removal is delayed and prolongs some infections, such as symptomatic shigellosis. Compromised GI defense mechanisms may predispose patients to particular infections (eg, achlorhydria predisposes to salmonellosis). Normal bowel flora can inhibit pathogens; alteration of this flora with antibiotics can allow overgrowth of inherently pathogenic microorganisms (eg, *Salmonella typhimurium*) or superinfection with ordinarily commensal organisms (eg, *Candida albicans*).

**GU tract:** GU tract barriers include the length of the urethra (20 cm) in men, the acid pH of the vagina in women, and the hypertonic state of the kidney medulla. The kidneys also produce and excrete large amounts of Tamm-Horsfall mucoprotein, which binds certain bacteria, facilitating their harmless excretion.

**Nonspecific Immune Responses**
Cytokines (including IL-1, IL-6, tumor necrosis factor, interferon-γ) are produced principally by macrophages and activated lymphocytes and mediate an acute-phase response that develops regardless of the inciting microorganism (see also p. 1084). The response involves fever and increased production of neutrophils by the bone marrow. Endothelial cells also produce large amounts of IL-8, which attracts neutrophils.

The inflammatory response directs immune system components to injury or infection sites and is manifested by increased blood supply and vascular permeability, which allows chemotactic peptides, neutrophils, and mononuclear cells to leave the intravascular compartment. Microbial spread is limited by engulfment of microorganisms by phagocytes (e.g., neutrophils, macrophages). Phagocytes are drawn to microbes via chemotaxis and engulf them, releasing phagocytic lysosomal contents that help destroy microbes. Oxidative products such as hydrogen peroxide are generated by the phagocytes and kill ingested microbes. When quantitative or qualitative defects in neutrophils result in infection, the infection is usually prolonged and recurrent and responds slowly to antimicrobial drugs. Staphylococci, gram-negative organisms, and fungi are the pathogens usually responsible.

**Specific Immune Responses**

After infection, the host can produce a variety of antibodies, complex glycoproteins known as immunoglobulins that bind to specific microbial antigenic targets. Antibodies can help eradicate the infecting organism by attracting the host's WBCs and activating the complement system. The complement system (see p. 1085) destroys cell walls, usually through the classic pathway. Complement can also be activated on the surface of some microorganisms via the alternative pathway. Antibodies can also promote the deposition of substances known as opsonins (e.g., the complement protein C3b) on the surface of microorganisms, which helps promote phagocytosis. Opsonization is important for eradication of encapsulated organisms such as pneumococci and meningococci.

**Factors Facilitating Microbial Invasion**

Microbial invasion can be facilitated by virulence factors, microbial adherence, resistance to antimicrobials, and defects in host defense mechanisms.

**Virulence Factors**

Virulence factors assist pathogens in invasion and resistance of host defenses; these factors include

- Capsules
- Enzymes
- Toxins

**Capsules:** Some organisms (e.g., certain strains of pneumococci, meningococci, type B *Haemophilus influenzae*) have capsules that prevent opsonic antibodies from binding and thus are more virulent than nonencapsulated strains.

**Enzymes:** Bacterial proteins with enzymatic activity (e.g., protease, hyaluronidase, neuraminidase, elastase, collagenase) facilitate local tissue spread. Invasive organisms (e.g., *Shigella flexneri*, *Yersinia enterocolitica*) can penetrate and traverse intact eukaryotic cells, facilitating entry from mucosal surfaces.

Some bacteria (e.g., *Neisseria gonorrhoeae*, *H. influenzae*, *Proteus mirabilis*, clostridial species, *Streptococcus pneumoniae*) produce IgA-specific proteases that cleave and inactivate secretory IgA on mucosal surfaces.

**Toxins:** Organisms may release toxins (called exotoxins), which are protein molecules that may cause the disease (e.g., diphtheria, cholera, tetanus, botulism) or increase the severity of the disease. Most toxins bind to specific target cell receptors. With the exception of preformed toxins responsible for food-borne...
illnesses, toxins are produced by organisms during the course of infection.

Endotoxin is a lipopolysaccharide produced by gram-negative bacteria and is part of the cell wall. Endotoxin triggers humoral enzymatic mechanisms involving the complement, clotting, fibrinolytic, and kinin pathways and causes much of the morbidity in gram-negative sepsis.

**Other factors:** Many microorganisms have mechanisms that impair antibody production by inducing suppressor cells, blocking antigen processing, and inhibiting lymphocyte mitogenesis.

Resistance to the lytic effects of serum complement confers virulence. Among species of *N. gonorrhoeae*, resistance predisposes to disseminated rather than localized infection.

Some organisms resist the oxidative steps in phagocytosis. For example, *Legionella* and *Listeria* either do not elicit or actively suppress the oxidative step, whereas other organisms produce enzymes (eg, catalase, glutathione reductase, or superoxide dismutase) that mitigate the oxidative products.

**Microbial Adherence**

Adherence to surfaces helps microorganisms establish a base from which to penetrate tissues. Among the factors that determine adherence are adhesins (microbial molecules that mediate attachment to a cell) and host receptors to which the adhesins bind. Host receptors include cell surface sugar residues and cell surface proteins (eg, fibronectin) that enhance binding of certain gram-positive organisms (eg, staphylococci). Other determinants of adherence include fine structures on certain bacterial cells (eg, streptococci) called fibrillae, by which some bacteria bind to human epithelial cells. Other bacteria, such as Enterobacteriaceae (eg, *Escherichia coli*), have specific adhesive organelles called fimbriae or pili. Fimbriae enable the organism to attach to almost all human cells, including neutrophils and epithelial cells in the GU tract, mouth, and intestine.

**Biofilm:** Biofilm is a slime layer that can form around certain bacteria and confer resistance to phagocytosis and antibiotics. It develops around *Pseudomonas aeruginosa* in the lungs of patients with cystic fibrosis and around coagulase-negative staphylococci on synthetic medical devices, such as IV catheters, prosthetic vascular grafts, and suture material. Factors that affect the likelihood of biofilm developing on such medical devices include the material's roughness, chemical composition, and hydrophobicity.

**Antimicrobial Resistance**

Genetic variability among microbes is inevitable. Use of antimicrobial drugs eventually selects for survival of strains that are capable of resisting them.

In many cases, resistant bacterial strains have acquired genes that are encoded on plasmids or transposons and that enable the microorganisms to synthesize enzymes that

- Modify or inactivate the antimicrobial agent
- Change the bacterial cell's ability to accumulate the antimicrobial agent
- Resist inhibition by the antimicrobial agent

Minimizing inappropriate use of antibiotics is important for public health. Resistance among bacteria is discussed on p. 1184.

**Defects in Host Defense Mechanisms**

Two types of immune deficiency states affect the host's ability to fight infection: Primary immune deficiency and secondary (acquired) immune deficiency.

**Primary immune deficiencies** are genetic in origin; > 100 primary immune deficiency states have been
described. Most primary immune deficiencies are recognized during infancy; however, up to 40% are recognized during adolescence or adulthood.

**Acquired immune deficiencies** are caused by another disease (eg, cancer, HIV infection, chronic disease) or by exposure to a chemical or drug that is toxic to the immune system.

**Mechanisms:** Defects in immune responses may involve

- Cellular immunity
- Humoral immunity
- Phagocytic system
- Complement system

Cellular deficiencies are typically T-cell or combined immune defects. T cells contribute to the killing of intracellular organisms; thus, patients with T-cell defects can present with opportunistic infections such as *Pneumocystis jirovecii* or cryptococcal infections. Chronicity of these infections can lead to failure to thrive, chronic diarrhea, and persistent oral candidiasis.

Humoral deficiencies are typically caused by the failure of B cells to make functioning immunoglobulins. Patients with this type of defect usually have infections involving encapsulated organisms (eg, *H. influenzae*, streptococci). Patients can present with poor growth, diarrhea, and recurrent sinopulmonary infections.

A defect in the phagocytic system affects the immediate immune response to bacterial infection and can result in development of recurrent abscesses, severe pneumonias, or delayed umbilical cord separation.

Primary complement system defects are particularly rare. Patients with this type of defect may present with recurrent infections with pyogenic bacteria (eg, encapsulated bacteria, *Neisseria* sp) and have an increased risk of autoimmune disorders (eg, SLE).

**Manifestations of Infection**

Manifestations may be local (eg, cellulitis, abscess) or systemic, most often fever (see p. 1152). Manifestations may develop in multiple organ systems. Severe, generalized infections may have life-threatening manifestations (eg, sepsis, septic shock—see p. 2299). Most manifestations resolve with successful treatment of the underlying infection.

**Clinical:** Most infections increase the pulse rate and body temperature, but others (eg, typhoid fever, tularemia, brucellosis, dengue) may not elevate the pulse rate commensurate with the degree of fever. Hypotension can result from hypovolemia or septic shock. Hyperventilation and respiratory alkalosis are common.

Alterations in sensorium (encephalopathy) may occur in severe infection regardless of whether CNS infection is present. Encephalopathy is most common and serious in the elderly and may cause anxiety, confusion, delirium, stupor, seizures, and coma.

**Hematologic:** Infectious diseases commonly increase the numbers of mature and immature circulating neutrophils. Mechanisms include demargination and release of immature granulocytes from bone marrow, IL-1- and IL-6-mediated release of neutrophils from bone marrow, and colony-stimulating factors elaborated by macrophages, lymphocytes, and other tissues. Exaggeration of these phenomena (eg, in trauma, inflammation, and similar stresses) can result in release of excessive numbers of immature leukocytes into the circulation (leukemoid reaction), with leukocyte counts up to 25 to 30 × 10⁹/L.

Conversely, some infections (eg, typhoid fever, brucellosis) commonly cause neutropenia. In
overwhelming, severe infections, profound neutropenia is often a poor prognostic sign. Characteristic morphologic changes in the neutrophils of septic patients include Dohle bodies, toxic granulations, and vacuolization.

Anemia can develop despite adequate tissue iron stores. If anemia is chronic, plasma iron and total iron-binding capacity may be decreased. Serious infection, particularly with gram-negative organisms, may cause disseminated intravascular coagulation (DIC—see p. 976).

**Other organ systems:** Pulmonary compliance may decrease, progressing to acute respiratory distress syndrome (ARDS) and respiratory muscle failure.

Renal manifestations range from minimal proteinuria to acute renal failure, which can result from shock and acute tubular necrosis, glomerulonephritis, or tubulointerstitial disease.

Hepatic dysfunction, including cholestatic jaundice (often a poor prognostic sign) or hepatocellular dysfunction, occurs with many infections, even though the infection does not localize to the liver. Upper GI bleeding due to stress ulceration may occur during sepsis.

Endocrinologic dysfunctions include increased production of thyroid-stimulating hormone, vasopressin, insulin, and glucagon; breakdown of skeletal muscle proteins and muscle wasting secondary to increased metabolic demands; and bone demineralization. Hypoglycemia occurs infrequently in sepsis, but adrenal insufficiency should be considered in patients with hypoglycemia and sepsis. Hyperglycemia may be an early sign of infection in diabetics.

**Fever**

Fever is elevated body temperature (> 37.8° C orally or > 38.2° C rectally) or an elevation above a person's known normal daily value. Elevated body temperature that is not caused by a resetting of the temperature set point in the hypothalamus is commonly called hyperthermia. Many patients use "fever" very loosely, often meaning that they feel too warm, too cold, or sweaty, but they have not actually measured their temperature.

Symptoms are due mainly to the condition causing the fever, although fever itself can cause discomfort.

**Pathophysiology**

During a 24-h period, temperature varies from lowest levels in the early morning to highest in late afternoon. Maximum variation is about 0.6° C.

Body temperature is determined by the balance between heat production by tissues, particularly the liver and muscles, and heat loss from the periphery. Normally, the hypothalamic thermoregulatory center maintains the internal temperature between 37° and 38° C. Fever results when something raises the hypothalamic set point, triggering vasoconstriction and shunting of blood from the periphery to decrease heat loss; sometimes shivering, which increases heat production, is induced. These processes continue until the temperature of the blood bathing the hypothalamus reaches the new set point. Resetting the hypothalamic set point downward (eg, with antipyretic drugs) initiates heat loss through sweating and vasodilation. The capacity to generate a fever is reduced in certain patients (eg, alcoholics, the very old, the very young).

**Pyrogens** are substances that cause fever. Exogenous pyrogens are usually microbes or their products. The best studied are the lipopolysaccharides of gram-negative bacteria (commonly called endotoxins) and *Staphylococcus aureus* toxin, which causes toxic shock syndrome. Exogenous pyrogens usually cause fever by inducing release of endogenous pyrogens (eg, IL-1, tumor necrosis factor [TNF], interferon-γ, IL-6), which raise the hypothalamic set point. Prostaglandin E₂ synthesis appears to play a critical role.

**Consequences of fever:** Although many patients worry that fever itself can cause harm, the modest transient core temperature elevations (ie, 38° to 40°) caused by most acute illnesses are well tolerated by
healthy adults. However, extreme temperature elevation (typically > 41° C) may be damaging. Such elevation is more typical of severe environmental hyperthermia but sometimes results from exposure to illicit drugs (eg, cocaine, phencyclidine), anesthetics, or antipsychotic drugs. At this temperature, protein denaturation occurs, and inflammatory cytokines that activate the inflammatory cascade are released. As a result, cellular dysfunction occurs, leading to malfunction and ultimately failure of most organs; the coagulation cascade is also activated, leading to disseminated intravascular coagulation.

Because fever can increase the BMR by about 10 to 12% for every 1° C increase over 37° C, fever may physiologically stress adults with preexisting cardiac or pulmonary insufficiency. Fever can also worsen mental status in patients with dementia.

Fever in healthy children can cause febrile seizures (see p. 2898).

Etiology

Many disorders can cause fever. They are broadly categorized as

• Infectious (most common)
• Neoplastic
• Inflammatory (including rheumatic, nonrheumatic, and drug-related)

The cause of an acute (ie, duration ≤ 4 days) fever in adults is highly likely to be infectious. When patients present with fever due to a noninfectious cause, the fever is almost always chronic or recurrent. Also, an isolated, acute febrile event in patients with a known inflammatory or neoplastic disorder is still most likely to be infectious. In healthy people, an acute febrile event is unlikely to be the initial manifestation of a chronic illness.

Infectious causes: Virtually all infectious illnesses can cause fever. But overall, the most likely causes are

• Upper and lower respiratory tract infections
• GI infections
• UTIs
• Skin infections

Most acute respiratory tract and GI infections are viral.

Specific patient and external factors also influence which causes are most likely.

Patient factors include health status, age, occupation, and risk factors (eg, hospitalization, recent invasive procedures, presence of IV or urinary catheters, use of mechanical ventilation).

External factors are those that expose patients to specific diseases—eg, through infected contacts, local outbreaks, disease vectors (eg, mosquitoes, ticks), a common vehicle (eg, food, water), or geographic location (eg, residence in or recent travel to an endemic area).

Some causes appear to predominate based on these factors (see Table 129-1).

Evaluation

Two general issues are important in the initial evaluation of acute fever:
• Identifying any localizing symptoms (eg, headache, cough): These symptoms help narrow the range of possible causes. The localizing symptom may be part of the patient's chief complaint or identified only by specific questioning.

• Determining whether the patient is seriously or chronically ill (particularly if such illness is unrecognized): Many causes of fever in healthy people are self-limited, and many of the possible viral infections are difficult to diagnose specifically. Limiting testing to the seriously or chronically ill can help avoid many expensive, unnecessary, and often fruitless searches.

**History:** History of present illness should cover magnitude and duration of fever and method used to take the temperature. True rigors (severe, shaking, teeth-chattering chills—not simply feeling cold) suggest fever due to infection but are not otherwise specific. Pain is an important clue to the possible source; the patient should be asked about pain in the ears, head, neck, teeth, throat, chest, abdomen, flank, rectum, muscles, and joints.

Other localizing symptoms include nasal congestion and/or discharge, cough, diarrhea, and urinary symptoms (frequency, urgency, dysuria). Presence of rash (including nature, location, and time of onset in relation to other symptoms) and lymphadenopathy may help. Infected contacts and their diagnosis should be identified.

**Review of systems** should identify symptoms of chronic illness, including recurrent fevers, night sweats, and weight loss.

**Past medical history** should particularly cover the following:

• Recent surgery

• Known disorders that predispose to infection (eg, HIV infection, diabetes, cancer, organ transplantation, sickle cell disease, valvular heart disorders—particularly if an artificial valve is present)

• Other known disorders that predispose to fever (eg, rheumatologic disorders, SLE, gout, sarcoidosis, hyperthyroidism, cancer)

Questions to ask about recent travel include location, time since return, locale (eg, in back country, only in cities), vaccinations received before travel, and any use of prophylactic antimalarial drugs (if required).

All patients should be asked about possible exposures (eg, via unsafe food or water, insect bites, animal contact, or unprotected sex).

Vaccination history, particularly against hepatitis A and B and against organisms that cause meningitis, influenza, or pneumococcal infection, should be noted.

Drug history should include specific questions about the following:

• Drugs known to cause fever (see Table 129-1)

• Drugs that predispose to infection (eg, corticosteroids, anti-TNF drugs, chemotherapeutic and antirejection drugs, other immunosuppressants)

• Illicit use of injection drugs (predisposing to endocarditis, hepatitis, septic pulmonary emboli, and skin and soft-tissue infections)

**Physical examination:** Physical examination begins with confirmation of fever. Fever is most accurately diagnosed by measuring rectal temperature. Oral temperatures are normally about 0.6° C lower and may be falsely even lower for many reasons, such as recent ingestion of a cold drink, mouth breathing, hyperventilation, and inadequate measurement time (up to several minutes are required with mercury thermometers). Measurement
Table 129-1. Some Causes of Acute Fever

of tympanic membrane temperature by infrared sensor is less accurate than rectal temperature.

Other vital signs are reviewed for presence of tachypnea, tachycardia, or hypotension.

For patients with localizing symptoms, examination proceeds as discussed elsewhere in THE MANUAL. For febrile patients without localizing symptoms, a complete examination is necessary because clues to the diagnosis may be in any organ system.

The patient's general appearance, including any weakness, lethargy, confusion, cachexia, and distress, should be noted.

All of the skin should be inspected for rash, particularly petechial or hemorrhagic rash and any lesions or areas of erythema or blistering suggesting skin or soft-tissue infection. Axillae and epitrochlear and inguinal areas should be examined for adenopathy. In hospitalized patients, presence of any IVs, NGTs, urinary catheters, and any other tubes or lines inserted into the body should be noted. If patients have had recent surgery, surgical sites should be thoroughly inspected.

For the head and neck examination, the following should be done:

• Tympanic membranes: Examined for infection
• Sinuses (frontal and maxillary): Percussed
• Temporal arteries: Palpated for tenderness
• Nose: Inspected for congestion and discharge (clear or purulent)
• Eyes: Inspected for conjunctivitis or icterus
• Fundi: Inspected for Roth's spots (suggesting endocarditis)
• Oropharynx and gingiva: Inspected for inflammation or ulceration (including any lesions of candidiasis, which suggests immunocompromise)
• Neck: Flexed to detect discomfort, stiffness, or both, indicating meningismus, and palpated for adenopathy

The lungs are examined for crackles or signs of consolidation, and the heart is auscultated for murmurs (suggesting possible endocarditis).

The abdomen is palpated for hepatosplenomegaly and tenderness (suggesting infection).

The flanks are percussed for tenderness over the kidneys (suggesting pyelonephritis). A pelvic examination is done in women to check for cervical motion or adnexal tenderness; a genital examination is done in men to check for urethral discharge and local tenderness.

The rectum is examined for tenderness and swelling, suggesting perirectal abscess (which may be occult in immunosuppressed patients).

All major joints are examined for swelling, erythema, and tenderness (suggesting a joint infection or rheumatologic disorder). The hands and feet are inspected for signs of endocarditis, including splinter hemorrhages under the nails, painful erythematous subcutaneous nodules on the tips of digits (Osler's nodes), and nontender hemorrhagic macules on the palms or soles (Janeway lesions).

Red flags: The following findings are of particular concern:
• Altered mental status
• Headache, stiff neck, or both
• Petechial skin rash
• Hypotension
• Significant tachycardia or tachypnea
• Temperature > 40° C or < 35° C
• Recent travel to malaria-endemic area
• Recent use of immunosuppressants

**Interpretation of findings:** The degree of elevation in temperature usually does not predict the likelihood or cause of infection. Fever pattern, once thought to be significant, is not. Likelihood of serious illness is considered. If serious illness is suspected, immediate and aggressive testing and often hospital admission are needed.

Red flag findings strongly suggest a serious disorder. Headache, stiff neck, and petechial or purpuric rash suggest meningitis. Tachycardia (beyond the modest elevation normally present with fever) and tachypnea, with or without hypotension or mental status changes, suggest sepsis. Malaria should be suspected in patients who have recently traveled to an endemic area.

Immune compromise, whether caused by a known disorder or use of immunosuppressants or suggested by examination findings (eg, weight loss, oral candidiasis), is also of concern, as are other known chronic illnesses, injection drug use, and heart murmur.

The elderly, particularly those in nursing homes, are at particular risk (see Geriatrics Essentials on p. 1157).

**Localizing findings** identified by history or physical examination are evaluated and interpreted (see elsewhere in THE MANUAL). Other suggestive findings include generalized adenopathy and rash.

**Generalized adenopathy** may occur in older children and younger adults who have acute mononucleosis; it is usually accompanied by significant pharyngitis, malaise, and hepatosplenomegaly. Primary HIV infection or secondary syphilis should be suspected in patients with generalized adenopathy, sometimes accompanied by arthralgias, rash, or both. HIV infection develops 2 to 6 wk after exposure (although patients may not always report unprotected sexual contact or other risk factors). Secondary syphilis is usually preceded by a chancre, with systemic symptoms developing 4 to 10 wk later.

Fever and rash have many infectious and drug causes. Petechial or purpuric rash is of particular concern; it suggests possible meningococcemia, Rocky Mountain spotted fever (particularly if the palms or soles are involved), and, less commonly, some viral infections (eg, dengue fever, hemorrhagic fevers). Other suggestive skin lesions include the classic erythema migrans rash of Lyme disease, target lesions of Stevens-Johnson syndrome, and the painful, tender erythema of cellulitis and other bacterial soft-tissue infections. The possibility of delayed drug hypersensitivity (even after long periods of use) should be kept in mind.

If no localizing findings are present, healthy people with acute fever and only nonspecific findings (eg, malaise, generalized aches) most likely have a self-limited viral illness, unless a history of exposure to infected contacts (including a new, unprotected sexual contact), to disease vectors, or in an endemic area (including recent travel) suggests otherwise.

Patients with significant underlying disorders are more likely to have an occult bacterial or parasitic
infection. Injection drug users and patients with a prosthetic heart valve may have endocarditis. Immunocompromised patients are predisposed to infection caused by certain microorganisms (see Table 129-1).

Drug fever (with or without rash) is a diagnosis of exclusion, often requiring a trial of stopping the drug. One difficulty is that if antibiotics are the cause, the illness being treated may also cause fever. Sometimes a clue is that the fever and rash begin after clinical improvement from the initial infection and without worsening or reappearance of the original symptoms (eg, in a patient being treated for pneumonia, fever reappears without cough, dyspnea, or hypoxia).

**Testing:** Testing depends on whether localized findings are present.

If **localizing findings are present,** testing is guided by clinical suspicion and findings (see also elsewhere in THE MANUAL), as for the following:

- Mononucleosis or HIV infection: Serologic testing
- Rocky Mountain spotted fever: Biopsy of skin lesions to confirm the diagnosis (acute serologic testing is unhelpful)
- Bacterial or fungal infection: Blood cultures to detect possible bloodstream infections
- Meningitis: Immediate lumbar puncture and IV antibiotics (head CT should be done before lumbar puncture if patients are at risk of brain herniation; IV antibiotics must be given immediately after blood cultures are obtained and before head CT is done)
- Specific disorders based on exposure (eg, to contacts, to vectors, or in endemic areas): Testing for those disorders, particularly a peripheral blood smear for malaria

If **no localizing findings are present** in otherwise healthy patients and serious illness is not suspected, patients can usually be observed at home without testing. In most, symptoms resolve quickly; the few who develop worrisome or localizing symptoms should be reevaluated and tested based on the new findings.

If serious illness is suspected in patients who have no localizing findings, testing is needed. Patients with red flag findings suggesting sepsis require cultures (urine and blood), chest x-ray, and evaluation for metabolic abnormalities with measurement of serum electrolytes, glucose, BUN, creatinine, lactate, and liver enzymes. CBC is typically done, but sensitivity and specificity for diagnosing serious bacterial infection are low. However, WBC count is important prognostically for patients who may be immunosuppressed (ie, a low WBC count may be associated with a poor prognosis).

Patients with certain underlying disorders may need testing even if they have no localizing findings and do not appear seriously ill. Because of the risk and devastating consequences of endocarditis, febrile injection drug users are usually admitted to the hospital for serial blood cultures and often echocardiography. Patients taking immunosuppressants require CBC; if neutropenia is present, testing is initiated and chest x-ray is done, as are cultures of blood, sputum, urine, stool, and any suspicious skin lesions. Many with neutropenia are admitted to be given IV antibiotics, but certain patients can be sent home provided daily follow-up is available.

Febrile elderly patients often require testing (see Geriatrics Essentials on p. 1157).

**Treatment**

Specific causes are treated with anti-infective therapy; empiric anti-infective therapy is required when suspicion of serious infection is high.

Whether fever due to infection should be treated is controversial. Experimental evidence, but not clinical studies, suggests that fever enhances host defenses.
Fever should probably be treated in certain patients at particular risk, including adults with cardiac or pulmonary insufficiency or with dementia. Drugs that inhibit brain cyclooxygenase effectively reduce fever:

- Acetaminophen 650 to 1000 mg po q 6 h
- Ibuprofen 400 to 600 mg po q 6 h

The daily dose of acetaminophen should not exceed 4 g to avoid toxicity; patients should be warned not to simultaneously take nonprescription cold or flu remedies that contain acetaminophen. Other NSAIDs (eg, aspirin, naproxen) are also effective antipyretics. Salicylates should not be used to treat fever in children with viral illnesses because use of salicylates has been associated with Reye's syndrome.

If temperature is ≥ 41°C, other cooling measures (eg, evaporative cooling with tepid water mist, cooling blankets) should also be started.

**Geriatrics Essentials**

In the frail elderly, infection is less likely to cause fever, and even when elevated by infection, temperature may be lower than the standard definition of fever. Similarly, other inflammatory symptoms, such as focal pain, may be less prominent. Frequently, alteration of mental status or decline in daily functioning may be the only other initial manifestations of pneumonia or UTI.

In spite of their less severe manifestations of illness, the febrile elderly are significantly more likely to have a serious bacterial illness than are febrile younger adults. As in younger adults, the cause is commonly a respiratory infection or UTI, but in the elderly, skin and soft-tissue infections are among the top causes.

Focal findings are evaluated as for younger patients. But unlike younger patients, elderly patients probably require urinalysis, urine culture, and chest x-ray. Blood cultures should be done to exclude septicemia; if septicemia is suspected or vital signs are abnormal, patients should be admitted to the hospital.

**Key Points**

- Most fevers in healthy people are due to viral respiratory tract or GI infections.
- Localizing symptoms guide evaluation.
- Underlying chronic disorders, particularly those impairing the immune system, must be considered.

**Fever of Unknown Origin**

FUO is body temperature ≥ 38.3°C rectally that does not result from transient and self-limited illness, rapidly fatal illness, or disorders with clear-cut localizing symptoms or signs or with abnormalities on common tests such as chest x-ray, urinalysis, or blood cultures.

FUO is currently classified into 4 distinct categories:

- **Classic FUO:** Fever for ≥ 3 wk with no identified cause after 3 days of hospital evaluation or ≥ 3 outpatient visits
- **Nosocomial FUO:** Fever in hospitalized patients receiving acute care and with no infection present or incubating at admission if the diagnosis remains uncertain after ≥ 3 days of appropriate evaluation, including incubation of microbiologic cultures for ≥ 2 days
- **Neutropenic FUO:** Fever in patients who have < 500 neutrophils/μL or who are expected to have this level within 2 days if the diagnosis remains uncertain after ≥ 3 days of appropriate evaluation, including incubation of microbiologic cultures for ≥ 2 days
**HIV-associated FUO:** Fever in patients with confirmed HIV infection for > 4 wk as outpatients or > 3 days as inpatients if the diagnosis remains uncertain after ≥ 3 days of appropriate evaluation, including incubation of microbiologic cultures for ≥ 2 days

**Etiology**

Causes of FUO are usually divided into 4 categories (see [Table 129-2]):

- Infectious (25 to 50%)
- Connective tissue disorders (10 to 20%)
- Neoplastic (5 to 35%)
- Miscellaneous (15 to 25%)

Infections are the most common cause of FUO. In patients with HIV infection, opportunistic infections (eg, TB; infection by atypical mycobacteria, disseminated fungi, or cytomegalovirus) should be sought.

Common connective tissue disorders include SLE, RA, giant cell arteritis, vasculitis, and juvenile RA of adults.

The most common neoplastic causes are lymphoma, leukemia, renal cell carcinoma, hepatocellular carcinoma, and metastatic carcinomas. However, the incidence of neoplastic causes of FUO has been decreasing, probably because ultrasonography and CT are widely used during initial evaluation.

**[Table 129-2. Some Causes of FUO]**

Important miscellaneous causes include drug reactions, deep venous thrombosis, recurrent pulmonary emboli, sarcoidosis, inflammatory bowel disease, and factitious fever.

No cause of FUO is identified in about 10% of adults.

**Evaluation**

In puzzling cases, such as FUO, assuming that all information was gathered or was gathered accurately by previous clinicians is usually a mistake. Clinicians should be aware of what patients previously reported (to resolve discrepancies) but should not simply copy details of previously recorded history (eg, family history, social history). Initial errors of omission have been perpetuated through many clinicians over many days of hospitalization, causing much unnecessary testing. Even when initial evaluation was thorough, patients often remember new details when questioning is repeated.

Conversely, clinicians should not ignore previous test results and should not repeat tests without considering how likely results are to be different (eg, because the patient's condition has changed, because a disorder develops slowly).

**History:** History aims to uncover focal symptoms and facts (eg, travel, occupation, family history, exposure to animal vectors, dietary history) that suggest a cause.

**History of present illness** should cover duration and pattern (eg, intermittent, constant) of fever. Fever patterns usually have little or no significance in the diagnosis of FUO, although a fever that occurs every other day (tertian) or every 3rd day (quartan) may suggest malaria in patients with risk factors. Focal pain often indicates the location (although not the cause) of the underlying disorder. Clinicians should ask generally, then specifically, about discomfort in each body part.

**Review of systems** should include nonspecific symptoms, such as weight loss, anorexia, fatigue, night
sweats, and headaches. Also, symptoms of connective tissue disorders (eg, myalgias, arthralgias, rashes) and GI disorders (eg, diarrhea, steatorrhea, abdominal discomfort) should be sought.

Past medical history should include disorders known to cause fever, such as cancer, TB, connective tissue disorders, alcoholic cirrhosis, inflammatory bowel disease, rheumatic fever, and hyperthyroidism. Clinicians should note disorders or factors that predispose to infection, such as immunocompromise (eg, due to disorders such as HIV infection, cancer, diabetes, or use of immunosuppressants), structural heart disorders, urinary tract abnormalities, operations, and insertion of devices (eg, IV lines, pacemakers, joint prostheses).

Drug history should include questions about specific drugs known to cause fever.

Social history should include questions about risk factors for infection such as injection drug use, high-risk sexual practices (eg, unprotected sex, multiple partners), infected contacts (eg, with TB), travel, and possible exposure to animal or insect vectors. Risk factors for cancer, including smoking, alcohol use, and occupational exposure to chemicals, should also be identified.

Family history should include questions about inherited causes of fever (eg, familial Mediterranean fever). Medical records are checked for previous test results, particularly those that effectively rule out certain disorders.

Physical examination: The general appearance, particularly for cachexia, jaundice, and pallor, is noted.

The skin is thoroughly inspected for focal erythema (suggesting a site of infection) and rash (eg, malar rash of SLE); inspection should include the perineum and feet, particularly in diabetics, who are prone to infections in these areas. Clinicians should also check for cutaneous findings of endocarditis, including painful erythematous subcutaneous nodules on the tips of digits (Osler's nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), petechiae, and splinter hemorrhages under the nails.

The entire body (particularly over the spine, bones, joints, abdomen, and thyroid) is palpated for areas of tenderness, swelling, or organomegaly; digital rectal examination and pelvic examination are included. The teeth are percussed for tenderness (suggesting apical abscess). During palpation, any regional or systemic adenopathy is noted; eg, regional adenopathy is characteristic of cat-scratch disease in contrast to the diffuse adenopathy of lymphoma.

The heart is auscultated for murmurs (suggesting bacterial endocarditis) and rubs (suggesting pericarditis due to a rheumatologic or infectious disorder).

Sometimes key physical abnormalities in patients with FUO are or seem so subtle that repeated physical examinations may be necessary to suggest causes (eg, by detecting new adenopathy, heart murmurs, rash, or nodularity and weak pulsations in the temporal artery).

Red flags: The following are of particular concern:

- Immunocompromise
- Heart murmur
- Presence of inserted devices (eg, IV lines, pacemakers, joint prostheses)
- Recent travel to endemic areas

Interpretation of findings: After a thorough history and physical examination, the following scenarios are typical:

- Localizing symptoms or signs that were not present, not detected, or not managed during previous examinations are discovered. These findings are interpreted and investigated as indicated (see Table 129-2).
• More commonly, evaluation detects only nonspecific findings that occur in many different causes of FUO, but it identifies risk factors that can help guide testing (eg, travel to an endemic area, exposure to animal vectors). Sometimes risk factors are less specific but may suggest a class of illness; eg, weight loss without anorexia is more consistent with infection than cancer, which usually causes anorexia. Possible causes should be investigated further.

• In the most difficult scenario, patients have only nonspecific findings and no or multiple risk factors, making a logical, sequential approach to testing essential. Initial testing is used to narrow the diagnostic possibilities and guide subsequent testing.

**Testing:** Previous test results, particularly for cultures, are reviewed. Cultures for some organisms may require a long time to become positive.

As much as possible, clinical information is used to focus testing (see Table 129-2). For example, housebound elderly patients with headache would not be tested for tick-borne infections or malaria, but those disorders should be considered in younger travelers who have hiked in an endemic area. Elderly patients require evaluation for giant cell arteritis; younger patients do not.

In addition to specific testing, the following should usually be done:

• CBC with differential

• ESR

• Liver function tests

• Serial blood cultures (ideally before antimicrobial therapy)

• HIV antibody test, RNA concentration assays, and PCR assay

• Tuberculin skin test

Even if done earlier, these tests may suggest a helpful trend.

Urinalysis, urine culture, and chest x-ray, usually already done, are repeated only if findings indicate that they should be.

Any available fluid or material from abnormal areas identified during the evaluation is cultured (eg, for bacteria, mycobacteria, fungi, viruses, or specific fastidious bacteria as indicated). Organism-specific tests, such as PCR and serologic titers (acute and convalescent), are helpful mainly when guided by clinical suspicion, not done in a shotgun approach.

Serologic tests, such as antinuclear antibody (ANA) and rheumatoid factor, are done to screen for rheumatologic disorders.

**Imaging tests** are guided by symptoms and signs. Typically, areas of discomfort should be imaged—eg, in patients with back pain, MRI of the spine (to check for infection or tumor); in patients with abdominal pain, CT of the abdomen. However, CT of the chest, abdomen, and pelvis should be considered to check for adenopathy and occult abscesses even when patients do not have localizing symptoms or signs. If blood cultures are positive or new heart murmurs or peripheral signs suggest endocarditis, echocardiography is done.

In general, CT is useful for delineating abnormalities localized to the abdomen or chest. MRI is more sensitive than CT for detecting most causes of FUO involving the CNS and should be done if a CNS cause is being considered. Venous duplex imaging may be useful for identifying cases of deep venous thrombosis. Radionuclide scanning with indium-111-labeled granulocytes may help localize some infectious or inflammatory processes. This technique has generally fallen out of favor because it is...
thought to contribute very little to diagnosis, but some reports suggest that it provides a higher diagnostic yield than CT. PET may also be useful in detecting the focus of fever.

**Biopsy** may be required if an abnormality is suspected in tissue that can be biopsied (e.g., liver, bone marrow, skin, pleura, lymph nodes, intestine, muscle). Biopsy specimens should be evaluated by histopathologic examination and cultured for bacteria, fungi, viruses, and mycobacteria or sent for molecular (PCR) diagnostic testing. Muscle biopsy or skin biopsy of rashes may confirm vasculitis. Bilateral temporal artery biopsy may confirm giant cell arteritis in elderly patients with unexplained ESR elevation.

**Treatment**

Treatment focuses on the causative disorder. Antipyretics should be used judiciously, considering the duration of fever.

**Geriatrics Essentials**

Causes of FUO in the elderly are usually similar to those in the general population, but connective tissue disorders are identified more often. The most common causes are

- Giant cell arteritis
- Leukemias
- Lymphomas
- Abscesses
- TB

**Key Points**

- Classic FUO is body temperature ≥ 38.3°C rectally for ≥ 3 wk with no identified cause after 3 days of hospital investigation or ≥ 3 outpatient visits.

- Identified causes can be categorized as infectious, rheumatologic, neoplastic, or miscellaneous.

- Evaluation should be based on synthesis of history and physical examination, with particular consideration of risk factors and likely causes based on individual circumstances.

**Abscesses**

Abscesses are collections of pus in confined tissue spaces, usually caused by bacterial infection. Symptoms include local pain, tenderness, warmth, and swelling (if abscesses are near the skin layer) or constitutional symptoms (if abscesses are deep). Imaging is often necessary for diagnosis of deep abscesses. Treatment is surgical drainage and often antibiotics.

**Etiology**

Numerous organisms can cause abscesses, but *Staphylococcus aureus* is the most common. Organisms may enter the tissue by

- Direct implantation (e.g., penetrating trauma with a contaminated object)
- Spread from an established, contiguous infection
- Dissemination via lymphatic or hematogenous routes from a distant site
• Migration from a location where there are resident flora into an adjacent, normally sterile area because natural barriers are disrupted (eg, by perforation of an abdominal viscus causing an intra-abdominal abscess)

Abscesses may begin in an area of cellulitis (see p. 694) or in compromised tissue where leukocytes accumulate. Progressive dissection by pus or necrosis of surrounding cells expands the abscess. Highly vascularized connective tissue may then surround the necrotic tissue, leukocytes, and debris to wall off the abscess and limit further spread.

Predisposing factors to abscess formation include impaired host defense mechanisms (eg, impaired leukocyte defenses), the presence of foreign bodies, obstruction to normal drainage (eg, in the urinary, biliary, or respiratory tracts), tissue ischemia or necrosis, hematoma or excessive fluid accumulation in tissue, and trauma.

Symptoms and Signs

The symptoms and signs of cutaneous and subcutaneous abscesses are pain, heat, swelling, tenderness, and redness. If superficial abscesses are ready to spontaneously rupture, the skin over the center of the abscess may thin, sometimes appearing white or yellow because of the underlying pus (termed pointing). Fever may occur, especially with surrounding cellulitis. For deep abscesses, local pain and tenderness and systemic symptoms, especially fever, as well as anorexia, weight loss, and fatigue are typical. The predominant manifestation of some abscesses is abnormal organ function (eg, hemiplegia due to a brain abscess).

Complications of abscesses include bacteremic spread, rupture into adjacent tissue, bleeding from vessels eroded by inflammation, impaired function of a vital organ, and inanition due to anorexia and increased metabolic needs.

Diagnosis

• Clinical evaluation

• Sometimes ultrasonography or CT

Diagnosis of cutaneous and subcutaneous abscesses is by physical examination. Diagnosis of deep abscesses often requires imaging. Ultrasonography is noninvasive and detects many soft-tissue abscesses; CT is accurate for most, although MRI is usually more sensitive.

Treatment

• Surgical drainage

• Sometimes antibiotics

Superficial abscesses may resolve with heat and oral antibiotics. However, healing usually requires drainage.

Minor cutaneous abscesses may require only incision and drainage. All pus, necrotic tissue, and debris should be removed. Eliminating open (dead) space by packing with gauze or by placing drains may be necessary to prevent reformation of the abscess. Predisposing conditions, such as obstruction of natural drainage or the presence of a foreign body, require correction.

Deep abscesses can sometimes be adequately drained by percutaneous needle aspiration (typically guided by ultrasonography or CT); this method often avoids the need for open surgical drainage.

Spontaneous rupture and drainage may occur, sometimes leading to the formation of chronic draining sinuses. Without drainage, an abscess occasionally resolves slowly after proteolytic digestion of the pus.
produces a thin, sterile fluid that is resorbed into the bloodstream. Incomplete resorption may leave a
cystic loculation within a fibrous wall that may become calcified.

If the abscess is deep or if there is surrounding cellulitis, systemic antimicrobial drugs are indicated as
adjunctive therapy; they are usually ineffective without drainage. Empiric antimicrobial therapy is based
on location and likely infecting pathogen. Gram stain, culture, and susceptibility results guide further
antimicrobial therapy.

**Bacteremia**

(See also Neonatal Sepsis on p. 2832 and Occult Bacteremia on p. 2841.)

**Bacteremia is the presence of bacteria in the bloodstream. It can occur spontaneously, during
certain tissue infections, with use of indwelling GU or IV catheters, or after dental, GI, GU,
wound-care, or other procedures. Bacteremia may cause metastatic infections, including
endocarditis, especially in patients with valvular heart abnormalities. Transient bacteremia is
often asymptomatic but may cause fever. Development of other symptoms usually suggests
more serious infection, such as sepsis or septic shock (see p. 2299).

Bacteremia may be transient and cause no sequelae, or it may have metastatic or systemic
consequences. Systemic consequences include systemic inflammatory response syndrome and septic
shock.

**Etiology**

Bacteremia has many possible causes, including

- Catheterization of an infected lower urinary tract
- Surgical treatment of an abscess or infected wound
- Colonization of indwelling devices, especially IV and intracardiac catheters, urethral catheters, and
  ostomy devices and tubes

Gram-negative bacteremia secondary to infection usually originates in the GU or GI tract or in the skin of
patients with decubitus ulcers. Chronically ill and immunocompromised patients have an increased risk of
gram-negative bacteremia. They may also develop bacteremia with gram-positive cocci, anaerobes, and
fungi. Staphylococcal bacteremia is common among injection drug users and patients with IV catheters.
*Bacteroides* bacteremia may develop in patients with infections of the abdomen and the pelvis,
particularly the female genital tract. If an infection in the abdomen causes bacteremia, the organism is
most likely a gram-negative bacillus. If an infection above the diaphragm causes bacteremia, the
organism is most likely gram-positive.

**Pathophysiology**

Transient or sustained bacteremia can cause metastatic infection of the meninges or serous cavities,
such as the pericardium or larger joints. Metastatic abscesses may occur almost anywhere. Multiple
abscess formation is especially common with staphylococcal bacteremia. Bacteremia may cause
endocarditis (see p. 2193), most commonly with enterococcal, streptococcal, or staphylococcal bacteremia and less commonly
with gram-negative bacteremia or fungemia. Patients with structural heart disease (eg, valvular disease,
certain congenital anomalies), prosthetic heart valves, or other intravascular prostheses are predisposed
to endocarditis. Staphylococci can cause bacterial endocarditis, particularly in injection drug users, and
may involve the tricuspid valve.

**Symptoms and Signs**

Some patients are asymptomatic or have only mild fever. Development of symptoms such as tachypnea,
shaking chills, persistent fever, altered sensorium, hypotension, and GI symptoms (abdominal pain, nausea, vomiting, diarrhea) suggests sepsis or septic shock. Septic shock develops in 25 to 40% of patients with significant bacteremia.

**Diagnosis**

If bacteremia, sepsis, or septic shock is suspected, cultures are obtained of blood and any other appropriate specimens (see p. 1166).

**Treatment**

• Antibiotics

In patients with suspected bacteremia, empiric antibiotics are given after appropriate cultures are obtained. Early treatment of bacteremia with an appropriate antimicrobial regimen appears to improve survival. Continuing therapy involves adjusting antibiotics according to the results of culture and susceptibility testing, surgically draining any abscesses, and usually removing any internal devices that are the suspected source of bacteria.

**Biological Warfare and Terrorism**

Biological warfare is the use of microbiological agents for hostile purposes. Such use is contrary to international law and has rarely taken place during formal warfare in modern history, despite the extensive preparations and stockpiling of biological agents carried out during the 20th century by most major powers. For a variety of reasons (including uncertain military efficacy and the threat of massive retaliation), experts consider the use of biological agents in formal warfare unlikely. The area of most concern is the use of such agents by terrorist groups. Biological agents are thought by some people to be an ideal weapon for terrorists. These agents may be delivered clandestinely, and they have delayed effects, allowing the user to remain undetected.

Potential biological agents include anthrax, botulinum toxin, brucellosis, encephalitis, viruses, hemorrhagic fever viruses (Ebola and Marburg), plague, tularemia, and smallpox. Each of these agents is potentially fatal and, except for anthrax and botulinum toxin, can be passed from person to person. Anthrax is of most concern; anthrax spores are relatively easy to prepare and spread through the air, creating the potential for distribution by airplane. Theoretically, 1 kg of anthrax could kill 10,000 people, although technical difficulties with preparing the spores in a sufficiently fine powder would probably limit actual deaths to a fraction of this number. Some other potential agents, including *Yersinia pestis*, *Francisella tularensis*, viral hemorrhagic fever viruses, smallpox virus, and botulinum toxin, can potentially be aerosolized as bioweapons.

Despite these theoretical concerns, the only successful terrorist use of anthrax—multiple pieces of contaminated mail delivered to a variety of locations in the US in 2001—resulted in only a handful of deaths and serious infections (total of 22 cases). A larger number of people were contaminated with anthrax spores without developing illness. However, there was extreme public anxiety related to these incidents, which may have been a major goal of the terror group responsible.

In addition to the actual infections, an even greater number of false threats of anthrax have been reported. In 1999, the FBI received an average of 1 false report/day of alleged anthrax use. False reports, both hoaxes and alarmed citizens misperceiving harmless material for anthrax, increased even more after the 2001 anthrax attack in the US.

The only other successful use of a biological agent by a terror group in the US occurred in 1984. In this event, 751 people were stricken with diarrhea when a salad bar in Oregon was intentionally contaminated with *Salmonella*. The bacteria were introduced by a religious cult trying to influence the results of a local election. No one died, and the election was not affected.

**Defense against bioterrorism** involves several factors:
• Intelligence to disrupt terrorists before they can use the weapons

• Early detection

• Availability of protective antibiotics

• Preparedness of public health infrastructure to coordinate management of an infectious disease outbreak

• Vaccination of selected populations (eg, the military)
Chapter 130. Laboratory Diagnosis of Infectious Disease

Introduction

Laboratory tests may identify organisms directly (eg, visually, using a microscope, growing the organism in culture) or indirectly (eg, identifying antibodies to the organism). General types of tests include microscopy, culture, immunologic tests (agglutination tests such as latex agglutination, enzyme immunoassays, Western blot, precipitation tests, and complement fixation tests), and nucleic and non-nucleic acid-based identification methods. Culture is normally the gold standard for identification of organisms, but results may not be available for days or weeks, and not all pathogens can be cultured, making alternative tests useful. When a pathogen is cultured and identified, the laboratory can also assess its susceptibility to antimicrobial drugs.

Some tests (eg, Gram stain, routine aerobic culture) can detect a large variety of pathogens and are commonly done for many suspected infectious illnesses. However, because some pathogens are missed on these tests, clinicians must be aware of the limitations of each test for each suspected pathogen. In such cases, clinicians should request tests specific for the suspected pathogen (eg, special stains or culture media) or advise the laboratory to select more specific tests.

Microscopy

Microscopy can be done quickly, but accuracy depends on the experience of the microscopist and quality of equipment. Regulations often limit physicians’ use of microscopy for diagnostic purposes outside a certified laboratory.

Most specimens are treated with stains that color pathogens, causing them to stand out from the background, although wet mounts of unstained samples can be used to detect fungi, parasites (including helminth eggs and larvae), vaginal clue cells, motile organisms (eg, *Trichomonas*), and syphilis (via darkfield microscopy). Visibility of fungi can be increased by applying 10% potassium hydroxide (KOH) to dissolve surrounding tissues and nonfungal organisms.

The clinician orders a stain based on the likely pathogens, but no stain is 100% specific. Most samples are treated with Gram stain and, if mycobacteria are suspected, with an acid-fast stain. However, some pathogens are not easily visible using these stains; if these pathogens are suspected, different stains or other identification methods are required. Because microscopic detection usually requires a microbe concentration of about $1 \times 10^5$ cells/mL, most body fluid specimens (eg, CSF) are concentrated (eg, by centrifugation) before examination.

**Gram stain:** The Gram stain classifies bacteria according to whether they retain crystal violet stain (gram-positive—blue) or not (gram-negative—red) and highlights cell morphology (eg, bacilli, cocci) and cell arrangement (eg, clumps, chains, diploids). Such characteristics can direct antibiotic therapy pending definitive identification. To do a Gram stain, technicians heat-fix specimen material to a slide and stain it by sequential exposure to Gram’s crystal violet, iodine, decolorizer, and counterstain (typically safranin).

**Acid-fast and moderate (modified) acid-fast stains:** These stains are used to identify acid-fast organisms (*Mycobacterium* sp) and moderately acid-fast organisms (primarily *Nocardia* sp). These stains are also useful for staining *Rhodococcus* and related genera, as well as oocysts of some parasites (eg, *Cryptosporidium*).

Although detection of mycobacteria in sputum requires only about 5,000 to 10,000 organisms/mL, mycobacteria are often present in lower levels, so sensitivity is limited. Usually, several mL of sputum are decontaminated with Na hydroxide and concentrated by centrifugation for acid-fast staining. Specificity is better, although some moderately acid-fast organisms are difficult to distinguish from mycobacteria.

**Fluorescent stains:** These stains allow detection at lower concentrations ($1 \times 10^4$ cells/mL). Examples are acridine orange (bacteria and fungi), auramine-rhodamine and auramine O (mycobacteria), and calcofluor white (fungi, especially dermatophytes).
Coupling a fluorescent dye to an antibody directed at a pathogen (direct or indirect immunofluorescence) should theoretically increase sensitivity and specificity. However, these tests are difficult to read and interpret, and few (e.g., *Pneumocystis* and *Legionella* direct fluorescent antibody tests) are commercially available and commonly used.

**India ink (colloidal carbon) stain:** This stain is used to detect mainly *Cryptococcus neoformans* and other encapsulated fungi in a cell suspension (e.g., CSF sediment). The background field, rather than the organism itself, is stained, making any capsule around the organism visible as a halo. In CSF, the test is not as sensitive as cryptococcal antigen. Specificity is also limited; leukocytes may appear encapsulated.

**Wright's stain and Giemsa stain:** These stains are used for detection of parasites in blood, *Histoplasma capsulatum* in phagocytes and tissue cells, intracellular inclusions formed by viruses and chlamydia, trophozoites of *Pneumocystis jirovecii*, and some intracellular bacteria.

**Trichrome stain (Gomori-Wheatley stain) and iron hematoxylin stain:** These stains are used to detect intestinal protozoa.

The Gomori-Wheatley stain is used to detect microsporidia. It may miss helminth eggs and larvae and does not reliably identify *Cryptosporidium*. Fungi and human cells take up the stain.

The iron hematoxylin stain differentially stains cells, cell inclusions, and nuclei. Helminth eggs may stain too dark to permit identification.

**Culture**

Culture is microbial growth on or in a nutritional solid or liquid medium; increased numbers of organisms simplify identification. Culture also facilitates testing of antimicrobial susceptibility.

Communication with the laboratory is essential. Although most specimens are placed on general purpose media (e.g., blood or chocolate agar), some pathogens require inclusion of specific nutrients and inhibitors or other special conditions (see Table 130-1); if one of these pathogens is suspected or if the patient has been taking antimicrobials, the laboratory should be advised. The specimen's source is reported so that the laboratory can differentiate pathogens from site-specific normal flora.

Specimen collection is important. The wrong type of swab can produce false-negative results. Wooden-shafted swabs are toxic to some viruses. Cotton-tipped swabs are toxic for some bacteria and chlamydiae. Blood cultures require decontamination and disinfection of the skin (e.g., povidone iodine swab, allowed to dry, removed with 70% alcohol). Multiple samples, each from a different site are generally used; they are taken nearly simultaneously with fever spikes if possible. Normal flora of skin and mucous membranes that grows in only a single blood sample is usually interpreted as contamination. If a blood specimen is obtained from a central line, a peripheral blood specimen should also be obtained to help differentiate systemic bacteremia from catheter infection. Cultures from infected catheters generally turn positive more quickly and contain more organisms than simultaneously drawn peripheral blood cultures. Some fungi, particularly molds (e.g., *Aspergillus* sp), usually cannot be cultured from blood.

[Table 130-1, Selective Media for Isolation of Common Bacteria]

The specimen must be transported rapidly, in the correct medium, and in conditions that limit growth of any potentially contaminating normal flora. For accurate quantification of the pathogen, additional pathogen growth must be prevented; specimens should be transported to the laboratory immediately or, if transport is delayed, refrigerated (in most cases).

Certain cultures have special considerations.

**Anaerobic bacteria** should not be cultured from sites where they are normal flora because differentiation of pathogens from normal flora may be impossible. Specimens must be shielded from air, which can be
difficult. For swab specimens, anaerobic transport media are available. Specimens collected with a syringe (eg, abscess contents) should be transported in the syringe.

**Mycobacteria** are difficult to culture. Specimens containing normal flora (eg, sputum) must first be decontaminated and concentrated. *Mycobacterium tuberculosis* and some other mycobacteria grow slowly. Growth of *M. tuberculosis* is typically faster in liquid than in solid media; routine use of automated systems with liquid media can result in growth within 2 wk vs ≥ 4 wk on solid media such as Lowenstein-Jensen agar. In addition, few organisms may be present in a specimen. Multiple specimens from the same site may help maximize yield. Specimens should be allowed to grow for 8 wk before being discarded. If an atypical mycobacterium is suspected, the laboratory should be notified.

**Viruses** are generally cultured from swabs and tissue specimens usually transported in media that contain antibacterial and antifungal agents. Specimens are inoculated onto tissue cultures that support the suspected virus and inhibit all other microbes. Viruses that are highly labile (eg, varicella zoster) should be inoculated onto tissue cultures within 1 h of collection. Standard tissue cultures are most sensitive. Rapid tissue cultures (shell vials) may provide more rapid results. Some common viruses cannot be detected using routine culture methods and require alternative methods for diagnosis (eg, enzyme immunoassay for Epstein-Barr virus, hepatitis B and E viruses, HIV, and human T-lymphotropic virus; serologic tests for hepatitis A and D viruses; nucleic acid-based methods for HIV).

Fungi specimens obtained from nonsterile sites must be inoculated onto media containing antibacterial agents. Specimens should be allowed to grow for 4 wk before being discarded.

**Susceptibility Testing**

Susceptibility tests determine a microbe’s vulnerability to antimicrobial drugs by exposing a standardized concentration of organism to specific concentrations of antimicrobial drugs. Susceptibility testing can be done for bacteria, fungi, and viruses. For some organisms, results obtained with one drug predict results with similar drugs. Thus, not all potentially useful drugs are tested.

Susceptibility testing occurs in vitro and may not account for many in vivo factors (eg, pharmacodynamics and pharmacokinetics, site-specific drug concentrations, host immune status, site-specific host defenses) that influence treatment success. Thus, susceptibility test results do not always predict treatment outcome.

Susceptibility testing can be done qualitatively, semiquantitatively, or using nucleic acid-based methods. Testing can also determine the effect of combining different antimicrobials (synergy testing).

**Qualitative methods:** Qualitative methods are less precise than semiquantitative. Results are usually reported as susceptible (S), intermediate (I), or resistant (R). The commonly used disk diffusion method (also known as the Kirby-Bauer test) is appropriate for rapidly growing organisms. It places antibiotic-impregnated disks on agar plates inoculated with the test organism. After incubation (typically 16 to 18 h), the diameter of the zone of inhibition around each disk is measured. Each organism-antibiotic combination has different diameters signifying S, I, or R.

Other methods that require less rigid adherence to test parameters can be used to rapidly screen for resistance of a single organism to a single drug or drug class or to specific antimicrobial combinations (eg, oxacillin resistance of methicillin-resistant *Staphylococcus aureus*, β-lactamase production).

**Semiquantitative methods:** Semiquantitative methods determine the minimal concentration of a drug that inhibits growth of a particular organism in vitro. This minimum inhibitory concentration (MIC) is reported as a numerical value that may then be translated to 1 of 3 groupings: S (sensitive), I (intermediate), or R (resistant). MIC determination is used primarily for bacteria, including mycobacteria and anaerobes, and is sometimes used for fungi, especially *Candida* sp, obtained from sterile sites. Minimal killing (bactericidal) concentration (MBC) can also be determined but is technically difficult, and standards for interpretation have not been agreed on. The value of MBC testing is that it indicates whether a drug may be bacteriostatic or bactericidal.
The antibiotic can be diluted in agar or broth, which is then inoculated with the organism. Broth dilution is the gold standard but is labor intensive because only one drug concentration can be tested per tube. A more efficient method uses a strip of polyester film impregnated with antibiotic in a concentration gradient along its length. The strip is laid on an agar plate containing the inoculum, and the MIC determined by the location on the strip where inhibition begins; multiple antibiotics can be tested on one plate.

The MIC allows correlation between drug susceptibility of the organism and the achievable tissue concentration of drug not bound to protein (free drug). If the tissue concentration of free drug is higher than the MIC, successful treatment is likely. Similarly, reports of S, I, and R are correlated with MIC but generally are not tissue concentration-specific. That is, they are usually based on achievable serum or plasma concentration of free drug.

**Nucleic acid-based methods:** These tests incorporate nucleic acid techniques similar to those used for organism identification (see p. 1170) but modified to detect known resistance genes or mutations. An example is mecA, a gene for oxacillin resistance in *S. aureus*; if this gene is present, the organism is considered resistant to all β-lactam drugs regardless of apparent susceptibility results. However, although a number of such genes are known, their presence does not uniformly confer in vivo resistance. Also, because new mutations or other resistance genes may be present, their absence does not guarantee drug sensitivity. For these reasons and because the tests are limited in number, expensive, and not widely available, nucleic acid methods have not replaced standard culture and routine susceptibility testing.

**Immunologic Tests**

Immunologic tests use an antigen to detect antibodies to a pathogen or use an antibody to detect an antigen of the pathogen in the patient's specimen. Handling varies, but if testing is to be delayed, the specimen should typically be refrigerated or frozen to prevent overgrowth of bacterial contaminants.

**Agglutination tests:** In agglutination tests (eg, latex agglutination, coaggregation), a particle (latex bead or bacterium) is coupled to a reagent antigen or antibody. The resulting particle complex is mixed with the specimen (eg, CSF, serum); if the target antibody or antigen is present in the specimen, it cross-links the particles, producing measurable agglutination.

If results are positive, the body fluid is serially diluted and tested. Agglutination with more dilute solutions indicates higher concentrations of the target antigen or antibody. The titer is correctly reported as the reciprocal of the most dilute solution yielding agglutination; eg, 32 indicates that agglutination occurred in a solution diluted to 1/32 of the starting concentration.

Usually, agglutination tests are rapid but less sensitive than many other methods. They can also determine serotypes of some bacteria.

**Complement fixation:** This test measures complement-consuming (complement-fixing) antibody in serum or CSF. The test is used for diagnosis of some viral and fungal infections, particularly coccidioidomycosis. The specimen is incubated with known quantities of complement and the antigen that is the target of the antibody being measured. The degree of complement fixation indicates the relative quantity of the antibody in the specimen. The test can measure IgM and IgG antibody titers or can be modified to detect certain antigens. It is accurate but has limited applications, is labor intensive, and requires numerous controls.

**Enzyme immunoassays:** These tests use antibodies linked to enzymes to detect antigens and to detect and quantify antibodies. The enzyme immunoassay (EIA) and enzyme-linked immunosorbent assay (ELISA) are examples. Because sensitivities of most enzyme immunoassays are high, they are usually used for screening. Titers can be determined by serially diluting the specimen as for agglutination tests.

Test sensitivities, although usually high, can vary, sometimes according to patient age, microbial serotype, specimen type, or stage of clinical disease.

**Precipitation tests:** These tests measure an antigen or antibody in body fluids by the degree of visible precipitation of antigen-antibody complexes within a gel (agarose) or in solution. There are many types of...
precipitation tests (eg, Ouchterlony double diffusion, counter immunoelectrophoresis), but their applications are limited. Usually, a blood specimen is mixed with test antigen to detect patient antibodies, most often in suspected fungal infection or pyogenic meningitis. Because a positive result requires a large amount of antibody or antigen, sensitivity is low.

**Western blot test:** This test detects antimicrobial antibodies in the patient's sample (eg, serum, other body fluid) by their reaction with target antigens (eg, viral components) that have been immobilized onto a membrane by blotting.

The Western blot typically has good sensitivity, although often less than that of screening tests such as ELISA, but generally is highly specific. Thus, it is usually used to confirm a positive result obtained with a screening test.

Technical modifications of the Western blot are the line immunoassay (LIA); the recombinant immunoblot assay (RIBA), which uses synthetic or recombinant-produced antigens; and immunochromatographic assays, which can rapidly screen specimens for specific microbial antigens or patient antibodies.

### Non-Nucleic Acid-Based Identification Methods

Once an organism has been isolated by culture, it must be identified. Non-nucleic acid-based identification methods use phenotypic (functional or morphologic) characteristics of organisms rather than genetic identification.

Characteristics of an organism's growth on culture media, such as colony size, color, and shape, provide clues to species identification and, combined with Gram stain, direct further testing. Numerous biochemical tests are available; each is restricted to organisms of a certain type (eg, aerobic or anaerobic bacteria). Some assess an organism's ability to use different substrates for growth. Others assess presence or activity of key enzymes (eg, coagulase, catalase). Tests are done sequentially, with previous results determining the next test to be used. The sequences of tests are myriad and differ somewhat among laboratories.

Non-nucleic acid-based identification tests may involve manual methods, automated systems, or chromatographic methods. Some commercially available kits contain a battery of individual tests that may be done simultaneously using a single specimen and may be useful for a wider range of organisms. Multiple test systems can be highly accurate but may require several days to yield results.

**Chromatographic methods:** Microbial components or products are separated and identified using high-performance liquid chromatography (HPLC) or gas chromatography. Usually, identification is by comparison of an organism's fatty acids to a database. Chromatographic methods can be used to identify aerobic and anaerobic bacteria, mycobacteria, and fungi. Test accuracy depends on the conditions used to culture the specimen and the quality of the database, which may be inaccurate or incomplete.

### Nucleic Acid-Based Identification Methods

Nucleic acid-based methods detect organism-specific DNA or RNA sequences extracted from the microorganism. Sequences may or may not be amplified in vitro. Nucleic acid-based methods are generally specific and highly sensitive and can be used for all categories of microbes. Results can be provided rapidly. Because each test typically is specific to a single organism, the clinician must know the diagnostic possibilities and request tests accordingly. For example, if a patient has symptoms suggesting influenza but the influenza season is over, doing a more general viral diagnostic test (eg, viral culture) rather than a specific flu test is better because another virus (eg, parainfluenza, adenovirus) may be the cause.

Nucleic acid-based tests are qualitative, but quantification methods exist for a limited but increasing number of infections (eg, HIV, cytomegalovirus, human T-cell lymphotropic virus); these methods can be useful for diagnosis and for monitoring response to treatment.

Techniques that do not involve nucleic acid amplification are used if the organism has been first cultured...
or is present in high concentration in the specimen (eg, in pharyngitis caused by group A Streptococcus, in genital infections caused by Chlamydia trachomatis or Neisseria gonorrhoeae).

**Amplification:** Nucleic acid amplification techniques take tiny amounts of DNA or RNA, replicate them many times, and thus can detect minute traces of an organism in a specimen, avoiding the need for culture. These techniques are particularly useful for organisms that are difficult to culture or identify using other methods (eg, viruses, obligate intracellular pathogens, fungi, mycobacteria, some other bacteria) or that are present in low numbers.

These tests may involve target amplification (eg, PCR, reverse transcriptase-PCR [RT-PCR], strand displacement amplification, transcription amplification), signal amplification (eg, branched DNA assays, hybrid capture), probe amplification (eg, ligase chain reaction, cleavase-invader, cycling probes), or postamplification analysis (eg, sequencing of the amplified product, microarray analysis, and melting curve analysis, as is done in real-time PCR).

Appropriate specimen collection and storage before arrival at the molecular diagnostic laboratory are critical. Because amplification methods are so sensitive, false positives from trace contamination of the specimen or equipment can easily occur. Despite high sensitivity, false negatives sometimes occur even when a patient is symptomatic (eg, in West Nile virus infection). False-negative results can be minimized by

- Avoiding use of swabs with wooden shafts or cotton tips
- Transporting specimens rapidly
- Freezing or refrigerating specimens if transport is likely to take > 2 h

Freezing is the typical storage method for nucleic acid amplification assays. However, specimens should be refrigerated rather than frozen if labile viruses (eg, varicella-zoster virus, influenza virus, HIV-2) are suspected or if viral cultures are also to be done (frozen specimens may not be usable for standard cultures).
Chapter 131. Immunization

Introduction

Immunity can be achieved actively by using antigens (eg, vaccines, toxoids) or passively by using antibodies (eg, immune globulins, antitoxins). A toxoid is a bacterial toxin that has been modified to be nontoxic but that can still stimulate antibody formation. A vaccine is a suspension of whole (live or inactivated) or fractionated bacteria or viruses rendered nonpathogenic. For vaccines available in the US, see Table 131-1. The most current recommendations for immunization are available at the Centers for Disease Control and Prevention (CDC) web site.

Vaccines should be given exactly as recommended on the package insert; however, the interval between a series of doses may be lengthened without losing efficacy. Injection vaccines are usually given IM into the mid-lateral thigh (in infants and toddlers) or into the deltoid muscle (in school-aged children and adults). Parents should keep a written history of each child's vaccinations.

Table 131-1. Vaccines Available in the US

Risks, Restrictions, and High-Risk Groups

Live-microbial vaccines should not be given simultaneously with blood, plasma, or immune globulin, which can interfere with development of desired antibodies; ideally, such vaccines should be given 2 wk before or 6 to 12 wk after the immune globulins.

Immunocompromised patients should not receive live-virus vaccines, which could provoke severe or fatal infections. In patients receiving short-term (ie, < 14 days) immunosuppressive therapy (eg, corticosteroids, antimetabolites, alkylating compounds, radiation), live-virus vaccines should be withheld until after treatment. Patients receiving longer-term immunosuppressive therapy may receive inactivated vaccines such as DTaP; ≥ 3 mo after immunosuppressive therapy is stopped, they should be given an additional dose of inactivated vaccine and may receive live-virus vaccines.

Asplenic patients are predisposed to overwhelming bacteremic infection, usually due to Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type b (Hib). They should be given the following:

- Hib conjugate vaccine (HbCV)
- Meningococcal polysaccharide vaccine
- Annual influenza vaccine
- Pneumococcal conjugate (if age < 5 yr) or polysaccharide (if age > 5 yr) vaccine

Before solid organ transplantation, patients should receive all appropriate vaccines. Patients who have had hematopoietic cell transplantation should be considered unimmunized and should receive repeat doses of all appropriate vaccines.

Patients with AIDS should generally receive inactivated vaccines (eg, DTP, polio [IPV], HbCV) according to routine recommendations but should usually not receive live-virus or bacterial vaccines (eg, measles-mumps-rubella, OPV, BCG). However, they can receive measles-mumps-rubella if immunosuppression is not severe because naturally occurring measles can cause severe, often fatal infection in AIDS patients, and measles-mumps-rubella vaccine rarely causes serious complications.

Risks of vaccines should be discussed with patients. Parents should give written consent for vaccination of their children. In the US, selected events that occur after routine vaccination must be reported to the manufacturer, the US Department of Health and Human Services, and the Centers for Disease Control...
and Prevention's Vaccine Adverse Event Reporting System (VAERS). Forms and instructions can be obtained by calling 800-822-7967 (Health and Human Services) or from the VAERS web site (http://vaers.hhs.gov).

A temperature of > 39° C requires delaying vaccination, but minor infections, such as the common cold (even with low-grade fever), do not. Some vaccines produced in cell culture systems contain trace amounts of egg antigens. Although egg allergies are often considered contraindications to these vaccines, the vaccines do not appear to cause significant adverse reactions in patients who can eat foods that contain eggs, such as bread or cookies. A history of other allergic reactions may contraindicate use of certain vaccines (see Table 131-2).

Pregnancy is a relative contraindication to vaccination with human papillomavirus (HPV), measles-mumps-rubella, pneumococcal pneumonia, varicella, and other live-virus vaccines.

Concern has been raised about the safety in infants of thimerosal, an Hg-based preservative present in some vaccines, but there is no evidence of harm. In particular, there is no convincing evidence that vaccines containing thimerosal are related to the development of autism. Nevertheless, most manufacturers have developed thimerosal-free vaccines for use in infants. Information about vaccines that currently contain low levels of Hg or thimerosal is available at the Institute for Vaccine Safety web site.

Patients with a fluctuating or progressive neurologic disorder, such as Guillain-Barre syndrome, should not be vaccinated until their condition has been stable for at least 1 yr because cerebral irritation is a risk. If a neurologic disorder is stable, vaccinations should proceed normally. The risk in patients with multiple sclerosis is unknown.

**Routine Vaccinations**

For the schedule of vaccinations for infants and children, see Table 268-10 on p. 2718 (see also the Centers for Disease Control and Prevention's [CDC's] National Immunization Program 2010 Childhood and Adolescent Immunization Schedule at www.cdc.gov/vaccines/recs/schedules/).

For vaccinations to be considered for all adults, see Table 131-2 (see also the CDC's National Immunization Program Adult Immunization Recommendations at www.cdc.gov/vaccines/recs/schedules/adult-schedule). Uses of nonroutine active vaccines (eg, for rabies, typhoid, yellow fever, and mycobacterial infections) and some routine vaccinations are discussed under specific disorders elsewhere in THE MANUAL.

**Diphtheria-Tetanus-Pertussis**

**Preparations:** Diphtheria (D) vaccines contain toxoids prepared from Corynebacterium diphtheriae. Tetanus (T) vaccines contain toxoids prepared from Clostridium tetani. Acellular (a) pertussis (P) vaccines contain semipurified or purified components of Bordetella pertussis. Whole-cell pertussis vaccine is no longer available in the US because of concerns about adverse effects, but it is still available in other parts of the world. There are 2 preparations of the acellular vaccine:

- DTaP for children < 7 yr
- Tdap for adolescents and adults

Tdap contains lower doses of diphtheria and pertussis components (indicated by the lower case d and p).

**Administration:** The vaccine is given as 5 primary and 1 booster IM injections during childhood as follows: the first 3 doses at 2-mo intervals, starting at age 2 mo; the 4th at age 12 to 15 mo; and the last before school entry at age 4 to 6 yr. A single booster of Tdap is given at age 11 or 12 yr.
Adverse effects: Adverse effects are rare and are mostly attributable to the pertussis component. They include encephalopathy within 7 days; a seizure, with or without fever, within 3 days; persistent, severe, inconsolable screaming or crying for ≥ 3 h; collapse or shock within 48 h; temperature of ≥ 40.5°C, unexplained by another cause, within 48 h; and immediate severe or anaphylactic reaction to the vaccine. These reactions contraindicate further use of pertussis vaccine; combined diphtheria and tetanus vaccine is available without the pertussis component.

Mild adverse effects include redness, swelling, and soreness at the injection site.

Tetanus-Diphtheria

Although tetanus is rare in the US, it has a high mortality rate. Because one third of cases occur unpredictably (after minor or inapparent injuries), universal tetanus vaccination remains necessary.

Preparations: The most widely used preparations combine tetanus toxoid with diphtheria toxoid (Td for adults, DT for children); a preparation with only tetanus toxoid (TT) is also available. Td contains a lower dose of diphtheria toxoid than DTaP and DT, which are used in children.

Administration: Td boosters, 0.5 mL IM, are given every 10 yr after the Tdap booster that is given at age 11 to 12 yr. Boosters are needed to maintain immunity. Because the incidence of pertussis is increasing, at least one booster before age 65 should be Tdap. Adults who missed the primary series of vaccinations in childhood should receive it as adults.

Adverse effects: Adverse effects are very rare. They include anaphylactic reactions, Guillain-Barre syndrome, and brachial neuritis. Mild effects include redness, swelling, and soreness at the injection site.

Haemophilus influenzae Type b

Preparations: These vaccines are prepared from the purified capsule of Haemophilus influenzae type b (Hib). All Hib vaccines use polyribosylribitol phosphate (PRP) as the polysaccharide, but 4 different protein carriers produce 4 different Hib conjugate vaccines: diphtheria toxoid (PRP-D), Neisseria meningitidis outer membrane protein (PRP-OMP), tetanus toxoid (PRP-T), and diphtheria mutant carrier protein CRM197 (HbOC).

Administration: A primary series is given in 3 IM doses at age 2, 4, and 6 mo or in 2 IM doses at age 2 and 4 mo, depending on the formulation. In either case, a booster is recommended at age 12 to 15 mo. Some adults at increased risk (eg, because of AIDS or asplenia) may benefit from this vaccine.

Adverse effects: Adverse effects are rare. They can include pain, redness, and swelling at the injection site.

Hepatitis A

Preparations: Hepatitis A vaccines are prepared from formalin-inactivated, cell culture-derived hepatitis A virus. There are 2 formulations; either can be used in children or adults.

Administration: The vaccine is given in 2 IM doses 6 mo apart. It is recommended for children aged 12 to 18 mo and for older children and adults who are at increased of the disease (see Table 131-2).

Adverse effects: No serious adverse effects have been reported. Mild effects include pain and occasionally induration at the injection site.

Hepatitis B

Preparations: Hepatitis B vaccine uses recombinant DNA technology. Single-antigen and combination
formulations are available.

**Administration:** The vaccine is given in 2 or 3 IM doses, depending on the formulation. Universal vaccination is recommended beginning at birth.

**Adverse effects:** Serious adverse effects are very rare and include anaphylaxis. Mild effects include pain at the injection site and occasionally an increase in temperature to > 38°C.

**Human Papillomavirus**

**Preparations:** Recombinant technology is used to prepare the vaccine. The vaccine is made from HPV-like particles (VLP) from serotypes 6, 11, 16, and 18, which cause 70% of cervical cancers and 90% of genital warts.

**Administration:** The vaccine is given in 3 IM doses: initially, then at 1 to 2 and 4 to 6 mo after the initial dose. It is recommended for females aged 11 to 13 but can be given as early as age 9 or up to age 26 for catch-up. Vaccination is not recommended after age 26.

**Adverse effects:** No serious adverse effects have been reported. Mild effects include redness, swelling, and tenderness at the injection site.

**Influenza**

**Preparations:** Influenza vaccines may be inactivated trivalent vaccines (TIV) or live-attenuated vaccines (LAIV). Each type targets 3 virus strains (2 from influenza A and 1 from influenza B). Because antigenic drift is continual, 1 or 2 strains are changed each year in anticipation of the expected predominant influenza strains. An inactivated vaccine against avian influenza has been developed but is not commercially available. It is being nationally stockpiled in case person-to-person transmission of avian influenza becomes possible.

**Administration:** The vaccine is required annually for at-risk patients because of antigenic drift. Because outbreaks usually begin in early winter or midwinter, the vaccine is given in the fall, usually October and November in the Northern Hemisphere.

TIV, given as a single IM injection, is recommended for people at high risk of serious sequelae, including children aged 6 mo to 8 yr and anyone > 50 yr (see Table 131-2), as well as anyone who requests vaccination.

LAIV, given as an intranasal spray, is indicated for healthy people aged 2 to 49 yr; it is contraindicated during pregnancy.

**Adverse effects:** Rarely, TIV has adverse effects, such as Guillain-Barre syndrome, anaphylactic reactions, soreness at the injection site, and fever. Adverse effects of LAIV are unusual; they include possible triggering of asthma and transmission of the virus to unimmunized contacts.

Egg protein is used in both vaccine types; thus, the vaccine is contraindicated for people who have severe anaphylactic reactions to egg protein.

**Measles, Mumps, and Rubella**

**Preparations:** The vaccine contains live-attenuated virus prepared in chicken embryo cell cultures. Measles vaccine is available as a single-antigen (measles-only) vaccine or combined with rubella (MR), mumps and rubella (MMR), or mumps, rubella, and varicella (MMRV). There are also single-antigen vaccines for mumps, rubella, and varicella.

**Administration:** Most commonly, the combination vaccine MMR or MMRV is given sc. The vaccine should be given to all children in their 2nd yr of life, typically at age 12 to 15 mo, with a 2nd dose at age 4 to 6 yr. Adults at risk include those who have never received the vaccine and have never become...
naturally infected. Generally, people born before 1956 are considered immune because infection during their childhood was ubiquitous. Unless the vaccine is contraindicated, people who were born after 1956 and have not had 2 doses of the vaccine or the infections should receive at least one dose of the combined vaccine; people who have been or are likely to be exposed (eg, college students, health care workers, international travelers) should receive a 2nd dose.

Although the components of the vaccine can be given separately, the combined form is preferred because people who need one vaccine probably need all 3, and revaccination poses no particular risk.

**Adverse effects:** A mild, noncommunicable infection occurs in 15% of vaccine recipients. Symptoms appear 7 to 11 days after immunization and include fever, malaise, and a measles-like exanthem. Mumps vaccine has adverse effects only rarely; they include encephalitis (only from a Japanese mumps vaccine strain), seizures, nerve deafness, parotitis, purpura, rash, and pruritus.

Rubella vaccine can cause joint pain, usually in the small peripheral joints 2 to 8 wk after immunization, in < 1% of infants but in ≤ 26% of women. Rash or lymphadenopathy occasionally occurs. The vaccine is not recommended for pregnant women because of the theoretic risk to the fetus. However, inadvertent administration during pregnancy does not necessarily mean a therapeutic abortion is recommended because the actual fetal risk may be nil.

With all of the vaccine formulations, local adverse effects are unusual and include soreness at the injection site.

**Pneumococcal Disease**

**Preparations:** Pneumococcal conjugate vaccine (PCV7) contains 7 purified capsular polysaccharides of *Streptococcus pneumoniae*; each is coupled to a variant of diphtheria toxin. Pneumococcal polysaccharide vaccine (PPV23) contains antigens from the 23 most virulent of the 83 subtypes of *S. pneumoniae*. Unlike the older 23-valent vaccine, PCV7 can stimulate antibody responses in infants. It also seems to confer greater protection against invasive pneumococcal disorders than PPV23. PPV23 reduces bacteremia by 56 to 81% in adults overall but is less effective in debilitated elderly people. It reduces pneumonia incidence only minimally.

**Administration:** PCV7 is recommended as a 4-dose IM series for infants at age 2, 4, 6, and 12 to 15 mo. Children at high risk of pneumococcal disease (eg, children with sickle cell disease, asplenia, or a chronic disorder) should receive a dose of PPV23 at age 24 mo and an additional dose 3 to 5 yr after the first. PPV23 should be given to any older child or adult at high risk of pneumococcal disease (see Table 131-2). One immunization is recommended for lifetime protection; however, revaccination after 5 yr should be considered for patients at particularly high risk.

**Adverse effects:** Adverse effects are usually mild and include fever, irritability, drowsiness, anorexia, vomiting, and local erythema.

**Poliomyelitis**

**Preparations:** Inactivated poliovirus vaccine (IPV) contains a mixture of formalin-inactivated poliovirus types 1, 2, and 3. IPV may contain trace amounts of streptomycin, neomycin, and polymyxin B. A combination vaccine with IPV, DTaP, and hepatitis B is also available. The live-attenuated oral formulation is no longer available in the US because it causes polio in about 1 of every 2.4 million people who receive the vaccine.

**Administration:** A 4-dose IM series is given at age 2 mo, 4 mo, 6 to 18 mo, and 4 to 6 yr. Typically, a combination vaccine is used for the first 3 vaccinations and a single-antigen vaccine for the last dose.

**Adverse effects:** No adverse effects have been associated with IPV. Because it may contain trace amounts of neomycin, streptomycin, and polymyxin B, people who are sensitive to any of these drugs may have an allergic reaction to the vaccine.
**Varicella**

**Preparations:** The vaccine contains an attenuated wild strain of varicella and trace amounts of gelatin and neomycin. It is available as a single-antigen vaccine or as a combination vaccine with MMR.

**Administration:** The vaccine is given sc in 2 doses: at age 12 to 15 mo and at age 4 to 6 yr. The 2nd dose is a new recommendation; thus, a catch-up dose is suggested for children, adolescents, and adults who have received only one dose. The vaccine should be given to all children and to young adults not previously infected, especially health care practitioners and close contacts of immunocompromised patients. If adults have not had varicella, levels of protective antibodies should be measured to determine the need for vaccination. No immune globulins, particularly varicella-zoster immune globulin, should be given within 5 mo before or 2 mo after vaccination because immune globulins may prevent development of protective antibodies.

**Adverse effects:** Adverse effects are minimal and include transient pain, tenderness, and redness at the injection site. Occasionally, within 1 mo of vaccination, a mild maculopapular or varicella-like rash develops. Patients who develop this rash should avoid contact with immunocompromised people until it resolves. Spread of the virus from vaccine recipients to susceptible people has been documented in < 1% of recipients but only from those who developed a rash.

Because Reye's syndrome can develop, recipients < 16 yr should avoid salicylates for 6 wk.

**Herpes Zoster**

**Preparations:** The vaccine contains an attenuated wild strain of varicella, similar to the varicella vaccine but with a higher amount of the attenuated virus.

**Administration:** The vaccine is recommended for adults ≥ 60 yr regardless of prior infection. It is given sc.

**Adverse effects:** No serious adverse effects have been reported. Soreness at the site of the injection may occur.

**Simultaneous Administration of Different Vaccines**

Simultaneous administration is safe, effective, and convenient; it is particularly recommended when children may be unavailable for future vaccination or when adults require multiple simultaneous vaccines (eg, before international travel). Simultaneous administration may involve combination vaccines (see Table 131-1) or use of ≥ 1 single-antigen vaccines. More than one vaccine may be given at the same time using different injection sites and syringes. If live-virus vaccines (varicella and MMR) are not given at the same time, they should be given at least 4 wk apart.

**Immunizations for Travelers**

Immunizations may be required for travel to areas where infectious diseases are endemic. The Centers for Disease Control and Prevention can provide information; a telephone service (1-877-394-8747) and web site (wwwnc.cdc.gov/travel/content/vaccinations.aspx) are available 24 h/day.

**Passive Immunization**

Passive immunization is provided in the following circumstances:

- When people cannot synthesize antibody
- When people have been exposed to a disease that they are not immune to or that is likely to cause complications
- When people have a disease and the effects of the toxin must be ameliorated
For immune globulins and antitoxins available in the US, see Table 131-3.

Human immune globulin (IG): IG is a concentrated antibody-containing solution prepared from plasma obtained from normal donors. It consists primarily of IgG, although trace amounts of IgA, IgM, and other serum proteins may be present. IG very rarely contains transmissible viruses (eg, hepatitis B or C, HIV) and is stable for many months if stored at 4°C. IG is given IM. Because maximal serum antibody levels may not occur until about 48 h after IM injection, IG must be given as soon after exposure as possible. Half-life of IG in the circulation is about 3 wk.

IG may be used for prophylaxis in hepatitis A, measles, immunoglobulin deficiency, varicella (in immunocompromised patients when varicella-zoster IG is unavailable), and rubella exposure during the 1st trimester of pregnancy.

[Table 131-3, Immune Globulins and Antitoxins* Available in the US]

IG provides only temporary protection; the antibody content against specific agents varies by as much as 10-fold among preparations. Administration is painful, and anaphylaxis can occur.

IV immune globulin (IVIG) was developed to provide larger and repeated doses of human immune globulin. IVIG is used to treat or prevent severe bacterial and viral infections, autoimmune disorders, and immunodeficiency disorders, particularly the following:

- Kawasaki disease
- HIV infection in children
- Chronic B-cell lymphocytic leukemia
- Primary immunodeficiencies
- Autoimmune thrombocytopenic purpura
- Prevention of graft-vs-host disease

IVG or a specific monoclonal antibody against RSV is available for prevention of RSV in children who are < 24 mo and have bronchopulmonary dysplasia or a history of premature birth (< 35 wk gestation).

Adverse effects are uncommon, although fever, chills, headache, faintness, nausea, vomiting, hypersensitivity, anaphylactic reactions, coughing, and volume overload have occurred.

Subcutaneous immune globulin (SCIG) is also prepared from pooled human plasma; SCIG is intended for home use in patients with a primary immunodeficiency.

Injection site reactions are common, but systemic adverse effects (eg, fever, chills) are much less common than with IVIG.

Hyperimmune globulin: Hyperimmune globulin is prepared from the plasma of people with high titers of antibody against a specific organism or antigen. It is derived from people convalescing from natural infections or donors artificially immunized.

Hyperimmune globulins are available for hepatitis B, respiratory syncytial virus (RSV), rabies, tetanus, cytomegalovirus, vaccinia, and varicella-zoster. Administration is painful, and anaphylaxis may occur.
Chapter 132. Bacteria and Antibacterial Drugs

Introduction

Bacteria are microorganisms that have circular double-stranded DNA and (except for mycoplasmas) cell walls. Most bacteria live extracellularly. Some bacteria (e.g., *Salmonella typhi*; *Neisseria gonorrhoeae*; *Legionella*, *Mycobacterium*, *Chlamydia*, and *Chlamydophila* spp) preferentially reside and replicate intracellularly. Some bacteria such as chlamydiae and rickettsiae are obligate intracellular pathogens (i.e., able to grow, reproduce, and cause disease only within the cells of the host). Others (e.g., *Salmonella typhi*, *Brucella* sp, *Francisella tularensis*, *N. gonorrhoeae*, *N. meningitidis*, *Legionella* and *Listeria* spp, *Mycobacterium tuberculosis*) are facultative intracellular pathogens.

Many bacteria are present in humans as normal flora, often in large numbers and in many areas (e.g., in the GI tract). Only a few bacterial species are human pathogens.

Bacteria are classified by the following criteria (see Table 132-1).

**Morphology**: Bacteria may be cylindric (bacilli), spherical (cocci), or spiral (spirochetes). A few coccal, many bacillary, and most spirochetal species are motile.

**Staining**: The most common stain for general bacterial identification is Gram stain. Gram-positive bacteria retain crystal violet dye (appearing dark blue) after iodine fixation and alcohol decolorization; gram-negative bacteria do not. Gram-negative bacteria have an additional outer membrane containing lipopolysaccharide (endotoxin), increasing the virulence of these bacteria. (For other factors that enhance bacterial pathogenicity, see Factors Facilitating Microbial Invasion on p. 1150.) Ziehl-Neelsen stain (acid-fast stain) is used to identify mainly mycobacteria, particularly *M. tuberculosis*. It also can identify *Nocardia* sp. Carbolfuchsin is applied with heat, followed by decolorization with hydrochloric acid and ethanol and counterstaining with methylene blue.

**Encapsulation**: Some bacteria are enclosed in capsules; for some encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*), the capsule helps protect them from ingestion by phagocytes. Encapsulation increases bacterial virulence.

**Oxygen requirements**: Aerobic bacteria (obligate aerobes) require O\(_2\) to produce energy and to grow in culture. They produce energy using aerobic cellular respiration.

Anaerobic bacteria (obligate anaerobes) do not require O\(_2\) and do not grow in culture if air is present. They produce energy using fermentation or anaerobic respiration. Anaerobic bacteria are common in the GI tract, vagina, dental crevices, and wounds when blood supply is impaired.

Facultative bacteria can grow with or without O\(_2\). They produce energy by fermentation or anaerobic respiration when O\(_2\) is absent and by aerobic cellular respiration when O\(_2\) is present. Microaerophilic bacteria prefer a reduced O\(_2\) tension (e.g., 2 to 10%). Chlamydiae are obligate intracellular parasites that acquire energy from the host cell and do not produce it themselves.

**Antibacterial Drugs**

Antibacterial drugs are derived from bacteria or molds or are synthesized de novo. Technically, "antibiotic" refers only to antimicrobials derived from bacteria or molds but is often (including in THE MANUAL) used synonymously with "antibacterial drug."
Antibiotics have many mechanisms of action, including inhibiting cell wall synthesis, activating enzymes that destroy the cell wall, increasing cell membrane permeability, and interfering with protein synthesis and nucleic acid metabolism.

Antibiotics sometimes interact with other drugs, raising or lowering serum levels of other drugs by increasing or decreasing their metabolism or by various other mechanisms (see Table 132-2). The most clinically important interactions involve drugs with a low therapeutic ratio (ie, toxic levels are close to therapeutic levels). Also, other drugs can increase or decrease levels of antibiotics.

Many antibiotics are chemically related and are thus grouped into classes. Although drugs within each class share structural and functional similarities, they often have different pharmacology and spectra of activity.

Selection and Use of Antibiotics

Antibiotics should be used only if clinical or laboratory evidence suggests bacterial infection. Use for viral illness or undifferentiated fever is inappropriate, subjects patients to drug complications without any benefit, and contributes to bacterial resistance. Certain bacterial infections (eg, abscesses, infections with foreign bodies) require surgical intervention and do not respond to antibiotics alone.

Spectrum of activity: Cultures and antibiotic sensitivity testing are essential for selecting a drug for serious infections. However, treatment must often begin before culture results are available, necessitating selection according to the most likely pathogens (empiric antibiotic selection). Whether chosen according to culture results or not, drugs with the narrowest spectrum of activity that can control the infection should be used. For empiric treatment of serious infections that may involve any one of several pathogens (eg, fever in neutropenic patients) or that may be due to multiple pathogens (eg, polymicrobial anaerobic infection), a broad spectrum of activity is desirable. The most likely pathogens and their susceptibility to antibiotics vary according to geographic location (within cities or even within a hospital) and can change from month to month.

For serious infections, combinations of antibiotics are often necessary because multiple species of bacteria may be present or because combinations act synergistically against a single species of bacteria. Synergism is usually defined as a more rapid and complete bactericidal action from a combination of antibiotics than occurs with either antibiotic alone. A common example is a cell wall-active antibiotic (eg, a β-lactam, vancomycin) plus an aminoglycoside.

Effectiveness: In vivo antibiotic effectiveness involves many factors, including

- Pharmacology (eg, absorption, distribution, concentration in fluids and tissues, protein binding, rate of metabolism or excretion)
- Pharmacodynamics (ie, the time course of antibacterial effects exerted by drug levels in blood and at the site of infection)
- Drug interactions or inhibiting substances
- Host defense mechanisms

[Table 132-2, Common Effects of Antibiotics on Other Drugs]

- In vitro killing power but usually only if the site of infection (eg, in meningitis or endocarditis) is resistant to treatment or if systemic host defenses are weak (eg, in neutropenic or other immunocompromised patients)

Bactericidal drugs kill bacteria in vitro. Bacteriostatic drugs slow or stop in vitro bacterial growth. These definitions are not absolute; bacteriostatic drugs may kill some bacteria, and bactericidal drugs may not kill all of the bacteria in vitro. More precise quantitative methods identify the minimum in vitro
concentration at which an antibiotic can inhibit growth (minimum inhibitory concentration, or MIC) or kill (minimum bactericidal concentration, or MBC).

The predominant determinant of bacteriologic response to antibiotics is the time that blood levels of the antibiotic exceed the MIC (time-dependence) or the peak blood level relative to MIC (concentration-dependence).

β-Lactams and vancomycin exhibit time-dependent bactericidal activity. Increasing their concentration above the MIC does not increase their bactericidal activity, and their in vivo killing is generally slow. In addition, because there is no or very brief residual inhibition of bacterial growth after concentrations fall below the MIC (postantibiotic effect, or PAE), β-lactams and vancomycin are most often effective when serum levels of free drug (drug not bound to serum protein) exceed the MIC for ≥ 50% of the time. Because ceftriaxone has a long serum half-life, free serum levels exceed the MIC of very susceptible pathogens for the entire 24-h dosing interval. However, for β-lactams that have serum half-lives of ≤ 2 h, frequent dosing or continuous infusion is required. For vancomycin, trough levels should be maintained at least at 10 to 15 μg/mL.

Aminoglycosides, fluoroquinolones, and daptomycin exhibit concentration-dependent bactericidal activity. Increasing their concentrations from levels slightly above the MIC to levels far above the MIC increases their rate of bactericidal activity and decreases the bacterial load. In addition, if concentrations exceed the MIC even briefly, aminoglycosides and fluoroquinolones have a PAE on residual bacteria; duration of PAE is also concentration-dependent. If PAEs are long, drug levels can be below the MIC for extended periods without loss of efficacy, allowing less frequent dosing. Consequently, aminoglycosides and fluoroquinolones are usually most effective as intermittent boluses that reach peak free serum levels ≥ 10 times the MIC of the bacteria.

Route: For many antibiotics, oral administration results in therapeutic blood levels nearly as rapidly as IV administration. However, IV administration is preferred in the following circumstances:

• Oral antibiotics cannot be tolerated (eg, because of vomiting).
• Oral antibiotics cannot be absorbed (eg, because of malabsorption after intestinal surgery).
• Intestinal motility is impaired (eg, because of opioid use).
• No oral formulation is available (eg, for aminoglycosides).
• Patients are critically ill, possibly impairing GI tract perfusion or making even the brief delay with oral administration detrimental.

Special populations: Doses and scheduling of antibiotics may need to be adjusted for the following:

• Infants
• The elderly
• Patients with renal failure (see Table 132-3)
• Patients with hepatic insufficiency (most commonly for cefoperazone, ceftriaxone, chloramphenicol, clindamycin, metronidazole, nafcillin, rifabutin, and rifampin)

Pregnancy and breastfeeding affect choice of antibiotic. Penicillins, cephalosporins, and erythromycin are among the safest antibiotics during pregnancy; tetracyclines are contraindicated. Most antibiotics reach sufficient concentrations in breast milk to affect a breastfed baby, sometimes contraindicating their use in women who are breastfeeding.

Duration: Antibiotics should be continued until objective evidence of systemic infection (eg, fever,
symptoms, abnormal laboratory findings) is absent for several days. For some infections (eg, endocarditis, TB, osteomyelitis), antibiotics are continued for weeks or months to prevent relapse.

**Complications:** Complications of antibiotic therapy include superinfection by nonsusceptible bacteria or fungi and cutaneous, renal, hematologic, and GI adverse effects. Adverse effects frequently require stopping the causative drug and substituting another antibiotic to which the bacteria are susceptible; sometimes, no alternatives exist.

**Antibiotic Resistance**

Resistance to an antibiotic may be inherent in a particular bacterial species or may be acquired through mutations or acquisition of genes for antibiotic resistance that are obtained from another organism. Different mechanisms for resistance are encoded by these genes (see Table 132-4). Resistance genes can be transmitted between 2 bacterial cells by the following mechanisms:

- Transformation (uptake of naked DNA from another organism)
- Transduction (infection by a bacteriophage)
- Conjugation (exchange of genetic material in the form of either plasmids, which are pieces of independently replicating extra-chromosomal DNA, or transposons, which are movable pieces of chromosomal DNA) Plasmids and transposons, which can rapidly disseminate resistance genes

Antibiotic use preferentially eliminates non-resistant bacteria, increasing the proportion of resistant bacteria that remain. Antibiotic use has this effect not only on pathogenic bacteria but also on normal flora; resistant normal flora can become a reservoir for resistance genes that can spread to pathogens.

**Aminoglycosides**

Aminoglycosides (see Table 132-5) have concentration-dependent bactericidal activity. They bind to the 30S ribosome, thereby inhibiting bacterial protein synthesis.

**Pharmacology**

Aminoglycosides are poorly absorbed orally but are well absorbed from the peritoneum, pleural cavity, and joints (and should never be instilled in these body cavities) and from denuded skin. Aminoglycosides are usually given IV. Aminoglycosides are distributed well into ECF except for vitreous humor, CSF, respiratory secretions, and bile (particularly in patients with biliary obstruction). Intravitreous injection is required to treat endophthalmitis. Intraventricular injection is often required to reach intraventricular levels high enough to treat meningitis.

**Indications**

Aminoglycosides are used for

- Serious gram-negative bacillary infections (especially those due to *Pseudomonas aeruginosa*)
Aminoglycosides are active against most gram-negative aerobic and facultative anaerobic bacilli but lack activity against anaerobes and most gram-positive bacteria, except for most staphylococci; however, some gram-negative bacilli and methicillin-resistant staphylococci are resistant.

Aminoglycosides that are active against *P. aeruginosa* include tobramycin (particularly), gentamicin, and amikacin. Streptomycin, neomycin, and kanamycin are not active against *P. aeruginosa*. Gentamicin and tobramycin have similar antimicrobial spectra against gram-negative bacilli, but tobramycin is more active against *P. aeruginosa*, and gentamicin is more active against *Serratia marcescens*. Amikacin is frequently active against gentamicin- and tobramycin-resistant pathogens.

Aminoglycosides are infrequently used alone, typically for plague and tularemia. They are usually used with a broad-spectrum β-lactam for severe infection suspected to be due to a gram-negative bacillary species. However, because of increasing aminoglycoside resistance, a fluoroquinolone can be substituted for the aminoglycoside in initial empiric regimens, or if the pathogen is found to be susceptible to the accompanying antibiotic, the aminoglycoside can be stopped after 2 to 3 days unless an aminoglycoside-sensitive *P. aeruginosa* is identified.

Gentamicin or, less commonly, streptomycin may be used with other antibiotics to treat endocarditis due to streptococci or enterococci. Enterococcal resistance to aminoglycosides has become a common problem. Because treatment of enterococcal endocarditis requires prolonged use of a potentially nephrotoxic and ototoxic aminoglycoside plus a bacterial cell wall-active drug (eg, penicillin, vancomycin) to achieve bactericidal synergy, the choice of aminoglycoside must be based on special in vitro susceptibility testing. Susceptibility only to high levels of aminoglycosides in vitro predicts synergy when low-dose aminoglycoside therapy is combined with a cell wall-active drug. If the strain is susceptible to high levels of gentamicin and streptomycin, gentamicin is preferred because serum levels can be readily determined and toxicity is less. High-level enterococcal resistance to gentamicin in vitro does not rule out susceptibility of these strains to high levels of streptomycin; in such cases, streptomycin should be used. Few therapeutic options are available for endocarditis due to enterococci that are resistant to high levels of gentamicin and streptomycin; no synergistic cell wall-active drug/aminoglycoside combination exists for endocarditis due to such strains, but long courses of a cell wall-active drug alone or combined with daptomycin or linezolid have had limited success.

Streptomycin has limited uses because of resistance and toxicity. It is used with other antibiotics to treat TB.

Because of toxicity, neomycin and kanamycin are limited to topical use in small amounts. Neomycin is available for eye, ear, oral, and rectal use and as a bladder irrigant. Oral neomycin is used topically against intestinal flora to prepare the bowel before surgery and to treat hepatic coma.

**Contraindications**

Aminoglycosides are contraindicated in patients who are allergic to them.

**Use During Pregnancy and Breastfeeding**

Aminoglycosides are in pregnancy category D (there is evidence of human risk, but clinical benefits may outweigh risk). Aminoglycosides enter breast milk but are not well absorbed orally. Thus, they are considered compatible with use during breastfeeding.

**Adverse Effects**

All aminoglycosides cause

- Renal toxicity (often reversible)
- Vestibular and auditory toxicity (often irreversible)
• Prolongation of effects of neuromuscular blockers

Symptoms and signs of vestibular damage are vertigo, nausea, vomiting, nystagmus, and ataxia.

**Risk factors** for renal, vestibular, and auditory toxicity are

- Frequent or very high doses
- Very high blood levels of the drug
- Long duration of therapy (particularly > 3 days)
- Older age
- A preexisting renal disorder
- Coadministration of vancomycin, cyclosporine, or amphotericin B
- For renal toxicity, coadministration of contrast agents
- For auditory toxicity, preexisting hearing problems and coadministration of loop diuretics

Patients receiving aminoglycosides for > 2 wk and those at risk of vestibular and auditory toxicity should be monitored with serial audiography. At the first sign of toxicity, the drug should be stopped (if possible), or dosing should be adjusted.

Aminoglycosides can prolong the effect of neuromuscular blockers (eg, succinylcholine, curare-like drugs) and worsen weakness in disorders affecting neuromuscular transmission (eg, myasthenia gravis). These effects are particularly likely when the drug is given too rapidly or serum levels are excessively high. The effects sometimes resolve more rapidly if patients are given neostigmine or IV Ca. Other neurologic effects include paresthesias and peripheral neuropathy.

Hypersensitivity reactions are uncommon. High oral doses of neomycin can cause malabsorption.

**Dosing considerations:** Because toxicity depends more on duration of therapeutic levels than on peak levels and because efficacy is concentration-dependent rather than time-dependent, frequent doses are avoided. Once/day IV dosing is preferred for most indications except enterococcal endocarditis. IV aminoglycosides are given slowly (30 min for divided daily dosing or 30 to 45 min for once/day dosing).

In patients with normal renal function, once/day dosing of gentamicin or tobramycin is 5 mg/kg (7 mg/kg if patients are critically ill) q 24 h, and once/day dosing for amikacin is 15 mg/kg q 24 h. If patients respond to the higher dose of gentamicin clinically and renal function continues to be normal, the once/day dose can be reduced to the lower dose after the first few days of treatment.

In critically ill patients, peak serum levels should be determined after the first dose. In all patients, peak and trough levels are measured after the 2nd or 3rd dose (when the daily dose is divided) or when therapy lasts > 3 days, as well as after the dose is changed. Serum creatinine is measured every 2 to 3 days, and if it is stable, serum aminoglycoside levels need not be measured again. Peak concentration is the level 60 min after an IM injection or 30 min after the end of a 30-min IV infusion. Trough levels are measured during the 30 min before the next dose.

Peak levels in serum of at least 10 times the MIC are desirable. Dosing is adjusted to ensure a therapeutic peak serum level (to facilitate concentration-dependent activity) and nontoxic trough levels.
In critically ill patients, who are likely to have expanded volumes of distribution and who are given higher initial doses, target peak serum levels are 16 to 24 μg/mL for gentamicin and tobramycin and 56 to 64 μg/mL for amikacin. For gentamicin and tobramycin, trough levels should be < 1 μg/mL at 18 to 24 h after the first dose with once/day dosing and between 1 and 2 μg/mL with divided daily dosing.

For patients with renal insufficiency, the loading dose is the same as that for patients with normal renal function; usually, the dosing interval is increased rather than the dose decreased. Guidelines for maintenance doses based on serum creatinine or creatinine clearance values are available (see Table 132-6), but they are not precise, and measurement of blood levels is preferred.

If patients are taking a high dose of a β-lactam (eg, piperacillin, ticarcillin) and an aminoglycoside, the high serum levels of the β-lactam can inactivate the aminoglycoside in vitro in serum specimens obtained to determine drug levels unless the specimen is assayed immediately or frozen. If patients with renal failure are concurrently taking an aminoglycoside and a high-dose β-lactam, the serum aminoglycoside level may be lower because interaction in vivo is prolonged.

**Spectinomycin**

Spectinomycin is a bacteriostatic antibiotic chemically related to the aminoglycosides. Spectinomycin binds to the 30S subunit of the ribosome, thus inhibiting bacterial protein synthesis. Its activity is restricted to gonococci. Spectinomycin is excreted by glomerular filtration.

**Indications** include

- Gonococcal urethritis
- Cervicitis
- Proctitis

Spectinomycin is not effective for gonococcal pharyngitis. It is reserved for patients who cannot be treated with ceftriaxone, cefpodoxime, cefixime, or a fluoroquinolone.

**Adverse effects**, including hypersensitivity reactions and fever, are rare.

**β-Lactams**

β-Lactams are antibiotics that have a β-lactam ring nucleus. Subclasses include

- Cephalosporins and cephamycins (cephems)
- Carbacephem (loracarbef)
- Penicillins
- Clavams
- Carbapenems
- Monobactams

All β-lactams bind to and inactivate enzymes required for bacterial cell wall synthesis.

**Cephalosporins**

Cephalosporins are bactericidal (see Table 132-7). They inhibit enzymes in the cell wall of susceptible bacteria, disrupting cell synthesis.
Pharmacology

Cephalosporins penetrate well into most body fluids and the ECF of most tissues, especially when inflammation (which enhances diffusion) is present. However, the only cephalosporins that reach CSF levels high enough to treat meningitis are

- Ceftriaxone
- Cefotaxime
- Ceftazidime
- Cefepime

All cephalosporins penetrate poorly into ICF and the vitreous humor.

Most cephalosporins are excreted primarily in urine, so their doses must be adjusted in patients with renal insufficiency. Cefoperazone and ceftriaxone, which have significant biliary excretion, do not require such dose adjustment.

Indications

Cephalosporins are bactericidal for most of the following:

- Gram-positive bacteria
- Gram-negative bacteria

Cephalosporins are classified in generations (see Table 132-7). The 1st-generation drugs are effective mainly against gram-positive organisms. Higher generations generally have expanded spectra against aerobic gram-negative bacilli. The 5th-generation cephalosporin ceftobiprole, which is not yet available in the US, is active against methicillin-resistant *Staphylococcus aureus*. Cephalosporins have the following limitations:

- Lack of activity against enterococci
- Lack of activity against methicillin-resistant staphylococci (except for ceftobiprole)
- Lack of activity against anaerobic gram-negative bacilli (except for cefotetan and cefoxitin)

First-generation cephalosporins: These drugs have excellent activity against

- Gram-positive cocci

Oral 1st-generation cephalosporins are commonly used for uncomplicated skin and soft-tissue infections, which are usually due to staphylococci and streptococci. Parenteral cefazolin is frequently used for endocarditis due to methicillin-sensitive *S. aureus* and for prophylaxis before cardiothoracic, orthopedic, abdominal, and pelvic surgery.

Second-generation cephalosporins and cephemycins: Second-generation cephalosporins are active against

- Gram-positive cocci
• Certain gram-negative bacilli

Cephamycins are active against

• *Bacteroides* sp, including *B. fragilis*

These drugs may be slightly less active against gram-positive cocci than 1st-generation cephalosporins. Second-generation cephalosporins and cephamycins are often used for polymicrobial infections that include gram-negative bacilli and gram-positive cocci. Because cephamycins are active against *Bacteroides* sp, they can be used when anaerobes are suspected (eg, in intra-abdominal sepsis, decubitus ulcers, and diabetic foot infections). However, in some medical centers, these bacilli are no longer reliably susceptible to cephamycins.

**Third-generation cephalosporins:** These drugs are active against

• *Haemophilus influenzae* and some Entero-bacteriaceae (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*) that do not produce ampC β-lactamase or extended-spectrum β-lactamase (ESBL)

Ceftazidime and cefoperazone are also active against

• *Pseudomonas aeruginosa*

Some 3rd-generation cephalosporins have relatively poor activity against gram-positive cocci. Oral cefixime and cefibuten have little activity against *S. aureus* and, if used for skin and soft-tissue infections, should be restricted to uncomplicated infections due to streptococci. These cephalosporins have many clinical uses, as does the 4th-generation cephalosporin (see Table 132-8).

**Fourth-generation cephalosporin:** The 4th-generation cephalosporin cefepime has activity against

• Gram-positive cocci (similar to cefotaxime)

• Gram-negative bacilli (enhanced activity), including *P. aeruginosa* (similar to ceftazidime), ESBL-producing *K. pneumoniae* and *E. coli*, and ampC β-lactamase-producing Enterobacteriaceae, such as *Enterobacter* sp

**Fifth-generation cephalosporin:** The 5th-generation cephalosporin ceftobiprole is active against

• Methicillin-resistant *S. aureus*

[Table 132-8, Some Clinical Uses of 3rd- and 4th-Generation Cephalosporins]

**Contraindications**

Cephalosporins are contraindicated in patients who are allergic to them or who have had an anaphylactic reaction to penicillins.

**Use During Pregnancy and Breastfeeding**

Cephalosporins are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not).

Cephalosporins enter breast milk and may alter bowel flora of the infant. Thus, use during breastfeeding is often discouraged.

**Adverse Effects**

Significant adverse effects include
Significant adverse effects include:

- Hypersensitivity reactions (most common)
- *Clostridium difficile*-induced diarrhea (pseudomembranous colitis)
- Leukopenia
- Thrombocytopenia
- Positive Coombs' test (although hemolytic anemia is very uncommon)

Hypersensitivity reactions are the most common systemic adverse effects; rash is common, but immediate IgE-mediated urticaria and anaphylaxis are rare.

Cross-sensitivity between cephalosporins and penicillins is uncommon; cephalosporins can be given cautiously to patients with a history of delayed hypersensitivity to penicillin if necessary. However, cephalosporins should not be used in patients who have had an anaphylactic reaction to penicillin. Pain at the IM injection site and thrombophlebitis after IV use may occur.

Cefamandole (no longer available in the US), cefoperazone, and cefotetan may have a disulfiram-like effect when ethanol is ingested, causing nausea and vomiting. Cefamandole, cefoperazone, and cefotetan may elevate the PT/INR and PTT, an effect that is reversible with vitamin K.

### Contraindications

Ceftriaxone is contraindicated as follows:

- Ceftriaxone IV must not be coadministered with Ca-containing IV solutions (including continuous Ca-containing infusions such as parenteral nutrition) in neonates ≤ 28 days because precipitation of ceftriaxone-Ca salt is a risk. Fatal reactions with ceftriaxone-Ca precipitates in the lungs and kidneys of neonates have been reported. In some cases, different infusion lines were used, and ceftriaxone and Ca-containing solutions were given at different times. To date, no intravascular or pulmonary precipitates have been reported in patients other than neonates who are treated with ceftriaxone and Ca-containing IV solutions. However, because an interaction between ceftriaxone and IV Ca-containing solutions is theoretically possible in patients other than neonates, ceftriaxone and Ca-containing solutions should not be mixed or given within 48 h of each other (based on 5 half-lives of ceftriaxone) —even via different infusion lines at different sites—to any patient regardless of age. No data on potential interaction between ceftriaxone and oral Ca-containing products or on interaction between IM ceftriaxone and Ca-containing products (IV or oral) are available.

- Ceftriaxone should not be given to hyperbilirubinemic and preterm neonates because in vitro, ceftriaxone can displace bilirubin from serum albumin, potentially triggering kernicterus.

### Penicillins

Penicillins (see Table 132-9) are bactericidal by unknown mechanisms but perhaps by activating autolytic enzymes that destroy the cell wall in some bacteria. Some bacteria produce β-lactamase, which inactivates the drug; this effect can be blocked by adding a β-lactamase inhibitor (clavulanate, sulbactam, or tazobactam). However, available β-lactamase inhibitors do not inhibit ampC β-lactamases, commonly produced by *Enterobacter*, *Serratia*, *Citrobacter*, *Providencia*, and *Morganella* spp or by *P. aeruginosa*, and these drugs may only partially inhibit ESBL produced by some *K. pneumoniae*, *E. coli*, and other Enterobacteriaceae.

[Table 132-9: Penicillins]

### Pharmacology
Food does not interfere with absorption of amoxicillin, but penicillin G should be given 1 h before or 2 h after a meal. Amoxicillin has generally replaced ampicillin for oral use because amoxicillin is absorbed better, has fewer GI effects, and can be given less frequently.

Penicillins are distributed rapidly in the ECF of most tissues, particularly when inflammation is present.

All penicillins except nafcillin are excreted in urine and reach high levels in urine. Parenteral penicillin G is rapidly excreted (serum half-life 0.5 h), except for repository forms (the benzathine or procaine salt of penicillin G); these forms are intended for deep IM injection only and provide a tissue depot from which absorption takes place over several hours to several days. Benzathine penicillin reaches its peak level more slowly and is generally longeracting than procaine penicillin.

**Indications**

Penicillin G-like drugs (including penicillin V) are primarily used against

- Gram-positive bacteria
- Some gram-negative cocci (eg, meningococci)

A minority of gram-negative bacilli are also susceptible to large parenteral doses of penicillin G. Most staphylococci, most *Neisseria gonorrhoeae*, many anaerobic gram-negative bacilli, and about 30% of *H. influenzae* are resistant. Penicillin G is the drug of choice for syphilis and, with gentamicin, for endocarditis due to susceptible enterococci.

Benzathine penicillin G is available as pure benzathine penicillin, a mixture of equal amounts of benzathine and procaine penicillin G, and a mixture of 0.9 million units benzathine and 0.3 million units procaine penicillin G. Of the 3 products, only pure benzathine penicillin is recommended for treating syphilis and preventing rheumatic fever. Whether the mixture of equal amounts is effective in treating syphilis is unknown. Pure benzathine penicillin and the mixture of equal amounts are indicated for treating URIs and skin and soft-tissue infections caused by susceptible streptococci.

**Amoxicillin and ampicillin:** These drugs are more active against

- Enterococci
- Certain gram-negative bacilli, such as non-β-lactamase-producing *H. influenzae, E. coli*, and *P. mirabilis; Salmonella* sp; and *Shigella* sp

The addition of a β-lactamase inhibitor allows use against methicillin-sensitive staphylococci, *H. influenzae, N. gonorrhoeae, Moraxella catarhalis, Bacteroides* sp, *E. coli*, and *K. pneumoniae*. Ampicillin is indicated primarily for infections typically caused by susceptible gram-negative bacteria:

- UTIs
- Meningococcal meningitis
- Biliary sepsis
- Respiratory infections
- *Listeria* meningitis
- Enterococcal infections
- Some typhoid fever and typhoid carriers

**Penicillinase-resistant penicillins:** These drugs are used primarily for
• Penicillinase-producing methicillin-sensitive S. aureus

These drugs are also used to treat some S. pneumoniae, group A streptococcal, and methicillin-sensitive coagulase-negative staphylococcal infections.

**Broad-spectrum (antipseudomonal) penicillin:** These drugs have activity against

• Bacteria susceptible to ampicillin

• Some strains of *Enterobacter* and *Serratia* spp

• Many strains of *P. aeruginosa*

Ticarcillin is less active against enterococci than piperacillin. The addition of a β-lactamase inhibitor enhances activity against β-lactamase-producing methicillin-sensitive *S. aureus, E. coli, K. pneumoniae, H. influenzae*, and gram-negative anaerobic bacilli, but not against gram-negative bacilli that produce amPC β-lactamase, and may only partially inhibit ESBL produced by some *K. pneumoniae, E. coli*, and other Enterobacteriaceae. Broad-spectrum penicillins exhibit synergy with aminoglycosides and are usually used with this class to treat *P. aeruginosa* infections.

**Contraindications**

Penicillins are contraindicated in patients who have had serious allergic reactions to them.

**Use During Pregnancy and Breastfeeding**

Penicillins are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not).

Penicillins enter breast milk in small amounts. Their use is usually considered compatible with breastfeeding.

**Adverse Effects**

Adverse effects include

• Hypersensitivity reactions, including rashes (most common)

Other adverse effects occur less commonly.

**Hypersensitivity:** Most adverse effects are hypersensitivity reactions:

• Immediate reactions: Anaphylaxis (which can cause death within minutes), urticaria and angioedema (in 1 to 5/10,000 injections), and death (in about 0.3/10,000 injections)

• Delayed reactions (in up to 8% of patients): Serum sickness, rashes (eg, macular, papular, morbilliform), and exfoliative dermatitis (which usually appears after 7 to 10 days of therapy)

Most patients who report an allergic reaction to penicillin do not react to subsequent exposure to penicillin. Although small, risk of an allergic reaction is about 10 times higher for patients who have had a previous allergic reaction. Many patients report adverse reactions to penicillin that are not truly allergic (eg, GI adverse effects, nonspecific symptoms). If patients have a vague or inconsistent history of penicillin allergy and taking alternative antibiotics is not effective or convenient, skin testing may be done (see p. 1123). Desensitization may be attempted in patients with a positive skin test if there is no alternative to a penicillin-type drug. However, patients with a history of anaphylaxis to penicillin should not be given any β-lactam again (including for skin testing), except in very rare circumstances when no substitute can be found. In such cases, special precautions and desensitization regimens are required.
Rashes: Rashes occur more often with ampicillin and amoxicillin than with other penicillins. Patients with infectious mononucleosis often develop a nonallergic rash, typically maculopapular, usually beginning between days 4 and 7 of treatment.

Other adverse effects: Penicillins can also cause

- CNS toxicity (eg, seizures) if doses are high, especially in patients with renal insufficiency
- Nephritis
- *C. difficile*-induced diarrhea (pseudomembranous colitis)
- Coombs’-positive hemolytic anemia
- Leukopenia
- Thrombocytopenia

Leukopenia seems to occur most often with nafcillin. Any penicillin used in very high IV doses can interfere with platelet function and cause bleeding, but ticarcillin is the most common cause, especially in patients with renal insufficiency.

Other adverse effects include pain at the IM injection site, thrombophlebitis when the same site is used repeatedly for IV injection, and, with oral formulations, GI disturbances. Rarely, black tongue, due to irritation of the glossal surface and keratinization of the superficial layers, occurs, usually when oral formulations are used. Ticarcillin in high doses may cause Na overload because ticarcillin is a disodium salt. Ticarcillin can also cause hypokalemic metabolic alkalosis because the large amount of nonabsorbable anion presented to the distal tubules alters H⁺ ion excretion and secondarily results in K⁺ loss.

Dosing Considerations

Because penicillins, except nafcillin, reach high levels in urine, doses must be reduced in patients with severe renal insufficiency. Probenecid inhibits renal tubular secretion of many penicillins, increasing blood levels. It is sometimes given to maintain high blood levels.

Other β-Lactams

Carbapenems (imipenem, meropenem, doripenem, and ertapenem) are parenteral bactericidal antibiotics that have an extremely broad spectrum. They are active against

- *H. influenzae*
- Anaerobes
- Most Enterobacteriaceae (including those that produce ampC β-lactamase and ESBL, although *P. mirabilis* tends to have higher imipenem MICs)
- Methicillin-sensitive staphylococci and streptococci, including *S. pneumoniae* (except possibly strains with reduced penicillin sensitivity)

Most *Enterococcus faecalis* and many *P. aeruginosa* strains, including those resistant to broad-spectrum penicillins and cephalosporins, are susceptible to imipenem, meropenem, and doripenem but are resistant to ertapenem. Carbapenems are active synergistically with aminoglycosides against *P. aeruginosa. E. faecium* and methicillin-resistant staphylococci are resistant.
Many multidrug-resistant hospital-acquired bacteria are sensitive only to carbapenems. However, expanded use of carbapenems has resulted in some carbapenem resistance.

Imipenem and meropenem penetrate into CSF when meninges are inflamed. Meropenem is used for gram-negative bacillary meningitis; imipenem is not used in meningitis because it may cause seizures. Most seizures occur in patients who have CNS abnormalities or renal insufficiency and who are given inappropriately high doses.

Aztreonam is a parenteral bactericidal antibiotic; it is as active as ceftazidime against

- Enterobacteriaceae that do not produce ampC β-lactamase or ESBL
- *P. aeruginosa*

Aztreonam is not active against anaerobes. Gram-positive bacteria are resistant to aztreonam (in contrast to cephalosporins). Aztreonam acts synergistically with aminoglycosides. Because the metabolic products of aztreonam differ from those of other β-lactams, cross-hypersensitivity is unlikely. Thus, aztreonam is used mainly for

- Severe aerobic gram-negative bacillary infections, including meningitis, in patients who have a serious β-lactam allergy but who nevertheless require β-lactam therapy

Other antibiotics are added to cover any suspected gram-positive cocci and anaerobes. The dose is reduced in renal failure.

Chloramphenicol

Chloramphenicol is primarily bacteriostatic. It binds to the 50S subunit of the ribosome, thereby inhibiting bacterial protein synthesis.

**Pharmacology**

Chloramphenicol is well absorbed orally. Parenteral therapy should be IV.

Chloramphenicol is distributed widely in body fluids, including CSF, and is excreted in urine. Because of hepatic metabolism, active chloramphenicol does not accumulate when renal insufficiency is present.

**Indications**

Chloramphenicol has a wide spectrum of activity against

- Gram-positive and gram-negative cocci and bacilli (including anaerobes)
- *Rickettsia, Mycoplasma, Chlamydia, and Chlamydophila* spp

Because of bone marrow toxicity, the availability of alternative antibiotics, and the emergence of resistance, chloramphenicol is no longer a drug of choice for any infection, except for

- Serious infections due to a few multidrug-resistant bacteria that remain susceptible to this antibiotic

However, when chloramphenicol has been used to treat meningitis caused by relatively penicillin-resistant pneumococci, outcomes have been discouraging, probably because chloramphenicol has poor bactericidal activity against these strains.

**Contraindications**

Chloramphenicol is contraindicated if another drug can be used instead.
Use During Pregnancy and Breastfeeding

Use of chloramphenicol during pregnancy results in fetal drug levels almost as high as maternal levels. Gray baby syndrome is a theoretical concern, particularly near term, but there is no clear evidence of fetal risk.

Chloramphenicol enters breast milk. Safety during breastfeeding has not been determined.

Adverse Effects

Adverse effects include

• Bone marrow depression (most serious)
• Nausea, vomiting, and diarrhea
• Gray baby syndrome (in neonates)

There are 2 types of bone marrow depression:

• Reversible dose-related interference with iron metabolism: This effect is most likely with high doses or prolonged treatment or in patients with a severe liver disorder.
• Irreversible idiosyncratic aplastic anemia: This anemia occurs in < 1/25,000 treated patients. It may not develop until after therapy is stopped. Chloramphenicol should not be used topically because small amounts may be absorbed and, rarely, cause aplastic anemia.

Hypersensitivity reactions are uncommon. Optic and peripheral neuritis may occur with prolonged use.

The neonatal gray baby syndrome, which involves hypothermia, cyanosis, flaccidity, and circulatory collapse, is often fatal. The cause is high blood levels, which occur because the immature liver cannot metabolize and excrete chloramphenicol. To avoid the syndrome, clinicians should not give infants ≤ 1 mo > 25 mg/kg/day initially, and doses should be adjusted based on blood levels of the drug.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that has a unique mechanism of action. It binds to the bacterial cell membranes, causing rapid depolarization of the membrane due to K efflux and associated disruption of DNA, RNA, and protein synthesis; the result is rapid concentration-dependent bacterial death.

Indications

Daptomycin has activity against the following:

• Gram-positive bacteria (broad-spectrum activity)
• Multidrug-resistant gram-positive bacteria (because cross-resistance with other classes of antibiotics does not occur)

Daptomycin is used mainly for infections caused by

• Vancomycin- and methicillin-resistant Staphylococcus aureus
• Vancomycin-resistant enterococci
• Pneumococci with reduced penicillin sensitivity
However, methicillin-resistant *S. aureus* and vancomycin-resistant enterococci may become resistant during daptomycin therapy, resulting in relapsing or persistent infection.

Daptomycin is inferior to ceftriaxone for pneumonia, presumably because daptomycin can bind to pulmonary surfactant, reducing daptomycin's activity in the alveolar epithelial lining fluid.

**Contraindications**

Daptomycin is contraindicated in patients who have had an allergic reaction to it.

**Use During Pregnancy and Breastfeeding**

Daptomycin is in pregnancy category B (animal studies show no risk and human evidence is incomplete).

Whether daptomycin enters breast milk and is safe to use during breastfeeding is unknown.

**Adverse Effects**

Adverse effects include

- Eosinophilic pneumonia
- Myopathy

Chronic use may cause reversible organizing pneumonia with eosinophilic pulmonary infiltrates, presumably because daptomycin binds to pulmonary surfactant and thus accumulates in the alveolar spaces.

Skeletal myopathy due to daptomycin is reversible but seldom occurs with once/day dosing.

**Dosing Considerations**

Daptomycin is given parenterally once/day. Over 90% is bound to serum protein. Dosing is adjusted for renal failure. Because daptomycin can cause reversible skeletal myopathy, patients should be monitored for muscle pain or weakness, and serum creatine kinase levels should be checked weekly.

**Fluoroquinolones**

Fluoroquinolones (see Table 132-10) exhibit concentration-dependent bactericidal activity by inhibiting the activity of DNA gyrase and topoisomerase, enzymes essential for bacterial DNA replication. Fluoroquinolones are divided into 2 groups, based on antimicrobial spectrum and pharmacology:

- Older group: Ciprofloxacin, norfloxacin, and ofloxacin
- Newer group: Gemifloxacin, levofloxacin, and moxifloxacin

Some newer fluoroquinolones have been withdrawn because of toxicity; they include trovafloxacin (because of severe hepatic toxicity) and gatifloxacin (because of hypoglycemia and hyperglycemia).

**Pharmacology**

Oral absorption is diminished by coadministration of cations (aluminum, Mg, Ca, zinc, and iron preparations). After oral and parenteral administration, fluoroquinolones are widely distributed in most extracellular and intracellular fluids and are concentrated in the prostate, lungs, and bile.
Most fluoroquinolones are metabolized in the liver and excreted in urine, reaching high levels in urine. Moxifloxacin is eliminated primarily in bile.

**Indications**

Fluoroquinolones are active against the following:

- *Neisseria* sp
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Mycoplasma* sp
- *Chlamydia* sp
- *Chlamydophila* sp
- *Legionella* sp
- Enterobacteriaceae
- *Pseudomonas aeruginosa* (particularly ciprofloxacin)
- *Mycobacterium tuberculosis*
- Some atypical mycobacteria
- Methicillin-sensitive staphylococci

Nosocomial methicillin-resistant staphylococci are usually resistant. Older fluoroquinolones have poor activity against streptococci and anaerobes. Newer fluoroquinolones have reliable activity against streptococci (including *Streptococcus pneumoniae* with reduced penicillin sensitivity) and some anaerobes. As use has increased, resistance, particularly to older fluoroquinolones, is developing among Enterobacteriaceae, *P. aeruginosa*, *S. pneumoniae*, and *Neisseria* sp. Nonetheless, fluoroquinolones have many clinical uses (see Table 132-11).

Fluoroquinolones are no longer recommended for treatment of gonorrhea in the US because of increasing resistance.

**Contraindications**

Contraindications include

- Previous allergic reaction to the drugs
- Certain disorders that predispose to arrhythmias (eg, QT-interval prolongation, uncorrected hypokalemia or hypomagnesemia, significant bradycardia)
- Use of drugs known to prolong the QT interval or to cause bradycardia (eg, metoclopramide, cisapride, erythromycin, clarithromycin, classes la and III antiarrhythmics, tricyclic antidepressants)

Fluoroquinolones have traditionally been considered to be contraindicated in children because they may cause cartilage lesions if growth plates are open. However, some experts, who challenge this view
because evidence is weak, have recommended prescribing fluoroquinolones as a 2nd-line antibiotic and restricting use to a few specific situations, including *P. aeruginosa* infections in patients with cystic fibrosis, prophylaxis and treatment of bacterial infections in immunocompromised patients, life-threatening multiresistant bacterial infections in neonates and infants, and *Salmonella* or *Shigella* GI tract infections.

**Use During Pregnancy and Breastfeeding**

Fluoroquinolones are in pregnancy category C (animal studies show some risk, evidence in human and animal studies is inadequate, but clinical benefit sometimes exceeds risk).

[Table 132-11. Some Clinical Uses of Fluoroquinolones]

Fluoroquinolones enter breast milk. Use during breastfeeding is not recommended.

**Adverse Effects**

Serious adverse effects are uncommon; main concerns include the following:

- Upper GI adverse effects occur in about 5% of patients because of direct GI irritation and CNS effects.

- CNS adverse effects (eg, mild headache, drowsiness, insomnia, dizziness, mood alteration) occur in < 5%. NSAIDs may enhance the CNS stimulatory effects of fluoroquinolones. Seizures are rare, but fluoroquinolones should not be used in patients with CNS disorders.

- Tendinopathy, including rupture of the Achilles tendon, may occur even after short-term use of fluoroquinolones.

- QT-interval prolongation can occur, potentially leading to ventricular arrhythmias and sudden cardiac death.

- Fluoroquinolone use has been strongly associated with *Clostridium difficile*-associated diarrhea (pseudomembranous colitis), especially that due to the hypervirulent *C. difficile* ribotype 027.

Diarrhea, leukopenia, anemia, and photosensitivity are uncommon. Rash is uncommon unless gemifloxacin is used for > 1 wk and is more likely to develop in women < 40. Nephrotoxicity is rare.

**Dosing Considerations**

Dose reduction, except for moxifloxacin, is required for patients with renal insufficiency. Older fluoroquinolones are normally given twice/day; newer ones and an extended-release form of ciprofloxacin are given once/day.

Ciprofloxacin raises theophylline levels, sometimes resulting in theophylline-related adverse effects.

**Lincosamides, Oxazolidinones, and Streptogramins**

Lincosamides (clindamycin), oxazolidinones (linezolid), streptogramins (dalfopristin [streptogramin A] and quinupristin [streptogramin B]) are grouped together because they have a similar mode of antibacterial action and similar antibacterial spectra. Macrolides (see p. 1212) and the ketolide telithromycin (see p. 1214) may be included with this group for similar reasons. All inhibit protein synthesis by binding to the 50S ribosomal subunit. Cross-resistance occurs among the following antibiotics because they bind to the same target:

- Macrolides
- Clindamycin
- Quinupristin
• Telithromycin (to some extent)

However, cross-resistance does not occur between these antibiotics and dalfopristin and linezolid, which bind to different targets on the 50S ribosomal subunit.

Lincosamides

Clindamycin is primarily bacteriostatic. It binds to the 50S subunit of the ribosome, thus inhibiting bacterial protein synthesis.

Pharmacology

Clindamycin is absorbed well orally and can be given parenterally. Clindamycin diffuses well into body fluids except CSF; it is concentrated in phagocytes. Most of the drug is metabolized; metabolites are excreted in bile and urine.

Indications

The spectrum of activity for clindamycin is similar to that of the macrolide erythromycin (see Table 132-13 on p. 1213) except that clindamycin is

• Effective for infections due to anaerobes (particularly Bacteroides sp, including B. fragilis), community-acquired methicillin-resistant Staphylococcus aureus, and macrolide-resistant, clindamycin-susceptible Streptococcus pneumoniae

• Not reliably active against mycoplasmas, chlamydiae, Chlamydophila sp, and legionellae

Aerobic gram-negative bacilli and enterococci are resistant.

Clindamycin is usually used for anaerobic infections; however, clindamycin resistance has emerged among these organisms in some regions. Because these infections often also involve aerobic gram-negative bacilli, additional antibiotics are also used. Clindamycin is part of combination therapy for the following:

• Infections caused by toxigenic streptococci (because clindamycin decreases the bacteria’s toxin production)

• Cerebral toxoplasmosis

• Babesiosis

• Falciparum malaria

• Pneumocystis jirovecii pneumonia

Clindamycin can be used for infections (eg, skin and soft-tissue infections) in communities where community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) is common; whether clindamycin is useful depends on local resistance patterns.

Clindamycin can be used for infections due to clindamycin- and erythromycin-susceptible strains. However, some CA-MRSA strains are clindamycin-susceptible and erythromycin-resistant; erythromycin resistance in these strains may be due to an active efflux mechanism or to erythromycin-inducible modification of the ribosomal target. If the infecting strain of clindamycin-susceptible CA-MRSA is resistant to erythromycin because of the efflux mechanism, patients can be expected to respond to clindamycin. However, if the strain is erythromycin-resistant because of erythromycin-inducible ribosomal target modification, patients may not respond clinically to clindamycin because certain mutants can emerge during clindamycin therapy; these mutants are resistant to clindamycin and erythromycin because
of constitutive modification of the ribosomal target. (Constitutive means that resistance is always present regardless of whether an inducer, such as erythromycin, is present.)

Erythromycin resistance due to efflux can be differentiated from that due to inducible ribosomal target modification with a commonly used double disk diffusion assay (D test). A clindamycin disk is placed at a standard distance from an erythromycin disk on an agar plate streaked with a standard inoculum of the CA-MRSA strain in question. Zone of growth inhibition (shaped like the letter "D") around the clindamycin disk, with a flattened zone nearest the erythromycin disk indicates inducible ribosomal resistance. Patients who have moderate to severe infection with an inducible ribosomal-resistant CA-MRSA strain and a positive D test should not be treated with clindamycin.

Clindamycin cannot be used for CNS infections (other than cerebral toxoplasmosis) because penetration into the brain and CSF is poor.

Topical clindamycin is used for acne.

**Contraindications**

Clindamycin is contraindicated in patients who have had an allergic reaction to it or have a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

**Use During Pregnancy and Breastfeeding**

Clindamycin is in pregnancy category B (animal studies show no risk but human evidence is inadequate, or animal studies show risk and human studies do not).

Clindamycin enters breast milk. Use during breastfeeding is not recommended.

**Adverse Effects**

The main adverse effect is:

- *Clostridium difficile*-associated diarrhea (pseudomembranous colitis)

Clindamycin, penicillins, cephalosporins, and, most recently, fluoroquinolones have been associated with *C. difficile*-associated diarrhea. Clindamycin has been associated with *C. difficile*-associated diarrhea in up to 10% of patients regardless of route, including topical.

Hypersensitivity reactions may occur. If not swallowed with water, clindamycin may cause esophagitis.

**Dosing Considerations**

Dose adjustments are not required for renal failure. Clindamycin is given q 6 to 8 h.

**Oxazolidinones**

Linezolid has activity against the following:

- Streptococci
- *Enterococci* (*Enterococcus faecalis* and *E. faecium*)
- Staphylococci, including strains resistant to other classes of antibiotics
- Mycobacteria
- Anaerobes, such as *Fusobacterium*, *Prevotella*, *Porphyromonas*, and *Bacteroides* spp and peptostreptococci
Contraindications

Linezolid is contraindicated in patients with a prior allergic reaction to it.

Linezolid is a reversible, nonselective monamine oxidase inhibitor (MAOI). Thus, linezolid, when used with drugs that have serotonergic activity (eg, SSRIs, MAOIs, tricyclic antidepressants, L-tryptophan, amphetamines, lithium), has the potential for causing serotonin syndrome, a hyperserotonergic state characterized by mental status changes, neurologic abnormalities, and autonomic instability.

Linezolid is contraindicated in the following patients unless they are carefully observed for symptoms and signs of serotonin syndrome:

- Those who have taken MAO inhibitors (eg, phenelzine, isocarboxazid), serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 1B,1D receptor agonists (triptans), meperidine, or buspirone within 2 wk
- Those with carcinoid syndrome

Linezolid should not be given to the following patients unless they are monitored for potential increases in BP:

- Those taking any of the following: sympathomimetic drugs (eg, pseudoephedrine), vasopressors (eg, epinephrine, norepinephrine), dopaminergic drugs (eg, dopamine, dobutamine)
- Those with uncontrolled hypertension
- Those with thyrotoxicosis
- Those with a pheochromocytoma

Use During Pregnancy and Breastfeeding

Linezolid is in pregnancy category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes exceeds risk).

Whether linezolid is excreted in breast milk or is safe to use during breastfeeding is unknown.

Adverse Effects

Adverse effects include

- Reversible myelosuppression
- Irreversible peripheral neuropathy
- Reversible optic neuropathy
- Serotonin syndrome

Adverse effects are minimal, although reversible myelosuppression, including thrombocytopenia, leukopenia, and anemia, occurs in about 3% of patients, usually when therapy is used > 2 wk. Consequently, CBC is monitored weekly, especially when therapy lasts > 2 wk. Peripheral and optic neuropathy may occur with prolonged use, and patients taking long-term linezolid therapy should be closely monitored for these disorders.

Streptogramins
Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin, a naturally occurring streptogramin. Quinupristin/dalfopristin (Q/D) is given together in a fixed 30/70 combination; this combination has synergistic bactericidal activity against the following:

- Streptococci and staphylococci, including strains resistant to other antibiotic classes
- Some gram-negative anaerobic bacilli
- *Clostridium perfringens*
- *Peptostreptococcus* sp
- Atypical respiratory pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*)

Q/D inhibits *E. faecium*, including vancomycin-resistant strains. *E. faecalis* is resistant.

Q/D is given via a central IV catheter because phlebitis frequently occurs when Q/D is given via a peripheral vein. Up to 30% of patients develop significant myalgias.

Dosage reduction is required for severe hepatic insufficiency but not for renal insufficiency.

Q/D may inhibit drugs that are metabolized by the cytochrome P-450 (CYP450) 3A4 isoenzyme system.

### Macrolides

Macrolides (see Table 132-12) are primarily bacteriostatic; by binding to the 50S subunit of the ribosome, they inhibit bacterial protein synthesis.

### Pharmacology

Dirithromycin is a prodrug that is converted to its active form during intestinal absorption. Except for telithromycin, macrolides are relatively poorly absorbed orally. Food has the following effects on absorption:

- For dirithromycin and extended-release clarithromycin, increased absorption
- For immediate-release clarithromycin tablet or suspension, no effect
- For azithromycin capsules and erythromycin (including base and stearate formulations), decreased absorption

All macrolides diffuse well into body fluids, except CSF, and are concentrated in phagocytes. Excretion is mainly in bile.

### Indications

Macrolides are active against

- Aerobic and anaerobic gram-positive cocci, except for most enterococci, many *Staphylococcus aureus* strains (especially methicillin-resistant strains), and some *Streptococcus pneumoniae* and *S. pyogenes* strains
- *Mycoplasma pneumoniae*
- *Chlamydia trachomatis*
Bacteroides fragilis is resistant. Clarithromycin and azithromycin have enhanced activity against Haemophilus influenzae and activity against Mycobacterium avium complex.

Macrolides have been considered the drug of choice for group A streptococcal and pneumococcal infections when penicillin cannot be used. However, pneumococci with reduced penicillin sensitivity are often resistant to macrolides, and in some communities, up to 20% of S. pyogenes are macrolide-resistant. Because they are active against atypical respiratory pathogens, they are often used empirically for lower respiratory tract infections, but another drug is often necessary to cover macrolide-resistant pneumococci. Macrolides have other clinical uses (see Table 132-13). Macrolides are not used to treat meningitis.

**Contraindications**

Macrolides are contraindicated in patients who have had an allergic reaction to them.

Concomitant administration of macrolides with astemizole, cisapride, pimozide, or terfenadine is contraindicated. Postmarketing surveillance has reported cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, torsades de pointes) when clarithromycin or erythromycin was coadministered with astemizole, cisapride, pimozide, or terfenadine; this effect was most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Deaths have been reported.

**Use During Pregnancy and Breastfeeding**

Erythromycin and azithromycin are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Erythromycin is considered safer because clinical use has been much more extensive.

Clarithromycin is in category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk).

Erythromycin is considered compatible with breastfeeding. Safety of other macrolides during breastfeeding is unknown.

**Adverse Effects**

Main concerns include

- GI disturbances (mainly with erythromycin)
- QT-interval prolongation by erythromycin
• Inhibition of hepatic metabolism, leading to numerous drug interactions

Erythromycin commonly causes dose-related GI disturbances, including nausea, vomiting, abdominal cramps, and diarrhea; disturbances are less common with clarithromycin and azithromycin. Taking the drug with food may help

(Table 132-13. Some Clinical Uses of Macrolides)

decrease GI disturbances. Erythromycin may cause dose-related tinnitus, dizziness, and reversible hearing loss. Cholestatic jaundice occurs most commonly with erythromycin estolate. Jaundice usually appears after 10 days of use, primarily in adults but can occur earlier if the drug has been given previously. Erythromycin is not given IM because it causes severe pain; when given IV, it may cause phlebitis or pain. Hypersensitivity reactions are rare.

Erythromycin causes QT-interval prolongation and predisposes to ventricular tachyarrhythmia, especially in women, in patients who have QT-interval prolongation or electrolyte abnormalities, and in patients taking another drug that may prolong the QT interval.

Dosing Considerations

For azithromycin and dirithromycin, no dosage adjustment is required for renal insufficiency.

Erythromycin and, to some extent, clarithromycin interact with numerous drugs because they inhibit hepatic metabolism via the cytochrome P-450 (CYP450) system. Azithromycin is the least likely to interact with other drugs. Interactions may occur when erythromycin or clarithromycin are taken with the following:

• Warfarin: Further elevation of the PT/INR
• Lovastatin and simvastatin: Rhabdomyolysis
• Midazolam and triazolam: Somnolence
• Theophylline: Nausea, vomiting, and seizures
• Tacrolimus, cyclosporine, and ergot alkaloids: Elevated serum levels of these drugs

Telithromycin

Telithromycin is a ketolide antibiotic. Ketolides are chemically related to macrolides and inhibit bacterial ribosomal protein synthesis without inducing resistance to macrolides, clindamycin, or streptogramins.

Telithromycin is rapidly absorbed orally with or without food and is metabolized primarily in the liver.

Indications

Telithromycin is active against erythromycin-susceptible staphylococci and streptococci and multidrug-resistant S. pneumoniae. Telithromycin is also active against erythromycin-susceptible enterococci, Bordetella pertussis, H. influenzae, Helicobacter pylori, Moraxella catarrhalis, M. pneumoniae, C. pneumoniae, and Legionella, Prevotella, and Peptostreptococcus spp.

Because of safety concerns, telithromycin is recommended only for the treatment of adults ≥ 18 yr with community acquired mild to moderate pneumonia due to the following:

• S. pneumoniae (including multidrug-resistant strains, ie, penicillin-resistant S. pneumoniae; isolates resistant to ≥ 2 of the following: penicillin, 2nd-generation cephalosporins [eg, cefuroxime], macrolides, tetracyclines, trimethoprim/sulfamethoxazole)

• H. influenzae
• *M. catarrhalis*

• *C. pneumoniae*

• *M. pneumoniae*

**Contraindications**

Contraindications include

• Previous allergic reaction to telithromycin or any macrolide

• Previous hepatitis or jaundice after taking telithromycin or a macrolide

• Concurrent use of pimozide or cisapride because of cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, torsades de pointes)

• Myasthenia gravis because telithromycin may exacerbate symptoms and fatal respiratory failure has occurred in patients with this disorder

**Use During Pregnancy and Breastfeeding**

Telithromycin is in pregnancy category C because animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk.

Safety of telithromycin during breastfeeding is unknown.

**Adverse Effects**

Adverse effects include

• GI disturbances

• QT-interval prolongation

• Severe hepatitis

Diarrhea, nausea, vomiting, and dizziness are the most common adverse effects. Prolongation of the QT interval, hyperbilirubinemia, elevation of liver enzymes, transient loss of consciousness (sometimes associated with vagal syndrome), and visual disturbances (particularly a slowed ability to accommodate and to release accommodation) are less common. Severe hepatotoxicity, which may require liver transplantation and which may be fatal, may occur.

Cross-sensitivity with macrolides can occur.

**Dosing Considerations**

Telithromycin inhibits cytochrome P-450 (CYP450) 3A4, increasing levels of the following drugs:

• Digoxin: Digoxin adverse effects or serum levels should be monitored.

• Ergot alkaloids: Concomitant use should be avoided.

• Benzodiazepines: Concomitant use requires caution.

• Metoprolol: Concomitant use in patients with heart failure requires caution.
Metronidazole

Metronidazole is bactericidal. It enters bacterial cell walls and interrupts DNA.

**Pharmacology**

Oral metronidazole is absorbed well. It is usually given IV only if patients cannot be treated orally. It is distributed widely in body fluids and penetrates into CSF, resulting in high concentrations. Metronidazole is metabolized presumably in the liver and excreted mainly in urine, but elimination is not decreased in patients with renal insufficiency.

**Indications**

Metronidazole is active against

- All obligate anaerobic bacteria (it is inactive against facultative anaerobic and aerobic bacteria)
- Certain protozoan parasites (eg, *Trichomonas vaginalis*, *Entamoeba histolytica*, *Giardia intestinalis* [lamblia])

Metronidazole is used primarily for infections caused by obligate anaerobes, often with other antimicrobials. Metronidazole is the drug of choice for bacterial vaginosis. The drug has other clinical uses (see Table 132-14).

**Contraindications**

Metronidazole is contraindicated in patients who have had an allergic reaction to it.

**Use During Pregnancy and Breastfeeding**

Metronidazole is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Nonetheless, metronidazole should be avoided during the 1st trimester because mutagenicity is a concern.

[Table 132-14, Some Clinical Uses of Metronidazole]

Metronidazole enters breast milk; use during breastfeeding is not recommended.

**Adverse Effects**

Adverse effects include
• GI disturbances
• CNS effects and peripheral neuropathy
• Disulfiram-like reaction

Nausea, vomiting, headache, seizures, syncope, other CNS effects, and peripheral neuropathy can occur; rash, fever, and reversible neutropenia have been reported. Metronidazole can cause a metallic taste and dark urine. A disulfiram-like reaction may occur if alcohol is ingested within 7 days of use.

Dosing Considerations

Metronidazole doses are not decreased in patients with renal failure but are usually decreased 50% in patients with significant liver disease.

Metronidazole inhibits metabolism of warfarin and may increase its anticoagulant effect.

Mupirocin

Mupirocin inhibits bacterial RNA and protein synthesis. It is available only as a 2% topical preparation, which is bactericidal against staphylococci and β-hemolytic streptococci. Systemic absorption of topical mupirocin is negligible.

Mupirocin is used for impetigo and for minor superficial secondarily infected skin lesions. Mupirocin can also eradicate *Staphylococcus aureus* nasal carriage, although relapse rates may be high. Chronic therapy leads to mupirocin-resistant staphylococci.

Mupirocin is nontoxic but, when applied to denuded skin or mucous membranes, may cause itching and burning.

Nitrofurantoin

Nitrofurantoin is bactericidal; the exact mechanism is unknown.

Nitrofurantoin is available only for oral use.

Pharmacology

After a single dose, serum drug levels are very low, but urine drug levels are therapeutic.

Indications

Nitrofurantoin is active against common uropathogens, such as

• *Escherichia coli*

• *Staphylococcus saprophyticus*

• *Enterococcus faecalis*

*E. faecium*, including vancomycin-resistant strains, and *Klebsiella* and *Enterobacter* sp are less susceptible. Most strains of *Proteus*, *Providencia*, *Morganella*, *Serratia*, *Acinetobacter*, and *Pseudomonas* spp are resistant. There is no cross-resistance with other antibiotic classes.

Nitrofurantoin is used only for

• Treatment or prophylaxis of uncomplicated UTI
In women with recurrent UTIs, it may decrease the number of episodes.

**Contraindications**

Contraindications to nitrofurantoin use include

- Previous allergic reaction to it
- Renal insufficiency (creatinine clearance < 60 L/min)
- Age < 1 mo

**Use During Pregnancy and Breastfeeding**

Nitrofurantoin is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Nonetheless, nitrofurantoin is contraindicated at term and during labor or delivery because it interferes with immature enzyme systems in RBCs of neonates, damaging the cells and resulting in hemolytic anemia.

Nitrofurantoin enters breast milk and is contraindicated during the first month of breast-feeding.

**Adverse Effects**

Adverse effects include

- GI disturbances
- Pulmonary toxicity
- Peripheral neuropathy
- Hemolytic anemia
- Hepatic toxicity

Common adverse effects are nausea and vomiting, which are less likely with the macrocrystalline form. Fever, rash, acute hypersensitivity pneumonitis (accompanied by fever and eosinophilia), and chronic progressive pulmonary interstitial fibrosis may occur. Paresthesias may result and may be followed by a severe ascending motor and sensory polyneuropathy if the drug is continued, especially in patients with renal failure. Leukopenia and hepatic toxicity (acute cholestatic or chronic active hepatitis) have been reported, and hemolytic anemia can occur in patients with G6PD deficiency and in infants < 1 mo. Chronic pulmonary and hepatic reactions occur when the drug is used for > 6 mo.

**Polypeptides**

Polypeptide antibiotics disrupt bacterial cell walls (see Table 132-15).

Bacitracin is a polypeptide antibiotic that inhibits cell wall synthesis and is active against gram-positive bacteria.

Colistin (polymyxin E) and polymyxin B are cationic polypeptide antibiotics that disrupt the outer bacterial cell membrane by binding to the anionic outer membrane, which contains lipopolysaccharide (endotoxin), and thereby neutralizing the bacteria’s toxicity.

Colistin methane sulfonate (colistimethate sodium [CMS]) is a parenteral preparation of a prodrug that is transformed in blood and urine to colistin. CMS is less toxic than colistin.
Polypeptides are usually used topically; systemic absorption is negligible.

**Indications**

Polymyxin B and colistin have rapid concentration-dependent bactericidal activity against

- Most facultative and aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* and *Acinetobacter* sp

These drugs are not active against *Proteus, Providencia, Burkholderia, and Serratia* spp and some obligate anaerobes, including *Bacteroides fragilis* and gram-positive bacteria. Development of resistance is uncommon.

Polypeptides are used for several types of infections (see Table 132-16).

**Contraindications**

All polypeptides are contraindicated in patients who have had an allergic reaction to them. CMS and polymyxin B should not be given simultaneously with drugs that block neuromuscular transmission or are nephrotoxic (eg, aminoglycosides, curare-like drugs).

**Use During Pregnancy and Breastfeeding**

Bacitracin may pose minimal risk during pregnancy and breastfeeding because systemic absorption is minimal; however, safety has not been established.

Polymyxin B is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not).

[Table 132-15. Polypeptides]

Colistin is in pregnancy category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk); this drug crosses the placenta. Whether use during breastfeeding is safe is unknown.

**Adverse Effects**

Adverse effects include

- Nephrotoxicity
- Central and peripheral neurotoxicity

Polymyxins are nephrotoxic. CMS and polymyxin B may cause circumoral and extremity paresthesias, vertigo, slurred speech, and muscle weakness and respiratory difficulty due to neuromuscular blockade, especially in patients with renal insufficiency.

**Rifamycins**

The rifamycins are bactericidal and inhibit bacterial DNA-dependent RNA polymerase, suppressing RNA synthesis (see Table 132-17).

**Rifampin and Rifabutin**

Rifampin and rifabutin have similar pharmacology, antimicrobial spectra, and adverse effects.
Pharmacology

Oral absorption is good, producing wide distribution in body tissues and fluids, including CSF. Rifampin is concentrated in polymorpho-nuclear granulocytes and macrophages, facilitating clearance of bacteria from abscesses. It is metabolized in the liver and eliminated in bile and, to a much lesser extent, in urine.

Indications

Rifampin is active against

- Most gram-positive and some gram-negative bacteria
- *Mycobacterium* sp

Resistance develops rapidly, so rifampin is rarely used alone. Rifampin is used with other antibiotics for

- TB (see p. 1307)
- Atypical mycobacterial infection (rifampin is active against many nontuberculous mycobacteria, but rapidly growing mycobacteria, such as *M. fortuitum* or *M. chelonae*, are naturally resistant)
- Leprosy (with dapsone with or without clofazimine)
- Staphylococcal infections, including osteomyelitis, prosthetic valve endocarditis, and

[Table 132-16, Some Clinical Uses of Polypeptides]

infections involving foreign bodies such as a prosthetic joint (with other antistaphylococcal antibiotics)

- *Legionella* infections (older data suggest better outcomes for rifampin when used with erythromycin; use of rifampin with azithromycin or a fluoroquinolone offers no advantage)

- Pneumococcal meningitis when organisms are susceptible to rifampin (with vancomycin)

[Table 132-17, Rifamycins]

with or without ceftriaxone or cefotaxime for ceftriaxone- or cefotaxime-resistant organisms [MIC > 4 μg/mL]) or when expected clinical or microbiologic response is delayed

Rifampin can be used alone for prophylaxis of close contacts of patients with meningococcal or *Haemophilus influenzae* type b meningitis.

Rifabutin and rifampin are equally efficacious in regimens for TB in HIV-positive and HIV-negative patients.

**Rifabutin** is more active than rifampin against *M. avium* complex and is used preferentially in multidrug regimens for these infections, but otherwise, rifampin is preferred.

Contraindications

Rifampin and rifabutin are contraindicated in patients who have had an allergic reaction to them.

Use During Pregnancy and Breastfeeding

Rifabutin is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Safety during breast-feeding is unknown.
Rifampin is in pregnancy category C (animal studies show some risk [in this case, teratogenicity], evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk). The drug crosses the placenta. Still, if risk of maternal TB is moderate or high, treatment is thought to be less harmful for the fetus than untreated maternal TB and is thus recommended. Because of potential tumorigenicity shown in animal studies, a decision to stop breastfeeding or to stop the drug should be made, depending on the importance of the drug to the mother.

**Adverse Effects**

Adverse effects include

- Hepatitis (most serious)
- GI disturbances
- CNS effects
- Myelosuppression

Hepatitis occurs much more often when isoniazid or pyrazinamide is used concurrently with rifampin. During the first week of therapy, rifampin may cause a transient rise in unconjugated serum bilirubin, which results from competition between rifampin and bilirubin for excretion and which is not in itself an indication for interrupting treatment.

CNS effects may include headache, drowsiness, ataxia, and confusion. Rash, fever, leukopenia, hemolytic anemia, thrombocytopenia, interstitial nephritis, acute tubular necrosis, renal insufficiency, and interstitial nephritis are generally considered to be hypersensitivity reactions and occur when therapy is intermittent or when treatment is resumed after interruption of a daily dosage regimen; they are reversed when rifampin is stopped.

Less serious adverse effects are common; they include heartburn, nausea, vomiting, and diarrhea. Rifampin colors urine, saliva, sweat, sputum, and tears red-orange.

**Dosing Considerations**

If patients have a liver disorder, liver function tests should be done before rifampin therapy is started and every 2 to 4 wk during therapy, or an alternate drug should be used. Dose adjustments are unnecessary for renal insufficiency.

Rifampin interacts with many drugs because it is a potent inducer of hepatic cytochrome P-450 (CYP450) microsomal enzymes. Rifampin accelerates elimination and thereby may decrease the effectiveness of the following drugs: ACE inhibitors, atovaquone, barbiturates, β-blockers, Ca channel blockers, chloramphenicol, clarithromycin, oral and systemic hormone contraceptives, corticosteroids, cyclosporine, dapsone, digoxin, doxycycline, fluconazole, haloperidol, itraconazole, ketoconazole, the nonnucleoside reverse transcriptase inhibitors delavirdine and nevirapine, opioid analgesics, phenytoin, protease inhibitors, quinidine, sulfonylureas, tacrolimus, theophylline, thyroxine, tocainide, tricyclic anti-depressants, voriconazole, warfarin, and zidovudine. To maintain optimum therapeutic effect of these drugs, clinicians may have to adjust the dosage when rifampin is started or stopped. Conversely, protease inhibitors, as well as other drugs (eg, azoles, the macrolide clarithromycin, nonnucleoside reverse transcriptase inhibitors) inhibit CYP450 enzymes and increase levels of rifamycins and thus potentially increase the frequency of toxic reactions. For example, uveitis occurs more commonly when rifabutin is used with clarithromycin or azoles.

**Rifaximin**

Rifaximin is a derivative of rifamycin that is poorly absorbed after oral administration; 97% is recovered primarily unchanged in feces. Rifaximin can be used for empiric treatment of traveler's diarrhea, which is caused primarily by enterotoxigenic and enteraggregative *Escherichia coli*. Rifaximin is not known to be
effective for diarrhea due to enteric pathogens other than \textit{E. coli}. Because rifaximin is not systemically absorbed, it should not be used to treat infectious diarrhea caused by invasive enteric bacterial pathogens (eg, salmonellae, \textit{Campylobacter} sp).

The dose is 200 mg q 8 h for 3 days in adults and children > 12 yr.

Adverse effects include nausea, vomiting, abdominal pain, and flatulence.

\textbf{Sulfonamides}

Sulfonamides (see \textbf{Table 132-18}) are synthetic bacteriostatic antibiotics that competitively inhibit conversion of \(p\)-aminobenzoic acid to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis. Humans do not synthesize folate but acquire it in their diet, so their DNA synthesis is less affected.

Two sulfonamides, sulfisoxazole and sulfamethizole, are available as single drugs for oral use. Sulfamethoxazole may be combined with trimethoprim (TMP/SMX—see p. \textbf{1221}). Sulfadoxine plus pyrimethamine is available (but not in the US) as an oral, fixed combination for malaria due to chloroquine-resistant \textit{Plasmodium falciparum}.

Sulfonamides available for topical use include silver sulfadiazine, vaginal cream and suppositories containing sulfanilamide, and ophthalmic sulfacetamide.

\textbf{Pharmacology}

Most sulfonamides are readily absorbed orally and, when applied to burns, topically. Sulfonamides are distributed throughout the body. They are metabolized mainly by the liver and excreted by the kidneys. Sulfonamides compete for bilirubin-binding sites on albumin.

\textbf{Table 132-18. Sulfonamides}

\textbf{Indications}

Sulfonamides are active against

- A broad spectrum of gram-positive and many gram-negative bacteria
- \textit{Plasmodium} and \textit{Toxoplasma} spp

However, resistance is widespread, and resistance to one sulfonamide indicates resistance to all.

Sulfasalazine can be used orally for inflammatory bowel disease. Sulfonamides are most commonly used with other drugs (eg, for nocardiosis, UTI, and chloroquine-resistant falciparum malaria).

Topical sulfonamides can be used to treat the following:

- Burns: Silver sulfadiazine and mafenide acetate
- Vaginitis: Vaginal cream and suppositories with sulfanilamide
- Superficial ocular infections: Ophthalmic sulfacetamide

\textbf{Contraindications}

Sulfonamides are contraindicated in patients who have had an allergic reaction to them or who have porphyria. Sulfonamides do not eradicate group A streptococci in patients with pharyngitis and should not be used to treat group A streptococcal pharyngitis.
Use During Pregnancy and Breastfeeding

Most sulfonamides are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). However, use near term and in breastfeeding mothers is contraindicated, as is use in patients < 2 mo (except as adjunctive therapy with pyrimethamine to treat congenital toxoplasmosis). If used during pregnancy or in neonates, these drugs increase blood levels of unconjugated bilirubin and increase risk of kernicterus in the fetus or neonate.

Sulfonamides enter breast milk.

Adverse Effects

Adverse effects can result from oral and sometimes topical sulfonamides; effects include

• Hypersensitivity reactions, such as rashes, Stevens-Johnson syndrome (see p. 689), vasculitis, serum sickness, drug fever, anaphylaxis, and angioedema

• Crystalluria, oliguria, and anuria

• Hematologic reactions, such as agranulocytosis, thrombocytopenia, and, in patients with G6PD deficiency, hemolytic anemia

• Kernicterus in neonates

• Photosensitivity

• Neurologic effects, such as insomnia, and headache

Hypothyroidism, hepatitis, and activation of quiescent SLE may occur in patients taking sulfonamides. These drugs can exacerbate porphyrias.

Incidence of adverse effects is different for the various sulfonamides, but cross-sensitivity is common.

Sulfasalazine can reduce intestinal absorption of folate (folic acid). Thus, use of this drug may trigger folate deficiency in patients with inflammatory bowel disease, which also reduces absorption, especially if dietary intake is also inadequate.

Mafenide may cause metabolic acidosis by inhibiting carbonic anhydrase.

Dosing Considerations

To avoid crystalluria, clinicians should hydrate patients well (eg, to produce a urinary output of 1200 to 1500 mL/day). Sulfonamides can be used in patients with renal insufficiency, but peak plasma levels should be measured and sulfamethoxazole levels should not exceed 120 μg/mL. Sulfonamides can potentiate sulfonylureas (with consequent hypoglycemia), phenytoin (with increased adverse effects), and coumarin anticoagulants.

Trimethoprim and Sulfamethoxazole

Trimethoprim is available as a single drug or in combination with sulfamethoxazole. The drugs act synergistically to block sequential steps in bacterial folate metabolism. Trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate, and sulfamethoxazole inhibits conversion of p-aminobenzoic acid to dihydropteroate. This synergy results in maximal antibacterial activity, which is often bactericidal.

Trimethoprim/sulfamethoxazole (TMP/SMX) is available as a fixed combination consisting of a 1:5 ratio (80 mg TMP plus 400 mg SMX or a double-strength tablet of 160 mg TMP plus 800 mg SMX).
Pharmacology

Both drugs are well absorbed orally and are excreted in the urine. They have a serum half-life of about 11 h in plasma and penetrate well into tissues and body fluids, including CSF. TMP is concentrated in prostatic tissue.

Indications

TMP and TMP/SMX are active against (see Table 132-19)

- A broad spectrum of gram-positive bacteria (including some methicillin-resistant *Staphylococcus aureus*)
- A broad spectrum of gram-negative bacteria

The combination is inactive against anaerobes, *Treponema pallidum*, *Mycobacterium tuberculosis*, *Mycoplasma* sp, and *Pseudomonas aeruginosa*. Enterococci, many Enterobacteriaceae, and *Streptococcus pneumoniae* strains are resistant. TMP/SMX is not clinically effective for group A streptococcal pharyngitis.

[Table 132-19, Some Indications for TMP/SMX]

TMP alone is especially useful for chronic bacterial prostatitis and for prophylaxis and treatment of UTI in patients allergic to sulfonamides.

Contraindications

TMP/SMX is contraindicated in patients who have had an allergic reaction to either drug. Relative contraindications include folate deficiency, liver dysfunction, and renal insufficiency.

Use During Pregnancy and Breastfeeding

TMP/SMX is in pregnancy category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk). However, use near term is contraindicated; if used during pregnancy or in neonates, TMP/SMX increases blood levels of unconjugated bilirubin and increases risk of kernicterus in the fetus or neonate.

Sulfonamides enter breast milk and use during breastfeeding is usually discouraged.

Adverse Effects

Adverse effects include

- Those associated with sulfonamide
- Folate deficiency
- Hyperkalemia (TMP can decrease renal tubular K excretion, leading to hyperkalemia)
- Renal insufficiency

Renal failure in patients with underlying renal insufficiency is probably secondary to interstitial nephritis or tubular necrosis. Also, TMP competitively inhibits renal tubular creatinine secretion and may cause an artificial increase in serum creatinine, although GFR remains unchanged. Increases in serum creatinine are more likely in patients with preexisting renal insufficiency and especially in those with diabetes mellitus.

Most adverse effects are the same as for sulfonamides. TMP has adverse effects identical to those of
SMX, but they are less common. Nausea, vomiting, and rash occur most often. AIDS patients have a high incidence of adverse effects, especially fever, rash, and neutropenia.

Folate deficiency (resulting in macrocytic anemia) can also occur. Use of folinic acid can prevent or treat macrocytic anemia, leukopenia, and thrombocytopenia, which sometimes occur with prolonged TMP/SMX use.

Rarely, severe hepatic necrosis occurs. The drug may also cause a syndrome resembling aseptic meningitis.

**Dosing Considerations**

TMP/SMX may increase warfarin activity and levels of phenytoin, methotrexate, and rifampin. SMX can increase the hypoglycemic effects of sulfonylureas.

**Tetracyclines**

Tetracyclines (see Table 132-20) are bacteriostatic antibiotics that bind to the 30S subunit of the ribosome, thus inhibiting bacterial protein synthesis.

**Pharmacology**

About 60 to 80% of tetracycline and ≥ 90% of doxycycline and minocycline are absorbed after oral use. However, absorption is decreased by metallic cations (eg, aluminum, Ca, Mg, iron); thus, tetracyclines cannot be taken with preparations containing these substances (eg, antacids, many vitamin and mineral supplements). Food decreases absorption of tetracycline but not of doxycycline or minocycline.

Tetracyclines penetrate into most body tissues and fluids. All are concentrated in unobstructed bile. However, CSF levels are not reliably therapeutic. Minocycline is the only tetracycline that reaches high concentrations in tears and saliva. Tetracycline and minocycline are excreted primarily in urine. Doxycycline is excreted primarily in the intestinal tract.

**Indications**

Tetracyclines are effective against infections caused by the following:

- Rickettsiae
- Spirochetes (eg, *Treponema pallidum, Borrelia burgdorferi*)
  - *Helicobacter pylori*
- *Vibrio* sp
- *Yersinia pestis*
- *Francisella tularensis*
- *Brucella* sp
- *Bacillus anthracis*
- *Plasmodium vivax*
- *Plasmodium falciparum*
- *Mycoplasma* sp
• *Chlamydia* and *Chlamydophila* sp

• Some methicillin-resistant *Staphylococcus aureus*

About 5 to 10% of pneumococcal strains and many group Aβ-hemolytic streptococci, many gram-negative bacillary uropathogens, and penicillinase-producing gonococci are resistant.

**Table 132-20. Tetracyclines**

Tetracyclines are interchangeable for most indications, although minocycline has been most studied for methicillin-resistant *S. aureus* infections. Doxycycline is usually preferred for all of the following because it is better tolerated and can be given twice/day:

• Infections caused by rickettsiae and *Chlamydia, Chlamydophila, Mycoplasma, and Vibrio* spp

• Acute exacerbations of chronic bronchitis

• Lyme disease

• Brucellosis

• Anthrax

• Plague

• Tularemia

• Granuloma inguinale

• Syphilis

• Prophylaxis of malaria caused by chloroquine-resistant *P. falciparum*

Because of its high concentration in tears and saliva, minocycline is the only tetracycline that can eradicate meningococci in carriers and is an alternate to rifampin for this indication.

**Contraindications**

Tetracyclines are contraindicated in patients who have had an allergic reaction to them, patients with renal insufficiency (except for doxycycline, which has no dosage adjustment for renal insufficiency), and children ≤ 8 yr (except sometimes for inhalational anthrax).

**Use During Pregnancy and Breastfeeding**

Tetracyclines are in pregnancy category D (there is evidence of human risk, but clinical benefits may outweigh risk). Tetracyclines cross the placenta, enter fetal circulation, accumulate in fetal bones, and, if used during the 2nd or 3rd trimester, may cause permanent discoloration of teeth. Hepatotoxicity may occur in pregnant women, particularly after IV administration and in those with azotemia or pyelonephritis. Taking high doses during pregnancy can lead to fatty degeneration of the liver, which may be fatal.

Tetracyclines enter breast milk, but usually in small amounts (particularly tetracycline). Use during breastfeeding is usually discouraged.

**Adverse Effects**

Adverse effects include
- GI disturbances
- *Clostridium difficile*-induced diarrhea (pseudomembranous colitis)
- Candidiasis
- Photosensitivity
- Bone and dental effects in children
- Fatty liver
- Vestibular dysfunction (with minocycline)

All oral tetracyclines cause nausea, vomiting, and diarrhea and can cause *C. difficile*-induced diarrhea (pseudomembranous colitis) and candidal superinfections. If not swallowed with water, tetracyclines can cause esophageal erosions. Photosensitivity due to tetracyclines may manifest as an exaggerated sunburn reaction. Bone and dental effects include staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in children ≤ 8 yr and in fetuses. In infants, tetracyclines may cause idiopathic intracranial hypertension and bulging fontanelles.

Excessive blood levels due to use of high doses or renal insufficiency may lead to fatal acute fatty degeneration of the liver, especially during pregnancy.

Minocycline commonly causes vestibular dysfunction, particularly in women, limiting its use. Use of minocycline has been associated with development of autoimmune disorders such as SLE and polyarteritis nodosa, which may be reversible.

Tetracycline can exacerbate azotemia in patients with renal insufficiency. Expired tetracycline pills can degenerate and, if ingested, cause Fanconi syndrome. Patients should be instructed to discard the drugs when they expire.

**Dosing Considerations**

Doxycycline, excreted primarily in the intestinal tract, requires no dose reduction in renal insufficiency.

Tetracyclines may decrease the effectiveness of oral contraceptives and potentiate the effects of oral anticoagulants.

**Tigecycline**

Tigecycline, a derivative of the tetracycline minocycline, is the first available glycylcycline. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. It is bacteriostatic.

Tigecycline is given IV. Tigecycline has a large volume of distribution (> 12 L/kg), penetrating well into bone, lung, liver, and kidney tissues. A half-life of 36 h should provide for once/day dosing. Most of the drug is excreted in bile and feces.

**Indications**

Tigecycline is effective against many resistant bacteria, including those with resistance to tetracyclines. Tigecycline is active against

- Many gram-positive bacteria, including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae* with reduced penicillin sensitivity, vancomycin-sensitive *Enterococcus faecalis*, vancomycin-resistant *E. faecium*, and *Listeria* sp
- Many gram-negative bacteria, such as multidrug-resistant *Acinetobacter baumannii*, *Stenotrophomonas*
*maltophilia, Haemophilus influenzae,* and most *Enterobacteriaceae* (including some strains that produce extended-spectrum β-lactamases [ESBLs] and other strains that were carbapenem-resistant based on production of a carbapenemase or metallo-β-lactamase)

- Many atypical respiratory pathogens (chlamydiae, *Mycoplasma* sp), *Mycobacterium abscessus, M. fortuitum,* and anaerobes, including *Bacteroides fragilis, Clostridium perfringens,* and *C. difficile*

It is not effective against *Pseudomonas aeruginosa, Providencia* sp, *Morganella morganii,* or *Proteus* sp.

Tigecycline is indicated for complicated skin and soft-tissue infections and complicated intra-abdominal infections, but the drug shows promise for other infections as well. Clinically, tigecycline is used mainly for the following:

- Complicated intra-abdominal infections, including abscesses, appendicitis, cholecystitis, diverticulitis, perforations, and peritonitis
- Complicated skin and soft-tissue infections, including abscesses and infected burns or ulcers
- Community-acquired bacterial pneumonia caused by *S. pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *H. influenzae* (β-lactamase negative isolates), and *Legionella pneumophila*
- Ventilator-associated hospital-acquired pneumonia due to multidrug resistant pathogens

**Contraindications**

Tigecycline is contraindicated in patients who have had an allergic reaction to it and in children ≤ 8 yr.

**Use During Pregnancy and Breastfeeding**

Tigecycline is in pregnancy category D (there is evidence of human risk, but clinical benefits may outweigh risk); it, like tetracyclines, can affect fetal bones and teeth.

Whether tigecycline enters breast milk and is safe to use during breastfeeding is unknown.

**Adverse Effects**

Adverse effects include

- Nausea, vomiting, and diarrhea
- Photosensitivity
- Hepatotoxicity

Nausea and vomiting are common. Increases in serum amylase, total bilirubin concentration, PT, and transaminases can occur in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Many of tigecycline's adverse effects are similar to those of tetracyclines (eg, photosensitivity).

**Dosing Considerations**

Dose is adjusted in patients with hepatic dysfunction but not in those with renal dysfunction. Serum levels of warfarin may increase, but INR does not appear to increase.

**Vancomycin**

Vancomycin is a time-dependent bactericidal antibiotic that inhibits cell wall synthesis.
Pharmacology

Vancomycin is not appreciably absorbed from a normal GI tract after oral administration. Given parenterally, it penetrates into bile and pleural, pericardial, synovial, and ascitic fluids. However, penetration into even inflamed CSF is low and erratic. Vancomycin is excreted unchanged by glomerular filtration.

Indications

Vancomycin is active against

• Most gram-positive cocci and bacilli, including almost all Staphylococcus aureus and coagulase-negative staphylococcal strains that are resistant to penicillins and cephalosporins.

• Many strains of enterococci (via a bacteriostatic mechanism)

However, many strains of enterococci and some strains of S. aureus are resistant.

Vancomycin is the drug of choice for serious infection and endocarditis caused by the following:

• Methicillin-resistant S. aureus

• Methicillin-resistant coagulase-negative staphylococci

• Streptococcus pneumoniae

• β-Hemolytic streptococci (when β-lactams cannot be used because of drug allergy or resistance)

• Corynebacterium group JK

• Viridans streptococci (when β-lactams cannot be used because of drug allergy or resistance)

• Enterococci, (when β-lactams cannot be used because of drug allergy or resistance)

However, vancomycin is less effective than antistaphylococcal β-lactams for S. aureus endocarditis. Vancomycin is used with other antibiotics when treating methicillin-resistant coagulase-negative staphylococcal prosthetic valve endocarditis or enterococcal endocarditis. Vancomycin has also been used as an alternative drug for pneumococcal meningitis caused by strains with reduced penicillin sensitivity; however, the erratic penetration of vancomycin into CSF (especially during concomitant use of dexamethasone) and reports of clinical failures make it less than optimal when used alone to treat pneumococcal meningitis. Before dental procedures likely to result in bacteremia are done, vancomycin is used to prevent endocarditis in penicillin-allergic high-risk patients who cannot tolerate oral antibiotics.

Oral vancomycin is used to treat Clostridium difficile-induced diarrhea (pseudomembranous colitis) only if patients do not respond to metronidazole.

Contraindications

Vancomycin is contraindicated in patients who have had an allergic reaction to it.

Use During Pregnancy and Breastfeeding

Vancomycin has not had adverse effects in animals, and evidence in human studies is inadequate. Oral vancomycin tablets are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Oral-solution vancomycin and IV vancomycin are in category C (animal studies show some risk, evidence in human and animal studies is inadequate, but clinical benefit sometimes exceeds risk).
Vancomycin enters breast milk, and so its use during breastfeeding is discouraged; however, because oral absorption is poor from a normal GI tract, adverse effects in infants are usually considered unlikely.

**Adverse Effects**

The main concern is

• Hypersensitivity

Hypersensitivity reactions (eg, rash, fever, reversible neutropenia and thrombocytopenia) may occur, especially when therapy lasts for > 2 wk. Nephrotoxicity is rare unless high doses are used or an aminoglycoside is given concomitantly. Phlebitis occurs uncommonly during IV infusion. Infusion should be given over at least 60 min to avoid the red-person syndrome, a histamine-mediated reaction that can cause pruritus and flushing on the face, neck, and shoulders.

Dose-related ototoxicity is unusual with current formulations.

**Dosing Considerations**

Doses used for meningitis must be higher than usual. Dose reduction is required in renal insufficiency. In critically ill patients, serum levels should be measured after the 2nd or 3rd dose and kept between 10 and 15 μg/mL (trough levels).

Vancomycin MIC has been increasing in the past decade. *S. aureus* with vancomycin MIC of ≤ 2 μg/mL are considered sensitive; those with vancomycin MIC of 4 to 8 μg/mL are considered intermediate, and those with vancomycin MIC of > 8 μg/mL are considered resistant. However, infections due to *S. aureus* with vancomycin MIC of 2 to 8 μg/mL may respond suboptimally to standard dosing and require higher doses with trough levels between 15 to 20 μg/mL, but this approach may be complicated by increased rates of nephrotoxicity.
Chapter 133. Gram-Positive Cocci

Introduction

Many gram-positive cocci are commensal organisms that cause infection only when they find their way into normally sterile areas. They are the most common cause of skin infections and a frequent cause of pneumonia and septicemia. Although they are generally susceptible to a broad range of antibiotics, certain strains have developed resistance to many available antimicrobial drugs.

Pneumococcal Infections

Streptococcus pneumoniae (pneumococci) are gram-positive, α-hemolytic, aerobic, encapsulated diplococci. In the US, pneumococcal infection annually causes about 7 million cases of otitis media, 500,000 cases of pneumonia, 50,000 cases of sepsis, 3,000 cases of meningitis, and 40,000 deaths. Diagnosis is by Gram stain and culture. Treatment depends on the resistance profile and includes a β-lactam, a macrolide, a respiratory fluoroquinolone, and sometimes vancomycin.

Pneumococci are fastidious microorganisms that require catalase to grow on agar plates. In the laboratory, pneumococci are identified by α-hemolysis on blood agar, sensitivity to optochin, and lysis by bile salts.

Pneumococci commonly colonize the human respiratory tract, particularly in winter and early spring. Spread is via airborne droplets. True epidemics of pneumococcal infections are rare.

Serotypes: The pneumococcus capsule consists of a complex polysaccharide that determines serologic type and contributes to virulence and pathogenicity. Virulence varies somewhat within serologic types because of differences in DNA composition.

Currently, > 90 different serotypes have been identified, but most serious infections are caused by serotypes 4, 6, 9, 14, 18, 19, and 23. These serotypes cause about 90% of invasive infections in children and 60% in adults. However, these patterns are slowly changing, in part because of the widespread use of polyvalent vaccine. Serotype 19A, a nonvaccine serotype that is highly virulent and multi-drug-resistant, has emerged as an important cause of respiratory tract infection and invasive disease.

Risk factors: Patients most susceptible to serious and invasive pneumococcal infections are those with chronic illness (eg, chronic cardiopulmonary disease, diabetes, liver disease, alcoholism), immunosuppression (eg, HIV), functional or anatomic asplenia, or sickle cell disease, as well as residents of long-term care facilities, smokers, aborigines, Alaskan natives, and certain American Indian populations. The elderly, even those without other disease, tend to have a poor prognosis with pneumococcal infections. Damage to the respiratory epithelium by chronic bronchitis or common respiratory viral infections, notably influenza, may predispose to pneumococcal invasion.

Diseases Caused by Pneumococci

Pneumococcal diseases include

• Otitis media
• Pneumonia
• Sinusitis
• Meningitis
• Endocarditis
• Septic arthritis
• Peritonitis (rare)

Primary infection usually involves the middle ear or lungs. The diseases listed below are further discussed elsewhere in THE MANUAL.

**Pneumococcal bacteremia** can occur in immunocompetent and immunosuppressed patients; patients who have had splenectomy are at particular risk. Bacteremia may be the primary infection, or it may accompany the acute phase of any focal pneumococcal infection. When bacteremia is present, secondary seeding of distant sites may cause infections such as septic arthritis, meningitis, and endocarditis. Despite treatment, the overall mortality rate for bacteremia is 15 to 20% in children and adults and 30 to 40% in the elderly; risk of death is highest during the first 72 h.

**Pneumonia** (see p. 1923) is the most frequent serious infection caused by pneumococci; it may manifest as lobar pneumonia or, less commonly, as bronchopneumonia. About 4 million cases of community-acquired pneumonia occur each year in the US; when community-acquired pneumonia requires hospitalization, pneumococci are the most common etiologic agent in patients of all ages. Pleural effusion occurs in up to 40% of patients, but most effusions resolve during drug treatment; only about 2% of patients develop empyema, which may become loculated, thick, and fibrinopurulent. Lung abscess formation is rare.

**Acute otitis media** in infants (after the neonatal period) and children is caused by pneumococci in about 30 to 40% of cases (see p. 448). More than one third of children in most populations develop acute pneumococcal otitis media during the first 2 yr of life, and pneumococcal otitis commonly recurs. Relatively few serotypes of *S. pneumoniae* are responsible for most cases. After universal immunization of infants in the US beginning in 2000, nonvaccine serotypes of *S. pneumoniae* (particularly serotype 19A) have become the most common pneumococcal cause of acute otitis media. Complications include mild conductive hearing loss, vestibular balance dysfunction, tympanic membrane perforation, mastoiditis, petrositis, and labyrinthitis. Intracranial complications are rare in developed countries but may include meningitis, epidural abscess, brain abscess, lateral venous sinus thrombosis, cavernous sinus thrombosis, subdural empyema, and carotid artery thrombosis.

**Paranasal sinusitis** (see p. 479) may be caused by pneumococci and may become chronic and polymicrobial. Most commonly, the maxillary and ethmoid sinuses are affected. Infection of the sinuses may extend into the cranium, causing cavernous sinus thrombosis; brain, epidural, or subdural abscesses; septic cortical thrombophlebitis; or meningitis.

**Acute purulent meningitis** (see p. 1735) is frequently caused by pneumococci and may be secondary to bacteremia from other foci (notably pneumonia); direct extension from infection of the ear, mastoid process, or paranasal sinuses; or basilar fracture of the skull involving one of these sites or the cribiform plate. Complications after pneumococcal meningitis include hearing loss (in up to 50% of patients), seizures, learning disabilities, mental dysfunction, and palsies.

**Endocarditis** (see p. 2193) may result from pneumococcal bacteremia, even in patients without valvular heart disease, but is rare. Pneumococcal endocarditis may produce a corrosive valvular lesion, with sudden rupture or fenestration, leading to rapidly progressive heart failure.

**Septic arthritis**, similar to septic arthritis caused by other gram-positive cocci, is usually a complication of pneumococcal bacteremia from another site (see Acute Infectious Arthritis on p. 365).

**Spontaneous pneumococcal peritonitis** occurs most often in patients with cirrhosis and ascites, with no features to distinguish it from spontaneous bacterial peritonitis of other causes (see p. 106).

**Diagnosis**

• Gram stain and culture
Pneumococci are readily identified by their typical appearance on Gram stain as lancet-shaped diplococci. The characteristic capsule can be best detected using the Quellung test. In this test, application of antiserum followed by staining with India ink causes the capsule to appear like a halo around the organism. The capsule is also visible in smears stained with methylene blue. Culture confirms identification; antimicrobial susceptibility testing should be done. Serotyping and genotyping of isolates can be helpful for epidemiologic reasons (eg, to follow the spread of specific clones and antimicrobial resistance patterns).

**Treatment**

- A β-lactam or macrolide

If pneumococcal infection is suspected, initial therapy pending susceptibility studies should be determined by local resistance patterns. Although preferred treatment for pneumococcal infections is a β-lactam or macrolide antibiotic, treatment has become more challenging because resistant strains have emerged. Strains highly resistant to penicillin, ampicillin, and other β-lactams are common worldwide. The most common predisposing factor to β-lactam resistance is use of these drugs within the past several months.

Intermediately resistant organisms may be treated with usual or high doses of penicillin G or another β-lactam.

Seriously ill patients with nonmeningeal infections caused by organisms that are highly resistant to penicillin can often be treated with ceftriaxone or cefotaxime. Very high doses of parenteral penicillin G (20 to 40 million units/day IV for adults) also work, unless the minimum inhibitory concentration of the isolate is very high. Fluoroquinolones (eg, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin) are effective for respiratory infections with highly penicillin-resistant pneumococci in adults.

All penicillin-resistant isolates have been susceptible to vancomycin so far, but parenteral vancomycin does not always produce concentrations in CSF adequate for treatment of meningitis (especially if corticosteroids are also being used). Therefore, in patients with meningitis, ceftriaxone or cefotaxime, rifampin, or both are commonly used with vancomycin.

**Prevention**

Infection produces type-specific immunity that does not generalize to other serotypes. Otherwise, prevention involves

- Vaccination
- Prophylactic antibiotics

**Vaccines:** Two pneumococcal vaccines are available: a conjugated vaccine against 7 serotypes (PCV7) and a polyvalent polysaccharide vaccine directed against the 23 serotypes (PPV23) that account for 80 to 95% of serious pneumococcal infections.

**Conjugated vaccine** is recommended for all children aged 6 wk through 59 mo. The schedule varies depending on age and underlying medical conditions (see *Table 268-10* on p. 2718). If vaccination is begun at age ≤ 6 mo, children should receive a 3-dose primary series at about 2-mo intervals, followed by a 4th dose at age 12 to 15 mo. The customary age for the first dose is 2 mo. If vaccination is begun at age 7 to 11 mo, a 2-dose primary series and a booster are given. From age 12 to 23 mo, 2 doses and no booster are given. From age 24 mo to 9 yr, children receive 1 dose.

**Polysaccharide vaccine** is ineffective in children < 2 yr but reduces pneumococcal bacteremia by 50% in adults. There is no documented reduction in pneumonia. Protection generally lasts many years, but revaccination after ≥ 5 yr may be desirable in highly susceptible people. The polysaccharide vaccine is indicated for adults ≥ 65 yr and people 2 to 64 yr with increased susceptibility (see p. 1226) and before splenectomy. It is not recommended for children < 2 yr or anyone hypersensitive to the vaccine's
components.

**Prophylactic antibiotics**: For functional or anatomic asplenic children < 5 yr, penicillin V 125 mg po bid is recommended. The duration for chemoprophylaxis is empiric, but some experts continue prophylaxis throughout childhood and into adulthood for high-risk patients with asplenia. Penicillin 250 mg po bid is recommended for older children or adolescents for at least 1 yr after splenectomy.

**Staphylococcal Infections**

Staphylococci are gram-positive, aerobic organisms. *Staphylococcus aureus* is the most pathogenic; it typically causes skin infections and sometimes pneumonia, endocarditis, and osteomyelitis. It commonly leads to abscess formation. Some strains elaborate toxins that cause gastroenteritis, scalded skin syndrome, and toxic shock syndrome. Diagnosis is by Gram stain and culture. Treatment is usually with penicillinase-resistant b-lactams, but because antibiotic resistance is common, vancomycin or other newer antibiotics may be required. Some strains are partially or totally resistant to all but the newest antibiotics, which include linezolid, quinupristin/dalfopristin, daptomycin, telavancin, dalbavancin, and tigecycline.

The ability to clot blood by producing coagulase determines the virulence of the several species of staphylococci. Coagulase-positive *Staphylococcus aureus* is among the most ubiquitous and dangerous human pathogens, for both its virulence and its ability to develop antibiotic resistance. Coagulase-negative species such as *S. epidermidis* are increasingly associated with hospital-acquired infections; *S. saprophyticus* causes urinary infections. *S. lugdunensis*, a coagulase-negative species, has recently been found to cause invasive disease with virulence similar to that of *S. aureus*. Unlike most coagulase-negative staphylococcal species, *S. lugdunensis* often remains sensitive to penicillinase-resistant β-lactam antibiotics.

Pathogenic staphylococci are ubiquitous. They are carried, usually transiently, in the anterior nares of about 30% of healthy adults and on the skin of about 20%. Rates are higher in hospital patients and personnel.

**Risk factors**: Neonates and breastfeeding mothers are predisposed to staphylococcal infections, as are patients with influenza, chronic bronchopulmonary disorders (eg, cystic fibrosis, emphysema), leukemia, tumors, transplants, implanted prostheses or other foreign bodies, burns, chronic skin disorders, surgical incisions, diabetes mellitus, or indwelling intravascular plastic catheters. Patients receiving adrenal steroids, irradiation, immunosuppressants, or antitumor chemotherapy are also at increased risk. Predisposed patients may acquire antibiotic-resistant staphylococci from other patients, health care personnel, or inanimate objects in health care settings. Transmission via the hands of personnel is the most common means of spread, but airborne spread can also occur.

**Diseases Caused by Staphylococci**

Staphylococci cause disease by

- Direct tissue invasion
- Sometimes exotoxin production

*S. aureus* bacteremia, which frequently causes metastatic foci of infection, may occur with any localized staphylococcal infection but is particularly common with infection related to intravascular catheters or other foreign bodies. It may also occur without any obvious primary site. *S. epidermidis* and other coagulase-negative staphylococci increasingly cause hospital-acquired bacteremia associated with intravascular catheters and other foreign bodies because they can form biofilms on these materials. They are important causes of morbidity (especially prolongation of hospitalization) and mortality in debilitated patients. The diseases listed below are further discussed elsewhere in THE MANUAL.

**Direct invasion**: Most staphylococcal disease results from direct tissue invasion. Examples are
• Skin infections
• Pneumonia
• Endocarditis
• Osteomyelitis
• Septic arthritis

**Skin infections** are the most common form of staphylococcal disease (see p. 694). Superficial infections may be diffuse, with vesicular pustules and crusting (impetigo) or sometimes cellulitis or with focal and nodular abscesses (furuncles and carbuncles). Deeper cutaneous abscesses are common. Severe necrotizing skin infections may occur. Staphylococci are commonly implicated in wound and burn infections, postoperative incision infections, and mastitis or breast abscess in breastfeeding mothers.

**Neonatal infections** usually appear within 6 wk after birth and include skin lesions with or without exfoliation, bacteremia, meningitis, and pneumonia.

**Pneumonia** that occurs in a community setting is not common but may develop in patients who have influenza, who are receiving corticosteroids or immunosuppressants, or who have chronic bronchopulmonary or other high-risk diseases. However, *S. aureus* is a common cause of hospital-acquired pneumonia. Staphylococcal pneumonia is occasionally characterized by formation of lung abscesses followed by rapid development of pneumatoceles and empyema. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) often causes severe necrotizing pneumonia.

**Endocarditis** can develop, particularly in IV drug abusers and patients with prosthetic heart valves. Because intravascular catheter use and implantation of cardiac devices have increased, *S. aureus* has become a leading cause of bacterial endocarditis. *S. aureus* endocarditis is an acute febrile illness often accompanied by visceral abscesses, embolic phenomena, pericarditis, subungal petchiae, subconjunctival hemorrhage, purpuric lesions, heart murmurs, and heart failure secondary to cardiac valve damage.

**Osteomyelitis** occurs more commonly in children, causing chills, fever, and pain over the involved bone. Redness and swelling subsequently appear. Articular infection may occur; it frequently results in effusion, suggesting septic arthritis rather than osteomyelitis.

**Toxin-mediated disease**: Staphylococci may produce multiple toxins. Some have local effects; others trigger cytokine release from certain T cells, causing serious systemic effects (eg, skin lesions, shock, organ failure, death). Panton-Valentine leukocidin (PVL) is a toxin produced by strains infected with a certain bacteriophage. PVL is typically present in strains of CA-MRSA and has been thought to mediate the ability to necrotize; however, this effect has not been verified.

Toxin-mediated staphylococcal diseases include the following:

• Toxic shock syndrome
• Staphylococcal scalded skin syndrome
• Staphylococcal food poisoning

**Toxic shock syndrome** (see p. 1235) may result from use of vaginal tampons or occur as a complication of a seemingly minor postoperative infection. Although most cases have been due to methicillin-susceptible *S. aureus* (MSSA), cases due to MRSA are becoming more frequent.

**Staphylococcal scalded skin syndrome** (see p. 701 and Plate 45), which is caused by several toxins termed exfoliatins, is an exfoliative dermatitis of childhood characterized by large bullae and peeling of the upper layer of skin. Eventually, exfoliation occurs.
**Staphylococcal food poisoning** is caused by ingesting a preformed heat-stable staphylococcal enterotoxin. Food can be contaminated by staphylococcal carriers or people with active skin infections. In food that is incompletely cooked or left at room temperature, staphylococci reproduce and elaborate enterotoxin. Many foods can serve as growth media, and despite contamination, they have a normal taste and odor. Severe nausea and vomiting begin 2 to 8 h after ingestion, typically followed by abdominal cramps and diarrhea. The attack is brief, often lasting < 12 h.

**Diagnosis**

- Gram stain and culture

Diagnosis is by Gram stain and culture of infected material. Susceptibility tests should be done because methicillin-resistant organisms are now common and require alternative therapy.

When staphylococcal scalded skin syndrome is suspected, cultures should be obtained from blood, urine, the nasopharynx, the umbilicus, abnormal skin, or any suspected focus of infection; the intact bullae are sterile. Although the diagnosis is usually clinical, a biopsy of the affected skin may help confirm the diagnosis.

Staphylococcal food poisoning is usually suspected because of case clustering (eg, within a family, attendees of a social gathering, or customers of a restaurant). Confirmation (typically by the health department) entails isolating staphylococci from suspect food and sometimes testing for enterotoxins.

X-ray changes of osteomyelitis may not be apparent for 10 to 14 days, and bone rarefaction and periosteal reaction may not be detected for even longer. Abnormalities in MRI, CT, or radionuclide bone scans are often apparent earlier. Bone biopsy (open or percutaneous) should be done for pathogen identification and susceptibility testing.

**Screening:** Some institutions that have a high incidence of MRSA nosocomial infections routinely screen admitted patients for MRSA (active surveillance) by using rapid laboratory techniques to evaluate nasal swab specimens. Some institutions screen only high-risk patients (eg, those who are admitted to the ICU, who have had previous MRSA infection, or who are about to undergo vascular, orthopedic, or cardiac surgeries). Quick identification of MRSA allows carriers to be placed in contact isolation. This practice decreases the spread of MRSA and may decrease the incidence of nosocomial infections with MRSA.

**Treatment**

- Local measures (eg, debridement, removal of catheters)

- Antibiotics selected based on severity of infection and local resistance patterns

Management includes abscess drainage, debridement of necrotic tissue, removal of foreign bodies (including intravascular catheters), and use of antibiotics. Initial choice and dosage of antibiotics depend on infection site, illness severity, and probability that resistant strains are involved. Thus, it is essential to know local resistance patterns for initial therapy (and ultimately, to know actual drug susceptibility).

Treatment of toxin-mediated staphylococcal disease (the most serious of which is toxic shock syndrome) involves decontamination of the toxin-producing area (exploration of surgical wounds, irrigation, debridement), intensive support (including vasopressors and respiratory assistance), electrolyte balancing, and antimicrobials. In vitro evidence supports a preference for protein synthesis inhibitors (eg, clindamycin 900 mg IV q 8 h) over other classes of antibiotics. IV immune globulin has been beneficial in severe cases.

**Antibiotic resistance:** Many staphylococcal strains produce penicillinase, an enzyme that inactivates several β-lactam antibiotics; these strains are resistant to penicillin G, ampicillin, and antipseudomonal penicillins. Most community-acquired strains are susceptible to penicillinase-resistant penicillins (eg, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin), cephalosporins, carbapenems (eg, imipenem,
meropenem, ertapenem, doripenem), macrolides, fluoroquinolones, trimethoprim-sulfamethoxazole (TMP/SMX), gentamicin, vancomycin, and teicoplanin.

MRSA isolates have become common, especially in hospitals. In addition, CA-MRSA has emerged over the past several years in many geographic regions. CA-MRSA tends to be less resistant to multiple drugs than hospital-acquired MRSA. These strains, although resistant to most β-lactams, are usually susceptible to TMP/SMX, doxycycline, or minocycline and are often susceptible to clindamycin, but there is the potential for emergence of clindamycin resistance by strains inducibly resistant to erythromycin (laboratories may report these strains as D-test positive). Vancomycin is effective against most MRSA, sometimes with the addition of rifampin and an amino-glycoside for serious infections.

Vancomycin-resistant S. aureus (VRSA) and vancomycin-intermediate-susceptible S. aureus (VISA) strains have appeared in the US. These organisms may require linezolid, quinupristin/dalfopristin, or daptomycin.

Because incidence of MRSA has increased, initial empiric treatment for serious staphylococcal infections (particularly those that occur in a health care setting) should include a drug with reliable activity against MRSA. Thus, for proven or suspected bloodstream infections, vancomycin or daptomycin would be appropriate. For pneumonia, vancomycin or linezolid should be used because daptomycin is not reliably active in the lungs.

Table 133-1 summarizes treatment options.

Prevention

Aseptic precautions (eg, thoroughly washing hands between patient examinations, sterilizing shared equipment) help decrease spread in institutions. Strict isolation procedures should be used for patients harboring resistant microbes until their infections have been cured. An asymptomatic nasal carrier need not be isolated unless the strain is MRSA or is the suspected source of an outbreak. Cloxacillin, dicloxacillin, TMP/SMX, ciprofloxacin (each of these drugs is often combined with rifampin), and topical mupirocin have been useful in treating MRSA in carriers, but the organism recurs in up to 50% and frequently becomes resistant.

Staphylococcal food poisoning can be prevented by appropriate food preparation. Patients with staphylococcal skin infections should not handle food, and food should be consumed immediately or refrigerated and not kept at room temperature.

Streptococcal and Enterococcal Infections

(See also Pneumococcal Infections on p. 1225, Rheumatic Fever on p. 2661, and Tonsillopharyngitis on p. 473.)

Streptococci are gram-positive aerobic organisms that cause many disorders, including pharyngitis, pneumonia, wound and skin infections, sepsis, and endocarditis. Symptoms vary with the organ infected. Sequelae include rheumatic fever and glomerulonephritis. Clinical diagnoses are confirmed by Gram stain and culture. Most strains are sensitive to penicillin, with the exception of enterococci, which can be resistant to multiple drugs. Recently, macrolide-resistant strains have emerged.

Classification: Three different types of streptococci are initially differentiated by their appearance when they are grown on sheep blood agar. β-Hemolytic streptococci produce zones of clear hemolysis around each colony, α-hemolytic streptococci (including viridans group streptococci) are surrounded by green discoloration resulting from incomplete hemolysis, and γ-hemolytic streptococci are nonhemolytic.

Subsequent classification, based on carbohydrates in the cell wall, divides streptococci into Lancefield
groups A through H and K through T (see Table 133-2). Viridans streptococci form a separate group that is difficult to classify. In the Lancefield classification, enterococci were initially included among the group D streptococci. More recently, enterococci have been classified as a separate genus.

Virulence factors: Many streptococci elaborate virulence factors, including streptolysins, DNAases, and hyaluronidase, which contribute to tissue destruction and spread of infection. A few strains release exotoxins that activate certain T cells, triggering release of cytokines, including tumor necrosis factor-α, interleukins, and other immunomodulators. These cytokines activate the complement, coagulation, and fibrinolytic systems, leading to shock, organ failure, and death.

Diseases Caused by Streptococci

The most significant streptococcal pathogen is *S. pyogenes*, which is β-hemolytic and in Lancefield group A and is thus denoted as group A β-hemolytic streptococci (GABHS). The 2 most common acute diseases due to GABHS are pharyngitis and skin infections; in addition, delayed, nonsuppurative complications (rheumatic fever, acute glomerulonephritis) sometimes occur ≥ 2 wk after infection.

Disease caused by other streptococcal species is less prevalent and usually involves soft-tissue infection or endocarditis (see Table 133-2). Some non-GABHS infections occur predominantly in certain populations (eg, group B streptococci in neonates and postpartum women, enterococci in hospitalized patients).

Infections can spread through the affected tissues and along lymphatic channels to regional lymph nodes. They can also cause local suppurative complications, such as peritonsillar abscess, otitis media, sinusitis, and

[Table 133-2. Classification of Streptococci]

bacteremia. Suppuration depends on the severity of infection and the susceptibility of tissue.

Streptococcal pharyngitis is usually caused by GABHS. About 20% of patients present with sore throat, fever, a beefy red pharynx, and a purulent tonsillar exudate. The remainder have less prominent symptoms, and the examination resembles that of viral pharyngitis. The cervical and submaxillary nodes may enlarge and become tender. Streptococcal pharyngitis can lead to peritonsillar abscess (see p. 474). Cough, laryngitis, and stuffy nose are not characteristic of streptococcal pharyngeal infection; their presence suggests another cause (usually viral or allergic). An asymptomatic carrier state may exist in as many as 20%.

Scarlet fever is uncommon today. Scarlet fever is caused by group A (and occasionally by group B or C) streptococcal strains that produce an erythrogenic toxin, leading to a diffuse pink-red cutaneous flush that blanches with pressure. The rash is seen best on the abdomen or lateral chest as dark red lines in skinfolds (Pastia's lines) or as circumoral pallor. A strawberry tongue (inflamed papillae protruding through a bright red coating) also occurs and must be differentiated from that seen in toxic shock syndrome (see p. 1235) and Kawasaki disease (see p. 2935). Characteristic numerous small (1- to 2-mm) papular elevations, giving a sandpaper quality to the skin, may be present. The upper layer of the previously reddened skin often desquamates after fever subsides. Other symptoms are similar to those in streptococcal pharyngitis, and the course and management of scarlet fever are the same as those of other group A infections.

Skin infections include impetigo (see p. 699) and cellulitis (see p. 694). Cellulitis may spread rapidly because of the numerous lytic enzymes and toxins produced mainly by group A streptococci. Erysipelas (see p. 696) is a particular form of streptococcal cellulitis.

Necrotizing fasciitis due to *S. pyogenes* is a severe dermal (or rarely muscular) infection that spreads along fascial planes (see p. 700). Inoculation originates through the skin or bowel, and the defect may be surgical, trivial, distant from the disease site, or occult, as with colonic diverticula or an appendiceal abscess. Necrotizing fasciitis is prevalent among IV drug abusers. Formerly known as streptococcal
gangrene and popularized as the flesh-eating bacteria, the same syndrome may also be polymicrobial, involving a host of aerobic and anaerobic flora, including Clostridium perfringens. When necrotizing fasciitis occurs in the perineum, it is called Fournier's gangrene (see Plate 61). Comorbid conditions, such as impaired immunity, diabetes, and alcoholism, are common. Symptoms begin with fever and exquisite localized pain; pain increases rapidly over time and is often the first (and sometimes only) manifestation. Diffuse or local erythema may be present. Thrombosis of the microvasculature causes ischemic necrosis, leading to rapid spread and disproportionally severe toxicity. In 20 to 40% of patients, adjacent muscles are invaded. Shock and renal dysfunction are common. Mortality is high, even with treatment.

Other serious streptococcal infections include septicemia, puerperal sepsis, endocarditis, and pneumonia.

**Streptococcal toxic shock syndrome** (see p. 1235), similar to that caused by S. aureus, may result from toxin-producing strains of GABHS. Patients are usually otherwise healthy children or adults with skin and soft-tissue infections.

**Delayed complications:** The mechanism by which certain strains of GABHS cause delayed complications is unclear but may involve cross-reactivity of streptococcal antibodies against host tissue.

**Rheumatic fever** (see p. 2861), an inflammatory disorder, occurs in < 3% of patients in the weeks after untreated GABHS upper respiratory tract infection. It is much less common today than in the preantibiotic era. Diagnosis is based on a combination of arthritis, carditis, chorea, specific cutaneous manifestations, and laboratory test results (Jones criteria). One of the most important reasons for treating strep throat is to prevent rheumatic fever.

**Poststreptococcal acute glomerulonephritis** (see p. 2392) is an acute nephritic syndrome following pharyngitis or skin infection due to a certain limited number of nephritogenic strains of GABHS (eg, types 12 and 49). After a throat or skin infection with one of these strains, about 10 to 15% of patients develop acute glomerulonephritis. It is most common among children, occurring 1 to 3 wk after infection. Nearly all children, but somewhat fewer adults, recover without permanent renal damage. Antibiotic treatment of GABHS infection has little effect on development of glomerulonephritis.

**PANDAS syndrome** (pediatric autoimmune neuropsychiatric disorder associated with group A streptococci) refers to a subset of obsessive disorders or tic disorders in children thought to be exacerbated by GABHS infection.

Certain forms of psoriasis (eg, guttate) may also be related to β-hemolytic streptococcal infections.

**Diagnosis**

• Culture

• Sometimes rapid antigen tests or antibody titers

Streptococci are readily identified by culture on a sheep blood agar plate.

**Rapid antigen-detection tests** that can detect GABHS directly from throat swabs are available. Many tests use enzyme immunoassay, but more recently, tests using optical immunoassay have become available. These rapid tests have high specificity (> 95%) but vary considerably in sensitivity (55% to 80 to 90% for the newer optical immunoassay test). Negative results should be confirmed by culture (particularly if use of a macrolide is being considered because of potential resistance).

During convalescence, evidence of infection can be obtained indirectly by demonstrating antistreptococcal antibodies in serum. Antibodies are most useful in diagnosis of poststreptococcal diseases, such as rheumatic fever and glomerulonephritis. Confirmation requires that sequential specimens show a rise in titer because a single value may be high because of a long antecedent infection. Serum specimens need not be taken more often than every 2 wk and may be taken every 2 mo. To be considered significant, a rise (or fall) in titer should span at least 2 serial dilutions. The antistreptolysin O (ASO) titer rises in only 75 to 80% of infections. For completeness in difficult cases, any
one of the other tests (antihyaluronidase, antideoxyribonuclease B, antinicotinamide adenine dinucleotidase, antistreptokinase) can also be used. Penicillin given within the first 5 days for symptomatic streptococcal pharyngitis may delay the appearance and decrease the magnitude of the ASO response. Patients with streptococcal pyoderma usually do not have a significant ASO response but may have a response to other antigens (ie, anti-DNAase, antihyaluronidase).

**Treatment**

- **Usually penicillin**

**Pharyngitis:** Ordinarily, pharyngeal GABHS infections, including scarlet fever, are self-limited. Antibiotics shorten the course in young children, especially those with scarlet fever, but have only modest effect on symptoms in adolescents and adults. However, antibiotics help prevent local suppurative complications (eg, peritonsillar abscess), otitis media, and rheumatic fever.

Penicillin is the drug of choice. No isolate of GABHS has demonstrated penicillin resistance clinically, probably because it lacks altered penicillin-binding proteins, has an inefficient gene transfer mechanism for resistance, or both. However, some streptococcal strains appear to have in vitro tolerance to penicillin; the clinical significance of such strains is unclear.

A single injection of benzathine penicillin G, 600,000 units IM for small children (< 27.3 kg) or 1.2 million units IM for adolescents and adults usually suffices. Oral penicillin V may be used if the patient can be trusted to maintain the regimen for the required 10 days; penicillin V 500 mg (250 mg for children < 27 kg) po bid or tid is given. Oral cephalosporins are also effective. Cefdinir, cefpodoxime, and azithromycin can be used for a 5-day course of therapy. Delaying treatment 1 to 2 days until laboratory confirmation increases neither the duration of disease nor the incidence of complications.

When penicillin or a β-lactam is contraindicated, erythromycin 250 mg po qid or clindamycin 300 mg po tid may be given for 10 days, although resistance of GABHS to macrolides has been detected. Some authorities recommend in vitro confirmation of susceptibility if a macrolide is to be used and there is macrolide resistance in the community. Clindamycin 5 mg/kg po qid is preferred in children who have relapses of chronic tonsillitis, possibly because it has good activity against penicillinase-producing staphylococci or anaerobes coinfecting the tonsillar crypts and inactivating penicillin G and because it appears to halt exotoxin production more rapidly than other drugs. Amoxicillin/clavulanate is also effective. Ceftriaxone is commercially available, but its use is not recommended. TMP/SMX, some of the fluoroquinolones, and tetracyclines are unreliable for treating GABHS.

Sore throat, headache, and fever can be treated with analgesics or antipyretics. Bed rest and isolation are unnecessary. Close contacts who are symptomatic or have a history of poststreptococcal complications should be examined for streptococci.

**Skin infection:** Cellulitis is often treated without doing a culture because isolating organisms can be difficult. Thus, regimens effective against both streptococci and staphylococci are used (see p. 695).

Necrotizing fasciitis should be treated in an ICU. Extensive (sometimes repeated) surgical debridement is required. A recommended initial antibiotic regimen is a β-lactam (often a broad-spectrum drug until etiology is confirmed by culture) plus clindamycin. Although streptococci remain susceptible to β-lactam antibiotics, animal studies show that penicillin is not always effective against a large bacterial inoculum because the streptococci are not rapidly growing.

**Other streptococcal infections:** Drugs of choice for treating group B, C, and G infections are penicillin, ampicillin, or vancomycin. Cephalosporins or macrolides are usually effective, but susceptibility tests must guide therapy, especially in very ill, immunocompromised, or debilitated people and in people with foreign bodies at the infection site. Surgical wound drainage and debridement as adjuncts to antimicrobial therapy may be lifesaving.

*S. bovis* is relatively susceptible to antibiotics. Although vancomycin-resistant *S. bovis* isolates have been reported, the organism remains susceptible to penicillin and aminoglycosides.
Most viridans streptococci are often susceptible to penicillin G and other β-lactams. Resistance is growing, and therapy for such strains should be dictated by results of in vitro susceptibility tests.

**Enterococcal Infections**

*Enterococcus faecalis* and *E. faecium* cause endocarditis, UTI, intra-abdominal infection, cellulitis, and wound infection as well as concurrent bacteremia.

Enterococci associated with endocarditis are difficult to eradicate unless a combination of a cell wall-active drug (eg, penicillin, ampicillin, vancomycin) plus an aminoglycoside (eg, gentamicin, streptomycin) is used.

For complicated skin infections due to vancomycin-susceptible enterococci, daptomycin and tigecycline are effective treatment options. Tigecycline is recommended for complicated intra-abdominal infections.

**Resistance:** Vancomycin-resistant enterococci (VRE) may exist; they may be resistant to other glycopeptides (eg, teicoplanin), aminoglycosides, and cell wall-active β-lactams (eg, penicillin G, ampicillin). When identified, infected patients are strictly isolated. Recommended treatment includes streptogramins (quinupristin/dalfopristin for *Enterococcus faecium* only) and oxazolidinones (linezolid). Daptomycin and tigecycline have in vitro activity against VRE and may be off-label treatment options.

β-Lactamase-producing enterococci are occasionally encountered. Combination β-lactam/β-lactamase inhibitor antibiotics (eg, piperacillin/tazobactam, ampicillin/sulbactam) or vancomycin can be used.

**Toxic Shock Syndrome**

Toxic shock syndrome (TSS) is caused by staphylococcal or streptococcal exotoxins. Symptoms include high fever, hypotension, diffuse erythematous rash, and multiple organ dysfunction, which may rapidly progress to severe and intractable shock. Diagnosis is made clinically and by isolating the organism. Treatment includes antibiotics, intensive support, and immune globulin.

TSS is caused by exotoxin-producing cocci. Strains of phage-group 1 *Staphylococcus aureus* elaborate the TSS toxin-1 (TSST-1) or related exotoxins; certain strains of *Streptococcus pyogenes* produce at least 2 exotoxins.

**Staphylococcal toxic shock:** Women who have preexisting staphylococcal colonization of the vagina and who use tampons are at highest risk. Mechanical or chemical factors related to tampon use probably enhance production of the exotoxin or facilitate its entry into the bloodstream through a mucosal break or via the uterus. Estimates made from small series suggest about 3 cases/100,000 menstruating women still occur, and cases are still reported in women who do not use tampons, in women who have had surgery, and in postpartum women. About 15% of cases occur postpartum or as a complication of postoperative staphylococcal wound infections, which frequently appear insignificant. Cases have also been reported in patients with influenza, osteomyelitis, or cellulitis.

Mortality from staphylococcal TSS is < 3%. Recurrences are common among women who continue to use tampons during the first 4 mo after an episode.

**Streptococcal toxic shock:** The syndrome is similar to that caused by *S. aureus*, but mortality is higher (20 to 60%). In addition, about 50% of patients have *S. pyogenes* bacteremia, and 50% have necrotizing fasciitis (neither is common with staphylococcal TSS). Patients are usually otherwise healthy children or adults. Primary infections in skin and soft tissue are more common than in other sites. In contrast to staphylococcal TSS, streptococcal TSS is more likely to cause acute respiratory distress syndrome (ARDS) and less likely to cause a typical cutaneous reaction.

*S. pyogenes* TSS is defined as any group A β-hemolytic streptococci (GABHS) infection associated with shock and organ failure. Risk factors for GABHS TSS include minor trauma, surgical procedures, viral infections (eg, varicella), and use of NSAIDs.
**Symptoms and Signs**

Onset is sudden, with fever (39° to 40.5°C, which remains elevated), hypotension, a diffuse macular erythroderma, and involvement of at least 2 other organ systems.

Staphylococcal TSS is likely to cause vomiting, diarrhea, myalgia, elevated CK, mucositis, hepatic damage, thrombocytopenia, and confusion. The staphylococcal TSS rash is more likely to desquamate, particularly on the palms and soles, between 3 and 7 days after onset.

Streptococcal TSS commonly causes respiratory distress syndrome, coagulopathy, and hepatic damage and is more likely to cause fever, malaise, and severe pain at the site of a soft-tissue infection.

Renal impairment is frequent and common to both. The syndrome may progress within 48 h to syncope, shock, and death. Less severe cases of staphylococcal TSS are fairly common.

**Diagnosis**

- **Clinical evaluation**
- **Cultures**

Diagnosis is made clinically and by isolating the organism from blood cultures (for *Streptococcus*) or from the local site. TSS resembles Kawasaki disease, but Kawasaki disease usually occurs in children < 5 yr of age and does not cause shock, azotemia, or thrombocytopenia; the skin rash is maculopapular. Other disorders to be considered are scarlet fever, Reye's syndrome, staphylococcal scalded skin syndrome, meningococcemia, Rocky Mountain spotted fever, leptospirosis, and viral exanthematous diseases. These disorders are ruled out by specific clinical differences, cultures, and serologic tests.

Specimens for culture should be taken from any lesions, the nose (for staphylococci), throat (for streptococci), vagina (for both), and blood. MRI or CT of soft tissue is helpful in localizing sites of infection. Continuous monitoring of renal, hepatic, bone marrow, and cardiopulmonary function is necessary.

**Treatment**

- **Local measures (eg, decontamination, debridement)**
- **Fluid resuscitation and circulatory support**
- **Aβ-lactam (eg, penicillin) plus clindamycin**

Patients suspected of having TSS should be hospitalized immediately and treated intensively. Tampons, diaphragms, and other foreign bodies should be removed at once. Suspected primary sites should be decontaminated thoroughly. Decontamination includes reinspection and irrigation of surgical wounds, even if they appear healthy; repeated debridement of devitalized tissues; and irrigation of potential naturally colonized sites (sinuses, vagina). Fluids and electrolytes are replaced to prevent or treat hypovolemia, hypotension, and shock. Because fluid loss into tissues can occur throughout the body (because of systemic capillary leak syndrome and hypoalbuminemia), shock may be profound and resistant. Aggressive fluid resuscitation and circulatory support are sometimes required.

Obvious infections should be treated. If *S. pyogenes* is isolated, a β-lactam (eg, penicillin) plus clindamycin (900 mg IV q 8 h) continued for 14 days is the most effective antibiotic treatment. If methicillin-resistant *S. aureus* (MRSA—see p. 1230) is suspected or confirmed, vancomycin, daptomycin, linezolid, or tigecycline is indicated. Antibiotics given during the acute illness may eradicate pathogen foci and prevent recurrences. Passive immunization to TSS toxins with IV immune globulin (400 mg/kg) has been helpful in severe cases of both types of TSS and lasts for weeks, but the disease may not induce active immunity, so recurrences are possible.
If a test for seroconversion of the serum antibody responses to TSST-1 in acute- and convalescent-phase paired sera is negative, women who have had staphylococcal TSS should probably refrain from using tampons and cervical caps, plugs, and diaphragms. Advising all women, regardless of TSST-1 antibody status, to change tampons frequently or use napkins instead and to avoid hyperabsorbent tampons seems prudent.
Chapter 134. Gram-Positive Bacilli

Introduction

Gram-positive bacilli cause anthrax, diphtheria, erysipelothricosis, listeriosis, and nocardiosis. Serious symptoms caused by anthrax and diphtheria are due to powerful toxins produced by the organisms.

Anthrax

Anthrax is caused by *Bacillus anthracis*, toxin-producing, encapsulated, aerobic or facultative anaerobic organisms. Anthrax, an often fatal disease of animals, is transmitted to humans by contact with infected animals or their products. In humans, infection typically occurs through the skin. Inhalation infection is less common; oropharyngeal, meningeal, and GI infections are rare. For inhalation and GI infections, nonspecific local symptoms are typically followed in several days by severe systemic illness, shock, and often death. Empiric treatment is with ciprofloxacin or doxycycline. A vaccine is available.

Etiology

Anthrax is an important domestic animal disease, occurring in goats, cattle, sheep, and horses. Anthrax also occurs in wildlife, such as hippos, elephants, and Cape buffalo. It is rare in humans and occurs mainly in countries that do not prevent industrial or agricultural exposure to infected animals or their products (eg, hides). The incidence of natural infection has decreased, particularly in the developed world.

However, the potential use of anthrax as a biological weapon has increased fear of this pathogen. Spores have been prepared in very finely powdered form (weaponized) to be used as agents of warfare and bioterrorism (see p. 1164); in anthrax bioattacks of 2001, spores were spread via the United States Postal Service.

Pathophysiology

*Bacillus anthracis* readily form spores when they dry—an environmental condition unfavorable for growth. Spores resist destruction and can remain viable in soil, wool, and animal hair for decades. Spores germinate and begin multiplying rapidly when they enter an environment rich in amino acids and glucose (eg, tissue, blood).

Human infection can be acquired by

- Cutaneous contact (most common)
- Ingestion
- Inhalation

Cutaneous infection is usually acquired by contact with infected animals or sporecontaminated animal products. Open wounds or abrasions increase susceptibility, but infection may occur when skin is intact. Skin infection may be transmitted from person to person by direct contact or fomites.

GI (including oropharyngeal) infection may occur after ingestion of inadequately cooked meat containing the vegetative forms of the organism, usually when a break in the pharyngeal or intestinal mucosa facilitates invasion. Ingested anthrax spores can cause lesions from the oral cavity to the cecum. Released toxin causes hemorrhagic necrotic ulcers and mesenteric lymphadenitis, which may lead to intestinal hemorrhage, obstruction, or perforation.

Pulmonary infection (inhalation anthrax), caused by inhaling spores, is almost always due to occupational exposure to contaminated animal products (eg, hides) and is often fatal.
GI and inhalation anthrax are not transmitted from person to person.

After entering the body, spores germinate inside macrophages, which migrate to regional lymph nodes where the bacteria multiply. In inhalation anthrax, spores are deposited in alveolar spaces, where they are ingested by macrophages, which migrate to mediastinal lymph nodes, usually causing a hemorrhagic mediastinitis. Bacteremia may occur in any form of anthrax and occurs in nearly all fatal cases; meningeal involvement is common.

**Virulence factors:** The virulence of *B. anthracis* is due to its antiphagocytic capsule, its toxins (factors), and its rapid replication capability.

The predominant toxins are edema toxin and lethal toxin. Protective antigen binds to target cells and facilitates cellular entry of edema toxin and lethal toxin. Edema toxin causes massive local edema. Lethal toxin triggers a massive release of cytokines from macrophages, which is responsible for the sudden death common in anthrax infections.

**Symptoms and Signs**

Most patients present within 1 to 6 days of exposure, but for inhalation anthrax, the incubation period can be > 6 wk.

**Cutaneous anthrax** begins as a painless, pruritic, red-brown papule 1 to 10 days after exposure to infective spores. The papule enlarges with a surrounding zone of brawny erythema and marked edema (see Plate 58). Vesiculation and induration are present. Central ulceration follows, with serosanguineous exudation and formation of a black eschar (the malignant pustule). Local lymphadenopathy is common, occasionally with malaise, myalgia, headache, fever, nausea, and vomiting. It may take several weeks for the wound to heal and the edema to resolve.

**GI anthrax** ranges from asymptomatic to fatal. Fever, nausea, vomiting, abdominal pain, and bloody diarrhea are common. Ascites may be present. Intestinal necrosis and septicemia with potentially lethal toxicity ensue.

**Oropharyngeal anthrax** manifests as edematous lesions with central necrotic ulcers on the tonsils, posterior pharyngeal wall, or hard palate. Soft-tissue swelling in the neck is marked, and cervical lymph nodes are enlarged. Symptoms include hoarseness, sore throat, fever, and dysphagia. Airway obstruction may occur.

**Inhalation anthrax** begins insidiously as a flu-like illness. Within a few days, fever worsens, and chest pain and severe respiratory distress develop, followed by cyanosis, shock, and coma. Severe hemorrhagic necrotizing lymphadenitis develops and spreads to adjacent mediastinal structures. Serosanguineous transudation, pulmonary edema, and bloody pleural effusion occur. Typical bronchopneumonia does not occur. Hemorrhagic meningoencephalitis or GI anthrax may develop.

**Diagnosis**

- Gram stain and culture

Occupational and exposure history is important. Cultures and Gram stain of samples from clinically identified sites, including cutaneous or mucosal lesions, pleural fluid, CSF, ascites, or stool, should be done. Sputum examination and Gram stain are unlikely to identify inhalation anthrax because airspace disease is frequently absent. A PCR test and immunohistochemical methods can help. Nasal swab testing for spores in people potentially exposed to inhalation anthrax is not recommended because the predictive value is unknown.

Chest x-ray (or CT) should be done if pulmonary symptoms are present. It typically shows widening of the mediastinum (because of enlarged hemorrhagic lymph nodes) and pleural effusion. Pneumonic infiltrates are uncommon. Lumbar puncture should be done if patients have meningeal signs or a change in mental status. An enzyme-linked immunosorbent assay (ELISA) is available, but confirmation requires a 4-fold
change in antibody titer from acute to convalescent specimens.

**Prognosis**

Mortality in untreated anthrax varies depending on infection type:

- Inhalation and meningeval anthrax: 100%
- Cutaneous anthrax: 10 to 20%
- GI anthrax: About 50%
- Oropharyngeal anthrax: 12.4 to 50%

**Treatment**

- Ciprofloxacin or doxycycline

Cutaneous anthrax without significant edema or systemic symptoms is treated with ciprofloxacin 500 mg (10 to 15 mg/kg for children) po q 12 h or doxycycline 100 mg (2.5 mg/kg for children) po q 12 h for 7 to 10 days. Treatment is extended to 60 days if concomitant inhalation exposure was possible. Children and pregnant or breastfeeding women, who typically should not be given ciprofloxacin or doxycycline, should nonetheless be given one of these drugs; however, if prolonged treatment is needed, they may be switched to amoxicillin 500 mg (15 to 30 mg/kg for children) tid after 14 to 21 days if the organism is shown to be susceptible to penicillin. Mortality is rare with treatment, but the lesion will progress through the eschar phase.

Inhalation and other forms of anthrax, including cutaneous anthrax with significant edema or systemic symptoms, require therapy with 2 or 3 drugs: ciprofloxacin 400 mg (10 to 15 mg/kg for children) IV q 12 h or doxycycline 100 mg (2.5 mg/kg for children) IV q 12 h, plus penicillin, ampicillin, imipenem/cilastatin, meropenem, rifampin, vancomycin, clindamycin, or clarithromycin. Corticosteroids may be useful for meningitis and severe mediastinal edema but have not been evaluated adequately. Ca channel blockers, ACE inhibitors, and specific hyperimmune globulin for *B. anthracis* may be considered. With early diagnosis and intensive support, including mechanical ventilation, fluids, and vasopressors, mortality may be reduced to 50%. If treatment is delayed (usually because the diagnosis is missed), death is likely.

**Drug resistance** is a theoretical concern. Although normally sensitive to penicillin, *B. anthracis* manifests inducible β-lactamases, so single-drug therapy with a penicillin or a cephalosporin is not recommended. Biological warfare researchers may have created strains of anthrax that are resistant to multiple antibiotics, but these strains have not yet been encountered in a clinical situation.

**Prevention**

An anthrax vaccine, composed of a cellfree culture filtrate, is available for people at high risk (eg, military personnel, veterinarians, laboratory technicians, employees of textile mills processing imported goat hair). A separate veterinary vaccine is also available. Repeated vaccination is required to ensure protection. Local reactions from vaccine can occur.

Limited data suggest that cutaneous anthrax does not result in acquired immunity, particularly if early effective antimicrobial therapy was used. Inhalation anthrax may provide some immunity in patients who survive, but data are very limited.

**Postexposure prophylaxis:** Postexposure measures include

- Antibiotics
- Vaccination
Asymptomatic people (including pregnant women and children) exposed to inhaled anthrax require prophylaxis with oral ciprofloxacin 500 mg (10 to 15 mg/kg for children) q 12 h or doxycycline 100 mg (2.5 mg/kg for children) q 12 h for 60 days. If the organism has been shown to be susceptible to penicillin, amoxicillin 500 mg (25 to 30 mg/kg for children) tid is an option when ciprofloxacin and doxycycline are contraindicated.

The Centers for Disease Control and Prevention (CDC) recommends that the anthrax vaccine be administered with antibiotic prophylaxis to patients exposed to anthrax spores. Postexposure antibiotic treatment is extended to 100 days in patients who are vaccinated.

**Diphtheria**

Diphtheria is an acute pharyngeal or cutaneous infection by *Corynebacterium diphtheriae*; some strains produce an exotoxin. Symptoms are either nonspecific skin infections or pseudomembranous pharyngitis followed by myocardial and neural tissue damage secondary to the exotoxin. Diagnosis is clinical and confirmed by culture. Treatment is with antitoxin and penicillin or erythromycin. Childhood vaccination should be routine.

*Corynebacterium diphtheriae* usually infect the nasopharynx (respiratory diphtheria) or skin.

**Diphtheria toxin:** Diphtheria strains infected by a β-phage, which carries a toxin-encoding gene, produce a potent toxin. This toxin first causes inflammation and necrosis of local tissues and then can damage the heart, nerves, and sometimes the kidneys. Nontoxigenic strains of *C. diphtheriae* can also cause nasopharyngeal infection and sometimes systemic disease (eg, endocarditis, septic arthritis).

**Epidemiology and transmission:** Humans are the only known reservoir for *C. diphtheriae*. The organism is spread by

- Respiratory droplets
- Contact with nasopharyngeal secretions
- Contact with infected skin lesions
- Fomites (rare)

A carrier state is common in endemic regions but not in developed countries; most patients who are adequately treated do not become carriers. Patients with clinical illness or asymptomatic carriers may transmit the infection.

Poor personal and community hygiene contributes to the spread of cutaneous diphtheria. In the US, indigent adults living in endemic areas are particularly at risk.

Diphtheria is endemic in many counties in Africa, South America, South and Southeast Asia, the Middle East, Haiti, and the Dominican Republic (travel information about diphtheria is available at the Centers for Disease Control and Prevention [CDC] web site). Diphtheria is now rare in developed countries because childhood immunization is widespread. However, after the breakup of the former Soviet Union, vaccination rates in its constituent countries fell, followed by a marked rise in diphtheria cases.

**Symptoms and Signs**

Symptoms vary depending on where the infection is and on whether the strain produces toxin. Most respiratory infections are caused by toxigenic strains. Cutaneous infections are caused by toxigenic and nontoxigenic strains. Toxin is poorly absorbed from the skin; thus, toxin complications are rare in cutaneous diphtheria.

**Pharyngeal infection:** After an incubation period, which averages 5 days, and a prodromal period of between 12 and 24 h, patients develop mild sore throat, dysphagia, low-grade fever, and tachycardia.
Nausea, emesis, chills, headache, and fever are more common among children.

If a toxigenic strain is involved, the characteristic membrane appears in the tonsillar area. It may initially appear as a white, glossy exudate but typically becomes dirty gray, tough, fibrinous, and adherent so that removal causes bleeding. Local edema may cause a visibly swollen neck (bull neck), hoarseness, stridor, and dyspnea. The membrane may extend to the larynx, trachea, and bronchi and may partially obstruct the airway or suddenly detach, causing complete obstruction.

Mild disease with a serosanguineous or purulent discharge and irritation of the external nares and upper lip occurs in patients who have only nasal diphtheria.

**Skin infection:** Skin lesions usually occur on the extremities and are varied in appearance, often indistinguishable from chronic skin conditions (eg, eczema, psoriasis, impetigo). A few patients have nonhealing, punched-out ulcers, occasionally with a grayish membrane. Pain, tenderness, erythema, and exudate are typical. If exotoxin is produced, lesions may be numb. Concomitant nasopharyngeal infection occurs in 20 to 40% by direct or indirect inoculation with the organism, often from preexisting chronic skin lesions.

**Complications:** The main complications are cardiac and neurologic.

**Myocarditis** is usually evident by the 10th to 14th day but can appear any time during the 1st to 6th wk, even while local respiratory symptoms are subsiding; risk of cardiac toxicity is related to degree of local infection. Insufficient ECG changes occur in 20 to 30% of patients, but atrioventricular dissociation, complete heart block, and ventricular arrhythmias may occur and are associated with a high mortality rate. Heart failure may develop.

**Nervous system toxicity** is uncommon (about 5%) and limited to patients with severe respiratory diphtheria. The toxin causes a demyelinating polyneuropathy that affects cranial and peripheral nerves. The toxic effects usually begin during the 1st wk of illness with loss of ocular accommodation and bulbar palsy, causing dysphagia and nasal regurgitation. Peripheral neuropathy appears during the 3rd to 6th wk. It is both motor and sensory, although motor symptoms predominate. Resolution occurs over many weeks.

**Diagnosis**

- **Gram stain and culture**

Diphtheria needs to be considered in patients with nonspecific findings of pharyngitis, cervical adenopathy, and low-grade fever if they also have systemic toxicity plus hoarseness, palatal paralysis, or stridor. The appearance of the characteristic membrane suggests the diagnosis.

Gram stain of the membrane may reveal gram-positive bacilli with metachromatic (beaded) staining in typical Chinese-character configuration. Material for culture should be obtained from below the membrane, or a portion of membrane itself should be submitted. The laboratory should be notified that *C. diphtheriae* is suspected, so that special culture media (Loeffler's or Tindale's) can be used. In vitro testing for toxin production (modified Elek test) is done to differentiate toxigenic from nontoxigenic strains.

Cutaneous diphtheria should be considered when a patient develops skin lesions during an outbreak of respiratory diphtheria. Swab or biopsy specimens should be cultured. Patients with cutaneous diphtheria may be co-infected with group A streptococci or *Staphylococcus aureus*.

**Treatment**

- **Diphtheria antitoxin**

- **Penicillin or erythromycin**

Symptomatic patients with respiratory diphtheria should be hospitalized in an ICU to monitor for...
Diphtheria antitoxin must be given without waiting for culture confirmation because the antitoxin neutralizes only toxin not yet bound to cells. The use of antitoxin for cutaneous disease, without evidence of respiratory disease, is of questionable value because toxic sequelae have rarely been reported in cutaneous diphtheria; however, some experts recommend it. In the US, antitoxin must be obtained from the CDC at 770-488-7100 (see also the CDC’s notice regarding availability of diphtheria antitoxin). CAUTION: Diphtheria antitoxin is derived from horses; therefore, a skin (or conjunctival) test to rule out sensitivity should always precede administration (see p. 1115). The dose, ranging from 20,000 to 100,000 units IM or IV, is determined by the site and severity of symptoms, duration of the disease, and complications. If an allergic reaction occurs, 0.3 to 1 mL epinephrine 1:1000 (0.01 mL/kg) should immediately be injected sc, IM, or slowly IV. In highly sensitive patients, IV administration of antitoxin is contraindicated.

Antibiotics are required to eradicate the organism and prevent spread; they are not substitutes for antitoxin. Adults may be given either procaine penicillin G 600,000 units IM q 12 h or erythromycin 250 to 500 mg IV or po q 6 h for 14 days. Children should be given procaine penicillin G 12,500 to 25,000 units/kg IM q 12 h or erythromycin 10 to 15 mg/kg (maximum, 2 g/day) po or IV q 6 h. Organism elimination should be documented by 2 consecutive negative throat and/or nasopharyngeal cultures after completion of antibiotics.

Vaccination is required after recovery for patients who had diphtheria because infection does not guarantee immunity.

Recovery from severe diphtheria is slow, and patients must be advised against resuming activities too soon. Even normal physical exertion may harm patients recovering from myocarditis. Overall mortality is 3%; it is higher in those with delayed presentation or myocarditis and in children < 15 yr.

For cutaneous diphtheria, thorough cleansing of the lesion with soap and water and administration of systemic antibiotics for 10 days are recommended.

Prevention

Prevention consists of infection control measures plus

- Vaccination (primary and postexposure)
- Antibiotics

Vaccination: The vaccine for diphtheria contains diphtheria toxoid; it is available only in combination with other vaccines.

Everyone should be vaccinated at prescribed intervals using diphtheria-tetanus-acellular pertussis (DTaP) vaccine for children and tetanus-diphtheria (Td) or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) for adolescents and adults (see p. 1173). (See also the CDC's National Immunization Program 2009 Childhood and Adolescent Immunization Schedule and their Adult Immunization Recommendations.)

After exposure, diphtheria immunization should be updated in all contacts (including hospital personnel) who have not completed a primary series or who have gone > 5 yr since their last booster dose. The vaccine should also be given if immunization status is unknown. An age-appropriate diphtheria toxoid-containing vaccine is used.

Postexposure antibiotics: All close contacts should be examined; surveillance for evidence of disease is maintained for 7 days. Nasopharyngeal and throat cultures for C. diphtheriae should be done regardless of immunization status.
Asymptomatic contacts should be treated with erythromycin 250 to 500 mg (10 to 15 mg/kg for children) po q 6 h for 7 days or, if adherence is uncertain, a single dose of penicillin G benzathine (600,000 units IM for patients < 30 kg and 1.2 million units IM for those > 30 kg).

If cultures are positive, an additional 10-day course of erythromycin should be given; carriers should not be given antitoxin. After 3 days of treatment, carriers can safely resume work while continuing to take antibiotics. Cultures should be repeated; 24 h after the completion of antimicrobial therapy, 2 consecutive culture sets of the nose and throat should be collected 24 h apart. If results are positive, another course of antibiotics is given and cultures are done again.

**Erysipelothricosis**

*Erysipelothricosis* is infection caused by *Erysipelothrix rhusiopathiae*. The most common symptom is erysipeloid, an acute but slowly evolving localized cellulitis. Diagnosis is by culture of a biopsy specimen or occasionally PCR testing. Treatment is with antibiotics.

*Erysipelothrix rhusiopathiae* (formerly *E. insidiosa*) are capsulated, nonsporulating, nonmotile, microaerophilic bacilli with worldwide distribution; they are primarily saprophytes. They may infect a variety of animals, including insects, shellfish, fish, birds, and mammals (especially swine). In humans, infection is chiefly occupational and typically follows a penetrating wound in people who handle edible or nonedible animal matter (eg, infected carcasses, rendered products [grease, fertilizer], bones, shells). Most commonly, patients handle fish or work in slaughterhouses. Infection can also result from cat or dog bites. Nondermal infection is rare, usually occurring as arthritis or endocarditis.

**Symptoms and Signs**

Within 1 wk of injury, a characteristic raised, purplish red, nonvesiculated, indurated, maculopapular rash appears, accompanied by itching and burning. Local swelling, although sharply demarcated, may inhibit use of the hand, the usual site of infection. The lesion's border may slowly extend outward, causing discomfort and disability that may persist for 3 wk. The disease is usually self-limited. Regional lymphadenopathy occurs in about one third of cases. It rarely becomes generalized cutaneous disease, which is characterized by purple skin lesions that expand as the lesion's center clears, plus bullous lesions at the primary or distant sites.

Bacteremia is rare and is more often a primary infection than dissemination from cutaneous lesions. It may result in septic arthritis or infective endocarditis, even in people without known valvular heart disease. Endocarditis tends to involve the aortic valve, and the mortality rate and percentage of patients needing cardiac valve replacement are unusually high.

**Diagnosis**

• **Culture**

Culture of a full-thickness biopsy specimen is superior to needle aspiration of the advancing edge of a lesion because organisms are located only in deeper parts of the skin. Culture of exudate obtained by abrading a florid papule may be diagnostic. Isolation from synovial fluid or blood is necessary for diagnosis of erysipelothrical arthritis or endocarditis. *E. rhusiopathiae* may be misidentified as lactobacilli or enterococci. PCR amplification may aid rapid diagnosis.

**Treatment**

• **Penicillin, ciprofloxacin, or erythromycin**

For *localized cutaneous disease*, usual treatment is penicillin V, ampicillin, ciprofloxacin, or erythromycin (macrolides may not be consistently active) 500 mg po qid for 7 days. Tetracyclines and cephalosporins are also effective. *E. rhusiopathiae* are resistant to sulfonamides and vancomycin.

**Severe diffuse cutaneous or systemic infection** is best treated with IV penicillin G (12 to 20 million
units/day), ceftriaxone (2 g IV once/day), or a fluoroquinolone (eg, ciprofloxacin 400 mg IV q 12 h).

**Endocarditis** is treated with penicillin G 25,000 to 30,000 units/kg IV q 4 h for 4 wk. Cephalosporins and fluoroquinolones are alternatives.

The same drugs and doses are appropriate for arthritis (given for at least 1 wk after defervescence or cessation of effusion), but repeated needle aspiration drainage of the infected joint is also necessary.

**Listeriosis**

(See also Neonatal Listeriosis on p. 2829.)

Listeriosis is bacteremia, meningitis, cerebritis, dermatitis, an oculoglandular syndrome, intrauterine and neonatal infections, or rarely endocarditis caused by *Listeria* sp. Symptoms vary with the organ system affected and include intrauterine death in perinatal infection. Diagnosis is by laboratory isolation. Treatment includes penicillin, ampicillin (often with aminoglycosides), and trimethoprim/sulfamethoxazole.

*Listeria* are small, non-acid-fast, noncapsulated, nonsporulating, β-hemolytic, aerobic, and facultative anaerobic gram-positive bacilli that have characteristic tumbling motility. They are present worldwide in the environment and in the gut of humans, nonhuman mammals, birds, arachnids, and crustaceans. There are several species of *Listeria*, but *L. monocytogenes* is the only pathogen in humans. Incidence in the US is ≥ 7 cases/1,000,000 people/yr, peaking in the summer; attack rates are highest in neonates and in adults ≥ 60 yr.

Because *L. monocytogenes* is ubiquitous in the environment, opportunities for contamination are numerous during the food production process. Infection usually occurs via ingestion of contaminated dairy products, raw vegetables, or meats and is favored by the ability of *L. monocytogenes* to survive and grow at refrigerator temperatures. Infection may also occur by direct contact and during slaughter of infected animals.

**Risk factors:** Glucocorticoid therapy is the most important predisposing factor in nonpregnant adults. Because *L. monocytogenes* multiplies intracellularly, control of listeriosis requires cell-mediated immunity; thus, immunocompromised patients are at high risk. Pregnant women are also at increased risk of developing listerial infection, which can spread antepartum and intrapartum from mother to child and can cause abortion or early infant death.

**Symptoms and Signs**

Primary listerial bacteremia is rare and causes high fever without localizing symptoms and signs. Endocarditis, peritonitis, osteomyelitis, cholecystitis, and pleuropneumonia may occur. Listerial bacteremia during pregnancy can cause intrauterine infection, chorioamnionitis, premature labor, fetal death, or neonatal infections.

Meningitis is due to *Listeria* in about 20% of cases in neonates and in patients > 60 yr. Twenty percent of cases progress to cerebritis, either diffuse encephalitis or, rarely, rhombencephalitis and abscesses; rhombencephalitis manifests as altered consciousness, cranial nerve palsies, cerebellar signs, and motor or sensory loss.

Oculoglandular listeriosis can cause ophthalmitis and regional lymph node enlargement. It may follow conjunctival inoculation and, if untreated, may progress to bacteremia and meningitis.

**Diagnosis**

- **Culture**

Listerial infections are diagnosed by culture of blood or CSF. The laboratory must be informed when *L. monocytogenes* is suspected because the organism is easily confused with diphtheroids. In all listerial
infections, IgG agglutinin titers peak 2 to 4 wk after onset.

Treatment

• Ampicillin, usually with an aminoglycoside

Listerial meningitis is best treated with ampicillin 2 g IV q 4 h. Most authorities recommend adding an aminoglycoside based on synergy in vitro. Children receive ampicillin 50 to 100 mg/kg IV q 6 h. Cephalosporins are not effective.

Endocarditis and primary listerial bacteremia are treated with ampicillin 2 g IV q 4 h plus gentamicin (for synergy) given for 6 wk (for endocarditis) or 2 wk (for bacteremia) beyond defervescence. Oculoglandular listeriosis and listerial dermatitis should respond to erythromycin 10 mg/kg po q 6 h, continued until 1 wk after defervescence. Cephalosporins have no in vitro activity and should not be used. Trimethoprim/sulfamethoxazole 5/25 mg/kg IV q 8 h is an alternative.

Nocardiosis

Nocardiosis is an acute or chronic, often disseminated, suppurative or granulomatous infection caused by various aerobic soil saprophytes of the genus *Nocardia*. Pneumonia is typical, but skin and CNS infections are common. Diagnosis is by culture and special stains. Treatment is usually with sulfonamides.

*Nocardia* are obligate aerobic, partially acidfast, beaded, branching, gram-positive bacilli. Several *Nocardia* sp, in the family Actinomycetaceae, cause human disease.

*N. asteroides* is the most common human pathogen; it usually causes pulmonary and disseminated infection.

*N. brasiliensis* most commonly causes skin infection, particularly in tropical climates. Infection is via inhalation or by direct inoculation of the skin.

Other *Nocardia* sp sometimes cause localized or, occasionally, systemic infections.

Nocardiosis occurs worldwide in all age groups, but incidence is higher in older adults, especially men. Person-to-person spread is rare.

**Risk factors:** Lymphoreticular cancers, organ transplantation, high-dose corticosteroid or other immunosuppressive therapy, and underlying pulmonary disease are predisposing factors, but about one half of patients have no preexisting disease. Nocardiosis is also an opportunistic infection in patients with advanced HIV infection.

**Symptoms and Signs**

Nocardiosis usually begins as a subacute pulmonary infection that resembles actinomycosis, but *Nocardia* are more likely to disseminate locally or hematogenously. Dissemination with abscess formation may involve any organ but most commonly affects the brain, skin, kidneys, bone, or muscle.

The most common symptoms of pulmonary involvement—cough, fever, chills, chest pain, weakness, anorexia, and weight loss—are nonspecific and may resemble those of TB or suppurative pneumonia. Pleural effusion may also occur. Metastatic brain abscesses, occurring in 30 to 50% of cases, usually cause severe headaches and focal neurologic abnormalities. Infection may be acute, subacute, or chronic.

Skin or subcutaneous abscesses occur frequently, sometimes as a primary local inoculation. They may appear as firm cellulitis, a lymphocutaneous syndrome, or an actinomycetoma. The lymphocutaneous syndrome consists of a primary pyoderma lesion and lymphatic nodules resembling sporotrichosis. An actinomycetoma begins as a nodule, suppurates, spreads along fascial planes, and drains through
chronic fistulas.

**Diagnosis**

- Microscopic examination or culture

Diagnosis is by identification of *Nocardia* sp in tissue or in culture of samples from localized lesions identified by physical examination, x-ray, or other imaging studies. Clumps of beaded, branching filaments of gram-positive bacteria (which may be weakly acid-fast) are often seen. *Nocardia* do not have a clubbed appearance, as do *Actinomyces israelii*.

**Prognosis**

Without treatment, pulmonary and disseminated nocardiosis are usually fatal. Among patients who are treated with appropriate antibiotics, the mortality rate is highest (> 50%) in immunocompromised patients with disseminated infections and lowest (about 10%) in immunocompetent patients with lesions restricted to the lungs. Cure rates for patients with skin infection are usually > 95%.

**Treatment**

- Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole or high doses of a sulfonamide alone (sulfamethoxazole or sulfisoxazole) are used. Because most cases respond slowly, a dose that maintains a sulfonamide blood concentration of 12 to 15 mg/dL (eg, with sulfadiazine 4 to 6 g/day po) must be continued for several months.

When sulfonamide hypersensitivity or refractory infection is present, amikacin, a tetracycline (particularly minocycline), imipenem cilastatin, ceftriaxone, cefotaxime, extended-spectrum fluoroquinolones (eg, moxifloxacin), or cycloserine can be used. In vitro susceptibility data should guide the choice of alternative drugs.
Chapter 135. Gram-Negative Bacilli

Introduction

Gram-negative bacilli are responsible for numerous diseases. Some are commensal organisms present among normal intestinal flora. These commensal organisms plus others from animal or environmental reservoirs may cause disease. UTIs, diarrhea, peritonitis, and bloodstream infections are commonly caused by gram-negative bacilli. Plague, cholera, and typhoid fever are rare but serious gram-negative infections.

Bartonella Infections

*Bartonella* sp are gram-negative bacteria previously classified as Rickettsiae. They cause several uncommon diseases: cat-scratch disease, an acute febrile anemia, a chronic cutaneous eruption, and disseminated disease in immunocompromised hosts (see Table 135-1).

Cat-Scratch Disease

*(Cat-Scratch Fever)*

Cat-scratch disease is infection caused by *Bartonella henselae*. Symptoms are a local papule and regional lymphadenitis. Diagnosis is clinical and confirmed by biopsy. Treatment is with local heat application and analgesics.

The domestic cat is a major reservoir for *B. henselae*. The prevalence of *B. henselae* antibodies in US cats is 14 to 50%. About 99% of patients report contact with cats, most of which are healthy. The cat flea may be an additional vector. Children are most often affected.

Symptoms and Signs

Within 3 to 10 days after a scratch, most patients develop an erythematous, crusted papule (rarely, a pustule) at the scratch site. Regional lymphadenopathy develops within 2 wk. The nodes are initially firm and tender, later becoming fluctuant, and may drain with fistula formation. Fever, malaise, headache, and anorexia may accompany lymphadenopathy.

Unusual manifestations occur in 5 to 14% of patients: Parinaud’s oculoglandular syndrome (conjunctivitis associated with palpable preauricular nodes) in 6%, neurologic manifestations (encephalopathy, seizures, neuroretinitis, myelitis, paraplegia, cerebral arteritis) in 2%, and hepatosplenic granulomatous disease in <1%. Severe disseminated illness may occur in patients with AIDS.

Lymphadenopathy subsides spontaneously within 2 to 5 mo. Complete recovery is usual, except in severe neurologic or hepatosplenic disease, which may be fatal or have residual effects.

Diagnosis

Diagnosis is confirmed by positive serum Ab titers or PCR testing of samples from lymph node aspirates. Immunocompromised patients and patients with systemic symptoms should also have blood cultures. Lymph node aspirates are rarely culture-positive.

Treatment

• Local heat and analgesics
Sometimes antibiotics for immunocompromised patients

Treatment in immunocompetent patients is local heat application and analgesics. If a lymph node is fluctuant, needle aspiration usually relieves the pain.

Antibiotic treatment is not clearly beneficial and generally should not be given for localized infection. Ciprofloxacin, gentamicin, or doxycycline may be used for bacteremia in AIDS patients. Prolonged therapy is usually necessary (eg, weeks to months) for bacteremia to clear. In vitro antibiotic susceptibilities often do not correlate with clinical results; testing often shows sensitivity to trimethoprim/sulfamethoxazole (TMP/SMX) and cephalosporins, but these drugs are clinically ineffective.

Oroya Fever and Verruga Peruana

Oroya fever and verruga peruana are infections caused by *Bartonella bacilliformis*. Oroya fever occurs after initial exposure; verruga peruana occurs after recovery from the primary infection.

Endemic only to the Andes Mountains in Colombia, Ecuador, and Peru, both diseases are passed from human to human by the *Phlebotomus* sandfly.

**Oroya fever**: Symptoms include fever and profound anemia, which may be sudden or indolent in onset. The anemia is primarily hemolytic, but myelosuppression also occurs. Muscle and joint pain, severe headache, and often delirium and coma may occur. Superimposed bacteremia caused by *Salmonella* or other coliform organisms may occur. Mortality rates may exceed 50% in untreated patients.

Diagnosis is confirmed by blood cultures. Because Oroya fever is often complicated by *Salmonella* bacteremia, chloramphenicol 500 to 1000 mg po q 6 h for 7 days is the treatment of choice; some clinicians add another antibiotic, typically a β-lactam, but TMP/SMX, macrolides, and fluoroquinolones have also been used successfully.

**Verruga peruana**: This disorder manifests as multiple skin lesions that strongly resemble bacillary angiomatosis, usually occurring on the limbs and face. The lesions may persist for months and may be accompanied by pain and fever.

Verruga peruana is diagnosed by its appearance and sometimes by biopsy showing dermal angiogenesis. Treatment with most antibiotics produces remission, but relapse is common and requires prolonged therapy. Typical treatment is streptomycin 15 to 20 mg/kg IM once/day for 10 days or rifampin 10 mg/kg po once/day for 10 to 14 days. Ciprofloxacin 500 mg po bid for 7 to 10 days has been used successfully, as has azithromycin.

Bacillary Angiomatosis

*(Epithelioid Angiomatosis)*

**Bacillary angiomatosis is skin infection caused by *Bartonella henselae* or *B. quintana*.**

Bacillary angiomatosis almost always occurs in immunocompromised people and is characterized by protuberant, reddish, berry-like lesions on the skin, often surrounded by a collar of scale. Lesions bleed profusely if traumatized. They may resemble Kaposi’s sarcoma or pyogenic granulomas. Infection is spread by lice and ticks and probably by fleas from household cats. Disease may spread throughout the reticuloendothelial system, particularly in AIDS patients.

Diagnosis relies on histopathology of the skin lesions, cultures, and PCR analysis. The laboratory should be notified that *Bartonella* is suspected because special stains and prolonged culture growth are necessary.

Treatment is with erythromycin 500 mg po q 6 h or doxycycline 100 mg po q 12 h, continued for at least 3 mo.
Trench Fever

(Wolhynia, Shin Bone, or Quintan Fever)

Trench fever is a louse- or tick-borne disease caused by *Bartonella quintana* or *B. henselae* and observed originally in military populations during World Wars I and II. Symptoms are an acute, recurring febrile illness, occasionally with a rash. Diagnosis is by blood culture. Treatment is with a macrolide or doxycycline.

Humans are the only reservoir. *B. quintana* is transmitted to humans when feces from infected lice are rubbed into abraded skin or the conjunctiva. *B. henselae* is transmitted by tick bites. Trench fever is endemic in Mexico, Tunisia, Eritrea, Poland, and the former Soviet Union and is reappearing in the homeless population in the US.

After a 14- to 30-day incubation period, onset is sudden, with fever, weakness, dizziness, headache, and severe back and leg pains. Fever may reach 40.5° C and persist for 5 to 6 days. In about half the cases, fever recurs 1 to 8 times at 5- to 6-day intervals. A transient macular or papular rash and, occasionally, hepatomegaly and splenomegaly occur. Relapses are common and have occurred up to 10 yr after the initial attack.

**Diagnosis**

Trench fever should be suspected in people living where louse infestation is heavy. Leptospirosis, typhus, relapsing fever, and malaria must be considered.

The organism is identified by blood culture, although growth may take 1 to 4 wk. The disease is marked by persistent bacteremia during the initial attack, during relapses, and throughout the asymptomatic periods between relapses.

**Treatment**

Although recovery is usually complete in 1 to 2 mo and mortality is negligible, bacteremia may persist for months after clinical recovery, and prolonged (> 1 mo) macrolide or doxycycline treatment may be needed. Body lice must be controlled (see p. 711). Patients with chronic bacteremia should be monitored for signs of endocarditis.

Brucellosis

(Undulant, Malta, Mediterranean, or Gibraltar Fever)

Brucellosis is caused by *Brucella* sp. Symptoms begin as an acute febrile illness with few or no localized signs and progress to a chronic stage with relapses of fever, weakness, sweats, and vague aches and pains. Diagnosis is by culture, usually from the blood. Optimal treatment usually requires 2 antibiotics—doxycycline or trimethoprim/sulfamethoxazole plus streptomycin or rifampin.

The causative organisms of human brucellosis are *B. abortus* (from cattle), *B. melitensis* (from sheep and goats), and *B. suis* (from hogs). *B. canis* (from dogs) has caused sporadic infections. The most common sources of infection are farm animals and raw dairy products. Deer, bison, horses, moose, caribou, hares, chickens, and desert rats may also be infected; humans can acquire the infection from these animals as well.

Brucellosis is acquired by direct contact with secretions and excretions of infected animals and by ingesting undercooked meat, raw milk, or milk products containing viable organisms. Brucellosis is rarely transmitted from person to person. Most prevalent in rural areas, brucellosis is an occupational disease of meatpackers, veterinarians, hunters, farmers, and livestock producers. Brucellosis is rare in the US, Europe, and Canada, but cases occur in the Middle East, Mediterranean regions, Mexico, and Central America.
Patients with acute, uncomplicated brucellosis usually recover in 2 to 3 wk, even without treatment. Some go on to subacute, intermittent, or chronic disease.

**Complications:** Complications are rare but include subacute bacterial endocarditis, meningitis, encephalitis, neuritis, orchitis, cholecystitis, hepatic suppuration, and osteomyelitis (particularly sacroiliac or vertebral).

**Symptoms and Signs**

The incubation period varies from 5 days to several months and averages 2 wk. Onset may be sudden, with chills and fever, severe headache, joint and low back pain, malaise, and occasionally diarrhea. Or onset may be insidious, with mild prodromal malaise, muscular pain, headache, and pain in the back of the neck, followed by a rise in evening temperature. As the disease progresses, temperature increases to 40 to 41° C, then subsides gradually to normal or near-normal with profuse sweating in the morning.

Typically, intermittent fever persists for 1 to 5 wk, followed by a 2- to 14-day remission when symptoms are greatly diminished or absent. In some patients, fever may be transient. In others, the febrile phase recurs once or repeatedly in waves (undulations) and remissions over months or years and may manifest as FUO.

After the initial febrile phase, anorexia, weight loss, abdominal and joint pain, headache, backache, weakness, irritability, insomnia, depression, and emotional instability may occur. Constipation is usually pronounced. Splenomegaly appears, and lymph nodes may be slightly or moderately enlarged. Up to 50% of patients have hepatomegaly.

**Diagnosis**

- Blood cultures
- Acute and convalescent serologic testing

Blood cultures should be obtained; growth may take > 7 days, so the laboratory should be notified of the suspicion of brucellosis.

Acute and convalescent sera should be obtained 3 wk apart. A 4-fold increase or an acute titer of 1:160 or higher is considered diagnostic, particularly if a history of exposure and characteristic clinical findings are present. The WBC count is normal or reduced with relative or absolute lymphocytosis during the acute phase.

**Treatment**

- Doxycycline plus streptomycin

Activity should be restricted in acute cases, with bed rest recommended during febrile episodes.

If antibiotics are given, combination therapy is preferred. Doxycycline 100 mg po bid for 3 to 6 wk plus streptomycin 1 g IM q 12 to 24 h for 14 days lowers the rate of relapses. In children < 8 yr, trimethoprim/sulfamethoxazole (TMP/SMX) and either IM streptomycin or oral rifampin for 4 to 6 wk have been used. Severe musculoskeletal pains, especially over the spine, may require analgesia.

Pasteurization of milk helps prevent brucellosis. Cheese that is made from unpasteurized milk and is aged < 3 mo may be contaminated. People handling animals or carcasses likely to be infected should wear goggles and rubber gloves and protect skin breaks from exposure. Programs to detect infection in animals, eliminate infected animals, and vaccinate young seronegative cattle and swine are required in the US and in several other countries. Immunity after human infection is short-lived, lasting about 2 yr.

**Campylobacter and Related Infections**
Campylobacter infections commonly cause diarrhea and occasionally bacteremia, with consequent endocarditis, osteomyelitis, or septic arthritis.

Campylobacter sp are motile, curved, microaerophilic, gram-negative bacilli that normally inhabit the GI tract of many domestic animals and fowl. Several species are human pathogens. The major pathogens are C. jejuni and C. fetus. C. jejuni causes diarrhea in all age groups, although peak incidence appears to be from age 1 to 5 yr. C. jejuni accounts for more cases of diarrhea in the US than Salmonella and Shigella combined. C. fetus and several others typically cause bacteremia in adults, more often when underlying predisposing diseases, such as diabetes, cirrhosis, or cancer, are present. In patients with immunoglobulin deficiencies, these organisms may cause difficult-to-treat, relapsing infections. C. jejuni can cause meningitis in infants.

Contact with infected animals and ingestion of contaminated food (especially under-cooked poultry) or water have been implicated in outbreaks. However, in sporadic cases, the source of the infecting organism is frequently obscure.

Complications: C. jejuni diarrheal illness is associated with subsequent development (up to 30% of cases) of Guillain-Barre syndrome because of cross-reaction between C. jejuni antibodies and surface components of peripheral nerves.

Postinfectious (reactive) arthritis may occur in HLA-B27-positive patients a few days to several weeks after an episode of C. jejuni diarrhea.

Focal extraintestinal infections (eg, endocarditis, meningitis, septic arthritis) occur rarely.

Symptoms and Signs

The most common manifestation is watery and sometimes bloody diarrhea. Fever (38 to 40° C), which follows a relapsing or intermittent course, is the only constant feature of systemic Campylobacter infection, although abdominal pain and hepatosplenomegaly are frequent.

Patients can also present with subacute bacterial endocarditis, reactive arthritis, meningitis, or an indolent FUO rather than with diarrheal illness. Joint involvement with reactive arthritis is usually monoarticular, affecting the knees; symptoms resolve spontaneously over 1 wk to several months.

Diagnosis

• Stool culture
• Sometimes blood cultures

Diagnosis, particularly to differentiate Campylobacter infection from ulcerative colitis (see p. 172), requires microbiologic evaluation. Stool culture should be obtained plus blood cultures for patients with signs of focal infection or serious systemic illness. WBCs are present in stained smears of stool.

Treatment

• Sometimes erythromycin

Most enteric infections resolve spontaneously; if they do not, erythromycin 500 mg po q 6 h for 5 days may be helpful. For patients with extraintestinal infections, antibiotics (eg, imipenem, gentamicin, ampicillin, erythromycin) should be given for 2 to 4 wk to prevent relapses.

Cholera

Cholera is an acute infection of the small bowel by Vibrio cholerae, which secretes a toxin that causes copious watery diarrhea, leading to dehydration, oliguria, and circulatory collapse.
Infection is typically through contaminated water or seafood. Diagnosis is by culture or serology. Treatment is vigorous rehydration and electrolyte replacement plus doxycycline.

The causative organism, \textit{V. cholerae}, serogroups 01 and 0139, is a short, curved, motile, aerobic bacillus that produces enterotoxin, a protein that induces hypersecretion of an isotonic electrolyte solution by the small-bowel mucosa. Both the El Tor and classic biotypes of \textit{V. cholerae} can cause severe disease. However, mild or asymptomatic infection is much more common with the El Tor biotype.

Cholera is spread by ingestion of water, seafood, or other foods contaminated by the excrement of people with symptomatic or asymptomatic infection. Cholera is endemic in portions of Asia, the Middle East, Africa, South and Central America, and the Gulf Coast of the US. Cases transported into Europe, Japan, and Australia have caused localized outbreaks. In endemic areas, outbreaks usually occur during warm months. The incidence is highest in children. In newly affected areas, epidemics may occur during any season, and all ages are equally susceptible. A milder form of gastroenteritis is caused by noncholera vibrios (see p. 1249).

Susceptibility to infection varies and is greater for people with blood type O. Because vibrios are sensitive to gastric acid, hypochlorhydria and achlorhydria are predisposing factors. People living in endemic areas gradually acquire a natural immunity.

**Symptoms and Signs**

The incubation period is 1 to 3 days. Cholera can be subclinical, a mild and uncomplicated episode of diarrhea, or a fulminant, potentially lethal disease. Abrupt, painless, watery diarrhea and vomiting are usually the initial symptoms. Significant nausea is typically absent. Stool loss in adults may exceed 1 L/h but is usually much less. The resultant severe water and electrolyte depletion leads to intense thirst, oliguria, muscle cramps, weakness, and marked loss of tissue turgor, with sunken eyes and wrinkling of skin on the fingers. Hypovolemia, hypoosmolality, oliguria and anuria, and severe metabolic acidosis with K+ depletion (but normal serum Na+ concentration) occur. If cholera is untreated, circulatory collapse with cyanosis and stupor may follow. Prolonged hypovolemia can cause renal tubular necrosis.

Most patients are free of \textit{V. cholerae} within 2 wk after cessation of diarrhea; chronic biliary tract carriers are rare.

**Diagnosis**

- Stool culture and serotyping

Diagnosis is confirmed by stool culture and subsequent serotyping. Cholera can be distinguished from clinically similar disease caused by enterotoxin-producing strains of \textit{Escherichia coli} and occasionally by \textit{Salmonella} and \textit{Shigella}. Serum electrolytes, BUN, and creatinine should be measured.

**Treatment**

- Fluid replacement

- Doxycycline, furazolidone, or trimethoprim/sulfamethoxazole (TMP/SMX), depending on results of susceptibility testing

Replacement of fluid loss is essential. Mild cases can be treated with standard oral replacement formulas (see p. 2809). Rapid correction of severe hypovolemia is lifesaving. Prevention or correction of metabolic acidosis and hypokalemia is important. For hypovolemic and severely dehydrated patients, IV replacement with isotonic fluids should be used (for details on fluid resuscitation, see pp. 2297 and 2807). Water should also be given freely by mouth. To replace K+ losses, KCl 10 to 15 mEq/L can be added to the IV solution, or KHCO$_3$ 1 mL/kg po of a 100-g/L solution can be given qid. K+ replacement is especially important for children, who tolerate hypokalemia poorly.
Once intravascular volume is restored, amounts for replacement of continuing losses should equal measured stool volume. Adequacy of hydration is confirmed by frequent clinical evaluation (pulse rate and strength, skin turgor, urine output). Plasma, plasma volume expanders, and vasopressors should \textit{not} be used in place of water and electrolytes.

Oral glucose-electrolyte solution is effective in replacing stool losses and may be used after initial IV rehydration, and it may be the only means of rehydration in epidemic areas where supplies of parenteral fluids are limited. Patients who have mild or moderate dehydration and who can drink may be rehydrated exclusively with the oral solution (about 75 mL/kg in 4 h). Those with more severe dehydration need more and may need to receive the fluid by nasogastric tube. The oral solution recommended by the WHO contains 20 g glucose, 3.5 g NaCl, 2.9 g trisodium citrate and dihydrate (or 2.5 g NaHCO$_3$), and 1.5 g KCl per liter of drinking water. This solution should be continued ad libitum after rehydration in amounts at least equal to continuing stool and vomitus losses. Solid food should be given only after vomiting stops and appetite returns.

Early treatment with an effective oral antimicrobial eradicates vibrios, reduces stool volume by 50%, and stops diarrhea within 48 h. The choice of antimicrobial should be based on the susceptibility of \textit{V. cholerae} isolated from the community.

Drugs effective for susceptible strains include

- Doxycycline: For adults, a single dose of 300 mg po
- Furazolidone: For adults, 100 mg po qid for 72 h; for children, 1.5 mg/kg qid for 72 h
- TMP/SMX: For adults, one double-strength tablet bid; for children, 5 mg/kg (of the TMP component) bid for 72 h

**Prevention**

For control of cholera, human excrement must be correctly disposed of, and water supplies purified. In endemic regions, drinking water should be boiled or chlorinated, and vegetables and fish cooked thoroughly.

A killed oral whole cell-B subunit vaccine (not available in the US) provides 85% protection against the 01 serogroup for 4 to 6 mo. Protection lasts up to 3 yr in adults but wanes rapidly in children and is greater for the classic than for the El Tor biotype. There is no cross-protection between 01 and 0139 serogroups. Vaccines proven effective against both sero-groups are a future goal. The parenteral cholera vaccine is not recommended because of its low efficacy, short duration (43% for 3 mo), and frequent severe adverse effects.

Prompt prophylaxis with doxycycline 100 mg po q 12 h in adults (TMP/SMX can be used for prophylaxis in children < 9 yr) can decrease secondary cases among household contacts of cholera patients, but mass prophylaxis is inappropriate and some strains are not sensitive.

**Noncholera \textit{Vibrio} Infections**

Noncholera vibrios include \textit{Vibrio parahaemolyticus}, \textit{V. mimicus}, \textit{V. alginolyticus}, \textit{V. hollisae}, and \textit{V. vulnificus}; these vibrios are sometimes called nonagglutinable vibrios (ie, they do not agglutinate with serum from cholera patients). They typically inhabit warm salt water or mixed salt and fresh water (eg, in estuaries).

\textit{V. parahaemolyticus}, \textit{V. mimicus}, and \textit{V. hollisae} usually cause food-borne outbreaks of diarrhea, typically involving inadequately cooked seafood (usually shellfish). \textit{V. parahaemolyticus} infections typically occur in Japan and in coastal areas of the US. The organisms damage intestinal mucosa but do not produce enterotoxin or invade the bloodstream. Also, wound infection may develop when
contaminated warm seawater enters a minor wound.

*V. alginolyticus* and *V. vulnificus* can cause serious wound infection; neither causes enteritis. *V. vulnificus*, when ingested by a compromised host (often someone with chronic liver disease or immunodeficiency), can cross the intestinal mucosa without causing enteritis and cause septicemia with a high mortality rate; occasionally, otherwise healthy people develop such infections.

**Symptoms and Signs**

After a 15- to 24-h incubation period, enteric illness begins suddenly with cramping abdominal pain, large amounts of watery diarrhea (stools may be bloody and contain PMNs), tenesmus, weakness, and sometimes nausea, vomiting, and low-grade fever. Symptoms subside spontaneously in 24 to 48 h.

Cellulitis can rapidly develop in contaminated wounds in some cases (typically those involving *V. vulnificus*) and progress to necrotizing fasciitis with typical hemorrhagic, bullous lesions.

*V. vulnificus* septicemia causes shock, bullous skin lesions, and often manifestations of disseminated intravascular coagulation (eg, thrombocytopenia, hemorrhage); mortality rate is high.

**Diagnosis**

- **Cultures**

Wound and bloodstream infections are readily diagnosed with routine cultures. When enteric infection is suspected, *Vibrio* organisms can be cultured from stool on thiosulfate citrate bile salts sucrose medium. Contaminated seafood also yields positive cultures.

**Treatment**

- **Ciprofloxacin or doxycycline for enteric infection**

- **Antibiotics and often debridement for wound infection**

Noncholera *Vibrio* enteric infections can be treated with a single dose of ciprofloxacin 1 g po or doxycycline 300 mg po. For diarrhea, close attention to volume repletion and replacement of lost electrolytes are needed.

For wound infections, antibiotics are used—typically, doxycycline 100 mg po q 12 h, with or without a 3rd-generation cephalosporin for severe wound infection or septicemia. Patients with necrotizing fasciitis require surgical debridement.

**Escherichia Coli Infections**

*Escherichia coli* are the most numerous aerobic commensal inhabitants of the large intestine. Certain strains cause diarrhea, and all can cause infection when they invade sterile sites (eg, the urinary tract). Diagnosis is by standard culture techniques. Toxin assays may help identify the cause of diarrhea. Treatment with antibiotics is guided by susceptibility testing.

**Diseases caused by *E. coli***: Most commonly, *E. coli* cause UTIs, which usually represent ascending infection (ie, from the perineum via the urethra).

*E. coli* normally inhabit the GI tract; however, some strains have acquired genes that enable them to cause intestinal infection. When ingested, the following strains can cause diarrhea:

- **Enterohemorrhagic**: These strains (eg, type O157:H7—see below) produce several cytotoxins, neurotoxins, and enterotoxins, including Shiga toxin, and cause bloody diarrhea; hemolytic-uremic syndrome develops in 2 to 7% of cases (see p. 961). Such strains have most often been acquired from undercooked ground beef but may also be acquired from infected people by the fecaloral route when...
hygiene is inadequate.

- Enterotoxigenic: These strains can cause watery diarrhea, particularly in infants and travelers (see p. 150).
- Enteroinvasive: These strains can cause inflammatory diarrhea.
- Enteropathogenic: These strains can cause watery diarrhea, particularly in infants.
- Enteroaggregative: Some strains are emerging as potentially important causes of persistent diarrhea in patients with AIDS and in children in tropical areas.

Other strains are capable of causing extra-intestinal infection if normal intestinal anatomic barriers are disrupted (eg, by ischemia, inflammatory bowel disease, or trauma), in which case the organism may spread to adjacent structures or invade the bloodstream. Hepatobiliary, peritoneal, cutaneous, and pulmonary infections also occur. *E. coli* bacteraemia may also occur without an evident portal of entry.

In neonates, particularly preterm infants, *E. coli* bacteraemia and meningitis (caused by strains with the K1 capsule, a marker for neuroinvasiveness) are common (see Neonatal Bacterial Meningitis on p. 2830 and Neonatal Sepsis on p. 2832).

**Diagnosis**

- **Culture**

Samples of blood, stool, or other clinical material are sent for culture. If an enterohemorrhagic strain is suspected, the laboratory must be notified because special culture media are required.

**Treatment**

- **Various antibiotics depending on site of infection and susceptibility testing**

Treatment must be started empirically based on the site and severity of infection (eg, mild bladder infection, urosepsis) and then modified based on antibiotic susceptibility testing. Many strains are resistant to ampicillin and tetracyclines, so other drugs should be used; they include ticarcillin, piperacillin, cephalosporins, aminoglycosides, trimethoprim/sulfamethoxazole (TMP/SMX), and fluoroquinolones.

Surgery may be required to drain pus, debride necrotic lesions, or remove foreign bodies.

**E. coli O157:H7 Infection**

*E. coli* O157:H7 typically causes acute bloody diarrhea, which may lead to hemolytic-uremic syndrome. Symptoms are abdominal cramps and diarrhea that may be grossly bloody. Fever is not prominent. Diagnosis is by stool culture and toxin assay. Treatment is supportive; antibiotic use is controversial.

**Epidemiology**

Although > 100 serotypes of *E. coli* produce Shiga and Shiga-like toxins, *E. coli* O157:H7 is the most common in North America. In some parts of the US and Canada, *E. coli* O157:H7 infection may be a more common cause of bloody diarrhea than shigellosis or salmonellosis. *E. coli* O157:H7 infection can occur in people of all ages, although severe infection is most common among children and the elderly.

*E. coli* O157:H7 has a bovine reservoir, so outbreaks and sporadic cases occur after ingestion of undercooked beef (especially ground beef) or unpasteurized milk. Food or water contaminated with cow manure or raw ground beef can also transmit infection. The organism can also be transmitted by the fecal-oral route, especially among infants in diapers (eg, via inadequately chlorinated children's wading pools).
After ingestion, *E. coli* O157:H7 and similar strains of *E. coli* (termed enterohemorrhagic *E. coli*) produce high levels of various toxins in the large intestine; these toxins are closely related to the potent cytotoxins produced by *Shigella dysenteriae* type 1. These toxins appear to directly damage mucosal cells and vascular endothelial cells in the gut wall. If absorbed, they exert toxic effects on other vascular endothelia (eg, renal).

**Symptoms and Signs**

*E. coli* O157:H7 infection typically begins acutely with severe abdominal cramps and watery diarrhea that may become grossly bloody within 24 h. Some patients report diarrhea as being “all blood and no stool,” which has given rise to the term hemorrhagic colitis. Fever, usually absent or low grade, occasionally reaches 39° C. Diarrhea may last 1 to 8 days in uncomplicated infections.

About 5% of cases (mostly children < 5 yr and adults > 60 yr) are complicated by hemolytic-uremic syndrome (see p. 961), which typically develops in the 2nd wk of illness. Death may occur, especially in the elderly, with or without this complication.

**Diagnosis**

- Stool cultures
- Sometimes rapid stool assay for Shiga toxin

*E. coli* O157:H7 infection should be distinguished from other infectious diarrheas by isolating the organism from stool cultures. Often, the clinician must specifically ask the laboratory to test for the organism. Because bloody diarrhea and severe abdominal pain without fever suggest various noninfectious etiologies, *E. coli* O157:H7 infection should be considered in suspected cases of ischemic colitis, intussusception, and inflammatory bowel disease. A rapid stool assay for Shiga toxin may help. Patients at risk of noninfectious diarrheas may need sigmoidoscopy. If done, sigmoidoscopy may reveal erythema and edema; barium enema typically shows evidence of edema with thumbprinting.

**Treatment**

- Supportive care

The mainstay of treatment is supportive. Although *E. coli* is sensitive to most commonly used antibiotics, antibiotics have not been shown to alleviate symptoms, reduce carriage of the organism, or prevent hemolytic-uremic syndrome. Fluoroquinolones are suspected of increasing release of enterotoxins.

In the week after infection, patients at high risk of developing hemolytic-uremic syndrome (eg, children < 5 yr, the elderly) should be observed for early signs, such as proteinuria, hematuria, red cell casts, and rising serum creatinine. Edema and hypertension develop later. Patients who develop complications are likely to require intensive care, including dialysis and other specific therapies, at a tertiary medical center.

**Prevention**

Correct disposal of the stool of infected people, good hygiene, and careful hand washing with soap limit spread of infection. Preventive measures that may be effective in the day care setting include grouping children known to be infected with *E. coli* O157:H7 or requiring 2 negative stool cultures before allowing infected children to attend. Pasteurization of milk and thorough cooking of beef prevent food-borne transmission.

Reporting outbreaks of bloody diarrhea to public health authorities is important because intervention can prevent additional infections.

*Haemophilus Infections*
*Haemophilus* sp cause numerous mild and serious infections, including bacteremia, meningitis, pneumonia, otitis media, cellulitis, and epiglottitis. Diagnosis is by culture and serotyping. Treatment is with antibiotics.

Many *Haemophilus* sp are normal flora in the upper respiratory tract and rarely cause illness. Pathogenic strains enter the upper respiratory tract through droplet inhalation or direct contact. Spread is rapid in nonimmune populations. Children, particularly males, blacks, and Native Americans, are at highest risk of serious infection. Overcrowded living conditions and day care center attendance predispose to infection, as do immunodeficiency states, asplenia, and sickle cell disease.

There are several pathogenic species of *Haemophilus*; the most common is *H. influenzae*, which has 6 distinct encapsulated serotypes (a through f) and numerous nonencapsulated, nontypeable strains. Before the use of *H. influenzae* type b (Hib) conjugate vaccine, most cases of serious, invasive disease were caused by type b.

**Diseases caused by *Haemophilus* sp: *H. influenzae* causes many childhood infections, including meningitis, bacteremia, septic arthritis, pneumonia, tracheobronchitis, otitis media, conjunctivitis, sinusitis, and acute epiglottitis. These infections, as well as endocarditis and UTIs, may occur in adults, although far less commonly. These illnesses are discussed elsewhere in THE MANUAL.**

Nontypeable *H. influenzae* strains cause mainly mucosal infections (eg, otitis media, sinusitis, conjunctivitis, bronchitis). Occasionally, nonencapsulated strains cause invasive infections in children, but they may cause up to half of serious *H. influenzae* infections in adults.

*H. influenzae* biogroup aegyptius (formerly called *H. aegyptius*) may cause mucopurulent conjunctivitis and bacteremic Brazilian purpuric fever. *H. ducreyi* causes chancroid (see p. 1468). *H. parainfluenzae* and *H. aphrophilus* are rare causes of bacteremia, endocarditis, and brain abscess.

**Diagnosis**

- Cultures
- Sometimes serotyping

Diagnosis is by culture of blood and body fluids. Strains involved in invasive illness should be serotyped.

**Treatment**

- Various antibiotics depending on site and severity of infection

Treatment depends on nature and location of the infection, but doxycycline, fluoroquinolones, 2nd- and 3rd-generation cephalosporins, and carbapenems are used for invasive disease. The Hib vaccine has markedly reduced the rate of bacteremia. Children with serious illness are hospitalized with contact and respiratory isolation for 24 h after starting antibiotics.

Antibiotic choices depend strongly on the site of infection and require susceptibility testing; many isolates in the US produce β-lactamase. For invasive illness, including meningitis, cefotaxime or ceftriaxone is recommended. For less serious infections, oral cephalosporins, macrolides, and amoxicillin/clavulanate are generally effective. (See individual disease entries for specific recommendations.)

**Prevention**

Hib conjugate vaccines are available for children ≥ 2 mo of age and have reduced invasive infections (eg, meningitis, epiglottitis, bacteremia) by 99%. A primary series is given at age 2, 4, and 6 mo or at age 2 and 4 mo, depending on the vaccine product. A booster at age 12 to 15 mo is indicated.

Contacts within the household may have asymptomatic *H. influenzae* carriage. Unimmunized or incompletely immunized household contacts < 4 yr are at risk of illness and should receive a dose of
vaccine. In addition, all household members (except pregnant women) should receive prophylaxis with rifampin 600 mg (20 mg/kg for children) po once/day for 4 days. Nursery or day care contacts should receive prophylaxis if ≥ 2 cases of invasive disease occurred in 60 days. The benefit of prophylaxis if only one case occurred has not been established.

**HACEK Infections**

The HACEK group includes weakly virulent, gram-negative organisms that primarily cause endocarditis.

The HACEK group of nonmotile, gram-negative bacilli or coccobacilli contains a number of minimally pathogenic, slow-growing, fastidious genera. Their primary pathology is endocarditis in susceptible people; about 1% of endocarditis cases are due to this group. The group consists of

- *Haemophilus* sp, which may cause respiratory infections or, less commonly, endocarditis
- *Actinobacillus actinomycetemcomitans*, which usually occurs with *A. israelii* in actinomycosis (see *Actinomycosis* on p. 1289)
- *Cardiobacterium hominis*
- *Eikenella corrodens*, which usually occurs in human bite wounds, endocarditis, brain and visceral abscesses, osteomyelitis, respiratory infections, uterine infections related to intrauterine devices, and mixed soft-tissue infections
- *Kingella kingae*

Antibiotic sensitivities differ among species, so treatment should be directed by susceptibility testing.

**Klebsiella, Enterobacter, and Serratia Infections**

*Klebsiella, Enterobacter, and Serratia* are closely related normal intestinal flora that rarely cause disease in normal hosts.

Infections with *Klebsiella, Enterobacter, and Serratia* are usually hospital-acquired and occur mainly in patients with diminished resistance. Usually, *Klebsiella, Enterobacter, and Serratia* cause a wide variety of infections, including bacteremia, surgical site infections, intravascular catheter infections, and respiratory or urinary tract infections that manifest as pneumonia, cystitis, or pyelitis and that may progress to lung abscess, empyema, and septicemia. *Klebsiella* pneumonia, a rare and severe disease with dark brown or red currant-jelly sputum, lung abscess formation, and empyema, is most common among diabetics and alcoholics. *Serratia*, particularly *S. marcescens*, has greater affinity for the urinary tract. *Enterobacter* can cause otitis media, cellulitis, and neonatal sepsis.

Treatment is with 3rd-generation cephalosporins, cefepime, carbapenems, fluoroquinolones, piperacillin/tazobactam, or aminoglycosides. However, because some isolates are resistant to multiple antibiotics, susceptibility testing is essential. *Klebsiella* strains that produce extended-spectrum β-lactamase (ESBL) may develop resistance to cephalosporins during treatment, particularly with ceftazidime. *Enterobacter* strains may be resistant to most β-lactam antibiotics, including 3rd-generation cephalosporins; the β-lactamase enzyme they produce is not inhibited by the usual β-lactamase inhibitors (clavulanate, tazobactam, sulbactam). However, these *Enterobacter* strains may be susceptible to carbapenems (eg, imipenem, meropenem, ertapenem).

**Legionella Infections**

*Legionella pneumophila* most often causes pneumonia with extrapulmonary features. Diagnosis requires specific growth media, serologic testing, or PCR analysis. Treatment is with doxycycline, macrolides, or fluoroquinolones.
The first appearance of this organism was in 1976 at a convention of the American Legion—thus, the name Legionnaires' disease. This disease is the pneumonic form of an infection usually caused by *Legionella pneumophila* serogroups 1 through 6. Nonpneumonic infection is called Pontiac fever.

The organisms are often present in soil and freshwater. A building's water supply is often the source of a Legionella outbreak. *Legionella* organisms are embedded in a biofilm that forms on the inside of water pipes and containers. The infection is usually acquired by inhaling aerosols of contaminated water (eg, as generated by shower heads, misters, whirlpool baths, or water cooling towers for air-conditioning).

**Diseases caused by Legionella sp:** The lungs are the most common site of infection; community- and hospital-acquired pneumonia may occur.

Extrapulmonary foci of infection occur most frequently in hospitalized patients and most commonly involve the heart. Other sites include the CNS, liver, and intestines. Immunocompromised patients, patients with diabetes mellitus, cigarette smokers, the elderly, and patients with chronic lung disease are principally affected.

**Symptoms and Signs**

Legionnaires' disease is a flu-like syndrome with acute fever, chills, malaise, myalgias, headache, or confusion. Nausea, loose stools or watery diarrhea, abdominal pain, cough, and arthralgias also frequently occur. Pneumonic manifestations may include dyspnea, pleuritic pain, and hemoptysis.

Mortality is low in otherwise healthy people but can reach 50% in hospital-acquired outbreaks.

**Diagnosis**

- Direct fluorescent antibody staining
- Sputum culture
- Rapid urinary antigen test (for serogroup 1 only)

Direct fluorescent antibody staining of sputum or lavage fluid is frequently used. In addition, PCR with DNA probing is available. A urinary antigen test is 70% sensitive and 100% specific 3 days after symptom onset but detects only *L. pneumophila* (serogroups 1 through 6) and not non-*pneumophila Legionella*. Paired acute and convalescent antibody assays may yield a delayed diagnosis. A 4-fold increase or an acute titer of ≥ 1:128 is considered diagnostic.

Diagnosis is by culture of sputum or bronchoalveolar lavage fluid; blood cultures are unreliable. Slow growth on laboratory media may delay identification for 3 to 5 days.

Chest x-ray should be done; it usually shows patchy and rapidly asymmetrically progressive infiltrates (even when effective antibiotic therapy is used), with or without small pleural effusions.

**Treatment**

- Fluoroquinolones
- Doxycycline

A fluoroquinolone given IV or po for 2 to 3 wk is the preferred regimen. Doxycycline is also highly effective. Azithromycin is effective, but erythromycin may be ineffective. Rifampin may be added for severe infections.

**Melioidosis**
Melioidosis is an infection caused by *Burkholderia* (formerly *Pseudomonas*) *pseudomallei*. Manifestations include pneumonia, septicemia, and localized infection in various organs. Diagnosis is by staining or culture. Treatment with antibiotics, such as ceftazidime, is prolonged.

The organism can be isolated from soil and water and is endemic in Southeast Asia; Australia; Central, West, and East Africa; India; and China. Humans may contract melioidosis by contamination of skin abrasions or burns, ingestion, or inhalation but not directly from infected animals or other humans. In endemic areas, melioidosis is likely to occur in patients with AIDS.

**Symptoms and Signs**

Infection may be asymptomatic or remain latent for years. Mortality is < 10%, except in acute septicemic melioidosis, which is frequently fatal.

**Acute pulmonary infection** is the most common form. It varies from mild to overwhelming necrotizing pneumonia. Onset may be abrupt or gradual, with headache, anorexia, pleuritic or dull aching chest pain, and generalized myalgia. Fever is usually > 39° C. Cough, tachypnea, and rales are characteristic. Sputum may be blood-tinged. Chest x-rays usually show upper lobe consolidation, frequently cavitating and resembling TB. Nodular lesions, thin-walled cysts, and pleural effusion may also occur. The WBC count ranges from normal to 20,000/μL.

**Disseminated septicemic infection** begins abruptly, with septic shock and multiple organ involvement manifested by disorientation, extreme dyspnea, severe headache, pharyngitis, upper abdominal colic, diarrhea, and pustular skin lesions. High fever, hypotension, tachypnea, a bright erythematous flush, and cyanosis are present. Muscle tenderness may be striking. Signs of arthritis or meningitis sometimes occur. Pulmonary signs may be absent or may include rales, rhonchi, and pleural rubs.

**Nondisseminated septicemic infection** occurs when bacteremia involves only a single organ. It does not usually lead to shock.

**Localized (chronic suppurative) infection** causes secondary abscesses, most often in the skin, lymph nodes, or bone. Patients may be afebrile. An acute suppurative form is uncommon.

**Diagnosis**

- Staining and culture

*B. pseudomallei* can be identified in exudates by methylene blue or Gram stain and by culture. Chest x-rays usually show irregular, nodular (4 to 10 mm) densities. The liver and spleen may be palpable. Liver function tests, AST, and bilirubin are often abnormal. The WBC count is normal or slightly increased.

**Treatment**

- Sometimes trimethoprim/sulfamethoxazole (TMP/SMX) or ceftazidime

Asymptomatic infection needs no treatment. Mildly ill patients are given TMP/SMX, one double-strength tablet po bid for a minimum of 30 days. Moderately or seriously ill patients are given ceftazidime 30 mg/kg IV q 6 h for 2 to 4 wk (imipenem, meropenem, and piperacillin are acceptable substitutes), then oral TMP/SMX or amoxicillin/clavulanate for 30 to 120 days.

**Pertussis**

(Whooping Cough)

**Pertussis** is a highly communicable disease occurring mostly in children and adolescents and caused by *Bordetella pertussis*. Symptoms are initially those of nonspecific URI followed by paroxysmal or spasmodic coughing that usually ends in a prolonged, high-pitched, crowing inspiration (the whoop). Diagnosis is by nasopharyngeal culture, PCR, and serologic assays.
Treatment is with macrolide antibiotics.

Pertussis is endemic throughout the world. Its incidence in the US cycles every 3 to 4 yr. In a given unimmunized locality, it becomes epidemic every 2 to 4 yr. It occurs at all ages, but 71% of cases occur in children < 5 yr, and 38% of cases, including nearly all deaths, occur in infants < 6 mo. Mortality is about 1 to 2% in children < 1 yr and is highest during the first month of life. Most deaths are caused by bronchopneumonia and cerebral complications. It is also serious in the elderly. One attack does not confer life-long natural immunity, but secondary attacks are usually mild and often unrecognized.

Transmission via aerosols of *B. pertussis* (a small, nonmotile, gram-negative coccobacillus) from infected patients, particularly in the catarrhal and early paroxysmal stages, causes disease in 90 to 100% of close contacts. Transmission by contact with contaminated articles is rare. Patients are usually not infectious after the 3rd wk of the paroxysmal phase.

**Diseases caused by pertussis:** Respiratory complications, including asphyxia in infants, are most common. Otitis media occurs frequently. Bronchopneumonia (common among the elderly) may be fatal at any age. Seizures are common among infants but rare in older children. Hemorrhage into the brain, eyes, skin, and mucous membranes can result from severe paroxysms and consequent anoxia. Cerebral hemorrhage, cerebral edema, and toxic encephalitis may result in spastic paralysis, intellectual disability (mental retardation), or other neurologic disorders. Umbilical herniation and rectal prolapse occasionally occur.

**Parapertussis:** This disease, caused by *B. parapertussis*, may be clinically indistinguishable from pertussis but is usually milder and less often fatal.

**Symptoms and Signs**

The incubation period averages 7 to 14 days (maximum 3 wk). *B. pertussis* invades respiratory mucosa, increasing the secretion of mucus, which is initially thin and later viscid and tenacious. Uncomplicated disease lasts about 6 to 10 wk and consists of 3 stages:

- **Catarrhal**
- **Paroxysmal**
- **Convalescent**

The catarrhal stage begins insidiously, generally with sneezing, lacrimation, or other signs of coryza; anorexia; listlessness; and a troublesome, hacking nocturnal cough that gradually becomes diurnal. Hoarseness may occur. Fever is rare.

After 10 to 14 days, the paroxysmal stage begins with an increase in the severity and frequency of the cough. Repeated bouts of ≥ 5 rapidly consecutive forceful coughs occur during a single expiration and are followed by the whoop—a hurried, deep inspiration. Copious viscid mucus may be expelled or bubble from the nares during or after the paroxysms. Vomiting is characteristic. In infants, choking spells (with or without cyanosis) may be more common than whoops.

Symptoms diminish as the convalescent stage begins, usually within 4 wk of onset. Average duration of illness is about 7 wk (range 3 wk to 3 mo). Paroxysmal coughing may recur for months, usually induced in the still sensitive respiratory tract by irritation from a URI.

**Diagnosis**

- **Nasopharyngeal cultures**

The catarrhal stage is often difficult to distinguish from bronchitis or influenza. Adenovirus infections and TB should also be considered.
Cultures of nasopharyngeal specimens are positive for *B. pertussis* in 80 to 90% of cases in the catarrhal and early paroxysmal stages. Because special media and prolonged incubation are required, the laboratory should be notified that pertussis is suspected. Specific fluorescent antibody testing of nasopharyngeal smears accurately diagnoses pertussis but is not as sensitive as culture. PCR can also be used. The WBC count is usually between 15,000 and 20,000/μL but may be normal or as high as 60,000/μL, usually with 60 to 80% small lymphocytes.

Parapertussis is differentiated by culture or the fluorescent antibody technique.

**Treatment**

- Supportive care
- Erythromycin or azithromycin

Hospitalization with respiratory isolation is recommended for seriously ill infants. Isolation is continued until antibiotics have been given for 5 days.

In infants, suction to remove excess mucus from the throat may be lifesaving. O₂ and tracheostomy or nasotracheal intubation is occasionally needed. Expectorants, cough suppressants, and mild sedation are of little value. Because any disturbance can precipitate serious paroxysmal coughing with anoxia, seriously ill infants should be kept in a darkened, quiet room and disturbed as little as possible. Patients treated at home should be quarantined, particularly from susceptible infants, for at least 4 wk from disease onset and until symptoms have subsided.

Antibiotics given during the catarrhal stage may ameliorate the disease. After paroxysms are established, antibiotics usually have no clinical effect but are recommended to limit spread. Preferred drugs are erythromycin 10 to 12.5 mg/kg po q 6 h (maximum 2 g/day) for 14 days or azithromycin 10 to 12 mg/kg po once/day for 5 days. Antibiotics should also be used for bacterial complications (eg, bronchopneumonia, otitis media).

**Prevention**

Active immunization is part of standard childhood vaccination. Five doses of vaccine are given (usually combined with diphtheria and tetanus [DTP or DTaP]) at age 2, 4, and 6 mo; boosters are given at 15 to 18 mo and 4 to 6 yr. Significant adverse effects from the pertussis component of the vaccine include encephalopathy within 7 days; seizure, with or without fever, within 3 days; persistent, severe, inconsolable screaming or crying for ≥ 3 h; collapse or shock within 48 h; fever ≥ 40.5° C within 48 h; and immediate severe or anaphylactic reaction. These reactions contraindicate further use of pertussis vaccine; combined diphtheria and tetanus vaccine is available without the pertussis component. The acellular vaccine (DTaP) is better tolerated.

Immunity after natural infection lasts about 20 yr. Passive immunization is unreliable and is not recommended.

Close contacts < 7 yr who have had < 4 doses of vaccine should be vaccinated. Contacts of all ages, whether vaccinated or not, should receive a 10-day course of erythromycin 500 mg po qid or 10 to 12.5 mg/kg po qid.

**Plague and Other Yersinia Infections**

(Bubonic Plague; Pestis; Black Death)

Plague is caused by *Yersinia pestis*. Symptoms are either severe pneumonia or massive lymphadenopathy with high fever, often progressing to septicemia. Diagnosis is epidemiologic and clinical, confirmed by culture and serologic testing. Treatment is with streptomycin or doxycycline.
Yersinia (formerly Pasteurella) pestis is a short bacillus that often shows bipolar staining (especially with Giemsa stain) and may resemble a safety pin.

Plague occurs primarily in wild rodents (e.g., rats, mice, squirrels, prairie dogs) and is transmitted from rodent to human by the bite of an infected rat flea vector. Human-to-human transmission occurs by inhaling droplet nuclei from patients with pulmonary infection (primary pneumonic plague), which is highly contagious. In endemic areas in the US, several cases may have been caused by household pets, especially cats. Transmission from cats can be by bite or, if the cat has pneumonic plague, by inhalation of infected droplets.

Massive human epidemics (e.g., the Black Death of the Middle Ages) have occurred. More recently, plague has occurred sporadically or in limited outbreaks. In the US, > 90% of human plague occurs in the Southwest, especially New Mexico, Arizona, California, and Colorado. Yersinia is considered a possible agent of bioterrorism.

**Symptoms and Signs**

In **bubonic plague**, the most common form, the incubation period is usually 2 to 5 days but varies from a few hours to 12 days. Onset of fever of 39.5 to 41°C is abrupt, often with chills. The pulse may be rapid and thready; hypotension may occur. Enlarged lymph nodes (buboes) appear with or shortly after the fever. The femoral or inguinal lymph nodes are most commonly involved, followed by axillary, cervical, or multiple nodes. Typically, the nodes are extremely tender and firm, surrounded by considerable edema. They may suppurate in the 2nd wk. The overlying skin is smooth and reddened but often not warm. A primary cutaneous lesion, varying from a small vesicle with slight local lymphangitis to an eschar, occasionally appears at the bite. The patient may be restless, delirious, confused, and uncoordinated. The liver and spleen may be enlarged. Bubonic plague may be complicated by pneumonic plague.

**Primary pneumonic plague** has a 2- to 3-day incubation period, followed by abrupt onset of high fever, chills, tachycardia, chest pain, and headache, often severe. Cough, not prominent initially, develops within 24 h. Sputum is mucoid at first, rapidly develops blood specks, and then becomes uniformly pink or bright red (resembling raspberry syrup) and foamy. Tachypnea and dyspnea are present, but pleuritic chest pain is not. Signs of consolidation are rare, and rales may be absent.

**Septicemic plague** may occur with the bubonic form or without the bubonic form (called primary septicemic plague) as an acute, fulminant illness. Abdominal pain, presumably due to mesenteric lymphadenopathy, occurs in 40% of patients. Disseminated intravascular coagulopathy, gangrene of the extremities (hence, the name Black Death), and multiorgan failure eventually develop. Pharyngeal plague and plague meningitis are less common forms.

**Pestis minor**, a more benign form of bubonic plague, usually occurs only in endemic areas. Lymphadenitis, fever, headache, and prostration subside within a week.

The mortality rate for untreated patients with bubonic plague is about 60%; most deaths result from septicemia in 3 to 5 days. Most untreated patients with pneumonic plague die within 48 h of symptom onset. Septicemic plague may be fatal before bubonic or pulmonary manifestations predominate.

**Diagnosis**

- **Staining, cultures, and serologic testing**

Diagnosis is made by stain and culture of the organism, typically by needle aspiration of a bubo (surgical drainage may disseminate the organism); blood and sputum cultures should also be obtained. Other tests include immunofluorescent staining and serology; a titer of > 1:16 or a 4-fold rise between acute and convalescent titers is positive. PCR testing, if available, is diagnostic. Prior vaccination does not exclude plague; clinical illness may occur in vaccinated people.

Patients with pulmonary symptoms or signs should have a chest x-ray, which shows a rapidly progressing pneumonia in pneumonic plague. The WBC count is usually 10,000 to 20,000/μL with numerous immature
neutrophils.

**Treatment**

- Streptomycin
- Alternatively, doxycycline, gentamicin, or chloramphenicol

Immediate treatment reduces mortality to < 5%. In septicemic or pneumonic plague, treatment must begin within 24 h with streptomycin 15 mg/kg (up to 1 g) IM bid for 10 days or until 3 days after temperature has returned to normal. Doxycycline 100 mg IV or po q 12 h is an alternative. Gentamicin and chloramphenicol are also effective.

Chloramphenicol is preferred for patients with infection of tissue spaces into which other drugs pass poorly (eg, plague meningitis, endophthalmitis). Chloramphenicol should be given in a loading dose of 25 mg/kg IV, followed by 12.5 mg/kg IV or po q 6 h.

Routine isolation precautions are adequate for patients with bubonic plague. Those with primary or secondary pneumonic plague require strict respiratory isolation.

**Prevention**

All pneumonic plague contacts should be under medical surveillance. Temperature should be taken q 4 h for 6 days. They and others in close contact with plague patients or with contaminated fluids or tissue should receive prophylaxis with doxycycline 100 mg po q 12 h (for children < 8 yr, trimethoprim/sulfamethoxazole [TMP/SMX] 20 mg/kg [of the SMX component] q 12 h). Travelers should be given prophylaxis with doxycycline 100 mg po q 12 h during exposure periods. Plague vaccine is available but is recommended mainly for laboratory workers and researchers because immunity requires about 1 mo to develop.

Rodents should be controlled and repellents used to minimize flea bites.

**Other Yersinia Infections**

*Yersinia enterocolitica* and *Y. pseudotuberculosis* are zoonoses acquired by ingestion of contaminated food or water; they occur worldwide.

*Y. enterocolitica* is a common cause of diarrheal disease and mesenteric adenitis that clinically mimics appendicitis. *Y. pseudotuberculosis* most commonly causes mesenteric adenitis and has been suspected in cases of interstitial nephritis, hemolytic-uremic syndrome, and a scarlet fever-like illness. Both species can cause pharyngitis, septicemia, focal infections in multiple organs, postinfectious erythema nodosum, and reactive arthritis. In patients with chronic liver disease or iron overload, mortality from septicemia may be as high as 50%, even with treatment.

The organisms can be identified in standard cultures from normally sterile sites. Selective culture methods are required for nonsterile specimens. Serologic assays are available but difficult and not standardized. Diagnosis, particularly of reactive arthritis, requires a high index of suspicion and close communication with the clinical laboratory.

Treatment of diarrhea is supportive because the disease is self-limited. Septic complications require β-lactamase-resistant antibiotics guided by susceptibility testing.

Prevention focuses on food handling and preparation, household pets, and epidemiology of suspected outbreaks.

**Proteeae Infections**

*The Proteae are normal fecal flora that often cause infection in patients whose normal flora*
have been disturbed by antibiotic therapy.

The Proteae constitute at least 3 genera of gram-negative organisms:

- **Proteus**: *P. mirabilis*, *P. vulgaris*, and *P. myxofaciens*
- **Morganella**: *M. morganii*
- **Providencia**: *P. rettgeri*, *P. alcalifaciens*, and *P. stuartii*

However, *P. mirabilis* causes most human infections. These organisms are normal fecal flora and are present in soil and water. They are often present in superficial wounds, draining ears, and sputum, particularly in patients whose normal flora has been eradicated by antibiotic therapy. They may cause bacteremia and deep-seated infections, particularly in the ears and mastoid sinuses, peritoneal cavity, and urinary tract of patients with chronic UTIs or with renal or bladder stones.

*P. mirabilis* is often sensitive to ampicillin, carbenicillin, ticarcillin, piperacillin, cephalosporins, and aminoglycosides and resistant to tetracyclines. Multidrug-resistant *P. mirabilis* is an emerging problem. Indole-positive species (*P. vulgaris*, *M. morganii*, *P. rettgeri*) tend to be more resistant but generally are sensitive to fluoroquinolones, carbapenems, piperacillin/tazobactam, 3rd-generation cephalosporins, and cefixime.

**Pseudomonas and Related Infections**

*Pseudomonas aeruginosa* and other members of this group of gram-negative bacilli are opportunistic pathogens that frequently cause hospital-acquired infections, particularly in ventilator patients, burn patients, and patients with chronic debility. Many sites can be infected, and infection is usually severe. Diagnosis is by culture. Antibiotic choice varies with the pathogen and must be guided by susceptibility testing because resistance is common.

**Epidemiology**

*Pseudomonas* is ubiquitous and favors moist environments. In humans, *P. aeruginosa* is the most common pathogen, but infection may result from *P. paucimobilis*, *P. putida*, *P. fluorescens*, or *P. acidovorans*. Other important hospital-acquired pathogens formerly classified as *Pseudomonas* include *Burkholderia cepacia* and *Stenotrophomonas maltophilia*. *B. pseudomallei* causes a distinct disease known as melioidosis that is limited mostly to the Asian tropics (see p. 1254).

*P. aeruginosa* is present occasionally in the axilla and anogenital areas of normal skin but rarely in stool unless antibiotics are being given. In hospitals, the organism is frequently present in sinks, antiseptic solutions, and urine receptacles. Transmission to patients by health care practitioners may occur, especially in burn and neonatal ICUs, unless infection control practices are meticulously followed.

**Diseases Caused by Pseudomonas**

Most *P. aeruginosa* infections occur in hospitalized patients, particularly those who are debilitated or immunocompromised. *P. aeruginosa* is a common cause of infections in ICUs. HIV-infected patients, particularly those in advanced stages, are at risk of community-acquired *P. aeruginosa* infections.

*Pseudomonas* infections can develop in many anatomic sites, including skin, subcutaneous tissue, bone, ears, eyes, urinary tract, and heart valves. The site varies with the portal of entry and the patient’s vulnerability. In hospitalized patients, the first sign may be overwhelming gram-negative sepsis.

**Skin and soft-tissue infections**: In burns, the region below the eschar can become heavily infiltrated with organisms, serving as a focus for subsequent bacteremia—an often lethal complication.

Deep puncture wounds of the foot are often infected by *P. aeruginosa*. Draining sinuses, cellulitis, and
osteomyelitis may result. Drainage from puncture wounds often has a sweet, fruity smell.

Folliculitis acquired in hot tubs is often caused by *P. aeruginosa*.

External otitis, common in tropical climates, is the most common form of *Pseudomonas* infection involving the ear. A more severe form, referred to as malignant external otitis (see p. 455), can develop in diabetic patients. It is manifested by severe ear pain, often with unilateral cranial nerve palsies, and requires parenteral therapy.

Ecthyma gangrenosum is a skin lesion that occurs in neutropenic patients and is usually caused by *P. aeruginosa*. It is characterized by erythematous, centrally ulcerated, purple-black areas about 1 cm in diameter occurring most often in the axillary, inguinal, or anogenital areas.

**Respiratory tract infections:** *P. aeruginosa* is a frequent cause of ventilator-associated pneumonia. In HIV-infected patients, *Pseudomonas* most commonly causes pneumonia or sinusitis. *Pseudomonas* bronchitis is common late in the course of cystic fibrosis. Isolates from patients with cystic fibrosis have a characteristic mucoid colonial morphology.

**Other infections:** *Pseudomonas* is a common cause of nosocomial UTI, especially in patients who have had urologic manipulation or obstructive uropathy. *Pseudomonas* commonly colonizes the urinary tract in catheterized patients, especially those who have received broad-spectrum antibiotics.

Ocular involvement generally manifests as corneal ulceration, most often after trauma, but contamination of contact lenses or lens fluid has been implicated in some cases.

Rarely, *Pseudomonas* causes acute bacterial endocarditis, usually on prosthetic valves in patients who have had open-heart surgery or on natural valves in IV drug abusers.

**Bacteremia:** Many *Pseudomonas* infections can cause bacteremia. In nonintubated patients without a detectable urinary focus, especially if infection is due to a species other than *P. aeruginosa*, bacteremia suggests contaminated IV fluids, drugs, or antiseptics used in placing the IV catheter.

**Diagnosis**

• Culture

Diagnosis depends on culturing the organism from the site of infection: blood, skin lesions, drainage fluid, urine, CSF, or eye. Localized infection may produce a fruity smell, and pus may be greenish.

**Treatment**

• Various antibiotics depending on site and severity of infection and susceptibility testing

**Localized infection:** Hot-tub folliculitis resolves spontaneously and does not require antibiotic therapy.

External otitis is treated with 1% acetic acid irrigations or topical drugs such as polymyxin B or colistin. More severe infection is treated with fluoroquinolones.

Focal soft-tissue infection may require early surgical debridement of necrotic tissue and drainage of abscesses in addition to antibiotics.

Small corneal ulcers are treated with ciprofloxacin 0.3% or levofloxacin 0.5%. Fortified (higher than stock concentration) antibiotic drops, such as tobramycin 15 mg/mL, are used for more significant ulcers. Frequent dosing (eg, q 1 h around the clock) is necessary initially. Eye patching is contraindicated because it produces a dark warm environment that favors bacterial growth and prevents administration of topical drugs.
Asymptomatic bacteriuria is not treated with antibiotics, except during pregnancy and before urologic manipulation. Patients with symptomatic UTIs can often be treated with levofloxacin 500 mg po once/day or ciprofloxacin 400 mg po bid.

Systemic infection: Parenteral therapy is required, typically with an aminoglycoside plus an antipseudomonal β-lactam, an anti-pseudomonal cephalosporin (eg, cefepime, cefoperazone), or the carbapenems meropenem or imipenem.

Right-sided endocarditis can be treated with antibiotics, but usually the infected valve must be removed to cure an infection involving the mitral, aortic, or prosthetic valve.

In neutropenic patients with marginal renal function, nonaminoglycoside combinations, such as double β-lactams or a β-lactam plus a fluoroquinolone, are also satisfactory.

*P. aeruginosa* resistance may occur among patients treated with ceftazidime, ciprofloxacin, gentamicin, meropenem, or imipenem.

**Salmonella Infections**

The 2200 known serotypes of *Salmonella* may be grouped into

- Those highly adapted to human hosts: This group includes *S. typhi* and *S. paratyphi* types A, B (also called *S. schottmulleri*), and C (also called *S. hirschfeldii*), which are pathogenic only in humans and commonly cause enteric (typhoid) fever.

- Those adapted to nonhuman hosts or causing disease almost exclusively in animals. Two strains within this group, *S. dublin* and *S. choleraesuis*, also cause disease in humans.

- Those unadapted to specific hosts: This group, designated *S. enteritidis*, includes > 2000 serotypes that cause gastroenteritis and accounts for 85% of all *Salmonella* infections in the US.

**Typhoid Fever**

Typhoid fever is a systemic disease caused by *Salmonella typhi*. Symptoms are high fever, prostration, abdominal pain, and a rose-colored rash. Diagnosis is clinical and confirmed by culture. Treatment is with ceftriaxone or ciprofloxacin.

**Epidemiology**

About 400 to 500 cases of typhoid fever are reported annually in the US, mainly among US travelers returning from endemic regions. Typhoid bacilli are shed in stool of asymptomatic carriers or in stool or urine of people with active disease. Inadequate hygiene after defecation may spread *S. typhi* to community food or water supplies. In endemic areas where sanitary measures are generally inadequate, *S. typhi* is transmitted more frequently by water than by food. In developed countries, transmission is chiefly by food that has been contaminated during preparation by healthy carriers. Flies may spread the organism from feces to food. Occasional transmission by direct contact (fecal-oral route) may occur in children during play and in adults during sexual practices. Rarely, hospital personnel who have not taken adequate enteric precautions have acquired the disease when changing soiled bedclothes.

The organism enters the body via the GI tract and gains access to the bloodstream via the lymphatic channels. Intestinal ulceration, hemorrhage, and perforation may occur in severe cases.

**Carrier state:** About 3% of untreated patients, referred to as chronic enteric carriers, harbor organisms in their gallbladder and shed them in stool for > 1 yr. Some carriers have no history of clinical illness. Most of the estimated 2000 carriers in the US are elderly women with chronic biliary disease. Obstructive uropathy related to schistosomiasis may predispose certain typhoid patients to urinary carriage. Epidemiologic data indicate that typhoid carriers are more likely than the general population to develop hepatobiliary cancer.
Symptoms and Signs

The incubation period (usually 8 to 14 days) is inversely related to the number of organisms ingested. Onset is usually gradual, with fever, headache, arthralgia, pharyngitis, constipation, anorexia, and abdominal pain and tenderness. Less common symptoms include dysuria, nonproductive cough, and epistaxis.

Without treatment, the temperature rises in steps over 2 to 3 days, remains elevated (usually 39.4 to 40°C) for another 10 to 14 days, begins to fall gradually at the end of the 3rd wk, and reaches normal levels during the 4th wk. Prolonged fever is often accompanied by relative bradycardia and prostration. CNS symptoms such as delirium, stupor, or coma occur in severe cases. In about 10% of patients, discrete pink, blanching lesions (rose spots) appear in crops on the chest and abdomen during the 2nd wk and resolve in 2 to 5 days. Splenomegaly, leukopenia, anemia, liver function abnormalities, proteinuria, and a mild consumption coagulopathy are common. Acute cholecystitis and hepatitis may occur.

Late in the disease, when intestinal lesions are most prominent, florid diarrhea may occur, and the stool may contain blood (occult in 20% of patients, gross in 10%). In about 2% of patients, severe bleeding occurs during the 3rd wk, with a mortality rate of about 25%. An acute abdomen and leukocytosis during the 3rd wk may suggest intestinal perforation, which usually involves the distal ileum and occurs in 1 to 2% of patients. Pneumonia may develop during the 2nd or 3rd wk and may be due to secondary pneumococcal infection, although S. typhi can also cause pulmonary infiltrates. Bacteremia occasionally leads to focal infections such as osteomyelitis, endocarditis, meningitis, soft-tissue abscesses, glomerulitis, or GU tract involvement. Atypical presentations, such as pneumonitis, fever only, or, very rarely, symptoms consistent with UTI, may delay diagnosis. Convalescence may last several months.

In 8 to 10% of untreated patients, symptoms and signs similar to the initial clinical syndrome recur about 2 wk after defervescence. For unclear reasons, antibiotic therapy during the initial illness increases the incidence of febrile relapse to 15 to 20%. If antibiotics are restarted at the time of relapse, the fever abates rapidly, unlike the slow defervescence that occurs during the primary illness. Occasionally, a 2nd relapse occurs.

Diagnosis

• Cultures

Other infections causing a similar presentation include other Salmonella infections, the major rickettsioses, leptospirosis, disseminated TB, malaria, brucellosis, tularemia, infectious hepatitis, psittacosis, Versinia enterocolitica infection, and lymphoma. Early in its clinical course, typhoid fever may resemble malaria.

Cultures of blood, stool, and urine should be obtained. Blood cultures are usually positive only during the first 2 wk of illness, but stool cultures are usually positive during the 3rd to 5th wk. If these cultures are negative and typhoid fever is strongly suspected, culture from a bone marrow biopsy specimen may reveal the organism.

Typhoid bacilli contain antigens (O and H) that stimulate the host to form corresponding antibodies. A 4-fold rise in O and H antibody titers in paired specimens obtained 2 wk apart suggests S. typhi infection. However, this test is only moderately (70%) sensitive and lacks specificity; many nontyphoidal Salmonella strains cross-react, and liver cirrhosis causes false-positives.

Prognosis

Without antibiotics, the mortality rate is about 12%. With prompt therapy, the mortality rate is 1%. Most deaths occur in malnourished people, infants, and the elderly. Stupor, coma, or shock reflects severe disease and a poor prognosis. Complications occur mainly in patients who are untreated or in whom treatment is delayed.
Treatment

• Ceftriaxone

• Sometimes a fluoroquinolone

Preferred antibiotics include ceftriaxone 1 g IM or IV q 12 h (25 to 37.5 mg/kg in children) for 14 days and various fluoroquinolones (eg, ciprofloxacin 500 mg po bid for 10 to 14 days, levofloxacin 500 mg po or IV once/day for 14 days, moxifloxacin 400 mg po or IV once/day for 14 days). Chloramphenicol 500 mg po or IV q 6 h is still widely used, but resistance is increasing. Fluoroquinolones may be used in children. Alternative therapies, depending on in vitro sensitivity, include amoxicillin 25 mg/kg po qid, trimethoprim/sulfamethoxazole (TMP/SMX) 320/1600 bid or 10 mg/kg (of the TMP component) bid, and azithromycin 1 g po on day 1, then 500 mg once/day for 6 days.

Corticosteroids may be added to antibiotics to treat severe toxicity. Defervescence and clinical improvement usually follow. Prednisone 20 to 40 mg once/day po (or equivalent) for the first 3 days of treatment usually suffices. Higher doses of corticosteroids (dexamethasone 3 mg/kg IV initially, followed by 1 mg/kg q 6 h for 48 h total), are used in patients with marked delirium, coma, or shock.

Nutrition should be maintained with frequent feedings. While febrile, patients are usually kept on bed rest. Salicylates (which may cause hypothermia and hypotension), as well as laxatives and enemas, should be avoided. Diarrhea may be minimized with a clear liquid diet; parenteral nutrition may be needed temporarily. Fluid and electrolyte therapy and blood replacement may be needed.

Intestinal perforation and associated peritonitis call for surgical intervention and broader gram-negative and anti-<i>Bacteroides fragilis</i> coverage.

Relapses are treated the same as the initial illness, although duration of antibiotic therapy seldom needs to be > 5 days.

Patients must be reported to the local health department and prohibited from handling food until proven free of the organism. Typhoid bacilli may be isolated for as long as 3 to 6 mo after the acute illness in people who do not become carriers. Thereafter, 3 stool cultures at weekly intervals must be negative to exclude a carrier state.

**Carriers:** Carriers with normal biliary tracts should be given antibiotics. The cure rate is about 60% with amoxicillin 2 g po tid for 4 wk.

In some carriers with gallbladder disease, eradication has been achieved with TMP/SMX and rifampin. In other cases, cholecystectomy with 1 to 2 days of preoperative antibiotics and 2 to 3 days of postoperative antibiotics is effective.

Prevention

Drinking water should be purified, sewage should be disposed of effectively, milk should be pasteurized, chronic carriers should avoid handling food, and adequate patient isolation precautions should be implemented. Special attention to enteric precautions is important. Travelers in endemic areas should avoid ingesting raw leafy vegetables, other foods stored or served at room temperature, and untreated water. Unless water is known to be safe, it should be boiled or chlorinated before drinking.

A live-attenuated oral typhoid vaccine is available (Ty21a strain) and is about 70% effective. It is given every other day for a total of 4 doses. Because the vaccine contains living <i>S. typhi</i> organisms, it is contraindicated in patients who are immunosuppressed. In the US, the Ty21a vaccine is not used in children < 6 yr. An alternative is the single-dose, IM Vi polysaccharide vaccine, which is 64 to 72% effective and is well tolerated, but it is not used in children < 2 yr.

**Nontyphoidal <i>Salmonella</i> Infections**
Nontyphoidal salmonellae, mainly *Salmonella enteritidis*, primarily cause gastroenteritis, bacteremia, and focal infection. Symptoms may be diarrhea, high fever with prostration, or symptoms of focal infection. Diagnosis is by cultures of blood, stool, or site specimens. Treatment, when indicated, is with trimethoprim/sulfamethoxazole or ciprofloxacin, with surgery for abscesses, vascular lesions, and bone and joint infections.

Most nontyphoidal *Salmonella* infections are caused by *S. enteritidis*. These infections are common and remain a significant public health problem in the US. Many serotypes of *S. enteritidis* have been given names and are referred to informally as if they were separate species even though they are not. The most common *Salmonella* serotypes in the US include *S. typhimurium*, *S. heidelberg*, *S. newport*, *S. infantis*, *S. agona*, *S. montevideo*, and *S. saint-paul*.

Human disease occurs by direct and indirect contact with numerous species of infected animals, the foodstuffs derived from them, and their excreta. Infected meat, poultry, raw milk, eggs, and egg products are common sources of *Salmonella*. Other reported sources include infected pet turtles and reptiles, carmine red dye, and contaminated marijuana.

**Risk factors**: Subtotal gastrectomy, achlorhydria (or ingestion of antacids), sickle cell anemia, splenectomy, louse-borne relapsing fever, malaria, bartonellosis, cirrhosis, leukemia, lymphoma, and HIV infection are all risk factors for *Salmonella* infection.

**Diseases caused by nontyphoidal *Salmonella* sp**: Each *Salmonella* serotype can cause any or all of the clinical syndromes described below, although given serotypes tend to produce specific syndromes. Enteric fever, for instance, is caused by *S. paratyphi* types A, B, and C.

An asymptomatic carrier state may also occur. However, carriers do not appear to play a major role in large outbreaks of nontyphoidal gastroenteritis. Persistent shedding of organisms in the stool for ≥ 1 yr occurs in only 0.2 to 0.6% of patients with nontyphoidal *Salmonella* infections.

**Symptoms and Signs**

*Salmonella* infection may manifest as

- Gastroenteritis
- Enteric fever
- Bacteremia
- Focal disease

**Gastroenteritis** usually starts 12 to 48 h after ingestion of organisms, with nausea and cramping abdominal pain followed by diarrhea, fever, and sometimes vomiting. Usually, the stool is watery but may be a pastelike semisolid. Rarely, mucus or blood is present. The disease is usually mild, lasting 1 to 4 days. Occasionally, a more severe, protracted illness occurs.

**Enteric fever** in a less severe form than typhoid is characterized by fever, prostration, and septicemia.

**Bacteremia** is relatively uncommon in patients with gastroenteritis. However, *S. choleraesuis*, *S. typhimurium*, and *S. heidelberg*, among others, can cause a sustained and frequently lethal bacteremic syndrome lasting ≥ 1 wk, with prolonged fever, headache, malaise, and chills but rarely diarrhea. Patients may have recurrent episodes of bacteremia or other invasive infections (eg, septic arthritis) due to *Salmonella*. Multiple *Salmonella* infections in a patient without other risk factors should prompt HIV testing.

**Focal Salmonella infection** can occur with or without sustained bacteremia, causing pain in or referred
from the involved organ—the GI tract (liver, gallbladder, appendix), endothelial surfaces (eg, atherosclerotic plaques, iliofemoral or aortic aneurysms, heart valves), pericardium, meninges, lungs, joints, bones, GU tract, or soft tissues. Preexisting solid tumors are occasionally seeded and develop abscesses that may, in turn, become a source of *Salmonella* bacteremia. *S. choleraesuis* and *S. typhimurium* are the most common causes of focal infection.

**Diagnosis**

- **Cultures**

Diagnosis is by isolating the organism from stool or another infected site. In bacteremic and focal forms, blood cultures are positive, but stool cultures are generally negative. In stool specimens stained with methylene blue, WBCs are often seen, indicating inflammatory colitis.

**Treatment**

- **Supportive care**

- **Ciprofloxacin or trimethoprim/sulfamethoxazole (TMP/SMX) only for high-risk patients and patients with systemic or focal infections**

Gastroenteritis is treated symptomatically with oral or IV fluids (see p. 149). Antibiotics do not hasten resolution, may prolong excretion of the organism, and are unwarranted in uncomplicated cases. However, in elderly nursing home residents, infants, and patients with HIV infection, increased mortality dictates treatment with antibiotics. Antibiotic resistance is more common with nontyphoidal *Salmonella* than with *S. typhi*. TMP/SMX 5 mg/kg (of the TMP component) po q 12 h for children and ciprofloxacin 500 mg po q 12 h for adults are acceptable regimens. Nonimmunocompromised patients should be treated for 3 to 5 days; patients with AIDS may require prolonged suppression to prevent relapses. Systemic or focal disease should be treated with antibiotic doses as outlined above for typhoid fever. Sustained bacteremia is generally treated for 4 to 6 wk. Abscesses should be drained surgically. At least 4 wk of antibiotic therapy should follow surgery. Infected aneurysms and heart valves and bone or joint infections usually require surgical intervention and prolonged courses of antibiotics. The prognosis is usually good, unless severe underlying disease is present.

**Carriers:** Asymptomatic carriage is usually self-limited, and antibiotic treatment is rarely required. In unusual cases (eg, in food handlers or health care workers), eradication may be attempted with ciprofloxacin 500 mg po q 12 h for 1 mo. Follow-up stool cultures should be obtained in the weeks after drug administration to document elimination of *Salmonella*.

**Prevention**

Preventing contamination of foodstuffs by infected animals and humans is paramount. Preventive measures for travelers discussed on p. 1261 also apply to most other enteric infections. Case reporting is essential.

**Shigellosis**

**(Bacillary Dysentery)**

Shigellosis is an acute infection of the intestine caused by *Shigella* sp. Symptoms include fever, nausea, vomiting, and diarrhea that is usually bloody. Diagnosis is clinical and confirmed by stool culture. Treatment is supportive, mostly with rehydration; antibiotics (eg, ampicillin, trimethoprim/sulfamethoxazole) are optional.

The genus *Shigella* is distributed worldwide and is the typical cause of inflammatory dysentery, responsible for 5 to 10% of diarrheal illness in many areas. *Shigella* is divided into 4 major subgroups: A, B, C, and D, which are subdivided into serologically determined types. *S. flexneri* and *S. sonnei* are more widespread than *S. boydii* and the particularly virulent *S. dysenteriae*. *S. sonnei* is the most common...
isolate in the US.

The source of infection is the feces of infected people or convalescent carriers. Direct spread is by the fecal-oral route. Indirect spread is by contaminated food and fomites. Flies serve as vectors. Epidemics occur most frequently in overcrowded populations with inadequate sanitation. Shigellosis is particularly common among younger children living in endemic areas. Adults usually have less severe disease.

Convalescents and subclinical carriers may be significant sources of infection, but true long-term carriers are rare. Infection imparts little or no immunity.

*Shigella* organisms penetrate the mucosa of the colon, causing mucus secretion, hyperemia, leukocytic infiltration, edema, and often superficial mucosal ulcerations. *Shigella dysenteriae* type 1 (not commonly present in the US, except in travelers returning from endemic areas) produces Shiga toxin, which causes marked watery diarrhea and sometimes hemolytic-uremic syndrome.

**Symptoms and Signs**

The incubation period is 1 to 4 days. The most common presentation, watery diarrhea, is indistinguishable from other bacterial, viral, and protozoan infections that induce secretory activity of intestinal epithelial cells.

In adults, initial symptoms may be episodes of gripping abdominal pain, urgency to defecate, and passage of formed feces that temporarily relieves the pain. These episodes recur with increasing severity and frequency. Diarrhea becomes marked, with soft or liquid stools containing mucus, pus, and often blood. Rectal prolapse and consequent fecal incontinence may result from severe tenesmus. However, adults may present without fever, with nonbloody and nonmucoid diarrhea, and with little or no tenesmus. The disease usually resolves spontaneously in adults—mild cases in 4 to 8 days, severe cases in 3 to 6 wk. Significant dehydration and electrolyte loss with circulatory collapse and death occur mainly in debilitated adults and children < 2 yr.

Rarely, shigellosis starts suddenly with rice-water or serous (occasionally bloody) stools. The patient may vomit and rapidly become dehydrated. Infection may manifest as delirium, seizures, and coma but with little or no diarrhea. Death may occur in 12 to 24 h.

In young children, onset is sudden, with fever, irritability or drowsiness, anorexia, nausea or vomiting, diarrhea, abdominal pain and distention, and tenesmus. Within 3 days, blood, pus, and mucus appear in the stools. The number of stools may increase to ≥ 20/day, and weight loss and dehydration become severe. If untreated, children may die in the first 12 days. If children survive, acute symptoms subside by the 2nd wk.

**Complications:** The hemolytic-uremic syndrome may complicate shigellosis due to *S. dysenteriae* type 1 in children. Secondary bacterial infections may occur, especially in debilitated and dehydrated patients. Severe mucosal ulcerations may cause significant acute blood loss. Patients (particularly those with the HLA-B27 genotype) may develop reactive arthritis (arthritis, conjunctivitis, urethritis) after shigellosis (and other enteritides).

Other complications are uncommon but include seizures in children, myocarditis, and, rarely, intestinal perforation. Infection does not become chronic and is not an etiologic factor in ulcerative colitis.

**Diagnosis**

- Stool cultures

Diagnosis is facilitated by a high index of suspicion during outbreaks and in endemic areas and by the presence of fecal leukocytes on smears stained with methylene blue or Wright's stain. Stool cultures are diagnostic and should be obtained. In patients with symptoms of dysentery (bloody and mucoid stools), the differential diagnosis should include invasive *Escherichia coli*, *Salmonella*, *Yersinia*, and *Campylobacter* infections; amebiasis; and viral diarrheas.
The mucosal surface, as seen through a proctoscope, is diffusely erythematous with numerous small ulcers. Although leukopenia or marked leukocytosis may be present, it averages 13,000/μL. Hemoconcentration is common, as is diarrhea-induced metabolic acidosis.

**Treatment**

- Supportive care
- For severely ill or at-risk patients, a fluoroquinolone or trimethoprim/sulfamethoxazole (TMP/SMX)

Fluid loss is treated symptomatically with oral or IV fluids (see p. 149). Antibiotics can reduce the symptoms and shedding of *Shigella* but are not necessary for healthy adults with mild illness. However, certain patients, including the following, should usually be treated:

- Children
- The elderly
- Debilitated patients
- Patients with severe disease

For adults, a fluoroquinolone, such as ciprofloxacin 500 mg po q 12 h for 3 to 5 days, or TMP/SMX one double-strength tablet q 12 h is the treatment of choice. For children, treatment is TMP/SMX 4 mg/kg (of the TMP component) po q 12 h. Many *Shigella* isolates are likely to be resistant to ampicillin and tetracycline.

**Prevention**

Hands should be washed thoroughly before handling food, and soiled garments and bedclothes should be immersed in covered buckets of soap and water until they can be boiled. Appropriate isolation techniques (especially stool isolation) should be used with patients and carriers.

A live oral vaccine is being developed, and field trials in endemic areas hold promise. However, immunity is generally type specific.

**Tularemia**

*(Rabbit or Deer Fly Fever)*

*Tularemia* is a febrile disease caused by *Francisella tularensis*; it may resemble typhoid fever. Symptoms are a primary local ulcerative lesion, regional lymphadenopathy, profound systemic symptoms, and, occasionally, atypical pneumonia. Diagnosis is primarily epidemiologic and clinical and supported by serologic tests. Treatment is with streptomycin, gentamicin, chloramphenicol, or doxycycline.

There are 7 clinical syndromes associated with tularemia (see Table 135-2). The causative organism, *F. tularensis*, is a small, pleomorphic, nonmotile, nonsporulating aerobic bacillus that enters the body by

- Ingestion of contaminated food or water
- Bite of an infected arthropod vector (ticks, deer flies, fleas)
- Inhalation
- Direct contact with infected tissues or material
The organism can penetrate apparently unbroken skin but may actually enter through microlesions.

There are 2 types of *F. tularensis*: type A and type B. Type A, a more virulent serotype for humans, usually occurs in rabbits and rodents in the US and Canada. Type B usually causes a mild ulceroglandular infection and occurs in water and aquatic animals in Europe and Asia.

Hunters, butchers, farmers, and fur handlers are most commonly infected. In winter months, most cases result from contact (especially during skinning) with infected wild rabbits. In summer months, infection usually follows handling of other infected animals or birds or bites of infected ticks or other arthropods. Rarely, cases result from eating undercooked infected meat, drinking contaminated water, or mowing fields in endemic areas. In the Western states, ticks, deer flies, horse flies, and direct contact with infected animals are other sources of infection. Human-to-human transmission has not been reported. Laboratory workers are at particular risk because infection is readily acquired during normal handling of infected specimens. Tularemia is considered a possible agent of bioterrorism.

In disseminated cases, characteristic focal necrotic lesions in various stages of evolution are scattered throughout the body. They are 1 mm to 8 cm and whitish yellow; they are seen externally as the primary lesions on the fingers, eyes, or mouth and commonly occur in lymph nodes, spleen, liver, kidneys, and lungs. In pneumonia, necrotic foci occur in the lungs. Although severe systemic toxicity may occur, no toxins have been demonstrated.

**Symptoms and Signs**

Onset occurs suddenly, 1 to 10 (usually 2 to 4) days after exposure, with headache, chills, nausea, vomiting, fever of 39.5° to 40° C, and severe prostration. Extreme weakness, recurring chills, and drenching sweats develop. Clinical manifestations depend to some extent on the type of exposure (see Table 135-2).

Within 24 to 48 h, an inflamed papule appears at the site of exposure (finger, arm, eye, roof of the mouth), except in glandular or typhoidal tularemia. The papule rapidly becomes pustular and ulcerates, producing a clean ulcer crater with a scanty, thin, colorless exudate. Ulcers are usually single on the extremities but multiple in the mouth or eyes. Usually, only one eye is affected. Regional lymph nodes enlarge and may suppurate and drain profusely. A typhoid-like state frequently develops by the 5th day, and the patient may develop atypical pneumonia, sometimes accompanied by delirium.

Pneumonic tularemia can occur after inhalation or by hematogenous spread from another type of tularemia; it develops in 10 to 15% of ulceroglandular tularemia cases and in about 50% of typhoidal tularemia cases. Although signs of consolidation are frequently present, reduced breath sounds and occasional rales may be the only physical findings in tularemic pneumonia. A dry, nonproductive cough is associated with a retrosternal burning sensation. A nonspecific roseola-like rash may appear at any stage of the disease. Splenomegaly and perisplenitis may occur. In untreated cases, temperature remains elevated for 3 to 4 wk and resolves gradually. Mediastinitis, lung abscess, and meningitis are rare complications.

Mortality is almost nil in treated cases and about 6% in untreated cases of ulceroglandular tularemia. Mortality rates are higher for type A infection and for typhoidal, septicemic, and pneumonic tularemia; they are as high as 33% for untreated cases. Death usually results from overwhelming infection, pneumonia, meningitis, or peritonitis. Relapses can occur in inadequately treated cases. One attack confers immunity.

**Diagnosis**

- Cultures
- Acute and convalescent serologic testing
Diagnosis is suspected based on a history of contact with rabbits or wild rodents or exposure to arthropod vectors, the sudden onset of symptoms, and the characteristic primary lesion.

Patients should have cultures of blood and relevant clinical material (eg, sputum, lesions); routine cultures may be negative, and the laboratory should be notified that tularemia is suspected so that appropriate media can be used (and appropriate safety precautions ensured). Acute and convalescent antibody titers should be done 2 wk apart. A 4-fold rise or a single titer > 1:128 is diagnostic. The serum of patients with brucellosis may cross-react to *F. tularensis* antigens but usually in much lower titers. Fluorescent antibody staining is used by some laboratories. Leukocytosis is common, but the WBC count may be normal with an increase only in the proportion of PMNs.

Because this organism is highly infectious, samples and culture media suspected of tularemia should be handled with extreme caution and, if possible, processed by a high-level biosafety containment-equipped laboratory with a level 3 rating.

**Treatment**

- Streptomycin (plus chloramphenicol for meningitis)

The preferred drug is streptomycin 7.5 to 10 mg/kg (up to 1 g) IM q 12 h for 7 to 14 days or, if in a bioterrorism setting, 15 mg/kg IM q 12 h. For children, the streptomycin dose is 10 to 15 mg/kg IM q 12 h. Chloramphenicol 12.5 to 25 mg/kg IV q 6 h is added if there is evidence of meningitis.

Alternatives to streptomycin include gentamicin 1 to 2 mg/kg IM or IV q 8 h, doxycycline 100 mg po q 12 h, chloramphenicol 12.5 to 25 mg/kg IV q 6 h (oral form not available in US), and ciprofloxacin 500 mg po q 12 h. However, relapses occasionally occur with these drugs, and they may not prevent node suppuration.

Continuous wet saline dressings are beneficial for primary skin lesions and may diminish the severity of lymphangitis and lymphadenitis. Surgical drainage of large abscesses is rarely necessary unless therapy is delayed. In ocular tularemia, applying warm saline compresses and using dark glasses give some relief. In severe cases, 2% homatropine 1 to 2 drops q 4 h may relieve symptoms. Intense headache usually responds to oral opioids (eg, oxycodone or hydrocodone with acetaminophen).

**Prevention**

When entering endemic areas, people should use tick-proof clothing and repellents. A thorough search for ticks should be done after leaving tick-infested areas. Ticks should be removed at once (see Sidebar 139-1 on p. 1283). When handling rabbits and rodents, especially in endemic areas, people should wear protective clothing, including rubber gloves and face masks, because organisms may be present in the animal and in tick feces on the animal’s fur. Wild birds and game must be thoroughly cooked before eating. Water that may be contaminated must be disinfected before use.

No vaccine is currently available. Antibiotic prophylaxis with 14 days of oral doxycycline or ciprofloxacin is recommended after high-risk exposure (eg, a laboratory accident).
Chapter 136. Spirochetes

Introduction

The family Spirochaetales is distinguished by the helical shape of the bacteria. They are too thin to be visualized using routine microscopy but can be viewed using darkfield microscopy. There are 3 genera: *Treponema*, *Leptospira*, and *Borrelia*. The spirochetal disease syphilis is discussed on p. 1475.

Bejel, Pinta, and Yaws

Bejel, pinta, and yaws (endemic treponematoses) are chronic, tropical, nonvenereal spirochetal infections spread by body contact. Symptoms of bejel are mucous-membrane and cutaneous lesions, followed by bone and skin gummas. Yaws causes periostitis and dermal lesions. Pinta lesions are confined to the dermis. Diagnosis is clinical and epidemiologic. Treatment is with penicillin.

The causative agents, *Treponema pallidum* subsp *endemicum* (bejel), *T. pallidum* subsp *pertenue* (yaws), and *T. carateum* (pinta), are morphologically and serologically indistinguishable from the agent of syphilis, *T. pallidum* subsp *pallidum*. As in syphilis, the typical course is an initial mucocutaneous lesion followed by diffuse secondary lesions, a latent period, and late destructive disease.

Transmission is by close skin contact—sexual or not—primarily between children living in conditions of poor hygiene. Bejel (endemic syphilis) occurs mainly in arid countries of the eastern Mediterranean and West Africa (Sahel). Transmission results from mouth-to-mouth contact or sharing eating and drinking utensils. Yaws (frambesia) occurs in humid equatorial countries where transmission is favored by scanty clothing and skin trauma. Pinta occurs among the natives of Mexico, Central America, and South America and is not very contagious. Transmission probably requires contact with broken skin.

Symptoms and Signs

**Bejel** begins in childhood as a mucous patch (usually on the buccal mucosa), which may go unnoticed; it is followed by papulosquamous and erosive papular lesions of the trunk and extremities that are similar to yaws. Periostitis of the leg bones is common. Later, gummatous lesions of the nose and soft palate develop.

**Yaws**, after an incubation period of several weeks, begins at the site of inoculation as a red papule that enlarges, erodes, and ulcerates. The surface resembles a strawberry, and the exudate is rich in spirochetes. The lesion heals but is followed after months to a year by successive generalized eruptions that resemble the primary lesion. These lesions often develop in moist areas of the axillae, skinfolds, and mucosal surfaces; they heal slowly and may recur. Keratotic lesions may develop on the palms and soles, causing painful ulcerations (crab yaws). Five to 10 yr later, destructive lesions may develop; they include periostitis (particularly of the tibia), proliferative exostoses of the nasal portion of the maxillary bone (goundou), juxta-articular nodules, gummatous skin lesions, and, ultimately, mutilating facial ulcers, particularly around the nose (gangosa).

**Pinta** lesions are confined to the dermis. They begin at the inoculation site as a small papule that enlarges and becomes hyperkeratotic; they develop mainly on the extremities, face, and neck. After 3 to 9 mo, further thickened and flat lesions (pintids) appear all over the body and over bony prominences. Still later, some lesions become slate blue or depigmented, resembling vitiligo.

Diagnosis

- Clinical evaluation

Diagnosis is based on the typical appearance of lesions in people from endemic areas. Serologic tests for syphilis (the Venereal Disease Research Laboratory [VDRL] and fluorescent treponemal antibody absorption tests) are positive; thus, differentiation from venereal syphilis is clinical. Early lesions are often
darkfield-positive for spirochetes and are indistinguishable from *T. pallidum* subsp *pallidum*.

**Treatment**

- Penicillin

Active disease is treated with 1 dose of penicillin benzathine 1.2 million units IM. Children < 45 kg should receive 600,000 units IM. Public health control includes active case finding and treatment of family and close contacts with penicillin benzathine.

**Leptospirosis**

Leptospirosis is an infection caused by one of several pathogenic serotypes of *Leptospira*. Symptoms are biphasic. Both phases involve acute febrile episodes; the 2nd phase sometimes includes hepatic, renal, and meningeal involvement. Diagnosis is by darkfield microscopy, culture, and serologic testing. Treatment is with doxycycline or penicillin.

Leptospirosis, a zoonosis occurring in many domestic and wild animals, may cause inapparent illness or serious, even fatal disease. There is a carrier state in which animals shed leptospires in their urine for years. Human infections are acquired by direct contact with infected urine or tissue or indirectly by contact with contaminated water or soil. Outbreaks frequently follow exposure to contaminated flood water. Abraded skin and exposed mucous membranes (conjunctival, nasal, oral) are the usual entry portals. Leptospirosis can be an occupational disease (eg, of farmers or sewer and abattoir workers), but in the US, most patients are exposed incidentally during recreational activities (eg, swimming in contaminated water). Dogs and rats are other common probable sources. The 40 to 100 annual US cases occur mainly in late summer and early fall. Because distinctive clinical features are lacking, probably many more cases are not diagnosed and reported.

**Symptoms and Signs**

The incubation period ranges from 2 to 20 (usually 7 to 13) days. The disease is characteristically biphasic. The septicemic phase starts abruptly, with headache, severe muscular aches, chills, fever, cough, chest pain, and, in some patients, hemoptysis. Conjunctival suffusion usually appears on the 3rd or 4th day. Splenomegaly and hepatomegaly are uncommon. This phase lasts 4 to 9 days, with recurrent chills and fever that often spikes to > 39° C. Defervescence follows. The 2nd, or immune, phase occurs between the 6th and 12th day of illness, correlating with appearance of antibodies in serum. Fever and earlier symptoms recur, and meningitis may develop. Iridocyclitis, optic neuritis, and peripheral neuropathy occur infrequently. If acquired during pregnancy, leptospirosis, even during the convalescent period, may cause abortion.

**Weil’s syndrome** (icteric leptospirosis) is a severe form with jaundice and usually azotemia, anemia, diminished consciousness, and continued fever. Onset is similar to that of less severe forms. However, hemorrhagic manifestations, which are due to capillary injury and include epistaxis, petechiae, purpura, and ecchymoses, then develop and rarely progress to subarachnoid, adrenal, or GI hemorrhage. Thrombocytopenia may occur. Signs of hepatocellular and renal dysfunction appear from the 3rd to 6th day. Renal abnormalities include proteinuria, pyuria, hematuria, and azotemia. Hepatocellular damage is minimal, and healing is complete.

Mortality is nil in anicteric patients. With jaundice, the mortality rate is 5 to 10%; it is higher in patients > 60 yr.

**Diagnosis**

- Blood cultures
- Serologic testing

Similar symptoms can result from viral meningoencephalitis, hemolytic fever with renal syndrome due to
hantaviruses, other spirochetal infections, influenza, and hepatitis. The history of biphasic illness may help differentiate leptospirosis. Leptospirosis should be considered in any patient with FUO if they might have been exposed to leptospires.

Patients with suspected leptospirosis should have blood cultures, acute and convalescent (3- to 4-wk) antibody titers, CBC, serum chemistries, and liver function tests. Meningeal findings mandate lumbar puncture; the CSF cell count is between 10 and 1000/μL (usually < 500/μL), with predominantly mononuclear cells. CSF glucose is normal; protein is < 100 mg/dL. CSF bilirubin levels are higher than serum bilirubin levels.

The peripheral blood WBC count is normal or slightly elevated in most patients but may reach 50,000/μL in severely ill patients with jaundice. The presence of > 70% neutrophils helps differentiate leptospirosis from viral illnesses. Serum bilirubin is elevated out of proportion to elevations in serum amino-transferases. In jaundiced patients, bilirubin levels are usually < 20 mg/dL (< 342 μmol/L) but may reach 40 mg/dL (684 μmol/L) in severe infection.

**Treatment**

- Penicillin
- Doxycycline

Antibiotic therapy is most effective when begun early in the infection. In severe illness, penicillin G 5 to 6 million units IV q 6 h or ampicillin 500 to 1000 mg IV q 6 h is recommended. In less severe cases, doxycycline 100 mg po q 12 h, ampicillin 500 to 750 mg po q 6 h, or amoxicillin 500 mg po q 6 h may be given for 5 to 7 days. In severe cases, supportive care, including fluid and electrolyte therapy, is also important. Patient isolation is not required, but urine must be handled and disposed of carefully.

Doxycycline 200 mg po given once/wk during a period of known geographic exposure prevents disease.

**Lyme Disease**

*Lyme disease* is a tick-transmitted infection caused by *Borrelia burgdorferi*. Early symptoms include an erythema migrans rash, which may be followed weeks to months later by neurologic, cardiac, or joint abnormalities. Diagnosis is primarily clinical in early-stage disease, but serologic testing can help diagnose cardiac, neurologic, and rheumatologic complications that occur later in the disease. Treatment is with antibiotics such as doxycycline or ceftriaxone.

**Epidemiology**

Lyme disease was recognized in 1975 because of close clustering of cases in Lyme, Connecticut and is now the most commonly reported tick-borne illness in the US. It has been reported in 49 states, but > 90% of cases occur from Massachusetts to Maryland and in Wisconsin, Minnesota, California, and Oregon. Lyme disease also occurs in Europe, across the former Soviet Union, and in China and Japan. Onset is usually in the summer and early fall. Most patients are children and young adults living in heavily wooded areas.

Lyme disease is transmitted primarily by 4 *Ixodes* sp world wide: *Ixodes scapularis* (the deer tick) in the northeastern and north central US, *I. pacificus* in the western US, *I. ricinus* in Europe, and *I. persulcatus* in Asia. In the US, the white-footed mouse is the primary animal reservoir for *Borrelia burgdorferi* and the preferred host for nymphal and larval forms of the deer tick. Deer are hosts for adult ticks but do not carry *Borrelia*. Other mammals (eg, dogs) can be incidental hosts and can develop Lyme disease. In Europe, sheep host the organism.

**Pathophysiology**

*B. burgdorferi* enters the skin at the site of the tick bite. After 3 to 32 days, the organisms migrate locally in the skin around the bite, spread via the lymphatics to cause regional adenopathy or disseminate in
blood to organs or other skin sites. Initially, an inflammatory reaction (erythema migrans) occurs before significant antibody response to infection (serologic conversion).

**Symptoms and Signs**

Lyme disease has 3 stages:

- **Early localized**
- **Early disseminated**
- **Late**

The early and late stages are usually separated by an asymptomatic interval.

**Early localized**: Erythema migrans (EM), the hallmark and best clinical indicator of Lyme disease, is the first sign of the disease. It occurs in at least 75% of patients, beginning as a red macule or papule at the site of the tick bite, usually on the proximal portion of an extremity or the trunk (especially the thigh, buttock, or axilla), between 3 and 32 days after a tick bite (see Plate 60). The area expands, often with clearing between the center and periphery resembling a bull's eye, to a diameter ≤ 50 cm. Darkening erythema may develop in the center, which may be hot to the touch and indurated. Without therapy, EM typically fades within 3 to 4 wk.

Soon after onset, nearly one half of untreated patients develop multiple, usually smaller lesions without indurated centers. Cultures of biopsy samples of these secondary lesions have been positive, indicating dissemination of infection. EM generally lasts a few weeks (average, 3 to 4 wk). Evanescent lesions may appear during resolution. Mucosal lesions do not occur.

**Early disseminated**: Symptoms of early-disseminated disease begin days or weeks after the appearance of the primary lesion when the bacteria spread through the body. This musculoskeletal, flu-like syndrome, consisting of malaise, fatigue, chills, fever, headache, stiff neck, myalgias, and arthralgias, may last for weeks. Because symptoms are often nonspecific, the diagnosis is frequently missed if EM is absent; a high index of suspicion is required. Frank arthritis is rare at this stage. Less common are backache, nausea and vomiting, sore throat, lymphadenopathy, and splenomegaly.

Symptoms are characteristically intermittent and changing, but malaise and fatigue may linger for weeks. Some patients develop symptoms of fibromyalgia. Resolved skin lesions may reappear faintly, sometimes before recurrent attacks of arthritis, in late-stage disease.

**Neurologic abnormalities** develop in about 15% of patients within weeks to months of EM (generally before arthritis occurs), commonly last for months, and usually resolve completely. Most common are lymphocytic meningitis (CSF pleocytosis of about 100 cells/μL) or meningoencephalitis, cranial neuritis (especially Bell's palsy, which may be bilateral), and sensory or motor radiculoneuropathies, alone or in combination.

**Myocardial abnormalities** occur in about 8% of patients within weeks of EM. They include fluctuating degrees of atrioventricular block (1st-degree, Wenckebach, or 3rd-degree) and, rarely, myopericarditis with chest pain, reduced ejection fractions, and cardiomegaly.

**Late**: In untreated Lyme disease, the late stage begins months to years after initial infection. Arthritis develops in about 60% of patients within several months, occasionally up to 2 yr, of disease onset (as defined by EM). Intermittent swelling and pain in a few large joints, especially the knees, typically recur for several years. Affected knees commonly are much more swollen than painful; they are often hot, but rarely red. Baker cysts may form and rupture. Malaise, fatigue, and low-grade fever may precede or accompany arthritis attacks. In about 10% of patients, knee involvement is chronic (unremittent for ≥ 6 mo). Other late findings (occurring years after onset) include an antibiotic-sensitive skin lesion (acrodematitis chronica atrophicans) and chronic CNS abnormalities, either polyneuropathy or a subtle encephalopathy with mood, memory, and sleep disorders.
Diagnosis

• Clinical evaluation, supported by acute and convalescent serologic testing

Cultures of blood and relevant body fluids (eg, CSF, joint fluid) may be obtained, primarily to diagnose other pathogens. Acute (IgM) and convalescent (IgG) antibody titers may be helpful; positive enzyme-linked immunosorbent assay (ELISA) titers should be confirmed by Western blot. However, seroconversion may be late (eg, > 4 wk) or occasionally absent (eg, if patients received prior antibiotic therapy), and positive IgG titers alone represent previous exposure. PCR testing of CSF or synovial fluid is often positive when those sites are involved. Consequently, diagnosis depends on both test results and the presence of typical findings. A classic EM rash strongly suggests Lyme disease, particularly when supported by other elements (eg, recent tick bite, exposure to endemic area, typical systemic symptoms).

In the absence of rash, diagnosis is more difficult. Early-disseminated disease may mimic idiopathic RA in children and reactive arthritis and atypical RA in adults. Important negative RA findings in adults include usually absent morning stiffness, subcutaneous nodules, iridocyclitis, mucosal lesions, rheumatoid factor, and antinuclear antibodies.

In the US, human granulocytic anaplasmosis and babesiosis are also transmitted by *I. scapularis* and have a common geographic distribution in the northeastern and upper Midwest. Patients ill with any one of the diseases transmitted by *I. scapularis* may be concurrently infected with the other diseases it transmits. A clinician should suspect that patients with Lyme disease also have babesiosis if they have hemolytic anemia and thrombocytopenia or that they also have human granulocytic anaplasmosis if they have hepatitis, leukopenia, or thrombocytopenia. Human monocytotropic ehrlichiosis, which is caused by *Ehrlichia chaffeensis* and transmitted by the Lone Star tick, *Amblyomma americanum*, occurs mainly in the southeastern and south central US and is unlikely to be confused with Lyme disease.

Lyme disease may manifest with a musculoskeletal aseptic meningitis syndrome in summer. Although ehrlichiosis, a rickettsial infection, is transmitted by the same tick (see p. 1286), clinical coinfection is rare. The lack of leukopenia, thrombocytopenia, elevated aminotransferases, and inclusion bodies in neutrophils helps distinguish Lyme disease from human granulocytic anaplasmosis. Lack of hemolytic anemia (unelevated LDH) and thrombocytopenia helps exclude babesiosis. Acute rheumatic fever is considered in the occasional patient with migratory polyarthralgias and either an increased PR interval or chorea (as a manifestation of meningoencephalitis). However, patients with Lyme disease rarely have heart murmurs or evidence of a preceding streptococcal infection.

Late-stage disease lacks axial involvement, which distinguishes it from spondyloarthropathies with peripheral joint involvement. Lyme disease may cause Bell's palsy and can mimic other causes of lymphocytic meningitis, or peripheral neuropathies.

In areas where Lyme disease is endemic, many patients report arthralgias, fatigue, difficulty concentrating, or other nonspecific symptoms. Without a history of EM or other symptoms of early-localized or early-disseminated Lyme disease, few of these patients actually have Lyme disease. In such patients, elevated IgG titers (with normal IgM titers) indicate past exposure, not current or persistent infection, and may lead to long and unnecessary courses of antibiotic therapy.

Treatment

• Multiple alternatives that vary with stage of disease but typically include amoxicillin, doxycycline, and ceftriaxone

Most features of Lyme disease respond to antibiotics, but treatment of early disease is most successful. In late-stage disease, antibiotics eradicate the bacteria, relieving the arthritis in most people. However, a few genetically predisposed people have persistent arthritis even after the infection has been eliminated because of continued inflammation.

*Table 136-3* shows adult treatment regimens for various presentations of Lyme disease. Treatment in children is similar except that doxycycline is avoided in children < 8 yr and doses are adjusted based on
weight (see Table 132-3 on p. 1185).

For symptomatic relief, NSAIDs may be used. Complete heart block may require a temporary pacemaker. Tense knee joints due to effusions require aspiration. Some genetically predisposed patients with arthritis of the knee that persists despite antibiotic therapy may respond to arthroscopic synovectomy.

Prevention

Precautions against tick bite (see Sidebar 139-1 on p. 1283) should be taken by people in endemic areas. Deer tick nymphs, which attack humans, are small and difficult to see. Once attached to the skin, they gorge on blood for days. Transmission of *B. burgdorferi* does not usually occur until the infected tick has been in place for > 36 h. Thus, searching for ticks after potential exposure and removing them promptly can help prevent infection.

A single dose of doxycycline 200 mg po has been shown to reduce the likelihood of Lyme disease after a deer tick bite. Patients with a known tick bite can easily be instructed to monitor the bite site and seek care if rash or other symptoms occur; the diagnostic dilemma of Lyme is most prominent when there is no history of tick bite.

A vaccine, which had adverse effects similar to symptoms of Lyme disease and was only moderately effective, has been removed from the market.

Rat-Bite Fever

*Rat-bite fever is caused by either *Streptobacillus moniliformis* or *Spirillum minus*. Symptoms of the streptobacillary form include fever, rash, and arthralgias. The spirillary form causes relapsing fever, rash, and regional lymphadenitis. Diagnosis is clinical and confirmed by culture and sometimes rising antibody titers. Treatment is with penicillin or doxycycline.*

Rat-bite fever is transmitted to humans in up to 10% of rat bites. However, there may be no history of rat bite. Rat-bite fever is most commonly caused by rat bites but can be caused by the bite of any rodent or of a carnivore that preys on rodents. Both the streptobacillary and spirillary forms affect mainly urban dwellers living in crowded conditions and biomedical laboratory personnel. In the US and Europe, rat-bite fever is usually due to *S. moniliformis*; in Asia, it is usually due to *S. minus*.

**Streptobacillary rat-bite fever:** This form is caused by the pleomorphic gram-negative bacillus *S. moniliformis*, an organism present in the oropharynx of healthy rats. Epidemics have been associated with ingestion of unpasteurized milk contaminated by *S. moniliformis* (Haverhill fever), but infection is usually a consequence of a bite by a wild rat or mouse. Other rodents and weasels have also been implicated.

The primary wound usually heals promptly, but after an incubation period of 1 to 22 (usually < 10) days, a viral-like syndrome develops abruptly, causing chills, fever, vomiting, headache, and back and joint pains. Most patients develop a morbilliform, petechial, or vesicular rash on the hands and feet about 3 days later. Polyarthralgia or arthritis, usually affecting the large joints asymmetrically, develops in many patients within 1 wk and, if untreated, may persist for several days or months. Bacterial endocarditis and abscesses in the brain or other tissues are rare but serious. Some patients have infected pericardial effusion and infected amniotic fluid. Haverhill fever resembles percutaneously acquired rat-bite fever, but with more prominent pharyngitis and vomiting.

Diagnosis is confirmed by culturing the organism from blood or joint fluid. Measurable agglutinins develop during the 2nd or 3rd wk and are diagnostically important if the titer increases. PCR or enzyme-linked immunosorbent assay (ELISA) tests may be helpful. The WBC count ranges between 6,000 and 30,000/μL. The streptobacillary form usually can be differentiated clinically from the spirillary form.
Spirillary rat-bite fever (sodoku): *S. minus* infection is acquired through a rat bite or occasionally a mouse bite. The wound usually heals promptly, but inflammation recurs at the site after 4 to 28 (usually > 10) days, accompanied by a relapsing fever and regional lymphadenitis. A roseolar-urticarial rash sometimes develops but is less prominent than the streptobacillary rash. Systemic symptoms commonly accompany fever, but arthritis is rare. In untreated patients, 2- to 4-day cycles of fever usually recur for 4 to 8 wk, but febrile episodes rarely recur for > 1 yr.

Diagnosis is by direct visualization or culture of *Spirillum* from blood smears or tissue from lesions or lymph nodes, or by Giemsa stain or darkfield examination of blood from inoculated mice. The WBC count ranges between 5,000 and 30,000/μL. The Venereal Disease Research Laboratory (VDRL) results are false-positive in half the patients. The disease may easily be confused with malaria or *Borrelia recurrentis* infection; both are characterized by relapsing fever.

Treatment is the same as for the streptobacillary form.

**Relapsing Fever**

(Tick, Recurrent, or Famine Fever)

Relapsing fever is a recurring febrile disease caused by several species of *Borrelia* and transmitted by lice or ticks. Symptoms are recurrent febrile episodes with headache, myalgia, and vomiting lasting 3 to 5 days, separated by intervals of apparent recovery. Diagnosis is clinical, confirmed by staining of peripheral blood smears. Treatment is with a tetracycline or erythromycin.

The insect vector may be soft ticks of the genus *Ornithodoros* or the human body louse, depending on geographic location. Louseborne relapsing fevers are rare in the US and endemic only in the highlands of Central and East Africa and the Andes of South America; the tick-borne fevers are endemic in the Americas, Africa, Asia, and Europe. In the US, the disease is generally confined to the western states, where occurrence is highest between May and September.

The louse is infected by feeding on a febrile patient. If the louse is crushed on a new host, *Borrelia* are released and can enter abraded skin or bites. Intact lice do not transmit disease. Ticks acquire the spirochetes from rodent reservoirs. Humans are infected when spirochetes in the tick's saliva or excreta enter the skin rapidly as the tick bites. Congenital borreliosis has also been reported.

The mortality rate is generally < 5% with treatment but may be considerably higher in very young, pregnant, old, malnourished, or debilitated people or during epidemics of louse-borne fever.

**Symptoms and Signs**

Because the tick feeds transiently and painlessly at night, most patients do not report a history of tick bite but may report an overnight exposure to caves or rustic dwellings. When present, louse infestation is usually obvious.

The incubation period ranges from 3 to 11 days (median, 6 days). Sudden chills mark the onset, followed by high fever, tachycardia, severe headache, vomiting, muscle and joint pain, and often delirium. An erythematosus macular or purpuric rash may appear early over the trunk and extremities. Conjunctival, subcutaneous, or submucous hemorrhages may be present. Fever remains high for 3 to 5 days, then clears abruptly, indicating a turning point in the disease. The duration of illness ranges from 1 to 54 days (median, 18 days). Later in the several weeks' course of the disease, jaundice, hepatomegaly, splenomegaly, myocarditis, and heart failure may occur, especially in louse-borne disease. Other symptoms may include ophthalmitis, iridocyclitis, exacerbation of asthma, and erythema multiforme. Meningismus is rare. Spontaneous abortion can occur.
The patient is usually asymptomatic for several days to ≥ 1 wk between the initial episode and the first relapse. Relapses, related to the cyclic development of the parasites, occur with a sudden return of fever and often arthralgia and all the former symptoms and signs. Jaundice is more common during relapse. The illness clears as before, but 2 to 10 similar episodes may follow at intervals of 1 to 2 wk. The episodes become progressively less severe, and patients eventually recover as they develop immunity.

Diagnosis

- Darkfield microscopy

The diagnosis is suggested by recurrent fever and confirmed by visualization of spirochetes in the blood during a febrile episode. The spirochetes may be seen on darkfield examination or Wright's- or Giemsa-stained thick and thin blood smears. (Acridine orange stain for examining blood or tissue is more sensitive than Wright's or Giemsa stain.) Serologic tests are unreliable. Mild polymorphonuclear leukocytosis may occur. Serologic tests for syphilis and Lyme disease may be falsely positive.

Differential diagnosis includes Lyme arthritis, malaria, dengue, yellow fever, leptospirosis, typhus, influenza, and enteric fevers.

Treatment

- Tetracycline, doxycycline, or erythromycin

In relapsing fever transmitted by ticks, tetracycline or erythromycin 500 mg po q 6 h is given for 5 to 10 days. A single 500-mg oral dose of either drug cures louse-transmitted fever. Doxycycline 100 mg po q 12 h for 5 to 10 days is also effective. Children < 8 yr are given erythromycin estolate 10 mg/kg po tid. When vomiting or severe disease precludes oral administration, doxycycline 1 to 2 mg/kg may be given IV q 12 to 24 h to children > 8 yr. Children < 8 yr are given penicillin G 25,000 units/kg IV q 6 h.

Therapy should be started early during fever. A Jarisch-Herxheimer reaction may occur within 2 h of starting therapy. Severity of the Jarisch-Herxheimer reaction may be lessened by giving acetaminophen 650 mg po 2 h before and 2 h after the first dose of doxycycline or erythromycin.

Dehydration and electrolyte imbalance should be corrected with parenteral fluids. Acetaminophen with oxycodone or hydrocodone may be used for severe headache. Nausea and vomiting should be treated with prochlorperazine 5 to 10 mg po or IM once/day to qid. If heart failure occurs, specific therapy is indicated.
Chapter 137. Neisseriaceae

Introduction

All pathogenic aerobic gram-negative cocci belong to the Neisseriaceae family, which is composed of 5 genera:

- *Acinetobacter*
- *Kingella*
- *Moraxella* (including 2 subgenera, *Moraxella* and *Branhamella)*
- *Neisseria*
- *Oligella*

Of these, *Neisseria* includes the most important human pathogens, *N. meningitidis* and *N. gonorrhoeae*. Numerous saprophytic Neisseriaceae commonly inhabit the oropharynx, vagina, or colon but rarely cause human disease. *Moraxella catarrhalis* causes otitis media in children and sinusitis. Over half a dozen other *Moraxella* sp and the related *Kingella kingae* cause infections in the CNS, respiratory tract, urinary tract, endocardium, bones, and joints.

Humans are the only reservoir of *Neisseria*, and person-to-person spread is the prime mode of transmission. Both *N. meningitidis* (meningococcus) and *N. gonorrhoeae* can exist in an asymptomatic carrier state. Carrier states are particularly important with meningococcus because of its association with epidemics. Gonorrhea is discussed on p. 1471.

*Acinetobacter* Infections

*Acinetobacter* sp can cause suppurative infections in any organ system; these bacteria are often opportunists in hospitalized patients.

*Acinetobacter* is ubiquitous and can survive on dry surfaces for up to a month, increasing the likelihood of patients being colonized and medical equipment being contaminated. There are many species of *Acinetobacter*; all can cause human disease, but *A. baumannii* (AB) accounts for about 80% of infections.

Diseases Caused by *Acinetobacter*

AB infections typically occur in critically ill, hospitalized patients. Crude death rates associated with AB infection are 19 to 54%.

The most common site for infection is the respiratory system. *Acinetobacter* easily colonize tracheostomy sites and can cause community-acquired bronchiolitis and tracheobronchitis in healthy children and tracheobronchitis in immunocompromised adults. Hospital-acquired *Acinetobacter* pneumonias are frequently multilobar and complicated. Secondary bacteremia and septic shock are associated with a poor prognosis.

*Acinetobacter* sp can also cause suppurative infections (eg, abscesses) in any organ system, including the lungs, urinary tract, skin, and soft tissues; bacteremia may occur. Rarely, these organisms cause meningitis (primarily after neurosurgical procedures), cellulitis, or phlebitis in patients with an indwelling venous catheter, ocular infections, native or prosthetic valve endocarditis, osteomyelitis, septic arthritis, and pancreatic and liver abscesses.

The significance of isolates from clinical specimens is difficult to determine because they often represent colonization.
**Risk factors:** Risk factors for infection depend on the type of infection (hospital-acquired, community-acquired, multidrug resistant—see Table 137-1).

**Drug resistance:** Recently, multidrug resistant (MDR) AB has emerged. Spread in ICUs has been attributed to colonized health care practitioners, contaminated common equipment, and contaminated parenteral nutrition solutions.

**Treatment**

- Typically empiric multidrug therapy for serious infections

In patients with localized cellulitis or phlebitis associated with a foreign body (eg, IV catheter, suture), removal of the foreign body plus local care is usually sufficient. Tracheobronchitis after endotracheal intubation may resolve with pulmonary toilet alone. Patients with more extensive infections should be treated with antibiotics and with debridement if necessary.

AB has long had intrinsic resistance to many antimicrobials. MDR-AB can be resistant to $\geq 3$ classes of antimicrobials; some isolates are resistant to all. Possible options include a carbapenem (eg, meropenem, imipenem, doripenem), a $\beta$-lactam/$\beta$-lactamase inhibitor (eg, ampicillin/sulbactam), colistin, or a fluoroquinolone plus an aminoglycoside, rifampin, or both. Sulbactam (a $\beta$-lactamase inhibitor) has intrinsic bactericidal activity against many MDR-AB strains. Tigecycline, a glycyclcline antibiotic, is also effective; however, borderline activity and emergence of resistance during therapy has been reported.

Mild to moderate infections may respond to monotherapy. Traumatic wound infections can be treated with minocycline. Serious infections are treated with combination therapy—typically, imipenem, or a $\beta$-lactam/$\beta$-lactamase inhibitor plus an aminoglycoside.

To prevent spread, health care practitioners should use contact precautions (hand washing, barrier precautions) and appropriate ventilator care and cleaning for patients colonized or infected with MDR-AB.

**Kingella Infections**

*Kingella* organisms colonize the human respiratory tract. They cause skeletal infections, endocarditis, and bacteremia and, rarely, pneumonia, epiglottitis, meningitis, abscesses, and ocular infections.

*Kingella* are short, nonmotile, gram-negative coccobacilli that occur in pairs or short chains. The organisms are slow-growing and fastidious. *Kingella* are recovered from the human respiratory tract and are a rare cause of human disease.

Among *Kingella* species, *K. kingae* is the most frequent human pathogen; these organisms frequently colonize the respiratory mucous membranes. Children aged 6 mo to 4 yr have the highest rates of colonization and invasive disease from this and other respiratory tract pathogens such as *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Infection has a seasonal distribution, with more cases in fall and winter.

**Diseases Caused By Kingella**

The most common manifestations of *K. kingae* disease are

- Skeletal infections
- Endocarditis
• Bacteremia

Rare manifestations include pneumonia, epiglottitis, meningitis, abscesses, and ocular infections.

The most common skeletal infection is septic arthritis, which most frequently affects large, weight-bearing joints, especially the knee and ankle. Osteomyelitis most frequently involves bones of the lower extremities. Onset is insidious, and diagnosis is often delayed. Hematogenous invasion of intervertebral disks can occur, most commonly in the lumbar intervertebral spaces.

*Kingella* endocarditis has been reported in all age groups. Endocarditis may involve native or prosthetic valves. *Kingella* is a component of the so-called HACEK group (*Haemophilus aphrophilus* and *H. parainfluenzae, Actinobacillus, Cardiobacterium, Eikenella, Kingella*—see p. 1252), which includes fastidious gram-negative bacteria capable of causing endocarditis.

Diagnosis requires laboratory isolation from suspected fluids or tissues.

**Treatment**

• A penicillin or cephalosporin

*Kingella* organisms are generally susceptible to various penicillins and cephalosporins. However, antimicrobial susceptibility testing is needed to guide therapy. Other useful drugs include aminoglycosides, trimethoprim/sulfamethoxazole, tetracyclines, erythromycin, and ciprofloxacin.

**Meningococcal Diseases**

*Meningococci* (*Neisseria meningitidis*) cause meningitis and septicemia. Symptoms, usually severe, include headache, nausea, vomiting, photophobia, lethargy, rash, multiple organ failure, shock, and disseminated intravascular coagulation. Diagnosis is clinical, confirmed by culture. Treatment is penicillin or a 3rd-generation cephalosporin.

Worldwide, the incidence of endemic meningococcal disease is 0.5 to 5/100,000, with an increased number of cases during winter and spring in temperate climates. Local outbreaks occur most frequently in sub-Saharan Africa between Senegal and Ethiopia, an area known as the meningitis belt. In major African epidemics, attack rates range from 100 to 800/100,000.

In the US, the annual incidence ranges from 0.5 to 1.1/100,000. Most cases are sporadic, typically in children < 2 yr; < 2% occur in outbreaks. Outbreaks tend to occur in semiclosed communities (eg, military recruit camps, college dormitories, schools, day-care centers) and often involve patients aged 5 to 19 yr.

**Diseases Caused by Meningococci**

Over 90% of meningococcal infections involve

• Meningitis

• Septicemia

Infections of lungs, joints, respiratory passageways, GU organs, eyes, endocardium, and pericardium are less common.

**Pathophysiology**

Meningococci can colonize the oropharynx and nasopharynx of asymptomatic carriers. A combination of factors is probably responsible for transition from carrier state to invasive disease. Despite documented high rates of colonization, transition to invasive disease is rare and occurs primarily in previously uninfected patients. Transmission usually occurs via direct contact with respiratory secretions from a
nasopharyngeal carrier. Carrier rates rise dramatically during epidemics.

After invading the body, _N. meningitidis_ causes meningitis and severe bacteremia in children and adults, resulting in profound vascular effects. Infection can rapidly become fulminant and is associated with a mortality rate of 10 to 15%. Of patients who recover, 10 to 15% have serious sequelae, such as permanent hearing loss, intellectual disability, or loss of phalanges or limbs.

**Risk factors:** Children aged 6 mo to 3 yr are the most frequently infected. Other high-risk groups include adolescents, military recruits, college freshmen living in dormitories, people with complement deficiencies, and microbiologists working with _N. meningitidis_ isolates. Infection or vaccination confers serogroup-specific immunity.

**Symptoms and Signs**

Patients with meningitis frequently report fever, headache, and stiff neck (see also Acute Bacterial Meningitis on p. 1735). Other symptoms include nausea, vomiting, photophobia, and lethargy. A maculopapular or hemorrhagic petechial rash often appears soon after disease onset. Meningeal signs are often apparent during physical examination. Fulminant meningococcemia syndromes include Waterhouse-Friderichsen syndrome (septicemia, profound shock, cutaneous purpura, adrenal hemorrhage), sepsis with multiple organ failure, shock, and disseminated intravascular coagulation. A rare, chronic meningococcemia causes recurrent mild symptoms.

**Diagnosis**

- **Gram stain and culture**

_Neisseria_ are small, gram-negative cocci readily identified with Gram stain and by other standard bacteriologic identification methods. Serologic methods, such as latex agglutination and coagglutination tests, allow rapid presumptive diagnosis of _N. meningitides_ in blood, CSF, synovial fluid, and urine. However, both positive and negative results should be confirmed by culture. PCR for _N. meningitidis_ has been developed but is not commercially available.

**Treatment**

- **Ceftriaxone**
- **Dexamethasone**

While awaiting definitive identification of the causal organism, immunocompetent adults suspected of having meningococcal infection are given a 3rd-generation cephalosporin (eg, cefotaxime 2 g IV q 6 h, ceftriaxone 2 g IV q 12 h) plus vancomycin 500 to 750 mg IV q 6 h or 1 g IV q 12 h or q 8 h. In immunocompromised patients and patients > 50 yr, coverage for _Listeria monocytogenes_ should be considered by adding ampicillin 2 g IV q 4 h.

Once _N. meningitidis_ has been definitively identified, the preferred treatment is ceftriaxone 2 g IV q 12 h or penicillin 4 million units IV q 4 h.

Corticosteroids decrease the incidence of neurologic complications in children and adults. When corticosteroids are used, they should be given with or before the first dose of antibiotics. Dexamethasone 0.15 mg/kg IV q 6 h in children (10 mg q 6 h in adults) is given for 4 days.

**Prevention**

**Antibiotic prophylaxis:** Close contacts of people with meningococcal disease are at increased risk of acquiring disease and should receive a prophylactic antibiotic. Options include

- **Rifampin** 600 mg (for children > 1 mo, 10 mg/kg; for children < 1 mo, 5 mg/kg) po q 12 h for 4 doses
Ceftriaxone 250 mg (for children < 15 yr, 125 mg) IM for 1 dose

In adults, a fluoroquinolone (ciprofloxacin or levofloxacin 500 mg or ofloxacin 400 mg) po for 1 dose

Azithromycin is not routinely recommended, but a recent study showed that a single 500-mg dose was equivalent to rifampin for chemoprophylaxis and so could be an alternative for patients with contraindications to recommended drugs.

Ciprofloxacin-resistant meningococcal disease has been reported in several countries (Greece, England, Wales, Australia, Spain, Argentina, France, India). More recently, 2 US states (North Dakota, Minnesota) reported ciprofloxacin-resistant meningococci and so recommended that ciprofloxacin chemoprophylaxis not be used as preventive treatment for people who have had close contact with someone diagnosed with meningococcal disease.

**Vaccination:** A meningococcal conjugate vaccine is available in the US. The vaccine includes 4 of the 5 serogroups of meningococcus (all but B). A one-time routine vaccination is recommended for all children between the age of 11 and 18 yr. Vaccination is also recommended for people who are aged 19 to 55 and at risk, including military recruits, college freshmen living in a dormitory, travelers to hyperendemic or epidemic areas, and people with laboratory or industrial exposure to *N. meningitidis* aerosols. Adults and children aged 2 to 10 yr with terminal complement component deficiencies or functional or actual asplenia should also be vaccinated.

**Moraxella Catarrhalis Infection**

*Moraxella catarrhalis* causes ear and upper and lower respiratory infections.

Previously classified as *Micrococcus*, then *Neisseria*, and also known as *Branhamella catarrhalis*, this organism is a frequent cause of otitis media in children, acute and chronic sinusitis at all ages, and lower respiratory infection in adults with chronic lung disease. It is the 2nd most common bacterial cause of COPD exacerbations after nontypeable *Haemophilus influenzae*. *M. catarrhalis* pneumonia resembles pneumococcal pneumonia. Although bacteremia is rare, half of patients die within 3 mo because of intercurrent diseases.

The prevalence of *M. catarrhalis* colonization depends on age. About 1 to 5% of healthy adults have upper respiratory tract colonization. Nasopharyngeal colonization with *M. catarrhalis* is common throughout infancy, may be increased during winter months, and is a risk factor for acute otitis media; early colonization is a risk factor for recurrent otitis media. Substantial regional differences in colonization rates occur. Living conditions, hygiene, environmental factors (eg, household smoking), genetic characteristics of the populations, host factors, and other factors may contribute to these differences.

The organism appears to spread contiguously from its colonizing position in the respiratory tract to the infection site.

There is no pathognomonic feature of *M. catarrhalis* otitis media, acute or chronic sinusitis, or pneumonia. In lower respiratory disease, patients experience increased cough, purulent sputum production, and increased dyspnea.

These gram-negative cocci resemble *Neisseria* sp but can be readily distinguished by routine biochemical tests after culture isolation from infected fluids or tissues.

All strains now produce β-lactamase. The organism is generally susceptible to β-lactam/β-lactamase inhibitors, sulfamethoxazole, tetracyclines, extended-spectrum oral cephalosporins, aminoglycosides, macrolides, and fluoroquinolones.

**Oligella Infections**

*Oligella* sp causes infection primarily of the GU tract.
The genus *Oligella* contains 2 species, *Oligella urethralis* and *O. ureolytica*.

*O. urethralis* is a commensal of the GU tract, and most clinical isolates are from the urine, predominantly from men. Although symptomatic infections are rare, bacteremia, septic arthritis that mimics gonococcal arthritis, and peritonitis have been reported.

*O. ureolytica* also occurs primarily in the urine, usually from patients with long-term urinary catheters or other urinary drainage systems. These patients have a propensity to develop urinary stones, possibly because the organism hydrolyzes urea and alkalinizes urine, leading to precipitation of phosphates. Bacteremia has occurred in a patient with obstructive uropathy.

Diagnosis is by culture.

Because these organisms are rarely isolated, antimicrobial susceptibility data are limited; most are sensitive to β-lactam antibiotics. However, a β-lactam-producing strain and strains resistant to ciprofloxacin have been identified.
Chapter 138. Chlamydia and Mycoplasmas

Chlamydia

Three species of *Chlamydia* cause human disease, including sexually transmitted diseases and pneumonias. Most are susceptible to azithromycin, doxycycline, and some fluoroquinolones.

Chlamydiae are nonmotile, obligate intracellular organisms. Although originally considered viruses because they require a cellular host, they are now known to be bacteria; they contain DNA, RNA, and ribosomes and make their own proteins and nucleic acids. However, because they synthesize most of their own metabolic intermediates, they cannot make their own ATP and thus are energy parasites.

Three species cause human disease:

- *Chlamydia trachomatis*
- *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*
- *Chlamydophila* (formerly *Chlamydia*) *psittaci*

*C. trachomatis* has 18 immunologically defined serovars. Serovars A, B, Ba, and C cause trachoma and inclusion conjunctivitis; D through K cause sexually transmitted diseases (STDs) localized to mucosal surfaces; L1, L2, and L3 cause STDs that lead to invasive lymph node disease (lymphogranuloma venereum). In the US, *C. trachomatis* is the most common bacterial cause of STDs, including nongonococcal urethritis (see p. 1468) and epididymitis in men; cervicitis, urethritis, and pelvic inflammatory disease in women; and proctitis, lymphogranuloma venereum, and reactive arthritis (Reiter's syndrome) in both sexes. Maternal transmission of *C. trachomatis* causes neonatal conjunctivitis and pneumonia. The organism is occasionally isolated from the throat in adults but rarely causes symptomatic pharyngitis.

*C. pneumoniae* can cause pneumonia (especially in children and young adults) that may be clinically indistinguishable from pneumonia caused by *Mycoplasma pneumoniae*. In some patients with *C. pneumoniae*, pneumonia, hoarseness, and sore throat may precede coughing, which may be persistent and complicated by bronchospasm. From 6 to 19% of community-acquired pneumonia cases are due to *C. pneumoniae*, but chlamydial pneumonia is uncommon among children < 5 yr. No seasonal variations in occurrence have been observed. The organism has been found in atheromatous lesions, and infection may be associated with increased risk of coronary artery disease, although proof of a connection has not yet been established.

*C. psittaci* causes psittacosis. Strains causing human disease are usually transmitted from psittacine birds (eg, parrots), causing a disseminated disease characterized by pneumonitis.

Diagnosis

- Clinical evaluation
- Sometimes nucleic acid-based testing

The diagnosis is sometimes made without testing (eg, in men with typical nongonococcal urethritis). However, because many cases are asymptomatic, especially in women, routine testing for genital infection has been recommended and is increasingly common. In cases of urethritis, diagnosis is often made by excluding gonorrhea as a cause or by presuming that both chlamydial infection and gonorrhea are present.

*C. trachomatis* can be isolated by diagnostic cell culture but is best identified in genital samples using nucleic acid amplification tests (NAATs) such as PCR because these tests are more sensitive than cell culture and have less stringent sample handling requirements. NAATs for genital infection can be done.
using noninvasively obtained samples, such as urine or vaginal swabs obtained by the patient or clinician. An enzyme-linked immunosorbent assay (ELISA) or a direct immunofluorescent slide test can detect antigens in genital and ocular infections, but both are less sensitive than culture or NAATs. Serologic tests are useful in diagnosing pneumonia in infants and lymphogranuloma venereum.

A primary clue to diagnosis of C. psittaci infection is close contact with birds, typically parrots or parakeets.

**Screening:** Because chlamydial genital infection is so common and often causes mild or nonspecific symptoms (particularly in women), routine screening of asymptomatic people at high risk of STDs is recommended. People who should be screened include

- People with a history of a previous STD
- People with high-risk behaviors
- Sexually active adolescents and young adults < 24 yr
- Pregnant women < 24 yr

**Treatment**

- Azithromycin or doxycycline

Uncomplicated lower genital tract infection is typically treated with a single dose of azithromycin (1 g po) or with a 7-day regimen of doxycycline (100 mg po bid) or some fluoroquinolones (eg, levofloxacin 500 mg po once/day). Treatment of presumed chlamydial infection is routine when gonorrhea is present (see also p. 1473). Pelvic inflammatory disease, lymphogranuloma venereum, or epididymitis is usually treated for 2 wk.

Specific infections are discussed elsewhere in THE MANUAL: Psittacosis and C. pneumoniae pneumonia on p. 1924, lymphogranuloma venereum and urethritis on p. 1474, epididymitis on p. 2455, reactive arthritis on p. 343, neonatal conjunctivitis and neonatal pneumonia on pp. 2824 and 2832, and trachoma and inclusion conjunctivitis on p. 583.

**Mycoplasmas**

Mycoplasmas are ubiquitous bacteria that differ from other prokaryotes in that they lack a cell wall. *Mycoplasma pneumoniae* is a common cause of pneumonia, particularly community-acquired. Increasing evidence suggests that *M. genitalium* and *Ureaplasma urealyticum* cause some cases of nongonococcal urethritis. They (and *M. hominis*) are often present in patients with other urogenital infections (eg, vaginitis, cervicitis, pyelonephritis, pelvic inflammatory disease) and some nonurogenital infections, but whether they cause these infections is not clear.

Mycoplasmas are not visible with light microscopy. Culture is technically difficult and often unavailable, but laboratory diagnosis is sometimes possible with DNA probes or by detection of antibodies or antigens; frequently, diagnosis must be clinical.

Macrolides are usually the antimicrobials of choice. Most species are also sensitive to fluoroquinolones and tetracyclines.
Chapter 139. Rickettsiae and Related Organisms

Introduction

Rickettsial diseases (rickettsioses) and related diseases (ehrlichiosis, Q fever) are caused by a group of gram-negative, obligately intracellular coccobacilli. Most have an arthropod vector. Symptoms usually include sudden-onset fever with severe headache, malaise, prostration, and, in most cases, a characteristic rash. Diagnosis is clinical, confirmed by immunofluorescence assay or PCR. Treatment is with tetracyclines or chloramphenicol.

Although rickettsiae require living cells for growth, they are true bacteria because they have metabolic enzymes and cell walls, use O$_2$, and are susceptible to antibiotics. Rickettsiae (except *Coxiella burnetii*, the causative agent of Q fever, which is no longer classified with the Rickettsiae) have an animal reservoir and usually an arthropod vector that infects humans (see Table 139-1).

Rickettsiae multiply at the site of arthropod attachment and often produce a local lesion (eschar). They penetrate the skin or mucous membranes; some (*Rickettsia rickettsii*) multiply in the endothelial cells of small blood vessels, causing vasculitis, and others (*Ehrlichia* sp) replicate in WBCs. The endovasculitis of *R. rickettsii* causes a rash, encephalitic signs, and gangrene of skin and tissues. Patients seriously ill with a rickettsial disease of the typhus or spotted fever group or with ehrlichiosis may have ecchymotic skin necrosis, digital gangrene, circulatory collapse, shock, oliguria, anuria, azotemia, anemia, hyponatremia, hypochloremia, edema, delirium, and coma.

Diagnosis

- Clinical features
- Biopsy of rash
- Serologic testing not useful acutely
- PCR for *Ehrlichia* sp

Differentiating rickettsial from other infections:

Rickettsial and related diseases must be differentiated from other acute infections, primarily meningococcemia, rubeola, and rubella. A history of louse or flea contact, tick bite, or presence in a known endemic area is helpful, but such history is often absent. Clinical features may help distinguish diseases:

- Meningococcemia: The rash may be pink, macular, maculopapular, or petechial in the subacute form and petechially confluent or ecchymotic in the fulminant form. The rash develops rapidly in acute meningococcal disease and, when ecchymotic, is usually tender when palpated.

- Rubeola: The rash begins on the face, spreads to the trunk and arms, and soon becomes confluent.

- Rubella: The rash usually remains discrete. Postauricular lymph node enlargement and lack of toxicity suggest rubella.

Differentiating among rickettsial diseases: Rickettsial and related diseases must also be differentiated from each other. Clinical features allow some differentiation, but overlap is considerable:

- Rocky Mountain spotted fever (RMSF): The rash usually appears on about the 4th febrile day as blanching macules on the extremities and gradually becomes petechial as it spreads to the trunk, palms, and soles over several days. Some patients with RMSF never develop a rash.
• **Epidemic typhus:** The rash usually appears initially in the axillary folds and on the trunk. Later, it spreads peripherally, rarely involving the palms, soles, and face. Severe physiologic and pathologic abnormalities similar to those of RMSF occur.

• **Murine typhus:** The rash is nonpurpuric, nonconfluent, and less extensive, and renal and vascular complications are uncommon.

• **Scrub typhus:** Manifestations are similar to those of RMSF and epidemic typhus.

**[Table 139-1. Diseases Caused by Rickettsia, Ehrlichia, and Coxiella Spp]**

However, scrub typhus occurs in different geographic areas, and frequently, an eschar develops with satellite adenopathy.

• **Rickettsialpox:** This disease is mild, and the rash, in the form of vesicles with surrounding erythema, is sparse and may resemble varicella.

• **African tick bite fever (due to *R. africae*):** Symptoms are similar to those of other rickettsial diseases. The rash is characterized by multiple black eschars on the distal extremities with regional adenopathy.

**Testing:** Knowledge of residence and recent travel often helps in diagnosis because many rickettsiae are localized to certain geographic areas. However, testing is usually required.

The most useful tests for *R. rickettsii* are indirect immunofluorescence assay (IFA) and PCR of a biopsy specimen of the rash. Culture is difficult and not clinically useful. For *Ehrlichia* sp, PCR of blood is the best test. Serologic tests are not useful for acute diagnosis because they usually become positive only during convalescence.

**Treatment**

• **Tetracyclines**

Because diagnostic tests can take time and may be insensitive, antibiotics are usually begun presumptively to prevent significant deterioration, death, and prolonged recovery. Tetracyclines are first-line treatment: doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. IV preparations are used in patients too ill to take oral drugs. Although tetracyclines can cause tooth staining in children, experts think that a course of doxycycline is warranted. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment. Both drugs are rickettsiostatic, not rickettsicidal. Ciprofloxacin and other fluoroquinolones are effective against certain rickettsiae, but extensive clinical experience is lacking.

Because severely ill patients with RMSF or epidemic typhus may have a marked increase in capillary permeability in later stages, IV fluids should be given cautiously to maintain BP while avoiding worsening pulmonary and cerebral edema. Heparin is not recommended in patients who develop disseminated intravascular coagulation.

**Eastern Tick-Borne Rickettsioses**

**Eastern tick-borne rickettsioses (ETBR)** are caused by various rickettsiae transmitted by ixodid ticks. Symptoms are an initial skin lesion, satellite adenopathy, and an erythematous maculopapular rash.

ETBR include North Asian tick-borne rickettsiosis, Queensland tick typhus, African tick typhus, and Mediterranean spotted fever (boutonneuse fever). The causative agents belong to the spotted fever group of rickettsiae.

The epidemiology of these tick-borne rickettsioses resembles that of spotted fever in the Western Hemisphere. Ixodid ticks and wild animals maintain the rickettsiae in nature. If humans intrude
accidentally into the cycle, they become infected. In certain areas, the cycle of boutonneuse fever involves domiciliary environments, with the brown dog tick, *Rhipicephalus sanguineus*, as the dominant vector.

### Symptoms and Signs

The symptoms and signs are similar for all ETBR and generally milder than with spotted fever. After an incubation period of 5 to 7 days, fever, malaise, headache, and conjunctival injection develop. With the onset of fever, a small buttonlike ulcer 2 to 5 mm in diameter with a black center appears (an eschar or, in boutonneuse fever, *tache noire*). Usually, the regional or satellite lymph nodes are enlarged. On about the 4th day of fever, a red maculopapular rash appears on the forearms and extends to most of the body, including the palms and soles. Fever lasts into the 2nd wk.

Complications and death are rare except among elderly or debilitated patients. However, the disease should not be ignored; a fulminant form of vasculitis can occur.

### Diagnosis

For diagnosis, see p. 1280.

### Treatment

- Doxycycline or ciprofloxacin

Treatment is doxycycline 100 mg po bid for 5 days or ciprofloxacin 500 to 750 mg po bid for 5 days. Measures can be taken to prevent tick bites (see Sidebar 139-1).

### Epidemic Typhus

(European, Classic, or Louse-Borne Typhus; Jail Fever)

**Epidemic typhus is caused by *Rickettsia prowazekii*. Symptoms are prolonged high fever, intractable headache, and a maculopapular rash.**

Humans are the natural reservoir for *R. prowazekii*, which is prevalent worldwide and transmitted by body lice when louse feces are scratched or rubbed into bite or other wounds (or sometimes the mucous membranes of the eyes or mouth). In the US, humans may occasionally contract epidemic typhus after contact with flying squirrels.

Fatalities are rare in children < 10 yr, but mortality increases with aging and may reach 60% in untreated patients > 50 yr.

### Symptoms and Signs

After an incubation period of 7 to 14 days, fever, headache, and prostration suddenly occur. Temperature reaches 40° C in several days and remains high, with slight morning remission, for about 2 wk. Headache is generalized and intense. Small, pink macules, which appear on the 4th to 6th day, rapidly cover the body, usually in the axillae and on the upper trunk and not on the palms, soles, and face. Later, the rash becomes dark and maculopapular. In severe cases, the rash becomes petechial and hemorrhagic. Splenomegaly sometimes occurs. Hypotension occurs in most seriously ill patients. Vascular collapse, renal insufficiency, encephalitic signs, ecchymosis with gangrene, and pneumonia are poor prognostic signs.

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**Sidebar 139-1 Tick Bite Prevention**

Preventing tick access to skin includes
• Staying on paths and trails

• Tucking trousers into boots or socks

• Wearing long-sleeved shirts

• Applying repellents with diethyltoluamide (DEET) to skin surfaces

DEET should be used cautiously in very young children because toxic reactions have been reported. Permethrin on clothing effectively kills ticks. Frequent searches for ticks, particularly in hairy areas and on children, are essential in endemic areas.

Engorged ticks should be removed with care and not crushed between the fingers because crushing the tick may result in disease transmission. The tick's body should not be grasped or squeezed. Gradual traction on the head with a small forceps dislodges the tick. The point of attachment should be swabbed with alcohol. Petroleum jelly, alcohol, lit matches, and other irritants are not effective and should not be used.

No practical means are available to rid entire areas of ticks, but tick populations may be reduced in endemic areas by controlling small-animal populations.

Diagnosis

Louse infestation is usually obvious and strongly suggests typhus if history (eg, living in or visiting an endemic area) suggests possible exposure. For details of diagnosis, see p. 1280.

Treatment

• Doxycycline

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment.

Prevention

Immunization and louse control are highly effective for prevention. However, vaccines are not available in the US. Lice may be eliminated by dusting infested people with malathion or lindane.
Brill-Zinsser Disease

Brill-Zinsser disease is a recrudescence of epidemic typhus, occurring years after an initial attack.

Patients with Brill-Zinsser disease acquired epidemic typhus earlier or lived in an endemic area. Apparently, when host defenses falter, viable organisms retained in the body are activated, causing recurrent typhus; thus, disease is sporadic, occurring at any season and in the absence of infected lice. Lice that feed on patients may acquire and transmit the agent.

Symptoms and signs are almost always mild and resemble those of epidemic typhus, with similar circulatory disturbances and hepatic, renal, and CNS changes. The remittent febrile course lasts about 7 to 10 days. The rash is often evanescent or absent. Mortality is nil.

For diagnosis and treatment, see p. 1283.

Murine (Endemic) Typhus

(Rat-Flea Typhus; Urban Typhus of Malaya)

Murine typhus is caused by Rickettsia typhi, which is transmitted to humans by rat fleas; it is clinically similar to but milder than epidemic typhus, causing chills, headache, fever, and rash.

Animal reservoirs include wild rats, mice, and other rodents. Rat fleas and probably cat fleas transmit the agent to humans. Distribution is sporadic but worldwide; the incidence is low but higher in rat-infested areas.

After an incubation of 6 to 18 days (mean 10 days), a shaking chill accompanies headache and fever. The fever lasts about 12 days; then temperature gradually returns to normal. The rash and other manifestations are similar to those of epidemic typhus but are much less severe. The early rash is sparse and discrete. Mortality is low but is higher in elderly patients.

Diagnosis

Murine typhus is identified by immunofluorescence assay (IFA), immunohistology of a skin biopsy, PCR, and enzyme-linked immunosorbent assay (ELISA).

Treatment

• Doxycycline

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment. (For details of treatment, see p. 1282.)

Incidence has been decreased by reducing rat and rat flea populations. No effective vaccine exists.

Rickettsialpox

(Vesicular Rickettsiosis)

Rickettsialpox is caused by Rickettsia akari. Symptoms are an initial local lesion and a generalized papulovesicular rash.

Rickettsialpox occurs in many areas of the US and in Russia, Korea, and Africa. The vector, a small, colorless mite, is widely distributed. It infects the house mouse and some species of wild mice. Humans may be infected by chigger (mite larvae) or adult mite bites.
An eschar appears about 1 wk before onset of fever as a small papule 1 to 1.5 cm in diameter, then develops into a small ulcer with a dark crust that leaves a scar when it heals. Regional lymphadenopathy is present. An intermittent fever lasts about 1 wk, with chills, profuse sweating, headache, photophobia, and muscle pains. Early in the febrile course, a generalized maculopapular rash with intraepidermal vesicles appears, sparing the palms and soles. The disease is mild; no deaths have been reported. For details of diagnosis, see p. 1280.

Treatment is doxycycline 100 mg po bid for 5 days or ciprofloxacin 750 mg po bid for 5 days.

For prophylaxis, mouse harborage must be destroyed, and the vector controlled by residual insecticides.

**Rocky Mountain Spotted Fever**

(Spotted Fever; Tick Fever; Tick Typhus)

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and transmitted by ixodid ticks. Symptoms are high fever, severe headache, and rash.

**Epidemiology**

RMSF is limited to the Western Hemisphere. Initially recognized in the Rocky Mountain states, it occurs in practically all of the US, especially the Atlantic states, and throughout Central and South America. In humans, infection occurs mainly from March to September, when adult ticks are active and people are most likely to be in tick-infested areas. In southern states, sporadic cases occur throughout the year. The incidence is highest in children < 15 yr and in people who frequent tick-infested areas for work or recreation.

Hard-shelled ticks (family Ixodidae) harbor *R. rickettsii*, and infected females transmit the agent to their progeny. These ticks are the natural reservoirs. *Dermacentor andersoni* (wood tick) is the principal vector in the western US. *D. variabilis* (dog tick) is the vector in the eastern and southern US. RMSF is probably not transmitted directly from person to person.

**Pathophysiology**

Small blood vessels are the sites of the characteristic pathologic lesions. Rickettsiae propagate within damaged endothelial cells, and vessels may become blocked by thrombi, producing vasculitis in the skin, subcutaneous tissues, CNS, lungs, heart, kidneys, liver, and spleen. Disseminated intravascular coagulation often occurs in severely ill patients (see p. 976).

**Symptoms and Signs**

The incubation period averages 7 days but varies from 3 to 12 days; the shorter the incubation period, the more severe the infection. Onset is abrupt, with severe headache, chills, prostration, and muscular pains. Fever reaches 39.5 to 40°C within several days and remains high (for 15 to 20 days in severe cases), although morning remissions may occur. Between the 1st and 6th day of fever, most patients develop a rash on the wrists, ankles, palms, soles, and forearms that rapidly extends to the neck, face, axillae, buttocks, and trunk. Initially macular and pink, it becomes maculopapular and darker. In about 4 days, the lesions become petechial and may coalesce to form large hemorrhagic areas that later ulcerate.

Neurologic symptoms include headache, restlessness, insomnia, delirium, and coma, all indicative of encephalitis. Hypotension develops in severe cases. Hepatomegaly may be present, but jaundice is infrequent. Nausea and vomiting are common. Localized pneumonitis may occur. Untreated patients may develop pneumonia, tissue necrosis, and circulatory failure, sometimes with brain and heart damage. Cardiac arrest with sudden death occasionally occurs in fulminant cases.

**Diagnosis**
Clinicians should suspect RMSF in any seriously ill patient who lives in or near a wooded area anywhere in the Western Hemisphere and has unexplained fever, headache, and prostration, with or without a history of tick contact. A history of tick bite is elicited in about 70% of patients.

**Treatment**

- **Doxycycline**

Starting antibiotics early significantly reduces mortality, from about 20 to 5%, and prevents most complications. If patients who have been in an endemic area have a tick bite but no clinical signs, antibiotics should not be given immediately.

If fever, headache, and malaise occur with or without a rash, antibiotics should be started promptly. Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment.

No effective vaccine is available. Measures can be taken to prevent tick bites (see Sidebar 139-1).

**Scrub Typhus**

(Tsutsugamushi Disease; Mite-Borne Typhus; Tropical Typhus)

*Scrub typhus is a mite-borne disease caused by Rickettsia tsutsugamushi. Symptoms are fever, a primary lesion, a macular rash, and lymphadenopathy.*

*R. tsutsugamushi* is transmitted by trombiculid mites, which feed on forest and rural rodents, including rats, voles, and field mice. Human infection follows a chigger (mite larva) bite.

**Symptoms**

After an incubation period of 6 to 21 days (mean 10 to 12 days), fever, chills, headache, and generalized lymphadenopathy start suddenly. At onset of fever, an eschar often develops at the site of the chigger bite. The typical lesion, common in whites but rare in Asians, begins as a red, indurated lesion about 1 cm in diameter; it eventually vesiculates, ruptures, and becomes covered with a black scab. Regional lymph nodes enlarge. Fever rises during the 1st wk, often to 40 to 40.5°C. Headache is severe and common, as is conjunctival injection. A macular rash develops on the trunk during the 5th to 8th day of fever, often extending to the arms and legs. It may disappear rapidly or become maculopapular and intensely colored. Cough is present during the 1st wk of fever, and pneumonitis may develop during the 2nd wk.

In severe cases, pulse rate increases; BP drops; and delirium, stupor, and muscular twitching develop. Splenomegaly may be present, and interstitial myocarditis is more common than in other rickettsial diseases. In untreated patients, high fever may persist ≥ 2 wk, then falls gradually over several days. With therapy, defervescence usually begins within 36 h. Recovery is prompt and uneventful.

**Diagnosis**

For details of diagnosis, see p. 1280.

**Treatment**

- **Doxycycline**

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po
Clearing brush and spraying infested areas with residual insecticides eliminate or decrease mite populations. Insect repellents (eg, diethyltoluamide [DEET]) should be used when exposure is likely.

**Ehrlichiosis**

*Ehrlichiosis* is caused by rickettsial-like bacteria of the genus *Ehrlichia* transmitted to humans by ticks. Symptoms resemble those of Rocky Mountain spotted fever except that a rash is much less common. Onset of illness, with fever, chills, headache, and malaise, is abrupt.

Most cases have been identified in the southeastern and south central US. Three species of *Ehrlichia* are human pathogens in the US: *E. chaffeensis* causes human monocytic ehrlichiosis; *Anaplasma phagocytophila* (formerly *E. phagocytophila*) and *E. ewingii* cause human granulocytic ehrlichiosis. The difference in the primary target cell results in only minor differences in clinical manifestations.

These obligate, intracellular bacteria appear as small cytoplasmic inclusions in lymphocytes and neutrophils. Infections are transmitted to humans via tick bites, sometimes via contact with animals that carry the brown dog tick or deer tick.

**Symptoms and Signs**

Although some infections are asymptomatic, most cause an abrupt onset of illness with fever, chills, headache, and malaise, usually beginning about 12 days after the tick bite. Some patients develop a maculopapular or petechial rash involving the trunk and extremities, although rash is rare with *E. ewingii*. Abdominal pain, vomiting and diarrhea, disseminated intravascular coagulation, seizures, and coma may occur.

**Diagnosis**

- PCR testing of a blood sample

Diagnostic serologic tests are available, but PCR of blood is more sensitive and specific and can result in an early diagnosis. Cytoplasmic ehrlichial inclusions in monocytes or neutrophils may be detected. Blood and liver functions tests may detect hematologic and hepatic abnormalities, such as leukopenia, thrombocytopenia, and elevated aminotransferase levels.

**Treatment**

- Doxycycline

Treatment is best started before laboratory results return. When treatment is started early, patients generally respond rapidly and well. A delay in treatment may lead to serious complications, including viral and fungal super-infections and death in 2 to 5%.

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment.

Measures can be taken to prevent tick bites (see Sidebar 139-1).

**Q Fever**

*Q* fever is an acute or chronic disease caused by the rickettsial-like bacillus *Coxiella burnetii*. Acute disease causes sudden onset of fever, headache, malaise, and interstitial pneumonitis. Chronic disease manifestations reflect the organ system affected. Diagnosis is confirmed by several serologic techniques, isolation of the organism, or PCR. Treatment is with doxycycline or chloramphenicol.
Coxiella burnetii is a small, intracellular, pleomorphic bacillus that is no longer classified as Rickettsia. Molecular studies have reclassified it as Proteobacteria in the same group as Legionella sp.

Q fever can be acute or chronic. Acute disease causes a febrile illness that often affects the respiratory system, although sometimes the liver is involved. Chronic Q fever usually manifests as endocarditis or hepatitis; osteomyelitis may occur.

Worldwide in its distribution, Q fever is maintained as an inapparent infection in domestic or farm animals. Sheep, cattle, and goats are the principal reservoirs for human infection. C. burnetii persists in stool, urine, milk, and tissues (especially the placenta), so that fomites and infective aerosols form easily. C. burnetii is also maintained in nature through an animal-tick cycle.

Etiology

Cases occur among workers whose occupations bring them in close contact with farm animals or their products. Transmission is usually by inhalation of infected aerosols, but the disease can also be contracted by ingesting infective raw milk. C. burnetii is very virulent, resists inactivation, and remains viable in dust and stool for months; even a single organism can cause infection. Very rarely, the disease is transmitted from person to person.

Symptoms and Signs

The incubation period averages 18 to 21 days (range 9 to 28 days). Some infections are minimally symptomatic; however, most patients have influenza-like symptoms. Onset is abrupt, with fever, severe headache, chills, severe malaise, myalgia, anorexia, and sweats. Fever may rise to 40°C and persist 1 to > 3 wk. Respiratory symptoms (a dry nonproductive cough, pleuritic chest pain) appear 4 to 5 days after onset of illness. These symptoms may be particularly severe in elderly or debilitated patients. During examination, lung crackles are commonly noted, and findings suggesting consolidation may be present. Unlike rickettsial diseases, acute Q fever does not cause a rash.

Acute hepatic involvement, occurring in some patients, resembles viral hepatitis, with fever, malaise, hepatomegaly with right upper abdominal pain, and possibly jaundice. Headache and respiratory signs are frequently absent. Chronic Q fever hepatitis may manifest as FUO. Liver biopsy may show granulomas, which should be differentiated from other causes of liver granulomas (eg, TB, sarcoidosis, histoplasmosis, brucellosis, tularemia, syphilis).

Endocarditis resembles viridans group subacute bacterial endocarditis (see p. 2193); the aortic valve is most commonly affected, but vegetations may occur on any valve. Marked finger clubbing, arterial emboli, hepatomegaly, splenomegaly, and a purpuric rash may occur.

The mortality rate is only 1% of untreated patients but is higher in those with endocarditis. Some patients with neurologic involvement have residual impairment.

Diagnosis

• Immunofluorescence assay of infected tissue

Symptoms do not readily suggest the diagnosis. Early on, Q fever resembles many infections (eg, influenza, other viral infections, salmonellosis, malaria, hepatitis, brucellosis). Later, it resembles many forms of bacterial, viral, and mycoplasmal pneumonias. Contact with animals or animal products is an important clue.

Immunofluorescence assay (IFA) of infected tissue is the diagnostic method of choice; alternatively, enzyme-linked immunosorbent assay (ELISA) may be done. Acute and convalescent serum specimens (typically complement fixation) may be used. PCR can identify the organism in biopsy specimens. C. burnetii may be isolated from clinical specimens, but only by special research laboratories; routine blood and sputum cultures are negative.
Patients with respiratory symptoms or signs require chest x-ray; findings may include atelectasis, pleural-based opacities, pleural effusion, and lobar consolidation. The gross appearance of the lungs may resemble bacterial pneumonia but, histologically, more closely resembles psittacosis and some viral pneumonias.

In acute Q fever, CBC may be normal, but about 30% of patients have an elevated WBC count. Alkaline phosphatase, AST, and ALT levels are mildly elevated to 2 to 3 times the normal level in typical cases. If obtained, liver biopsy specimens often show diffuse granulomatous changes.

**Treatment**

- **Doxycycline**

Primary treatment is doxycycline 200 mg po once followed by 100 mg po bid until the patient improves, has been afebrile for about 5 days, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment. Fluoroquinolones and macrolides are also effective.

For endocarditis, treatment needs to be prolonged (months to years to lifelong). Clinical signs, ESR, blood count, and antibody titers should be monitored to determine when to stop treatment. A tetracycline plus rifampin or ciprofloxacin is usually preferred. Some experts use hydroxychloroquine as an additional drug. When antibiotic treatment is only partially effective, damaged valves must be replaced surgically, although some cures have occurred without surgery. Clear-cut regimens for chronic hepatitis have not been determined.

**Prevention**

Vaccines are effective and should be used to protect slaughterhouse and dairy workers, rendering-plant workers, herders, woolsorters, farmers, and other people at risk. These vaccines are not available commercially but may be obtained from special laboratories (eg, the US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland).
Chapter 140. Anaerobic Bacteria

Introduction

Bacteria can be classified by their need and tolerance for O\textsubscript{2}:

• Facultative bacteria, which grow in the presence or absence of O\textsubscript{2}

• Microaerophilic bacteria, which tolerate low O\textsubscript{2} concentrations but grow better anaerobically or with > 10% CO\textsubscript{2}

• Obligate anaerobic bacteria, which are intolerant of O\textsubscript{2}

Obligate anaerobes replicate at sites with low oxidation-reduction potential (eg, necrotic, devascularized tissue). Obligate anaerobes have been categorized based on their O\textsubscript{2} tolerance: strict anaerobes grow in ≤ 0.4% O\textsubscript{2}; moderate anaerobes grow in 0.8 to 2.5% O\textsubscript{2}; and aerotolerant anaerobes grow in ≥ 2.5% O\textsubscript{2}. The obligate anaerobes that commonly cause infection can tolerate atmospheric O\textsubscript{2} for at least 8 h and frequently for up to 72 h.

Obligate anaerobes are major components of the normal microflora on mucous membranes, especially of the mouth, lower GI tract, and vagina; these anaerobes cause disease when normal mucosal barriers break down.

Gram-negative anaerobes and some of the infections they cause include

• \textit{Bacteroides} (most common): Intra-abdominal infections

• \textit{Fusobacterium}: Abscesses, wound infections, and pulmonary and intracranial infections

• \textit{Porphyromonas}: Aspiration pneumonia and periodontitis

• \textit{Prevotella}: Intra-abdominal and soft-tissue infections

Gram-positive anaerobes and some of the infections they cause include

• \textit{Actinomyces}: Head, neck, abdominal, and pelvic infections and aspiration pneumonia

• \textit{Clostridium}: Gas gangrene due to \textit{C. perfringens}, food poisoning due to \textit{C. perfringens type A}, botulism due to \textit{C. botulinum}, tetanus due to \textit{C. tetani}, and \textit{C. difficile}-induced diarrhea (pseudomembranous colitis)

• \textit{Peptostreptococcus}: Oral, respiratory, and intra-abdominal infections

• \textit{Propionibacterium}: Foreign body infections (eg, in a cerebrospinal fluid shunt, prosthetic joint, or cardiac device)

Anaerobic infections are typically suppurative, causing abscess formation and tissue necrosis (often the result of thrombophlebitis, gas formation, or both). Many anaerobes produce tissue-destructive enzymes as well as some of the most potent paralytic toxins known.

Clues to anaerobic infection include

• Polymicrobial results on Gram stain or culture

• Gas in pus or infected tissues
• Foul odor of pus or infected tissues

• Necrotic infected tissues

• Site of infection near mucosa where anaerobic microflora normally reside

**Testing:** Specimens for anaerobic culture should be obtained by aspiration or biopsy from normally sterile sites. Delivery to the laboratory should be prompt, and transport devices should provide an O2-free atmosphere of carbon dioxide, hydrogen, and nitrogen. Swabs are best transported in an anaerobically sterilized, semisolid medium such as Cary-Blair transport medium.

**Clostridia**

Clostridia are spore-forming, gram-positive bacilli present widely in dust, soil, and vegetation and as normal flora in mammalian GI tracts.

Nearly 100 *Clostridium* sp have been identified, but only 25 to 30 commonly cause human or animal disease.

**Pathophysiology**

The pathogenic species produce tissue-destructive and neural exotoxins that are responsible for disease manifestations. Clostridia may become pathogenic when tissue O2 tension and pH are low. Such an anaerobic environment may develop in ischemic or devitalized tissue, as occurs in primary arterial insufficiency or after severe penetrating or crushing injuries. The deeper and more severe the wound, the more prone the patient is to clostridial infection, especially if there is even minimal contamination by foreign matter. Clostridial disease can also occur after injection of street drugs. Serious noninfectious disease can occur after ingestion of home-canned foods in which clostridia have produced toxins.

**Diseases Caused by Clostridia**

Diseases caused by clostridia include

• Botulism (due to *C. botulinum*)

• *C. difficile*-induced colitis

• Gastroenteritis

• Soft-tissue infections

• Tetanus (due to *C. tetani*)

• Enteritis necroticans (due to *C. perfringens* type C)

• Neutropenic enterocolitis (due to *C. septicum*)

The most frequent clostridial infection is minor, self-limited gastroenteritis, typically due to *C. perfringens* type A. Serious clostridial diseases are relatively rare but can be fatal. Abdominal disorders, such as cholecystitis, peritonitis, ruptured appendix, and bowel perforation can involve *C. perfringens*, *C. ramosum*, and many others. Muscle necrosis and soft-tissue infection, which is characterized by crepitant cellulitis, myositis, and clostridial myonecrosis, can be caused by *C. perfringens*. Tissue necrosis can be caused by *C. septicum*. Clostridia also appear as components of mixed flora in common mild wound infections; their role in such infections is unclear.

Hospital-acquired clostridial infection is increasing, particularly in postoperative and immunocompromised patients. Severe clostridial sepsis may complicate intestinal perforation and obstruction.
Actinomycosis

Actinomycosis is a chronic localized or hematogenous infection caused by *Actinomyces israelii*. Symptoms are a local abscess with multiple draining sinuses, a TB-like pneumonitis, and low-grade septicemia. Diagnosis is by the typical appearance plus laboratory identification. Treatment is with a long course of antibiotics and surgery.

The causative organisms, *Actinomyces* sp (most commonly *A. israelii*), are often present commensally on the gums, tonsils, and teeth. However, many, if not most, infections are polymicrobial, with other bacteria (oral anaerobes, staphylococci, streptococci, *Aggregatibacter* [previously *Actinobacillus*] *actinomycetemcomitans*, Enterobacteriaceae) frequently cultured from lesions.

Actinomycosis most often occurs in adult males and takes several forms:

- **Cervicofacial (lumpy jaw):** The most common portal of entry is decayed teeth.
- **Thoracic:** Pulmonary disease results from aspiration of oral secretions.
- **Abdominal:** Disease presumably results from a break in the mucosa of a diverticulum or the appendix or from trauma.
- **Uterine:** This localized pelvic form is a complication of certain types of intrauterine device (IUD).
- **Generalized:** Rarely, the infection spreads from primary sites, presumably by hematogenous seeding.

**Symptoms and Signs**

The characteristic lesion is an indurated area of multiple, small, communicating abscesses surrounded by granulation tissue. Lesions tend to form sinus tracts that communicate to the skin and drain a purulent discharge containing "sulfur" granules (rounded or spherical, usually yellowish, and ≤ 1 mm in diameter). Infection spreads to contiguous tissues, but only rarely hematogenously.

The **cervicofacial form** usually begins as a small, flat, hard swelling, with or without pain, under the oral mucosa or the skin of the neck or as a subperiosteal swelling of the jaw. Subsequently, areas of softening appear and develop into sinuses and fistulas that discharge the characteristic sulfur granules. The cheek, tongue, pharynx, salivary glands, cranial bones, meninges, or brain may be affected, usually by direct extension.

In the **abdominal form**, the intestines (usually the cecum and appendix) and the peritoneum are infected. Pain, fever, vomiting, diarrhea or constipation, and emaciation are characteristic. One or more abdominal masses develop and cause signs of partial intestinal obstruction. Draining sinuses and intestinal fistulas may develop and extend to the external abdominal wall.

In the **localized pelvic form**, patients who use an IUD have vaginal discharge and pelvic or lower abdominal pain.

In the **thoracic form**, lung involvement resembles TB. Extensive invasion may occur before chest pain, fever, and productive cough appear. Perforation of the chest wall, with chronic draining sinuses, may result.

In the **generalized form**, infection spreads hematogenously to multiple areas, including the skin, vertebral bodies, brain, liver, kidneys, ureters, and, in women, pelvic organs. Diverse symptoms (eg, back pain, headache, abdominal pain) related to these sites may occur.

**Diagnosis**

- Microscopy
• Culture

Diagnosis is suspected clinically and by x-ray. It is confirmed by identification of *A. israelii* in sputum, pus, or a biopsy specimen by microscopy and by culture.

In pus or tissue, the microorganism appears as the distinctive sulfur granules or as tangled masses of branched and unbranched wavy bacterial filaments, pus cells, and debris, surrounded by an outer zone of radiating, club-shaped, hyaline, and refractive filaments that take hematoxylin-eosin stain in tissue but are positive on Gram stain.

Lesions in any location may simulate malignant growths. Lung lesions must be distinguished from those of TB and cancer. Most abdominal lesions occur in the ileocecal region and are difficult to diagnose, except during laparotomy or when draining sinuses appear in the abdominal wall. Aspiration liver biopsy should be avoided because it can cause a persistent sinus.

**Prognosis**

The disease is slowly progressive. Prognosis relates directly to early diagnosis and is most favorable in the cervicofacial form and progressively worse in the thoracic, abdominal, and generalized forms, especially if the CNS is involved.

**Treatment**

• High-dose penicillin

Most patients respond to antibiotics, although response is usually slow because of extensive tissue induration and the relatively avascular nature of the lesions. Therefore, treatment must be continued for at least 8 wk and occasionally for ≥ 1 yr, until symptoms and signs have resolved.

High doses of penicillin G (eg, 3 to 5 million units IV q 6 h) are usually effective. Penicillin V 1 g po qid may be substituted after about 2 to 6 wk. Tetracycline 500 mg po q 6 h may be given instead of penicillin. Minocycline, clindamycin, and erythromycin have also been successful. Antibiotic regimens may be broadened to cover other pathogens cultured from lesions.

Anecdotal reports suggest that hyperbaric O₂ therapy is helpful.

Extensive and repeated surgical procedures may be required. Sometimes small abscesses can be aspirated; large ones are drained, and fistulas are excised surgically.

**Botulism**

Botulism is neuromuscular poisoning due to *Clostridium botulinum* toxin. Botulism may occur without infection if toxin is ingested. Symptoms are symmetric cranial nerve palsies accompanied by a symmetric descending weakness and flaccid paralysis without sensory deficits. Diagnosis is clinical and by laboratory identification of toxin. Treatment is with support and antitoxin.

*C. botulinum* elaborates 7 types of antigenically distinct neurotoxins, which interfere with release of acetylcholine at peripheral nerve endings. Four of the toxins (types A, B, E, and rarely F) affect humans. Types A and B are highly poisonous proteins resistant to digestion by GI enzymes. About 50% of food-borne outbreaks in the US are caused by type A toxin, followed by types B and E. Type A toxin occurs predominantly west of the Mississippi River, type B in the eastern states, and type E in Alaska and the Great Lakes area (type E is frequently associated with ingestion of fish products). Type A toxin is used therapeutically to relieve excess muscle activity; botulinum toxin has also been developed as a bioweapon.

Botulism occurs in 3 forms:
In food-borne botulism, neurotoxin produced in contaminated food is eaten. Neurotoxin is elaborated in vivo by *C. botulinum* in infected tissue in wound botulism and in the large intestine in infant botulism (see p. 1292).

*C. botulinum* spores are highly heat-resistant and may survive boiling for several hours at 100°C. However, exposure to moist heat at 120°C for 30 min kills the spores. Toxins, on the other hand, are readily destroyed by heat, and cooking food at 80°C for 30 min safeguards against botulism. Toxin production (especially type E) can occur at temperatures as low as 3°C (ie, inside a refrigerator) and does not require strict anaerobic conditions.

**Sources of infection:** Home-canned foods, particularly low-acid foods, are the most common sources, but commercially prepared foods have been implicated in about 10% of outbreaks. Vegetables, fish, fruits, and condiments are the most common vehicles, but beef, milk products, pork, poultry, and other foods have been involved. Of outbreaks caused by seafood, type E causes about 50%; types A and B cause the rest. In recent years, foods that are not canned (eg, foil-wrapped baked potatoes, chopped garlic in oil, patty melt sandwiches) have caused restaurant-associated outbreaks.

*C. botulinum* spores are common in the environment, and many cases may be caused by ingestion or inhalation of dust or by absorption through the eyes or a break in the skin.

Injecting drugs with unsterilized needles can cause wound botulism. Injecting contaminated heroin into a muscle or under the skin (skin popping) is riskiest.

**Symptoms and Signs**

**Food-borne botulism:** Symptoms begin abruptly, usually 18 to 36 h after toxin ingestion, although the incubation period may vary from 4 h to 8 days. Nausea, vomiting, abdominal cramps, and diarrhea frequently precede neurologic symptoms. Neurologic symptoms are characteristically bilateral and symmetric, beginning with the cranial nerves and followed by descending weakness or paralysis. There are no sensory disturbances, and the sensorium usually remains clear.

Common initial symptoms and signs include dry mouth, blurred or double vision, drooping eyelids, slurred speech, and difficulty swallowing. Pupillary light reflex is diminished or totally lost. Dysphagia can lead to aspiration pneumonia. Muscles of respiration and of the extremities and trunk progressively weaken in a descending pattern. Fever is absent, and the pulse remains normal or slow unless intercurrent infection develops. Constipation is common after neurologic impairment appears. Major complications include respiratory failure caused by diaphragmatic paralysis and pulmonary infections.

**Wound botulism:** Neurologic symptoms appear, as in food-borne botulism, but there are no GI symptoms or evidence implicating food as a cause. A history of a traumatic injury or a deep puncture wound in the preceding 2 wk may suggest the diagnosis. A thorough search should be made for breaks in the skin and for skin abscesses caused by self-injection of illegal drugs.

**Diagnosis**

- Toxin assays
- Sometimes electromyography

Botulism may be confused with Guillain-Barre syndrome, poliomyelitis, stroke, myasthenia gravis, tick paralysis, and poisoning caused by curare or belladonna alkaloids. Electromyography shows
characteristic augmented response to rapid repetitive stimulation in most cases.

In food-borne botulism, the pattern of neuromuscular disturbances and ingestion of a likely food source are important diagnostic clues. The simultaneous presentation of at least 2 patients who ate the same food simplifies diagnosis, which is confirmed by demonstrating *C. botulinum* toxin in serum or stool or by isolating the organism from stool. Finding *C. botulinum* toxin in suspect food identifies the source.

In wound botulism, finding toxin in serum or isolating *C. botulinum* organisms on anaerobic culture of the wound confirms the diagnosis.

Toxin assays are done only by certain laboratories, which may be located through local health authorities or the Centers for Disease Control and Prevention (CDC).

**Treatment**

- **Supportive care**
- **Equine trivalent antitoxin**

Anyone known or thought to have been exposed to contaminated food must be carefully observed. Administration of activated charcoal may be helpful. Patients with significant symptoms often have impaired airway reflexes, so if charcoal is used, it should be given via gastric tube, and the airway should be protected by a cuffed endotracheal tube.

The greatest threat to life is respiratory impairment and its complications. Patients should be hospitalized and closely monitored with serial measurements of vital capacity. Progressive paralysis prevents patients from showing signs of respiratory distress as their vital capacity decreases. Respiratory impairment requires management in an ICU, where intubation and mechanical ventilation are readily available. Improvements in such supportive care have reduced the mortality rate to < 10%.

Nasogastric intubation is the preferred method of alimentation because it simplifies management of calories and fluids, stimulates intestinal peristalsis (which eliminates *C. botulinum* from the gut), allows the use of breast milk in infants, and avoids the potential infectious and vascular complications inherent in IV alimentation.

Patients with wound botulism require wound debridement and parenteral antibiotics such as penicillin or metronidazole.

**Antitoxin**: Trivalent equine antitoxin (A, B, E) is available from the CDC through state health departments. Antitoxin does not inactivate toxin that is already bound at the neuromuscular junction; therefore, preexisting neurologic impairment cannot be reversed rapidly. (Ultimate recovery depends on regeneration of nerve endings, which may take weeks or months.) However, antitoxin may slow or halt further progression. In patients with wound botulism, antitoxin can reduce complications and mortality rate. Antitoxin should be given as soon as possible after clinical diagnosis and not delayed to await culture results. Antitoxin is less likely to be of benefit if given > 72 h after symptom onset.

In the US, botulism equine trivalent antitoxin is given as a single 10-mL dose containing 7500 IU of antitoxin A, 5500 IU of antitoxin B, and 8500 IU of antitoxin E. All patients who require the antitoxin must be reported to state health authorities or the CDC. Antitoxin is available only through the CDC, the telephone number is 404-639-2206 weekdays and 404-639-2888 for all other times. Because antitoxin is derived from horse serum, there is a risk of anaphylaxis or serum sickness. (For precautions, see Drug Hypersensitivity on p. 1122; for treatment, see Anaphylaxis on p. 1120.)

**Prevention**

Because even minute amounts of *C. botulinum* toxin can cause serious illness, all materials suspected of containing toxin require special handling. Toxoids are available for active immunization of people working...
with *C. botulinum* or its toxins. Details regarding specimen collection and handling can be obtained from state health departments or the CDC.

Correct canning and adequate heating of home-canned food before serving are essential. Canned foods showing evidence of spoilage and swollen or leaking cans should be discarded.

**Infant Botulism**

**Infant botulism results from ingestion of *C. botulinum* spores, their colonization of the large intestine, and toxin production in vivo.**

Infant botulism occurs most often in infants < 6 mo. The youngest reported patient was 2 wk, and the oldest was 12 mo. Unlike food-borne botulism, infant botulism is not caused by ingestion of a preformed toxin. Most cases are idiopathic, although some have been traced to ingestion of honey, which may contain *C. botulinum* spores; thus, infants < 12 mo should not be fed honey.

**Symptoms and Signs**

Constipation is present initially in 90% of cases and is followed by neuromuscular paralysis, beginning with the cranial nerves and proceeding to peripheral and respiratory musculature. Cranial nerve deficits typically include ptosis, extraocular muscle palsies, weak cry, poor suck, decreased gag reflex, pooling of oral secretions, poor muscle tone (floppy baby syndrome), and an expressionless face. Severity varies from mild lethargy and slowed feeding to severe hypotonia and respiratory insufficiency.

**Diagnosis**

Infant botulism may be confused with sepsis, congenital muscular dystrophy, spinal muscular atrophy, hypothyroidism, and benign congenital hypotonia. Finding *C. botulinum* toxin or organisms in the stool establishes the diagnosis.

**Treatment**

- Human botulism antitoxin

Infants are hospitalized, and supportive care (eg, ventilatory support) is given as needed.

Specific treatment is with human botulism immune globulin. Treatment is started as soon as the diagnosis is suspected; waiting for confirmatory test results is dangerous. The dose is 50 mg/kg IV once, given slowly. The horse serum antitoxin used in adults is not recommended for infants.

Antibiotics are not given because they may lyse *C. botulinum* in the gut and increase toxin availability.

**Clostridium Difficile-Induced Diarrhea**

(Pseudomembranous Colitis)

Toxins produced by *Clostridium difficile* strains in the GI tract cause pseudomembranous colitis, typically after antibiotic use. Symptoms are diarrhea, sometimes bloody, rarely progressing to sepsis and acute abdomen. Diagnosis is by identifying *C. difficile* toxin in stool. Treatment is with oral metronidazole or vancomycin.

*C. difficile* is the most common cause of antibiotic-associated colitis and is typically hospital-acquired. *C. difficile*-induced diarrhea occurs in up to 8% of hospitalized patients and is responsible for 20 to 30% of cases of hospital-acquired diarrhea. Extremes of age, severe underlying disease, prolonged hospital stay, and living in a nursing home are risk factors.

*C. difficile* is carried asymptptomatically by 15 to 70% of neonates, 3 to 8% of healthy adults, and perhaps 20% of hospitalized adults (more in long-term care facilities) and is common in the environment (eg, soil,
water, household pets). Disease may result from overgrowth of intrinsic organisms or infection from an external source. Health care workers are frequently the source of transmission.

Recently, a more virulent strain, BI/NAP1/027, has become prominent in hospital out-breaks. This strain produces substantially more toxin, causes more severe illness with greater chance of relapse, is more transmissible, and responds less well to antibiotic treatment.

**Pathophysiology**

Antibiotic-induced changes in GI flora are the dominant predisposing factor. Although most antibiotics have been implicated, cephalosporins (particularly 3rd-generation), penicillins (particularly ampicillin and amoxicillin), clindamycin, and fluoroquinolones pose the highest risk. *C. difficile*-induced colitis may also follow use of certain antineoplastic drugs.

The organism secretes both a cytotoxin and an enterotoxin. The main effect is on the colon, which secretes fluid and develops characteristic pseudomembranes—discrete yellow-white plaques that are easily dislodged. Plaques may coalesce in severe cases. Toxic megacolon, which rarely develops, is somewhat more likely after use of antimotility drugs. Limited tissue dissemination occurs very rarely, as does sepsis and acute abdomen. Reactive arthritis has occurred after *C. difficile*-induced diarrhea.

**Symptoms and Signs**

Symptoms typically begin 5 to 10 days after starting antibiotics but may occur on the first day or up to 2 mo later. Diarrhea may be mild and semiformed or frequent and watery. Cramping or pain is common, but nausea and vomiting are rare. The abdomen may be slightly tender.

Patients with significant colitis or toxic megacolon have more pain and appear very ill, with tachycardia and abdominal distention and tenderness. Peritoneal signs are present in those with perforation.

**Diagnosis**

- Stool assay for toxin
- Sometimes sigmoidoscopy

Diagnosis should be suspected in any patient who develops diarrhea within 2 mo of antibiotic use or 72 h of hospital admission. Diagnosis is confirmed by stool (sample, not swab) assay for *C. difficile* toxin. A new real-time PCR test for the toxin gene tcdB may be superior to current assays. A single sample is usually adequate, but repeat samples should be submitted when suspicion is high and the first sample is negative. Fecal leukocytes are often present but not specific.

Sigmoidoscopy, which can confirm the presence of pseudomembranes, should be done if patients have ileus or if toxin assays are non-diagnostic. Abdominal x-rays, CT, or both are usually done if fulminant colitis, perforation, or megacolon is suspected.

**Treatment**

- Oral metronidazole or vancomycin

Metronidazole 250 mg po q 6 h or 500 mg po q 8 h for 10 days is the therapy of choice. If patients do not respond within 48 h, vancomycin 125 to 500 mg po q 6 h for 10 days may be given. Some patients require bacitracin 500 mg po q 6 h for 10 days, cholestyramine resin, or *Saccharomyces boulardii* yeast. Relapses occur in 15 to 20% of patients. Nitazoxanide 500 mg po q 12 h appears to be comparable to oral vancomycin 125 mg but is not commonly used in the US. A few patients require total colectomy for cure.

Infection control measures are vital to reduce the spread of *C. difficile* among patients and health care workers.
**Clostridial Intra-Abdominal Infections**

Clostridia, primarily *Clostridium perfringens*, are common in mixed intra-abdominal infections due to a ruptured viscus or pelvic inflammatory disease.

*Clostridium* sp are common residents of the GI tract and are present in many abdominal infections, generally mixed with other enteric organisms. Clostridia are often the primary agents in emphysematous cholecystitis, gas gangrene of the uterus (previously common with septic abortion), certain other female genital tract infections (tubo-ovarian, pelvic, and uterine abscesses), and infection after perforation in colon carcinoma.

The primary organisms are *C. perfringens* and, in the case of colon carcinoma, *C. septicum*. The organism produces exotoxins (lecithinases, hemolysins, collagenases, proteases, lipases) that can cause suppuration. Gas formation is common. Clostridial septicemia may cause hemolytic anemia because lecithinase disrupts RBC membranes. With severe hemolysis and coexisting toxicity, acute renal failure can occur.

Symptoms are similar to those of other abdominal infections (eg, pain, fever, abdominal tenderness, a toxic appearance). In uterine infection, gas sometimes escapes through the cervix. Rarely, acute tubular necrosis develops.

**Diagnosis**

- Gram stain and culture

Early diagnosis requires a high index of suspicion. Early and repeated Gram stains and cultures of the site, pus, lochia, and blood are indicated. Because *C. perfringens* can occasionally be isolated from healthy vagina and lochia, cultures are not specific. X-rays may show local gas production (eg, in the biliary tree, gallbladder wall, or uterus).

**Treatment**

- Surgical debridement
- High-dose penicillin

Treatment is surgical debridement and penicillin G 5 million units IV q 6 h for at least 1 wk. Organ removal (eg, hysterectomy) may be necessary and can be lifesaving if debridement is insufficient. If acute tubular necrosis develops, dialysis is needed. The usefulness of hyperbaric O₂ has not been established.

**Clostridial Necrotizing Enteritis**

(Enteritis Necroticans; Pigbel)

Clostridial necrotizing enteritis is necrotizing inflammation of the jejunum and ileum caused by *Clostridium perfringens*.

*C. perfringens* occasionally causes severe inflammatory disease in the small bowel (primarily, the jejunum). Inflammation is segmental, involving small or large patches with varying degrees of hemorrhage and necrosis. Perforation may occur.

Disease is caused by clostridial β-toxin, which is very sensitive to proteolytic enzymes and is inactivated by normal cooking. Disease occurs primarily in populations with multiple risk factors, including protein deprivation (causing inadequate synthesis of protease enzymes), poor food hygiene, episodic meat feasting, staple diets containing trypsin inhibitors (eg, sweet potatoes), and *Ascaris* infestation (these parasites secrete a trypsin inhibitor). These factors are typically present collectively only in the hinterlands of New Guinea and parts of Africa, Central and South America, and Asia. In New Guinea, the
disease is known as pigbel and is usually spread through contaminated pork, other meats, and perhaps peanuts.

Severity varies from mild diarrhea to a fulminant course of severe abdominal pain, vomiting, bloody stool, and sometimes death within 24 h.

Treatment is with antibiotics (penicillin G, metronidazole). Perhaps 50% of seriously ill patients require surgery for perforation, persistent intestinal obstruction, or failure to respond to antibiotics. An experimental toxoid vaccine has been used successfully in endemic areas but is not available commercially.

**Neutropenic enterocolitis (typhilitis):** This similar syndrome develops in the cecum of neutropenic patients (e.g., those with leukemia or receiving cancer chemotherapy). It may be associated with sepsis due to *Clostridium septicum*. Symptoms are fever, abdominal pain, and diarrhea.

Treatment is with antibiotics, but surgery may be necessary.

**Neonatal necrotizing enterocolitis:** Neonatal necrotizing enterocolitis (see p. 2803), which occurs in neonatal ICUs, may be caused by *C. perfringens*, *C. butyricum*, or *C. difficile*, although the role of these organisms needs further study.

**Clostridium perfringens Food Poisoning**

*Clostridium perfringens* food poisoning is acute gastroenteritis caused by ingestion of contaminated food.

*C. perfringens* is widely distributed in feces, soil, air, and water. Contaminated meat has caused many outbreaks. When meat contaminated with *C. perfringens* is left at room temperature, the organism multiplies and produces toxin. Outbreaks typically occur in commercial establishments and rarely at home. Once inside the GI tract, *C. perfringens* produces an enterotoxin that acts on the small bowel. Only *C. perfringens* type A has been definitively linked to this food poisoning syndrome. The enterotoxin produced is sensitive to heat (> 75°C).

Mild gastroenteritis is most common, with onset of symptoms 6 to 24 h after ingestion of contaminated food. The most common symptoms are watery diarrhea and abdominal cramps. Vomiting is unusual. Symptoms typically resolve within 24 h; severe or fatal cases rarely occur.

Diagnosis is based on epidemiologic evidence and isolation of large numbers of organisms from contaminated food or from stools of affected people or on direct identification of enterotoxin in stool samples.

To prevent disease, people should promptly refrigerate leftover cooked meat and reheat it thoroughly (internal temperature, 75°C) before serving.

Treatment is supportive (see p. 149); antibiotics are not given.

**Clostridial Soft-Tissue Infections**

Clostridial soft-tissue infections include cellulitis, myositis, and clostridial myonecrosis. They usually occur after trauma. Symptoms may include edema, pain, gas with crepitation, foul-smelling exudates, intense coloration of the site, and progression to shock and renal failure. Diagnosis is by inspection and smell, confirmed by culture. Treatment is with penicillin and surgical debridement. Hyperbaric O₂ is sometimes beneficial.

*Clostridium perfringens* is the most common species involved. Infection develops hours or days after injury, usually in an extremity after severe crushing or penetrating trauma devitalizes tissue, creating anaerobic conditions. The presence of foreign material (even if sterile) markedly increases risk of
clostridial infection. Infection may also occur in operative wounds, particularly in patients with underlying occlusive vascular disease. Rarely, spontaneous cases occur, usually involving C. septicum originating from occult colon perforation in patients with colon cancer, diverticulitis, or bowel ischemia. Infection typically results in gas collection in soft tissues.

In suitable conditions (low oxidation-reduction potential, low pH), as occur in devitalized tissue, infection progresses rapidly, from initial injury through shock, toxic delirium, and death within as little as 1 day.

**Symptoms and Signs**

**Clostridial cellulitis** occurs as a localized infection in a superficial wound, usually ≥ 3 days after injury. Infection may spread extensively along fascial planes, often with evident crepitation and abundant gas bubbling, but toxicity is much less severe than with extensive myonecrosis, and pain is minimal. Bullae are frequently evident, with foul-smelling, serous, brown exudate. Discoloration and gross edema of the extremity are rare. Clostridial skin infections associated with primary vascular occlusion of an extremity rarely progress to severe toxic myonecrosis or extend beyond the line of demarcation.

**Clostridial myositis** (suppurative infection of muscle without necrosis) is most common among parenteral drug users. It resembles staphylococcal pyomyositis and lacks the systemic symptoms of clostridial myonecrosis. Edema, pain, and frequently gas in the tissues occur. The infection spreads rapidly and may progress to myonecrosis.

In **clostridial myonecrosis** (gas gangrene), initial severe pain is common, sometimes even before other findings. The wound site may be pale initially, but it becomes red or bronze, often with blebs or bullae, and finally turns blackish green. The area is tensely edematous and tender to palpation. Crepitation is less obvious early than it is in clostridial cellulitis but is ultimately palpable in about 80%. Wounds and drainage have a particularly foul odor.

With progression, patients appear toxic, with tachycardia, pallor, and hypotension. Shock and renal failure occur, although patients often remain alert until the terminal stage. Unlike clostridial uterine infection, overt hemolysis is rare in gas gangrene of the extremities, even in terminally ill patients. Whenever massive hemolysis occurs, mortality of 70 to 100%, due to acute renal failure and septicemia, can be expected.

**Diagnosis**

- Clinical evaluation
- Gram stain and culture

Early suspicion and intervention are essential; clostridial cellulitis responds well to treatment, but myonecrosis has a mortality rate of ≥ 40% with treatment and 100% without treatment.

Although localized cellulitis, myositis, and spreading myonecrosis may be clinically distinct, differentiation often requires surgical exploration. In myonecrosis, muscle tissue is visibly necrotic; the affected muscle is a lusterless pink, then deep red, and finally gray-green or mottled purple and does not contract with stimulation. X-rays may show local gas production, and CT and MRI delineate the extent of gas and necrosis.

Wound exudate should be cultured for anaerobic and aerobic organisms. Because of their short generation time, anaerobic cultures of Clostridia may be positive in as little as 6 h. However, other anaerobic and aerobic bacteria, including members of the Enterobacteriaceae family and Bacteroides, Streptococcus, and Staphylococcus spp, alone or mixed, can cause severe clostridia-like cellulitis, extensive fasciitis, or myonecrosis (see Necrotizing Sub-cutaneous Infection on p. 700). Also, many wounds, particularly if open, are contaminated with both pathogenic and nonpathogenic clostridia that are not responsible for the infection.

The presence of clostridia is significant when
• Gram stain shows them in large numbers.
• Few PMNs are found in the exudates.
• Free fat globules are demonstrated with Sudan stain.

However, if PMNs are abundant and the smear shows many chains of cocci, an anaerobic streptococcal or staphylococcal infection should be suspected. Abundant gram-negative bacilli may indicate infection with one of the Enterobacteriaceae or a Bacteroides sp (see also Mixed Anaerobic Infections on p. 1299). Detection of clostridial toxins in the wound or blood is useful only in the rare case of wound botulism (see p. 1291).

Treatment

• Drainage and debridement
• Penicillin plus clindamycin

When clinical signs of clostridial infection (eg, gas, myonecrosis) are present, rapid, aggressive intervention is mandatory. Thorough drainage and debridement are as important as antibiotics; both should be instituted rapidly. Penicillin G is the drug of choice; 1 to 2 million units IV q 2 to 3 h should be given immediately for severe cellulitis and myonecrosis. Addition of clindamycin 600 mg IV q 6 h is beneficial. If gram-negative organisms are seen or suspected, a broad-spectrum antibiotic (eg, ticarcillin plus clavulanate, ampicillin plus sulbactam, piperacillin plus tazobactam) should be added.

Hyperbaric O$_2$ therapy may be helpful in extensive myonecrosis, particularly in the extremities, as a supplement to antibiotics and surgery. Hyperbaric O$_2$ therapy may salvage tissue and lessen mortality and morbidity if it is started early, but it should not delay surgical debridement.

Tetanus

(LOCKJAW)

Tetanus is acute poisoning from a neurotoxin produced by Clostridium tetani. Symptoms are intermittent tonic spasms of voluntary muscles. Spasm of the masseters accounts for the name lockjaw. Diagnosis is clinical. Treatment is with immune globulin and intensive support.

Tetanus bacilli form durable spores that occur in soil and animal feces and remain viable for years. Worldwide, tetanus is estimated to cause over half a million deaths annually, mostly in neonates and young children, but the disease is so rarely reported that all figures are only rough estimates. In the US, only 37 cases were reported in 2001. Disease incidence is directly related to the immunization level in a population, attesting to the effectiveness of preventive efforts. In the US, well over half of elderly patients have inadequate antibody levels and account for one third to one half of cases. Most of the rest occur in inadequately immunized patients aged 20 to 59. Patients < 20 account for < 10%. Patients with burns, surgical wounds, or a history of injection drug abuse are especially prone to developing tetanus. However, tetanus may follow trivial or even inapparent wounds. Infection may also develop postpartum in the uterus (maternal tetanus) and in a neonate’s umbilicus (tetanus neonatorum).

Pathophysiology

Manifestations of tetanus are caused by an exotoxin (tetanospasmin). The toxin may enter the CNS along the peripheral motor nerves or may be bloodborne to nervous tissue. Tetanospasmin binds irreversibly to the ganglioside membranes of nerve synapses, blocking release of inhibitory transmitter from nerve terminals and thereby causing a generalized tonic spasticity, usually with superimposed intermittent tonic seizures. Disinhibition of autonomic neurons and loss of control of adrenal catecholamine release cause autonomic instability and a hypersympathetic state. Once bound, the toxin cannot be neutralized.
Most often, tetanus is generalized, affecting skeletal muscles throughout the body. However, tetanus is sometimes localized to muscles near an entry wound.

**Symptoms and Signs**

The incubation period ranges from 2 to 50 days (average, 5 to 10 days). Symptoms include

- Jaw stiffness (most frequent)
- Difficulty swallowing
- Restlessness
- Irritability
- Stiff neck, arms, or legs
- Headache
- Sore throat
- Tonic spasms

Later, patients have difficulty opening their jaw (trismus).

**Spasms:** Facial muscle spasm produces a characteristic expression with a fixed smile and elevated eyebrows (risus sardonicus). Rigidity or spasm of abdominal, neck, and back muscles—even opisthotonos—may occur. Sphincter spasm causes urinary retention or constipation. Dysphagia may interfere with nutrition. Characteristic painful, generalized tonic spasms with profuse sweating are precipitated by minor disturbances such as a draft, noise, or movement. Mental status is usually clear, but coma may follow repeated spasms. During generalized spasms, patients are unable to speak or cry out because of chest wall rigidity or glottal spasm. Spasms also interfere with respiration, causing cyanosis or fatal asphyxia. The immediate cause of death may not be apparent.

Respiratory failure is the most common cause of death. Laryngeal spasm and rigidity and spasms of the abdominal wall, diaphragm, and chest wall muscles cause asphyxiation. Hypoxemia can also induce cardiac arrest, and pharyngeal spasm leads to aspiration of oral secretions with subsequent pneumonia, contributing to a hypoxic death.

**Autonomic instability:** Temperature is only moderately elevated unless a complicating infection, such as pneumonia, is present. Respiratory and pulse rates are increased. Reflexes are often exaggerated. Protracted tetanus may manifest as a very labile and overactive sympathetic nervous system, including periods of hypertension, tachycardia, and myocardial irritability.

**Localized tetanus:** In localized tetanus, there is spasticity of muscles near the entry wound but no trismus; spasticity may persist for weeks.

**Cephalic tetanus** is a form of localized tetanus that affects the cranial nerves. It is more common among children; in them, it may occur with chronic otitis media or may follow a head wound. Incidence is highest in Africa and India. All cranial nerves can be involved, especially the 7th. Cephalic tetanus may become generalized.

**Tetanus neonatorum:** Tetanus in neonates is usually generalized and frequently fatal. It often begins in an inadequately cleansed umbilical stump in children born of inadequately immunized mothers. Onset during the first 2 wk of life is characterized by rigidity, spasms, and poor feeding. Bilateral deafness may occur in surviving children.

**Diagnosis**
• Clinical evaluation

A history of a recent wound in a patient with muscle stiffness or spasms is a clue. Tetanus can be confused with meningocencephalitis of bacterial or viral origin, but the combination of an intact sensorium, normal CSF, and muscle spasms suggests tetanus. Trismus must be distinguished from peritonsillar or retropharyngeal abscess or another local cause. Phenothiazines can induce tetanus-like rigidity (eg, dystonic reaction, neuroleptic malignant syndrome).

* C. tetani* can sometimes be cultured from the wound, but culture is not sensitive.

### Prognosis

Tetanus has a worldwide mortality rate of 50%, 15 to 60% in untreated adults, and 80 to 90% in neonates even if treated. Mortality is highest at the extremes of age and in drug abusers. The prognosis is poorer if the incubation period is short and symptoms progress rapidly or if treatment is delayed. The course tends to be milder when there is no demonstrable focus of infection.

### Treatment

• Supportive care, particularly respiratory support

• Wound debridement

• Tetanus antitoxin

• Benzodiazepines for muscle spasms

• Metronidazole or penicillin

• Sometimes drugs for autonomic dysfunction

Therapy requires maintaining adequate ventilation. Additional interventions include early and adequate use of human immune globulin to neutralize nonfixed toxin; prevention of further toxin production; sedation; control of muscle spasm, hypertonicity, fluid balance, and intercurrent infection; and continuous nursing care.

**General principles:** The patient should be kept in a quiet room. Three principles should guide all therapeutic interventions: prevent further toxin release by debriding the wound and giving an antibiotic (see p. 1298); neutralize toxin outside the CNS with human tetanus immune globulin and tetanus toxoid, taking care to inject into different body sites and thus avoid neutralizing the antitoxin; and minimize the effect of toxin already in the CNS.

**Wound care:** Because dirt and dead tissue promote *C. tetani* growth, prompt, thorough debridement, especially of deep puncture wounds, is essential. Antibiotics are not substitutes for adequate debridement and immunization.

**Antitoxin:** The benefit of human-derived antitoxin depends on how much tetanospasmin is already bound to the synaptic membranes—only free toxin is neutralized. For adults, human tetanus immune globulin 3000 units IM is given once; this large volume may be split and given at separate sites. Dose can range from 1,500 to 10,000 units, depending on wound severity, although some authorities feel that 500 units are adequate. Antitoxin of animal origin is far less preferable because it does not maintain the patient's serum antitoxin level well and risk of serum sickness is considerable. If horse serum must be used, the usual dose is 50,000 units IM or IV (CAUTION: See Drug Hypersensitivity on p. 1122). If necessary, immune globulin or antitoxin can be injected directly into the wound, but this injection is not as important as good wound care.

**Management of muscle spasm:** Drugs are used to manage spasms.
Benzodiazepines are the standard of care to control rigidity and spasms. They block reuptake of an endogenous inhibiting neuro-transmitter, γ-aminobutyric acid (GABA), at the GABA\textsubscript{A} receptor.

Diazepam can help control seizures, counter muscle rigidity, and induce sedation. Dosage varies and requires meticulous titration and close observation. The most severe cases may require 10 to 20 mg IV q 3 h (not exceeding 5 mg/kg). Less severe cases can be controlled with 5 to 10 mg po q 2 to 4 h. Dosage varies by age:

- Infants > 30 days: 1 to 2 mg IV given slowly, repeated q 3 to 4 h as necessary
- Young children: 0.1 to 0.8 mg/kg/day up to 0.1 to 0.3 mg/kg IV q 4 to 8 h
- Children > 5 yr: 5 to 10 mg IV q 3 to 4 h
- Adults: 5 to 10 mg po q 4 to 6 h or up to 40 mg/h IV drip

Diazepam has been used most extensively, but midazolam (adults, 0.1 to 0.3 mg/kg/h IV infusion; children, 0.06 to 0.15 mg/kg/h IV infusion) is water soluble and preferred for prolonged therapy. Midazolam reduces risk of lactic acidosis due to propylene glycol solvent, which is required for diazepam and lorazepam, and reduces risk of long-acting metabolites accumulating and causing coma.

Benzodiazepines may not prevent reflex spasms, and effective respiration may require neuromuscular blockade with vecuronium 0.1 mg/kg IV or other paralytic drugs and mechanical ventilation. Pancuronium has been used but may worsen autonomic instability. Vecuronium is free of adverse cardiovascular effects but is short-acting. Longer-acting drugs (eg, pipecuronium, rocuronium) also work, but no randomized clinical comparative trials have been done.

Intrathecal baclofen (a GABA\textsubscript{A} agonist) is effective but has no clear advantage over benzodiazepines. It is given by continuous infusion; effective doses range between 20 and 2000 μg/day. A test dose of 50 μg is given first; if response is inadequate, 75 μg may be given 24 h later, and 100 μg 24 h after that. Patients who do not respond to 100 μg are not candidates for chronic infusion. Coma and respiratory depression requiring ventilatory support are potential adverse effects.

Dantrolene (loading dose 1.0 to 1.5 mg/kg IV, followed by infusion of 0.5 to 1.0 mg/kg q 4 to 6 h for ≤ 25 days) relieves muscle spasticity. Dantrolene given orally can be used in place of infusion therapy for up to 60 days. Hepatotoxicity and expense limit its use.

Management of autonomic dysfunction: Morphone may be given q 4 to 6 h to control autonomic dysfunction, especially cardiovascular; total daily dose is 20 to 180 mg. β-Blockade with long-acting drugs such as propranolol is not recommended. Sudden cardiac death is a feature of tetanus, and β-blockade can increase risk; however, esmolol, a short-acting β-blocker, has been used successfully. Atropine at high doses has been used; blockade of the parasympathetic nervous system markedly reduces excessive sweating and secretions. Lower mortality has been reported in clonidine-treated patients than in those treated with conventional therapy.

Mg sulfate at doses that maintain serum levels between 4 to 8 mEq/L (eg, 4 g bolus followed by 2 to 3 g/h) has a stabilizing effect, eliminating catecholamine stimulation. Patellar tendon reflex is used to assess overdosage. Tidal volume may be impaired, so ventilatory support must be available.

Pyridoxine (100 mg once/day) lowers mortality in neonates. Other drugs that may prove useful include Na valproate (which blocks GABA-aminotransferase, inhibiting GABA catabolism), ACE inhibitors (which inhibit angiotensin II and reduce norepinephrine release from nerve endings), dexmedetomidine (a potent α-2 adrenergic agonist), and adenosine (which reduces presynaptic norepinephrine release and antagonizes the inotropic effect of catecholamines). Corticosteroids are of unproven benefit; their use is not recommended.

Antibiotics: The role of antibiotic therapy is minor compared with wound debridement and general
support. Typical antibiotics include penicillin G 6 million units IV q 6 h, doxycycline 100 mg po bid, and metronidazole 500 mg po q 6 to 8 h.

**Supportive care:** In moderate or severe cases, patients should be intubated. Mechanical ventilation is essential when neuromuscular blockade is required to control muscle spasms that impair respirations.

IV hyperalimentation avoids the hazard of aspiration secondary to gastric tube feeding. Because constipation is usual, stools should be kept soft. A rectal tube may control distention. Bladder catheterization is required if urinary retention occurs.

Chest physiotherapy, frequent turning, and forced coughing are essential to prevent pneumonia. Analgesia with opioids is often needed.

**Prevention**

A series of 4 primary immunizations against tetanus, followed by boosters every 10 yr, with the adsorbed (for primary immunization) or fluid (for boosters) toxoid is superior to giving antitoxin at the time of injury. Tetanus toxoid comes by itself, combined with diphtheria in both adult (Td) and child strengths (DT), and combined with diphtheria and pertussis (DTP). For routine diphtheria, tetanus, and pertussis immunization and booster recommendations, see Ch. 131. Adults need to maintain immunity with regular boosters q 10 yr. Immunization in an unimmunized or inadequately immunized pregnant woman produces both active and passive immunity in the fetus and should be given at a gestational age of 5 to 6 mo with a booster at 8 mo. Passive immunity develops when maternal toxoid is given before a gestational age of 6 mo.

After injury, tetanus vaccination is given depending on wound type and vaccination history; tetanus immune globulin may also be indicated (see **Table 140-1**). Patients not previously vaccinated are given a 2nd and 3rd dose of toxoid at monthly intervals.

Because tetanus infection does not confer immunity, patients who have recovered from clinical tetanus should be vaccinated.

**Mixed Anaerobic Infections**

Anaerobes can infect normal hosts and hosts with compromised resistance or damaged tissues. Symptoms depend on site of infection. Anaerobes are often accompanied by aerobic organisms. Diagnosis is clinical combined with Gram stain and anaerobic cultures. Treatment is with antibiotics and surgical drainage and debridement.

Hundreds of species of nonsporulating anaerobes are part of the normal flora of the skin, mouth, GI tract, and vagina. If this commensal relationship is disrupted (eg, by surgery, other trauma, poor blood supply, or tissue necrosis), a few of these species can cause infections with high morbidity and mortality. After becoming established in a primary site, organisms can spread hematogenously to distant sites. Because aerobic and anaerobic bacteria are frequently present in the same infected site, appropriate procedures for isolation and culture are necessary to keep from overlooking the anaerobes. Anaerobes can be the main cause of infection in the pleural spaces and lungs; in intra-abdominal, gynecologic, CNS, upper respiratory tract, and cutaneous diseases; and in bacteremia.

**Etiology**

The principal anaerobic gram-positive cocci that cause disease are peptococci and peptostreptococci, which are part of the normal flora of the mouth, upper respiratory tract, and large intestine. The principal anaerobic gram-negative bacilli include *Bacteroides fragilis*, *Prevotella melaninogenica*, and *Fusobacterium* sp. The *B. fragilis* group is part of the normal bowel flora and includes the anaerobic pathogens most frequently isolated from intra-abdominal
infections. Organisms in the *Prevotella* group and *Fusobacterium* sp are part of the normal oral flora.

**Pathophysiology**

Anaerobic infections can usually be characterized as follows:

- They tend to occur as localized collections of pus or abscesses.
- The reduced O₂ tension and low oxidation-reduction potential that prevail in avascular and necrotic tissues are critical for their survival.
- When bacteremia occurs, it usually does not lead to disseminated intravascular coagulation (DIC) and purpura.

Some anaerobic bacteria possess distinct virulence factors. The virulence factors of *B. fragilis* probably account for its frequent isolation from clinical specimens despite its relative rarity in normal flora. This organism has a polysaccharide capsule that apparently stimulates abscess formation. An experimental model of intra-abdominal sepsis has shown that *B. fragilis* alone can cause abscesses, whereas other *Bacteroides* sp require the synergistic effect of another organism. Another virulence factor, a potent endotoxin, is implicated in septic shock associated with severe *Fusobacterium* pharyngitis.

Morbidity and mortality rates for anaerobic and mixed bacterial sepsis are as high as those for sepsis caused by a single aerobic organism. Anaerobic infections are often complicated by deep-seated tissue necrosis. The overall mortality rate for severe intra-abdominal sepsis and mixed anaerobic pneumonias tends to be high. *B. fragilis* bacteremia has a high mortality rate, especially in the elderly and in patients with cancer.

**Symptoms and Signs**

Patients usually have fever, rigors, and critical illness; shock may develop. DIC may occur in *Fusobacterium* sepsis.

For specific infections (and symptoms) caused by mixed anaerobic organisms, see elsewhere in THE MANUAL and Table 140-2. Anaerobes are rare in UTI, septic arthritis, and infective endocarditis.

**Diagnosis**

- Clinical suspicion
- Gram stain and culture

[Table 140-2, Disorders Often Caused by Mixed* Anaerobic Organisms]

Clinical clues to the presence of anaerobic organisms include

- Infection adjacent to mucosal surfaces that bear anaerobic flora
- Ischemia, tumor, penetrating trauma, foreign body, or perforated viscus
- Spreading gangrene involving skin, subcutaneous tissue, fascia, and muscle
- Feculent odor in pus or infected tissues
- Abscess formation
- Gas in tissues
• Septic thrombophlebitis

• Failure to respond to antibiotics that do not have significant anaerobic activity

Anaerobic infection should be suspected when any wound smells foul or when a Gram stain of pus from an infected site shows mixed pleomorphic bacteria. Only specimens from normally sterile sites should be cultured because commensal contaminants may easily be mistaken for pathogens.

Gram stains and aerobic cultures should be obtained for all specimens. Gram stain, particularly in *Bacteroides* infection, and cultures for all anaerobes may be falsely negative. Antibiotic sensitivity testing of anaerobes is exacting, and data may not be available for ≥ 1 wk after initial culture. However, if the species is known, sensitivity patterns can usually be predicted. Therefore, many laboratories do not routinely test anaerobic organisms for sensitivity.

**Treatment**

• Drainage and debridement

• Antibiotic choice varying by site of infection

In established infection, pus is drained, and devitalized tissue, foreign bodies, and necrotic tissue are removed. Organ perforations must be treated by closure or drainage. Whenever possible, blood supply should be reestablished. Septic thrombophlebitis may require vein ligation as well as antibiotics.

Because anaerobic culture results may not be available for 3 to 5 days, antibiotics are started. Antibiotics sometimes work even when some of the bacterial species in a mixed infection are resistant to the antibiotic, especially if surgical debridement and drainage are adequate.

Oropharyngeal anaerobic infections may not respond to penicillin and thus require a drug effective against penicillin-resistant anaerobes (see below). Oropharyngeal infections and lung abscesses should be treated with clindamycin or a β-lactam/β-lactamase combination such as amoxicillin/clavulanate. In patients allergic to penicillin, clindamycin or metronidazole (plus a drug active against aerobes) is useful.

GI or female pelvic anaerobic infections are likely to contain obligate anaerobic gram-negative bacilli such as *B. fragilis* plus facultative gram-negative bacilli such as *Escherichia coli*; antibiotic regimens must be active against both. Resistance of *B. fragilis* and other obligate anaerobic gram-negative bacilli to penicillins and 3rd- and 4th-generation cephalosporins occurs. However, the following drugs have excellent in vitro activity against *B. fragilis* and are effective: metronidazole, carbapenems (eg, imipenem/cilastatin, meropenem, ertapenem), β-lactam/β-lactamase combinations (eg, piperacillin/tazobactam, ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate), tigecycline, and moxifloxacin. No single regimen appears to be superior. Drugs that are somewhat less predictably active in vitro against *B. fragilis* but are usually effective include clindamycin, cefoxitin, and cefotetan. All except clindamycin and metronidazole can be used as monotherapy because these drugs also have good activity against facultative anaerobic gram-negative bacilli.

Metronidazole is active against clindamycin-resistant *B. fragilis*, has unique anaerobic bactericidal activity, and usually avoids the pseudomembranous colitis sometimes associated with clindamycin. Concerns about metronidazole’s potential mutagenicity have not been of clinical consequence.

Because many regimens are available to treat GI or female pelvic anaerobic infections, use of a potentially nephrotoxic aminoglycoside (to cover enteric gram-negative bacilli) plus an antibiotic active against *B. fragilis* is no longer warranted.

**Prevention**

• Metronidazole plus gentamicin or ciprofloxacin
Before elective colorectal surgery, patients should have bowel preparation consisting of

• Cathartics

• Enemas

• Antibiotics

Most surgeons give both oral and parenteral antibiotics. For emergency colorectal surgery, parenteral antibiotics are used alone. Examples of oral regimens are neomycin plus erythromycin or neomycin plus metronidazole; these drugs are given no more than 18 to 24 h before the procedure. Examples of parenteral preoperative regimens are cefotetan, cefoxitin, or cefazolin plus metronidazole. Preoperative parenteral antibiotics control bacteremia, reduce secondary or metastatic suppurative complications, and prevent local spread of infection around the surgical site.

For patients with confirmed allergy or adverse reaction to β-lactams, one of the following regimens is recommended: clindamycin plus gentamicin, aztreonam, or ciprofloxacin; or metronidazole plus gentamicin or ciprofloxacin.
Chapter 141. Mycobacteria

Introduction

Mycobacteria are small, slow-growing, aerobic bacilli distinguished by a complex, lipid-rich cell envelope responsible for their characterization as acid-fast (ie, resistant to decolorization by acid after staining with carbol fuchsin) and their imperviousness to Gram stain. The most common mycobacterial infection is tuberculosis; others include leprosy and various diseases caused by *Mycobacterium avium* complex.

Tuberculosis

(See also Perinatal Tuberculosis on p. 2838.)

Tuberculosis (TB) is a chronic, progressive infection with a period of latency following initial infection. It occurs most commonly in the lungs. Pulmonary symptoms include productive cough, chest pain, and dyspnea. Diagnosis is most often by sputum culture and smear. Treatment is with multiple antimicrobial drugs.

TB is a leading infectious cause of morbidity and mortality in adults worldwide, killing about 1.5 million people every year. HIV/AIDS is an increasingly prominent factor predisposing to TB infection and mortality in parts of the world where both infections are prevalent.

Etiology

TB properly refers only to disease caused by *Mycobacterium tuberculosis*. Similar disease occasionally results from the closely related mycobacteria, *M. bovis, M. africanum*, and *M. microti*.

TB results almost exclusively from inhalation of airborne particles (droplet nuclei) containing *M. tuberculosis*. They disperse primarily through coughing, singing, and other forced respiratory maneuvers by people who have active pulmonary TB and whose sputum contains a significant number of organisms (typically enough to render the smear positive). People with pulmonary cavitory lesions are especially infectious. Droplet nuclei containing tubercle bacilli may remain suspended in room air currents for several hours, increasing the chance of spread. However, once these droplets land on a surface, it is difficult to resuspend the organisms (eg, by sweeping the floor, shaking out bed linens) as respirable particles. Although such actions can resuspend dust particles containing tubercle bacilli, these particles are far too large to reach the alveolar surfaces necessary to initiate infection. Fomites (eg, contaminated surfaces, food, and personal respirators) do not appear to facilitate spread.

Although there is wide variability, patients with pulmonary TB infect about 7 close contacts, on average, but most of those infected do not develop active disease. Transmission is enhanced by frequent or prolonged exposure to a patient who is dispersing large numbers of tubercle bacilli in overcrowded, enclosed, poorly ventilated spaces; thus, people living in poverty or in institutions are at particular risk. Health care practitioners who have close contact with active cases have increased risk. However, once effective treatment begins, cough rapidly decreases, organisms are inactivated, and within weeks, TB is no longer contagious.

Much less commonly, spread results from aerosolization of organisms after irrigation of infected wounds, in mycobacteriology laboratories, or in autopsy rooms. TB of the tonsils, lymph nodes, abdominal organs, bones, and joints was once commonly caused by ingestion of milk or milk products (eg, cheese) contaminated with *M. bovis*, but this transmission route has been largely eradicated in developed countries by slaughter of cows that test positive on a tuberculin skin test and by pasteurization of milk. Tuberculosis due to *M. bovis* still occurs in developing countries and in immigrants from developing countries where bovine tuberculosis is endemic (eg, some Latin American countries).

Risk factors: HIV infection is the greatest single medical risk factor because cell-mediated immunity, which is impaired by HIV, is essential for defense against TB; other immunosuppressive illnesses (eg, diabetes) or therapies (eg, tumor necrosis factor [TNF] inhibitors, corticosteroids) increase risk but less...
than HIV.

Age has traditionally been considered an independent risk factor because the elderly have more years of potential exposure and are more likely to have impaired immunity. However, in the US, the difference in the age-specific case rate is no longer as large, probably because the incidence of infectious cases (and hence lifetime risk of significant exposure) has declined.

Epidemiology

About one third of the world's population is infected. Of these, perhaps only 15 million have active disease at any given time. In 2006, an estimated 9.2 million new TB cases occurred worldwide (139/100,000). Of these, Africa and Southeast Asia each accounted for about 3 million cases, and the Western Pacific region for about 2 million. Case rates vary very widely by country, age, race, sex, and socioeconomic status. India and China reported the largest numbers of new cases, but South Africa has the largest case rate: 940/100,000.

In the US, the case rate has declined 10-fold since 1953. In 2007, 13,299 cases were reported to the CDC for a case rate of 4.4/100,000 (ranging from 0.4 in Wyoming to 10.2 in Washington DC). Over half of these cases occurred in patients born outside the US in high-prevalence areas. The TB rate among foreign-born people (20.7/100,000) was nearly 10 times the rate among US-born people (2.1/100,000). Blacks accounted for 45% of cases among the US-born. In the southeastern US and inner cities throughout the US, poor US-born blacks, the homeless, people in jails and prisons, and other disenfranchised minorities contribute disproportionately to the case rate. In such high-risk populations, case rates can approach those in high-burden parts of the world.

A resurgence of TB occurred in parts of the US and other developed countries between 1985 and 1992; it was associated with several factors, including HIV coinfection, homelessness, a deteriorated public health infrastructure, and the appearance of multidrug-resistant TB (MDR-TB). Although substantially controlled in the US by public health and institutional infection control measures, the problem of MDR-TB, including extensively drug-resistant TB (XDR-TB), appears to be growing around the world, fueled by poor treatment supervision, weak retreatment regimens, inadequate drug supplies, HIV coinfection, institutional transmission, and inadequate diagnostic laboratory facilities. Control efforts, including prolonged (eg, > 18 mo) use of 2nd-line antibiotics, treatment of adverse drug reactions, community-based supervision, social and emotional support, and improved institutional transmission control are raising hopes for better global control of MDR-TB. Treatment of XDR-TB has less favorable outcomes, and the mortality rate is extremely high in patients coinfected with HIV despite concomitant antiretroviral therapy.

Pathophysiology

Tubercle bacilli initially cause a primary infection, which only rarely causes acute illness. Most (about 95%) primary infections are asymptomatic and followed by a latent (dormant) phase. However, a variable percentage of latent infections subsequently reactivate with symptoms and signs of disease. Infection is usually not transmissible in the primary stage and is never contagious in the latent stage.

Primary infection: Infection requires inhalation of particles small enough to traverse the upper respiratory defenses and deposit deep in the lung, usually in the subpleural airspaces of the lower lung. Large droplets tend to lodge in the more proximal airways and typically do not result in infection. Infection usually begins from a single initial focus.

To initiate infection, tubercle bacilli must be ingested by alveolar macrophages. Tubercle bacilli that are not killed by the macrophages actually replicate inside them, ultimately killing the host macrophage (with the help of CD8 lymphocytes); inflammatory cells are attracted to the area, causing a focal pneumonia that evolves into the characteristic tubercles seen histologically. In the early weeks of infection, some infected macrophages migrate to regional lymph nodes (eg, hilar, mediastinal), where they access the bloodstream. Organisms may then spread hematogenously to any part of the body, particularly the apical-posterior portion of the lungs, epiphyses of the long bones, kidneys, vertebral bodies, and meninges.
In 95% of cases, after about 3 wk of uninhibited growth, the immune system suppresses bacillary replication before symptoms or signs develop. Foci of infection in the lung or other sites resolve into epithelioid cell granulomas, which may have caseous and necrotic centers. Tubercle bacilli can survive in this material for years; the balance between the host's resistance and microbial virulence determines whether the infection ultimately resolves without treatment, remains dormant, or becomes active. Infectious foci may leave fibronodular scars in the apices of one or both lungs (Simon foci), calcified scars from the primary infection (Ghon foci), or calcified hilar lymph nodes. The tuberculin skin test (see p. 1305) and the newer interferon-γ release assay become positive.

Less often, the primary focus immediately progresses, causing acute illness with pneumonia (sometimes cavitary), pleural effusion, and marked mediastinal or hilar lymph node enlargement (which, in children, may compress bronchi). Small pleural effusions are predominantly lymphocytic, typically contain few organisms, and clear within a few weeks. This sequence may be more common among young children and recently infected or reinfected immunosuppressed patients. Extrapulmonary TB at any site can sometimes manifest without evidence of lung involvement. TB lymphadenopathy is the most common extrapulmonary presentation; however, meningitis is the most feared because of its high mortality in the very young and very old.

**Active disease:** In about 10% of immunocompetent patients, latent infection develops into active disease, although the percentage varies significantly by age and other risk factors. In 50 to 80% of those who develop active disease, TB reactivates within the first 2 yr, but it can occur decades later. Any organ initially seeded may become a site of reactivation, but reactivation occurs most often in the lung apices, presumably because of favorable local conditions such as high O₂ tension. Ghon foci and affected hilar lymph nodes are much less likely to be sites of reactivation.

Conditions that facilitate activation include impaired immunity (particularly HIV infection), certain immunosuppressants (eg, corticosteroids, infliximab, other TNF inhibitors), gastrectomy, jejunoileal bypass surgery, silicosis, renal insufficiency, stress, diabetes, head or neck cancer, significant weight loss, adolescence, and advanced age (particularly > 70 yr).

TB damages tissues through delayed-type hypersensitivity (DTH—see p. 1109), typically producing granulomatous necrosis with a caseous histologic appearance. Lung lesions are characteristically but not invariably cavitary, especially in immunosuppressed patients with impaired DTH. Pleural effusion is less common than in progressive primary TB but may result from direct extension or hematogenous spread. Rupture of a large tuberculous lesion into the pleural space may cause empyema with or without bronchopleural fistula and sometimes causes pneumothorax. In the prechemotherapy era, TB empyema sometimes complicated medically induced pneumothorax therapy and was usually rapidly fatal, as was sudden massive hemoptysis due to erosion of a pulmonary artery by an enlarging cavity.

The course varies greatly, depending on the virulence of the organism and the state of host defenses. The course may be rapid among blacks, American Indians, and other populations who have not had as many centuries of selective pressure to develop innate or natural immunity as descendents of the European and American TB epidemics have had. The course is often more indolent in the latter populations.

Acute respiratory distress syndrome (ARDS), which appears to be due to hypersensitivity to TB antigens, develops rarely after diffuse hematogenous spread or rupture of a large cavity with spillage into the lungs.

**Symptoms and Signs**

In active pulmonary TB, even moderate or severe disease, patients may have no symptoms, except "not feeling well," anorexia, fatigue, and weight loss, which develop gradually over several weeks, or they may have more specific symptoms. Cough is most common. At first, it may be minimally productive of yellow or green sputum, usually on rising, but cough may become more productive as the disease progresses. Hemoptysis occurs only with cavitary TB (sometimes due to fungal growth in a cavity). Low-grade fever is common but not invariable. Drenching night sweats are a classic symptom but are neither common in nor specific for TB. Dyspnea may result from lung parenchymal damage, spontaneous pneumothorax, or pleural TB with effusion.
With HIV coinfection, the clinical presentation is often atypical because DTH is impaired; patients are more likely to have symptoms of extrapulmonary or disseminated disease.

**Diagnosis**

- Chest x-ray
- Tuberculin skin test
- Acid-fast stain and culture
- When available, DNA-based testing

Pulmonary TB is often suspected based on chest x-rays taken while evaluating respiratory symptoms (cough > 3 wk, hemoptysis, chest pain, dyspnea), an unexplained illness, FUO, or a positive tuberculin skin test (see p. 1305).

Initial tests are chest x-ray, sputum examination, and tuberculin skin testing. If the chest x-ray is highly characteristic (upper lobe lung cavitation) in patients with TB risk factors, sputum examination is still required, but skin testing is often not done.

**Chest x-ray:** In adults, a multinodular infiltrate above or behind the clavicle (the most characteristic location, most visible in an apical-lordotic view or with CT) suggests reactivation of TB. Middle and lower lung infiltrates are nonspecific but should prompt suspicion of primary TB in patients (usually young) whose symptoms or exposure history suggests recent infection, particularly if there is pleural effusion. Calcified hilar nodes may be present; they may result from primary TB infection but also may result from histoplasmosis in areas where histoplasmosis is endemic (eg, the Ohio River Valley).

**Sputum examination:** Sputum is tested for the presence of acid-fast bacilli (AFB). Tubercle bacilli are nominally gram-positive but take up Gram stain inconsistently; samples are best prepared with Ziehl-Neelsen or Kinyoun stains for conventional light microscopy or fluorochrome stains for fluorescent microscopy.

If patients cannot produce sputum spontaneously, aerosolized hypertonic saline can be used to induce it. If induction is unsuccessful, bronchial washings, which are particularly sensitive, can be obtained by fiberoptic bronchoscopy. Because induction of sputum and bronchoscopy entail some risk of infection for medical staff, these procedures should be done as a last resort in selected cases when MDR-TB is not likely. Appropriate precautions (eg, negative-pressure room, N-95 or other fitted respirators) should be used.

In addition to acid-fast staining, sputum can be tested using nucleic acid amplification techniques (NAAT) for TB; this test can shorten the time needed to diagnose TB from 1 to 2 wk to 1 to 2 days. However, in low-prevalence situations, this test is usually done only on smear-positive specimens. It is approved for smear-negative specimens and is indicated when suspicion is high and a rapid diagnosis is essential for medical or public health reasons.

If NAAT and AFB smear results are positive, patients are presumed to have TB and treatment can be started. If the NAAT result is positive and the AFB smear result is negative, an additional specimen is tested using NAAT; patients can be presumed to have TB if ≥ 2 specimens are NAAT-positive. If NAAT and AFB smear results are negative, clinical judgment is used to determine whether to begin anti-TB treatment while awaiting results of culture.

The finding of acid-fast bacilli in a sputum smear is strong presumptive evidence of TB, but definitive diagnosis requires a positive sputum culture or NAAT. Culture is also required for isolating bacteria for drug-susceptibility testing and genotyping.

**Drug susceptibility tests (DSTs)** should be done on initial isolates from all patients to identify an
effective anti-TB regimen. These tests should be repeated if patients continue to produce culture-positive sputum after 3 mo of treatment or if cultures become positive after a period of negative cultures. Results of DSTs may take up to 8 wk if conventional bacteriologic methods are used. However, several new molecular DSTs can detect drug resistance in a sputum sample within hours.

**Tests of other specimens:** Transbronchial biopsies can be done on infiltrative lesions, and samples are submitted for culture, histologic evaluation, and molecular testing. Gastric washings, which are culture-positive in a minority of samples, are no longer commonly used except in small children, who usually cannot produce a good sputum specimen. Ideally, biopsied samples of other tissue should be cultured fresh, but NAAT can be used for fixed tissues (eg, for biopsied lymph node if histologic examination unexpectedly detects granulomatous changes). The latter use of NAAT has not been approved but can be extremely useful, although positive and negative predictive values have not been established.

**Skin testing:** Multiple-puncture devices (tine test) are no longer recommended. The tuberculin skin test (TST; Mantoux or PPD—purified protein derivative) is usually done, although it is a test of infection, latent or active, and is not diagnostic of active disease. The standard dose in the US of 5 tuberculin units (TU) of PPD in 0.1 mL of solution is injected on the volar forearm. It is critical to give the injection intradermally, not subcutaneously. A well-demarcated bleb or wheal should result immediately. The diameter of induration (not erythema) transverse to the long axis of the arm is measured 48 to 72 h after injection. Recommended cutoff points for a positive reaction depend on the clinical setting:

- **5 mm:** Patients at high risk of developing active TB if infected, such as those who have chest x-ray evidence of past TB, who are immunosuppressed because of HIV infection or drugs (eg, TNF-α inhibitors, corticosteroid use equivalent to prednisone 15 mg/day for > 1 mo), or who are close contacts of patients with infectious TB

- **10 mm:** Patients with some risk factors, such as injection drug users, recent immigrants from high-prevalence areas, residents of high-risk settings (eg, prisons, homeless shelters), patients aged > 70 yr, those with certain disorders (eg, silicosis, renal insufficiency, diabetes, head or neck cancer), and those who have had gastrectomy or jejunoileal bypass surgery

- **15 mm:** Patients with no risk factors (who typically should not be tested)

Results can be falsely negative, most often in patients who are febrile, elderly, HIV-infected (especially if CD4+ count is < 200 cells/μL), or very ill, many of whom show no reaction to any skin test (anergy). Anergy probably occurs because inhibiting antibodies are present or because so many T cells have been mobilized to the disease site that too few remain to produce a significant skin reaction.

**Other tests:** New blood tests based on the release of interferon-γ by lymphocytes exposed in vitro to TB-specific antigens are now available and are likely to soon replace the TST for routine testing for TB infection. Although results of interferon-γ release assays (IGRAs) are not always concordant with TST, these tests appear to be as sensitive as and more specific than TST in contact investigations. Importantly, they are often negative in patients with remote TB infection. Long-term studies are being done to see whether TST-positive, IGRA-negative patients (particularly those with immunosuppression) are at low risk of reactivation.

**Prognosis**

In immunocompetent patients with drug-susceptible pulmonary TB, even severe disease and large cavities usually resolve if appropriate therapy is instituted and completed. Still, TB causes or contributes to death in about 10% of cases, often in patients who are debilitated for other reasons. Disseminated TB and TB meningitis may be fatal in up to 25% of cases despite optimal treatment.

TB is much more aggressive in immunocompromised patients and, if not appropriately and aggressively treated, may be fatal in as little as 2 mo from its initial symptom, especially with MDR-TB, in which mortality can approach 90%. With effective antiretroviral therapy (and appropriate anti-TB treatment), the prognosis for immunocompromised patients, even with MDR-TB, may approach that of immunocompetent patients. However, poorer outcomes should be expected for patients with XDR-TB because there are so
few effective drugs.

**Treatment**

Most patients with uncomplicated TB and all patients with complicating illnesses (eg, AIDS, hepatitis, diabetes), adverse drug reactions, or drug resistance should be referred to a TB specialist. However, most TB can be fully treated at home with instructions on how to avoid spreading disease; these measures include

- Staying at home
- Avoiding visitors (previously exposed family members may stay)
- Covering coughs with a tissue or hand

Surgical face masks for TB patients are stigmatizing and are generally not recommended for cooperative patients. For drug-susceptible TB that is being treated effectively, precautions must be continued for at least 2 wk in or outside the hospital. For patients with MDR-TB and XDR-TB, response to treatment may be slower, and the consequences of transmission greater; thus, precautions are continued longer, until there is clear evidence of treatment response.

**Hospitalization:** The main indications for hospitalization are

- Serious concomitant illness
- Need for diagnostic procedures
- Social issues (eg, homelessness)
- Need for respiratory isolation, as for people living in congregate settings where previously unexposed people would be regularly encountered

Initially, all hospitalized patients should be in respiratory isolation, ideally in a negative-pressure room with 6 to 12 air changes/h. Anyone entering the room should wear a respirator (not a surgical mask) that has been appropriately fitted and that meets National Institute for Occupational Safety and Health certification (N-95 or greater). Because risk of exposing other hospitalized patients is high, release from respiratory isolation usually requires 3 negative sputum smears over 2 days, including at least one early-morning negative specimen.

**Public health considerations:** To improve treatment adherence, ensure cure, and limit transmission and the development of drug-resistant strains, public health programs closely monitor treatment, even if patients are being treated by a private physician. In most states, TB care (including skin testing, chest x-rays, and drugs) is available free through public health clinics to reduce barriers to treatment.

Increasingly, optimal patient case management includes supervision by public health personnel of the ingestion of every dose of drug, a strategy known as directly observed therapy (DOT). DOT increases the likelihood that the full treatment course will be completed from 61% to 86% (91% with enhanced DOT, in which incentives and enablers such as transportation vouchers, child care, outreach workers, and meals are provided). DOT is particularly important

- For children and adolescents
- For patients with HIV infection, psychiatric illness, or substance abuse
- After treatment failure, relapse, or development of drug resistance

In some programs, selective self-administered treatment (SAT) is an option for patients who are committed to treatment; ideally, fixed-dose combination drug preparations are used to avoid the possibility of
monotherapy, which can lead to drug resistance. Mechanical drug monitors have been advocated to improve adherence with SAT.

Public health departments usually visit homes to evaluate potential barriers to treatment (eg, extreme poverty, unstable housing, child care problems, alcoholism, mental illness) and to check for other active cases and close contacts. Close contacts are people who share the same breathing space for prolonged periods, typically household residents, but often include people at work, school, and places of recreation. The precise duration and degree of contact that constitutes risk vary because TB patients vary greatly in infectiousness. For patients who are highly infectious as evidenced by multiple family members with disease or positive skin tests, even relatively casual contacts (eg, passengers on the bus they ride) should be referred for skin testing and evaluation for latent infection (see p. 1310); patients who do not infect any household contacts are less likely to infect casual contacts.

**First-line drugs:** The first-line drugs isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) are used together in initial treatment (for regimens and doses, see p. 1310 and Table 141-1).

INH is given orally once/day, has good tissue penetration (including CSF), and is

[Table 141-1. Dosing of First-Line Anti-TB Drugs*]

highly bactericidal. It remains the single most useful and least expensive drug for TB treatment. However, inconsistent drug levels and decades of uncontrolled use (often as monotherapy) in many countries (especially in East Asia) have greatly increased the percentage of resistant strains. In the US, about 10% of isolates are INH-resistant. INH is safe during pregnancy.

Adverse reactions include rash, fever, and, rarely, anemia and agranulocytosis. INH causes harmless, transient aminotransferase elevations in up to 20% of patients and symptomatic (usually reversible) hepatitis in about 1/1000 (more often in patients > 35 yr, alcoholics, postpartum women, and patients with chronic liver disease). Monthly liver function testing is not recommended unless patients have risk factors for liver disease. Patients with unexplained fatigue, anorexia, nausea, vomiting, or jaundice may have hepatic toxicity; treatment is suspended and liver function tests are obtained. Those with symptoms and any significant aminotransferase elevation (or asymptomatic elevation > 5 times normal) by definition have hepatic toxicity, and INH is stopped. After recovery from mild aminotransferase elevations and symptoms, patients can be safely challenged with a half-dose for 2 to 3 days. If this dose is tolerated (typically in about half of patients), the full dose may be restarted with close monitoring for symptoms and liver function deterioration. If patients are receiving INH, RIF, and PZA, all drugs must be stopped, and the challenge done with each drug separately. INH or PZA, rather than RIF, is the more likely cause of hepatotoxicity. Peripheral neuropathy can result from INH-induced pyridoxine (vitamin B$_6$) deficiency, most likely in pregnant or breastfeeding women, undernourished patients, patients with diabetes mellitus or HIV infection, alcoholics, patients with cancer or uremia, and the elderly. A daily dose of pyridoxine 25 to 50 mg can prevent this complication, although pyridoxine is usually not needed in children and healthy young adults. INH delays hepatic metabolism of phenytoin, requiring dose reduction. INH can also cause a violent reaction to disulfiram, a drug occasionally used for alcoholism.

RIF, given orally, is bactericidal, is well absorbed, penetrates well into cells and CSF, and acts rapidly. It also eliminates dormant organisms in macrophages or caseous lesions that can cause late relapse. Thus, RIF should be used throughout the course of therapy. Adverse effects include cholestatic jaundice (rare), fever, thrombocytopenia, and renal failure. RIF adds only slightly to the hepatotoxicity of INH. RIF has many significant drug interactions. It accelerates metabolism of anticoagulants, oral contraceptives, corticosteroids, digitoxin, oral antihyperglycemic drugs, methadone, and many other drugs. The interactions of rifamycins and many antiretroviral drugs is particularly complex; combined use requires specialized expertise. RIF is safe during pregnancy.

The following newer rifamycins are available for special situations:

- **Rifabutin** is used for patients taking drugs (particularly antiretroviral drugs) that have unacceptable interactions with RIF. Its action is similar to RIF, but when used with clarithromycin or fluconazole, it has
been associated with uveitis.

- **Rifapentine** is used in one dose/wk regimens (see Table 141-1) but is not used in children or patients with HIV (because of unacceptable treatment failure rates) or extrapulmonary TB.

**PZA** is an oral bactericidal drug. When used during the intensive initial 2 mo of treatment, it shortens therapy to 6 mo and prevents development of resistance to RIF.

Its major adverse effects are GI upset and hepatitis. It often causes hyperuricemia, which is generally mild and only rarely induces gout. It is contraindicated in pregnancy. PZA plus rifampin is no longer recommended as a 2-mo regimen for latent TB because excessive hepatotoxicity can occur.

**EMB** is given orally and is the best tolerated of the first-line drugs. Its main toxicity is optic neuritis, which is more common at higher doses (eg, 25 mg/kg) and in patients with impaired renal function. Patients present initially with an inability to distinguish blue from green, followed by impairment of visual acuity and color vision and should be questioned monthly regarding their vision. Caution is warranted if communication is limited by language and cultural barriers. For similar reasons, EMB is usually avoided in young children who cannot read eye charts but can be used if needed because of drug resistance or drug intolerance. Another drug is substituted for EMB if optic neuritis occurs. EMB can be used safely during pregnancy. Resistance to EMB is less common than that to the other first-line drugs.

**Second-line drugs:** Other antibiotics are active against TB and are used primarily when patients have MDR-TB or do not tolerate one of the first-line drugs. The 2 most important classes are aminoglycosides (and the closely related polypeptide drug, capreomycin) and fluoroquinolones.

**Streptomycin**, the most commonly used aminoglycoside, is very effective and bactericidal. Resistance is still relatively uncommon in the US but is more common globally. CSF penetration is poor, and intrathecal administration should not be used if other effective drugs are available.

Dose-related adverse effects include renal tubular damage, vestibular damage, and ototoxicity. The dose is about 15 mg/kg IM (maximum: usually 1 g for adults, reduced to 0.75 g [10 mg/kg] for those ≥ 60 yr). To limit dose-related adverse effects, clinicians give one dose only 5 days/wk for > 2 mo. Then it may be given twice/wk for another 2 mo if necessary. In patients with renal insufficiency, dosing frequency should be reduced (eg, 12 to 15 mg/kg/dose 2 or 3 times/wk). Patients should be monitored with appropriate testing of balance, hearing, and serum creatinine levels. Adverse effects include rash, fever, agranulocytosis, and serum sickness. Flushing and tingling around the mouth commonly accompany injection but subside quickly. Streptomycin is contraindicated during pregnancy because it may damage the 8th cranial nerve in the fetus.

**Kanamycin** and **amikacin** may remain effective even if streptomycin resistance has developed. Their renal and neural toxicities are similar to those of streptomycin.

**Capreomycin**, a related nonaminoglycoside parenteral bactericidal drug, has dosage, effectiveness, and adverse effects similar to those of aminoglycosides. It is an important drug for MDR-TB because isolates resistant to streptomycin are often susceptible to capreomycin, and it is somewhat better tolerated than aminoglycosides when prolonged administration is required.

Some **fluoroquinolones** (levofloxacin, moxifloxacin) are the most active and safest TB drugs after INH and RIF, but they are not first-line drugs for TB susceptible to INH and RIF. Moxifloxacin appears to be as active as INH when used with RIF.

Other 2nd-line drugs include ethionamide, cycloserine, and para-aminosalicylic acid (PAS). These drugs are less effective and more toxic than the first-line drugs but are essential in treatment of MDR-TB.

**Drug resistance:** Treatment with any single antibiotic always results in survival of a very few (about 1 in a million) organisms that have acquired spontaneous resistance mutations. Incomplete or erratic therapy selects for these resistant organisms, making treatment adherence particularly important in prevention of
resistance. Multiple drugs are used concurrently for TB so that organisms resistant to one drug are killed by the others; simultaneous spontaneous mutations to multiple drugs are unlikely. However, once a strain resistant to a single drug has developed and proliferated, it may acquire resistance to additional drugs through the same process; thus, MDRTB can occur by stepwise acquired resistance to INH, RIF, and often other drugs. Some resistant strains appear to be less fit (i.e., less transmissible and virulent); others have acquired compensatory mutations that restore fitness, allowing disease progression and transmission to occur.

Once a drug-resistant strain develops in a patient, it can spread from person to person (primary drug resistance). Uninhibited transmission of drug-resistant strains in congregate settings, such as hospitals, clinics, prisons, shelters, and refugee camps, is a major barrier to global control.

Several new anti-TB drugs that may be active against resistant strains are in preclinical or clinical development but will not be available for several more years. Furthermore, unless treatment programs are strengthened (e.g., by full supervision of each dose), stepwise resistance to new drugs is likely.

**MDR-TB** is TB resistant in vitro to both isoniazid and rifampin, with or without resistance to other drugs. Numerous outbreaks of MDR-TB have been reported, and the global burden is rising. The Stop TB Partnership estimates that 780,000 new cases of MDR-TB will occur between 2006 and 2015. In parts of the world where resistance testing is inadequate or unavailable, many patients who do not respond to first-line therapy probably have MDR-TB that is undiagnosed. MDR-TB has major negative implications for TB control; alternative treatments require a longer treatment course with less effective, more toxic, and more expensive 2nd-line drugs.

**XDR-TB** is MDR-TB that is also resistant to fluoroquinolones and injectable drugs (e.g., streptomycin, amikacin, kanamycin, capreomycin). TB strains that are resistant to other drug combinations but that do not meet the definitions of MDR or XDR are termed polyresistant. Because the fluoroquinolones and injectables are important for treatment of MDR-TB, XDR-TB has dire therapeutic implications. Although some patients can be cured, mortality is higher and depends on the number of effective drugs remaining and the extent of lung destruction. Surgery to remove localized areas of lung destruction plays an important role in the treatment of advanced cases of MDR-TB or XDR-TB but is not widely available in high-burden regions.

**Treatment regimens:** Treatment of all patients with new, previously untreated TB should consist of a

- 2-mo initial, intensive phase
- 4- or 7-mo continuation phase

**Initial intensive-phase therapy** is with 4 antibiotics: INH, RIF, PZA, and EMB (see Table 141-1 for dosing). These drugs can be given daily throughout this phase or daily for 2 wk, followed by doses 2 or 3 times/wk for 6 wk. Intermittent administration (usually with higher doses) is usually satisfactory because of the slow growth of tubercle bacilli and the residual postantibiotic effect on growth (after antibiotic inhibition, bacterial growth is often delayed well after antibiotics are below the minimal inhibitory concentration). However, daily therapy is recommended for patients with MDR-TB or HIV coinfection. Regimens involving less than daily dosing must be carried out as DOT because each dose becomes more important.

After 2 mo of intensive 4-drug treatment, PZA and usually EMB are stopped, depending on the drug susceptibility pattern of the original isolate.

**Continuation-phase treatment** depends on results of drug susceptibility testing of initial isolates (where available), the presence or absence of a cavitary lesion on the initial chest x-ray, and results of cultures taken at 2 mo. If positive, 2-mo cultures indicate the need for a longer course of treatment. If both culture and smear are negative, regardless of the chest x-ray, or if the culture or smear is positive but x-ray showed no cavitation, INH and RIF are continued for 4 more mo (6 mo total). If the x-ray showed cavitation and the culture or smear is positive, INH and RIF are continued for 7 more mo (9 mo total). In either regimen, EMB is stopped if the initial culture shows no resistance to any drug. Continuation-phase
drugs can be given daily or, if patients are not HIV-positive, 2 or 3 times/wk. Patients who have negative culture and smears at 2 mo and no cavitation on chest x-ray and who are HIV-negative may receive once/wk INH plus rifapentine.

For both initial and continuation phases, the total number of doses (calculated by doses/wk times number of weeks) should be given; thus if any doses are missed, treatment is extended and not stopped at the end of the time period.

Management of drug-resistant TB varies with the pattern of drug resistance. Generally, MDR-TB requires prolonged (eg, 18 to 24 mo) treatment with the remaining active first-line drugs (including PZA, if the strain is susceptible) with addition of an injectable, a fluoroquinolone, and other 2nd-line drugs as needed to build a 4- or 5-drug regimen that the infecting strain is known or likely to be susceptible to (ie, based on testing, a known source-case, prior treatment, or drug susceptibility patterns in the community). Managing the adverse effects of these long, complex regimens is challenging. MDR-TB should always be treated by a TB specialist experienced with these cases. Fully supervised treatment is essential to avoid additional drug resistance through nonadherence.

Other treatments: Surgical resection of a persistent TB cavity is occasionally necessary. The main indication for resection is persistent, culture-positive MDR-TB or XDR-TB in patients with a destroyed lung region into which antibiotics cannot penetrate. Other indications include uncontrollable hemoptysis and bronchial stenosis.

Corticosteroids are sometimes used to treat TB when inflammation is a major cause of morbidity and are indicated for patients with acute respiratory distress syndrome or closed-space infections, such as meningitis and pericarditis. Dexamethasone 12 mg po or IV q 6 h is given to adults and children > 25 kg; children < 25 kg are given 8 mg. Treatment is continued for 2 to 3 wk. Corticosteroids that are needed for other indications pose no danger to patients who have active TB and who are receiving an effective TB regimen.

Screening

Screening for latent TB infection (LTBI) is done with TST or IGRA. Indications for testing include

- Close contact with a person who has active pulmonary TB
- Chest x-ray evidence of past TB infection
- Risk factors for exposure to TB (eg, people who have immigrated within 5 yr from high-risk areas, indigent patients, IV drug users, selected US health care practitioners such as respiratory therapists and practitioners working with high-risk populations)
- Risk factors for development of active TB (eg, HIV infection or other impaired immunity, gastrectomy, jejunoileal bypass surgery, silicosis, renal insufficiency, diabetes, head or neck cancer, age > 70 yr)
- Therapeutic immunosuppression with corticosteroids, TNF inhibitors, or cancer chemotherapy

In the US, most children and other people without specific TB risk factors should not be tested to avoid false-positive reactions.

A positive TST or IGRA test result (see p. 1305 for criteria) suggests LTBI. Patients with a positive TST or IGRA result are evaluated for other risk factors and have a chest x-ray. Those with x-ray abnormalities suggesting TB require evaluation for active TB as above, including sputum examination and culture. Updated guidelines for testing and treatment of LTBI are available at the Centers for Disease Control and Prevention (CDC) web site (www.cdc.gov).

Booster reaction: Some patients with remote TB exposure, BCG vaccination, or infection with nontuberculous mycobacteria may have a negative TST or IGRA; however, the TST itself may serve as an immune booster so that a subsequent test done as little as 1 wk or as much as several years later may
be positive (booster reaction). Thus, in people who are tested regularly (eg, health care workers), the 2nd routine test will be positive, giving the false appearance of recent infection (and hence mandating further testing and treatment). If recurrent testing for LTBI is indicated, a 2nd TST should be done 1 to 4 wk after the first to identify a booster reaction (because conversion in that brief interval is highly unlikely). Subsequent TST is done and interpreted normally.

The new IGRAs for LTBI do not involve injection of antigens and thus do not cause boosting. They also are not influenced by preexisting hypersensitivity from BCG vaccination or infection with environmental mycobacteria other than *M. kansasii*, *M. szulgai*, and *M. marinum*.

**Treatment of LTBI:** Treatment is indicated principally for

- People whose TST converted from negative to positive within the previous 2 yr
- People with x-ray changes consistent with old TB and no evidence of active TB

Other indications for preventive treatment include

- People who, if infected, are at high risk of developing active TB (eg, HIV-infected people, people with drug-induced immunosuppression)
- Any child < 5 yr who is a close contact of a person with smear-positive TB, regardless of whether there was TST conversion

Other people with an incidental positive TST or IGRA but without these risk factors are often treated for LTBI, but physicians should balance individual risks of drug toxicity against the benefits of treatment.

Treatment generally consists of INH unless resistance is suspected (eg, in exposure to a known INH-resistant case). The dose is 300 mg once/day for 6 to 9 mo for most adults and 10 mg/kg for 9 mo for children. HIV-infected patients and people with abnormal chest x-rays consistent with old TB also require 9 mo of therapy. An alternative for patients resistant to or intolerant of INH is RIF 600 mg once/day for 4 mo.

The main limitations of treatment of LTBI are poor adherence and hepatotoxicity. Used for LTBI, INH causes clinical hepatitis in 1/1000 cases; hepatitis usually reverses if INH is stopped promptly. Patients being treated for LTBI should be instructed to stop the drug if they experience any new symptoms, especially unexplained fatigue, loss of appetite, or nausea. Hepatitis due to RIF is less common than with INH, but drug interactions are frequent. Monthly visits to monitor symptoms and to encourage treatment completion are standard good clinical and public health practice.

**Prevention**

General preventive measures (eg, staying at home, avoiding visitors, covering coughs with a tissue or hand—see p. 1306) are followed.

**Vaccination:** The BCG vaccine, made from an attenuated strain of *M. bovis* is given to > 80% of the world’s children, primarily in high-burden countries. Overall average efficacy is probably only 50%. However, although BCG is not believed to prevent TB infection, it reduces the rate of extrathoracic TB in children, especially TB meningitis, and therefore is considered worthwhile. BCG has few indications in the US, except unavoidable exposure of a child to an infectious TB case that cannot be effectively treated (ie, highly resistant MDR-TB) and possibly previously uninfected health care workers exposed to MDRTB or XDR-TB on a regular basis.

Although BCG vaccination often converts the TST, the reaction is usually smaller than the response to natural TB infection, and it usually wanes more quickly. The TST reaction due to BCG is rarely > 15 mm and rarely > 10 mm 15 yr after BCG administration. CDC recommends that all TST reactions in children who have had BCG be attributed to TB infection (and treated accordingly) because untreated latent infection can have serious complications. IGRAs for LTBI are not influenced by BCG vaccination.
Special Populations

**Children:** Primary TB in children can spread to the vertebrae (Pott's disease) or the highly vascular epiphyses of long bones. Young children may also rapidly develop serious TB, possibly miliary TB, TB meningitis, or cavitary disease, even before the TST becomes positive. However, most children have few symptoms other than a brassy cough, and the primary focus usually resolves spontaneously with or without treatment. The most common sign is hilar lymphadenopathy, but segmental atelectasis is possible. Adenopathy may progress, even after chemotherapy is started, and may cause lobar atelectasis, which usually clears during treatment. Cavitary disease is less common than in adults, and most children harbor far fewer organisms and are not infectious. Except for dosage adjustments, treatment of children is similar to that of adults (see Table 141-1).

**The elderly:** Reactivated disease can involve any organ, but particularly the lungs, brain, kidneys, long bones, vertebrae, or lymph nodes. Reactivation may cause few symptoms and can be overlooked for weeks or months, delaying appropriate evaluation. The frequent presence of other disorders in old age further complicates the diagnosis. At any age, recent transmission may cause apical, middle-lobe, or lower-lobe pneumonia as well as pleural effusion in previously tuberculin-negative nursing home residents. The pneumonia may not be recognized as TB and may persist and spread to other people despite broad-spectrum antibiotic treatment. In the US, miliary TB and TB meningitis, commonly thought to affect mainly young children, are more common among the elderly.

INH is hepatotoxic in up to 4 to 5% of patients > 65 yr (compared with < 1% of patients < 65 yr). In the elderly, chemoprophylaxis is indicated only if the TST increases ≥ 15 mm from a previously negative reaction. TST sensitivity can be poor in the elderly. Close contacts of an active case and others at high risk and with a negative TST or IGRA should be considered for preventive treatment unless contraindicated.

**HIV-infected patients:** TST sensitivity is generally poor in immunocompromised patients (who may be anergic). In some studies, IGRAs appear to perform better than the TST in immunocompromised patients, although this advantage has not yet been established.

In HIV-infected patients with LTBI, active TB develops in about 5 to 10%/yr; whereas in people who are not immunocompromised, it develops in about the same percentage over a lifetime. In the early 1990s, half of HIV-infected TB patients who were untreated or infected with an MDR strain died, with median survival of only 60 days. Now, outcomes are somewhat better in developed countries because of earlier TB diagnosis and antiretroviral therapy, but TB in HIV patients remains a serious concern. In developing countries, mortality continues to be high among patients coinfected with HIV and MDR-TB or XDR-TB.

Dissemination of bacilli during primary infection is usually much more extensive in patients with HIV infection. Consequently, a larger proportion of TB is extrapulmonary. Tuberculomas are more common and more destructive. HIV reduces both inflammatory reaction and cavitation of pulmonary lesions. As a result, a chest x-ray may show a nonspecific pneumonia or even be normal, even though AFB are present in sufficient numbers to appear on a sputum smear. Smear-negative TB is more common when HIV coinfection is present.

TB may develop early in AIDS and may be its presenting manifestation. Hematogenous dissemination of TB in patients with HIV infection causes a serious, often baffling illness with symptoms of both infections. In AIDS patients, a mycobacterial illness that develops while the CD4 count is ≥ 200/μL is almost always TB. By contrast, depending on the probability of TB exposure, a mycobacterial infection that develops while the CD4 count is < 50/μL is usually due to *M. avium* complex (see p. 1314), which is not contagious and is predominantly an infection of the blood and bone marrow, not the lungs.

TB in HIV-infected patients generally responds well to usual regimens when in vitro testing shows sensitivity. However, for MDRTB strains, outcomes are not as favorable because the drugs are more toxic and less effective. Therapy for susceptible TB should be continued for 6 to 9 mo after conversion of sputum cultures to negative but may be shortened to 6 mo if 3 separate pretreatment sputum smears are negative, suggesting a low burden of organisms. Current recommendations suggest that if the sputum
Extrapulmonary Tuberculosis

TB outside the lung usually results from hematogenous dissemination. Sometimes infection directly extends from an adjacent organ. Symptoms vary by site but generally include fever, malaise, and weight loss.

**Miliary TB:** Also known as generalized hematogenous TB, miliary TB occurs when a tuberculous lesion erodes into a blood vessel, disseminating millions of tubercle bacilli into the bloodstream and throughout the body. The lungs and bone marrow are most often affected, but any site may be involved. Miliary TB is most common among children < 4 yr, immunocompromised people, and the elderly.

Symptoms include fever, chills, weakness, malaise, and often progressive dyspnea. Intermittent dissemination of tubercle bacilli may lead to a prolonged FUO. Bone marrow involvement may cause anemia, thrombocytopenia, or a leukemoid reaction.

**Genitourinary TB:** Infection of the kidneys may manifest as pyelonephritis (eg, fever, back pain, pyuria) without the usual urinary pathogens on routine culture (sterile pyuria). Infection commonly spreads to the bladder and, in men, to the prostate, seminal vesicles, or epididymis, causing an enlarging scrotal mass. Infection may spread to the perinephric space and down the psoas muscle, sometimes causing an abscess on the anterior thigh.

Salpingo-oophoritis can occur after menarche, when the fallopian tubes become vascular. Symptoms include chronic pelvic pain and sterility or ectopic pregnancy due to tubal scarring.

**TB meningitis:** Meningitis often occurs in the absence of infection at other extrapulmonary sites. In the US, it is most common among the elderly and immunocompromised, but in areas where TB is common among children, TB meningitis usually occurs between birth and 5 yr. At any age, meningitis is the most serious form of TB and has high morbidity and mortality. It is the one form of TB believed to be prevented in childhood by vaccination with BCG.

Symptoms are low-grade fever, unremitting headache, nausea, and drowsiness, which may progress to stupor and coma. Kernig's and Brudzinski's signs may be positive. Stages are

1. Clear sensorium with abnormal CSF
2. Drowsiness or stupor with focal neurologic signs
3. Coma

Stroke may result from thrombosis of a major cerebral vessel. Focal neurologic symptoms suggest a tuberculous mass intracranial lesion (tuberculoma).

**TB peritonitis:** Peritoneal infection represents seeding from abdominal lymph nodes or from salpingo-oophoritis. Peritonitis is particularly common among alcoholics with cirrhosis.

Symptoms may be mild, with fatigue, abdominal pain, and tenderness, or severe enough to mimic acute abdomen.

**TB pericarditis:** Pericardial infection may develop from foci in mediastinal lymph nodes or from pleural TB. In some high-incidence parts of the world, TB pericarditis is a common cause of heart failure.

Patients may have a pericardial friction rub, pleuritic and positional chest pain, or fever. Pericardial tamponade may occur, causing dyspnea, neck vein distention, paradoxical pulse, muffled heart sounds, and possibly hypotension.
**TB lymphadenitis:** Usually, the hilar lymph nodes are involved. Other nodes are generally not involved unless the inoculum is large or poorly contained, allowing organisms to reach the thoracic duct, where they disseminate into the bloodstream. Most infected nodes heal, but reactivation commonly occurs. Infection in supraclavicular nodes may inoculate anterior cervical nodes, eventually resulting in scrofula (TB lymphadenitis in the neck).

Affected nodes are swollen and may be mildly tender or drain. Adjacent nodes sometimes coalesce into an irregular mass.

**TB of bones and joints:** Weight-bearing joints are most commonly involved, but bones of the wrist, hand, and elbow may also be affected, especially after injury.

Pott's disease is spinal infection, which begins in a vertebral body and often spreads to adjacent vertebrae, with narrowing of the disk space between them. Untreated, the vertebrae may collapse, possibly impinging on the spinal cord. Symptoms include progressive or constant pain in involved bones and chronic or subacute arthritis (usually monoarticular). In Pott's disease, spinal cord compression produces neurologic deficits, including paraplegia; paravertebral swelling may result from an abscess.

**Gastrointestinal TB:** Because the entire GI mucosa resists TB invasion, infection requires prolonged exposure and enormous inocula. It is very unusual in developed countries where bovine TB is rare.

Ulcers of the mouth and oropharynx may develop from eating *M. bovis*-contaminated dairy products; primary lesions may also occur in the small bowel. Intestinal invasion generally causes hyperplasia and an inflammatory bowel syndrome with pain, diarrhea, obstruction, and hematochezia. It may also mimic appendicitis. Ulceration and fistulas are possible.

**TB of the liver:** Liver infection is common in patients with advanced pulmonary TB and widely disseminated or miliary TB. However, the liver generally heals without sequelae when the principal infection is treated. TB in the liver occasionally spreads to the gallbladder, leading to obstructive jaundice.

**Other sites:** Rarely, TB may develop on abraded skin in patients with cavitary pulmonary TB. TB may infect the wall of a blood vessel and has even ruptured the aorta. Adrenal involvement, leading to Addison's disease, formerly was common but now is rare. Tubercle bacilli may spread to tendon sheaths (tuberculous tenosynovitis) by direct extension from adjacent lesions in bone or hematogenously from any infected organ.

**Diagnosis**

- Chest x-ray
- Tuberculin skin test
- Acid-fast stain and culture
- When available, DNA-based testing

Testing is similar to that for pulmonary TB (see p. 1304), including chest x-ray, tuberculin skin testing (TST), and microscopic analysis (with appropriate staining) and cultures of affected body fluids (CSF, urine, or pleural, pericardial, or joint fluid) and tissue for mycobacteria. However, cultures and smears are often negative because few organisms may be present; in this case, nucleic acid amplification techniques (NAAT) may be helpful. If all tests are negative and miliary TB is still a concern, biopsies of the bone marrow and the liver are done. Blood culture results are positive in about 50% of patients with disseminated TB; such patients are often immunocompromised by HIV infection or another immunosuppressive condition. If TB is highly suspected based on other features (eg, granuloma seen on biopsy, positive TST plus unexplained lymphocytosis in pleural fluid or CSF), treatment should usually proceed despite inability to demonstrate TB organisms.
Chest x-ray may show signs of primary or active TB; in miliary TB, it shows thousands of 2- to 3-mm interstitial nodules evenly distributed through both lungs. TST and IGRA may initially be negative, but a repeat test in a few weeks is likely to be positive. If it is not, the diagnosis of TB should be questioned or causes of anergy sought.

Other imaging studies are done based on clinical findings. Abdominal or GU involvement usually requires CT or ultrasonography; renal lesions are often visible. Bone and joint involvement requires CT or MRI; MRI is preferable for spinal disease.

Body fluids typically show lymphocytosis. The most suggestive CSF constellation also includes a glucose level < 50% of that in the serum and an elevated protein level.

**Treatment**

Drug treatment is the most important modality and follows standard regimens and principles (see p. 1307). Six to 9 mo of therapy is probably adequate for most sites except the meninges, which require treatment for 9 to 12 mo. Corticosteroids may help in pericarditis and meningitis (for dosing, see p. 1310).

**Surgery** is required for the following:

- To drain empyema, cardiac tamponade, and CNS abscess
- To close bronchopleural fistulas
- To resect infected bowel
- To decompress spinal cord encroachment

Surgical debridement is sometimes needed in Pott's disease to correct spinal deformities or to relieve cord compression if there are neurologic deficits or pain persists; fixation of the vertebral column by bone graft is required in only the most advanced cases. Surgery is usually not necessary for TB lymphadenitis except for diagnostic purposes.

**Other Mycobacterial Infections Resembling Tuberculosis**

Mycobacteria other than the tubercle bacillus sometimes infect humans. These organisms are commonly present in soil and water and are much less virulent in humans than is *M. tuberculosis*. Infections with these organisms have been called atypical, environmental, and nontuberculous mycobacterial infections. Most exposures and infections by these organisms do not cause disease, which usually requires a defect in local or systemic host defenses; the frail elderly are sometimes infected. *M. avium* complex (MAC)—the closely related species of *M. avium* and *M. intracellulare*—accounts for most diseases. Other causative species are *M. kansasii*, *M. xenopi*, *M. marinum*, *M. ulcerans*, and the *M. fortuitum* complex (*M. fortuitum*, *M. abscessus*, and *M. chelonae*). Person-to-person transmission has not been documented.

The lungs are the most common site; most lung infections involve MAC but may be due to *M. kansasii*, *M. xenopi*, or *M. abscessus*. Occasional cases involve lymph nodes, bones and joints, the skin, and wounds. However, incidence of disseminated MAC disease is increasing in HIV-infected patients, and resistance to anti-TB drugs is the rule (except for *M. kansasii* and *M. xenopi*).

Nontuberculous mycobacterial infections are best managed by a specialist with particular expertise in that area. The American Thoracic Society publishes updated diagnostic and therapeutic guidelines on the diagnosis and management of these challenging infections.

**Pulmonary disease**: The typical patient is a middle-aged or older white man with previous lung problems such as chronic bronchitis, emphysema, healed TB, bronchiectasis, or silicosis. MAC also commonly causes pulmonary disease in middle-aged and elderly women with bronchiectasis, scoliosis, pectus excavatum, or mitral valve prolapse but without known underlying lung abnormalities. This syndrome appears to be increasing in frequency for unknown reasons.
Cough and expectoration are common, often associated with fatigue, weight loss, and low-grade fever. The course may be slowly progressive or stable for long periods. Respiratory insufficiency and persistent hemoptysis may develop. Fibronodular infiltrates on chest x-ray resemble those of pulmonary TB, but cavitation tends to be thin-walled, and pleural effusion is rare. So-called tree-and-bud infiltrates are also characteristic of MAC disease.

Determination of drug susceptibility may be helpful for certain organism/drug combinations but can be done only in highly specialized laboratories.

For moderately symptomatic disease due to MAC with positive sputum smears and cultures, clarithromycin 500 mg po bid or azithromycin 600 mg once/day, rifampin (RIF) 600 mg po once/day, and ethambutol (EMB) 15 to 25 mg/kg po once/day should be used for 12 to 18 mo or until cultures are negative for 12 mo. For progressive cases unresponsive to standard drugs, combinations of 4 to 6 drugs that include clarithromycin 500 mg po bid or azithromycin 600 mg once/day, rifabutin 300 mg po once/day, ciprofloxacin 250 to 500 mg po or IV bid, clofazimine 100 to 200 mg po once/day, and amikacin 10 to 15 mg/kg IV once/day may be tried. Resection surgery is recommended in exceptional cases involving well-localized disease in young, otherwise healthy patients. *M. kansasii* and *M. xenopi* infections respond to isoniazid, rifabutin, and EMB, with or without streptomycin or clarithromycin, given for 18 to 24 mo. All nontuberculous mycobacteria are resistant to pyrazinamide.

**Lymphadenitis:** In children 1 to 5 yr, chronic submaxillary and submandibular cervical lymphadenitis is commonly due to MAC or *M. scrofulaceum*. It is presumably acquired by oral ingestion of soil organisms. Diagnosis is usually by excisional biopsy. Usually, excision is adequate treatment and chemotherapy is not required.

**Cutaneous disease:** Swimming pool granuloma is a protracted but self-limited superficial granulomatous ulcerating disease usually caused by *M. marinum* contracted from swimming in contaminated pools or from cleaning a home aquarium. *M. ulcerans* and *M. kansasii* are occasionally involved. Lesions, reddish bumps enlarging and turning purple, most frequently occur on the upper extremities or knees. Healing may occur spontaneously, but minocycline or doxycycline 100 to 200 mg po once/day, clarithromycin 500 mg po bid, or RIF plus EMB for 3 to 6 mo have been effective against *M. marinum*.

**Wounds and foreign body infections:** *M. fortuitum* complex has caused serious infections of penetrating wounds in the eyes and skin (especially feet) and in patients receiving contaminated materials (eg, porcine heart valves, breast implants, bone wax).

Treatment usually requires extensive debridement and removal of the foreign material. Useful drugs include imipenem 1 g IV q 6 h, levofloxacin 500 mg IV or po once/day, clarithromycin 500 mg po bid, trimethoprim/sulfamethoxazole 1 double-strength tablet po bid, doxycycline 100 to 200 mg po once/day, cefoxitin 2 g IV q 6 to 8 h, and amikacin 10 to 15 mg/kg IV once/day, for 3 to 6 mo. Combination therapy is recommended with at least 2 drugs that have in vitro activity. Infections caused by *M. abscessus* and *M. chelonae* are resistant to most antibiotics, have proved extremely difficult or impossible to cure and should be referred to an experienced specialist.

**Disseminated disease:** MAC causes disseminated disease commonly in patients with advanced AIDS and occasionally in those with other immunocompromised states, including organ transplantation and hairy cell leukemia. In AIDS patients, disseminated MAC usually develops late (unlike TB, which develops early), occurring simultaneously with other opportunistic infections.

Disseminated MAC disease causes fever, anemia, thrombocytopenia, diarrhea, and abdominal pain (features similar to Whipple's disease). Diagnosis can be confirmed by cultures of blood or bone marrow or by biopsy (eg, percutaneous fine-needle biopsy of liver or necrotic lymph nodes). Organisms may be identified in stool and respiratory specimens, but organisms from these specimens may represent colonization rather than true disease.

Combination therapy to clear bacteremia and alleviate symptoms usually requires 2 to 3 drugs; one is
clarithromycin 500 mg po bid or azithromycin 600 mg po once/day, plus EMB 15 to 25 mg/kg once/day. Sometimes rifabutin 300 mg once/day is also given. After successful treatment, chronic suppression with clarithromycin or azithromycin plus EMB is necessary to prevent relapse.

HIV-infected patients with a CD4 count < 100 cells/μL require prophylaxis for disseminated MAC with azithromycin 1.2 g po once/week or clarithromycin 500 mg po bid.

**Leprosy**

(*Hansen's Disease*)

Leprosy is a chronic infection caused by the acid-fast bacillus *Mycobacterium leprae*, which has a unique tropism for peripheral nerves, skin, and mucous membranes. Symptoms are myriad and include anesthetic polymorphic skin lesions and peripheral neuropathy. Diagnosis is clinical and confirmed by biopsy. Treatment is typically with dapsone plus other antimycobacterial drugs.

Because without treatment, people with leprosy are visibly disfigured and often have significant disability, they have long been feared and shunned by others. Although leprosy is not highly contagious, rarely causes death, and can be effectively treated with antibiotics, it still causes anxiety. As a result, people with leprosy and their family members often have psychologic and social problems.

**Epidemiology**

During 2007, > 250,000 new cases were reported. About 90% of these cases occurred in the following 8 countries (from the most cases to the least): India, Brazil, Indonesia, Congo, Bangladesh, Nigeria, Nepal, and Ethiopia. In 2006, 137 new cases were reported in the US. Cases occurred in 30 states, but more than half occurred in 6 states: California, Florida, Louisiana, Massachusetts, New York, and Texas. Most cases of leprosy in the US involve people who emigrated from developing countries.

Leprosy can develop at any age but appears most often in people aged 5 to 15 yr or > 30.

**Pathophysiology**

Humans are the main natural reservoir for *M. leprae*. Armadillos are the only confirmed source other than humans, although other animal and environmental sources may exist.

How leprosy is spread is unclear. It is thought to be passed from person to person through nasal droplets and secretions. Casual contact (eg, simply touching someone with the disease) and short-term contact does not seem to spread the disease. About half of people with leprosy probably contracted it through close, long-term contact with an infected person. Even after contact with the bacteria, most people do not contract leprosy; health care workers often work for many years with people who have leprosy without contracting the disease. Most (95%) immunocompetent people who are infected with *M. leprae* do not develop leprosy because of effective immunity. People who do develop leprosy probably have a poorly defined genetic predisposition.

*M. leprae* grow slowly (doubling in 2 wk). The usual incubation period ranges from 6 mo to 10 yr. Once infection develops, hematogenous dissemination can occur.

**Classification:** Leprosy can be categorized by type and number of skin areas affected:

- **Paucibacillary:** ≤ 5 skin lesions with no bacteria detected on samples from those areas
- **Multibacillary:** ≥ 6 skin lesions, bacteria detected on samples from skin lesions, or both

Leprosy can also be classified by cellular response and clinical findings:

- **Tuberculoid**
• Lepromatous

• Borderline

People with tuberculoid leprosy typically have a strong cell-mediated response, which limits disease to a few skin lesions (paucibacillary), and the disease is milder, less common, and less contagious. People with lepromatous or borderline leprosy typically have poor cell-mediated immunity to *M. leprae* and have more severe, systemic infection with widespread bacterial infiltration of skin, nerves, and other organs (eg, nose, testes, kidneys). They have more skin lesions (multibacillary), and the disease is more contagious.

In both classifications, the type of leprosy dictates long-term prognosis, likely complications, and duration of antibiotic treatment.

**Symptoms and Signs**

Symptoms usually do not begin until > 1 yr after infection (average 5 to 7 yr). Once symptoms begin, they progress slowly.

Leprosy affects mainly the skin and peripheral nerves. Nerve involvement causes numbness and weakness in areas controlled by the affected nerves.

• **Tuberculoid leprosy:** Skin lesions consist of one or a few hypoesthetic, centrally hypopigmented macules with sharp, raised borders. The rash, as in all forms of leprosy, is nonpruritic. Areas affected by this rash are numb because of damage to the underlying nerves, which may be palpably enlarged.

• **Lepromatous leprosy:** Much of the skin and many areas of the body, including the kidneys, nose, and testes, may be affected. Patients have skin macules, papules, nodules, or plaques, often symmetric. Peripheral neuropathy is more severe than in tuberculoid leprosy, with more areas of numbness; certain muscle groups may be weak. Patients may develop gynecomastia or lose eyelashes and eyebrows or digits.

• **Borderline leprosy:** Features of both tuberculoid and lepromatous leprosy are present. Without treatment, borderline leprosy may become less severe and more like the tuberculoid form, or it may worsen and become more like the lepromatous form.

**Complications:** The most severe complications result from the peripheral neuropathy, which causes deterioration of the sense of touch and a corresponding inability to feel pain and temperature. Patients may unknowingly burn, cut, or otherwise harm themselves. Repeated damage may lead to loss of digits. Muscle weakness can result in deformities (eg, clawing of the 4th and 5th fingers caused by ulnar nerve involvement, foot drop caused by peroneal nerve involvement).

Papules and nodules can be particularly disfiguring on the face.

Other areas of the body may be affected:

• **Feet:** Plantar ulcers with secondary infection are a major cause of morbidity, making walking painful.

• **Nose:** Damage to the nasal mucosa can result in chronic nasal congestion and nosebleeds and, if untreated, erosion and collapse of the nasal septum.

• **Eyes:** Iritis may lead to glaucoma, and corneal insensitivity may lead to scarring and blindness.

• **Sexual function:** Men with lepromatous leprosy may have erectile dysfunction and infertility. The infection can reduce testosterone and sperm production by the testes.

• **Kidneys:** Amyloidosis and consequent renal failure occasionally occur in lepromatous leprosy.
Leprosy reactions: During the course of untreated or even treated leprosy, the immune system may produce inflammatory reactions. There are 2 types.

Type 1 reactions result from a spontaneous increase in cell-mediated immunity. These reactions can cause fever and inflammation of the preexisting skin and peripheral nerve lesions, resulting in skin edema, erythema, and tenderness and worsening nerve function. These reactions, particularly if not treated early, contribute significantly to nerve damage. Because the immune response is increased, these reactions are termed reversal reactions, despite the apparent clinical worsening.

Type 2 reactions (erythema nodosum leprosum, or ENL) are systemic inflammatory reactions that appear to be a vasculitis or panniculitis and probably involve circulating immune complex deposition or increased T-helper cell function. They have become less common since clofazimine was added to the drug regimen. Patients may develop erythematous and painful papules or nodules that may pustulate and ulcerate and cause fever, neuritis, lymphadenitis, orchitis, arthritis (particularly in large joints, usually knees), and glomerulonephritis. Hemolysis or bone marrow suppression may cause anemia, and hepatic inflammation may cause mild abnormalities in liver function tests.

Diagnosis

• Microscopic examination of skin biopsy specimen

Diagnosis is suggested by the clinical picture of skin lesions and peripheral neuropathy and confirmed by microscopic examination of biopsy specimens; the organism does not grow on artificial culture media. Biopsy specimens should be taken from the advancing edge of tuberculoid lesions or, in lepromatous leprosy, from nodules or plaques.

Serum IgM antibodies to *M. leprae* are specific but insensitive (present in only two thirds of patients with tuberculoid leprosy). Diagnostic usefulness is further limited in endemic areas because such antibodies may be present in asymptomatic infection.

Treatment

• Long-term, multidrug regimens with dapsone, rifampin, and sometimes clofazimine

• Sometimes lifelong maintenance antibiotics

Antibiotics can stop the progression of leprosy but do not reverse any nerve damage or deformity. Thus, early detection and treatment are vitally important. Because of antibiotic resistance, multidrug regimens are used. The drugs chosen depend on the type of leprosy; multibacillary leprosy requires more intensive regimens and a longer duration than paucibacillary does. Advice about diagnosis and treatment is available from the National Hansen's Disease Program in Baton Rouge, LA (1-800-642-2477). Standard regimens recommended by the WHO differ somewhat from those used in the US.

Multibacillary: The standard WHO regimen includes dapsone, rifampin, and clofazimine. Patients take rifampin 600 mg and clofazimine 300 mg po once/mo under a health care practitioner's supervision and dapsone 100 mg plus clofazimine 50 mg once/day without supervision. This regimen is continued for 12 to 24 mo, depending on disease severity.

In the US, the regimen is rifampin 600 mg po once/day and dapsone 100 mg po once/day for 3 yr. Dapsone is continued indefinitely for lepromatous leprosy and for 10 yr for borderline leprosy.

Paucibacillary: In the standard WHO regimen, patients take rifampin 600 mg po once/mo with supervision and dapsone 100 mg once/day without supervision for 6 mo. People who have only a single skin lesion are given a single dose of rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg.

In the US, the regimen is rifampin 600 mg po once/day and dapsone 100 mg po once/day for 6 mo. Dapsone is continued for 3 yr for indeterminate and tuberculoid leprosy and for 5 yr for borderline leprosy.
tuberculoid.

**Drugs for leprosy:** Dapsone is relatively inexpensive and generally safe to use. Adverse effects include hemolysis and anemia (which are generally mild) and allergic dermatoses (which can be severe); rarely, dapsone syndrome (exfoliative dermatitis, high fever, mononucleosis-like WBC differential) occurs.

Rifampin, is primarily bactericidal for *M. leprae* and is even more effective than dapsone. However, if given at the recommended US dosage of 600 mg po once/day, it is too expensive for many developing countries. Adverse effects include hepatotoxicity, flu-like syndromes, and, rarely, thrombocytopenia and renal failure.

Clofazimine is extremely safe. The main side effect is temporary skin pigmentation.

**Leprosy reactions:** Patients with type 1 reactions (except minor skin inflammation) are given prednisone 40 to 60 mg po once/day initially, followed by low maintenance doses (often as low as 10 to 15 mg once/day) for a few months. Minor skin inflammation should not be treated.

First and 2nd episodes of ENL may be treated, if mild, with aspirin or, if significant, with 1 wk of prednisone 40 to 60 mg po once/day plus antimicrobials. For recurrent cases, thalidomide 100 to 300 mg po once/day is the drug of choice (in the US, available through the National Hansen's Disease Program). However, because of its teratogenicity, thalidomide should not be given to women who may become pregnant. Adverse effects are mild constipation, mild leukopenia, and sedation.

**Prevention**

Because leprosy is not very contagious, risk of spread is low. Only the untreated lepromatous form is contagious, but even then the infection is not easily spread. Once treatment has begun, leprosy cannot be spread. Avoiding contact with bodily fluids from and the rash on infected people is the best prevention.

The BCG vaccine, used to prevent TB, provides some protection against leprosy but is not often used.
Chapter 142. Fungi

Introduction

(See also Ch. 82.)

Fungal infections are often classified as opportunistic or primary. Opportunistic infections are those that develop mainly in immunocompromised hosts; primary infections can develop in immunocompetent hosts. Fungal infections can be systemic or local. Local fungal infections typically involve the skin (see p. 703), mouth (see p. 509), and vagina (see p. 2544) and may occur in normal or immunocompromised hosts.

Opportunistic fungal infections: Many fungi are opportunists and are usually not pathogenic except in an immunocompromised host. Causes of immunocompromise include AIDS, azotemia, diabetes mellitus, bronchiectasis, emphysema, TB, lymphoma, leukemia, other hematologic cancers, burns, and therapy with corticosteroids, immunosuppressants, or antimetabolites. Patients who spend more than several days in an ICU can become compromised because of medical procedures, underlying disorders, and undernutrition.

Typical opportunistic systemic fungal infections (mycoses) include

- Candidiasis
- Aspergillosis
- Mucormycosis (zygomycosis)
- Fusariosis

Systemic mycoses affecting severely immunocompromised patients often manifest acutely with rapidly progressive pneumonia, fungemia, or manifestations of extrapulmonary dissemination.

Primary fungal infections: These infections usually result from inhalation of fungal spores, which can cause a localized pneumonia as the primary manifestation of infection. In immunocompetent patients, systemic mycoses typically have a chronic course; disseminated mycoses with pneumonia and septicemia are rare and, if lung lesions develop, usually progress slowly. Months may elapse before medical attention is sought or a diagnosis is made. Symptoms are rarely intense in such chronic mycoses, but fever, chills, night sweats, anorexia, weight loss, malaise, and depression may occur. Various organs may be infected, causing symptoms and dysfunction.

Primary fungal infections may have a characteristic geographic distribution, which is especially true for the endemic mycoses caused by certain dimorphic fungi. For example,

- **Coccidioidomycosis:** Confined primarily to the southwestern US and northern Mexico
- **Histoplasmosis:** Occurring primarily in the eastern and Midwestern US
- **Blastomycosis:** Confined to North America and Africa

- **Paracoccidioidomycosis (formerly, South American blastomycosis):** Confined to that continent

However, travelers can manifest disease any time after returning from endemic areas.

When fungi disseminate from a primary focus in the lung, the manifestations may be characteristic, as for the following:

- **Cryptococcosis:** Usually, chronic meningitis
- **Progressive disseminated histoplasmosis:** Generalized involvement of the reticuloendothelial
system (liver, spleen, bone marrow)

- **Blastomycosis:** Single or multiple skin lesions or involvement of the prostate

**Diagnosis**

- Cultures and stains (typically for fungi and mycobacteria)
- Sometimes serologic tests (mainly for *Aspergillus, Candida, Coccidioides*, and *Cryptococcus*)
- Rarely biopsy

If clinicians suspect an acute or a chronic primary fungal infection, they should obtain a detailed travel and residential history to determine whether patients may have been exposed to certain endemic mycoses, perhaps years previously.

Pulmonary fungal infections must be distinguished from TB, tumors, and chronic pneumonias caused by nonfungal organisms. Specimens are obtained for fungal and acid-fast bacilli culture and histopathology. Sputum samples may be adequate, but occasionally bronchoalveolar lavage, transthoracic needle biopsy, or even surgery may be required to obtain an acceptable specimen.

Fungi that cause primary systemic infections are readily recognized by their histopathologic appearance. However, identifying the specific fungus may be difficult and usually requires fungal culture. The clinical significance of positive sputum cultures may be unclear if they show commensal organisms (eg, *Candida albicans*) or fungi ubiquitous in the environment (eg, *Aspergillus* sp). Therefore, evidence of tissue invasion is required for a diagnosis of candidiasis, aspergillosis, or other opportunistic fungal infections (eg, fusariosis, pseudallescheriasis) because these fungi may not be causing the symptoms.

**Serologic tests** may be used to check for many systemic mycoses if culture and histopathology are unavailable or unrevealing, although few provide definitive diagnoses. Particularly useful tests include the following:

- Measurement of organism-specific antigens, most notably from *Cryptococcus neoformans, Histoplasma capsulatum*, and *Aspergillus* sp
- Measurement of histoplasmin in urine to diagnose histoplasmosis
- Complement fixation assays and newer enzyme immunoassays for anticoxidiodial antibodies, which are satisfactorily specific and do not require proof of rising levels (high titers confirm the diagnosis and indicate high risk of extrapulmonary dissemination)
- Detection of antibodies in CSF of patients with chronic meningitis to confirm the diagnosis

Most other tests for antifungal antibodies have low sensitivity, specificity, or both and, because measurement of acute and convalescent titers is required, cannot be used to guide initial therapy.

**Antifungal Drugs**

Drugs for systemic antifungal treatment include amphotericin B (and its lipid formulations), various azole derivatives, echinocandins, and flucytosine (see **Table 142-1**).

**Table 142-1. Some Drugs for Systemic Fungal Infections**

Amphotericin B, an effective but relatively toxic drug, has long been the mainstay of antifungal therapy for invasive and serious mycoses. However, newer potent and less toxic triazoles and echinocandins are now often recommended as first-line drugs for many invasive fungal infections. These drugs have markedly changed the approach to antifungal therapy, sometimes even allowing oral treatment of chronic
Amphotericin B

Amphotericin B has been the mainstay of antifungal therapy for invasive and serious mycoses, but other antifungals (eg, voriconazole, posaconazole, the echinocandins) are now considered first-line drugs for many of these infections.

For chronic mycoses, conventional amphotericin B is usually started at ≥ 0.3 mg/kg IV once/day, increased as tolerated to the desired dose (0.4 to 1.0 mg/kg; generally not > 50 mg/day); many patients tolerate the target dose on the first day. If patients tolerate the target dose, twice that dose can be given on a more convenient alternate-day schedule. Extended treatment courses may be even less frequent (eg, 3 times/wk).

For acute, life-threatening mycoses, amphotericin B is started at 0.6 to 1.0 mg/kg IV once/day. For certain rapidly progressive opportunistic mycoses (eg, invasive aspergillosis), daily doses as high as 1.5 mg/kg have been used, usually divided into 2 or 3 infusions. These doses must be decreased to about 0.5 mg/kg/day as nephrotoxicity develops.

For chronic meningitis, intrathecal amphotericin B injections can be used but are now rarely needed because potent triazoles (eg, voriconazole, posaconazole) are an effective alternative. Administration is usually via direct intracisternal injection or through a subcutaneous Ommaya-type reservoir connected to an intraventricular catheter. Headache, nausea, and vomiting may occur, but adding dexamethasone to each intrathecal injection may lessen these effects. Amphotericin B can also be given as lumbar intrathecal injections. At the time of injection, ≥ 10 mL of CSF is withdrawn into a syringe containing amphotericin B diluted in 5% D/W to 0.2 mg/mL. Doses of 0.05 to 0.5 mg are then injected over 2 min or more. Doses are gradually increased as tolerated, peaking with a regimen of 0.5 mg 3 times/wk.

Formulations: There are 2 formulations of amphotericin:

• Standard (conventional)

• Lipid-based

The standard formulation, colloidal amphotericin B deoxycholate, must always be given in 5% D/W because salts can precipitate the drug. It is usually given over 2 to 3 h, although more rapid infusions over 20 to 60 min can be used in selected patients. However, more rapid infusions usually have no advantage. Many patients experience chills, fever, nausea, vomiting, anorexia, headache, and, occasionally, hypotension during and for several hours after an infusion. Amphotericin B may also cause chemical thrombophlebitis when given via peripheral veins. Pretreatment with acetaminophen or NSAIDs is often used; if these drugs are ineffective, hydrocortisone 25 to 50 mg or diphenhydramine 25 mg is sometimes added to the infusion or given as a separate IV bolus. Often, hydrocortisone can be tapered and omitted during extended therapy. Severe chills and rigors can be relieved or prevented by meperidine 50 to 75 mg IV.

Several lipid vehicles reduce the toxicity of amphotericin B (particularly nephrotoxicity and infusion-related symptoms). Three preparations are available:

• Amphotericin B lipid complex

• Liposomal amphotericin B

• Amphotericin B cholesteryl sulfate

The first 2 lipid formulations are preferred over conventional amphotericin B because they cause fewer infusion-related symptoms and less nephrotoxicity. Amphotericin B cholesteryl sulfate does not provide any advantages over conventional amphotericin B.
Adverse effects: The main adverse effects are

- Nephrotoxicity (most common)
- Bone marrow suppression

Renal impairment is the major toxic risk of amphotericin B therapy. Serum creatinine and BUN should be monitored before treatment and at regular intervals during treatment: several times/wk for the first 2 to 3 wk, then 1 to 4 times/mo as clinically indicated. Amphotericin B is unique among nephrotoxic antimicrobial drugs because it is not eliminated appreciably via the kidneys and does not accumulate as renal failure worsens. Nevertheless, dosages should be lowered if serum creatinine rises to > 3.0 to 3.5 mg/dL (> 265 to 309 μmol/L) or BUN rises to > 50 mg/dL (> 18 mmol urea/L). Acute nephrotoxicity can be reduced by aggressive IV hydration with saline before amphotericin B infusion; at least 1 L of normal saline should be given before amphotericin infusion. Mild to moderate renal function abnormalities induced by amphotericin B usually resolve gradually after therapy is completed. Permanent damage occurs primarily after prolonged treatment; after > 4 g total dose, about 75% of patients have persistent renal insufficiency.

Amphotericin B also frequently suppresses bone marrow function, manifested primarily by anemia. Hepatotoxicity or other untoward effects are unusual.

Azole Antifungals

Azoles block the synthesis of ergosterol, an important component of the fungal cell membrane. They can be given orally to treat chronic mycoses. The first such oral drug, ketoconazole, has largely been supplanted by more effective, less toxic triazole derivatives, such as fluconazole, itraconazole, posaconazole, and voriconazole. Drug interactions can occur with all azoles but are less likely with fluconazole.

Fluconazole: This water-soluble drug is absorbed almost completely after an oral dose. It is excreted largely unchanged in urine and has a half-life of > 24 h, allowing single daily doses. It has high penetration into CSF (≥ 70% of serum levels) and has been especially useful in treating cryptococcal and coccidioidal meningitis. It is also one of the first-line drugs for treatment of candidemia in non-neutropenic patients. Doses range from 200 to 400 mg po once/day to as high as 160 mg once/day in some seriously ill patients and in patients infected with Candida glabrata or other Candida sp (not C. albicans); daily doses of ≥ 1000 mg have been given and had acceptable toxicity.

Adverse effects that occur most commonly are GI discomfort and skin rash. More severe toxicity is unusual, but the following have occurred: hepatic necrosis, Stevens-Johnson syndrome, anaphylaxis, alopecia, and, when taken after the 1st trimester of pregnancy, congenital fetal anomalies.

Drug interactions occur less often with fluconazole than with other azoles. However, fluconazole sometimes elevates serum levels of cyclosporine, rifabutin, phenytoin, tacrolimus, warfarin-type oral anticoagulants, sulfonyleurea drugs (eg, tolbutamide), and zidovudine. Rifampin may lower fluconazole blood levels.

Itraconazole: This drug has become the standard treatment for lymphocutaneous sporotrichosis as well as for mild or moderately severe histoplasmosis, blastomycosis, and paracoccidioidomycosis. It is also effective in mild cases of invasive aspergillosis, some cases of coccidioidomycosis, and certain types of chromoblastomycosis. Itraconazole can clear some types of fungal meningitis, but it is not the drug of choice. Because of its high lipid solubility and protein binding, itraconazole blood levels tend to be low, but tissue levels are typically high. Drug levels are negligible in urine and CSF. Use of itraconazole is likely to decline as use of voriconazole and posaconazole increases.

Adverse effects with doses of up to 400 mg/day most commonly are GI, but a few men have reported erectile dysfunction, and higher doses may cause hypokalemia, hypertension, and edema. Other reported adverse effects include allergic rash, hepatitis, and hallucinations.

Drug and food interactions can be significant. Acidic drinks (eg, cola, acidic fruit juices) or food
(especially high-fat foods) improves absorption from the GI tract. However, absorption may be reduced if itraconazole is taken with prescription or OTC drugs used to lower gastric acidity. Several drugs, including rifampin, rifabutin, didanosine, phenytoin, and carbamazepine, may decrease serum itraconazole levels. Itraconazole also inhibits metabolic degradation of other drugs, elevating blood levels with potentially serious consequences. Serious, even fatal cardiac arrhythmias may occur if itraconazole is used with cisapride (not available in the US) or some antihistamines (eg, terfenadine, astemizole, perhaps loratadine). Rhabdomyolysis has been associated with itraconazole-induced elevations in blood levels of cyclosporine or statins. Blood levels of digoxin, tacrolimus, oral anticoagulants, or sulfonylureas may increase when these drugs are used with itraconazole.

**Posaconazole**: The triazole posaconazole is an oral suspension; it is not available in tablet or IV formulations. This drug is highly active against yeasts and molds and effectively treats various opportunistic mold infections, such as those due to dematiaceous (dark-walled) fungi (eg, *Cladophialophora* sp). Posaconazole is also being evaluated as prophylaxis in neutropenic patients with various cancers.

**Adverse effects** for posaconazole, as for other triazoles, include a prolonged QT interval and interaction with many drugs, including rifampin, statins, various immunosuppressants, and barbiturates.

**Voriconazole**: This broad-spectrum triazole can be used as first-line therapy for serious *Aspergillus* infections; most clinical mycologists consider it the treatment of choice for *Aspergillus* infections in immunocompetent and immunocompromised hosts. Voriconazole can also be used to treat *Scedosporium apispermum* and *Fusarium* infections. Additionally, the drug is effective in candidal esophagitis and other candidal infections; it has activity against a broader spectrum of *Candida* sp than does fluconazole.

**Adverse effects** that must be monitored for include hepatotoxicity, visual disturbances, hallucinations, and dermatologic reactions. This drug can prolong the QT interval. Also, there are numerous drug-drug interactions, notably with certain immunosuppressants used after organ transplantation.

**Echinocandins**

Echinocandins are water-soluble lipopeptides that inhibit glucan synthase. Their mechanism of action is unique among antifungal drugs; echinocandins target the fungal cell wall, making them attractive because they lack cross-resistance with other drugs and their target is fungal and has no mammalian counterpart. Echinocandins available in the US are anidulafungin, caspofungin, and micafungin. There is little evidence to suggest that one is better than the other, but anidulafungin appears to interact with fewer drugs than the other two.

These drugs can be used to treat various forms of candidiasis, aspergillosis, and other mycoses.

**Flucytosine**

Flucytosine, a nucleic acid analog, is water soluble and well absorbed after oral administration. Preexisting or emerging resistance is common, so it is almost always used with another antifungal, usually amphotericin B. Flucytosine plus amphotericin B is used primarily to treat cryptococcosis but is also valuable for some cases of disseminated candidiasis, other yeast infections, and severe invasive aspergillosis. Flucytosine plus antifungal azoles may be beneficial in treating cryptococcosis and some other mycoses.

The usual dose (12.5 to 37.5 mg/kg po qid) leads to high drug levels in serum, urine, and CSF. Major adverse effects are bone marrow suppression (thrombocytopenia and leukopenia), hepatotoxicity, and enterocolitis; only degree of bone marrow suppression is proportional to serum levels. Because flucytosine is cleared primarily by the kidneys, blood levels rise if nephrotoxicity develops during concomitant use with amphotericin B, particularly when amphotericin B is used in doses > 0.4 mg/kg/day. Flucytosine serum levels should be monitored, and the dosage should be adjusted to keep levels between 40 and 90 μg/mL. CBC and renal and liver function tests should be done twice/wk. If blood levels are unavailable, therapy is begun at 25 mg/kg qid, and dosage is decreased if renal function deteriorates.
Aspergillus

Aspergillosis is an opportunistic infection caused by inhaling spores of the mold *Aspergillus*; the spores invade blood vessels, causing hemorrhagic necrosis and infarction. Symptoms may be those of asthma, pneumonia, sinusitis, or rapidly progressing systemic illness. Diagnosis is primarily clinical but may be aided by imaging, histopathology, and specimen staining and culture. Treatment is with voriconazole, amphotericin B (or its lipid formulations), caspofungin, itraconazole, or flucytosine. Fungus balls may require surgical resection. Recurrence is common.

*Aspergillus* sp are among the most common environmental molds, frequently present in or on the following:

- Decaying vegetation (eg, compost heaps)
- Insulating materials
- Air conditioning or heating vents
- Operating pavilions and patient rooms
- Hospital implements
- Airborne dust

Pathophysiology

Invasive infections are usually acquired by inhalation of spores or, occasionally, by direct invasion through damaged skin.

Major risk factors include

- Neutropenia
- Long-term high-dose corticosteroid therapy
- Organ transplantation (especially bone marrow transplantation)
- Hereditary disorders of neutrophil function (eg, chronic granulomatous disease)
- AIDS

*Aspergillus* sp tends to infect open spaces, such as pulmonary cavities caused by previous lung disorders (eg, bronchiectasis, tumor, TB), the sinuses, or ear canals (otomycosis). Such infections tend to be locally invasive and destructive, although systemic spread sometimes occurs, particularly in immunocompromised patients.

*A. fumigatus* is the most common cause of invasive pulmonary disease; *A. flavus* most often causes invasive extrapulmonary disease, probably because these patients are more severely immunosuppressed than patients infected with *A. fumigatus*.

Focal infections, typically in the lung, sometimes form a fungus ball (aspergilloma), a characteristic growth of tangled masses of hyphae, with fibrin exudate and few inflammatory cells, typically encapsulated by fibrous tissue. Occasionally, there is some local invasion of tissue at the periphery of the cavity, but usually the fungus just resides within the cavity with no appreciable local invasion.

A chronic form of invasive aspergillosis occasionally occurs, particularly in patients with chronic
granulomatous disease, which is characterized by a hereditary phagocytic cell defect. *Aspergillus* sp can also cause endophthalmitis after trauma or surgery to the eye (or by hematogenous seeding) and infections of intravascular and intracardiac prostheses.

Primary superficial aspergillosis is uncommon but may occur in burns; beneath occlusive dressings; after corneal trauma (keratitis); or in the sinuses, mouth, nose, or ear canal.

**Allergic bronchopulmonary aspergillosis** is a hypersensitivity reaction to *A. fumigatus* that results in lung inflammation unrelated to fungal invasion of tissues (see p. 1887).

**Symptoms and Signs**

Chronic pulmonary aspergillosis causes cough, often with hemoptysis and shortness of breath. If untreated, invasive pulmonary aspergillosis usually causes rapidly progressive, ultimately fatal respiratory failure.

Extrapulmonary invasive aspergillosis begins with skin lesions, sinusitis, or pneumonia and may involve the liver, kidneys, brain, and other tissues; it is often rapidly fatal.

Aspergillosis in the sinuses can form an aspergilloma or cause allergic fungal sinusitis or a chronic, slowly invasive granulomatous inflammation with fever, rhinitis, and headache. Patients may have necrosing cutaneous lesions overlying the nose or sinuses, palatal or gingival ulcerations, signs of cavernous sinus thrombosis, or pulmonary or disseminated lesions.

**Diagnosis**

- Usually fungal culture and histopathology of tissue samples

Because *Aspergillus* sp are common in the environment, positive sputum cultures may be due to environmental contamination or noninvasive colonization in patients with chronic lung disease; positive cultures are significant mainly when obtained from patients with increased susceptibility due to immunosuppression or when there is high suspicion due to typical imaging findings. Conversely, sputum cultures from patients with aspergillomas or invasive pulmonary aspergillosis are often negative because cavities are often walled off from airways and because invasive disease progresses mainly by vascular invasion and tissue infarction.

Chest x-rays are taken, and CT of sinuses is done if sinus infection is suspected. A movable fungus ball within a cavitary lesion is characteristic on both, although most lesions are focal and solid. Sometimes imaging detects a halo sign (a thin air shadow surrounding a nodule), representing cavitation within a necrotic lesion. Diffuse, generalized pulmonary infiltrates are seen in some patients.

Culture and histopathology of a tissue sample are usually necessary for confirmation; the sample is typically taken from the lungs via bronchoscopy and from the sinuses via anterior rhinoscopy. Because cultures take time and histopathology results may be false-negative, most decisions to treat are based on strong presumptive clinical evidence. Large vegetations often release sizable emboli that may occlude blood vessels and provide specimens for diagnosis.

Various serologic assays exist but are of limited value for rapid diagnosis of acute, life-threatening invasive aspergillosis. Detection of antigens such as galactomannans can be specific but is not sufficiently sensitive to identify most cases in their early stages. Blood cultures are almost always negative, even in rare cases of endocarditis.

**Treatment**

- Voriconazole or amphotericin B

- Sometimes surgery for aspergillomas
Invasive infections usually require aggressive treatment with IV amphotericin B or voriconazole (generally considered the first-choice drug). Oral itraconazole (but not fluconazole) can be effective in some cases. Caspofungin or other echinocandins may be used as salvage therapy. Combination therapy with azoles and echinocandins or with amphotericin B and echinocandins has been effective in some patients.

Usually, complete cure requires reversal of immunosuppression (eg, resolution of neutropenia, discontinuation of corticosteroids). Recrudescence is common if neutropenia recurs.

Aspergillomas neither require nor respond to systemic antifungal therapy but may require resection because of local effects, especially hemoptysis.

Blastomycosis

(Gilchrist's Disease; North American Blastomycosis)

Blastomycosis is a pulmonary disease caused by inhaling spores of the dimorphic fungus *Blastomyces dermatitidis*; occasionally, the fungi spread hematogenously, causing extrapulmonary disease. Symptoms result from pneumonia or from dissemination to multiple organs, most commonly the skin. Diagnosis is clinical, by chest x-ray, or both and is confirmed by laboratory identification of the fungi. Treatment is with itraconazole, fluconazole, or amphotericin B.

In North America, the endemic area for blastomycosis includes

- Ohio-Mississippi River valleys (extending into the middle Atlantic and Southeastern states)
- Northern Midwest
- Upstate New York
- Southern Canada

Infection also occurs in the Middle East and Africa.

Immunocompetent people can contract this infection. Although blastomycosis may be more common and more severe in immunocompromised patients, it is a less common opportunistic infection than histoplasmosis or coccidioidomycosis.

*B. dermatitidis* grows as a mold at room temperature in soil enriched with animal excreta and in moist, decaying, acidic organic material, often near rivers. In the lungs, inhaled spores convert into large (15 to 20 μm) invasive yeasts, which form characteristic broad-based buds.

Once in the lungs, infection may

- Remain localized in the lungs
- Disseminate hematogenously

Hematogenous dissemination can cause focal infection in numerous organs, including the skin, prostate, epididymides, testes, kidneys, vertebrae, ends of long bones, subcutaneous tissues, brain, oral or nasal mucosa, thyroid, lymph nodes, and bone marrow.

Symptoms and Signs

**Pulmonary:** Pulmonary blastomycosis may be asymptomatic or cause an acute, self-limited disease that often goes unrecognized. It can also begin insidiously and develop into a chronic, progressive infection. Symptoms include a productive or dry hacking cough, chest pain, dyspnea, fever, chills, and drenching
sweats.
Pleural effusion occurs occasionally. Some patients have rapidly progressive infections, and acute respiratory distress syndrome may develop.

**Extrapulmonary:** In extrapulmonary disseminated blastomycosis, symptoms depend on the organ involved. Skin lesions are by far the most common; they may be single or multiple and may occur with or without clinically apparent pulmonary involvement. Papules or papulopustules usually appear on exposed surfaces and spread slowly. Painless miliary abscesses, varying from pinpoint to 1 mm in diameter, develop on the advancing borders. Irregular, wartlike papillae may form on surfaces. As lesions enlarge, the centers heal, forming atrophic scars. When fully developed, an individual lesion appears as an elevated verrucous patch, usually ≥ 2 cm wide with an abruptly sloping, purplish red, abscess-studded border. Ulceration may occur if bacterial superinfection is present.

If bone lesions develop, overlying areas are sometimes swollen, warm, and tender. Genital lesions cause painful epididymal swelling, deep perineal discomfort, or prostatic tenderness detected during rectal examination.

**Diagnosis**

- Chest x-ray
- Fungal cultures

A chest x-ray should be taken. Focal or diffuse infiltrates may be present, sometimes as patchy bronchopneumonia fanning out from the hilum. These findings must be distinguished from other causes of pneumonia (eg, other mycoses, TB, tumors). Skin lesions can be mistaken for sporotrichosis, TB, iodism, or basal cell carcinoma. Genital involvement may mimic TB.

Cultures of infected material are done; they are definitive when positive. The organism's characteristic appearance, seen during microscopic examination of tissues or sputum, is also frequently diagnostic. Serologic testing is not sensitive but is useful if positive.

**Treatment**

- For mild to moderate disease, itraconazole
- For severe, life-threatening infection, amphotericin B

Untreated blastomycosis is usually slowly progressive and is rarely ultimately fatal. Treatment depends on severity of the infection. For mild to moderate disease, itraconazole 200 to 400 mg po once/day is used. Fluconazole appears less effective, but 400 to 800 mg po once/day may be tried in itraconazole-intolerant patients with mild disease. For severe, life-threatening infections, IV amphotericin B is usually effective.

Voriconazole and posaconazole are highly active against *B. dermatitidis*, but their role has not yet been defined.

**Candidiasis (Invasive)**

(See also pp. 703, 1102, and 2544.)

*Candidiasis* is infection by *Candida* sp (most often *C. albicans*), manifested by mucocutaneous lesions, fungemia, and sometimes focal infection of multiple sites. Symptoms depend on the site of infection and include dysphagia, skin and mucosal lesions, blindness, vaginal symptoms (itching, burning, discharge), fever, shock, oliguria, renal shutdown, and disseminated intravascular coagulation. Diagnosis is confirmed by histopathology and cultures from normally
sterile sites. Treatment is with amphotericin B, fluconazole, echinocandins, voriconazole, or posaconazole.

Candida sp are commensal organisms that inhabit the GI tract and sometimes the skin (see p. 703). Unlike other systemic mycoses, candidiasis results from endogenous organisms. Most infections are caused by C. albicans or C. tropicalis; however, C. glabrata (formerly Torulopsis glabrata) is increasingly involved in fungemia, UTIs, and, occasionally, pneumonia or other focal disease.

Candida sp account for about 80% of major systemic fungal infections and are the most common cause of fungal infections in immunocompromised patients. Candidal infections are one of the most common hospital-acquired infections.

Candidiasis involving the mouth and esophagus is a defining opportunistic infection in AIDS. Although mucocutaneous candidiasis is frequently present in HIV-infected patients, hematogenous dissemination is unusual until immunosuppression becomes profound. Neutropenic patients (eg, those receiving cancer chemotherapy) are at high risk of developing life-threatening disseminated candidiasis.

Candidemia may occur in nonneutropenic patients during prolonged hospitalization. This bloodstream infection is often related to one or more of the following:

• Multiple trauma
• Surgical procedures
• Multiple courses of broad-spectrum antibacterial therapy
• IV hyperalimentation

IV lines and the GI tract are the usual portals of entry. Candidemia often prolongs hospitalization and increases mortality due to concurrent disorders. Prolonged or untreated candidemia may lead to endocarditis or meningitis as well as to focal involvement of skin, subcutaneous tissues, bones, joints, liver, spleen, kidneys, eyes, and other tissues. Endocarditis is commonly related to IV drug abuse, valve replacement, or intravascular trauma induced by indwelling IV catheters.

All forms of disseminated candidiasis should be considered serious, progressive, and potentially fatal.

Symptoms and Signs

Esophagitis is most often manifested by dysphagia. Symptoms of respiratory tract infections (eg, cough) are nonspecific.

Candidemia usually causes fever, but no symptoms are specific. Some patients develop a syndrome resembling bacterial sepsis, with a fulminating course that may include shock, oliguria, renal shutdown, and disseminated intravascular coagulation.

Candidal endophthalmitis starts as white retinal lesions that are initially asymptomatic but can progress, opacifying the vitreous and causing potentially irreversible scarring and blindness. In neutropenic patients, retinal hemorrhages occasionally also occur, but actual infection of the eye is rare.

Papulonodular skin lesions may also develop, especially in neutropenic patients, in whom they indicate widespread hematogenous dissemination to other organs. Symptoms of other focal infection depend on the organ involved.

Diagnosis

• Histopathology and fungal cultures

Because Candida spp are commensal, their culture from sputum, the mouth, the vagina, urine, stool, or
skin does not necessarily signify an invasive, progressive infection. A characteristic clinical lesion must also be present, histopathologic evidence of tissue invasion (eg, yeasts, pseudohyphae, or hyphae in tissue specimens) must be documented, and other etiologies must be excluded. Positive cultures of blood, CSF, pericardium or pericardial fluid or tissue biopsy specimens provide definitive evidence that systemic therapy is needed.

Serologic assays do not have sufficient specificity or sensitivity to be useful.

**Treatment**

- **Amphotericin B** for severe illness, otherwise an echinocandin or azole

Predisposing conditions (eg, neutropenia, immunosuppression, use of broad-spectrum antibacterial antibiotics, hyperalimentation, presence of indwelling lines) should be reversed or controlled if possible. IV amphotericin B is recommended for most severely ill patients, especially those who are immunosuppressed. Echinocandins are an alternative to amphotericin B in adults with or without neutropenia. Fluconazole 400 to 800 mg po once/day is also considered a first-line drug (unless *C. krusei* or *C. glabrata* is involved) for nonneutropenic patients and may be effective in patients with neutropenia.

Esophageal candidiasis is treated with fluconazole 200 to 400 mg po or IV once/day or itraconazole 200 mg po once/day. If these drugs are ineffective or if infection is severe, voriconazole 4 mg/kg po or IV bid, posaconazole 400 mg po bid, or one of the echinocandins may be used. These drugs are also effective for bloodstream and other hematogenously disseminated infections.

**Coccidioidomycosis**

(San Joaquin Fever; Valley Fever)

*Coccidioidomycosis* is a pulmonary or hematogenously spread disseminated disease caused by the fungus *Coccidioides immitis*; it usually occurs as an acute benign asymptomatic or self-limited respiratory infection. The organism occasionally disseminates to cause focal lesions in other tissues. Symptoms, if present, are those of lower respiratory infection or low-grade nonspecific disseminated disease. Diagnosis is suspected based on clinical and epidemiologic characteristics and confirmed by chest x-ray, culture, and serologic testing. Treatment, if needed, is usually with fluconazole, itraconazole, newer triazoles, or amphotericin B.

In North America, the endemic area for coccidioidomycosis includes

- The southwestern US
- Northern Mexico

The affected areas of the southwestern US include Arizona, the central valley of California, parts of New Mexico, and Texas west of El Paso. The area extends into northern Mexico, and foci occur in parts of Central America and Argentina.

**Pathophysiology**

Infections are acquired by inhaling spore-laden dust. Because of travel and delayed onset of clinical manifestations, infections can become evident outside endemic areas.

Once inhaled, *C. immitis* spores convert to large tissue-invasive spherules. As spherules enlarge and then rupture, each releases thousands of small endospores, which may form new spherules. Pulmonary disease is characterized by an acute, subacute, or chronic granulomatous reaction with varying degrees of fibrosis. Lesions may cavitate or form nodular-like coin lesions.

Sometimes disease progresses, with widespread lung involvement, dissemination, or both; focal lesions may form in almost any other tissue, most commonly in skin, subcutaneous tissues, bones (osteomyelitis),
and meninges (meningitis). Progressive disease is more common among men and is more likely to occur in the following contexts:

- HIV infection
- Use of immunosuppressants
- Advanced age
- 2nd half of pregnancy or postpartum
- Certain ethnic backgrounds (Filipino, African American, Native American, Hispanic, and Asian, in decreasing order of relative risk)

Symptoms and Signs

**Primary coccidioidomycosis:** Most patients are asymptomatic, but nonspecific respiratory symptoms resembling those of influenza, acute bronchitis, or, less often, acute pneumonia or pleural effusion sometimes occur. Symptoms, in decreasing order of frequency, include fever, cough, chest pain, chills, sputum production, sore throat, and hemoptysis.

Physical signs may be absent or limited to scattered rales with or without areas of dullness to percussion over lung fields. Some patients develop hypersensitivity to the localized respiratory infection, manifested by arthritis, conjunctivitis, erythema nodosum, or erythema multiforme.

Primary pulmonary lesions sometimes leave nodular coin lesions that must be distinguished from tumors, TB, and other granulomatous infections. Sometimes residual cavitary lesions develop; they may vary in size over time and often appear thin-walled. A small percentage of these cavities fail to close spontaneously. Hemoptysis or the threat of rupture into the pleural space occasionally necessitates surgery.

**Progressive coccidioidomycosis:** Nonspecific symptoms develop a few weeks, months, or occasionally years after primary infection; they include low-grade fever, anorexia, weight loss, and weakness.

Extensive pulmonary involvement may cause progressive cyanosis, dyspnea, and mucopurulent or bloody sputum. Symptoms of extrapulmonary lesions depend on the site. Draining sinus tracts sometimes connect deeper lesions to the skin. Localized extrapulmonary lesions often become chronic and recur frequently, sometimes long after completion of seemingly successful antifungal therapy.

Untreated disseminated coccidioidomycosis is usually fatal and, if meningitis is present, is uniformly fatal without prolonged and possibly lifelong treatment. Mortality rates in patients with advanced HIV infection exceed 70% within 1 mo of diagnosis; whether treatment can alter mortality rates is unclear.

**Diagnosis**

- Cultures (routine or fungal)
- Microscopic examination of specimens to check for *C. immitis* spherules
- Serologic testing

Eosinophilia may be an important clue in identifying coccidioidomycosis. The diagnosis is suspected based on history and typical physical findings, when apparent; chest x-ray findings can help confirm the diagnosis, which can be established by fungal culture or by visualization of *C. immitis* spherules in sputum, pleural fluid, CSF, exudate from draining lesions, or biopsy specimens. Intact spherules are usually 20 to 80 μm in diameter, thick-walled, and filled with small (2 to 4 μm) endospores. Endospores released into tissues from ruptured spherules may be mistaken for nonbudding yeasts.
Serologic testing for anticoccidioidal antibodies using an immunodiffusion kit (for IgG and IgM antibodies) and complement fixation (for IgG antibodies) are the most useful tests. Titers ≥ 1:4 in serum are consistent with current or recent infection, and higher titers (≥ 1:32) signify an increased likelihood of extrapulmonary dissemination. However, immunocompromised patients may have low titers. Titers should decline during successful therapy. The presence of complement-fixing antibodies in CSF is diagnostic of coccidioidal meningitis and is important because CSF cultures are rarely positive.

Delayed cutaneous hypersensitivity to coccidioidin or spherulin usually develops within 10 to 21 days after acute infections in immunocompetent patients but is characteristically absent in progressive disease. Because this test is positive in most people in endemic areas, its primary value is for epidemiologic studies rather than for diagnosis.

**Treatment**

- Usually antifungal drugs

Treatment for primary coccidioidomycosis is controversial in low-risk patients. Some experts give fluconazole because its toxicity is low and there is a small risk of hematogenous seeding, especially to bone or brain. In addition, symptoms resolve more quickly in treated patients than in those who are not treated with an antifungal. Others think that fluconazole may blunt the immune response and that risk of hematogenous seeding in primary infection is too low to warrant use of fluconazole. High complement fixation titers indicate spread and the need for treatment.

Mild to moderate nonmeningeal extrapulmonary involvement should be treated with fluconazole ≥ 400 mg po once/day or voriconazole 200 mg po or IV bid. For severe illness, amphotericin B 0.5 to 1.0 mg/kg IV over 2 to 6 h once/day is given for 4 to 12 wk until total dose reaches 1 to 3 g, depending on degree of infection. Patients can usually be switched to an oral azole once they have been stabilized, usually within several weeks.

Patients with HIV- or AIDS-associated coccidioidomycosis require maintenance therapy to prevent relapse; fluconazole 200 mg po once/day or itraconazole 200 mg po or IV bid usually is sufficient, and weekly IV amphotericin B may suffice for azole-intolerant patients. Lipid formulations of amphotericin B are preferred over conventional amphotericin B.

For meningeal coccidioidomycosis, fluconazole is used. The optimal dose is unclear; oral doses of 800 to 1200 mg once/day may be more effective than 400 mg/day. If amphotericin B is used, intrathecal injections are needed, either intraventricularly via a subcutaneous reservoir or intracisternally. Treatment for meningeal coccidioidomycosis must be continued for many months, probably lifelong. Surgical removal of involved bone may be necessary to cure osteomyelitis.

**Cryptococcosis**

(European Blastomycosis; Torulosis)

Cryptococcosis is a pulmonary or disseminated infection acquired by inhalation of soil contaminated with the encapsulated yeast *Cryptococcus neoformans*. Symptoms are those of pneumonia, menigitis, or involvement of skin, bones, or viscera. Diagnosis is clinical and microscopic, confirmed by culture or fixed-tissue staining. Treatment, when necessary, is with azoles or amphotericin B, with or without flucytosine.

Distribution is worldwide. Cryptococcosis is a defining opportunistic infection for AIDS, although patients with Hodgkin lymphoma, other lymphomas, or sarcoidosis and those taking long-term corticosteroid therapy are also at increased risk.

**Pathophysiology**

Cryptococcosis is acquired by inhalation and thus typically affects the lungs. Many patients present with
asymptomatic, self-limited primary lung lesions. In immunocompetent patients, the isolated pulmonary lesions usually heal spontaneously without disseminating, even without antifungal therapy.

After inhalation, Cryptococcus may disseminate, frequently to the brain and meninges, typically manifesting as microscopic multifocal intracerebral lesions. Meningeal granulomas and larger focal brain lesions may be evident. Although pulmonary involvement is rarely dangerous, meningitis is life-threatening and requires aggressive therapy.

Focal sites of dissemination may also occur in skin, the ends of long bones, joints, liver, spleen, kidneys, prostate, and other tissues. Except for those in the skin, these lesions usually cause few or no symptoms. Rarely, pyelonephritis occurs with renal papillary necrosis.

Involved tissues typically contain cystic masses of yeasts that appear gelatinous because of accumulated cryptococcal capsular polysaccharide, but acute inflammatory changes are minimal or absent.

**Symptoms and Signs**

Manifestations depend on the affected area.

**CNS:** Because inflammation is not extensive, fever is usually low grade or absent, and meningismus is uncommon. In patients with AIDS, cryptococcal meningitis may cause minimal or no symptoms, but headache frequently occurs. Because most symptoms of cryptococcal meningitis result from cerebral edema, they are usually nonspecific (eg, headache, blurred vision, confusion, depression, agitation, other behavioral changes). Except for ocular or facial palsies, focal signs are rare until relatively late in the course. Blindness may develop because of cerebral edema or direct involvement of the optic tracts.

**Lungs:** Many patients are asymptomatic. Those with pneumonia usually have cough and other nonspecific respiratory symptoms. However, AIDS-associated cryptococcal pulmonary infection may manifest as severe, progressive pneumonia with acute dyspnea and an x-ray pattern suggesting Pneumocystis infection.

**Skin:** Dermatologic spread can manifest as pustular, papular, nodular, or ulcerated lesions, which sometimes resemble acne, molluscum contagiosum, or basal cell carcinoma.

**Diagnosis**

- Culture of CSF, sputum, urine, and blood
- Fixed-tissue specimen staining

Clinical diagnosis is suggested by symptoms of an indolent infection in immunocompetent patients and a more severe, progressive infection in immunocompromised patients. Chest x-ray, urine collection, and lumbar puncture are done first.

Culture of *C. neoformans* is definitive. CSF, sputum, and urine yield organisms most often, and blood cultures may be positive, particularly in patients with AIDS. In disseminated cryptococcosis with meningitis, *C. neoformans* is frequently cultured from urine (prostatic foci of infection sometimes persist despite successful clearance of organisms from the CNS). Diagnosis is strongly suggested if experienced observers identify encapsulated budding yeasts in smears of body fluids, secretions, exudates, or other specimens. In fixed tissue specimens, encapsulated yeasts may also be identified and confirmed as *C. neoformans* by positive mucicarmine or Masson-Fontana staining.

Elevated CSF protein and a mononuclear cell pleocytosis are usual in cryptococcal meningitis, although neutrophilia occasionally predominates. Glucose is frequently low, and encapsulated yeasts forming narrow-based buds can be seen on India ink smears in most patients, especially in those who have AIDS and who typically have a higher fungal burden than those without HIV infection. In some patients with AIDS, CSF parameters are normal, except for the presence of numerous yeasts on India ink preparation. The latex test for cryptococcal capsular antigen is positive in CSF or blood specimens or both in > 90% of
patients with meningitis and is generally specific, although false-positive results may occur, usually with titers ≤ 1:8, especially if rheumatoid factor is also present.

**Treatment**

- Usually antifungal drugs

**Patients without AIDS:** Patients may need no treatment for localized pulmonary involvement, confirmed by normal CSF parameters, negative cultures of CSF and urine, and no evidence of cutaneous, bone, or other extrapulmonary lesions. Some experts give a course of fluconazole to prevent hematogenous dissemination and to shorten the course of the illness.

In patients without meningitis, localized lesions in skin, bone, or other sites require systemic antifungal therapy, typically fluconazole 400 mg po once/day for 3 to 6 mo. For more severe disease, amphotericin B 0.5 to 1.0 mg/kg IV once/day with flucytosine 25 mg/kg po q 6 h is given for several weeks.

For meningitis, the standard regimen is amphotericin B 0.7 to 1.0 mg/kg IV once/day plus flucytosine 25 mg/kg po q 6 h for 6 to 10 wk; alternatively, this regimen can be used for 2 wk, followed by fluconazole 400 mg po once/day for 10 wk. After these regimens, patients with AIDS are given fluconazole 200 mg po once/day until the CD4 count is > 200 for at least 6 mo.

Cryptococcal antigen titers should be monitored at the start and end of therapy. However, if the patient is not improving with antifungal drugs, titers should be rechecked while the patient continues to receive therapy; the titers should steadily decline during successful therapy. In general, cultures should become and remain negative for at least 2 wk before treatment is ended.

**Patients with AIDS:** All patients require treatment. In isolated pulmonary or urinary tract disease, fluconazole 400 mg po once/day is given. For more severe disease, fluconazole 400 mg po once/day plus flucytosine 25 mg/kg po qid is used for 10 wk. For meningitis, the standard regimen is amphotericin B 0.7 to 1.0 mg/kg IV once/day plus flucytosine 25 mg po q 6 h for the first 2 wk of treatment; the entire induction phase of therapy lasts 6 to 10 wk. Alternatively, this regimen can be used for 2 wk, followed by fluconazole 400 mg po once/day for 10 wk total. Once induction therapy is completed, long-term suppressive (maintenance) therapy is required.

Nearly all AIDS patients need maintenance therapy for life. Fluconazole 200 mg po once/day is preferred, but itraconazole at the same dose is acceptable; however, itraconazole serum levels should be measured to make sure that patients are absorbing the drug. Weekly doses of IV amphotericin B also can be used, but this regimen has mostly been replaced by one of the azoles.

**Histoplasmosis**

**Histoplasmosis** is a pulmonary and hematogenous disease caused by *Histoplasma capsulatum*; it is often chronic and usually follows an asymptomatic primary infection. Symptoms are those of pneumonia or of nonspecific chronic illness. Diagnosis is by chest x-ray, identification of the organism in sputum or tissue, or both. Treatment, when necessary, is with amphotericin B or an azole.

Histoplasmosis occurs worldwide.

In the US, the endemic area for histoplasmosis includes

- The Ohio-Mississippi River valleys extending into parts of northern Maryland, southern Pennsylvania, central New York, and Texas

Microfoci have been noted in other states, such as Florida.

*H. capsulatum* grows as a mold in nature or in culture at room temperature but converts to a small (1 to 5 μm in diameter) yeast cell at 37° C and during invasion of host cells. Infection follows inhalation of conidia.
(spores produced by the mycelial form of the fungus) in soil or dust contaminated with bird or bat droppings. Severe disease is more common after heavy, prolonged exposure and in men, infants, or people with compromised T-cell-mediated immunity.

Initial infection occurs in the lungs and usually remains there but may spread hematogenously to other organs if it is not controlled by normal cell-mediated host defenses. Progressive disseminated histoplasmosis is one of the defining opportunistic infections for AIDS.

Symptoms and Signs

Most histoplasmosis infections are asymptomatic or so mild that patients do not seek medical attention. The disease has 3 main forms.

**Acute primary histoplasmosis** is a syndrome with fever, cough, myalgias, chest pain, and malaise of varying severity. Acute pneumonia (evident on physical examination and chest x-ray) sometimes develops.

**Chronic cavitary histoplasmosis** is characterized by pulmonary lesions that are often apical and resemble cavitary TB. Manifestations are worsening cough and dyspnea, progressing eventually to disabling respiratory dysfunction. Dissemination does not occur.

**Progressive disseminated histoplasmosis** characteristically includes generalized involvement of the reticuloendothelial system, with hepatosplenomegaly, lymphadenopathy, bone marrow involvement, and sometimes oral or GI ulcerations. The course is usually subacute or chronic, with only nonspecific, often subtle symptoms (eg, fever, fatigue, weight loss, weakness, malaise); the condition of HIV-positive patients may inexplicably worsen. The CNS may become involved, causing meningitis or focal brain lesions. Adrenal infection is rare but may result in Addison’s disease. Severe pneumonia is rare, but patients with AIDS may develop severe acute pneumonia with hypoxia suggesting *Pneumocystis jirovecii* infection, as well as hypotension, mental status changes, coagulopathy, or rhabdomyolysis.

Fibrosing mediastinitis, a chronic but rare form, ultimately causes circulatory compromise.

Patients with histoplasmosis may lose vision, but organisms are not present in ocular lesions, antifungal chemotherapy is not helpful, and the link to *H. capsulatum* infection is unclear.

Diagnosis

• Histopathology and cultures

• Antigen testing

The index of suspicion must be high because symptoms are nonspecific. Chest x-rays should be done and may show the following:

• **In acute infection:** Normal or a diffuse nodular or miliary pattern

• **In chronic pulmonary histoplasmosis:** Cavitary lesions in most patients

• **In progressive disease:** Hilar adenopathy with diffuse nodular infiltrates in about 50% of patients

Bronchiolavage or tissue biopsy may be necessary to obtain histology specimens; serologic testing and culture of urine, blood, and sputum specimens are also done.

Microscopic histopathology can strongly suggest the diagnosis, particularly in patients with AIDS and extensive infections; in such patients, intracellular yeasts may be seen in Wright’s- or Giemsa-stained peripheral blood oruffy coat specimens. Fungal culture confirms the diagnosis. Lysis-centrifugation or culture ofuffy coat improves the yield from blood specimens.

A test for *H. capsulatum* antigen is sensitive and specific, particularly when simultaneous serum and urine
specimens are tested; however, cross-reactivity with other fungi (Coccidioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Penicillium marneffei) has been noted.

Prognosis

The acute primary form is almost always self-limited, although very rarely, death occurs after massive infection. Chronic cavitary histoplasmosis can cause death due to severe respiratory insufficiency. Untreated progressive disseminated histoplasmosis has a mortality rate of > 90%.

Treatment

• Sometimes no treatment
• Sometimes azole antifungal drugs
• Amphotericin B for serious illness

Acute primary histoplasmosis requires no antifungal therapy unless there is no spontaneous improvement after 1 mo; itraconazole 200 mg po once/day for 6 to 12 wk is then used. Fluconazole and other azoles are also effective. Severe pneumonia requires more aggressive therapy with amphotericin B.

For chronic cavitary histoplasmosis, itraconazole 200 mg po once/day or bid is given for 12 to 24 mo. Other azoles or amphotericin B is used if patients are seriously ill or do not respond to or tolerate itraconazole.

For severe disseminated histoplasmosis, amphotericin B 0.5 to 1.0 mg/kg IV once/day for 4 to 12 wk is the treatment of choice. Patients without AIDS can be switched to itraconazole 200 mg po once/day after they become afebrile and require no ventilatory or BP support. For mild disseminated disease, itraconazole 200 mg po once/day or bid for 9 mo can be used. In patients with AIDS, itraconazole is given indefinitely to prevent relapse. Fluconazole may be less effective, but voriconazole and posaconazole are very active against H. capsulatum and may be very effective in the treatment of patients with histoplasmosis. Further data and experience are required to determine which drug is the best in each clinical situation. Intermittent doses of IV amphotericin B can be used for chronic suppression in azole-intolerant patients with AIDS.

Mucormycosis

(Zygomycosis)

Mucormycosis refers to infection caused by diverse fungal species, including Rhizopus, Rhizomucor, Absidia, and Mucor. Symptoms most frequently result from invasive necrotic lesions in the nose and palate, causing pain, fever, orbital cellulitis, proptosis, and purulent nasal discharge. CNS symptoms may follow. Pulmonary symptoms are severe and include productive cough, high fever, and dyspnea. Diagnosis is primarily clinical, requires a high index of suspicion, and is confirmed by histopathology and culture. Treatment is with IV amphotericin B and surgery to remove necrotic tissue.

Infection is most common among immunocompromised people, in patients with poorly controlled diabetes, and in patients receiving the iron-chelating drug deferoxamine.

The most common form of mucormycosis is

• Rhinocerebral

However, primary cutaneous, pulmonary, or GI lesions sometimes develop, and hematogenous dissemination to other sites can occur.

Symptoms and Signs
Rhinocerebral infections are usually severe and frequently fatal unless diagnosed early and treated aggressively. Necrotic lesions appear on the nasal mucosa or sometimes the palate. Vascular invasion by hyphae leads to progressive tissue necrosis that may involve the nasal septum, palate, and bones surrounding the orbit or sinuses. Manifestations may include pain, fever, orbital cellulitis, proptosis, purulent nasal discharge, and mucosal necrosis.

Progressive extension of necrosis to the brain can cause signs of cavernous sinus thrombosis, seizures, aphasia, or hemiplegia. Pulmonary infections resemble invasive aspergillosis. Pulmonary symptoms (eg, productive cough, high fever, dyspnea) are severe. Cutaneous *Rhizopus* infections have developed under occlusive dressings but more often result from trauma when the injured areas are contaminated with soil.

**Diagnosis**

- Examination of tissue samples for nonseptate hyphae

Diagnosis requires a high index of suspicion and painstaking examination of tissue samples for large nonseptate hyphae with irregular diameters and right-angle branching patterns; the examination must be thorough because much of the necrotic debris contains no organisms. For unclear reasons, cultures may be negative, even when hyphae are clearly visible in tissues. CT and x-rays often underestimate or miss significant bone destruction.

**Treatment**

- Control of underlying condition
- Amphotericin B
- Surgical debridement

Effective therapy requires that diabetes be controlled or, if at all possible, immunosuppression be reversed or deferoxamine be stopped.

IV amphotericin B must be used because azoles are ineffective, although recent evidence suggests that posaconazole with or without an echinocandin may be effective. Most experts use high doses of lipid formulations of amphotericin B (up to 10 to 20 mg/kg/day).

Complete surgical debridement of necrotic tissue is critical.

**Mycetoma**

(Maduromycosis; Madura Foot)

*Mycetoma* is a chronic, progressive local infection caused by fungi or bacteria and involving the feet, upper extremities, or back. Symptoms include tumefaction and formation of sinus tracts. Diagnosis is clinical, confirmed by microscopic examination of exudates and culture. Treatment includes antimicrobials, surgical debridement, and sometimes amputation.

Bacteria, primarily *Nocardia* sp and other actinomycetes, cause > one half of the cases. The remainder are caused by about 20 different fungal species. When caused by fungi, the lesions are sometimes called eumycetoma.

Mycetoma occurs mainly in tropical or subtropical areas, including the southern US, and is acquired when organisms enter through sites of local trauma on bare skin of the feet or on the extremities or backs of workers carrying contaminated vegetation or other objects. Men aged 20 to 40 are most often affected, presumably because of trauma incurred while working outdoors.

Infections spread through contiguous subcutaneous areas, resulting in tumefaction and formation of
multiple draining sinuses that exude characteristic grains of clumped organisms. Microscopic tissue reactions may be primarily suppurative or granulomatous depending on the specific causative agent. As the infection progresses, bacterial superinfections can develop.

Symptoms and Signs

The initial lesion may be a papule, a fixed subcutaneous nodule, a vesicle with an indurated base, or a subcutaneous abscess that ruptures to form a fistula to the skin surface. Fibrosis is common in and around early lesions. Tenderness is minimal or absent unless acute suppurative bacterial superinfection is present.

Infection progresses slowly over months or years, gradually extending to and destroying contiguous muscles, tendons, fascia, and bones. Neither systemic dissemination nor symptoms and signs suggesting generalized infection occur. Eventually, muscle wasting, deformity, and tissue destruction prevent use of affected limbs. In advanced infections, involved extremities appear grotesquely swollen, forming a club-shaped mass of cystic areas. The multiple draining and intercommunicating sinus tracts and fistulas in these areas discharge thick or serosanguineous exudates containing characteristic grains.

Diagnosis

- Examination and culture of exudates

Causative agents can be identified presumptively by gross and microscopic examination of grains from exudates, which contain irregularly shaped, variably colored, 0.5- to 2-mm granules. Crushing and culture of these granules provides definitive identification. Exudate specimens may yield multiple bacteria and fungi, some of which are potential causes of superinfections.

Treatment

- Antibacterial or antifungal drugs
- Sometimes surgery

Treatment may be required for > 10 yr. Death may result from bacterial superinfection and sepsis if treatment is neglected.

In infections caused by *Nocardia* (see p. 1242), sulfonamides and certain other antibacterial drugs, sometimes in combination, are used.

In infections caused by fungi, certain potential causative organisms may be at least partially sensitive to amphotericin B, itraconazole, or ketoconazole, but many are resistant to all antifungal drugs. Relapses occur after antifungal therapy in most patients, and many patients do not improve or worsen during treatment.

Surgical debridement is necessary, and limb amputation may be needed to prevent potentially fatal severe secondary bacterial infections.

**Paracoccidioidomycosis**

(South American Blastomycosis)

**Paracoccidioidomycosis** is progressive mycosis of the lungs, skin, mucous membranes, lymph nodes, and internal organs caused by *Paracoccidioides brasiliensis*. Symptoms are skin ulcers, adenitis, and pain due to abdominal organ involvement. Diagnosis is clinical and microscopic, confirmed by culture. Treatment is with azoles (eg, itraconazole), amphotericin B, or sulfonamides.

Infections occur only in discrete foci in South and Central America, most often in men aged 20 to 50,
especially coffee growers of Colombia, Venezuela, and Brazil. Although a relatively unusual opportunistic infection, paracoccidioidomycosis sometimes occurs in immunocompromised patients, including those with AIDS. Although specific natural sites for *Paracoccidioides brasiliensis* remain undefined, it is presumed to exist in soil as a mold, with infection due to inhalation of conidia (spores produced by the mycelial form of the fungus). Conidia convert to invasive yeasts in the lungs and are assumed to spread to other sites via blood and lymphatics.

**Symptoms and Signs**

Most people who inhale conidia of *P. brasiliensis* do not become ill; illness, if it occurs, usually manifests as acute pneumonia, which may spontaneously resolve. Clinically apparent infections can become chronic and progressive but are not usually fatal. There are 3 patterns:

- **Mucocutaneous:** Infections most often involve the face, especially at the nasal and oral mucocutaneous borders. Yeasts are usually abundantly present within pinpoint lesions throughout granular bases of slowly expanding ulcers. Regional lymph nodes enlarge, become necrotic, and discharge necrotic material through the skin.

- **Lymphatic:** Cervical, supraclavicular, or axillary nodes enlarge but are painless.

- **Visceral:** Typically, focal lesions cause enlargement mainly of the liver, spleen, and abdominal lymph nodes, sometimes causing abdominal pain.

Infections may be mixed, involving combinations of all 3 patterns.

**Diagnosis**

Clinical findings suggest the diagnosis. Culture is diagnostic, although observation of large (often > 15 μm) yeasts that form characteristic multiple buds (pilot wheel) in specimens provides strong presumptive evidence.

**Treatment**

- **Antifungal drugs**

  Azoles are highly effective. Oral itraconazole is generally considered the drug of choice, primarily because it costs less than other azoles that are available in endemic areas. IV amphotericin B can also eliminate the infection and is often used in very severe cases. Sulfonamides, which are widely used in some countries because they are inexpensive, can suppress growth and cause lesions to regress but are not curative.

**Pigmented Fungi**

(Chromoblastomycosis; Chromomycosis; Phaeohyphomycosis; Verrucous Dermatitis)

Chromoblastomycosis is a cutaneous infection caused by dematiaceous (pigmented) fungi. Symptoms are ulcerating nodules on exposed body parts; extracutaneous infections (termed phaeohyphomycosis) in subcutaneous tissues, sinuses, the brain, and other tissues may occur. Diagnosis is by appearance, histopathology, and culture. Treatment is with itraconazole, another azole, or flucytosine and surgical excision.

Chromoblastomycosis is a cutaneous infection affecting normal, immunocompetent people mostly in tropical or subtropical areas; it is characterized by formation of papillomatous nodules that tend to ulcerate. Pigmented fungi have been increasingly recognized as opportunists affecting immunosuppressed patients. These infections are caused by many kinds of dark, melanin-pigmented dematiaceous fungi including species of *Bipolaris, Cladophialophora, Cladosporium, Drechslera, Exophiala, Fonsecaea, Phialophora, Xylohypha, Ochronosis, Rhinocladiella, Scolecobasidium,* and *Wangiella.*
Symptoms and Signs

Most infections begin on the foot or leg, but other exposed body parts may be infected, especially where the skin is broken. Early small, itchy, enlarging papules may resemble dermatophytosis (ringworm). These papules extend to form dull red or violaceous, sharply demarcated patches with indurated bases. Several weeks or months later, new lesions, projecting 1 to 2 mm above the skin, may appear along paths of lymphatic drainage. Hard, dull red or grayish cauliflower-shaped nodular projections may develop in the center of patches and gradually extend to cover extremities for up to 4 to 15 yr. Lymphatics may be obstructed, itching may persist, and secondary bacterial superinfections may develop, causing ulcerations and occasionally septicemia.

Extracutaneous infections (phaeohyphomycosis) may occur. They include invasive sinusitis, sometimes with bone necrosis, as well as subcutaneous nodules or abscesses, keratitis, lung masses, osteomyelitis, mycotic arthritis, intramuscular abscess, endocarditis, brain abscess, and chronic meningitis.

Dematiaceous fungi only rarely cause fatal infections in patients who have normal, intact host defense mechanisms. Life-threatening illnesses occur more often in immunocompromised patients.

Diagnosis

• Culture

• Sometimes tissue staining

Late chromoblastomycosis lesions have a characteristic appearance, but early lesions may be mistaken for dermatophytoses. Phaeohyphomycosis must be distinguished from myriad other infectious and noninfectious conditions by histopathology and culture.

Dematiaceous fungi are frequently discernible in tissue specimens stained with conventional hematoxylin and eosin; they appear as septate, brownish bodies, reflecting their natural melanin content. Fontana-Masson staining for melanin confirms their presence. Culture is needed to identify the causative species.

Treatment

• Itraconazole, sometimes with flucytosine

• Often surgery

Itraconazole is the most effective drug, although not all patients respond. Flucytosine is sometimes added to prevent relapse. Fluconazole seldom causes lesions to regress, and amphotericin B is ineffective. The role of voriconazole and posaconazole has not yet been determined.

Many cases require surgical excision for cure.

Sporotrichosis

Sporotrichosis is a cutaneous infection caused by the saprophytic mold *Sporothrix schenckii*. Pulmonary and hematogenous involvement is uncommon. Symptoms are cutaneous nodules that spread via lymphatics and break down into abscesses and ulcers. Diagnosis is by culture. Treatment is with itraconazole or amphotericin B.

*Sporothrix schenckii* resides on rose or barberry bushes, in sphagnum moss, and in other mulches. Horticulturists, gardeners, farm laborers, and timber workers are most often infected, typically after minor trauma involving contaminated material. In contrast to the other dimorphic fungi, *S. schenckii* is not usually inhaled but enters the body through small cuts and abrasions in the skin.

Symptoms and Signs
Lymphocutaneous infections are most common. They characteristically involve one hand and arm, although they can occur anywhere on the body; primary lesions may occur on exposed surfaces of the feet or face.

A primary lesion may appear as a small, nontender papule or, occasionally, as a slowly expanding subcutaneous nodule that eventually becomes necrotic and sometimes ulcerates. Typically, a few days or weeks later, a chain of draining lymph nodes begins to enlarge slowly but progressively, forming movable subcutaneous nodules. Without treatment, overlying skin reddens and may later necrose, sometimes causing an abscess, ulceration, and bacterial superinfection. Systemic symptoms and signs of infection are notably absent.

Lymphocutaneous sporotrichosis is chronic and indolent; it is potentially fatal only if bacterial superinfections cause sepsis.

Rarely, in patients without primary lymphocutaneous lesions, hematogenous spread leads to indolent infections of multiple peripheral joints, sometimes bones, and, less often, genitals, liver, spleen, kidneys, or meninges. Equally rare is chronic pneumonia caused by inhaling spores and manifested by localized infiltrates or cavities, most often in patients with preexisting chronic lung disease.

**Diagnosis**

- **Culture**

The illness must be differentiated from local infections caused by *Mycobacterium tuberculosis*, atypical mycobacteria, *Nocardia*, or other organisms. During the early, nondisseminated stage, the primary lesion is sometimes misdiagnosed as a spider bite. Culture of tissue from the active infection site provides the definitive diagnosis. *S. schenckii* yeasts can be seen only rarely in fixed-tissue specimens, even with special staining. Serologic tests are not available.

**Treatment**

- **Itraconazole**

Oral itraconazole, given for 3 to 6 mo, is the treatment of choice. Severe infection and infection in patients with AIDS require IV amphotericin B. AIDS patients may require lifelong maintenance therapy with itraconazole. Voriconazole and posaconazole may have a role.

**Miscellaneous Opportunistic Fungi**

Many yeasts and molds can cause opportunistic, even life-threatening infections in immunocompromised patients. These infections only rarely affect immunocompetent people. Yeasts tend to cause fungemia as well as focal involvement of skin and other sites.

*Trichosporon beigelii* (most now known as *T. asahii*) and *Blastoschizomyces capitatus* particularly affect neutropenic patients.

*Malassezia furfur* fungemia typically affects infants and debilitated adults receiving lipid-containing IV hyperalimentation infusions.

*Penicillium marneffei* was recognized as an opportunistic invader in Southeast Asian patients with AIDS, and cases have been recognized in the US. *P. marneffei* skin lesions may resemble molluscum contagiosum.

Especially in neutropenic patients, various environmental molds, including species of *Fusarium* and *Scedosporium*, both of which are becoming more frequent, can cause focal vasculitic lesions mimicking invasive aspergillosis.
Specific diagnosis requires culture and species identification and is crucial because not all of these organisms respond to any single antifungal drug. For example, *Scedosporium* sp are typically resistant to amphotericin B. Optimal regimens of antifungal therapy for each member of this group of fungal opportunists must be defined.
Chapter 143. Approach to Parasitic Infections

Introduction

Parasitic infections are responsible for substantial morbidity and mortality worldwide. They are prevalent in Central and South America, Africa, and Asia. They are much less common in Australia, Canada, Europe, Japan, New Zealand, and the US. By far, the greatest impact is on residents of developing areas, but parasitic infections are encountered in developed countries among immigrants and travelers returning from endemic regions and, on occasion, even among residents who have not traveled, particularly those with AIDS or other causes of immunodeficiency.

Many parasitic infections are spread through fecal contamination of food or water. They are most frequent in impoverished areas where sanitation and hygiene are poor. Some parasites, such as the hookworm, can enter the skin during contact with infected dirt or, in the case of schistosomes, with freshwater. Others, such as malaria, are transmitted by arthropod vectors. Rarely, parasites are transmitted via blood transfusions or shared needles or congenitally from mother to fetus.

Some parasites are endemic in the US and other developed countries. Examples are the pinworm, Enterobius vermicularis, Trichomonas vaginalis, toxoplasmosis, and enteric parasites such as Giardia intestinalis (lamblia) and Cryptosporidium spp.

Taxonomically, parasites can be divided into 2 major groups:

• Protozoa

• Helminths (worms)

The characteristics of protozoan and helminthic infections vary in important ways.

Protozoa: Protozoa are single-celled organisms that multiply by simple binary division (see Chs. 147 and 148). Protozoa can multiply in their human hosts, increasing in number to cause overwhelming infection. With rare exceptions, protozoan infections do not cause eosinophilia.

Helminths: Helminths are multicellular and have complex organ systems. Helminths can be further divided into

• Roundworms (nematodes—see Ch. 144)

• Flatworms (platyhelminthes), which include tapeworms (cestodes—see Ch. 146)

• Flukes (trematodes—see Ch. 145)

Some parasites have adapted to living in the lumen of the intestine where conditions are anaerobic; others reside in blood or tissues in aerobic conditions.

In contrast to protozoa, helminths do not multiply in humans but can elicit eosinophilic responses when they migrate through tissue. Most helminths have complex life cycles that involve substantial time outside their human hosts. Exceptions are Strongyloides stercoralis, Capillaria philippinensis, and Hymenolepis nana, which can increase in number because of autoinfection. In strongyloidiasis, autoinfection can result in life-threatening, disseminated hyperinfections in immunosuppressed people, particularly those taking corticosteroids.

The severity of helminthic infections usually correlates with the worm burden, but there are exceptions as when a single ascaris causes life-threatening pancreatitis by migrating into the pancreatic duct. The worm burden depends on the degree of environmental exposure, parasite factors, and the host's genetically determined immune responses. If a person moves from an endemic area, the number of adult worms diminishes over time. Although a few parasites (eg, Clonorchis sinensis) can survive for decades, many
species have life spans of only a few years or less. More information about parasitic infections is available at the CDC's Division of Parasitic Diseases.

**Diagnosis**

Methods for the diagnosis of specific parasitic infections are discussed in the chapters to follow and are summarized in Table 143-1.

Parasitic infections should be considered in the differential diagnosis of clinical syndromes in residents of or travelers to areas where sanitation and hygiene are poor or where vector-borne diseases are endemic. For example, fever in the returning traveler suggests the possibility of malaria. Experience indicates that immigrants from developing areas to developed countries who return home to visit friends and relatives are at particular risk. They frequently do not seek or cannot afford pretravel advice on disease prevention and are more likely to enter high-risk settings than tourists who stay at resort facilities. Although less frequent, the possibility of an endemic or imported parasitic infection must also be considered in residents of developed countries who present with suggestive clinical syndromes, even if they have not traveled.

Historical information, physical findings, and laboratory data may also suggest specific parasitic infections. For example, eosinophilia is common when helminths migrate through tissue and suggests a parasitic infection in an immigrant or returning traveler.

Physicians with expertise in parasitic infections and tropical medicine are available for consultation at many major medical centers, travel clinics, and public health facilities.

"Laboratory Identification of Parasites of Public Health Concern" provides detailed descriptions of diagnostic methods and is available from the Centers for Disease Control and Prevention (CDC) at www.dpd.cdc.gov/dpdx.

**GI tract parasites:** Various stages of protozoa and helminths that infect the GI tract are typically shed in the stool. Routine detection requires examination of stool specimens, preferably 3 collected on different days, because shedding can be sporadic. With some parasites, relatively sensitive and specific assays are available to detect antigens in stool.

Freshly passed stools uncontaminated with urine, water, dirt, or disinfectants should be sent to the laboratory within 1 h; unformed or watery stools are most likely to contain motile trophozoites. If not examined immediately, stools should be refrigerated, but not frozen. Portions of fresh stools should also be emulsified in fixative to preserve GI protozoa. Concentration techniques can be used to improve sensitivity. Anal cellophane tape or swabs may collect pinworm or tapeworm eggs. If strongyloidiasis is suspected, fresh stool should be smeared on an agar plate and incubated to identify the tracks of migrating larvae. Antibiotics, x-ray contrast material, purgatives, and antacids can hinder detection of ova and parasites for several weeks. Serologic assays, antigen detection tests (eg, for *Giardia intestinalis*, *Cryptosporidium* sp, or *Entamoeba histolytica*), or PCR testing may aid in diagnosis (see Table 143-2). Sensitivity of stool examinations for ova and parasites is low enough that when clinical suspicion is strong, empirical treatment may be given.

**Sigmoidoscopy or colonoscopy** should be considered when routine stool examinations are negative and amebiasis is suspected in patients with persistent GI symptoms. Sigmoidoscopic specimens should be collected with a curet or spoon (cotton swabs are not suitable) and processed immediately for microscopy. Duodenal aspirates or small-bowel biopsy specimens may be necessary for diagnosis of such infections as cryptosporidiosis and microsporidiosis.

[Table 143-2. Serologic and Molecular Tests for Parasitic Infection]
Serologic testing for parasitic infections: Some parasites can be detected by serologic tests (see Table 143-2).

Treatment

Advice for treating parasitic infections is available from experts at major medical and public health centers and travel clinics, in textbooks of infectious diseases and tropical medicine, and in summary form from *The Medical Letter on Drugs and Therapeutics*. Drugs for unusual parasitic infections can be obtained from the manufacturer or from the CDC Drug Service.

Prevention

Despite substantial investment and research, no vaccines are yet available for prevention of human parasitic infections. Prevention is based on avoidance strategies.

Transmission of most intestinal parasites can be prevented by

• Sanitary disposal of feces

• Adequate cooking of food

• Provision of purified water

For the international traveler, the best advice is "cook it, boil it, peel it, or forget it." When followed, these measures substantially reduce the risk of intestinal parasitic infections as well as risk of bacterial and viral gastroenteritis. Meat, particularly pork, and fish, particularly freshwater varieties, should be thoroughly cooked before ingestion. Other safety measures include removing litter boxes from areas where food is prepared to prevent toxoplasmosis. People should not swim in freshwater lakes, streams, or rivers in areas where schistosomiasis is endemic or walk barefoot in areas where hookworms are found.

The risk of malaria and many other vector-borne diseases can be decreased by wearing long-sleeved shirts and pants and applying diethyltoluamide (DEET)-containing insect repellants to exposed skin and permethrin to clothing. Window screens, air-conditioning, and mosquito nets impregnated with permethrin or other insecticides provide further protection. In addition, prophylactic antimalarial drugs should be taken by those traveling in endemic regions.

Travelers to rural Latin America should not sleep in adobe dwellings where reduviid bugs can transmit Chagas disease. In Africa, travelers should avoid bright colors and wear long-sleeved shirts and pants to avoid tsetse flies in regions where African sleeping sickness occurs.

Country-specific recommendations for travel are available from the CDC web site (www.cdc.gov/travel) and in *CDC Health Information for International Travel 2010*. 
Chapter 144. Nematodes (Roundworms)

**Introduction**

Nematodes are nonsegmented cylindric worms ranging from 1 mm to 1 m in length. Nematodes have a body cavity, distinguishing them from tapeworms and flukes. Depending on the species, different stages in the life cycle are infectious to humans. Hundreds of millions of humans are infected with nematodes; the most common are *Ascaris*, hookworms, and *Trichuris*.

**Angiostrongyliasis**

Angiostrongyliasis is infection with larvae of worms of the genus *Angiostrongylus*; intestinal symptoms or eosinophilic meningitis occurs depending on the infecting species.

*Angiostrongylus* are parasites of rats. Excreted larvae are taken up by intermediate hosts (snails and slugs) and transport hosts (certain crabs and freshwater shrimp). Human infection is acquired by ingestion of raw or undercooked snails or slugs or transport hosts; it is unclear whether larval contamination of vegetables (eg, in slime from snails or slugs that crawl on the food) can cause infection.

*A. cantonensis* infection occurs predominantly in Southeast Asia and the Pacific Basin, although infection has been reported elsewhere. The larvae migrate from the GI tract to the meninges, where they cause eosinophilic meningitis, with fever, headache, and meningismus. Occasionally, ocular invasion occurs.

*A. costaricensis* infection occurs in the Americas. Adult worms reside in arterioles of the ileocecal area, and eggs can be released into the intestinal tissues, resulting in local inflammation with abdominal pain, vomiting, and fever. Abdominal angiostrongyliasis mimics appendicitis; a painful right lower quadrant mass may develop.

Diagnosis is suspected based on a history of ingesting potentially contaminated material. Patients with meningeal findings require lumbar puncture; CSF shows eosinophilia, but parasites are rarely visible. Diagnosis of GI infection is difficult because larvae and eggs are not present in stool; however, if surgery is done (eg, for suspected appendicitis), eggs and larvae can be identified in tissues removed during surgery.

*A. cantonensis* meningitis is treated with analgesics, corticosteroids, and removal of CSF at frequent intervals to reduce CNS pressure. Most patients have a self-limited course and recover completely.

Treatment of *A. costaricensis* infection is controversial. Anthelmintics do not appear to be effective and may be harmful because of the inflammatory response provoked by antigen released from dead parasites.

**Anisakiasis**

Anisakiasis is infection with larvae of worms of the genus *Anisakis* and related genera such as *Pseudoterranova*. Infection is acquired by eating raw or poorly cooked saltwater fish; larvae burrow into the mucosa of the GI tract, causing discomfort.

*Anisakis* is a parasite that resides in the GI tract of marine mammals. Excreted eggs hatch into free-swimming larvae, which are ingested by fish and squid; human infection is acquired by ingestion of these intermediate hosts in a raw or undercooked state. Thus, infection is particularly common in locations and cultures in which raw fish is traditionally consumed. Larvae burrow into the stomach and small bowel.

Symptoms typically include abdominal pain, nausea, and vomiting; intestinal infection may create an inflammatory mass causing symptoms resembling Crohn's disease.

**Diagnosis**
• Upper endoscopy

Diagnosis is usually made by upper endoscopy; stool examination is unhelpful, but a serologic test is available in some countries. Infection typically resolves spontaneously after several weeks; rarely, it persists for months. Endoscopic removal of the larvae is curative.

Treatment

• Albendazole

Treatment with albendazole 400 mg po as a single dose may be effective. Cooking to > 50° C (> 122° F) or freezing for > 24 h destroys larvae; they may resist pickling, salting, and smoking.

Ascariasis

Ascariasis is infection with *Ascaris lumbricoides*. Light infections may be asymptomatic. Early symptoms are pulmonary (cough, wheezing); later symptoms are GI, with cramps or abdominal pain due to obstruction of GI lumina (intestines or biliary or pancreatic ducts) by adult worms. Chronically infected children may develop undernutrition. Diagnosis is by identifying eggs or adult worms in stool, adult worms that migrate from the nose or mouth, or larvae in sputum during the pulmonary migration phase. Treatment is with albendazole, mebendazole, or pyrantel pamoate.

Pathophysiology

Ingested eggs hatch in the duodenum, and the resulting larvae penetrate the wall of the small bowel and migrate via the portal circulation through the liver to the heart and lungs. Larvae lodge in the alveolar capillaries, penetrate alveolar walls, and ascend the bronchial tree into the oropharynx. They are swallowed and return to the small bowel, where they develop into adult worms, which mate and release eggs into the stool. The life cycle is completed in about 2 to 3 mo; adult worms live 1 to 2 yr.

A tangled mass of worms resulting from heavy infection can obstruct the bowel, particularly in children. Aberrantly migrating individual adult worms occasionally obstruct the biliary or pancreatic ducts, causing cholecystitis or pancreatitis; cholangitis, liver abscess, and peritonitis are less common. Fever due to other illnesses or certain drugs (eg, albendazole, mebendazole, tetrachloroethylene) may trigger aberrant migration.

Etiology

Ascariasis occurs worldwide. It is concentrated in tropical and subtropical areas with poor sanitation, but transmission also occurs in rural areas of the southeastern US. Ascariasis is the most prevalent intestinal helminth infection in the world. Current estimates suggest that > 1.3 billion people are infected, and about 20,000 infected people (mostly children) die each year of bowel or biliary obstruction. An estimated 4 million people in the US are infected.

Symptoms and Signs

Larvae migrating through the lungs may cause cough, wheezing, and occasionally hemoptysis or other respiratory symptoms. Adult worms in small numbers usually do not cause GI symptoms, although passage of an adult worm by mouth or rectum may bring an otherwise asymptomatic patient to medical attention. Bowel or biliary obstruction causes cramping abdominal pain, nausea, and vomiting. Jaundice is uncommon. Even moderate infections can lead to undernutrition in children. The pathophysiology is unclear and may include competition for nutrients, impairment of absorption, and depression of appetite.

Diagnosis

• Microscopic examination of stool
Diagnosis is by microscopic detection of eggs in stools. Occasionally, larvae can be found in sputum during the pulmonary phase.

Eosinophilia can be marked while larvae migrate though the lungs but usually subsides later when adult worms reside in the intestine. Chest x-ray during the pulmonary phase may show infiltrates (Loffler's syndrome).

**Treatment**

- **Abendazole**

  All infections should be treated. Albendazole 400 mg po once, mebendazole 100 mg po bid for 3 days, or ivermectin 150 to 200 μg/kg once is effective. Albendazole, mebendazole, and ivermectin should not be used during pregnancy. Nitazoxanide is effective for mild *Ascaris* infections but less so for heavy infections. Piperazine, once widely used, has been replaced by less toxic alternatives.

Obstructive complications may respond to anthelmintic therapy or require surgical or endoscopic extraction of adult worms.

**Prevention**

Prevention requires adequate sanitation. Uncooked or unwashed vegetables should be avoided in areas where human feces are used as fertilizer.

**Dracunculiasis**

*(Guinea Worm Disease; Fiery Serpent)*

**Dracunculiasis is infection with Dracunculus medinensis. Symptoms are a painful, inflamed skin lesion, which contains an adult worm, and debilitating arthritis. Diagnosis is by inspection. Treatment is slow removal of the adult worm.**

Twenty years ago, dracunculiasis was endemic in much of tropical Africa, Yemen, India, and Pakistan. Today, because of international efforts to interrupt transmission, infection occurs mainly within a narrow belt of African countries and Yemen.

**Pathophysiology**

Humans become infected by drinking water containing infected microcrustaceans (copepods). The larvae are released, penetrate the bowel wall, and mature in the abdominal cavity into adult worms in about 1 yr. After mating, the male dies, and the gravid female migrates through subcutaneous tissues, usually to the distal lower extremities. The cephalic end of the worm produces an indurated papule that vesiculates and eventually ulcerates. On contact with water, a loop of the worm's uterus prolapses through the skin and discharges motile larvae. Worms that do not reach the skin die and disintegrate or become calcified. Larvae are ingested by copepods.

In most endemic areas, transmission is seasonal and each infectious episode lasts about 1 yr.

**Symptoms and Signs**

Infection is initially asymptomatic; symptoms usually develop when the worm erupts. Local symptoms include intense itching and a burning pain at the site of the skin lesion. Urticaria, erythema, dyspnea, vomiting, and pruritus are thought to reflect allergic reactions to worm antigens. If the worm is broken during expulsion or extraction, a severe inflammatory reaction ensues with disabling pain. Symptoms subside and the ulcer heals once the adult worm is expelled. In about 50% of cases, secondary bacterial infections occur along the track of the emerging worm. Chronic sequelae include fibrous ankylosis of joints and contraction of tendons.
Diagnosis

- Clinical evaluation

Diagnosis is obvious once the white, filamentous adult worm appears at the cutaneous ulcer. Calcified worms can be localized with x-ray examination; they have been found in Egyptian mummies. Serodiagnostic tests are not specific.

Treatment

- Manual removal

Treatment consists of slow removal of the adult worm over days to weeks by rolling it on a stick. Surgical removal under local anesthesia is an option but is seldom available in endemic areas. There are no effective drugs for this disease; the beneficial effect of metronidazole (250 mg tid for 10 days) has been ascribed to the drug's anti-inflammatory and antibacterial properties rather than to anthelmintic effects.

Prevention

Filtering drinking water through a piece of cheesecloth, chlorination, or boiling effectively protects against dracunculiasis.

Filarial Nematode Infections

Threadlike adult filarial worms reside in lymphatic or subcutaneous tissues. Gravid females produce live offspring (microfilariae) that circulate in blood or migrate through tissues. When ingested by a suitable bloodsucking insect (mosquitoes or flies), microfilariae develop into infective larvae that are inoculated or deposited in the skin of the next host during the insect bite. Life cycles of all filarial worms are similar except for the site of infection. Only a few filarial species infect humans.

Subcutaneous filariasis is caused by *Loa loa* (the African eye worm) and *Onchocerca volvulus*.

Lymphatic filariasis is caused by *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*.

Dirofilariasis

(Dog Heartworm Infection)

*Dirofilaria immitis* is the dog heartworm, which is transmitted to humans by infected mosquitoes.

Symptomatic human infection is very rare, but larvae may become encapsulated in infarcted lung tissue and produce well-defined pulmonary nodules.

Patients may have chest pain, cough, and occasionally hemoptysis. Many patients remain asymptomatic, and a pulmonary nodule, which may suggest a tumor, is discovered during routine chest x-ray.

Diagnosis is by histologic examination of a surgical specimen. No treatment is indicated in humans; infection is self-limited.

Loiasis

Loiasis is infection with *Loa loa*. Symptoms include localized angioedema (Calabar swellings) and subconjunctival migration of adult worms. Diagnosis is by detecting microfilariae in peripheral blood or seeing worms migrating across the eye. Treatment is with diethylcarbamazine.

Loiasis is confined to the rain forest belt of western and central Africa. Humans are the only known
natural reservoir for this parasite.

*Loa loa* microfilariae are transmitted by day-biting tabanid flies (*Chrysops* [deerfly or horsefly]). Microfilariae mature to adult worms in the subcutaneous tissues of the human host; females are 40 to 70 mm long, and males are 30 to 34 mm long. The adults produce more microfilariae. Adults migrate in subcutaneous tissues and the eye, and microfilariae circulate in blood. Flies become infected when they ingest blood from a human host during the day (when microfilaremia levels are the highest).

Occasionally, infection causes cardiomyopathy, nephropathy, or encephalitis.

**Symptoms and Signs**

Infection produces areas of angioedema (Calabar swellings) that develop anywhere on the body but predominantly on the extremities; they are presumed to reflect hypersensitivity reactions to allergens released by migrating adult worms. In native residents, swellings usually last 1 to 3 days but are more frequent and severe in visitors. Worms may also migrate subconjunctivally across the eyes. This migration may be unsettling, but residual eye damage is uncommon.

Nephropathy generally manifests as proteinuria with or without mild hematuria and is believed to be due to immune complex deposition. Encephalopathy is usually mild, with vague CNS symptoms.

**Diagnosis**

- Microscopic examination of blood samples

Microscopic detection of microfilariae in peripheral blood establishes the diagnosis. Blood samples should be drawn around noontime, when microfilaremia levels are the highest. Serologic tests for antibodies do not differentiate *Loa loa* from other filarial nematode infections.

**Treatment**

- Diethylcarbamazine

Diethylcarbamazine (DEC) is the only drug that kills microfilariae and adult worms. Patients with microfilariae in the blood are given DEC 50 mg po on day 1, 50 mg po tid on day 2, 100 mg tid on day 3, then 2 mg/kg tid on days 4 through 14. A single dose of 6 mg/kg has been used in mass treatment programs. Multiple courses may be necessary before resolution is complete.

DEC transiently exacerbates proteinuria and, in heavily infected patients, may trigger encephalopathy, leading to coma and death. Such patients may benefit from apheresis or initial treatment with albendazole, and multiple courses of therapy may be necessary. Ivermectin has also been used to reduce microfilaremia, but albendazole is preferred because its onset of action is slower and risk of precipitating encephalopathy is lower.

**Prevention**

DEC 300 mg po once/wk can be used to prevent infection. Using insect repellents (including permethrin-impregnated clothing) and wearing long-sleeved and long-legged clothing may reduce the number of bites by infected flies. Because the flies are day-biting, mosquito (bed) nets do not help.

**Bancroftian and Brugian Lymphatic Filariasis**

Lymphatic filariasis is infection with any of 3 species of *Filarioidea*. Acute symptoms include fever, lymphadenitis, lymphangitis, funiculitis, and epididymitis. Chronic symptoms include abscesses, hyperkeratosis, polyarthritis, hydroceles, lymphedema, and elephantiasis. Tropical pulmonary eosinophilia with bronchospasm, fever, and pulmonary infiltrates is another manifestation of infection. Diagnosis is by detection of microfilariae in blood, ultrasound visualization of adult worms, or serologic testing. Treatment is with diethylcarbamazine;

1500
antibiotics are used for complicating bacterial cellulitis.

Etiology

Lymphatic filariasis is caused by *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*. Transmission is by mosquitoes. Infective larvae from the mosquito migrate to the lymphatics, where they develop into threadlike adult worms within 6 to 12 mo. Females are 80 to 100 mm long; males are about 40 mm long. Gravid adult females produce microfilariae that circulate in blood.

Bancroftian filariasis is present in tropical and subtropical areas of Africa, Asia, the Pacific, and the Americas, including Haiti. Brugian filariasis is endemic in South and Southeast Asia. Current estimates suggest that about 120 million people are infected.

Symptoms and Signs

Infection can result in microfilaremia without overt clinical manifestations. Symptoms and signs are caused primarily by adult worms. Microfilaremia gradually disappears after people leave the endemic area.

**Acute inflammatory filariasis** consists of 4- to 7-day episodes (often recurrent) of fever and inflammation of lymph nodes with lymphangitis (termed acute adenolymphangitis [ADL]) or acute epididymitis and spermatic cord inflammation. Localized involvement of a limb may cause an abscess that drains externally and leaves a scar. ADL is often associated with secondary bacterial infections. ADL episodes usually precede onset of chronic disease by ≥ 2 decades. Acute filariasis is more severe in previously unexposed immigrants to endemic areas than in native residents.

**Chronic filarial disease** develops insidiously after many years. In most patients, asymptomatic lymphatic dilation occurs, but chronic inflammatory responses to adult worms and secondary bacterial infections may result in chronic lymphedema of the affected body area or in scrotal hydroceles. Chronic pitting lymphedema of a lower extremity can progress to elephantiasis. Increased local susceptibility to bacterial and fungal infections contributes to the development of elephantiasis. Other forms of chronic filarial disease are caused by disruption of lymphatic vessels or aberrant drainage of lymph fluid, leading to chyluria and chyloceles.

**Extralymphatic signs** include chronic microscopic hematuria and proteinuria and mild polyarthritis, all presumed to result from immune complex deposition.

**Tropical pulmonary eosinophilia** (TPE) is an uncommon manifestation with recurrent bronchospasm, transitory lung infiltrates, low-grade fever, and marked eosinophilia. It is most likely due to hypersensitivity reactions to microfilariae. Chronic TPE can lead to pulmonary fibrosis.

Diagnosis

- Microscopic examination of blood samples

Microscopic detection of microfilariae in blood establishes the diagnosis. Filtered or centrifuged concentrates of blood are more sensitive than thick blood films. Blood samples must be obtained when microfilaremia peaks—at night where *W. bancrofti* is endemic, but during the day in many Pacific islands where *B. malayi* and *B. timori* occur. Viable adult worms can be visualized in dilated lymphatics by ultrasonography; their movement has been called the filarial dance.

A rapid-format immunochromatographic antigen test specific for *W. bancrofti* has recently been evaluated in the field. Antibody detection is of limited value; there is substantial antigenic cross-reactivity between filariae and other helminths, and a positive serologic test does not distinguish between past and current infection. PCR-based assays for DNA of *W. bancrofti* and *B. malayi* are available in research settings.

Treatment

- **Diethylcarbamazine**
Optimal treatment is uncertain. Diethylcarbamazine (DEC) kills microfilariae and a variable proportion of adult worms. The DEC dose in patients with heavy microfilaremia is 50 mg po on day 1, 50 mg tid on day 2, 100 mg tid on day 3, then 2 mg/kg tid on days 4 to 14. A single dose of albendazole (400 mg po) with either ivermectin (200 μg/kg po) or DEC (6 mg/kg) rapidly reduces microfilaremia levels, but ivermectin does not kill adult worms.

Also, doxycycline has been given long-term (eg, 8 wk). Doxycycline kills Wolbachia endosymbiont bacteria within filaria, leading to death of the worms.

Acute attacks of ADL usually resolve spontaneously, although antibiotics may be required to control secondary bacterial infections. Whether DEC therapy prevents or lessens chronic lymphedema remains controversial.

Chronic lymphedema requires meticulous skin care, including use of systemic antibiotics to treat secondary bacterial infections; these antibiotics may slow or prevent progression to elephantiasis. Conservative measures such as elastic bandaging of the affected limb reduce swelling. Surgical decompression using nodal-venous shunts to improve lymphatic drainage offers some long-term benefit in extreme cases of elephantiasis. Massive hydroceles can also be managed surgically.

TPE responds to DEC (2 mg/kg tid for 12 to 21 days), but relapses occur in up to 25% of patients and require additional courses of therapy.

Prevention

Avoiding mosquito bites in endemic areas is the best protection (eg, by using diethyltoluamide [DEET], permethrin-impregnated clothing, and bed nets). Chemoprophylaxis with DEC or combinations of antifilarial drugs (ivermectin/albendazole or ivermectin/DEC) can suppress microfilaremia and thereby reduce transmission of the parasite by mosquitoes in endemic communities. DEC has even been used as an additive to table salt in some endemic areas.

Onchocerciasis

(River Blindness)

Onchocerciasis is infection with the filarial nematode Onchocerca volvulus. Symptoms are subcutaneous nodules, pruritus, adenopathy, lymphatic obstruction, chronic skin disease, and eye lesions that may lead to blindness. Diagnosis is by finding microfilariae in skin snips, the cornea, or the anterior chamber of the eye; identifying adult worms in subcutaneous nodules; or using PCR or DNA probes. Treatment is with ivermectin.

Pathophysiology

Onchocerciasis is spread by blackflies (Simulium sp) that breed in swiftly flowing streams (hence, the term river blindness). Infective larvae inoculated into the skin during the bite of a blackfly develop into adult worms in 12 to 18 mo. Adult female worms may live up to 15 yr in subcutaneous nodules. Females are 33 to 50 cm long; males are 19 to 42 mm long. Mature female worms produce microfilariae that migrate mainly through the skin and invade the eyes.

Etiology

About 18 million people are infected; about 270,000 are blind and an additional 500,000 are visually impaired. Onchocerciasis is the 2nd leading cause of blindness worldwide (after trachoma). Onchocerciasis is most common in tropical and sub-Saharan regions of Africa. Small foci exist in Yemen, southern Mexico, Guatemala, Ecuador, Colombia, Venezuela, and the Brazilian Amazon. Blindness due to onchocerciasis is fairly rare in the Americas.

Symptoms and Signs
Onchocerciasis typically affects

• Skin (nodules, dermatitis)

• Eyes

**Nodules:** The subcutaneous (or deeper) nodules (onchocercoma) that contain adult worms may be visible or palpable but are otherwise asymptomatic. They are composed of inflammatory cells and fibrotic tissue in various proportions. Old nodules may caseate or calcify.

**Dermatitis:** Onchocercal dermatitis is caused by the microfilarial stage of the parasite. Intense pruritus may be the only symptom in lightly infected people. Skin lesions usually consist of a nondescript maculopapular rash with secondary excoriations, scaling ulcerations and lichenification, and mild to moderate lymphadenopathy. Premature wrinkling, skin atrophy, enlargement of inguinal or femoral nodes, lymphatic obstruction, patchy hypopigmentation, and transitory localized areas of edema and erythema can occur.

Onchocercal dermatitis is generalized in most patients, but a localized and sharply delineated form of eczematous dermatitis with hyperkeratosis, scaling, and pigment changes (Sowdah) is common in Yemen and Saudi Arabia.

**Eye disease:** Ocular involvement ranges from mild visual impairment to complete blindness. Lesions of the anterior portion of the eye include

• Punctate (snowflake) keratitis (an acute inflammatory infiltrate surrounding dying microfilariae that resolves without causing permanent damage)

• Sclerosing keratitis (an ingrowth of fibrovascular scar tissue that may cause subluxation of the lens and blindness)

• Anterior uveitis or iridocyclitis (which may deform the pupil)

Chorioretinitis, optic neuritis, and optic atrophy may also occur.

**Diagnosis**

• Microscopic examination of a skin sample

Demonstration of microfilariae in skin snips is the traditional diagnostic method (see Table 143-1 on p. 1337). Microfilariae may also be visible in the cornea and anterior chamber of the eye during slit-lamp examination. PCR-based methods to detect parasite DNA in skin snips may be more sensitive than standard techniques but are available only in research settings. Antibody detection is of limited value; there is substantial antigenic cross-reactivity among filaria and other helminths, and a positive serologic test does not distinguish between past and current infection. Palpable nodules (or deep nodules detected by ultrasonography or MRI) can be excised and examined for adult worms, but this procedure is rarely necessary.

**Treatment**

• Ivermectin

Ivermectin is given as a single oral dose of 150 μg/kg, repeated q 6 to 12 mo until patients are asymptomatic. Ivermectin reduces microfilariae in the skin and eyes and decreases production of microfilariae for many months. It does not appear to kill adult worms in standard regimens but inhibits microfilarial release from female worms. Adverse effects are qualitatively similar to those of diethylcarbamazine (DEC) but are much less common and less severe. DEC is no longer used for onchocerciasis because it can cause a severe hypersensitivity (Mazzotti) reaction, which can further
damage skin and eyes and lead to cardiovascular collapse.

Long-term use (eg, 6 wk) of doxycycline, which targets *Wolbachia* endosymbiont bacteria, with or without a single dose of ivermectin has produced long periods of amicrofilaremia.

**Prevention**

No drug has been shown to protect against infection with *O. volvulus*. However, annual or semiannual administration of ivermectin effectively controls disease and may decrease transmission. Surgical removal of accessible onchocercomas can also reduce skin microfilaria counts, but it has been replaced by ivermectin therapy.

*Simulium* bites can be minimized by avoiding fly-infested areas, by wearing protective clothing, and possibly by liberally applying insect repellents.

**Hookworm Infection**

*(Ancylostomiasis)*

**Ancylostomiasis** is infection with the hookworm *Ancylostoma duodenale* or *Necator americanus*. Symptoms include rash at the site of larval entry and sometimes abdominal pain or other GI symptoms during early infection. Later, iron deficiency may develop because of chronic blood loss. Hookworms are a major cause of iron deficiency anemia in endemic regions. Diagnosis is by finding eggs in stool. Treatment is with albendazole, mebendazole, or pyrantel pamoate.

**Pathophysiology**

Both hookworm species have similar life cycles. Eggs passed in the stool hatch in 1 to 2 days (if they are deposited in a warm, moist place on loose soil) and release rhabditiform larvae, which molt once to become slender filariform larvae in 5 to 10 days. The larvae can survive 3 to 4 wk if environmental conditions are favorable. Filariform larvae penetrate human skin when people walk barefoot on infested soil. The larvae reach the lungs via blood vessels, penetrate into pulmonary alveoli, ascend the bronchial tree to the epiglottis, and are swallowed. The larvae develop into adults in the small bowel; there, they attach to the wall, feeding on blood. Adult worms may live ≥ 2 yr.

Chronic blood loss leads to iron deficiency anemia. Development of anemia depends on worm burden and the amount of absorbable iron in the diet.

**Etiology**

The estimated prevalence of hookworm infection is about 1 billion, mostly in developing areas. Both *A. duodenale* and *N. americanus* occur in Africa, Asia, and the Americas. Only *A. duodenale* occurs in the Middle East, North Africa, and southern Europe. *N. americanus* predominates in the Americas and Australia; it was once widely distributed in the southern US and is still endemic on islands of the Caribbean and in Central and South America.

**Other hookworms:** *A. braziliense* and *A. caninum* are hookworms that have cats and dogs as the primary hosts. These hookworms cannot complete their life cycle in humans. If their larvae penetrate human skin, they typically wander in the skin, causing cutaneous larva migrans (see p. 710), rather than migrate to the intestine.

Rarely, a few *A. caninum* larvae migrate to the intestine, where they may cause eosinophilic enterocolitis. However, they do not cause significant blood loss and anemia, and because they do not mature to full adulthood, they do not lay eggs (making diagnosis difficult). Such intestinal infection may be asymptomatic or cause acute abdominal pain and eosinophilia.

**Symptoms and Signs**
Hookworm infection is often asymptomatic. However, a pruritic papulovesicular rash (ground itch, cutaneous larva migrans) may develop at the site of larval penetration, usually on the feet. Migration of large numbers of larvae through the lungs occasionally causes Loffler's syndrome, with cough, wheezing, and sometimes hemoptysis. During the acute phase, adult worms in the intestine may cause colicky epigastric pain, anorexia, flatulence, diarrhea, and weight loss. Chronic infection can lead to iron deficiency anemia, and heavy infection can lead to hypoproteinemia, causing pallor, dyspnea, weakness, tachycardia, lassitude, and peripheral edema. A low-grade eosinophilia is often present. Chronic blood loss may lead to severe anemia, heart failure, and anasarca and, in pregnant women, to growth retardation in the fetus.

**Diagnosis**

- Microscopic examination of stool

*A. duodenale* and *N. americanus* produce thin-shelled oval eggs that are readily detected in fresh stool. If the stool is not kept cold and examined within several hours, the eggs may hatch and release larvae that may be confused with those of *Strongyloides stercoralis*. Nutritional status, anemia, and iron stores should be evaluated.

**Treatment**

- Albendazole or mebendazole

Albendazole 400 mg po as a single dose or mebendazole 100 mg po bid for 3 days or 500 mg as a single dose is given. Pyrantel pamoate 11 mg/kg po once/day (1 g maximum) for 3 days is also effective. These drugs should not be used during pregnancy.

General support and correction of iron deficiency anemia are needed if infection is heavy.

**Prevention**

Preventing unhygienic defecation and avoiding direct skin contact with the soil are effective in preventing infection but difficult to implement in many endemic areas. Periodic mass treatment of susceptible populations at 3- to 4-mo intervals has been used in high-risk areas.

Hookworm treatment for cats and dogs is the primary means for preventing cutaneous larva migrans.

**Pinworm Infestation**

(Enterobiasis; Oxyuriasis)

*Enterobiasis* is an intestinal infestation by the pinworm *Enterobius vermicularis*, usually in children. Its major symptom is perianal itching. Diagnosis is by visual inspection for threadlike worms in the perianal area or the cellophane tape test for ova. Treatment is with pyrantel pamoate, mebendazole, or albendazole.

Pinworm infestation is the most common helminthic infection in the US.

**Pathophysiology**

Infestation usually results from transfer of ova from the perianal area to fomites (clothing, bedding, furniture, rugs, toys), from which the ova are picked up by the new host, transmitted to the mouth, and swallowed. Thumb sucking is a risk factor. Reinfestation (autoinfestation) easily occurs through finger transfer of ova from the perianal area to the mouth. Pinworm infections have also been attributed to anilingus among adults.

Pinworms reach maturity in the lower GI tract within 2 to 6 wk. The female worm migrates to the perianal region (usually at night) to deposit ova. The sticky, gelatinous substance in which the ova are deposited...
and the movements of the female worm cause perianal pruritus. The ova can survive on fomites as long as 3 wk at normal room temperature.

**Symptoms and Signs**

Most infected people have no symptoms or signs, but some experience perianal pruritus and develop perianal excoriations from scratching. Rarely, migrating female worms ascend the human female genital tract, causing vaginitis and, even less commonly, peritoneal lesions.

Many other conditions (eg, abdominal pain, insomnia, seizures) have been attributed to pinworm infestation, but a causal relationship is unlikely. Pinworms have been found obstructing the appendiceal lumen in cases of appendicitis, but the presence of the parasites may be coincidental.

**Diagnosis**

- Examination of the perianal region for worms, ova, or both

Pinworm infestation can be diagnosed by finding the female worm, which is about 10 mm long (males average 3 mm), in the perianal region 1 or 2 h after a child goes to bed at night or in the morning or by using a low-power microscope to identify ova on cellophane tape. The ova are obtained in the early morning before the child arises by patting the perianal skin-folds with a strip of cellophane tape, which is then placed sticky side down on a glass slide and viewed microscopically. The 50 by 30 μm ova are oval with a thin shell that contains a curled-up larva. A drop of toluene placed between tape and slide dissolves the adhesive and eliminates air bubbles under the tape, which can hamper identification of the ova. This procedure should be repeated on 5 successive mornings if necessary. Eggs may also be encountered, but less frequently, in stool, urine, or vaginal smears.

**Treatment**

- Mebendazole or albendazole

Because pinworm infestation is seldom harmful, prevalence is high, and reinfection is common, treatment is indicated only for symptomatic infections. However, most parents actively seek treatment when their children have pinworms.

A single dose of mebendazole 100 mg po (regardless of age) or albendazole 400 mg po, repeated in 2 wk, is effective in eradicating pinworms (but not ova) in > 90% of cases. A single dose of pyrantel pamoate 11 mg/kg po (maximum 1 g) initially and repeated after 2 wk is also effective.

Reinfestation is common because viable ova may be excreted for 1 wk after therapy, and ova deposited in the environment before therapy can survive 3 wk. Multiple infestations within the household are common, and treatment of the entire family may be necessary. Clothing, bedding, and other articles should be washed frequently, and the environment vacuumed.

Carbolated petrolatum or other antipruritic creams or ointments applied to the perianal region may relieve itching.

**Strongyloidiasis**

*(Threadworm Infection)*

**Strongyloidiasis** is infection with *Strongyloides stercoralis*. Findings include rash and pulmonary symptoms (including cough and wheezing), eosinophilia, and abdominal pain with diarrhea. Diagnosis is by finding larvae in stool or small-bowel contents or by detection of antibodies in blood. Treatment is with ivermectin, thiabendazole, or albendazole.

Strongyloidiasis is endemic throughout the tropics and subtropics, including rural areas of the southern US, at sites where bare skin is exposed to contaminated soil and conditions are unsanitary. *Strongyloides*
*Fulleborni*, which infects chimpanzees and baboons, can cause limited infections in humans.

**Pathophysiology**

Adult worms live in the mucosa and submucosa of the duodenum and jejunum. Released eggs hatch in the bowel lumen, liberating rhabditiform larvae. Most of the larvae are excreted in the stool. After a few days in soil, they develop into infectious filariform larvae. Like hookworms, *Strongyloides* larvae penetrate human skin, migrate via the bloodstream to the lungs, break through pulmonary capillaries, ascend the respiratory tract, are swallowed, and reach the intestine, where they mature in about 2 wk. In the soil, larvae that do not contact humans may develop into free-living adult worms that can reproduce for several generations before their larvae reenter a human host.

Some rhabditiform larvae convert within the intestine to infectious filariform larvae that immediately reenter the bowel wall, short-circuiting the life cycle (internal autoinfection). Sometimes filariform larvae are passed in stool and reenter through the skin of the buttocks and thighs (external autoinfection). Autoinfection explains why strongyloidiasis can persist for many decades and helps account for the extremely high worm burdens in the hyperinfection syndrome.

Hyperinfection may result from a newly acquired *Strongyloides* infection or from activation of a previously asymptomatic one. In either case, it can result in disseminated disease involving organs not usually part of the parasite’s normal life cycle (eg, CNS, skin, liver, heart). Hyperinfection usually occurs in patients who are taking corticosteroids or who have impaired cell-mediated immunity, particularly those infected with the human T-lymphotropic virus 1 (HTLV-1). However, hyperinfection and disseminated strongyloidiasis are less common than might be predicted among patients with HIV/AIDS, even those living in areas where *Strongyloides* is highly endemic.

**Symptoms and Signs**

Infection may be asymptomatic.

Larva currens (creeping infection) is a form of cutaneous larva migrans specific to *Strongyloides* infection; it results from autoinfection. The eruption begins in the perianal region and rapidly spreads, causing intense pruritus, but nonspecific maculopapular or urticarial eruptions may also occur.

Pulmonary symptoms are uncommon, although heavy infections may cause Loffler’s syndrome, with cough, wheezing, and eosinophilia. GI symptoms include anorexia, epigastric pain and tenderness, diarrhea, nausea, and vomiting. In heavy infections, malabsorption and protein-losing enteropathy may result in weight loss and cachexia.

**Hyperinfection syndrome**: GI and pulmonary symptoms are often prominent. Ileus, obstruction, massive GI bleeding, severe malabsorption, and peritonitis may occur. Pulmonary symptoms include dyspnea, hemoptysis, and respiratory failure. Infiltrates may be seen on chest x-ray.

Other symptoms depend on the organ involved. CNS involvement includes parasitic meningitis, brain abscess, and diffuse invasion of the brain. Secondary gram-negative meningitis and bacteremia, which occurs with high frequency, probably reflect disruption of bowel mucosa, carriage of bacteria on migrating larvae, or both. Liver infection may result in cholestatic and granulomatous hepatitis. Infection may be fatal in immunocompromised patients, even with treatment.

**Diagnosis**

- Microscopic examination of stool
- Sometimes enzyme immunoassay

Microscopic examination of a single stool sample detects larvae in about 25% of uncomplicated infections. Repeated examination of concentrated stool or the agar-plate method raises sensitivity to ≥ 85%. If the specimen stands at room temperature for several hours, rhabditiform larvae may transform...
into longer filariform larvae, leading to erroneous diagnosis of hyperinfection. Sampling of the proximal small bowel by aspiration may be positive in low-level infections and should be done endoscopically to permit biopsy of suspicious duodenal and jejunal lesions. In hyperinfection syndrome, filariform larvae may be found in stool, duodenal contents, sputum, and bronchial washings and, uncommonly, in CSF, urine, or pleural or ascitic fluid. Chest x-rays may show diffuse interstitial infiltrates, consolidation, or abscess.

Several immunodiagnostic tests are available for strongyloidiasis. Enzyme immunoassay (EIA) is recommended because of its greater sensitivity (> 90%). IgG antibodies can usually be detected even in immunocompromised patients with disseminated strongyloidiasis. Cross-reactions in patients with filariasis or other nematode infections may result in false-positive tests. Antibody test results cannot be used to differentiate current from past infection. A positive test warrants continuing efforts to establish a parasitologic diagnosis. Serologic monitoring may be useful in follow-up because antibody levels decrease within 6 mo of successful chemotherapy.

Eosinophilia is often present but can be suppressed by drugs such as corticosteroids or cytotoxic chemotherapeutic drugs.

**Treatment**

- **Ivermectin**

Ivermectin 200 μg/kg po once/day for 2 days is used for uncomplicated infection and is generally well tolerated. Albendazole 400 mg po bid for 7 days is an alternative. In immunocompromised patients, prolonged therapy or repeated courses may be needed. Combined therapy with albendazole and ivermectin has been used for hyperinfections. In severely ill patients who are unable to take oral drugs, veterinary parenteral or rectal preparations of ivermectin have been used.

Cure should be documented by repeated stool examinations.

**Prevention**

Prevention of primary infections is the same as for hookworms. To prevent potentially fatal hyperinfection syndrome, clinicians should do several stool examinations and serologic testing in patients with possible exposure to *Strongyloides* (even in the distant past), with unexplained eosinophilia, or with symptoms that suggest strongyloidiasis before corticosteroids or other immunosuppressants are used. If patients are infected, treatment for strongyloidiasis should be instituted and parasitologic cure should be documented before immunosuppression. Immunosuppressed people who have recurrent strongyloidiasis require additional courses of treatment until cured.

**Toxocariasis**

(Visceral or Ocular Larva Migrans)

Toxocariasis is human infection with nematode ascarid larvae that ordinarily infect animals. Symptoms are fever, anorexia, hepatosplenomegaly, rash, pneumonitis, asthma, or visual impairment. Diagnosis is by enzyme immunoassay. Treatment is with albendazole or mebendazole. Corticosteroids may be added for severe symptoms or eye involvement.

**Pathophysiology**

The eggs of *Toxocara canis*, *T. cati*, and other animal ascarid helminths mature in soil and infect dogs, cats, and other animals. Humans may accidentally ingest eggs in soil contaminated by stool from infected animals or may ingest infected transfer hosts (eg, rabbits). The eggs hatch in the human intestine. Larvae penetrate the bowel wall and may migrate through the liver, lungs, CNS, eyes, or other tissues. Tissue damage is caused by focal eosinophilic granulomatous reactions to the migrating larvae. The larvae usually do not complete their development in the human body but can remain alive for many months.
Symptoms and Signs

**Visceral larva migrans (VLM):** This syndrome consists of fever, anorexia, hepatosplenomegaly, rash, pneumonitis, and asthmatic symptoms, depending on the affected organs.

VLM occurs mostly in 2- to 5-yr-old children with a history of geophagia. The syndrome is self-limiting in 6 to 18 mo if egg intake ceases. Deaths due to invasion of the brain or heart occur rarely.

**Ocular larva migrans (OLM):** This syndrome, also called ocular toxocariasis, usually has no or very mild systemic manifestations. OLM lesions consist mostly of granulomatous reactions to a larva in the retina; the larva may cause visual impairment.

OLM occurs in older children and less commonly in young adults. The lesion may be confused with retinoblastoma or other intraocular tumors.

**Diagnosis**

- Enzyme immunoassay plus clinical findings

Diagnosis is based on clinical, epidemiologic, and serologic findings. Enzyme immunoassay (EIA) is currently recommended. Isoagglutinins are frequently elevated, but this finding is nonspecific. Hyperglobulinemia, leukocytosis, and marked eosinophilia are common.

Biopsies of the liver or other affected organs may show eosinophilic granulomatous reactions, but larvae are difficult to find in tissue sections and biopsies are low yield. Stool examinations are worthless. OLM should be distinguished from retinoblastoma to prevent unnecessary surgical enucleation of the eye.

**Treatment**

- Mebendazole or albendazole
- Symptomatic treatment

Mebendazole 100 to 200 mg po bid for 5 days or albendazole 400 mg po bid for 5 days is often used, but the optimal duration of therapy has not been determined.

Antihistamines may suffice for mild symptoms. Corticosteroids (prednisone 20 to 40 mg po once/day) are indicated for patients with severe symptoms. Corticosteroids, both local and oral, are also indicated for acute OLM.

Laser photocoagulation has been used to kill larvae in the retina.

**Prevention**

Infection with *T. canis* in puppies is common in the US; infection with *T. cati* in cats is less common. Both animals should be dewormed regularly. Contact with dirt or sand contaminated with animal feces should be minimized. Sandboxes should be covered.

**Baylisascariasis**

Baylisascariasis is infection with the raccoon ascarid, *Baylisascaris procyonis*, which may cause fatal CNS infection in humans.

Infection usually occurs in children who play in dirt or with articles contaminated with raccoon feces. It occurs in the US, particularly in the Middle Atlantic, Midwest, and Northeast. Although baylisascariasis is rare in people, it is of concern because a large number of raccoons live near humans and the infection rate of *B. procyonis* in these animals is high.
Migration of the larvae through a wide variety of tissues (liver, heart, lungs, brain, eyes) results in VLM and OLM syndromes, similar to those due to toxocariasis. However, in contrast to *Toxocara* larvae, *Baylisascaris* larvae continue to grow to a large size (up to 24 cm for females and 12 cm for males) within the CNS and cause eosinophilic meningoencephalitis. Tissue damage and symptoms and signs of baylisascariasis are often severe because *Baylisascaris* larvae continue to grow, tend to wander widely, and do not readily die.

Diagnosis is difficult because serologic tests are not widely available. Viewing a larva during ocular examination is often a clue.

Treatment is similar to that of other causes of VLM and OLM.

**Trichinosis**

(Trichiniasis)

Trichinosis is infection with *Trichinella spiralis* or related *Trichinella* species. Symptoms include initial GI irritation followed by periorbital edema, muscle pain, fever, and eosinophilia. Diagnosis is clinical and with serologic tests. Muscle biopsy may be diagnostic but is seldom necessary. Treatment is with mebendazole or albendazole plus prednisone if symptoms are severe.

Trichinosis occurs worldwide. In addition to the classic agent *Trichinella spiralis*, trichinosis can be caused by *T. pseudospiralis*, *T. nativa*, *T. nelsoni*, and *T. britovi* in different geographic locations.

**Pathophysiology**

The life cycle is maintained by animals that are fed (eg, pigs, horses) or eat (eg, bears, foxes, boars) other animals whose striated muscles contain encysted infective larvae (eg, rodents). Humans become infected by eating raw, undercooked, or processed meat from infected animals, most commonly pigs, wild boar, or bear. Larvae excyst in the small bowel, penetrate the mucosa, and become adults in 6 to 8 days. Females are about 2.2 mm long, and males are about 1.2 mm long. Mature females release living larvae for 4 to 6 wk and then die or are expelled. Newborn larvae migrate through the bloodstream and body but ultimately survive only within striated skeletal muscle cells. Larvae fully encyst in 1 to 2 mo and remain viable for several years as intracellular parasites. Dead larvae eventually are resorbed or calcify. The cycle continues only if encysted larvae are ingested by another carnivore.

**Symptoms and Signs**

Many infections are asymptomatic or mild. During the 1st wk, nausea, abdominal cramps, and diarrhea may occur. One to 2 wk after infection, systemic symptoms and signs begin: facial or periorbital edema, myalgia, persistent fever, headache, and subconjunctival hemorrhages and petechiae. Eye pain and photophobia often precede myalgia.

Symptoms due to muscle invasion may mimic polymyositis. The muscles of respiration, speech, mastication, and swallowing may be painful. Severe dyspnea may occur in heavy infections.

Fever is generally remittent, rising to 39° C or higher, remaining elevated for several days, and then falling gradually. Eosinophilia usually begins when newborn larvae invade tissues, peaks 2 to 4 wk after infection, and gradually declines as the larvae encyst.

In heavy infections, the inflammation may cause complications: cardiac (myocarditis, heart failure, arrhythmia), neurologic (encephalitis, meningitis, visual or auditory disorders, seizures), or pulmonary (pneumonitis, pleurisy). Death may result from myocarditis or encephalitis.

Symptoms and signs gradually resolve, and most disappear by about the 3rd mo, when the larvae have become fully encysted in muscle cells and eliminated from other organs and tissues. Vague muscular pains and fatigue may persist for months. Recurrent infections with *T. nativa* in northern latitudes can cause chronic diarrhea.
Diagnosis

• Enzyme immunoassay
• Rarely biopsy

No specific tests to diagnose the intestinal stage are available. After the 2nd wk of infection, a muscle biopsy may detect larvae and cysts but is seldom necessary. Diffuse inflammation in muscle tissue indicates recent infection.

A number of serologic tests have been used, but enzyme immunoassay (EIA) using *T. spiralis* excretory-secretory (ES) antigen seems to be the quickest way to detect the infection and is used in the US. Antibodies are often not detectable for the first 3 to 5 wk of infection, so tests should be repeated at weekly intervals if results are initially negative. Because antibodies may persist for years, serologic tests are of most value if they are initially negative and then positive. Serologic tests and muscle biopsy are complementary tests: Either one can be negative in a given patient with trichinosis. Skin testing with larval antigens is unreliable.

Muscle enzymes (creatine kinase and LDH) are elevated in 50% of patients and correlate with abnormal electromyograms.

Trichinosis must be differentiated from

• Acute rheumatic fever, acute arthritis, angioedema, and myositis
• Febrile illnesses such as TB, typhoid fever, sepsis, and undulant fever
• Pneumonitis
• Neurologic manifestations of meningitis, encephalitis, and poliomyelitis
• Eosinophilia due to Hodgkin lymphoma, eosinophilic leukemia, polyarteritis nodosa, or disease caused by other migrating nematodes

Treatment

• Symptomatic treatment

• Mebendazole or albendazole to eliminate adult worms

Anthelmintics eliminate adult worms from the GI tract but probably have little effect on encysted larvae. Mebendazole 200 to 400 mg po tid for 3 days, then 400 to 500 mg tid for 10 days or albendazole 400 mg bid for 8 to 14 days may be used.

Analgesics (eg, NSAIDs, opioids) may help relieve muscle pains. For severe allergic manifestations or myocardial or CNS involvement, prednisone 20 to 60 mg po once/day is given for 3 or 4 days, then tapered over 10 to 14 days.

Prevention

Trichinosis is prevented by cooking meat thoroughly until brown (71°C [160°F] throughout). Larvae can usually be killed by freezing the meat at -17°C (1°F) for 3 wk or -30°C (-22°F) for 6 days, but *T. nativa* is relatively resistant. Smoking, microwave cooking, or salting meat does not reliably kill larvae.

Domestic swine should not be fed uncooked meat products.

**Trichuriasis**
(Whipworm Infection; Trichocephalasis)

**Trichuriasis is infection with** *Trichuris trichiura*. **Symptoms may include abdominal pain, diarrhea, and, in heavy infections, anemia and undernutrition. Diagnosis is by finding eggs in stool. Treatment is with mebendazole or albendazole.**

Infection is spread via the fecal-oral route. Ingested eggs hatch and enter the crypts of the small bowel as larvae. After maturing for 1 to 3 mo, the worms migrate to the cecum and ascending colon, where they attach to the superficial epithelium, mate, and lay eggs.

**Adult worms may live 7 to 10 yr.**

Trichuriasis is the 3rd most common roundworm infection. An estimated 800 million people are infected worldwide. *Trichuris trichiura* occurs principally in developing tropical or subtropical areas, but infections also occur in the southern US. Children are most affected.

Light infections are often asymptomatic. Heavy infections cause abdominal pain, anorexia, and diarrhea and may result in anemia or retarded growth. Very heavy infections may cause weight loss, anemia, and rectal prolapse, particularly in children.

**Diagnosis**

- Microscopic examination of stool

Diagnosis is made by microscopic examination of stool; the characteristic lemon-shaped eggs with clear opercula at both ends are readily apparent. When colonoscopy is done for other indications, wiggling adult worms may be seen protruding into the bowel lumen. CBC is done to check for anemia.

**Treatment**

- Mebendazole

Mebendazole 100 mg po bid for 3 days or 500 mg as a single dose is recommended. Alternatively, albendazole 400 mg po once/day for 3 days or ivermectin 200 μg/kg po once/day for 3 days may be used. These drugs should not be used during pregnancy.

Prevention is possible through good sanitation and personal hygiene.
Flukes are parasitic flatworms that infect the blood vessels, GI tract, lungs, or liver. They are often categorized according to the organ system they invade:

- **Schistosoma** sp: Vasculature of the GI or GU system
- **Fasciolopsis buski, Heterophyes heterophyes**, and related organisms: Lumen of the GI tract
- **Clonorchis sinensis, Fasciola hepatica, and Opisthorchis** sp: Liver
- **Paragonimus westermani** and related species: Lungs and other organs such as the CNS

### Clonorchiasis

(Oriental Liver Fluke Infection)

Clonorchiasis is infection with the liver fluke *Clonorchis sinensis*. Infection is acquired by eating undercooked freshwater fish. Symptoms include fever, chills, epigastric pain, tender hepatomegaly, diarrhea, and mild jaundice. Diagnosis is by identifying eggs in the feces or duodenal contents. Treatment is with praziquantel or albendazole.

*Clonorchis* is endemic in the Far East, especially in Korea, Japan, Taiwan, and southern China, and infection occurs elsewhere among immigrants and people eating fish imported from endemic areas.

### Pathophysiology

Adult *C. sinensis* worms live in the bile ducts. Eggs are passed in the stool and ingested by snails. Cercariae (free-swimming larvae) released from infected snails subsequently infect a variety of freshwater fish. Humans become infected by eating raw, dried, salted, or pickled fish containing encysted metacercariae (resting or maturing stage). Metacercariae are released in the duodenum, enter the common bile duct through the ampulla of Vater, and migrate to smaller intrahepatic ducts (or occasionally the gallbladder and pancreatic ducts), where they mature into adult worms in about 1 mo. The adults may live ≥ 20 yr and grow to about 10 to 25 mm by 3 to 5 mm.

### Symptoms and Signs

Light infections are usually asymptomatic. Heavier infections can cause fever, chills, epigastric pain, tender hepatomegaly, mild jaundice, and eosinophilia. Later, diarrhea may occur. Chronic cholangitis in heavy infections may progress to atrophy of liver parenchyma, portal fibrosis, and cirrhosis. Jaundice may occur if a mass of flukes obstructs the biliary tree. Other complications include supplicative cholangitis, chronic pancreatitis, and, late in the course, cholangiocarcinoma.

### Diagnosis

- Microscopic examination of stool

Diagnosis is by finding eggs in the feces or duodenal contents. The eggs are difficult to distinguish from those of *Metagonimus, Heterophyes*, and *Opisthorchis*. Occasionally, the diagnosis is made by identifying adult flukes in surgical specimens or by doing percutaneous transhepatic cholangiography.

Other tests are nondiagnostic but may be abnormal: alkaline phosphatase, bilirubin, and eosinophil counts may be elevated. A plain abdominal x-ray occasionally shows intrahepatic calcification. Hepatic ultrasonography may show ductal irregularities and evidence of scarring.
Treatment

• Praziquantel or albendazole

Treatment is with praziquantel 25 mg/kg po tid for 2 days or albendazole 10 mg/kg po once/day for 7 days. Biliary obstruction may require surgery. Freshwater fish from endemic waters should be thoroughly cooked and not eaten raw, pickled, or wine-soaked.

Fascioliasis

Fascioliasis is infection with the liver fluke *Fasciola hepatica*, which is acquired by eating contaminated watercress or other water plants.

*F. hepatica* is the sheep and cattle liver fluke. Incidental human fascioliasis, acquired by eating watercress contaminated by sheep or cattle dung, occurs in Europe, Africa, China, and South America but is rare in the US.

In acute infection, immature flukes migrate through the intestinal wall, the peritoneal cavity, the liver capsule, and the parenchyma of the liver before entering the biliary ducts where they mature to adulthood in about 3 to 4 mo.

Acute infection causes abdominal pain, hepatomegaly, nausea, vomiting, intermittent fever, urticaria, eosinophilia, malaise, and weight loss due to liver damage. Chronic infection may be asymptomatic or lead to intermittent biliary tract obstruction. Ectopic lesions may occur in the intestinal wall, lungs, or other organs.

CT frequently shows hypodense lesions in the liver. Antibody detection assays are useful in the early stages of disease. Eggs may be recovered in the stool or, during chronic infection, in duodenal or biliary materials.

Treatment is with triclabendazole (10 mg/kg po once or twice) where it is available. Alternatively, nitazoxanide 500 mg bid po for 7 days or bithionol 30 to 50 mg/kg po every other day for 10 to 15 doses may be used. Treatment failures are common with praziquantel.

Fasciolopsiasis

Fasciolopsiasis is infection with the intestinal fluke *Fasciolopsis buski*, which is acquired by eating aquatic plants.

*F. buski* is present in the intestine of pigs in many parts of Asia. Human infection is acquired by eating aquatic plants (eg, water chestnuts) that bear infectious metacercariae (encysted stage). Adult worms attach to and ulcerate the mucosa of the proximal small bowel. They grow to about 20 to 75 mm by 8 to 20 mm. Adults have a life span of about 1 yr.

Most infections are light and asymptomatic, but heavy infections may cause diarrhea, abdominal pain, and signs of malabsorption.

Diagnosis is made by finding eggs or, less commonly, adult worms in the feces.

Treatment is with praziquantel 25 mg/kg po tid for 1 day.

Heterophyiasis and Related Trematode Infections

Heterophyiasis is infection with the intestinal fluke *Heterophyes heterophyes*, which is acquired by eating infected raw or undercooked fish from freshwater or brackish water.

*Heterophyes heterophyes* and several related trematodes are endemic in the Far East, Middle East, and Egypt. Infection is acquired by eating infected raw or undercooked fish from freshwater or brackish water.
containing metacercariae (encysted stage). After ingestion, metacercariae excyst and attach to the mucosa of the small intestine. There, they develop into adults, growing to about 1.0 to 1.7 mm by 0.3 to 0.4 mm. Salmon live part of their lives in freshwater and can be infected with *Nanophyetus salmincola*.

Adult flukes can cause abdominal pain and diarrhea. Diagnosis is by finding eggs in the feces. Treatment is with praziquantel 25 mg/kg po tid for 1 day.

**Opisthorchiasis**

Opisthorchiasis is infection with 1 of 2 species of the liver fluke *Opisthorchis*, which is acquired by eating infected raw or undercooked fish.

Opisthorchiasis occurs in cats and dogs in eastern and central Europe, Siberia, and parts of Asia, such as Thailand and Cambodia. The life cycle of *Opisthorchis* requires both snails and fish. Human disease resembles clonorchiasis and is acquired by eating raw or undercooked freshwater fish that contains infectious metacercariae (encysted stage). After ingestion, metacercariae excyst and ascend through the ampulla of Vater into the biliary ducts, where they attach to the mucosa and mature. Adult flukes grow to 5 to 10 mm by 1 to 2 mm (*O. viverrini*) or 7 to 12 mm by 2 to 3 mm (*O. felineus*).

Symptoms include vague GI discomfort or bowel symptoms (diarrhea or constipation). Rarely, infection causes cholangitis or cholangiocarcinoma.

Diagnosis is by finding eggs in the feces. Praziquantel 25 mg/kg po tid for 2 days is the treatment of choice.

**Paragonimiasis**

(Oriental Lung Fluke Infection; Endemic Hemoptysis)

Paragonimiasis is infection with the lung fluke *Paragonimus westermani* and related species. Humans are infected by eating raw, pickled, or poorly cooked freshwater crustaceans.

Symptoms include chronic cough, chest pain, dyspnea, and hemoptysis. Allergic skin reactions and CNS abnormalities due to ectopic flukes, including seizures, aphasia, paresis, and visual disturbances, can also occur. Diagnosis is by identifying eggs in sputum, stool, or pleural or peritoneal fluid. Serologic tests are also available. Praziquantel is the treatment of choice; bithionol is an alternative.

Although > 30 species of *Paragonimus* exist and 10 have been reported to infect humans, *P. westermani* is the most frequent cause of disease. The most important endemic areas are in the Far East, principally Korea, Japan, Taiwan, the highlands of China, and the Philippines. Endemic foci also exist in West Africa and in parts of South and Central America.

**Pathophysiology**

Eggs passed in sputum or feces develop for 2 to 3 wk in freshwater before miracidia (first larval stage) hatch. The miracidia invade snails; there, they develop, multiply, and eventually emerge as cercariae (free-swimming larvae). Cercariae penetrate freshwater crabs or crayfish and encyst to form metacercariae. Humans become infected by eating raw, pickled, or poorly cooked crustaceans. Metacercariae excyst in the human GI tract, penetrate the intestinal wall, move into the peritoneal cavity, then through the diaphragm into the pleural cavity; they enter lung tissue, encyst, and develop into hemaphroditic adult worms, which grow to about 7.5 to 12 mm by 4 to 6 mm. Worms may also reach the brain, liver, lymph nodes, skin, and spinal cord and develop there. However, in these organs, the life cycle cannot be completed because the eggs have no way to exit the body. Adult flukes may persist for 20 to 25 yr.

Other hosts include pigs, dogs, and a variety of feline species.

**Symptoms and Signs**
Most damage is to the lungs, but other organs may be involved. About 25 to 45% of all extrapulmonary infections affect the CNS. Manifestations of pulmonary infection develop slowly and include chronic cough, chest pain, hemoptysis, and dyspnea; the clinical picture resembles and is often confused with TB. Cerebral infections manifest as space-occupying lesions, often within a year after the onset of pulmonary disease. Seizures, aphasia, paresis, and visual disturbances occur. Migratory allergic skin lesions similar to those of cutaneous larva migrans are common in infections with *P. skrjabini* but also occur with other species.

**Diagnosis**

* Microscopic examination of sputum and stool

Diagnosis is by identifying the characteristic large operculated eggs in sputum or stool. Occasionally, eggs may be found in pleural or peritoneal fluid. Eggs may be difficult to find because they are released intermittently and in small numbers. Concentration techniques increase sensitivity.

X-rays provide ancillary information but are not diagnostic; chest x-rays and CT may show a diffuse infiltrate, nodules and annular opacities, cavitations, lung abscesses, pleural effusion, and pneumothorax. Serologic tests may assist in diagnosis of light or extrapulmonary infections.

**Treatment**

* Praziquantel

Praziquantel 25 mg/kg po tid for 2 days cures 80 to 100% of pulmonary infections and is the drug of choice. Bithionol 30 to 50 mg/kg po every other day for 10 to 15 doses is an alternative but has more adverse effects. Praziquantel is used to treat extrapulmonary infections, but multiple courses may be required. Surgery may be needed to excise skin lesions or, rarely, brain cysts.

The best prevention is to avoid eating raw or undercooked freshwater crabs and crayfish from endemic waters.

**Schistosomiasis**

*(Bilharziasis)*

Schistosomiasis is infection with blood flukes of the genus *Schistosoma*, which are acquired transcutaneously by swimming or wading in contaminated freshwater. The organisms infect the vasculature of the GI or GU system. Acute symptoms are dermatitis, followed several weeks later by fever, chills, nausea, abdominal pain, diarrhea, malaise, and myalgia. Chronic symptoms vary with species but include bloody diarrhea (eg, with *S. mansoni*) or hematuria (eg, with *S. haematobium*). Diagnosis is by identifying eggs in stool, urine, or biopsy specimens. Serologic tests may be sensitive and specific but do not provide information about the worm burden or clinical status. Treatment is with praziquantel.

**Etiology**

Schistosomiasis is by far the most important trematode infection. *Schistosoma* is the only trematode that invades through the skin; all other trematodes infect only via ingestion. About 200 million people are infected worldwide. The risk of infection is spreading as new dams are built in endemic areas.

Five species of schistosomes infect humans; all have similar life cycles involving freshwater snails. *S. haematobium* causes urinary tract disease; the other *Schistosoma* sp cause intestinal disease. Geographic distribution differs by species:

* *S. haematobium*: Widely distributed over the African continent with smaller foci in the Middle East and India
S. mansoni: Widespread in Africa and the only species in the Western Hemisphere, endemic in Brazil, Surinam, and Venezuela and on some Caribbean islands

S. japonicum: Only in Asia, mainly in China and the Philippines

S. mekongi: Laos and Cambodia

S. intercalatum: Central Africa

The disease may be imported in travelers and immigrants from endemic areas, but transmission does not occur within the US and Canada.

Pathophysiology

Adult worms live and copulate within the veins of the mesentery (typically S. japonicum and S. mansoni) or bladder (typically S. haematobium—see Fig. 145-1). Some eggs penetrate the intestinal or bladder mucosa and are passed in stool or urine; other eggs remain within the host organ or are transported through the portal system to the liver and occasionally to other sites (eg, lungs, CNS, spinal cord). Excreted eggs hatch in freshwater, releasing miracidia (first larval stage), which enter snails. After multiplication, thousands of free-swimming cercariae are released. Cercariae penetrate human skin within a few minutes after exposure and transform into schistosomula, which travel through the bloodstream to the liver, where they mature into adults. The adults then migrate to their ultimate home in the intestinal veins or the venous plexus of the GU tract.

Eggs appear in stool or urine 1 to 3 mo after cercarial penetration.

Estimates of the adult worm life span range from 3 to 7 yr. The females range in size from 7 to 20 mm; males are slightly smaller.

Symptoms and Signs

Schistosome dermatitis: This pruritic papular rash (see also Dermatitis Caused by Avian and Animal Schistosomes on p. 1360) develops where the cercariae penetrate the skin in previously sensitized people.

Acute schistosomiasis: Acute schistosomiasis (Katayama fever) occurs with onset of egg laying, typically 2 to 4 wk after heavy exposure. Symptoms include fever, chills, cough, nausea, abdominal pain, malaise, myalgia, urticarial rashes, and marked eosinophilia, resembling serum sickness. Manifestations are more common and usually more severe in visitors than in residents of endemic areas and typically last for several weeks.

Chronic schistosomiasis: Chronic schistosomiasis results mostly from host responses to eggs retained in tissues. Early on, intestinal mucosal ulcerations caused by S. mansoni or S. japonicum may bleed and result in bloody diarrhea. As lesions progress, focal fibrosis, strictures, fistulas, and papillomatous growths may develop. With S. haematobium, ulcers in the bladder wall may cause dysuria, hematuria, and urinary frequency. Over time, chronic cystitis develops. Strictures may lead to hydronephrosis and hydroureter. Papillomatous masses in the bladder are common, and squamous cell carcinoma may develop. Blood loss from both GI and GU tracts frequently results in anemia.

Secondary bacterial infection of the GU tract is common, and persistent Salmonella septicemia may occur with S. mansoni. Several species, notably S. haematobium, can cause genital disease in both men and women, resulting in numerous symptoms including infertility.

[Fig. 145-1. Simplified Schistosoma life cycle.]

Granulomatous reactions to eggs of S. mansoni and S. japonicum in the liver usually do not compromise
liver function but may cause fibrosis and cirrhosis, which can lead to portal hypertension and subsequent hematemesis due to esophageal varices. Eggs in the lungs may produce granulomas and focal obliterative arteritis, which may cause pulmonary hypertension and cor pulmonale. Eggs lodged in the spinal cord can cause transverse myelitis, and those in the CNS can cause seizures.

Diagnosis

- Microscopic examination of stool

Stool (S. japonicum, S. mansoni, S. mekongi, S. intercalatum) or urine (S. haematobium, occasionally S. japonicum) is examined for eggs. Repeated examinations using concentration techniques may be necessary. Geography is a primary determinant of species, so a history of exposure should be communicated to the laboratory. If the clinical picture suggests schistosomiasis but no eggs are found after repeated examination of urine or feces, intestinal or bladder mucosa can be biopsied to check for eggs.

Depending on the antigens used, serologic tests may be sensitive and specific for infection, but they do not provide information about worm burden, clinical status, or prognosis.

Treatment

- Praziquantel

Single-day oral treatment with praziquantel (20 mg/kg bid for S. haematobium, S. mansoni, and S. intercalatum; 20 mg/kg tid for S. japonicum and S. mekongi) is recommended. However, treatment does not affect developing schistosomula and thus may not abort an early infection. Adverse effects are generally mild and include abdominal pain, diarrhea, headache, and dizziness. Therapeutic failures have been reported, but it is difficult to determine whether they are due to reinfection or drug-resistant strains.

Oxamniquine (not available in the US) has been effective in treating infection due to S. mansoni in some areas where praziquantel has been less effective. African strains are more resistant to this drug than South American strains and require higher doses.

Patients should be examined for living eggs 3 and 6 mo after treatment. Retreatment is indicated if egg excretion has not decreased markedly.

Prevention

Scrupulously avoiding contact with contaminated freshwater prevents infection. The sanitary disposal of urine and feces reduces the likelihood of infection. Adult residents of endemic areas are more resistant to reinfection than children, suggesting the possibility of acquired immunity. Vaccine development is under way.

Dermatitis Caused by Avian and Animal Schistosomes

(Cercarial Dermatitis; Clam Diggers' Itch; Swimmers' Itch)

Cercarial dermatitis, a skin condition, occurs when Schistosoma sp that cannot develop in humans penetrate the skin during contact with contaminated freshwater or brackish water.

Cercariae of Schistosoma sp that infect birds and mammals other than humans can penetrate the skin. Although the organisms do not develop in humans, humans may become sensitized and develop pruritic maculopapular, then vesicular skin lesions at the site of penetration. Skin lesions may be accompanied by a systemic febrile response that runs for 5 to 7 days and resolves spontaneously.

Ocean-related schistosome dermatitis (clam diggers' itch) occurs on all Atlantic, Gulf, Pacific, and Hawaiian coasts. It is very common in muddy flats off Cape Cod. Freshwater schistosome dermatitis (swimmers' itch) is common in the lakes of northern Michigan, Wisconsin, and Minnesota.
Diagnosis is based on clinical findings. Most cases do not require medical attention.

Treatment is symptomatic with cool compresses, baking soda, or antipruritic lotions. Topical corticosteroids can also be used.
Chapter 146. Cestodes (Tapeworms)

Introduction

All tapeworms (cestodes) cycle through 3 stages—eggs, larvae, and adults. Adults inhabit the intestines of definitive hosts, mammalian carnivores. Several of the adult tapeworms that infect humans are named after their intermediate host: the fish tapeworm (*Diphyllobothrium latum*), the beef tapeworm (*Taenia saginata*), and the pork tapeworm (*Taenia solium*). Eggs laid by adult tapeworms living in the intestines of definitive hosts are excreted with feces into the environment and ingested by an intermediate host (typically another species), in which larvae develop, enter the circulation, and encyst in the musculature or other organs. When the intermediate host is eaten, cysts develop into adult tapeworms in the intestines of the definitive host, restarting the cycle. With some cestode species (eg, *T. solium*), the definitive host can also serve as an intermediate host; tissue cysts develop instead of intestinal worms after eggs are ingested.

Adult tapeworms are multisegmented flat worms that lack a digestive tract and absorb nutrients directly from the host's small bowel. In the host's digestive tract, adult tapeworms can become large; the longest parasite in the world is the 40-m whale tapeworm, *Polygonoporus* sp. Tapeworms have 3 recognizable portions. The scolex (head) functions as an anchoring organ that attaches to intestinal mucosa. The neck is an unsegmented region with high regenerative capacity. If treatment does not eliminate the neck and scolex, the entire worm may regenerate. The rest of the worm consists of numerous proglottids (segments). Proglottids closest to the neck are undifferentiated. As proglottids move caudally, each develops hermaphroditic sex organs. Distal proglottids are gravid and contain eggs in a uterus.

In contrast to adult tapeworms, larvae can cause severe and even lethal disease, most importantly in the brain, but also in the liver, lungs, eyes, muscles, and subcutaneous tissues. In humans, *T. solium* causes cysticercosis, and *Echinococcus granulosus* and *E. multilocularis* cause hydatid disease. *Sparganum mansoni* and *T. multiceps* larvae can also infect humans.

Symptoms and Signs

Adult tapeworms are so well adapted to their hosts that they cause minimal symptoms. *Hymenolepis nana* is an exception and can cause abdominal discomfort, diarrhea, and weight loss. However, larvae may elicit intense immunologic reactions as they travel through tissues (hence inducing immunity) and cause severe disease when they settle in extraintestinal sites.

Diagnosis

Adult tapeworm infections are diagnosed by identifying eggs or gravid proglottid segments in stool. Larval disease is best identified by imaging (eg, brain CT or MRI) and, for some species, serologic tests.

Treatment

The anthelmintic drugs, praziquantel and niclosamide, are effective for most intestinal tapeworm infections. Some extraintestinal infections respond to anthelmintic treatment; others require surgical intervention.

Prevention

Prevention and control involve the following:

- Thorough cooking (to a temperature > 57° C [> 135° F]) of pork, beef, lamb, game meat, and fish
- Regular worming of dogs and cats
- Prevention of recycling through hosts (eg, dogs eating dead game or livestock)
• Reduction and avoidance of intermediate hosts such as rodents, fleas, and grain beetles

• Meat inspection

• Sanitary treatment of human waste

Prolonged freezing of meat is effective, pickling is variably effective, and smoking and drying are ineffective.

**Diphyllobothriasis**

*(Fish Tapeworm Infection)*

* [*Diphyllobothriasis* is infection with the intestinal tapeworm, *Diphyllobothrium latum*, a parasite of freshwater fish. Treatment is with praziquantel.]*

* *D. latum* is the largest parasite of humans (up to 10 m in length). It and *Sparganum mansoni* are the only human tapeworms with aquatic life cycles. In freshwater, eggs of *D. latum* from human feces hatch into free-swimming larvae, which are ingested by microcrustaceans. The microcrustaceans are ingested by fish, in which the larvae become infective.*

Diphyllobothriasis occurs worldwide, especially where cool lakes are contaminated by sewage. Infections in the US and northern Europe occur in people who eat raw freshwater fish. Infection is less common with current sewage treatment.

Infection is usually asymptomatic, but mild GI symptoms may be noted. Fish tapeworms take up dietary vitamin B12, occasionally resulting in vitamin B12 deficiency and megaloblastic anemia.

Diagnosis is by identification of characteristic operculated eggs or broad proglottids in stool.

**Treatment**

• Praziquantel or niclosamide

Treatment is with a single oral dose of praziquantel 5 to 10 mg/kg. Alternatively, a single 2-g dose of niclosamide is given as 4 tablets (500 mg each) that are chewed one at a time and swallowed. For children, the dose is 50 mg/kg once.

Vitamin B12 may be needed to correct the anemia. Thorough cooking of freshwater fish or freezing it at -10° C (14° F) for 48 h prevents infection.

**Dipylidium caninum Infection**

* [*Dipylidium caninum* can cause intestinal infection, which is typically asymptomatic.]*

* *D. caninum*, the double-pored tapeworm, is present in dogs and cats. Fleas are the intermediate host. Ingestion of an infected flea, usually by a young child, causes an asymptomatic, self-limited infection, but proglottids may be seen in stool.*

Treatment is with a single oral dose of praziquantel 5 to 10 mg/kg. Alternatively, a single 2-g dose of niclosamide is given as 4 tablets (500 mg each) that are chewed one at a time and swallowed. For children, the dose is 50 mg/kg once.

**Echinococcosis**

*(Hydatid Disease)*
Echinococcosis is infection with larvae of *Echinococcus granulosus* or *E. multilocularis* (alveolar hydatid disease). Symptoms depend on the organ involved—e.g., jaundice and abdominal discomfort with liver cysts or cough, chest pain, and hemoptysis with lung cysts. Cyst rupture can cause fever, urticaria, and serious anaphylactic reactions. Diagnosis is with imaging, examination of cyst fluid, or serologic tests. Treatment is with albendazole, surgery, or both or with cyst aspiration and instillation of a scolicidal agent.

**Etiology**

*Echinococcus granulosus* is common in sheep-raising areas of the Mediterranean, Middle East, Australia, New Zealand, South Africa, and South America. It requires canines as definitive hosts and herbivores (e.g., sheep, horses, deer) or humans as intermediate hosts. Foci also exist in regions of Canada, Alaska, and California.

*E. multilocularis* worms are present in foxes, and the hydatid larvae occur in small wild rodents. Infected dogs and other canines are the main link to occasional human infection. *E. multilocularis* occurs mainly in Central Europe, Alaska, Canada, and Siberia. Its range of natural infection in the continental US extends from Wyoming and the Dakotas to the upper Midwest. Rarely, *E. vogelii* or *E. oliganthus* causes polycystic hydatid disease in humans, primarily in the liver.

**Pathophysiology**

Ingested eggs from animal feces (which may be present in the fur of dogs or other animals) hatch in the gut. Larvae penetrate the intestinal wall, migrate via the circulation, and lodge in the liver or lungs or, less frequently, in the brain, bone, or other organs.

*E. granulosus* larvae develop slowly (usually over many years) into large unilocular, fluid-filled lesions—hydatid cysts. Brood capsules containing numerous small infective protoscolices form within these cysts. Large cysts may contain > 1 L of highly antigenic hydatid fluid as well as millions of protoscolices. Daughter cysts sometimes form in or outside primary cysts. If a cyst in the liver leaks or ruptures, infection can spread to the peritoneum.

*E. multilocularis* produces spongy masses that are locally invasive and difficult or impossible to treat surgically. Cysts occur primarily in the liver but can occur in the lungs, or other tissues.

**Symptoms and Signs**

Although many infections are acquired during childhood, clinical signs may not appear for years, except when cysts are in vital organs. Symptoms and signs may resemble those of a space-occupying tumor.

Liver cysts eventually cause abdominal pain or a palpable mass. Jaundice may occur if the bile duct is obstructed. Rupture into the bile duct, peritoneal cavity, or lung may cause fever, urticaria, or a serious anaphylactic reaction.

Pulmonary cysts can rupture, causing cough, chest pain, and hemoptysis.

**Diagnosis**

- Imaging
- Serologic testing
- Examination of cyst fluid

Pulmonary cysts are usually discovered on routine chest x-ray as round, often irregular pulmonary masses.

CT, MRI, and ultrasound findings may be pathognomonic if daughter cysts and hydatid sand
(protoscolices and debris) are present, but simple hydatid cysts may be difficult to differentiate from simple benign cysts, abscesses, or benign or malignant tumors. The presence of hydatid sand in aspirated cyst fluid is diagnostic.

Serologic tests (enzyme immunoassay, immunofluorescent assay, indirect hemagglutination assay) are variably sensitive but are useful if positive and should be done. CBC may detect eosinophilia.

Treatment

• Surgical removal or aspiration followed by instillation of a scolicidal agent

• Sometimes albendazole

Surgery, sometimes via laparoscopy, can be curative. Albendazole is often given before surgery to prevent metastatic infections that can occur if cyst contents spill during the procedure. In some centers, percutaneous aspiration under CT guidance is done, followed by instillation of a scolicidal agent (eg, hypertonic saline) and reaspiration (PAIR [percutaneous aspiration-injection-reaspiration]).

For *E. granulosus*, albendazole 400 mg po bid for 1 to 6 mo (7.5 mg/kg bid in children up to a maximum of 400 mg bid) is curative in 30 to 40% of patients and can be used to suppress growth in inoperable cases.

Prognosis for patients with *E. multilocularis* infection is poor unless the entire larval mass can be removed. Surgery is indicated if it is feasible, which depends on the size, location, and manifestations of the lesion. Albendazole in the above doses can suppress growth of inoperable lesions. Liver transplantation has been lifesaving in a few patients.

*Hymenolepis nana* Infection

(Dwarf Tapeworm Infection)

*Hymenolepis nana*, a tiny intestinal tapeworm, is the most common human cestode; infection is treated with praziquantel.

*Hymenolepis nana* is only 15 to 40 mm long. It requires only one host but can also cycle through two. Its larvae migrate only within the gut wall, and its life span is relatively short (4 to 6 wk). *H. nana* is more frequent in populations living in conditions of poverty and poor hygiene, particularly when fleas are present.

*H. nana* has 3 modes of infection:

• **Indirect 2-host cycle**: Rodents are the primary definitive hosts, and grain beetles, fleas, or other insects feed on contaminated rodent droppings as intermediate hosts; humans can become infected by ingesting parasitized insects.

• **Human-to-human oral-anal cycle**: Eggs are passed from one human to another or recycle externally in a single host.

• **Internal autoinfection**: Eggs hatch within the gut and initiate a 2nd generation without ever exiting the host. Autoinfection can result in massive numbers of worms, which can cause nausea, vomiting, diarrhea, abdominal pain, weight loss, and nonspecific systemic symptoms.

The pronounced cellular and humoral response to the tissue phase of *H. nana* infection probably provides some protection for adult humans living in endemic areas.

Diagnosis is made by finding eggs in stool samples.

Treatment
Praziquantel 25 mg/kg po once is the treatment of choice.

**Hymenolepis diminuta Infection**

*Hymenolepis diminuta* can cause intestinal infection.

*Hymenolepis diminuta*, the rat tapeworm, has a life cycle similar to the indirect cycle of *H. nana*, involving grain insects. *H. diminuta* rarely infects humans but can cause mild diarrhea.

Diagnosis is by finding characteristic eggs in stool.

Infection is effectively treated with praziquantel 25 mg/kg po once.

**Coenurusosis (Taenia multiceps or T. serialis Infection)**

*Taenia multiceps* and *T. serialis*, rare causes of human infection, are acquired by accidental ingestion of eggs from dog feces.

Canines are the definitive hosts for adult *Taenia multiceps* and *T. serialis* tapeworms; sheep and other herbivorous animals are intermediate hosts. Unwitting ingestion of material contaminated by dog feces causes human disease. The larvae invade and form a cyst (coenurus) in human tissue, usually in the CNS.

Symptoms require several years to develop and depend on the organ infected. Involvement of the brain causes increased intracranial pressure, seizures, loss of consciousness, and focal neurologic deficits.

Diagnosis is typically made after surgical removal, which is also the primary treatment. Surgery is typically done for symptomatic, space-occupying lesions.

**Sparganosis**

Sparganosis is infection with larvae of the tapeworm *Spirometra mansoni* and related species.

*Spirometra mansoni* affects dogs, cats, and other carnivores. Eggs are passed into freshwater where they are ingested by copepods (eg, *Cyclops*). Frogs, reptiles, and various small mammals ingest them and serve as intermediate hosts. Humans can become infected by accidental ingestion of copepods from water contaminated by cat or dog feces, ingestion of inadequately cooked flesh from another intermediate host, or contact with poultices containing flesh from these sources. In humans, larvae typically migrate to subcutaneous tissue or muscle and form slowly growing masses. Other sites, including the CNS, may be involved but are much less common. Symptoms are caused by mass effect.

Diagnosis is typically made after surgical removal, although it may be suggested when imaging detects a mass. Surgery is also the primary treatment and is typically done for symptomatic, space-occupying lesions.

**Taeniasis saginata**

(Beef Tapeworm Infection)

Infection with the beef tapeworm, *Taenia saginata*, may cause mild GI upset or passage of a motile segment in the stool. It is treated with praziquantel.

Cattle are intermediate hosts for *Taenia saginata*. Humans are infected by eating cysticerci (larval form) in raw or undercooked beef. The larvae mature in about 2 mo to adult worms that can live for several years; usually, only 1 or 2 adult worms are present.

Infection occurs worldwide but especially in cattle-raising regions of the tropics and subtropics in Africa, the Middle East, Eastern Europe, Mexico, and South America. Infection is uncommon in US cattle and is...
monitored by federal inspection.

Patients may be asymptomatic or have mild digestive symptoms. Passage of a motile segment often brings an otherwise asymptomatic patient to medical attention.

The stool should be examined for proglottids and eggs; eggs may also be present on anal swabs. The ova of *T. saginata* are indistinguishable from those of *T. solium* (pork tapeworm), as are the clinical features and management of intestinal infections due to the 2 tapeworms.

**Treatment**

- Praziquantel or niclosamide

Treatment is with a single oral dose of praziquantel 5 or 10 mg/kg. Alternatively, a single 2-g dose of niclosamide is given as 4 tablets (500 mg each) that are chewed one at a time and swallowed with a small amount of water. For children, the dose is 40 to 50 mg/kg once. Both drugs have cure rates of about 90%. Treatment can be considered successful when no proglottids are passed for 4 mo.

**Taeniasis Solium and Cysticercosis**

(Pork Tapeworm Infection)

Taeniasis solium is infection with adult *Taenia solium* worms that follows ingestion of contaminated pork, resulting in intestinal infection. Cysticercosis is infection with larvae of *T. solium*, which develop from ova excreted with human feces. Adult worms may cause mild GI symptoms or passage of a motile segment in the stool. Cysticercosis is usually asymptomatic unless larvae invade the CNS, resulting in neurocysticercosis, which can cause seizures and various other neurologic signs. Neurocysticercosis may be recognized on brain imaging studies. Less than half of patients with neurocysticercosis have adult *T. solium* in their intestines and thus eggs or proglottids in their stool. Adult worms can be eradicated with praziquantel. Treatment of symptomatic neurocysticercosis is with corticosteroids, anticonvulsants, and, in some situations, albendazole or praziquantel. Surgery may be required.

Presentation, diagnosis, and management of intestinal infection with the adult *T. solium* tapeworm are similar to those of beef tapeworm infection. However, humans may also act as intermediate hosts for *T. solium* larvae if they ingest *T. solium* eggs from human excreta (see Fig. 146-1). Another theory is that if an adult tapeworm is present in the intestine, gravid proglottids may be passed retrograde from the intestine to the stomach, where oncospheres (immature form of the parasite enclosed in an embryonic envelope) may hatch and migrate to subcutaneous tissue, muscle, viscera, and the CNS.

Adult tapeworms may reside in the small bowel for years. They may be 2 to 7 m long and produce < 1000 proglottids; each contains about 50,000 eggs.

Cysticercosis is prevalent, and neurocysticercosis is a major cause of seizure disorders in Latin America, Africa, Southeast Asia, and Eastern Europe. Infection in the US is most common among immigrants from those areas but has occurred in North Americans who have not traveled abroad but who have apparently been infected through exposure to immigrants harboring adult *T. solium*.

**Symptoms and Signs**

Humans infected with adult *T. solium* worms are asymptomatic or have mild GI complaints.

**Cysticercosis:** Viable cysticerci (larval form) in most organs cause minimal or no tissue reaction, but death of the cysts in the CNS can elicit an intense tissue response. Thus, symptoms often do not appear for years after infection. Infection in the brain (cerebral cysticercosis) may result in severe symptoms, resulting from mass effect and inflammation induced by degeneration of cysticerci and release of antigens.
Patients may present with seizures, signs of increased intracranial pressure, hydrocephalus, focal neurologic signs, altered mental status, or aseptic meningitis. Cysticerci may also infect the spinal cord, muscles, subcutaneous tissues, and eyes. Substantial secondary immunity develops after larval infection.

**Diagnosis**

- Microscopic examination of stool
- Imaging and serologic testing for patients with CNS symptoms

*T. solium* eggs are present in ≤50% of stool samples from patients with cysticercosis. Diagnosis is usually made when CT or MRI is done to evaluate neurologic symptoms. Scans may show solid nodules, cysts, calcified cysts, ring-enhancing lesions, or hydrocephalus. The CDC's (Centers for Disease Control and Prevention's) immunoblot assay (using a serum specimen) is highly specific and more sensitive than other enzyme immunoassays (particularly when >2 CNS lesions are present; sensitivity is lower when only a single cyst is present). Infection with adult *T. solium* worms can usually be diagnosed using stool samples.

**Treatment**

- **For intestinal infection:** Praziquantel
- **For cysticercosis:** Corticosteroids, anticonvulsants, and sometimes surgery

Intestinal infection is treated with praziquantel 5 to 10 mg/kg po as a single dose to eliminate adult worms.

Corticosteroids (prednisone 60 mg po once/day or dexamethasone 6 mg once/day) and anticonvulsants should be given to patients with symptomatic neurocysticercosis to reduce inflammation and symptoms.

The anthelmintic treatment of choice for cerebral cysticercosis is controversial. Not all patients respond to treatment, and not all patients must be treated (cysts may already be dead and calcified, or the inflammatory response to treatment may be worse than the disease). When anthelmintic treatment is used, albendazole 400 mg po bid for 8 to 30 days is the drug of choice; praziquantel 33.3 mg/kg po tid on day 1 followed by 16.6 mg/kg po tid for 29 days can also be used. Neither albendazole nor praziquantel should be used in patients with ocular or spinal cord involvement.

Surgery may be necessary for obstructive hydrocephalus (due to intraventricular cysticerci), infection of the 4th ventricle, and spinal and ocular cysticercosis.

*[Fig. 146-1. Taenia solium life cycle.]*
Chapter 147. Intestinal Protozoa

Introduction

The most important intestinal protozoan pathogens are *Entamoeba histolytica*, *Cryptosporidium* sp, *Giardia intestinalis* (*lambia*), *Cystoisospora* (*Isospora*) *belli*, *Cyclospora cayetanensis*, and members of the phylum Microsporidia. Multiple pathogenic parasites and nonpathogenic commensal organisms may be present in the intestine at the same time. Nonintestinal protozoan infections are covered in other chapters: For systemic protozoal diseases (malaria, babesiosis, leishmaniasis, toxoplasmosis, trypanosomiasis), see p. 1373; for nematode infections, see p. 1342; for fluke infections, see p. 1355; and for tapeworm infections, see p. 1360.

Intestinal protozoa are spread by the fecal-oral route, so infections are widespread in areas with inadequate sanitation and water treatment. They are also common in the US in settings where fecal incontinence and poor hygiene prevail, as occur in mental institutions and day care centers. Occasionally, large waterborne outbreaks of intestinal protozoan infection have occurred in the US (eg, the massive waterborne *Cryptosporidium* outbreak in Milwaukee in 1993). Some GI protozoa are spread sexually, especially with practices involving oral-anal contact, and several protozoan species cause severe opportunistic infections in patients with AIDS.

Diagnosis

Making a diagnosis based on symptoms and physical findings is difficult; stool testing for parasite antigens or microscopic examination of stool for cysts or organisms is necessary.

Fecal antigen tests that are sensitive and specific are available for

- *G. intestinalis*
- *Cryptosporidium* sp
- *E. histolytica*

Microscopic diagnosis may require several samples, concentration methods, and special stains; thus, the laboratory should be notified which pathogen or pathogens are suspected. Some patients require semi-invasive diagnostic techniques such as endoscopic biopsy (see Table 143-1 on p. 1337).

Amebiasis

(Entamebiasis)

Amebiasis is infection with *Entamoeba histolytica*. It is commonly asymptomatic, but symptoms ranging from mild diarrhea to severe dysentery may occur. Extraintestinal infections include liver abscesses. Diagnosis is by identifying *E. histolytica* in stool specimens or by serologic tests. Treatment for symptomatic disease is with metronidazole or tinidazole followed by paromomycin or other drugs active against cysts in the lumen.

Three species of *Entamoeba* are morphologically indistinguishable, but molecular techniques show that they are different species:

- *E. histolytica* (pathogenic)
- *E. dispar* (harmless colonizer, more common)
- *E. moshkovskii* (harmless colonizer)
Disease is caused by *E. histolytica* and tends to occur in regions with poor socioeconomic conditions and poor sanitation. Most infections occur in Central America, western South America, western and southern Africa, and the Indian subcontinent. In developed countries (eg, US), most cases occur among recent immigrants and travelers returning from endemic regions.

Worldwide each year, an estimated 40 to 50 million people develop amebic colitis or extraintestinal disease, and about 40,000 to 70,000 die.

**Pathophysiology**

*Entamoeba* sp exist in 2 forms:

- Trophozoite
- Cyst

The motile trophozoites feed on bacteria and tissue, reproduce, colonize the lumen and the mucosa of the large intestine, and sometimes invade tissues and organs. Trophozoites predominate in liquid stools but rapidly die outside the body. Some trophozoites in the colonic lumen become cysts that are excreted with stool.

Cysts predominate in formed stools and resist destruction in the external environment. They may spread directly from person to person or indirectly via food or water. Amebiasis can also be sexually transmitted by oral-anal contact.

*E. histolytica* trophozoites can adhere to and kill colonic epithelial cells and PMNs and can cause dysentery with blood and mucus but with few PMNs in stool. Trophozoites also secrete proteases that degrade the extracellular matrix and permit invasion into the intestinal wall and beyond. Trophozoites can spread via the portal circulation and cause necrotic liver abscesses. Infection may spread by direct extension from the liver to the right lung and pleural space or, rarely, through the bloodstream to the brain and other organs.

**Symptoms and Signs**

Most infected people are asymptomatic but chronically pass cysts in stools. Symptoms that occur with tissue invasion include intermittent diarrhea and constipation, flatulence, and cramping abdominal pain. Tenderness over the liver or ascending colon may occur, and stools may contain mucus and blood.

**Amebic dysentery**: This form, common in the tropics, manifests with episodes of frequent semiliquid stools that often contain blood, mucus, and live trophozoites. Abdominal findings range from mild tenderness to frank abdominal pain, with high fevers and toxic systemic symptoms. Abdominal tenderness frequently accompanies amebic colitis. Between relapses, symptoms diminish to recurrent cramps and loose or very soft stools, but emaciation and anemia may develop. Symptoms suggesting appendicitis may occur. Surgery in such cases may result in peritoneal spread of amebas.

**Chronic amebic infection**: This infection can mimic inflammatory bowel disease and manifests as intermittent nondysenteric diarrhea with abdominal pain, mucus, flatulence, and weight loss. Chronic infection may also manifest as tender, palpable masses or annular lesions (amebomas) in the cecum and ascending colon.

**Extraintestinal amebic disease**: Extraintestinal disease originates from infection in the colon and can involve any organ, but a liver abscess, usually single and in the right lobe, is the most common. It can manifest in patients who had no prior symptoms, is more common among men than among women (7:1 to 9:1), and may develop insidiously.

Symptoms include pain or discomfort over the liver, which is occasionally referred to the right shoulder, as well as intermittent fever, sweats, chills, nausea, vomiting, weakness, and weight loss. Jaundice is unusual and low grade when present. The abscess may perforate into the subphrenic space, right pleural
cavity, right lung, or other adjacent organs (eg, pericardium).

Skin lesions are occasionally observed, especially around the perineum and buttocks in chronic infection, and may also occur in traumatic or operative wounds.

**Diagnosis**

- **Intestinal infection:** Microscopic examination and, when available, enzyme immunoassay of stool
- **Extraintestinal infection:** Imaging and serologic testing or a therapeutic trial

Nondysenteric amebiasis may be misdiagnosed as irritable bowel syndrome, regional enteritis, or diverticulitis. A right-sided colonic mass may also be mistaken for cancer, TB, actinomycosis, or lymphoma.

Amebic dysentery may be confused with shigellosis, salmonellosis, schistosomiasis, or ulcerative colitis. In amebic dysentery, stools are usually less frequent and watery than those in bacillary dysentery. They characteristically contain tenacious mucus and flecks of blood. Unlike stools in shigellosis, salmonellosis, and ulcerative colitis, amebic stools do not contain large numbers of WBCs because trophozoites lyse them.

Hepatic amebiasis and amebic abscess must be differentiated from other hepatic infections and tumors.

Diagnosis of amebiasis is supported by finding amebic trophozoites, cysts, or both in stool or tissues; however, pathogenic *E. histolytica* are morphologically indistinguishable from nonpathogenic *E. dispar* and *E. moshkovskii*.

**Intestinal infection:** Identification of intestinal amebas may require examination of 3 to 6 stool specimens and concentration methods (see Table 143-1 on p. 1337). Antibiotics, antacids, antidiarrheals, enemas, and intestinal radiocontrast agents can interfere with recovery of the parasite and should not be given until the stool has been examined. *E. histolytica* also has to be distinguished from nonpathogenic amebas such as *E. coli*, *E. hartmanni*, *Endolimax nana*, and *Iodamoeba butschlii*.

In symptomatic patients, proctoscopy often shows characteristic flask-shaped mucosal lesions, which should be aspirated, and the aspirate should be examined for trophozoites. Biopsy specimens from rectosigmoid lesions may also show trophozoites.

**Extraintestinal infection:** This infection is more difficult to diagnose. Stool examination is usually negative, and recovery of trophozoites from aspirated pus is uncommon. If a liver abscess is suspected, ultrasonography, CT, or MRI should be done. They have similar sensitivity; however, no technique can differentiate amebic from pyogenic abscess with certainty.

Needle aspiration is reserved for lesions of uncertain etiology, those in which rupture seems imminent, and those that respond poorly to drug therapy. Abscesses contain thick, semifluid material ranging from yellow to chocolate-brown. A needle biopsy may show necrotic tissue, but motile amebas are difficult to find in abscess material, and amebic cysts are not present.

A therapeutic trial of an amebicide is often the most helpful diagnostic tool for an amebic liver abscess.

Serologic tests are positive in about 95% of patients with an amebic liver abscess, in > 70% of those with active intestinal infection, and in 10% of asymptomatic carriers. Enzyme immunoassay (EIA) is the most widely used. Antibody titers can confirm *E. histolytica* infection but may persist for months or years, making it impossible to differentiate acute from past infection in residents from areas with a high prevalence of infection. *E. histolytica*, *E. dispar*, and *E. moshkovskii* are morphologically indistinguishable, so microscopic examination cannot be used to differentiate them. A sensitive and specific antigen detection assay for the *E. histolytica* adherence lectin has been developed and is available. PCR-based assays are available in research settings.
Treatment

• Metronidazole or tinidazole initially

• Iodoquinol, paromomycin, or diloxanide furoate subsequently for cyst eradication

For mild to moderate GI symptoms, oral metronidazole 500 to 750 mg tid in adults (12 to 17 mg/kg tid in children) for 7 to 10 days is recommended. Metronidazole should not be given to pregnant women. Alcohol must be avoided because of the drug's disulfiram-like effect. Alternatively, tinidazole 2 g po once/day in adults (50 mg/kg [maximum 2 g] po once/day in children > 3 yr) for 3 days can be used. When taken with alcohol, tinidazole also has a disulfiram-like effect, and it should not be used during pregnancy; however, in terms of GI adverse effects, it is generally better tolerated than metronidazole.

For severe intestinal and extraintestinal amebiasis, metronidazole 750 mg tid in adults (12 to 17 mg/kg tid in children) for 7 to 10 days is used. Alternatively, tinidazole 2 g po once/day in adults (50 mg/kg [maximum 2 g] po once/day in children > 3 yr) for 5 days can be used.

A course of metronidazole or tinidazole should be followed by a 2nd oral drug to eradicate residual cysts in the lumen. Options are

• Iodoquinol 650 mg po tid in adults (10 to 13 mg/kg [maximum of 2 g/day] tid in children) for 20 days

• Paromomycin 8 to 11 mg/kg tid for 7 days

• Diloxanide furoate 500 mg po tid in adults (7 mg/kg po tid in children) for 10 days

Diloxanide furoate is not available commercially in the US.

Therapy should include rehydration with fluid and electrolytes and other supportive measures.

Asymptomatic people who pass E. histolytica cysts should be treated with paromomycin, iodoquinol, or diloxanide furoate (see above for doses). Although metronidazole and tinidazole have some activity against E. histolytica cysts, it is not sufficient for them to be used for cyst eradication.

Treatment is not necessary for E. dispar or E. moshkovskii infections. However, if fecal antigen testing to differentiate them from E. histolytica is not available, the decision to treat is made clinically (eg, by the likelihood of exposure to E. histolytica).

Prevention

Contamination of food and water with human feces must be prevented—a problem complicated by the high incidence of asymptomatic carriers. Uncooked foods, including salads and vegetables, and potentially contaminated water and ice should be avoided in developing areas. Boiling water kills E. histolytica cysts. The effectiveness of chemical disinfection with iodine- or chlorine-containing compounds depends on the temperature of the water and amount of organic debris in it. Portable filters provide various degrees of protection.

Work continues on the development of a vaccine, but none is available yet.

Cryptosporidiosis

Cryptosporidiosis is infection with Cryptosporidium. The primary symptom is watery diarrhea, often with other signs of GI distress. Illness is typically self-limited in immunocompetent patients but can be persistent and severe in patients with AIDS. Diagnosis is by identification of the organism or antigen in stool. Treatment, when necessary, is with nitazoxanide.

Pathophysiology
Cryptosporidia are coccidian protozoa that replicate in small-bowel epithelial cells of a vertebrate host. Infective oocysts are shed into the lumen and passed in stool. Very few oocysts (eg, < 100) are required to cause disease, thus increasing risk of person-to-person transmission. After ingestion by another vertebrate, the oocyst releases sporozoites that transform into trophozoites in epithelial cells, replicate, and then produce oocysts that are released into the lumen of the intestine to complete the cycle. Thin-walled oocysts are involved in autoinfection.

Oocysts are resistant to harsh conditions, including chlorine at levels usually used in public water treatment systems.

**Epidemiology**

*Cryptosporidium parvum* and *C. hominis* are responsible for most human cases. Infections result from fecally contaminated food or water, direct person-to-person contact, or zoonotic spread. The disease occurs worldwide. Cryptosporidiosis is responsible for 0.6 to 7.3% of diarrheal illness in developed countries and an even higher percentage in areas with poor sanitation. In Milwaukee, Wisconsin, > 400,000 people were affected during a waterborne outbreak in 1993, when the city's water supply was contaminated by run-off from dairy farms during spring rains and the filtration system was not working correctly.

Children, travelers to foreign countries, immunocompromised patients, and medical personnel caring for patients with cryptosporidiosis are at increased risk. Outbreaks have occurred in day care centers. Severe, chronic diarrhea due to cryptosporidiosis is a problem in patients with AIDS.

**Symptoms and Signs**

The incubation period is about 1 wk, and clinical illness occurs in > 80% of infected people. Onset is abrupt, with profuse watery diarrhea, abdominal cramping, and, less commonly, nausea, anorexia, fever, and malaise. Symptoms usually persist 1 to 2 wk, rarely ≥ 1 mo, and then abate. Fecal excretion of oocysts may continue for several weeks after symptoms have subsided. Asymptomatic shedding of oocysts is common among older children in developing countries.

In the immunocompromised host, onset may be more gradual, but diarrhea can be more severe. Unless the underlying immune defect is corrected, infection can persist, causing profuse intractable diarrhea for life. Fluid losses of > 5 to 10 L/day have been reported in some AIDS patients. The intestine is the most common site of infection in immunocompromised hosts; however, other organs (eg, biliary tract, pancreas, respiratory tract) may be involved.

**Diagnosis**

- Microscopic examination of stool (special techniques required)
- Enzyme immunoassay for fecal antigen

Identifying the acid-fast oocysts in stool confirms the diagnosis, but conventional methods of stool examination are unreliable. Oocyst excretion is intermittent, and multiple stool samples may be needed. Several concentration techniques increase the yield. *Cryptosporidium* oocysts can be identified by phase-contrast microscopy or by staining with modified Ziehl-Neelsen or Kinyoun techniques. Immunofluorescence microscopy with fluorescein-labeled monoclonal antibodies allows for greater sensitivity and specificity.

Enzyme immunoassay for fecal *Cryptosporidium* antigen is more sensitive than microscopic examination for oocysts. Intestinal biopsy can demonstrate *Cryptosporidium* within epithelial cells.

**Treatment**

- Nitazoxanide in patients without AIDS
Highly active antiretroviral therapy (HAART) in patients with AIDS

In immunocompetent people, cryptosporidiosis is self-limited. Nitazoxanide can be used; the recommended doses, given for 3 days, are

- Age 1 to 3 yr: 100 mg bid
- Age 4 to 11 yr: 200 mg bid
- Age > 12 yr: 500 mg bid

No drug has proved to be effective against Cryptosporidium in patients with advanced AIDS. Symptoms have abated after effective HAART in some AIDS patients. Supportive measures, oral and parenteral rehydration, and hyperalimentation are indicated for immunocompromised patients.

Prevention

Stools of patients with cryptosporidiosis are highly infectious; strict stool precautions should be observed. Special biosafety guidelines have been developed for handling clinical specimens. Boiling water is the most reliable decontamination method; only filters with pore sizes ≤ 1 μm (specified as "absolute 1 micron" or certified by NSF Standard No. 53) remove Cryptosporidium cysts.

Cystoisosporiasis and Cyclosporiasis

Cystoisosporiasis is infection with Cystoisospora (Isospora) belli; cyclosporiasis is infection with Cyclospora cayetanensis. Both organisms are coccidian protozoa. Symptoms include watery diarrhea with GI and systemic symptoms. Diagnosis is by detection of characteristic oocysts in stool or intestinal biopsy specimens. Treatment is usually with trimethoprim/sulfamethoxazole.

The life cycles of Cystoisospora belli and Cyclospora cayetanensis are similar to that of Cryptosporidium, except that oocysts must sporulate before becoming infective. Human cystoisosporiasis and cyclosporiasis are most common in tropical and subtropical climates. Transmission is by the fecal-oral route via contaminated food or drink. In North America, outbreaks of C. cayetanensis have been caused by ingestion of raspberries imported from Guatemala.

Symptoms and Signs

The primary symptom is sudden, nonbloody, watery diarrhea, with fever, abdominal cramps, nausea, anorexia, malaise, and weight loss. In immunocompetent patients, the illness usually resolves spontaneously but can last weeks.

In hosts with depressed cell-mediated immunity as occurs in AIDS, cystoisosporiasis and cyclosporiasis may cause severe, intractable, voluminous diarrhea resembling cryptosporidiosis. Extraintestinal disease in patients with AIDS may include cholecystitis and disseminated infection.

Diagnosis

- Microscopic examination of stool

Diagnosis is by detection of oocysts via microscopic examination of the stool. Detection is facilitated by staining stool samples with modified acid-fast stain. Multiple stool specimens may be needed because cyst secretion may be intermittent. Diagnosis is sometimes made only when intracellular parasite stages are detected in biopsies of intestinal tissue. In cystoisosporiasis, cysts autofluoresce when ultraviolet microscopy is used; the stool may contain Charcot-Leyden crystals (hexagonal, double-pointed, and often needlelike crystals) derived from eosinophils. Unlike other protozoan infections, cystoisosporiasis may result in peripheral blood eosinophilia.
Treatment

- Trimethoprim/sulfamethoxazole

Treatment of choice for both cystoisosporiasis and cyclosporiasis is double-strength trimethoprim/sulfamethoxazole (TMP/SMX): 160 mg TMP and 800 mg SMX po bid for 10 days for cystoisosporiasis or for 7 to 10 days for cyclosporiasis. Children are given 5 mg/kg TMP (and 25 mg/kg SMX) po bid for the same number of days.

In patients with AIDS, higher doses and longer duration may be needed, and treatment of acute infection is usually followed by long-term suppressive therapy.

Ciprofloxacin 500 mg po bid for 7 days has also been used to treat cystoisosporiasis and cyclosporiasis but appears to be less effective than TMP/SMX.

Prevention is as for cryptosporidiosis.

Giardiasis

Giardiasis is infection with the flagellated protozoan *Giardia intestinalis* (*lamblia*). Infection can be asymptomatic or cause symptoms ranging from intermittent flatulence to chronic malabsorption. Diagnosis is by identifying the organism in fresh stool or duodenal contents or by assays of *Giardia* antigen in stool. Treatment is with metronidazole, tinidazole, or nitazoxanide or, during pregnancy, paromomycin.

*Giardia* trophozoites firmly attach to the duodenal and proximal jejunal mucosa and multiply by binary fission. Some organisms transform into environmentally resistant cysts that are spread by the fecal-oral route. Waterborne transmission is the major source of giardiasis. Transmission can also occur by ingestion of contaminated food and by direct person-to-person contact, especially in mental institutions and day care centers or between sex partners. *Giardia* cysts remain viable in surface water and are resistant to routine levels of chlorination. Wild animals may also serve as reservoirs. Thus, mountain streams as well as chlorinated but poorly filtered municipal water supply systems have been implicated in waterborne epidemics.

Symptoms and Signs

Many cases are asymptomatic. However, asymptomatic people can pass infective cysts.

Symptoms of acute giardiasis usually appear 1 to 2 wk after infection. They are usually mild and include watery malodorous diarrhea, abdominal cramps and distention, flatulence, eructation, intermittent nausea, epigastric discomfort, and sometimes low-grade malaise and anorexia. Acute giardiasis usually lasts 1 to 3 wk. Malabsorption of fat and sugars can lead to significant weight loss in severe cases. Neither blood nor WBCs are present in stool.

A subset of infected patients develop chronic diarrhea with foul stools, abdominal distention, and malodorous flatus. Substantial weight loss may occur. Chronic giardiasis occasionally causes failure to thrive in children.

Diagnosis

- Enzyme immunoassay for antigen in stool
- Microscopic examination of stool

Enzyme immunoassay to detect parasite antigen in stool is more sensitive than microscopic examination. Characteristic trophozoites or cysts in stool are diagnostic, but parasite excretion is intermittent and at low levels during chronic infections. Thus, microscopic diagnosis may require repeated stool examinations. Sampling of the upper intestinal contents can also yield trophozoites but is seldom necessary. Specific
DNA probes are under evaluation.

**Treatment**

- Tinidazole, metronidazole, or nitazoxanide

For symptomatic infections, metronidazole 250 mg po tid in adults (5 mg/kg po tid in children) for 5 to 7 days can be used. Adverse effects include nausea, headaches, and a disulfiram-like effect if alcohol is consumed concurrently. Tinidazole 2 g once in adults (50 mg/kg [maximum 2 g] in children) is as effective as and less toxic than metronidazole. Neither of these drugs should be taken with alcohol.

Nitazoxanide is given orally for 3 days as follows: age 1 to 3 yr, 100 mg bid; age 4 to 11 yr, 200 mg bid; and age > 12 yr (including adults), 500 mg bid. It is available in liquid form for children.

Furazolidone and quinacrine are effective but are now rarely used because of potential toxicity.

Metronidazole and tinidazole should not be given to pregnant women. Nitazoxanide is in pregnancy category B. If therapy cannot be delayed because of symptoms, the nonabsorbable aminoglycoside paromomycin (8 to 11 mg/kg po tid for 5 to 10 days) is an option.

**Prevention**

Prevention requires appropriate public water treatment, hygienic food preparation, and appropriate fecal-oral hygiene. Water can be decontaminated by boiling. *Giardia* cysts resist routine levels of chlorination. Disinfection with iodine-containing compounds is variably effective and depends on the turbidity and temperature of the water and duration of treatment. Some handheld filtration devices can remove *Giardia* cysts from contaminated water, but the efficacy of various filter systems has not been fully assessed.

Treatment of asymptomatic cyst passers can theoretically reduce the spread of infection, but whether it is cost-effective remains unclear.

**Microsporidiosis**

Microsporidiosis is infection with microsporidia. Symptomatic disease develops predominantly in patients with AIDS and includes chronic diarrhea, disseminated infection, and corneal disease. Diagnosis is by demonstrating organisms in biopsy specimens, stool, urine, other secretions, or corneal scrapings. Treatment is with albendazole or fumagillin (depending on the infecting species and clinical syndrome), with topical fumagillin added for eye disease.

Microsporidia are obligate intracellular spore-forming protozoan parasites. At least 14 of the > 1200 species are associated with human disease. Spores of the organisms are acquired by ingestion, inhalation, direct contact with the conjunctiva, animal contact, or person-to-person transmission. Inside the host, they harpoon a host cell with their polar tubule or filament and inoculate it with an infective sporoplasm. Intracellularly, the sporoplasm divides and multiplies, producing sporoblasts that mature into spores; the spores can disseminate throughout the body or pass into the environment via respiratory aerosols, stool, or urine. An inflammatory response develops when spores are liberated from host cells.

Little is known about routes of transmission to humans or possible animal reservoirs. Microsporidia probably are a common cause of subclinical or mild self-limited illness in otherwise healthy people, but only a few cases of human infection were reported in the pre-AIDS era.

Microsporidia have emerged as opportunistic pathogens in patients with AIDS and, to a lesser degree, in those with other immunocompromising conditions. *Encephalitozoon bieneusi* and *E.* (formerly *Septata*) *intestinalis* can cause chronic diarrhea in patients with AIDS and CD4+ cell counts of < 100/μL. Microsporidian species can also infect the biliary tract, cornea, muscles, respiratory tract, GU system, and, occasionally, the CNS.

**Symptoms and Signs**

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Clinical illness caused by microsporidia varies with the parasite species and the immune status of the host. In patients with AIDS, various species cause chronic diarrhea, malabsorption, wasting, cholangitis, punctate keratoconjunctivitis, peritonitis, hepatitis, myositis, or sinusitis. Infections of kidneys, gallbladder, and sinuses have occurred. *Vittaforma (Nosema) corneum* and several other species can cause ocular infections ranging from punctuate keratopathy with redness and irritation to severe, vision-threatening stromal keratitis.

**Diagnosis**

- Light or electron microscopy with special stains

Infecting organisms can be demonstrated in specimens of affected tissue obtained by biopsy or in stool, urine, CSF, sputum, or corneal scrapings. Microsporidia are best seen with special staining techniques. Fluorescence brighteners (fluorochromes) are used to detect spores in tissues and smears. The quick-hot Gram chromotrope technique is the fastest. Immunoassay and PCR-based tests hold promise for the future.

Transmission electron microscopy is currently the most sensitive test and is used for speciation.

**Treatment**

- For immunocompetent patients: Supportive care
- For immunocompromised patients: Albendazole alone or with topical fumagillin for corneal disease

In immunocompetent patients, microsporidia infections are usually self-limited, and therapy is seldom necessary.

In immunocompromised patients, albendazole (400 mg po bid for 21 days in adults) may be effective in controlling intestinal infection with *E. intestinalis*. The drug reduces the number of organisms in small-bowel biopsies but does not eliminate infection. Fumagillin 20 mg po tid for 14 days has been used for *E. bieneusi*, but it has adverse effects (eg, bone marrow suppression).

Ocular lesions (due to *Brachiola algerae*, *E. hellem*, or *E. cuniculi*) have been treated with albendazole 400 mg bid plus fumagillin eyedrops. These drugs are also used for *V. corneum*, but they frequently fail, and keratoplasty may be required.

Albendazole 400 mg bid has been used for patients with disseminated disease and skin and deep muscle infection caused by numerous microsporidian species.

Treatment of AIDS with highly active antiretroviral therapy (HAART) is important and can lead to reduction in symptoms.
Chapter 148. Extraintestinal Protozoa

Introduction

Protozoa are motile, single-celled organisms that occur worldwide. Many of those that cause extraintestinal infections are transmitted by arthropod vectors. These infections include African trypanosomiasis, Chagas disease, leishmaniasis, and malaria. Toxoplasmosis is acquired through contaminated food. Free-living amebas are acquired through contact with surface water or soil.

African Trypanosomiasis

(African Sleeping Sickness)

African trypanosomiasis is infection with protozoa of the genus *Trypanosoma*, transmitted by the bite of a tsetse fly. Symptoms include characteristic skin lesions, intermittent fever, headache, rigors, transient edema, generalized lymphadenopathy, and often fatal meningoencephalitis. Diagnosis is by identification of the organism in blood, lymph node aspirate, or CSF or sometimes by serologic tests. Treatment is with suramin, pentamidine, melarsoprol, or eflornithine, depending on the infecting subspecies, clinical stage, and drug availability.

African trypanosomiasis is caused by *Trypanosoma brucei gambiense* in West and Central Africa and by *T. brucei rhodesiense* in East Africa; both species are endemic in Uganda. The organisms are transmitted by tsetse flies and occasionally by blood transfusion.

Pathophysiology

Metacyclic trypomastigotes inoculated by flies transform into bloodstream trypomastigotes, which multiply by binary fission and spread through the lymphatics and bloodstream after inoculation. Bloodstream trypomastigotes multiply until specific antibodies produced by the host sharply reduce parasite levels. However, a subset of parasites escape immune destruction by a change in their variant surface glycoprotein and start a new multiplication cycle. The cycle of multiplication and lysis repeats. Late in the course of infection, trypanosomes appear in the interstitial fluid of many organs, including the myocardium and eventually the CNS. The cycle is continued when a tsetse fly bites an infected human. Humans are the main reservoir of *T. b. gambiense*, but this species may also reside in animals. Wild game animals are the main reservoir of *T. b. rhodesiense*.

Symptoms and Signs

The disease has 3 stages:

- Cutaneous

- Hemolymphatic

- CNS

Cutaneous: A papule may develop at the site of the tsetse fly bite within a few days to 2 wk. It evolves into a dusky red, painful, indurated nodule (trypanosomal chancre). A chancre is present in about half of Caucasians with *T. b. rhodesiense* but is less common in Africans with *T. b. rhodesiense* and seldom occurs with *T. b. gambiense*.

Hemolymphatic: Over several months in *T. b. gambiense* infection but a period of weeks with *T. b. rhodesiense*, intermittent fever, headaches, rigors, and transient swellings develop. An evanescent, circinate erythematous rash may develop. It is most readily visible in light-skinned patients. Generalized lymphadenopathy often occurs. Winterbottom's sign (enlarged lymph nodes in the posterior cervical triangle) is characteristic with *T. b. gambiense* sleeping sickness.
CNS: In the Gambian form, CNS involvement occurs months to several years after onset of acute disease. In the Rhodesian form, disease is more fulminant, and CNS invasion often occurs within a few weeks. CNS involvement causes persistent headache, inability to concentrate, personality changes (eg, progressive lassitude and indifference), daytime somnolence, hyperphagia, tremor, ataxia, and terminal coma. Without treatment, death occurs within months of disease onset with *T. b. rhodesiense* and during the 2nd or 3rd yr with *T. b. gambiense*. Untreated patients die in coma of undernutrition or secondary infections.

**Diagnosis**

- Light microscopy of blood (thin or thick smears) or other fluid sample

Diagnosis is made by identifying trypanosomes in fluid from a chancre, lymph node aspirate, blood, bone marrow aspirate, or, during the late stage of infection, CSF. Preferred sources are blood smears for *T. b. rhodesiense* and fluid aspirated from an enlarged lymph node for *T. b. gambiense*. Wet preparations should be examined for motile trypanosomes, and smears should be fixed, stained with Giemsa (or Field's) stain, and examined. Concentration techniques (eg, centrifugation of blood or CSF) enhance sensitivity.

Antibody detection assays are not very useful clinically because seroconversion occurs after the onset of symptoms. However, a card agglutination test for *T. b. gambiense* is useful in mass screening programs to identify candidates for microscopic examination.

When the CNS is involved, lumbar puncture is done. CSF pressure is increased, and CSF has elevated levels of lymphocytes (≥ 5 cells/μL), total protein, and IgM. In addition to trypanosomes, characteristic Mott cells (plasma cells with cytoplasmic vacuoles that contain immunoglobulin [Russell bodies]) may be present.

Other, nonspecific laboratory findings include anemia, monocytosis, and markedly elevated serum levels of polyclonal IgM.

**Treatment**

- Without CNS involvement, pentamidine or eflorentine for *T. b. gambiense*; suramin for *T. b. rhodesiense*

- With CNS involvement, eflorentine or melarsoprol for *T. b. gambiense*; melarsoprol for *T. b. rhodesiense*

**Without CNS involvement:** Suramin and pentamidine are effective against bloodstream stages of both *T. brucei* subspecies but do not cross the blood-brain barrier and are not useful for CNS infection. Pentamidine is preferred for *T. b. gambiense*, and suramin is preferred for the hemolymphatic stage of *T. b. rhodesiense*. The dosage of pentamidine is 4 mg/kg IM or IV once/day for 7 days. An initial test dose of suramin 100 mg IV (to exclude hypersensitivity) is followed by 20 mg/kg (up to 1 g) IV on days 1, 3, 7, 14, and 21.

Eflornithine (availability limited) is effective against all stages of *T. b. gambiense* (but not *T. b. rhodesiense*) trypanosomiasis. Dosage is 100 mg/kg IV qid for 14 days. When available, it is the drug of choice for *T. b. gambiense*.

**With CNS involvement:** Melarsoprol, an organic arsenical, is used in most African countries for CNS disease. For *T. b. gambiense*, dosage is 2.2 mg/kg IV once/day for 10 days. Where available, eflornithine can be used in the regimen above for *T. b. gambiense* CNS disease. For *T. b. rhodesiense*, dosage is 2 to 3.6 mg/kg IV once/day for 3 days; after 7 days, 3.6 mg/kg once/day is given for 3 days, followed 7 days later by another 3-day course at this dose. Alternative regimens have been proposed for debilitated patients with severe CNS involvement.

Serious adverse effects include reactive encephalopathy and exfoliative dermatitis in addition to the usual
Gl and renal toxicity of arsenicals.

Corticosteroids have been used to decrease the risk of reactive encephalopathy.

Prevention

Prevention includes avoiding endemic areas and protecting against tsetse flies. Visitors to game parks should wear substantial wrist- and ankle-length clothing (tsetse flies bite through thin clothes) and use insect repellents with DEET (diethyltoluamide) appropriately.

Pentamidine can help prevent *T. b. gambiense* infection, but it may damage pancreatic β-cells, resulting in insulin release and hypoglycemia followed later by diabetes; thus, it is seldom used for prophylaxis.

**Babesiosis**

Babesiosis is infection with *Babesia* sp. Infections can be asymptomatic or cause a malaria-like illness with fever and hemolytic anemia. Disease is most severe in asplenic patients, the elderly, and patients with AIDS. Diagnosis is by identification of *Babesia* in a peripheral blood smear, serologic test, or PCR. Treatment, when needed, is with azithromycin plus atovaquone or with quinine plus clindamycin.

**Etiology**

In the US, *Babesia microti* is the most common cause of babesiosis. Rodents are the principal natural reservoir, and deer ticks of the family Ixodidae are the usual vectors. Larval ticks become infected while feeding on an infected rodent, then transform into nymphs that transmit the parasite to another animal or to a human. Adult ticks ordinarily feed on deer but may also transmit the parasite to humans. *Babesia* enter RBCs, mature, and then divide asexually. Infected erythrocytes eventually rupture and release organisms that invade other RBCs; thus, *Babesia* can also be transmitted by blood transfusion.

Endemic areas in the US include the islands and the mainland bordering Nantucket Sound in Massachusetts, eastern Long Island and Shelter Island in New York, coastal Connecticut, and New Jersey, as well as foci in Wisconsin and the upper Midwest. *Babesia duncani* has been isolated from patients in Washington and California. A currently unnamed strain designated MO-1 has been reported in patients in Missouri. Other *Babesia* sp transmitted by different ticks infect humans in areas of Europe. In Europe, *B. divergens* is the principle cause of babesiosis in patients who have had a splenectomy.

*Ixodes* ticks infected with *Babesia* are sometimes coinfected with *Borrelia burgdorferi* (which causes Lyme disease), *Anaplasma phagocytophilum* (which causes human granulocytic anaplasmosis), or both.

**Symptoms and Signs**

Asymptomatic infection may persist for months to years and remain subclinical throughout its course in otherwise healthy people, especially those < 40 yr.

When symptomatic, the illness usually starts after a 1- to 2-wk incubation period with malaise, fatigue, chills, fever, headache, myalgia, and arthralgia, which may last for weeks. Hepatosplenomegaly with jaundice, mild to moderately severe hemolytic anemia, mild neutropenia, and thrombocytopenia may occur.

Infection is sometimes fatal, particularly in the elderly, asplenic patients, and patients with AIDS. In such patients, babesiosis may resemble falciparum malaria, with high fever, hemolytic anemia, hemoglobinuria, jaundice, and renal failure. Splenectomy may cause previously acquired asymptomatic parasitemia to become symptomatic.

**Diagnosis**

- Light microscopy of blood smears
Most patients do not remember a tick bite, but they may report a history of travel to an endemic region. Diagnosis is usually made by finding *Babesia* in blood smears, but differentiation from *Plasmodium* species can be difficult. Tetrad forms (the so-called Maltese cross formation), although not common, are unique to *Babesia* and helpful diagnostically. Serologic and PCR tests are available. Antibody detection by indirect fluorescent antibody (IFA) testing using *B. microti* antigens can be helpful in patients with low-level parasitemia but may be falsely negative in those infected with other *Babesia* sp. PCR-based assays are available in research settings.

**Treatment**

- Atovaquone plus azithromycin

Asymptomatic patients require no treatment, but therapy is indicated for patients with persistent high fever, rapidly increasing parasitemia, and falling Hct. The combination of atovaquone 750 mg po q 12 h and azithromycin 600 mg po once/day for 7 to 10 days is as effective as traditional therapy with quinine plus clindamycin and has fewer adverse effects. Pediatric dosage is atovaquone 20 mg/kg bid plus azithromycin 12 mg/kg once/day for 7 to 10 days.

Alternatively, quinine 650 mg po tid for 7 days plus clindamycin 600 mg po tid or 1.2 g IV bid for 7 to 10 days can be used. Pediatric dosage is quinine 10 mg/kg po tid plus clindamycin 7 to 14 mg/kg po tid.

Exchange transfusion has been used in hypotensive patients with high parasitemia.

Standard tick precautions (see Sidebar 139-1 on p. 1283) should be taken by all people in endemic areas. Asplenic patients and patients with AIDS should be particularly cautious.

**Chagas Disease**

(American Trypanosomiasis)

*Chagas disease* is infection with *Trypanosoma cruzi*, transmitted by Triatominae bug bites. Symptoms begin with a skin lesion or unilateral periorbital edema, then progress to fever, malaise, generalized lymphadenopathy, and hepatosplenomegaly; years later, some patients develop chronic cardiomyopathy, megaesophagus, or mega-colon. Diagnosis is by detecting trypanosomes in peripheral blood or aspirates from infected organs. Antibody tests are sensitive and can be helpful. Treatment is with nifurtimox or benznidazole.

*T. cruzi* is transmitted by Triatominae (reduviid, kissing, or assassin) bugs.

**Pathophysiology**

While biting, infected bugs deposit feces containing metacyclic trypomastigotes on the skin. These infective forms enter through the bite wound or penetrate the conjunctivae or mucous membranes. The parasites invade macrophages at the site of entry and transform into amastigotes that multiply by binary fission; the amastigotes develop into trypomastigotes, enter the bloodstream and tissue spaces, and infect other cells. Cells of the reticuloendothelial system, myocardium, muscles, and nervous system are most commonly involved.

Infection can also be transmitted by blood transfusion, organ transplantation, or ingestion of uncooked food or drink (eg, drinks made from sugar cane juice) contaminated by infected reduviid bugs or their feces. Transplacental transmission is also possible.

**Etiology**

Infected Triatominae bugs are present in North, Central, and South America. More than 20 million people in the Americas are infected with *T. cruzi*, but the prevalence has been decreasing because of control...
measures. In some rural parts of South America, Chagas disease has been a leading cause of death. Nonhuman reservoirs include dogs, cats, opossums, rats, and many other animals.

Vector-borne disease is rare in the US, but some Latin American immigrants living in the US are chronically infected. These people are potential sources of transmission by blood transfusion or organ donation.

**Symptoms and Signs**

Acute infection is followed by a latent (indeterminate) period, which may remain asymptomatic or progress to chronic disease. Immunosuppression may reactivate latent infection, with high parasitemia and a 2nd acute stage, skin lesions, or brain abscesses. Congenital transmission occurs in 1 to 5% of pregnancies and results in abortion, stillbirth, or chronic neonatal disease with high mortality.

**Acute:** Acute infection in endemic areas usually occurs in childhood and can be asymptomatic. When present, symptoms start 1 to 2 wk after exposure. An indurated, erythematous skin lesion (a chagoma) appears at the site of parasite entry. When the inoculation site is the conjunctiva, unilateral periocular and palpebral edema with conjunctivitis and preauricular lymphadenopathy are collectively called Romana's sign.

Acute Chagas disease is fatal in a small percentage of patients; death results from acute myocarditis with heart failure or meningoencephalitis. In the remainder, symptoms subside without treatment.

Primary acute Chagas disease in immunocompromised patients, such as those with AIDS, may be severe and atypical, with skin lesions and, rarely, brain abscesses.

**Chronic:** Chronic disease develops in 20 to 40% after a latent phase that may last years or decades. The main effects are

- **Cardiac**
- **GI**

Chronic cardiomyopathy leads to flaccid enlargement of all chambers, apical aneurysms, and localized degenerative lesions in the conduction system. Patients may present with heart failure, syncope, sudden death due to heart block or ventricular arrhythmia, or thromboembolism. ECG may show right bundle branch or complete heart block.

GI disease causes symptoms resembling achalasia or Hirschsprung's disease. Chagas megaesophagus manifests as dysphagia and may lead to pulmonary infections caused by aspiration or to severe undernutrition. Mega-colon may result in long periods of obstipation and intestinal volvulus.

**Diagnosis**

- Light microscopy of blood smears (thin or thick) or another fluid sample

The number of trypanosomes in peripheral blood is large during the acute phase and readily detected by examining thin or thick smears. In contrast, few parasites are present in blood during latent infection or chronic disease. Definitive diagnosis may be made by examining aspirates from organs such as lymph nodes.

Serologic tests including indirect fluorescent antibody (IFA) and enzyme immunoassays (EIA) are sensitive but may yield false-positive results in patients with leishmaniasis or other diseases. Other diagnostic approaches include xenodiagnosis (examination of the intestinal contents of laboratory-raised bugs after they take a blood meal from a patient suspected of having Chagas disease) and detection of PCR-amplified parasite DNA in blood or tissue fluids.

**Treatment**
• Nifurtimox or benznidazole

• Supportive care

Treatment in the acute stage rapidly reduces parasitemia, shortens the clinical illness, and reduces risk of mortality due to chronic infection.

For indeterminate infections, treatment of children and young adults has been recommended but is not always curative. Treatment of older adults with indeterminate disease is controversial.

Once the signs of chronic Chagas disease appear, antiparasitic drugs are not helpful.

Supportive measures include treatment for heart failure, pacemakers for heart block, antiarrhythmic drugs, cardiac transplantation, esophageal dilation, botulinum toxin injection into the lower esophageal sphincter, and GI tract surgery.

The only effective drugs are

• **Nifurtimox**: For adults, 2 to 2.5 mg/kg po qid for 3 to 4 mo
  
  For children aged 11 to 16 yr, 3 to 3.75 mg/kg qid for 3 mo

  For children aged 1 to 10 yr, 4 to 5 mg/kg qid for 3 mo

• **Benznidazole**: For adults and children > 12 yr, 2.5 to 3.5 mg/kg po bid for 1 to 3 mo
  
  For children ≤ 12 yr, 5 mg/kg bid for 1 to 3 mo

Both drugs have substantial toxicity. The long treatment courses are often associated with GI adverse effects, peripheral neuropathy, poor tolerance, and low compliance.

**Prevention**

Plastering walls and replacing thatched roofs or repeated spraying of houses with residual insecticides (those that have prolonged duration of action) can control Triatominae bugs. Infection in travelers is rare and can be avoided by not sleeping in adobe dwellings or by using bed nets if sleeping in such dwellings is unavoidable.

Blood and organ donors are screened in many endemic areas and, since 2006, in the US to prevent transfusion and organ transplant-related Chagas disease.

**Free-Living Amebas**

Free-living amebas are protozoa that live independently in soil or water and do not require a human or animal host. They rarely cause disease, in contrast to the parasitic ameba *Entamoeba histolytica*, which is a common cause of intestinal infection (see p. 1367). Pathogenic free-living amebas are of the genera *Naegleria*, *Acanthamoeba*, and *Balamuthia*.

Three major syndromes occur:

• Primary amebic meningoencephalitis

• Granulomatous amebic encephalitis

• Amebic keratitis

*Acanthamoeba* can also cause skin lesions.
Primary Amebic Meningoencephalitis

Primary amebic meningoencephalitis is a generally fatal, acute CNS infection caused by *Naegleria fowleri*.

*Naegleria fowleri* inhabit bodies of warm fresh water worldwide. Swimming in contaminated water exposes nasal mucosa to the organism, which can enter the CNS via olfactory neuroepithelium and the cribriform plate. Most patients are healthy children or young adults.

Symptoms begin within 1 to 2 wk of exposure, sometimes with alteration of smell and taste. Fulminant meningoencephalitis ensues, with headache, meningismus, and mental status change, progressing to death within 10 days, usually due to cerebral herniation. Only a few patients survive.

Diagnosis is suspected based on history of swimming in fresh water, but confirmation is difficult because CT and routine CSF tests, although necessary to exclude other causes, are nonspecific. Wet mount of CSF should be done; it may demonstrate motile amebic trophozoites (which are destroyed by Gram stain techniques).

Optimal treatment is unclear. A reasonable regimen would include amphotericin B (given intravenously, intrathecally, or both) plus azithromycin or clarithromycin, azole antimicrobials (eg, ketoconazole, fluconazole, miconazole), and perhaps rifampin.

Granulomatous Amebic Encephalitis

Granulomatous amebic encephalitis is a generally fatal subacute CNS infection caused by *Acanthamoeba* sp in immunocompromised or debilitated hosts or by *Balamuthia mandrillaris*.

*Acanthamoeba* sp and *Balamuthia mandrillaris* are present worldwide in water, soil, and dust. Human exposure is common, but infection is rare. *Acanthamoeba* infection of the CNS occurs almost entirely in immunocompromised or otherwise debilitated patients, but *B. mandrillaris* may also infect healthy hosts. The entry portal is thought to be the skin or lower respiratory tract, with subsequent hematogenous dissemination to the CNS.

Onset is insidious, often with focal neurologic manifestations. Mental status change, seizures, and headache are common. *B. mandrillaris* may also cause skin lesions. Survival is highly unlikely (and only in immunocompetent patients); death occurs between 7 and 120 days after onset (average, 39 days).

Diagnosis is often postmortem. CT and routine CSF tests are obtained but are nonspecific. CT may show multiple nonenhancing lucent areas; in CSF, WBC count (predominantly lymphocytes) is elevated, but trophozoites are rarely seen. Visible skin lesions often contain amebas and should be biopsied; if detected, amebas may be cultured and tested for drug sensitivity. Brain biopsy is often positive.

Some patients with *Acanthamoeba* granulomatous encephalitis have responded to drug combinations, which may include pentamidine; sulfadiazine or trimethoprim/sulfamethoxazole; fluycytosine; fluconazole, ketoconazole, itraconazole, or voriconazole; amphotericin B; and other drugs. Skin infections caused by *Acanthamoeba* sp are usually treated with the same drugs and surgical debridement.

*B. mandrillaris* has been treated with a combination of pentamidine, fluycytosine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin combined with surgical resection.

Amebic Keratitis

Amebic keratitis is corneal infection with *Acanthamoeba* sp, typically occurring in contact lens wearers.

*Acanthamoeba* sp can cause chronic and progressively destructive keratitis in normal hosts. The main risk factor (85% of cases) is contact lens use, particularly if lenses are worn while swimming or if unsterile...
lens cleaning solution is used. Some infections follow corneal abrasion.

Lesions are typically very painful and produce a foreign body sensation. Initially, lesions have a dendriform appearance resembling herpes simplex keratitis. Later, there are patchy stromal infiltrates and sometimes a characteristic ring-shaped lesion. Anterior uveitis is usually also present. Vision is diminished.

Diagnosis is confirmed by examination of Giemsa- or trichrome-stained corneal scrapings and by culture on special media. Viral culture is done if herpes is considered.

**Treatment**

- Corneal debridement
- Topical propamidine plus a biguanide
- Perhaps systemic fluconazole or itraconazole

Early, superficial infection responds better to treatment. The encysted stage of the life cycle appears to cause most problems.

Epithelial lesions are debrided, and intensive drug therapy is applied. Topical propamidine isethionate 0.1% plus either polyhexamethylene biguanide or biguanide chlorhexidine drops is frequently the initial choice; for the first 3 days, drugs are given every 1 to 2 h. Other topical drugs that can be used include aminoglycosides, hexamidine diisethionate, miconazole, and neosporin.

Systemic treatment with fluconazole or itraconazole has also been used, particularly in patients with anterior uveitis or involvement of the sclera. Early recognition and treatment have eliminated the need for therapeutic keratoplasty in most instances, but it remains an option when pharmacologic therapy fails. Intensive treatment is required for the first month; it is tapered per clinical response but often continued for 6 to 12 mo. Recurrence is common if treatment is stopped prematurely.

**Prevention**

Contact lens solution should be kept clean. Nonsterile homemade contact lens solutions should not be used. Wearing contact lenses while swimming or showering should be avoided.

**Leishmaniasis**

Leishmaniasis is caused by species of *Leishmania*. Manifestations include cutaneous, visceral, and mucocutaneous syndromes. Cutaneous leishmaniasis causes painless chronic skin lesions ranging from nodules to large ulcers that can persist for months to years but eventually heal. Visceral leishmaniasis causes irregular fever, hepatosplenomegaly, pancytopenia, and polyclonal hypergammaglobulinemia with high mortality in untreated patients. Mucosal disease affects nasopharyngeal tissues and can cause gross mutilation of the nose and palate. Diagnosis is by demonstrating parasites in smears or cultures. Treatment is with liposomal amphotericin B, amphotericin B deoxycholate, pentavalent antimony compounds (sodium stibogluconate, meglumine antimonate), or miltefosine, depending on the causative species and clinical syndrome.

**Etiology**

Leishmaniasis is present in scattered areas worldwide. Human infection is caused by about 20 *Leishmania* sp that are morphologically indistinguishable but can be differentiated by laboratory analysis. *Leishmania* promastigotes are transmitted by sand flies (*Phlebotomus* sp, *Lutzomyia* sp) to vertebrate hosts. Vector sand flies are infected by biting infected humans or animals. Animal reservoirs vary with the *Leishmania* sp and location and include canines, rodents, and other animals. In the Indian subcontinent,
humans are the reservoir for *L. donovani*. Rarely, infection is spread by blood transfusion, shared needles, congenitally, or sexually.

**Pathophysiology**

After infection, promastigotes from the vector are phagocytized by host macrophages; inside these cells, they transform into amastigotes.

The parasites may remain localized in the skin or spread to internal organs or the mucosa of the nasopharynx, resulting in 3 major clinical forms of leishmaniasis:

• Cutaneous

• Visceral

• Mucosal

**Cutaneous leishmaniasis** is also known as oriental or tropical sore, Delhi or Aleppo boil, uta or chiclero ulcer, or forest yaws. The causative agents are *L. major* and *L. tropica* in southern Europe, Asia, and Africa; *L. mexicana* and related species in Mexico and Central and South America; and *L. braziliensis* and related species in Central and South America. Cases have occurred among US military personnel serving in Iraq and Afghanistan and among travelers to endemic areas in Central and South America, Israel, and elsewhere. Uncommonly, *L. braziliensis* spreads widely in the skin causing disseminated cutaneous leishmaniasis.

**Visceral leishmaniasis** (kala-azar, Dumdum fever) is typically caused by *L. donovani* or *L. infantum/chagasi* and occurs in India, Africa (particularly the Sudan), Central Asia, the Mediterranean basin, South and Central America, and infrequently China. Most cases occur in northeastern India. Parasites disseminate from the site of the sand fly bite in the skin to regional lymph nodes, the spleen, the liver, and bone marrow and cause symptoms. Subclinical infections are common; only a minority of infected patients develop progressive visceral disease. Symptomatic infection with *L. infantum/chagasi* is more common among children than adults. Visceral leishmaniasis is an opportunistic infection in patients with AIDS or other immunocompromising conditions.

**Mucosal leishmaniasis** (espundia) is caused mainly by *L. braziliensis*, but it occasionally occurs with other *Leishmania* sp in the Americas. The parasites spread from the initial skin lesion through lymphatics and blood to nasopharyngeal tissues. Symptoms and signs of mucosal disease develop months to years later.

**Symptoms and Signs**

In **cutaneous leishmaniasis**, a well-demarcated skin lesion develops at the site of a sand fly bite, usually within several weeks to months. Multiple lesions may occur after multiple infective bites or with metastatic spread. The initial lesion is often a papule that slowly enlarges, ulcerates centrally, and develops a raised, erythematous border where intracellular parasites are concentrated. Ulcers are painless and cause no systemic symptoms unless secondarily infected. Lesions typically heal spontaneously after several months but may persist for years. They leave a depressed, burn-like scar. The course depends on the infecting *Leishmania* sp and the host's immune status. Diffuse cutaneous leishmaniasis results in widespread nodular skin lesions resembling those of lepromatous leprosy. It results from cell-mediated anergy to the organism.

In **visceral leishmaniasis**, the clinical manifestations usually develop gradually over weeks to months after inoculation of the parasite. Irregular fever, hepatosplenomegaly, pancytopenia, and polyclonal hypergammaglobulinemia with a reversed albumin:globulin ratio occur. In some patients, there are twice-daily temperature spikes. Emaciation and death occur within months to years in patients with progressive infections. Those with asymptomatic, self-resolving infections and survivors (after successful treatment) are resistant to further attacks unless cell-mediated immunity is impaired (eg, by AIDS). Relapse may occur years after initial infection. After treatment for visceral leishmaniasis, patients in the Sudan and India
may develop post kalaazar dermal leishmaniasis (PKDL) with flat or nodular cutaneous lesions that contain many parasites. These lesions develop at the end of or within 6 mo of therapy in patients in the Sudan and 1 to 2 yr later in India. The lesions persist for a few months to a year in most patients in the Sudan but can last for years in India. PKDL lesions are thought to contribute to the spread of infection.

**Mucosal leishmaniasis** starts with a primary cutaneous ulcer. This skin lesion heals spontaneously, but months to years later, mucosal lesions develop, sometimes resulting in gross mutilations of the nose, palate, and face.

**Diagnosis**

- Light microscopy of tissue samples, touch preparations, or aspirates
- For visceral leishmaniasis, antibody titers
- For cutaneous leishmaniasis, sometimes skin testing (not available in the US)
- Culture (special media required)

A definite diagnosis is made by demonstrating organisms in Giemsa-stained smears or cultures of aspirates from the spleen, bone marrow, liver, or lymph nodes in visceral leishmaniasis or biopsy, aspirates, or touch preparations from the border of a cutaneous lesion. Parasites are usually difficult to isolate from mucosal lesions. Organisms causing simple cutaneous leishmaniasis can be differentiated from those capable of causing mucocutaneous leishmaniasis with specific DNA probes or monoclonal antibodies or by analysis of isoenzyme patterns of cultured parasites.

Serologic tests can help diagnose visceral leishmaniasis; high titers of antibodies to a recombinant leishmanial antigen (rk39) are present in most immunocompetent patients with visceral leishmaniasis. Antibodies may be absent in subclinical cases and in patients with cutaneous leishmaniasis or AIDS.

The leishmanin skin test is available outside the US. It is positive in patients with cutaneous and mucosal leishmaniasis but negative in those with active visceral leishmaniasis.

**Treatment**

- Liposomal amphotericin B
- Pentavalent antimony compounds
- Alternative drugs (eg, amphotericin B deoxycholate, miltefosine, paromomycin)

Supportive measures (eg, adequate nutrition, transfusions, antibiotics for secondary bacterial infection) may be needed for patients with visceral leishmaniasis. Reconstructive surgery may be required if mucocutaneous leishmaniasis grossly distorts the nose or palate, but surgery should be delayed for 6 to 12 mo after therapy to avoid losing grafts because of relapses. This form frequently relapses, as does the visceral form in patients with AIDS. Treatment with highly active antiretroviral therapy (HAART) may reduce risk of relapse.

Drugs are given; selection depends on the form of disease, infecting species, resistance pattern, and geographic location.

**Cutaneous leishmaniasis:** Parenteral pentavalent antimonials are often used for *Leishmania* sp acquired in regions where resistance is low if the lesion is potentially disfiguring or if the infecting species has the potential to disseminate and cause mucosal leishmaniasis. Drugs include sodium stibogluconate and meglumine antimonite. Doses of both are based on their pentavalent antimony content—20 mg/kg IV (slow infusion required) or IM once/day for 20 days. Adverse effects include nausea, vomiting, malaise; elevated amylase, liver enzymes, or both; and cardiotoxicity (arrhythmias, myocardial depression, heart failure, ECG changes, cardiac arrest). The incidence of side effects increases with age. The drug is
stopped if patients develop cardiotoxicity.

Alternatively, miltefosine may be effective at a dose of 2.5 mg/kg (maximum, 150 mg/day) po once/day for 28 days. Adverse effects include nausea, vomiting, transient aminotransferase elevations, and dizziness. Fluconazole or itraconazole is effective in some cases. Topical paromomycin 2 times a day for 10 to 20 days has been used for *L. major* infections.

Diffuse cutaneous leishmaniasis is relatively resistant to treatment.

**Visceral leishmaniasis:** Liposomal amphotericin B is the drug of choice in the US and wherever the drug is available; other lipid-associated amphotericin preparations have been used successfully. Immunocompetent patients are given liposomal amphotericin B 3 mg/kg IV once/day for 5 days and then once/day on days 14 and 21. Higher doses and longer regimens are used in patients with AIDS.

Pentavalent antimony compounds are used to treat visceral leishmaniasis in Latin America. Dosing is as for cutaneous disease (see p. 1380), except the drug is given for 28 days.

Drug resistance is an increasing problem with antimonials, particularly in India in patients with visceral leishmaniasis. In such cases, miltefosine 2.5 mg/kg po once/day (maximum 150 mg/day) for 28 days has been effective, but miltefosine resistance has also been reported. Alternatively, amphotericin B deoxycholate 1 mg/kg IV once/day for 15 to 20 days or every other day for up to 8 wk or paromomycin 15 mg/kg IM once/day for 21 days may be used for antimony-sensitive or -resistant strains.

**Mucosal leishmaniasis:** Pentavalent antimonials (as for visceral leishmaniasis), amphotericin B 0.5 to 1.0 mg/kg once/day or every other day for 8 wk, or miltefosine (as described for visceral leishmaniasis) may be used.

**Prevention**

For prevention, treatment of cases in a geographic area where humans are a reservoir, reduction of the vector population by spraying residual insecticide (one that has prolonged duration of action) in sites of domestic transmission, and elimination of nonhuman reservoirs may help. People in endemic areas should use insect repellents containing DEET (diethyltoluamide). Insect screens, bed nets, and clothing are more effective if treated with permethrin or pyrethrum because the small sand flies can penetrate mechanical barriers. Vaccines are not currently available.

**Malaria**

Malaria is infection with *Plasmodium* sp. Symptoms are fever (which may be periodic), chills, sweating, hemolytic anemia, and splenomegaly. Diagnosis is by seeing *Plasmodium* in a peripheral blood smear. Treatment and prophylaxis depend on the species and drug sensitivity and include chloroquine, quinine, the fixed combination of atovaquone and proguanil, mefloquine, doxycycline, and artemisinin derivatives. Patients infected with *P. vivax* and *P. ovale* also receive primaquine to prevent relapse.

Malaria is endemic in Africa, much of South and Southeast Asia, North and South Korea, Mexico, Central America, Haiti, the Dominican Republic, northern South America (including northern parts of Argentina), the Middle East (including Turkey, Syria, Iran, and Iraq), and Central Asia. There are 300 to 500 million infected people worldwide, with 1 to 2 million deaths yearly, most in children < 5 yr in Africa. Malaria once was endemic in the US but has been virtually eliminated. About 1500 cases/yr occur in the US. Nearly all are acquired abroad, but a small number result from blood transfusions or rare autochthonous transmission by local mosquitoes that feed on infected immigrants.

**Pathophysiology**

The *Plasmodium* species that are spread among humans are

- *P. falciparum*
• *P. vivax*
• *P. ovale*
• *P. malariae*

Also, simian malaria has been reported in humans; *P. knowlesi* is implicated most often. Whether *P. knowlesi* is transmitted from human to human via the mosquito, without the natural intermediate monkey host, has not been determined.

The basic elements of the life cycle are the same for all *Plasmodium* sp. Transmission begins when a female *Anopheles* mosquito feeds on a person with malaria and ingests blood containing gametocytes. During the following 1 to 2 wk, gametocytes inside the mosquito reproduce sexually and produce infective sporozoites. When the mosquito feeds on another human, sporozoites are inoculated and quickly reach the liver and infect hepatocytes. The parasites mature into tissue schizonts within hepatocytes. Each schizont produces 10,000 to 30,000 merozoites, which are released into the bloodstream 1 to 3 wk later when the hepatocyte ruptures. Each merozoite can invade an RBC and there transform into a trophozoite. Trophozoites grow and develop into erythrocyte schizonts; schizonts produce further merozoites, which 48 to 72 h later rupture the RBC and are released in plasma. These merozoites then rapidly invade new RBCs, repeating the cycle. Some trophozoites develop into gametocytes, which are ingested by an *Anopheles* mosquito. They undergo sexual union in the gut of the mosquito, develop into oocysts, and release infective sporozoites, which migrate to the salivary glands.

With *P. vivax* and *P. ovale* (but not *P. falciparum* or *P. malariae*), tissue schizonts may persist as hypnozoites in the liver for up to 3 yr. These dormant forms serve as time-release capsules, which cause relapses and complicate chemotherapy because they are not killed by most antimalarial drugs, which typically act on bloodstream parasites.

The pre-erythrocytic (hepatic) stage of the malarial life cycle is bypassed when infection is transmitted by blood transfusions, by sharing of contaminated needles, or congenitally. Therefore, these modes of transmission do not cause latent disease or delayed recurrences.

Rupture of RBCs during release of merozoites is responsible for the clinical symptoms. If severe, hemolysis causes anemia and jaundice, which are worsened by phagocytosis of infected RBCs in the spleen. Anemia may be severe in *P. falciparum* or chronic *P. vivax* infection but tends to be mild in *P. malariae* infection.

**Falciparum malaria:** Unlike other forms of malaria, *P. falciparum* causes microvascular obstruction because infected RBCs adhere to vascular endothelial cells. Ischemia develops with resultant tissue hypoxia, particularly in the brain, kidneys, lungs, and GI tract. Hypoglycemia and lactic acidosis are other potential complications.

**Resistance to infection:** Most West Africans have complete resistance to *P. vivax* because their RBCs lack the Duffy blood group, which is required for the attachment of *P. vivax* to RBCs; many African Americans also have such resistance. The development of *Plasmodium* in RBCs is retarded in patients with hemoglobin S, hemoglobin C, thalassemia, G6PD deficiency, or elliptocytosis.

Previous infections provide partial immunity. Once residents of hyperendemic areas leave, acquired immunity wanes over time (months to years), and symptomatic malaria may develop if they return home and become reinfected.

**Symptoms and Signs**

The incubation period is usually 12 to 17 days for *P. vivax*, 9 to 14 days for *P. falciparum*, 16 to 18 days or longer for *P. ovale*, and about 1 mo (18 to 40 days) or longer (years) for *P. malariae*. However, some strains of *P. vivax* in temperate climates may not cause clinical illness for months to > 1 yr after infection.
Manifestations common to all forms of malaria include

- Fever and rigor—the malarial paroxysm
- Anemia
- Jaundice
- Splenomegaly
- Hepatomegaly

The malarial paroxysm coincides with release of merozoites from ruptured RBCs. The classic paroxysm starts with malaise, abrupt chills and fever rising to 39 to 41°C, rapid and thready pulse, polyuria, headache, myalgia, and nausea. After 2 to 6 h, fever falls, and profuse sweating occurs for 2 to 3 h, followed by extreme fatigue. Fever is often hectic at the start of infection. In established infections, malarial paroxysms typically occur about every 2 to 3 days depending on the species; intervals are not rigid.

Splenomegaly usually becomes palpable by the end of the first week of clinical disease but may not occur with *P. falciparum*. The enlarged spleen is soft and prone to traumatic rupture. Splenomegaly may decrease with recurrent attacks of malaria as functional immunity develops. After many bouts, the spleen may become fibrotic and firm or, in some patients, becomes massively enlarged (tropical splenomegaly). Hepatomegaly usually accompanies splenomegaly.

*P. falciparum* causes the most severe disease because of its microvascular effects. It is the only species likely to cause fatal disease if untreated; nonimmune patients may die within days of their initial symptoms. Patients with cerebral malaria may develop symptoms ranging from irritability to seizures and coma. Acute respiratory distress syndrome (ARDS), diarrhea, icterus, epigastric tenderness, retinal hemorrhages, algid malaria (a shocklike syndrome), and severe thrombocytopenia may also occur. Renal insufficiency may result from volume depletion, vascular obstruction by parasitized erythrocytes, or immune complex deposition. Hemoglobinemia and hemoglobinuria resulting from intravascular hemolysis may progress to blackwater fever (so named based on the dark color of the urine), either spontaneously or after treatment with quinine. Hypoglycemia is common and may be aggravated by quinine treatment and associated hyperinsulinemia. Placental involvement may lead to spontaneous abortion, stillbirth, or sometimes congenital infection.

*P. vivax*, *P. ovale*, and *P. malariae* typically do not compromise vital organs. Mortality is rare and is mostly due to splenic rupture or uncontrolled hyperparasitemia in asplenic patients. The clinical course with *P. ovale* is similar to that of *P. vivax*. In established infections, temperature spikes occur at 48-h intervals. *P. malariae* infections may cause no acute symptoms, but low-level parasitemia may persist for decades and lead to immune complex-mediated nephritis or nephrosis or tropical splenomegaly; when symptomatic, fever tends to occur at 72-h intervals.

In patients who have been taking chemoprophylaxis (see p. 1389), malaria may be atypical. The incubation period may extend weeks after the drug is stopped. Those infected may develop headache, backache, and irregular fever. Parasites may initially be difficult to find in blood samples.

**Diagnosis**

- Light microscopy of blood (thin and thick smears)
- Sometimes rapid blood assays that detect *Plasmodium* antigens or enzymes

Fever and chills (particularly recurrent attacks) in a traveler returning from an endemic region should prompt immediate assessment for malaria. Most cases occur within the first 6 mo, but onset may take up to 2 yr or, rarely, longer.
Malaria is typically diagnosed by finding parasites on microscopic examination of thick or thin blood smears. The infecting species (which determines therapy and prognosis) is identified by characteristic features on smears (see Table 148-1). Blood smears should be repeated at 4- to 6-h intervals if the initial smear is negative.

Thin blood smears stained with Wright-Giemsa stain allow assessment of parasite morphology within RBCs and determination of percentage parasitemia. Thick smears are more sensitive but more difficult to prepare and interpret as the RBCs are lysed before staining.

Commercial rapid assays have been developed to diagnose malaria based on the presence of certain plasmodium antigens or enzymatic activities. Assays may involve detection of a histidine-rich protein 2 (HRP-2) associated with malaria parasites (especially *P. falciparum* and *P. vivax*) and detection of plasmodium-associated lactate dehydrogenase (pLDH). However, the rapid tests are no more sensitive for detecting low levels of parasitemia than evaluation of a blood smear by an experienced microscopist and do not detect dual infections.

PCR and species-specific DNA probes may be used but are not widely available. Serologic tests may reflect prior exposure and are not useful in the diagnosis of acute malaria.

[Table 148-1, Diagnostic Features of *Plasmodium* Species in Blood Smears]

**Treatment**

- Antimalarial drugs chosen by known resistance patterns of strain in area of acquisition

Malaria is particularly dangerous in children < 5 yr (mortality is highest in those < 2 yr), pregnant women, and previously unexposed visitors to endemic areas. In case of a febrile illness during travel in an endemic region, prompt professional medical evaluation is essential; when this is not possible, self-medication with atovaquone-proguanil can be used pending evaluation.

If *P. falciparum* is suspected, therapy should be initiated immediately, even if the initial smear is negative. *P. falciparum* and, more recently, *P. vivax* have become increasingly resistant to antimalarial drugs. Recommended dosages of antimalarial drugs are listed in Tables 148-2 and 148-3. Common adverse effects and contraindications are listed in Table 148-4.

[Table 148-2, Treatment of Malaria]

**Treatment of the acute attack:** Chloroquine is the drug of choice against *P. malariae*, *P. ovale*, and chloroquine-sensitive *P. falciparum* and *P. vivax*. Chloroquine resistance is common among *P. falciparum* strains throughout endemic areas, with the exception of Central America north and west of the Panama Canal, Mexico, Haiti, the Dominican Republic, Paraguay, northern Argentina, North and South Korea, Georgia, Armenia, most of rural China, and some Middle Eastern countries; current location of resistant strains is available from the CDC at http://cdc-malaria.ncsa.uiuc.edu/. Chloroquine resistance is not always complete, but chloroquine should be used only for malaria acquired in areas where *Plasmodium* sp are known to be sensitive.

Artemisinin derivatives, particularly artemether, artesunate, and the new synthetic arteether, are used globally for treatment of acute malaria in regions where chloroquine-resistance is present. They are usually used in combination with a 2nd drug (eg, lumefantrine); in areas where artemisinins were used as monotherapy for many years (China, Viet Nam, along the Thai-Cambodian border), resistance to artemisinins has been confirmed in *P. falciparum*. Artemisinin derivatives act more rapidly than other drugs and are well tolerated.

[Table 148-3, Prevention of Malaria]
Although artemisinins are embryotoxic and associated with a low incidence of teratogenicity in animals, they have not been reported to cause birth defects in humans. They are a pregnancy category C drug.

Uncomplicated chloroquine-resistant malaria can also be treated with atovaquone-proguanil. Quinine plus doxycycline has long been used for uncomplicated and complicated chloroquine-resistant infections, but quinine is associated with frequent side effects. If the patient is pregnant, quinine plus clindamycin can be used. Mefloquine is another option, but adverse effects are common.

IV quinidine, quinine dihydrochloride, or artesunate (available from the CDC) is used in patients unable to take oral drugs. If quinidine or quinine is used, hemodynamic and

Table 148-4. Adverse Reactions and Contraindications of Antimalarial Drugs

ECG monitoring is required; the infusion is slowed or temporarily suspended if the QT interval is > 0.6 sec or the QRS widens > 25% beyond baseline. Parenteral therapy should be continued until oral drug is tolerated. It is customary to supplement quinine and quinidine with doxycycline or clindamycin to prevent late recrudescences. These antibiotics act too slowly to be used alone for the treatment of acute malaria. Halofantrine (not available in the US) may prolong the QT interval and has been associated with sudden death.

Patients with falciparum malaria must be monitored closely for hypoglycemia and proper hydration. Exchange transfusions have been used in some patients with high parasitemia to remove infected RBCs, but there is no uniform agreement on this approach. After successful treatment, patients usually improve in 24 to 48 h, but symptoms can persist for 5 days with P. falciparum.

Chloroquine-resistant P. vivax is common in Papua New Guinea and Indonesia. It is treated with quinine plus doxycycline or with mefloquine.

Curative therapy for hypnozoites: The hypnozoite stage must be eliminated from the liver with primaquine to prevent relapses of P. vivax or P. ovale malaria. Primaquine may be given simultaneously with chloroquine or afterward. Some P. vivax strains are less sensitive and require repeated treatment with higher doses. Primaquine therapy is not necessary for P. falciparum or P. malariae because these Plasmodium sp do not have a persistent hepatic phase.

Prevention

Prophylactic antimalarial drugs and insect repellants reduce but do not eliminate risk of malaria. Vaccines are under development, but none is currently available.

Prophylaxis against mosquitoes includes using permethrin- or pyrethrum-containing residual insecticide sprays (which have prolonged duration of action) on clothing or in homes and outbuildings, placing screens on doors and windows, using mosquito netting (preferably impregnated with permethrin or pyrethrum) around beds, using mosquito repellents such as DEET (diethyltoluamide), and wearing protective clothing, especially between dusk and dawn, when Anopheles mosquitoes are active.

Chemoprophylaxis: Regimens and dosing vary by geographic location and patient characteristics (see Table 148-3). Information for travelers is available from the CDC at www.cdc.gov/malaria/travel/index.htm.

If exposure to P. vivax or P. ovale is intense or prolonged or if the traveler was splenectomized, a 14-day prophylactic course of primaquine phosphate on return helps reduce the risk of recurrence. The main adverse effect is hemolysis in people with G6PD deficiency. G6PD levels should be determined before the drug is used.

Malaria during pregnancy poses a serious threat to both mother and fetus. Chloroquine can be used in areas where Plasmodium sp are susceptible. In general, pregnant women should avoid travel to chloroquine-resistant areas. The safety of mefloquine during pregnancy has not been documented, but limited experience suggests that it may be used when the benefits are judged to outweigh the risks. Doxycycline, atovaquone-proguanil, and primaquine should not be used during pregnancy. Artemisinins
have a short half-life and are not useful for prophylaxis.

Toxoplasmosis

Toxoplasmosis is infection with *Toxoplasma gondii*. Symptoms range from none to benign lymphadenopathy (a mononucleosis-like illness) to life-threatening CNS disease or involvement of other organs in immunocompromised people. Retinochoroiditis, seizures, and intellectual disability occur in congenital infection. Diagnosis is by serologic tests, histology, or PCR. Treatment is most often with pyrimethamine plus either sulfadiazine or clindamycin. Corticosteroids are given concurrently for retinochoroiditis.

Human exposure to toxoplasmosis is common wherever cats are found; 20 to 40% of healthy adults in the US are seropositive. The risk of developing disease is very low except for a fetus infected in utero and people who are or become immunocompromised.

Pathophysiology

*T. gondii* is ubiquitous in birds and mammals. This obligate intracellular parasite invades and multiplies asexually as tachyzoites within the cytoplasm of any nucleated cell (see Fig. 148-1). When host immunity develops, multiplication of tachyzoites ceases and tissue cysts form; cysts persist in a dormant state for years, especially in brain and muscle. The dormant *Toxoplasma* forms within the cysts are called bradyzoites. Sexual reproduction of *T. gondii* occurs only in the intestinal tract of cats; the resultant oocysts passed in the feces remain infectious in moist soil for months.

Infection can occur by

- Ingestion of oocysts
- Ingestion of tissue cysts
- Transplacental transmission
- Blood transfusion or organ transplantation

Ingestion of oocysts in food or water contaminated with cat feces is the most common mode of oral infection. Infection can also occur by eating raw or undercooked meat containing tissue cysts, most commonly lamb, pork, or rarely beef. After ingestion of oocysts or tissue cysts, tachyzoites are released and spread throughout the body. This acute infection is followed by the development of protective immune responses and the formation of tissue cysts in many organs. The cysts can reactivate, primarily in immunocompromised patients. Toxoplasmosis reactivates in 30 to 40% of AIDS patients who are not taking antibiotic prophylaxis, but the widespread use of trimethoprim/sulfamethoxazole for *Pneumocystis* prophylaxis has dramatically reduced the incidence.

Toxoplasmosis can be transmitted transplacentally if the mother becomes infected during pregnancy or if immunosuppression reactivates a prior infection. Transmission of *Toxoplasma* to a fetus is extraordinarily rare in immunocompetent mothers who have had toxoplasmosis earlier in life. Transmission may occur via transfusion of whole blood or WBCs or via transplantation of an organ from a seropositive donor. In otherwise healthy people, congenital or acquired infection can reactivate in the retina. Past infection confers resistance to reinfection.

Symptoms and Signs

Infections may manifest in several ways:

- Acute toxoplasmosis
- CNS toxoplasmosis
• Congenital toxoplasmosis

• Ocular toxoplasmosis

• Disseminated or non-CNS disease in immunocompromised patients

**Acute toxoplasmosis:** Acute infection is usually asymptomatic, but 10 to 20% of patients develop bilateral, nontender cervical or axillary lymphadenopathy. A few of these also have a mild flu-like syndrome of fever, malaise, myalgia, hepatosplenomegaly, and less commonly, pharyngitis, which may mimic infectious mononucleosis. Atypical lymphocytosis, mild anemia, leukopenia, and slightly elevated liver enzymes are common. The syndrome may persist for weeks but is almost always self-limited.

**CNS toxoplasmosis:** Most patients with AIDS or other immunocompromised patients who develop toxoplasmosis due to reactivation present with ring-enhancing intracranial mass lesions or encephalitis. These patients typically have headache, altered mental status, seizures, coma, fever, and sometimes focal neurologic deficits, such as motor or sensory loss, cranial nerve palsies, visual abnormalities, and focal seizures.

**Congenital toxoplasmosis:** This type results from a primary, often asymptomatic infection acquired by the mother during pregnancy. Women infected before conception ordinarily do not transmit toxoplasmosis to the fetus unless the infection is reactivated during pregnancy.

by immunosuppression. Spontaneous abortion and stillbirth may occur. The percentage of surviving fetuses born with toxoplasmosis depends on when maternal infection is acquired; it increases from 15% during the 1st trimester to 30% during the 2nd to 60% during the 3rd.

Disease in neonates may be severe, particularly if acquired early in pregnancy; symptoms include jaundice, rash, hepatosplenomegaly, and the characteristic tetrad of abnormalities: bilateral retinochoroiditis, cerebral calcifications, hydrocephalus or microcephaly, and psychomotor retardation. Prognosis is poor.

Many children with less severe infections and most infants born to mothers infected during the 3rd trimester appear healthy at birth but are at high risk of seizures, intellectual disability, retinochoroiditis, or other symptoms developing months or even years later.

**Ocular toxoplasmosis:** This type usually results from congenital infection that is reactivated, often during the teens and 20s, but rarely, it occurs with acquired infections. Focal necrotizing retinitis and a secondary granulomatous inflammation of the choroid occur and may cause ocular pain, blurred vision, and sometimes blindness. Relapses are common.

**Disseminated infection and non-CNS involvement:** Disease outside the eye and CNS is much less common and occurs primarily in severely immunocompromised patients. They may present with pneumonitis, myocarditis, polymyositis, diffuse maculopapular rash, high fevers, chills, and prostration. In toxoplasmic pneumonitis, diffuse interstitial infiltrates may progress rapidly to consolidation and cause respiratory failure, whereas endarteritis may lead to infarction of small lung segments. Myocarditis, in which conduction defects are common but often asymptomatic, may rapidly lead to heart failure. Untreated disseminated infections are usually fatal.

**Diagnosis**

• Serologic testing

• For CNS involvement, CT or MRI and lumbar puncture

The diagnosis is usually made serologically using an indirect fluorescent antibody (IFA) test or enzyme immunoassay (EIA) for IgG and IgM antibodies. Specific IgM antibodies appear during the first 2 wk of
acute illness, peak within 4 to 8 wk, and eventually become undetectable, but they may be present for as long as 18 mo after acute infection. IgG antibodies arise more slowly, peak in 1 to 2 mo, and may remain high and stable for months to years. Specific IgM antibodies with low IgG are consistent with recent infection in immunocompetent patients. Acute infection should also be suspected if the IgG is positive in immunocompromised patients with encephalitis. Toxoplasma-specific IgG antibody levels in AIDS patients with Toxoplasma encephalitis are usually low to moderate but may be absent; IgM antibodies are not present. Past infection in a healthy person typically produces a negative IgM test and a positive IgG test. In patients with retinochoroiditis, low titers of IgG antibodies are usually present, but IgM antibodies are not detected.

The diagnosis of acute toxoplasmosis during pregnancy and in the fetus or neonate can be difficult, and consultation with an expert is recommended. If the patient is pregnant and IgG and IgM are positive, an IgG avidity test should be done. High avidity antibodies in the first 12 to 16 wk of pregnancy essentially rules out an infection acquired during gestation. But a low IgG avidity result cannot be interpreted as indicating recent infection because some patients have persistent low IgG avidity for many months after infection. Suspected recent infection in a pregnant woman should be confirmed before intervention by having samples tested at a toxoplasmosis reference laboratory. If the patient has clinical illness compatible with toxoplasmosis but the IgG titer is low, a follow-up titer 2 to 3 wk later should show an increase in antibody titer if the illness is due to acute toxoplasmosis, unless the host is severely immunocompromised.

In general, detection of specific IgM antibody in neonates suggests congenital infection. Maternal IgG crosses the placenta, but IgM does not. Detection of Toxoplasma-specific IgA antibodies is more sensitive than IgM in congenitally infected infants, but it is available only at special reference facilities (eg, Palo Alto Medical Foundation [telephone 650-853-4828]). They should be consulted when fetal or congenital infection is suspected.

Toxoplasma are occasionally demonstrated histologically. Tachyzoites, which are present during acute infection, take up Giemsa or Wright's stain but may be difficult to find in routine tissue sections. Tissue cysts do not distinguish acute from chronic infection. Toxoplasma must be distinguished from other intracellular organisms, such as Histoplasma, Trypanosoma cruzi, and Leishmania. PCR tests for parasite DNA in blood, CSF, or amniotic fluid are available at several reference laboratories. PCR-based analysis of amniotic fluid is the preferred method to diagnose toxoplasmosis during pregnancy.

If CNS toxoplasmosis is suspected, patients should have head CT with contrast agent, MRI, or both plus a lumbar puncture if there are no signs of increased intracranial pressure. MRI is more sensitive than CT. CSF may show lymphocytic pleocytosis and elevated protein levels. CT typically shows single or multiple dense, rounded, ring-enhancing lesions. Although these lesions are not pathognomonic, their presence in patients with AIDS and CNS symptoms warrants a trial of chemotherapy for T. gondii. If the suspected diagnosis of toxoplasmosis is correct, clinical or radiographic improvement should become evident within 7 to 14 days. If symptoms persist, a brain biopsy should be considered.

Treatment

- Pyrimethamine plus sulfadiazine (when treatment is indicated)

Most immunocompetent patients do not require therapy unless visceral disease is present or severe symptoms persist. However, specific treatment is indicated for acute toxoplasmosis of neonates, pregnant women, and immunocompromised patients.

The most effective regimen in immunocompetent patients is pyrimethamine plus sulfadiazine. Dosage for pyrimethamine is 50 to 100 mg po q 12 h for 1 day, then 25 to 100 mg once/day for 3 to 4 wk in adults (1 mg/kg q 12 h for 3 days, then 1 mg/kg once/day for 4 wk in children; maximum 25 mg/day). Dosage for sulfadiazine is 1 to 1.5 g po qid for 3 to 4 wk in adults (25 to 50 mg/kg qid for 4 wk in children). Higher doses of pyrimethamine are used in HIV-infected patients with CNS toxoplasmosis. Some clinicians use a loading dose of pyrimethamine 200 mg the first day, then 50 to 100 mg/day plus sulfadiazine for 4 to 6 wk. In patients who have or develop sulfonamide hypersensitivity, clindamycin 600 to 800 mg po tid is given instead of sulfonamides. Another option is atovaquone 1500 mg q 12 h plus pyrimethamine, starting with
a 200-mg loading dose followed by 75 mg/day for 6 wk. Relapses of toxoplasmosis are common in patients with AIDS, and suppressive treatment should continue indefinitely unless the CD4 count increases and remains above 200/µL. Pyrimethamine bone marrow suppression can be minimized with leucovorin (also called folinic acid; not folate, which blocks the therapeutic effect). The dosage is 10 to 25 mg po once/day. Patients with ocular toxoplasmosis should also be given corticosteroids.

Treatment of pregnant women with primary infection can decrease the incidence of fetal infection. Spiramycin 1 g po tid or qid has been used safely to reduce transmission in pregnant women during the 1st trimester (available from the FDA [telephone 301-827-2335]), but spiramycin is less active than pyrimethamine plus sulfonamide and does not cross the placenta. Spiramycin is continued until fetal infection is documented or excluded at the end of the 1st trimester. If no transmission has occurred, spiramycin can be continued to term. If the fetus is infected, pyrimethamine plus sulfadiazine is used. Pyrimethamine is a potent teratogen and should not be used during the 1st trimester. Consultation with an infectious diseases expert is recommended.

Congenitally infected infants should be treated with pyrimethamine every 2 to 3 days and with sulfadiazine once/day for about a year. Infants should also receive leucovorin while receiving pyrimethamine and for 1 wk after pyrimethamine is stopped to prevent bone marrow suppression.

**Prevention**

Washing hands thoroughly after handling raw meat, soil, or cat litter is essential. Food possibly contaminated with cat feces should be avoided. Meat should be cooked to 165 to 170° F.

Chemoprophylaxis is recommended for patients with HIV and a positive IgG *T. gondii* serologic test once CD4+ cell counts are < 100/µL. One double-strength tablet of trimethoprim/sulfamethoxazole once/day, which also is prophylactic against *Pneumocystis jiroveci*, is one regimen. Alternatively, pyrimethamine plus dapsone or atovaquone with or without pyrimethamine can be used.
Chapter 149. Viruses

Introduction

Viruses are the smallest parasites, ranging from 0.02 to 0.3 μm. They depend completely on cells (bacterial, plant, or animal) to reproduce. Viruses have an outer cover of protein, and sometimes lipid, and an RNA or DNA core. For infection to occur, the virus first attaches to the host cell. The viral DNA or RNA then enters the host cell and separates from the outer cover (uncoating) and replicates inside the host cell in a process that requires specific enzymes. Most RNA viruses replicate their nucleic acid in the cytoplasm, whereas most DNA viruses replicate in the nucleus. The host cell typically dies, releasing new viruses that infect other host cells.

The consequences of viral infection vary considerably. Many infections cause acute illness after a brief incubation period, but some are asymptomatic or cause minor symptoms that may not be recognized except in retrospect. Many viral infections are cleared by the body's defenses, but some remain in a latent state. In latent infection, viral RNA or DNA remains in host cells but does not cause disease for a long time, sometimes for many years. Latent viral infections may be transmissible during the asymptomatic period, facilitating person-to-person spread. Sometimes a trigger (particularly immunosuppression) causes reactivation. Common viruses that remain latent include

- Herpesviruses
- HIV
- Papovaviruses

Some disorders are caused by viral reactivation in the CNS after a very long latency period. These diseases include progressive multifocal leukoencephalopathy (due to the JC virus, a polyomavirus), subacute sclerosing panencephalitis (due to the measles virus), and progressive rubella panencephalitis (due to rubella virus). Creutzfeldt-Jakob disease and bovine spongiform encephalopathy were formerly termed slow viral diseases because they have lengthy incubations (years), but they are now known to be caused by prions; prions are proteinaceous disease-causing agents that are not bacterial, fungal, or viral and that contain no genetic material (see p. 1729).

Several hundred different viruses infect humans. Viruses that infect primarily humans often spread via respiratory and enteric excretions. Some are transmitted sexually and through transfer of blood. Some viruses are transmitted via arthropod vectors. Viruses exist worldwide, but their spread is limited by inborn resistance, prior immunizing infections or vaccines, sanitary and other public health control measures, and prophylactic antiviral drugs.

Zoonotic viruses (see Ch. 153) pursue their biologic cycles chiefly in animals; humans are secondary or accidental hosts. These viruses are limited to areas and environments able to support their nonhuman natural cycles of infection (vertebrates, arthropods, or both).

Viruses and cancer: Some viruses are oncogenic and predispose to certain cancers:

- **Papillomavirus**: Cervical and anal carcinomas
- **Human T-lymphotropic virus 1**: Certain types of human leukemia and lymphoma
- **Epstein-Barr virus**: Nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin lymphoma, and lymphomas in immunosuppressed organ transplant recipients
- **Hepatitis B and C viruses**: Hepatocellular carcinoma
- **Human herpesvirus 8**: Kaposi's sarcoma, primary effusion lymphomas, and multicentric Castleman disease (a lymphoproliferative disorder)
Diagnosis

Some viral disorders can be diagnosed clinically (eg, by well-known viral syndromes such as measles, rubella, roseola infantum, erythema infectiosum, and chickenpox) or epidemiologically (eg, during epidemic outbreaks such as influenza). Definitive laboratory diagnosis is necessary mainly when specific treatment may be helpful or when the agent may be a public health threat (eg, HIV). Typical hospital laboratories can test for some viruses, but for less common disorders (eg, rabies, Eastern equine encephalitis), specimens must be sent to state health laboratories or the Centers for Disease Control and Prevention.

Serologic examination during acute and convalescent stages is sensitive and specific but slow; more rapid diagnosis can sometimes be made using culture, PCR, or viral antigen tests. Histopathology with electron (not light) microscopy can sometimes help. For specific diagnostic procedures, see Ch. 130.

Treatment

**Antiviral drugs:** Progress in the use of antiviral drugs is occurring rapidly. Antiviral chemotherapy can be directed at various phases of viral replication: It can interfere with viral particle attachment to host cell membranes or uncoating of viral nucleic acids, inhibit a cellular receptor or factor required for viral replication, or block specific virus-coded enzymes and proteins that are produced in the host cells and that are essential for viral replication but not for normal host cell metabolism.

Antiviral drugs are most often used therapeutically or prophylactically against herpesviruses (including cytomegalovirus—see Ch. 151), respiratory viruses (see Ch. 150), and HIV (see Ch. 154). However, some drugs are effective against many different kinds of viruses. Some drugs active against HIV are used for other viral infections such as hepatitis B.

**Interferons:** Interferons are compounds released from infected host cells in response to viral or other foreign antigens. There are many different interferons, which have numerous effects such as blocking translation and transcription of viral RNA and stopping viral replication without disturbing normal host cell function. Interferons are sometimes given attached to polyethylene glycol (pegylated formulations), allowing slow, sustained release of the interferon.

Viral disorders sometimes treated with interferon therapy include

- Chronic hepatitis B and C
- Condyloma acuminata
- Hairy cell leukemia
- Kaposi's sarcoma

Adverse effects of interferons include fever, chills, weakness, and myalgia, typically starting 7 to 12 h after the first injection and lasting up to 12 h. Depression, hepatitis, and, when high doses are used, bone marrow suppression are also possible.

Prevention

**Vaccines:** Vaccines (see p. 1170) work by stimulating native immunity. Viral vaccines in general use include hepatitis A, hepatitis B, human papillomavirus, influenza, measles, mumps, poliomyelitis, rabies, rotavirus, rubella, varicella, and yellow fever. Adenovirus and smallpox vaccines are available but used only in high-risk groups (eg, military recruits).

**Immune globulins:** Immune globulins (see p. 1178) are available for passive immune prophylaxis in limited situations. They can be used preexposure (eg, for hepatitis A), postexposure (eg, for rabies or hepatitis), and for treating disease (eg, eczema vaccinatum).
Protective measures: Many viral infections can be prevented by commonsense protective measures (which vary depending on the transmission mode of a given agent). Important measures include hand washing, appropriate food preparation and water treatment, avoidance of contact with sick people, and safe-sex practices. For infections with an insect vector (eg, mosquitoes, ticks), avoiding the vector is important.

Types of Viral Disorders

Categorizing viral infections by the organ system most commonly affected (eg, lungs, GI tract, skin, liver, CNS, mucous membranes) can be clinically useful, although certain viral disorders (eg, mumps) are hard to categorize. Many specific viruses and the disorders they cause are also discussed elsewhere in THE MANUAL.

Respiratory infections: The most common viral infections are probably URIs. Respiratory infections are more likely to cause severe symptoms in infants, the elderly, and patients with a lung or heart disorder.

Respiratory viruses include influenza viruses (A, B, C), parainfluenza viruses 1 through 4, adenoviruses, respiratory syncytial virus, and rhinoviruses (see Table 149-1 and Ch. 150). They are typically spread from person to person by contact with infected respiratory droplets.

GI infections: Gastroenteritis is usually caused by viruses (Ch. 16) and transmitted from person-to-person by the oral-fecal route. Age group primarily affected depends on the virus:

- **Rotavirus**: Children
- **Norovirus**: Older children and adults
- **Astrovirus**: Usually infants and young children
- **Adenovirus 40 and 41**: Infants
- **Coronavirus-like agents**: Infants

Local epidemics may occur in children, particularly during colder months.

The main symptoms are vomiting and diarrhea.

No specific treatment is recommended, but supportive care, particularly rehydration, is important.

A rotavirus vaccine that is effective against most pathogenic strains is part of the recommended infant vaccination schedule (see Table 268-10 on p. 2718). Hand washing and good sanitation measures can help prevent spread.

Exanthematous infections: Some viruses cause only skin lesions (as in molluscum contagiosum and warts—see Ch. 84); others also cause systemic manifestations or lesions

**[Table 149-1, Some Respiratory Viruses]**

everse in the body (see Table 149-2). Transmission is typically from person to person; alphaviruses have a mosquito vector.

Hepatic infections: At least 5 specific viruses (hepatitis A, B, C, D, and E viruses) can cause hepatitis; each causes a specific type of hepatitis (see Table 149-3 and Ch. 28). Hepatitis D virus can infect only when hepatitis B is present. Transmission is from person to person by contact with infected blood or body secretions or by the fecal-oral route for hepatitis A and E.
Other viruses can affect the liver as part of their disease process. Common examples are cytomegalovirus, Epstein-Barr virus, and yellow fever virus. Less common examples are echovirus, coxsackievirus, and herpes simplex, rubeola, rubella, and varicella viruses.

[Table 149-2, Some Exanthematous Viruses]

[Table 149-3, Viral Hepatitis]

**Neurologic infections:** Most cases of encephalitis are caused by viruses (see Table 149-4 and p. 1726). Many of these viruses are transmitted to humans by blood-eating arthropods, mainly mosquitoes and ticks (see Ch. 153); these viruses are called arboviruses (arthropod-borne viruses). For such infections, prevention includes avoiding mosquito and tick bites.

**Hemorrhagic fevers:** Certain viruses cause fever and a bleeding tendency (see Table 149-5 and Ch. 153). Transmission may involve mosquitoes, ticks, or contact with infected animals (eg, rodents, monkeys, bats) and people. Prevention involves avoiding the means of transmission.

**Cutaneous or mucosal infections:** Some viruses cause skin or mucosal lesions that recur and may become chronic (see Table 149-7). Mucocutaneous infections are the most common type of herpes simplex virus infection (see p. 1417). Human papillomavirus causes warts (see pp. 715 and 1470); some subtypes cause cervical cancer (see p. 2576). Transmission is by person-to-person contact.

**Multisystem diseases:** Enteroviruses, which include coxsackieviruses and echoviruses

[Table 149-4, Some Neurologic Viruses]

[Table 149-5, Some Viruses that Cause Hemorrhagic Fever]

(see Ch. 152), can cause various multisystem syndromes, as can cytomegaloviruses (see Table 149-7 and p. 1416). Transmission is by the fecal-oral route.

**Nonspecific febrile illness:** Some viruses cause nonspecific symptoms, including fever, malaise, headaches, and myalgia (see Tables 149-8 and 153-1). Transmission is usually by an insect or arthropod vector.

Rift Valley fever rarely progresses to ocular disorders, meningoencephalitis, or a hemorrhagic form (which has a 50% mortality rate).

[Table 149-6, Some Viruses that Cause Recurrent or Chronic Skin or Mucosal Lesions]

[Table 149-7, Some Viruses that Cause Multisystem Disease]

[Table 149-8, Some Viruses that Cause Nonspecific Acute Febrile Illness]
Chapter 150. Respiratory Viruses

Introduction

(See also Bronchiolitis on p. 2878, Croup on p. 2879, and Pneumonia on p. 1923.)

Viral infections commonly affect the upper or lower respiratory tract. Although these infections can be classified by the causative virus (eg, influenza), they are generally classified clinically according to syndrome (eg, the common cold, bronchiolitis, croup). Although specific pathogens commonly cause characteristic clinical manifestations (eg, rhinovirus typically causes the common cold, respiratory syncytial virus [RSV] typically causes bronchiolitis), each can cause many of the viral respiratory syndromes (see Table 150-1).

Severity of viral respiratory illness varies widely; severe disease is more likely in the elderly and infants. Morbidity may result directly from viral infection or may be indirect, due to exacerbation of underlying cardiopulmonary conditions or bacterial superinfection of the lung, paranasal sinuses, or middle ear.

Diagnosis

Detection of viral pathogens by PCR, culture, or serologic tests is generally too slow to be useful for patient care but is useful for epidemiologic surveillance. More rapid diagnostic tests are available for influenza and RSV, but the utility of these tests for routine care is not clear; they should be reserved for situations in which pathogen-specific diagnosis affects clinical management. Management decisions are usually based on clinical data and epidemiology.

Treatment

Treatment of viral respiratory infections is usually supportive. Antibacterial drugs are ineffective against viral pathogens, and prophylaxis against secondary bacterial infections is not recommended. Antibiotics should be given only when secondary bacterial infections develop. In patients with chronic lung disease, antibiotics may be given with less restriction.

Aspirin should not be used in patients who are ≤18 yr and have respiratory infections because Reye's syndrome is a risk.

Some patients continue to cough for weeks after resolution of an URI; these symptoms may lessen with use of an inhaled bronchodilator or corticosteroids.

In some cases, antiviral drugs are useful. Amantadine, rimantadine, oseltamivir, and zanamivir are effective for influenza. Ribavirin, a guanosine analog that inhibits replication of many RNA and DNA viruses, may be considered for severely immunocompromised patients with lower respiratory tract infection due to RSV.

Adenovirus Infections

Infection with one of the many adenoviruses may be asymptomatic or result in specific syndromes, including mild respiratory infections, keratoconjunctivitis, gastroenteritis, cystitis, and primary pneumonia. Diagnosis is clinical. Treatment is supportive.

Adenoviruses are DNA viruses classified according to 3 major capsid antigens (hexon, penton, and fiber). Adenoviruses are commonly acquired by contact with secretions (including those on fingers of infected people) from an infected person or by contact with a contaminated object (eg, towel, instrument). Infection may be airborne or waterborne (eg, acquired while swimming). Asymptomatic respiratory or GI viral
shedding may continue for months, or even years.

### Symptoms and Signs

In immunocompetent hosts, most adenovirus infections are asymptomatic; when infections are symptomatic, a broad spectrum of clinical manifestations is possible. The most common syndrome, especially in children, involves fever that tends to be > 39°C and to last > 5 days. Sore throat, cough, rhinorrhea, or other respiratory symptoms may occur. A separate syndrome involves conjunctivitis, pharyngitis, and fever (pharyngoconjunctival fever). Rare adenoviral syndromes in infants include severe bronchiolitis (see p. 2878) and pneumonia. In closed populations of young adults (eg, military recruits), outbreaks of respiratory illness may occur; symptoms include fever and lower respiratory tract symptoms, usually tracheobronchitis but occasionally pneumonia.

Epidemic keratoconjunctivitis (see p. 581) is sometimes severe and occurs sporadically and in epidemics. Conjunctivitis is frequently bilateral. Preauricular adenopathy may develop. Chemosis, pain, and punctate corneal lesions that are visible with fluorescein staining may be present. Systemic symptoms and signs are mild or absent. Epidemic keratoconjunctivitis usually resolves within 3 to 4 wk, although corneal lesions may persist much longer.

Nonrespiratory adenoviral syndromes include hemorrhagic cystitis, diarrhea in infants, and meningoencephalitis.

Most patients recover fully. Even severe primary adenoviral pneumonia is not fatal except for rare fulminant cases, predominantly in infants, military recruits, and immunocompromised patients.

### Diagnosis

- Clinical evaluation

Laboratory diagnosis of adenovirus infection rarely affects management. During the acute illness, virus can be isolated from respiratory and ocular secretions and frequently from stool and urine. A 4-fold rise in the serum antibody titer indicates recent adenoviral infection.

### Treatment

- Symptomatic treatment

Treatment is symptomatic and supportive.

To minimize transmission, health care practitioners should change gloves and wash hands after examining infected patients, sterilize instruments adequately, and avoid using ophthalmologic instruments in multiple patients.

### Prevention

Vaccines containing live adenovirus types 4 and 7, given orally in an enteric-coated capsule, can reduce lower respiratory disease in military populations; however, these vaccines are no longer available.

### Common Cold

(Upper Respiratory Infection; Coryza)

The common cold is an acute, usually afebrile, self-limited viral infection causing upper respiratory symptoms, such as rhinorrhea, cough, and sore throat. Diagnosis is clinical. Hand washing helps prevent its spread. Treatment is supportive.

About 50% of all colds are caused by one of the > 100 serotypes of rhinoviruses. Coronavirus cause some outbreaks, and infections caused by influenza, parainfluenza, enterovirus, adenovirus, respiratory
syncytial viruses, and metapneumoviruses may also manifest as the common cold, particularly in patients who are experiencing reinfection.

Rhinovirus infections are most common during fall and spring and are less common during winter. Rhinoviruses are most efficiently spread by direct person-to-person contact, although spread may also occur via large-particle aerosols.

The most potent deterrent to infection is the presence of specific neutralizing antibodies in the serum and secretions, induced by previous exposure to the same or a closely related virus. Susceptibility to colds is not affected by exposure to cold temperature, host health and nutrition, or upper respiratory tract abnormalities (eg, enlarged tonsils or adenoids).

**Symptoms and Signs**

After an incubation period of 24 to 72 h, symptoms begin with a "scratchy" or sore throat, followed by sneezing, rhinorrhea, nasal obstruction, and malaise. Temperature is usually normal, particularly when the pathogen is a rhinovirus or coronavirus. Nasal secretions are watery and profuse during the first days but then become more mucoid and purulent. Mucopurulent secretions do not indicate a bacterial superinfection. Cough is usually mild but often lasts into the 2nd wk. Most symptoms due to uncomplicated colds resolve within 10 days. Colds may exacerbate asthma and chronic bronchitis.

Purulent sputum or significant lower respiratory tract symptoms are unusual with rhinovirus infection. Purulent sinusitis and otitis media may result from the viral infection itself or from secondary bacterial infection.

**Diagnosis**

- Clinical evaluation

Diagnosis is generally made clinically and presumptively, without diagnostic tests. Allergic rhinitis is the most important consideration in differential diagnosis.

**Treatment**

- Symptomatic treatment

No specific treatment exists. Antipyretics and analgesics may relieve fever and sore throat. Nasal decongestants may reduce nasal obstruction. Topical nasal decongestants are more effective than oral decongestants, but the use of topical drugs for > 3 to 5 days may result in rebound congestion. Rhinorrhea may be relieved with 1st-generation antihistamines (eg, chlorpheniramine) or intranasal ipratropium bromide (2 sprays of a 0.03% solution bid or tid); however, these drugs should be avoided in the elderly and people with benign prostatic hypertrophy or glaucoma. First-generation antihistamines frequently cause sedation, but 2nd-generation (nonsedating) antihistamines are ineffective for treating the common cold. Antihistamines and decongestants are not recommended for children < 4 yr.

Zinc, echinacea, and vitamin C have all been evaluated as common cold therapies, but none has been clearly shown to be beneficial.

**Prevention**

There are no vaccines. Polyvalent bacterial vaccines, citrus fruits, vitamins, ultraviolet light, glycol aerosols, and other folk remedies do not prevent the common cold. Hand washing and use of surface disinfectant in a contaminated environment may reduce spread of infection.

Antibiotics should not be given unless there is clear evidence of secondary bacterial infection. In patients with chronic lung disease, antibiotics may be given with less restriction.

**Influenza**
Influenza is a viral respiratory infection causing fever, coryza, cough, headache, and malaise. Mortality is possible during seasonal epidemics, particularly among high-risk patients (eg, those who are institutionalized, at the extremes of age, have cardiopulmonary insufficiency, or are in late pregnancy); during pandemics, even healthy, young patients may die. Diagnosis is usually clinical and depends on local epidemiologic patterns. High-risk patients, their caregivers and household contacts, health care practitioners, all people ≥ 50 yr, and all children aged 6 mo to 18 yr should receive annual influenza vaccination. Antiviral treatment reduces the duration of illness by about 1 day and should be specifically considered for high-risk patients.

Influenza refers to illness caused by the influenza viruses, but the term is commonly and incorrectly used to refer to similar illnesses caused by other viral respiratory pathogens. Influenza viruses are classified as types A, B, or C by their nucleoproteins and matrix proteins. Influenza C virus infection does not cause typical influenza illness and is not discussed here.

**Influenza antigens:** Hemagglutinin (HA) is a glycoprotein on the influenza surface that allows the virus to bind to cellular sialic acid and fuse with the host membrane. Neuraminidase (NA), another surface glycoprotein, enzymatically removes sialic acid, promoting viral dispersion from the infected cell.

**Antigenic drift** refers to relatively minor mutations in HA and NA of influenza A and B that result in the frequent emergence of new viral strains. The result is decreased protection by antibody generated to the previous strain.

**Antigenic shift** refers to a major change in NA or HA that occurs in influenza A (antigenic shift) at infrequent intervals (10 to 40 yr during the last century); as a result, the population has no immunity to the new virus, and pandemic influenza may occur.

**Epidemiology**

Influenza causes widespread sporadic illness yearly during fall and winter in temperate climates. Epidemics in the US occur about every 2 to 3 yr, most often caused by influenza A viruses. Pandemics due to new influenza A serotypes may cause particularly severe disease. Influenza B viruses typically cause mild disease but can cause epidemics with moderate or severe disease, usually in 3- to 5-yr cycles. Although most influenza epidemics result from a single serotype, different influenza viruses may appear sequentially in one location or may appear simultaneously, with one virus predominating in one location and another virus predominating elsewhere.

Seasonal epidemics often occur in 2 waves—the first in schoolchildren and their household contacts (generally younger people) and the 2nd mostly in housebound or institutionalized people, particularly the elderly.

Influenza viruses may be spread by airborne droplets, person-to-person contact, or contact with contaminated items. Airborne spread appears to be the most important mechanism.

**At-risk groups:** Certain patients are at high risk of complications from influenza:

- Children < 4 yr
- Adults > 65 yr
- People with chronic medical disorders (eg, cardiopulmonary disease, diabetes mellitus, renal or hepatic insufficiency, hemoglobinopathies, immuno deficiency)
- Women in the 2nd or 3rd trimester of pregnancy
- Patients with disorders that impair handling of respiratory secretions (eg, cognitive dysfunction,
neuromuscular disorders, stroke, seizure disorders)

• Patients ≤ 18 yr taking aspirin (because Reye's syndrome is a risk)

Morbidity and mortality in these patients may be due to exacerbation of underlying illness, acute respiratory distress syndrome, primary influenza pneumonia, or secondary bacterial pneumonia.

Symptoms and Signs

The incubation period ranges from 1 to 4 days with an average of about 48 h. In mild cases, many symptoms are like those of a common cold (eg, sore throat, rhinorrhea); mild conjunctivitis may also occur. Typical influenza in adults is characterized by sudden onset of chills, fever, prostration, cough, and generalized aches and pains (especially in the back and legs). Headache is prominent, often with photophobia and retrobulbar aching. Respiratory symptoms may be mild at first, with scratchy sore throat, substernal burning, nonproductive cough, and sometimes coryza. Later, lower respiratory tract illness becomes dominant; cough can be persistent, raspy, and productive. GI symptoms may occur and appear to be more common with the 2009 pandemic H1N1 strain. Children may have prominent nausea, vomiting, or abdominal pain, and infants may present with a sepsis-like syndrome.

After 2 to 3 days, acute symptoms rapidly subside, although fever may last up to 5 days. Cough, weakness, sweating, and fatigue may persist for several days or occasionally for weeks.

Complications: Pneumonia is suggested by a worsening cough, bloody sputum, dyspnea, and rales. Secondary bacterial pneumonia is suggested by persistence or recurrence of fever and cough after the primary illness appears to be resolving.

Encephalitis, myocarditis, and myoglobinuria, sometimes with renal failure, develop infrequently after influenza A or B infection. Reye's syndrome (see p. 2937)—characterized by encephalopathy; fatty liver; elevation of liver enzymes, ammonia, or both; hypoglycemia; and lipidemia—often occurs during epidemics of influenza B, particularly in children who have ingested aspirin.

Diagnosis

• Clinical evaluation

• Sometimes rapid diagnostic testing

• Pulse oximetry and chest x-ray for patients with severe respiratory symptoms

The diagnosis is generally made clinically in patients with a typical syndrome when influenza is known to be present in the community. Although many rapid diagnostic tests are available, their sensitivities and specificities vary widely in different studies and they usually add little to patient management. Diagnostic tests should be done when results will affect clinical decisions. Reverse transcriptase-PCR (RT-PCR) assays are sensitive and specific and can differentiate influenza types and subtypes. If this assay is quickly available, results may be used to select appropriate antiviral therapy. These tests are also useful to determine whether outbreaks of respiratory disease are due to influenza. Cell culture of nasopharyngeal swabs or aspirates takes several days and is not useful for patient management decisions.

If patients have lower respiratory tract symptoms and signs (eg, dyspnea, rales noted during lung examination), pulse oximetry to detect hypoxemia and a chest x-ray to detect pneumonia should be done. Primary influenza pneumonia appears as focal or diffuse interstitial infiltrates or as acute respiratory distress syndrome. Secondary bacterial pneumonia is more likely to be lobar or segmental.

Prognosis

Most patients recover fully, although full recovery often takes 1 to 2 wk. However, influenza and influenza-related pneumonia are important causes of increased morbidity or mortality in high-risk patients.
antiviral treatment in these patients appears to reduce the incidence of lower respiratory disease and hospitalization. Appropriate antibacterial therapy decreases the mortality rate due to secondary bacterial pneumonia.

**Treatment**

- Symptomatic treatment
- Sometimes antiviral drugs

Treatment for most patients is symptomatic, including rest, hydration, and antipyretics as needed, but aspirin is avoided in patients ≤ 18 yr. Complicating bacterial infections require appropriate antibiotics.

**Drugs for influenza:** Antiviral drugs given within 1 to 2 days of symptom onset decrease the duration of fever, severity of symptoms, and time to return to normal activity. Treatment with antiviral drugs is recommended for high-risk patients who develop influenza-like symptoms; this recommendation is based on data suggesting that early treatment may prevent complications in these patients.

Drugs for influenza include the following:

- Oseltamivir and zanamivir (neuraminidase inhibitors)
- Amantadine and rimantadine (adamantanes)

**Neuraminidase inhibitors** interfere with release of influenza virus from infected cells and thus halt spread of infection.

**Adamantanes** block the M2 ion channel and thus interfere with viral uncoating inside the cell. They are effective only against influenza A viruses (influenza B viruses lack the M2 protein).

Choice of antiviral drug is complicated by resistance of different influenza types and subtypes to different drugs (see Table 150-2). If RT-PCR testing is rapidly available, results can be used to direct treatment. If RT-PCR is not available, patients may be treated with zanamivir alone or with rimantadine plus oseltamivir.

Zanamivir is given by an inhaler, 2 puffs (10 mg) bid; it can be used in adults and children ≥ 7 yr. Zanamivir sometimes causes bronchospasm and should not be given to patients with reactive airway disease; some people cannot use the inhalation device.

Oseltamivir 75 mg po bid is given to patients > 12 yr; lower doses may be used in children as young as 1 yr. Oseltamivir may cause occasional nausea and vomiting. In children, oseltamivir may decrease the incidence of otitis media; however, no other data clearly show that treatment of influenza prevents complications.

Rimantadine is the preferred adamantane because it has fewer side effects and is better tolerated. Treatment is stopped 1 to 2 days after symptoms resolve or after 3 to 5 days. For rimantadine or amantadine, 100 mg po bid can be used. To avoid adverse effects due to drug accumulation, clinicians reduce the dose for children (2.5 mg/kg bid to a maximum of 150 mg/day for children < 10 yr or 200 mg/day for children ≥ 10 yr). In patients with impaired renal function, dose is adjusted according to creatinine clearance. The dose of rimantadine should not exceed 100 mg/day if patients have hepatic dysfunction. Dose-related nervousness, insomnia, or other CNS effects occur in about 10% of people receiving amantadine and in about 2% of people receiving rimantadine. These effects usually occur within 48 h after starting the drug, are more prominent in the elderly and in patients with CNS diseases or impaired renal function, and often resolve during continued use. Anorexia, nausea, and constipation may also occur.

**Prevention**
Influenza infections can largely be prevented by

- Annual vaccination
- Sometimes chemoprophylaxis (ie, with antiviral drugs)

[Table 150-2. Drug Sensitivities of Various Influenza Strains]

Prevention is indicated for all patients, but is especially important for high-risk patients and health care practitioners.

**Vaccines:** Vaccines are modified annually to include the most prevalent strains (usually 2 strains of influenza A and 1 of influenza B). When the vaccine contains the same HA and NA as the strains in the community, vaccination decreases infections by 70 to 90% in healthy adults. In the institutionalized elderly, vaccines are less effective for prevention but decrease the rate of pneumonia and death by 60 to 80%. Vaccine-induced immunity is decreased by antigenic drift and is absent if there is antigenic shift.

There are 2 types of vaccine:

- **Trivalent inactivated influenza vaccine (TIV)**
- **Live-attenuated influenza vaccine (LAIV)**

**TIV** is given by IM injection. Patients aged 6 mo to 35 mo are given 0.25 mL, and those ≥ 3 yr are given 0.5 mL. Adverse effects are usually limited to mild pain at the injection site; it lasts no more than a few days. Fever, myalgia, and other systemic effects are uncommon.

**LAIV** is given intranasally at a dose of 0.25 mL in each nostril. It may be used for healthy people aged 2 to 49 yr. The vaccine is not recommended for high-risk patients, pregnant women, household contacts of patients with severe immunodeficiency (eg, with hematopoietic stem cell transplants), or children who are receiving long-term aspirin therapy. Adverse effects associated with the vaccine are mild; rhinorrhea is the most common, and mild wheezing may occur. LAIV should not be given to children who are < 5 yr and have reactive airway disease (eg, known asthma, recurrent or recent wheezing episodes).

For both vaccines, children who are < 8 yr and have not been vaccinated should be given a primary dose and a booster dose 1 mo apart.

**Vaccination recommendations:** Annual vaccination is recommended for

- All children aged 6 mo to 18 yr
- All people ≥ 50 yr
- People who are aged 19 to 49 yr and have chronic health disorders (eg, immunosuppression, cardiopulmonary disorders, diabetes, renal failure, asthma) or who are residents of long-term care facilities
- Women who are pregnant or will be pregnant during influenza season
- People who wish to avoid having influenza
- Health care practitioners and other people in contact with people at high risk of influenza (eg, employees of long-term care facilities, household members and caregivers of at-risk people)

Influenza vaccine is given annually to maintain antibody titers and allow vaccine modification to compensate for antigenic drift. Vaccine is best given in the fall, so that antibody titers will be high during the winter influenza season (between November and March in the US).
Vaccination (both TIV and LAIV) should be avoided in people who

- Have a severe egg allergy
- Previously had a severe reaction to influenza vaccine
- Developed Guillain-Barre syndrome (GBS) within 6 wk of a previous influenza vaccination (it is not known whether influenza vaccination increases risk of recurrent GBS in patients who have previously had GBS that was not related to influenza vaccination)
- Have had GBS in the previous 6 wk, regardless of cause
- Are < 6 mo old

**Antiviral drugs:** Although vaccination is the preferred method of prevention, antiviral drugs are also effective. Prophylactic antiviral drugs are indicated when influenza is circulating in the community for patients

- Who have been vaccinated only within the previous 2 wk
- For whom vaccination is contraindicated
- Who are immunocompromised and thus may not respond to vaccination

Antiviral drugs do not impair development of immunity from the vaccine. They can be stopped 2 wk after vaccination. If vaccine cannot be given, antiviral drugs are continued for the duration of the epidemic.

If the circulating influenza types or subtypes are unknown, patients may be treated with either zanamivir alone (in patients for whom it is not contraindicated) or with a combination of rimantadine and oseltamivir.

**Avian Influenza**

**Avian influenza (bird flu) is caused by strains of influenza A that normally infect only wild birds (and sometimes pigs). Infections due to these strains have recently been detected in humans.**

Most human infections are caused by strains of avian influenza type H5N1, but H7N7, H7N3, and H9N2 have caused some human infections. Infections with these strains are asymptomatic in wild birds but can cause highly lethal illness in domestic birds.

The first human cases of H5N1 were discovered in Hong Kong in 1997. Spread to humans was contained by culling domestic bird populations. However, in 2003 and 2004, H5N1 infections in humans reappeared, and occasional cases continue to be reported, primarily in Asia and the Middle East. Human infections with other avian influenza strains have also been reported in Asia (H9N2), Canada (H7N3), and the Netherlands (H7N7). Although most cases occurred through exposure to infected birds, some person-to-person transmission probably occurred in the Netherlands and in Asia.

All influenza viruses are capable of rapid genetic change, raising the possibility that avian strains could acquire the ability to spread more easily from person to person via direct mutation or via recombination with human strains in a human or porcine host. Many experts are concerned that if these strains acquire the ability to spread efficiently from person to person, an influenza pandemic could result.

Human infection with avian influenza H5N1 strains can cause severe respiratory symptoms. Mortality was 33% in the 1997 outbreak and has been > 60% in subsequent infections. Infection with the H7 strains most commonly causes conjunctivitis, although in the Netherlands outbreak, a few patients had flu-like symptoms and one patient (of 83) died.

**Diagnosis**
An appropriate clinical syndrome in a patient exposed to a person known to be infected or to birds in an area with an ongoing avian influenza outbreak should prompt consideration of this infection. History of recent travel to regions with ongoing transmission from birds to humans (eg, Egypt, Indonesia, Vietnam) plus exposure to birds or infected people should prompt testing for influenza A by RT-PCR. Culture of the organism should not be attempted.

Suspected and confirmed cases are reported to the Centers for Disease Control and Prevention (CDC).

Treatment

• A neuraminidase inhibitor

Treatment with oseltamivir or zanamivir at usual doses is indicated. The H5N1 virus is resistant to amantadine and rimantadine; resistance to oseltamivir has also been reported.

H1N1 Swine Influenza

H1N1 swine influenza (flu) is caused by a new strain of H1N1 influenza A virus, which genetically is a combination of swine, avian, and human influenza viruses.

Most often, pigs are infected by strains of influenza that are slightly different from those that infect people. These strains very rarely spread to people, and when they do, they very rarely then spread from person to person. The H1N1 swine flu virus is a combination of swine, bird (avian), and human influenza viruses that spreads easily from person to person. The infection is not acquired through ingestion of pork and is acquired very rarely by contact with infected pigs.

In June 2009, the World Health Organization declared H1N1 swine flu a pandemic; it has spread to > 70 countries and to all 50 US states. The majority of the deaths occurred in Mexico. The attack rate and mortality for H1N1 swine flu are higher in young and middle-aged adults and lower in the elderly than they are for seasonal flu. The pandemic entered the post-pandemic period in August 2010.

Symptoms and Signs

Symptoms, signs, and complications resemble those of ordinary influenza (see p. 1406), although nausea, vomiting, and diarrhea may be more common. Symptoms are usually mild, but they can become severe, leading to pneumonia or respiratory failure.

Diagnosis

• Sometimes PCR testing of respiratory samples

Because H1N1 swine flu is the predominant strain of influenza currently circulating worldwide, the diagnosis should be considered in any patient with influenza-like symptoms.

A newly developed PCR test can detect the H1N1 virus in respiratory tract samples (eg, nasopharyngeal swabs, nasal washings, tracheal aspirates). Mildly ill patients do not require testing other than for epidemiologic or surveillance purposes; however, local hospital and public health requirements may vary. Usual rapid antigen detection tests have decreased sensitivity for H1N1 swine flu and generally have little clinical use in diagnosis.

Treatment

• Sometimes a neuraminidase inhibitor

Treatment focuses mainly on symptom relief (eg, acetaminophen or ibuprofen for fever and aches). Antiviral drugs may be used, particularly for high-risk patients (see p. 1407) and those who are seriously
ill. Oseltamivir and zanamivir appear to be effective; they are most effective when started within 48 h after symptom onset. In the US, the FDA has issued Emergency Use Authorizations for the use of oseltamivir in patients < 1 yr old and the use of peramivir, an IV neuraminidase inhibitor, in severely ill hospitalized patients.

Most patients recover fully without taking these drugs.

**Prevention**

Vaccines for H1N1 infection have been developed. Guidelines for use of these vaccines are similar to those for use of seasonal TIV and LAIV.

Commonsense steps (eg, staying home if influenza-like symptoms develop; thorough, frequent hand washing with soap and water or an alcohol-based hand sanitizer) are recommended to reduce the spread of infection.

**Parainfluenza Virus Infections**

Parainfluenza viruses include several closely related viruses that cause many respiratory illnesses varying from the common cold to an influenza-like syndrome or pneumonia; croup is the most common severe manifestation. Diagnosis is usually clinical. Treatment is supportive.

The parainfluenza viruses are paramyxoviruses types 1, 2, 3, and 4. They share antigenic cross-reactivity but tend to cause diseases of different severity. Type 4 has antigenic cross-reactivity with mumps and appears to be an uncommon cause of respiratory disease.

Childhood outbreaks of parainfluenza virus infections can occur in nurseries, pediatric wards, and schools. Types 1 and 2 tend to cause epidemics in the autumn, with each serotype occurring in alternate years. Type 3 disease is endemic and infects most children < 1 yr; incidence is increased in the spring.

Parainfluenza viruses can cause repeated infections, but reinfection generally causes milder illness. Thus, in immunocompetent adults, most infections are asymptomatic or mild.

The most common illness in children is an upper respiratory illness with no or low-grade fever.

Parainfluenza type 1 probably causes croup (laryngotracheobronchitis—see p. 2879), primarily in infants aged 6 to 36 mo. Croup begins with common cold symptoms. Later, fever, a barking cough, hoarseness, and stridor develop. Respiratory failure due to upper airway obstruction is a rare but potentially fatal complication.

Parainfluenza virus type 3 may cause pneumonia and bronchiolitis in young infants (see p. 2878). These illnesses are generally indistinguishable from disease caused by respiratory syncytial virus (see below) but are often less severe.

A specific viral diagnosis is unnecessary. Treatment is symptomatic.

**Respiratory Syncytial Virus and Human Metapneumovirus Infections**

Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) infections cause seasonal lower respiratory tract disease, particularly in infants and young children. Disease may be asymptomatic, mild, or severe, including bronchiolitis and pneumonia. Although diagnosis is usually clinical, laboratory diagnosis is readily available. Treatment is supportive.

RSV is an RNA virus, classified as a pneumovirus. Subgroups A and B have been identified. RSV is ubiquitous; almost all children are infected by age 4 yr. Outbreaks occur annually in winter or early spring. Because the immune response to RSV does not protect against reinfection, the attack rate is about 40% for all exposed people. However, antibody to RSV decreases illness severity. RSV is the most common cause of lower respiratory tract illness in young infants and is responsible for > 100,000 hospitalizations
annually in the US.

hMPV is a similar but separate virus. The seasonal epidemiology of hMPV appears to be similar to that of RSV, but the incidence of infection and illness appears to be substantially lower.

Symptoms and Signs

The most recognizable clinical syndromes are bronchiolitis (see p. 2878) and pneumonia. These illnesses typically begin with upper respiratory symptoms and fever, then progress over several days to dyspnea, cough, and wheezing. Apnea may be the initial symptom of RSV in infants < 6 mo. In healthy adults and older children, illness is usually mild and may be inapparent or manifested only as an afebrile common cold. However, patients who are elderly or immunocompromised or who have underlying cardiopulmonary disorders may develop severe disease.

RSV and hMPV illness appear to be similar.

Diagnosis

• Clinical evaluation

• Sometimes rapid antigen tests of nasal washings or swabs

RSV (and possibly hMPV) infection is suspected in infants and young children with bronchiolitis or pneumonia during RSV season. Because antiviral treatment is not typically recommended, a specific laboratory diagnosis is unnecessary for patient management. However, a laboratory diagnosis may facilitate hospital infection control by allowing segregation of children infected with the same virus. Rapid antigen tests with high sensitivities for RSV are available for use in children; nasal washings or swabs are used. These tests are insensitive in adults.

Treatment

• Supportive care

Treatment of RSV and hMPV infections is supportive and includes supplemental O₂ and hydration as needed (see Bronchiolitis on p. 2878).

Corticosteroids and bronchodilators are not generally helpful.

Antibiotics are reserved for patients with fever and evidence of pneumonia on chest x-ray (ie, who may have a bacterial superinfection).

Palivizumab (monoclonal antibody to RSV) is not effective for treatment.

Inhaled ribavirin, an antiviral drug with activity against RSV, has little or no efficacy, is potentially toxic to health care practitioners, and is no longer recommended except for infection in severely immunocompromised patients.

Prevention

Contact precautions (eg, hand washing, gloves, isolation) are important, particularly in hospitals.

Passive prophylaxis with palivizumab decreases the frequency of hospitalization in high-risk infants. It is cost-effective only for infants at high risk of hospitalization (ie, those < 2 yr with hemodynamically significant congenital heart disease or chronic lung disease requiring medical treatment in the preceding 6 mo, those who were born at < 29 wk gestation and are < 1 yr old at the start of RSV season, and those who were born at 29 to 32 wk gestation and are < 6 mo at the start of the season). The dose is 15 mg/kg IM. The first dose is given just before the usual onset of the RSV season (early November in North America). Subsequent doses are given at 1-mo intervals for the duration of the RSV season (usually a...
Coronavirus infections in humans most frequently cause common cold symptoms; however, in 2002, a relatively new coronavirus caused an outbreak of severe acute respiratory syndrome (SARS), which was much more severe than other coronavirus infections.

Coronaviruses are enveloped RNA viruses. Coronaviruses 229E and OC43 cause the common cold, and more recently, 2 new serotypes NL63 and HUK1 have also been associated with this syndrome. In late 2002, a relatively new coronavirus (SARS-CoV) caused an outbreak of SARS, an influenza-like illness that occasionally leads to progressively severe respiratory insufficiency.

SARS-CoV was a new human pathogen that was first detected in the Guangdong province of China in November 2002 and subsequently spread to >30 countries. As of mid-July 2003, > 8000 cases had been reported worldwide, with > 800 deaths (about 10% case mortality rate). This outbreak subsided, and no new cases have been identified since 2004.

Diagnosis is made clinically, and treatment is supportive.
Chapter 151. Herpesviruses

Introduction

Eight types of herpesviruses infect humans (see Table 151-1). After initial infection, all herpesviruses remain latent within specific host cells and may subsequently reactivate or be shed. Herpesviruses do not survive long outside a host; thus, transmission usually requires intimate contact, although varicellazoster virus (VZV) may spread by aerosol. In people with latent infection, the virus can reactivate without causing symptoms; in such cases, asymptomatic people can transmit infection. Epstein-Barr virus (EBV) and human herpesvirus type 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), are tightly linked with cancer.

Drug Treatment of Herpesviruses

Drugs that have activity against herpesviruses include acyclovir, cidofovir, famciclovir, fomivirsen, foscarnet, ganciclovir, idoxuridine, penciclovir, trifluridine, valacyclovir, valganciclovir, and vidarabine (see Table 151-2).

Chickenpox

(Varicella)

Chickenpox is an acute, systemic, usually childhood infection caused by the varicella-zoster virus (human herpesvirus type 3). It usually begins with mild constitutional symptoms that are followed shortly by skin lesions appearing in crops and characterized by macules, papules, vesicles, and crusting. Patients at risk of severe neurologic or other systemic complications (eg, pneumonia) include adults, neonates, and patients who are immunocompromised or have certain underlying medical conditions. Diagnosis is clinical. Those at risk of severe complications receive postexposure prophylaxis with immune globulin and, if disease develops, are treated with antiviral drugs (eg, valacyclovir, famciclovir, acyclovir). Vaccination provides effective prevention.

Chickenpox is caused by the varicella-zoster virus (human herpesvirus type 3); chickenpox is the acute invasive phase of the virus, and herpes zoster (shingles) represents reactivation of the latent phase (see p. 1420). Chickenpox, which is extremely contagious, is spread by infected droplets and is most communicable during the prodrome and early stages of the eruption. It is communicable from 48 h before the first skin lesions appear until the final lesions have crusted. Indirect transmission (by immune carriers) does not occur.

Epidemics occur in winter and early spring in 3- to 4-yr cycles. Some infants may have partial immunity, probably acquired transplacentally, until age 6 mo.

Symptoms and Signs

In immunocompetent children, chickenpox is rarely severe. In adults and immunocompromised children, infection can be serious. Mild headache, moderate fever, and malaise may occur 11 to 15 days after exposure, about 24 to 36 h before lesions appear. This prodrome is more likely in patients > 10 yr and is usually more severe in adults.

The initial rash, a macular eruption, may be accompanied by an evanescent flush. Within a few hours, lesions progress to papules and then characteristic, sometimes pathognomonic teardrop vesicles, often intensely itchy, on red bases. The lesions become pustular and then crust. Lesions initially develop on the face and trunk and erupt in successive crops; some macules appear just as earlier crops begin to crust.
The eruption may be generalized (in severe cases) or more limited but almost always involves the upper trunk. Ulcerated lesions may develop on the mucous membranes, including the oropharynx and upper respiratory tract, palpebral conjunctiva, and rectal and vaginal mucosa. In the mouth, vesicles rupture immediately, are indistinguishable from those of herpetic gingivostomatitis, and often cause pain during swallowing. Scalp lesions may result in tender, enlarged suboccipital and posterior cervical lymph nodes. New lesions usually cease to appear by the 5th day, and the majority are crusted by the 6th day; most crusts disappear < 20 days after onset.

**Complications:** Secondary bacterial infection (typically streptococcal or staphylococcal) of the vesicles may occur, causing cellulitis or rarely streptococcal toxic shock. Pneumonia may complicate severe chickenpox in adults, neonates, and immunocompromised patients of all ages but usually not in immunocompetent young children. Myocarditis, transient arthritis or hepatitis, and hemorrhagic complications may also occur.

Encephalopathy occurs in < 1/1000 cases, usually as the disease resolves or within the next 2 wk. Complete neurologic recovery is likely, although rarely, persistent deficits or death occurs. One of the most common neurologic complications is acute postinfectious cerebellar ataxia. Transverse myelitis, cranial nerve palsies, and multiple sclerosis-like clinical manifestations have also occurred. Reye's syndrome (see p. 2937), a rare but severe childhood complication, may begin 3 to 8 days after onset of the rash; aspirin increases the risk. In adults, encephalitis, which can be life threatening, occurs in 1 to 2/1000 cases of chickenpox.

**Diagnosis**

- **Clinical evaluation**

Chickenpox is suspected in patients with the characteristic rash, which is usually the basis for diagnosis. The rash may be confused with that of other viral skin infections. If the diagnosis is in doubt, laboratory confirmation can be done; it requires immunofluorescent detection of viral antigen in lesions or culture or serologic findings. Samples are generally obtained with scraping and transported to the laboratory in viral media.

**Prognosis**

Chickenpox in children is rarely severe. Severe or fatal disease is more likely in adults, patients with depressed T-cell immunity (eg, lymphoreticular cancer), and those receiving corticosteroids or chemotherapy.

**Treatment**

- **Symptomatic treatment**

- Valacyclovir or famciclovir for patients ≥ 12 yr, immunocompromised patients, and others at risk of severe disease

Mild cases require only symptomatic treatment. Relief of itching and prevention of scratching, which predisposes to secondary bacterial infection, may be difficult. Wet compresses or, for severe itching, systemic antihistamines and colloidal oatmeal baths may help. Simultaneous use of large doses of systemic and topical antihistamines can cause encephalopathy and should be avoided.

To prevent secondary bacterial infection, patients should bathe regularly and keep their underclothing and hands clean and their nails clipped. Antiseptics should not be applied unless lesions become infected; infection is treated with antibiotics.

Oral antivirals, when given to immunocompetent patients within 24 h of the rash's onset, slightly decrease symptom duration and severity. However, because the disease is generally benign in children, antiviral treatment is not routinely recommended. Oral valacyclovir, famciclovir, or acyclovir should be strongly considered for immunocompromised patients and for healthy people at risk of moderate to severe
disease, including all patients ≥ 12 yr, those with skin disorders (particularly eczema) or chronic lung
disease, and those receiving corticosteroid therapy. The dose is famciclovir 500 mg tid or valacyclovir 1 g
tid. Acyclovir is a less desirable choice because it has poorer oral bioavailability, but it can be given at 20
mg/kg qid with a maximum daily dose of 3200 mg. Immunocompromised children > 1 yr should be given
500 mg/m² q 8 h.

Patients should not return to school or work until the final lesions have crusted.

Prevention

Infection provides lifelong protection. Potentially susceptible people should take strict precautions to avoid
people capable of transmitting the infection.

Vaccination: All healthy children and susceptible adults should receive 2 doses of live-attenuated
varicella vaccine (see
Table 268-10 on p. 2718). Vaccination is particularly important for women of child-bearing age and adults
with underlying chronic medical conditions. Serologic testing to determine immune status before
vaccination in adults is usually not required. Although the vaccine may cause chickenpox in
immunocompetent patients, disease is usually mild (< 10 papules or vesicles) and brief and causes few
systemic symptoms.

Vaccination is contraindicated in

• Patients with moderate to severe concurrent illness

• Immunocompromised patients

• Pregnant women

• Patients taking high doses of systemic corticosteroids

• Children using salicylates

Postexposure prophylaxis: After exposure, chickenpox can be prevented or attenuated by IM
administration of varicella-zoster immune globulin, which is available as an investigational new drug from
FFF Enterprises (800-843-7477). Candidates for postexposure prophylaxis include people with leukemia,
immunodeficiencies, or other severe debilitating illness; susceptible pregnant women; and neonates
whose mother developed chickenpox within 5 days before or 2 days after delivery. The immune globulin
should be given within 4 days of exposure and may modify or prevent varicella. Vaccination should be
given as soon as possible in susceptible healthy patients eligible for vaccination, and vaccination can be
effective in preventing or ameliorating disease within 3 days and possibly up to 5 days after exposure.

Cytomegalovirus Infection

(Cytomegalic Inclusion Disease)

(See also Congenital and Perinatal Cytomegalovirus Infection on p. 2811.)

Cytomegalovirus (CMV) can cause infections that have a wide range of severity. A syndrome
that is similar to infectious mononucleosis but lacks severe pharyngitis is common. Severe
focal disease, including retinitis, can develop in HIV-infected patients and, rarely, in organ
transplant recipients and other immunocompromised patients. Severe systemic disease can
develop in neonates and immunocompromised patients. Laboratory diagnosis, helpful for
severe disease, may involve culture, serologic testing, biopsy, or antigen or nucleic acid
detection. Ganciclovir and other antiviral drugs are used to treat severe disease, particularly
retinitis.

CMV (human herpesvirus type 5) is transmitted through blood, body fluids, or transplanted organs.
Infection may be acquired transplacentally or during birth. Prevalence increases with age; 60 to 90% of adults have had CMV infection. Lower socioeconomic groups tend to have a higher prevalence.

Congenital infection (see p. 2811) may be asymptomatic or may cause abortion, stillbirth, or postnatal death. Complications include extensive hepatic or CNS damage.

Acquired infections are often asymptomatic. An acute febrile illness, termed CMV mononucleosis or CMV hepatitis, may cause hepatitis with elevated aminotransferases, atypical lymphocytosis similar to infectious (Epstein-Barr virus [EBV]) mononucleosis, and splenomegaly.

Postperfusion/posttransfusion syndrome can develop 2 to 4 wk after transfusion with blood products containing CMV. It causes fever lasting 2 to 3 wk and manifestations similar to CMV hepatitis.

In immunocompromised patients, CMV is a major cause of morbidity and mortality. Disease often results from reactivation of latent virus. The lungs, GI tract, or CNS may be involved. In the terminal phase of AIDS, CMV infection causes retinitis in up to 40% of patients and causes funduscopically visible retinal abnormalities. Ulcerative disease of the colon (with abdominal pain and GI bleeding) or of the esophagus (with odynophagia) may occur.

**Diagnosis**

- Usually clinical evaluation
- Urine culture in infants
- Often biopsy in immunocompromised patients

CMV infection is suspected in healthy people with mononucleosis-like syndromes; immunocompromised patients with GI, CNS, or retinal symptoms; and neonates with systemic disease.

CMV mononucleosis can sometimes be differentiated from infectious (EBV) mononucleosis by the absence of pharyngitis, a negative heterophil antibody test, and serologic testing. CMV infection can be differentiated from viral hepatitis by hepatitis serologic testing. Laboratory confirmation of primary CMV infection is necessary only to differentiate it from other, particularly treatable, conditions or serious disease.

Seroconversion can be demonstrated by development of CMV antibodies and indicates new CMV infection. However, much CMV disease occurs from reactivation of latent disease in the immunocompromised host. Reactivation of CMV can result in virus in the urine, other body fluids, or tissues but does not always indicate disease and may merely represent shedding. Therefore, biopsy showing CMV-induced abnormalities is often necessary to demonstrate invasive disease. Quantitative detection of CMV antigen or DNA in the peripheral blood can also be very helpful because elevated or rising CMV titers are often highly suggestive of invasive disease. Diagnosis in infants can be made by urine culture.

**Treatment**

- For serious disease, antivirals (eg, ganciclovir, valganciclovir, foscarnet, cidofovir)

**Retinitis:** CMV retinitis (see p. 611), which occurs mostly in AIDS patients, is treated with antivirals.

Most patients receive induction therapy with either ganciclovir 5 mg/kg IV bid for 2 to 3 wk or valganciclovir 900 mg po bid for 21 days. If induction fails more than once, another drug should be used. After induction, patients receive maintenance or suppressive therapy with valganciclovir 900 mg po once/day to delay progression. Maintenance therapy with ganciclovir 5 mg/kg IV once/day can also be used to prevent recurrence. Alternatively, foscarnet can be given with or without ganciclovir. Foscarnet 90 mg/kg IV q 12 h for 2 to 3 wk is used for induction, followed by 90 to 120 mg/kg IV once/day for
maintenance therapy. Adverse effects of IV foscarnet are significant and include nephrotoxicity, symptomatic hypocalcemia, hypomagnesemia, hyperphosphatemia, hypokalemia, and CNS effects. Combination therapy with ganciclovir and foscarnet increases efficacy as well as adverse effects.

Cidofovir therapy consists of 5 mg/kg IV once/wk (induction) for 2 wk, followed by a similar dose every other week for maintenance. Efficacy is similar to ganciclovir or foscarnet. Significant adverse effects, including renal failure, limit its use. Cidofovir may cause iritis or ocular hypotony. The potential for nephrotoxicity can be reduced by giving probenecid and prehydration with each dose. However, the adverse effects of probenecid, including rash, headache, and fever, may be significant enough to prevent its use.

Ganciclovir ocular implants can be used for prolonged treatment in some patients. Intraocular injections into the vitreous are given sometimes, primarily if other measures have failed or are contraindicated (salvage therapy). Such treatments include injection of ganciclovir or foscarnet. Potential adverse effects of ocular injection therapy include direct retinal toxicity, vitreous hemorrhage, endophthalmitis, retinal detachment, cystoid macular edema, and cataract formation.

Even patients receiving ocular injections and those with implants need systemic therapy to prevent CMV in the contralateral eye and extracocular tissues. Ultimately, improvement of CD4+ count to > 200 cells/μL with systemic retroviral therapy should prevent the need for ocular implants and chemoprophylaxis.

**Other CMV infections:** Anti-CMV drugs are used to treat severe disease other than retinitis but are less consistently effective than in retinitis. Ganciclovir plus immune globulin has been used to treat CMV pneumonia in bone marrow transplant recipients.

**Prevention**

Prophylaxis of CMV disease is necessary for solid organ or hematopoietic cell transplant recipients at risk of CMV disease. Drugs used include ganciclovir, valganciclovir, and valacyclovir.

**Herpes Simplex Virus Infections**

Herpes simplex viruses (human herpesviruses 1 and 2) commonly cause recurrent infection affecting the skin, mouth, lips, eyes, and genitals. Common severe infections include encephalitis, meningitis, neonatal herpes, and, in immunocompromised patients, disseminated infection. Mucocutaneous infections cause clusters of small painful vesicles on an erythematous base. Diagnosis is clinical; laboratory confirmation by culture, PCR, direct immunofluorescence, or serologic testing can be done. Treatment is symptomatic; antiviral therapy with acyclovir, valacyclovir, or famciclovir is helpful for severe infections and, if begun early, for recurrent or primary infections.

Both types of herpes simplex virus (HSV), HSV-1 and HSV-2, can cause oral or genital infection. Most often, HSV-1 causes gingivostomatitis, herpes labialis, and herpes keratitis. HSV-2 usually causes genital lesions. Transmission of HSV results from close contact with a person who is actively shedding virus. Viral shedding generally occurs from lesions but can occur even when lesions are not apparent.

After the initial infection, HSV remains dormant in nerve ganglia, from which it can periodically emerge, causing symptoms. Recurrent herpetic eruptions are precipitated by overexposure to sunlight, febrile illnesses, physical or emotional stress, immunosuppression, or unknown stimuli. Generally, recurrent eruptions are less severe and occur less frequently over time.

**Diseases Caused by Herpes Simplex**

Diseases include

- Mucocutaneous infection (most common)
- Ocular infection (herpes keratitis)
• CNS infection

• Neonatal herpes

HSV rarely causes fulminant hepatitis in the absence of cutaneous lesions. In patients with HIV infection, herpetic infections can be particularly severe. Progressive and persistent esophagitis, colitis, perianal ulcers, pneumonia, encephalitis, and meningitis may occur.

HSV outbreaks may be followed by erythema multiforme (see p. 686), possibly caused by an immune reaction to the virus. Eczema herpeticum (see p. 664) is a complication of HSV infection in which severe disease develops in skin regions with eczema.

Mucocutaneous infection: Lesions may appear anywhere on the skin or mucosa but are most frequent around or in the mouth or on the lips, conjunctiva and cornea, and genitals. Generally, after a prodromal period (typically < 6 h in recurrent HSV-1) of tingling discomfort or itching, clusters of small, tense vesicles appear on an erythematous base. Clusters vary in size from 0.5 to 1.5 cm but may coalesce. Lesions on the nose, ears, eyes, fingers, or genitals may be particularly painful. Vesicles typically persist for a few days, then rupture and dry, forming a thin, yellowish crust. Healing generally occurs 8 to 12 days after onset. Lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring. Skin lesions can develop secondary bacterial infection. In patients with depressed cell-mediated immunity due to HIV infection or other conditions, prolonged or progressive lesions may persist for weeks or longer. Localized infections can disseminate, particularly—and often dramatically—in immunocompromised patients.

Acute herpetic gingivostomatitis usually results from primary infection with HSV-1, typically in children. Occasionally, through oral-genital contact, the cause is HSV-2. Intraoral and gingival vesicles rupture, usually within several hours to 1 or 2 days, to form ulcers. Fever and pain often occur. Difficulty eating and drinking may lead to dehydration. After resolution, the virus resides dormant in the semilunar ganglion.

Herpes labialis is usually a secondary outbreak of HSV. It develops as ulcers (cold sores) on the vermillion border of the lip or, much less commonly, as ulcerations of the mucosa of the hard palate.

Herpetic whitlow, a swollen, painful, erythematous lesion of the distal phalanx (see p. 390), results from inoculation of HSV through the skin and is most common among health care practitioners.

Genital herpes is the most common ulcerative sexually transmitted disease in developed countries. It is usually caused by HSV-2, although 10 to 30% of cases involve HSV-1. Primary lesions develop 4 to 7 days after contact. The vesicles usually erode to form ulcers that may coalesce. Lesions may occur on the prepuce, glans penis, and penile shaft in men and on the labia, clitoris, perineum, vagina, and cervix in women. They may occur around the anus and in the rectum in men or women who engage in receptive rectal intercourse. Genital HSV infection may cause urinary hesitancy, dysuria, urinary retention, or constipation. Severe sacral neuralgia may occur. Scarring may follow healing, and recurrences occur in 80% of patients with HSV-2 and in 50% with HSV-1. Primary genital lesions are usually more painful, prolonged, and widespread and are more likely to be bilateral and involve regional adenopathy and constitutional symptoms than recurrent genital lesions. Recurrent lesions may have severe prodromal symptoms and may involve the buttock, groin, or thigh.

Herpes simplex keratitis: HSV infection of the corneal epithelium causes pain, tearing, photophobia, and corneal ulcers that often have a branching pattern (see p. 589).

Neonatal herpes simplex: Infection develops in neonates, including those whose mothers have no suggestion of current or past herpes infection. It is most commonly transmitted during birth through contact with vaginal secretions containing HSV and usually involves HSV-2. It usually develops between the 1st and 4th wk of life, often causing mucocutaneous vesicles or CNS involvement. It causes major morbidity and mortality (see p. 2827).
CNS infection: Herpes encephalitis (see also p. 1726) occurs sporadically and may be severe. Multiple early seizures are characteristic.

Aseptic meningitis (see p. 1741) may result from HSV-2. It is usually self-limited and may involve lumbosacral myeloradiculitis, which may cause urinary retention or obstipation.

Diagnosis

- Clinical evaluation
- Viral culture for serious disease
- PCR of CSF and MRI for HSV encephalitis

Diagnosis is often clinical based on characteristic lesions. Laboratory confirmation can be helpful, especially if infection is severe, the patient is immunocompromised or pregnant, or lesions are atypical. A Tzanck test (a superficial scraping from the base of a freshly ruptured vesicle stained with Wright's-Giemsa stain) often reveals multinucleate giant cells in HSV or varicella-zoster virus infection. Definitive diagnosis is with culture, seroconversion involving the appropriate serotype (in primary infections), and biopsy. Fluid and material for culture should be obtained from the base of a vesicle or of a freshly ulcerated lesion. HSV can sometimes be identified using direct immunofluorescence assay of scrapings of lesions. PCR of CSF and MRI are used to diagnose HSV encephalitis.

HSV should be distinguished from herpes zoster, which rarely recurs and usually causes more severe pain and larger groups of lesions that are distributed along a dermatome. Clusters of vesicles or ulcers on an erythematous base are unusual in genital ulcers other than herpes.

If herpes infections recur frequently, do not resolve, or do not respond to antiviral drugs as expected, immunocompromise, possibly due to HIV infection, should be suspected.

Treatment

- Usually acyclovir, valacyclovir, or famciclovir
- For keratitis, topical idoxuridine or trifluridine

Mucocutaneous infection: Isolated infections often go untreated without consequence. Acyclovir, valacyclovir, or famciclovir can be used to treat infection, especially when it is primary. Infection with acyclovir-resistant HSV is rare and occurs almost exclusively in immunocompromised patients. Foscarnet may be effective for acyclovir-resistant infections. Secondary bacterial infections are treated with topical antibiotics (eg, mupirocin or neomycin-bacitracin) or, if severe, with systemic antibiotics (eg, penicillinase-resistant β-lactams). All mucocutaneous herpes infections are treated symptomatically. Systemic analgesics may help.

Gingivostomatitis typically requires only symptom relief with topical anesthetics applied directly with a swab (eg, dyclonine 0.5% liquid or benzocaine 2 to 20% ointment q 2 h as needed). When many large areas are affected, 5% lidocaine viscous may be used as a mouth rinse 5 min before mealtime. (NOTE: Lidocaine must not be swallowed because it anesthetizes the oropharynx, hypopharynx, and possibly the epiglottis. Children must be watched for signs of aspiration.) Severe cases can be treated with acyclovir, valacyclovir, or famciclovir.

Herpes labialis responds to oral and topical acyclovir. The duration of a recurrent eruption may be decreased by about a day by applying penciclovir 1% cream q 2 h while awake for 4 days, beginning during the prodrome or when the first lesion appears. Toxicity appears to be minimal. Famciclovir 1500 mg as one dose or valacyclovir 2 g po q 12 h for 1 day can be used to treat recurrent herpes labialis. Acyclovir-resistant strains are resistant to penciclovir. Docosanol 10% cream may be effective when used 5 times/day.
Genital herpes is treated with antiviral drugs. Acyclovir 200 mg po 5 times/day for 10 days, valacyclovir 1 g po bid for 10 days, or famciclovir 250 mg po tid for 7 to 10 days can be used for primary eruptions. These drugs reduce viral shedding and symptoms in severe primary infections. However, even early treatment of primary infections does not prevent recurrences.

In recurrent eruptions, symptom duration and severity can be reduced marginally by antiviral treatment, particularly during the prodromal phase. Acyclovir 200 mg po q 4 h for 5 days, valacyclovir 500 mg po bid for 3 days, or famciclovir 1000 mg po bid for 1 day can be used. Patients with frequent eruptions (eg, > 6 eruptions/yr) may receive suppressive antiviral therapy with acyclovir 400 mg po bid, valacyclovir 500 to 1000 mg po once/day, or famciclovir 250 mg po bid. Doses should be adjusted for renal insufficiency. Adverse effects are infrequent with oral administration but may include nausea, vomiting, diarrhea, headache, and rash.

Herpes simplex keratitis: Treatment involves topical antivirals, such as idoxuridine or trifluridine, and should be supervised by an ophthalmologist (see p. 590).

Neonatal herpes simplex: Acyclovir 20 mg/kg IV q 8 h for 14 to 21 days should be used. A dose of 20 mg/kg IV q 8 h for 21 days is indicated for CNS and disseminated HSV disease.

CNS infection: Encephalitis is treated with acyclovir 10 mg/kg IV q 8 h for 14 to 21 days. Up to 20 mg/kg IV q 8 h can be used in children. Aseptic meningitis is usually treated with IV acyclovir. Acyclovir is generally very well tolerated. However, adverse effects can include phlebitis, renal dysfunction, and, rarely, neurotoxicity (lethargy, confusion, seizures, coma).

Herpes Zoster

(Shingles; Acute Posterior Ganglionitis)

Herpes zoster is infection that results when varicella-zoster virus reactivates from its latent state in a posterior dorsal root ganglion. Symptoms usually begin with pain along the affected dermatome, followed in 2 to 3 days by a vesicular eruption that is usually diagnostic. Treatment is antiviral drugs and possibly corticosteroids given within 72 h after skin lesions appear.

Chickenpox and herpes zoster are caused by the varicella-zoster virus (human herpesvirus type 3); chickenpox is the acute invasive phase of the virus (see p. 1412), and herpes zoster (shingles) represents reactivation of the latent phase. Herpes zoster inflames the sensory root ganglia, the skin of the associated dermatome, and sometimes the posterior and anterior horns of the gray matter, meninges, and dorsal and ventral roots. Herpes zoster frequently occurs in elderly and HIV-infected patients and is more severe in immunocompromised patients. There are no clear-cut precipitants.

Symptoms and Signs

Lancinating, dysesthetic, or other pain develops in the involved site, followed in 2 to 3 days by a rash, usually crops of vesicles on an erythematous base. The site is usually one or more adjacent dermatomes in the thoracic or lumbar region. Lesions are typically unilateral. The site is usually hyperesthetic, and pain may be severe. Lesions usually continue to form for about 3 to 5 days. Herpes zoster may disseminate to other regions of the skin and to visceral organs, especially in immunocompromised patients.

Fewer than 4% of patients with herpes zoster experience another outbreak. However, many, particularly the elderly, have persistent or recurrent pain in the involved distribution (postherpetic neuralgia), which may persist for months, years, or permanently. Infection in the trigeminal nerve is particularly likely to lead to severe, persistent pain. The pain of postherpetic neuralgia may be sharp and intermittent or constant and may be debilitating.

Geniculate zoster (Ramsay Hunt syndrome) results from involvement of the geniculate ganglion. Ear pain, facial paralysis, and sometimes vertigo occur. Vesicles erupt in the external auditory canal, and taste
may be lost in the anterior two thirds of the tongue (see also Herpes Zoster Oticus on p. 444).

**Ophthalmic herpes zoster** (see also p. 590) results from involvement of the gasserian ganglion, with pain and vesicular eruption in and around the eye, in the distribution of the ophthalmic division of the 5th cranial nerve. Vesicles on the tip of the nose (Hutchinson's sign) indicate involvement of the nasociliary branch and often severe ocular disease. However, eye involvement may occur in the absence of lesions on the tip of the nose.

**Intraoral zoster** is uncommon but may produce a sharp unilateral distribution of lesions. No intraoral prodromal symptoms occur.

**Diagnosis**

- **Clinical evaluation**

  Herpes zoster is suspected in patients with the characteristic rash and sometimes in patients with typical pain in a dermatomal distribution. Diagnosis is usually based on the virtually pathognomonic rash. If the diagnosis is equivocal, detecting multinucleate giant cells with a Tzanck test can confirm infection, but the Tzanck test is positive with herpes zoster or herpes simplex. Herpes simplex virus (HSV) may cause nearly identical lesions, but unlike herpes zoster, HSV tends to recur and is not dermatomal. Viruses can be differentiated by culture. Antigen detection from a biopsy sample can be useful.

**Treatment**

- **Symptomatic treatment**

  - **Antivirals (acyclovir, famciclovir, valacyclovir)** for immunocompromised or pregnant patients

  Wet compresses are soothing, but systemic analgesics are often necessary. Treatment with oral antivirals decreases the severity and duration of the acute eruption, the incidence of postherpetic neuralgia, and the rate of serious complications in immunocompromised patients and pregnant women. Treatment should start as soon as possible, ideally during the prodrome, and is likely to be ineffective if given > 72 h after skin lesions appear. Famciclovir 500 mg po tid for 7 days and valacyclovir 1 g po tid for 7 days have better bioavailability with oral dosing than acyclovir, and therefore for herpes zoster, they are generally preferred to oral acyclovir 800 mg 5 times/day for 7 to 10 days. Corticosteroids moderately increase the rate of healing and resolution of acute pain but do not decrease the incidence of postherpetic neuralgia.

  For immunocompromised patients, acyclovir is recommended at a dosage of 10 mg/kg IV q 8 h for 7 days for adults and 20 mg/kg IV q 8 h for 7 days for children < 12 yr.

  Management of postherpetic neuralgia can be particularly difficult. Treatments include gabapentin, cyclic antidepressants, and topical capsaicin or lidocaine ointment. Opioid analgesics may be necessary. Intrathecal methylprednisolone may be of benefit.

  For treatment of ophthalmic herpes zoster, an ophthalmologist should be consulted (see p. 591). For treatment of otic herpes zoster, an otolaryngologist should be consulted (see p. 445).

**Prevention**

Prevention involves preventing primary infection (chickenpox) by giving the varicella vaccine (see p. 1416) to children and susceptible adults. Adults ≥ 60 yr should have a single dose of zoster vaccine (a more potent preparation of varicella vaccine) whether they have had herpes zoster or not. This vaccine has been shown to decrease the incidence of zoster.

**Infectious Mononucleosis**

Infectious mononucleosis is caused by Epstein-Barr virus (EBV, human herpesvirus type 4), characterized by fatigue, fever, pharyngitis, and lymphadenopathy. Fatigue may persist weeks
or months. Severe complications, including splenic rupture and neurologic syndromes, occasionally occur. Diagnosis is clinical or with EBV serologic testing. Treatment is supportive.

EBV is a herpesvirus that infects 50% of children before age 5. Its host is humans.

Pathophysiology

After initial replication in the nasopharynx, the virus infects B cells, which are induced to secrete immunoglobulins, including heterophil antibodies. Morphologically abnormal (atypical) lymphocytes develop, mainly from CD8+ T cells.

After primary infection, EBV remains within the host, primarily in B cells, for life and undergoes intermittent asymptomatic shedding from the oropharynx. The virus is detectable in oropharyngeal secretions of 15 to 25% of healthy EBV-seropositive adults. Shedding increases in frequency and titer in immunocompromised patients (eg, organ allograft recipients, HIV-infected people).

EBV has not been recovered from environmental sources and is not very contagious. Transmission may occur via transfusion of blood products but much more frequently occurs via kissing between an uninfected and an EBV-seropositive person who is shedding the virus asymptomatically. Only about 5% of patients acquire EBV from someone who has acute infection. Early childhood transmission occurs more frequently among lower socioeconomic groups and in crowded conditions.

Complications: EBV is statistically associated with and likely has a causal role in Burkitt's lymphoma, certain B-cell tumors in immunocompromised patients, and nasopharyngeal carcinoma. EBV does not cause chronic fatigue syndrome. However, it may occasionally cause a syndrome of fever, interstitial pneumonitis, pancytopenia, and uveitis (ie, chronic active EBV).

Symptoms and Signs

In most young children, primary EBV infection is asymptomatic. Symptoms of infectious mononucleosis develop most often in older children and adults.

The incubation period is about 30 to 50 days. The triad of fever, pharyngitis, and adenopathy is present in most patients. Fatigue can last months but is usually maximal during the first 2 to 3 wk. Fever usually peaks in the afternoon or early evening, with a temperature around 39.5° C, although it may reach 40.5° C. Pharyngitis may be severe, painful, and exudative and may resemble streptococcal pharyngitis.

Adenopathy is usually symmetric and may involve any group of nodes, particularly the anterior and posterior cervical chains. Adenopathy may be the only manifestation.

Splenomegaly, which occurs in about 50% of cases, is maximal during the 2nd and 3rd wk and usually results in only a barely palpable splenic tip. Mild hepatomegaly and hepatic percussion tenderness may occur. Patients may have periorbital edema and palatal petechiae. Less frequent findings include maculopapular eruptions and jaundice.

Complications: Although recovery is usually complete, complications may be dramatic.

Neurologic complications are rare but may include encephalitis, seizures, Guillain-Barre syndrome, peripheral neuropathy, aseptic meningitis, myelitis, cranial nerve palsies, and psychosis. Encephalitis may manifest with cerebellar dysfunction, or it may be global and rapidly progressive, similar to herpes simplex encephalitis, but is usually self-limited.

Hematologic complications are usually self-limited. They include granulocytopenia, thrombocytopenia, and hemolytic anemia. Transient mild granulocytopenia or thrombocytopenia occurs in about 50% of patients; severe cases, associated with bacterial infection or bleeding, occur less frequently. Hemolytic anemia is often due to anti-i-specific antibodies.

Splenic rupture can have severe consequences. It can result from splenic enlargement and capsular swelling, which are maximal 10 to 21 days after presentation. A history of trauma is present only about
half of the time. Rupture is usually painful but occasionally causes painless hypotension. Treatment is discussed on p. 986.

**Respiratory complications** include, rarely, upper airway obstruction due to pharyngeal or paratracheal lymphadenopathy; respiratory complications may respond to corticosteroids. Clinically silent interstitial pulmonary infiltrates occur mostly in children and are usually visible on x-rays.

**Hepatic complications** include elevated aminotransferase levels (about 2 to 3 times normal, returning to baseline over 3 to 4 wk); they occur in about 95% of patients. If jaundice or more severe enzyme elevations occur, other causes of hepatitis should be investigated.

Overwhelming infection with EBV occurs sporadically but may cluster in families, particularly those with X-linked lymphoproliferative syndrome (see also p. 1108). Survivors of overwhelming primary EBV infection are at risk of developing agammaglobulinemia or lymphoma.

**Diagnosis**

- Heterophil antibody test
- Sometimes EBV serologic testing

Infectious mononucleosis should be suspected in patients with typical symptoms and signs. Exudative pharyngitis, anterior cervical lymphadenopathy, and fever may be clinically indistinguishable from those caused by group A β-hemolytic streptococci. However, posterior cervical or generalized adenopathy or hepatosplenomegaly suggests infectious mononucleosis. Moreover, detection of streptococci in the oropharynx does not exclude infectious mononucleosis.

Primary HIV infection (see p. 1438) can produce a clinical picture resembling acute EBV infection. If patients have risk factors for HIV infection, quantitative HIV RNA viral blood count, p24 antigen assay, and CD4 count, plus EBV serologic testing, should be done. HIV enzyme-linked immunosorbent assay (ELISA)/Western blot is usually negative during the acute infection and thus is not useful in early primary HIV infection.

Cytomegalovirus (CMV) may cause a syndrome similar to infectious mononucleosis, with atypical lymphocytosis as well as hepatosplenomegaly and hepatitis but usually not with severe pharyngitis. Toxoplasmosis, hepatitis B, rubella, or atypical lymphocytes associated with adverse drug reactions can also cause infectious mononucleosis-like syndromes. These syndromes can usually be distinguished by their other clinical features or by specific testing.

Laboratory diagnosis usually involves a CBC and EBV serologic testing. Lymphocytes that are morphologically atypical account for up to 80% of the WBCs. Although individual lymphocytes may resemble leukemic lymphocytes, lymphocytes are heterogeneous, which is unlikely in leukemia. Atypical lymphocytes may also be present in HIV or CMV infection, hepatitis B, influenza B, rubella, or other viral illnesses, so diagnosis requires serologic testing. However, very high atypical lymphocyte counts are typically seen only in primary EBV and CMV infection. Two serologic tests are used to diagnose acute EBV infection: heterophil antibody testing and specific EBV antibody testing.

Heterophil antibodies are measured using various card-agglutination (monospot) tests. However, heterophil antibodies are present in only 50% of patients < 5 yr and in about 80 to 90% of adolescents and adults. Importantly, the heterophil antibody test may be false-positive in some patients with acute HIV infection. The titer and prevalence of heterophil antibodies rise during the 2nd and 3rd wk of illness. Thus, if the diagnosis is strongly suspected but the heterophil antibody test is negative, repeating the test after 7 to 10 days of symptoms is reasonable. If the test remains negative, antibodies to EBV should be measured. The presence of IgM antibodies to the EBV viral capsid antigen (VCA) indicates primary EBV infection (these antibodies disappear within 3 mo after infection). EBV VCA-IgG antibodies develop later (perhaps after 8 wk) in acute EBV infection and persist for life. If EBV antibody titers are negative or indicate remote infection (ie, positive for IgG antibodies and negative for IgM antibodies), other diagnoses (eg, acute HIV infection, CMV infection) should be considered.
Prognosis

Infectious mononucleosis is usually self-limited. Duration of illness varies; the acute phase lasts about 2 wk. Generally, 20% of patients can return to school or work within 1 wk, and 50% within 2 wk. Fatigue may persist for several more weeks or, in 1 to 2% of cases, for months. Death occurs in < 1%, mostly resulting from complications (eg, encephalitis, splenic rupture, airway obstruction).

Treatment

• Supportive care

• Corticosteroids possibly helpful for severe disease

Treatment is supportive. Patients are encouraged to rest during the acute phase but can resume activity when fever, pharyngitis, and malaise abate. To prevent splenic rupture, patients should avoid heavy lifting and contact sports for 1 mo after presentation and until splenomegaly (which can be monitored by ultrasonography) resolves.

Although corticosteroids hasten defervescence and relieve pharyngitis, they generally should not be used in uncomplicated disease. Corticosteroids can be helpful for complications such as impending airway obstruction, severe thrombocytopenia, and hemolytic anemia. Although oral or IV acyclovir decreases oropharyngeal shedding of EBV, there is no convincing evidence to warrant its clinical use.

Roseola Infantum

(Exanthem Subitum; Pseudorubella)

Roseola infantum is an infection of infants or very young children caused by human herpesvirus 6 (HHV-6) or, less commonly, HHV-7. The infection causes high fever and a rubelliform eruption that occurs during or after defervescence, but localizing symptoms or signs are absent. Diagnosis is clinical, and treatment is symptomatic.

Roseola infantum is the most well-described illness to result from HHV-6. HHV-6 may also cause visceral disease in immunocompromised patients (eg, organ transplant recipients). Roseola infantum occurs most often in the spring and fall. Minor local epidemics have been reported.

Symptoms and Signs

The incubation period is about 5 to 15 days. Fever of 39.5 to 40.5° C begins abruptly and persists 3 to 5 days without any localizing symptoms or signs. Despite the high fever, the child is usually alert and active, although febrile seizures may occur. Cervical and posterior auricular lymphadenopathy often develops. Encephalitis or hepatitis occurs rarely.

The fever usually falls rapidly on the 4th day, and when the fall occurs, a macular or maculopapular exanthem usually appears prominently on the chest and abdomen and, to a lesser extent, on the face and extremities; it lasts for a few hours to 2 days and may be unnoticed in mild cases. In 70% of HHV-6 infections, the classic exanthem does not occur.

Diagnosis

If roseola is known to be in the community, it may be suspected when a child aged 6 mo to 3 yr develops typical symptoms and signs. Testing is rarely needed, but diagnosis can be confirmed by culture, PCR, or serologic tests.

Treatment

Treatment is generally symptomatic. Foscarnet or ganciclovir have been used to treat some
immunosuppressed patients with severe disease, although controlled trials are lacking. Foscarnet is more consistently active than ganciclovir against HHV-6.
Chapter 152. Enteroviruses

Introduction

Enteroviruses include

• Coxsackieviruses A1 to A22, A24, and B1 to 6
• Echoviruses (enteric cytopathic human orphan viruses) 1 to 7, 9, 11 to 21, 24 to 27, and 29 to 33
• Enteroviruses 68 to 71, 73 to 91, and 100 to 101
• Polioviruses types 1 to 3

Enteroviruses, along with rhinoviruses (see Common Cold on p. 1404) and human parechoviruses, are picornaviruses (pico, or small, RNA viruses). Human parechoviruses types 1 and 2 were previously named echovirus 22 and 23 but have now been reclassified. All enteroviruses are antigenically heterogeneous and have wide geographic distribution.

Enteroviruses are shed in respiratory secretions and stool and sometimes are present in the blood and CSF of infected patients. Infection is usually transmitted by direct contact with respiratory secretions or stool but can be transmitted by contaminated environmental sources (eg, water). Enteroviral diseases or epidemics in the US occur in summer and fall. Infection transmitted by a mother during delivery can cause severe disseminated neonatal infection, which may include hepatitis or hepatic necrosis, meningoencephalitis, myocarditis, or a combination.

Intact humoral immunity and B-cell function are required for control of enteroviral disease. Severe enteroviral infections (often manifesting as a slowly progressive meningoencephalitis) occur in patients with agammaglobulinemia but usually not in those with other immune deficiencies.

Diseases Caused by Enteroviruses

Enteroviruses cause various syndromes (see Table 152-1). Epidemic pleurodynia, hand-foot-and-mouth disease, herpangina, and poliomyelitis are caused almost exclusively by enteroviruses. Other disorders (eg, aseptic meningitis, myopericarditis) may be caused by enteroviruses or other organisms.

Aseptic meningitis: Aseptic meningitis is most common among infants and children. In infants and young children, the cause is frequently a group A or B coxsackievirus, an echovirus, or a human parechovirus. In older children and adults, other enteroviruses as well as other viruses may cause aseptic meningitis.

[Table 152-1. Syndromes Caused by Enteroviruses]

The course is usually benign. A rash may accompany enteroviral aseptic meningitis. Rarely, encephalitis, which may be severe, also occurs.

Although rarely clinically necessary, the causative virus can often be isolated in a sample from the throat, stool, or CSF or be identified by reverse transcriptase-PCR.

Hemorrhagic conjunctivitis: Rarely, this disorder occurs in epidemics in the US. Importation of the virus from Africa, Asia, Mexico, and the Caribbean may make outbreaks more common.

The eyelids rapidly swell. Hemorrhagic conjunctivitis, unlike uncomplicated conjunctivitis, often leads to subconjunctival hemorrhages or keratitis, causing pain, tearing, and photophobia. Systemic illness is uncommon. However, when hemorrhagic conjunctivitis is due to enterovirus 70, transient lumbosacral radiculomyelopathy or poliomyelitis-like illness (with paralysis) can occur but is rare. Recovery is usually complete within 1 to 2 wk of onset.
Coxsackievirus A24 also causes hemorrhagic conjunctivitis, but subconjunctival hemorrhage is less frequent, and neurologic complications have not been described. Most patients recover in 1 to 2 wk.

**Myopericarditis:** Cardiac infection may occur at any age, but most patients are 20 to 39 yr old. Patients may present with chest pain, arrhythmias, or heart failure. Recovery is usually complete, but some patients develop dilated cardiomyopathy. Diagnosis may require PCR of myocardial tissue.

Myocarditis neonatorum (cardiac infection at birth) is caused by group B coxsackieviruses and some echorviruses. It causes fever and heart failure and has a high mortality rate.

**Neonatal infection:** Usually, several days after birth, the neonate suddenly develops a syndrome resembling sepsis with fever, lethargy, disseminated intravascular coagulation, bleeding, and multiple organ (including heart) failure. CNS, hepatic, myocardial, pancreatic, or adrenal lesions may occur simultaneously. Recovery may occur within a few weeks, but death may result from circulatory collapse or, if the liver is involved, liver failure.

**Rashes:** Certain coxsackieviruses and echoviruses may cause rashes, often during epidemics. Rashes are usually nonpruritic, do not desquamate, and occur on the face, neck, chest, and extremities. They are sometimes maculopapular or morbilliform but occasionally hemorrhagic, petechial, or vesicular. Fever is common. Aseptic meningitis may develop simultaneously. The course is usually benign.

**Respiratory infections:** These infections may result from enteroviruses. Symptoms include fever, coryza, pharyngitis, and, in some infants and children, vomiting and diarrhea. Bronchitis and interstitial pneumonia occasionally occur in adults and children. The course is usually mild.

**Diagnosis**

Diagnosis of enteroviral diseases is clinical. Laboratory diagnosis is usually unnecessary but can often be made by culturing the virus, by detecting viral RNA using reverse transcriptase-PCR or, less commonly, by demonstrating seroconversion. Enteroviruses that cause aseptic meningitis can be cultured in a sample from the throat, stool, blood, or CSF.

**Treatment**

Treatment of enteroviral disease is supportive. Patients with agammaglobulinemia are treated with IV immune globulins with variable success.

**Epidemic Pleurodynia**

(Bornholm Disease)

**Epidemic pleurodynia is a febrile disorder caused most commonly by a group B coxsackievirus. Infection causes severe pleuritic chest or abdominal pain.**

Epidemic pleurodynia may occur at any age but is most common among children. Severe, frequently intermittent, often pleuritic pain begins suddenly in the epigastrum, abdomen, or lower anterior chest, with fever and often headache, sore throat, and malaise. The involved truncal muscles may become swollen and tender. Symptoms usually subside in 2 to 4 days but may recur within a few days and persist or recur for several weeks. Up to 5% of cases are complicated by aseptic meningitis, orchitis, and, less commonly, myopericarditis. After recovery, subsequent infection with another group B coxsackievirus is possible.

**Diagnosis**

• Clinical evaluation

Diagnosis may be obvious in a child who has unexplained severe pleuritic or abdominal pain during an epidemic. However, in other situations, symptoms may be hard to distinguish from those due to other
conditions that cause chest or abdominal pain.

Laboratory diagnosis is not routinely necessary; it consists of isolating the virus in a throat or stool culture or, less commonly, demonstrating seroconversion.

**Treatment**

Treatment includes NSAIDs and other symptomatic measures.

**Hand-Foot-and-Mouth Disease**

Hand-foot-and-mouth disease is a febrile disorder usually caused by coxsackievirus A16, enterovirus 71, or other enteroviruses. Infection causes a vesicular eruption of skin and mucosa.

The disease is most common among young children. The course is similar to that of herpangina (see below).

Children have a sore throat or mouth pain and may refuse to eat. Fever is common. Vesicles are distributed over the buccal mucosa and tongue, the hands and feet, and, occasionally, the buttocks or genitals; usually, the vesicles are benign and short-lived.

Infection with enterovirus 71 may be accompanied by severe neurologic manifestations (eg, meningitis, encephalitis, polio-like paralysis). Morbidity and mortality are significantly higher with enterovirus 71 than with coxsackievirus A16 or other enteroviruses.

The diagnosis of hand-foot-and-mouth disease is usually made clinically.

Treatment is symptomatic (see p. 512).

**Herpangina**

Herpangina is a febrile disorder caused by numerous group A coxsackieviruses and occasionally other enteroviruses. Infection causes oropharyngeal mucosal vesicular and ulcerative lesions.

Herpangina tends to occur in epidemics, most commonly in infants and children. It is characterized by sudden onset of fever with sore throat, headache, anorexia, and frequently neck pain. Infants may vomit. Within 2 days after onset, up to 20 (mean, 4 to 5) 1- to 2-mm diameter grayish papules develop and become vesicles with erythematous areolae. They occur most frequently on the tonsillar pillars but also on the soft palate, tonsils, uvula, or tongue. During the next 24 h, the lesions become shallow ulcers, seldom > 5 mm in diameter, and heal in 1 to 7 days.

Complications are unusual. Lasting immunity to the infecting strain follows, but repeated episodes caused by other group A coxsackieviruses or other enteroviruses are possible.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on symptoms and characteristic oral lesions. Confirmatory testing is not usually required but can be done by isolating the virus from the lesions, detecting virus by reverse transcriptase-PCR, or by demonstrating a rise in specific antibody titer.

Recurrent aphthous ulcers may appear similar. Rarely, Bednar's aphthous ulcers occur in the pharynx but usually without systemic symptoms. Herpetic stomatitis occurs sporadically and causes larger, more persistent, and more numerous ulcers throughout the oropharynx than herpangina. Coxsackievirus A10 causes lymphonodular pharyngitis, which is similar except that the papules become 2- to 3-mm whitish to

yellowish nodules instead of vesicles and ulcers.

Treatment

Treatment of herpangina is symptomatic (see p. 512).

Poliomyelitis

(Infantile Paralysis; Acute Anterior Poliomyelitis)

Poliomyelitis is an acute infection caused by a poliovirus. Manifestations include a nonspecific minor illness (abortive poliomyelitis), sometimes aseptic meningitis without paralysis (nonparalytic poliomyelitis), and, less often, flaccid weakness of various muscle groups (paralytic poliomyelitis). Diagnosis is clinical, although laboratory diagnosis is possible. Treatment is supportive.

Polioviruses have 3 serotypes. Type 1 is the most paralytogenic and used to be the most common cause of epidemics. Humans are the only natural host. Infection is highly transmittable via direct contact. Asymptomatic and minor infections (abortive poliomyelitis) are more common than nonparalytic or paralytic infections by ≥ 60:1 and are the main source of spread. Extensive vaccination has almost eradicated the disease in developed countries. However, cases still occur in regions with incomplete immunization, such as sub-Saharan Africa and southern Asia.

Pathophysiology

The virus enters the mouth via the fecal-oral route, then enters the lymphoid tissues of the GI tract. A primary (minor) viremia follows with spread of virus to the reticuloendothelial system. Infection may be contained at this point, or the virus may further multiply and cause several days of secondary viremia, culminating in the development of symptoms and antibodies.

In paralytic infections, poliovirus enters the CNS—whether via secondary viremia or via migration up peripheral nerves is unclear. Significant damage occurs in only the spinal cord and brain, particularly in the nerves controlling motor and autonomic function. Inflammation compounds the damage produced by primary viral invasion. Factors predisposing to serious neurologic damage include increasing age (throughout life), recent tonsillectomy or intramuscular injection, pregnancy, impairment of B-cell function, and physical exertion concurrent with onset of the CNS phase.

Poliovirus is present in the throat and feces during incubation and, after symptom onset, persists 1 to 2 wk in the throat and ≥ 3 to 6 wk in feces; the fecal-oral route is the usual method of transmission.

Symptoms and Signs

Most (90 to 95%) infections cause no symptoms. Symptomatic disease is classified as abortive poliomyelitis or as paralytic or nonparalytic poliomyelitis.

Abortive: Most symptomatic infections, particularly in young children, are minor, with 1 to 3 days of slight fever, malaise, headache, sore throat, and vomiting, which develop 3 to 5 days after exposure. There are no neurologic symptoms or signs, and physical examination is unremarkable except for the presence of fever.

Paralytic and nonparalytic: Paralytic poliomyelitis occurs in about 0.1% of all infections. It may develop without a preceding minor illness, particularly in older children and adults. Incubation is usually 7 to 14 days.

Common manifestations include aseptic meningitis, deep muscle pain, hyperesthesias, paresthesias, and, during active myelitis, urinary retention and muscle spasms. Asymmetric flaccid paralysis may develop and progress over 2 to 3 days. Encephalitic signs occasionally predominate.
Dysphagia, nasal regurgitation, and nasal voice are usually the earliest signs of bulbar involvement, but some patients have pharyngeal paralysis and cannot control oral secretions. As with skeletal muscle paralysis, bulbar involvement may worsen over 2 to 3 days and, in some patients, affects the respiratory and circulatory centers of the brain stem, leading to respiratory compromise. Infrequently, respiratory failure develops when the diaphragm or intercostal muscles are affected.

Some patients develop postpoliomyelitis syndrome (see below).

**Diagnosis**

- Lumbar puncture
- Viral culture (stool, throat, and CSF)
- Reverse transcriptase-PCR of blood or CSF
- Serologic testing for poliovirus serotypes, enteroviruses, and West Nile virus

When there are no CNS manifestations, symptomatic polio resembles other systemic viral infections and is typically not considered or diagnosed except during an epidemic.

Nonparalytic poliomyelitis resembles other viral meningitides. In such patients, lumbar puncture is usually done; typical CSF findings are normal glucose, mildly elevated protein, and a cell count of 10 to 500/μL (predominantly lymphocytes). Isolation of the virus from the throat, feces, or CSF or demonstration of a rise in specific antibody titer confirms infection with poliovirus but is usually not needed in patients with uncomplicated aseptic meningitis.

Asymmetric flaccid limb paralysis or bulbar palsies without sensory loss during an acute febrile illness in a nonimmunized child or young adult almost always indicates paralytic poliomyelitis. However, certain group A and B coxsackieviruses (especially A7), several echoviruses, and enterovirus type 71 may produce similar findings. West Nile virus infection can also cause an acute flaccid paralysis that is clinically indistinguishable from paralytic poliomyelitis due to polioviruses. Guillain-Barre syndrome (see p. 1788) causes flaccid paralysis but can be distinguished because it usually causes no fever, muscle weakness is symmetric, sensory deficits occur in 70% of patients, and CSF protein is usually elevated and CSF cell count is normal.

Epidemiologic clues (eg, immunization history, recent travel, age, season) can help suggest the cause. Because identification of poliovirus or another enterovirus as the cause of acute flaccid paralysis is important for public health reasons, viral culture of throat swabs, stool, and CSF and reverse transcriptase-PCR of CSF and blood should be done in all cases. Specific serologic testing for polioviruses, other enteroviruses, and West Nile virus should also be done.

**Prognosis**

In nonparalytic forms, recovery is complete.

In paralytic forms, about two thirds of patients have residual permanent weakness. Bulbar paralysis is more likely to resolve than peripheral paralysis. Mortality is 4 to 6% but increases to 10 to 20% in adults and in patients with bulbar disease.

**Postpoliomyelitis syndrome:** Muscle fatigue and decreased endurance, often accompanied by weakness, fasciculations, and atrophy, may develop years or decades after paralytic poliomyelitis, particularly in older patients and in patients who are severely affected initially. Damage usually occurs in previously affected muscle groups. The cause may be related to further loss of anterior horn cells due to aging in a population of neurons already depleted by earlier poliovirus infection. However, it rarely substantially increases disability.

**Treatment**
• Supportive care

Standard treatment is supportive and includes rest, analgesics, and antipyretics as needed. Specific antiviral therapy is not available.

During active myelitis, precautions to avoid complications of bed rest (eg, deep venous thrombosis, atelectasis, UTI) and prolonged immobility (eg, contractures) may be necessary. Respiratory failure may require mechanical ventilation. Mechanical ventilation or bulbar paralysis requires intensive pulmonary toilet measures.

Treatment of postpoliomyelitis syndrome is supportive.

Prevention

All infants and children should be immunized. The American Academy of Pediatrics recommends vaccination at ages 2 mo, 4 mo, and 6 to 18 mo and a booster dose at age 4 to 6 yr (see also p. 1177 and Table 268-10 on p. 2718). Childhood vaccination produces immunity in > 95% of recipients.

Salk inactivated poliovirus vaccine (IPV) is preferred to Sabin live-attenuated oral polio vaccine (OPV), which causes paralytic poliomyelitis in about 1 case per 2,400,000 doses and is thus no longer available in the US. Serious adverse effects have not been associated with IPV.

Adults are not routinely vaccinated. Nonimmunized adults traveling to endemic or epidemic areas should receive primary vaccination with IPV, including 2 doses given 4 to 8 wk apart and a 3rd dose given 6 to 12 mo later. At least 1 dose is given before travel. Immunized adults traveling to endemic or epidemic areas should be given 1 dose of IPV. Immunocompromised hosts and their household contacts should not be given OPV.
Chapter 153. Arboviridae, Arenaviridae, and Filoviridae

Introduction

Arbovirus (arthropod-borne virus) is a term applied to a group of viruses that are transmitted to vertebrates by certain types of blood-eating insects, chiefly mosquitoes and ticks (arthropods). Arbovirus is not part of the current viral classification system. Families in the current classification system that have some arbovirus members include

- Bunyaviridae (including bunyaviruses, phleboviruses, nairoviruses, and hantaviruses)
- Flaviviridae (including flaviviruses)
- Reoviridae (including coltiviruses and orbiviruses)
- Togaviridae (including alphaviruses)

Arenaviridae and Filoviridae (including Marburg and Ebola viruses) are not arboviruses.

Arboviruses number > 250 and are distributed worldwide; at least 80 cause human disease. Birds are often reservoirs for arboviruses, which are transmitted by mosquitoes to horses, other domestic animals, and humans. Most arboviral diseases are not transmissible by humans, perhaps because the typical viremia is inadequate to infect the arthropod vector; an exception is dengue fever, which can be transmitted from person to person via mosquitoes. Some infections (eg, West Nile virus, Colorado tick fever) can be spread by blood transfusion or organ donation. Reservoirs for Bunyaviridae include insects and vertebrates, often rodents. These viruses spread to humans directly from their reservoirs, but human-to-human transmission may occur.

Arenaviruses are usually transmitted by rodents and their excreta; in the case of Lassa fever, human-to-human transmission is possible.

Reservoirs for the Marburg and Ebola viruses are unknown, and human-to-human transmission occurs readily.

Many infections are asymptomatic. When symptomatic, they generally begin with a minor nonspecific flu-like illness that may evolve to one of a few syndromes (see Table 153-1). These syndromes include lymphadenopathy, rashes, aseptic meningitis, encephalitis, arthralgias, arthritis, and noncardiogenic pulmonary edema. Many cause fever and bleeding tendencies (hemorrhagic fever). Decreased synthesis of vitamin K-dependent coagulation factors, disseminated intravascular coagulation, and altered platelet function contribute to bleeding.

Laboratory diagnosis often involves viral cultures, PCR, electron microscopy, and antigen and antibody detection where available.

Treatment

- Supportive care
- Sometimes ribavirin

Treatment for most of these infections is supportive. In hemorrhagic fevers, bleeding may require phytonadione (see p. 46 under Vitamin K Deficiency). Transfusion of packed RBCs or fresh frozen plasma may also be necessary. Aspirin and other NSAIDs are contraindicated because of antiplatelet activity.
Ribavirin 30 mg/kg IV (maximum, 2 g) loading dose followed by 16 mg/kg IV (maximum, 1 g/dose) q 6 h for 4 days, then 8 mg/kg IV (maximum, 500 mg/dose) q 8 h for 6 days is recommended for hemorrhagic fever caused by arenaviruses or bunyaviruses including Lassa fever, Rift Valley fever, and Crimean-Congo hemorrhagic fever. For dosage in hemorrhagic fever with renal syndrome, see p. 1434. Antiviral treatment for other syndromes has not been adequately studied.

Prevention

Diseases transmitted by mosquitoes or ticks can often be prevented by wearing clothing that covers as much of the body as possible, using insect repellants, and minimizing the likelihood of exposure to the insect (eg, for mosquitoes, limiting time outdoors in wet areas; for ticks, see Sidebar 139-1 on p. 1283).

Diseases transmitted by rodent excreta can be prevented by sealing sites of potential rodent entry into homes and nearby buildings, preventing rodent access to food, and eliminating potential nesting sites around the home. Guidelines for cleaning and working in areas with potential rodent excreta are available through the Centers for Disease Control and Prevention (CDC).

Dengue

(Breakbone Fever; Dandy Fever)

Dengue is a mosquito-borne disease caused by a flavivirus. Dengue fever usually results in abrupt onset of high fever, headache, myalgias, arthralgias, and lymphadenopathy, followed by a rash that appears with a 2nd temperature rise after an afebrile period. Respiratory symptoms, such as cough, sore throat, and rhinorrhea, can occur. Dengue can also cause potentially fatal hemorrhagic fever with bleeding tendency and shock. Diagnosis involves serologic testing and PCR. Treatment is symptomatic and, for dengue hemorrhagic fever, includes meticulously adjusted intravascular volume replacement.

Dengue is endemic to the tropical regions of the world in latitudes from about 35° north to 35° south. Outbreaks are most prevalent in Southeast Asia but also occur in the Caribbean, including Puerto Rico and the US Virgin Islands, Oceania, and the Indian subcontinent; more recently, dengue incidence has increased in Central and South America. Each year, only about 100 to 200 cases are imported to the US by returning tourists, but an estimated 50 to 100 million cases occur worldwide, with about 20,000 deaths.

The causative agent, a flavivirus with 4 serogroups, is transmitted by the bite of Aedes mosquitoes. The virus circulates in the blood of infected humans for 2 to 7 days; Aedes mosquitoes may acquire the virus when they feed on humans during this period.

Symptoms and Signs

After an incubation period of 3 to 15 days, fever, chills, headache, retro-orbital pain with eye movement, lumbar backache, and severe prostration begin abruptly. Extreme aching in the legs and joints occurs during the first hours, accounting for the traditional name of breakbone fever. The temperature rises rapidly to up to 40° C, with relative bradycardia. Bulbar and palpebral conjunctival injection and a transient flushing or pale pink macular rash (particularly of the face) may occur. Cervical, epitrochlear, and inguinal lymph nodes are often enlarged.

Fever and other symptoms persist 48 to 96 h, followed by rapid defervescence with profuse sweating. Patients then feel well for about 24 h, after which fever may occur again (saddle-back pattern), typically with a lower peak temperature than the first. Simultaneously, a blanching maculopapular rash spreads from the trunk to the extremities and face.

Mild cases of dengue, usually lacking lymphadenopathy, remit in < 72 h. In more severe disease, asthenia may last several weeks. Death is rare. Immunity to the infecting strain is long-lasting, whereas broader immunity to other strains lasts only 2 to 12 mo.

Diagnosis
• Acute and convalescent serologic testing

Dengue fever is suspected in patients in endemic areas if they develop sudden fever, headache, myalgias, and adenopathy, particularly with the characteristic rash or recurrent fever. Evaluation should rule out alternative diagnoses, especially malaria and leptospirosis. Diagnostic studies include serologic testing, antigen detection, and PCR of blood. Serologic testing involves hemagglutination inhibiting or complement fixation tests using paired sera, but cross-reactions with other flavivirus antibodies are possible. Antigen detection is available in some parts of the world (not in the US), and PCR is usually done only in laboratories with special expertise. Although rarely done and difficult, cultures can be done using mosquitoes or specialized cell lines in specialized laboratories.

CBC may show leukopenia by the 2nd day of fever; by the 4th or 5th day, the WBC count may be 2000 to 4000/μL with only 20 to 40% granulocytes. Urinalysis may show moderate albuminuria and a few casts.

Treatment

• Supportive care

Treatment is symptomatic. Acetaminophen can be used, but NSAIDs, including aspirin, should be avoided because bleeding is a risk. Aspirin increases the risk of Reye's syndrome in children and should be avoided for that reason.

Prevention

People in endemic areas should try to prevent mosquito bites. To prevent further transmission by mosquitoes, patients with dengue should be kept under mosquito netting until the 2nd bout of fever has resolved. Vaccines are being evaluated.

Dengue Hemorrhagic Fever

(Philippine, Thai, or Southeast Asian Hemorrhagic Fever; Dengue Shock Syndrome)

Dengue hemorrhagic fever (DHF) is a variant presentation that occurs primarily in children < 10 yr living in areas where dengue is endemic. DHF requires prior infection with the dengue virus. It is an immunopathologic disease; dengue virus-antibody immune complexes trigger release of vasoactive mediators by macrophages. The mediators increase vascular permeability, causing vascular leakage, hemorrhagic manifestations, hemoconcentration, and serous effusions, which lead to circulatory collapse (ie, dengue shock syndrome).

Symptoms and Signs

In adults, DHF begins with abrupt fever and headache and is initially indistinguishable from classic dengue. Shock and increasing illness may develop rapidly 2 to 6 days after onset. Bleeding tendencies occur, usually as purpura, petechiae, or ecchymoses at injection sites; sometimes as hematemesis, melena, or epistaxis; and occasionally as subarachnoid hemorrhage. Hepatomegaly is common, as is bronchopneumonia with or without bilateral pleural effusions. Myocarditis can occur. Mortality is usually < 1% in experienced centers but otherwise can range up to 30%.

Diagnosis

• Clinical and laboratory criteria

DHF is suspected in children with WHO-defined clinical criteria for the diagnosis: sudden fever that stays high for 2 to 7 days, hemorrhagic manifestations, and hepatomegaly. Hemorrhagic manifestations include at least a positive tourniquet test and petechiae, purpura, ecchymoses, bleeding gums, hematemesis, or melena. The tourniquet test is done by inflating a BP cuff to midway between the systolic and diastolic BP for 15 min. The number of petechiae that form within a 2.5-cm diameter circle are counted; > 20
petechiae suggests capillary fragility.

CBC, coagulation tests, urinalysis, liver function tests, and dengue serologic tests should be done. Thrombocytopenia (≤ 100,000 platelets/μL) and a prolonged PT characterize the coagulation abnormalities. There may be mild proteinuria and increases in AST levels. Complement fixation antibody titers against flaviviruses are usually high.

Patients with WHO-defined clinical criteria plus thrombocytopenia (≤ 100,000/μL) or hemoconcentration (Hct increased by ≥ 20%) are presumed to have the disease.

Treatment

• Supportive care

Patients require intensive treatment to maintain euvoeemia. Both hypovolemia (which can cause shock) and overhydration (which can cause acute respiratory distress syndrome) should be avoided. Urine output and the degree of hemoconcentration can be used to monitor intravascular volume.

No antivirals have been shown to improve outcome.

Hantavirus Infection

Bunyaviridae contain the genus Hantavirus, which consists of at least 4 serogroups with 9 viruses causing 2 major, sometimes overlapping, clinical syndromes:

• Hemorrhagic fever with renal syndrome (HFRS)

• Hantavirus pulmonary syndrome (HPS)

Viruses causing HFRS are Hantaan, Seoul, Dobrava (Belgrade), and Puumala. Those causing HPS are Sin Nombre, Black Creek Canal, Bayou, and New York-1.

Hantaviruses occur throughout the world in wild rodents, which shed the virus throughout life in urine and feces. Transmission occurs between rodents. Transmission to humans is through inhalation of aerosols of rodent excreta. Recent evidence suggests human-to-human transmission may occur rarely. Naturally and laboratory-acquired infections are becoming more common.

Laboratory diagnosis of Hantavirus infection is established by serologic tests and reverse transcriptase-PCR (RT-PCR). Serologic tests include enzyme-linked immunosorbent assay (ELISA) and Western and strip immunoblot assays. Growth of the virus is technically difficult and requires a biosafety level 3 laboratory.

Hemorrhagic Fever With Renal Syndrome

(Epidemic Nephrosonephritis; Korean Hemorrhagic Fever; Nephropathia Epidemica)

Hemorrhagic fever with renal syndrome (HFRS) begins as a flu-like illness and may progress to shock, bleeding, and renal failure. Diagnosis is with serologic tests and PCR. Mortality is 6 to 15%. Treatment includes IV ribavirin.

Some forms of HFRS are mild (eg, nephropathia epidemica, caused by Puumala virus, as occur in Scandinavia, the western part of the former Soviet Union, and Europe). Others are severe (eg, those caused by Hantaan, Seoul, and Dobrava viruses, as occur in Korea or the Balkans).

Symptoms and Signs

Incubation is about 2 wk. In mild forms, infection is often asymptomatic. When symptoms occur, onset is sudden, with high fever, headache, backache, and abdominal pain. On the 3rd or 4th day, subconjunctival
hemorrhages, palatal petechiae, and a truncal petechial rash may appear. Diffuse reddening of the face that resembles sunburn, with dermatographism, occurs in > 90% of patients. Relative bradycardia is present, and transient mild hypotension occurs in about half of patients, with shock in a minority. After the 4th day, renal failure develops. About 20% of patients become mentally obtunded. Seizures or severe focal neurologic symptoms occur in 1%. The rash subsides; patients develop polyuria and recover over several weeks. Proteinuria, hematuria, and pyuria may develop.

Diagnosis

• Serologic testing or PCR

HFRS is suspected in patients with possible exposure if they have fever, a bleeding tendency, and renal failure. CBC, electrolyte levels, renal function tests, coagulation tests, and urinalysis are then done. During the hypotensive phase, Hct increases and leukocytosis and thrombocytopenia develop. Albuminuria, hematuria, and RBC and WBC casts may develop, usually between the 2nd and 5th day. During the diuretic phase, electrolyte abnormalities are common.

Diagnosis of HFRS is ultimately based on serologic testing or PCR.

Prognosis

Death can occur during the diuretic phase, secondary to volume depletion, electrolyte disturbances, or secondary infections. Recovery usually takes 3 to 6 wk but may take up to 6 mo. Overall, mortality is 6 to 15%, almost always occurring in patients with the more severe forms. Residual renal dysfunction is uncommon except in the severe form that occurs in the Balkans.

Treatment

• Ribavirin

• Sometimes renal dialysis

Treatment is with IV ribavirin: loading dose 33 mg/kg (maximum, 2.64 g), followed by 16 mg/kg q 6 h (maximum, 1.28 g q 6 h) for 4 days, then 8 mg/kg q 8 h (maximum, 0.64 g q 8 h) for 3 days. Supportive care, which may include renal dialysis, is critical, particularly during the diuretic phase.

Hantavirus Pulmonary Syndrome

Hantavirus pulmonary syndrome (HPS) occurs in the US primarily in the southwestern states. It begins as a flu-like illness and, within days, causes noncardiogenic pulmonary edema. Diagnosis is with serologic tests and reverse transcriptase-PCR. Mortality is 50 to 75%.

Treatment is supportive.

Most cases of HPS are caused by the Sin Nombre hantavirus (Four Corners virus, Muerto Canyon virus); others are caused by the Black Creek Canal virus or Bayou virus in the southeastern US, the New York virus on the East Coast of the US, or the Andes virus or Laguna Negra virus in South America. Infection is transmitted to humans via inhalation of excreta of sigmodontine rodents (especially the deer mouse). Most cases occur west of the Mississippi River in spring or summer, typically after heavy rains.

Symptoms and Signs

HPS begins as a nonspecific flu-like illness, with acute fever, myalgia, headache, and GI symptoms. Two to 15 days later (median 4 days), patients rapidly develop noncardiogenic pulmonary edema and hypotension. Several patients have had a combination of HFRS and HPS. Mild cases of HPS can occur.

Diagnosis

• Serologic testing or PCR
HPS is suspected in patients with possible exposure if they have unexplained clinical or radiographic pulmonary edema. Chest x-ray may show increased vascular markings, Kerley B lines, bilateral infiltrates, or pleural effusions. If HPS is suspected, echocardiography should be done to exclude cardiogenic pulmonary edema. CBC, liver function tests, and urinalysis are also usually done. HPS causes mild neutrophilic leukocytosis, hemoconcentration, and thrombocytopenia. Modest elevation of LDH, AST, and ALT, with decreased serum albumin, is typical. Urinalysis shows minimal abnormalities.

Diagnosis is with serologic testing or reverse transcriptase-PCR.

Prognosis

Patients who survive the first few days improve rapidly and recover completely over 2 to 3 wk, often without sequelae. Mortality is 50 to 75%.

Treatment

- Supportive care

Treatment is supportive. Mechanical ventilation, meticulous volume control, and vasopressors may be required. For severe cardiopulmonary insufficiency, extracorporeal mechanical oxygenation may be lifesaving. IV ribavirin is ineffective.

Lassa Fever

Lassa fever is an often fatal arenavirus infection that occurs mostly in Africa. It may involve multiple organ systems but spares the CNS. Diagnosis is with serologic tests and PCR. Treatment includes IV ribavirin.

Lassa fever outbreaks have occurred in Nigeria, Liberia, and Sierra Leone. Cases have been imported to the US and the United Kingdom. The reservoir is Mastomys natalensis, a rat that commonly inhabits houses in Africa. Most human cases probably result from contamination of food with rodent urine, but human-to-human transmission can occur via urine, feces, saliva, vomitus, or blood.

Symptoms and Signs

The incubation period is 5 to 16 days. Symptoms begin with gradually progressive fever, weakness, malaise, and GI symptoms (e.g., nausea, vomiting, diarrhea, dysphagia, stomach ache); symptoms and signs of hepatitis may occur. Over the subsequent 4 to 5 days, symptoms progress to prostration with sore throat, cough, chest pain, and vomiting. The sore throat becomes more severe during the first week; patches of white or yellow exudate may appear on the tonsils, often coalescing into a pseudomembrane.

In 60 to 80% of patients, systolic BP is < 90 mm Hg with pulse pressures of < 20 mm Hg, and relative bradycardia is possible. Facial and neck swelling and conjunctival edema occur in 10 to 30%. Occasionally, patients have tinnitus, epistaxis, bleeding from the gums and venipuncture sites, maculopapular rash, cough, and dizziness. Sensorineural hearing loss develops in 20%; it is often permanent.

In patients who will recover, defervescence occurs; fatally ill patients often develop shock, delirium, rales, pleural effusion, and, occasionally, generalized seizures. Pericarditis occasionally occurs. Degree of fever and aminotransferase levels correlate with disease severity. Late sequelae include alopecia, iridocyclitis, and transient blindness.

Diagnosis

- PCR or serologic testing

Lassa fever is suspected in patients with possible exposure if they have a viral prodrome followed by
unexplained disease of any organ system except the CNS. Liver function tests, urinalysis, serologic tests, and possibly CBC should then be done. Proteinuria is common and may be massive. AST and ALT levels rise (to 10 times normal), as do LDH levels. The most rapid diagnostic test is PCR, but demonstrating either Lassa IgM antibodies or a 4-fold rise in IgG antibody titer using an indirect fluorescent antibody technique is also diagnostic. Although the virus can be grown in cell culture, cultures are not routine. Because infection is a risk, particularly in patients with hemorrhagic fever, cultures must be handled only in a biosafety level 4 laboratory. Chest x-rays, obtained if lung involvement is suspected, may show basilar pneumonitis and pleural effusions.

Prognosis

Recovery or death usually occurs 7 to 31 days (average 12 to 15 days) after symptoms begin. Mortality is 16 to 45%. Disease is severe during pregnancy. Mortality is 50 to 92% in women who are pregnant or who have delivered within 1 mo. Most pregnant women lose the fetus.

Treatment

• Ribavirin

Ribavirin, if begun within the first 6 days, may reduce mortality up to 10-fold. Treatment with ribavirin is 30 mg/kg IV (maximum, 2 g) loading dose followed by 16 mg/kg IV (maximum, 1 g/dose) q 6 h for 4 days, then 8 mg/kg IV (maximum, 500 mg/dose) q 8 h for 6 days. Anti-Lassa fever plasma may be used as adjunctive therapy in very ill patients. Supportive treatment, including correction of fluid and electrolyte imbalances, is imperative. For infected pregnant women, particularly during the 3rd trimester, uterine evacuation appears to reduce maternal mortality.

Prevention

Universal precautions, airborne isolation (including use of goggles, high-efficiency masks, a negative-pressure room, and positive-pressure filtered air respirators), and surveillance of contacts are recommended.

Lymphocytic Choriomeningitis

Lymphocytic choriomeningitis is caused by an arenavirus. It usually causes a flu-like illness or aseptic meningitis, sometimes with rash, arthritis, orchitis, parotitis, or encephalitis. Diagnosis is by viral isolation or indirect immunofluorescence. Treatment is supportive.

Lymphocytic choriomeningitis is endemic in rodents. Human infection results most commonly from exposure to dust or food contaminated by the gray house mouse or hamsters, which harbor the virus and excrete it in urine, feces, semen, and nasal secretions. When transmitted by mice, the disease occurs primarily in adults during autumn and winter.

Symptoms and Signs

The incubation period is 1 to 2 wk. Most patients have no or minimal symptoms. Some develop a flu-like illness. Fever, usually 38.5 to 40° C, with rigors is accompanied by malaise, weakness, myalgia (especially lumbar), retro-orbital headache, photophobia, anorexia, nausea, and light-headedness. Sore throat and dysesthesis occur less often. After 5 days to 3 wk, patients may improve for 1 or 2 days. Many relapse with recurrent fever, headache, rashes, swelling of metacarpophalangeal and proximal interphalangeal joints, meningeal signs, orchitis, parotitis, or alopecia of the scalp.

Aseptic meningitis occurs in a minority of patients. Rarely, frank encephalitis, ascending paralysis, bulbar paralysis, transverse myelitis, or acute Parkinson's disease can occur. Neurologic sequelae are rare in meningitis but occur in up to 33% of patients with encephalitis. Infection may cause fetal abnormalities, including hydrocephalus and chorioretinitis.

Diagnosis
Lymphocytic choriomeningitis is suspected in patients with murine exposure and an acute illness, particularly aseptic meningitis or encephalitis. Aseptic meningitis may lower CSF glucose mildly but occasionally to as low as 15 mg/dL. CSF WBCs range from a few hundred to a few thousand cells, usually with > 80% lymphocytes. WBC counts of 2000 to 3000/μL and platelet counts of 50,000 to 100,000/μL typically occur during the first week of illness. Diagnosis can be made by isolating the virus from the blood or CSF or by indirect immunofluorescence assays of inoculated cell cultures, although these tests are most likely to be found in research laboratories. Diagnosis can also be made by detecting seroconversion of antibody to the virus.

**Treatment**

Treatment is supportive.

**Marburg and Ebola Virus Infections**

Marburg and Ebola are filoviruses that cause hemorrhage, multiple organ failure, and high mortality rates. Diagnosis is with enzyme-linked immunosorbent assay, PCR, or electron microscopy. Treatment is supportive. Strict isolation and quarantine measures are necessary to contain outbreaks.

Epidemics have occurred rarely and sporadically. Most index cases involve exposure to nonhuman primates from sub-Saharan Africa or the Philippines. The vector and reservoir are unknown, although the Marburg virus has been identified in bats, and cases have occurred in people exposed to bats.

Human-to-human transmission occurs via skin and mucous membrane contact with an infected person or other primate. Aerosol transmission has been postulated.

**Symptoms and Signs**

After an incubation period of 5 to 10 days, fever, myalgia, and headache occur, often with abdominal symptoms (nausea, vomiting, pain, diarrhea) and upper respiratory symptoms (cough, chest pain, pharyngitis). Photophobia, conjunctival injection, jaundice, and lymphadenopathy also occur. Delirium, stupor, and coma may occur, indicating CNS involvement. Hemorrhagic symptoms begin within the first few days and include petechiae, ecchymoses, and frank bleeding around puncture sites and mucous membranes. A maculopapular rash, primarily on the trunk, begins around day 5.

During the 2nd wk of symptoms, either defervescence occurs and patients begin recovery, or patients develop fatal multiple organ failure. Recovery is prolonged and may be complicated by recurrent hepatitis, uveitis, transverse myelitis, and orchitis. Mortality ranges from 25 to 90% (higher with Ebola).

**Diagnosis**

- Enzyme-linked immunosorbent blood assay and PCR
- Electron microscopy

Marburg or Ebola virus infection is suspected in patients with bleeding tendencies, fever, and travel to endemic areas or exposure to primates from these areas. CBC, routine blood chemistries, liver function and coagulation tests, and urinalysis are then done. Diagnostic tests include the enzyme-linked immunosorbent blood assay (ELISA) and PCR. The gold standard is detection of characteristic virions with electron microscopy of infected tissue (especially liver) or blood.

**Treatment**

- Supportive care
No effective antiviral therapy exists. Treatment is supportive and includes minimizing invasive procedures
and replacing depleted coagulation factors.

Prevention

A vaccine is currently in development. Mask-gown-glove precautions, thorough equipment sterilization,
hospital closures, and community education have shortened epidemics. All suspected cases, including the
cadavers, require strict isolation and special handling.

The US has strict quarantine procedures to prevent importation of infected monkeys.

Case reporting is required.

Yellow Fever

Yellow fever is a mosquito-borne flavivirus infection endemic in tropical South America and
sub-Saharan Africa. Symptoms may include sudden onset of fever, relative bradycardia,
headache, and, if severe, jaundice, hemorrhage, and multiple organ failure. Diagnosis is with
viral culture and serologic tests. Treatment is supportive. Prevention involves vaccination and
mosquito control.

In urban yellow fever, virus is transmitted by the bite of an *Aedes aegypti* mosquito infected about 2 wk
previously by feeding on a person with viremia. In jungle (sylvatic) yellow fever, the virus is transmitted by
*Haemagogus* and other forest canopy mosquitoes that acquire the virus from wild primates. Incidence is
highest during months of peak rainfall, humidity, and temperature in South America and during the late
rainy and early dry seasons in Africa.

Symptoms and Signs

Infection ranges from asymptomatic (in 5 to 50% of cases) to a hemorrhagic fever with 50% mortality.
Incubation lasts 3 to 6 days. Onset is sudden, with fever of 39 to 40° C, chills, headache, dizziness, and
myalgias. The pulse is usually rapid initially but, by the 2nd day, becomes slow for the degree of fever
(Faget's sign). The face is flushed, and the eyes are injected. Nausea, vomiting, constipation, severe
prostration, restlessness, and irritability are common. Mild disease may resolve after 1 to 3 days.
However, in moderate or severe cases, the fever falls suddenly 2 to 5 days after onset, and a remission
of several hours or days ensues. The fever recurs, but the pulse remains slow. Jaundice, extreme
albuminuria, and epigastric tenderness with hematemesis often occur together after 5 days of illness.
There may be oliguria, petechiae, mucosal hemorrhages, confusion, and apathy.

Disease may last > 1 wk with rapid recovery and no sequelae. In the most severe form (called malignant
yellow fever), delirium, intractable hiccups, seizures, coma, and multiple organ failure may occur
terminally. During recovery, bacterial superinfections, particularly pneumonia, can occur.

Diagnosis

• Viral culture or serologic testing

Yellow fever is suspected in patients in endemic areas if they develop sudden fever with relative
bradycardia and jaundice; mild disease often escapes diagnosis. CBC, urinalysis, liver function tests,
coagulation tests, viral blood culture, and serologic tests should be done. Leukopenia with relative
neutropenia is common, as are thrombocytopenia, prolonged clotting, and increased PT. Bilirubin and
aminotransferase levels may be elevated acutely and for several months. Albuminuria, which occurs in
90% of patients, may reach 20 g/L; it helps differentiate yellow fever from hepatitis. In malignant yellow
fever, hypoglycemia and hyperkalemia may occur terminally.

Diagnosis is confirmed by culture, serologic tests, PCR, or identification of characteristic midzonal
hepatocyte necrosis at autopsy. Suspected or confirmed cases must be quarantined. Needle biopsy of
the liver during illness is contraindicated because hemorrhage is a risk.

**Treatment**

- Supportive care

Up to 10% of patients with disease severe enough to be diagnosed die.

Treatment is mainly supportive. Bleeding may be treated with vitamin K. An H₂ blocker and sucralfate can be helpful as prophylaxis for GI bleeding and can be used in all patients ill enough to require hospitalization.

**Prevention**

Preventive measures include

- Mosquito avoidance
- Vaccination

The most effective way to prevent outbreaks is to reduce the number of mosquitoes and limit mosquito bites by using diethyltoluamide (DEET), mosquito netting, and protective attire. During jungle outbreaks, people should evacuate the area until they are immunized and mosquitoes are controlled.

For people traveling to endemic areas, active immunization with the 17D strain of live-attenuated yellow fever vaccine (0.5 mL sc q 10 yr) is indicated and is effective in 95%. In the US, the vaccine is given only at US Public Health Service-authorized Yellow Fever Vaccination Centers. The vaccine is contraindicated in pregnant women, in infants < 6 mo, and in people with compromised immunity. If infants aged 6 to 8 mo cannot avoid travel to an endemic area, parents should discuss vaccination with their physician since the vaccine is typically not offered until age 9 mo.

To prevent further mosquito transmission, infected patients should be isolated in rooms that are well screened and sprayed with insecticides.

**Other Infections**

**Chikungunya disease:** This disease is an acute febrile illness followed by more chronic polyarthritis. It is transmitted by *Aedes* mosquitoes and is common in Africa, India, Guam, Southeast Asia, New Guinea, and limited areas of Europe. Prevention involves avoiding mosquito bites.

**Mayaro disease:** This dengue-like disease is transmitted by mosquitoes. It is common in Brazil, Bolivia, and Trinidad. Prevention involves avoiding mosquito bites.

**Tick-borne encephalitis:** Initially, a mild flu-like illness occurs, accompanied by leukocytopenia and thrombocytopenia, which clears up within a few days. About 30% of patients develop more severe symptoms (eg, meningitis, meningoencephalitis). A vaccine is available in Europe and Russia.

**California encephalitis:** This encephalitis and related infections are transmitted by mosquitoes and occur in the US Midwest and probably worldwide. This infection causes symptoms (eg, fever, somnolence, obtundation, focal neurologic findings, seizures) primarily in children. Temporal lobe involvement may mimic herpes encephalitis; 20% of patients develop behavioral problems or recurrent seizures. Mortality rate is < 1%. No treatment is available.

**Omsk hemorrhagic fever and Kyasanur Forest disease:** These infections are transmitted by ticks or by direct contact with an infected animal (eg, rodent, monkey). Omsk hemorrhagic fever occurs in the former Soviet Union, including Siberia; Kyasanur Forest disease occurs in India. They are acute febrile illnesses accompanied by bleeding diathesis, low BP, leukopenia, and thrombocytopenia; some patients develop encephalitis in the 3rd wk. Mortality rate is < 3% for Omsk hemorrhagic fever and 3 to 5% for
Kyasanur Forest disease. Prevention involves avoiding tick bites and infected animals.

**Rift Valley fever:** This infection is spread by mosquitoes and transmitted by direct or indirect contact with the blood or organs of infected animals (eg, during slaughtering, butchering, or veterinary procedures), inhalation of infected aerosols, or ingestion of raw milk from infected animals. Rift Valley fever occurs in South Africa, eastern Africa, and Egypt. Rarely, it progresses to ocular disorders, meningoencephalitis, or a hemorrhagic form (which has a 50% mortality rate). A vaccine for livestock is available, and a human vaccine is under investigation.
Chapter 154. Human Immunodeficiency Virus

Introduction

(See also p. 2847, the National Institutes of Health's AIDSInfo web site, and the recommendations of the HIV Medicine Association of the Infectious Diseases Society of America: Primary care guidelines for the management of persons infected with HIV.)

Human immunodeficiency virus (HIV) infection results from 1 of 2 similar retroviruses (HIV-1 and HIV-2) that destroy CD4+ lymphocytes and impair cell-mediated immunity, increasing risk of certain infections and cancers. Initial infection may cause nonspecific febrile illness. Risk of subsequent manifestations—related to immunodeficiency—is proportional to the level of CD4+ lymphocytes. Manifestations range from asymptomatic carriage to AIDS, which is defined by serious opportunistic infections or cancers or a CD4 count of < 200/μL. HIV infection can be diagnosed by antibody or antigen testing. Screening should be routinely offered to all adults and adolescents. Treatment aims to suppress HIV replication by using combinations of drugs that inhibit HIV enzymes.

Retroviruses are enveloped RNA viruses defined by their mechanism of replication via reverse transcription to produce DNA copies that integrate in the host cell genome. Several retroviruses, including human T-lymphotropic virus (see Sidebar 154-1), cause disorders in people.

AIDS is defined as HIV infection that leads to any of the disorders in clinical category B or C of HIV infection (see Table 154-1) or a CD4+ T lymphocyte (helper cell—see p. 1082) count of < 200/μL. The disorders in categories B and C are

• Serious opportunistic infections

• Certain cancers, such as Kaposi's sarcoma and non-Hodgkin lymphoma, to which defective cell-mediated immunity predisposes

• Neurologic dysfunction

Sidebar 154-1 HTLV Infections

Infection with human T-lymphotropic virus (HTLV) 1 or 2 can cause T-cell leukemias and lymphomas, lymphadenopathy, hepatosplenomegaly, skin lesions, and immunocompromise. Some immunocompromised patients develop infections similar to those that occur in patients with AIDS. HTLV-1 can also cause myelopathy (see Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy on p. 1812).

Most cases are transmitted from mother to child by breastfeeding, but HTLV-1 can be transmitted sexually and through blood.

HIV-1 causes most HIV infections worldwide, but HIV-2 causes a substantial proportion of infections in parts of West Africa. In some areas of West Africa, both viruses are prevalent and may coinfect patients. HIV-2 appears less virulent than HIV-1.

HIV-1 originated in rural central Africa in the first half of the 20th century, when a closely related chimpanzee virus first infected humans. Epidemic global spread began in the late 1970s, and AIDS was recognized in 1981. More than 40 million people are infected worldwide. Of the 3 million annual deaths and 11,000 new daily infections, 95% occur in the developing world, one half are in women, and one seventh are in children < 15 yr.

Transmission
Transmission of HIV requires contact with body fluids—specifically blood, semen, vaginal secretions, breast milk, saliva, or exudates from wounds or skin and mucosal lesions—that contain free virions or infected cells. Transmission is more likely with higher levels of virions, as is typical during primary infection, even when people are asymptomatic. Transmission by saliva or droplets produced by coughing or sneezing, although conceivable, is extremely unlikely. HIV is not transmitted by casual nonsexual contact as may occur at work, school, or home.

Transmission is generally by

- Direct transfer of bodily fluids through sexual intercourse
- Sharing of blood-contaminated needles
- Childbirth
- Breastfeeding
- Medical procedures (eg, transfusions, exposure to contaminated instruments)

Sexual practices such as fellatio and cunnilingus appear to be relatively low risk but not absolutely safe (see Table 154-2). Risk does not increase significantly if semen or vaginal secretions are swallowed. However, open sores in the mouth may increase risk. The sexual practices with the highest risks are those that cause mucosal trauma, typically intercourse. Anal-receptive intercourse poses the highest risk. Mucous membrane inflammation facilitates HIV transmission; sexually transmitted diseases such as gonorrhea, chlamydia, trichomoniasis, especially those that cause ulceration (eg, chancroid, herpes, syphilis), increase risk. In heterosexuals, the estimated risk per coital act is about 1/1000; however, risk is increased in early and advanced stages of HIV infection when HIV concentrations in plasma and genital fluid are higher, in younger people, and in people with ulcerative genital diseases.

HIV can be transmitted from mother to offspring transplacentally or perinatally; without treatment, risk of transmission is about 25 to 35%. HIV is also excreted in breast milk, and breastfeeding by HIV-infected mothers may transmit HIV to about 75% of infants who had previously escaped infection. Because many women of childbearing age are infected, incidence of AIDS in children has increased (see p. 2847).

Risk of transmission after skin penetration with a medical instrument contaminated with infected blood is on average about 1/300 without treatment. Immediate antiretroviral treatment probably reduces risk to 1/1500. Risk appears to be higher if the wound is deep or if blood is inoculated (eg, with a contaminated hollow-bore needle). Risk of transmission from infected health care practitioners who take appropriate precautions is unclear but appears minimal. In the 1980s, one dentist transmitted HIV to ≥ 6 of his patients by unknown means. However, extensive investigations of patients cared for by other HIV-infected physicians, including surgeons, have uncovered few other cases.

Although screening of blood donors has minimized risk of transmission via transfusion, a small risk still exists because antibody-based screening tests may miss early infections (see Prevention on p. 1454). Current risk of transmitting HIV via blood transfusion is probably between 1/500,000 and 1/1,000,000 per unit transfused.

[Table 154-1, Clinical Categories of HIV Infection*]

[Table 154-2, HIV Transmission Risk of Several Sexual Activities]

**Epidemiology**

HIV has spread in 2 epidemiologically distinct patterns:

- Male homosexual intercourse or contact with infected blood (eg, through sharing needles in IV drug use)
users; before effective screening of donors, through transfusions)

• Heterosexual intercourse (affecting men and women equally)

The first pattern usually predominates in developed countries; the second pattern predominates in Africa, South America, and southern Asia. In some countries (eg, Brazil, Thailand), both patterns are common. In areas where heterosexual transmission is dominant, HIV infection follows routes of trade, transportation, and economic migration to cities and spreads secondarily to rural areas. In Africa, particularly southern Africa, the HIV epidemic has killed tens of millions of young adults, creating millions of orphans. Factors that perpetuate spread include poverty, poor education, a deficient system of medical care, and lack of effective drugs.

Many opportunistic infections that complicate HIV are reactivations of latent infections. Thus, epidemiologic factors that determine the prevalence of latent infections also influence risk of specific opportunistic infections. In many developing countries, prevalence of toxoplasmosis and TB is high in the general population, and thus enormous increases in active TB have followed the HIV epidemic in these countries. Similarly in the US, incidence of coccidiodomycosis, common in the Southwest, and histoplasmosis, common in the Midwest, has increased because of HIV infection. In the US and Europe, human herpesvirus 8 infection, which causes Kaposi's sarcoma, is common among homosexual and bisexual men but uncommon among other HIV patients. Thus, in the US, > 90% of AIDS patients who develop Kaposi's sarcoma are homosexual or bisexual men.

Pathophysiology

HIV attaches to and penetrates host T cells via CD4+ molecules and chemokine receptors (see Fig. 154-1). After attachment, HIV RNA and enzymes are released into the host cell. Viral replication requires that reverse transcriptase (an RNA-dependent DNA polymerase) copy HIV RNA, producing proviral DNA; this copying mechanism is prone to errors, resulting in frequent mutations. These mutations facilitate the generation of HIV that can resist control by the host's immune system and by antiretroviral drugs. Proviral DNA enters the host cell's nucleus and is integrated into the host DNA in a process that involves HIV integrase. With each cell division, the integrated proviral DNA is duplicated along with the host DNA. Proviral HIV DNA is transcribed to viral RNA and translated to HIV proteins, including the envelope glycoproteins 40 and 120. The HIV proteins are assembled into HIV virions at the inner cell membrane and budded from the cell surface;

[Fig. 154-1. Simplified HIV life cycle.]

each host cell may produce thousands of virions. After budding, protease, another HIV enzyme, cleaves viral proteins, converting the immature virion into a mature, infectious form.

Infected CD4+ lymphocytes produce > 98% of plasma HIV virions. A subset of infected CD4+ lymphocytes constitutes a reservoir of HIV that can reactivate (eg, if antiviral treatment is stopped). Virions have a plasma half-life of about 6 h. In moderate to heavy HIV infection, about \(10^8\) to \(10^9\) virions are created and removed daily. The high volume of HIV replication and high frequency of transcription errors by HIV reverse transcriptase result in many mutations, increasing the chance of producing strains resistant to host immunity and drugs.

Immune system: The main consequence of HIV infection is damage to the immune system, specifically loss of CD4+ lymphocytes, which are involved in cell-mediated and, to a lesser extent, humoral immunity. CD4+ lymphocyte depletion may result from the following:

• Direct cytotoxic effects of HIV replication

• Cell-mediated immune cytotoxicity

• Thymic damage that impairs lymphocyte production

Infected CD4+ lymphocytes have a half-life of about 2 days, which is much shorter than that of uninfected
CD4+ cells. Rates of CD4+ lymphocyte destruction correlate with plasma HIV level. Typically, during the initial or primary infection, HIV levels are highest (> $10^6$ copies/mL), and the CD4 count drops rapidly. The normal CD4 count is about 750/μL, and immunity is minimally affected if the count is > 350/μL. If the count drops below about 200/μL, a variety of opportunistic pathogens may produce clinical disease, often by reactivating from latent states.

The humoral immune system is also affected. Hyperplasia of B cells in lymph nodes occurs, causing lymphadenopathy, and secretion of antibodies to previously encountered antigens increases, often leading to hyperglobulinemia. Total antibody levels (especially IgG and IgA) and titers against previous antigens (eg, cytomegalovirus [CMV]) may be unusually high. However, response to new antigens (eg, in vaccines) decreases as the CD4 count decreases.

**Other tissues**: HIV also infects nonlymphoid monocytic cells (eg, dendritic cells in the skin, macrophages, brain microglia) and cells of the heart and kidneys, causing disease in the corresponding organ systems. HIV strains in several compartments, such as the nervous system (brain and CSF) and genital tract (semen), can be genetically distinct from those in plasma. Thus, HIV levels and resistance patterns in these compartments may differ from those in plasma.

**Disease progression**: Antibodies to HIV are measurable usually within a few weeks after primary infection; however, antibodies cannot fully control HIV infection because mutated forms of HIV that are not controlled by the patient's current antibodies are generated.

Risk and severity of opportunistic infections, AIDS, and AIDS-related cancers are determined by 2 factors:

- CD4 count
- Exposure to potentially opportunistic pathogens

Plasma HIV virion levels, expressed as HIV RNA copies/mL, stabilize after about 6 mo at values (set points) that vary widely among patients but average 30,000 to 100,000/mL (4.2 to 5 log10/mL). The higher the set point, the more quickly the CD4 count decreases to a level that seriously impairs immunity (< 200/μL) and results in the opportunistic infections and cancers that define AIDS. Risk of specific opportunistic infections increases below threshold CD4 counts of about 200/μL for some and 50/μL for others. For example, risk of *Pneumocystis jiroveci* pneumonia, toxoplastic encephalitis, and cryptococcal meningitis rises when the CD4 count is < 200/μL; CMV and *Mycobacterium avium* complex (MAC) infections are a risk when the CD4 count is < 50/μL. For every 3-fold (0.5 log10) increase in plasma HIV RNA in untreated patients, risk of progression to AIDS or death over the next 2 to 3 yr increases about 50%.

Without treatment, risk of progression to AIDS is about 1 to 2%/yr in the first 2 to 3 yr of infection and about 5 to 6%/yr thereafter. Eventually, AIDS almost invariably develops.

**Symptoms and Signs**

Initially, primary HIV infection may be asymptomatic or cause transient nonspecific symptoms (acute retroviral syndrome). Acute retroviral syndrome usually begins within 1 to 4 wk of infection and usually lasts 3 to 14 days; it is characterized by fever, malaise, rash, arthralgia, generalized lymphadenopathy, and sometimes aseptic meningitis. Symptoms are often mistaken for infectious mononucleosis or benign, nonspecific viral syndromes.

After the first symptoms disappear, most patients, even without treatment, have no symptoms or only a few, mild, intermittent, nonspecific symptoms for a highly variable time period (2 to 15 yr).

Symptoms may result from HIV directly or from opportunistic infections. The following are most common:

- Lymphadenopathy
• White plaques due to oral candidiasis
• Painful rash due to herpes zoster
• Diarrhea
• Fatigue
• Fever with intermittent sweats

Asymptomatic, mild-to-moderate cytopenias (eg, leukopenia, anemia, thrombocytopenia) are also common. In some patients, progressive wasting occurs.

Eventually, when the CD4 count drops to < 200/μL, nonspecific symptoms may worsen and a succession of AIDS-defining illnesses (those in category B or C of Table 154-1) develop. Evaluation may detect infection by *Mycobacterium* sp, *P. jirovecii*, *Cryptococcus neoformans*, or other fungi. Infections that also occur in the general population but suggest AIDS if they are unusually severe or frequently recur include herpes zoster, herpes simplex, vaginal candidiasis, and *Salmonella* sepsis. In patients with HIV infection, certain syndromes are common and may require different considerations (see Table 154-3). Some patients present with cancers (eg, Kaposi's sarcoma, B-cell lymphomas) that occur more frequently, are unusually severe, or have unique features in patients with HIV infection (see p. 1457). In other patients, neurologic dysfunction may occur.

[Table 154-3. Common Manifestations of HIV Infection by Organ System]

**Diagnosis**

• HIV antibody testing

• Nucleic acid amplification assays to determine HIV RNA level (viral load)

HIV infection is suspected in patients with persistent, unexplained, generalized adenopathy or any of the disorders in category B or C (see Table 154-1). It may also be suspected in high-risk patients with symptoms that could represent acute primary HIV infection.

Detection of antibodies to HIV is sensitive and specific except during the first few weeks after infection. Enzyme-linked immunosorbent assay (ELISA) to detect HIV antibodies is highly sensitive, but rarely, results are false-positive. Positive ELISA results are therefore confirmed with a more specific test such as Western blot. However, these tests have drawbacks:

• ELISA requires complex equipment.

• Western blot requires well-trained technicians and is expensive.

• The full testing sequence takes time.

Newer point-of-care tests using blood or saliva (eg, particle agglutination, immunoconcentration, immunochromatography) can be done quickly and simply, allowing testing in a variety of settings and immediate reporting to patients. Positive results of these tests should be confirmed by standard blood tests (eg, Western blot).

If HIV infection is suspected despite negative antibody test results (eg, during the first few weeks), plasma may be tested for HIV RNA (virion). The nucleic acid amplification assays used are highly sensitive and specific. HIV RNA assays require advanced technology, such as reverse transcription-PCR (RT-PCR) or branched DNA (bDNA) measurement, which are sensitive to extremely low HIV RNA levels. Measurement of p24 HIV antigen by ELISA is a less sensitive and less specific alternative for directly detecting HIV protein in blood.
When HIV is diagnosed, CD4 count and plasma HIV RNA level should be determined; both are useful for determining prognosis and monitoring treatment. The CD4 count is calculated as the product of the following:

- WBC count
- Percentage of WBCs that are lymphocytes
- Percentage of lymphocytes that are CD4+

Normally, the CD4 count in adults is about 750 ± 250/μL. Plasma HIV RNA level (viral load) reflects HIV replication rates. The higher the set point (the relatively stable virus levels that occur after primary infection), the more quickly the CD4 count decreases and the greater the risk of opportunistic infection, even in patients without symptoms.

HIV infection can be staged in order of increasing severity as category A, B, or C (see Table 154-1). Staging is by clinical manifestations or the CD4 count (A: ≥ 500; B: 200 to 499; and C: < 200/μL). The clinical category is determined by the most severe manifestation patients have had, past or present. Patients are never restaged to a less severe category.

**HIV-related conditions:** Diagnosis of the various opportunistic infections, cancers, and other syndromes that occur in HIV-infected patients is discussed elsewhere in THE MANUAL. Many have aspects unique to HIV infection (see Table 154-1 and p. 1457).

**Hematologic disorders** (eg, cytopenias, lymphomas, cancers) are common and may be usefully evaluated with bone marrow aspiration and biopsy. This procedure can also help diagnose disseminated infections with MAC, *M. tuberculosis*, *Cryptococcus*, *Histoplasma*, human parvovirus B19, *P. jirovecii*, and *Leishmania*. Most patients have normocellular or hypercellular marrow despite peripheral cytopenia, reflecting peripheral destruction. Iron stores are usually normal or increased, reflecting anemia of chronic disease (an iron-reutilization defect). Mild to moderate plasmacytosis, lymphoid aggregates, increased numbers of histiocytes, and dysplastic changes in hematopoietic cells are common.

**HIV-associated neurologic syndromes** can be differentiated via lumbar puncture with CSF analysis and contrast-enhanced CT or MRI (see Table 154-3 and elsewhere in THE MANUAL).

**Screening:** Screening antibody tests should be offered routinely to adults and adolescents, particularly pregnant women, regardless of their perceived risk. For people at highest risk, especially sexually active people who have multiple partners and who do not practice safe sex, testing should be repeated every 6 to 12 mo. Such testing is confidential and available, often free of charge, in many public and private facilities throughout the world.

**Prognosis**

Risk of AIDS, death, or both is predicted by the CD4 count in the short term and by plasma HIV RNA level in the longer term. For every 3-fold (0.5 log10) increase in viral load, mortality over the next 2 to 3 yr increases about 50%. HIV-associated morbidity and mortality vary by the CD4 count, with the most deaths from HIV-related causes occurring at counts of < 50/μL. However, with effective treatment, the HIV RNA level decreases to undetectable levels, CD4 counts often increase dramatically, and risk of illness and death falls.

A subgroup of HIV-infected persons (termed long-term nonprogressors) remains asymptomatic with high CD4 counts and low HIV levels in the blood without antiretroviral treatment. They usually have vigorous cellular and humoral immune responses to their infecting HIV strain as measured by assays in vitro. The specificity of this effective response is shown by examples of superinfection with a second strain of HIV to which their immune response is not as effective, resulting in their conversion to a more typical pattern of progression. Thus, their unusually effective response to the first strain did not apply to the second strain. These cases provide a rationale for counseling HIV-infected people not to expose themselves to possible HIV superinfection through unsafe sex or needle sharing.
Treatment

- Combinations of antiretroviral drugs

- Sometimes prophylaxis for opportunistic infections

Because adequate antiretroviral therapy can cause significant long-term morbidity, it is not recommended for everyone. Current indications include a CD4 count of < 350/μL and an HIV RNA level of > 55,000 copies/mL. Use of potent combinations of antiretroviral drugs for HIV therapy (highly active antiretroviral therapy [HAART]) aims to reduce the plasma HIV RNA level and restore the CD4 count (immune restoration or reconstitution). The lower the pretreatment CD4 count and the higher the HIV RNA level, the less likely treatment is to succeed; however, marked improvement is likely even in patients with advanced immunosuppression. The increase in CD4 count indicates a corresponding decrease in risk of opportunistic infections, other complications, and death. With immune restoration, patients, even those with complications that have no specific treatment (eg, HIV-induced cognitive dysfunction) or that were previously considered untreatable (eg, progressive multifocal leukoencephalopathy), may improve. Outcomes are also improved for patients with cancers (eg, lymphoma, Kaposi's sarcoma) and opportunistic infections.

HAART aims to suppress viral replication to undetectable levels; this goal can usually be achieved if patients take their drugs > 95% of the time. However, maintaining this degree of adherence is difficult. Partial suppression (failure to lower plasma levels to undetectable levels) may select for single or multiple mutations in HIV that make viruses completely or partially resistant and make subsequent treatment more likely to fail.

Patients beginning HAART sometimes deteriorate clinically, despite increasing CD4 counts, because of an immune reaction to subclinical opportunistic infections or to residual microbial antigens after successful treatment of opportunistic infections. These sometimes serious reactions are termed immune reconstitution inflammatory syndromes (IRIS). IRIS can complicate many infections and even cancers (eg, Kaposi's sarcoma) but is usually self-limited or responds to treatment with brief regimens of corticosteroids. Determining whether clinical deterioration is caused by treatment failure, IRIS, or both requires assessment of the persistence of active infection with cultures and can be difficult.

The success of HAART is assessed by measuring plasma HIV RNA levels every 4 to 8 wk for the first 4 to 6 mo or until HIV levels are undetectable (ie, < 50 copies/mL) and every 3 to 6 mo thereafter. Increasing levels are the earliest evidence of treatment failure and may precede a decreasing CD4 count by months. Maintaining patients on failing drug regimens contributes to development of HIV mutants that are more drug-resistant; however, compared with wild-type HIV, these mutants appear to reduce the CD4 count less.

If treatment fails, drug susceptibility (resistance) assays can determine the susceptibility of the dominant HIV strain to all available drugs. Genotypic and phenotypic assays are available and can help clinicians select a new regimen that should contain at least 2 and preferably 3 drugs. The dominant HIV strain in the blood of patients who are taken off antiretroviral therapy may revert over months to years to the wild type (which is susceptible) because resistant mutants replicate more slowly. Thus, if patients have not been treated recently, the full extent of resistance may not be apparent through resistance testing, but when treatment resumes, strains with resistance mutations often reemerge.

Several classes of antiretrovirals are used in HAART (see Table 154-4). There are 5 classes of antiretrovirals; 3 of them inhibit reverse transcriptase by blocking its RNA-dependent and DNA-dependent DNA polymerase activity.

- **Nucleoside reverse transcriptase inhibitors (NRTIs)** are phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and terminate synthesis of DNA chains.

- **Nucleotide reverse transcriptase inhibitors (nRTIs)** competitively inhibit the HIV reverse
transcriptase enzyme, as do NRTIs, but do not require initial phosphorylation.

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** bind directly to the reverse transcriptase enzyme.

- **Protease inhibitors (PIs)** inhibit the viral protease enzyme that is crucial to maturation of immature HIV virions after they bud from host cells.

- **Entry inhibitors (EIs)**, sometimes called fusion inhibitors, interfere with the binding of HIV to CD4+ receptors and chemokine receptors; this binding is required for HIV to enter cells. For example, CCR-5 inhibitors block the CCR-5 receptor.

- **Integrase inhibitors** prevent HIV DNA from being integrated into human DNA.

Combinations of 3 or 4 drugs from different classes are usually necessary to fully suppress replication of wild-type HIV. The specific drugs are chosen based on factors such as concomitant conditions (eg, hepatic dysfunction) and other drugs being taken (to avoid drug interactions). To maximize adherence, clinicians should choose an affordable, well-tolerated regimen that uses once/day (preferable) or bid dosing. Guidelines from expert panels for initiating, selecting, switching, and interrupting therapy and special issues in treating women and children change regularly and are updated at www.aidsinfo.nih.gov/guidelines. Interactions between antiretrovirals may synergistically increase efficacy. For example, a subtherapeutic dose of ritonavir (100 mg once/day) can be combined with another PI (eg, lopinavir, amprenavir, indinavir, atazanavir, tipranavir). Ritonavir inhibits the hepatic enzyme that metabolizes the other PI, increasing the other drug's levels and efficacy. Another example is lamivudine (3TC) plus zidovudine (ZDV). Use of either drug as monotherapy quickly results in resistance, but the mutation that produces resistance in response to 3TC increases the susceptibility of HIV to ZDV. Thus, used together, they are synergistic.

Conversely, interactions between antiretrovirals may decrease the efficacy of each drug. One drug may increase elimination of another drug (eg, by inducing hepatic cytochrome P-450 enzymes responsible for elimination). Another, poorly understood effect of some NRTI combinations (eg, ZDV plus stavudine [d4T]) results in decreased antiretroviral activity without increasing drug elimination.

Combining drugs often increases the risk that either drug will have an adverse effect. Possible mechanisms include the following:

- **Hepatic metabolism of PIs by cytochrome P-450**: The result is decreased metabolism (and increased levels) of other drugs.

- **Additive toxicities**: For example, combining NRTIs, such as d4T and didanosine (ddl), increases the chance of adverse metabolic effects and peripheral neuropathy.

Many drugs may interfere with antiretrovirals; thus, interactions should always be checked before any new drug is started. In addition to drug interactions, grapefruit juice and St. John's wort can decrease activity of some antiretroviral drugs and should be avoided.

**Adverse effects**: Antiretrovirals can have serious adverse effects (see Table 154-4). Some of these effects, notably anemia, pancreatitis, hepatitis, and glucose intolerance, can be detected by blood tests before they cause symptoms. Patients should be screened regularly, both clinically and with appropriate laboratory testing (CBC and blood tests for hyperglycemia, hyperlipidemia, hepatic damage, and renal function), especially when new drugs are started or unexplained symptoms develop.

**Metabolic effects** consist of interrelated syndromes of fat redistribution, hyperlipidemia, and insulin resistance. Subcutaneous fat is commonly redistributed from the face and distal extremities to the trunk.
and abdomen—a cosmetic effect that can stigmatize and distress patients. Treating the resulting deep facial grooves with injected collagen or polylactic acid can be beneficial. Hyperlipidemia and hyperglycemia due to insulin resistance may occur with lipodystrophy. Drugs from all classes appear to contribute to these metabolic effects. Some, such as ritonavir or d4T, do so commonly; others, such as atazanavir, appear to have minimal effects on lipid levels.

Mechanisms for metabolic effects appear to be multiple; one is mitochondrial toxicity. Risk of metabolic effects (highest with PIs) and mitochondrial toxicity (highest with NRTIs) varies by drug class and within drug classes (eg, among NRTIs, highest with d4T). Effects are dose-dependent and often begin in the first 1 to 2 yr of treatment. Nonalcoholic steatohepatitis and lactic acidosis are uncommon but can be lethal. Long-term effects and optimal management of metabolic effects are unclear. Lipid-lowering drugs (statins) and insulin-sensitizing drugs (glitazones) may help. (See also the recommendations of the HIV Medicine Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group: Guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving antiretroviral therapy.)

**Bone complications** of HAART include asymptomatic osteopenia and osteoporosis, which are common. Uncommonly, osteonecrosis of large joints such as the hip and shoulder causes severe joint pain and dysfunction. Mechanisms of bone complications are poorly understood.

Interruption of HAART is usually safe if all drugs are stopped simultaneously. Interruption may be necessary if intervening illnesses require treatment or if drug toxicity is intolerable or needs to be evaluated. After interruption to determine which drug is responsible for toxicity, clinicians can safely restart most drugs as monotherapy for up to a few days. **NOTE:** The most important exception is abacavir; patients who had fever or rash during previous exposure to abacavir may develop severe, potentially fatal hypersensitivity reactions with reexposure.

**End-of-life care:** Although antiretroviral therapy has dramatically increased life expectancy for patients with AIDS, many patients still deteriorate and die. Death may result from the following:

- Inability to take HAART consistently, resulting in progressive immunosuppression
- Occurrence of untreatable opportunistic infections and cancers
- Liver failure due to hepatitis B or C

Death is rarely sudden; thus, patients usually have time to make plans. Nonetheless, patients should record their plans for health care early, with clear instructions for end-of-life care. Other legal documents, including powers of attorney (see p. 3472) and wills, should be in place. These documents are particularly important for homosexual patients because protection of assets and rights (including visitation and decision-making) for their partners may be problems.

As patients near the end of life, clinicians may need to prescribe drugs to relieve pain, anorexia, agitation, and other distressing symptoms. The profound weight loss in many people during the last stages of AIDS makes good skin care difficult. The comprehensive support provided by hospice programs helps many patients because hospice providers are unusually skilled at symptom management, and they support caregivers and patient autonomy.

**Prevention**

Vaccines against HIV have been difficult to develop because HIV surface proteins mutate easily, resulting in an enormous diversity of antigenic types. Nonetheless, research continues, and various candidates are under study. At the present time, there is no effective AIDS vaccine.

**Prevention of transmission:** Vaginal microbicides (including antiretroviral drugs) inserted before sexual contact have proved ineffective, and some appear to increase risk for women, perhaps by damaging natural barriers to HIV.
Effective measures include the following:

- **Public education**: Education is effective and appears to have decreased rates of infection in some countries, notably Thailand and Uganda. Because sexual contact accounts for most cases, teaching people to avoid unsafe sex practices is the most relevant measure (see Table 154-2).

- **Safe sex practices**: Unless both partners are known to be free of HIV and remain monogamous, safe sex practices are essential. Safe sex practices are also advised when both partners are HIV-positive; unprotected sex between HIV-infected people may expose a person to resistant or more virulent strains of HIV and to other viruses (eg, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, hepatitis B virus) that cause severe disease in AIDS patients. Condoms offer the best protection. Oil-based lubricants should not be used because they may dissolve latex, increasing the risk of condom failure.

- **Counseling for parenteral drug users**: Counseling about the risk of sharing needles is important but is probably more effective if combined with provision of sterile needles, treatment of drug dependence, and rehabilitation.

- **Confidential testing for HIV infection**: Testing should be offered routinely to adolescents and adults in virtually all health care settings. To facilitate routine testing, some states no longer require written consent or extensive pre-test counseling.

- **Counseling for pregnant women**: If pregnant women test positive for HIV, risk of maternal-fetal transmission should be explained (see p. 2847). Monotherapy with ZDV or nevirapine reduces risk by two thirds, and 2- or 3-drug combination therapy probably reduces it even more. Some drugs can be toxic to the fetus or mother and cannot be guaranteed to prevent transmission. If treatment is indicated, combination therapy tailored to the woman's history and stage of pregnancy should be used throughout pregnancy. Cesarean delivery can reduce risk of transmission. Some women choose to terminate their pregnancy for this or other reasons.

- **Screening of blood and organs**: Transmission by blood transfusion is still possible because antibody results may be false-negative during early infection. Currently, screening blood for antibody and p24 antigen is mandated in the US and probably further reduces risk of transmission. Risk is reduced further by asking people with risk factors for HIV infection, even those with recent negative HIV antibody test results, not to donate blood or organs for transplantation.

- **Antiretrovirals**: Giving antiretrovirals to HIV-infected people reduces risk of transmission, but how much risk is reduced is unclear.

- **Circumcision of men**: In several African countries, circumcision reduced incidence by about 50%; it is probably also effective elsewhere.

- **Universal precautions**: Medical and dental health care practitioners should wear gloves in situations that may involve contact with any patient's mucous membranes or body fluids and should be taught how to avoid needlestick accidents. Home caregivers of patients with HIV infection should wear gloves if their hands may be exposed to body fluids. Surfaces or instruments contaminated by blood or other body fluids should be cleaned and disinfected. Effective disinfectants include heat, peroxide, alcohols, phenolics, and hypochlorite (bleach). Isolation of HIV-infected patients is unnecessary unless indicated by an opportunistic infection (eg, TB). Guidelines to prevent transmission from infected practitioners to patients have not been established.

**Postexposure prophylaxis (PEP)**: Potential consequences of exposure to HIV have prompted the development of policies and procedures, particularly preventive treatment, to decrease risk of infection to health care workers. Preventive treatment is indicated after penetrating injuries involving HIV-infected blood (usually needlesticks) or heavy exposure of mucous membranes (eye or mouth) to infected fluids. Other body fluids of concern include

- **Semen**
• Vaginal secretions

• Body fluids obviously contaminated with blood

After initial exposure to blood, the exposed area is immediately cleaned with soap and water for skin exposures and with antiseptic for puncture wounds. If mucous membranes are exposed, the area is flushed with large amounts of water.

The following are documented:

• Nature and time of the exposure

• Clinical information, including risk factors and serologic tests for HIV, about the source patient for the exposure and the person exposed

  **Nature of the exposure** is defined by

• Which body fluid was involved

• Whether exposure involved a penetrating injury (eg, needlestick, cut with sharp object)

• Whether the fluid had contact with nonintact skin (eg, abraded or chapped skin) or mucous membrane

**Risk of infection** is categorized as high or low:

• High: Involves a hollow-bore needle with visible blood, direct exposure to a needle from a vein or an artery of the source patient, or mucocutaneous exposure with a large amount of blood from a high-risk source (viral load > 1500 copies/mL)

• Low: Involves a solid needle, superficial injury, or a low-risk source (viral load < 1500 copies/mL) and includes most mucocutaneous exposures

Risk is about 0.3% after percutaneous exposure and about 0.09% after mucous membrane exposure.

**The source** is qualified by whether it is known or unknown; if the source is unknown (eg, a needle on the street or in a sharps disposal container), risk should be assessed based on the circumstances of the exposure (eg, whether the exposure occurred in an area where injection drug use is prevalent, whether a needle discarded in a drug-treatment facility was used). If the source is known but HIV status is not, the source is assessed for HIV risk factors, and prophylaxis is considered (see Table 154-5).

The goal is to start PEP as soon after exposure as possible if prophylaxis is warranted. CDC recommends providing PEP within 24 to 36 h after exposure; a longer interval after exposure requires the advice of an expert.

Use of PEP is determined by risk of infection; guidelines recommend antiretroviral therapy with 2 NRTIs (eg, ZDV plus 3TC) for low risk and the addition of one or more drugs (eg, 2 NRTIs plus a PI or an NNRTI) for high risk; drugs are given for 28 days. Nevirapine is avoided because of the rare possibility of severe hepatitis. Although evidence is not conclusive, ZDV alone probably reduces risk of transmission after needlestick injuries by about 80%. For detailed recommendations, see www.cdc.gov/mmwr/PDF/rr/rr5011.pdf or www.nccc.ucsf.edu/Hotlines/PEPline.html.

If the source's virus is known or suspected to be resistant to ≥ 1 drug, an expert in antiretroviral therapy and HIV transmission should be consulted. However, clinicians should not delay PEP pending expert consultation or drug susceptibility testing. Also, clinicians should provide immediate evaluation and face-to-face counseling and not delay follow-up care.

**Prevention of opportunistic infections:** Effective chemoprophylaxis is available for many opportunistic
infections and reduces rates of disease due to *P. jirovecii*, *Candida*, *Cryptococcus*, and MAC. If therapy restores CD4 counts to above threshold values for > 3 mo, chemoprophylaxis can be stopped.

**Primary prophylaxis** depends on CD count:

[Table 154-5. Postexposure Prophylaxis Recommendations]

- **CD4 count < 200/μL:** Prophylaxis against *P. jirovecii* pneumonia and toxoplasmic encephalitis is recommended. Double-strength trimethoprim/sulfamethoxazole (TMP/SMX) tablets given once/day or 3 times/wk are effective for both infections. Some adverse effects can be minimized with the 3 times/wk dose or by gradual dose escalation. Some patients who cannot tolerate TMP/SMX can tolerate dapsone (100 mg once/day). For the few patients who cannot tolerate either drug because of a troublesome adverse effect (eg, fever, neutropenia, rash), aerosolized pentamidine 300 mg once/day or atovaquone 1500 mg once/day can be used.

- **CD4 count < 75/μL:** Prophylaxis against disseminated MAC with azithromycin, clarithromycin, or rifabutin is recommended. Azithromycin can be given weekly as two 600-mg tablets; it provides protection (70%) similar to daily clarithromycin and does not interact with other drugs.

If latent TB is suspected (based on tuberculin skin tests, high-risk exposure, or prior history of infection), regardless of CD4 count, patients should be given either rifampicin 10 mg/kg po up to 600 mg or rifabutin 300 mg po daily plus either pyrazinamide 25 mg/kg po up to 2.5 g for 2 mo or isoniazid 5 mg/kg po up to 300 mg once/day for 9 mo to prevent reactivation.

For primary prophylaxis against some fungal infections (eg, esophageal candidiasis, cryptococcal meningitis or pneumonia), oral fluconazole 100 to 200 mg once/day or 400 mg weekly is successful but is infrequently used because the cost per infection prevented is high and diagnosis and treatment of these infections are usually successful.

**Secondary prophylaxis** is indicated if patients have had the following:

- Recurrent oral, vaginal, or esophageal candidiasis or cryptococcal infections: Fluconazole is used.

- Histoplasmosis: Itraconazole is used (see p. 1331).

- Latent toxoplasmosis: This disorder is indicated by serum antibodies (IgG) to *Toxoplasma gondii*. TMP/SMX (in doses used to prevent *P. jirovecii* pneumonia) is used to prevent reactivation and consequent toxoplasmic encephalitis. Latent infection is less common (about 15% of adults) in the US than in Europe and most developing countries.

- *P. jirovecii* pneumonia (see p. 1935)

- Herpes simplex infection (see p. 1417)

- Aspergillosis (possibly—see p. 1323)

Detailed guidelines for prophylaxis of fungal (including *Pneumocystis*), viral, mycobacterial, and toxoplasmic infections are available at www.aidsinfo.nih.gov/guidelines.

**Vaccination:** Vaccination (using nonviable vaccines) is indicated for pneumococcal disease (23-valent vaccine if the CD4 count is > 200/μL), influenza A (all patients annually), and hepatitis B and A (for patients at risk); these vaccines are effective less often in patients who are HIV-positive than in those who are HIV-negative. Vaccines against human papillomavirus and varicella (secondary boosting with varicella-zoster, consisting of high-titer live virus) would potentially be valuable in HIV-infected adults, and both are undergoing testing. But their safety needs to be evaluated because these live-virus vaccines are potentially dangerous for patients with severe immunosuppression. For children with HIV infection, vaccination recommendations vary (see p. 2857 and Table 281-4 on p. 2859).
Cancers Common in HIV-Infected Patients

Kaposi’s sarcoma (see p. 753), non-Hodgkin lymphoma (see p. 1020), and cervical cancer are AIDS-defining cancers in HIV-infected patients. Other cancers that appear to be increased in incidence or severity include Hodgkin lymphoma (especially the mixed cellularity and lymphocyte-depleted subtypes), primary CNS lymphoma, anal cancer, testicular cancer, melanoma and other skin cancers, and lung cancer. Leiomyosarcoma is a rare complication of HIV infection in children.

Non-Hodgkin lymphoma: Incidence is 50 to 200 times higher in HIV-infected patients. Most cases are B-cell, aggressive, high-grade histologic subtype lymphomas. At diagnosis, extranodal sites are usually involved; they include bone marrow, GI tract, and other sites that are unusual in non-HIV-associated non-Hodgkin lymphoma, such as the CNS and body cavities (eg, pleural, pericardial, peritoneal).

Common presentations include rapidly enlarging lymph nodes or extranodal masses or systemic symptoms (eg, weight loss, night sweats, fevers).

Diagnosis is by biopsy with histopathologic and immunochemical analysis of tumor cells. Abnormal circulating lymphocytes or unexpected cytopenias suggest involvement of the bone marrow, mandating bone marrow biopsy. Tumor staging may require CSF examination and CT or MRI of the chest, abdomen, and other areas where tumors are suspected.

Poor prognosis is predicted by the following:

- CD4 count of < 100/μL
- Age > 35 yr
- Poor functional status
- Bone marrow involvement
- History of opportunistic infections
- High-grade histologic subtype

Non-Hodgkin lymphoma is treated with systemic, multidrug chemotherapy (eg, cyclophosphamide, doxorubicin, and vincristine plus prednisone), usually combined with antiretrovirals, prophylactic antibiotics and antifungals, and hematologic growth factors. Therapy may be limited by severe myelosuppression, particularly when combinations of myelosuppressive antitumor or antiretroviral drugs are used. Another possible treatment is IV anti-CD20 monoclonal antibody (rituximab), which is effective for non-Hodgkin lymphoma in patients without HIV. Radiation therapy may debulk large tumors and control pain or bleeding.

Primary CNS lymphoma: Incidence is markedly increased in HIV-infected patients with very low CD4 counts (see also p. 1821). These lymphomas consist of intermediate- or high-grade malignant B cells, originating in CNS tissue, and do not spread systemically.

Presenting symptoms include headache, seizures, neurologic deficits (eg, cranial nerve palsies), and mental status change.

Acute treatment requires control of cerebral edema and whole-brain radiation therapy. Radiographic response is common, but median survival is < 6 mo. The role of antitumor chemotherapy is unclear, but highly active antiretroviral therapy (HAART) improves survival.

Cervical cancer: In HIV-infected women, incidence of human papillomavirus (HPV) infection is increased, oncogenic subtypes (types 16, 18, 31, 33, 35, and 39) persist, and the incidence of cervical intraepithelial dysplasia (CIN) is up to 60%, but increased incidence of cervical cancer has not been
proved. However, cervical cancers, if they occur, are more extensive, are more difficult to cure, and have higher recurrence rates after treatment. Confirmed risk factors for cancer include the following:

- Infection with HPV subtype 16 or 18
- CD4+ count of < 200/μL
- Age > 34 yr

HIV infection does not change the management of CIN or cervical cancer. Frequent Papanicolaou tests are important to monitor for progression. HAART may result in resolution of HPV infection and regression of CIN but has no clear effects on cancer.

**Squamous cell cancer of the anus and vulva:** Squamous cell cancers of the anus (see also p. 195) and vulva (see also p. 2581) are caused by the same oncogenic types of HPV as cervical cancers and occur more commonly in HIV-infected patients. The reason for the increased incidence in these patients appears to be the increased rate of high-risk behaviors (eg, anal-receptive intercourse) rather than HIV itself. Anal dysplasia is common, and squamous cell cancers can be very aggressive.

Treatments include surgical extirpation, radiation therapy, and combined chemotherapy with mitomycin or cisplatin and 5-fluorouracil.
Chapter 155. Other Viruses

Introduction

The number of viral diseases affecting humans is large. Most of these are discussed elsewhere in THE MANUAL. A few are not easily categorized and are discussed here. Most of these diseases tend to occur in children but can occur in adults.

Measles

(Measles)

Measles is a highly contagious, viral infection that is most common among children. It is characterized by fever, cough, coryza, conjunctivitis, enanthem (Koplik's spots) on the buccal or labial mucosa, and a maculopapular rash that spreads cephalocaudally. Diagnosis is usually clinical. Treatment is supportive. Vaccination is highly effective.

Worldwide, measles infects about 20 million people causing about 200,000 deaths annually, primarily in children. Measles is rare in the US because of routine childhood vaccination; an average of 63 cases/yr were reported to the Centers for Disease Control and Prevention (CDC) from 2000 to 2007. However, in 2008, 131 cases were reported from January to July.

Pathophysiology

Measles is caused by a paramyxovirus and is a human disease with no known animal reservoir or asymptomatic carrier state. It is extremely communicable; the secondary attack rate is > 90% among susceptible people who are exposed.

Measles is spread mainly by secretions from the nose, throat, and mouth during the prodromal or early eruptive stage. Communicability begins several days before and continues until several days after the rash appears. Measles is not communicable once the rash begins to desquamate.

Transmission is typically by large respiratory droplets that are discharged by cough and briefly remain airborne for a short distance. Transmission may also occur by small aerosolized droplets that can remain airborne (and thus can be inhaled) for up to 2 h in closed areas (eg, in an office examination room). Transmission by fomites seems less likely than airborne transmission because the measles virus is thought to survive only for a short time on dry surfaces.

An infant whose mother has had measles receives antibodies transplacentally; these antibodies are protective for most of the first 6 to 12 mo of life. Lifelong immunity is conferred by infection. In the US, many measles cases are imported by travelers or immigrants; indigenous transmission occurs primarily among unvaccinated people.

Symptoms and Signs

After a 7- to 14-day incubation period, measles begins with a prodrome of fever, coryza, hacking cough, and tarsal conjunctivitis. The pathognomonic Koplik's spots appear 2 to 4 days later, usually on the buccal mucosa opposite the 1st and 2nd upper molars. The spots resemble grains of white sand surrounded by red areolae. They may be extensive, producing diffuse mottled erythema of the buccal mucosa. Sore throat develops.

The rash (see Plate 65) appears 3 to 5 days after symptom onset, usually 1 to 2 days after Koplik's spots appear. It begins on the face in front of and below the ears and on the side of the neck as irregular macules, soon mixed with papules. Within 24 to 48 h, lesions spread to the trunk and extremities (including the palms and soles) as they begin to fade on the face. Petechiae or ecchymoses may occur with severe rashes.

During peak disease severity, a patient's temperature may exceed 40°C, with periorbital edema,
conjunctivitis, photophobia, a hacking cough, extensive rash, prostration, and mild itching. Constitutional symptoms and signs parallel the severity of the eruption and the epidemic. In 3 to 5 days, the fever falls, the patient feels more comfortable, and the rash fades rapidly, leaving a coppery brown discoloration followed by desquamation.

Immunocompromised patients may not have a rash and can develop severe, progressive giant cell pneumonia.

**Complications:** Complications include

- Atypical measles syndrome
- Pneumonia
- Bacterial superinfection
- Acute thrombocytopenic purpura
- Encephalitis
- Transient hepatitis
- Subacute sclerosing panencephalitis

**Atypical measles syndrome** usually occurs in people previously immunized with the original killed-virus measles vaccines, which have been unavailable since 1968. The older vaccines can alter disease expression after infection with wild-type measles. Atypical measles syndrome may begin abruptly, with high fever, prostration, headache, abdominal pain, and cough. The rash may appear 1 to 2 days later, often beginning on the extremities, and may be maculopapular, vesicular, urticarial, or purpuric. Edema of the hands and feet may occur. Pneumonia and hilar adenopathy are common and may be prolonged; chest x-ray abnormalities may persist for weeks to months. Symptomatic hypoxemia may occur.

**Pneumonia** due to measles virus infection of the lungs occurs in about 5% of patients, even during apparently uncomplicated infection; in infants, it is a common cause of death.

**Bacterial superinfections** include pneumonia and otitis media. Measles transiently suppresses delayed hypersensitivity, which can worsen active TB and temporarily prevent reaction to tuberculin and histoplasmin antigens in skin tests. Bacterial superinfection is suggested by pertinent focal signs or a relapse of fever, leukocytosis, or prostration.

**Acute thrombocytopenic purpura** may occur after infection resolves and cause a mild, self-limited bleeding tendency, although occasionally bleeding is severe.

**Encephalitis** occurs in 1/1000 to 2000 cases, usually 2 days to 2 wk after onset of the rash, often beginning with recrudescence of high fever, headache, seizures, and coma. CSF usually has a lymphocyte count of 50 to 500/μL and a mildly elevated protein level but may be normal initially. Encephalitis may resolve in about 1 wk or may persist longer, causing morbidity or death.

**Transient hepatitis** may occur during an acute infection.

**Subacute sclerosing panencephalitis** (SSPE) is a rare, progressive, ultimately fatal, late complication of measles (see p. 1466).

**Diagnosis**

- Clinical evaluation
- Serologic testing
• Viral detection via culture or reverse transcription-PCR

Typical measles may be suspected in an exposed patient who has coryza, conjunctivitis, photophobia, and cough but is usually suspected only after the rash appears. Diagnosis is usually clinical, by identifying Koplik’s spots or the rash. CBC is unnecessary but, if obtained, may show leukopenia with a relative lymphocytosis. Laboratory identification is necessary for public health and outbreak control purposes. It is most easily done by demonstration of the presence of measles IgM antibody in an acute serum specimen or by viral culture or reverse transcription-PCR of throat swabs, blood, nasopharyngeal swabs, or urine samples. A rise in IgG antibody levels between acute and convalescent sera is highly accurate, but obtaining this information delays diagnosis. All cases of suspected measles should be reported to the local health department even before laboratory confirmation.

Differential diagnosis includes rubella, scarlet fever, drug rashes (eg, from phenobarbital or sulfonamides), serum sickness, roseola infantum, infectious mononucleosis, erythema infectiosum (see p. 2840), and echovirus and coxsackievirus infections (see also Table 149-7). Atypical measles, because of its greater variability, can simulate even more conditions than typical measles. Some of these conditions can be distinguished from typical measles as follows:

• Rubella: A recognizable prodrome is absent, fever and other constitutional symptoms are absent or less severe, postauricular and suboccipital lymph nodes are enlarged (and usually tender), and duration is short.

• Drug rashes: A drug rash often resembles the measles rash, but a prodrome is absent, there is no cephalocaudal progression or cough, and there is usually a history of recent drug exposure.

• Roseola infantum: The rash resembles that of measles, but it seldom occurs in children > 3 yr. Initial temperature is usually high, Koplik’s spots and malaise are absent, and dermoe-verse and rash occur simultaneously.

Prognosis

Mortality is about 2/1000 in the US but is much higher in the developing world. Undernutrition and vitamin A deficiency may predispose to mortality. Vitamin A supplementation is recommended for populations at risk.

Treatment

• Supportive care

• For children, vitamin A

Treatment is supportive, including for encephalitis.

Vitamin A supplementation has been shown to reduce morbidity and mortality due to measles in children in the developing world. Because low serum levels of vitamin A are associated with severe disease due to measles, vitamin A treatment is recommended for all children with measles. The dose is given orally once/day for 2 days and depends on the child's age:

• > 1 yr: 200,000 IU
• 6 to 11 mo: 100,000 IU
• < 6 mo: 50,000 IU

In children with clinical signs of vitamin A deficiency, a single age-specific dose of vitamin A is repeated 2 to 4 wk later.
Prevention

A live-attenuated virus vaccine containing measles, mumps, and rubella is routinely given to children in most developed countries (see also p. 1177 and Table 268-10 on p. 2718). The first dose is recommended at age 12 to 15 mo but can be given as young as age 6 mo during a measles outbreak. Two doses are recommended; the second is given at age 4 to 6 yr. Infants immunized at < 1 yr of age still require 2 further doses given after the first birthday. Vaccine provides long-lasting immunity and has decreased measles incidence in the US by 99%. The vaccine causes mild or inapparent, noncommunicable infection. Fever > 38° C occurs 5 to 12 days after inoculation in < 5% of vaccinees and can be followed by a rash. CNS reactions are exceedingly rare; the vaccine does not cause autism.

Contraindications to the vaccine include generalized cancers (eg, leukemia, lymphoma), immunodeficiency, and therapy with immunosuppressants (eg, corticosteroids, irradiation, alkylating agents, antimetabolites). HIV infection is a contraindication only if immunosuppression is severe (CDC immunologic category 3 with CD4 < 15%); if not, the risks of wild measles outweigh the risk of acquiring measles from the live vaccine. Reasons to defer vaccination include pregnancy, serious febrile illness, active untreated TB, or administration of antibody (as whole blood, plasma, or any immune globulin). Duration of deferral depends on the type and dose of immune globulin preparation given but may be as long as 11 mo.

Postexposure prophylaxis: Prevention in susceptible contacts is possible by giving the vaccine within 3 days of exposure. If vaccine should be deferred, immune globulin 0.25 mL/kg IM (maximum dose, 15 mL) is given immediately, with vaccination given 5 to 6 mo later if medically appropriate (eg, if the patient is no longer pregnant). An exposed immunodeficient patient with a contraindication to vaccination is given immune globulin 0.5 mL/kg IM (maximum, 15 mL). Immune globulin should not be given simultaneously with vaccine.

Monkeypox

Monkeypox virus is structurally related to the smallpox virus and causes similar, but milder illness.

Monkeypox, like smallpox, is a member of the Orthopoxvirus group. Although the reservoir is unknown, monkeypox is endemic among rodents and monkeys in the rain forests of Africa, mostly in western and central Africa. Human disease occurs in Africa sporadically and in occasional epidemics.

In the US, an outbreak of monkeypox occurred in 2003, when infected rodents imported as pets from Ghana spread the virus to pet prairie dogs, which then infected people in the Midwest. The outbreak involved 35 confirmed, 13 probable, and 22 suspected cases in 6 states, but there were no deaths.

Monkeypox is probably transmitted from animals via wounds or mucous membranes. Person-to-person transmission occurs inefficiently, with an attack rate of 8 to 9%. Most patients are children. People who have received smallpox vaccine may be at reduced risk. In Africa, mortality rate ranges from 4 to 22%.

Clinically, monkeypox is similar to smallpox; however, skin lesions occur more often in crops, and lymphadenopathy may be more common.

Clinical differentiation of monkeypox from smallpox and chickenpox may be impossible. Diagnosis is by culture, PCR, immunohistochemistry, or electron microscopy, depending on which tests are available.

Treatment is supportive. Cases are reported to public health authorities.

Mumps

(Epidemic Parotitis)

Mumps is an acute, contagious, systemic viral disease, usually causing painful enlargement of
the salivary glands, most commonly the parotids. Complications may include orchitis, meningoencephalitis, and pancreatitis. Diagnosis is usually clinical; all cases are reported to public health authorities. Treatment is supportive. Vaccination is effective for prevention.

The causative agent, a paramyxovirus, is spread by droplets or saliva. The virus probably enters through the nose or mouth. It is in saliva up to 6 days before salivary gland swelling appears. It is also in blood and urine and, if the CNS is involved, in CSF. One attack usually confers permanent immunity.

Mumps is less communicable than measles. It occurs mainly in unimmunized populations, but outbreaks on college campuses among largely immunized populations have occurred. A combination of primary vaccine failure (failure to develop immunity after vaccination) and waning immunity may have played a part in these outbreaks. In 2006, there was a resurgence of mumps in the US with 6584 cases, which occurred primarily in young adults with prior vaccination. As with measles, mumps cases may be imported, leading to indigenous transmission, especially in congregate settings (eg, college campuses). Peak incidence of mumps is during late winter and early spring. Disease occurs at any age but is unusual in children < 2 yr, particularly those < 1 yr. About 25 to 30% of cases are clinically inapparent.

Symptoms and Signs

After a 14- to 24-day incubation period, most people develop headache, anorexia, malaise, and a low- to moderate-grade fever. The salivary glands become involved 12 to 24 h later, with fever up to 39.5 to 40° C. Fever persists 24 to 72 h. Glandular swelling peaks on about the 2nd day and lasts 5 to 7 days. Involved glands are extremely tender during the febrile period.

Parotitis is usually bilateral. Pain while chewing or swallowing, especially while swallowing acidic liquids such as vinegar or citrus juice, is its earliest symptom. It later causes swelling beyond the parotid in front of and below the ear. Occasionally, the submandibular and sublingual glands also swell and, more rarely, are the only glands affected. Submandibular gland involvement causes neck swelling beneath the jaw, and suprasternal edema may develop, perhaps because of lymphatic obstruction by enlarged salivary glands. When sublingual glands are involved, the tongue may swell. The oral duct openings of the affected glands are edematous and slightly inflamed. The skin over the glands may become tense and shiny.

Complications: Mumps may involve organs other than the salivary glands, particularly in postpubertal patients. Such complications include

• Orchitis or oophoritis
• Meningitis or encephalitis
• Pancreatitis

About 20% of postpubertal male patients develop orchitis (testicular inflammation), usually unilateral, with pain, tenderness, edema, erythema, and warmth of the scrotum. Some testicular atrophy may ensue, but testosterone production and fertility are usually preserved. In females, oophoritis (gonadal involvement) is less commonly recognized, is less painful, and does not impair fertility.

Meningitis, typically with headache, vomiting, stiff neck, and CSF pleocytosis, occurs in 1 to 10% of patients with parotitis. Encephalitis, with drowsiness, seizures, or coma, occurs in about 1/1000 to 5000 cases. About 50% of CNS mumps infections occur without parotitis.

Pancreatitis, typically with sudden severe nausea, vomiting, and epigastric pain, may occur toward the end of the first week. These symptoms disappear in about 1 wk, leading to complete recovery.

Prostatitis, nephritis, myocarditis, hepatitis, mastitis, polyarthritis, deafness, and lacrimal gland involvement occur extremely rarely. Inflammation of the thyroid and thymus glands may cause edema and swelling over the sternum, but sternal swelling more often results from submandibular gland involvement.
Diagnosis

• Clinical evaluation

• Serologic testing

• Viral detection via tissue culture or reverse transcription-PCR

Mumps is suspected in patients with salivary gland inflammation and typical systemic symptoms, particularly if there is parotitis or a known mumps outbreak. Laboratory testing is not needed to make a diagnosis but is strongly recommended for public health purposes. Other conditions can cause similar glandular involvement (see Table 155-1). Mumps is also suspected in patients with unexplained aseptic meningitis or encephalitis during mumps outbreaks. Lumbar puncture is necessary for patients with meningeval signs.

Laboratory diagnosis is necessary if disease is unilateral, is recurrent, occurs in previously immunized patients, or causes prominent involvement of tissues other than the salivary glands. Testing is also recommended for all patients with parotitis lasting ≥ 2 days without an identified cause. Acute and convalescent sera are tested by complement fixation or enzyme-linked immunosorbent assays (ELISA). If the laboratory is capable, the virus can usually be cultured from the throat, CSF, and occasionally the urine, or viral RNA can be detected by reverse transcription-PCR.

Other laboratory tests are generally unnecessary, although serum amylase level can also be measured; elevation suggests mumps. WBC count is nonspecific; it may be normal but usually shows slight leukopenia and neutropenia. In meningitis, CSF glucose is usually normal but is occasionally between 20 and 40 mg/dL (1.1 and 2.2 mmol/L), as in bacterial meningitis. CSF protein is only mildly elevated.

Prognosis

Uncomplicated mumps usually resolves, although a relapse occurs rarely after about 2 wk. Prognosis of patients with meningitis is usually good, although permanent sequelae, such as unilateral (or rarely bilateral) nerve deafness or facial paralysis, may result. Postinfectious encephalitis, acute cerebellar ataxia, transverse myelitis, and polynieritis occur rarely.

Treatment

• Supportive care

Treatment of mumps and its complications is supportive. The patient is isolated until glandular swelling subsides. A soft diet reduces pain caused by chewing. Acidic substances (eg, citrus fruit juices) that cause discomfort should be avoided.

Repeated vomiting due to pancreatitis may necessitate IV hydration. For orchitis, bed rest and support of the scrotum in cotton on an adhesive-tape bridge between the thighs to minimize tension or use of ice packs often relieves pain. Corticosteroids have not been shown to hasten resolution of orchitis.

Prevention

Vaccination with live mumps virus vaccine (see p. 1177 and Table 268-10 on p. 2718) provides effective prevention and causes no significant local or systemic reactions. Two doses, given as combined measles, mumps and rubella vaccine, are recommended for children; the first is given at age 12 to 15 mo, and the second at age 4 to 6 yr. Adults born during or after 1957 should have 1 dose, unless they have had mumps diagnosed by a health care practitioner. Pregnant women and people with an impaired immune system should not be given such live-attenuated vaccines.
Postexposure vaccination does not protect against mumps from that exposure. Mumps immune globulin and serum immune globulin are also not helpful.

**Rubella**

(German Measles; 3-Day Measles)

(See also p. 2820.)

**Rubella** is a contagious viral infection that may cause adenopathy, rash, and sometimes constitutional symptoms, which are usually mild and brief. Infection during early pregnancy can cause spontaneous abortion, stillbirth, or congenital defects. Diagnosis is usually clinical. Cases are reported to public health authorities. Treatment is usually unnecessary. Vaccination is effective for prevention.

Rubella is caused by an RNA virus, rubella virus, which is spread by respiratory droplets through close contact or through the air. Patients can transmit rubella during asymptomatic infection or from 10 days before the rash appears until 15 days after onset of the rash. Congenitally infected infants may transmit rubella for many months after birth. Rubella is less contagious than measles. Immunity appears to be lifelong after natural infection. However, in unvaccinated populations, 10 to 15% of young adults have not had childhood infection and are susceptible. At present, incidence in the US is at a historic low because of routine childhood vaccination; all cases since 2002 have been linked to importation.

**Symptoms and Signs**

Many cases are mild. After a 14- to 21-day incubation period, a 1- to 5-day prodrome, usually consisting of low-grade fever, malaise, and lymphadenopathy, occurs in adults but may be minimal or absent in children. Tender swelling of the suboccipital, postauricular, and posterior cervical glands is characteristic. There is pharyngeal injection at the onset.

The rash is similar to that of measles but is less extensive and more evanescent (see Plate 64); it is often the first sign in children. It begins on the face and neck and quickly spreads to the trunk and extremities. At onset, a blanching, macular erythema may appear, particularly on the face. On the 2nd day, the rash often becomes more scarlatiniform (pinpoint) with a reddish flush. Petechiae form on the soft palate (Forschheimer's spots), later coalescing into a red blush. The rash lasts 3 to 5 days.

Constitutional symptoms in children are absent or mild and may include malaise and occasional arthralgias. Adults usually have few or no constitutional symptoms but occasionally have fever, malaise, headache, stiff joints, transient arthritis, and mild rhinitis. Fever typically resolves by the 2nd day of the rash. Encephalitis has occurred rarely during large military outbreaks. Complete resolution is typical, but encephalitis is occasionally fatal. Thrombocytopenic purpura and otitis media occur rarely.

**Diagnosis**

- Clinical evaluation
- Serologic testing

Rubella is suspected in patients with characteristic adenopathy and rash. Laboratory diagnosis is necessary for pregnant women, patients with encephalitis, and neonates. Also, laboratory evaluation is strongly encouraged for all suspected cases of rubella for public health purposes. A ≥ 4-fold rise between acute and convalescent (4 to 8 wk) antibody titers confirms the diagnosis, as can serum rubella IgM antibody testing.

**Differential diagnosis** includes measles, scarlet fever, secondary syphilis, drug rashes, erythema
infectiosum (see p. 2840), and infectious mononucleosis as well as echovirus and coxsackievirus infections (see Table 149-7). Infections with enteroviruses and parvovirus B19 (erythema infectiosum) may be clinically indistinguishable. Rubella is differentiated from measles by the milder, more evanescent rash; milder and briefer constitutional symptoms; and absence of Koplik's spots, photophobia, and cough. Within a day of onset, scarlet fever usually causes more severe constitutional symptoms and pharyngitis than does rubella. In secondary syphilis, adenopathy is not tender, and the rash is usually prominent on the palms and soles. Also, laboratory diagnosis of syphilis is usually readily available. Infectious mononucleosis can be differentiated by its more severe pharyngitis, more prolonged malaise, and atypical lymphocytosis and by Epstein-Barr virus antibody testing (see p. 1422).

**Treatment**

- Supportive care

Treatment is symptomatic. No specific therapy for encephalitis is available.

**Prevention**

Live-virus vaccine is given routinely (see Table 268-10 on p. 2718). It produces immunity for ≥ 15 yr in > 95% of recipients and does not appear to transmit the infection. Because certain other infections are clinically indistinguishable from rubella, a reported history of rubella does not guarantee immunity.

Vaccination is given to children as combined measles, mumps and rubella vaccine in 2 doses; the first is given at age 12 to 15 mo, and the second at age 4 to 6 yr. One dose is recommended for all susceptible postpubertal people, especially college students, military recruits, health care practitioners, recent immigrants, and people working with young children. Routine vaccination is recommended for all susceptible mothers immediately after delivery. Screening women of childbearing age for rubella antibodies and immunizing those susceptible is also suggested. However, women receiving the vaccine should prevent conception for at least 28 days afterward. The vaccine virus may be capable of infecting a fetus during early pregnancy. The vaccine does not cause congenital rubella syndrome, but risk of fetal damage is estimated at ≤ 3%; use of vaccine is contraindicated throughout pregnancy.

Fever, rash, lymphadenopathy, polyneuropathy, arthralgia, and arthritis occur rarely after vaccination in children; painful joint swelling occasionally follows vaccination in adults, usually in women.

**Progressive Rubella Panencephalitis**

Progressive rubella panencephalitis is a neurologic disorder occurring in children with congenital rubella. It is presumably due to persistence or reactivation of rubella virus infection.

Some children with congenital rubella syndrome (eg, with deafness, cataracts, microcephaly, and intellectual disability) develop neurologic deficits in the early teens.

The diagnosis is considered when a child with congenital rubella develops progressive spasticity, ataxia, mental deterioration, and seizures. Testing involves at least CSF examination and serologic testing. CSF total protein and globulin and rubella antibody titers in CSF and serum are elevated. CT may show ventricular enlargement due to cerebellar atrophy and white matter disease. Brain biopsy may be necessary to exclude other causes of encephalitis or encephalopathy. Rubella virus usually cannot be recovered by viral culture or immunohistologic testing.

No specific treatment exists.

**Smallpox**

(Variola)

Smallpox is a highly contagious disease caused by the smallpox virus, an orthopoxvirus. It causes death in up to 30%. Indigenous infection has been eradicated. The main concern for
outbreaks is from bioterrorism. Severe constitutional symptoms and a characteristic pustular rash develop. Treatment is supportive. Prevention involves vaccination, which, because of its risks, is done selectively.

No cases of smallpox have occurred in the world since 1977 because of worldwide vaccination. In 1980, the World Health Organization (WHO) recommended discontinuation of routine smallpox vaccination. Routine vaccination in the US ended in 1972. Because humans are the only natural host of the smallpox virus and because the virus cannot survive > 2 days in the environment, WHO has declared natural infection eradicated. Recent concerns about terrorist access to existing stockpiles of smallpox virus raise the possibility of a recurrence (see p. 1164).

Because immunity declines over time, nearly all people—even those previously vaccinated—are now thought to be susceptible to smallpox.

Pathophysiology

There are at least 2 strains of smallpox virus. The more virulent strain causes variola major (classic smallpox); the less virulent strain causes variola minor (alastrim).

Smallpox is transmitted from person to person by direct contact or inhalation of droplet nuclei. Contaminated clothing or bed linens can also transmit infection. The infection is most communicable for the first 7 to 10 days after the rash appears. Once crusts form on the skin lesions, infectivity declines.

The attack rate is as high as 85% in unvaccinated people, and infection may lead to as many as 4 to 10 secondary cases from each primary case. However, infection tends to spread slowly and mainly among close contacts.

The virus invades the oropharyngeal or respiratory mucosa and multiplies in regional lymph nodes, causing subsequent viremia. It eventually localizes in small blood vessels of the dermis and the oropharyngeal mucosa. Other organs are seldom clinically involved, except for occasionally the CNS, with encephalitis. Secondary bacterial infection may develop in skin lesions.

Symptoms and Signs

**Variola major** has a 10- to 12-day incubation period (range 7 to 17 days), followed by a 2- to 3-day prodrome of fever, headache, backache, and extreme malaise. Sometimes severe abdominal pain and vomiting occur. After the prodrome, a maculopapular rash develops on the oropharyngeal mucosa, face, and arms, spreading shortly thereafter to the trunk and legs. The oropharyngeal lesions quickly ulcerate. After 1 or 2 days, the cutaneous lesions become vesicular, then pustular. Pustules are denser on the face and extremities than on the trunk, and they may appear on the palms. The pustules are round and tense and appear deeply embedded. Skin lesions of smallpox, unlike those of chickenpox, are all at the same stage of development on a given body part. After 8 or 9 days, the pustules become crusted. Severe residual scarring is typical. Mortality rate is about 30%, due to a massive inflammatory response causing shock and multiple organ failure; death usually occurs in the 2nd wk of illness.

**Variola minor** results in symptoms that are similar but much less severe, with a less extensive rash. Mortality rate is < 1%.

About 5 to 10% of people with smallpox develop either a hemorrhagic or a malignant variant. The hemorrhagic form is rarer and has a shorter, more intense prodrome, followed by generalized erythema and cutaneous and mucosal hemorrhage. It is uniformly fatal within 5 or 6 days. The malignant form has a similar, severe prodrome, followed by development of confluent, flat, nonpustular skin lesions. In the rare survivors, the epidermis frequently peels.

Diagnosis

- PCR
• Electron microscopy

Diagnosis is confirmed by documenting the presence of variola DNA by PCR of vesicular or pustular samples. Or the virus can be confirmed by electron microscopy or viral culture of material scraped from skin lesions (ideally, with subsequent confirmation by PCR). Suspected smallpox must be reported immediately to local public health agencies or the Centers for Disease Control and Prevention (CDC) at 770-488-7100. These agencies then arrange for testing in a laboratory with high-level containment capability (biosafety level 4).

Treatment

• Supportive care
• Isolation
• Possibly cidofovir

Treatment is generally supportive, with antibiotics for the occasional secondary bacterial infection. Antiviral drugs have never been used clinically, but cidofovir may be considered for use under an investigational new drug protocol sponsored by the CDC.

Isolation of people with smallpox is essential. In limited outbreaks, patients may be isolated in a hospital in a negative-pressure room equipped with high-efficiency particulate (HEPA) filters. In mass outbreaks, home isolation may be required. Contacts should be placed under surveillance, typically with daily temperature measurement, and isolated at home if they develop a temperature of > 38°C or other sign of illness.

Prevention

Smallpox vaccine consists of live vaccinia virus, which is related to smallpox and provides cross-immunity. Vaccine is administered with a bifurcated needle dipped in reconstituted vaccine. The needle is rapidly jabbed 15 times in an area about 5 mm in diameter and with sufficient force to draw a trace of blood. The vaccine site is covered with a dressing to prevent spread of the vaccine virus to other body sites. Fever, malaise, and myalgias are common the week after vaccination. Successful vaccination is indicated by development of a pustule by about the 7th day. Revaccination may cause only a papule surrounded by erythema, which peaks between 3 and 7 days. People without such signs of successful vaccination should be given another dose of vaccine.

Until an outbreak in the population occurs, preexposure vaccination remains recommended only for people at high risk of exposure to the virus (eg, laboratory technicians).

Vaccine complications: Risk factors for complications include extensive skin disorders (particularly eczema), immunosuppressive diseases or therapies, ocular inflammation, and pregnancy. Widespread vaccination is not recommended because of the risk. Serious complications occur in about 100 per million primary vaccines and include

• Postvaccinial encephalitis
• Progressive vaccinia
• Eczema vaccinatum
• Generalized vaccinia

Postvaccinial encephalitis occurs in about 1 of 300,000 recipients of primary vaccination, typically 8 to 15 days postvaccination.

Progressive vaccinia results in a nonhealing vaccinial (vesicular) skin lesion that spreads to adjacent skin
and ultimately other skin areas, bones, and viscera. Progressive vaccinia may occur after primary vaccination or revaccination but occurs almost exclusively in patients with an underlying defect in cell-mediated immunity; it can be fatal.

Eczema vaccinatum results in vaccinial skin lesions appearing on areas of active or even healed eczema.

Generalized vaccinia results from hematogenous dissemination of the vaccinia virus and causes vaccinia lesions at multiple body locations; it is usually benign. If there is inadvertent ocular viral implantation, vaccinia keratitis occurs rarely.

Some serious vaccine complications are treated with vaccinia immune globulin (VIG). In the past, high-risk patients who required vaccination because of viral exposure were simultaneously given VIG to try to prevent complications. The efficacy of this practice is unknown, and it is not recommended by the CDC. VIG is available only from the CDC.

**Postexposure prophylaxis:** Postexposure vaccination can prevent or significantly limit the severity of illness and is indicated for family members and close personal contacts of smallpox patients. Early administration is most effective, but some benefit is realized up to 4 days postexposure.

**Subacute Sclerosing Panencephalitis**

Subacute sclerosing panencephalitis (SSPE) is a progressive, usually fatal brain disorder occurring months to usually years after an attack of measles. It causes mental deterioration, myoclonic jerks, and seizures. Diagnosis involves EEG, CT, CSF examination, and measles serologic testing. Treatment is supportive.

SSPE is probably a persistent measles virus infection (see p. 1458). The measles virus is present in brain tissue.

SSPE occurs in about 7 to 110 cases per million people who had wild measles and in about 1 case per million people who received measles vaccine; all cases are probably due to unrecognized measles before vaccination. Males are more often affected. Onset is usually before age 20. SSPE is exceedingly rare in the US and Western Europe.

**Symptoms and Signs**

Often, the first signs are subtle—diminished performance in schoolwork, forgetfulness, temper tantrums, distractibility, and sleeplessness. However, hallucinations and myoclonic jerks may then occur, followed by generalized seizures. There is further intellectual decline and speech deterioration. Dystonic movements and transient opisthotonos occur. Later, muscular rigidity, dysphagia, cortical blindness, and optic atrophy may occur. Focal chorioretinitis and other funduscopic abnormalities are common. In the final phases, hypothalamic involvement may cause intermittent hyperthermia, diaphoresis, and pulse and BP disturbances.

**Diagnosis**

- Serologic testing
- EEG
- Neuroimaging

SSPE is suspected in young patients with dementia and neuromuscular irritability. EEG, CT or MRI, CSF examination, and measles serologic testing are done. EEG shows periodic complexes with high-voltage diphasic waves occurring synchronously throughout the recording. CT or MRI may show cortical atrophy or white matter lesions. CSF examination usually reveals normal pressure, cell count, and total protein content; however, CSF globulin is almost always elevated, constituting up to 20 to 60% of CSF protein. Serum and CSF contain elevated levels of measles virus antibodies. Anti-measles IgG appears to
increase as the disease progresses.

If test results are inconclusive, brain biopsy may be needed.

**Prognosis**

The disease is almost invariably fatal within 1 to 3 yr (often pneumonia is the terminal event), although some patients have a more protracted course. A few patients have remissions and exacerbations.

**Treatment**

- Supportive care

Anticonvulsants and other supportive measures are the only accepted treatments. Isoprinosine, interferon alfa, and lamivudine are controversial, and antiviral drugs have generally not proved helpful.
Chapter 156. Sexually Transmitted Diseases

Introduction

Sexually transmitted diseases (STDs), also termed sexually transmitted infections (STIs), can be caused by a number of microorganisms that vary widely in size, life cycle, symptoms, and susceptibility to available treatments.

Bacterial STDs include syphilis, gonorrhea, chancroid, lymphogranuloma venereum, granuloma inguinale, and chlamydial, mycoplasmal, and *Ureaplasma* infections.

Viral STDs include genital and anorectal warts, genital herpes (see p. 1418), molluscum contagiosum (see p. 715), and HIV infection (see p. 1438).

Parasitic infections that can be sexually transmitted include trichomoniasis (caused by protozoa), scabies (caused by mites—see p. 713), and pediculosis pubis (caused by lice—see p. 713).

Many other infections not considered primarily to be STDs—including salmonellosis, shigellosis, campylobacteriosis, amebiasis, giardiasis, hepatitis (A, B, and C), and cytomegalovirus infection—can be transmitted sexually.

Because sexual activity includes close contact with skin and mucous membranes of the genitals, mouth, and rectum, many organisms are efficiently spread between people. Inflammation or ulceration caused by some STDs (eg, herpes, chancroid) predisposes to transmission of others (eg, HIV). STD prevalence rates remain high in most of the world, despite diagnostic and therapeutic advances that can rapidly render patients with many STDs noninfectious. Factors impeding control of STDs include

- Unprotected sexual activity with multiple partners
- Difficulty talking about sexual issues for both physicians and patients
- Inadequate funding for new therapy and research
- Susceptibility to reinfection if both partners are not treated simultaneously
- Incomplete treatment, which leads to development of drug-resistant organisms
- International travel, which facilitates rapid global dissemination of STDs

Symptoms and signs vary depending on the infection. Many STDs cause genital lesions (see Table 156-1).

STDs are diagnosed and treated in a variety of settings; for many, diagnostic tests are limited or unavailable or patient follow-up is uncertain. Thus, identification of the causative organism is often not pursued, and initial treatment is often syndromic—ie, directed at the organisms most likely to cause the presenting syndrome (eg, urethritis, cervicitis, genital ulcers, pelvic inflammatory disease). Diagnostic testing is done more often when the diagnosis is unclear, when the infection is severe, when initial treatment is ineffective, or when other reasons (eg, public health surveillance, psychosocial reasons, including extreme mental distress and depression) are compelling.

STD control depends on

- Adequate facilities and personnel for diagnosis and treatment
- Public health programs for locating and treating recent sex partners of patients
- Follow-up for treated patients to ensure that they have been cured
• Education of health care practitioners and the public

• Avoidance of high-risk behaviors by patients

[Table 156-1. Differentiating Common Sexually Transmitted Genital Lesions]

Condoms and vaginal dams, if used correctly, greatly decrease risk. Vaccines are unavailable for most STDs, except for hepatitis A and B and human papillomavirus infection.

Chancroid

Chancroid is infection of the genital skin or mucous membranes caused by Haemophilus ducreyi and characterized by papules, painful ulcers, and enlargement of the inguinal lymph nodes leading to suppuration. Diagnosis is usually clinical because culturing the organism is difficult. Treatment is with a macrolide, ceftriaxone, or ciprofloxacin.

H. ducreyi is a short, slender, gram-negative bacillus with rounded ends. Chancroid occurs in rare outbreaks in developed countries but is a common cause of genital ulcers throughout much of the developing world and often acquired by men from prostitutes. Like other sexually transmitted diseases (STDs) causing genital ulcers, chancroid increases risk of HIV transmission.

Symptoms and Signs

After an incubation period of 3 to 7 days, small, painful papules appear and rapidly break down into shallow, soft, painful ulcers with ragged, undermined edges (ie, with overhanging tissue) and a red border. Ulcers vary in size and often coalesce. Deeper erosion occasionally leads to marked tissue destruction. The inguinal lymph nodes become tender, enlarged, and matted together, forming a pus-filled abscess (bubo). The skin over the abscess may become red and shiny and may break down to form a sinus. The infection may spread to other areas of skin, resulting in new lesions. Phimosis, urethral stricture, and urethral fistula may result from chancroid.

Diagnosis

• Clinical evaluation

• Sometimes culture or PCR

Chancroid is suspected in patients who have unexplained genital ulcers or buboes (which may be mistaken for abscesses) and who have been in endemic areas. Genital ulcers with other causes (see Table 156-1) may resemble chancroid.

If available, a sample of pus from a bubo or exudate from the edge of an ulcer should be sent to a laboratory that can identify H. ducreyi. However, diagnosis is usually based on clinical findings alone because culture of the bacteria is difficult and microscopic identification is confounded by the mixed flora in ulcers. PCR testing has a high sensitivity (98.4%) and a high specificity (99.6%) for H. ducreyi but is not widely available. Clinical diagnosis has a lower sensitivity (53 to 95%) and specificity (41 to 75%).

Serologic testing for syphilis and HIV and cultures for herpes should be done to exclude other causes of genital ulcers. However, interpretation of test results is complicated by the fact that genital ulcers due to other causes may be co-infected with H. ducreyi.

Treatment

• Antibiotics (various)

Treatment should be started promptly, without waiting for test results. One of the following is recommended:
A single-dose of azithromycin 1 g po or ceftriaxone 250 mg IM

Erythromycin 500 mg po qid for 7 days

Ciprofloxacin 500 mg po bid for 3 days

Patients treated for other causes of genital ulcers should be given antibiotics that also treat chancroid if chancroid is suspected and laboratory testing is impractical. Treatment of patients with HIV infection, particularly with single-dose regimens, may be ineffective.

Buboes can safely be aspirated for diagnosis or incised for symptomatic relief if patients are also given effective antibiotics. Sex partners should be examined, and patients should be followed for 3 mo.

**Chlamydial, Mycoplasmal, and Ureaplasmal Infections**

Sexually transmitted urethritis, cervicitis, proctitis, and pharyngitis not due to gonorrhea are caused predominantly by chlamydiae and infrequently by mycoplasmas or *Ureaplasma* sp. Chlamydiae may also cause salpingitis, epididymitis, perihepatitis, neonatal conjunctivitis, and infant pneumonia. Untreated chlamydial salpingitis can become chronic, causing minimal symptoms but having serious consequences. Diagnosis is by culture, immunoassay for antigens, or genetic methods. Treatment is with single-dose azithromycin or a week of ofloxacin, levofloxacin, erythromycin, or a tetracycline.

Several organisms can cause nongonococcal sexually transmitted cervicitis in women and urethritis, proctitis, and pharyngitis in both sexes. These organisms include *Chlamydia trachomatis* (responsible for about 50% of such cases of urethritis and most cases of mucopurulent cervicitis), *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and *Trichomonas vaginalis* (see p. 1481). Chlamydiae may also cause lymphogranuloma venereum (see p. 1474). The imprecise terms nonspecific "urethritis" and "nongonococcal urethritis" have been replaced by terms that specify the causative organism.

**Symptoms and Signs**

Men develop symptomatic urethritis after a 7- to 28-day incubation period, usually beginning with mild dysuria, discomfort in the urethra, and a clear to mucopurulent discharge. Discharge may be slight, and symptoms may be mild but are frequently more marked early in the morning; then, the urethral meatus is often red and blocked with dried secretions, which may also stain underclothes. Occasionally, onset is more acute, with dysuria, frequency, and a copious, purulent discharge that simulates gonococcal urethritis. Infection may progress to epididymitis. After rectal or orogenital contact with an infected person, proctitis or pharyngitis may develop.

Women are usually asymptomatic, although vaginal discharge, dysuria, increased urinary frequency and urgency, pelvic pain, dyspareunia, and symptoms of urethritis may occur. Cervicitis with yellow, mucopurulent exudate and cervical ectopy (expansion of the red endocervical epithelium onto the vaginal surfaces of the cervix) are characteristic. Pelvic inflammatory disease (salpingitis and pelvic peritonitis) may cause lower abdominal discomfort (typically bilateral) and marked tenderness when the abdomen, adnexa, and cervix are palpated. Fitz-Hugh-Curtis syndrome (perihepatitis) may cause right upper quadrant pain, fever, and vomiting.

Chlamydiae may be transferred to the eye, causing acute conjunctivitis.

Reactive arthritis (see p. 343) caused by immunologic reactions to genital and intestinal infections is an infrequent complication of chlamydial infections in adults. Reactive arthritis sometimes causes skin and eye lesions and noninfectious recurrent urethritis.

Infants born to women with chlamydial cervicitis may develop chlamydial pneumonia or ophthalmia neonatorum (neonatal conjunctivitis—see p. 2824).

**Diagnosis**
• Nucleic acid detection tests of cervical or urethral exudate or urine

Chlamydial, mycoplasmal, or ureaplasmal infection is suspected in patients with symptoms of urethritis, salpingitis, cervicitis, or unexplained proctitis, but similar symptoms can also result from gonococcal infection. If clinical evidence for urethritis is uncertain, finding ≥ 5 WBCs/high-power field in a urine sample confirms the diagnosis. Examination of first-voided, morning samples is most sensitive.

Samples of cervical or male urethral exudates are obtained to check for chlamydia. Nucleic acid-based tests (NAT) for chlamydial DNA may be done on nonamplified samples or may use one of several nucleic acid amplification techniques. Tests are usually done on swab samples, but amplified NAT tests are highly sensitive and specific and can also be done on urine, eliminating the need for doing an uncomfortable swab of the urethra or cervix. Amplification techniques should be routinely used in patients at high risk (eg, unprotected sex with new or multiple partners, history of prior sexually transmitted disease [STD], exchanging sex for drugs or money). Because gonococcal infection sometimes coexists, testing should also be done for that organism.

Detection of mycoplasmas and *Ureaplasma* sp is currently impractical in routine practice.

In the US, confirmed cases of chlamydial infection, gonorrhea, and syphilis must be reported to the public health system. A serologic test for syphilis (STS) should be done.

**Screening:** Urine testing using nucleic acid amplification tests (NAAT) is especially useful for screening asymptomatic people at high risk of STDs because genital examination is not necessary. People who should be screened include

• People with a history of a previous STD

• People with high-risk behaviors

• Sexually active adolescents and young adults < 24 yr

• Pregnant women < 24 yr

**Treatment**

• Oral antibiotics (various)

• Treatment of sex partners

Uncomplicated documented or suspected chlamydial, ureaplasmal, or mycoplasmal infections are treated with one of the following:

• A single dose of azithromycin 1 g po

• Doxycycline 100 mg po bid for 7 days

• Erythromycin base 500 mg po qid for 7 days

• Ofloxacin 300 mg po bid for 7 days

• Levofloxacin 500 mg po once/day for 7 days

For pregnant women, azithromycin 1 g po once should be used.

These regimens do not reliably treat gonorrhea, which coexists in many patients with chlamydial infections. Therefore, treatment should usually include a cephalosporin, such as a single dose of ceftriaxone 125 mg IM.
Patients who relapse (about 10%) are usually coinfected with microbes that do not respond to antichlamydial therapy, or they were reinfected since treatment. They may require further diagnostic evaluation and repeated or longer (21 to 28 days) courses, and their current sex partners should be treated. Patients should abstain from sexual intercourse until they and their partners complete treatment.

If chlamydial genital infections are untreated, symptoms and signs subside within 4 wk in about two thirds of patients. However, in women, asymptomatic cervical infection may persist, resulting in chronic endometritis, salpingitis, or pelvic peritonitis and their sequelae—pelvic pain, infertility, and increased risk of ectopic pregnancy. Because chlamydial infections can have serious long-term consequences for women, even when symptoms are mild or absent, detecting the infection in women and treating them and their male sex partners is crucial.

Genital Warts

(Condylomata Acuminata; Venereal Warts; Anogenital Warts)

Genital warts are lesions of the skin or mucous membranes of the genitals caused by certain types of human papillomavirus (HPV). Some types of HPV cause flat warts in the cervical canal or anus; these warts can become cancerous. Diagnosis of external warts is based on their clinical appearance. Multiple treatments exist, but few are highly effective unless applied repeatedly over weeks to months. Genital warts may resolve without treatment in immunocompetent patients but may persist and spread in patients with decreased cell-mediated immunity (eg, due to pregnancy or HIV infection).

In the US, an estimated 1.4 million people have genital warts at any given time. There are about 6 million new cases of genital HPV infection each year, and about 80% of women have been infected at least once by age 50. Most infections clear spontaneously within 1 to 2 yr, but some persist.

Etiology

There are > 70 known types of HPV. Some types cause common skin warts (see p. 715), but others infect primarily the skin and mucosa of the anogenital region. Important manifestations of anogenital HPV include

- Genital warts (condyloma acuminatum)
- Intraepithelial neoplasia and carcinoma of the cervix, anus, or penis
- Bladder and oral cancers
- Bowenoid papulosis

Condylomata acuminata are benign anogenital warts most often caused by HPV types 6 and 11. Low- and high-grade intraepithelial neoplasia and carcinoma may be caused by HPV types 16 and 18 and probably other types.

HPV is transmitted from lesions during skin-to-skin contact. The types that affect the anogenital region are usually transmitted sexually by penetrative vaginal or anal intercourse, but digital, oral, and nonpenetrative genital contact may be involved.

Genital warts are more common among immunocompromised patients. Growth rates vary, but pregnancy, immunosuppression, or maceration of the skin may accelerate the growth and spread of warts.

Symptoms and Signs

Warts appear after an incubation period of 1 to 6 mo. Visible anogenital warts are usually soft, moist, minute pink or gray polyps (raised lesions) that enlarge, may become pedunculated, have rough surfaces,
and may occur in clusters. They are usually asymptomatic, but some patients have itching, burning, or discomfort.

In men, warts occur most commonly under the foreskin, on the coronal sulcus, within the urethral meatus, and on the penile shaft. They may occur around the anus and in the rectum, especially in homosexual men. In women, warts occur most commonly on the vulva, vaginal wall, cervix, and perineum; the urethra and anal region may be affected. HPV types 16 and 18 usually cause flat endocervical or anal warts that are difficult to see and diagnose clinically.

Diagnosis

- Clinical evaluation, sometimes including colposcopy, anoscopy, or both

Genital warts are usually diagnosed clinically. Their appearance usually differentiates them from condyloma lata of secondary syphilis, which are flat-topped. However, serologic tests for syphilis (STS) should be done initially and after 3 mo. Biopsies of atypical, bleeding, ulcerated, or persistent warts may be necessary to exclude carcinoma. Endocervical and anal warts can be visualized only by colposcopy and anoscopy. Applying a 3 to 5% solution of acetic acid for a few minutes before colposcopy causes warts to whiten and enhances visualization and detection of small warts. Nucleic acid amplification tests (NAAT) for HPV DNA confirm the diagnosis and allow typing of HPV, but their role in HPV management is not yet clear.

Treatment

- Manual removal (eg, by cryotherapy, electro-cauterization, laser, or surgical excision)
- Topical treatment (eg, with antimitotics, caustics, or interferon inducers)

No treatment of anogenital warts is completely satisfactory, and relapses are frequent and require retreatment. In immunocompetent people, genital warts may resolve without treatment. In immunocompromised patients, warts may be less responsive to treatment.

Genital warts may be removed by cryotherapy, electro-cauterization, laser, or surgical excision; a local or general anesthetic is used depending on the size and number to be removed. Removal with a resectoscope may be the most effective treatment; a general anesthetic is used.

Topical antimitotics (eg, podophyllotoxin, podophyllin, 5-fluorouracil), caustics (eg, trichloroacetic acid), and interferon inducers (eg, imiquimod) are widely used but usually require multiple applications over weeks to months and are frequently ineffective. Before topical treatments are applied, surrounding tissue should be protected with petroleum jelly. Patients should be warned that after treatment, the area may be painful.

Interferon alfa (eg, interferon alfa-2b, interferon alfa-n3), intralesionally or IM, has cleared intractable lesions on the skin and genitals, but optimal administration and long-term effects are unclear. Also, in some patients with Bowenoid papulosis of the genitals (caused by type 16 HPV), lesions initially disappeared after treatment with interferon alfa but reappeared as invasive cancers.

For intraurethral lesions, thiotepa (an alkylating drug), instilled in the urethra, is effective. In men, 5-fluorouracil applied bid to tid is highly effective for urethral lesions, but rarely, it causes swelling, leading to urethral obstruction. Endocervical lesions should not be treated until Papanicolaou (Pap) test results rule out other cervical abnormalities (eg, dysplasia, cancer) that may dictate additional treatment.

By removing the moist underside of the prepuce, circumcision may prevent recurrences in uncircumcised men.

Sex partners of women with endocervical warts and of patients with Bowenoid papulosis should be counseled and screened regularly for HPV-related lesions. A similar approach can be used for HPV in the rectum.
Current sex partners of people with genital warts should be examined and, if infected, treated.

**Prevention**

A quadrivalent vaccine that protects against the 2 types of HPV (types 6 and 11) that cause > 90% of visible genital warts is available. This vaccine also protects against the 2 types of HPV (types 16 and 18) that cause most cervical cancers. The HPV vaccine has been recommended for girls and women aged 9 to 26 yr for prevention of initial infection. Three doses are given, preferably at age 11 to 12 yr. The vaccine should be administered before onset of sexual activity, but girls and women who are sexually active should still be vaccinated. The vaccine's role in preventing HPV in boys and men has not been established. A bivalent vaccine against HPV types 16 and 18 is awaiting approval.

Because of the location of these warts, condoms may not fully protect against infection.

**Gonorrhea**

Gonorrhea is caused by the bacteria *Neisseria gonorrhoeae*. It typically infects epithelia of the urethra, cervix, rectum, pharynx, or eyes, causing irritation or pain and purulent discharge. Dissemination to skin and joints, which is uncommon, causes sores on the skin, fever, and migratory polyarthritis or pauciarticular septic arthritis. Diagnosis is by microscopy, culture, or nucleic acid amplification tests. Several oral or injectable antibiotics can be used, but drug resistance is an increasing problem.

*N. gonorrhoeae* occurs only in humans and is almost always transmitted by sexual contact. Urethral and cervical infections are most common, but infection in the pharynx or rectum can occur after oral or anal intercourse, and conjunctivitis may follow contamination of the eye. After an episode of vaginal intercourse, likelihood of transmission from women to men is about 20%, but from men to women, it may be higher. Neonates can acquire conjunctival infection during passage through the birth canal (see p. 2824), and children may acquire gonorrhea as a result of sexual abuse.

In 10 to 20% of women, cervical infection ascends via the endometrium to the fallopian tubes (salpingitis) and pelvic peritoneum, causing pelvic inflammatory disease (PID—see p. 2545). Chlamydiae or intestinal bacteria may also cause PID. Gonorrheal cervicitis is commonly accompanied by dysuria or inflammation of Skene's ducts and Bartholin's glands. In a small fraction of men, ascending urethritis progresses to epididymitis. Disseminated gonococcal infection (DGI) due to hematogenous spread occurs in < 1% of cases, predominantly in women. DGI typically affects the skin, tendon sheaths, and joints. Pericarditis, endocarditis, meningitis, and perihepatitis occur rarely.

Coinfection with *Chlamydia trachomatis* occurs in 15 to 25% of infected heterosexual men and 35 to 50% of women.

**Symptoms and Signs**

About 10 to 20% of infected women and very few infected men are asymptomatic. About 25% of men have minimal symptoms.

**Male urethritis** has an incubation period from 2 to 14 days. Onset is usually marked by mild discomfort in the urethra, followed by more severe penile tenderness and pain, dysuria, and a purulent discharge. Urinary frequency and urgency may develop as the infection spreads to the posterior urethra. Examination detects a purulent, yellow-green urethral discharge, and the meatus may be inflamed.

**Epididymitis** usually causes unilateral scrotal pain, tenderness, and swelling. Rarely, men develop abscesses of Tyson's and Littre's glands, periurethral abscesses, or infection of Cowper's glands, the prostate, or the seminal vesicles.

**Cervicitis** usually has an incubation period of > 10 days. Symptoms range from mild to severe and include dysuria and vaginal discharge. During pelvic examination, clinicians may note a mucopurulent or
purulent cervical discharge, and the cervical os may be red and bleed easily when touched with the speculum. Urethritis may occur concurrently; pus may be expressed from the urethra when the symphysis pubis is pressed or from Skene's ducts or Bartholin's glands. Rarely, infections in sexually abused prepubertal girls cause dysuria, purulent vaginal discharge, and vulvar irritation, erythema, and edema.

PID occurs in 10 to 20% of infected women. PID may include salpingitis, pelvic peritonitis, and pelvic abscesses and may cause lower abdominal discomfort (typically bilateral), dyspareunia, and marked tenderness on palpation of the abdomen, adnexa, or cervix.

Fitz-Hugh-Curtis syndrome is gonococcal (or chlamydial) perihepatitis that occurs predominantly in women and causes right upper quadrant abdominal pain, fever, nausea, and vomiting, often mimicking biliary or hepatic disease.

Rectal gonorrhea is usually asymptomatic. It occurs predominantly in men practicing receptive anal intercourse and can occur in women who participate in anal sex. Symptoms include rectal itching, a cloudy rectal discharge, bleeding, and constipation—all of varying severity. Examination with a proctoscope may detect erythema or mucopurulent exudate on the rectal wall.

Gonococcal pharyngitis is usually asymptomatic but may cause sore throat. *N. gonorrhoeae* must be distinguished from *N. meningitidis*, a closely related organism that is often present in the throat without causing symptoms or harm.

Disseminated gonococcal infection (DGI), also called the arthritis-dermatitis syndrome, reflects bacteremia and typically manifests with fever, migratory pain or joint swelling (polyarthritis), and pustular skin lesions (see Plate 59). In some patients, pain develops and tendons (eg, at the wrist or ankle) redden or swell. Skin lesions occur typically on the arms or legs, have a red base, and are small, slightly painful, and often pustular. Genital gonorrhea, the usual source of disseminated infection, may be asymptomatic. DGI can mimic other disorders that cause fever, skin lesions, and polyarthritis (eg, the prodrome of hepatitis B infection or meningococcemia); some of these disorders may cause genital symptoms (eg, reactive arthritis—see p. 343).

Gonococcal septic arthritis is a more focal form of DGI that results in a painful arthritis with effusion, usually of 1 or 2 large joints such as the knees, ankles, wrists, or elbows. Some patients used to have or still have skin lesions of DGI. Onset is often acute, usually with fever, severe joint pain, and limitation of movement. Infected joints are swollen, and the overlying skin may be warm and red.

**Diagnosis**

- Gram staining and culture
- Nucleic acid-based testing

Gonorrhea is diagnosed when gonococci are detected via microscopic examination using Gram stain, culture, or a nucleic acid-based test of genital fluids, blood, or joint fluids (obtained by needle aspiration).

**Gram stain** is sensitive and specific for gonorrhea in men with urethral discharge; gram-negative intracellular diplococci typically are seen. Gram stain is much less accurate for infections of the cervix, pharynx, and rectum and is not recommended for diagnosis at these sites.

**Culture** is sensitive and specific, but because gonococci are fragile and fastidious, samples taken using a swab need to be rapidly plated on an appropriate medium (eg, modified Thayer-Martin) and transported to the laboratory in a CO₂-containing environment. Blood and joint fluid samples should be sent to the laboratory with notification that gonococcal infection is suspected.

Unamplified nucleic acid-based tests may be done on genital rectal or oral swabs. Most tests simultaneously detect gonorrhea and chlamydial infection and then differentiate between them in a subsequent specific test. Nucleic acid amplification tests (NAAT) further increase the sensitivity.
advisedly to enable testing of urine samples in both sexes.

In the US, confirmed cases of gonorrhea, chlamydial infection and syphilis must be reported to the public health system. A serologic test for syphilis (STS) and a screening test for chlamydial infection should be done.

**Men with urethritis:** Men with obvious discharge may be treated presumptively if likelihood of follow-up is questionable or if clinic-based diagnostic tools are not available. Samples for Gram staining can be obtained by touching a swab or slide to the end of the penis to collect discharge. Gram stain does not identify chlamydiae, so urine or swab samples for NAAT are obtained.

**Women with genital symptoms or signs:** A cervical swab should be sent for culture or nucleic acid-based testing. If a pelvic examination is not possible, NAAT of a urine sample can detect gonococcal (and chlamydial) infections rapidly and reliably.

**Pharyngeal or rectal exposures (either sex):** Swabs of the affected area are sent for culture or nucleic acid-based tests.

**Arthritis, DGI, or both:** An affected joint should be aspirated, and fluid should be sent for culture and routine analysis (see p. 286). Patients with skin lesions, systemic symptoms, or both should have blood, urethral, cervical, and rectal cultures or NAAT. In about 30 to 40% of patients with DGI, blood cultures are positive during the first week of illness. With gonococcal arthritis, blood cultures are less often positive, but cultures of joint fluids are usually positive. Joint fluid is usually cloudy to purulent because of large numbers of WBCs (typically > 20,000/μL).

**Screening:** Asymptomatic patients considered at high risk of sexually transmitted diseases (STDs) can be screened by NAAT of urine samples, thus not requiring invasive procedures to collect samples from genital sites. Patients at risk include:

- People with a history of a previous STD
- People with high-risk behaviors (eg, new or multiple sex partners, inconsistent use of condoms, exchange of sex for money or drugs)
- Sexually active adolescents and young adults < 24 yr
- Pregnant women < 24 yr

**Treatment**

- For uncomplicated infection, a single dose of ceftriaxone or cefixime
- For DGI with arthritis, a longer course of parenteral antibiotics
- Concomitant treatment for chlamydial infection
- Treatment of sex partners

Uncomplicated gonococcal infection of the urethra, cervix, rectum, and pharynx can be treated with a single dose of ceftriaxone 125 mg IM or cefixime 400 mg po. Previous alternative regimens with quinolones (eg, ciprofloxacin, levofloxacin, ofloxacin) are no longer recommended because of increasing drug resistance. Routinely, patients are simultaneously given a single dose of azithromycin 1 g po to treat chlamydial infection (see p. 1469) because it often coexists in patients with gonorrhea.

DGI with gonococcal arthritis is initially treated with IM or IV antibiotics (eg, ceftriaxone 1 g IM or IV q 24 h, ceftizoxime 1 g IV q 8 h, cefotaxime 1 g IV q 8 h) continued for 24 to 48 h once symptoms lessen, followed by 4 to 7 days of oral therapy. Antichlamydial therapy is also routinely given.
Gonococcal arthritis does not usually require joint drainage. Initially, the joint is immobilized in a functional position. Passive range-of-motion exercises should be started as soon as patients can tolerate them. Once pain subsides, more active exercises, with stretching and muscle strengthening, should begin. Over 95% of patients treated for gonococcal arthritis recover complete joint function. Because sterile joint fluid accumulations (effusions) may persist for prolonged periods, an anti-inflammatory drug may be beneficial.

Posttreatment cultures are unnecessary if symptomatic response is adequate. However, for patients with symptoms for > 7 days, cultures are repeated, and antimicrobial sensitivity testing is done. Patients should abstain from sexual activity until treatment is completed to avoid infecting sex partners.

**Sex partners:** All sex partners who have had sexual contact with the patient within 60 days should be tested for gonorrhea and other STDs and treated if results are positive. Sex partners with contact within 2 wk should be treated presumptively for gonorrhea (epidemiologic treatment).

**Expedited partner therapy (EPT)** involves giving patients a prescription or drugs to deliver to their partner. EPT may enhance partner adherence and reduce treatment failure due to reinfection. It may be most appropriate for partners of women with gonorrhea or chlamydial infection. However, a health care visit is preferable to ascertain histories of drug allergies and to screen for other STDs.

**Granuloma Inguinale**

(Donovanosis)

Granuloma inguinale is a progressive infection of genital skin caused by *Calymmatobacterium granulomatis*. Skin lesions are beefy red, raised, and often ulcerated. Diagnosis is by clinical criteria and microscopy. Treatment is with antibiotics, usually tetracyclines, macrolides, or trimethoprim/sulfamethoxazole.

The bacteria *Calymmatobacterium* (formerly *Donovania*) *granulomatis* are very rare in most of the world. Current epidemiologic data are unavailable, but historically, granuloma inguinale has been reported in areas such as Papua New Guinea, northern Australia, southern Africa, and parts of Brazil and India.

**Symptoms and Signs**

Sites of infection are

- Penis, scrotum, groin, and thighs in men (see Plate 63)
- Vulva, vagina, and perineum in women (see Plate 62)
- Anus and buttocks in patients who engage in anal-receptive intercourse
- Face in both sexes

After an incubation period of about 1 to 12 wk, a painless, red skin nodule slowly enlarges, becoming a raised, beefy red, moist, smooth, foul-smelling lesion. The lesion slowly enlarges and may spread to other skin areas. Lesions heal slowly, with scarring. Secondary infections with other bacteria are common and can cause extensive tissue destruction.

Occasionally, granuloma inguinale spreads through the bloodstream to the bones, joints, or liver; without treatment, anemia, wasting, and uncommonly death may occur.

**Diagnosis**

- Microscopic examination showing Donovan bodies in fluid from a lesion
Granuloma inguinale is suspected in patients from endemic areas with characteristic lesions. Diagnosis is confirmed microscopically by the presence of Donovan bodies (numerous bacilli in the cytoplasm of macrophages shown by Giemsa or Wright's stain) in smears of fluid from scrapings from the edge of lesions. These smears contain many plasma cells. Biopsy specimens are taken if the diagnosis is unclear or if adequate tissue fluid cannot be obtained because lesions are dry, sclerotic, or necrotic. The bacteria do not grow on ordinary culture media.

**Treatment**

- Antibiotics (various)

Many oral antibiotics kill the bacteria, but tetracyclines, macrolides, and trimethoprim/sulfamethoxazole (TMP/SMX) are most effective, followed by ceftriaxone, aminoglycosides, fluoroquinolones, and chloramphenicol. Recommended oral regimens include doxycycline 100 mg bid for 3 wk, TMP/SMX 160/800 mg bid for 3 wk, erythromycin 500 mg qid for 3 wk, or azithromycin 1 g/wk for 3 wk. IV or IM antibiotics (eg, ceftriaxone) are an alternative.

Response to treatment should begin within 7 days, but healing of extensive disease may be slow and lesions may recur, requiring longer treatment. HIV-infected patients may also require prolonged or intensive treatment. After apparently successful treatment, follow-up should continue for 6 mo. Current sex partners should be examined and, if infected, treated.

**Lymphogranuloma Venereum**

Lymphogranuloma venereum (LGV) is a chlamydial disease characterized by a small, often asymptomatic skin lesion, followed by regional lymphadenopathy in the groin or pelvis or by proctitis in homosexual men. Without treatment, LGV may cause obstruction of lymph flow and chronic swelling of genital tissues. Diagnosis is by clinical signs, but laboratory confirmation with serologic or immunofluorescent testing is usually possible. Treatment is 21 days of a tetracycline or erythromycin.

LGV is caused by serotypes L1, L2, and L3 of the bacteria *Chlamydia trachomatis*. These serotypes differ from those that cause trachoma, inclusion conjunctivitis, urethritis, and cervicitis because they can invade and reproduce in regional lymph nodes.

LGV occurs sporadically in the US but is endemic in parts of Africa, India, Southeast Asia, South America, and the Caribbean. It is diagnosed much more often in men than women.

**Symptoms and Signs**

The 1st stage begins after an incubation period of about 3 days with a small skin lesion at the site of entry. It may cause the overlying skin to break down (ulcerate) but heals so quickly that it may pass unnoticed.

The 2nd stage usually begins in men after about 2 to 4 wk, with the inguinal lymph nodes on one or both sides enlarging and forming large, tender, sometimes fluctuant masses (buboes). The buboes stick to deeper tissues and cause the overlying skin to become inflamed, sometimes with fever and malaise. In women, backache or pelvic pain is common; the initial lesions may be on the cervix or upper vagina, resulting in enlargement and inflammation of deeper perirectal and pelvic lymph nodes. Multiple draining sinus tracts may develop and discharge pus or blood.

In the 3rd stage, lesions heal with scarring, but sinus tracts can persist or recur. Persistent inflammation due to untreated infection obstructs the lymphatic vessels, causing swelling and skin sores.

In homosexual men, proctitis or proctocolitis with bloody purulent rectal discharges may occur in the 1st stage. In the chronic stages, colitis simulating Crohn's disease may cause tenesmus and strictures in the rectum or pain due to inflamed pelvic nodes.
Diagnosis

• Antibody detection

LGV is suspected in patients who have genital ulcers, swollen inguinal lymph nodes, or proctitis and who live in, have visited, or have sexual contact with people from areas where infection is common. LGV is also suspected in patients with buboes, which may be mistaken for abscesses caused by other bacteria.

Diagnosis has usually been made by detecting antibodies to chlamydial endotoxin; levels are usually elevated at presentation or shortly thereafter and remain elevated. Direct tests for chlamydial antigens with immunoassays (eg, enzyme-linked immunosorbent assay [ELISA]) or with immunofluorescence using monoclonal antibodies to stain pus or nucleic acid amplification tests may be available through reference laboratories (eg, Centers for Disease Control and Prevention in the US).

All sex partners should be evaluated. After apparently successful treatment, patients should be followed for 6 mo.

Treatment

• Oral tetracyclines or erythromycin

• Possibly drainage of buboes for symptomatic relief

Doxycycline 100 mg po bid, erythromycin 500 mg po qid, or tetracycline 500 mg po qid, each for 21 days, are effective for early disease. Azithromycin 1 g po once/wk for 1 to 3 wk is probably effective, but neither it nor clarithromycin has been adequately evaluated.

Swelling of damaged tissues in later stages may not resolve despite elimination of the bacteria. Buboes may be drained by needle or surgically if necessary for symptomatic relief, but most patients respond quickly to antibiotics. Buboes and sinus tracts may require surgery, but rectal strictures can usually be dilated.

Sexually Transmitted Enteric Infections

Various pathogens—bacterial (Shigella, Campylobacter, or Salmonella), viral (hepatitis A, B, and C viruses), and parasitic (Giardia sp or amebae)—are transmitted via sexual practices, especially those that can involve fecal-oral contamination. In order of decreasing risk, these practices are oral-rectal, anal-genital, oral-genital, and genital-genital intercourse.

Although some of the above pathogens may cause proctitis, they usually cause infection higher in the intestinal tract; symptoms include diarrhea, fever, bloating, nausea, and abdominal pain. Multiple infections are frequent, especially in people with many sex partners. Most of these pathogens can cause infections without symptoms; asymptomatic infections are the rule with Entamoeba dispar, which commonly occurs in homosexual men and was previously known as nonpathogenic Entamoeba histolytica. For diagnosis and treatment of these infections, see elsewhere in THE MANUAL.

Syphilis

(See also Congenital Syphilis on p. 2821.)

Syphilis is caused by the spirochete Treponema pallidum and is characterized by 3 sequential clinical, symptomatic stages separated by periods of asymptomatic latent infection. Common manifestations include genital ulcers, skin lesions, meningitis, aortic disease, and neurologic syndromes. Diagnosis is by serologic tests and adjunctive tests selected based on the disease stage. Penicillin is the drug of choice.

Syphilis is caused by T. pallidum, a spirochete that cannot survive for long outside the human body. T. pallidum enters through the mucous membranes or skin, reaches the regional lymph nodes within hours,
and rapidly spreads throughout the body.

Syphilis occurs in primary, secondary, and tertiary stages (see Table 156-2), with long latent periods between them. Infected people are contagious during the first 2 stages.

Infection is usually transmitted by sexual contact (including genital, orogenital, and anorectal) but may be transmitted non-sexually by skin contact or transplacentally (see p. 2821). Risk of transmission is about 30% from a single sexual encounter with a person who has primary syphilis and 60 to 80% from an infected mother to a fetus. Infection does not lead to immunity against reinfection.

**Symptoms and Signs**

Syphilis may manifest at any stage and may affect multiple or single organs, mimicking many other disorders. Syphilis may be accelerated by coexisting HIV infection; in these cases, eye involvement, meningitis, and other neurologic complications are more common and more severe.

**Primary syphilis:** After an incubation period of 3 to 4 wk (range 1 to 13 wk), a primary lesion (chancre—see Plate 66) develops at the site of inoculation. The initial red papule quickly forms a chancre, usually a painless ulcer with a firm base; when rubbed, it produces clear fluid containing numerous spirochetes. Nearby lymph nodes may be enlarged, firm, and nontender. Chancres can occur anywhere but are most common on the following:

- Penis, anus, and rectum in men
- Vulva, cervix, rectum, and perineum in women
- Lips or mouth in either sex

**Secondary syphilis:** The spirochete spreads in the bloodstream, producing widespread mucocutaneous lesions (see Plate 67), lymph node swelling, and, less commonly, symptoms in other organs. Symptoms typically begin 6 to 12 wk after the chancre appears; about 25% of patients still have a chancre. Fever, loss of appetite, nausea, and fatigue are common. Headache, hearing or balance problems, visual disturbances, and bone pain can also occur.

Over 80% of patients have mucocutaneous lesions; a wide variety of rashes and lesions occur, and any body surface can be affected. Without treatment, lesions may disappear in a few days to weeks, persist for months, or return after healing, but all eventually heal, usually without scarring.

**Syphilitic dermatitis** is usually symmetric and more marked on the palms and soles. The individual lesions are round, often scale, and may coalesce to produce larger lesions, but they generally do not itch or hurt. After lesions resolve, the affected areas may be lighter or darker than normal. If the scalp is involved, alopecia areata often occurs.

**Condyloma lata** are hypertrophic, flattened, dull pink or gray papules at mucocutaneous junctions and in moist areas of the skin (eg, in the perianal area, under the breasts); lesions are extremely infectious. Lesions of the mouth, throat, larynx, penis, vulva, or rectum are usually circular, raised, and often gray to white with a red border.

Secondary syphilis can affect any organ. About half of patients have lymphadenopathy, usually generalized, with nontender, firm, discrete nodes, and often hepatosplenomegaly. About 10% of patients have lesions of the eyes (uveitis), bones (periostitis), joints, meninges, kidneys (glomerulitis), liver
(hepatitis), or spleen. About 10 to 30% of patients have mild meningitis, but < 1% have meningeal symptoms, which can include headache, neck stiffness, cranial nerve lesions, deafness, and eye inflammation (eg, optic neuritis, retinitis).

**Latent period:** Symptoms and signs are absent, but antibodies, detected by serologic tests for syphilis (STS), persist. Because symptoms of primary and secondary syphilis are often minimal or ignored, patients frequently are first diagnosed during the latent stage when routine blood tests for syphilis are done. Syphilis may remain latent permanently, but relapses with contagious skin or mucosal lesions may occur during the early latent period (< 1 yr after infection). Patients are often given antibiotics for other disorders, which may cure latent syphilis and may account for the rarity of late-stage disease in developed countries.

**Late or tertiary syphilis:** About one third of untreated people develop late syphilis, although not until years to decades after the initial infection. Lesions may be clinically classified as benign tertiary syphilis, cardiovascular syphilis, or neurosyphilis.

**Benign tertiary gummatous syphilis** usually develops within 3 to 10 yr of infection and may involve the skin, bones, and internal organs. Gummas are soft, destructive, inflammatory masses that are typically localized but may diffusely infiltrate an organ or tissue; they grow and heal slowly and leave scars.

**Benign tertiary syphilis of bone** results in either inflammation or destructive lesions that cause a deep, boring pain, characteristically worse at night.

**Cardiovascular syphilis** usually manifests 10 to 25 yr after the initial infection as aneurysmal dilation of the ascending aorta, insufficiency of the aortic valve, or narrowing of the coronary arteries. Pulsations of the dilated aorta may cause symptoms by compressing or eroding adjacent structures in the chest. Symptoms include brassy cough, infections, and obstruction of breathing due to pressure on the trachea, hoarseness due to vocal cord paralysis resulting from compression of the left laryngeal nerve, and painful erosion of the sternum and ribs or spine.

**Neurosyphilis** has several forms:

- Asymptomatic neurosyphilis
- Meningovascular neurosyphilis
- Parenchymatous neurosyphilis
- Tabes dorsalis

**Asymptomatic neurosyphilis** causes mild meningitis in about 15% of patients originally diagnosed as having latent syphilis, in 25 to 40% of those with secondary syphilis, in 12% of those with cardiovascular syphilis, and in 5% of those with benign tertiary syphilis. Without treatment, it evolves to symptomatic neurosyphilis in 5%. If CSF examination does not detect evidence of meningitis 2 yr after the initial infection, neurosyphilis is unlikely to develop.

**Meningovascular neurosyphilis** results from inflammation of large- to medium-sized arteries of the brain or spinal cord; symptoms typically occur 5 to 10 yr after infection and range from none to strokes. Initial symptoms may include headache, neck stiffness, dizziness, behavioral abnormalities, poor concentration, memory loss, lassitude, insomnia, and blurred vision. Spinal cord involvement may cause weakness and wasting of shoulder-girdle and arm muscles, slowly progressive leg weakness with urinary or fecal incontinence or both, and, rarely, sudden paralysis of the legs due to thrombosis of spinal arteries.

**Parenchymatous neurosyphilis** (general paresis, or dementia paralytica) results when chronic meningoencephalitis causes destruction of cortical parenchyma. It usually develops 15 to 20 yr after initial infection and typically does not affect patients before their 40s or 50s. Behavior progressively deteriorates, sometimes mimicking a mental disorder or dementia. Irritability, difficulty concentrating,
deterioration of memory, defective judgment, headaches, insomnia, fatigue, and lethargy are common; seizures, aphasia, and transient hemiparesis are possible. Hygiene and grooming deteriorate. Patients may become emotionally unstable and depressed and have delusions of grandeur with lack of insight; wasting may occur. Tremors of the mouth, tongue, outstretched hands, and whole body may occur; other signs include pupillary abnormalities, dysarthria, hyperreflexia, and, in some patients, extensor plantar responses. Handwriting is usually shaky and illegible.

**Tabes dorsalis** (locomotor ataxia) involves slow, progressive degeneration of the posterior columns and nerve roots. It typically develops 20 to 30 yr after initial infection; mechanism is unknown. Usually, the earliest, most characteristic symptom is an intense, stabbing (lightning) pain in the back and legs that recurs irregularly. Gait ataxia, hyperesthesia, and paresthesia may produce a sensation of walking on foam rubber. Loss of bladder sensation leads to urine retention, incontinence, and recurrent infections. Erectile dysfunction is common.

Most patients with tabes dorsalis are thin and have characteristic sad facies and Argyll Robertson pupils (pupils that accommodate for near vision but do not respond to light). Optic atrophy may occur. Examination of the legs detects hypotonia, hyporeflexia, impaired vibratory and joint position sense, ataxia in the heel-shin test, absence of deep pain sensation, and Romberg's sign. Tabes dorsalis tends to be intractable even with treatment. Visceral crises (episodic pain) are a variant of tabes dorsalis; paroxysms of pain occur in various organs, most commonly in the stomach (causing vomiting) but also in the rectum, bladder, and larynx.

**Other lesions:** Syphilitic ocular and otic manifestations can occur at any stage of the disease. Ocular syndromes can affect virtually any part of the eye; they include interstitial keratitis, uveitis (anterior, intermediate, and posterior), chorioretinitis, retinitis, retinal vasculitis, and cranial nerve and optic neuropathies. Otosyphilis may affect the cochlea (causing hearing loss and tinnitus) or vestibular system (causing vertigo and nystagmus).

Trophic lesions, secondary to hypoesthesia of the skin or periarticular tissues, may develop in the later stages. Trophic ulcers may develop on the soles of the feet and penetrate as deeply as the underlying bone. Neurogenic arthropathy (Charcot's joints), a painless joint degeneration with bony swelling and abnormal range of movement, is a classic manifestation of neuropathy (see p. 348).

**Diagnosis**

- Serologic reaginic tests (rapid plasma reagin, Venereal Disease Research Laboratory) for screening
- Serologic treponemal tests (eg, fluorescent treponemal antibody absorption) for confirmation

Syphilis should be suspected in patients with typical mucocutaneous lesions or unexplained neurologic disorders, particularly in areas where the infection is prevalent. In such areas, it should also be considered in patients with a broad range of unexplained findings. Because clinical manifestations are so diverse and advanced stages are now relatively rare in most developed countries, syphilis may escape recognition. Patients with HIV and syphilis may have atypical or accelerated disease.

Diagnostic test selection depends on which stage of syphilis is suspected. Cases must be reported to public health agencies.

**Diagnostic tests for syphilis:** Tests include serologic tests for syphilis (STS), which consist of screening (reaginic) and confirmatory (treponemal) tests, and darkfield microscopy. *T. pallidum* cannot be grown in vitro.

**Reaginic tests** use lipid antigens (cardiolipin from bovine hearts) to detect reagin (human antibodies that bind to lipids). The Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are sensitive, simple, and inexpensive reaginic tests that are used for screening but are not specific for syphilis. Results may be presented qualitatively (eg, reactive, weakly reactive, borderline, or nonreactive) and quantitatively as titers (eg, positive at 1:16 dilution).
Many disorders other than treponemal infections (eg, SLE, antiphospholipid antibody syndromes) can produce a positive (biologically false-positive) reagin test result. CSF reaginic tests are reasonably sensitive for early disease but less so for late neurosyphilis. CSF reagin tests can be used to diagnose neurosyphilis or to monitor response to treatment by measuring antibody titers.

**Treponemal tests** detect antitreponemal antibodies qualitatively and are very specific for syphilis. They include the following:

- Fluorescent treponemal antibody absorption (FTA-ABS) test
- Microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP)
- *T. pallidum* hemagglutination assay (TPHA)

If they do not confirm treponemal infection after a positive reaginic test, the reaginic result is biologically false-positive. Treponemal tests of CSF are controversial, but some authorities believe the FTA-ABS test is sensitive.

Neither reaginic nor treponemal tests become positive until 3 to 6 wk after the initial infection. Thus, a negative result is common in early primary syphilis and does not exclude syphilis until after 6 wk. Reaginic titers decline after effective treatment, becoming negative by 1 yr in primary and by 2 yr in secondary syphilis. Treponemal tests usually remain positive for many decades, despite effective treatment.

**Darkfield microscopy** directs light obliquely through a slide of exudate from a chancre or lymph node aspirate to directly visualize spirochetes. Although the skills and equipment required are not usually available, darkfield microscopy is the most sensitive and specific test for early primary syphilis. The spirochetes appear against a dark background as bright, motile, narrow coils that are about 0.25 μm wide and 5 to 20 μm long. They must be distinguished morphologically from nonpathogenic spirochetes, which may be part of the normal flora, especially of the mouth.

**Primary syphilis:** Primary syphilis is usually suspected based on relatively painless genital (but occasionally extragenital) ulcers. Syphilitic ulcers should be differentiated from other sexually transmitted genital lesions (see Table 156-1). Co-infections with 2 ulcer-causing pathogens (eg, herpes simplex virus plus *T. pallidum*) are not rare.

Darkfield microscopy of exudate from a chancre or lymph node aspirate may be diagnostic. If results are negative or the test is unavailable, a reaginic STS is done. If results are negative or the test cannot be done immediately but a skin lesion has been present for < 3 wk (before the STS becomes positive) and an alternate diagnosis seems unlikely, treatment may be instituted, and the STS repeated in 2 to 4 wk. Patients with syphilis should be tested for other sexually transmitted diseases (STDs), including HIV, at diagnosis and 6 mo later.

**Secondary syphilis:** Because syphilis can mimic many diseases, it should be considered when any cutaneous eruption or mucosal lesion is undiagnosed, particularly if patients have any of the following:

- Generalized lymphadenopathy
- Lesions on the palms or soles
- Condyloma lata
- Risk factors (eg, HIV, multiple sex partners)

Clinically, secondary syphilis may be mistaken for a drug eruption, rubella, infectious mononucleosis, erythema multiforme, pityriasis rubra pilaris, fungal infection, or, particularly, pityriasis rosea. Condyloma lata may be mistaken for warts, hemorrhoids, or pemphigus vegetans; scalp lesions may be mistaken for ringworm or idiopathic alopecia areata.
Secondary syphilis is excluded by a negative reaginic STS, which is virtually always reactive during this stage, often with a high titer. A compatible syndrome with a positive STS (reaginic or treponemal) warrants treatment. Uncommonly, this combination represents latent syphilis coexisting with another skin disease. Patients with secondary syphilis should be tested for other STDs and for asymptomatic neurosyphilis.

**Latent syphilis:** Asymptomatic, latent syphilis is diagnosed when reaginic and treponemal STSs are positive in the absence of symptoms or signs of active syphilis. Such patients should have a thorough examination, particularly genital, skin, neurologic, and cardiovascular examinations, to exclude secondary and tertiary syphilis. Treatment and serologic follow-up for up to several years may be needed to ensure the success of therapy because reaginic STS titers decrease slowly.

Latent acquired syphilis must be differentiated from latent congenital syphilis (see p. 2821), latent yaws, and other treponemal infections.

**Late or tertiary syphilis:** Patients with symptoms or signs of tertiary syphilis (particularly unexplained neurologic abnormalities) require STS. If the test is reactive, the following should be done:

- Lumbar puncture for CSF examination (including STS)
- Imaging of the brain and aorta
- Screening of any other organ systems clinically suspected to be involved

At this stage of syphilis, a reaginic STS is nearly always positive, except in a few cases of tabes dorsalis.

In benign tertiary syphilis, differentiation from other inflammatory mass lesions or ulcers may be difficult without biopsy.

Cardiovascular syphilis is suggested by symptoms and signs of aneurysmal compression of adjacent structures, particularly stridor or hoarseness.

Syphilitic aortic aneurysm is suggested by aortic insufficiency without aortic stenosis and, on chest x-ray, by widening of the aortic root and linear calcification on the walls of the ascending aorta. Diagnosis of aneurysm is confirmed with aortic imaging (transesophageal echocardiography, CT, or MRI).

In neurosyphilis, most symptoms and signs, except for Argyll Robertson pupil, are non-specific, so that diagnosis relies heavily on a high index of clinical suspicion. Asymptomatic neurosyphilis is diagnosed based on abnormal CSF (typically, lymphocytic pleocytosis and elevated protein) and a reactive CSF reaginic test. In parenchymatous neurosyphilis, the CSF reaginic and serum treponemal tests are reactive and CSF typically has lymphocytic pleocytosis and elevated protein. If present, HIV may confound the diagnosis because it causes mild pleocytosis and various other neurologic symptoms.

In tabes dorsalis, serum reaginic tests may be negative if patients have been previously treated, but serum treponemal tests are usually positive. CSF usually has lymphocytic pleocytosis and elevated protein, and sometimes reaginic or treponemal test results are positive; however, in many treated patients, CSF is normal.

**Treatment**

- Sustained-release penicillin
- Treatment of sex partners

The treatment of choice in all stages of syphilis and during pregnancy is sustained-release penicillin (ie, benzathine penicillin). All sex partners within the past 3 mo (if primary syphilis is diagnosed) and within 1 yr (if secondary syphilis is diagnosed) should be evaluated and, if infected, treated.
Primary, secondary, and latent syphilis: Benzathine penicillin G 2.4 million units IM given once produces blood levels that are sufficiently high for 2 wk to cure primary, secondary, and early (< 1 yr) latent syphilis. Doses of 1.2 million units are usually given in each buttock to reduce local reactions. Additional injections of 2.4 million units should be given 7 and 14 days later for late (> 1 yr) latent syphilis or latent syphilis of unknown duration because treponemes occasionally persist in the CSF after single-dose regimens.

Patients with a history of IgE (anaphylactic or urticarial) allergic reactions to penicillin should not be treated with a cephalosporin because they may have an allergic reaction. Azithromycin 2 g po in a single dose or doxycycline 100 mg po bid for 14 days may be used, but efficacy of these drugs is not well-defined, particularly for late latent syphilis, and the 14-day regimen requires good adherence. If adherence to the 14-day regimen cannot be ensured, the risk of using a cephalosporin may be justifiable. Ceftriaxone 125 mg IM or IV once/day for 10 days has been effective in a limited number of patients.

Late or tertiary syphilis: Benign or cardiovascular tertiary syphilis can be treated in the same way as late latent syphilis.

For ocular syphilis or neurosyphilis, aqueous penicillin 3 to 4 million units IV q 4 h for 10 days (best penetrates the CNS but may be impractical) or procaine penicillin G 2.4 million units IM once/day plus 500 mg probenecid po qid is recommended; both drugs are given for 10 to 14 days, followed by benzathine penicillin 2.4 million units once/wk for 3 wk. For patients who have penicillin allergies, azithromycin and doxycycline are effective, so penicillin desensitization is usually not indicated. Ceftriaxone 2 g IM or IV once/day for 14 days can also be effective, but cross-sensitivity with cephalosporins is a concern so it is usually avoided.

Treatment of asymptomatic neurosyphilis appears to prevent the development of new neurologic deficits. Patients with neurosyphilis may be given oral or IM antipsychotics to help control paresis. Patients with tabes dorsalis and lightning pains should be given analgesics as needed; carbamazepine 200 mg po tid or qid sometimes helps.

Jarisch-Herxheimer reaction (JHR): Most patients with primary or secondary syphilis, especially those with secondary syphilis, have a JHR within 6 to 12 h of initial treatment. It typically manifests as malaise, fever, headache, sweating, rigors, anxiety, or a temporary exacerbation of the syphilitic lesions. The mechanism is not understood, and JHR may be misdiagnosed as an allergic reaction. JHR usually subsides within 24 h and poses no danger. However, patients with general paresis or a high CSF cell count may have a more serious reaction, including seizures or strokes, and should be warned and observed accordingly. Unanticipated JHR may occur if patients with undiagnosed syphilis are given antitreponemal antibiotics for other infections.

Posttreatment surveillance: After treatment, patients should have

- Examinations and reaginic tests at 3, 6, and 12 mo and annually thereafter until the test is nonreactive
- For neurosyphilis, CSF testing every 6 mo until CSF cell count is normal

The importance of repeated tests to confirm cure should be explained to patients before treatment. Examinations and reaginic tests should be done at 3, 6, and 12 mo after treatment and annually thereafter until the test is nonreactive. Failure of titers to decline by 4-fold at 6 mo suggests treatment failure and indicates the need for retreatment. After successful treatment, primary lesions heal rapidly, and plasma reaginic titers fall and usually become qualitatively negative within 9 to 12 mo. In about 15% of patients with primary or secondary syphilis treated as recommended, the reaginic titer does not decrease by 4-fold—the criterion used to define response at 1 yr after treatment. Treponemal tests may remain positive for decades or permanently and should not be measured to monitor progress. Serologic or clinical relapse, usually affecting the nervous system, may occur after 6 to 9 mo, but the cause may be reinfection rather than relapse.

Patients with neurosyphilis require CSF testing at 6-mo intervals until the CSF cell count is normal. In HIV-infected patients, persisting CSF pleocytosis may represent effects of HIV rather than persisting
neurosyphilis. Normal CSF, serologic test, and examination results for 2 yr indicates probable cure. If the CSF WBC count remains abnormal 2 yr after maximal treatment, it is unclear whether treatment should be continued. Indications for retreatment with a more intensive regimen of antibiotics include a reaginic test that remains reactive for > 2 yr, an increasing titer, and clinical relapse.

Trichomoniasis

Trichomoniasis is infection of the vagina or male genital tract with *Trichomonas vaginalis*. It can be asymptomatic or cause urethritis, vaginitis, or occasionally cystitis, epididymitis, or prostatitis. Diagnosis is by microscopic examination of vaginal or prostatic secretions or by urethral culture. Patients and sex partners are treated with metronidazole.

*T. vaginalis* is a flagellated, sexually transmitted protozoan that more often infects women (about 20% of women of reproductive age) than men. Infection may be asymptomatic in either sex, but asymptomatic is the rule for men. In men, protozoa may persist for long periods in the GU tract without causing symptoms; thus, protozoa may be transmitted unwittingly to sex partners. Trichomoniasis may account for up to 5% of nongonococcal, nonchlamydial urethritis in men in some areas. Coinfection with gonorrhea and other sexually transmitted diseases (STDs) is common.

Symptoms and Signs

In women, symptoms range from none to copious, yellow-green, frothy vaginal discharge with soreness of the vulva and perineum, dyspareunia, and dysuria. Asymptomatic infection may become symptomatic at any time as the vulva and perineum become inflamed and edema develops in the labia. The vaginal walls and surface of the cervix may have punctate, red "strawberry" spots. Urethritis and possibly cystitis may also occur.

Men are usually asymptomatic; however, sometimes urethritis results in a discharge that may be transient, frothy, or purulent or that causes dysuria and frequency, usually early in the morning. Often, urethritis is mild and causes only minimal urethral irritation and occasional moisture at the urethral meatus, under the foreskin, or both. Epididymitis and prostatitis are rare complications.

Diagnosis

- Microscopic examination of vaginal secretions
- Culture of male urine or urethral swab

Trichomoniasis is suspected in women with vaginitis, in men with urethritis, and in their sex partners. Suspicion is high if symptoms persist after patients have been evaluated and treated for other infections such as gonorrhea and chlamydial, mycoplasmal, and ureaplasmal infections.

In women, diagnosis is based on clinical criteria and in-office testing. Vaginal secretions are obtained from the posterior fornix. The pH is measured. Secretions are then placed on 2 slides; they are diluted with 10% K hydroxide on one slide (KOH wet mount) and with 0.9% NaCl on the other (saline wet mount). For the whiff test, the KOH wet mount is checked for a fishy odor, which results from amines produced in trichomonas vaginitis or bacterial vaginosis. The saline wet mount is examined microscopically as soon as possible to detect trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation. (Trichomonads are pear-shaped with flagella, often motile, and average 7 to 10 μm—about the size of WBCs—but occasionally reach 25 μm.) If trichomoniasis is present, numerous neutrophils are also present.

If results are inconclusive, cultures, which are more sensitive than microscopy, are done. Trichomoniasis is also commonly diagnosed when a Papanicolaou test is done.

In men, microscopy of urine is insensitive, although occasionally organisms are visible in a first-voided morning specimen or a centrifuged specimen. Cultures of urine and urethral swabs are more sensitive.
As with diagnosis of any STD, patients with trichomoniasis should be tested to exclude other common STDs such as gonorrhea and chlamydial infection.

**Treatment**

- Oral metronidazole or tinidazole
- Treatment of sex partners

Metronidazole or tinidazole 2 g po in a single dose cures up to 95% of women if sex partners are treated simultaneously. Effectiveness of single-dose regimens in men is not as clear, so treatment is typically with metronidazole or tinidazole 500 mg bid for 5 to 7 days. IV metronidazole cures some women when repeated oral doses are ineffective.

Metronidazole may cause leukopenia, disulfiram-like reactions to alcohol, or candidal superinfections. It is relatively contraindicated during early pregnancy, although it may not be dangerous to the fetus after the 1st trimester. Tinidazole has not been established as safe during pregnancy and so is not used.

Sex partners should be screened and treated for trichomoniasis and other STDs. If poor adherence to follow-up is likely, treatment can be initiated in sex partners of patients with documented trichomoniasis without confirming the diagnosis in the partner.
Introduction

Patients with mental complaints or concerns or disordered behavior present in a variety of clinical settings, including primary care and emergency treatment centers. Complaints or concerns may be new or a continuation of a history of mental problems. Complaints may be related to coping with a physical condition or be the direct effects of a physical condition. The method of assessment depends on whether the complaints constitute an emergency or are reported in a scheduled visit. In an emergency, a physician may have to focus on more immediate history, symptoms, and behavior to be able to make a management decision. In a scheduled visit, a more thorough assessment is appropriate.

Routine Psychiatric Assessment

Assessment includes a general medical and psychiatric history and a mental status examination.

History

The physician must determine whether the patient can provide a history, ie, whether the patient readily and coherently responds to initial questions. If not, information is sought from family and caregivers. Even when a patient is communicative, close family members, friends, or caseworkers may provide information that the patient has omitted. Receiving information that is not solicited by the physician does not violate patient confidentiality. Previous psychiatric assessments, treatments, and degree of adherence to past treatments are reviewed, and records from such care are obtained as soon as possible.

Conducting an interview hastily and indifferently with closed-ended queries (following a rigid system review) often prevents patients from revealing relevant information. Tracing the history of the presenting illness with open-ended questions, so that patients can tell their story in their own words, takes a similar amount of time and enables patients to describe associated social circumstances and reveal emotional reactions.

The interview should first explore what prompted the need (or desire) for psychiatric assessment (eg, unwanted or unpleasant thoughts, undesirable behavior). The interviewer then attempts to gain a broader perspective on the patient's personality by reviewing significant life events—current and past—and the patient's responses to them (see Table 157-1). Psychiatric, medical, social, and developmental history is also reviewed.

The personality profile that emerges may suggest traits that are adaptive (eg, resilience, conscientiousness) or maladaptive (eg, self-centeredness, dependency, poor tolerance of frustration) and may show the coping mechanisms used (see Table 163-1 on p. 1554). The interview may reveal obsessions (unwanted and distressing thoughts or impulses), compulsions (urges to do irrational or apparently useless acts), and delusions (fixed false beliefs) and may determine whether distress is expressed in physical symptoms (eg, headache, abdominal pain), mental symptoms (eg, phobic behavior, depression), or social behavior (eg, withdrawal, rebelliousness). The patient should also be asked about attitudes regarding psychiatric treatments, including drugs and psychotherapy, so that this information can be incorporated into the treatment plan.

The interviewer should establish whether a physical condition or its treatment is causing or worsening a mental condition (see p. 1467). In addition to having direct effects (eg, symptoms, including mental ones), many physical conditions cause enormous stress and require coping mechanisms to withstand the pressures related to the condition. Most patients with severe physical conditions experience some kind of adjustment disorder, and those with underlying mental disorders may become unstable.

Observation during an interview may provide evidence of mental or physical disorders. Body language may reveal evidence of attitudes and feelings denied by the patient. For example, does the patient fidget or pace back and forth despite denying anxiety? Does the patient seem sad despite denying feelings of
depression? General appearance may provide clues as well. For example, is the patient clean and well-kept? Is a tremor or facial droop present?

**Mental Status Examination**

A mental status examination uses observation and questions to evaluate several domains

[Table 157-1. Areas to Cover in the Initial Psychiatric Assessment]

of mental function, including speech, emotional expression, thinking and perception, and cognitive functions. Brief standardized screening questionnaires are available for assessing certain components of the mental status examination, including those specifically designed to assess orientation and memory. However, screening questionnaires cannot take the place of a broader, more detailed mental status examination (see Sidebar 168-1 on p. 1588).

**General appearance** should be assessed for unspoken clues to underlying conditions. Patients’ appearance can help determine whether they are unable to care for themselves (eg, they appear undernourished, disheveled, or dressed inappropriately for the weather or have significant body odor), are unable or unwilling to comply with social norms (eg, they are garbed in socially inappropriate clothing), or have engaged in substance abuse or attempted self-harm (eg, they have an odor of alcohol, scars suggesting IV drug abuse or self-inflicted injury).

**Speech** can be assessed by noting spontaneity, syntax, rate, and volume. A patient with depression may speak slowly and softly, whereas a patient with mania may speak rapidly and loudly. Abnormalities such as dysarthrias and aphasias may indicate a physical cause of mental status changes, such as head injury, stroke, brain tumor, or multiple sclerosis.

**Emotional expression** can be assessed by asking patients to describe their feelings. The patient's tone of voice, posture, hand gestures, and facial expressions are all considered. Mood (emotions patients report) and affect (emotional state interviewer notes) should be assessed.

**Thinking and perception** can be assessed by noticing not only what is communicated but also how it is communicated. Abnormal content may take the form of delusions (false, fixed beliefs), ideas of reference (notions that everyday occurrences have special meaning or significance personally intended for or directed to the patient), or obsessions. The physician can assess whether ideas seem to be linked and goal-directed and whether transitions from one thought to the next are logical. Psychotic or manic patients may have disorganized thoughts or an abrupt flight of ideas.

**Cognitive functions** include the patient's level of alertness; attentiveness or concentration; orientation to person, place, and time; memory; abstract reasoning; insight; and judgment. Abnormalities of cognition most often occur with delirium or dementia or with substance abuse or withdrawal but can also occur with depression.

**Medical Assessment of the Patient With Mental Symptoms**

Medical assessment of patients with mental symptoms seeks to identify 2 things:

* Physical disorders *mimicking* mental disorders

* Physical disorders *accompanying* mental disorders

Numerous physical disorders cause symptoms mimicking specific mental disorders (see Table 157-2). Other physical disorders may not mimic specific mental syndromes but instead change mood and energy.

Many drugs cause mental symptoms; the most common drug causes are

* CNS-active drugs (eg, anticonvulsants, antidepressants, antipsychotics, sedative/hypnotics, stimulants)
• Anticholinergics (eg, antihistamines)

• Corticosteroids

Numerous other therapeutic drugs and drug classes have also been implicated; they include some classes that may not ordinarily be considered (eg, antibiotics, antihypertensives). Drugs of abuse, particularly alcohol, amphetamines, cocaine, hallucinogens, and phencyclidine (PCP), particularly in overdose, are also frequent causes of mental symptoms. Withdrawal from alcohol, barbiturates, or benzodiazepines may cause mental symptoms (eg, anxiety) in addition to symptoms of physical withdrawal.

In addition to the problem of causing mental symptoms, patients with a mental disorder may develop a physical disorder (eg, meningitis, diabetic ketoacidosis) that causes new or worsened mental symptoms. Thus, a clinician should not assume that all mental symptoms in patients with a known mental disorder are due to that disorder. The clinician may need to be proactive in addressing possible physical causes for mental symptoms, especially in patients unable to describe their physical health because they have psychosis or dementia.

Patients presenting for psychiatric care occasionally have undiagnosed physical disorders (including substance abuse, diabetes, and hypothyroidism) that are not the cause of their mental symptoms but nonetheless require evaluation and treatment.

**Table 157-2. Selected Mental Symptoms Due to Physical Disorders**

**Evaluation**

Medical assessment by history, physical examination, and often brain imaging and laboratory testing is required for patients with

• New-onset mental symptoms

• Qualitatively different or atypical symptoms (ie, in a patient with a known or stable mental disorder)

• Mental symptoms that begin at an atypical age

The goal is to diagnose underlying and concomitant physical disorders rather than to make a specific psychiatric diagnosis.

**History**: History of present illness should note the nature of symptoms and their onset, particularly whether onset was sudden or gradual and whether symptoms followed any possible precipitants (eg, trauma, starting or stopping of a drug or abused substance). The clinician should ask whether patients have had previous episodes of similar symptoms, whether a mental disorder has been diagnosed and treated, and, if so, whether patients have stopped taking their drugs.

**Review of systems** seeks symptoms that suggest possible causes:

• Vomiting, diarrhea, or both: Dehydration, electrolyte disturbance

• Palpitations: Hyperthyroidism, drug effects including withdrawal

• Polyuria and polydipsia: Diabetes mellitus

• Tremors: Parkinson's disease, withdrawal syndromes

• Difficulty walking or speaking: Multiple sclerosis, Parkinson's disease, stroke

• Headache: CNS infection, complex migraine, hemorrhage, mass lesion

• Fever, cough, and dysuria: Systemic infection
Past medical history should identify known chronic physical disorders that can cause mental symptoms (eg, thyroid, liver, or kidney disease; diabetes; HIV infection). All prescription and OTC drugs should be reviewed, and patients should be queried about any alcohol or illicit substance use (amount and duration). Family history of physical disorders, particularly of thyroid disease and multiple sclerosis, is assessed. Risk factors for infection (eg, unprotected sex, needle sharing, recent hospitalization, residence in a group facility) are noted.

Physical examination: Vital signs are reviewed, particularly for fever, tachypnea, and tachycardia. Mental status is assessed (see p. 1588), particularly for signs of confusion or inattention. A full physical examination is done, although the focus is on signs of infection (eg, meningismus, lung congestion, flank tenderness), the neurologic examination (including gait testing), and funduscopy to detect signs of increased intracranial pressure (eg, papilledema, loss of venous pulsations). Signs of liver disease (eg, jaundice, ascites, spider angiomas) should be noted. The skin is carefully inspected for self-inflicted wounds or other evidence of external trauma (eg, bruising).

Interpretation of findings: Confusion and inattention (reduced clarity of awareness of the environment—see p. 1669), especially if of sudden onset, fluctuating, or both, indicate the presence of a physical disorder. However, the converse is not true (ie, a clear sensorium does not confirm that the cause is a mental disorder). Other findings that suggest a physical cause include:

- Abnormal vital signs (eg, fever, tachycardia, tachypnea)
- Meningeal signs
- Abnormalities noted during the neurologic examination
- Disturbance of gait, balance, or both
- Incontinence

Some findings help suggest a specific cause. Dilated pupils (particularly if accompanied by flushed, hot, dry skin) suggest anticholinergic drug effects. Constricted pupils suggest opioid drug effects or pontine hemorrhage. Rotary or vertical nystagmus suggests PCP intoxication, and horizontal nystagmus often accompanies diphenylhydantoin toxicity. A preceding history of relapsing-remitting neurologic symptoms, particularly when a variety of nerves appear to be involved, suggests multiple sclerosis. Stocking-glove paresthesias may indicate thiamin or vitamin B₁₂ deficiency. In patients with hallucinations, the type of hallucination is not particularly diagnostic except that command hallucinations or voices commenting on the patient's behavior probably represent a mental disorder.

Symptoms that began shortly after significant trauma or after beginning a new drug may be due to those events. Drug or alcohol abuse may or may not be the cause of mental symptoms; about 40 to 50% of patients with a mental disorder also have substance abuse (dual diagnosis).

Testing: Patients typically should have

- Pulse oximetry
- Fingerstick glucose testing
- Measurement of therapeutic drug levels

If patients with a known mental disorder have an exacerbation of their typical symptoms and they have no medical complaints, a normal sensorium, and a normal physical examination (including vital signs, pulse oximetry, and fingerstick glucose testing), they do not typically require further laboratory testing. Most other patients should have...
• Blood alcohol level, urine toxicology screens (which may also be required for inpatient admission at certain psychiatric facilities), and HIV testing

Many clinicians also measure

• Serum electrolytes (including Ca and Mg), BUN, and creatinine

Electrolyte and renal function tests may be diagnostic and help inform subsequent drug management (eg, for drugs that require adjustment in patients with renal insufficiency).

Other tests are commonly done based on specific findings:

• Head CT: Patients with new-onset mental symptoms or with delirium, headache, history of recent trauma, or focal neurologic findings (eg, weakness of an extremity)

• Lumbar puncture: Patients with meningeal signs or with normal head CT findings plus fever, headache, or delirium

• Thyroid function tests: Patients taking lithium, those with symptoms or signs of thyroid disease, and those > 40 yr with new-onset mental symptoms (particularly females or patients with a family history of thyroid disease)

• Chest x-ray, urinalysis and culture, CBC, C-reactive protein, and blood cultures: Patients with fever

• Liver function tests: Patients with symptoms or signs of liver disease, with history of alcohol or drug abuse, or with no obtainable history

Less often, findings may suggest testing for SLE, syphilis, demyelinating disorders, or vitamin B₁₂ or thiamin deficiency.

**Behavioral Emergencies**

Patients who are experiencing severe changes in mood, thoughts, or behavior or severe, potentially life-threatening drug adverse effects need urgent assessment and treatment. Non-specialists are often the first care providers for outpatients and inpatients on medical units, but whenever possible, such cases should also be evaluated by a psychiatrist.

When a patient's mood, thoughts, or behavior is highly unusual or disorganized, assessment must first determine whether the patient is a

• Threat to self

• Threat to others

The threat to self can include inability to care for self (leading to self-neglect) or suicidal behavior (see p. 1579). Self-neglect is a particular concern for patients with psychotic disorders, dementia, or substance abuse because their ability to obtain food, clothing, and appropriate protection from the elements is impaired.

Patients posing a threat to others include those who are actively violent, those who appear belligerent and hostile (ie, potentially violent), and those who do not appear threatening to the examiner and staff members but express intent to harm another person (eg, spouse, neighbor, public figure).

**Causes:** Aggressive, violent patients are often psychotic and have diagnoses such as polysubstance abuse, schizophrenia, delusional disorder, or acute mania. Other causes include physical disorders that cause acute delirium (see Table 157-2) and intoxication with alcohol or other substances, particularly methamphetamine, cocaine, and sometimes phencyclidine (PCP) and club drugs (eg, MDMA [3,4-
General Principles

Management typically occurs simultaneously with evaluation, particularly evaluation for a possible physical disorder (see p. 1487); it is a mistake to assume that the cause of abnormal behavior is a mental disorder or intoxication, even in patients who have a known psychiatric diagnosis or an odor of alcohol. Because patients are often unable or unwilling to provide a clear history, other collateral sources of information (eg, family members, friends, caseworkers, medical records) must be identified and consulted immediately.

actively violent patients must first be restrained by

- Physical means
- Drugs (chemical restraint)
- Both

Such interventions are done to prevent harm to patients and others and to allow evaluation of the cause of the behavior (eg, by taking vital signs and doing blood tests). Close monitoring, sometimes involving constant observation by a trained sitter, is required. Although clinicians must be aware of legal issues regarding involuntary treatment (see Sidebar 157-1 and p. 1492), such issues must not delay potentially lifesaving interventions.

Potentially violent patients require measures to defuse the situation. Measures that may help reduce agitation and aggressiveness include

- Moving patients to a calm, quiet environment (eg, a seclusion room, when available)
- Removing objects that could be used to inflict harm to self or others
- Expressing sympathetic concern for patients and their complaints
- Responding in a confident yet supportive manner

Speaking directly—mentioning that patients seem angry or upset, asking them if they intend to hurt someone—acknowledges their feelings and may elicit information; it does not make them more likely to act out.

Counterproductive measures include

- Arguing about the validity of patients’ fears and complaints
- Issuing threats (eg, to call police, to commit them)
- Speaking in a condescending manner
- Attempting to deceive patients (eg, hiding drugs in food, promising them they will not be restrained)

Staff and public safety: When hostile, aggressive patients are interviewed, staff safety must be considered. Most hospitals have a policy to search for weapons (manually, with metal detectors, or both) on patients presenting with disordered behavior.

Patients who are hostile but not yet violent typically do not assault staff members randomly; rather, they assault staff members who anger or appear threatening to them. Doors to rooms should be left open and staff members should avoid positioning themselves between patients and the door so that patients do not feel trapped or threatened; it is preferable that patients run out than assault staff members. Staff members may also avoid appearing threatening by sitting on the same level as patients. Staff members
may avoid angering patients by not responding to their hostility in kind, with loud, angry remarks or arguing. If patients nonetheless become increasingly agitated and violence appears impending, staff members should simply leave the room and summon sufficient additional staff to provide a show of force, which sometimes deters patients. Typically, at least 4 or 5 people should be present (some preferably young and male). However, the team should not bring restraints into the room unless they are definitely to be applied; seeing restraints may further agitate patients.

Verbal threats must be taken seriously. In most states, when a patient expresses the intention to harm a particular person, the evaluating physician is required to warn the intended victim and to notify a specified law enforcement agency. Specific requirements vary by state. Typically, state regulations also require reporting of suspected abuse of children, the elderly, and spouses.

**Physical Restraints**

Use of physical restraints is controversial and should be considered only when other methods have failed and a patient continues to pose a significant risk of harm to self or others. Restraints may be needed to hold the patient long enough to administer drugs, do a complete assessment, or both. Because restraints are applied without the patient's consent, certain legal and ethical issues should be considered (see Sidebar 157-1).

Restraints are used to

- Prevent clear, imminent harm to the patient or others
- Prevent the patient's medical treatment from being significantly disrupted (eg, by pulling out tubes or IVs) when consent to the treatment has been provided
- Prevent damage to physical surroundings, staff members, or other patients
- Prevent a patient who requires involuntary treatment from leaving (when a locked room is unavailable)

Restraints should not be used for

- Punishment
- Convenience of staff members (eg, to prevent wandering)

Caution is required in overtly suicidal patients, who could use the restraint as a suicide device.

**Procedure**: Restraints should be applied only by staff members adequately trained in correct techniques and in protecting patient rights and safety.

First, adequate staff are assembled in the room, and patients are informed that restraints must be applied. Patients are encouraged to cooperate to avoid a struggle. However, once the clinician has determined that restraints are necessary, there is no negotiation, and patients are told that restraints will be applied whether or not they agree. Some actually understand and appreciate having external limits on their behavior. In preparation for applying restraints, one person is assigned to each extremity and another to the patient's head. Then, each person simultaneously grasps their assigned extremity and places the patient supine on the bed; one physically fit person can typically control a single extremity of even large, violent patients (provided all extremities are grasped at the same time). However, an additional person is needed to apply the restraints. Rarely, upright patients who are extremely combative may first need to be sandwiched between 2 mattresses.

Leather restraints are preferred. One restraint is applied to each ankle and wrist and attached to the bed frame, not the rail. Restraints are not applied around the chest, neck, or head, and gags (eg, to prevent spitting and swearing) are forbidden. Patients who remain combative in restraints (eg, attempting to upset the stretcher, bite, or spit) require chemical restraint.
Complications: Agitated or violent people brought to the hospital by police are almost always in restraints (eg, handcuffs). Occasionally, young, healthy people have died in police restraints before or shortly after hospital arrival. The cause is often unclear but probably involves some combination of overexertion with subsequent metabolic derangement and hyperthermia, drug use, aspiration of stomach contents into the respiratory system, embolism in people left in restraints for a long time, and occasionally serious underlying medical disorders. Death is more likely if people are restrained in the hobble position, with one or both wrists shackled to the ankles behind their back; this type of restraint may cause asphyxia and should be avoided. Because of these complications, violent patients presenting in police custody should be evaluated promptly and thoroughly and not dismissed as mere sociobehavioral problems.

Sidebar 157-1 Regulatory Issues in Use of Physical Restraints in Aggressive, Violent Patients

Use of physical restraints should be considered a last resort, when other steps have not sufficiently controlled aggressive, potentially violent behavior. When restraints are needed for such a situation, they are legal in all states as long as their use is properly ordered and documented in the patient's medical record. Restraints have the advantage of being immediately removable, whereas drugs may alter symptoms enough or in a way that delays assessment.

The Joint Commission on Accreditation of Healthcare Organizations guidelines for use of restraints in the psychiatric setting state that restraints must be applied under the direction of a licensed independent practitioner (LIP). The LIP must assess the patient within the first hour of restraint placement. The order for continued restraint may be written for up to 4 h at a time. The patient must be evaluated by an LIP or registered nurse during the 4-h interval and before further continuation of the restraint order. At 8 h, the LIP must reevaluate the patient in person before continuing the restraint order.

Hospital accreditation standards require that patients in restraints be continuously observed by a trained sitter. Immediately after restraints have been applied, the patient must be monitored for signs of injury; circulation, range of motion, nutrition and hydration, vital signs, hygiene, and elimination are also monitored. Physical and mental comfort and readiness for discontinuation of restraints as appropriate are also assessed. These assessments should be done every 15 min.

Chemical Restraints

Drug therapy, if used, should target control of specific symptoms.

Drugs: Patients can usually be rapidly calmed or tranquilized using

- Benzodiazepines

- Antipsychotics (typically a conventional antipsychotic, but a 2nd-generation drug may be used)

These drugs are better titrated and act more rapidly and reliably when administered IV (see Table 157-3), but IM administration may be necessary when IV access cannot be achieved in struggling patients. Both classes of drug are effective sedatives for agitated, violent patients. Benzodiazepines are probably preferred for stimulant drug overdoses and for alcohol and benzodiazepine drug withdrawal syndromes, and antipsychotics are preferred for clear exacerbations of known mental disorders. Sometimes a combination of both drugs is more effective; when large doses of one drug are required, using another drug class may limit adverse effects.

Adverse effects of benzodiazepines: Parenteral benzodiazepines, particularly in the doses sometimes needed for extremely violent patients, may cause respiratory depression. Airway management with intubation and assisted ventilation may be required. The benzodiazepine antagonist, flumazenil, may be used, but caution is required because if sedation is significantly reversed, the original behavioral problem may reappear.

Benzodiazepines sometimes lead to further disinhibition of behavior.
Adverse effects of antipsychotic drugs: Antipsychotics, particularly dopamine-receptor antagonists, at therapeutic as well as toxic doses, can have acute extrapyramidal adverse effects (see Table 157-4), including acute dystonia and akathisia (an unpleasant sensation of motor restlessness). These adverse effects may be dose dependent and may resolve once the drug is stopped. Several antipsychotics, including thioridazine, haloperidol, olanzapine, risperidone, and ziprasidone, can cause long QT-interval syndrome and ultimately increase the risk of fatal arrhythmias. Neuroleptic malignant syndrome is also a possibility. For other adverse effects, see p. 1562.

Legal Considerations

Patients with severe changes in mood, thoughts, or behavior are usually hospitalized when their condition is likely to deteriorate without psychiatric intervention and when appropriate alternatives are not available.

[Table 157-3, Drug Therapy for Agitated or Violent Patients]

[Table 157-4, Treatment of Acute Adverse Effects of Antipsychotics]

Consent and involuntary treatment: If patients refuse hospitalization, the physician must decide whether to hold them against their will. Doing so may be necessary to ensure the immediate safety of the patient or of others or to allow completion of an assessment and implementation of treatment. Criteria and procedures for involuntary hospitalization vary by jurisdiction. Usually, temporary restraint requires a physician or psychologist and one additional clinician, family member, or close contact to certify that the patient has a mental disorder, is a danger to self or to others, and refuses voluntary treatment.

Danger to self includes but is not limited to

• Suicidal ideation or attempts

• Failure to attend to basic needs, including nutrition, shelter, and needed drugs

In most jurisdictions, knowledge of intent to commit suicide requires a health care practitioner to act immediately to prevent the suicide, for example, by notifying the police or another responsible agency.

Danger to others includes

• Homicidal intent

• Placing others in peril

• Failing to provide for the needs or safety of dependents because of the mental disorder
Chapter 158. Anxiety Disorders

Introduction

Everyone periodically experiences fear and anxiety. Fear is an emotional, physical, and behavioral response to an immediately recognizable external threat (eg, an intruder, a runaway car). Anxiety is a distressing, unpleasant emotional state of nervousness and uneasiness; its causes are less clear. Anxiety is less tied to the exact timing of a threat; it can be anticipatory before a threat, persist after a threat has passed, or occur without an identifiable threat. Anxiety is often accompanied by physical changes and behaviors similar to those caused by fear.

Some degree of anxiety is adaptive; it can help people prepare, practice, and rehearse so that their functioning is improved and can help them be appropriately cautious in potentially dangerous situations. However, beyond a certain level, anxiety causes dysfunction and undue distress. At this point, it is maladaptive and considered a disorder.

Anxiety occurs in a wide range of physical and mental disorders, but it is the predominant symptom of several. Anxiety disorders are more common than any other class of psychiatric disorder. However, they often are not recognized and consequently not treated. Left untreated, chronic, maladaptive anxiety can contribute to or interfere with treatment of some physical disorders.

Etiology

The causes of anxiety disorders are not fully known, but both mental and physical factors are involved. Many people develop anxiety disorders without any identifiable antecedent triggers. Anxiety can be a response to environmental stressors, such as the ending of a significant relationship or exposure to a life-threatening disaster. Some physical disorders can directly cause anxiety; they include the following:

- Hyperthyroidism
- Pheochromocytoma
- Hyperadrenocorticism
- Heart failure
- Arrhythmias
- Asthma
- COPD

Other physical causes include use of drugs; effects of corticosteroids, cocaine, amphetamines, and even caffeine can mimic anxiety disorders. Withdrawal from alcohol, sedatives, and some illicit drugs can also cause anxiety.

Symptoms and Signs

Anxiety can arise suddenly, as in panic, or gradually over many minutes, hours, or even days. Anxiety may last from a few seconds to years; longer duration is more characteristic of anxiety disorders. Anxiety ranges from barely noticeable qualms to complete panic. The ability to tolerate a given level of anxiety varies from person to person.

Anxiety disorders can be so distressing and disruptive that depression may result. Alternatively, an anxiety disorder and a depressive disorder may coexist, or depression may develop first, with symptoms and signs of an anxiety disorder occurring later.

Diagnosis
Exclusion of other causes

Assessment of severity

Deciding when anxiety is so dominant or severe that it constitutes a disorder depends on several variables, and physicians differ at what point they make the diagnosis. Physicians must first use history, physical examination, and appropriate laboratory tests to determine whether anxiety is due to a physical disorder or drug. They must also determine whether anxiety is better accounted for by another mental disorder. An anxiety disorder is present and merits treatment if the following apply:

- Other causes are not identified.
- Anxiety is very distressing.
- Anxiety interferes with functioning.
- Anxiety does not stop spontaneously within a few days.

Diagnosis of a specific anxiety disorder is based on its characteristic symptoms and signs. Clinicians usually use specific criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR), which describes the specific symptoms and requires exclusion of other causes of symptoms.

A family history of anxiety disorders (except acute and posttraumatic stress disorders) helps in making the diagnosis because some patients appear to inherit a predisposition to the same anxiety disorders that their relatives have, as well as a general susceptibility to other anxiety disorders. However, some patients appear to acquire the same disorders as their relatives through learned behavior.

Treatment

Treatments vary for the different anxiety disorders, but typically involve a combination of psychotherapy and drug treatment. The most common drug classes used are the benzodiazepines and SSRIs.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive, almost daily anxiety and worry for ≥ 6 mo about many activities or events. The cause is unknown, although it commonly coexists in people who have alcohol abuse, major depression, or panic disorder. Diagnosis is based on history and physical examination. Treatment is psychotherapy, drug therapy, or both.

GAD is common, affecting about 3% of the population within a 1-yr period. Women are twice as likely to be affected as men. The disorder often begins in childhood or adolescence but may begin at any age.

Symptoms and Signs

The focus of the worry is not restricted as it is in other mental disorders (eg, to having a panic attack, being embarrassed in public, or being contaminated); the patient has multiple worries, which often shift over time. Common worries include work and family responsibilities, money, health, safety, car repairs, and chores.

The course is usually fluctuating and chronic, with worsening during stress. Most people with GAD have one or more other comorbid psychiatric disorders, including major depression, specific phobia, social phobia, and panic disorder.

Diagnosis

- Clinical criteria
Diagnosis is clinical based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (see Table 158-1).

**Treatment**

- **Antidepressants and often benzodiazepines**

  Certain antidepressants, including SSRIs (eg, paroxetine, starting dose of 20 mg po once/day) and serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine extended-release, starting dose of 37.5 mg po once/day) are effective but typically only after being taken for at least a few weeks. Benzodiazepines (anxiolytics—see Table 158-2) in small to moderate doses are also often and more rapidly effective, although sustained use usually causes physical dependence. One strategy involves starting with concomitant use of a benzodiazepine and an antidepressant. Once the antidepressant becomes effective, the benzodiazepine is tapered.

  [Table 158-1. Diagnosis of Generalized Anxiety Disorder]

  Buspirone is also effective; the starting dose is 5 mg po bid or tid. However, buspirone can take at least 2 wk before it begins to help.

  Psychotherapy, usually cognitive-behavioral therapy, can be both supportive and problem-focused. Relaxation and biofeedback may be of some help, although few studies have documented their efficacy.

**Obsessive-Compulsive Disorder**

Obsessive-compulsive disorder (OCD) is characterized by anxiety-provoking ideas, images, or impulses (obsessions) and by urges (compulsions) to do something that will lessen the anxiety. The cause is unknown. Diagnosis is based on history. Treatment consists of psychotherapy, drug therapy, or, especially in severe cases, both.

OCD occurs about equally in men and women and affects about 2% of the population.

**Symptoms and Signs**

The dominant theme of the obsessive thoughts may be harm, risk, danger, contamination, doubt, loss, or aggression. Typically, affected people feel compelled to perform repetitive, purposeful rituals to balance their obsessions, as in the following:

- Washing to balance contamination
- Checking to balance doubt
- Hoarding to balance loss
- Avoiding people who may provoke them to balance fear of behaving aggressively

Most rituals, such as hand washing or checking locks, are observable, but some rituals, such as repetitive counting or statements muttered under the breath, are not.

At some point, people with OCD recognize that their obsessions do not reflect real risks and that the behaviors they perform to relieve their concern are unrealistic and excessive. Preservation of insight, although sometimes

[Table 158-2. Benzodiazepines]
slight, differentiates OCD from psychotic disorders, in which contact with reality is lost.

Because people with this disorder fear embarrassment or stigmatization, they often conceal their obsessions and rituals, on which they may spend several hours each day. Relationships often deteriorate, and performance in school or at work may decline. Depression is a common secondary feature.

**Diagnosis**

Diagnosis is clinical based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision.

**Treatment**

- Exposure and ritual prevention therapy
- Often antidepressants

Exposure and ritual prevention therapy is effective; its essential element is exposure to situations or people that trigger the anxiety-provoking obsessions and rituals. After exposure, patients forgo rituals, allowing the anxiety triggered by exposure to diminish through habituation. Improvement often continues for years, especially in patients who master the approach and use it even after formal treatment has ended. However, most patients have incomplete responses as they also do to drugs.

Many experts believe that combining psychotherapy and drug therapy is best, especially for severe cases. SSRIs (see p. 1543) and clomipramine (a tricyclic antidepressant with potent serotonergic effects) are effective. For most SSRIs, low doses (eg, fluoxetine 20 mg po once/day, fluvoxamine 100 mg po once/day, sertraline 50 mg po once/day, paroxetine 40 mg po once/day) are often as effective as larger ones.

**Panic Attacks and Panic Disorder**

A panic attack is the sudden onset of a discrete, brief period of intense discomfort, anxiety, or fear accompanied by somatic or cognitive symptoms. Panic disorder is occurrence of repeated panic attacks typically accompanied by fears about future attacks or changes in behavior to avoid situations that might predispose to attacks. Diagnosis is clinical. Isolated panic attacks may not require treatment. Panic disorder is treated with drug therapy, psychotherapy (eg, exposure therapy, cognitive-behavioral therapy), or both.

Panic attacks are common, affecting as many as 10% of the population in a single year. Most people recover without treatment; a few develop panic disorder. Panic disorder is uncommon, affecting 2 to 3% of the population in a 12-mo period. Panic disorder usually begins in late adolescence or early adulthood and affects women 2 to 3 times more often than men.

**Symptoms and Signs**

A panic attack involves the sudden onset of at least 4 of the 13 symptoms listed in Table 158-3. Symptoms usually peak within 10 min and dissipate within minutes thereafter, leaving little for a physician to observe. Although uncomfortable—at times extremely so—panic attacks are not medically dangerous.

Panic attacks may occur in any anxiety disorder, usually in situations tied to the core features of the disorder (eg, a person with a phobia of snakes may panic at seeing a snake). In pure panic disorder, however, some of the attacks occur spontaneously.

Most people with panic disorder anticipate and worry about another attack (anticipatory anxiety) and avoid places or situations where they have previously panicked. People with panic disorder often worry that they have a dangerous heart, lung, or brain disorder and repeatedly visit their family physician or an emergency department seeking help. Unfortunately, in these settings, attention is focused on physical
symptoms, and the correct diagnosis often is not made. Many people with panic disorder also have symptoms of major depression.

**Diagnosis**

Panic disorder is diagnosed after physical disorders that can mimic anxiety are eliminated and symptoms meet diagnostic criteria stipulated in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (DSM-IV-TR).

*Table 158-3. Symptoms of a Panic Attack*

**Treatment**

- Often antidepressants, benzodiazepines, or both
- Often nondrug measures (eg, exposure therapy, cognitive-behavioral therapy)

Some people recover without treatment, particularly if they continue to confront situations in which attacks have occurred. For others, especially without treatment, panic disorder follows a chronic waxing and waning course.

Patients should be told that treatment usually helps control symptoms. If avoidance behaviors have not developed, reassurance, education about anxiety, and encouragement to continue to return to and remain in places where panic attacks have occurred may be all that is needed. However, with a long-standing disorder that involves frequent attacks and avoidance behaviors, treatment is likely to require drug therapy combined with more intensive psychotherapy.

Many drugs can prevent or greatly reduce anticipatory anxiety, phobic avoidance, and the number and intensity of panic attacks:

- **Antidepressants**: The different classes—SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, tricyclics (TCAs), and monoamine oxidase inhibitors (MAOIs)—are similarly effective. However, SSRIs and SNRIs offer a potential advantage of fewer adverse effects in comparison with other antidepressants.

- **Benzodiazepines**: These anxiolytics—(see *Table 158-2*) work more rapidly than antidepressants but are more likely to cause physical dependence and such adverse effects as somnolence, ataxia, and memory problems.

- **Antidepressants plus benzodiazepines**: These drugs are sometimes used in combination initially; the benzodiazepine is slowly tapered after the antidepressant becomes effective.

Panic attacks often recur when drugs are stopped.

Different forms of psychotherapy are effective. Exposure therapy, in which patients confront their fears, helps diminish the fear and complications caused by fearful avoidance. For example, patients who fear that they will faint during a panic attack are asked to spin in a chair or to hyperventilate until they feel faint, thereby learning that they will not faint during an attack. Cognitive-behavioral therapy involves teaching patients to recognize and control their distorted thinking and false beliefs and to modify their behavior so that it is more adaptive. For example, if patients describe acceleration of their heart rate or shortness of breath in certain situations or places and fear that they are having a heart attack, they are taught the following:

- Not to avoid those situations
- To understand that their worries are unfounded
- To respond instead with slow, controlled breathing or other methods that promote relaxation
Phobic Disorders

Phobic disorders consist of persistent, unreasonable, intense fears (phobias) of situations, circumstances, or objects. The fears provoke anxiety and avoidance. Phobic disorders are classified as general (agoraphobia and social phobia) or specific. The causes of phobias are unknown. Phobic disorders are diagnosed based on history. Treatment for agoraphobia and social phobia is drug therapy, psychotherapy (eg, exposure therapy, cognitive-behavioral therapy), or both. Some phobias, including specific phobias, are treated mainly with exposure therapy.

Symptoms and Signs

Symptoms depend on the type of phobic disorder, which is classified as general (agoraphobia and social phobia) or specific.

Agoraphobia: Agoraphobia is fear of and anticipatory anxiety about being trapped in situations or places without a way to escape easily and without help if intense anxiety develops. The situations are avoided or they may be endured but with substantial anxiety. Agoraphobia can occur alone or as part of panic disorder.

Agoraphobia without panic disorder affects about 4% of women and 2% of men during any 12-mo period. Peak age at onset is the early 20s; first appearance after age 40 is unusual.

Common examples of situations or places that create fear and anxiety include standing in line at a bank or at a supermarket checkout, sitting in the middle of a long row in a theater or classroom, and using public transportation, such as a bus or an airplane. Some people develop agoraphobia after a panic attack in a typical agoraphobic situation. Others simply feel uncomfortable in such a situation and may never or only later have panic attacks there. Agoraphobia often interferes with function and, if severe enough, can cause people to become housebound.

Social phobia (social anxiety disorder): Social phobia is fear of and anxiety about being exposed to certain social or performance situations. These situations are avoided or endured with substantial anxiety. People with social phobia recognize that their fear is unreasonable and excessive.

Social phobia affects about 9% of women and 7% of men during any 12-mo period, but the lifetime prevalence may be at least 13%. Men are more likely than women to have the most severe form of social anxiety, avoidant personality disorder (see p. 1555).

Fear and anxiety in people with social phobia often centers on being embarrassed or humiliated if they fail to meet expectations. Often the concern is that their anxiety will be apparent through sweating, blushing, vomiting, or trembling (sometimes as a quavering voice) or that the ability to keep a train of thought or find words to express themselves will be lost. Usually, the same activity done alone causes no anxiety. Situations in which social phobia is common include public speaking, acting in a theatrical performance, and playing a musical instrument. Other potential situations include eating with others, signing their name before witnesses, or using public bathrooms.

A more generalized type of social phobia causes anxiety in a broad array of social situations.

Specific phobias: A specific phobia is fear of and anxiety about a particular situation or object (see Table 158-4). The situation or object is usually avoided when possible, but if exposure occurs, anxiety quickly develops. The anxiety may intensify to the level of a panic attack. People with specific phobias typically recognize that their fear is unreasonable and excessive.

Specific phobias are the most common anxiety disorders. Among the most frequent are fear of animals (zoophobia), heights (acrophobia), and thunderstorms (astraphobia or brontophobia). Specific phobias affect about 13% of women and 4% of men during any 12-mo period. Some cause little inconvenience—eg, fear of snakes (ophidiophobia) in city dwellers, unless they are asked to hike in an area where
snakes are found. However, other phobias interfere severely with functioning—e.g., fear of closed places (claustrophobia), such as elevators, in people who must work on an upper floor of a skyscraper. Phobia of blood (hemophobia), injections (trypanophobia), needles or other sharp objects (belonephobia), or injury (traumatophobia) occurs to some degree in at least 5% of the population. People

**Table 158-4.** Some Common Phobias*

with a phobia of blood, needles, or injury, unlike those with other phobias or anxiety disorders, can actually faint because an excessive vasovagal reflex causes bradycardia and orthostatic hypotension.

**Diagnosis**

Diagnosis is clinical based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision.

**Prognosis**

If untreated, agoraphobia usually waxes and wanes in severity. Agoraphobia may disappear without formal treatment, possibly because some affected people conduct their own form of exposure therapy. But if agoraphobia interferes with functioning, treatment is needed.

Social phobia is almost always chronic, and treatment is needed.

The prognosis for specific phobias is more variable when untreated because it may be easy to avoid the situation or object that causes fear and anxiety.

**Treatment**

- Exposure therapy
- For agoraphobia and social phobia, often cognitive-behavioral therapy
- Sometimes limited use of a benzodiazepine or β-blocker

Because many phobic disorders involve avoidance, exposure therapy, a form of psychotherapy, is the treatment of choice. With structure and support from a clinician who prescribes exposure homework, patients seek out, confront, and remain in contact with what they fear and avoid until their anxiety is gradually relieved through a process called habituation. Exposure therapy helps > 90% of those who carry it out faithfully and is almost always the only treatment needed for specific phobias. Cognitive-behavioral therapy is effective for agoraphobia and social phobia. Cognitive-behavioral therapy involves teaching patients to recognize and control their distorted thinking and false beliefs as well as instructing them on exposure therapy. For example, patients who describe acceleration of their heart rate or shortness of breath in certain situations or places learn by being repeatedly exposed to those situations that their worries about having a heart attack are unfounded and are taught to respond instead with slow, controlled breathing or other methods that promote relaxation.

Very short-term therapy with a benzodiazepine (e.g., lorazepam 0.5 to 1.0 mg po) or a β-blocker (propranolol is generally preferred—10 to 40 mg po), ideally about 1 to 2 h before the exposure, is occasionally useful when exposure to an object or situation cannot be avoided (e.g., when a person who has a phobia of flying must fly on short notice) or when cognitive-behavioral therapy is either unwanted or has not been successful.

Many people with agoraphobia also have panic disorder, and many of them benefit from drug therapy with an SSRI. SSRIs and benzodiazepines are effective for social phobia, but SSRIs are probably preferable in most cases because, unlike benzodiazepines, they are unlikely to interfere with cognitive-behavioral therapy. β-Blockers are useful for phobias related to public performance.

**Stress Disorders**
Stress disorders include acute stress disorder and posttraumatic stress disorder.

**Acute Stress Disorder**

*Acute stress disorder is a brief period of intrusive recollections occurring within 4 wk of witnessing or experiencing an overwhelming traumatic event.*

In acute stress disorder, people have been through a traumatic event, have recurring recollections of the trauma, avoid stimuli that remind them of the trauma, and have increased arousal. Symptoms begin within 4 wk of the traumatic event and last a minimum of 2 days but, unlike posttraumatic stress disorder, last no more than 4 wk. People with this disorder experience dissociative symptoms.

**Diagnosis**

Diagnosis is based on criteria recommended by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (see *Table 158-5*); these criteria include dissociative symptoms.

**Treatment**

- **Nondrug measures**

Many people recover once they are removed from the traumatic situation, shown understanding and empathy, and given an opportunity to describe the event and their reaction to it. To prevent or minimize this disorder, some experts recommend systematic debriefing to assist people who were involved in or witnessed a traumatic event as they process what has happened and reflect on its effect. In one approach to debriefing, the event is referred to as the critical incident and the debriefing is referred to as critical incident stress debriefing (CISD). Other experts have expressed concern and some studies show that CISD may be not be as helpful as supportive, empathic interviewing, may be quite distressful for some patients, and may even impede natural recovery.

Drugs to assist sleep may help, but other drugs are generally not indicated.

*[Table 158-5, Diagnosis of Acute Stress Disorder]*

**Posttraumatic Stress Disorder**

*Posttraumatic stress disorder (PTSD) is recurring, intrusive recollections of an overwhelming traumatic event. The pathophysiology of the disorder is incompletely understood. Symptoms also include avoidance of stimuli associated with the traumatic event, nightmares, and flashbacks. Diagnosis is based on history. Treatment consists of exposure therapy and drug therapy.*

When terrible things happen, many people are lastingly affected; in some, the effects are so persistent and severe that they are debilitating and constitute a disorder. Generally, events likely to evoke PTSD are those that invoke feelings of fear, helplessness, or horror. These events might include experiencing serious injury or the threat of death or witnessing others being seriously injured, threatened with death, or actually dying. Combat, sexual assault, and natural or man-made disasters are common causes of PTSD.

Lifetime prevalence approaches 8%, with a 12-mo prevalence of about 5%.

**Symptoms and Signs**

Most commonly, patients have frequent, unwanted memories replaying the triggering event. Nightmares of the event are common. Much rarer are transient waking dissociative states in which events are relived as if happening (flashback), sometimes causing patients to react as if in the original situation (eg, loud noises such as fireworks might trigger a flashback of being in combat, which in turn might cause patients
to seek shelter or prostrate themselves on the ground for protection).

Patients avoid stimuli associated with the trauma and often feel emotionally numb and disinterested in daily activities. Sometimes the onset of symptoms is delayed, occurring many months or even years after the traumatic event. PTSD is considered chronic if present > 3 mo. Depression, other anxiety disorders, and substance abuse are common among patients with chronic PTSD.

In addition to trauma-specific anxiety, patients may experience guilt because of their actions during the event or because they survived when others did not.

**Diagnosis**

Diagnosis is clinical based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (see Table 158-6).

**Treatment**

- Exposure therapy or other psychotherapy, including supportive psychotherapy
- SSRI or other drug therapy

If untreated, chronic PTSD often diminishes in severity without disappearing, but some people remain severely impaired. The primary form of psychotherapy used, exposure therapy, involves exposure to situations that the person avoids because they may trigger recollections of the trauma. Repeated exposure in fantasy to the traumatic experience itself usually lessens distress after some initial increase in discomfort. Stopping certain ritual behaviors, such as excessive washing to feel clean after a sexual assault, also helps.

Drug therapy, particularly with SSRIs (see p. 1543), is effective. Drugs with mood-stabilizing effects, such as valproate, carbamazepine, and topiramate, can help reduce arousal, nightmares, and flashbacks.

Because the anxiety is often intense, supportive psychotherapy plays an important role. Therapists must be openly empathic and sympathetic, recognizing and acknowledging patients’ mental pain and the reality of the traumatic events. Therapists must also encourage patients to face the memories through desensitizing exposure and learning techniques to control anxiety. For survivor guilt, psychotherapy aimed at helping patients understand and modify their self-critical and punitive attitudes may be helpful.
Chapter 159. Dissociative Disorders

Introduction

Everyone occasionally experiences a failure in the normal automatic integration of memories, perceptions, identity, and consciousness. For example, people may drive somewhere and then realize that they do not remember many aspects of the drive because they are preoccupied with personal concerns, a program on the radio, or conversation with a passenger. Typically, such a failure, referred to as nonpathologic dissociation, does not disrupt everyday activities.

People with a dissociative disorder may totally forget a series of normal behaviors occupying minutes or hours and may sense missing a period of time in their experience. Dissociation thus disrupts the continuity of self and the recollection of life events. People may experience the following:

• Poorly integrated memory (dissociative amnesia)
• Fragmentation of identity and memory (dissociative fugue or dissociative identity disorder)
• Disruption of experience and self-perception (depersonalization disorder)

Dissociative disorders are usually attributed to overwhelming stress. Such stress may be generated by traumatic events or by intolerable inner conflict.

Depersonalization Disorder

Depersonalization disorder consists of persistent or recurrent feelings of being detached from one's body or mental processes, usually with a feeling of being an outside observer of one's life. The disorder is often triggered by severe stress. Diagnosis is based on symptoms after other possible causes are ruled out. Treatment consists of psychotherapy.

About 20 to 40% of the general population have had a transient experience of depersonalization, frequently occurring in connection with life-threatening danger, acute drug intoxication (marijuana, hallucinogens, ketamine, Ecstasy), sensory deprivation, or sleep deprivation. Depersonalization can also occur as a symptom in many other mental disorders as well as in physical disorders such as seizure disorders (ictal or postictal). When depersonalization occurs independently of other mental or physical disorders and is persistent or recurrent, depersonalization disorder is present. It is estimated to occur in about 2% of the general population.

Symptoms and Signs

Patients feel detached from their body, mind, feelings, or sensations. Most patients also say they feel unreal (derealization), like an automaton, or as if they were in a dream or in some other way detached from the world. Some patients cannot recognize or describe their emotions (alexithymia). Patients may describe themselves as the "walking dead." Symptoms are almost always distressing and, when severe, profoundly intolerable. Anxiety and depression are common.

Symptoms are often chronic; about one third of patients have recurrent episodes, and two thirds have continuous symptoms. Episodic symptoms sometimes become continuous.

Patients often have great difficulty describing their symptoms and may fear or believe they are going crazy. They always retain the knowledge that their unreal experiences are not real but rather are just the way that they feel. This awareness differentiates depersonalization disorder from a psychotic disorder, in which such insight is always lacking.

Diagnosis

• Medical and psychiatric evaluation
Diagnosis is based on symptoms after ruling out physical disorders, ongoing substance abuse, and other mental disorders (especially anxiety, depression, and other dissociative disorders). Initial evaluation should include MRI and EEG to rule out physical causes, particularly if symptoms or progression are atypical. Urine toxicology tests may also be indicated.

Psychologic tests and special structured interviews and questionnaires are helpful.

**Prognosis**

Patients often improve without intervention. Complete recovery is possible for many patients, especially if symptoms result from treatable or transient stresses or have not been protracted. In others, depersonalization becomes more chronic and refractory.

Even persistent or recurrent depersonalization symptoms may cause only minimal impairment if patients can distract themselves from their subjective sense of self by keeping their mind busy and focusing on other thoughts or activities. Some patients become disabled by the chronic sense of estrangement, by the accompanying anxiety or depression, or both.

**Treatment**

- **Psychotherapy**

  Treatment must address all stresses associated with onset of the disorder as well as earlier stresses (eg, childhood emotional abuse or neglect), which may have predisposed patients to late onset of depersonalization.

  Various psychotherapies (eg, psychodynamic psychotherapy, cognitive-behavioral therapy) are successful for some patients:

  - Cognitive techniques can help block obsessive thinking about the unreal state of being.
  - Behavioral techniques can help patients engage in tasks that distract them from the depersonalization.
  - Grounding techniques use the 5 senses (eg, by playing loud music or placing a piece of ice in the hand) to help patients feel more connected to themselves and the world and more real in the moment.
  - Psychodynamic therapy focuses on underlying conflicts that make certain affects intolerable to the self and thus dissociated.
  - Moment-to-moment tracking and labeling of affect and dissociation in therapy sessions works well for some patients.

  Various drugs have been used, but none have clearly demonstrable efficacy. However, some patients are apparently helped by serotonin reuptake inhibitors, lamotrigine, opioid antagonists, anxiolytics, and stimulants. However, these drugs may largely be targeting other mental disorders (eg, anxiety, depression) that are often associated with or precipitated by depersonalization.

**Dissociative Amnesia**

Dissociative amnesia is inability to recall important personal information that is too extensive to be explained by normal forgetfulness. Diagnosis is based on history after ruling out other causes of amnesia. Treatment is psychotherapy, sometimes combined with hypnosis or drug-facilitated interviews.

The information lost would normally be part of conscious awareness and would be described as autobiographic memory—eg, the story of one's life: who one is, where one went, to whom one spoke, and what one did, said, thought, experienced, and felt. Although the forgotten information may be inaccessible to consciousness, it sometimes continues to influence behavior.
Dissociative amnesia is likely underdetected. Prevalence, although not well-established, has been estimated at 2 to 6% in the general population. Dissociative amnesia is most commonly diagnosed in young adults. The amnesia appears to be caused by traumatic or stressful experiences endured or witnessed (eg, physical or sexual abuse, rape, combat, abandonment during natural disasters, death of a loved one, financial troubles) or by tremendous internal conflict (eg, turmoil over guilt-ridden impulses, apparently unresolvable interpersonal difficulties, criminal behaviors).

Symptoms and Signs

The main symptom is memory loss, usually of information regarding traumatic or stressful events or entire periods of the patient's life. Characteristically, patients experience one or more episodes in which they forget some or all of the events that occurred during a period of time. These periods, or gaps in memory, may represent only a few hours or can encompass years. Usually, the forgotten period of time is clearly demarcated.

Patients seen shortly after they become amnestic may appear confused. Some are very distressed; others are indifferent. Some, especially if the amnesia is for the remote past, may not even be aware of it, and if they present for psychiatric help, the presenting complaint is often different.

Diagnosis

• Medical and psychiatric examination

Diagnosis requires a medical and psychiatric examination. Initial evaluation should include MRI to rule out structural causes, EEG to rule out a seizure disorder, and blood and urine tests to rule out toxic causes, such as illicit drug use. Psychologic testing can help better characterize the nature of the dissociative experiences.

Prognosis

Most patients recover their missing memories, and amnesia resolves. However, some are never able to reconstruct their missing past. The prognosis is determined mainly by the patient's life circumstances, particularly stresses and conflicts associated with the amnesia, and by the patient's overall mental adjustment.

Treatment

• To recover memory, a supportive environment and sometimes hypnosis or a drug-induced hypnotic state

• Psychotherapy to deal with issues associated with recovered memories

If memory of only a very short time period is lost, supportive treatment is usually adequate, especially if patients have no apparent need to recover the memory of some painful event.

Treatment for more severe memory loss begins with creation of a safe and supportive environment. This measure alone frequently leads to gradual recovery of missing memories. When it does not or when the need to recover memories is urgent, questioning patients while they are under hypnosis or, rarely, in a drug-induced (barbiturate or benzodiazepine) semihypnotic state can be successful. These strategies must be done gently because the traumatic circumstances that stimulated memory loss are likely to be recalled and to be very upsetting. The questioner also must carefully phrase questions so as not to suggest the existence of an event and risk creating a false memory. The accuracy of memories recovered with such strategies can be determined only by external corroboration. However, regardless of the degree of historical accuracy, filling in the gap as much as possible is often therapeutically useful in restoring continuity to the patient's identity and sense of self and in creating a cohesive narrative. Once the amnesia is lifted, treatment helps with the following:

• Giving meaning to the underlying trauma or conflict
• Resolving problems associated with the amnestic episode
• Enabling patients to move on with their life

**Dissociative Fugue**

Dissociative fugue is one or more episodes of amnesia in which patients cannot recall some or all of their past and either lose their identity or form a new identity. The episodes, called fugues, result from trauma or stress. Dissociative fugue often manifests as sudden, unexpected, purposeful travel away from home. Diagnosis is based on history, after ruling out other causes of amnesia. Treatment consists of psychotherapy, sometimes combined with hypnosis or drug-facilitated interviews.

The incidence of dissociative fugue has been estimated at ≤ 0.2%, but the rate increases in connection with wars, accidents, and natural disasters.

**Etiology**

Causes are similar to those of dissociative amnesia (see p. 1503), with some additional factors (eg, prolonged and escalating subacute stress, extreme intrapsychic conflict, intense struggle between a wish to escape from one's life as is and a very harsh superego).

Fugues are often mistaken for malingering (see p. 1574) because like malingering, fugues may absolve people of accountability for their actions or of certain responsibilities or remove them from hazardous situations. However, unlike malingering, fugues are spontaneous, unplanned, and not faked. Many fugues appear to represent disguised wish fulfillment, the only permissible means of escape from severe distress, especially for people with a rigid conscience. For example, a financially distressed executive leaves a hectic life and lives as a farm hand in the country. A fugue may also remove the person from an embarrassing situation or intolerable stress or may be related to issues of rejection or separation. For example, the fugue may say, in effect, "I am not the man who found his wife to be unfaithful." Some fugues may be an alternative response to suicidal or homicidal impulses.

About half of people have only one dissociative fugue, and the others have a few episodes over their lifetime. When dissociative fugue recurs more than a few times, people usually have an underlying dissociative identity disorder.

**Symptoms and Signs**

The length of a fugue may range from hours to months, occasionally longer. During the fugue, people may appear and act normal or be only mildly confused. They may assume a new name and identity and engage in complex social interactions. However, at some point, confusion about the new identity or a return of the original identity may make them aware of amnesia or cause distress. When the fugue ends, shame, discomfort, grief, depression, intense conflict, and suicidal or aggressive impulses may appear—people must deal with what they left behind. Failure to remember events that occurred during the fugue may cause confusion, distress, or even terror. When the fugue ends, many people recall their past identity and life up to fugue onset; however, for some, recalling is a lengthier and more gradual process, and some aspects of their autobiographic past may never be recalled. A very few people remember nothing or almost nothing about their past indefinitely.

**Diagnosis**

• Clinical evaluation (usually the disorder is diagnosed retrospectively)

A fugue in progress is rarely recognized. It may be suspected when people seem confused about their identity, puzzled about their past, or confrontational when their new identity is challenged. Often, the fugue is not diagnosed until people abruptly return to their pre-fugue identity and are distressed to find themselves in unfamiliar circumstances.
The diagnosis is usually made retrospectively, based on documentation of the circumstances before travel, the travel itself, and the establishment of an alternate life. When clinicians suspect that a fugue is faked, cross-checking information from multiple sources may reveal inconsistencies that preclude the diagnosis.

**Prognosis**

Most fugues are brief and self-limited. Impairment after the fugue ends is usually mild and short-lived. However, if the fugue was prolonged and complications due to behavior before or during the fugue are significant, people may have considerable difficulties trying to return to their pre-fugue identity—eg, a soldier who returns after a fugue may be charged with desertion, or a person who marries during a fugue may have inadvertently become a bigamist.

**Treatment**

- During fugue, restoring missing information
- After fugue ends, psychotherapy

Rarely, people are identified while still in a fugue. In such cases, the following are important:

- Recovering information (possibly with help from law enforcement and social services personnel) about their true identity
- Figuring out why it was abandoned
- Facilitating its restoration

Treatment after the fugue ends involves psychotherapy, sometimes combined with hypnosis or drug-facilitated (barbiturate or benzodiazepine) interviews. However, efforts to restore memory of the fugue period are often unsuccessful. Regardless, a psychiatrist can help people explore how they handle the types of situations, conflicts, and affects that precipitated the fugue and thus foster better future adaptations and solutions and help prevent fugue recurrences.

**Dissociative Identity Disorder**

Dissociative identity disorder, formerly called multiple personality disorder, is characterized by ≥ 2 identities (called alters or self-states) that alternate. The disorder includes inability to recall important personal information relating to some of the identities. The cause is almost invariably overwhelming childhood trauma, and the disorder is best viewed as a developmental disorder in which extreme trauma interferes with formation of a single cohesive identity. Diagnosis is based on history, sometimes with hypnosis or drug-facilitated interviews. Treatment is long-term psychotherapy, sometimes with drug therapy.

What is known by one identity may or may not be known by another. Some identities appear to know and interact with others in an elaborate inner world, and some identities do this more than others. The system must be mapped out by the psychiatrist over time.

This disorder may be present in about 1% of the general population.

**Etiology**

Dissociative identity disorder is attributed to the interaction of the following:

- Overwhelming stress (typically extreme childhood mistreatment)
- Insufficient nurturing and compassion in response to overwhelmingly hurtful experiences during
childhood

• Dissociative capacity (ability to uncouple one’s memories, perceptions, or identity from conscious awareness)

Children are not born with a sense of a unified identity; it develops from many sources and experiences. In overwhelmed children, many parts of what should have blended together remain separate. Chronic and severe abuse (physical, sexual, or emotional) and neglect during childhood are frequently reported by and documented in patients with dissociative identity disorder. Some patients have not been abused but have experienced an important early loss (such as death of a parent), serious medical illness, or other overwhelmingly stressful events.

In contrast to most children who achieve cohesive, complex appreciation of themselves and others, severely mistreated children may go through phases in which different perceptions, memories, and emotions of their life experiences are kept segregated. Such children may over time develop an increasing ability to escape the mistreatment by "going away" or retreating into their own mind. Each developmental phase or traumatic experience may be used to generate a different self-state.

Symptoms and Signs

Several symptoms are characteristic:

• Fluctuating symptom pictures

• Fluctuating levels of function from highly effective to disabled

• Severe headaches or other pains

• Time distortions, time lapses, and amnesia

• Depersonalization and derealization

Depersonalization refers to feeling unreal, removed from one's self, and detached from one's physical and mental processes. Patients feel like an observer of their life, as if they were watching themselves in a movie. Patients may even feel as if transiently they do not inhabit their bodies. Derealization refers to experiencing familiar people and surroundings as if they were unfamiliar, strange, or unreal.

Patients typically lose time; they experience frequent bouts of amnesia after which they may discover objects or samples of handwriting that they cannot account for or recognize. They may also find themselves in different places from where they last remember being and have no idea why or how they got there. They may refer to themselves in the first person plural (we) or in the third person (he, she, they), sometimes without knowing why.

The switching of identities and the amnestic barriers between them frequently result in chaotic lives. Because the identities often interact with each other, patients typically report hearing inner conversations between other personalities, which comment on or address them. Thus, patients may be misdiagnosed with a psychotic disorder. Although these voices are experienced as hallucinations, they have a distinctly different quality from the typical hallucinations of psychotic disorders such as schizophrenia.

Patients often have a remarkable array of symptoms that can resemble those of anxiety disorders, mood disorders, posttraumatic stress disorder, personality disorders, eating disorders, bipolar disorder, schizophrenia, and seizure disorders. Suicidal ideation and attempts are common, as are episodes of self-mutilation. Many patients abuse substances.

Diagnosis

• Detailed interviews, sometimes with hypnosis or facilitated by drugs
Patients typically have been diagnosed with at least 3 different mental disorders and have been treated unsuccessfully. On average, these patients are in the mental health system for about 6 to 8 yr before the disorder is accurately diagnosed. The skepticism of some physicians regarding the validity of dissociative identity disorder can contribute to misdiagnosis.

The diagnosis requires knowledge of and specific questions about dissociative phenomena. Prolonged interviews, hypnosis, or drug-facilitated (barbiturate or benzodiazepine) interviews are sometimes used, and patients may be asked to keep a journal between visits. All of these measures encourage a shift of personality states during the evaluation. The clinician may over time attempt to map out the different self-states and their interrelationships. Specially designed structured interviews and questionnaires can be very helpful, especially for clinicians who have less experience with this disorder.

The clinician may also attempt to directly contact other identities by asking to speak to the part of the mind involved in behaviors for which patients had amnesia or that were experienced in a depersonalized or derealized way.

Prognosis

Symptoms wax and wane spontaneously, but dissociative identity disorder does not resolve spontaneously. Patients can be divided into groups based on their symptoms:

1: Symptoms are mainly dissociative and posttraumatic. These patients generally function well and recover completely with treatment.

2: Dissociative symptoms are combined with prominent symptoms of other disorders, such as personality disorders, mood disorders, eating disorders, and substance abuse disorders. These patients improve more slowly, and treatment may be less successful or longer and more crisis-ridden.

3: Patients not only have severe symptoms due to coexisting mental disorders but may also remain deeply emotionally attached to their abusers. These patients can be challenging to treat, often requiring longer treatments that typically aim to help control symptoms more than to achieve integration.

Treatment

• Supportive care, including drug treatment as needed for associated symptoms

• Long-term integration of identity states when possible

Integration of the identity states is the most desirable outcome. Drugs are widely used to help manage symptoms of depression, anxiety, impulsivity, and substance abuse but do not relieve dissociation per se; treatment to achieve integration centers on psychotherapy. For patients who cannot or will not strive for integration, treatment aims to facilitate cooperation and collaboration among the identities and to reduce symptoms.

The first priority of psychotherapy is to stabilize patients and ensure safety, before evaluating traumatic experiences and exploring problematic identities. Some patients benefit from hospitalization, during which continuous support and monitoring are provided as painful memories are addressed. Hypnosis may help with accessing the identities, facilitating communication between them, and stabilizing and interpreting them. Modified exposure techniques can be used to gradually desensitize patients to traumatic memories, which are sometimes tolerated only in small fragments.

As the reasons for dissociations are addressed and worked through, therapy can move toward reconnecting, integrating, and rehabilitating the patient's alternate selves, relationships, and social functioning. Some integration occurs spontaneously during treatment. Integration can be encouraged by negotiating with and arranging the unification of the identities or facilitated with imagery and hypnotic suggestion.
Chapter 160. Drug Use and Dependence

Introduction

Some people who use drugs use large enough amounts often enough and long enough to become dependent.

Definitions

A single definition for drug dependence is elusive. Concepts that aid in defining drug dependence are tolerance and psychologic and physical dependence.

Tolerance describes the need to progressively increase the drug dose to produce the effect originally achieved with smaller doses.

Psychologic dependence includes feelings of satisfaction and a desire to repeat the drug experience or to avoid the discontent of not having it. This anticipation of effect is a powerful factor in the chronic use of psychoactive drugs and, with some drugs, may be the only obvious reason for intense craving and compulsive use. Craving and compulsion to use a drug lead to using it in larger amounts, more frequently, or over a longer period than was intended when use began. Psychologic dependence involves giving up social, occupational, or recreational activities because of drug use, as well as persistent use despite knowing that the drug is likely causing a physical or mental problem. Drugs that cause psychologic dependence often have ≥ 1 of the following effects:

- Reduced anxiety and tension
- Elation, euphoria, or other pleasurable mood changes
- Feelings of increased mental and physical ability
- Altered sensory perception
- Changes in behavior

Drugs that cause chiefly psychologic dependence include marijuana, amphetamine, 3,4-methylenedioxyamphetamine (MDMA), and hallucinogens, such as lysergic acid diethylamide (LSD), mescaline, and psilocybin.

Physical dependence is manifested by a withdrawal (abstinence) syndrome, in which untoward physical effects occur when the drug is stopped or when its effect is counteracted by a specific antagonist. Drugs that cause strong physical dependence include heroin, alcohol, benzodiazepines, and cocaine. Abstinence syndromes are drug-specific or drug class-specific and may vary considerably based on the amount and frequency of use and on patient characteristics, which may affect how patients experience withdrawal.

Addiction, a concept without a consistent, universally accepted definition, is used here to refer to compulsive use and overwhelming involvement with a drug, including spending an increasing amount of time obtaining the drug, using the drug, or recovering from its effects. It may occur without physical dependence. Addiction implies the risk of harm and the need to stop drug use, regardless of whether the addict understands and agrees.

Drug abuse is definable only in terms of societal disapproval. Drug abuse may involve the following:

- Experimental and recreational use of drugs, which is usually illegal
- Unsanctioned or illegal use of psychoactive drugs to relieve problems or symptoms
- Use of drugs because of dependence or the need to prevent withdrawal
Illicit drug use, although usually considered abuse simply because it is illegal, does not always involve dependence. Use of legal substances, such as alcohol and prescription drugs, may involve dependence and abuse. Abuse of prescription and illegal drugs cuts across all socioeconomic groups.

**Recreational drug use** has increasingly become a part of Western culture, although in general, it is not sanctioned by society. Some users apparently are unharmed; they tend to use drugs episodically in relatively small doses, precluding clinical toxicity and development of tolerance and physical dependence. Many recreational drugs (eg, crude opium, alcohol, marijuana, caffeine, hallucinogenic mushrooms, coca leaf) are "natural" (ie, close to plant origin); they contain a mixture of relatively low concentrations of psychoactive compounds and are not isolated psychoactive compounds. Recreational drugs are most often taken orally or inhaled. Taking these drugs by injection makes it harder to predict and control desired and unwanted effects.

**Intoxication** refers to development of a reversible substance-specific syndrome of mental and behavioral changes that may involve altered perception, euphoria, cognitive impairment, impaired judgment, impaired physical and social functioning, mood lability, belligerence, or a combination. Taken to the extreme, intoxication can lead to overdose, significant morbidity, and risk of death.

**Narcotics and scheduled drugs:** Narcotics are drugs that cause insensibility or stupor (narcosis), but the term is typically restricted to drugs that bind to opiate receptors: opium, opium derivatives, and their semisynthetic and synthetic analogues. However, the US government classifies cocaine as a narcotic, even though it does not bind to opiate receptors or have morphine-like effects. Many narcotics (specifically opioids) are used therapeutically to induce anesthesia and to relieve pain, cough, and diarrhea. The morphine-like effects of opioids are welcomed in most clinical situations but contribute to the attractiveness of narcotics for abuse.

In the US, the Comprehensive Drug Abuse Prevention and Control Act of 1970 and subsequent modifications require the pharmaceutical industry to maintain physical security of and strict record keeping for certain classes of drugs (controlled substances—see Table 160-1). Controlled substances are divided into 5 schedules (or classes) on the basis of their potential for abuse, accepted medical use, and accepted safety under medical supervision. The schedule classification determines how a substance must be controlled.

- **Schedule I:** These substances have a high potential for abuse, no accredited medical use, and a lack of accepted safety. They can be used only under government-approved research conditions.

- **Schedule II to IV:** Going from schedule II to IV, these drugs have progressively less potential for abuse. They have an accredited medical use. Prescriptions for these drugs must bear the physician's federal Drug Enforcement Administration (DEA) license number.

- **Schedule V:** These substances are least likely to be abused. Some Schedule V drugs do not require a prescription.

[Table 160-1: Some Examples of Controlled Substances]

State schedules may vary from federal schedules.

**Drug Dependence**

People usually progress from experimentation to occasional use and then to dependence. This progression is complex and only partially understood. The process depends on interaction between the drug, user, and setting.

**Drug:** Commonly used psychoactive drugs vary in their potential for creating dependence.

**User:** The user's predisposing physical characteristics (probably including genetic predisposition), personal characteristics, and circumstances (eg, coexistence of other disorders) influence whether drug
dependence develops. For example, sadness, emotional distress that is symptomatically relieved by the
drug, and a sense of social alienation may lead to increased use and dependence or addiction.
Psychiatric disorders increase the risk of becoming drug dependent.

Patients with chronic pain (eg, back pain, pain due to sickle cell disease, neuropathic pain, fibromyalgia)
often require narcotics for relief; many subsequently become dependent, and a few become addicted.
However, in many of these patients, nonnarcotic drugs and other treatments (see p. 1629) are not
adequate to relieve pain and suffering.

Few differences exist between the biochemical, drug dispositional, and physical responsiveness of
people who become addicted or dependent and those who do not, although such differences have been
vigorously sought. However, exceptions exist; nonalcoholic relatives of alcoholics have a diminished
physical response to alcohol. Consequently, they need to drink more to get the desired effect.

A neural substrate for reinforcement (the tendency to seek more drugs and other stimuli) has been
identified in animal models. In these studies, self-administration of such drugs as opioids, cocaine,
amphetamine, nicotine, and benzodiazepines is associated with enhanced dopaminergic transmission in
specific mid-brain and cortical circuits. This finding suggests the existence of a brain reward pathway
involving dopamine in the mammalian brain. However, evidence that hallucinogens and cannabinoids
activate this system is insufficient, and not everyone who experiences these rewards becomes dependent
or addicted.

An addictive personality has been described variously by behavioral scientists, but little scientific
evidence backs this concept.

Setting: Cultural and social factors include peer or group pressure and environmental stress (particularly
if accompanied by feelings of impotence to effect change or to accomplish goals).

Physicians may inadvertently contribute to harmful use of psychoactive drugs by overzealously
prescribing them to patients for stress relief or may be manipulated by patients to overprescribe the
drugs. Many social factors and the mass media may contribute to the expectation that drugs can safely
relieve all distress and gratify all needs.

Injection Drug Use

A number of drugs of abuse are given by injection to achieve a more rapid or potent effect or both. Drugs
are typically injected IV but may be injected sc, IM, or even sublingually. Users typically access peripheral
veins, but when these have sclerosed because of chronic use, some learn to inject into large central
veins (eg, internal jugular, femoral, axillary).

Complications

People who inject illicit drugs risk not only the adverse pharmacodynamic effects of the drugs but also
complications related to contaminants, adulterants, and infectious agents that may be injected with the
drug.

Adulterants: Some drug users crush tablets of prescription drugs, dissolve them, and inject the solution
IV, thus injecting themselves with an array of filler agents commonly present in tablets, including cellulose,
talc, and cornstarch. Filler agents can become trapped by the pulmonary capillary bed and result in
chronic inflammation and foreign body granulomatosis. Filler agents can also damage the endothelium of
heart valves, thus increasing the risk of endocarditis.

Street drugs such as heroin and cocaine are often "cut" with various adulterants (eg, amphetamines,
clenbuterol, dextromethorphan, fentanyl, ketamine, lidocaine, lysergic acid diethylamide [LSD],
pseudoephedrine, quinine, scopolamine, xylazine). Adulterants may be added to enhance mind-altering
properties or to substitute for pure drug; their presence can make diagnostic and therapeutic decisions
difficult.
**Infectious agents:** Needle sharing and use of nonsterile techniques can lead to many infectious complications. Injection site complications include cutaneous abscesses, cellulitis, lymphangitis, lymphadenitis, and thrombophlebitis. Distant focal infectious complications due to septic emboli and bacteremia include bacterial endocarditis and abscesses in various organs and sites. Septic lung emboli and osteomyelitis (particularly lumbar vertebral) are particularly common. Infectious spondylitis and sacroiliitis may occur.

Systemic infectious diseases are primarily hepatitis B and C and HIV infection. IV drug users are at high risk of pneumonia, resulting from aspiration or hematogenous spread of bacteria. Other infections that are not directly caused by drug injection but are common among IV drug users include TB, syphilis, and other sexually transmitted diseases. Even botulism and tetanus can result from IV drug abuse.

**Diagnosis**

- History, physical examination, or both

Some patients readily admit to injection drug use, but for others, a thorough physical examination is needed to detect evidence of injection. Chronic IV drug use can be confirmed by observing track marks due to repeated injections into subcutaneous veins. Track marks are a linear area of tiny, dark punctate lesions (needle punctures) surrounded by an area of darkened or discolored skin due to chronic inflammation. Track marks are often found in easily accessible sites (eg, antecubital fossa, forearms), but some drug users try to hide evidence of their injections by choosing less obvious sites (eg, axillae). Subcutaneous injection (skin popping) can cause characteristic circular scars or ulcers; there may be signs of previous abscesses. Addicts may deny stigmata of drug use by attributing track marks to frequent blood donations, bug bites, or previous trauma.

**Treatment**

- Prevention and treatment of infectious complications

Drug users, especially those with a history of injection drug use, should be thoroughly evaluated for viral hepatitis, HIV infection, and the wide range of other infectious diseases common among these patients (eg, TB, syphilis, other sexually transmitted diseases). Also, vaccination to prevent hepatitis, influenza, pneumococcal infection, and other infections should be offered to all appropriate patients.

The AIDS epidemic has triggered a harm-reduction movement, which aims to reduce the harm of drug use without necessarily requiring cessation. For example, providing clean needles and syringes for users who cannot stop injecting drugs reduces the spread of HIV and hepatitis.

Treatment of infectious complications is the same as that for similar infections resulting from other conditions; it includes use of antibiotics and incision and drainage of abscesses. Treatment may be complicated by difficulty obtaining venous access (and keeping the patient from using it to inject more drugs) and by poor adherence to treatment regimens.

**Drug Testing**

Drug testing is done primarily to screen people systematically or randomly for evidence of use of one or more substances with potential for abuse. Testing is done in the following circumstances:

- Certain groups of people, commonly including students, athletes, and prisoners
- People who are applying for or who already hold certain types of jobs (eg, pilots, commercial truck drivers)
- People who have been involved in motor vehicle or boating accidents or accidents at work
- People who have attempted suicide by unclear means
• People in a court-ordered treatment program or with terms of probation or parole requiring abstinence (to monitor adherence)

• People in a substance abuse treatment program (as a standard feature, to obtain objective evidence about substance abuse and thus optimize treatment)

• People required to participate in a drug testing program as part of custody or parental rights

Notification or consent may be a requirement before testing, depending on jurisdiction and circumstances. Mere documentation of use may be sufficient for legal purposes; however, testing cannot determine frequency and intensity of substance use and thus cannot distinguish casual users from those with more serious problems. Also, drug testing targets only a limited number of substances and thus does not identify many others. The clinician must use other measures (e.g., thorough history, questionnaires) to identify the degree to which substance use has affected each patient's life.

Alcohol, marijuana, cocaine, natural and semisynthetic opioids, amphetamines, and phencyclidine are the substances most commonly tested for. Testing for benzodiazepines and barbiturates may also be done. Urine, blood, breath, saliva, sweat, or hair samples may be used. Urine testing is most common because it is noninvasive, quick, and able to qualitatively detect a wide range of drugs. The window of detection depends on the frequency and amount of drug intake but is about 1 to 4 days for most drugs. Because cannabinoid metabolites persist, urine tests for marijuana can remain positive longer after use is stopped. Blood testing can be used to quantify levels of certain drugs but is less commonly done because it is invasive and the window of detection for many drugs is much shorter, often only hours. Hair analysis is not as widely available but provides the longest window of detection, ≥ 100 days for some drugs.

Validity of testing depends on the type of test done. Screening tests are typically rapid qualitative urine immunoassays. Such screening tests are associated with a number of false-positive and false-negative results, and they do not detect meperidine and fentanyl. Lysergic acid diethylamide (LSD), gamma hydroxybutyrate (GHB), mescaline, and inhaled hydrocarbons are not detected on readily available screens. Confirmatory tests, which may require several hours, typically use gas chromatography or mass spectroscopy.

False results: Several factors can produce false-negative results, particularly in urine testing. Patients may submit samples provided by others (presumably drug-free). This possibility can be eliminated by directly observing sample collection and by sealing samples immediately with tamper-evident seals. Some people attempt to defeat urine drug testing by drinking large quantities of fluids or by taking diuretics before the test; however, samples that appear too clear can be rejected if specific gravity of the sample is very low.

False positives can result from ingesting prescription and nonprescription therapeutic drugs and from consuming certain foods. Poppy seeds may produce false-positive results for opioids. Pseudoephedrine, tricyclic antidepressants, and quetiapine may produce false-positive results for amphetamines, and ibuprofen may produce false-positive results for marijuana.

Body Packing

Body packing is the voluntary or coerced swallowing of drug-filled packets to smuggle drugs across borders or other security checkpoints.

Body packing often involves drugs with a high street value (primarily heroin or cocaine). The drugs may be placed in condoms or in packets enclosed by several layers of polyethylene or latex and sometimes covered with an outer layer of wax. After body packers (“mules”) swallow multiple packets, they typically take antimotility drugs to decrease intestinal motility until the packets can be retrieved. Rupture of one or more packets is a risk, resulting in abrupt toxicity and overdose. Specific symptoms depend on the drug, but intractable seizures, tachycardia, hypertension, and hyperthermia are common with cocaine, and coma and respiratory depression are common with heroin. Intestinal obstruction or rupture and peritonitis are also risks.
Body stuffing is similar to body packing; it occurs when people about to be apprehended by law enforcement swallow drug packets to avoid detection. Sometimes packets are placed in the rectum or vagina. Body stuffing usually involves much smaller amounts of drugs than does body packing, but the drugs are usually less securely wrapped, so overdose is still a concern.

Diagnosis

Suspected body packers are usually brought to medical attention by law enforcement officials, but clinicians should consider body packing if recent travelers and newly incarcerated people present with coma or seizures of unknown etiology. Body packing can sometimes be confirmed when packets are detected during rectal examination. Plain x-rays can often confirm the presence of packets in the GI tract.

Treatment

- Supportive treatment for complications

Treatment of patients with symptoms of overdose (and presumed packet rupture) is supportive and includes airway protection, respiratory and circulatory support, and anticonvulsants, depending on patient symptoms. Sometimes, specific antidotes are indicated (see under specific drugs). Usually, unruptured packets can be removed by whole-bowel irrigation. However, once packets rupture, immediate surgical or endoscopic removal (depending on location in the GI tract) of all packets is indicated but can rarely be done in time; death commonly occurs because the quantity of drug released is large. Patients with intestinal obstruction or perforation also need immediate surgery. Activated charcoal may be helpful but is contraindicated in patients with obstruction or perforation.

Asymptomatic body packers should be observed for development of symptoms until the packets are passed and followed by several packet-free stools. Some clinicians use whole-bowel irrigation with a polyethylene glycol solution with or without metoclopramide as a promotility agent. Emergency endoscopy is not indicated for asymptomatic patients.

Opioids

Opioids are euphoriants that, in high doses, cause sedation and respiratory depression. Respiratory depression can be managed with specific antidotes (eg, naloxone) or with endotracheal intubation and mechanical ventilation. Withdrawal manifests initially as anxiety and drug craving, followed by increased respiratory rate, diaphoresis, yawning, lacrimation, rhinorrhea, mydriasis, and stomach cramps and later by piloerection, tremors, muscle twitches, tachycardia, hypertension, fever, chills, anorexia, nausea, vomiting, and diarrhea. Diagnosis is clinical plus with urine tests. Withdrawal can be treated by substitution with a long-acting opioid (eg, methadone) or buprenorphine (a mixed opioid agonist-antagonist).

"Opioid" is a term for a number of natural substances (originally derived from the opium poppy) and their semisynthetic and synthetic analogues that bind to specific opioid receptors. Opioids, which are potent analgesics with a limited role in management of cough and diarrhea, are also common drugs of abuse because of their wide availability and euphoriant properties (see also p. 1623).

Pathophysiology

There are 3 main opioid receptors: delta, kappa, and mu. They occur throughout the CNS but particularly in areas and tracts associated with pain perception. Receptors are also located in some sensory nerves, on mast cells, and in some cells of the GI tract.

Opioid receptors are stimulated by endogenous endorphins, which generally produce analgesia and a sense of well-being. Opioids are used therapeutically primarily as analgesics. Opioids vary in their receptor activity, and some (eg, buprenorphine) have combined agonist and antagonist actions. Compounds with pure antagonist activity (eg, naloxone, naltrexone) are available.

Exogenous opioids can be taken by almost any route: orally, intravenously, subcutaneously, rectally,
through the nasal membranes, or inhaled as smoke. Peak effects are reached about 10 min after IV injection, 10 to 15 min after nasal insufflation, and 90 to 120 min after oral ingestion, although time to peak effects and duration of effect vary considerably depending on the specific drug.

**Chronic effects:** Tolerance develops quickly, with escalating dose requirements. Tolerance to the various effects of opioids frequently develops unevenly. Heroin users, for example, may become relatively tolerant to the drug's euphoric and respiratory depression effects but continue to have constricted pupils and constipation.

A minor withdrawal syndrome may occur after only several days' use. Severity of the syndrome increases with the size of the opioid dose and the duration of dependence.

Long-term effects of the opioids themselves are minimal; even decades of methadone use appear to be well tolerated physiologically, although some long-term opioid users experience chronic constipation, excessive sweating, peripheral edema, drowsiness, and decreased libido. However, many long-term users who inject opioids have adverse effects from contaminants (eg, talc) and adulterants (eg, nonprescription stimulant drugs) and cardiac, pulmonary, and hepatic damage due to infections such as HIV infection and hepatitis B or C, which are spread by needle sharing and nonsterile injection techniques (see p. 1509).

**Pregnancy:** Use of opioids during pregnancy can result in physical dependence in the fetus (see p. 2800).

**Symptoms and Signs**

**Acute effects:** Acute intoxication is characterized by euphoria and drowsiness. Mast cell effects (eg, flushing, itching) are common, particularly with morphine. GI effects include nausea, vomiting, decreased bowel sounds, and constipation.

**Toxicity or overdose:** The main toxic effect is decreased respiratory rate and depth, which can progress to apnea. Other complications (eg, pulmonary edema, which usually develops within minutes to a few hours after opioid overdose) and death result primarily from hypoxia. Pupils are miotic. Delirium, hypotension, bradycardia, decreased body temperature, and urinary retention may also occur.

Normeperidine, a metabolite of meperidine, accumulates with repeated use (including therapeutic); it stimulates the CNS and may cause seizure activity.

**Serotonin syndrome** (see p. 3269) occasionally occurs when fentanyl, meperidine, or oxycodone is taken concomitantly with other drugs that have serotonergic effects (eg, SSRIs, monoamine oxidase inhibitors). This syndrome consists of one or more of the following:

- Hypertonia
- Tremor and hyperreflexia
- Spontaneous clonus
- Inducible clonus plus agitation or diaphoresis
- Ocular clonus plus agitation or diaphoresis
- Temperature > 38° plus ocular or inducible clonus

**Withdrawal:** The withdrawal syndrome usually includes symptoms and signs of CNS hyperactivity. Onset and duration of the syndrome depend on the specific drug and its half-life. Symptoms may appear as early as 4 h after the last dose of heroin, peak within 48 to 72 h, and subside after about a week. Anxiety and a craving for the drug are followed by increased resting respiratory rate (> 16 breaths/min), usually with diaphoresis, yawning, lacrimation, rhinorrea, mydriasis, and stomach cramps. Later, piloerection
(gooseflesh), tremors, muscle twitching, tachycardia, hypertension, fever and chills, anorexia, nausea, vomiting, and diarrhea may develop. Opioid withdrawal does not cause fever, seizures, or altered mental status. Although it may be distressingly symptomatic, opioid withdrawal is not fatal.

The withdrawal syndrome in people who were taking methadone (which has a long half-life) develops more slowly and may be less acutely severe than heroin withdrawal, although users may describe it as worse. Even after the withdrawal syndrome remits, lethargy, malaise, anxiety, and disturbed sleep may persist up to several months. Drug craving may persist for years.

Diagnosis

Diagnosis is usually made clinically and sometimes with urine drug testing (see p. 1510); laboratory tests are done as needed to identify drug-related complications. Drug levels are not measured.

Treatment

- Supportive therapy
- For withdrawal, sometimes drug therapy (eg, with an opioid agonist, opioid agonist-antagonist, opioid antagonist, or clonidine)

Toxicity or overdose: Treatment to maintain the airway and support breathing is the first priority.

- Naloxone 0.4 mg IV
- Sometimes endotracheal intubation

Patients with spontaneous respirations can be treated with an opioid antagonist, typically naloxone 0.4 mg IV (for children < 20 kg, 0.1 mg/kg); naloxone has no agonist activity and a very short half-life (see Table 340-8 on p. 3345). Naloxone rapidly reverses unconsciousness and apnea due to an opioid in most patients. If IV access is not immediately available, IM or sc administration is also effective. A 2nd or 3rd dose can be given if there is no response within 2 min. Almost all patients respond to three 0.4-mg doses. If they do not, the patient's condition is unlikely to be due to an opioid overdose, although massive opioid overdose may require higher doses of naloxone. Because some patients become agitated, delirious, and combative as consciousness returns and because naloxone precipitates acute withdrawal, soft physical restraints should be applied before naloxone is given. To ameliorate withdrawal in long-term users, some experts suggest titrating very small doses of naloxone (0.1 mg) when the clinical situation does not require emergency total reversal.

Apneic patients require endotracheal intubation. These patients should probably not receive total naloxone reversal because they may become agitated and belligerent when they suddenly regain consciousness.

In general, patients treated for overdose should be hospitalized and observed for at least 24 h because the duration of action of naloxone is less than that of some opioids, and overdose symptoms can redevelop. Respiratory depression may recur within several hours, especially with methadone or sustained-released oxycodone or morphine tablets. If respiratory depression recurs, naloxone should be readministered at an appropriate dose. Continuous naloxone infusion may be helpful for recurrent respiratory depression; two thirds of the dose that relieved respiratory depression is given hourly. Patients should be observed until no naloxone pharmacologic activity is present and they have no opioid-related symptoms. The serum half-life of naloxone is about 1 h, so an observation period of 2 to 3 h after use of naloxone should clarify disposition. The half-life of IV heroin is relatively short, and recurrent respiratory depression after naloxone reversal of IV heroin is rare.

Acute pulmonary edema is treated with supplemental O₂ and often noninvasive or invasive modalities of breathing support (eg, bilevel positive airway pressure [BiPAP], endotracheal intubation).

Withdrawal and detoxification: Treatment may involve several strategies:
• No treatment ("cold turkey")
• Substitution with methadone or buprenorphine
• Clonidine to relieve symptoms
• Long-term support and possibly naltrexone

The withdrawal syndrome is self-limited and, although severely uncomfortable, is not life threatening. Minor metabolic and physical withdrawal effects may persist up to 6 mo. Withdrawal is typically managed in outpatient settings, unless patients require hospitalization for concurrent medical or mental health problems.

Options for management of withdrawal include allowing the process to run its course ("cold turkey") after the patient's last opioid dose and giving another opioid (substitution) that can be tapered on a controlled schedule. Clonidine can provide some symptom relief during withdrawal.

**Methadone substitution** is the preferred method of managing opioid withdrawal for more seriously addicted patients because at appropriate doses, it has a long half-life and less profound sedation and euphoria. Any physician can initiate methadone substitution during hospitalization or for 3 days in an outpatient setting, but further treatment is continued in a licensed methadone treatment program. Methadone is given orally in the smallest amount that prevents severe but not necessarily all symptoms of withdrawal. Typical dose range is 15 to 30 mg once/day; doses ≥ 25 mg can result in dangerous levels of sedation in patients who have not developed tolerance. Symptom scales are available for estimating the appropriate dose. Higher doses should be given when evidence of withdrawal is observed. After the appropriate dose has been established, it should be reduced progressively by 10 to 20%/day unless the decision is made to continue the drug at a stable dose (methadone maintenance—see p. 1515). During tapering of the drug, patients commonly become anxious and request more of the drug. Methadone withdrawal for addicts who have been in a methadone maintenance program may be particularly difficult because their dose of methadone may be as high as 100 mg once/day; in these patients, the dose should be gradually reduced to 60 mg once/day over several weeks before attempting complete detoxification.

**Buprenorphine**, a mixed opioid agonist-antagonist usually given sublingually, also has been successfully used in withdrawal. It is available in a combination formulation with naloxone to prevent diversion to IV use. The first dose is given when the first signs of withdrawal appear. The dose needed to effectively control severe symptoms is titrated as quickly as possible; sublingual doses of 8 to 16 mg/day are typically used. Buprenorphine is then tapered over several weeks. Protocols for using buprenorphine for detoxification or maintenance therapy are available at the US Department of Health and Human Services web site.

**Clonidine**, a centrally acting adrenergic drug, can suppress symptoms and signs of opioid withdrawal. Starting dosages are 0.1 mg po q 4 to 6 h and may be increased to 0.2 mg po q 4 to 6 h as tolerated. Clonidine can cause hypotension and drowsiness, and its withdrawal may precipitate restlessness, insomnia, irritability, tachycardia, and headache.

**Rapid and ultrarapid protocols** have been evaluated for managing withdrawal and detoxification. In rapid protocols, combinations of naloxone, nalmefene, and naltrexone are used to induce withdrawal, and clonidine and various adjuvant drugs are used to suppress withdrawal symptoms. Some rapid protocols use buprenorphine to suppress opioid withdrawal symptoms. Ultrarapid protocols may use large boluses of naloxone and diuretics to enhance excretion of the opioids while patients are under general anesthesia; these ultrarapid protocols are not recommended because they have a high risk of complications and no substantial additional benefit.

Clinicians must understand that detoxification is not treatment per se. It is only the first step and must be followed by an ongoing treatment program, which may involve various kinds of counseling and possibly nonopioid antagonists (eg, naltrexone).
Opioid Abuse and Rehabilitation

Heroin is commonly abused, and abuse of prescription analgesic opioids (eg, morphine, oxycodone, hydrocodone, fentanyl) is increasing; some of the increase is due to people who began taking them for legitimate medical purposes. Patients with chronic pain requiring long-term use should not be routinely labeled addicts, although they commonly have tolerance and physical dependence.

Treatment

• For severe, relapsing dependence, maintenance preferred to opioid withdrawal
• For maintenance, buprenorphine or methadone
• Ongoing counseling and support

Physicians must be fully aware of federal, state, and local regulations concerning use of an opioid drug to treat an addict. To comply, physicians must establish the existence of physical opioid dependence. In the US, treatment is further complicated by negative societal attitudes toward addicts (including the attitudes of law enforcement officers, physicians, and other health care practitioners) and toward treatment programs, which some view as abetting drug consumption. In most cases, physicians should refer opioid-dependent patients to specialized treatment centers. If trained to do so, physicians may provide office-based treatment for selected patients. In European countries, access to methadone or buprenorphine maintenance programs and alternative maintenance strategies is easier, and the stigma attached to prescribing psychoactive drugs is less.

Maintenance: Long-term maintenance using an oral opioid such as methadone or buprenorphine (an opioid agonist-antagonist) is an alternative to opioid substitution with tapering. Oral opioids suppress withdrawal symptoms and drug craving without providing a significant high or oversedation and, by eliminating the supply problems of addicts, enable them to be socially productive. In the US, thousands of opioid addicts are in licensed methadone maintenance programs. For many, such programs work. However, because the participants continue to take an opioid, many people in society disapprove of these programs.

Eligibility criteria include the following:

• A positive drug screen for opioids
• Physical dependence for > 1 yr of continuous opioid use or intermittent use for even longer
• Evidence of withdrawal or physical findings confirming drug use

Clinicians and patients need to decide whether a withdrawal (detoxification) or opioid maintenance approach is indicated. Generally, patients with severe, chronic, relapsing dependence do much better with opioid maintenance. Withdrawal and detoxification, although effective in the short term, have poor outcomes in patients with severe opioid dependence. Whichever course is chosen, it must be accompanied by ongoing counseling and supportive measures.

Methadone is commonly used. Physicians can begin the substitution, but then use of methadone must be supervised in a licensed methadone treatment program.

Buprenorphine is being used increasingly for maintenance. Its effectiveness is comparable to that of methadone, and because it blocks receptors, it inhibits concomitant illicit use of heroin or other opioids. Buprenorphine can be prescribed for office-based treatment by specially trained physicians, including primary care physicians, who have received the required training and have been certified by the federal government. The typical dosage is an 8- or 16-mg sublingual tablet once/day. Many patients prefer this option because it eliminates the need for attending a methadone clinic. Buprenorphine is also available in combination with naloxone; the addition of naloxone may further discourage illicit opioid use. The combination formulation is used in office-based treatment.
Naltrexone, an opioid antagonist, blocks the effects of heroin. The usual dosage is 50 mg po once/day or 350 mg/wk po in 2 or 3 divided doses. A once-monthly depot IM formulation is also available. Because naltrexone is an opioid antagonist and has no direct agonist effects on opioid receptors, naltrexone is often unacceptable to opioid-dependent patients, especially those who have chronic, relapsing opioid dependence. For such patients, opioid maintenance treatment is much more effective. Naltrexone may be useful for patients with less severe dependence, early-stage opioid dependence, and strong motivation to remain abstinent. For example, opioid-dependent health care practitioners whose future employment is at risk if opioid use persists may be excellent candidates for naltrexone.

Levomethadyl acetate (LAAM), a longer-acting opioid related to methadone, is no longer used because it causes QT-interval abnormalities in some patients. LAAM could be used only 3 times/wk, thereby reducing the expense and problems of daily client visits or take-home drugs. A dose of 100 mg 3 times/wk is comparable to methadone 80 mg once/day.

**Support:** Most treatment of opioid dependence occurs in outpatient settings, typically in licensed opioid maintenance programs but increasingly in physician's offices.

The therapeutic community concept, pioneered by Daytop Village and Phoenix House, involves nondrug treatment in communal residential centers, where drug users receive training, education, and redirection to help them build new lives. Residency is usually 15 mo. These communities have helped, even transformed, some users. However, initial dropout rates are extremely high. Questions of how well these communities work, how many will be opened, and how much funding society will give remain unanswered.

**Alcohol**

Alcohol (ethanol) is a CNS depressant. Large amounts consumed rapidly can cause respiratory depression, coma, and death. Large amounts chronically consumed damage the liver and many other organs. Alcohol withdrawal manifests as a continuum, ranging from tremor to seizures, hallucinations, and life-threatening autonomic instability in severe withdrawal (delirium tremens). Diagnosis is clinical.

About 45 to 50% of adults are current drinkers, 20% are former drinkers, and 30 to 35% are lifetime abstainers. For most drinkers, the frequency and amount of alcohol consumption does not impair physical or mental health or the ability to safely carry out daily activities. However, acute alcohol intoxication is a significant factor in injuries, particularly those due to interpersonal violence, suicide, and motor vehicle crashes. Chronic abuse interferes with the ability to socialize and work. About 7 to 10% of adults meet criteria for an alcohol use disorder (abuse or dependence) in any given year. Binge drinking, defined as consuming ≥ 5 drinks per occasion for men and ≥ 4 drinks per occasion for women, is a particular problem among younger people.

**Pathophysiology**

One serving of alcohol (one 12-oz can of beer, one 6-oz glass of wine, or 1.5 oz of distilled liquor) contains 10 to 15 g of ethanol. Alcohol is absorbed into the blood mainly from the small bowel, although some is absorbed from the stomach. Alcohol accumulates in blood because absorption is more rapid than oxidation and elimination. The concentration peaks about 30 to 90 min after ingestion if the stomach was previously empty. About 5 to 10% of ingested alcohol is excreted unchanged in urine, sweat, and expired air; the remainder is metabolized mainly by the liver, where alcohol dehydrogenase converts ethanol to acetaldehyde. Acetaldehyde is ultimately oxidized to CO₂ and water at a rate of 5 to 10 mL/h (of absolute alcohol); each milliliter yields about 7 kcal. Alcohol dehydrogenase in the gastric mucosa accounts for some metabolism; much less gastric metabolism occurs in women.

Alcohol exerts its effects by several mechanisms. Alcohol binds directly to γ-aminobutyric acid (GABA) receptors in the CNS, causing sedation. Alcohol also directly affects cardiac, hepatic, and thyroid tissue.

**Chronic effects:** Tolerance to alcohol develops rapidly; similar amounts cause less intoxication.
Tolerance is caused by adaptational changes of CNS cells (cellular, or pharmacodynamic, tolerance) and by induction of metabolic enzymes. People who develop tolerance may reach an incredibly high blood alcohol content (BAC). However, ethanol tolerance is incomplete, and considerable intoxication and impairment occur with a large enough amount. But even these drinkers may die of respiratory depression secondary to alcohol overdose. Alcohol-tolerant people are susceptible to alcoholic ketoacidosis (see p. 886), especially during binge drinking. Alcohol-tolerant people are cross-tolerant of many other CNS depressants (eg, barbiturates, nonbarbiturate sedatives, benzodiazepines).

The physical dependence accompanying tolerance is profound, and withdrawal has potentially fatal adverse effects.

Chronic heavy alcohol intake typically leads to liver disorders (eg, fatty liver, alcoholic hepatitis, cirrhosis); the amount and duration required vary (see p. 235). Patients with a severe liver disorder often have coagulopathy due to decreased hepatic synthesis of coagulation factors, increasing the risk of significant bleeding due to trauma (eg, from falls or vehicle crashes) and of GI bleeding (eg, due to gastritis, from esophageal varices due to portal hypertension); alcohol abusers are at particular risk of GI bleeding.

Chronic heavy intake also commonly causes the following:

- Gastritis
- Pancreatitis
- Cardiomyopathy, often accompanied by arrhythmias and hypertension
- Peripheral neuropathy
- Brain damage, including Wernicke's encephalopathy, Korsakoff's psychosis, Marchiafava-Bignami disease, and alcoholic dementia
- Certain cancers (eg, head and neck, esophageal), especially when drinking is combined with smoking

Indirect long-term effects include undernutrition, particularly vitamin deficiencies.

On the other hand, low to moderate levels of alcohol consumption (≤ 1 to 2 drinks/day) may decrease the risk of death due to cardiovascular disorders. Numerous explanations, including increased high density lipoprotein (HDL) levels and a direct antithrombotic effect, have been suggested. Nonetheless, alcohol should not be recommended for this purpose, especially when there are several safer, more effective approaches to reduce cardiovascular risk.

Special populations: Young children who drink alcohol are at significant risk of hypoglycemia because alcohol impairs gluconeogenesis and their smaller stores of glycogen are rapidly depleted. Women may be more sensitive than men, even on a per-weight basis, because their gastric (first-pass) metabolism of alcohol is less. Drinking during pregnancy increases the risk of fetal alcohol syndrome (see p. 2799).

Symptoms and Signs

Acute effects: Symptoms progress proportionately to the BAC. Actual levels required to cause given symptoms vary with tolerance, but in typical users

- 20 to 50 mg/dL: Tranquility, mild sedation, and some decrease in fine motor coordination
- 50 to 100 mg/dL: Impaired judgment and a further decrease in coordination
- 100 to 150 mg/dL: Unsteady gait, nystagmus, slurred speech, loss of behavioral inhibitions, and memory impairment
- 150 to 300 mg/dL: Delirium and lethargy (likely)
Emesis is common with moderate to severe intoxication; because emesis usually occurs with obtundation, aspiration is a significant risk.

In most US states, the legal definition of intoxication is a BAC of ≥ 0.08 to 0.10% (≥ 80 to 100 mg/dL); 0.08 is used most commonly.

**Toxicity or overdose:** In alcohol-naive people, a BAC of 300 to 400 mg/dL often causes unconsciousness, and a BAC ≥ 400 mg/dL may be fatal. Sudden death due to respiratory depression or arrhythmias may occur, especially when large quantities are drunk rapidly. This problem is emerging in US colleges but has been known in other countries where it is more common. Other common effects include hypotension and hypoglycemia.

The effect of a particular BAC varies widely; some chronic drinkers seem unaffected and appear to function normally with a BAC in the 300 to 400 mg/dL range, whereas non-drinkers and social drinkers are impaired at a BAC that is inconsequential in chronic drinkers.

**Chronic effects:** Stigmata of chronic use include Dupuytren's contracture of the palmar fascia, vascular spiders, and, in men, signs of hypogonadism and feminization (eg, smooth skin, lack of male-pattern baldness, gynecomastia, testicular atrophy). Undernutrition may lead to enlarged parotid glands.

**Withdrawal:** A continuum of symptoms and signs of CNS (including autonomic) hyperactivity may accompany cessation of alcohol intake.

A mild withdrawal syndrome includes tremor, weakness, headache, sweating, hyperreflexia, and GI symptoms. Symptoms usually begin within about 6 h of cessation. Some patients have generalized tonic-clonic seizures (called alcoholic epilepsy, or rum fits) but usually not > 2 in short succession.

Alcoholic hallucinosis (hallucinations without other impairment of consciousness) follows abrupt cessation from prolonged, excessive alcohol use, usually within 12 to 24 h. Hallucinations are typically visual. Symptoms may also include auditory illusions and hallucinations that frequently are accusatory and threatening; patients are usually apprehensive and may be terrified by the hallucinations and by vivid, frightening dreams. The syndrome may resemble schizophrenia, although thought is usually not disordered and the history is not typical of schizophrenia. Symptoms do not resemble the delirious state of an acute organic brain syndrome as much as does delirium tremens (DT) or other pathologic reactions associated with withdrawal. Consciousness remains clear, and the signs of autonomic lability that occur in DT are usually absent. When hallucinosis occurs, it usually precedes DT and is transient.

DT usually begins 48 to 72 h after alcohol withdrawal; anxiety attacks, increasing confusion, poor sleep (with frightening dreams or nocturnal illusions), profuse sweating, and severe depression also occur. Fleeting hallucinations that arouse restlessness, fear, and even terror are common. Typical of the initial delirious, confused, and disoriented state is a return to a habitual activity; eg, patients frequently imagine that they are back at work and attempt to do some related activity. Autonomic lability, evidenced by diaphoresis and increased pulse rate and temperature, accompanies the delirium and progresses with it. Mild delirium is usually accompanied by marked diaphoresis, a pulse rate of 100 to 120 beats/min, and a temperature of 37.2 to 37.8°C. Marked delirium, with gross disorientation and cognitive disruption, is accompanied by significant restlessness, a pulse of > 120 beats/min, and a temperature of > 37.8°C; risk of death is high.

During DT, patients are suggestible to many sensory stimuli, particularly to objects seen in dim light. Vestibular disturbances may cause them to believe that the floor is moving, the walls are falling, or the room is rotating. As the delirium progresses, resting tremor of the hand develops, sometimes extending to the head and trunk. Ataxia is marked; care must be taken to prevent self-injury. Symptoms vary among patients but are usually the same for a particular patient with each recurrence.

**Diagnosis**

- Usually clinical
• Acute: BAC, evaluation to rule out hypoglycemia and occult trauma

• Chronic: CBC, Mg, liver function tests, and PT/PTT

• Withdrawal: Evaluation to rule out CNS injury and infection

In acute intoxication, laboratory tests, except for fingerstick glucose to rule out hypoglycemia and tests to determine BAC, are generally not helpful; diagnosis is usually made clinically. Confirmation by breath or blood alcohol levels is useful for legal purposes (eg, to document intoxication in drivers or employees who appear impaired). However, finding a low BAC in patients who have altered mental status and smell of alcohol is helpful because it expedites the search for an alternate cause. Clinicians should not assume that a high BAC in patients with apparently minor trauma accounts for their obtundation, which may be due to intracranial injury or other abnormalities. Such patients should also have toxicology tests to search for evidence of toxicity due to other substances.

Chronic alcohol abuse and dependence are clinical diagnoses; experimental markers of long-term use have not proved sufficiently sensitive or specific for general use. However, heavy alcohol users may have a number of metabolic derangements that are worth screening for, so CBC, electrolytes (including Mg), liver function tests including coagulation profile (PT/PTT), and serum albumin are often recommended.

In severe withdrawal and toxicity, symptoms may resemble those of CNS injury or infection, so medical evaluation with CT and lumbar puncture may be needed. Patients with mild symptoms do not require routine testing unless improvement is not marked within 2 to 3 days.

**Treatment**

• Supportive measures

• For withdrawal, benzodiazepines

**Toxicity or overdose:** Treatment may include the following:

• Airway protection

• Sometimes IV fluids with thiamin, Mg, and vitamins

The first priority is ensuring an adequate airway; endotracheal intubation and mechanical ventilation are required for apnea or inadequate respirations. IV hydration is needed for hypotension or evidence of volume depletion but does not significantly enhance ethanol clearance. When IV fluids are used, a single dose of thiamin 100 mg IV is given to treat or prevent Wernicke's encephalopathy. Many clinicians also add multivitamins and Mg to the IV fluids.

Disposition of the acutely intoxicated patient depends on clinical response, not a specific BAC.

**Withdrawal:** Patients with severe withdrawal or DT should be managed in an ICU until these symptoms abate. Treatment may include the following to prevent Wernicke-Korsakoff syndrome and other complications:

• IV thiamin

• Benzodiazepines

Thiamin 100 mg IV is given to prevent Wernicke-Korsakoff syndrome.

Alcohol-tolerant people are cross-tolerant of some drugs commonly used to treat withdrawal (eg, benzodiazepines).
Benzodiazepines are the mainstay of therapy. Dosage and route depend on degree of agitation, vital signs, and mental status. Diazepam, given 5 to 10 mg IV or po hourly until sedation occurs, is a common initial intervention; lorazepam 1 to 2 mg IV or po is an alternative. Chlordiazepoxide 50 to 100 mg po q 4 to 6 h, then tapered, is an older acceptable alternative for less severe cases of withdrawal. Phenobarbital may help if benzodiazepines are ineffective, but respiratory depression is a risk with concomitant use. Phenothiazines and haloperidol are not recommended initially because they may lower the seizure threshold. For patients with a significant liver disorder, a short-acting benzodiazepine (lorazepam) or one metabolized by glucuronidation (oxazepam) is preferred. (NOTE: Benzodiazepines may cause intoxication, physical dependence, and withdrawal in alcoholics and therefore should not be continued after the detoxification period. Carbamazepine 200 mg po qid may be used as an alternative and then tapered.) For severe hyperadrenergic activity or to reduce benzodiazepine requirements, short-term therapy (12 to 48 h) with titrated β-blockers (eg, metoprolol 25 to 50 mg po or 5 mg IV q 4 to 6 h) and clonidine 0.1 to 0.2 mg IV q 2 to 4 h can be used.

A seizure, if brief and isolated, needs no specific therapy; however, some clinicians routinely give a single dose of lorazepam 1 to 2 mg IV as prophylaxis against another seizure. Repeated or longer-lasting (ie, > 2 to 3 min) seizures should be treated and often respond to lorazepam 1 to 3 mg IV. Routine use of phenytoin is unnecessary and unlikely to be effective. Outpatient therapy with phenytoin is rarely indicated for patients with simple alcohol withdrawal seizures when no other source of seizure activity has been identified because seizures occur only under the stress of alcohol withdrawal, and patients who are withdrawing or heavily drinking may not take the anticonvulsant.

DT may be fatal and thus must be treated promptly with high-dose IV benzodiazepines, preferably in an ICU. Dosing is higher and more frequent than in mild withdrawal. Very high doses of benzodiazepines may be required, and there is no maximum dose or specific treatment regimen. Diazepam 5 to 10 mg IV or lorazepam 1 to 2 mg IV q 10 min is given as needed to control delirium; some patients require several hundred milligrams over the first few hours. Patients refractory to high-dose benzodiazepines may respond to phenobarbital 120 to 240 mg IV q 20 min as needed. Severe drug-resistant DT can be treated with a continuous infusion of lorazepam, diazepam, midazolam, or propofol, usually with concomitant mechanical ventilation. Physical restraints should be avoided if possible to minimize additional agitation, but patients must not be allowed to elope, remove IVs, or otherwise endanger themselves. Intravascular volume must be maintained with IV fluids, and large doses of vitamins B and C, particularly thiamin, must be given promptly. Appreciably elevated temperature with DT is a poor prognostic sign.

Alcohol Problems and Rehabilitation

Definitions

At-risk drinking is defined solely by quantity and frequency of drinking:

• > 14 drinks/wk or 4 drinks per occasion for men

• > 7 drinks/wk or 3 drinks per occasion for women

Compared with lesser amounts, these amounts are associated with increased risk of a wide variety of medical and psychosocial complications.

Alcohol abuse refers to a maladaptive pattern of episodic drinking that results in failure to fulfill obligations, drinking in physically hazardous situations (eg, driving, boating), legal problems, or social and interpersonal problems without evidence of dependence.

Alcohol dependence refers to frequent consumption of large amounts of alcohol with ≥ 3 of the following:

• Tolerance

• Withdrawal symptoms
• Drinking larger amounts than intended

• Persistent desire to reduce use without success

• Substantial time spent obtaining, drinking, or recovering from alcohol

• Sacrifice of other life events for drinking

• Continued use despite physical or psychologic problems

Alcoholism is often used as an equivalent term for alcohol dependence, especially when drinking results in significant toxicity and tissue damage.

**Etiology**

The maladaptive pattern of drinking that constitutes alcohol abuse may begin with a desire to reach a state of feeling high. Some drinkers who find the feeling rewarding then focus on repeatedly reaching that state. Many who abuse alcohol chronically have certain personality traits: feelings of isolation, loneliness, shyness, depression, dependency, hostile and self-destructive impulsivity, and sexual immaturity. Alcoholics may come from a broken home and have a disturbed relationship with their family. Societal factors—attitudes transmitted through the culture or child rearing—affect patterns of drinking and consequent behavior. However, such generalizations should not obscure the fact that alcohol use disorders can occur in anyone, regardless of their age, sex, background, ethnicity, or social situation. Thus, clinicians should screen for alcohol problems in all patients.

The incidence of alcohol abuse and dependence is higher in biologic children of people with alcohol problems than in adoptive children, and the percentage of biologic children of alcoholics who are problem drinkers is greater than that of the general population. There is evidence of genetic or biochemical predisposition, including data that suggest some people who become alcoholics are less easily intoxicated; ie, they have a higher threshold for CNS effects.

**Symptoms and Signs**

Serious social consequences usually occur. Frequent intoxication is obvious and destructive; it interferes with the ability to socialize and work. Injuries are common. Eventually, failed relationships and job loss due to absenteeism may result. People may be arrested because of alcohol-related behavior or be apprehended for driving while intoxicated, often losing driving privileges for repeated offenses; in most US states, the maximum legal blood alcohol concentration (BAC) while driving is 80 mg/dL (0.08%), and this level is likely to be reduced in the future.

**Diagnosis**

• Clinical evaluation

• Screening

Some alcohol-related problems are diagnosed when people seek medical treatment for their drinking or for obvious alcohol-related illness (eg, delirium tremens, cirrhosis). However, many of these people remain unrecognized for a long time. Female alcoholics are, in general, more likely to drink alone and are less likely to manifest some of the social signs. Therefore, many governmental and professional organizations recommend alcohol screening during routine health care visits. A scaled approach (see [Table 160-2](#)) can help identify patients who require more detailed questioning; several validated detailed questionnaires are available.
Treatment

- Rehabilitation programs
- Outpatient counseling
- Self-help groups
- Consideration of drugs (eg, naltrexone, disulfiram)

All patients should be counseled to decrease their alcohol use to below at-risk levels.

For patients identified as at-risk drinkers, treatment may begin with a brief discussion of the medical and social consequences and a recommendation to reduce or cease drinking, with follow-up regarding compliance (see Table 160-3).

For patients with more serious problems, particularly after less intensive measures have been unsuccessful, a rehabilitation program is often the best approach. Rehabilitation programs combine psychotherapy, including one-on-one and group therapy, with medical supervision. For most patients, outpatient rehabilitation is sufficient; how long patients remain enrolled in programs varies, typically weeks to months, but longer if needed. Inpatient rehabilitation programs are reserved for patients with more severe alcohol dependence and those with significant and comorbid medical, psychoactive, and substance abuse problems. Treatment duration is usually briefer (typically days to weeks) than that of outpatient programs and may be dictated in part by patients’ insurance.

Psychotherapy involves techniques that enhance motivation and teach patients to avoid circumstances that precipitate drinking. Social support of abstinence, including the support of family and friends, is important.

Maintenance: Maintaining sobriety is difficult. Patients should be warned that after a few weeks, when they have recovered from their last bout, they are likely to find an excuse to drink. They should also be told that although they may be able to practice controlled drinking for a few days or, rarely, a few weeks, they will most likely lose control eventually.

In addition to the counseling provided in outpatient and inpatient alcohol treatment programs, self-help groups and certain drugs may help prevent relapse in some patients.

Alcoholics Anonymous (AA) is the most common self-help group. Patients must find an AA group they feel comfortable in. AA provides patients with nondrinking friends who are always available and a nondrinking environment in which to socialize. Patients also hear others discuss every rationalization they have ever used for their own drinking. The help they give other alcoholics may give them the self-regard and confidence formerly found only in alcohol. Many alcoholics are reluctant to go to AA and find individual counseling or group or family treatment more acceptable. Alternative organizations, such as LifeRing Recovery (Secular Organizations for Sobriety), exist for patients seeking another approach.

Drug therapy should be used with counseling rather than as sole treatment.

Disulfiram, the first drug available to prevent relapse in alcohol dependence, interferes with the metabolism of acetaldehyde (an intermediary product in the oxidation of alcohol) so that acetaldehyde accumulates. Drinking alcohol within 12 h of taking disulfiram causes

[Table 160-3, Brief Interventions for Alcohol Problems]

facial flushing in 5 to 15 min, then intense vasodilation of the face and neck with suffusion of the conjunctivae, throbbing headache, tachycardia, hyperpnea, and sweating. With high doses of alcohol, nausea and vomiting may follow in 30 to 60 min and may lead to hypotension, dizziness, and sometimes fainting and collapse. The reaction can last up to 3 h. Few patients risk drinking alcohol while taking
disulfiram because of the intense discomfort. Drugs that contain alcohol (eg, tinctures; elixirs; some OTC liquid cough and cold preparations, which contain as much as 40% alcohol) must also be avoided. Disulfiram is contraindicated during pregnancy and in patients with cardiac decompensation. It may be given on an outpatient basis after 4 or 5 days of abstinence. The initial dosage is 0.5 g po once/day for 1 to 3 wk, followed by a maintenance dosage of 0.25 g once/day. Effects may persist for 3 to 7 days after the last dose. Periodic physician visits are needed to encourage continuation of disulfiram as part of an abstinence program. Disulfiram's general usefulness has not been established, and many patients are nonadherent. Adherence usually requires adequate social support, such as observation of drinking. For these reasons, use of disulfiram is now limited. Disulfiram is most effective when given under close supervision to highly motivated patients.

Naltrexone, an opioid antagonist (see p. 1515), decreases the relapse rate and number of drinking days in most patients who take it consistently. Naltrexone 50 mg po once/day is typically given, although there is evidence that higher doses (eg, 100 mg once/day) may be more effective in some patients. Even with counseling, adherence rates with oral naltrexone are modest. A long-acting depot form is also available: 380 mg IM once/mo. Naltrexone is contraindicated in patients with acute hepatitis or liver failure and in those who are opioid dependent.

Acamprosate, a synthetic analogue of γ-aminobutyric acid, is given as 2 g po once/day. Acamprosate may decrease the relapse rate and number of drinking days in patients who relapse.

Nalmefene, an opioid antagonist, and topiramate are under study for their ability to decrease alcohol craving.

Wernicke's Encephalopathy

Wernicke's encephalopathy is characterized by acute onset of confusion, nystagmus, partial ophthalmoplegia, and ataxia due to thiamin deficiency. Diagnosis is primarily clinical. The disorder may remit with treatment, persist, or degenerate into Korsakoff's psychosis. Treatment consists of thiamin and supportive measures.

Wernicke's encephalopathy results from inadequate intake or absorption of thiamin plus continued carbohydrate ingestion. Severe alcoholism is a common underlying condition. Excessive alcohol intake interferes with thiamin absorption from the GI tract and hepatic storage of thiamin; the poor nutrition associated with alcoholism often precludes adequate thiamin intake. Wernicke's encephalopathy may also result from other conditions that cause prolonged undernutrition or vitamin deficiency (eg, recurrent dialysis, hyperemesis, starvation, gastric plication, cancer, AIDS). Loading carbohydrates in patients with thiamin deficiency (ie, refeeding after starvation or giving IV dextrose-containing solutions to high-risk patients) can trigger Wernicke's encephalopathy.

Not all thiamin-deficient alcohol abusers develop Wernicke's encephalopathy, suggesting that other factors may be involved. Genetic abnormalities that result in a defective form of transketolase, an enzyme that processes thiamin, may be involved.

Characteristically, CNS lesions are symmetrically distributed around the 3rd ventricle, aqueduct, and 4th ventricle. Changes in the mamillary bodies, dorsomedial thalamus, locus ceruleus, periaqueductal gray matter, ocular motor nuclei, and vestibular nuclei are common.

Symptoms and Signs

Clinical changes occur suddenly. Oculomotor abnormalities, including horizontal and vertical nystagmus and partial ophthalmoplegias (eg, lateral rectus palsy, conjugate gaze palsies), are common. Pupils may be abnormal; they are usually sluggish or unequal.

Vestibular dysfunction without hearing loss is common, and the oculovestibular reflex may be impaired. Gait ataxia may result from vestibular disturbances and cerebellar dysfunction; gait is wide-based and slow, with short-spaced steps.
Global confusion is often present; it is characterized by profound disorientation, indifference, inattention, drowsiness, or stupor. Peripheral nerve pain thresholds are often elevated, and many patients develop severe autonomic dysfunction characterized by sympathetic hyperactivity (eg, tremor, agitation) or hypoactivity (eg, hypothermia, postural hypotension, syncope). In untreated patients, stupor may progress to coma, then to death.

**Diagnosis**

- Clinical evaluation

Diagnosis is clinical and depends on recognition of underlying undernutrition or vitamin deficiency. There are no characteristic abnormalities in CSF, evoked potentials, brain imaging, or EEG. However, these tests, as well as laboratory tests (eg, blood tests, glucose, CBC, liver function tests, ABG measurements, toxicology screening), should be done to rule out other etiologies. Thiamin levels are not routinely measured.

**Prognosis**

Prognosis depends on timely diagnosis. If begun in time, treatment may correct all abnormalities. Ocular symptoms usually begin to abate within 24 h after early thiamin administration. Ataxia and confusion may persist days to months. Untreated, the disorder progresses; mortality is 10 to 20%. Of surviving patients, 80% develop Korsakoff psychosis; the combination is called Wernicke-Korsakoff syndrome.

**Treatment**

- Parenteral thiamin
- Parenteral Mg

Treatment consists of immediate administration of thiamin 100 mg IV or IM, continued daily for at least 3 to 5 days. Mg is a necessary cofactor in thiamin-dependent metabolism, and hypomagnesemia should be corrected using Mg sulfate 1 to 2 g IM or IV q 6 to 8 h or Mg oxide 400 to 800 mg po once/day. Supportive treatment includes rehydration, correction of electrolyte abnormalities, and general nutritional therapy, including multivitamins. Patients with advanced disease require hospitalization. Alcohol cessation is mandatory.

Because Wernicke's encephalopathy is preventable, all undernourished patients should be treated with parenteral thiamin (typically 100 mg IM followed by 50 mg po once/day) plus vitamin B_{12} and folate (1 mg po once/day for both), particularly if IV dextrose is necessary. Thiamin is also prudent before any treatment is begun in patients who present with a reduced level of consciousness. Patients who are undernourished should continue to receive thiamin as outpatients.

**Korsakoff's Psychosis**

Korsakoff's psychosis is a late complication of persistent Wernicke's encephalopathy and results in memory deficits, confusion, and behavioral changes.

Korsakoff's psychosis (Korsakoff's amnestic syndrome) occurs in 80% of untreated patients with Wernicke's encephalopathy. Why Korsakoff's psychosis develops in only some patients with Wernicke's encephalopathy is unclear. A severe or repeated attack of post-alcoholic delirium tremens can trigger Korsakoff's psychosis whether or not a typical attack of Wernicke's encephalopathy has occurred first.

Other triggers include head injury, subarachnoid hemorrhage, thalamic hemorrhage, thalamic ischemic stroke, and, infrequently, tumors affecting the paramedian posterior thalamic region.

**Symptoms and Signs**

Immediate memory is severely affected; retrograde and anterograde amnesia occurs in varying degrees.
Patients tend to draw on memory of remote events, which appears to be less affected than memory of recent events. Disorientation to time is common. Emotional changes are common; they include apathy, blandness, or mild euphoria with little or no response to events, even frightening ones. Spontaneity and initiative may be decreased.

Confabulation is often a striking early feature. Bewildered patients unconsciously fabricate imaginary or confused accounts of events they cannot recall; these fabrications may be so convincing that the underlying disorder is not detected.

**Diagnosis**

Diagnosis is based on typical symptoms in patients with a history of severe chronic alcohol dependence. Other causes of symptoms (eg, CNS injury or infection) must be ruled out.

**Prognosis**

Prognosis is fairly good for patients with head injury, subarachnoid hemorrhage, or both; the amnesia is transient. Prognosis is poor when the cause is thiamin deficiency or stroke; prolonged institutional care is required for about 25% of patients, and only about 20% recover completely. However, they may improve up to 12 to 24 mo after onset, and patients should not be prematurely institutionalized.

**Treatment**

Treatment consists of thiamin and adequate hydration.

**Marchiafava-Bignami Disease**

**Marchiafava-Bignami disease is a rare demyelination of the corpus callosum that occurs in chronic alcoholics, predominantly men.**

Pathology and circumstances link this disorder to osmotic demyelination syndrome (previously called central pontine myelinolysis), of which it may be a variant (see p. 828). In Marchiafava-Bignami disease, agitation and confusion occur with progressive dementia and frontal release signs. Some patients recover over several months; others experience seizures and coma, which may precede death.

**Anxiolytics and Sedatives**

Anxiolytics and sedatives (hypnotics) include benzodiazepines, barbiturates, and related drugs. High doses can cause stupor and respiratory depression, which is managed with intubation and mechanical ventilation. Chronic users may have a withdrawal syndrome of agitation and seizures, so dependence is managed by slow tapering with or without substitution (ie, with pentobarbital or phenobarbital).

The therapeutic benefit of anxiolytics and sedatives is well-established, but their value in alleviating stress and anxiety is also probably the reason that they are abused so frequently. Abused anxiolytics and sedatives include benzodiazepines, barbiturates, and other drugs taken to promote sleep.

**Pathophysiology**

Benzodiazepines and barbiturates potentiate γ-aminobutyric acid (GABA) at specific receptors thought to be located near GABA receptors. The exact mechanism of this potentiation process remains unclear but may be related to opening of chloride channels, producing a hyperpolarized state within the postsynaptic neuron.

**Chronic effects:** Patients taking high doses of sedatives frequently have difficulty thinking, slow speech and comprehension (with some dysarthria), poor memory, faulty judgment, narrowed attention span, and emotional lability. In susceptible patients, psychologic dependence on the drug may develop rapidly. The extent of physical dependence is related to dose and duration of use; eg, pentobarbital 200 mg/day taken
for many months may not induce significant tolerance, but 300 mg/day for > 3 mo or 500 to 600 mg/day for 1 mo may induce a withdrawal syndrome when the drug is stopped. Tolerance and tachyphylaxis develop irregularly and incompletely; thus, considerable behavioral, mood, and cognitive disturbances persist, even in regular users, depending on the dosage and the drug’s pharmacodynamic effects. Some cross-tolerance exists between alcohol and barbiturates and nonbarbiturate anxiolytics and sedatives, including benzodiazepines. (Barbiturates and alcohol are strikingly similar in the dependence, withdrawal symptoms, and chronic intoxication they cause.)

**Pregnancy:** Prolonged use of barbiturates during pregnancy can cause withdrawal in the neonate (see p. 2799).

### Symptoms and Signs

**Toxicity or overdose:** The signs of progressive anxiolytic and sedative intoxication are depression of superficial reflexes, fine lateral-gaze nystagmus, slightly decreased alertness with coarse or rapid nystagmus, ataxia, slurred speech, and postural unsteadiness.

Increasing toxicity can cause nystagmus on forward gaze, miosis, somnolence, marked ataxia with falling, confusion, stupor, respiratory depression, and, ultimately, death. Overdose of a benzodiazepine rarely causes hypotension, and these drugs do not cause arrhythmias.

**Withdrawal:** When intake of therapeutic doses of anxiolytics and sedatives is stopped or reduced below a critical level, a self-limited mild withdrawal syndrome can ensue. After only a few weeks, attempts to stop using the drug can exacerbate insomnia and result in restlessness, disturbing dreams, frequent awakening, and feelings of tension in the early morning.

Withdrawal from benzodiazepines is rarely life threatening. Symptoms can include tachypnea, tachycardia, tremulousness, hyperreflexia, confusion, and seizures. Onset may be slow because the drugs remain in the body a long time. Withdrawal may be most severe in patients who used drugs with rapid absorption and a quick decline in serum levels (eg, alprazolam, lorazepam, triazolam). Many people who misuse benzodiazepines have been or are heavy users of alcohol, and a delayed benzodiazepine withdrawal syndrome may complicate alcohol withdrawal.

Withdrawal from barbiturates taken in large doses causes an abrupt, potentially life-threatening withdrawal syndrome similar to delirium tremens. Occasionally, even after properly managed withdrawal over 1 to 2 wk, a seizure occurs. Without treatment, withdrawal of a short-acting barbiturate causes the following:

- Within the first 12 to 20 h: Increasing restlessness, tremulousness, and weakness
- By the 2nd day: More prominent tremulousness, sometimes increased deep tendon reflexes, and increased weakness
- During the 2nd and 3rd days: Seizures (in 75% of patients who were taking ≥ 800 mg/day), sometimes progressing to status epilepticus and death
- From the 2nd to the 5th day: Delirium, insomnia, confusion, frightening visual and auditory hallucinations, and often hyperpyrexia and dehydration

### Diagnosis

- Clinical evaluation

Diagnosis is usually made clinically. Drug levels are not measured. Benzodiazepines and barbiturates are usually included in routine immunoassay-based urine drug screens (see p. 1510).

### Treatment
Toxicity or overdose: Acute intoxication generally requires nothing more than observation, although the airway and respirations should be carefully assessed. If ingestion was within 1 h, the gag reflex is preserved, and the patient can protect the airway; 50 g of activated charcoal may be given to reduce further absorption; however, this intervention has not been shown to reduce morbidity or mortality. Occasionally, intubation and mechanical ventilation are required.

The benzodiazepine receptor antagonist flumazenil can reverse severe sedation secondary to benzodiazepine overdose. Dose is 0.2 mg IV given over 30 sec; 0.3 mg may be given after 30 sec, followed by 0.5 mg q 1 min to total 3 mg. However, its clinical usefulness is not well-defined because most people who overdose on benzodiazepines recover with only supportive care, and occasionally flumazenil precipitates seizures. Contraindications to flumazenil include long-term benzodiazepine use (because flumazenil may precipitate withdrawal), an underlying seizure disorder, presence of twitching or other motor abnormalities, a concomitant epileptogenic drug overdose (especially of tricyclic antidepressants), and cardiac arrhythmias.

If barbiturate overdose is diagnosed, urine should be alkalinized to increase excretion.

Withdrawal and detoxification: Severe acute withdrawal requires hospitalization, preferably in an ICU, and use of appropriate doses of IV benzodiazepines.

One approach for managing sedative dependence is to withdraw the drug on a strict schedule while monitoring signs of withdrawal. Often, switching to a long-acting drug, which is easier to taper, is better.

As for alcohol withdrawal, patients going through anxiolytic or sedative withdrawal require close monitoring, preferably in an inpatient setting if a moderate to severe withdrawal reaction is expected.

Marijuana (Cannabis)

Marijuana is a euphoriant that can cause sedation or dysphoria in some users. Overdose does not occur. Psychologic dependence can develop with chronic use, but very little physical dependence is clinically apparent. Withdrawal is uncomfortable but requires only supportive treatment.

Marijuana is the most commonly used illicit drug; it is typically used episodically without evidence of social or psychologic dysfunction.

In the US, marijuana is commonly smoked in cigarettes, made from the flowering tops and leaves of the dried plant, or as hashish, the pressed resin of the plant. Much less commonly, marijuana is taken orally. Dronabinol, a synthetic oral form of the active ingredient, Δ-9-tetrahydrocannabinol (THC), is used to treat nausea and vomiting associated with cancer chemotherapy and to enhance appetite in AIDS patients.

Pathophysiology

Δ-9-THC binds at cannabinoid receptors, which are present throughout the brain.

Chronic effects: Any drug that causes euphoria and diminishes anxiety can cause dependence, and marijuana is no exception. However, heavy use and reports of inability to stop are unusual. Critics of marijuana cite much scientific data regarding adverse effects, but most claims of significant biologic effect are unsubstantiated. Findings are sparse even among relatively heavy users and in areas intensively investigated (eg, immunologic and reproductive function). However, high-dose smokers develop pulmonary symptoms (episodes of acute bronchitis, wheezing, coughing, and increased phlegm), and
pulmonary function may be altered, manifested as large airway changes of unknown significance. Even daily smokers do not develop obstructive airway disease. There is no evidence of increased risk of head and neck or airway cancers, as there is with tobacco. In a few case-control studies, diminished cognitive function was identified in small samples of long-term high-dose users; this finding needs to be confirmed. A sense of diminished ambition and energy is often described.

The effect of prenatal marijuana use on neonates is not clear. Decreased fetal weight has been reported, but when all factors (eg, maternal alcohol and tobacco use) are accounted for, the effect on fetal weight appears less. THC is secreted in breast milk. Although harm to breastfed infants has not been shown, breastfeeding mothers, like pregnant women, should avoid using marijuana.

**Symptoms and Signs**

Intoxication and withdrawal are not life threatening.

**Acute effects:** Within minutes, smoking marijuana produces a dreamy state of consciousness in which ideas seem disconnected, unanticipated, and free-flowing. Time, color, and spatial perceptions may be altered. In general, intoxication consists of a feeling of euphoria and relaxation (a high). These effects last 4 to 6 h after inhalation.

Many of the other reported psychologic effects seem to be related to the setting in which the drug is taken. Anxiety, panic reactions, and paranoia have occurred, particularly in naive users. Marijuana may exacerbate or even precipitate psychotic symptoms in schizophrenics, even those being treated with antipsychotics.

Physical effects are mild in most patients. Tachycardia, conjunctival injection, and dry mouth occur regularly. Concentration, sense of time, fine coordination, depth perception, tracking, and reaction time can be impaired for up to 24 h—all hazardous in certain situations (eg, driving, operating heavy equipment). Appetite often increases.

**Withdrawal:** Cessation after 2 to 3 wk of frequent, heavy use can cause a mild withdrawal syndrome, which typically begins about 12 h after the last use. Symptoms consist of insomnia, irritability, depression, nausea, and anorexia; symptoms peak at 2 to 3 days and last up to 7 days.

**Diagnosis**

- Clinical evaluation

Diagnosis is usually made clinically. Drug levels are not measured. Most routine urine drug screens include marijuana (see p. 1510).

**Treatment**

- Supportive measures

Treatment is usually unnecessary; for patients experiencing significant discomfort, treatment is supportive. Management of abuse typically consists of behavioral therapy in an outpatient drug treatment program.

**Cocaine**

Cocaine is a sympathomimetic drug with CNS stimulant and euphoriant properties. High doses can cause panic, schizophrenic-like symptoms, seizures, hyperthermia, hypertension, arrhythmias, stroke, aortic dissection, intestinal ischemia, and MI. Toxicity is managed with supportive care, including IV benzodiazepines (for agitation, hypertension, and seizures) and cooling techniques (for hyperthermia). Withdrawal manifests primarily as depression, difficulty concentrating, and somnolence (cocaine washout syndrome).
Most cocaine users are episodic recreational users. However, about 25% (or more) of users meet criteria for abuse or dependence. Use among adolescents has declined recently. Availability of highly biologically active forms, such as crack cocaine, has worsened the problem of cocaine dependence. Most cocaine in the US is about 50 to 60% pure; it may contain a wide array of fillers, adulterants, and contaminants.

Most cocaine in the US is volatilized and inhaled, but it may be snorted, or injected IV. For inhalation, the powdered hydrochloride salt is converted to a more volatile form, usually by adding NaHCO₃, water, and heat. The resultant precipitate (crack cocaine) is volatilized by heating (it is not burned) and inhaled. Onset of effect is quick, and intensity of the high rivals IV injection. Tolerance to cocaine occurs, and withdrawal from heavy use is characterized by somnolence, difficulty concentrating, increased appetite, and depression. The tendency to continue taking the drug is strong after a period of withdrawal.

Pathophysiology

Cocaine, an alkaloid present in the leaves of the coca plant, enhances norepinephrine, dopamine, and serotonin activity in the central and peripheral nervous systems.

Enhancement of dopamine activity is the likely cause of the drug's intended effects and thus of the reinforcement that contributes to developing abuse and dependence.

Norepinephrine activity accounts for the sympathomimetic effects: tachycardia, hypertension, mydriasis, diaphoresis, and hyperthermia.

Cocaine also blocks Na channels, accounting for its action as a local anesthetic. Cocaine causes vasoconstriction and thus can affect almost any organ. MI, cerebral ischemia and hemorrhage, aortic dissection, intestinal ischemia, and renal ischemia are possible sequelae.

Onset of cocaine's effects depends on mode of use:

- IV injection and smoking: Immediate onset, peak effect after about 3 to 5 min, and duration of about 15 to 20 min
- Intranasal use: Onset after about 3 to 5 min, peak effect at 20 to 30 min, and duration of about 45 to 90 min
- Oral use: Onset after about 10 min, peak effect at about 60 min, and duration of about 90 min

Because cocaine is such a short-acting drug, heavy users may inject it or smoke it repeatedly every 10 to 15 min.

Pregnancy: Use of cocaine during pregnancy can affect the fetus; the rate of placental abruption and spontaneous abortion is higher (see p. 2799).

Symptoms and Signs

Acute effects: Effects may differ depending on mode of use. When injected or smoked, cocaine causes hyperstimulation, alertness, euphoria, a sense of increased energy, and feelings of competence and power. The excitation and high are similar to those produced by injecting amphetamine. These feelings are less intense and disruptive in users who snort cocaine powder.

Users who smoke the drug may develop pneumothorax or pneumomediastinum, causing chest pain, dyspnea, or both. Myocardial ischemia due to cocaine use may also cause chest pain ("cocaine chest pain"), but cocaine can also cause chest pain in the absence of myocardial ischemia; the mechanism is unclear. Arrhythmias and conduction abnormalities may occur. Cardiac effects may result in sudden death. Binges, often over several days, lead to an exhaustion syndrome, involving intense fatigue and need for sleep.

Toxicity or overdose: An overdose may cause severe anxiety, panic, agitation, aggression,
sleeplessness, hallucinations, paranoid delusions, impaired judgment, tremors, seizures, and delirium. Mydriasis and diaphoresis are apparent, and heart rate and BP are increased. Death may result from MI or arrhythmias.

Severe overdose causes a syndrome of acute psychosis (eg, schizophrenic-like symptoms), hypertension, hyperthermia, rhabdomyolysis, coagulopathy, renal failure, and seizures. Patients with extreme clinical toxicity may, on a genetic basis, have decreased (atypical) serum cholinesterase, an enzyme needed for clearance of cocaine.

The concurrent use of cocaine and alcohol produces a condensation product, cocaethylene, which has stimulant properties and may contribute to toxicity.

**Chronic effects:** Severe toxic effects occur in compulsive heavy users. Myocardial fibrosis, left ventricular hypertrophy, and cardiomyopathy can develop. Rarely, repeated snorting causes nasal septal perforation due to local ischemia. Cognitive impairment, including impaired attention and verbal memory, occurs in some heavy users. Users who inject cocaine are subject to the typical infectious complications (see p. 1510).

**Withdrawal:** The main symptoms are depression, difficulty concentrating, and somnolence (cocaine washout syndrome). Appetite is increased.

**Diagnosis**

- Clinical evaluation

Diagnosis is usually made clinically. Drug levels are not measured. The cocaine metabolite, benzoylecgonine, is part of most routine urine drug screens (see p. 1510).

**Treatment**

- IV benzodiazepines
- Avoidance of β-blockers
- Cooling for hyperthermia as needed

**Toxicity or overdose:** Treatment of mild cocaine intoxication is generally unnecessary because the drug is extremely short-acting. Benzodiazepines are the preferred initial treatment for most toxic effects, including CNS excitation and seizures, tachycardia, and hypertension. Lorazepam 2 to 3 mg IV q 5 min titrated to effect may be used. High doses and a continuous infusion may be required. Propofol infusion, with mechanical ventilation, may be used for resistant cases. Hypertension that does not respond to benzodiazepines is treated with IV nitrates (eg, nitroprusside) or phentolamine; β-blockers are not recommended because they allow continued α-adrenergic stimulation. Hyperthermia can be life threatening and should be managed aggressively with sedation plus evaporative cooling, ice packs, and maintenance of intravascular volume and urine flow with IV normal saline solution. Phenothiazines lower seizure threshold, and their anticholinergic effects can interfere with cooling; thus, they are not preferred for sedation. Occasionally, severely agitated patients must be pharmacologically paralyzed and mechanically ventilated to ameliorate acidosis, rhabdomyolysis, or multisystem dysfunction.

Cocaine-related chest pain is evaluated as for any other patient with potential myocardial ischemia or aortic dissection, with chest x-ray, serial ECG, and serum cardiac markers. As discussed above, β-blockers are contraindicated, and benzodiazepines are a first-line drug. If coronary vasodilation is required after benzodiazepines are given, nitrates are used, or phentolamine 1 to 5 mg IV given slowly can be considered.

**Abuse:** Heavy users and people who inject the drug IV or smoke it are most likely to become dependent. Light users and people who take the drug nasally or orally are at lower risk of becoming dependent. Stopping sustained use requires considerable assistance, and the depression that may result requires
close supervision and treatment. Many outpatient therapies, including support and self-help groups and cocaine hotlines, exist. Inpatient therapy is used primarily when it is required by physical or mental comorbidity or when outpatient therapy has repeatedly been unsuccessful.

For treatment of infants born to cocaine-addicted mothers, see Prenatal Drug Exposure on p. 2799.

Amphetamines

Amphetamines are sympathomimetic drugs with CNS stimulant and euphoriant properties whose toxic adverse effects include delirium, hypertension, seizures, and hyperthermia (which can cause rhabdomyolysis and renal failure). Toxicity is managed with supportive care, including IV benzodiazepines (for agitation, hypertension, and seizures) and cooling techniques (for hyperthermia). There is no stereotypical withdrawal syndrome.

The original drug in this class, amphetamine, has been modified by various substitutions on its phenyl ring, resulting in many variations, including methamphetamine, methylenediooxymethamphetamine (MDMA or Ecstasy), methylenedioxyethylamphetamine (MDEA), and numerous others.

Some amphetamines, including dextroamphetamine, methamphetamine, and the related methylphenidate, are widely used medically to treat attention-deficit hyperactivity disorder, obesity, and narcolepsy, thus creating a supply subject to diversion for illicit use. Methamphetamine is easily manufactured illicitly.

Pathophysiology

Amphetamines enhance release of catecholamines, increasing intrasynaptic levels of norepinephrine, dopamine, and serotonin. The resulting marked α- and β-receptor stimulation and general CNS excitation account for the "desired" effects of increased alertness, euphoria, and anorexia, as well as the adverse effects of delirium, hypertension, hyperthermia, and seizures. Effects of amphetamines are similar, varying in intensity and duration of psychoactive effects; MDMA and its relatives have more mood-enhancing properties, perhaps related to a greater effect on serotonin. Amphetamines can be taken orally as pills or capsules, nasally by inhaling or smoking, or by injection.

Chronic effects: Repeated use of amphetamines induces dependence. Tolerance develops slowly, but amounts several 100-fold greater than the amount originally used may eventually be ingested or injected. Tolerance to various effects develops unequally. Tachycardia and increased alertness diminish, but hallucinations and delusions may occur.

Amphetamines typically cause erectile dysfunction in men but enhance sexual desire. Use is associated with unsafe sex practices, and users are at increased risk of sexually transmitted infections, including HIV infection. Amphetamine abusers are prone to injury because the drug produces excitation and grandiosity followed by excess fatigue and sleepiness.

Symptoms and Signs

Acute effects: Many psychologic effects of amphetamines are similar to those of cocaine; they include increased alertness and concentration, euphoria, and feelings of well-being and grandiosity. Palpitations, tremor, diaphoresis, and mydriasis may also occur during intoxication.

Binges (perhaps over several days) lead to an exhaustion syndrome, involving intense fatigue and need for sleep after the stimulation phase.

Toxicity or overdose: Tachycardia, arrhythmias, chest pain, hypertension, dizziness, nausea, vomiting, and diarrhea can occur. CNS effects include acute delirium and toxic psychosis. Overdose can also cause stroke (usually hemorrhagic), seizures, muscle rigidity, and hyperthermia (> 40° C); all of these effects may precipitate rhabdomyolysis, which can lead to renal failure.

Chronic effects: A paranoid psychosis may result from long-term use; rarely, the psychosis is precipitated by a single high dose or by repeated moderate doses. Typical features include delusions of
persecution, ideas of reference (notions that everyday occurrences have special meaning or significance personally meant for or directed to the patient), and feelings of omnipotence. Some users experience a prolonged depression, during which suicide is possible. Recovery from even prolonged amphetamine psychosis is usual but is slow. The more florid symptoms fade within a few days or weeks, but some confusion, memory loss, and delusional ideas commonly persist for months.

Users have a high rate of severe tooth decay affecting multiple teeth; causes include decreased salivation, acidic combustion products, and poor oral hygiene.

**Withdrawal:** Although no stereotypical withdrawal syndrome occurs when amphetamines are stopped, EEG changes occur, considered by some experts to fulfill the physical criteria for dependence. Abruptly stopping use may uncover or exacerbate underlying depression or precipitate a serious depressive reaction. Withdrawal is often followed by 2 or 3 days of intense fatigue or sleepiness and depression.

**Diagnosis**

- Clinical evaluation

- Testing as needed to exclude serious nondrug-related disorders (eg, causing altered mental status)

Diagnosis is usually made clinically, although when history of drug use and the diagnosis are unclear, tests are done as indicated for the undifferentiated patient with altered mental status, hyperpyrexia, or seizures. Evaluation then typically includes CT, lumbar puncture, and laboratory tests to identify infections and metabolic abnormalities. Amphetamines are usually part of routine urine drug screens (see p. 1510), which are done unless history of ingestion is clear; specific drug levels are not measured. Immunoassay urine screening tests for amphetamines may produce false-positive results and may not detect methamphetamine and methylphenidate.

**Treatment**

- IV benzodiazepines

- IV nitrates for hypertension unresponsive to benzodiazepines as needed

- Cooling for hyperthermia as needed

**Toxicity or overdose:** When significant oral toxicity is recent (eg, < 1 to 2 h), activated charcoal may be given to limit absorption, although this intervention has not been shown to reduce morbidity or mortality. Urinary acidification hastens amphetamine excretion, but it may worsen myoglobin precipitation in the renal tubules and thus is not recommended.

Benzodiazepines are the preferred initial treatment for CNS excitation, seizures, tachycardia, and hypertension. Lorazepam 2 to 3 mg IV q 5 min titrated to effect may be used. High doses or a continuous infusion may be required. Propofol, with mechanical ventilation, may be required for severe agitation. Hypertension that does not respond to benzodiazepines is treated with nitrates (occasionally nitroprusside) or other antihypertensives as needed, depending on the severity of the hypertension. β-Blockers (eg, metoprolol 2 to 5 mg IV) may be used for severe ventricular arrhythmias or tachycardia.

Hyperthermia can be life threatening and should be managed aggressively with sedation plus evaporative cooling, ice packs, and maintenance of intravascular volume and urine flow with IV normal saline solution.

Phenothiazines lower seizure threshold, and their anticholinergic effects can interfere with cooling; thus, they are not preferred for sedation.

**Withdrawal and rehabilitation:** No specific treatment is needed. BP and mood should be monitored initially. Patients whose depression persists for more than a brief period after amphetamines are stopped may respond to antidepressants.
Cognitive-behavioral therapy (a form of psychotherapy) is effective in some patients. There are no other proven treatments for rehabilitation and maintenance after detoxification.

**Methylenedioxymethamphetamine (Ecstasy, MDMA)**

MDMA (3,4-Methylenedioxymethamphetamine) is an amphetamine analog with stimulant and hallucinogenic effects.

MDMA acts primarily on neurons that produce and release serotonin, but it also affects dopaminergic neurons. MDMA is usually taken as a pill; effects begin 30 to 60 min after ingestion and typically last 4 to 6 h. MDMA is often used at dance clubs, concerts, and rave parties.

**Symptoms and Signs**

MDMA causes a state of excitement and disinhibition and accentuates physical sensation, empathy, and feelings of interpersonal closeness. Toxic effects are similar to those of the other amphetamines but are less common, perhaps because use is more likely to be intermittent. However, even with casual use, significant problems such as hyperthermia and centrally mediated hyponatremia may occur. The effects of intermittent, occasional use are uncertain. Rarely, fulminant hepatic failure occurs.

Chronic, repeated use may cause problems similar to those of amphetamines, including dependence. Some users develop paranoid psychosis. Cognitive decline may also occur with repeated, frequent use.

**Diagnosis**

MDMA may not be detected by routine urine immunoassay drug screens.

**Treatment**

Treatment for acute toxicity and dependency is similar to that for amphetamines, although treatment for acute overdose is less commonly needed.

**Hallucinogens**

Hallucinogens are a diverse group of drugs that can cause highly unpredictable, idiosyncratic reactions. Intoxication typically causes hallucinations, with altered perception, impaired judgment, ideas of reference, and depersonalization. There is no stereotypical withdrawal syndrome. Diagnosis is clinical. Treatment is supportive.

Traditional hallucinogens include lysergic acid diethylamide (LSD), psilocybin, and mescaline. All are derived from natural products:

- **LSD** from a fungus that often contaminates wheat and rye flour
- **Psilocybin** from several types of mushrooms
- **Mescaline** from the peyote cactus

Dozens of newer synthetic compounds ("designer drugs") have been produced, usually based on tryptamine or phenylethylamine molecules. Tryptamines include N,N-dimethyltryptamine (DMT) and 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT).

To complicate matters, many illicit drugs sold under one name actually contain another drug of abuse—often ketamine or phencyclidine (PCP), anesthetic drugs, dextromethorphan, or other drugs.

Some other drugs, including marijuana, also have hallucinogenic properties. The term hallucinogen persists, although use of these drugs may not cause hallucinations. Alternative terms, such as psychedelic and psychotomimetic, are even less appropriate.
Pathophysiology

LSD, psilocybin, and many designer hallucinogens are serotonin receptor agonists. For mescaline, a phenylethylamine similar to amphetamines, the exact mechanism has not been determined.

Mode of use and effects vary:

- LSD is taken orally from drug-impregnated blotter paper or as tablets. Onset of action is usually 30 to 60 min after ingestion; duration of effects can be 12 to 24 h.
- Psilocybin is taken orally; effects usually last about 4 to 6 h.
- Mescaline is taken orally as peyote buttons. Onset of effects is usually 30 to 90 min after ingestion; duration of effects is about 12 h.
- DMT, when smoked, has onset in 2 to 5 min; duration of effects is 20 to 60 min (accounting for its street name, "businessman's lunch").

A high degree of tolerance for LSD develops and disappears rapidly. Users tolerant of any of these drugs are cross-tolerant of the other drugs. Psychologic dependence varies greatly; there is no evidence of physical dependence or a withdrawal syndrome.

Symptoms and Signs

Intoxication results in altered perceptions, including synesthesias (eg, seeing sounds, hearing colors), intensification of sensations, enhanced empathy, depersonalization (feeling the self is not real), a distorted sense of the environment's reality, and changes in mood (usually euphoric, sometimes depressive). Users often refer to the combination of these effects as a trip. Periods of intense psychologic effects may alternate with periods of lucidity. LSD may also have several physical effects, including mydriasis, blurred vision, sweating, palpitations, and impaired coordination. Many other hallucinogens cause nausea and vomiting. With all, judgment is impaired.

Responses to hallucinogens depend on several factors, including the user's expectations, ability to cope with perceptual distortions, and the setting. With LSD, delusions and true hallucinations occur but are rare, as are anxiety attacks, extreme apprehensiveness, and panic states. Psilocybin and mescaline are more likely to cause hallucinations. When hallucinogenic reactions occur, they usually subside quickly if treated appropriately in a secure setting. However, some people (especially after using LSD) remain disturbed and may have a persistent psychotic state. Whether drug use has precipitated or uncovered preexisting psychotic potential or can cause this state in previously stable people is unclear.

Some people, especially long-term or repeat users (particularly of LSD), experience apparent drug effects long after they have stopped drug use. These episodes (flashbacks) are usually visual illusions but can include distortions of virtually any sensation (including self-image or perceptions of time or space) and hallucinations. Flashbacks can be precipitated by use of marijuana, alcohol, or barbiturates or by stress or fatigue or can occur without apparent reason. Mechanisms are not known. Flashbacks tend to subside within 6 to 12 mo.

Diagnosis

- Clinical evaluation

Diagnosis is usually made clinically. Drug levels are not measured. Except for PCP, most hallucinogens are not included in routine urine drug screens (see p. 1510).

Treatment

- For acute intoxication, supportive measures and relief of anxiety
For persistent psychosis, psychiatric care

A quiet, calming environment with reassurance that the bizarre thoughts, visions, and sounds are due to the drug and will go away soon usually suffices. Anxiolytics (eg, lorazepam, diazepam) may help reduce severe anxiety.

Persistent psychotic states or other mental disorders require appropriate psychiatric care. Flashbacks that are transient or not unduly distressing to the patient require no special treatment. However, flashbacks associated with anxiety and depression may require anxiolytics as for acute adverse reactions.

**Ketamine and Phencyclidine**

Ketamine and phencyclidine are related drugs that can cause intoxication, sometimes with confusion or a catatonic state. Overdose can cause coma and, rarely, death.

Ketamine and phencyclidine (PCP) are chemically related anesthetics. These drugs are often used to adulterate or pass for other hallucinogens such as LSD.

Ketamine is available in liquid or powder form. When used illicitly, the powder form is typically snorted but can be taken orally. The liquid form is taken IV, IM, or sc.

PCP, once common, is no longer being legally manufactured. It is illegally manufactured and sold on the street under names such as angel dust; it is sometimes sold in combination with marijuana.

**Symptoms and Signs**

Intoxication, characterized by a giddy euphoria, occurs with lower doses; euphoria is often followed by bursts of anxiety or mood lability. Overdose causes a withdrawn state of depersonalization and disassociation; when doses are higher still, disassociation can become severe (known as a k-hole), with combativeness, ataxia, dysarthria, muscular hypertonicity, nystagmus, hyperreflexia, and myoclonic jerks. With very high doses, acidosis, hyperthermia, tachycardia, severe hypertension, seizures, and coma may occur; deaths are unusual. Acute effects generally fade after 30 min.

**Diagnosis**

- Clinical evaluation

Diagnosis is usually clinical. Ketamine is not detected by routine urine drug screens; high-performance liquid chromatography testing must be requested when ketamine use must be confirmed.

**Treatment**

- Supportive measures

Patients should be kept in a quiet, calming environment and closely observed. Benzodiazepines can be used to manage seizures. Further treatment is rarely needed.

**Volatile Nitrites**

Nitrites (poppers, as amyl, butyl, or isobutyl nitrite, sold with street names such as Locker Room and Rush) may be inhaled to enhance sexual pleasure. There is little evidence of significant risk, although nitrites and nitrates cause vasodilation, with brief hypotension, dizziness, and flushing, followed by reflex tachycardia (see Table 340-8 on p. 3345). Nitrites may cause methemoglobinemia. However, they are dangerous when combined with drugs used for erectile enhancement; the combination can lead to severe hypotension and death.

**Volatile Solvents**
Inhalation of volatile industrial solvents and solvents from aerosol sprays can cause a state of intoxication. Chronic use can result in neuropathies and hepatotoxicity.

Use of volatile solvents (eg, acetates, alcohol, chloroform, ether, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, ketones) continues to be an endemic problem among adolescents. Common commercial products (eg, glues and adhesives, paints, cleaning fluids) contain these substances; thus, children and adolescents can easily obtain them. About 10% of adolescents in the US have reportedly inhaled volatile solvents.

Volatile solvents temporarily stimulate the CNS before depressing it. Partial tolerance and psychologic dependence develop with frequent use, but a withdrawal syndrome does not occur.

Symptoms and Signs

Acute symptoms of dizziness, drowsiness, slurred speech, and unsteady gait occur early. Impulsiveness, excitement, and irritability may occur. As effects on the CNS increase, illusions, hallucinations, and delusions develop. Users experience a euphoric, dreamy high, culminating in a short period of sleep. Delirium with confusion, psychomotor clumsiness, emotional lability, and impaired thinking develop. The intoxicated state may last from minutes to > 1 h.

Sudden death can result from respiratory arrest or airway occlusion due to CNS depression or arrhythmias (perhaps due to myocardial sensitization).

Complications of chronic use may result from the effect of the solvent or from other toxic ingredients (eg, lead in gasoline). Carbon tetrachloride may cause a syndrome of hepatic and renal failure. Toluene may cause degeneration of CNS white matter. Injuries to brain, peripheral nerves, liver, kidneys, and bone marrow may result from heavy exposure or hypersensitivity.

Diagnosis

Volatile solvents are not detected by routine drug screens.

Treatment

Treatment of solvent-dependent adolescents is difficult, and relapse is frequent. However, most users stop solvent use by the end of adolescence. Intensive attempts to broadly improve patients’ social skills and status in family, school, and society may help. For symptoms and treatment of poisoning with specific solvents, see Table 340-8 on p. 3345.

Gamma Hydroxybutyrate

Gamma hydroxybutyrate causes intoxication resembling alcohol or ketamine intoxication and, especially when combined with alcohol, can lead to respiratory depression, seizures, and rarely death.

Gamma hydroxybutyrate (GHB, also called "G") is similar to the neurotransmitter γ-aminobutyric acid (GABA), but it can cross the blood-brain barrier and so can be taken by mouth. It is similar to ketamine in its effects but lasts longer and is far more dangerous.

GHB produces feelings of relaxation and tranquility. It may also cause fatigue and disinhibition. At higher doses, GHB may cause dizziness, loss of coordination, nausea, and vomiting. Coma and respiratory depression may also occur. Combining GHB and any other sedative, especially alcohol, is extremely dangerous. Most deaths have occurred when GHB was taken with alcohol.

Withdrawal symptoms occur if GHB is not taken for several days after previous frequent use.

Treatment is directed at symptoms. Mechanical ventilation may be needed if breathing is affected. Most
people recover rapidly, although effects may not fade for 1 to 2 h.

**Anabolic Steroids**

Anabolic steroids are often used to enhance physical performance and promote muscle growth. When used inappropriately, chronically at high doses and without medical supervision, they can cause erratic and irrational behavior and a wide range of physical adverse effects.

Anabolic steroids include testosterone and any drugs chemically and pharmacologically related to testosterone that promote muscle growth; numerous drugs are available. Anabolic steroids are used clinically to treat low testosterone levels (see Male Hypogonadism on p. 2340). Additionally, because anabolic steroids are antianabolic and improve protein utilization, they are sometimes given to burn, bedbound, or other debilitated patients to prevent muscle wasting. Some physicians prescribe them to patients with AIDS-related wasting or with cancer. However, there are few data to recommend such therapy and little guidance on how supplemental androgens may affect underlying disorders. Testosterone has been reputed to benefit wound healing and muscle injury, although few data support these claims.

Anabolic steroids are used illicitly to increase lean muscle mass and strength; resistance training and a certain diet can enhance these effects. There is no direct evidence that anabolic steroids increase endurance or speed, but substantial anecdotal evidence suggests that athletes taking them can perform more frequent high-intensity workouts. Muscle hypertrophy is unequivocal.

Estimates of lifetime incidence of anabolic steroid abuse range from 0.5 to 5% of the population, but subpopulations vary significantly (eg, higher rates for bodybuilders and competitive athletes). In the US, the reported rate of use is 6 to 11% among high school-aged males, including an unexpected number of nonathletes, and about 2.5% among high school-aged females.

**Pathophysiology**

Anabolic steroids have androgenic effects (eg, changes in hair or in libido, aggressiveness) and anabolic effects (eg, increased protein utilization, increased muscle mass). Androgenic effects cannot be separated from the anabolic, but some anabolic steroids have been synthesized to minimize the androgenic effects.

Testosterone is rapidly degraded by the liver; oral testosterone is inactivated too rapidly to be effective, and injectable testosterone must be modified (eg, by esterification) to retard absorption or delay breakdown. Analogs modified by 17α-alkylation are often effective orally, but adverse effects may be increased. Transdermal preparations are also available.

**Chronic effects**: Adverse effects vary significantly by dose and drug. There are few adverse effects at physiologic replacement doses (eg, methyltestosterone 10 to 50 mg/day or its equivalent). Athletes may use doses 10 to 50 times this range. At high doses, some effects are clear; others are equivocal (see Table 160-4). Uncertainties exist because most studies involve abusers who may not report doses accurately and who also use black market drugs, many of which are counterfeit and contain (despite labeling) varying doses and substances.

Athletes may take steroids for a certain period, stop, then start again (cycling) several times a year. Intermittently stopping the drugs is believed to allow endogenous testosterone levels, sperm count, and the hypothalamic-pituitary-gonadal axis to return to normal. Anecdotal evidence suggests that cycling may decrease harmful effects and the need for increasing drug doses to attain the desired effect.

Athletes frequently use many drugs simultaneously (a practice called stacking) and alternate routes of administration (oral, IM, or transdermal). Increasing the dose through a cycle (pyramiding) may result in doses 5 to 100 times the physiologic dose. Stacking and pyramiding are intended to increase receptor binding and minimize adverse effects, but these benefits have not been proved.

[Table 160-4, Adverse Effects of Anabolic Steroids]
Symptoms and Signs

The most characteristic sign is a rapid increase in muscle mass. The rate and extent of increase are directly related to the doses taken. Patients taking physiologic doses have slow and often unnoticeable growth; those taking megadoses may increase lean body weight by several pounds per month. Increases in energy level and libido (in men) occur but are more difficult to identify.

Psychologic effects (usually only with very high doses) are often noticed by family members:

• Wide and erratic mood swings
• Irrational behavior
• Increased aggressiveness ("roid rage")
• Irritability
• Increased libido
• Depression

Increased acne is common in both sexes; libido may increase or, less commonly, decrease; aggressiveness and appetite may increase. Gynecomastia, testicular atrophy, and decreased fertility may occur in males. Virilizing effects (eg, alopecia, enlarged clitoris, hirsutism, deepened voice) are common among females. Also, breast size may decrease; vaginal mucosa may atrophy; and menstruation may change or stop. Virilization and gynecomastia may be irreversible.

Diagnosis

• Urine testing

A urine screen usually identifies users of anabolic steroids. Metabolites of anabolic steroids can be detected in urine up to 6 mo (even longer for some types of anabolic steroids) after the drugs are stopped. Testosterone taken exogenously is indistinguishable from endogenous testosterone. However, if high levels of testosterone are detected, the ratio between testosterone and epitestosterone (an endogenous steroid that chemically is nearly identical to testosterone) is measured. Normally, the ratio is < 6:1; if exogenous testosterone is being used, the ratio is higher.

Treatment

• Cessation of use

The main treatment is cessation of use. Although physical dependence does not occur, psychologic dependence, particularly in competitive bodybuilders, may exist. Gynecomastia may require surgical reduction.

Prevention

Physicians caring for adolescents and young adults should be alert to the signs of steroid abuse and teach patients about its risks. Education about anabolic steroids should start by the beginning of middle school. Use of programs that teach alternative, healthy ways to increase muscle size and improve performance through good nutrition and weight training techniques may help.

Substance Use in Children and Adolescents

Substance use is common among children, especially adolescents. Regardless of economic or ethnic background, alcohol, tobacco, and marijuana are consistently the most commonly used substances. Use of other substances, including amphetamines and methamphetamines, inhalants, hallucinogens, cocaine,
anabolic steroids, opioids, and so-called date rape drugs and club drugs (eg, methylenedioxymethamphetamine [MDMA], ketamine, gamma hydroxybutyrate), is less common, and the prevalence of use of each varies more over time. Of growing concern is a reported increase in the prevalence of prescription opioid abuse.

Children and adolescents use drugs for a variety of reasons. Some do so to escape from perceived pressures (eg, parental pressure, societal pressure) or to challenge authority; others are disposed to novelty seeking and risk taking. Influence of peers and the media’s portrayal of substances such as alcohol are other commonly cited reasons. Poor self-control, lack of parental monitoring, or various psychologic disorders (eg, conduct disorder, attention-deficit/hyperactivity disorder, depression) may increase risk. Parental attitudes and the examples that parents set in their own use of alcohol, tobacco, prescription drugs, and other substances are a powerful influence.

Diagnosis

• Screening

Primary care physicians should be prepared to screen their adolescent patients for use of alcohol and drinking and provide counseling and, when necessary, referral to other treatment services and resources. The CRAFFT questionnaire is one validated screening tool. Patients with ≥ 2 positive answers require further evaluation. Physicians ask patients whether they do or have done the following:

• C: Ride in a Car driven by someone (including themselves) who is "high" or has been drinking alcohol or using drugs

• R: Drink alcohol or use drugs to Relax, feel better about themselves, or fit in

• A: Drink alcohol or use drugs while they are Alone

• F: Forget things they did while drinking or using drugs

• F: Are ever told by family members or Friends that they should drink or use drugs less

• T: Get into Trouble while drinking or using drugs
Chapter 161. Eating Disorders

Introduction

Eating disorders are grouped into 3 categories: anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified (EDNOS). Within EDNOS, provisional diagnostic criteria are provided for binge eating disorder.

Anorexia Nervosa

Anorexia nervosa is characterized by a relentless pursuit of thinness, a morbid fear of obesity, a refusal to maintain a minimally normal body weight, resulting in body weight below the normal range and, in women, amenorrhea. Diagnosis is clinical. Most treatment is with some form of psychologic therapy. Olanzapine may help with weight gain.

Anorexia nervosa occurs predominantly in girls and young women. Onset is usually during adolescence. The exact etiology is unknown. Other than being female, few risk factors have been identified. In Western society, obesity is considered unattractive and unhealthy, and the desire to be thin is pervasive, even among children. More than 50% of prepubertal girls diet or take other measures to control their weight. Excessive concern about weight or a history of dieting appears to indicate increased risk, and some genetic predisposition probably exists. Studies of identical twins have shown a concordance of < 50%. Family and social factors probably play a role. Many patients belong to middle or upper socioeconomic classes; are meticulous, compulsive, and intelligent; and have very high standards for achievement and success.

Two types of anorexia nervosa are recognized:

- Restricting type: Patients restrict food intake but do not regularly engage in binge eating or purging behavior.
- Binge-eating/purging type: Patients regularly binge, then induce vomiting, misuse laxatives, diuretics, or enemas, or a combination.

Binges are defined as consumption of a much larger amount of food than most people would eat in a similar time period under similar circumstances with loss of control, ie, perceived inability to resist or stop eating.

Pathophysiology

Endocrine abnormalities are common; they include low levels of luteinizing hormone (decreased secretion), low levels of thyroxine (T₄) and triiodothyronine (T₃), and increased cortisol secretion. Menses usually cease. Bone mass declines. In severely undernourished patients, virtually every major organ system may malfunction.

Dehydration and metabolic alkalosis may occur, and serum K may be low; all are aggravated by induced vomiting and laxative or diuretic use.

Cardiac muscle mass, chamber size, and output decrease; mitral valve prolapse is commonly detected. Some patients have prolonged QT intervals (even when corrected for heart rate), which, with the risks imposed by electrolyte disturbances, may predispose to tachyarrhythmias. Sudden death, most likely due to ventricular tachyarrhythmias, may occur.

Symptoms and Signs

Anorexia nervosa may be mild and transient or severe and long-standing. Most patients are lean yet are concerned about body weight and restrict food intake. Preoccupation and anxiety about weight increase,
even as emaciation develops.

Anorexia is a misnomer because appetite remains until patients become cachectic. Patients are preoccupied with food:

• They study diets and calories.
• They hoard, conceal, and waste food.
• They collect recipes.
• They prepare elaborate meals for other people.

Patients are often manipulative, lying about food intake and concealing behavior, such as induced vomiting. Binge-eating/purging occurs in 30 to 50% of patients. The others simply restrict their food intake.

Many anorectics also exercise excessively to control weight. Even patients who appear cachectic tend to remain very active (including pursuing vigorous exercise programs), are free of symptoms of nutritional deficiencies, and have no unusual susceptibility to infections.

Reports of bloating, abdominal distress, and constipation are common. Patients usually lose interest in sex. Depression occurs frequently.

Common physical findings include bradycardia, low BP, hypothermia, lanugo hair or slight hirsutism, and edema. Body fat is usually greatly reduced. Patients who vomit frequently may have eroded dental enamel, painless salivary gland enlargement, and an inflamed esophagus.

Diagnosis

• Clinical criteria

Denial is a prominent feature, and patients resist evaluation and treatment. They are usually brought to the physician's attention by family members or by intercurrent illness.

Clinical characteristics include the following:

• Body weight ≤ 85% of expected weight (with a BMI of < 17.5 kg/m²)
• Fear of obesity
• Denial of illness (body image disturbance)
• Amenorrhea in females

Patients should otherwise appear well. The key to diagnosis is eliciting the central fear of fatness, which is not diminished by weight loss.

Differential diagnosis: Another mental disorder, such as schizophrenia or primary depression, may cause similar findings.

Rarely, a severe physical disorder may cause substantial weight loss. Disorders to consider include malabsorption syndromes (eg, due to inflammatory bowel disease or celiac sprue), new-onset type 1 diabetes, adrenal insufficiency, and CNS tumors. Amphetamine abuse may cause similar symptoms.

Prognosis

Without treatment, mortality rates approach 10%; unrecognized mild disease probably rarely leads to
death. With treatment, one half of patients regain most or all of lost weight and reverse any endocrine and other complications. About one fourth have intermediate outcomes and may relapse. The remaining one fourth have a poor outcome, including relapses and persistent physical and mental complications.

Treatment

- Nutrition supplementation
- Psychologic therapy (eg, cognitive-behavioral treatment)
- For adolescents, family therapy

Treatment may require life-saving short-term intervention to restore body weight. When weight loss has been severe or rapid or when weight has fallen below about 75% of ideal, prompt restoration of weight becomes critical, and hospitalization should be considered. If any doubt exists, patients should be hospitalized. Removing patients from their home sometimes reverses a downhill course, but psychiatric treatment is also required.

Nutritional therapy, which begins by providing about 30 to 40 kcal/kg/day, can produce weight gains of up to 1.5 kg/wk during inpatient care and 0.5 kg/wk during outpatient care. Oral feedings are best, but very resistant, undernourished patients occasionally require nasogastric feedings. Loss of bone mass should be treated with elemental Ca 1200 to 1500 mg/day, vitamin D 600 to 800 IU/day, and, if severe, a bisphosphonate.

Once nutritional, fluid, and electrolyte status has been stabilized, long-term treatment begins. Outpatient psychologic therapy is the cornerstone of treatment. Cognitive-behavioral therapy is the modality of choice, done over a period of 1 yr for weight-restored patients and up to 2 yr for low-weight patients. Results are best in adolescents who have had the disorder < 6 mo. Family therapy, particularly using the Maudsley model, is useful for adolescents. This model has 3 phases:

- Family members are taught how to refeed the adolescent (eg, through a supervised family meal) and thus restore the adolescent's weight (in contrast to many approaches, this model does not assign blame to the family or the adolescent).
- Control over eating is gradually returned to the adolescent.
- After the adolescent is able to maintain the restored weight, therapy focuses on engendering a healthy adolescent identity.

Treatment is complicated by patients' abhorrence of weight gain, denial of illness, and manipulative behavior. The physician should attempt to provide a calm, concerned, stable relationship while encouraging a reasonable caloric intake.

Although psychologic therapy is primary, drugs are sometimes used. Second-generation antipsychotics (eg, olanzapine 10 mg po once/day) may help produce weight gain and relieve the morbid fear of obesity. Fluoxetine, beginning with 20 mg once/day, may help prevent relapse after weight has been restored.

Bulimia Nervosa

Bulimia nervosa is characterized by recurrent episodes of binge eating followed by some form of excessive compensatory behavior such as purging (self-induced vomiting, laxative or diuretic abuse), fasting, or driven exercise occurring at least 2 times/wk for 3 mo. Diagnosis is based on history and examination. Treatment is with psychologic therapy and antidepressants.

Bulimia nervosa affects about 1.6% of adolescent and young women and 0.5% of men of comparable age. Those affected are persistently and overly concerned about body shape and weight. Unlike patients with anorexia nervosa, those with bulimia nervosa are usually of normal weight.
Pathophysiology

Serious fluid and electrolyte disturbances, especially hypokalemia, occur occasionally. Very rarely, the stomach ruptures or the esophagus is torn during a binge, leading to life-threatening complications.

Because substantial weight loss does not occur, the serious nutritional deficiencies that occur with anorexia nervosa are not present. Cardiomyopathy may result from long-term abuse of syrup of ipecac to induce vomiting.

Symptoms and Signs

Patients typically describe binge-purge behavior. Binges involve rapid consumption of an amount of food definitely larger than most people would eat in a similar period of time under similar circumstances accompanied by feelings of loss of control.

Patients tend to consume high-calorie foods (eg, ice cream, cake). The amount of food consumed in a binge varies, sometimes involving thousands of calories. Binges tend to be episodic, are often triggered by psychosocial stress, may occur as often as several times a day, and are carried out in secret.

Binging is followed by purging: self-induced vomiting, use of laxatives or diuretics, excessive exercise, or fasting.

Patients are typically of normal weight; a minority is overweight or obese. Most symptoms and physical complications result from purging. Self-induced vomiting leads to erosion of dental enamel of the front teeth, painless parotid (salivary) gland enlargement, and an inflamed esophagus. Danger signs include

• Swollen parotid glands
• Scars on the knuckles (from induced vomiting)
• Dental erosion

Patients with bulimia nervosa tend to be more aware of and remorseful or guilty about their behavior than those with anorexia nervosa and are more likely to acknowledge their concerns when questioned by a sympathetic physician. They also appear less introverted and more prone to impulsive behavior, drug and alcohol abuse, and overt depression.

Diagnosis

• Clinical criteria

Criteria for diagnosis include the following:

• Recurrent binge eating (the uncontrolled consumption of unusually large amounts of food) at least twice/wk for 3 mo
• Recurrent inappropriate compensatory behavior to influence body weight (at least twice/wk for 3 mo)
• Self-evaluation unduly influenced by body shape and weight concerns

Treatment

• Cognitive-behavioral therapy (CBT)
• Interpersonal psychotherapy (IPT)
• SSRIs
CBT is the treatment of choice. Therapy usually involves 16 to 20 individual sessions over 4 to 5 mo, although it can also be done as group therapy. Treatment aims to increase motivation for change, replace dysfunctional dieting with a regular and flexible pattern of eating, decrease undue concern with body shape and weight, and prevent relapse. CBT eliminates binge eating and purging in about 30% to 50% of patients. Many others show improvement; some drop out of treatment or do not respond. Improvement is usually well-maintained over the long-term.

In IPT, the emphasis is on helping patients identify and alter current interpersonal problems that may be maintaining the eating disorder. The treatment is both nondirective and noninterpretive and does not focus directly on eating disorder symptoms. IPT can be considered an alternative when CBT is unavailable.

SSRIs used alone reduce the frequency of binge eating and vomiting, although long-term outcomes are unknown. SSRIs are also effective in treating comorbid anxiety and depression.

**Binge Eating Disorder**

*Binge eating disorder is characterized by recurrent episodes of consuming large amounts of food with a feeling of loss of control. It is not followed by inappropriate compensatory behavior, such as self-induced vomiting or laxative abuse. Diagnosis is clinical.*

Binge eating disorder affects about 3.5% of women and 2.0% of men in the general population. Unlike bulimia nervosa, binge eating disorder occurs most commonly among obese people and contributes to excessive caloric intake; it may be present in ≥ 30% of patients in some weight reduction programs. Compared with people with anorexia nervosa or bulimia nervosa, those with binge eating disorder are older and more likely to be men.

People with binge eating disorder are usually distressed by it, especially if they are trying to lose weight. Clinical depression and preoccupation with body shape, weight, or both are more common in obese people with binge eating disorder than in obese people who are not binge eaters.

**Diagnosis**

- **Clinical criteria**

Diagnosis requires binge eating for 2 days/wk for at least 6 mo and a sense of lack of control over eating, according to research criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision. Other criteria include presence of ≥ 3 of the following:

- Eating much more rapidly than normal
- Eating until feeling uncomfortably full
- Eating large amounts of food when not feeling physically hungry
- Eating alone because of embarrassment
- Feeling disgusted, depressed, or guilty after overeating

**Treatment**

- Cognitive-behavioral therapy (CBT)
- Sometimes interpersonal psychotherapy (IPT)
- Consideration of drug therapy with SSRIs or sibutramine

CBT is the most researched and best supported treatment. IPT and dialectical behavior therapy may also
be effective. Both CBT and IPT result in remission rates of ≥ 60%; improvement is usually well-maintained over the long-term. These treatments do not produce significant weight loss in obese patients.

Conventional behavioral weight loss treatment has short-term effectiveness in reducing binge eating, but patients tend to relapse. Antidepressant drugs also have short-term effectiveness in eliminating binge eating, but long-term effectiveness is unknown. Initial results with the appetite-suppressing drug sibutramine are promising.
Chapter 162. Mood Disorders

Introduction

(For mood disorders in children, see p. 3055.)

Mood disorders are emotional disturbances consisting of prolonged periods of excessive sadness, excessive joyousness, or both. Mood disorders are categorized as depressive or bipolar. Anxiety and related disorders (see p. 1493) also affect mood.

Sadness and joy (elation) are part of everyday life. Sadness is a universal response to defeat, disappointment, and other discouraging situations. Joy is a universal response to success, achievement, and other encouraging situations. Grief, a form of sadness, is considered a normal emotional response to a loss. Bereavement refers specifically to the emotional response to death of a loved one.

A mood disorder is diagnosed when sadness or elation is overly intense and persistent and is accompanied by a requisite number of other mood disorder symptoms. In such cases, intense sadness is termed depression, and intense elation is termed mania. Depressive disorders are characterized by depression; bipolar disorders are characterized by varying combinations of depression and mania.

Lifetime risk of suicide (see p. 1579) for people with a depressive disorder is 2 to 15%, depending on severity of the disorder. Risk is further increased in the following cases:

- At the start of treatment, when psychomotor activity is returning to normal but mood is still dark
- During mixed bipolar states
- At personally significant anniversaries
- By severe anxiety
- By alcohol and substance use

Other complications include disability ranging from mild to complete inability to function, maintain social interaction, and participate in routine activities; impaired food intake; severe anxiety; alcoholism; and other drug dependencies.

Depressive Disorders

Depressive disorders are characterized by sadness severe enough or persistent enough to interfere with function and often by decreased interest or pleasure in activities. Exact cause is unknown but probably involves heredity, changes in neurotransmitter levels, altered neuroendocrine function, and psychosocial factors. Diagnosis is based on history. Treatment usually consists of drugs, psychotherapy, or both and sometimes electroconvulsive therapy.

The term depression is often used to refer to any of several depressive disorders. Three are classified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revision (DSM-IV-TR) by specific symptoms:

- Major depressive disorder (often called major depression)
- Dysthymia
- Depressive disorder not otherwise specified

Two others are classified by etiology:
• Depressive disorder due to a general physical condition

• Substance-induced depressive disorder

Depressive disorders occur at any age but typically develop during the mid teens, 20s, or 30s. In primary care settings, as many as 30% of patients report depressive symptoms, but < 10% have major depression.

The term depression is often used to describe the low or discouraged mood that results from disappointments or losses. However, a better term for such a mood is demoralization. The negative feelings of demoralization, unlike those of depression, resolve when circumstances or events improve; the low mood usually lasts days rather than weeks or months, and suicidal thoughts and prolonged loss of function are much less likely.

Etiology

Exact cause is unknown, but genetic and environmental factors contribute.

Heredity accounts for about half of the etiology (less so in late-onset depression). Thus, depression is more common among 1st-degree relatives of depressed patients, and concordance between identical twins is high. Also, genetic factors probably influence the development of depressive responses to adverse events.

Other theories focus on changes in neurotransmitter levels, including abnormal regulation of cholinergic, catecholaminergic (noradrenergic or dopaminergic), and serotonergic (5-hydroxytryptamine) neurotransmission. Neuroendocrine dysregulation may be a factor, with particular emphasis on 3 axes: hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, and growth hormone.

Psychosocial factors also seem to be involved. Major life stresses, especially separations and losses, commonly precede episodes of major depression; however, such events do not usually cause lasting, severe depression except in people predisposed to a mood disorder.

People who have had an episode of major depression are at higher risk of subsequent episodes. People who are introverted and who have anxious tendencies may be more likely to develop a depressive disorder. Such people often do not develop the social skills to adjust to life pressures. Depression may also develop in people with other mental disorders.

Women are at higher risk, but no theory explains why. Possible factors include greater exposure to or heightened response to daily stresses, higher levels of monoamine oxidase (the enzyme that degrades neurotransmitters considered important for mood), higher rates of thyroid dysfunction, and endocrine changes that occur with menstruation and at menopause. In postpartum depression (see p. 2689), symptoms develop within 4 wk after delivery; endocrine changes have been implicated, but the specific cause is unknown.

In seasonal affective disorder, symptoms develop in a seasonal pattern, typically during autumn or winter; the disorder tends to occur in climates with long or severe winters.

Depressive symptoms or disorders may accompany various physical disorders, including thyroid and adrenal gland disorders, benign and malignant brain tumors, stroke, AIDS, Parkinson's disease, and multiple sclerosis (see Table 162-1). Certain drugs, such as corticosteroids, some β-blockers, interferon, and reserpine, can also result in depressive disorders. Abuse of some recreational drugs (eg, alcohol, amphetamines) can lead to or accompany depression. Toxic effects or withdrawal of drugs may cause transient depressive symptoms.

Symptoms and Signs

Depression causes cognitive, psychomotor, and other types of dysfunction (eg, poor concentration,
fatigue, loss of sexual desire, loss of pleasure), as well as a depressed mood. Other mental symptoms or disorders (eg, anxiety and panic attacks) commonly coexist, sometimes complicating diagnosis and treatment.

Patients with all forms of depression are more likely to abuse alcohol or other recreational drugs in an attempt to self-treat sleep disturbances or anxiety symptoms; however, depression is a less common cause of alcoholism and drug abuse than was once thought. Patients are also more likely to become heavy smokers and to neglect their health, increasing the risk of development or progression of other disorders (eg, COPD).

Table 162-1: Some Causes of Symptoms in Depression and Mania

Depression may reduce protective immune responses. Depression increases risk of cardiovascular disorders, MIs, and stroke, perhaps because in depression, cytokines and factors that increase blood clotting are elevated and heart rate variability is decreased—all potential risk factors for cardiovascular disorders.

Major depression (unipolar disorder): Periods (episodes) that include ≥ 5 mental or physical symptoms and last ≥ 2 wk are classified as major depression. One of the symptoms must be sadness deep enough to be described as despondency or despair (often called depressed mood) or loss of interest or pleasure in usual activities (anhedonia). Other mental symptoms include feelings of worthlessness or guilt, recurrent thoughts of death or suicide, and a reduced ability to concentrate. Physical symptoms include changes in weight or appetite, loss of energy, fatigue, psychomotor retardation or agitation, and sleep disorders (eg, insomnia, hypersomnia, early morning awakening). Patients may appear miserable, with tearful eyes, furrowed brows, down-turned corners of the mouth, slumped posture, poor eye contact, lack of facial expression, little body movement, and speech changes (eg, soft voice, lack of prosody, use of monosyllabic words). Appearance may be confused with Parkinson's disease. In some patients, depressed mood is so deep that tears dry up; they report that they are unable to experience usual emotions and feel that the world has become colorless and lifeless. Nutrition may be severely impaired, requiring immediate intervention. Some depressed patients neglect personal hygiene or even their children, other loved ones, or pets.

Major depression is often divided into subgroups:

- **Psychotic:** This subgroup is characterized by delusions, often of having committed unpardonable sins or crimes, of harboring incurable or shameful disorders, or of being persecuted. Patients with delusions may also have auditory or visual hallucinations (eg, hearing accusatory or condemning voices). If only voices are described, careful consideration should be given to whether the voices represent true hallucinations.

- **Catatonic:** This subgroup is characterized by severe psychomotor retardation or excessive purposeless activity, withdrawal, and, in some patients, grimacing and mimicry of speech (echolalia) or movement (echopraxia).

- **Melancholic:** This subgroup is characterized by loss of pleasure in nearly all activities, inability to respond to pleasurable stimuli, unchanging emotional expression, excessive or inappropriate guilt, early morning awakening, marked psychomotor retardation or agitation, and significant anorexia or weight loss.

- **Atypical:** This subgroup is characterized by a brightened mood in response to positive events and rejection sensitivity, resulting in depressed overreaction to perceived criticism or rejection, feelings of leaden paralysis or anergy, weight gain or increased appetite, and hypersomnia. Symptoms tend to worsen as the day passes.

**Dysthymia:** Low-level or subthreshold depressive symptoms that persist for ≥ 2 yr are classified as dysthymia. Symptoms typically begin insidiously during adolescence and follow a low-grade course over many years or decades (diagnosis requires a course of ≥ 2 yr); dysthymia may intermittently be complicated by episodes of major depression. Affected patients are habitually gloomy, pessimistic,
humorless, passive, lethargic, introverted, hypercritical of self and others, and complaining. Patients with chronic depressive states, whether dysthymia or chronic major depression, are also more likely to have underlying anxiety, substance use, or personality (ie, borderline personality) disorders.

**Depression not otherwise specified (NOS):** Clusters of symptoms that do not meet criteria for other depressive disorders are classified as depression NOS. For example, minor depressive disorder may involve ≥ 2 wk of any of the symptoms of major depression but fewer symptoms than the 5 required for diagnosing major depression. Brief depressive disorder involves the same symptoms required for diagnosing major depression but lasts only 2 days to 2 wk. Premenstrual dysphoric disorder involves a depressed mood, anxiety, and decreased interest in activities but only during most menstrual cycles, beginning in the luteal phase and ending within a few days after onset of menses.

**Mixed anxiety-depression:** Although not considered a type of depression in DSM-IV-TR, this condition, also called anxious depression, refers to concurrent mild symptoms common to anxiety and depression. The course is usually chronically intermittent. Because depressive disorders are more serious, patients with mixed anxiety-depression should be treated for depression.

**Diagnosis**

- Clinical criteria (DSM-IV-TR)
- CBC, thyroid-stimulating hormone, vitamin B₁₂, and folate levels to rule out physical disorders that can cause depression

Diagnosis is based on identifying the symptoms and signs (see p. 1539). Several brief questionnaires are available for screening. They help elicit some depressive symptoms but cannot be used alone for diagnosis. Specific close-ended questions help determine whether patients have symptoms required by DSM-IV-TR criteria for diagnosis of major depression.

Severity is determined by the degree of pain and disability (physical, social, occupational) and by duration of symptoms. A physician should gently but directly ask patients about any thoughts and plans to harm themselves or others (see p. 1579). Psychosis and catatonia indicate severe depression. Melancholic features indicate severe or moderate depression. Coexisting physical conditions, substance abuse disorders, and anxiety disorders may add to severity.

**Differential diagnosis:** Depressive disorders must be distinguished from demoralization. Other mental disorders (eg, anxiety disorders) can mimic or obscure the diagnosis of depression. Sometimes more than one disorder is present. Major depression (unipolar disorder) must be distinguished from bipolar disorder (see p. 1548).

In elderly patients, depression can manifest as dementia of depression (formerly called pseudodementia), which causes many of the symptoms and signs of dementia such as psychomotor retardation and decreased concentration (see p. 1673). However, early dementia may cause depression. In general, when the diagnosis is uncertain, treatment of a depressive disorder should be tried.

Differentiating chronic depressive disorders, such as dysthymia, from substance abuse disorders may be difficult, particularly because they can coexist and may contribute to each other.

Physical disorders must also be excluded as a cause of depressive symptoms. Hypothyroidism often causes symptoms of depression and is common, particularly among the elderly. Parkinson's disease, in particular, may manifest with symptoms that mimic depression (eg, loss of energy, lack of expression, paucity of movement). A thorough neurologic examination is needed to exclude this disorder.

**Testing:** No laboratory findings are pathognomonic for depressive disorders. Tests for limbic-diencephalic dysfunction are rarely indicated or helpful. However, laboratory testing is necessary to exclude physical conditions that can cause depression. Tests include CBC, TSH levels, and routine electrolyte, vitamin B₁₂, and folate levels. Testing for illicit drug use is sometimes appropriate.
Treatment

• Support

• Psychotherapy

• Drugs

Symptoms may remit spontaneously, particularly when they are mild or of short duration. Mild depression may be treated with general support and psychotherapy. Moderate to severe depression is treated with drugs, psychotherapy, or both and sometimes electroconvulsive therapy. Some patients require a combination of drugs. Improvement may not be apparent until after 1 to 4 wk of drug treatment.

Depression, especially in patients who have had > 1 episode, is likely to recur; therefore, severe cases often warrant long-term maintenance drug therapy.

Most people with depression are treated as outpatients. Patients with significant suicidal ideation, particularly when family support is lacking, require hospitalization, as do those with psychotic symptoms or physical debilitation.

Depressive symptoms in patients with substance abuse disorders often resolve within a few months of stopping substance use. Antidepressant treatment is much less likely to be effective while substance abuse continues.

If a physical disorder or drug toxicity could be the cause, treatment is directed first at the underlying disorder. However, if the diagnosis is in doubt or if symptoms are disabling or include suicidal ideation or hopelessness, a therapeutic trial with an antidepressant or a mood-stabilizing drug may help.

Initial support: Until definite improvement begins, a physician should see patients weekly or biweekly to provide support and education and to monitor progress. Telephone calls may supplement office visits.

Patients and loved ones may be worried or embarrassed about the idea of having a mental disorder. The physician can help by explaining that depression is a serious medical disorder caused by biologic disturbances and requires specific treatment and that the prognosis with treatment is good. Patients and loved ones should be reassured that depression does not reflect a character flaw (eg, laziness, weakness). Telling patients that the path to recovery often fluctuates helps them put feelings of hopelessness in perspective and improves adherence.

Encouraging patients to gradually increase simple activities (eg, taking walks, exercising regularly) and social interactions must be balanced with acknowledging their desire to avoid activities. The physician can suggest that patients avoid self-blame and explain that dark thoughts are part of the disorder and will go away.

Psychotherapy: Psychotherapy, often as cognitive-behavioral therapy (individual or group), alone is often effective for milder forms of depression. Cognitive-behavioral therapy is increasingly used to combat the inertia and self-defeating mental set of depressed patients. However, cognitive-behavioral therapy is most useful when combined with antidepressants to treat moderate to severe depression. Cognitive-behavioral therapy may improve coping skills and enhance gains by providing support and guidance, by removing cognitive distortions that prevent adaptive action, and by encouraging patients to gradually resume social and occupational roles. Couple therapy may help reduce conjugal tensions and disharmony. Long-term psychotherapy is usually unnecessary except for patients who have long-term interpersonal conflicts or who are unresponsive to brief therapy.

Selective serotonin reuptake inhibitors (SSRIs): These drugs prevent reuptake of serotonin (5-hydroxytryptamine [5-HT]). SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Although these drugs have the same mechanism of action, differences in their clinical properties make selection important. SSRIs have a wide therapeutic margin; they are relatively easy to administer, with little need for dose adjustment (except for fluvoxamine).
By preventing reuptake of 5-HT presynaptically, SSRIs result in more 5-HT to stimulate postsynaptic 5-HT receptors. SSRIs are selective to the 5-HT system but not specific for the different 5-HT receptors. They stimulate 5-HT₁ receptors, with antidepressant and anxiolytic effects, but they also stimulate 5-HT₂ receptors, commonly causing anxiety, insomnia, and sexual dysfunction, and 5-HT₃ receptors, commonly causing nausea and headache. Thus, SSRIs can paradoxically relieve and cause anxiety.

A few patients may seem more agitated, depressed, and anxious within a week of starting SSRIs or increasing the dose. Patients and their loved ones should be warned of this possibility and instructed to call the physician if symptoms worsen with treatment. This situation should be closely monitored because some patients, especially younger children and adolescents, become increasingly suicidal if agitation, increased depression, and anxiety are not detected and rapidly treated. Recent studies have determined that children, adolescents, and young adults have an increased rate of suicidal ideation, suicide gestures, and suicide attempts during the first few months of taking SSRIs (the same concern may apply to serotonin modulators, serotonin-norepinephrine reuptake inhibitors, and norepinephrine-dopamine reuptake inhibitors); physicians must balance this risk with clinical need.

Sexual dysfunction (especially difficulty achieving orgasm but also decreased libido and erectile dysfunction) occurs in one third or more of patients. Some SSRIs cause weight gain. Others, especially fluoxetine, may cause anorexia in the first few months. SSRIs have few anticholinergic, adrenolytic, and cardiac conduction effects. Sedation is minimal or nonexistent, but in the early weeks of treatment, some patients tend to be sleepy during the day. Loose stools or diarrhea occurs in some patients.

Drug interactions are relatively uncommon; however, fluoxetine, paroxetine, and fluvoxamine can inhibit cytochrome P-450 (CYP450) isoenzymes, which can lead to serious drug interactions. For example, these drugs can inhibit the metabolism of certain β-blockers, including propranolol and metoprolol, potentially resulting in hypotension and bradycardia. Discontinuation symptoms (eg, irritability, anxiety, nausea) can occur if the drug is stopped abruptly; such effects are less likely with fluoxetine.

**Serotonin modulators (5-HT₂ blockers):** These drugs block primarily the 5-HT₂ receptor and inhibit reuptake of 5-HT and norepinephrine. Serotonin modulators include nefazodone, trazodone, and mirtazapine. Serotonin modulators have antidepressant and anxiolytic effects but do not cause sexual dysfunction. Unlike most antidepressants, nefazodone does not suppress REM (rapid eye movement) sleep and produces restful sleep. Nefazodone can significantly interfere with drug-metabolizing liver enzymes and has been associated with liver failure.

Trazodone is related to nefazodone but does not inhibit 5-HT reuptake presynaptically. Unlike nefazodone, trazodone has caused priapism (in 1/1000) and, as an α₁-noradrenergic blocker, may cause orthostatic (postural) hypotension. It is very sedating, so its use in antidepressant doses (> 200 mg/day) is limited. It is most often given in 50- to 100-mg doses at bedtime to depressed patients with insomnia.

Mirtazapine inhibits 5-HT reuptake and blocks α₂-adrenergic autoreceptors, as well as 5-HT₂ and 5-HT₃ receptors. The result is increased serotonergic function and increased noradrenergic function without sexual dysfunction or nausea. It has no cardiac adverse effects, has minimal interaction with drug-metabolizing liver enzymes, and is generally well tolerated, although it does cause sedation and weight gain, mediated by H₁ (histamine) blockade.

**Serotonin-norepinephrine reuptake inhibitors:** These drugs (eg, venlafaxine, duloxetine) have a dual 5-HT and norepinephrine mechanism of action, as do tricyclic antidepressants. However, their toxicity approximates that of SSRIs. Nausea is the most common problem during the first 2 wk; modest dose-dependent increases in BP occur with high doses. Discontinuation symptoms (eg, irritability, anxiety, nausea) often occur if the drug is stopped suddenly. Duloxetine resembles venlafaxine in effectiveness and adverse effects.

**Norepinephrine-dopamine reuptake inhibitors:** By mechanisms not clearly understood, these drugs favorably influence catecholaminergic, dopaminergic, and noradrenergic function. They do not affect the 5-HT system.
Bupropion is currently the only drug in this class. It can help depressed patients with concurrent attention-deficit/hyperactivity disorder or cocaine dependence and those trying to stop smoking. Bupropion causes hypertension in a very few patients but has no other effects on the cardiovascular system. Bupropion can cause seizures in 0.4% of patients taking doses > 150 mg tid (or > 200 mg sustained-release [SR] bid or > 450 mg extended-release [XR] once/day); risk is increased in patients with bulimia. Bupropion does not have sexual adverse effects and interacts little with coadministered drugs, although it does inhibit the CYP2D6 hepatic enzyme. Agitation, which is common, is considerably attenuated by using the SR or XR form.

**Heterocyclic antidepressants:** This group of drugs, once the mainstay of treatment, includes tricyclic (tertiary amines amitriptyline and imipramine and their secondary amine metabolites nortriptyline and desipramine), modified tricyclic, and tetracyclic antidepressants. Acutely, these drugs increase the availability of primarily norepinephrine and, to some extent, 5-HT by blocking reuptake in the synaptic cleft. Long-term use downregulates α1-adrenergic receptors on the postsynaptic membrane—a possible final common pathway of their antidepressant activity.

Although effective, these drugs are now rarely used because overdose causes toxicity and they have more adverse effects than other antidepressants. The more common adverse effects of heterocyclics are due to their muscarinic-blocking, histamine-blocking, and α1-adrenolytic actions. Many heterocyclics have strong anticholinergic properties and are thus unsuitable for the elderly and for patients with benign prostatic hypertrophy, glaucoma, or chronic constipation. All heterocyclics, particularly maprotiline and clomipramine, lower the threshold for seizures.

**Monoamine oxidase inhibitors (MAOIs):** These drugs inhibit the oxidative deamination of the 3 classes of biogenic amines (norepinephrine, dopamine, 5-HT) and other phenylethylamines. MAOIs have little or no effect on normal mood. Their primary value is for treating refractory or atypical depression when SSRIs, tricyclic antidepressants, and sometimes even electroconvulsive therapy is ineffective.

MAOIs marketed as antidepressants in the US (eg, phenelzine, tranylcypromine, isocarboxazid) are irreversible and nonselective (inhibiting MAO-A and MAO-B). Another MAOI (selegiline), which inhibits only MAO-B at lower doses, is available as a patch.

MAOIs that inhibit MAO-A and MAO-B can cause hypertensive crises if a sympathomimetic drug or food containing tyramine or dopamine is ingested concurrently. This effect is called the cheese reaction because mature cheese has a high tyramine content. MAOIs are used infrequently because of concern about this reaction. The lower dosage of the selegiline patch is considered safe to use without specific dietary restrictions, unless the dosage must be higher than starting levels (a 6-mg patch). More selective and reversible MAOIs (eg, moclobemide, befloxatone), which inhibit MAO-A, are not yet available in the US; they are relatively free of these interactions. To prevent hypertension and febrile crises, patients taking MAOIs should avoid sympathomimetic drugs (eg, pseudoephedrine), dextromethorphan, reserpine, and meperidine as well as malted beers, Chianti wines, sherry, liqueurs, and overripe or aged foods that contain tyramine or dopamine (eg, bananas, fava or broad beans, yeast extracts, canned figs, raisins, yogurt, cheese, sour cream, soy sauce, pickled herring, caviar, liver, extensively tenderized meats). Patients can carry 25-mg tablets of chlorpromazine and, as soon as signs of such a hypertensive reaction occur, take 1 or 2 tablets as they head to the nearest emergency department.

Common adverse effects include erectile dysfunction (least common with tranylcypromine), anxiety, nausea, dizziness, insomnia, pedal edema, and weight gain. MAOIs should not be used with other classes of antidepressants, and at least 2 wk (5 wk with fluoxetine, which has a long half-life) should elapse between use of the 2 classes of drugs. MAOIs used with antidepressants that affect the 5-HT system (eg, SSRIs, nefazodone) may cause neuroleptic malignant syndrome (malignant hyperthermia, muscle breakdown, renal failure, seizures, and eventual death). Patients who are taking MAOIs and who also need antiasthmatic or antiallergic drugs, a local anesthetic, or a general anesthetic should be treated by a psychiatrist plus an internist, a dentist, or an anesthesiologist with expertise in neuropsychopharmacology.

**Drug choice and administration:** Choice of drug may be guided by past response to a specific
antidepressant. Otherwise, SSRIs are often the initial drugs of choice. Although the different SSRIs are equally effective for typical cases, certain properties of the drugs make them more or less appropriate for certain patients (see Table 162-2).

If one SSRI is ineffective, another SSRI can be substituted, but an antidepressant from a different class may be more likely to help. Tranylcypromine in high doses (20 to 30 mg po bid) is often effective for depression refractory to sequential trials of other antidepressants; it should be given by a physician experienced in use of MAOIs. Psychologic support of patients and loved ones is particularly important in refractory cases.

Insomnia, a common adverse effect of SSRIs, is treated by reducing the dose or adding a low dose of trazodone or another sedating antidepressant. Initial nausea and loose stools usually resolve, but throbbing headaches do not always go away, necessitating a change in drug class. An SSRI should be stopped if it causes agitation. When decreased libido, impotence, or anorgasmia occur during SSRI therapy, dose reduction may help, or a change can be made to another drug class.

SSRIs, which tend to stimulate many depressed patients, should be given in the morning. Giving the entire heterocyclic antidepressant dose at bedtime usually makes sedatives unnecessary, minimizes adverse effects during the day, and improves adherence. MAOIs are usually given in the morning and early afternoon to avoid excessive stimulation.

Therapeutic response with most classes of antidepressants usually occurs in about 2 to 3 wk (sometimes as early as 4 days or as late as 8 wk). For a first episode of mild or moderate depression, the antidepressant should be given for 6 mo, then tapered gradually over 2 mo. If the episode is severe or is a recurrence or if there is suicidal risk, the dose that produces full remission should be continued during maintenance.

For psychotic depression, imipramine appears to be more effective than monotherapy with antidepressants from other classes; dosing this drug can be guided by steady-state plasma levels. The addition of an antipsychotic may improve the likelihood of response, but antipsychotic monotherapy appears to be ineffective.

Continued therapy with an antidepressant for 6 to 12 mo (up to 2 yr in patients > 50) is usually needed to prevent relapse. Most antidepressants, especially SSRIs, should be tapered off (by decreasing the dose by about 25%/wk) rather than stopped abruptly; stopping SSRIs abruptly may result in discontinuation syndrome (nausea, chills, muscles aches, dizziness, anxiety, irritability, insomnia, fatigue). The likelihood and severity of withdrawal varies inversely with the half-life of the SSRI.

Medicinal herbs are used by some patients. St. John's wort (see p. 3431) may be effective for mild depression, although data are contradictory. St. John's wort may interact with other antidepressants and other drugs. A number of placebo-controlled studies of ω-3 supplementation, used as augmentation or as monotherapy, have suggested that eicosapentaenoic acid 1 to 2 g once/day has useful antidepressant effects.

**Electroconvulsive therapy (ECT):** Severe suicidal depression, depression with agitation or psychomotor retardation, delusional depression, or depression during pregnancy is often treated with ECT if drugs are ineffective. Patients who have stopped eating may need ECT to prevent death. ECT is also effective for psychotic depression. Response to 6 to 10 ECT treatments is usually dramatic and may be lifesaving. Relapse after ECT is common, and drug therapy is often maintained after ECT is stopped.

**Phototherapy:** Phototherapy is best known for its effects on seasonal depression but can also be effective in other types of depression. Treatment can be provided at home with 2,500 to 10,000 lux at a distance of 30 to 60 cm for 30 to 60 min/day (longer with a less intense light source). In patients who go to sleep late at night and rise late in the morning, phototherapy is most effective in the morning.
sometimes supplemented with 5 to 10 min of exposure between 3 PM and 7 PM. For patients who go to sleep and rise early, phototherapy is most effective between 3 PM and 7 PM.

**Other therapies:** Psychostimulants (eg, dextroamphetamine, methylphenidate) are sometimes used, often with antidepressants; however, they have not been well studied in controlled clinical trials.

Vagus nerve stimulation involves intermittently stimulating the vagus nerve via an implanted pulse generator. It may be useful for depression refractory to other treatments but usually takes 3 to 6 mo to be effective.

Deep brain stimulation and transcranial magnetic stimulation are still under study.

**Bipolar Disorders**

Bipolar disorders are characterized by episodes of mania and depression, which may alternate, although many patients have a predominance of one or the other. Exact cause is unknown, but heredity, changes in the level of brain neurotransmitters, and psychosocial factors may be involved. Diagnosis is based on history. Treatment consists of mood-stabilizing drugs, sometimes with psychotherapy.

Bipolar disorders usually begin in the teens, 20s, or 30s. Lifetime prevalence is about 4%. Rates are about equal for men and women.

Bipolar disorders are classified as

- **Bipolar I disorder:** Defined by the presence of at least one full-fledged (ie, disrupting normal social and occupational function) manic or mixed episode and usually depressive episodes
- **Bipolar II disorder:** Defined by the presence of major depressive episodes with at least one hypomanic episode but no full-fledged manic episodes
- **Bipolar disorder not otherwise specified (NOS):** Disorders with clear bipolar features that do not meet the specific criteria for other bipolar disorders

**Etiology**

Exact cause is unknown. Heredity plays a significant role. There is also evidence of dysregulation of serotonin and norepinephrine. Psychosocial factors may be involved. Stressful life events are often associated with initial development of symptoms and later exacerbations, although cause and effect have not been established. Certain drugs can trigger exacerbations in some patients with bipolar disorder; these drugs include sympathomimetics (eg, cocaine, amphetamines), alcohol, and certain antidepressants (eg, tricyclics, MAOIs).

**Symptoms and Signs**

Bipolar disorder begins with an acute phase of symptoms, followed by a repeating course of remission and relapse. Remissions are usually complete, although some patients have residual symptoms. Relapses are discrete episodes of more intense symptoms that are manic, depressive, hypomanic, or a mixture of depressive and manic features. Episodes last anywhere from a few weeks to 3 to 6 mo. Cycles—time from onset of one episode to that of the next—vary in length among patients. Some patients have infrequent episodes, perhaps only a few over a lifetime, whereas others have rapid-cycling forms (usually defined as ≥ 4 episodes/yr). Only a minority alternate back and forth between mania and depression with each cycle; in most, one or the other predominates to some extent.

**Mania:** A manic episode is defined as ≥ 1 wk of a persistently elevated, expansive, or irritable mood plus ≥ 3 additional symptoms:

- Inflated self-esteem or grandiosity
• Decreased need for sleep
• Greater talkativeness than usual
• Persistent elevation of mood
• Flight of ideas or racing of thoughts
• Distractibility
• Increased goal-directed activity

Manic patients are inexhaustibly, excessively, and impulsively involved in various pleasurable, high-risk activities (eg, gambling, dangerous sports, promiscuous sexual activity) without insight into possible harm. Symptoms are so severe that they impair functioning; unwise investments, spending sprees, and other personal choices may have irreparable consequences.

Typically, patients in a manic episode are exuberant and flamboyantly or colorfully dressed; they have an authoritative manner with a rapid, unstoppable flow of speech. Patients may make clang associations (new thoughts that are triggered by word sounds rather than meaning). Easily distracted, patients may constantly shift from one theme or endeavor to another. However, they tend to believe they are in their best mental state. Lack of insight and an increased capacity for activity often lead to intrusive behavior and can be a dangerous combination. Interpersonal friction results and may cause patients to feel that they are being unjustly treated or persecuted. As a result, patients may become a danger to themselves or to other people. Accelerated mental activity is experienced as racing thoughts by patients and is observed as flights of ideas by the physician.

**Manic psychosis** is a more extreme manifestation, with psychotic symptoms that may be difficult to distinguish from schizophrenia. Patients may have extreme grandiose or persecutory delusions (eg, of being Jesus or being pursued by the FBI), occasionally with hallucinations. Activity level increases markedly; patients may race about and scream, swear, or sing. Mood lability increases, often with increasing irritability. Full-blown delirium (delirious mania) may appear, with complete loss of coherent thinking and behavior.

**Hypomania:** A hypomanic episode is a less extreme variant of mania involving a distinct episode that lasts ≥ 4 days and is distinctly different from the patient's usual nondepressed mood. During the hypomanic period, mood brightens, the need for sleep decreases, and psychomotor activity accelerates. For some patients, hypomanic periods are adaptive because they produce high energy, creativity, confidence, and supernormal social functioning. Many do not wish to leave the pleasurable, euphoric state. Some function quite well, and in most, functioning is not markedly impaired. However, in some patients, hypomania manifests as distractibility, irritability, and labile mood, which the patient and others find less attractive.

**Depression:** A depressive episode has features typical of major depression (see p. 1538), including depressed mood, anhedonia, psychomotor retardation, and feelings of pessimism and guilt. Sleeping and eating often increase. Delusions of guilt accompanied by self-loathing are common in psychotic depression, and some patients have hallucinations.

**Mixed state:** A mixed episode blends depressive and manic or hypomanic features; the criteria for both mania and depression are met. For example, patients may momentarily switch to tearfulness during the height of mania, or their thoughts may race during a depressive period. Often, the switch follows circadian factors (eg, going to bed depressed and waking early in the morning in a hypomanic state). In at least one third of people with bipolar disorder, the entire episode is mixed. A common presentation consists of a dysphorically excited mood, crying, curtailed sleep, racing thoughts, grandiosity, psychomotor restlessness, suicidal ideation, persecutory delusions, auditory hallucinations, indecisiveness, and confusion. This presentation is called dysphoric mania (ie, prominent depressive symptoms superimposed on manic psychosis).
Diagnosis

• Clinical criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision)

• Thyroxine (T4) and thyroid-stimulating hormone (TSH) levels to exclude hyperthyroidism

• Exclusion of stimulant drug abuse clinically or by urine testing

Diagnosis is based on identification of symptoms of mania or hypomania as described above, plus a history of remission and relapse. Some patients who present with depressive symptoms may have previously experienced hypomania or mania but do not report it unless they are specifically questioned. Skillful questioning may reveal morbid signs (eg, excesses in spending, impulsive sexual escapades, stimulant drug abuse), although such information is more likely to be provided by relatives. All patients must be asked gently but directly about suicidal ideation, plans, or activity.

Similar acute manic or hypomanic symptoms may result from stimulant abuse, a schizoaffective disorder (bipolar type), or physical disorders such as hyperthyroidism or pheochromocytoma. A review of substance use (especially of amphetamines and cocaine) and urine drug screening can help identify drug causes. However, because drug use may simply have triggered an episode in a patient with bipolar disorder, seeking evidence of symptoms (manic or depressive) not related to drug use is important. Patients with a schizoaffective disorder rarely return to normal between episodes, and they do not show the interest in connecting with other people manifested by patients with mania (except those with the most florid type). Patients with hyperthyroidism typically have other physical symptoms and signs (see p. 781), but thyroid function testing (T4 and TSH levels) is a reasonable screen for new patients. Patients with pheochromocytoma are markedly hypertensive; if not, testing is not indicated.

Patients with bipolar disorder may also have anxiety disorders (eg, social phobia, panic attacks, obsessive-compulsive disorders), possibly confusing the diagnosis.

Treatment

• Mood stabilizers (eg, lithium, certain anticonvulsants), a 2nd-generation antipsychotic, or both

• Support and psychotherapy

Treatment usually has 3 phases:

• Acute: To stabilize and control the initial, sometimes severe manifestations

• Continuation: To attain full remission

• Maintenance or prevention: To keep patients in remission

Although most patients with hypomania can be treated as outpatients, severe mania or depression often requires inpatient management.

Drugs for bipolar disorder include mood stabilizers and 2nd-generation antipsychotics. These drugs are used alone or in combination for all phases of treatment, although at different dosages.

Mood stabilizers consist of lithium and certain anticonvulsants, especially valproate, carbamazepine, and lamotrigine. Second-generation antipsychotics include aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Specific antidepressants (eg, SSRIs) are sometimes added for severe depression, but antidepressants (particularly heterocyclics) may trigger mania, and their effectiveness continues to be studied. They are not recommended as sole therapy for depressive episodes.

Electroconvulsive therapy (ECT) is sometimes used for depression refractory to treatment and is also effective for mania. Phototherapy can be useful in treating seasonal bipolar I or bipolar II disorder (with
autumn-winter depression and spring-summer hypomania). It is probably most useful as augmentative therapy.

**Drug selection and use**: Choice of drug can be difficult because all drugs have significant adverse effects, drug interactions are common, and no drug is universally effective. Selection should be based on what has previously been effective and well tolerated in a given patient. If there is no prior experience (or it is unknown), choice is based on the patient's medical history (vis-a-vis the adverse effects of the specific mood stabilizer) and the severity of symptoms.

For severe manic psychosis, in which immediate patient safety and management is compromised, urgent behavioral control usually requires a sedating 2nd-generation antipsychotic, sometimes supplemented initially with a benzodiazepine such as lorazepam or clonazepam 2 to 4 mg IM or po tid.

For less severe acute episodes in patients without contraindications (eg, renal disorders), lithium is a good first choice for both mania and depressive episodes. Because its onset is slow (4 to 10 days), patients with significant symptoms may also be given an anticonvulsant or a 2nd-generation antipsychotic. For those with depression, lamotrigine may be a good choice of anticonvulsant.

Once remission is achieved, preventive treatment with mood stabilizers is indicated for all bipolar I patients. If episodes recur during maintenance treatment, clinicians should determine whether adherence is poor and, if so, whether nonadherence preceded or followed recurrence. Reasons for nonadherence should be explored to determine whether a change in mood stabilizer type or dosing would render treatment more acceptable.

**Lithium**: As many as two thirds of patients with uncomplicated bipolar disorder may respond to lithium, which attenuates bipolar mood swings but has no effect on normal mood. Whether lithium or another mood stabilizer is being used, breakthroughs are more likely in patients who have mixed states, rapid-cycling forms of bipolar disorder, comorbid anxiety, substance abuse, or a neurologic disorder.

Lithium carbonate is started at 300 mg po bid or tid and titrated, based on steady-state blood levels and tolerance, to a range of 0.8 to 1.2 mEq/L. Levels should be drawn after 5 days at a stable dose and 12 h after the last dose. Target drug levels for maintenance are lower, about 0.6 to 0.7 mEq/L. Higher maintenance levels are more protective against manic (but not depressive) episodes but have more adverse effects. Adolescents, whose glomerular function is excellent, need higher doses; elderly patients need lower doses.

Lithium can cause sedation and cognitive impairment directly or indirectly (by causing hypothyroidism) and often exacerbates acne and psoriasis. The most common acute, mild adverse effects are fine tremor, fasciculation, nausea, diarrhea, polyuria, polydipsia, and weight gain (partly attributed to drinking high-calorie beverages). These effects are usually transient and often respond to decreasing the dose slightly, dividing the dose (eg, tid), or using slow-release forms. Once dosage is established, the entire dose should be given after the evening meal. This dosing may improve adherence. A β-blocker (eg, atenolol 25 to 50 mg po once/day) can control severe tremor; however, some β-blockers (eg, propranolol) may worsen depression.

Acute lithium toxicity is manifested initially by gross tremor, increased deep tendon reflexes, persistent headache, vomiting, and confusion and may progress to stupor, seizures, and arrhythmias. Toxicity is more likely to occur in elderly patients, in patients with decreased creatinine clearance, and in those with Na loss (eg, due to fever, vomiting, diarrhea, or use of diuretics). Thiazide diuretics, ACE inhibitors, and NSAIDs other than aspirin may contribute to hyperlithemia. Lithium blood levels should be measured every 6 mo and whenever the dose is changed.

Long-term effects include hypothyroidism, particularly when there is a family history of hypothyroidism, and renal damage involving the distal tubule (mainly in patients with a history of renal parenchymal disease). Therefore, TSH levels should be monitored when lithium is started and annually thereafter if there is a family history of thyroid dysfunction or every other year for all other patients. Levels should also be measured whenever symptoms suggest thyroid dysfunction (including when mania recurs) because hypothyroidism may blunt the effect of mood stabilizers. BUN and creatinine should be measured at
baseline, 2 or 3 times during the first 6 mo, and then once or twice a year.

**Anticonvulsants:** Anticonvulsants that act as mood stabilizers, especially valproate and carbamazepine, are often used for acute mania and for mixed states (mania and depression). Lamotrigine is also effective for mood-cycling and for depression; unlike some antidepressants, it does not induce mania. The precise mechanism of action for anticonvulsants in bipolar disorder is unknown but may involve γ-aminobutyric acid mechanisms and ultimately G-protein signaling systems. Their main advantages over lithium include a wider therapeutic margin and lack of renal toxicity.

For valproate, a loading dose of 20 mg/kg is given, then 250 to 500 mg po tid (extended-release formulation can be used); target blood levels are between 50 and 125 μg/mL. Adverse effects include nausea, headache, sedation, dizziness, and weight gain; rare serious effects include hepatotoxicity and pancreatitis.

Carbamazepine should not be loaded; it should be started at 200 mg po bid and be increased gradually in 200-mg/day increments to target levels between 4 and 12 μg/mL (maximum, 800 mg bid). Adverse effects include nausea, dizziness, sedation, and unsteadiness. Very severe effects include aplastic anemia and agranulocytosis.

Lamotrigine is started at 25 mg po once/day for 2 wk, then 50 mg once/day for 2 wk, then 100 mg/day for 1 wk, and then can be increased by 50 mg each week as needed up to 200 mg once/day. Dosage is lower for patients taking valproate and higher for patients taking carbamazepine. Lamotrigine can cause rash and, rarely, the life-threatening Stevens-Johnson syndrome (see p. 689), particularly if the dosage is increased more rapidly than recommended. While taking lamotrigine, patients should be encouraged to report any new rash, hives, fever, swollen glands, sores in the mouth and on the eyes, and swelling of the lips or tongue.

**Antipsychotics:** Acute manic psychosis is being increasingly managed with 2nd-generation antipsychotics, such as risperidone (usually 4 to 6 mg po once/day), olanzapine (usually 10 to 20 mg po once/day), quetiapine (200 to 400 mg po bid), ziprasidone (40 to 80 mg po bid), and aripiprazole (10 to 30 mg po once/day). In addition, evidence suggests that these drugs may enhance the effects of mood stabilizers after the acute phase.

Although any of these drugs may have extrapyramidal adverse effects and cause akathisia, risk is lower with more sedating drugs such as quetiapine and olanzapine. Less immediate adverse effects include substantial weight gain and development of the metabolic syndrome (including weight gain, excess abdominal fat, insulin resistance, and dyslipidemia); risk may be lower with the least sedating 2nd-generation antipsychotics, ziprasidone and aripiprazole. For extremely hyperactive psychotic patients with poor food and fluid intake, an antipsychotic given IM plus supportive care in addition to lithium or an anticonvulsant may be appropriate.

**Precautions during pregnancy:** Lithium use during pregnancy has been associated with an increased risk of cardiovascular malformations (particularly Ebstein's anomaly). However, the absolute risk of this particular malformation is quite low. Taking lithium during pregnancy appears to increase the relative risk of any congenital anomaly by about 2-fold, a risk similar to the 2- to 3-fold increased risk of congenital anomalies associated with use of carbamazepine or lamotrigine and is substantially lower than the risk associated with use of valproate.

Extensive study of the use of 1st-generation antipsychotics and tricyclic antidepressants during early pregnancy has not revealed causes for concern. The same appears to be true of SSRIs, except for paroxetine. Data about the risks of 2nd-generation antipsychotics to the fetus are sparse as yet, even though these drugs are being more widely used for all phases of bipolar disorder.

Use of drugs (particularly lithium and SSRIs) before parturition may have carry-over effects on neonates.

Treatment decisions are complicated by the fact that with unplanned pregnancy, teratogenic effects may already have taken place by the time practitioners' become aware of the issue. Consultation with a perinatal psychiatrist should be considered. In all cases, discussing the risks and benefits of treatment.
with patients is important.

**Education and psychotherapy:** Enlisting the support of loved ones is crucial to preventing major episodes. Group therapy is often recommended for patients and their partner; there, they learn about bipolar disorder, its social sequelae, and the central role of mood stabilizers in treatment. Individual psychotherapy may help patients better cope with problems of daily living and adjust to a new way of identifying themselves.

Patients, particularly those with bipolar II disorder, may not adhere to mood-stabilizer regimens because they believe that these drugs make them less alert and creative. The physician can explain that decreased creativity is relatively uncommon because mood stabilizers usually provide opportunity for a more even performance in interpersonal, scholastic, professional, and artistic pursuits.

Patients should be counseled to avoid stimulant drugs and alcohol, to minimize sleep deprivation, and to recognize early signs of relapse. If patients tend to be financially extravagant, finances should be turned over to a trusted family member. Patients with a tendency to sexual excesses should be given information about conjugal consequences (eg, divorce) and infectious risks of promiscuity, particularly AIDS.

**Cyclothymic Disorder**

Cyclothymic disorder is characterized by hypomanic and mini-depressive periods that last a few days, follow an irregular course, and are less severe than those in bipolar disorder. Diagnosis is clinical and based on history. Management consists primarily of education, although some patients with functional impairment require drug therapy.

Cyclothymic disorder is commonly a precursor of bipolar II disorder. However, it can also occur as extreme moodiness without becoming a major mood disorder. In chronic hypomania, a form rarely seen clinically, elated periods predominate, with habitual reduction of sleep to < 6 h. People with this form are constantly overcheerful, self-assured, over-energetic, full of plans, improvident, overinvolved, and meddlesome; they rush off with restless impulses and may act in an overfamiliar manner with people.

For some people, cyclothymic and chronic hypomanic dispositions contribute to success in business, leadership, achievement, and artistic creativity; however, they more often have serious detrimental interpersonal and social consequences. Consequences often include instability with an uneven work and schooling history, impulsive and frequent changes of residence, repeated romantic or marital breakups, and an episodic abuse of alcohol and drugs.

**Treatment**

- Supportive care
- Sometimes a mood stabilizer

Patients should be taught how to live with the extremes of their temperamental inclinations; however, living with cyclothymic disorder is not easy because interpersonal relationships are often stormy. Jobs with flexible hours are advised. Patients with artistic inclinations should be encouraged to pursue careers in the arts because the excesses and fragility of cyclothymia may be better tolerated there.

The decision to use a mood stabilizer depends on the balance between functional impairment and the social benefits or creative spurts that patients may experience. Divalproex 500 to 1000 mg po once/day is often better tolerated than equivalent doses of lithium. Antidepressants should be avoided unless depressive symptoms are severe and prolonged because switching and rapid cycling are risks.

Support groups (eg, Depression and Bipolar Support Alliance in Chicago) can help patients by providing a forum to share their common experiences and feelings.
Chapter 163. Personality Disorders

Introduction

(See also Dissociative Identity Disorder on p. 1505.)

Personality disorders are pervasive, inflexible, and stable patterns of behavior that cause significant distress or functional impairment. Ten distinct personality disorders have been identified and grouped into 3 clusters. All are believed to be caused by a combination of genetic and environmental factors. Diagnosis is clinical. Treatment is with psychotherapy and sometimes drug therapy.

Personality traits are patterns of thinking, perceiving, reacting, and relating that are relatively stable over time and in various situations. Personality traits are usually evident from late adolescence or early adulthood, and although many traits persist throughout much of life, some fade with aging and some can be modified. Personality disorders exist when these traits become so rigid and maladaptive that they impair functioning. Mental coping mechanisms (defenses) that are used unconsciously at times by everyone tend to be immature and maladaptive in people with personality disorders (see Table 163-1).

People with personality disorders are often frustrating and even infuriating to people around them (including physicians). Most are distressed about their lives and have impaired work or social relationships. Personality disorders often coexist with mood, anxiety, substance abuse, and eating disorders. People with severe personality disorders are at high risk of hypochondriasis and violent or self-destructive behaviors. They may have inconsistent, detached, overemotional, abusive, or irresponsible styles of parenting, leading to physical and mental problems in their children.

About 13% of the general population is affected. Antisocial personality disorder occurs in about 2%, with men outnumbering women 6:1. Borderline personality disorder occurs in about 1%, with women outnumbering men 3:1.

Classification

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) recognizes 10 distinct personality disorders and divides them into 3 clusters:

A: Odd/eccentric

B: Dramatic/erratic

C: Anxious/fearful

Cluster A: Patients tend to be detached and distrustful.

Paranoid personality involves coldness and distancing in relationships, with a need for control and a tendency toward jealousy if attachments are formed. Affected people are often secretive and untrusting. They tend to be suspicious of changes and frequently find hostile and malevolent motives behind other people's acts. Often, these hostile motives represent projections (see Table 163-1) of their own hostilities onto others. Their reactions sometimes surprise or scare others. They then use the resulting anger of or rejection by others (ie, projective identification) to justify their original feelings. Paranoid people tend to feel a sense of righteous indignation and often take legal action against others. These people may be highly efficient and conscientious, although they usually need to work in relative isolation. This disorder must be differentiated from paranoid schizophrenia.
Schizoid personality is characterized by introversion, social withdrawal, isolation, and emotional coldness and distancing. Affected people are often absorbed in their own thoughts and feelings and fear closeness and intimacy with other people. They are reticent, are given to daydreaming, and prefer theoretical speculations to practical action.

Schizotypal personality, like schizoid personality, involves social withdrawal and emotional coldness but also includes oddities of thinking, perception, and communication, such as magical thinking, clairvoyance, ideas of reference, or paranoid ideation. These oddities suggest schizophrenia (see p. 1559) but are never severe enough to meet its criteria. People with schizotypal personality are believed to have a muted expression of the genes that cause schizophrenia.

Cluster B: Patients tend to be emotionally unstable, impulsive, and intense.

Borderline personality is marked by unstable self-image, mood, behavior, and relationships. Affected people tend to believe they were deprived of adequate care during childhood and consequently feel empty, angry, and entitled to nurturance. As a result, they relentlessly seek care and are sensitive to its perceived absence. Their relationships tend to be intense and dramatic. When feeling cared for, they appear like lonely waifs who seek help for depression, substance abuse, eating disorders, and past mistreatments. When they fear the loss of the caring person, they frequently express inappropriate and intense anger. These mood shifts are typically accompanied by extreme changes in their view of the world, themselves, and other people—eg, from bad to good, from hated to loved. When they feel abandoned, they dissociate or become desperately impulsive. Their concept of reality is sometimes so poor that they have brief episodes of psychotic thinking, such as paranoid delusions and hallucinations. They often become self-destructive and may cut themselves (self-mutilate) or attempt suicide. They initially tend to evoke intense, nurturing responses in caretakers, but after repeated crises, vague unfounded complaints, and failures to adhere to therapeutic recommendations, they are viewed as help-rejecting complainers. Borderline personality tends to become milder or to stabilize with aging.

Antisocial personality is marked by the callous disregard for the rights and feelings of other people. Affected people exploit others for materialistic gain or personal gratification. They become frustrated easily and tolerate frustration poorly. Characteristically, they act out (see Table 163-1) their conflicts impulsively and irresponsibly, sometimes with hostility and violence. They usually do not anticipate the consequences of their behaviors and typically do not feel remorse or guilt afterward. Many of them have a well-developed capacity for glibly rationalizing their behavior or blaming it on others. Dishonesty and deceit permeate their relationships. Punishment rarely modifies their behavior or improves their judgment. Antisocial personality often leads to alcoholism, drug addiction, promiscuity, failure to fulfill responsibilities, frequent relocation, and difficulty abiding by laws. Life expectancy is decreased, but the disorder tends to diminish or stabilize with age.

Narcissistic personality involves grandiosity. Affected people have an exaggerated sense of superiority and expect to be treated with deference. Their relationships are characterized by a need to be admired, and they are extremely sensitive to criticism, failure, or defeat. When confronted with a failure to fulfill their high opinion of themselves, they can become enraged or seriously depressed and suicidal. They often believe other people envy them. They may exploit others because they think their superiority justifies it.

Histrionic personality involves conspicuous attention seeking. Affected people are also overly conscious of appearance and are dramatic. Their expression of emotions often seems exaggerated, childish, and superficial. Still, they frequently evoke sympathetic or erotic attention from other people. Relationships are often easily established and overly sexualized but tend to be superficial and transient. Behind their seductive behaviors and their tendency to exaggerate somatic problems (ie, hypochondriasis) often lie more basic wishes for dependency and protection.

Cluster C: Patients tend to be nervous and passive or rigid and preoccupied.

Dependent personality is characterized by the surrender of responsibility to other people. Affected people may submit to others to gain and maintain support. For example, they often allow the needs of people they depend on to supersede their own. They lack self-confidence and feel intensely inadequate about taking care of themselves. They believe that others are more capable, and they are reluctant to
express their views for fear that their aggressiveness will offend the people they need. Dependency in other personality disorders may be hidden by obvious behavioral problems; eg, histrionic or borderline behaviors mask underlying dependency.

Avoidant personality is marked by hypersensitivity to rejection and fear of starting relationships or anything new because of the risk of failure or disappointment. Because affected people have a strong conscious desire for affection and acceptance, they are openly distressed by their isolation and inability to relate comfortably to other people. They respond to even small hints of rejection by withdrawing.

Obsessive-compulsive personality is characterized by conscientiousness, orderliness, and reliability, but inflexibility often makes affected people unable to adapt to change. They take responsibilities seriously, but because they hate mistakes and incompleteness, they can become entangled with details and forget their purpose. As a result, they have difficulty making decisions and completing tasks. Such problems make responsibilities a source of anxiety, and they rarely enjoy much satisfaction from their achievements. Most obsessive-compulsive traits are adaptive, and as long as they are not too marked, people who have them often achieve much, especially in the sciences and other academic fields in which order, perfectionism, and perseverance are desirable. However, they can feel uncomfortable with feelings, interpersonal relationships, and situations in which they lack control, they must rely on other people, or events are unpredictable.

Other personality types: Several other personality types have been described but are not classified as disorders in the DSM-IV-TR.

Passive-aggressive (negativistic) personality typically produces the appearance of ineptness or passivity, but these behaviors are covertly designed to avoid responsibility or to control or punish other people. Passive-aggressive behavior is often evidenced by procrastination, inefficiency, or unrealistic protests of disability. Frequently, affected people agree to do tasks they do not want to do and then subtly undermine completion of the tasks. Such behavior usually serves to deny or conceal hostility or disagreements.

Cyclothymic personality (see also p. 1552) alternates between high-spirited buoyancy and gloomy pessimism; each mood lasts weeks or longer. Characteristically, the rhythmic mood changes are regular and occur without justifiable external cause. When these features do not interfere with social adaptation, cyclothymia is considered a temperament and is present in many gifted and creative people.

Depressive personality is characterized by chronic moroseness, worry, and self-consciousness. Affected people have a pessimistic outlook, which impairs their initiative and disheartens other people. Self-satisfaction seems undeserved and sinful. They unconsciously believe their suffering is a badge of merit needed to earn the love or admiration of others.

Diagnosis

• DSM-IV-TR criteria

Specific personality disorders are diagnosed based on DSM-IV-TR criteria. The general criteria in DSM-IV-TR emphasize the need to consider whether other mental or physical disorders (eg, depression, substance abuse, hyperthyroidism) can account for the patient's patterns of behavior.

Patients' emotional reactions and their perspectives on what causes their problems and how other people treat them can provide information about their disorder. Diagnosis is based on observing repetitive patterns of behavior or perceptions that cause distress and impair social functioning. Because the patient often lacks insight into these patterns, physicians may initially seek information from and evaluation by others who interact with the patient. Often, physicians suspect a personality disorder based on their own discomfort, typically if they begin to feel angry or defensive.

Treatment

• Comprehensive approach, often requiring prolonged treatment
Although treatment differs according to the type of personality disorder, some general principles apply:

- Family members and friends can act in ways that either reinforce or diminish the patient's problematic behavior or thoughts; thus, their involvement is helpful and often essential.

- An early effort should be made to get patients to see that the problem is really based on who they are.

- Treating a personality disorder takes a long time; repetitious confrontation in prolonged psychotherapy or by peer encounters is usually required to make patients aware of their defenses, beliefs, and maladaptive behavior patterns.

Because personality disorders are particularly difficult to treat, therapists need experience, enthusiasm, and an understanding of the patient's expected areas of emotional sensitivity and usual ways of coping. Kindness and guidance alone do not change personality disorders. Treatment may involve a combination of psychotherapy and drug therapy. However, symptoms typically are not very responsive to drugs.

Relief of anxiety or depression is the first goal, and drug therapy can be helpful. Reducing environmental stress can also quickly relieve such symptoms.

Maladaptive behaviors, such as recklessness, social isolation, lack of assertiveness, or temper outbursts, can be changed in months. Group therapy and behavior modification, sometimes within day hospital or residential settings, are effective. Participation in self-help groups or family therapy can also help change socially undesirable behaviors. Behavioral change is most important for patients with borderline, antisocial, or avoidant personality disorder. Dialectical behavioral therapy (DBT) is effective for borderline personality disorder. DBT, which involves weekly individual psychotherapy and group therapy as well as telephone contact with therapists between scheduled sessions, seeks to help patients understand their behaviors and teach them problem solving and adaptive behaviors. Psychodynamic therapy is effective for patients with borderline and avoidant personality disorders. Such therapies help patients with personality disorders reorganize feeling states in themselves and think about the effect their behaviors have on other people.

Interpersonal problems, such as dependency, distrust, arrogance, and manipulativeness, usually take > 1 yr to change. The cornerstone for effecting interpersonal changes is individual psychotherapy that helps patients understand the sources of their interpersonal problems. A therapist must repeatedly point out the undesirable consequences of the patient's thought and behavior patterns and must sometimes set limits on the patient's behavior. Such therapy is essential for patients with histrionic, dependent, or passive-aggressive personality disorder. For some patients with personality disorders that involve how attitudes, expectations, and beliefs are mentally organized (eg, narcissistic or obsessive-compulsive types), psychoanalysis is recommended, usually for ≥ 3 yr.
Chapter 164. Schizophrenia and Related Disorders

Introduction

Schizophrenia and related disorders—brief psychotic disorder, delusional disorder, schizoaffective disorder, and schizophreniform disorder—are characterized by psychotic symptoms. Psychotic symptoms include delusions, hallucinations, disorganized thinking and speech, and bizarre and inappropriate behavior.

Brief Psychotic Disorder

Brief psychotic disorder consists of delusions, hallucinations, or other psychotic symptoms for at least 1 day but < 1 mo, with eventual return to normal premorbid functioning. It is typically caused by severe stress in susceptible people.

Brief psychotic disorder is uncommon. Preexisting personality disorders (eg, paranoid, histrionic, narcissistic, schizotypal, borderline) predispose to its development. A major stressor, such as loss of a loved one, may precipitate the disorder. The disorder causes at least one psychotic symptom:

• Delusions
• Hallucinations
• Disorganized speech
• Grossly disorganized or catatonic behavior

This disorder is not diagnosed if a psychotic mood disorder, a schizoaffective disorder, schizophrenia, a physical disorder, or an adverse drug effect (prescribed or illicit) better accounts for the symptoms. Differentiating between brief psychotic disorder and schizophrenia in a patient without any prior psychotic symptoms is based on duration of symptoms; if the duration exceeds 1 mo, the patient no longer meets required diagnostic criteria for brief psychotic disorder.

Treatment is similar to that of an acute exacerbation of schizophrenia; supervision and short-term treatment with antipsychotics may be required.

Delusional Disorder

Delusional disorder is characterized by nonbizarre delusions (false beliefs) that persist for at least 1 mo, without other symptoms of schizophrenia.

Delusional disorder is distinguished from schizophrenia by the presence of delusions without other symptoms of schizophrenia. The delusions tend to be nonbizarre and involve situations that could occur, such as being followed, poisoned, infected, loved at a distance, or deceived by one's spouse or lover.

In contrast to schizophrenia, delusional disorder is relatively uncommon. Onset generally occurs in middle or late adult life. Psychosocial functioning is not as impaired as it is in schizophrenia, and impairments usually arise directly from the delusional belief.

When delusional disorder occurs in elderly patients, it is sometimes called paraphrenia. It may coexist with mild dementia. The physician must be careful to distinguish delusions from elder abuse being reported by a mildly demented elderly patient.

Symptoms and Signs

Delusional disorder may arise from a preexisting paranoid personality disorder (see p. 1553). In such people, a pervasive distrust and suspiciousness of others and their motives begins in early adulthood and extends throughout life. Early symptoms may include the feeling of being exploited, preoccupation with
the loyalty or trustworthiness of friends, a tendency to read threatening meanings into benign remarks or events, persistent bearing of grudges, and a readiness to respond to perceived slights.

Several subtypes of delusional disorder are recognized:

• **Erotomanic**: Patients believe that another person is in love with them. Efforts to contact the object of the delusion through telephone calls, letters, surveillance, or stalking are common. People with this subtype may have conflicts with the law related to this behavior.

• **Grandiose**: Patients believe they have a great talent or have made an important discovery.

• **Jealous**: Patients believe that their spouse or lover is unfaithful. This belief is based on incorrect inferences supported by dubious evidence. They may resort to physical assault.

• **Persecutory**: Patients believe that they are being plotted against, spied on, maligned, or harassed. They may repeatedly attempt to obtain justice through appeals to courts and other government agencies and may resort to violence in retaliation for the imagined persecution.

• **Somatic**: The delusion relates to a bodily function; eg, patients believe they have a physical deformity, odor, or parasite.

**Diagnosis**

Diagnosis depends largely on making a clinical assessment, obtaining a thorough history, and ruling out other specific conditions associated with delusions. Assessment of dangerousness, especially the extent to which patients are willing to act on their delusion, is very important.

**Prognosis**

Delusional disorder does not usually lead to severe impairment or change in personality, but delusional concerns may gradually progress. Most patients can remain employed.

**Treatment**

Treatment aims to establish an effective physician-patient relationship and to manage complications. If patients are assessed to be dangerous, hospitalization may be required. Insufficient data are available to support the use of any particular drug, although antipsychotics sometimes suppress symptoms.

A long-term treatment goal of shifting the patient's major area of concern away from the delusional locus to a more constructive and gratifying area is difficult but reasonable.

**Schizoaffective Disorder**

Schizoaffective disorder is characterized by significant mood symptoms, psychosis, and other symptoms of schizophrenia. It is differentiated from schizophrenia by occurrence of ≥ 1 episodes of depressive or manic symptoms.

Schizoaffective disorder is considered when a psychotic patient also demonstrates mood symptoms. The diagnosis requires that significant mood symptoms (depressive or manic) be present for a substantial portion of the total duration of illness, concurrent with symptoms of schizophrenia. Differentiating schizoaffective disorder from schizophrenia and mood disorders may require longitudinal assessment of symptoms and symptom progression. The prognosis is somewhat better than that for schizophrenia but worse than that for mood disorders.

**Treatment**

• Often a combination of drugs, psychotherapy, and community support
Because schizoaffective disorder often leads to long-term disability, comprehensive treatment (including drugs, psychotherapy, and community support) is often required.

For treatment of the manic type, antipsychotics combined with lithium, carbamazepine, or valproate may be more effective than antipsychotics alone.

For treatment of the depressive type, antipsychotics are commonly combined with antidepressants. Antidepressants should usually be introduced once positive psychotic symptoms are stabilized. SSRIs are preferred because of their safety profile. Second-generation antipsychotics may be more effective than conventional antipsychotics in alleviating depression associated with psychosis.

**Schizophrenia**

Schizophrenia is characterized by psychosis (loss of contact with reality), hallucinations (false perceptions), delusions (false beliefs), disorganized speech and behavior, flattened affect (restricted range of emotions), cognitive deficits (impaired reasoning and problem solving), and occupational and social dysfunction. The cause is unknown, but evidence for a genetic component is strong. Symptoms usually begin in adolescence or early adulthood. One or more episodes of symptoms must last ≥ 6 mo before the diagnosis is made. Treatment consists of drug therapy, psychotherapy, and rehabilitation.

Worldwide, the prevalence of schizophrenia is about 1%. The rate is comparable among men and women and relatively constant cross-culturally. The rate is higher among lower socioeconomic classes in urban areas, perhaps because its disabling effects lead to unemployment and poverty. Similarly, a higher prevalence among single people may reflect the effect of illness or illness precursors on social functioning. The average age at onset is 18 yr in men and 25 yr in women. Onset is rare in childhood, but early-adolescent onset or late-life onset (when it is sometimes called paraphrenia) may occur.

**Etiology**

Although its specific cause is unknown, schizophrenia has a biologic basis, as evidenced by alterations in brain structure (eg, enlarged cerebral ventricles, decreased size of the anterior hippocampus and other brain regions) and by changes in neurotransmitters, especially altered activity of dopamine and glutamate. Some experts suggest that schizophrenia occurs in people with neurodevelopmental vulnerabilities and that the onset, remission, and recurrence of symptoms are the result of interactions between these enduring vulnerabilities and environmental stressors.

**Neurodevelopmental vulnerability:** Vulnerability may result from genetic predisposition; intrauterine, birth, or postnatal complications; or viral CNS infections. Maternal exposure to famine and influenza during the 2nd trimester of pregnancy, birth weight < 2500 g, Rh incompatibility during a 2nd pregnancy, and hypoxia increase risk.

Although most people with schizophrenia do not have a family history, genetic factors have been implicated. People who have a 1st-degree relative with schizophrenia have about a 10% risk of developing the disorder, compared with a 1% risk among the general population. Monozygotic twins have a concordance of about 50%. Sensitive neurologic and neuropsychiatric tests suggest that aberrant smooth-pursuit eye tracking, impaired cognition and attention, and deficient sensory gating occur more commonly among patients with schizophrenia than among the general population. These markers (endophenotypes) also occur among 1st-degree relatives of people with schizophrenia and may represent the inherited component of vulnerability.

**Environmental stressors:** Stressors can trigger the emergence or recurrence of symptoms in vulnerable people. Stressors may be primarily biochemical (eg, substance abuse, especially marijuana) or social (eg, becoming unemployed or impoverished, leaving home for college, breaking off a romantic relationship, joining the Armed Forces); however, these stressors are not causative. There is no evidence that schizophrenia is caused by poor parenting.

Protective factors that may mitigate the effect of stress on symptom formation or exacerbation include
good social support, coping skills, and antipsychotics (see Treatment on p. 1562).

**Symptoms and Signs**

Schizophrenia is a chronic illness that may progress through several phases, although duration and patterns of phases can vary. Patients with schizophrenia tend to develop psychotic symptoms an average of 12 to 24 mo before presenting for medical care.

**Phases:** In the premorbid phase, patients may show no symptoms or may have impaired social competence, mild cognitive disorganization or perceptual distortion, a diminished capacity to experience pleasure (anhedonia), and other general coping deficiencies. Such traits may be mild and recognized only in retrospect or may be more noticeable, with impairment of social, academic, and vocational functioning.

In the prodromal phase, subclinical symptoms may emerge; they include withdrawal or isolation, irritability, suspiciousness, unusual thoughts, perceptual distortions, and disorganization. Onset of overt schizophrenia (delusions and hallucinations) may be sudden (over days or weeks) or slow and insidious (over years).

In the middle phase, symptomatic periods may be episodic (with identifiable exacerbations and remissions) or continuous; functional deficits tend to worsen.

In the late illness phase, the illness pattern may be established, and disability may stabilize or even diminish.

**Symptom categories:** Generally, symptoms are categorized as

- **Positive:** An excess or distortion of normal functions
- **Negative:** Diminution or loss of normal functions
- **Disorganized:** Thought disorders and bizarre behavior
- **Cognitive:** Deficits in information processing and problem solving

Patients may have symptoms from one or all categories.

**Positive symptoms** can be further categorized as delusions and hallucinations. Delusions are erroneous beliefs. In persecutory delusions, patients believe they are being tormented, followed, tricked, or spied on. In delusions of reference, patients believe that passages from books, newspapers, song lyrics, or other environmental cues are directed at them. In delusions of thought withdrawal or thought insertion, patients believe that others can read their mind, that their thoughts are being transmitted to others, or that thoughts and impulses are being imposed on them by outside forces. Hallucinations may be auditory, visual, olfactory, gustatory, or tactile, but auditory hallucinations are by far the most common. Patients may hear voices commenting on their behavior, conversing with one another, or making critical and abusive comments. Delusions and hallucinations may be extremely vexing to patients.

**Negative (deficit) symptoms** include blunted affect, poverty of speech, anhedonia, and asociality. With blunted affect, the patient's face appears immobile, with poor eye contact and lack of expressiveness. Poverty of speech refers to decreased speech and terse replies to questions, creating the impression of inner emptiness. Anhedonia may be reflected by a lack of interest in activities and increased purposeless activity. Asociality is shown by a lack of interest in relationships. Negative symptoms often lead to poor motivation and a diminished sense of purpose and goals.

**Disorganized symptoms,** which can be considered a type of positive symptom, involve thought disorders and bizarre behaviors. Thinking is disorganized, with rambling, non-goal-directed speech that shifts from one topic to another. Speech can range from mildly disorganized to incoherent and incomprehensible. Bizarre behavior may include childlike silliness, agitation, and inappropriate appearance, hygiene, or conduct. Catatonia is an extreme behavior that can include maintaining a rigid
posture and resisting efforts to be moved or engaging in purposeless and unstimulated motor activity.

**Cognitive deficits** include impairment in attention, processing speed, working memory, abstract thinking, problem solving, and understanding of social interactions. The patient's thinking may be inflexible, and the ability to problem solve, understand the viewpoints of other people, and learn from experience may be diminished. Symptoms of schizophrenia typically impair the ability to function and often markedly interfere with work, social relations, and self-care. Unemployment, isolation, deteriorated relationships, and diminished quality of life are common outcomes. Severity of cognitive impairment is a major determinant of overall disability.

**Subtypes:** Five subtypes of schizophrenia have been described:

- **Paranoid:** Characterized by delusions or auditory hallucinations, with preservation of cognition and affect
- **Disorganized:** Characterized by disorganized speech, disorganized behavior, and flat or inappropriate affect
- **Catatonic:** Characterized by physical symptoms, including either immobility or excessive motor activity and the assumption of bizarre postures
- **Residual:** A clear history of schizophrenia with more prominent symptoms, followed by a prolonged period of mild negative symptoms
- **Undifferentiated:** A mixture of symptoms from the other subtypes

Alternatively, some experts classify schizophrenia into deficit and nondeficit subtypes based on the presence and severity of negative symptoms, such as blunted affect, lack of motivation, and diminished sense of purpose. Patients with the deficit subtype have prominent negative symptoms unaccounted for by other factors (eg, depression, anxiety, an understimulating environment, drug adverse effects). Those with the nondeficit subtype may have delusions, hallucinations, and thought disorders but are relatively free of negative symptoms.

**Suicide:** About 10% of patients with schizophrenia commit suicide. Suicide is the major cause of premature death among people with schizophrenia and explains, in part, why on average the disorder reduces life span by 10 yr. Patients who have paranoid subtypes with late onset and good premorbid functioning—the very patients with the best prognosis for recovery—are also at the greatest risk of suicide. Because these patients retain the capacity for grief and anguish, they may be more prone to act in despair based on a realistic recognition of the effect of their disorder (see also p. 1579).

**Violence:** Schizophrenia is a relatively modest risk factor for violent behavior. Threats of violence and minor aggressive outbursts are far more common than seriously dangerous behavior. Patients more likely to engage in significant violence include those with substance abuse, persecutory delusions, or command hallucinations and those who do not take their prescribed drugs. A very few severely depressed, isolated, paranoid patients attack or murder someone whom they perceive as the single source of their difficulties (eg, an authority, a celebrity, their spouse).

**Diagnosis**

- **Combination of history, symptoms, and signs**

No definitive test for schizophrenia exists. Diagnosis is based on a comprehensive assessment of history, symptoms, and signs. Information from collateral sources, such as family members, friends, teachers, and coworkers, is often important. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (DSM-IV-TR), the diagnosis requires both of the following:

- ≥ 2 characteristic symptoms (delusions, hallucinations, disorganized speech, disorganized behavior, negative symptoms) for a significant portion of a 1-mo period
• Prodromal or attenuated signs of illness with social, occupational, or self-care impairments evident for a 6-mo period that includes 1 mo of active symptoms

Psychosis due to other medical disorders or substance abuse must be ruled out by history and examination that includes laboratory tests and neuroimaging (see p. 1487). Although some patients with schizophrenia have structural brain abnormalities present on imaging, these abnormalities are insufficiently specific to have diagnostic value.

Other mental disorders with similar symptoms include several that are related to schizophrenia: brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and delusional disorder. In addition, mood disorders can cause psychosis in some people. Certain personality disorders (especially schizotypal) cause symptoms similar to those of schizophrenia, although they are usually milder and do not involve psychosis.

Prognosis

During the first 5 yr after onset of symptoms, functioning may deteriorate and social and work skills may decline, with progressive neglect of self-care. Negative symptoms may increase in severity, and cognitive functioning may decline. Thereafter, the level of disability tends to plateau. Some evidence suggests that severity of illness may lessen in later life, particularly among women. Spontaneous movement disorders may develop in patients who have severe negative symptoms and cognitive dysfunction, even when antipsychotics are not used.

Prognosis varies depending on the subtype. Patients with paranoid schizophrenia tend to be less severely disabled and more responsive to available treatments. Patients with the deficit subtype are typically more disabled, have a poorer prognosis, and are more resistant to treatment.

Schizophrenia can occur with other mental disorders. When associated with significant obsessive-compulsive symptoms (see p. 1495), prognosis is particularly poor; with symptoms of borderline personality disorder (see p. 1555), prognosis is better. About 80% of people with schizophrenia experience one or more episodes of major depression at some time in their life.

For the first year after diagnosis, prognosis is closely related to adherence to prescribed psychoactive drugs. Overall, one third of patients achieve significant and lasting improvement; one third improve somewhat but have intermittent relapses and residual disability; and one third are severely and permanently incapacitated. Only about 15% of all patients fully return to their pre-illness level of functioning.

Factors associated with a good prognosis include

• Good premorbid functioning (eg, good student, strong work history)

• Late and/or sudden onset of illness

• Family history of mood disorders other than schizophrenia

• Minimal cognitive impairment

• Few negative symptoms

• Paranoid or nondeficit subtype

Factors associated with a poor prognosis include

• Young age at onset

• Poor premorbid functioning
• Family history of schizophrenia

• Disorganized or deficit subtype with many negative symptoms

Men have poorer outcomes than women; women respond better to treatment with antipsychotics.

Substance abuse is a significant problem in up to 50% of patients with schizophrenia. Anecdotal evidence suggests that use of marijuana and other hallucinogens is highly disruptive for patients with schizophrenia and should be strongly discouraged. Comorbid substance abuse is a significant predictor of poor outcome and may lead to drug nonadherence, repeated relapse, frequent rehospitalization, declining function, and loss of social support, including homelessness.

Treatment

• Antipsychotic drugs

• Rehabilitation, including community support services

• Psychotherapy

The time between onset of psychotic symptoms and first treatment correlates with the rapidity of initial treatment response, quality of treatment response, and severity of negative symptoms. When treated early, patients tend to respond more quickly and fully. Without ongoing use of antipsychotics after an initial episode, 70 to 80% of patients have a subsequent episode within 12 mo. Continuous use of antipsychotics can reduce the 1-yr relapse rate to about 30%.

General goals are to reduce severity of psychotic symptoms, prevent recurrences of symptomatic episodes and associated deterioration of functioning, and help patients function at the highest level possible. Antipsychotics, rehabilitation with community support services, and psychotherapy are the major components of treatment. Because schizophrenia is a long-term and recurrent illness, teaching patients illness self-management skills is a significant overall goal.

Drugs are divided into conventional antipsychotics and 2nd-generation antipsychotics (SGAs) based on their specific neurotransmitter receptor affinity and activity. SGAs may offer some advantages both in terms of modestly greater efficacy (although recent evidence casts doubt on SGAs' advantage as a class) and reduced likelihood of an involuntary movement disorder and related adverse effects. However, risk of metabolic syndrome (excess abdominal fat, insulin resistance, dyslipidemia, and hypertension) is greater with SGAs than with conventional antipsychotics.

**Conventional antipsychotics:** These drugs (see Table 164-1) act primarily by blocking the dopamine-2 receptor (dopamine-2 blockers). Conventional antipsychotics can be classified as high, intermediate, or low potency. High-potency antipsychotics have a higher affinity for dopamine receptors and less for α-adrenergic and muscarinic receptors. Low-potency antipsychotics, which are rarely used, have less affinity for dopamine receptors and relatively more affinity for α-adrenergic, muscarinic, and histaminic receptors. Different drugs are available in tablet, liquid, and short- and long-acting IM preparations. A specific drug is selected primarily based on adverse effect profile, required route of administration, and the patient's previous response to the drug.

Two conventional antipsychotics (and one SGA) are available as long-acting depot preparations (see Table 164-2). These preparations are useful for eliminating drug nonadherence. They may also help patients who, because of disorganization, indifference, or denial of illness, cannot reliably take daily oral drugs.

Conventional antipsychotics have several adverse effects, such as sedation, cognitive blunting, dystonia and muscle stiffness, tremors, elevated prolactin levels, and weight gain (for treatment of adverse effects, see Table 157-4 on p. 1493). Akathisia (motor restlessness) is particularly unpleasant and may lead to
nonadherence. These drugs may also cause tardive dyskinesia, an involuntary movement disorder most often characterized by puckering of the lips and tongue, writhing of the arms or legs, or both. The incidence of tardive dyskinesia is about 5%/yr of drug exposure among patients taking conventional antipsychotics. In about 2%, tardive dyskinesia is severely disfiguring. In some patients, tardive dyskinesia persists indefinitely, even after the drug is stopped. Because of this risk, patients receiving long-term maintenance therapy should be evaluated at least every 6 mo. Rating instruments, such as the Abnormal Involuntary Movement Scale, may be used (see Table 164-3). Neuroleptic malignant syndrome, a rare but potentially fatal adverse effect, is characterized by rigidity, fever, autonomic instability, and elevated CK.

About 30% of patients with schizophrenia do not respond to conventional antipsychotics. They may respond to clozapine, an SGA.

Second-generation antipsychotics: SGAs block dopamine receptors more selectively than conventional antipsychotics, decreasing the likelihood of extrapyramidal (motor) adverse effects. Although greater binding to serotonergic receptors was initially thought to contribute to the efficacy of SGAs, recent studies suggest this binding is unrelated to efficacy or adverse effect profile. SGAs also do the following:

- Tend to alleviate positive symptoms
- May lessen negative symptoms to a greater extent than do conventional antipsychotics (although such differences have been questioned)
- May cause less cognitive blunting
- Are less likely to have extrapyramidal (motor) adverse effects
- Have a lower risk of causing tardive dyskinesia
- Increase prolactin slightly or not at all (except risperidone, which increases prolactin as much as do conventional antipsychotics)

Clozapine, the first SGA, is the only SGA shown to be effective in up to 50% of patients resistant to conventional antipsychotics. Clozapine reduces negative symptoms, has few or no motor adverse effects, and has minimal risk of causing tardive dyskinesia, but it has other adverse effects, including sedation, hypotension, tachycardia, weight gain, type 2 diabetes, and increased salivation. It also may cause seizures in a dose-dependent fashion. The most serious adverse effect is agranulocytosis, which can occur in about 1% of patients. Consequently, frequent monitoring of WBCs is required, and clozapine is generally reserved for patients who have responded inadequately to other drugs.

Newer SGAs (see Table 164-4) provide some of the benefits of clozapine without the risk of agranulocytosis and are generally preferable to conventional antipsychotics for treatment of an acute episode and for prevention of recurrence. However, in a recent, large, long-term, controlled clinical trial, symptom relief using any of 4 SGAs (olanzapine, risperidone, quetiapine, ziprasidone) was no greater than that with perphenazine, a conventional antipsychotic. A follow-up study, in which patients who left the study prematurely were randomized to one of the 3 other study SGAs or to clozapine, demonstrated a clear advantage of clozapine over the other SGAs. Hence, clozapine seems to be the only effective treatment for patients who have failed treatment with a conventional antipsychotic or an SGA. However, clozapine remains underused, probably because of lower tolerability and need for continuous blood monitoring.

Newer SGAs are very similar to each other in efficacy but differ in adverse effects, so drug choice is based on individual response and on other drug characteristics. For example, olanzapine, which has a
relatively high rate of sedation, may be prescribed for patients with prominent agitation or insomnia; less sedating drugs might be preferred for patients with lethargy. A 4- to 8-wk trial is usually required to assess efficacy. After acute symptoms have stabilized, maintenance treatment is initiated; for it, the lowest dose that prevents symptom recurrence is used. Risperidone is the only SGA available in a long-acting injectable formulation.

Weight gain, hyperlipidemia, and elevated risk of type 2 diabetes are the major adverse effects of SGAs. Thus, before treatment with SGAs is begun, all patients should be screened for risk factors, including personal or family history of diabetes, weight, waist circumference, BP, and fasting plasma glucose and lipid profile. Those found to have or to be at significant risk of metabolic syndrome may be better treated with ziprasidone or aripiprazole than the other SGAs. Patient and family education regarding symptoms and signs of diabetes, including polyuria, polydipsia, weight loss, and diabetic ketoacidosis (nausea, vomiting, dehydration, rapid respiration, clouding of sensorium), should be provided. In addition, nutritional and physical activity counseling should be provided to all patients when they start taking an SGA. All patients taking an SGA require periodic monitoring of weight, body mass index, and fasting plasma glucose and referral for specialty evaluation if they develop hyperlipidemia or type 2 diabetes.

Rehabilitation and community support services: Psychosocial skill training and vocational rehabilitation programs help many patients work, shop, and care for themselves; manage a household; get along with others; and work with mental health care practitioners. Supported employment, in which patients are placed in a competitive work setting and provided with an on-site job coach to promote adaptation to work, may be particularly valuable. In time, the job coach acts only as a backup for problem solving or for communication with employers.

Support services enable many patients with schizophrenia to reside in the community. Although most can live independently, some require supervised apartments where a staff member is present to ensure drug adherence. Programs provide a graded level of supervision in different residential settings, ranging from 24-h support to periodic home visits. These programs help promote patient autonomy while providing sufficient care to minimize the likelihood of relapse and need for inpatient hospitalization. Assertive community treatment programs provide services in the patient's home or other residence and are based on high staff-to-patient ratios; treatment teams directly provide all or nearly all required treatment services.

Hospitalization or crisis care in a hospital alternative may be required during severe relapses, and involuntary hospitalization may be necessary if patients pose a danger to themselves or others. Despite the best rehabilitation and community support services, a small percentage of patients, particularly those with severe cognitive deficits and those poorly responsive to drug therapy, require long-term institutional or other supportive care.

Psychotherapy: The goal of psychotherapy is to develop a collaborative relationship between the patients, family members, and physician so that patients can learn to understand and manage their illness, take drugs as prescribed, and handle stress more effectively. Although individual psychotherapy plus drug therapy is a common approach, few empirical guidelines are available. Psychotherapy that begins by addressing the patient's basic social service needs, provides support and education regarding the nature of the illness, promotes adaptive activities, and is based on empathy and a sound dynamic understanding of schizophrenia is likely to be most effective. Many patients need empathic psychologic support to adapt to what is often a lifelong illness that can substantially limit functioning.

For patients who live with their families, psychoeducational family interventions can reduce the rate of relapse. Support and advocacy groups, such as the National Alliance for the Mentally Ill, are often helpful.
Schizophreniform Disorder

Schizophreniform disorder is characterized by symptoms identical to those of schizophrenia but that last ≥ 1 mo but < 6 mo.

At presentation, schizophrenia is likely to be suspected. Psychosis secondary to substance abuse or to a physical disorder must also be ruled out. Differentiating between schizophreniform disorder and schizophrenia in a patient without any prior psychotic symptoms is based on duration of symptoms. If duration of symptoms or disability exceeds 6 mo, the patient no longer meets required diagnostic criteria for schizophreniform disorder, and the diagnosis is likely to be schizophrenia, although the acute psychosis may also evolve into a psychotic mood disorder, such as bipolar or schizoaffective disorder. Longitudinal observation is often required to establish the diagnosis and appropriate treatment.

Treatment with antipsychotics and supportive psychosocial care is indicated. After symptoms resolve, drug treatment is continued for 12 mo and then gradually tapered while closely monitoring for the return of psychotic symptoms.

Substance-Induced Psychotic Disorder

Psychotic symptoms, particularly delusions and hallucinations, can result from a wide variety of substances, including alcohol, amphetamines, marijuana, cocaine, hallucinogens, inhalants, opioids, phencyclidine, and certain sedatives and anxiolytics.

Diagnosis

The diagnosis is made when symptoms begin during or < 1 mo after intoxication with or withdrawal from the implicated substance and after other psychotic disorders are ruled out. Because symptoms may overlap with brief psychotic disorder, schizophreniform disorder, and acute episodes of psychotic mania or schizophrenia, differentiating these conditions may be difficult. Diagnosis may require several days of observation.

Treatment

• Symptomatic

Treatment may vary depending on the drug involved. Hallucinogen and phencyclidine psychosis may not respond well to antipsychotics. A supportive approach is preferred, with reassuring, structured, and protective surroundings. Agitation may be best treated with short-acting benzodiazepines, such as lorazepam given po or IM.
Chapter 165. Sexuality and Sexual Disorders

Introduction

(For sexual dysfunction in men, see p. 2345; for sexual dysfunction in women, see p. 2521.)

Accepted norms of sexual behavior and attitudes vary greatly within and among different cultures. Health care practitioners should never be judgmental of sexual behaviors, even under societal pressure. Generally, what is normal and abnormal cannot be defined medically. However, when sexual behavior or difficulties bother a patient or the patient's partner or cause harm, treatment is warranted.

Societal attitudes about sexuality also change with time, as has occurred with the following:

- **Masturbation**: Once widely regarded as a perversion and a cause of mental disorders, masturbation is now recognized as a normal sexual activity throughout life. It is considered abnormal only when it inhibits partner-oriented behavior, is done in public, or is sufficiently compulsive to cause distress. About 97% of males and 80% of females masturbate. Although masturbation is harmless, guilt created by the disapproval and punitive attitudes of other people may cause considerable distress and impair sexual performance. Masturbation often continues at some level even in a sexually healthy relationship.

- **Homosexuality**: Homosexuality has not been considered a disorder by the American Psychiatric Association for > 3 decades. About 4 to 5% of the population identify themselves as exclusively homosexual for their entire lives. Like heterosexuality, homosexuality results from complex biologic and environmental factors leading to an ability to become sexually aroused by people of the same sex. Like heterosexuality, homosexuality is not a matter of choice.

- **Promiscuity**: Frequent sexual activity with many partners, often involving anonymous or one-time-only encounters, may indicate a diminished capacity for intimacy. However, promiscuity is not in itself evidence of a psychosexual disorder. Casual sex is common, although the fear of AIDS, herpes simplex infections, and other sexually transmitted diseases has resulted in a decrease.

- **Extramarital sex**: Most cultures discourage extramarital sexual activity but accept premarital or nonmarital sexual activity as normal. In the US, most people engage in sexual activity before marriage or without marriage as part of the trend toward more sexual freedom in developed countries. Extramarital sex occurs frequently among married people despite social taboos. This behavior has the potential to pass diseases to unsuspecting spouses.

Accepted norms of sexual behavior and attitudes are influenced greatly by parents. A forbidding, puritanical rejection of physical affection, including touching, by a parent engenders guilt and shame in children and inhibits their capacity for enjoying sex and developing healthy intimate relationships as adults. Relations with parents may be damaged by excessive emotional distance, by punitive behaviors, or by overt seductiveness and sexual exploitation. Children exposed to verbal and physical hostility, rejection, and cruelty are likely to develop problems with sexual and emotional intimacy. For example, love and sexual arousal may become dissociated, so that although emotional bonds can be formed with people from the same social class or intellectual circle, sexual relationships can be formed only with those for whom there is no emotional intimacy, typically those who are perceived to be of a lower class or in some way depreciated (eg, prostitutes, anonymous partners).

Well-informed health care practitioners can offer sensitive, disciplined advice on sexuality and should not miss opportunities for helpful intervention. Behaviors that place patients at risk of sexually transmitted diseases must be addressed. Practitioners have an opportunity to recognize and address psychosexual issues, including sexual dysfunction (see pp. 2345 and 2521), gender identity problems, and paraphilias.

Gender Identity Disorder and Transsexualism

Gender identity disorder is characterized by a strong, persistent cross-gender identification; people believe they are victims of a biologic accident and are cruelly imprisoned in a body incompatible with their subjective gender identity. Those with the most extreme form of gender
identity disorder are called transsexuals. These disorders are considered mental disorders because the body does not match the person's psychologic (felt) gender.

Core gender identity is a subjective sense of knowing to which gender one belongs, ie, the awareness that "I am a male" or "I am a female." Gender identity is the inner sense of masculinity or femininity. Gender role is the objective, public expression of being male, female, or androgynous (blended). It is everything that people say and do to indicate to others or to themselves the degree to which they are male or female. For most people, there is congruity between their anatomic sex, gender identity, and gender role. However, those with gender identity disorder experience some degree of incongruity between their anatomic sex and their gender identity. The incongruity experienced by transsexuals is usually complete, severe, disturbing, and long-standing. Labeling the condition a "disorder" can add to the distress that frequently occurs, and the term should not be construed as being judgmental. Treatment is aimed at helping patients adapt rather than trying to dissuade them from their identity; in any case, the latter approach is ineffective.

Gender role behaviors fall on a continuum of traditional masculinity or femininity, with a growing cultural recognition that some people do not fit into the traditional male-female dichotomy. Western cultures are more tolerant of tomboyish behaviors in young girls (generally not considered a gender identity disorder) than effeminate or "sissy" behaviors in boys. Many boys role-play as girls or mothers, including trying on their sister's or mother's clothes. Usually, this behavior is part of normal development. Only in extreme cases does this behavior and an associated expressed wish to be the other sex persist. Most boys with gender identity disorder of childhood do not have the disorder as adults, but many are homosexual or bisexual as adults.

Etiology

Although biologic factors (eg, genetic complement, prenatal hormonal milieu) largely determine gender identity, the formation of a secure, unconflicted gender identity and gender role is influenced by social factors (eg, the character of the parents' emotional bond, the relationship that each parent has with the child). Rarely, transsexualism is associated with genital ambiguity or a genetic abnormality (eg, Turner's syndrome, Klinefelter's syndrome).

When sex labeling and rearing are confusing (eg, in cases of ambiguous genitals or genetic syndromes altering genital appearance, such as androgen insensitivity syndrome), children may become uncertain about their gender identity or role, although the level of importance of environmental factors remains controversial. However, when sex labeling and rearing are unambiguous, even the presence of ambiguous genitals often does not affect a child's gender identity.

Symptoms and Signs

Childhood gender identity problems are usually present by age 2. Children experiencing difficulty with gender identity commonly do the following:

• Prefer cross-dressing

• Insist that they are of the other sex

• Intensely and persistently desire to participate in the stereotypical games and activities of the other sex

• Have negative feelings toward their genitals

For example, a young girl may insist she will grow a penis and become a boy; she may stand to urinate. A boy may fantasize about being female, and avoid rough-and-tumble play and competitive games. He may sit to urinate and wish to be rid of his penis and testes. For boys with a gender identity disorder, distress at the physical changes of puberty is often followed by a request during adolescence for feminizing somatic treatments. Most children with these disorders are not evaluated until they are age 6 to 9, at a point when the disorder is already chronic.
Although most transsexuals began having gender identity problems in early childhood, some do not present until adulthood. Male-to-female transsexuals may be cross-dressers first and only later in life come to accept their cross-gender identity. Marriage and military service are common among transsexual men who seek to run from their cross-gender feelings. Once they accept their cross-gender (transgender) feelings, many transsexuals adopt a convincing public feminine gender role. Some are satisfied with mastering a more feminine appearance and obtaining an identity card (eg, driver's license) as a female to help them work and live in society as women. Others experience problems, which may include depression and suicidal behavior.

**Diagnosis**

Diagnosis in children requires the presence of both of the following:

- Cross-gender identification (the desire to be or insistence that they are the other sex)
- A sense of discomfort about their sex or sense of substantial inappropriateness in their gender role

Cross-gender identification must not be merely a desire for perceived cultural advantages of being the other sex. For example, a boy who says he wants to be a girl so that he will receive the same special treatment his younger sister receives is not likely to have gender identity disorder.

Assessment of adults focuses on determining whether there is significant distress or obvious impairment in social, occupational, or other important areas of functioning.

**Treatment**

- For selected, motivated patients, hormone therapy, sex reassignment surgery, and psychotherapy

Cross-gender behavior, such as cross-dressing, may not require treatment if it occurs without concurrent psychologic distress or functional impairment or if a person has a physical intersex condition (eg, congenital adrenal hyperplasia, ambiguous genitals, androgen insensitivity syndrome).

Most transsexuals who request treatment are natal males who claim a feminine gender identity and regard their genitals and masculine features with repugnance. However, as treatments improve, female-to-male transsexualism is increasingly seen in medical and psychiatric practice. Transsexuals’ primary objective in seeking medical help is not to obtain psychologic treatment but to obtain hormones and genital surgery that will make their physical appearance approximate their felt gender identity. The combination of psychotherapy, hormonal reassignment, and sex reassignment surgery is often curative when the disorder is appropriately diagnosed and clinicians follow the internationally accepted standards of care for the treatment of gender identity disorders, available from the World Professional Association for Transgender Health (WPATH).

**Male-to-female transsexualism:** Taking moderate doses of a feminizing hormone (eg, ethinyl estradiol 0.1 mg once/day) plus electrolysis and other feminizing treatments may make the adjustment to a feminine gender role more stable.

Many male-to-female transsexuals request sex reassignment surgery. Surgery involves removal of the penis and testes and creation of an artificial vagina. A part of the glans penis is retained as a clitoris, which is usually sexually sensitive and retains the capacity for orgasm in most cases. The decision to pursue sex reassignment surgery often raises important social problems for patients. Many of these patients are married and have children. A parent or spouse who changes sex will have substantial adjustment issues in all intimate relationships and may lose loved ones in the process. In follow-up studies, genital surgery has helped some transsexuals live happier and more productive lives and so is justified in highly motivated, appropriately assessed and treated transsexuals who have completed a 1- to 2-yr real-life experience in the opposite gender role. Before surgery, transsexuals often need assistance with passing in public, including help with gestures and voice modulation. Participation in gender support groups, available in most large cities, is usually helpful.
Female-to-male transsexualism: Patients ask for mastectomy early, then hysterectomy and oophorectomy. Androgenic hormones (eg, IM testosterone ester preparations 300 to 400 mg q 3 wk or equivalent doses of androgen transdermal patches or gels) are given to permanently alter the voice, induce a more masculine muscle and fat distribution, and promote growth of facial and body hair.

Patients may opt for an artificial phallus (neophallus) to be fashioned from skin transplanted from the inner forearm (phalloplasty) or for a micropenis to be created from fat tissue removed from the testosterone-hypertrophied clitoris (metoidioplasty). Surgery may help certain patients achieve greater adaptation and life satisfaction. Similar to male-to-female transsexuals, female-to-male transsexuals should live in the male gender role for at least 1 yr before surgery. Anatomic results of neophallus surgical procedures are often less satisfactory in terms of function and appearance than neovaginal procedures for male-to-female transsexuals. Complications are common, especially in procedures that involve extending the urethra into the neophallus.

Paraphilias

Paraphilias are recurrent, intense, sexually arousing fantasies, urges, or behaviors that are distressing or disabling and that involve inanimate objects, children or other nonconsenting adults, or suffering or humiliation of oneself or the partner.

Sexual preferences that seem unusual to another person or health care practitioner do not constitute paraphilia simply because they are unusual. The arousal patterns are considered pathologic only when the following apply:

• They become obligatory for sexual functioning (ie, erection or orgasm cannot occur without the stimulus).

• They involve inappropriate partners (eg, children, nonconsenting adults).

• They cause significant distress or impairment in social, occupational, or other important areas of functioning.

People with a paraphilia may have an impaired or nonexistent capacity for affectionate, reciprocal emotional and sexual intimacy with a consenting partner. Other aspects of personal and emotional adjustment may be impaired as well.

The pattern of disturbed erotic arousal is usually fairly well developed before puberty. At least 3 processes are involved:

• Anxiety or early emotional trauma interferes with normal psychosexual development.

• The standard pattern of arousal is replaced by another pattern, sometimes through early exposure to highly charged sexual experiences that reinforce the person's experience of sexual pleasure.

• The pattern of sexual arousal often acquires symbolic and conditioning elements (eg, a fetish symbolizes the object of arousal but may have been chosen because the fetish was accidentally associated with sexual curiosity, desire, and excitement).

Whether all paraphilic development results from these psychodynamic processes is controversial, and some evidence of altered brain functioning is present in some paraphilias (eg, pedophilia).

In most cultures, paraphilias are far more common among males. Biologic reasons for the unequal distribution may exist but are poorly defined.

Many of the paraphilias are rare. The most common are pedophilia, voyeurism, transvestic fetishism, and exhibitionism. Some paraphilias (such as pedophilia) are illegal and may result in being imprisoned and being labeled and registered as a sex offender for life. Some of these offenders have significant personality disorders accompanying the paraphilia (eg, antisocial, narcissistic), which make treatment
difficult. Often, more than one paraphilia is present.

**Fetishism**

**Fetishism is use of an inanimate object (the fetish) as the preferred method of producing sexual excitement.** However, in common parlance, the word is often used to describe particular sexual interests, such as sexual role-playing, preference for certain physical characteristics, and preferred sexual activities.

Common fetishes include aprons, shoes, leather or latex items, and women's underclothing. The fetish may replace typical sexual activity with a partner or may be integrated into sexual activity with a willing partner. Minor fetishistic behavior as an adjunct to consensual sexual behavior is not considered a disorder because distress, disability, and significant dysfunction are absent. More intense, obligatory fetishistic arousal patterns may cause problems in a relationship or become all-consuming and destructive in a person's life.

**Transvestic fetishism:** Heterosexual males who dress in women's clothing typically begin such behavior in late childhood (see also Gender Identity Disorder and Transsexualism on p. 1568). A more common term for transvestite is cross-dresser. This behavior is associated, at least initially, with sexual arousal.

Cross-dressing per se is not a disorder because this behavior does not always cause distress or impairment. Personality profiles of cross-dressing men are generally similar to age- and race-matched norms. When their partner is cooperative, these men have intercourse in partial or full feminine attire. When their partner is not cooperative, they may feel anxiety, depression, guilt, and shame associated with the desire to cross-dress.

Most transvestites do not present for treatment. Those who do are usually brought in by an unhappy spouse, referred by courts, or self-referred out of concern about experiencing negative social and employment consequences. Some transvestites present for treatment of comorbid gender dysphoria, substance abuse, or depression. Social and support groups for transvestites are usually very helpful. No drugs are reliably effective; psychotherapy is aimed at self-acceptance and modulating risky behaviors.

**Exhibitionism**

**Exhibitionism is characterized by achievement of sexual excitement through genital exposure, usually to an unsuspecting stranger. It may also refer to a strong desire to be observed by other people during sexual activity.**

Exhibitionists (usually male) may masturbate while exposing or fantasizing about exposing themselves. They may be aware of their need to surprise, shock, or impress the unwilling observer. The victim is almost always a female adult or a child of either sex. Actual sexual contact is rarely sought. Age at onset is usually the mid 20s; occasionally, the first act occurs during preadolescence or middle age. About 30% of apprehended male sex offenders are exhibitionists. They have the highest recidivism rate of all sex offenders; about 20 to 50% are re-arrested. Most exhibitionists are married, but the marriage is often troubled by poor social and sexual adjustment, including frequent sexual dysfunction. Very few females are diagnosed as exhibitionists; society sanctions some exhibitionistic behaviors in females (through media and entertainment venues).

For some people, exhibitionism is expressed as a strong desire to have other people watch their sexual acts. What appeals to such people is not the act of surprising an audience but rather of being seen by a consenting audience. People with this form of exhibitionism may make pornographic films or become adult entertainers. They are rarely troubled by this desire and thus may not have a psychiatric disorder.

**Treatment**

When laws are broken and sex offender status is conferred, treatment usually begins with psychotherapy, support groups, and SSRIs (see p. 1573). If these drugs are ineffective, antiandrogens should be considered; full informed consent and appropriate monitoring of liver function and serum testosterone
level are required.

**Voyeurism**

Voyeurism is achievement of sexual arousal by observing people who are naked, disrobing, or engaging in sexual activity. When observation is of unsuspecting people, this sexual behavior often leads to problems with the law and relationships.

Desire to watch others in sexual situations is common and not in itself abnormal. Voyeurism usually begins during adolescence or early adulthood. Adolescent voyeurism is generally viewed more leniently; few teenagers are arrested. When voyeurism is pathologic, voyeurs spend considerable time seeking out viewing opportunities. Orgasm is usually achieved by masturbating during or after the voyeuristic activity. Voyeurs do not seek sexual contact with the people being observed.

In many cultures, voyeurs have ample legal opportunities to watch sexual activity.

**Treatment**

When laws are broken and sex offender status is conferred, treatment usually begins with therapy, support groups, and SSRIs (see p. 1573). If these drugs are ineffective, antiandrogens should be considered; full informed consent and appropriate monitoring of liver function and serum testosterone levels are required.

**Sexual Masochism**

Sexual masochism is intentional participation in an activity that involves being humiliated, beaten, bound, or otherwise abused to experience sexual excitement.

Sadomasochistic fantasies and sexual behavior between consenting adults is very common. Masochistic activity tends to be ritualized and chronic. For most participants, the humiliation and beating are simply acted out; participants know that it is a game and carefully avoid actual humiliation or injury. However, some masochists increase the severity of their activity with time, potentially leading to serious injury or death.

Masochistic activities may be the preferred or exclusive mode of producing sexual excitement. People may act on their masochistic fantasies themselves (eg, binding themselves, piercing their skin, applying electrical shocks, burning themselves) or seek out a partner who may be a sexual sadist. Activities with a partner include bondage, blindfolding, spanking, flagellation, humiliation by means of urination or defecation on the person, forced cross-dressing, or simulated rape.

Treatment of this disorder is often ineffective.

**Sexual Sadism**

Sexual sadism is infliction of physical or mental suffering (eg, humiliation, terror) on the sex partner to stimulate sexual excitement and orgasm.

Most sexual sadists have insistent, persistent fantasies in which sexual excitement results from suffering inflicted on the partner, consenting or not. Mild sadism is a common sexual practice; when it becomes pathologic is a matter of degree. Sexual sadism is not rape, a complex amalgam of sex and power over the victim. Sexual sadism is diagnosed in < 10% of rapists.

Most sadistic sexual behavior occurs between consenting adults. As is the case with masochism, sadism is usually limited in scope and not harmful. In some people, the behaviors escalate to the point of harm. When practiced with nonconsenting partners, sexual sadism constitutes criminal activity and is likely to continue until the sadist is apprehended. Sexual sadism is particularly dangerous when associated with antisocial personality disorder (see p. 1555). This combination of disorders is particularly recalcitrant to any form of psychiatric treatment.
Pedophilia

(See also p. 3063.)

Pedophilia is a preference for sexual activity with prepubertal children. Pedophilia often leads to imprisonment; medical management should include drugs and psychotherapy.

Sexual offenses against children constitute a significant proportion of reported criminal sexual acts. Arbitrarily, the age of a person with pedophilia is set at ≥ 16 yr, with the age difference between offender and child victim set at ≥ 5 yr. The age of the child is usually ≤ 13 yr. For older adolescents with pedophilia (ie, 17 to 18 yr old), no precise age difference is specified; clinical and legal judgment is relied on. Legal criteria may be different from psychiatric criteria.

Most pedophiles are male. Attraction may be to young boys, girls, or both. But pedophiles prefer opposite-sex to same-sex children 2:1. In most cases, the adult is known to the child and may be a family member, stepparent, or a person with authority (eg, a teacher). Looking or touching seems more prevalent than genital contact. Homosexual males typically have a less close acquaintanceship with the child. Pedophiles may be attracted only to children (exclusive) or also adults (nonexclusive).

Some pedophiles limit their sexual activities to their own children or to close relatives (incest). Predatory pedophiles, many of whom have antisocial personality disorder, may use force and threaten to physically harm the child or the child's pets if the abuse is disclosed. The course of pedophilia is chronic, and perpetrators often have or develop substance abuse or dependence and depression. Pervasive family dysfunction, including marital conflict, is common.

Identifying a pedophile often poses an ethical crisis for health care practitioners. They can try to protect the privacy of the patient but must protect the community of children. Practitioners should know the reporting requirements in their state. If practitioners have reasonable suspicion of child sexual or physical abuse, it must be reported to authorities.

Treatment

• Psychotherapy
• Treatment of associated disorders
• Drug treatment (eg, antiandrogens, SSRIs)

Long-term individual or group psychotherapy is usually necessary and may be especially helpful when it is part of multimodal treatment that includes social skills training, treatment of comorbid physical and mental disorders (eg, seizure disorders, attention deficit disorder, depression), and drug treatment. Treatment is less effective when court ordered, although many adjudicated sex offenders have benefited from treatments, such as group psychotherapy and antiandrogens.

In the US, IM medroxyprogesterone acetate is the treatment of choice; cypreterone is used in Europe. Typical doses are medroxyprogesterone 200 mg IM 2 to 3 times/wk for 2 wk, followed by 200 mg 1 to 2 times/wk for 4 wk, then 200 mg q 2 to 4 wk. Serum testosterone should be monitored and maintained in the normal female range (< 62 ng/dL). Treatment is usually long-term because deviant fantasies usually recur weeks to months after treatment is stopped. Drugs that inhibit gonadotropin release (eg, leuprolide, goserelin), given IM, have also been used. Liver function tests and serum testosterone levels should be monitored as required.

The usefulness of antiandrogens in female pedophiles is less well established.

In addition to antiandrogens, SSRIs (eg, high-dose fluoxetine 60 to 80 mg po once/day or fluvoxamine 200 to 300 mg po once/day) may be useful. Drugs are most effective when used as part of a multimodal treatment program.
Some pedophiles who are committed to treatment and monitoring can refrain from pedophilic activity and be reintegrated into society.
Chapter 166. Somatoform and Factitious Disorders

Introduction

Somatization is the expression of mental phenomena as physical (somatic) symptoms. Typically, the symptoms cannot be explained by a physical disorder. Disorders characterized by somatization extend in a continuum from those in which symptoms develop unconsciously and nonvolitionally to those in which symptoms develop consciously and volitionally. This continuum includes somatoform disorders, factitious disorders, and malingering. Somatization typically leads to seeking medical evaluation and treatment.

Somatoform disorders are characterized by physical symptoms that are not fully explained by another disorder—physical or mental. Symptoms of somatoform disorders are not volitional. Somatoform disorders are distressing and often impair social, occupational, academic, or other aspects of functioning. These disorders include body dysmorphic disorder, conversion disorder, hypochondriasis, pain disorder, somatization disorder, undifferentiated somatoform disorder, and somatoform disorder not otherwise specified. Body dysmorphic disorder differs somewhat from other somatoform disorders in that it is characterized by preoccupation with perceived defects in physical appearance.

Factitious disorders involve the conscious and volitional feigning of symptoms without any external incentive (eg, time off from work) and is thus distinguished from malingering. Patients gain gratification from assuming the sick role through the simulation, exaggeration, or aggravation of symptoms and signs. Symptoms and signs may be mental, physical, or both. The most severe and chronic form is Munchausen syndrome.

Malingering is intentional feigning of physical or mental symptoms motivated by an external incentive (eg, feigning illness to avoid work or military duty, to evade criminal prosecution, or to obtain financial compensation or drugs for abuse). Malingering is suspected in the following cases:

• Patients report symptoms, yet little is detected through unannounced observation, physical examination, or laboratory testing.

• The claimed disability and objective findings are markedly discrepant.

• Patients do not cooperate with efforts to diagnose or treat potential causes of symptoms.

Body Dysmorphic Disorder

Body dysmorphic disorder is preoccupation with an imagined or a slight defect in appearance that causes significant distress or impairment of social, occupational, academic, or other aspects of functioning. Diagnosis is based on history. Treatment consists of drug therapy, psychotherapy, or both.

Body dysmorphic disorder usually begins during adolescence and may be somewhat more common among women.

Symptoms and Signs

Symptoms may develop gradually or abruptly. Although intensity may vary, the disorder is usually chronic unless patients are appropriately treated. Concerns commonly involve the face or head but may involve any body part or several parts and may change from one part to another. For example, patients may be concerned about thinning hair, acne, wrinkles, scars, vascular markings, color of complexion, or excessive facial or body hair. Or they may focus on the shape or size of the nose, eyes, ears, mouth, breasts, buttocks, legs, or other body part. Men may have a form of the disorder called muscle dysmorphia, which involves preoccupation with the idea that their body is not sufficiently lean and muscular.

Patients usually spend many hours a day worrying about their perceived defects. Most check themselves often in mirrors, others avoid mirrors, and still others alternate between the 2 behaviors. Other common
Compulsive behaviors include excessive grooming, skin picking, reassurance seeking, and clothes changing. Most try to camouflage their imagined defects—eg, by growing a beard to hide perceived scars or by wearing a hat to cover slightly thinning hair. Many undergo cosmetic, medical (most often, dermatologic), dental, or surgical treatment to correct their perceived defect, but such treatment is usually unsuccessful and may intensify their preoccupation. Men with muscle dysmorphia may use androgen supplements.

Because people with body dysmorphic disorder feel self-conscious about their appearance, they may avoid going out in public. For most, social, occupational, academic, and other aspects of functioning are impaired because of their concerns about appearance. Some leave their homes only at night; others, not at all. Social isolation, repeated hospitalization, and suicidal behavior may result.

**Diagnosis**

**History**

Because many patients are too embarrassed and ashamed to reveal their symptoms, the disorder may go undiagnosed for years. It is distinguished from normal concerns about appearance because the preoccupations are time-consuming and cause significant distress, impairment in functioning, or both.

Diagnosis is based on history. If the only concern is body shape and weight, an eating disorder may be the more accurate diagnosis (see p. 1535); if the only concern is the appearance of sex characteristics, gender identity disorder may be considered (see p. 1568).

**Treatment**

Serotonin reuptake inhibitors are often effective and are currently the drug of choice; relatively high doses are often required. Cognitive-behavioral therapy that specifically targets symptoms of body dysmorphic disorder is currently the psychotherapy of choice.

**Conversion Disorder**

Conversion disorder consists of symptoms or deficits that develop unconsciously and nonvolitionally and usually involve motor or sensory function. Manifestations resemble a neurologic or other physical disorder but rarely conform to known pathophysiologic mechanisms or anatomic pathways. Onset, exacerbation, or maintenance of conversion symptoms is typically attributed to mental factors, such as stress. Diagnosis is based on history after excluding physical disorders as the cause. Treatment begins by establishing a consistent, supportive physician-patient relationship; psychotherapy can help, as may hypnosis.

Conversion disorder tends to develop during late childhood to early adulthood but may occur at any age. It is more common among women.

**Symptoms and Signs**

Symptoms often develop abruptly, and onset can often be linked to a stressful event. Symptoms involve apparent deficits in voluntary motor or sensory function and sometimes include seizures, thus suggesting a neurologic or general physical disorder. For example, patients may present with impaired coordination or balance, weakness, paralysis of an arm or a leg, loss of sensation in a body part, seizures, blindness, double vision, deafness, aphonia, difficulty swallowing, sensation of a lump in the throat, or urinary retention.

The symptoms are severe enough to cause significant distress or impair social, occupational, or other important areas of functioning. Patients may have a single episode or sporadic repeated ones; symptoms may become chronic. Typically, episodes are brief.

**Diagnosis**
The diagnosis is considered only after a physical examination and tests rule out physical disorders that can fully account for the symptoms and their effects.

Treatment

A consistently trustful and supportive physician-patient relationship is essential. Collaborative treatment that involves a psychiatrist and a physician from another field (eg, neurologist, internist) seems most helpful. After the physician has excluded a physical disorder and reassured patients that the symptoms do not indicate a serious underlying disorder, patients may begin to feel better, and symptoms may fade.

The following treatments may help:

• Hypnosis may help by enabling patients to control the effects of stress and their mental state on their bodily functions.

• Narcoanalysis is a rarely used procedure similar to hypnosis except that patients are given a sedative to induce a state of semisleep.

• Psychotherapy, including cognitive-behavioral therapy, is effective for some people.

Any coexisting psychiatric disorders (eg, depression) should be treated.

Hypochondriasis

Hypochondriasis is preoccupation with the fear of having, or with the idea that one has, a serious disease, based on misinterpretation of nonpathologic physical symptoms or normal bodily functions. Hypochondriasis is nonvolitional; the exact cause is unknown. Diagnosis is confirmed when fears and symptoms persist for ≥ 6 mo despite reassurance after thorough medical evaluation. Treatment includes establishing a consistent, supportive physician-patient relationship; cognitive-behavioral therapy and drug therapy may help.

Hypochondriasis most commonly begins during early adulthood and appears to occur equally among men and women.

Symptoms and Signs

A wide array of fears may derive from misinterpreting nonpathologic physical symptoms or normal bodily functions (eg, borborygmi, abdominal bloating and crampy discomfort, heartbeat, sweating). The location, quality, and duration of symptoms are often described in minute detail, but symptoms are usually not associated with abnormal physical findings. Symptoms impair social and occupational functioning or cause significant distress.

The course is often chronic—fluctuating in some, steady in others. Some patients recover.

Diagnosis

The diagnosis is suggested by the history and confirmed when symptoms persist ≥ 6 mo despite appropriate medical evaluation that excludes a physical disorder and reassurance, and when the symptoms are not better accounted for by depression or another mental disorder.

Treatment

Treatment is difficult because patients believe that something is seriously wrong and that the physician has failed to find the real cause. A trusting relationship with a caring, reassuring physician can nonetheless prove beneficial. If symptoms are not adequately relieved, patients may benefit from a psychiatric referral while continuing under the care of the primary physician.

Treatment with SSRIs may be helpful, as may cognitive-behavioral therapy.
Munchausen Syndrome

Munchausen syndrome, a severe and chronic form of factitious disorder, consists of intentional production or feigning of physical symptoms or signs without an external incentive; the motivation for this behavior is to assume the sick role. Symptoms are usually acute, dramatic, and convincing and are accompanied by a tendency to wander from one physician or hospital to another for treatment. The exact cause is unknown, although stress and a severe personality disorder, most often borderline personality disorder, are often implicated.

Patients with Munchausen syndrome may simulate many physical symptoms or conditions (eg, MI, hematemesis, hemoptysis, diarrhea, FUO). Their abdominal wall may be crisscrossed by scars, or a digit or a limb may have been amputated. Fevers are often due to self-inflicted injection with bacteria; *Escherichia coli* is often the infecting organism. These patients initially and sometimes chronically become the responsibility of medical or surgical clinics. Nevertheless, the disorder is a mental problem, is more complex than simple dishonest simulation of symptoms, and is associated with severe emotional difficulties.

Patients may have prominent histrionic or borderline personality features and are usually intelligent and resourceful. They know how to simulate disease and are sophisticated regarding medical practices. They differ from malingerers because although their deceits and simulations are conscious and volitional, their behavior is not motivated by external incentives, such as economic gain. It is unclear what they gain beyond medical attention for their suffering, and their motivations and quest for attention are largely unconscious and obscure.

Patients may have an early history of emotional and physical abuse. Patients may also have experienced a severe illness during childhood or had a seriously ill relative. Patients appear to have problems with their identity as well as unstable relationships. Feigning illness may be a way to increase or protect self-esteem by blaming failures on their illness, by being associated with prestigious physicians and medical centers, and by appearing unique, heroic, or medically knowledgeable and sophisticated.

Diagnosis

Diagnosis is based on history and examination, along with any tests necessary to exclude physical disorders. Less severe forms of factitious disorder may also involve the feigning of physical or mental symptoms (eg, depression, hallucinations, delusions, symptoms of posttraumatic stress disorder), with an apparent goal to assume the sick role. These forms are not considered Munchausen, which is more severe and chronic, with recurrent hospitalization, peregrination, and pseudologia fantastica (lying in a manner that is intriguing to the listener).

Treatment

• No clearly effective treatments

Treatment is usually challenging, and there are no clearly effective treatments. Patients may obtain initial relief by having their treatment demands met, but their symptoms typically escalate, ultimately surpassing what physicians are willing or able to do. Confrontation or refusal to meet treatment demands often results in angry reactions, and patients usually move from one physician or hospital to another (called peregrination). Recognizing the disorder and requesting psychiatric or psychologic consultation early is important, so that risky invasive testing, surgical procedures, and excessive or unwarranted use of drugs can be avoided.

A nonaggressive, nonpunitive, nonconfrontational approach should be used to present the diagnosis of Munchausen syndrome or other forms of factitious disorder to patients. To avoid suggesting guilt or reproach, a physician can present the diagnosis as a cry for help. Alternatively, some experts recommend providing mental health treatment without requiring patients to admit their role in causing their illness. In either case, conveying that the physician and patient can cooperatively resolve the problem is helpful.
Munchausen Syndrome by Proxy

Munchausen syndrome by proxy is a variant in which caregivers (usually a parent) intentionally produce or feign physical or mental symptoms or signs in a person in their care (usually a child).

The caregiver falsifies history and may injure the child with drugs or other agents or add blood or bacterial contaminants to urine specimens to simulate disease. The caregiver seeks medical care for the child and appears to be deeply concerned and protective. The child typically has a history of frequent hospitalizations, usually for a variety of nonspecific symptoms, but no firm diagnosis. Victimized children may be seriously ill and sometimes die.

Pain Disorder

(Somatoform Pain Disorder)

Pain disorder consists of pain in one or more anatomic sites severe enough to warrant clinical attention and to cause clinically significant distress or impairment of social, occupational, or other functioning. Mental factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of symptoms, but the pain is not intentionally produced or feigned. Some patients may recall an initial stimulus that produced acute pain. Diagnosis is based on history. Treatment begins by establishing a consistent, supportive physician-patient relationship; drug therapy and psychotherapy can also help.

The proportion of people whose chronic pain is strongly influenced by mental factors is unknown. However, pain is rarely, if ever, "all in a patient's head"; apperception of pain involves sensory and emotional components (see p. 1620). In some cases, both mental and physical factors have important roles in the onset, severity, exacerbation, or maintenance of the pain.

Symptoms and Signs

Physical pain may occur in mood and anxiety disorders, but in pain disorder, pain is a major complaint and is severe enough to warrant clinical attention. Any body part may be affected; the back, head, abdomen, and chest are commonly involved. The pain may be acute or chronic (≥ 6 mo).

Diagnosis

Diagnosis is based on history after excluding a physical disorder that would adequately explain the pain and its onset, severity, duration, and maintenance and the degree of disability. Detection of mental or social stressors may help explain the disorder.

Treatment

• Effective treatment of pain

• For chronic pain, measures that correct dysfunction caused by pain's effects (eg, psychotherapy, various drugs)

A thorough medical evaluation, followed by reassurance, may be sufficient. Sometimes, empathetically pointing out a relationship with an obvious mental or social stressor is effective. However, many patients develop chronic problems and are difficult to treat. They may visit many physicians with an expressed wish to find a cure and are at risk of developing dependence on opioids or benzodiazepines.

For acute pain, the primary goal is to relieve the pain with analgesics, most commonly NSAIDs and acetaminophen. Antidepressants and anticonvulsants are sometimes added.

For chronic pain (lasting ≥ 6 mo), it is important to not only manage the pain but also to reduce the pain's effect on the patient's life and functioning. Psychotherapy and various drugs (eg, analgesics, antidepressants, anticonvulsants) may help. Opioids can be safely and effectively used for chronic pain,
although some patients abuse and become dependent on them, especially those with a history of substance abuse and dependence. All patients need ongoing monitoring for abuse and dependence. Thorough regular reevaluations by a caring, empathetic physician, who remains alert to the possibility of a new significant physical disorder while protecting the patient from unnecessary tests or procedures, offers hope for long-term palliation.

Somatization Disorder

Somatization disorder is characterized by multiple physical complaints (eg, pain; GI, sexual, and neurologic symptoms) over several years that cannot be explained fully by a physical disorder. Symptoms usually begin before age 30 and are not intentionally produced or feigned. Diagnosis is based on history after excluding physical disorders. Treatment focuses on establishing a consistent, supportive physician-patient relationship that avoids exposing the patient to unnecessary diagnostic testing and therapies.

Somatization disorder is often familial, although the etiology is unknown. Somatization disorder occurs more often in women. Male relatives of affected women have an increased risk of antisocial personality and substance-related disorders.

Symptoms and Signs

Recurring and multiple physical complaints usually begin before age 30. Severity may fluctuate, but symptoms persist for at least several years. Complete symptom relief for any extended period is rare. Some people become more overtly depressed.

Any body part may be affected, and specific symptoms and their frequency vary among cultures. In the US, typical symptoms include headache, nausea and vomiting, bloating, abdominal pain, diarrhea or constipation, dysuria, dysmenorrhea, dyspareunia, and loss of sexual desire. Men frequently complain of erectile or ejaculatory dysfunction. Neurologic symptoms are also present. Anxiety and depression may occur. Typically, patients are dramatic and emotional when recounting their symptoms, often referring to them as "unbearable," "beyond description," or "the worst imaginable."

Patients may become dependent on others, demanding help and emotional support and becoming angry when they feel their needs are not met. They may also threaten or attempt suicide. Often dissatisfied with their medical care, they typically go from one physician to another or seek treatment from several physicians concurrently.

The intensity and persistence of symptoms may reflect a strong desire to be cared for. Symptoms may help patients avoid responsibilities but may also prevent pleasure and act as punishment, suggesting underlying feelings of unworthiness and guilt.

Diagnosis

• Usually clinical criteria

Patients are unaware of their underlying mental problem and believe that they have physical ailments, so they pressure physicians for tests and treatments. Physicians usually do many examinations and tests to eliminate a physical disorder as the cause. Because such patients may develop concurrent physical disorders, appropriate examinations and tests should also be done when symptoms change significantly or when objective signs develop. Patients, even those who have a satisfactory relationship with a primary physician, are commonly referred to a psychiatrist.

Specific diagnostic criteria include the following:

• Onset of multiple physical symptoms before age 30

• Symptoms occurring over several years
• Treatment seeking or impaired functioning

• Pain affecting ≥ 4 body parts

• ≥ 2 GI symptoms other than pain (eg, nausea, bloating, food intolerance)

• ≥ 1 sexual or reproductive symptom other than pain (eg, sexual indifference, erectile dysfunction)

• ≥ 1 neurologic symptom other than pain (eg, weakness, imbalance, loss of sensation)

The diagnosis is supported by the dramatic nature of the complaints and the patient's sometimes exhibitionistic, dependent, and suicidal behavior. Somatization disorder is distinguished from generalized anxiety disorder, conversion disorder, and major depression by the predominance, multiplicity, and persistence of physical symptoms.

Patients who do not meet the above diagnostic criteria for somatization disorder but who have ≥ 6 mo of ≥ 1 physical complaints that are not fully explained by a physical disorder or another mental disorder and who have clinically significant distress or impairment in functioning, are said to have undifferentiated somatoform disorder.

**Treatment**

Treatment is usually difficult. Drug treatment of concurrent mental disorders (eg, depression) may help. Psychotherapy, particularly cognitive-behavioral therapy, may also help. Patients benefit from having a supportive relationship with a primary care physician, who coordinates all of their health care, offers symptomatic relief, sees them regularly, and protects them from unnecessary tests and procedures.
Chapter 167. Suicidal Behavior

Introduction

Suicidal behavior includes 3 types of self-destructive acts: completed suicide, attempted suicide, and suicide gestures. Thoughts and plans about suicide are referred to as suicide ideation.

Completed suicide is a suicidal act that results in death. Attempted suicide is an act intended to be self-lethal, but one that does not result in death. Frequently, suicide attempts involve at least some ambivalence about wishing to die and may be a cry for help. Suicide gestures are attempts that involve an action with a very low lethal potential (eg, inflicting superficial scratches on the wrist, overdosing on vitamins). Suicide gestures and suicide ideation may reflect pleas for help from people who still wish to live. However, they should not be dismissed lightly.

Epidemiology

Statistics on suicidal behavior are based mainly on death certificates and inquest reports and underestimate the true incidence. Suicide ranks 11th among causes of death in the US, with 32,439 completed suicides in 2004. It is the 3rd leading cause of death among people 10 to 24 yr. Men ≥ 75 have the highest rate of death by suicide. In all age groups, male deaths by suicide outnumber female deaths by 4:1.

Each year, an estimated > 700,000 people attempt suicide. About 25 attempts are made for every death that occurs by suicide. However, 3.5 to 12.5% of people who make an attempt eventually die by suicide because many people make repeated attempts. About 20 to 30% of people who attempt suicide try again within 1 yr. Women attempt suicide twice as often as men, but men complete suicide 4 times more often than women.

People in a secure relationship have a significantly lower suicide rate than single people. Attempted and completed suicide rates are higher among those who live alone. Suicide is less common among practicing members of most religious groups (particularly Roman Catholics).

Group suicides, whether of many people or only 2 (such as lovers or spouses), represent an extreme form of personal identification with others.

A suicide note is left by about 1 in 6 people who complete suicide. The content may indicate the mental disorder that led to the suicidal act.

Etiology

Suicidal behaviors usually result from the interaction of several factors. The primary remediable risk factor in suicide is

• Depression

Suicide and suicide attempts appear to be more common among patients with anxiety disorders, and severe anxiety is associated with major depression or bipolar disorders.

Other factors include the following:

• Social factors

• Personality abnormalities

• Traumatic childhood experiences

• Serious physical disorders
Alcohol and drugs of abuse

Serious psychiatric disorders

Certain social factors (eg, disappointment, loss) and personality abnormalities (eg, impulsivity, aggression) appear associated with suicide. Traumatic childhood experiences, particularly the distresses of a broken home, parental deprivation, and abuse, are significantly more common among people who commit suicidal acts. Suicide is sometimes the final act in a course of self-destructive behavior, such as alcoholism, reckless driving, and violent antisocial acts. Often, one factor (commonly disruption of an important relationship) is the last straw. Serious physical disorders, especially those that are chronic and painful, play an important role in about 20% of suicides among the elderly.

Alcohol and drugs of abuse may increase disinhibition and impulsivity, as well as worsen mood, a potentially lethal combination. About 30% of people who attempt suicide have consumed alcohol before the attempt, and about one half of them were intoxicated at the time. Alcoholics are suicide-prone even when sober.

Some patients with schizophrenia commit suicide, sometimes because of depression, to which these patients are prone. The suicide method may be bizarre and violent. Attempted suicide is uncommon, although it may be the first sign of psychiatric disturbance, occurring early in schizophrenia.

People with personality disorders are prone to attempted suicide—especially emotionally immature people with a borderline or an antisocial personality disorder because they tolerate frustration poorly and react to stress impetuously with violence and aggression.

Aggression toward others is sometimes evident in suicidal behavior. Rarely, former lovers or estranged spouses are involved in murder-suicides; one person murders the other, then commits suicide.

Methods

Choice of methods is determined by many things, including cultural factors and availability as well as the seriousness of intent. Some methods (eg, jumping from heights) make survival virtually impossible, whereas others (eg, drug ingestion) may allow rescue. However, using a method that proves not to be fatal does not necessarily imply that the intent was less serious.

A bizarre method suggests an underlying psychosis. Drug ingestion is the most common method used in suicide attempts. Violent methods, such as shooting and hanging, are uncommon among attempted suicides. Some methods, such as driving over cliffs, can endanger others. Suicide by police is a bizarre form of suicide; people commit an act (eg, brandishing a weapon) that forces law enforcement agents to kill them.

For completed suicides, firearms are most commonly used by both men (74%) and women (31%), followed by hanging in men and drug ingestion in women.

Management of Suicidal Acts

A health care practitioner who foresees the likelihood of suicide in a patient is, in most jurisdictions, required to inform an empowered agency to intervene. Failure to do so can result in criminal and civil actions. Such patients should not be left alone until they are in a secure environment. They should be transported to a secure environment (often a psychiatric facility) by trained professionals (eg, ambulance, police), never by family members or friends.

Any suicidal act, regardless of whether it is a gesture or an attempt, must be taken seriously. Every person with a serious self-injury should be evaluated and treated for the physical injury. If an overdose of a potentially lethal drug is confirmed, immediate steps are taken to prevent absorption and expedite excretion, administer any available antidote, and provide supportive treatment (see Ch. 340).
Initial assessment can be done by any health care practitioner trained in the assessment and management of suicidal behavior. However, all patients require psychiatric assessment as soon as possible. A decision must be made as to whether patients need to be admitted and whether involuntary commitment or restraint is necessary. Patients with a psychotic disorder, delirium, or epilepsy and some with severe depression and an unresolved crisis should be admitted to a psychiatric unit.

After a suicide attempt, the patient may deny any problems because the severe depression that led to the suicidal act may be followed by a short-lived mood elevation. Nonetheless, the risk of later, completed suicide is high unless the patient's problems are resolved.

Psychiatric assessment identifies some of the problems that contributed to the attempt and helps the physician plan appropriate treatment. It consists of the following:

• Establishing rapport

• Understanding the suicide attempt, its background, the events preceding it, and the circumstances in which it occurred

• Appreciating the current difficulties and problems

• Thoroughly understanding personal and family relationships, which are often pertinent to the suicide attempt

• Fully assessing the patient's mental state, with particular emphasis on recognizing depression, anxiety, agitation, panic attacks, severe insomnia, other mental disorders, and alcohol or drug abuse (many of these problems require specific treatment in addition to crisis intervention)

• Interviewing close family members and friends

• Contacting the family physician

Prevention

Prevention requires identifying at-risk people and initiating appropriate interventions (see Table 167-1).

Although some attempted or completed suicides are a surprise and shock, even to close relatives and associates, clear warnings may have been given to family members, friends, or health care practitioners. Warnings are often explicit, as when patients actually discuss plans or suddenly write or change a will. However, warnings can be more subtle, as when patients make comments about having nothing to live for or being better off if dead.

On average, primary care physicians encounter ≥ 6 potentially suicidal people in their practice each year. About 77% of people who commit suicide were seen by a physician within 1 yr before killing themselves, and about 32% had been under the care of a mental health care practitioner during the preceding year. Because severe and painful physical disorders, substance abuse, and mental disorders (particularly depression) are often a factor

[Table 167-1, Risk Factors and Warning Signs for Suicide]

in suicide, recognizing these possible factors and initiating appropriate treatment are important contributions a physician can make to suicide prevention.

Each depressed patient should be questioned about thoughts of suicide. The fear that such inquiry may implant the idea of self-destruction is baseless. Inquiry helps the physician obtain a clearer picture of the depth of the depression, encourages constructive discussion, and conveys the physician's awareness of the patient's deep despair and hopelessness.
Even people threatening imminent suicide (eg, those who call and declare that they are going to take a lethal dose of a drug or who threaten to jump from a high height) may have some desire to live. The physician or another person to whom they appeal for help must support the desire to live. Emergency psychiatric aid for suicidal people includes the following:

- Establishing a relationship and open communication with them
- Reminding them of their identity (ie, using their name repeatedly)
- Helping sort out the problem that has caused the crisis
- Offering constructive help with the problem
- Encouraging them to take positive action
- Reminding them that family and friends care for them and want to help

**Treatment of depression and risk of suicide:** People with depression have a significant risk of suicide and should be carefully monitored for suicidality (suicidal behaviors and ideation). Risk of suicide may be increased early in the treatment of depression, when psychomotor retardation and indecisiveness have been ameliorated but the depressed mood is only partially lifted. When antidepressants are started or when doses are increased, a few patients experience agitation, anxiety, and increasing depression, which may increase suicidality. Recent public health warnings about the possible association between antidepressant use and suicidality in children, adolescents, and young adults have led to a significant reduction (> 20%) in antidepressant prescriptions to these populations. However, youth suicide rates increased by 14% during this period. Thus, by discouraging drug treatment of depression, these warnings may have resulted in more, not fewer, deaths by suicide. Together, these findings suggest that the best approach is to encourage treatment, but with appropriate precautions (dispensing antidepressants in sublethal amounts, giving a clear warning to patients and to family members and significant others to be alert for worsening symptoms or suicidal ideation, and, if either occurs, immediately calling the prescribing clinician or seek care elsewhere).

**Effects of Suicide**

Any suicidal act has a marked emotional effect on all involved. The physician, family members, and friends may feel guilt, shame, and remorse at not having prevented a suicide, as well as anger toward the deceased or others. The physician can provide valuable assistance to the deceased’s family members and friends in dealing with their feelings of guilt and sorrow.

**Assisted Suicide**

Assisted suicide refers to the assistance given by physicians or other practitioners to people who wish to end their life. Assistance may be requests about drugs that can be saved up to provide a lethal dose, about instructions for a painless way to commit suicide, or for administration of a lethal dose of drug.

Assisted suicide is controversial and is illegal in most states in the US. Nonetheless, patients with painful, debilitating, and untreatable conditions may initiate a discussion about it with a physician. Assisted suicide may pose difficult ethical issues for physicians.
13 - Neurologic Disorders

Chapter 168. Approach to the Neurologic Patient

Introduction

Patients with neurologic symptoms are approached in a stepwise manner termed the neurologic method, which consists of the following:

- Identifying the anatomic location of the lesion or lesions causing symptoms
- Identifying the pathophysiology involved
- Generating a differential diagnosis
- Selecting specific, appropriate tests

Identifying the anatomy and pathophysiology of the lesion through careful history taking and an accurate neurologic examination markedly narrows the differential diagnosis and thus the number of tests needed. This approach should not be replaced by reflex ordering of CT, MRI, and other laboratory testing; doing so leads to error and unnecessary cost.

To identify the anatomic location, the examiner considers questions such as

- Is the lesion in one or multiple locations?
- Is the lesion confined to the nervous system, or is it part of a systemic disorder?
- What part of the nervous system is affected?

Specific parts of the nervous system to be considered include the cerebral cortex, subcortical white matter, basal ganglia, thalamus, cerebellum, brain stem, spinal cord, brachial or pelvic plexus, peripheral nerves, neuromuscular junction, and muscle.

Once the location of the lesion is identified, categories of pathophysiologic causes are considered; they include

- Vascular
- Infectious
- Neoplastic
- Degenerative
- Traumatic
- Toxic-metabolic
- Immune-mediated

When appropriately applied, the neurologic method provides an orderly approach to even the most complex case, and clinicians are far less likely to be fooled by neurologic mimicry—eg, when symptoms of an acute stroke are actually due to a brain tumor or when rapidly ascending paralysis suggesting Guillain-Barre is actually due to spinal cord compression.

History
The history is the most important part of the neurologic evaluation. Patients should be put at ease and allowed to tell their story in their own words. Usually, a clinician can quickly determine whether a reliable history is forthcoming or whether a family member should be interviewed instead.

Specific questions clarify the quality, intensity, distribution, duration, and frequency of each symptom. What aggravates and attenuates the symptom and whether past treatment was effective should be determined. Specific disabilities should be described quantitatively (eg, walks at most 25 ft before stopping to rest), and their effect on the patient's daily routine noted. Past medical history and a complete review of systems are essential because neurologic complications are common in other disorders, especially alcoholism, diabetes, cancer, vascular disorders, and HIV infection. Family history is important because migraine and many metabolic, muscle, nerve, and neurodegenerative disorders are inherited. Social, occupational, and travel history provides information about unusual infections and exposure to toxins and parasites.

Sometimes neurologic symptoms and signs are functional or hysterical, reflecting a psychiatric disorder. Typically, such symptoms and signs do not conform to the rules of anatomy and physiology, and the patient is often depressed or unusually frightened. However, functional and physical disorders sometimes coexist, and distinguishing them can be challenging.

**Neurologic Examination**

The neurologic examination begins with careful observation of the patient entering the examination area and continues during history taking. The patient's speed, symmetry, and coordination while moving to the examining table are noted, as are posture and gait. The patient's demeanor, dress, and responses provide information about mood and social adaptation. Abnormalities in language, speech, or praxis; neglect of space; unusual posturing; and other disorders of movement may be apparent before formal testing.

As information is obtained, a skilled examiner may include certain components of the examination and exclude others based on a preliminary hypothesis about the anatomy and pathophysiology of the problem. If the examiner is less skilled, complete neurologic screening is done.

**Mental status:** (See also Ch. 157.) The patient's attention span is assessed first; an inattentive patient cannot cooperate fully and hinders testing. Any hint of cognitive decline requires examination of mental status (see Sidebar 168-1), which involves testing multiple aspects of cognitive function (eg, orientation to time, place, and person; attention and concentration; memory; verbal and mathematical abilities; judgment; reasoning). Loss of orientation to person (ie, not knowing one's own name) occurs only when obtundation, delirium, or dementia is severe; when it occurs as an isolated symptom, it suggests malingering. Insight into illness and fund of knowledge in relation to educational level are assessed, as are affect and mood (see p. 1538).

The patient is asked to follow a complex command that involves 3 body parts and discriminates between right and left (eg, "Put your right thumb in your left ear, and stick out your tongue"). The patient is asked to name simple objects and body parts and to read, write, and repeat simple phrases; if deficits are noted, other tests of aphasia are needed (see p. 1642). Spatial perception can be assessed by asking the patient to imitate simple and complex finger constructions and to draw a clock, cube, house, or interlocking pentagons; the effort expended is often as informative as the final product. This test may identify impersistence, perseveration, micrographia, and hemispatial neglect. Praxis (cognitive ability to do complex motor movements) can be assessed by asking the patient to use a toothbrush or comb, light a match, or snap the fingers.

**Cranial nerves:** (See also Ch. 181.) Smell, a function of the 1st (olfactory) cranial nerve, is usually evaluated only after head trauma or when lesions of the anterior fossa (eg, meningioma) are suspected or patients report abnormal smell or taste. The patient is asked to identify odors (eg, soap, coffee, cloves) presented to each nostril. Alcohol, ammonia, and other irritants, which test the nociceptive receptors of the 5th (trigeminal) cranial nerve, are used only when malingering is suspected.

The 2nd (optic), 3rd (oculomotor), 4th (trochlear), and 6th (abducens) cranial nerves involve the visual
system.

For the **2nd cranial nerve**, visual acuity is tested using a Snellen chart for distance vision and a handheld chart for near vision; each eye is assessed individually, with the other eye covered. Color perception is tested using standard pseudoisochromatic Ishihara or Hardy-Rand-Ritter plates that have numbers or figures embedded in a field of specifically colored dots. Visual fields are tested by directed confrontation in all 4 visual quadrants. Direct and consensual pupillary responses are tested (see also p. 1745). Funduscopic examination is also done.

For the **3rd, 4th, and 6th cranial nerves**, eyes are observed for symmetry of movement, globe position, asymmetry or droop of the eyelids (ptosis), and twitches or flutters of globes or lids. Extraocular movements controlled by these nerves are tested by asking the patient to follow a moving target (eg, examiner's finger, penlight) to all 4 quadrants (including across the midline); this test can detect nystagmus and palsies of ocular muscles. Anisocoria or differences in pupillary size should be noted in a dimly lit room. The pupillary light response is tested for symmetry and briskness.

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**Sidebar 168-1 Examination of Mental Status**

The mental status examination is an assessment of current mental capacity through evaluation of general appearance, behavior, any unusual or bizarre beliefs and perceptions (eg, delusions, hallucinations), mood, and all aspects of cognition (eg, attention, orientation, memory).

Examination of mental status is done in anyone with an altered mental status or evolving impairment of cognition whether acute or chronic. Many screening tools are available; the Mini-Mental State Examination is one of the most commonly used. Baseline results are recorded, and the examination is repeated yearly and whenever a change in mental status is suspected.

Patients should be told that recording of mental status is routine and that they should not be embarrassed by its being done.

The examination is done in a quiet room, and the examiner should make sure that patients can hear the questions clearly. Patients who do not speak English as their primary language should be questioned in the language they speak fluently.

Mental status examination evaluates different areas of cognitive function. The examiner must first establish that the patient is attentive—eg, by asking the patient to immediately repeat 3 words. Testing an inattentive patient further is not useful.

The parameters of cognitive function to be tested include the following:

- **Orientation**
  - Person (What is your name?)
  - Time (What is today's date?)
  - Place (What is the name of this place?)

- **Short-term memory**
  Ask the patient to recall 3 objects after a 3-min delay.

- **Long-term memory**
  Ask the patient a question about the past, such as "What color suit did you wear at your wedding?" or "What was the make of your first car?"

- **Math**
  Use any simple mathematical test. Serial 7s are common: The patient is asked to start with 100 and to subtract 7, then 7 from 93, etc. Alternatively, ask how many nickels are in $1.35.

- **Word finding**
  Ask the patient to name as many objects in a single category, such as articles of clothing or animals, as possible in 1 min.
Concentration

Ask the patient to spell a 5-letter word forward and backward. "World" is commonly used.

Naming objects

Present an object, such as a pen, book, or ruler, and ask the patient to name it.

Following commands

Start with a 1-step command, such as "Touch your nose with your right hand." Then test a 3-step command, such as "Take this piece of paper in your right hand. Fold it in half. Put the paper on the floor."

Writing

Ask the patient to write a sentence. The sentence should contain a subject and an object and should make sense. Spelling errors should be ignored.

Spatial orientation

Ask the patient to draw a house or a clock and mark the clock with a specific time. Or ask the patient to draw 2 intersecting pentagons.

Abstract reasoning

Ask the patient to identify a unifying theme between 3 or 4 objects (e.g., all are fruit, all are vehicles of transportation, all are musical instruments). Ask the patient to interpret a moderately challenging proverb, such as "People who live in glass houses should not throw stones."

Judgment

Ask the patient about a hypothetical situation requiring good judgment, such as "What would you do if you found a stamped letter on the sidewalk?" Placing it in the mailbox is the correct answer; opening the letter suggests a personality disorder.

For the 5th (trigeminal) nerve, the 3 sensory divisions (ophthalmic, maxillary, mandibular) are evaluated by using a pinprick to test facial sensation and by brushing a wisp of cotton against the lower or lateral cornea to evaluate the corneal reflex. If facial sensation is lost, the angle of the jaw should be examined; sparing of this area (innervated by spinal root C2) suggests a trigeminal deficit. A weak blink due to facial weakness (e.g., 7th cranial nerve paralysis) should be distinguished from depressed or absent corneal sensation, which is common in contact lens wearers. A patient with facial weakness feels the cotton wisp normally on both sides, even though blink is decreased. Trigeminal motor function is tested by palpating the masseter muscles while the patient clenches the teeth and by asking the patient to open the mouth against resistance. If a pterygoid muscle is weak, the jaw deviates to that side when the mouth is opened.

The 7th (facial) cranial nerve is evaluated by checking for hemifacial weakness. Asymmetry of facial movements is often more obvious during spontaneous conversation, especially when the patient smiles or, if obtunded, grimaces at a noxious stimulus; on the weakened side, the nasolabial fold is depressed and the palpebral fissure is widened. If the patient has only lower facial weakness (i.e., furrowing of the forehead and eye closure are preserved), etiology of 7th nerve weakness is central rather than peripheral. Taste in the anterior two thirds of the tongue can be tested with sweet, sour, salty, and bitter solutions applied with a cotton swab first on one side of the tongue, then on the other. Hyperacusis may be detected with a vibrating tuning fork held next to the ear.

Because the 8th (vestibulocochlear, acoustic, auditory) cranial nerve carries auditory and vestibular input, evaluation involves testing hearing (see p. 431) and balance.

The 9th (glossopharyngeal) and 10th (vagus) cranial nerves are usually evaluated together. Whether the palate elevates symmetrically is noted. A tongue blade is used to touch one side of the posterior pharynx, then the other, and symmetry of the gag reflex is observed; bilateral absence of the gag reflex is common among healthy people and may not be significant. In an unresponsive, intubated patient, suctioning the endotracheal tube normally triggers coughing. If hoarseness is noted, the vocal cords are inspected. Isolated hoarseness (with normal gag and palatal elevation) should prompt a search for lesions (e.g., mediastinal lymphoma, aortic aneurysm) compressing the recurrent laryngeal nerve.

The 11th (spinal accessory) cranial nerve is evaluated by testing the muscles it supplies. For the sternocleidomastoid, the patient is asked to turn the head against resistance supplied by the examiner's hand while the examiner palpates the active muscle (opposite the turned head). For the upper trapezius, the patient is asked to elevate the shoulders against resistance supplied by the examiner.

The 12th (hypoglossal) cranial nerve is evaluated by asking the patient to extend the tongue and inspecting it for atrophy, fasciculations, and weakness (deviation is toward the side of a lesion).
Motor system: The limbs and shoulder girdle should be fully exposed, then inspected for atrophy, hypertrophy, asymmetric development, fasciculations, myotonia, tremor, and other involuntary movements, including chorea (brief, jerky movements), athetosis (continuous, writhing movements), and myoclonus (shocklike contractions of a muscle). Passive flexion and extension of the limbs in a relaxed patient provide information about muscle tone. Decreased muscle bulk indicates atrophy, but bilateral atrophy or atrophy in large or concealed muscles, unless advanced, may not be obvious. In the elderly, loss of some muscle mass is common. Hypertrophy occurs when one muscle must work harder to compensate for weakness in another; pseudohypertrophy occurs when muscle tissue is replaced by excessive connective tissue or storage material.

Fasciculations (brief, fine, irregular twitches of the muscle visible under the skin) are relatively common. Although they can occur in normal muscle, particularly in calf muscles of the elderly, fasciculations usually indicate lesions of the lower motor neuron (eg, nerve degeneration or injury and regeneration). Myotonia (slowed relaxation of muscle after a sustained contraction or direct percussion of the muscle) indicates myotonic dystrophy and may be demonstrated by inability to quickly open a clenched hand. Increased resistance followed by relaxation (clasp-knife phenomenon) and spasticity indicates upper motor neuron lesions. Lead-pipe rigidity, often with cogwheeling, suggests a basal ganglia disorder.

Muscle strength: Patients who report weakness may mean fatigue, clumsiness, or true muscle weakness. Thus, the examiner must define the precise character of symptoms, including exact location, time of occurrence, precipitating and ameliorating factors, and associated symptoms and signs (see Weakness on p. 1597). Limbs are inspected for weakness (when extended, a weak limb drifts downward), tremor, and other involuntary movements. The strength of specific muscle groups is tested against resistance, and one side of the body is compared with the other. However, pain may preclude a full effort during strength testing. With hysterical weakness, resistance to movement may be initially normal, followed by a sudden giving way.

Subtle weakness may be indicated by decreased arm swing while walking, pronator drift in an outstretched arm, decreased spontaneous use of a limb, an externally rotated leg, slowing of rapid alternating movements, or impairment of fine dexterity (eg, ability to fasten a button, open a safety pin, or remove a match from its box). Subtle motor weakness can often be detected by Tiller and mini-Tiller testing. With each hand, the patient makes a fist (in the Tiller test) or a fist with the index finger extended (in the mini-Tiller test) and then rotates the 2 around each other. The weaker limb becomes fixed in space while the stronger revolves around it.

Strength should be graded. The following scale, originally developed by The Medical Research Council of the United Kingdom, is now used universally:

0: No visible muscle contraction
1: Visible muscle contraction with no or trace movement
2: Limb movement when gravity is eliminated
3: Movement against gravity but not resistance
4: Movement against resistance supplied by the examiner
5: Full strength

The difficulty with this and similar scales is the large range in strength possible between grades 4 and 5. Distal strength can be semiquantitatively measured with a handgrip ergometer or with an inflated BP cuff squeezed by the patient.

Functional testing often provides a better picture of the relationship between strength and disability. As the patient does various maneuvers, deficiencies are noted and quantified as much as possible (eg, number of squats done or steps climbed). Rising from a squatting position or stepping onto a chair tests proximal leg strength; walking on the heels and on tiptoe tests distal strength. Pushing with the arms to
get out of a chair indicates quadriceps weakness. Swinging the body to move the arms indicates shoulder girdle weakness. Rising from the supine position by turning prone, kneeling, and using the hands to climb up the thighs and slowly push erect (Gowers' sign) suggests pelvic girdle weakness.

**Gait, stance, and coordination:** Normal gait, stance, and coordination require integrity of the motor, vestibular, and proprioceptive pathways (see also Ch. 183). A lesion in any of the pathways causes characteristic deficits: Cerebellar ataxia requires a wide gait for stability; dropfoot causes a steppage gait (lifting the leg higher than normal to avoid catching the foot on surface irregularities); pelvic muscle weakness causes waddling; and spastic leg causes scissoring and circumduction. Patients with impaired proprioception must constantly observe placement of their feet to avoid tripping or falling. Coordination can be tested with finger-to-nose or knee-to-shin maneuvers, which help detect ataxic movements.

**Sensation:** The best screening test for sensory loss uses a safety pin to lightly prick the face, torso, and 4 limbs; the patient is asked whether the pinprick feels the same on both sides and whether the sensation is dull or sharp. The pin is discarded after use to avoid potential transmission of bloodborne disorders (eg, HIV infection, hepatitis).

Cortical sensory function is evaluated by asking the patient to identify a familiar object (eg, coin, key) placed in the palm of the hand (stereognosis) and numbers written on the palm (graphesthesis) and to distinguish between 1 and 2 simultaneous, closely placed pinpricks on the fingertips (2-point discrimination).

Temperature sense can be tested with a cold tuning fork that has one prong rubbed warm by the examiner’s palm or with test tubes containing warm and cold water.

Joint position sense is tested by moving the terminal phalanges of the patient's fingers, then the toes, up or down a few degrees. If the patient cannot identify these tiny movements with eyes closed, larger up-and-down movements are tried before testing the next most proximal joints (eg, testing the ankles if toe movement is not perceived). Pseudoathetosis refers to involuntary writhing, snakelike movements of a limb that result from severe loss of position sense; motor pathways, including those of the basal ganglia, are preserved. The brain cannot sense where the limb is in space so the limb moves on its own, and the patient must use vision to control the limb's movements. Typically, when the eyes are closed, the patient cannot locate the limb in space. Inability to stand with feet together and eyes closed (Romberg test) indicates impaired position sense in the lower extremities. When cerebellar disease is present, the patient stands with the feet apart but as close together as possible without falling and only then closes the eyes. Rarely, a positive result is due to severe bilateral loss of vestibular function (eg, aminoglycoside toxicity).

To test vibration sense, the examiner places a finger under the patient's distal interphalangeal joint and presses a lightly tapped 128-cycle tuning fork on top of the joint. The patient should note the end of vibration about the same time as the examiner, who feels it through the patient's joint.

A cotton wisp can be used to test light touch.

If sensation is impaired, the anatomic pattern suggests location of the lesion (see Figs. 168-1, 168-2, and 168-3):

- Stocking-glove distribution: Distal peripheral nerves
- Single dermatomal or nerve branch distribution: Isolated nerves (mononeuritis multiplex) or nerve roots (radiculopathy)
- Sensation reduced below a certain dermatomal level: Spinal cord
- Saddle area sensory loss: Cauda equina
- Crossed face-body pattern: Brain stem
• Hemisensory loss: Brain

• Midline hemisensory loss: Thalamus or functional (psychiatric)

Location of the lesion is confirmed by determining whether motor weakness and reflex changes follow a similar pattern. Patchy sensory, motor, and reflex deficits in a limb suggest lesions of the brachial or pelvic plexus.

**Reflexes:** Deep tendon (muscle stretch) reflex testing evaluates afferent nerves, synaptic connections within the spinal cord, motor nerves, and descending motor pathways. Lower motor neuron lesions (eg, affecting the anterior horn cell, spinal root, or peripheral nerve) depress reflexes; upper motor neuron lesions (ie, non-basal ganglia disorders anywhere above the anterior horn cell) increase reflexes (see p. [1791](#)).

Reflexes tested include the biceps (innervated by C5 and C6), radial brachialis (by

[Fig. 168-1. Sensory dermatomes.]

[Fig. 168-2. Cutaneous nerve distribution: upper limb.] C6), triceps (by C7), quadriceps knee jerk (by L4), and ankle jerk (by S1). Any asymmetric increase or depression is noted. Jendrassik's maneuver can be used to augment hypoactive reflexes: The patient locks the hands together and pulls vigorously apart as a tendon in the lower extremity is tapped. Alternatively, the patient can push the knees together against each other, while the upper limb tendon is tested.

[Fig. 168-3. Cutaneous nerve distribution: lower limb.] Lightly stroking the 4 quadrants of the abdomen should elicit a superficial abdominal reflex. Depression of this reflex may be due to a central lesion, obesity, or lax skeletal muscles (eg, after pregnancy); its absence may indicate spinal cord injury.

Pathologic reflexes (eg, Babinski's, Chaddock's, Oppenheim, snout, root, grasp) are reversions to primitive responses and indicate loss of cortical inhibition.

**Babinski's, Chaddock's, and Oppenheim reflexes** all evaluate the plantar response. The normal reflex response is flexion of the great toe. An abnormal response is slower and consists of extension of the great toe with fanning of the other toes and often knee and hip flexion. This reaction is of spinal reflex origin and indicates spinal disinhibition due to an upper motor neuron lesion. For Babinski's reflex, the lateral sole of the foot is firmly stroked from the heel to the ball of the foot with a tongue blade or end of a reflex hammer. The stimulus must be noxious but not injurious; stroking should not veer too medially, or it may inadvertently induce a primitive grasp reflex. In sensitive patients, the reflex response may be masked by quick voluntary withdrawal of the foot, which is not a problem in Chaddock's or Oppenheim reflex testing. For Chaddock's reflex, the lateral foot, from lateral malleolus to small toe, is stroked with a blunt instrument. For the Oppenheim reflex, the anterior tibia, from just below the patella to the foot, is firmly stroked with a knuckle.

The **snout reflex** is present if tapping a tongue blade across the lips causes pursing of the lips.

The **rooting reflex** is present if stroking the lateral upper lip causes movement of the mouth toward the stimulus.

The **grasp reflex** is present if gently stroking the palm of the patient's hand causes the fingers to flex and grasp the examiner's finger.

The **palmomental reflex** is present if stroking the palm of the hand causes contraction of the ipsilateral mentalis muscle of the lower lip.
**Hoffmann's sign** is present if flicking the nail on the 3rd or 4th finger elicits involuntary flexion of the distal phalanx of the thumb and index finger.

For the **glabellar sign**, the forehead is tapped to induce blinking; normally, each of the first 5 taps induces a single blink, then the reflex fatigues. Blinking persists in patients with diffuse cerebral dysfunction.

Testing for **clonus** (rhythmic, rapid alternation of muscle contraction and relaxation caused by sudden, passive tendon stretching) is done by rapid dorsiflexion of the foot at the ankle. Sustained clonus indicates an upper motor neuron disorder.

**Sphincteric reflexes** may be tested during the rectal examination. To test sphincteric tone (S2 to S4 nerve root levels), the examiner inserts a gloved finger into the rectum and asks the patient to squeeze it. Alternatively, the perianal region is touched lightly with a cotton wisp; the normal response is contraction of the external anal sphincter (anal wink reflex). Rectal tone typically becomes lax in patients with acute spinal cord injury or cauda equine syndrome.

For the **bulbospongiosus reflex**, which tests S2 to S4 levels, the dorsum of the penis is tapped; normal response is contraction of the bulbospongiosus muscle.

For the **cremasteric reflex**, which tests the L2 level, the medial thigh 7.6 cm (3 in) below the inguinal crease is stroked upward; normal response is elevation of the ipsilateral testis.

**Autonomic nervous system**: (See also p. 1615.) Assessment involves checking for postural hypotension, heart rate changes in response to the Valsalva maneuver, decreased or absent sweating, and evidence of Horner's syndrome (unilateral ptosis, pupillary constriction, facial anhidrosis). Disturbances of bowel, bladder, sexual, and hypothalamic function should be noted.

**Cerebrovascular examination**: In a patient presenting with acute stroke, radial pulse and BP in the 2 arms are compared to check for painless aortic dissection, which can occlude a carotid artery and cause stroke. The skin, sclerae, fundi, oral mucosae, and nail beds are inspected for hemorrhages and evidence of cholesterol or septic emboli; auscultation over the heart can detect new or evolving murmurs and arrhythmias. Bruits over the cranium may indicate an arteriovenous malformation or fistula or, occasionally, redirected blood flow across the circle of Willis after carotid occlusion. Auscultation over the carotid arteries can detect bruits near the bifurcation; vigorous palpation should be avoided. By running the bell of the stethoscope down the neck toward the heart, the examiner may identify a change in character that can distinguish a bruit from a systolic heart murmur. Decreased vigor of the carotid upstroke suggests a stenotic lesion.

Peripheral pulses are palpated to check for peripheral vascular disease. The temporal arteries are palpated; enlargement or tenderness may suggest temporal arteritis.

**Neurologic Diagnostic Procedures**

Diagnostic procedures should not be used for preliminary screening, except perhaps in emergencies when a complete neurologic evaluation is impossible. Evidence uncovered during the history and physical examination should guide testing.

**Lumbar puncture (spinal tap)**: Lumbar puncture is used to evaluate intracranial pressure and CSF composition (see Table 168-1), to therapeutically reduce intracranial pressure (eg, pseudotumor), and to administer intrathecal drugs or a radiopaque agent for myelography.

**Relative contraindications** include

- Infection at the puncture site
• Bleeding diathesis

• Increased intracranial pressure due to an intracranial mass lesion, obstructed CSF outflow (eg, due to aqueductal stenosis or Chiari I malformation), or spinal cord CSF blockage (eg, due to tumor cord compression)

If papilledema or focal neurologic deficits are present, CT or MRI should be done before lumbar puncture to rule out presence of a mass that could precipitate transtentorial or cerebellar herniation.

[Table 168-1. Cerebrospinal Fluid Abnormalities in Various Disorders]

For the procedure, the patient is typically in the left lateral decubitus position. A cooperative patient is asked to hug the knees and curl up as tightly as possible. Assistants may have to hold patients who cannot maintain this position, or the spine may be flexed better by having patients, particularly obese patients, sit on the side of the bed and lean over a bedside tray table. An area 20 cm in diameter is washed with iodine, then wiped with alcohol to remove the iodine and prevent its introduction into the subarachnoid space. A lumbar puncture needle with stylet is inserted into the L4- to-L5 interspace (the L4 spinous process is typically on a line between the posterior-superior iliac crests); the needle is aimed rostrally toward the patient's umbilicus and always kept parallel to the floor. Entrance into the subarachnoid space is usually accompanied by a discernible pop; the stylet is withdrawn to allow CSF to flow out. Opening pressure is measured with a manometer; 4 tubes are each filled with about 2 to 10 mL of CSF for testing. The puncture site is then covered with a sterile adhesive strip. A post-lumbar puncture headache (see p. 1724) occurs in about 10% of patients.

Normal CSF is clear and colorless; ≥ 300 cells/μL produces cloudiness or turbidity. Bloody fluid may indicate a traumatic puncture (pushing the needle in too far, into the venous plexus along the anterior spinal canal) or subarachnoid hemorrhage. A traumatic puncture is distinguished by gradual clearing of the CSF between the 1st and 4th tubes (confirmed by decreasing RBC count), absence of xanthochromia (yellowish CSF due to lysed RBCs) in a centrifuged sample, and fresh, uncrenated RBCs. With intrinsic subarachnoid hemorrhage, the CSF remains uniformly bloody throughout collection; xanthochromia is often present if several hours have passed after ictus; and RBCs are usually older and crenated. Faintly yellow fluid may also be due to senile chromogens, severe jaundice, or increased protein (> 100 mg/dL).

Cell count and differential and glucose and protein levels aid in the diagnosis of many neurologic disorders (see Table 168-1). If infection is suspected, the centrifuged CSF sediment is stained for bacteria (Gram stain), for TB (acid-fast stain or immunofluorescence), and for Cryptococcus sp (India ink). Larger amounts of fluid (10 mL) improve the chances of detecting the pathogen, particularly acidfast bacilli and certain fungi, in stains and cultures. In early meningococcal meningitis or severe leukopenia, CSF protein may be too low for bacterial adherence to the glass slide during Gram staining, producing a false-negative result. Mixing a drop of aseptic serum with CSF sediment prevents this problem. When hemorrhagic meningoencephalitis is suspected, a wet mount is used to search for amebas. Latex particle agglutination and coagglutination tests may allow rapid bacterial identification, especially when stains and cultures are negative (eg, in partially treated meningitis). CSF should be cultured aerobically and anaerobically and for acid-fast bacilli and fungi. Except for enteroviruses, viruses are seldom isolated from the CSF. Viral antibody panels are available. Venereal Disease Research Laboratories (VDRL) testing and cryptococcal antigen testing are often routinely done. PCR tests for herpes simplex virus and other CNS pathogens are increasingly available.

Normally, CSF: blood glucose ratio is about 0.6, and except in severe hypoglycemia, CSF glucose is typically > 50 mg/dL (> 2.78 mmol/L). Increased CSF protein (> 50 mg/dL) is a sensitive but nonspecific index of disease; protein increases to > 500 mg/dL in purulent meningitis, advanced TB meningitis, complete block by spinal cord tumor, or a bloody puncture. Special examinations for globulin (normally < 15%), oligoclonal banding, and myelin basic protein aid in diagnosis of a demyelinating disorder.

CT: CT provides rapid, noninvasive imaging of the brain and skull. CT is superior to MRI in visualizing fine bone detail in (but not the contents of) the posterior fossa, base of the skull, and spinal canal. A radiopaque contrast agent helps detect brain tumors and abscesses. Noncontrast CT is used to rapidly detect acute hemorrhage and various gross structural changes without concern about contrast allergy or
renal failure. With an intrathecal agent, CT can outline abnormalities encroaching on the brain stem, spinal cord, or spinal nerve roots (eg, meningeal carcinoma, herniated disk) and may detect a syrinx in the spinal cord. CT angiography using a contrast agent can show the cerebral blood vessels, obviating the need for MRI or angiography.

Adverse effects of contrast agents (see p. 3403) include allergic reactions and contrast nephropathy.

MRI: MRI provides better resolution of neural structures than CT. This difference is most significant clinically for visualizing cranial nerves, brain stem lesions, abnormalities of the posterior fossa, and the spinal cord; CT images of these regions are often marred by bony streak artifacts. Also, MRI is better for detecting demyelinating plaques, early infarction, subclinical brain edema, cerebral contusions, incipient transtentorial herniation, abnormalities of the craniocervical junction, and syringomyelia. MRI is especially valuable for identifying spinal abnormalities (eg, tumor, abscess) compressing the spinal cord and requiring emergency intervention.

MRI is contraindicated in patients who have had a pacemaker or cardiac or carotid stents for < 6 wk or who have ferromagnetic aneurysm clips or other metallic objects that may overheat or be displaced within the body by the intense magnetic field.

Visualization of inflammatory, demyelinated, and neoplastic lesions may require enhancement with IV paramagnetic contrast agents (eg, gadolinium). Although gadolinium is thought to be much safer than contrast agents used with CT, nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) has been reported in patients with impaired renal function and acidosis.

There are several MRI techniques (see p. 3406); choice of technique depends on the specific tissue, location, and suspected disorder. Diffusion-weighted imaging (DWI) allows rapid, early detection of ischemic stroke. Perfusion-weighted imaging (PWI) can detect areas of hypoperfusion in early ischemic stroke but cannot yet reliably distinguish areas with benign oligemia from those with injurious hypoperfusion that results in infarction. Diffusion tensor imaging (DTI) is an extension of DWI that can show white matter tracts in 3 dimensions (tractography) and can be used to monitor the integrity of CNS tracts affected by aging and disease. Functional MRI (fMRI) detects brain regions activated (shown by increased flow of oxygenated blood) by a specific cognitive or motor task, but its clinical use is still being defined.

Magnetic resonance angiography (MRA) uses MRI with or without a contrast agent to show cerebral vessels and major arteries and their branches in the head and neck. Although MRA has not replaced cerebral angiography, it is used when cerebral angiography cannot be done (eg, because the patient refuses or has increased risk). As a check for stroke, MRA tends to exaggerate severity of arterial narrowing and thus does not usually miss occlusive disease of large arteries.

Magnetic resonance venography (MRV) uses MRI to show the major veins and dural sinuses of the cranium. MRV obviates the need for cerebral angiography in diagnosing cerebral venous thrombosis and is useful for monitoring thrombus resolution and guiding the duration of anticoagulation. Magnetic resonance spectroscopy can measure metabolites in the brain regionally to distinguish tumors from abscess or stroke.

Echoencephalography: Ultrasonography can be used at the bedside (usually in the neonatal ICU) to detect hemorrhage and hydrocephalus in children < 2 yr. CT has replaced echoencephalography in older children and adults.

Cerebral catheter angiography: X-rays taken after a radiopaque agent is injected via an intraarterial catheter show individual cerebral arteries and venous structures of the brain. With digital data processing (digital subtraction angiography), small amounts of agent can produce high-resolution images. Cerebral angiography supplements CT and MRI in delineating the site and vascularity of intracranial lesions; it has been the gold standard for diagnosing stenotic or occluded arteries, congenitally absent vessels, aneurysms, and arteriovenous malformations. Vessels, as small as 0.1 mm, can be visualized. However, its use has decreased dramatically with the advent of MRA and CT angiography. It is still routinely used
when cerebral vasculitis is suspected and when angiographic interventions (e.g., angioplasty, stent placement, intra-arterial thrombolysis, aneurysm obliteration) may be necessary.

**Duplex Doppler ultrasonography:** This noninvasive procedure can assess dissection, stenosis, occlusion, and ulceration of the carotid bifurcation. It is safe and rapid, but it does not provide the detail of angiography. It is preferable to periorbital Doppler ultrasonography and oculoplethysmography for evaluating patients with carotid artery transient ischemic attacks and is useful for following an abnormality over time. Transcranial Doppler ultrasonography helps evaluate residual blood flow after brain death, vasospasm of the middle cerebral artery after subarachnoid hemorrhage, and vertebrobasilar stroke.

**Myelography:** X-rays are taken after a radiopaque agent is injected into the subarachnoid space via lumbar puncture. MRI has replaced myelography for evaluation of intraspinal abnormalities, but CT myelography is still done when MRI is unavailable. Contraindications are the same as those for lumbar puncture. Myelography may exacerbate the effects of spinal cord compression, especially if too much fluid is removed too rapidly.

**EEG:** Electrodes are distributed over the brain to detect electrical changes associated with seizure disorders, sleep disorders, and metabolic or structural encephalopathies. Twenty electrodes are distributed symmetrically over the scalp. The normal awake EEG shows 8- to 12-Hz, 50-μV sinusoidal alpha waves that wax and wane over the occipital and parietal lobes and > 12-Hz, 10- to 20-μV beta waves frontally, interspersed with 4- to 7-Hz theta waves. The EEG is examined for asymmetries between the 2 hemispheres (suggesting a structural disorder), for excessive slowing (appearance of 1- to 4-Hz, 50- to 350-μV delta waves, as occurs in depressed consciousness, encephalopathy, and dementia), and for abnormal wave patterns.

Abnormal wave patterns may be nonspecific (e.g., epileptiform sharp waves) or diagnostic (e.g., 3-Hz spike and wave discharges for absence seizures, 1-Hz periodic sharp waves for Creutzfeldt-Jakob disease). The EEG is particularly useful for appraising episodic altered consciousness of uncertain etiology. If a seizure disorder is suspected and the routine EEG is normal, maneuvers that electrically activate the cortex (e.g., hyperventilation, photic stimulation, sleep, sleep deprivation) can sometimes elicit evidence of a seizure disorder. Nasopharyngeal leads can sometimes detect a temporal lobe seizure focus when the EEG is otherwise uninformative. Continuous ambulatory monitoring of the EEG (with or without video monitoring) over 24 h can often determine whether fleeting memory lapses, subjective auras, or unusual episodic motor behavior is due to seizure activity.

**Measurement of evoked responses (potentials):** Visual, auditory, or tactile stimuli are used to activate corresponding areas of the cerebral cortex, resulting in focal cortical electrical activity. Ordinarily, these small potentials are lost in EEG background noise, but computer processing cancels out the noise to reveal a waveform. Latency, duration, and amplitude of the evoked responses indicate whether the tested sensory pathway is intact.

Evoked responses are particularly useful for detecting clinically inapparent deficits in a demyelinating disorder, appraising sensory systems in infants, substantiating deficits suspected to be histrionic, and following the subclinical course of disease. For example, visual evoked responses may detect unsuspected optic nerve damage by multiple sclerosis. When integrity of the brain stem is in question, brain stem auditory evoked responses is an objective test. Somatosensory evoked responses may pinpoint the physiologic disturbance when a structural disorder (e.g., metastatic carcinoma that invades the plexus and spinal cord) affects multiple levels of the neuraxis.

**Electromyography and nerve conduction velocity studies:** When determining whether weakness is due to a nerve, muscle, or neuromuscular junction disorder is clinically difficult, these studies can identify the affected nerves and muscles.

In electromyography, a needle is inserted in a muscle, and electrical activity is recorded while the muscle is contracting and resting. Normally, resting muscle is electrically silent; with minimal contraction, action potentials of single motor units appear. As contraction increases, the number of potentials increases, forming an interference pattern. Denervated muscle fibers are recognized by increased activity with needle insertion and abnormal spontaneous activity (fibrillations and fasciculations); fewer motor units are
recruited during contraction, producing a reduced interference pattern. Surviving axons branch to innervate adjacent muscle fibers, enlarging the motor unit and producing giant action potentials. In muscle disorders, individual fibers are affected without regard to their motor units; thus, amplitude of their potentials is diminished, but the interference pattern remains full.

In nerve conduction velocity studies, a peripheral nerve is stimulated with electrical shocks at several points along its course to a muscle, and the time to initiation of contraction is recorded. The time an impulse takes to traverse a measured length of nerve determines conduction velocity. The time required to traverse the segment nearest the muscle is called distal latency. Similar measurements can be made for sensory nerves. When weakness is due to a muscle disorder, nerve conduction is normal. In neuropathy, conduction is often slowed, and the response pattern may show a dispersion of potentials due to unequal involvement of myelinated and unmyelinated axons. A nerve can be repeatedly stimulated to evaluate the neuromuscular junction for fatigability; eg, a progressive decremental response occurs in myasthenia gravis.

**Weakness**

Weakness is one of the most common reasons patients present to primary care clinicians. Weakness is loss of muscle strength, although many patients also use the term when they feel generally fatigued or have functional limitations (eg, due to pain or limited joint motion) even though muscle strength is normal.

Weakness may affect a few or many muscles and develop suddenly or gradually. Other symptoms may be present depending on the cause. Weakness of specific muscle groups can cause disorders of eye movement, dysarthria, dysphagia, or respiratory weakness.

**Pathophysiology**

Voluntary movement is initiated in the cerebral motor cortex, at the posterior aspect of the frontal lobe. The neurons involved (upper motor or corticospinal tract neurons) synapse with neurons in the spinal cord (lower motor neurons). Lower motor neurons transmit impulses to the neuromuscular junction to initiate muscle contraction. Common mechanisms of weakness thus include dysfunction of

- Upper motor neurons (corticospinal and corticobulbar tract lesions)
- Lower motor neurons (eg, due to peripheral polyneuropathies or anterior horn cell lesions)
- Neuromuscular junction
- Muscle (eg, due to myopathies)

The location of certain lesions correlates with physical findings:

- Upper motor neuron dysfunction (except in the uncommon case when all other nearby motor pathways are affected) disinhibits lower motor neurons, resulting in increased muscle tone (spasticity) and increased muscle stretch reflexes (hyperreflexia). An extensor plantar (Babinski's) reflex is specific for upper motor neuron (corticospinal tract) dysfunction.

- Lower motor neuron dysfunction disrupts reflex arcs, causing hyporeflexia and decreased muscle tone (flaccidity), and may cause fasciculations; with time, muscles atrophy.

- Peripheral polyneuropathies tend to be most noticeable in the longest nerves (ie, weakness is more prominent in the distal limb than the proximal and in legs more than arms) and produce signs of lower motor neuron dysfunction (eg, decreased reflexes and muscle tone).

- The most common disorder of the neuromuscular junction—myasthenia gravis—typically causes fluctuating weakness that worsens with activity and lessens with rest.

- Diffuse muscle dysfunction (eg, in myopathies) tends to be most noticeable in the largest muscle groups
Etiology

The many causes of muscle weakness are categorized by location of the lesion (see Table 168-2). Usually, lesions in a given location manifest similar clinical findings. However, some disorders have characteristics of lesions in more than one location. For example, patients with amyotrophic lateral sclerosis (ALS) may have findings of both upper and lower motor neuron dysfunction. Disorders of the spinal cord may affect tracts from upper motor neurons, lower motor neurons (anterior horn cells), or both.

Common causes of focal weakness include

• Stroke (the most common cause of unilateral weakness)

• Neuropathies, including those that are caused by trauma or entrapment (eg, carpal tunnel syndrome) and that are immunemediated (eg, Bell's palsy)

• Spinal root entrapment (eg, herniated intervertebral disk)

• Spinal cord compression (eg, cervical spondylosis, epidural cancer metastasis, trauma)

• Multiple sclerosis

The most common causes of generalized weakness are

• Generalized muscle wasting due to prolonged immobilization in an ICU (ICU myopathy)

• Critical illness polyneuropathy (ICU neuropathy)

• Common myopathies (eg, alcoholic myopathy, hypokalemia, corticosteroid myopathy)

• Use of paralytic drugs in a critical care patient

Fatigue: Many patients report weakness when their problem is fatigue. Fatigue can prevent maximal effort and muscle performance during strength testing. Common causes of fatigue include acute severe illness of almost any cause, cancers, chronic infections (eg, HIV, hepatitis, endocarditis, mononucleosis), endocrine disorders, renal failure, hepatic failure, heart failure, and anemia. Patients with fibromyalgia, depression, or chronic fatigue syndrome may report weakness or fatigue but have no defined objective abnormalities.

Evaluation

Evaluation should try to distinguish true muscular weakness from fatigue, then check for findings that help establish the mechanism and, when possible, the cause.

History: History of present illness should begin with open-ended questions, asking patients to describe in detail what they are experiencing as weakness. Then, specific questions can be asked, particularly about the ability to do specific tasks, including brushing teeth or hair, speaking, swallowing, rising from a chair, climbing stairs, and walking. Clinicians should also ask about the onset (sudden or gradual) and progression (eg, constant, worsening, intermittent) of symptoms. Close questioning is needed to differentiate sudden onset from sudden recognition; patients may suddenly recognize symptoms only after slowly progressive weakness crosses a threshold that prevents them from doing some normally routine task (eg, walking, tying shoes). Important associated symptoms include sensory changes, double vision, memory loss, difficulty using...
language, seizures, and headaches. Factors that worsen weakness, such as heat (suggesting multiple sclerosis) or repetitive use of a muscle (suggesting myasthenia gravis), are noted.

**Review of systems** should seek symptoms suggesting possible causes, including rash (dermatomyositis, Lyme disease, syphilis); fevers (chronic infection); muscle pain (myositis); neck pain (cervical myelopathy); vomiting or diarrhea (botulism); shortness of breath (heart failure, a pulmonary disorder, anemia); anorexia and weight loss (cancer, other chronic illness); change in color of urine (porphyria, liver or kidney disorder); heat or cold intolerance (thyroid dysfunction); and depressed mood, poor concentration, anxiety, and loss of interest in usual activities (mood disorder).

**Past medical history** should identify known disorders that can cause weakness or fatigue, including thyroid, liver, kidney, or adrenal disorders; cancer or risk factors for cancer (paraneoplastic syndromes—eg, Eaton-Lambert syndrome) such as heavy smoking; osteoarthritis (cervical myelopathy); and infections. Clinicians should assess risk factors for possible causes, including those for infection (eg, unprotected sexual intercourse, blood transfusions, exposure to TB) and stroke (eg, hypertension, atrial fibrillation, atherosclerosis). Complete drug history should be reviewed.

**Family history** should include known hereditary disorders (eg, hereditary muscle disorders, channelopathies, metabolic myopathies, hereditary neuropathies) and presence of similar symptoms in family members (suggesting a possible unrecognized hereditary disorder). Hereditary motor neuropathies often go unrecognized in families because of variable, incomplete phenotypic expression. Hammer toes, high arches in the feet, and poor performance in sports may indicate an undiagnosed hereditary motor neuropathy.

**Social history** should note use of alcohol (suggesting alcoholic myopathy), illicit drug use (suggesting increased risk of HIV/AIDS, bacterial infections, TB, or stroke due to cocaine use), occupational or other exposure to toxins (eg, organophosphate insecticides, heavy metals, industrial solvents), recent travel (suggesting Lyme disease, tick paralysis, diphtheria, or a parasitic infection), and social stressors (suggesting depression).

**Physical examination:** A complete neurologic and muscle examination is done to identify localizing or diagnostic findings. Key findings usually involve

- Cranial nerves
- Motor function
- Reflexes

**Cranial nerve examination** includes inspection of the face for gross asymmetry and ptosis; mild facial asymmetry can be normal. Extraocular movements and facial muscles, including masseters (for strength), are tested. Palatal weakness is suggested by a nasal voice quality; testing the gag reflex and looking at the palate directly are less helpful. Tongue weakness is suggested by inability to clearly articulate certain consonants (eg, saying "ta-ta-ta") and slurring of speech (lingual dysarthria). Mild asymmetry during tongue protrusion may be normal. Sternocleidomastoid and trapezius strength is tested by having the patient rotate the head and shrug the shoulders against resistance. The patient is asked to blink repeatedly to see whether blinking fatigues.

**Motor examination** includes inspection, assessment of tone, and strength testing. The body is inspected for kyphoscoliosis (sometimes suggesting chronic weakness of paraspinal muscles) and for surgical and traumatic scars. Dystonic posturing (eg, torticollis) may interfere with movement, mimicking weakness. Muscles are inspected for fasciculations and atrophy; both may begin focally or asymmetrically in ALS. Fasciculations may be most visible in the tongue in patients with advanced ALS. Diffuse atrophy may be most evident in the hands, face, and shoulder girdle.

Muscle tone is assessed using passive motion. Tapping a muscle (eg, hypothenar) may induce fasciculations in neuropathies or a myotonic contraction in myotonic dystrophy.
Strength testing should include muscles that are proximal, distal, extensor, and flexor. Some tests of large, proximal muscles include standing from a sitting position; squatting and rising; and flexing, extending, and turning the head against resistance. Motor strength is often rated on a 0 to 5 scale (see p. 1590).

Although these numbers seem objective, rating strength between 3 and 5 (the typical levels during early weakness, when diagnosis usually occurs) is rather subjective; if symptoms are unilateral, comparison with the unaffected side improves discrimination. Describing specifically what the patient can or cannot do is often more useful than simply assigning a number for level of weakness, particularly for assessing changes in weakness over time. A cognitive deficit may cause motor impersistence (inability to focus attention on completing a motor task), motor perseveration, apraxia, or incomplete effort. Malingering and other functional weakness is often characterized by give-way weakness, in which normal strength of effort suddenly gives way.

**Coordination** testing includes finger-to-nose and heel-to-shin maneuvers and toe-heel tandem gait to check for cerebellar dysfunction, which can accompany cerebellar stroke, vermian atrophy (eg, due to alcohol abuse), some hereditary spinocerebellar ataxias, multiple sclerosis, and the Miller Fisher variant of Guillain-Barre syndrome.

**Gait** is observed for ignition failure (temporary freezing in place when starting to walk, followed by festination, as occurs in Parkinson's disease) and apraxia, as when feet stick to the floor (normal-pressure hydrocephalus, other frontal lobe disorders); festination (Parkinson's disease); limb asymmetry, as when patients drag a leg, have reduced arm swing, or both (hemispheric stroke); ataxia (midline cerebellar disease); and instability during turns (parkinsonism). Walking on the toes and heels is tested; distal muscle weakness makes these maneuvers difficult. Walking on the heels is particularly difficult when corticospinal tract lesions are the cause of weakness. Spastic gait is notable for scissoring (legs flexed slightly at the hips and knees, giving the appearance of crouching, with the knees and thighs hitting or crossing in a scissors-like movement) and walking on the toes. A steppage gait may occur with perineal palsy (drop foot).

**Sensation** is tested; sensory deficits can help localize some lesions causing weakness (eg, sensory level localizes the lesion to a spinal cord segment) or suggest certain specific causes of weakness (eg, distal sensory loss helps confirm clinical suspicion of Guillain-Barre syndrome).

A bandlike tingling and pressure is a spinal cord sign that occurs with both intrinsic and extrinsic lesions.

**Reflexes** are tested. If deep tendon reflexes appear absent, they may be elicited by augmentation with Jendrassik's maneuver (eg, trying to pull the hands apart while they are clasped together). Hyporeflexia may be normal, particularly with aging, but findings should be symmetric and augmentation should elicit reflexes that are otherwise absent. The plantar reflex (extensor, flexor) is tested. The classic Babinski's reflex (the great toe extends and the other toes fan apart) is highly specific for a corticospinal tract lesion. A normal jaw jerk and hyperreflexic arms and legs suggest a cervical lesion affecting the corticospinal tract, usually cervical stenosis. Anal tone, anal wink reflex, or both are reduced or absent in spinal cord injury but are preserved in ascending paralysis due to Guillain-Barre syndrome. Abdominal reflexes are absent below the level of spinal cord injury. A cremasteric reflex can test the integrity of the upper lumbar cord and roots in males.

Evaluation also includes testing for back tenderness to percussion (present with vertebral inflammation, some vertebral tumors, and epidural abscess), straight leg raising (painful with sciatica), and checking for scapular winging (suggesting weakness of the shoulder girdle muscles).

**General examination:** If patients have no objective motor weakness, the general examination is particularly important; in such patients, nonneuromuscular disorders should be sought.

Signs of respiratory distress (eg, tachypnea, weak inspiration) are noted. The skin is examined for jaundice, pallor, rash, and striae. Other important findings during inspection include the moon facies of Cushing's syndrome and the parotid enlargement, smooth hairless skin, ascites, and vascular spiders of chronic alcohol use. The neck, axillae, and inguinal area should be palpated for adenopathy; any thyromegaly is noted.
Heart and lungs are auscultated for crackles, wheezes, prolonged expiration, murmurs, and gallops. The abdomen is palpated for masses, including, if spinal cord dysfunction is possible, a grossly enlarged bladder. A rectal examination is done to check for heme-positive stool. Joint range of motion is assessed.

If tick paralysis is suspected, the skin, particularly the scalp, should be thoroughly inspected for ticks.

**Red flags:** The following findings are of particular concern:

- Weakness that becomes severe over a few days or less
- Dyspnea
- Inability to raise the head against gravity
- Bulbar symptoms (eg, difficulty chewing, talking, and swallowing)
- Loss of ambulation

**Interpretation of findings:** The history helps differentiate weakness from fatigue, defines the time course of the illness, and gives clues to the anatomic pattern of weakness. Weakness and fatigue tend to cause different symptoms:

- **Weakness:** Patients typically complain that they cannot do specific tasks. They may also report limb heaviness or stiffness. Weakness usually has a particular pattern in time, anatomy, or both.

- **Fatigue:** Fatigue reported as "weakness" tends to have no temporal pattern (eg, "tired all of the time") or anatomic pattern (eg, "weak everywhere"); complaints center more on being tired than on being unable to do specific tasks.

**The temporal pattern** of symptoms is useful.

- Weakness that becomes severe within minutes or less is usually caused by severe trauma or stroke; in stroke, weakness is usually unilateral and can be mild or severe. Sudden weakness, numbness, and severe pain localized to a limb are more likely caused by local arterial occlusion and limb ischemia, which can be differentiated by vascular assessment (eg, pulse, color, temperature, capillary refill, differences in Doppler-measured limb BPs). Spinal cord compression can also cause paralysis that evolves over minutes (but usually over hours or days) and is readily distinguished by incontinence and clinical findings of a discrete cord sensory and motor level.

- Weakness that progresses steadily over hours to days may be caused by acute or subacute disorders (eg, spinal cord compression, transverse myelitis, spinal cord ischemia or hemorrhage, Guillain-Barre syndrome, sometimes muscle wasting caused by a critical illness, rhabdomyolysis, botulism, organophosphate poisoning).

- Weakness that progresses over weeks to months may be caused by subacute or chronic disorders (eg, cervical myelopathy, most inherited and acquired polyneuropathies, myasthenia gravis, motor neuron disorders, acquired myopathies, most tumors).

- Weakness that fluctuates from day to day may be caused by multiple sclerosis and sometimes metabolic myopathies.

- Weakness that fluctuates over the course of a day may be caused by myasthenia gravis, Eaton-Lambert syndrome, or periodic paralysis.

**The anatomic pattern** of weakness is characterized by specific motor tasks that are difficult to do. Anatomic patterns suggest certain diagnoses:
• Proximal muscle weakness impairs reaching upward (eg, combing hair, lifting objects over the head),
  ascending stairs, or getting up from a sitting position; this pattern is typical of myopathies.

• Distal muscle weakness impairs tasks such as stepping over a curb, holding a cup, writing, buttoning, or
  using a key; this pattern is typical of polyneuropathies and myotonic dystrophy. Many disorders (eg,
  chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis,
  radiculopathies, Eaton-Lambert syndrome) cause proximal and distal weakness, but one pattern may be
  more prominent at first.

• Bulbar weakness can cause facial weakness, dysarthria, and dysphagia, with or without impairment of
  ocular movements; these manifestations are typical of certain neuromuscular disorders, such as
  myasthenia gravis, Eaton-Lambert syndrome, or botulism, but also certain motor neuron disorders, such
  as ALS or progressive supranuclear bulbar palsy.

Physical examination further helps localize the lesion. First, general patterns are discerned:

• Weakness primarily of proximal muscles suggests myopathy.

• Weakness accompanied by hyperreflexia and increased muscle tone suggests upper motor neuron
  (corticospinal or other motor tract) dysfunction, particularly if an extensor plantar (Babinski's) reflex is
  present.

• Disproportionate impairment of fine finger dexterity (eg, fine pincer movements, playing the piano) with
  relatively preserved grip strength indicates selective disruption of the corticospinal (pyramidal) tract.

• Complete paralysis accompanied by absent reflexes and severely depressed muscle tone (flaccidity)
  occurs in sudden, severe spinal cord injury (spinal shock).

• Weakness accompanied by hyporeflexia, decreased muscle tone (with or without fasciculations), and
  chronic muscle atrophy suggests lower motor neuron dysfunction.

• Weakness that is most noticeable in muscles innervated by the longest nerves (ie, distal more than
  proximal, legs more than arms), particularly with loss of distal sensation, suggests lower motor neuron
  dysfunction due to peripheral polyneuropathy.

• Absence of neurologic abnormalities (ie, normal reflexes, no muscle wasting or fasciculations, normal
  strength or poor effort during strength testing) or poor effort in patients with tiredness or with weakness
  that has no temporal or anatomic pattern suggests fatigue rather than true muscular weakness.
  However, if weakness is intermittent and is absent at the time of examination, abnormalities may be
  missed.

Additional findings can help localize the lesion more precisely. For example, weakness accompanied by
upper motor signs plus other signs such as aphasia, mental status abnormalities, or other cortical
function suggests a brain lesion. Unilateral upper motor neuron signs (spasticity, hyperreflexia,
extensor plantar response) and weakness involving an arm and a leg on the same side of the body
suggest a contralateral hemispheric lesion, most often a stroke. Upper or lower motor neuron signs (or
both) plus loss of sensation below a segmental spinal cord level and loss of bowel or bladder control (or
both) suggest a spinal cord lesion. Weakness with lower motor neuron signs may result from a disorder
affecting one or more peripheral nerves; such a disorder has very specific patterns of weakness (eg, wrist
drop in radial nerve injury). When the brachial or pelvic plexus is damaged, motor, sensory, and reflex
deficits are often patchy and do not follow any one peripheral nerve pattern.

Determination of a specific causative disorder: Sometimes combinations of findings suggest a cause
(see
Table 168-3).

If no symptoms or signs of true weakness (eg, characteristic anatomic and temporal pattern,
objective signs) are present and patients complain only of overall weakness, fatigue, or lack of energy,
clinicians should consider nonneurologic disorders. However, among elderly patients who feel too weak to walk, determining the contribution of muscle weakness may be difficult because gait dysfunction is often multifactorial (see Geriatrics Essentials on p. 1606). Patients with many disorders may be functionally limited but lack true loss of muscle strength. For example, cardiopulmonary dysfunction or anemia can cause fatigue due to dyspnea or exercise intolerance. Joint dysfunction (eg, due to arthritis) or muscle pain (eg, due to polymyalgia rheumatica or fibromyalgia) may make doing physical tasks difficult. These and other physical disorders that cause complaints of weakness (eg, influenza, infectious mononucleosis, renal failure) typically are already diagnosed or are suggested by findings during the history, physical examination, or both.

[Table 168-3. Findings Related to Weakness Suggesting a Specific Disorder]

In general, if history and physical examination do not detect abnormalities suggesting physical disorders, these disorders are unlikely; disorders that cause constant, generalized fatigue with no physiologic temporal or anatomic pattern (eg, depression, chronic fatigue syndrome) should be considered.

Testing: Testing may be unnecessary in patients with fatigue rather than weakness. Although many tests can be done if patients have true muscular weakness, such testing is often only adjunctive.

If no true weakness is present, other clinical findings (eg, dyspnea, pallor, jaundice, heart murmur), if present, are used to guide testing.

If patients have no abnormal clinical findings, test results are unlikely to be abnormal. In such cases, testing practices vary widely. If done, initial tests usually include some combination of CBC, electrolytes, glucose, Ca, Mg, kidney and liver function tests, thyroid-stimulating hormone (TSH), ESR, and hepatitis C serologic testing.

If sudden or severe general weakness or any respiratory symptoms are present, forced vital capacity and maximal inspiratory force must be tested to assess risk of acute ventilatory failure. Patients with vital capacity < 15 mL/kg or inspiratory force < 20 cm H2O are at increased risk.

If true weakness is present (and usually after risk of acute ventilatory failure is assessed), initial testing typically focuses on determining the mechanism of weakness. Unless the cause is obvious, routine laboratory tests (CBC, electrolytes, glucose, Ca, Mg, kidney and liver function tests, TSH, ESR, hepatitis C serologic testing) are usually done.

If brain upper motor neuron dysfunction is suspected as the cause of weakness, the key test is MRI. CT is used when MRI testing is not possible (eg, in patients with a cardiac pacemaker).

If myelopathy is suspected, MRI can detect lesions in the spinal cord. It also detects other causes of paralysis that may mimic myelopathy, including lesions of the cauda equina, spinal roots, and brachial and pelvic plexuses. CT myelography may be used when MRI testing is not available. Other tests are done (see Table 168-2). CSF analysis may be unnecessary for some disorders diagnosed during imaging (eg, epidural tumor) and is contraindicated if CSF block (eg, due to epidural spinal cord compression) is suspected.

If polyneuropathies, myopathies, or neuromuscular junction disorders are suspected, the key tests that help differentiate these mechanisms of weakness are electrodiagnostic studies (electromyography and nerve conduction velocity studies).

After nerve injury, changes in nerve conductance and muscle denervation can take up to a few weeks to develop, so electrodiagnostic studies may not help when the disorder is acute. However, these studies can help differentiate among certain acute disorders, such as acute demyelinating neuropathy (eg, Guillain-Barre syndrome), acute botulism, and other acute neuromuscular junction disorders.

If myopathy is suspected (suggested by muscle weakness, muscle cramping, and pain), muscle enzymes (eg, CK, aldolase, LDH) may be measured. Elevated levels are consistent with myopathy but can also be high in neuropathies (reflecting muscle atrophy) and very high in ischemic rhabdomyolysis. Also, levels
may not be high in all myopathies. Regular crack cocaine use can also cause chronically moderately elevated CK levels (mean value, 400 IU/L).

Clinicians can use MRI to identify muscle inflammation, as occurs in inflammatory myopathies. Muscle biopsy may be necessary ultimately to diagnose myopathy. MRI or electromyography can help find a suitable site for muscle biopsy. However, needlestick artifact can mimic muscle pathology and must be avoided; thus, biopsy should never be done in the same muscle tested by electromyography.

If motor neuron disorders (eg, ALS) are suspected, tests include electromyography and nerve conduction velocity studies to confirm the diagnosis and exclude treatable disorders that mimic motor neuron disorders (eg, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block). Brain MRI may show degeneration of the corticospinal tracts when ALS is advanced. Spinal cord MRI (or CT myelography) is done routinely to rule out spinal cord compression or other myelopathies (see Table 168-2).

Testing for specific disorders may be needed:

- If findings suggest myasthenia gravis, edrophonium test and acetylcholine receptor antibody levels
- If findings suggest vasculitis, autoantibody testing
- If family history suggests a hereditary disorder, genetic testing
- If findings suggest polyneuropathy, other tests (see Table 168-2)
- If myopathy is unexplained by drugs, metabolic, or endocrine disorders, possibly muscle biopsy

Treatment

Causes are treated. For patients with life-threatening, acute weakness, ventilatory support may be needed. Physical and occupational therapy can help people adapt to permanent weakness and minimize loss of function.

Geriatrics Essentials

Some decrease in deep tendon reflexes is normal with aging, but asymmetry or absence of these reflexes with augmentation is abnormal.

Because the elderly are more likely to have preexisting sarcopenia, bed rest can cause debilitating muscle wasting rapidly, sometimes after only several days.

The elderly take more drugs and are more susceptible to drug-induced myopathies, neuropathies, and fatigue; thus, drugs are a common cause of weakness in the elderly.

Feeling too weak to walk often has multiple causes. Factors may include muscle weakness (eg, caused by stroke, use of certain drugs, myelopathy due to cervical spondylosis, or muscle atrophy), but also hydrocephalus, parkinsonism, painful arthritis, and age-related loss of neural networks mediating postural stability (vestibular system, proprioceptive pathways), coordination (cerebellum, basal ganglia), vision, and praxis (frontal lobe). Evaluation should focus on reversible factors.

Physical therapy and rehabilitation are generally helpful no matter what the etiology of the weakness is.

Key Points

- True loss of muscle strength must be distinguished from a feeling of fatigue.
- Fatigue with no anatomic or temporal pattern of weakness in patients with a normal physical examination may reflect chronic fatigue syndrome, an as yet undiscovered systemic illness (eg, severe
anemia, hypothyroidism, Addison's disease), a psychologic problem (eg, depression), or an adverse drug effect.

- Initial evaluation of true muscle weakness focuses on determining whether weakness is caused by dysfunction of the brain, spinal cord, plexuses, peripheral nerves, neuromuscular junction, or muscles.

- Hyperreflexia and increased muscle tone (spasticity), particularly if Babinski's reflex is present, suggest an upper motor neuron (eg, corticospinal tract) lesion in the brain or spinal cord; MRI is usually required.

- Hyporeflexia, decreased muscle tone, muscle atrophy, and muscle fasciculations suggest a lower motor neuron lesion.

- Hyporeflexia and predominantly distal muscle weakness, particularly with distal sensory deficits or paresthesias, suggest polyneuropathy.

- Difficulty climbing stairs, combing hair, and standing up with predominantly proximal muscle weakness and intact sensation suggests myopathy.

- Physical therapy is usually helpful in improving strength no matter what the cause is.
Chapter 169. Neurotransmission

Introduction

A neuron generates and propagates an action potential along its axon, then transmits this signal across a synapse by releasing neurotransmitters, which trigger a reaction in another neuron or an effector cell (eg, muscle cells, most exocrine and endocrine cells). The signal may stimulate or inhibit the receiving cell, depending on the neurotransmitter and receptor involved.

In the CNS, interconnections are complex. An impulse from one neuron to another may pass from axon to cell body, axon to dendrite (a neuron's receiving branches), cell body to cell body, or dendrite to dendrite. A neuron can simultaneously receive many impulses—excitatory and inhibitory—from other neurons and integrate simultaneous impulses into various patterns of firing.

Propagation: Action potential propagation along an axon is electrical, caused by the exchanges of Na$^+$ and K$^+$ ions across the axonal membrane. A particular neuron generates the same action potential after each stimulus, conducting it at a fixed velocity along the axon. Velocity depends on axonal diameter and degree of myelination and ranges from 1 to 4 m/sec in small unmyelinated fibers to 75 m/sec in large myelinated ones. Propagation speed is higher in myelinated fibers because the myelin cover has regular gaps (nodes of Ranvier) where the axon is exposed. The electrical impulse jumps from one node to the next, skipping the myelinated section of the axon. Thus, disorders that alter the myelin cover (eg, multiple sclerosis) interfere with impulse propagation, causing various neurologic symptoms.

Transmission: Impulse transmission is chemical, caused by release of specific neurotransmitters from the nerve ending (terminal). Neurotransmitters diffuse across the synaptic cleft and bind briefly to specific receptors on the adjoining neuron or effector cell. Depending on the receptor, the response may be excitatory or inhibitory.

One type of synapse, the electrical synapse, does not involve neurotransmitters; ion channels directly connect the cytoplasm of the presynaptic and postsynaptic neurons. This type of transmission is the fastest.

The nerve cell body produces enzymes that synthesize most neurotransmitters, which are stored in vesicles at the nerve terminal (see Fig. 169-1). The amount in one vesicle (usually several thousand molecules) is a quantum. A membrane action potential arriving at the terminal opens axonal Ca channels; Ca inflow releases neurotransmitter molecules from many vesicles by fusing the vesicle membranes to the nerve terminal membrane. Membrane fusion generates an opening through which the molecules are expelled into the synaptic cleft via exocytosis.

The amount of neurotransmitters in the terminal is typically independent of nerve activity and kept relatively constant by modifying uptake of neurotransmitter precursors or the activity of enzymes involved in neurotransmitter synthesis or destruction. Stimulation of presynaptic receptors can decrease presynaptic neurotransmitter synthesis, and blockade can increase it.

The neurotransmitter-receptor interaction must be terminated quickly to allow rapid, repeated activation of receptors. One of the following can happen to neurotransmitters that have interacted with receptors:

- They can be quickly pumped back into the presynaptic nerve terminals by active, ATP-dependent processes (reuptake).

- They can be destroyed by enzymes near the receptors.

- They can diffuse into the surrounding area and be removed.

Neurotransmitters taken up by the nerve terminals are repackaged in vesicles for reuse.
**Receptors:** Neurotransmitter receptors are protein complexes that span the cell membrane. Their nature determines whether a given neurotransmitter is excitatory or inhibitory. Receptors that are continuously stimulated by neurotransmitters or drugs become desensitized (downregulated); those that are not stimulated by their neurotransmitter or are chronically blocked by drugs become supersensitive (upregulated). Downregulation or upregulation of receptors strongly influences the development of tolerance and physical dependence. These concepts are particularly important in organ or tissue transplantation, in which denervation deprives receptors of their neurotransmitter. Withdrawal symptoms can be explained at least in part by a rebound phenomenon due to altered receptor affinity or density.

Most neurotransmitters interact primarily with postsynaptic receptors, but some receptors are located on presynaptic neurons, providing fine control of neurotransmitter release.

**[Fig. 169-1. Neurotransmission.]**

One family of receptors, termed ionotropic receptors (eg, \(N\)-methyl-D-glutamate, kinate-quisqualate, nicotinic acetylcholine, glycine, and \(\gamma\)-aminobutyric acid [GABA] receptors), consist of ion channels that open when bound to the neurotransmitter and effect a very rapid response. In the other family, termed metabotropic receptors (eg, serotonin, \(\alpha\)- and \(\beta\)-adrenergic, and dopaminergic receptors), neurotransmitters interact with G proteins and activate another molecule (2nd messenger such as cAMP) that catalyzes a chain of events through protein phosphorylation, Ca mobilization, or both; cellular changes mediated by 2nd messengers are slower and permit finer tuning of the rapid ionotropic neurotransmitter response. Far more neurotransmitters activate specific receptors than 2nd messengers.

**Major Neurotransmitters and Receptors**

At least 100 substances can act as neurotransmitters; about 18 are of major importance. Several occur in slightly different forms.

**Glutamate and aspartate:** These amino acids are the major excitatory neurotransmitters in the CNS. They occur in the cortex, cerebellum, and spinal cord. In neurons, synthesis of nitric oxide (NO) increases in response to glutamate. Excess glutamate can be toxic, increasing intracellular Ca, free radicals, and proteinase activity. These neurotransmitters may contribute to tolerance to opioid therapy and mediate hyperalgesia.

GABA receptors are classified as GABA\(_A\) (activating chloride channels) and GABA\(_B\) (potentiating cAMP formation). GABA\(_A\) receptors are the site of action for several neuroactive drugs, including benzodiazepines, barbiturates, picrotoxin, and muscimol. GABA\(_B\) receptors are activated by baclofen, used to treat muscle spasms (eg, in multiple sclerosis).

**Serotonin:** Serotonin (5-hydroxytryptamine, or 5-HT) is generated by the raphe nucleus and midline neurons of the pons and upper brain stem. Tryptophan is hydroxylated by tryptophan hydroxylase to 5-hydroxytryptophan, then decarboxylated to serotonin. Serotonin levels are controlled by the uptake of tryptophan and intraneuronal monoamine oxidase (MAO), which breaks down serotonin. Ultimately, serotonin is excreted in the urine as 5-hydroxyindooacetic acid or 5-HIAA.

Serotoninergic (5-HT) receptors (with at least 15 subtypes) are classified as 5-HT\(_1\) (with 4 subtypes), 5-HT\(_2\), and 5-HT\(_3\). Selective serotonin receptor agonists (eg, sumatriptan) can abort migraines.
Acetylcholine: Acetylcholine is the major neurotransmitter of the bulbospinal motor neurons, autonomic preganglionic fibers, postganglionic cholinergic (parasympathetic) fibers, and many neurons in the CNS (eg, basal ganglia, motor cortex). It is synthesized from choline and acetyl coenzyme A by choline acetyltransferase, and its action is rapidly terminated via local hydrolysis to choline and acetate by acetylcholinesterase. Acetylcholine levels are regulated by choline acetyltransferase and by choline uptake. Levels of this neurotransmitter are decreased in patients with Alzheimer's disease.

Cholinergic receptors are classified as nicotinic N\(_1\) (in the adrenal medulla and autonomic ganglia) or N\(_2\) (in skeletal muscle) or muscarinic M\(_1\) through M\(_5\) (widely distributed in the CNS). M\(_1\) occurs in the autonomic nervous system, striatum, cortex, and hippocampus; M\(_2\) occurs in the autonomic nervous system, heart, intestinal smooth muscle, hindbrain, and cerebellum.

Dopamine: Dopamine interacts with receptors on some peripheral nerve fibers and many central neurons (eg, in the substantia nigra, midbrain, ventral tegmental area, and hypothalamus). The amino acid tyrosine is taken up by dopaminergic neurons and converted by tyrosine hydroxylase to 3,4-dihydroxyphenylalanine (dopa), which is decarboxylated by aromatic-L-amino-acid decarboxylase to dopamine. After release and interaction with receptors, dopamine is actively pumped back (reuptake) into the nerve terminal. Tyrosine hydroxylase and MAO (which breaks down dopamine) regulate dopamine levels in nerve terminals.

Dopaminergic receptors are classified as D\(_1\) through D\(_5\). D\(_3\) and D\(_4\) receptors play a role in thought control (limiting the negative symptoms of schizophrenia); D\(_2\) receptor activation controls the extrapyramidal system. However, receptor affinity does not predict functional response (intrinsic activity); eg, ropinirole, which has high affinity for the D\(_3\) receptor, has intrinsic activity via activation of D\(_2\) receptors.

Norepinephrine: Norepinephrine is the neurotransmitter of most postganglionic sympathetic fibers and many central neurons (eg, in the locus caeruleus and hypothalamus). The precursor tyrosine is converted to dopamine, which is hydroxylated by dopamine β-hydroxylase to norepinephrine. After release and interaction with receptors, some norepinephrine is degraded by catechol O-methyltransferase (COMT), and the remainder is actively taken back into the nerve terminal, where it is degraded by MAO. Tyrosine hydroxylase, dopamine β-hydroxylase, and MAO regulate intraneuronal norepinephrine levels.

Adrenergic receptors are classified as α\(_1\) (postsynaptic in the sympathetic system), α\(_2\) (presynaptic in the sympathetic system and postsynaptic in the brain), β\(_1\) (in the heart), or β\(_2\) (in other sympathetically innervated structures).

Endorphins and enkephalins: Endorphins and enkephalins are opioids. Endorphins are large polypeptides that activate many central neurons (eg, in the hypothalamus, amygdala, thalamus, and locus caeruleus). The cell body contains a large polypeptide called proopiomelanocortin, the precursor of α-, β-, and γ-endorphins. This polypeptide is transported down the axon and cleaved into fragments; one is β-endorphin, contained in neurons that project to the periaqueductal gray matter, limbic structures, and major catecholamine-containing neurons in the brain. After release and interaction with receptors, β-endorphin is hydrolyzed by peptidases.

Met-enkephalin and leu-enkephalin are small polypeptides present in many central neurons (eg, in the globus pallidus, thalamus, caudate, and central gray matter). Their precursor, proenkephalin, is formed in the cell body, then split by specific peptidases into the active peptides. These substances are also localized in the spinal cord, where they modulate pain signals. The neurotransmitters of pain signals in the posterior horn of the spinal cord are glutamate and substance P. Enkephalins decrease the amount of neurotransmitter released and hyperpolarize (make more negative) the postsynaptic membrane, reducing the generation of action potentials and pain perception at the level of the postcentral gyrus. After release and interaction with peptidergic receptors, enkephalins are hydrolyzed into smaller, inactive peptides and amino acids. Rapid inactivation of exogenous enkephalins prevents these substances from being clinically useful. More stable molecules (eg, morphine) are used as analgesics instead.
Endorphin-enkephalin (opioid) receptors are classified as $\mu_1$ and $\mu_2$ (affecting sensorimotor integration and analgesia), $\delta_1$ and $\delta_2$ (affecting motor integration, cognitive function, and analgesia), and $\kappa_1$, $\kappa_2$, and $\kappa_3$ (affecting water balance regulation, analgesia, and food intake). $\sigma$-Receptors, currently classified as nonopioid and mostly localized in the hippocampus, bind PCP. New data suggest the presence of many more receptor subtypes, with pharmacologic implications. Components of the molecular precursor to the receptor protein can be rearranged during receptor synthesis to produce several receptor variants (eg, 27 splice variants of the $\mu$ opioid receptor). Also, 2 receptors can combine (dimerize) to form a new receptor.

**Other neurotransmitters:** Dynorphins are a group of 7 peptides with similar amino acid sequences. They, like enkephalins, are opioids.

Substance P, a peptide, occurs in central neurons (in the habenula, substantia nigra, basal ganglia, medulla, and hypothalamus) and is highly concentrated in the dorsal root ganglia. Its release is triggered by intense afferent painful stimuli. It modulates the neural response to pain and mood; it modulates nausea and vomiting through the activation of NK1A receptors that are localized in the brain stem.

Nitric oxide (NO) is a labile gas that mediates many neuronal processes. It is generated from arginine by NO synthase. Neurotransmitters that increase intracellular $\text{Ca}^{++}$ (eg, substance P, glutamate, acetylcholine) stimulate NO synthesis in neurons that express NO synthetase. NO may be an intracellular messenger; it may diffuse out of a cell into a 2nd neuron and produce physiologic responses (eg, long-term potentiation [strengthening of certain presynaptic and postsynaptic responses—a form of learning]) or enhance glutamate (NMDA-receptor-mediated) neurotoxicity (eg, in Parkinson's disease, stroke, or Alzheimer's disease).

Substances with less firmly established roles in neurotransmission include histamine, vasopressin, vasoactive intestinal peptide, camosine, bradykinin, cholecystokinin, bombesin, somatostatin, corticotropin releasing factor, neurotensin, and possibly adenosine.

**Disorders Associated With Defects in Neurotransmission**

Disorders or substances that alter the production, release, reception, breakdown, or reuptake of neurotransmitters or that change the number and affinity of receptors can cause neurologic or psychiatric symptoms and cause disease (see Table 169-1). Drugs that modify neurotransmission can alleviate many of these disorders (eg, Parkinson's disease, depression).

[Table 169-1, Examples of Disorders Associated with Defects in Neurotransmission]
Chapter 170. Autonomic Nervous System

Introduction

The autonomic nervous system (ANS) regulates physiologic processes. Regulation occurs without conscious control, ie, autonomously. The 2 major divisions are the sympathetic and parasympathetic systems.

Disorders of the ANS cause autonomic insufficiency or failure and can affect any system of the body.

Anatomy

The ANS receives input from parts of the CNS that process and integrate stimuli from the body and external environment. These parts include the hypothalamus, nucleus of the solitary tract, reticular formation, amygdala, hippocampus, and olfactory cortex.

The sympathetic and parasympathetic systems each consist of 2 sets of nerve bodies: one set (called preganglionic) in the CNS, with connections to another set in ganglia outside the CNS. Efferent fibers from the ganglia (postganglionic fibers) lead to effector organs (see Fig. 170-1).

Sympathetic: The preganglionic cell bodies of the sympathetic system are located in the intermediolateral horn of the spinal cord between T1 and L2 or L3. The sympathetic ganglia are adjacent to the spine and consist of the vertebral (sympathetic chain) and prevertebral ganglia, including the superior cervical, celiac, superior mesenteric, inferior mesenteric, and aorticorenal ganglia. Long fibers run from these ganglia to effector organs, including the smooth muscle of blood vessels, viscera, lungs, scalp (piloerector muscles), and pupils; the heart; and glands (sweat, salivary, and digestive).

Parasympathetic: The preganglionic cell bodies of the parasympathetic system are located in the brain stem and sacral portion of the spinal cord. Preganglionic fibers exit the brain stem with the 3rd, 7th, 9th, and 10th (vagus) cranial nerves and exit the spinal cord at S2 and S3; the vagus nerve contains about 75% of all parasympathetic fibers. Parasympathetic ganglia (eg, ciliary, sphenopalatine, otic, pelvic, and vagal ganglia) are located within the effector organs, and postganglionic fibers are only 1 or 2 mm long. Thus, the parasympathetic system can produce specific, localized responses in effector organs, such as blood vessels of the head, neck, and thoraco-abdominal viscera; lacrimal and salivary glands; smooth muscle of glands and viscera (eg, liver, spleen, colon, kidneys, bladder, genitals); and ocular muscles.

Physiology

The ANS controls BP, heart rate, body temperature, weight, digestion, metabolism, fluid and electrolyte balance, sweating, urination, defecation, sexual response, and other processes. Many organs are controlled primarily by either the sympathetic or parasympathetic system, although they may receive input from both; occasionally, functions are reciprocal (eg, sympathetic input increases heart rate; parasympathetic decreases it).

The sympathetic nervous system is catabolic; it activates fight-or-flight responses. The parasympathetic nervous system is anabolic; it conserves and restores (see Table 170-1).

Two major neurotransmitters in the ANS are

- **Acetylcholine**: Fibers that secrete acetylcholine (cholinergic fibers) include all preganglionic fibers, all postganglionic parasympathetic fibers, and some postganglionic sympathetic fibers (those that innervate piloerectors, sweat glands, and blood vessels).

- **Norepinephrine**: Fibers that secrete norepinephrine (adrenergic fibers) include most postganglionic sympathetic fibers. Sweat glands on the palms and soles also respond to adrenergic stimulation to some degree.
There are different subtypes of adrenergic receptors (see p. 1609) and cholinergic receptors (see p. 1608), which vary by location.

**Etiology**

Disorders causing autonomic insufficiency or failure can originate in the peripheral or central nervous system and may be primary or secondary to other disorders.

The most common causes of autonomic insufficiency are

- Peripheral neuropathies
- Aging
- Parkinson's disease

Other causes include

- Autoimmune autonomic neuropathy
- Multiple system atrophy
- Spinal cord disorders
- Drugs
- Disorders of the neuromuscular junction (eg, botulism, Lambert-Eaton syndrome)

**Evaluation**

**History:** Symptoms suggesting autonomic insufficiency include

- Orthostatic hypotension
- Heat intolerance
- Loss of bladder and bowel control
- Erectile dysfunction (an early symptom)

Other possible symptoms include dry eyes and dry mouth, but they are less specific.

**Physical examination:** Important parts of the examination include the following:

- Postural BP and heart rate: In a normally hydrated patient, a sustained (eg, > 1 min) decrease of ≥ 20 mm Hg in systolic BP or a decrease of ≥ 10 mm Hg in diastolic BP with standing suggests autonomic insufficiency. Heart rate change with respiration and standing should be noted; absence of physiologic sinus arrhythmia and failure of heart rate to increase with standing indicate autonomic insufficiency. In contrast, patients with postural tachycardia syndrome, a benign disorder, typically have postural tachycardia without hypotension (see p. 2035).

- Eye examination: Miosis and mild ptosis (Horner's syndrome) suggest a sympathetic lesion. A dilated, unreactive pupil (Adie's pupil) suggests a parasympathetic lesion.
• GU and rectal reflexes: Abnormal GU and rectal reflexes may indicate ANS deficits. Testing includes the cremasteric reflex (normally, stroking the upper inner thigh results in retraction of the testes), anal wink reflex (normally, stroking perianal skin results in contraction of the anal sphincter), and bulbocavernosus reflex (normally, squeezing the glans penis or clitoris results in contraction of the anal sphincter).

**Laboratory testing:** If patients have symptoms and signs suggesting autonomic insufficiency, sudomotor, cardiovagal, and adrenergic testing is usually done to help determine severity and distribution of the insufficiency.

**Sudomotor testing** includes the following:

• Quantitative sudomotor axon-reflex test: This test evaluates integrity of postganglionic neurons using iontophoresis; electrodes filled with acetylcholine are placed on the legs and wrist to stimulate sweat glands, and the volume of sweat is then measured. The test can detect decreased or absent sweat production.

• Thermoregulatory sweat test: This test evaluates both preganglionic and postganglionic pathways. After a dye is applied to the skin, patients enter a closed compartment that is heated to cause maximal sweating. Sweating causes the dye to change color, so that areas of anhidrosis and hypohidrosis are apparent and can be calculated as a percentage of BSA.

**Cardiovagal testing** evaluates heart rate response (via ECG rhythm strip) to deep breathing and to the Valsalva maneuver. If the ANS is intact, heart rate varies with these maneuvers; normal responses to deep breathing and the Valsalva ratio vary by age.

**Adrenergic testing** evaluates response of beat-to-beat BP to the following:

• Head-up tilt: Blood is shifted to dependent parts, causing reflex responses in BP and heart rate. This test helps differentiate autonomic neuropathies from postural tachycardia syndrome.

• Valsalva maneuver: This maneuver increases intrathoracic pressure and reduces venous return, causing BP changes and reflex vasoconstriction.

With the head-up tilt test and Valsalva maneuvers, the pattern of responses is an index of adrenergic function.

**Plasma norepinephrine** levels can be measured with patients supine and then after they stand for > 5 min. Normally, levels increase after standing. If patients have autonomic insufficiency, levels may not increase with standing and may be low in the supine position, particularly in postganglionic disorders (eg, autonomic neuropathy, pure autonomic failure).

**Autonomic Neuropathies**

**Autonomic neuropathies are peripheral nerve disorders with disproportionate involvement of autonomic fibers.**

The best known autonomic neuropathies are those accompanying peripheral neuropathy due to diabetes, amyloidosis, or autoimmune disorders. Autoimmune autonomic neuropathy is an idiopathic disorder that often develops after a viral infection; onset may be subacute. Autonomic insufficiency is usually a late manifestation in alcoholic neuropathy.

Common symptoms of autonomic neuropathies include orthostatic hypotension, neurogenic bladder, erectile dysfunction, gastroparesis, and intractable constipation. When somatic fibers are involved, sensory loss in a stocking-and-glove distribution and distal weakness may occur (see also Ch. 185).
Clinical evaluation

Diagnosis is based on demonstration of autonomic failure (see p. 1617) and of a specific cause of neuropathy (e.g., diabetes, amyloidosis). Autoimmune autonomic neuropathy may be suspected after a viral infection. Ganglionic anti-acetylcholine receptor antibody A3 is present in about one half of patients with autoimmune autonomic neuropathy and is occasionally present in patients with other autonomic neuropathies.

Treatment

Underlying disorders are treated. Autoimmune autonomic neuropathy may respond to immunotherapy; plasma exchange or IV γ-globulin can be used for more severe cases.

Horner's Syndrome

Horner's syndrome is ptosis, miosis, and anhidrosis due to dysfunction of cervical sympathetic output.

Etiology

Horner's syndrome results when the cervical sympathetic pathway running from the hypothalamus to the eye is disrupted. The causative lesion may be primary (including congenital) or secondary to another disorder. Lesions are usually divided into:

- Central (e.g., brain stem ischemia, syringomyelia, brain tumor)
- Peripheral (e.g., Pancoast's tumor, cervical adenopathy, neck and skull injuries, aortic or carotid dissection, thoracic aortic aneurysm)

Peripheral lesions may be preganglionic or postganglionic in origin.

Symptoms and Signs

Symptoms include ptosis, miosis, anhidrosis, and hyperemia of the affected side. In the congenital form, the iris does not become pigmented and remains blue-gray.

Diagnosis

- Cocaine eye drop test
- MRI or CT to diagnose cause

Liquid cocaine 10% can be applied to the affected eye; poor pupillary dilation after 30 min indicates Horner's syndrome. If results are positive, 1% hydroxyamphetamine solution or 5% N-methyl hydroxyamphetamine can be applied to the eye 48 h later to determine whether the lesion is preganglionic (if the pupil dilates) or postganglionic (if the pupil does not dilate). Patients with Horner's syndrome require MRI or CT of the brain, spinal cord, chest, or neck, depending on clinical suspicion.

Treatment

The cause, if identified, is treated; there is no treatment for primary Horner's syndrome.

Multiple System Atrophy

Multiple system atrophy is a relentlessly progressive neurodegenerative disorder causing pyramidal, cerebellar, and autonomic dysfunction. It includes 3 disorders previously thought to be distinct: olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome. Symptoms include hypotension, urinary retention, constipation, ataxia, rigidity, and postural
Multiple system atrophy affects about twice as many men as women. Mean age at onset is about 53 yr; after symptoms appear, patients live about 9 to 10 yr.

Etiology
Etiology is unknown, but neuronal degeneration occurs in several areas of the brain; the area and amount damaged determine initial symptoms. A characteristic finding is cytoplasmic inclusion bodies containing α-synuclein within oligodendroglial cells.

Symptoms and Signs
Initial symptoms vary but include a combination of parkinsonism unresponsive to levodopa, cerebellar abnormalities, and symptoms due to autonomic insufficiency.

Parkinsonian symptoms: These symptoms predominate in striatonigral degeneration. They include rigidity, bradykinesia, postural instability, and jerky postural tremor. High-pitched, quavering dysarthria is common. In contrast to Parkinson's disease, multiple system atrophy usually does not cause resting tremor and dyskinesia, and symptoms respond poorly and transiently to levodopa.

Cerebellar abnormalities: These abnormalities predominate in olivopontocerebellar atrophy. They include ataxia, dysmetria, dysdiadochokinesia (difficulty performing rapidly alternating movements), poor coordination, and abnormal eye movements.

Autonomic symptoms: Typically, autonomic insufficiency causes orthostatic hypotension (symptomatic fall in BP when a person stands, often with syncope—see p. 2035), urinary retention or incontinence, constipation, and erectile dysfunction.

Other autonomic symptoms, which may occur early or late, include decreased sweating, difficulty breathing and swallowing, fecal incontinence, and decreased tearing and salivation. REM sleep behavior disorder (eg, speech or skeletal muscle movement during REM sleep) and respiratory stridor are common. Patients are often unaware of REM sleep behavior disorder. Patients may have nocturnal polyuria; contributing factors may include a circadian decrease in arginine vasopressin and treatments used to increase blood volume.

Diagnosis
• Clinical evaluation (parkinsonism or cerebellar symptoms that respond poorly to levodopa plus autonomic failure)

• MRI

Diagnosis is suspected clinically, based on the combination of autonomic failure and parkinsonism or cerebellar symptoms. Similar symptoms may result from Parkinson's disease, Lewy body dementia, pure autonomic failure, autonomic neuropathies, progressive supranuclear palsy, multiple cerebral infarcts, or drug-induced parkinsonism.

No diagnostic test is definitive, but MRI abnormalities in the striatum, pons, and cerebellum strongly suggest the disorder. Multiple system atrophy can be diagnosed antemortem based on these findings plus symptoms of generalized autonomic failure and lack of response to levodopa.

Treatment
• Supportive care

There is no specific treatment, but symptoms are managed as follows:
• Orthostatic hypotension: Treatment includes intravascular volume expansion with salt and water supplementation and sometimes fludrocortisone 0.1 to 0.4 mg po once/day. Use of compression garments for the lower body (eg, abdominal binder, Jobst stockings) and α-adrenoreceptor stimulation with midodrine 10 mg po tid may help. However, midodrine also increases peripheral vascular resistance and supine BP, which may be problematic. Raising the head of the bed about 10 cm reduces nocturnal polyuria and supine hypertension and may reduce morning orthostatic hypotension.

• Parkinsonism: Levodopa/carbidopa 25/100 mg po at bedtime or pergolide 0.1 mg po once/day, titrated upward to 0.25 to 1.0 mg tid, may be tried to relieve rigidity and other parkinsonian symptoms, but these drugs are usually ineffective or provide modest benefit.

• Urinary incontinence: If the cause is detrusor hyperreflexia, oxybutynin chloride 5 mg po tid or tolterodine 2 mg po bid may be used.

• Urinary retention: Many patients must self-catheterize their bladder.

• Constipation: A high-fiber diet and stool softeners can be used; for refractory cases, enemas may be necessary.

• Erectile dysfunction: Drugs such as sildenafil 50 mg po prn and various physical means can be used (see p. 2347).

**Pure Autonomic Failure**

**Pure autonomic failure results from neuronal loss in autonomic ganglia, causing orthostatic hypotension and other autonomic symptoms.**

Pure autonomic failure, previously called idiopathic orthostatic hypotension or Bradbury-Eggleston syndrome, denotes generalized autonomic failure without CNS involvement. This disorder differs from multiple system atrophy because it lacks central or preganglionic involvement. Pure autonomic failure affects more women, tends to begin during a person's 40s or 50s, and does not result in death.

Etiology is usually unknown. Some cases are due to a synucleinopathy (see p. 1765); occasionally, the cause is an autoimmune autonomic neuropathy.

The main symptom is orthostatic hypotension; there may be other autonomic symptoms, such as decreased sweating, heat intolerance, urinary retention, bladder spasms (possibly causing incontinence), erectile dysfunction, fecal incontinence or constipation, and pupillary abnormalities.

**Diagnosis**

• Clinical evaluation

Diagnosis is by exclusion. The norepinephrine level is usually < 100 pg/mL supine and does not increase with standing. Postural tachycardia syndrome can be differentiated because with standing, it does not usually cause hypotension, the norepinephrine level increases, and heart rate increases by > 30 beats/min or to 120 beats/min within 10 min.

**Treatment**

Treatment is symptomatic:

• Orthostatic hypotension: Vasopressors and support hose

• Constipation: High-fiber diet and stool softeners
• Bladder spasms: Bladder antispasmodics

• Urinary retention: Possibly self-catheterization of the bladder

• Sweating abnormalities: Avoidance of hot conditions
Chapter 171. Pain

Introduction

Pain is the most common reason patients seek medical care. Pain has sensory and emotional components and is often classified as acute or chronic. Acute pain is frequently associated with anxiety and hyperactivity of the sympathetic nervous system (eg, tachycardia, increased respiratory rate and BP, diaphoresis, dilated pupils). Chronic pain does not involve sympathetic hyperactivity but may be associated with vegetative signs (eg, fatigue, loss of libido, loss of appetite) and depressed mood. People vary considerably in their tolerance for pain.

Pathophysiology

Acute pain, which usually occurs in response to tissue injury, results from activation of peripheral pain receptors and their specific A delta and C sensory nerve fibers (nociceptors). Chronic pain (see p. 1629) related to ongoing tissue injury is presumably caused by persistent activation of these fibers. Chronic pain may also result from ongoing damage to or dysfunction of the peripheral or central nervous system (which causes neuropathic pain) (see p. 1632).

Nociceptive pain may be somatic or visceral. Somatic pain receptors are located in skin, subcutaneous tissues, fascia, other connective tissues, peristomeum, endosteum, and joint capsules. Stimulation of these receptors usually produces sharp or dull localized pain, but burning is not uncommon if the skin or subcutaneous tissues are involved. Visceral pain receptors are located in most viscera and the surrounding connective tissue. Visceral pain due to obstruction of a hollow organ is poorly localized, deep, and cramping and may be referred to remote cutaneous sites. Visceral pain due to injury of organ capsules or other deep connective tissues may be more localized and sharp.

Although pain of predominantly psychologic origin is far less common than nociceptive or neuropathic pain, psychologic factors commonly contribute to chronic pain and may contribute to pain-related disability. Pain thought to be caused predominantly by psychologic factors is sometimes called psychogenic pain; however, psychophysiologic pain is a more accurate term because the pain results from interaction of physiologic and psychologic phenomena. This type of pain can be categorized in terms of defined somato-form disorders (eg, chronic pain disorders, somatization disorders, hypochondriasis—see p. 1573) in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).

Many pain syndromes are multifactorial. For example, chronic low back pain and most cancer pain syndromes have a prominent nociceptive component but may also involve neuropathic pain (due to nerve damage).

Pain transmission and modulation: Pain fibers enter the spinal cord at the dorsal root ganglia and synapse in the dorsal horn. From there, fibers cross to the other side and travel up the lateral columns to the thalamus and then to the cerebral cortex.

Repetitive stimulation (eg, from a prolonged painful condition) can sensitize neurons in the dorsal horn of the spinal cord so that a lesser peripheral stimulus causes pain (wind-up phenomenon). Peripheral nerves and nerves at other levels of the CNS may also be sensitized, producing long-term synaptic changes in cortical receptive fields (remodeling) that maintain exaggerated pain perception.

Substances released when tissue is injured, including those involved in the inflammatory cascade, can sensitize peripheral nociceptors. These substances include vasoactive peptides (eg, calcitonin gene-related protein, substance P, neurokinin A) and other mediators (eg, prostaglandin E2, serotonin, bradykinin, epinephrine).

The pain signal is modulated at multiple points in both segmental and descending pathways by many neurochemical mediators, including endorphins (eg, enkephalin) and monoamines (eg, serotonin, norepinephrine). These mediators interact in poorly understood ways to exaggerate or reduce the
perception of and response to pain. They mediate the potential benefit of CNS-active drugs (eg, opioids, antidepressants, anticonvulsants, membrane stabilizers) that interact with specific receptors and neurochemicals in the treatment of chronic pain.

Psychologic factors are important modulators. They not only affect verbal expression of pain (ie, whether patients appear stoic or sensitive) but also generate neural output that modulates neurotransmission along pain pathways. Psychologic reaction to protracted pain interacts with other CNS factors to induce long-term changes in pain perception.

**Evaluation**

Clinicians should evaluate the cause, severity, and nature of the pain and its effect on activities and psychologic well-being. Evaluation of the cause of acute pain (eg, back pain, chest pain—see elsewhere in THE MANUAL) differs from that of chronic pain (see p. 1630).

The history should include the following information about the pain:

- Quality (eg, burning, cramping, aching, deep, superficial, boring, shooting)
- Severity
- Location
- Radiation pattern
- Duration
- Timing (including pattern and degree of fluctuation and frequency of remissions)
- Exacerbating and relieving factors

The patient's level of function should be assessed, focusing on activities of daily living (eg, dressing, bathing), employment, avocations, and personal relationships (including sexual).

The patient's perception of pain can represent more than the disorder's intrinsic physiologic processes. What pain means to the patient should be determined, with emphasis on psychologic issues, depression, and anxiety. Reporting pain is more socially acceptable than reporting anxiety or depression, and appropriate therapy often depends on sorting out these divergent perceptions. Pain and suffering should also be distinguished, especially in cancer patients (see p. 1075); suffering may be due as much to loss of function and fear of impending death as to pain. Whether secondary gain (external, incidental benefits of a disorder—eg, time off, disability payments) contributes to pain or pain-related disability should be considered. The patient should be asked whether litigation is ongoing or financial compensation for injury will be sought. A personal or family history of chronic pain can often illuminate the current problem. Whether family members perpetuate chronic pain (eg, by constantly asking about the patient's health) should be considered.

Patients and sometimes family members and caregivers should be asked about the use, efficacy, and adverse effects of prescription and OTC drugs and other treatments and about alcohol and recreational or illicit drug use.

**Pain severity:** Pain severity should be assessed before and after potentially painful interventions. In verbal patients, self-report is the gold standard, and external signs of pain or distress (eg, crying, wincing, rocking) are secondary. For patients who have difficulty communicating and for young children, nonverbal indicators (behavioral and sometimes physiologic) may need to be the primary source of information.

Formal measures (see Fig. 171-1) include verbal category scales (eg, mild, moderate, severe), numeric scales, and the Visual Analog Scale (VAS). For the numeric scale, patients are asked to rate their pain from 0 to 10 (0 = no pain;
10 = “the worst pain ever”). For the VAS, patients make a hash mark representing their degree of pain on an unmarked 10-cm line with the left side labeled “no pain” and the right side labeled “unbearable pain.” The pain score is distance in mm from the left end of the line. Children and patients with limited literacy or known developmental problems may select from images of faces ranging from smiling to contorted with pain or from fruits of varying sizes to convey their perception of pain severity. When measuring pain, the examiner should specify a time period (eg, “on average during the past week”).

**Demented and aphasis patients:** Assessing pain in patients with disorders affecting cognition, speech, or language (eg, dementia, aphasis) can be difficult. Pain is suggested by facial grimacing, frowning, or repetitive eye blinking. Sometimes caregivers can describe behaviors that suggest pain (eg, sudden social withdrawal, irritability, grimacing). Pain should be considered in patients who have difficulty communicating and who inexplicably change their behavior. Many patients who have difficulty communicating can communicate meaningfully when an appropriate pain scale is used. For example, the Function Pain Scale has been validated and can be used in nursing home patients who have Mini-Mental State Examination scores of ≥ 17.

**Patients receiving neuromuscular blockade:** No validated instruments are available to assess pain when neuromuscular blockade is used to facilitate mechanical ventilation. If the patient is given a sedative, the dose can be adjusted until there is no evidence of consciousness. In such cases, specific analgesics are not needed. If, however, the patient is sedated but continues to have evidence of consciousness (eg, blinking, some eye movement response to command), pain treatment should be considered based on the degree of pain usually caused by the condition (eg, burns, trauma). If a potentially painful procedure (eg, turning a bedbound patient) is required, pretreatment with the selected analgesic or anesthetic should be given.

**Treatment of Pain**

Nonopioid and opioid analgesics are the main drugs used to treat pain. Antidepressants, anticonvulsants, and other CNS-active drugs may also be used for chronic or neuropathic pain and are first-line therapy for some conditions. Neuraxial infusion, nerve stimulation, injection therapies, and neural blockade can help selected patients. Cognitive-behavioral interventions (eg, incremental gains in function; changes in relationships in the home; systematic use of relaxation techniques, hypnosis, or biofeedback; graduated exercise) may reduce pain and pain-related disability and help patients cope.

**Nonopioid Analgesics**

Acetaminophen and NSAIDs are often effective for mild to moderate pain (see Table 171-1). Of these, only ketorolac can be given parenterally. Nonopioids do not cause physical dependence or tolerance.

Acetaminophen has no anti-inflammatory or antiplatelet effects and does not cause gastric irritation.

NSAIDs include nonselective COX (COX-1 and COX-2) inhibitors and selective COX-2 inhibitors (coxibs); all are effective analgesics. Aspirin is the least expensive but has prolonged antiplatelet effects. Coxibs have lowest risk of ulcer formation and GI upset. However, when a coxib is used with low-dose aspirin, it may have no GI benefit over other NSAIDs. Recent studies suggest that inhibition of COX-2, which occurs with both nonselective COX inhibitors and coxibs, is associated with a prothrombotic effect that can increase risk of MI, stroke, and claudication. This effect appears to be drug-related, as well as dose- and duration-related. Although there is some evidence that the risk is very low with some of the nonselective COX inhibitors (eg, ibuprofen, naproxen) and coxibs (celecoxib), it is prudent to consider the potential for prothrombotic effects as a risk of all NSAID therapy.

If an NSAID is likely to be used only short-term, significant adverse effects are unlikely, regardless of the drug used. Some clinicians use a coxib first whenever therapy is likely to be long-term (eg, months).
because the risk of GI adverse effects is lower; others limit coxib use to patients predisposed to GI 
adverse effects (eg, the elderly, patients taking corticosteroids, those with a history of peptic ulcer 
disease or GI upset due to other NSAIDs) and those who are not doing well with nonselective NSAIDs or 
who have a history of intolerance to them. Although data are still limited, the prothrombotic risk suggests 
that all NSAIDs should be used cautiously in patients with clinically significant atherosclerosis or multiple 
cardiovascular risk factors. All NSAIDs should be used cautiously in patients with renal insufficiency; 
coxibs are not renal-sparing.

If initial recommended doses provide inadequate analgesia, a higher dose is given, up to the conventional 
safe maximum dose. If analgesia remains inadequate, the drug should be stopped. If pain is not severe, 
another NSAID may be tried because response varies from drug to drug. It is prudent during long-term 
NSAID therapy to monitor for occult blood in stool and changes in CBC, electrolytes, and hepatic and 
renal function.

**Opioid Analgesics**

"Opioid" is a generic term for natural or synthetic substances that bind to specific opioid receptors in the 
CNS, producing an agonist action. Opioids are also called narcotics. Some opioids used for analgesia 
have both agonist and antagonist actions. Potential for abuse among those with a known history of abuse 
or addiction may be less with agonist-antagonists than with pure agonists, but agonist-antagonist drugs 
have a ceiling effect for analgesia and induce a withdrawal syndrome in patients already physically 
dependent on opioids. In general, acute pain is best treated with short-acting pure agonist drugs, and 
chronic pain is

[Table 171-1. Nonopioid Analgesics]

best treated with longer-acting pure agonist drugs (see 
Tables 171-2 and 
171-3).

Opioid analgesics are useful in managing severe acute or chronic pain. They are often underused, 
resulting in needless pain and suffering because clinicians often underestimate the required dosage, 
overestimate the duration of action and risk of adverse effects, and have unreasonable concerns about 
addiction (see p. 1512). Physical dependence (development of withdrawal symptoms when a drug is 
stopped) should be assumed to exist in all patients treated with opioids for more than a few days. 
However, addiction (loss of control, compulsive use, craving and use despite harm) is very rare in 
patients with no history of substance abuse. Before opioid therapy is initiated, clinicians should ask about 
risk factors for abuse and addiction. These risk factors include prior alcohol or drug abuse, a family 
history of alcohol or drug abuse, and a prior major psychiatric disorder. If risk factors are present, 
treatment may still be appropriate; however, the clinician should use more controls to prevent abuse (eg, 
small prescriptions, frequent visits, no refills for "lost" prescriptions) or should refer the patient to a pain 
specialist or an addiction medicine specialist experienced in pain management.

**Route of administration:** Almost any route can be used. The oral or transdermal route is preferred for 
long-term use; both are effective

[Table 171-2. Opioid Analgesics]

and provide stable blood levels. Modified-release oral and transdermal forms allow less frequent dosing, 
which is particularly important for providing overnight relief. Formulations of fentanyl are now available for 
delivery through the oral mucosa. Lozenges are used for sedation in children and as treatment of 
breaththrough pain. Effervescent tablets are available for breakthrough pain. Breakthrough pain has been 
targeted by these formulations because they have a relatively more rapid onset than the oral route; other 
rapid-onset, transmucosal

[Table 171-3. Equianalgesic Doses of Opioid Analgesics*]

formulations of fentanyl and other drugs are in development.
The IV route provides the most rapid onset and thus the easiest titration, but duration of analgesia is short. Large, rapid fluctuations in blood levels (bolus effect) can lead to toxicity at peak levels early in the dosing interval or later to breakthrough pain at trough levels. Continuous IV infusion, sometimes with patient-controlled supplemental doses, eliminates this effect but requires an expensive pump; this approach is used most often for postoperative pain.

The IM route provides analgesia longer than IV but is painful, and absorption can be erratic; it is not recommended. Long-term continuous SC infusion can be used, particularly for cancer pain.

Intraspinal opioids (eg, morphine 5 to 10 mg epidurally or 0.5 to 1 mg intrathecally for acute pain) can provide relief, which is prolonged when a hydrophilic drug like morphine is used; they are typically used postoperatively. Implanted infusion devices can provide long-term neuraxial infusion. These devices can also be used with other drugs (eg, local anesthetics, clonidine, ziconotide).

**Dosing and titration:** Initial dose is modified according to the patient's response; it is increased incrementally until analgesia is satisfactory or adverse effects limit treatment. Sedation and respiratory rate are monitored when opioids are given parenterally to relatively opioid-naive patients. The elderly are more sensitive to opioids and are predisposed to adverse effects; opioid-naive elderly patients typically require lower doses than younger patients. Neonates, especially when premature, are also sensitive to opioids, because they lack adequate metabolic pathways to eliminate them.

For moderate, transient pain, an opioid may be given prn. For severe or ongoing pain, doses should be given regularly, without waiting for severe pain; supplemental doses are given as needed when treating cancer pain and are typically considered case by case when treating chronic noncancer pain. A common error is prescribing short-acting drugs at long intervals, allowing breakthrough pain.

For patient-controlled analgesia, a bolus dose (in a postoperative setting, typically morphine 1 mg q 6 min) is provided when patients push a button; a baseline infusion (eg, morphine 0.5 to 1 mg/h) may or may not be given. The physician controls the amount and interval of the bolus. Patients with prior opioid exposure or with chronic pain require a higher bolus and baseline infusion dose; the infusion dose is further adjusted based on response.

Patients with dementia cannot use patient-controlled analgesia, nor can young children; however, adolescents often can.

During long-term treatment, the effective opioid dose can remain constant for prolonged periods. Some patients need intermittent dose escalation, typically in the setting of physical changes that suggest an increase in the pain (eg, progressive neoplasm). Fear of tolerance should not inhibit appropriate early, aggressive use of an opioid. If a previously adequate dose becomes inadequate, that dose must usually be increased by 30 to 100% to control pain.

Nonopioid analgesics (eg, acetaminophen, NSAIDs) are often given concomitantly. Products containing both drugs are convenient, but the nonopioid may limit upward titration of the opioid dose.

**Adverse effects:** In opioid-naive patients, adverse effects common at the start of therapy include sedation, mental clouding, constipation, nausea, vomiting, and itching. Respiratory depression is serious but is rare when opioids are given at appropriate doses. Because steady-state plasma levels are not approached until 4 to 5 half-lives have passed, drugs with a long half-life (particularly levorphanol and methadone) have a risk of delayed toxicity as plasma levels rise. Modified-release opioids typically require several days to approach steady-state levels.

In the elderly, opioids tend to have more adverse effects (commonly, constipation and sedation or mental clouding). Opioids may cause urinary retention in men with benign prostatic hyperplasia.

Although tolerance to opioid-induced sedation, mental clouding, and nausea usually develops within days, tolerance to opioid-induced constipation and urinary retention usually occurs much more slowly. Any adverse effect may be persistent in some patients and this is much more likely with constipation.
Opioids should be used cautiously in patients with certain disorders:

- Hepatic disorders because drug metabolism is delayed, particularly with modified-release preparations
- COPD because respiratory depression is a risk
- Some neurologic disorders, such as dementia and encephalopathy, because delirium is a risk
- Severe renal insufficiency because metabolites may accumulate and cause problems; accumulation is least likely with fentanyl and methadone

Constipation is common among patients who take opioids for more than a few days. For prevention in predisposed patients (eg, the elderly), dietary fiber and fluids should be increased, and a stimulant laxative (eg, senna—see p. 87) should be given. Persisting constipation can be managed with Mg citrate 90 mL po q 2 to 3 days, lactulose 15 mL po bid, or propylethylene glycol powder (dose is adjusted as needed). Some patients require regular enemas.

While sedated after taking an opioid, patients should not drive and should take precautions to prevent falls and other accidents. If sedation impairs quality of life, certain stimulant drugs may be given intermittently (eg, before a family gathering or other event that requires alertness) or, to some patients, regularly. Drugs that can be effective are methylphenidate (initially, 5 to 10 mg po bid), dextroamphetamine (initially, 2.5 to 10 mg po bid), or modafinil (initially, 100 to 200 mg po once/day). These drugs are typically given in the morning and as needed later. The maximum dose of methylphenidate seldom exceeds 60 mg/day. For some patients, caffeine-containing beverages provide enough stimulation. Stimulants may also potentiate analgesia.

Nausea can be treated with hydroxyzine 25 to 50 mg po q 6 h, metoclopramide 10 to 20 mg po q 6 h, or an antiemetic phenothiazine (eg, prochlorperazine 10 mg po or 25 mg rectally q 6 h).

Respiratory depression is rare with conventional doses and with long-term use. If it occurs acutely, ventilatory assistance may be needed until the opioid's effect can be reversed by an opioid antagonist.

For urinary retention, double voiding or using Crede's method during voiding may help; some patients benefit from adding an α-adrenergic blocker such as tamsulosin 0.4 mg po once/day (starting dose).

Opioids can cause neuroendocrine effects, typically reversible hypogonadism. Symptoms may include fatigue, loss of libido, infertility due to low levels of sex hormones, and, in women, amenorrhea.

**Opioid antagonists:** Opioid antagonists are opioid-like substances that bind to opioid receptors but produce little or no agonist activity. They are used mainly to reverse symptoms of opioid overdose, particularly respiratory depression.

Naloxone acts in < 1 min when given IV and slightly less rapidly when given IM. It can also be given sublingually or endotracheally. Duration of action is about 60 to 120 min. However, opioid-induced respiratory depression usually lasts longer than the duration of antagonism; thus, *repeated doses of naloxone and close monitoring are necessary*. The dose for acute opioid overdosage is 0.4 mg IV q 2 to 3 min pm. For patients receiving long-term opioid therapy, naloxone should be used only to reverse respiratory depression and must be given more cautiously to avoid precipitating withdrawal or recurrent pain. A reasonable regimen is 1 mL of a dilute solution (0.4 mg in 10 mL saline) IV q 1 to 2 min, titrated to adequate respirations (not alertness). Nalmefene is similar to naloxone, but its duration of action is about 4 to 8 h. Nalmefene is occasionally used to ensure prolonged opioid reversal.

Naltrexone, an orally bioavailable opioid antagonist, is given as adjunctive therapy in opioid and alcohol addiction. It is long-acting and generally well tolerated.

**Adjuvant Analgesic Drugs**
Many drugs are used as adjuvant analgesics, including anticonvulsants (eg, pregabalin, gabapentin) and antidepressants (eg, tricyclics, duloxetine, venlafaxine, bupropion), and many others (see Table 171-4). These drugs have many uses, most notably to relieve pain with a neuropathic component. Gabapentin is the most widely used drug for such purposes. The dose often needs to be high, up to 1200 mg tid or sometimes higher. Pregabalin is similar to gabapentin but has more stable pharmacokinetics; some patients who do not respond well to gabapentin do respond to pregabalin and visa versa. Duloxetine is a new mixed mechanism (serotonin and norepinephrine) reuptake inhibitor, which has good evidence of analgesic efficacy in diabetic neuropathic pain and fibromyalgia.

Topical drugs are also widely used. Capsaicin cream, topical NSAIDS, other compounded creams (eg, local anesthetics), and a lidocaine 5% patch have little risk of adverse effects; they should be considered for many types of pain.

**Neural Blockade**

Interrupting nerve transmission in peripheral or central pain pathways via drugs or physical methods provides short-term and sometimes long-term relief. Neuroablation (pathway destruction is used rarely; it is typically reserved for patients with an advanced disorders and a short life expectancy.

Local anesthetic drugs (eg, lidocaine) can be given IV, intrathecally, intrapleurally, transdermally, sc, or epidurally. Epidural analgesia using local anesthetics or opioids is particularly useful for some types of postoperative pain. Long-term epidural drug administration is occasionally used for patients with localized pain and a short life expectancy. Generally, for long-term neuraxial infusion, an intrathecal route via an implanted pump is preferred.

Neuroablation involves interrupting a nociceptive pathway surgically or using radio-frequency energy to produce a lesion. The procedure is used mainly for cancer pain. Somatic pain is more responsive than visceral pain. Neuroablation of the ascending spinothalamic tract (cordotomy) is usually used; it provides relief for several years, although numbness and dysesthesias develop. Neuroablation of the dorsal roots (rhizotomy) is used when a specific dermatome can be identified.

**Neuromodulation**

Stimulation of neural tissues may decrease pain, presumably by activating endogenous pain modulatory pathways. The most common method is transcutaneous electrical nerve stimulation (TENS), which applies a small current to the skin. Also, electrodes may be implanted along peripheral nerves or along the dorsal columns in the epidural space. Stimulation of brain structures (deep brain stimulation and motor cortex stimulation) has also been used, but evidence of benefit is slight.

**Geriatrics Essentials**

In the elderly, the most common causes of pain are musculoskeletal disorders. However, pain is often chronic and multifactorial, and the causes may not be clear.

**NSAIDs:** Risk of ulcers and GI bleeding due to NSAIDs for people > 65 is 3 to 4 times higher than that for middle-aged people. Risk depends on drug dose and duration of therapy. Elderly patients at high risk of GI adverse effects may benefit from concomitant use of cytoprotective drugs (usually, a proton pump inhibitor; occasionally, the prostaglandin misoprostol).

The newly recognized risk of cardiovascular toxicity, which presumably occurs with nonselective COX-1 and COX-2 inhibitors and with selective COX-2 inhibitors (coxibs), is particularly relevant to the elderly, who are more likely to have cardiovascular risk factors (eg, a history of MI or cerebrovascular or peripheral vascular disease). These drugs should be prescribed cautiously for such patients.

Both nonselective and selective NSAIDs can impair renal function and cause Na and water retention; they should be used cautiously in the elderly, particularly in those who have a renal or hepatic disorder, heart failure, or hypovolemia. Rarely, NSAIDs cause cognitive impairment and personality changes in the elderly. Indomethacin causes more confusion in the elderly than other NSAIDs and should be avoided.
Given the overall greater risk of serious toxicity in the elderly, low doses of NSAIDs should be used if possible, and using short-term therapy or interrupted therapy to confirm effectiveness should be considered.

**Opioids:** In the elderly, opioids have a longer half-life and possibly a greater analgesic effect than in younger patients. Opioid agonist-antagonists often have psychotomimetic effects (eg, delirium) in the elderly and should usually be avoided. Opioids can contribute to constipation and urinary retention in patients of any age, but the effects tend to be more problematic in the elderly.

**Chronic Pain**

(See also Fibromyalgia on p. 375.)

**Chronic pain is pain that persists or recurs for > 3 mo, persists > 1 mo after resolution of an acute tissue injury, or accompanies a nonhealing lesion.** Causes include chronic disorders (eg, cancer, arthritis, diabetes) and injuries (eg, herniated disk, torn ligament), and many primary pain disorders (eg, neuropathic pain, fibromyalgia, chronic headache). Various drugs and psychologic treatments are used.

Unresolved, long-lasting disorders (eg, cancer, RA, herniated disk) that produce ongoing nociceptive stimuli may account completely for chronic pain. Alternatively, injury, even mild injury, may lead to long-lasting changes (sensitization) in the nervous system—from peripheral receptors to the cerebral cortex—that may produce persistent pain in the absence of ongoing nociceptive stimuli. With sensitization, discomfort that is due to a nearly resolved disorder and might otherwise be perceived as mild or trivial is instead perceived as significant pain. Psychologic factors may also amplify persistent pain. Thus, chronic pain commonly appears out of proportion to identifiable physical processes. In some cases (eg, chronic back pain after injury), the original precipitant of pain is obvious; in others (eg, chronic headache, atypical facial pain, chronic abdominal pain), the precipitant is remote or occult.

In most patients, physical processes are undeniably involved in sustaining chronic pain and are sometimes (eg, in cancer pain) the main factor. However, even in these patients, psychologic factors usually also play a role. Patients who have to continually prove that they are sick to obtain medical care, insurance coverage, or work relief may unconsciously reinforce their pain perceptions, particularly when litigation is involved. This response differs from malingering, which is conscious exaggeration of symptoms for secondary gain (eg, time off, disability payments). Various factors in the patient's environment (eg, family members, friends) may reinforce behaviors that perpetuate chronic pain.

Chronic pain can lead to psychologic problems. Constant, unremitting pain limits activities and may cause depression and anxiety, interrupt sleep, and interfere with almost all activities. Distinguishing cause from effect is often difficult.

**Symptoms and Signs**

Chronic pain often leads to vegetative signs (eg, lassitude, sleep disturbance, decreased appetite, loss of taste for food, weight loss, diminished libido, constipation), which develop gradually; depression may develop. Patients may become inactive, withdraw socially, and become preoccupied with physical health. Psychologic and social impairment may be severe, causing virtual lack of function.

Some patients, particularly those without a clear-cut ongoing cause, have a history of failed medical and surgical treatments, multiple (and duplicative) diagnostic tests, use of many drugs (sometimes involving abuse or addiction), and inappropriate use of health care.

**Diagnosis**

- Evaluation for organic cause initially and if symptoms change

An organic cause should always be sought—even if a prominent psychologic contribution to the pain is
likely. Physical processes associated with the pain should be evaluated appropriately and characterized. However, once a full evaluation is done, repeating tests in the absence of new findings is not useful. The best approach is often to stop testing and focus on relieving pain and restoring function.

The effect of pain on the patient's life should be evaluated; evaluation by an occupational therapist may be necessary. Formal psychiatric evaluation should be considered if a coexisting psychiatric disorder (eg, major depression) is suspected as cause or effect.

Treatment

• Often multimodal therapy (eg, analgesics, physical methods, psychologic treatments)

Specific causes should be treated. Early, aggressive treatment of acute pain is always preferable and may limit or prevent sensitization and remodeling and hence prevent progression to chronic pain.

Drugs or physical methods may be used. Psychologic and behavioral treatments are usually helpful. Many patients who have marked functional impairment or who do not respond to a reasonable attempt at management by their physician benefit from the multidisciplinary approach available at a pain clinic.

Many patients prefer to have their pain treated at home, even though an institution may offer more advanced modalities of pain management. Also, pain control may be compromised by certain practices in institutions; for example, they restrict visiting hours, use of televisions and radios (which provide useful distraction), and use of heating pads (for fear of thermal injury).

Drugs: Analgesics include NSAIDs, opioids, and adjuvant analgesics (eg, antidepressants, anticonvulsants—see p. 1628 and Table 171-4). One or more drugs may be appropriate.

Table 171-4. Drugs for Neuropathic Pain

Adjuvant analgesics are most commonly used for neuropathic pain. For persistent, moderate-to-severe pain that impairs function, opioids should be considered after determining the following:

• What conventional treatment practice is

• Whether other treatments are reasonable

• Whether the patient has an unusually high risk of adverse effects from an opioid

• Whether the patient is likely to be a responsible drug user

Prescription drug abuse may be a problem, and physicians should not offer long-term opioid therapy unless they can assess risk of abuse, monitor patients appropriately, and respond reasonably to problematic drug use. As pain lessens, patients usually need help reducing use of opioids. If depression coexists with pain, antidepressants should be used.

Depending on the condition, trigger point injection, joint or spinal injections, nerve blocks, or neuraxial infusion may be appropriate.

Physical methods: Many patients benefit from physical therapy or occupational therapy. Spray-and-stretch techniques can relieve myofascial trigger points. Some patients require an orthosis. Spinal cord stimulation may be appropriate.

Psychologic treatments: Behavioral treatments can improve patient function, even without reducing pain. Patients should keep a diary of daily activities to pinpoint areas amenable to change. The physician should make specific recommendations for gradually increasing physical activity and social engagement. Activities should be prescribed in gradually increasing units of time; pain should not, if at all possible, be allowed to abort the commitment to greater function. When activities are increased in this way, reports of pain often decrease.
Various cognitive techniques of pain control (eg, relaxation training, distraction techniques, hypnosis, biofeedback) may be useful. Patients may be taught to use distraction by guided imagery (organized fantasy evoking calm and comfort—eg, imagining resting on a beach or lying in a hammock). Other cognitive-behavioral techniques (eg, self-hypnosis) may require training by specialists.

Behavior of family members or fellow workers that reinforces pain behavior (eg, constant inquiries about the patient's health or insistence that the patient do no chores) should be discouraged. The physician should avoid reinforcing pain behavior, discourage maladaptive behaviors, applaud progress, and provide pain treatment while emphasizing return of function.

Neuropathic Pain

Neuropathic pain results from damage to or dysfunction of the peripheral or central nervous system, rather than stimulation of pain receptors. Diagnosis is suggested by pain out of proportion to tissue injury, dysesthesia (eg, burning, tingling), and signs of nerve injury detected during neurologic examination. Although neuropathic pain responds to opioids, treatment is often with adjuvant drugs (eg, antidepressants, anticonvulsants, baclofen, topical drugs).

Pain can develop after injury to any level of the nervous system, peripheral or central; the sympathetic nervous system may be involved (causing sympathetically maintained pain). Specific syndromes include postherpetic neuralgia (see p. 1420), root avulsions, painful traumatic mononeuropathy, painful polyneuropathy (particularly due to diabetes), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, phantom pain), and complex regional pain syndrome (reflex sympathetic dystrophy and causalgia—see p. 1633).

Etiology

Peripheral nerve injury or dysfunction can result in neuropathic pain. Examples are mononeuropathies (eg, carpal tunnel syndrome, radiculopathy), plexopathies (typically caused by nerve compression, as by a neuroma, tumor, or herniated disk), and polyneuropathies (typically caused by various metabolic neuropathies—see Table 185-1 on p. 1785). Mechanisms presumably vary and may involve an increased number of Na channels on regenerating nerves.

Central neuropathic pain syndromes appear to involve reorganization of central somatosensory processing; the main categories are deafferentation pain and sympathetically maintained pain. Both are complex and, although presumably related, differ substantially.

Deafferentation pain is due to partial or complete interruption of peripheral or central afferent neural activity. Examples are postherpetic neuralgia, central pain (pain after CNS injury), and phantom pain (pain felt in the region of an amputated body part). Mechanisms are unknown but may involve sensitization of central neurons, with lower activation thresholds and expansion of receptive fields.

Sympathetically maintained pain depends on efferent sympathetic activity. Complex regional pain syndrome sometimes involves sympathetically maintained pain. Other types of neuropathic pain may have a sympathetically maintained component. Mechanisms probably involve abnormal sympathetic-somatic nerve connections (ephapses), local inflammatory changes, and changes in the spinal cord.

Symptoms and Signs

Dysesthesias (spontaneous or evoked burning pain, often with a superimposed lancinating component) are typical, but pain may also be deep and aching. Other sensations—eg, hyperesthesia, hyperalgesia, allodynia (pain due to a nonnoxious stimulus), and hyperpathia (particularly unpleasant, exaggerated pain response)—may also occur. Symptoms are long-lasting, typically persisting after resolution of the primary cause (if one was present) because the CNS has been sensitized and remodeled.
Diagnosis

Clinical evaluation

Neuropathic pain is suggested by its typical symptoms when nerve injury is known or suspected. The cause (eg, amputation, diabetes) may be readily apparent. If not, the diagnosis often can be assumed based on the description. Pain that is ameliorated by sympathetic nerve block is sympathetically maintained pain.

Treatment

Multimodal therapy (eg, psychologic treatments, physical methods, antidepressants or anticonvulsants, sometimes surgery)

Without concern for diagnosis, rehabilitation, and psychosocial issues, treatment has a limited chance of success. For peripheral nerve lesions, mobilization is needed to prevent trophic changes, disuse atrophy, and joint ankylosis. Surgery may be needed to alleviate compression. Psychologic factors must be constantly considered from the start of treatment. Anxiety and depression must be treated appropriately. When dysfunction is entrenched, patients may benefit from the comprehensive approach provided by a pain clinic.

Several classes of drugs are moderately effective (see Table 171-4), but complete or near-complete relief is unlikely. Antidepressants and anticonvulsants are most commonly used. Evidence of efficacy is strong for several antidepressants and anticonvulsants.

Opioid analgesics can provide some relief but are less effective than for nociceptive pain; adverse effects may prevent adequate analgesia. Topical drugs and a lidocaine-containing patch may be effective for peripheral syndromes. Sympathetic blockade is usually ineffective except for some patients with complex regional pain syndrome.

Complex Regional Pain Syndrome

(Reflex Sympathetic Dystrophy and Causalgia)

Complex regional pain syndrome (CRPS) is chronic neuropathic pain that follows soft-tissue or bone injury (type I) or nerve injury (type II) and lasts longer and is more severe than expected for the original tissue damage. Other manifestations include autonomic changes (eg, sweating, vasomotor abnormalities), motor changes (eg, weakness, dystonia), and trophic changes (eg, skin or bone atrophy, hair loss, joint contractures). Diagnosis is clinical. Treatment includes drugs, physical therapy, and sympathetic blockade.

CRPS type I was previously known as reflex sympathetic dystrophy, and type II as causalgia. Both types occur most often in young adults and are 2 or 3 times more common among women.

Etiology

CRPS type I typically follows an injury (usually of a hand or foot), most commonly after crush injuries, especially in a lower limb. It may follow amputation, acute MI, stroke, or cancer (eg, lung, breast, ovary, CNS); no precipitant is apparent in about 10% of patients. CRPS type II is similar to type I but involves overt damage to a peripheral nerve.

Pathophysiology

Pathophysiology is unclear, but peripheral nociceptor and central sensitization and release of neuropeptides (substance P, calcitonin gene-related peptide) help maintain pain and inflammation. The sympathetic nervous system is more involved in CRPS than in other neuropathic pain syndromes: Central sympathetic activity is increased, and peripheral nociceptors are sensitized to norepinephrine (a...
sympathetic neurotransmitter); these changes may lead to sweating abnormalities and poor blood flow due to vasoconstriction. Nonetheless, only some patients respond to sympathetic manipulation (ie, central or peripheral sympathetic blockade).

**Symptoms and Signs**

Symptoms vary greatly and do not follow a pattern; they include sensory, focal autonomic (vasomotor or sudomotor), and motor abnormalities.

Pain—burning or aching—is common. It does not follow the distribution of a single peripheral nerve; it may worsen with changes in environment or emotional stress. Allodynia and hyperalgesia may occur. Pain often causes patients to limit use of an extremity.

Cutaneous vasomotor changes (eg, red, mottled, or ashen color; increased or decreased temperature) and sudomotor abnormalities (dry or hyperhidrotic skin) may be present. Edema may be considerable and locally confined. Other symptoms include trophic abnormalities (eg, shiny, atrophic skin; cracking or excess growth of nails; bone atrophy; hair loss) and motor abnormalities (weakness, tremors, spasm, dystonia with fingers fixed in flexion or equinovarus position of foot). Range of motion is often limited, sometimes leading to joint contractures. Symptoms may interfere with fitting a prosthesis after amputation.

Psychologic distress (eg, depression, anxiety, anger) is common, fostered by the poorly understood cause, lack of effective therapy, and prolonged course.

**Diagnosis**

- Clinical evaluation

The following clinical criteria must be present to establish the diagnosis of CRPS:

- Occurrence of pain (usually burning)
- Allodynia or hyperalgesia
- Focal autonomic dysregulation (vasomotor or sudomotor abnormalities)
- No evidence of another disorder that could explain the symptoms

If another disorder is present, CRPS should be considered possible or probable.

Other symptoms and findings may support the diagnosis: edema, trophic abnormalities, or a change in temperature of the affected area. Thermography may be used to document the temperature change if clinical evaluation is equivocal and if this finding would help establish the diagnosis. Bone changes (eg, demineralization on x-ray, increased uptake on a triple-phase radionuclide bone scan) may be detected and are usually evaluated only if the diagnosis is equivocal. However, imaging tests may also be abnormal after trauma in patients without CRPS.

Sympathetic nerve block (cervical stellate ganglion or lumbar) can be used for diagnosis and treatment. However, false-positive and false-negative results are common because not all CRPS pain is sympathetically maintained and nerve block may also affect nonsympathetic fibers. In another test of sympathetic involvement, a patient is given IV infusions of saline (placebo) or phentolamine 1 mg/kg over 10 min while pain scores are recorded; a decrease in pain after phentolamine but not placebo indicates sympathetically maintained pain.

**Prognosis**

Prognosis varies and is difficult to predict. CRPS may remit or remain stable for years; in a few patients, it progresses, spreading to other areas of the body.
Treatment

- Multimodal therapy (e.g., drugs, physical therapy, sympathetic blockade, psychologic treatments, neuromodulation)

Treatment is complex and often unsatisfactory, particularly if begun late. It includes drugs, physical therapy, sympathetic blockade, psychologic treatments, and neuromodulation. Few controlled trials have been done.

Many of the drugs used for neuropathic pain, including tricyclic antidepressants, anticonvulsants, and corticosteroids (see Table 171-4), may be tried; none is known to be superior. Long-term treatment with opioid analgesics may be useful for selected patients.

In some patients with sympathetically maintained pain, regional sympathetic blockade relieves pain, making physical therapy possible. Oral analgesics (NSAIDs, opioids, and various adjuvant analgesics) may also relieve pain sufficiently to allow rehabilitation.

For neuromodulation, implanted spinal cord stimulators are being increasingly used. Transcutaneous electrical nerve stimulation (TENS), applied at multiple locations with different stimulation parameters, should be given a long trial. Other methods of neuromodulation include brisk rubbing of the affected part (counterirritation) and acupuncture. No one form of neuromodulation is known to be more effective than another, and a poor response to one form does not mean a poor response to another.

Neuraxial infusion with opioids, anesthetics, and clonidine may help, and intrathecal baclofen has reduced dystonia in a few patients.

Physical therapy is essential. Goals include strengthening, increased range of motion, and vocational rehabilitation.
Chapter 172. Function and Dysfunction of the Cerebral Lobes

Introduction

The cerebrum is divided by a longitudinal fissure into 2 hemispheres, each containing 5 discrete lobes. The frontal, temporal, parietal, and occipital lobes cover the brain's surface; the insula is hidden under the Sylvian fissure (see Fig. 172-1). Although specific functions are attributed to each lobe, most activities require coordination of multiple areas in both hemispheres. For example, although the occipital lobe is essential to visual processing, parts of the parietal, temporal, and frontal lobes on both sides also process complex visual stimuli.

Function is extensively lateralized. Visual, tactile, and motor activities of the left side of the body are directed predominantly by the right hemisphere and vice versa. Certain complex functions involve both hemispheres but are directed predominantly by one (cerebral dominance). For example, the left hemisphere is typically dominant for language, and the right is dominant for spatial attention.

The cerebral cortex contains the primary sensory and motor areas as well as multiple association areas. The primary sensory areas receive somesthetic, auditory, visual, olfactory, and gustatory stimuli from specialized sensory organs and peripheral receptors. Sensory stimuli are further processed in association areas that relate to one or more senses. The primary motor cortex generates volitional body movements; motor association areas help plan and execute complex motor activity. Some cortical areas are heteromodal. They are not restricted to any single motor or sensory function but receive convergent information from multiple sensory and motor areas of the brain. Heteromodal association areas in the frontal, temporal, and parietal lobes integrate sensory data, motor feedback, and other information with instinctual and acquired memories. This integration facilitates learning and creates thought, expression, and behavior.

Frontal lobes: The frontal lobes are anterior to the central sulcus. They are essential for planning and executing learned and purposeful behaviors; they are also the site of many inhibitory functions. There are several functionally distinct areas in the frontal lobes:

• The primary motor cortex is the most posterior part of the precentral gyrus. The primary motor cortex on one side controls all moving parts on the contralateral side of the body (shown on a spatial map called a homunculus—see Fig. 172-2); 90% of motor fibers from each hemisphere cross the midline in the brain stem. Thus, damage to the motor cortex of one hemisphere causes weakness or paralysis mainly on the contralateral side of the body.

• The medial frontal cortex (sometimes called the medial prefrontal area) is important in arousal and motivation. If lesions in this area are large and extend to the most anterior part of the cortex (frontal pole), patients sometimes become abulic (apathetic, inattentive, and markedly slow to respond).

• The orbital frontal cortex (sometimes called the orbital prefrontal area—see Fig. 172-1) helps modulate social behaviors. Patients with orbital frontal lesions can become emotionally labile, indifferent to the implications of their actions, or both. They may be alternately euphoric, facetious, vulgar, and indifferent to social nuances. Bilateral acute trauma to this area may make patients boisterously talkative, restless, and socially intrusive. With aging and in many types of dementia, disinhibition and abnormal behaviors can develop; these changes probably result from degeneration of the frontal lobe, particularly the orbital frontal cortex.

• The left posteroinferior frontal cortex (sometimes called Broca's area or the posteroinferior prefrontal area—see Fig. 172-1) controls expressive language function. Lesions in this area cause expressive aphasia (impaired expression of words—see p. 1640).
• The dorsolateral frontal cortex (sometimes called the dorsolateral prefrontal area) manipulates very recently acquired information—a function called working memory. Lesions in this area can impair the ability to retain information and process it in real time (eg, to spell words backwards or to alternate between letters and numbers sequentially).

**Parietal lobes:** Several areas in the parietal lobes have specific functions.

• The primary somatosensory cortex, located in the postrolandic area (postcentral gyrus) in the anterior parietal lobes, integrates somesthetic stimuli for recognition and recall of form, texture, and weight. The primary somatosensory cortex on one side receives all somatosensory input from the contralateral side of the body (see Fig. 172-2). Lesions of the anterior parietal lobe can cause difficulty recognizing objects by touch (astereognosis).

• Areas posterolateral to the postcentral gyrus generate visual-spatial relationships and integrate these perceptions with other sensations to create awareness of trajectories of moving objects. These areas also mediate proprioception (awareness of the position of body parts in space).

• Parts of the midparietal lobe of the dominant hemisphere are involved in abilities such as calculation, writing, left-right orientation, and finger recognition. Lesions in the angular gyrus can cause deficits in writing, calculating, left-right disorientation, and finger-naming (Gerstmann's syndrome).

• The nondominant parietal lobe integrates the contralateral side of the body with its environment, enabling people to be aware of this environmental space, and is important for abilities such as drawing. Acute injury to the nondominant parietal lobe may cause neglect of the contralateral side (usually the left), resulting in decreased awareness of that part of the body, its environment, and any associated injury to that side (anosognosia). For example, patients with large right parietal lesions may deny the existence of left-sided paralysis. Patients with smaller lesions may lose the ability to do learned motor tasks (eg, dressing, other well-learned activities)—a spatial-manual deficit called apraxia.

**Temporal lobes:** The temporal lobes are integral to auditory perception, receptive components of language, visual memory, declarative (factual) memory, and emotion. Patients with right temporal lobe lesions commonly lose the ability to interpret nonverbal auditory stimuli (eg, music). Left temporal lobe lesions interfere greatly with the recognition, memory, and formation of language.

Patients with epileptogenic foci in the medial limbic-emotional parts of the temporal lobe commonly have complex partial seizures, characterized by uncontrollable feelings and autonomic, cognitive, or emotional dysfunction. Occasionally, such patients have personality changes, characterized by humorlessness, philosophic religiosity, and obsessiveness.

**Occipital lobes:** The occipital lobes contain the primary visual cortex and visual association areas. Lesions in the primary visual cortex lead to a form of central blindness called Antón's syndrome; patients become unable to recognize objects by sight and are generally unaware of their deficits. Seizures in the occipital lobe can cause visual hallucinations, often consisting of lines or meshes of color superimposed on the contralateral visual field.

**Insula:** The insula integrates sensory and autonomic information from the viscera. It plays a role in certain language functions, as evidenced by aphasia in patients with some insular lesions. The insula processes aspects of pain and temperature sensation and possibly taste.

**Pathophysiology**

Cerebral dysfunction may be focal or global. Focal and global processes may also affect subcortical systems, altering arousal (eg, causing stupor or coma) or integration of thought (eg, causing delirium).

**Focal dysfunction** usually results from structural abnormalities (eg, tumors, stroke, trauma, malformations, gliosis, demyelination). Manifestations depend on the lesion's location, size, and development rate. Lesions that are < 2 cm in diameter or that develop very slowly may be asymptomatic.
Larger lesions, rapidly developing lesions (over weeks or months rather than years), and lesions that simultaneously affect both hemispheres are more likely to become symptomatic. Focal lesions in white matter can interrupt the connectivity between brain areas and cause the disconnection syndrome (inability to do a task that requires coordinated activity of ≥ 2 brain regions, despite retention of basic functions of each region).

**Global dysfunction** is caused by toxicmetabolic disorders or sometimes by diffuse inflammation, vasculopathy, major trauma, or disseminated cancer; these disorders affect multiple dimensions of cerebral function.

**Recovery:** Recovery from brain injury depends in part on the plasticity (ability of an area of the brain to alter its function) of the remaining cerebrum, a capacity that varies from person to person and is affected by age and general health. Plasticity is most prominent in the developing brain. For example, if the dominant hemisphere language areas are severely damaged before age 8 yr, the opposite hemisphere can often assume near-normal language function. Although capacity for recovery from brain injury is considerable after the first decade of life, severe damage more often results in permanent deficits. Gross reorganization of brain function after injury in adults is uncommon, although plasticity remains operative in certain specific areas of the brain throughout life.

**Cerebral dysfunction syndromes:** Specific syndromes include agnosia, amnesia, aphasia, and apraxia. Psychiatric conditions (eg, depression, psychosis, anxiety disorders) sometimes include similar elements.

**Diagnosis**

In general, diagnosis is clinical, often assisted by neuropsychologic testing. Diagnosis of the cause usually requires laboratory tests (blood and sometimes CSF analysis) and brain imaging, either structural (CT, MRI) or functional (PET, single-photon emission CT).

**Agnosia**

Agnosia is inability to identify an object using one or more of the senses. Diagnosis is clinical, often including neuropsychologic testing, with brain imaging (eg, CT, MRI) to identify the cause. Prognosis depends on the nature and extent of damage and patient age. There is no specific treatment, but occupational therapy may help patients compensate.

Agnosias are uncommon. They result from damage to (eg, by infarct, tumor, trauma) or degeneration of areas of the brain that integrate perception, memory, and identification.

Discrete brain lesions can cause different forms of agnosia, which may involve any sense. Typically, only one sense is affected. Examples are hearing (auditory agnosia, the inability to identify objects through sound such as a ringing telephone), taste (gustatory agnosia), smell (olfactory agnosia), touch (tactile agnosia), and sight (visual agnosia).

Other forms of agnosia involve very specific and complex processes within one sense. For example, prosopagnosia is inability to identify well-known faces, including those of close friends, or to otherwise distinguish individual objects among a class of objects, despite the ability to identify generic facial features and objects.

Anosognosia often accompanies damage to the right, nondominant parietal lobe. Patients deny their deficit, insisting that nothing is wrong even when one side of their body is completely paralyzed. When shown the paralyzed body part, patients may deny that it is theirs. In an often related phenomenon, patients ignore the paralyzed or desensitized body parts (hemi-inattention) or the space around them (hemineglect). Hemineglect most often involves the left side of the body.

Occipitotemporal lesions may cause an inability to recognize familiar places (environmental agnosia), visual disturbances (visual agnosia), or color blindness (achromatopsia). Right-sided temporal lesions may cause an inability to interpret sounds (auditory agnosia) or impaired music perception (amusia).
Diagnosis

• Bedside and neuropsychologic testing

• Brain imaging

At bedside, patients are asked to identify common objects through sight, touch, or another sense. If hemineglect is suspected, patients are asked to identify the paralyzed parts of their body or objects in their hemivisual fields. Physical examination is done to detect primary deficits in individual senses or communication that may interfere with testing for agnosias. For example, if light touch is defective, patients may not sense an object even when cortical function is intact. Also, aphasias may interfere with patient's expression. Neuropsychologic testing may help identify more subtle agnosias.

Brain imaging (eg, CT or MRI with or without angiographic protocols) is required to characterize a central lesion (eg, infarct, hemorrhage, mass) and to check for atrophy suggesting a degenerative disorder.

Prognosis

Recovery may be influenced by size and location of lesions, degree of impairment, and patient age. Most recovery occurs within the first 3 mo but may continue to a variable degree up to a year.

Treatment

There is no specific treatment. Rehabilitation with speech or occupational therapists can help patients learn to compensate for their deficits.

Amnesias

Amnesia is partial or total inability to recall past experiences. It may result from traumatic brain injury, degeneration, metabolic disorders, seizure disorders, or psychologic disturbances. Diagnosis is clinical but often includes neuropsychologic testing and brain imaging (eg, CT, MRI). Treatment is directed at the cause.

Processing of memories involves registration (taking in new information), encoding (forming associations, time stamps, and other processes necessary for retrieval), and retrieval. Deficits in any of these steps can cause amnesia. Amnesia, by definition, results from impairment of memory functions, not impairment of other functions (eg, attention, motivation, reasoning, language), which may cause similar symptoms.

Amnesia can be classified as follows:

• Retrograde: Amnesia for events before the causative event

• Anterograde: Inability to store new memories after the causative event

• Global: Amnesia for information related to all senses and past times

• Sense-specific: Amnesia for events processed by one sense—eg, an agnosia

Amnesia may be transient (as occurs after brain trauma), fixed (as occurs after a serious event such as encephalitis, global ischemia, or cardiac arrest), or progressive (as occurs with degenerative dementias, such as Alzheimer’s disease).

Memory deficits more commonly involve facts (declarative memory) and, less commonly, skills (procedural memory).

Etiology
Amnesia can result from diffuse cerebral impairment, bilateral lesions, or multifocal injuries that impair memory-storage areas in the cerebral hemispheres. Predominant pathways for declarative memory are located along the medial parahippocampal region and hippocampus as well as in the inferomedial temporal lobes, orbital surface of the frontal lobes (basal forebrain), and diencephalon (which contains the thalamus and hypothalamus). Of these structures, the hippocampal gyri, hypothalamus, nuclei of the basal forebrain, and dorsomedial thalamic nuclei are critical. The amygdaloid nucleus contributes emotional amplifications to memory. The thalamic intralaminar nuclei and brain stem reticular formation stimulate the imprinting of memories. Bilateral damage to the mediodorsal nuclei of the thalamus severely impairs recent memory and the ability to form new memories; the most common causes are

- Thiamin deficiency
- Hypothalamic tumors
- Vertebrobasilar ischemia

Other causes of amnesia include the following:

- Bilateral damage to the medial temporal lobes (especially the hippocampus)
- Degenerative dementias
- Severe brain trauma
- Global brain anoxia or ischemia
- Alcoholic-nutritional disorders (eg, Wernicke's encephalopathy, Korsakoff's psychosis—see pp. 1522 and 1523)
- Various drug intoxications (eg, chronic solvent sniffing, amphotericin B or lithium toxicity)

Posttraumatic amnesias for the periods immediately before and after concussion or more severe head trauma seem to result from medial temporal lobe injury. More severe injuries may affect larger areas of memory storage and recall, as can many diffuse cerebral disorders that cause dementia.

Psychologic disturbances of memory result from extreme psychologic trauma or stress (see p. 1503).

With aging, many people gradually develop noticeable problems with memory, often first for names, then for events, and occasionally for spatial relationships. This widely experienced so-called benign senescent forgetfulness has no proven relationship to dementia, although some similarities are hard to overlook. People who have a subjective memory problem, who perform worse on objective memory tests, but who otherwise have intact cognition and daily function may have amnestic mild cognitive impairment (amnestic MCI). People with amnestic MCI are more likely to develop Alzheimer's disease than agematched people without memory problems.

**Diagnosis**

- Bedside testing

Simple bedside tests (eg, 3-item recall, location of objects previously hidden in the room) and formal tests (eg, word list learning tests such as the California Verbal Learning Test and the Buschke Selective Reminding Test) can help identify verbal memory loss. Assessment of nonverbal memory is more difficult but may include recall of visual designs or a series of tones. Clinical findings usually suggest causes and any necessary tests.

**Treatment**

- Treatment directed at the cause
Any underlying disorder or psychologic cause must be treated. However, some patients with acute amnesia improve spontaneously. Certain disorders that cause amnesia (eg, Alzheimer's disease, Korsakoff's psychosis, herpes encephalitis) can be treated; however, treatment of the underlying disorder may or may not lessen the amnesia. If it does not, no specific measures can hasten recovery or improve the outcome.

**Transient Global Amnesia**

Transient global amnesia is disturbed memory typically caused by vascular or ischemic lesions in the brain. Diagnosis is primarily clinical but includes laboratory tests and CT, MRI, or both to evaluate central circulation. The amnesia typically remits spontaneously but may recur. There is no specific treatment, but underlying abnormalities are corrected.

Transient global amnesia is typically caused by ischemia (eg, due to atherosclerosis, thrombosis, or thromboembolism) that transiently affects the posteromedial thalamus or hippocampus bilaterally, but this amnesia can be caused by seizure activity or migraines.

A distinct benign form of transient global amnesia can follow excessive alcohol ingestion, moderately large sedative doses of barbiturates, use of several illicit drugs, or sometimes relatively small doses of benzodiazepines (especially midazolam and triazolam).

**Symptoms and Signs**

Patients present with acute global amnesic confusion that usually lasts 6 to 12 h but may last from 30 min to 24 h (rarely). Patients have a retrograde memory deficit that can extend back for several years; they are often disoriented to time and place but usually not to personal identity. Anterograde memory is less disturbed. Many patients are anxious or agitated and may repeatedly ask questions about transpiring events. Language function, attention, visual-spatial skills, and social skills are retained. Impairments gradually resolve as the episode subsides.

The benign transient amnesia after substance ingestion is distinct because it is selectively retrograde (ie, for events during and preceding intoxication), relates specifically to drug-accompanied events, does not cause confusion (once acute intoxication resolves), and recurs only if similar amounts of the same drug are ingested.

**Diagnosis**

- Primarily clinical evaluation
- Brain imaging

Diagnosis is primarily clinical. Neurologic examination typically does not detect any abnormalities other than disturbed memory. Brain ischemia must be ruled out (see p. 1648). Laboratory tests should include CBC, coagulation tests, and evaluation for hypercoagulable states. CT, MRI, or both, with or without angiographic protocols, are done. EEG usually shows nonspecific abnormalities and is unnecessary unless a seizure is suspected or episodes recur.

**Prognosis**

Prognosis is good. Symptoms typically last < 24 h. As the disorder resolves, the amnesia lessens, but memory for events during the attack may be lost. Usually, episodes do not recur, unless the cause is seizures or migraines. Overall lifetime recurrence rate is about 5 to 25%.

**Treatment**

No specific treatment is indicated. However, underlying ischemia (see p. 1649) or seizure (see p. 1692) should be treated.
Aphasia

Aphasia is language dysfunction that may involve impaired comprehension or expression of words or nonverbal equivalents of words. It results from dysfunction of the language centers in the cerebral cortex and basal ganglia or of the white matter pathways that connect them. Diagnosis is clinical, often including neuropsychologic testing, with brain imaging (CT, MRI) to identify cause. Prognosis depends on the cause and extent of damage and on patient age. There is no specific treatment, but speech therapy may promote recovery.

Language function resides predominantly in the following:

- Posterosuperior temporal lobe, which contains Wernicke's area
- Adjacent inferior parietal lobe
- Posterior inferior part of the frontal lobe just anterior to the motor cortex, which contains Broca's area
- Subcortical connection between those regions—usually in the left hemisphere, even in left-handed people

Damage to any part of this roughly triangular area (eg, by infarct, tumor, trauma, or degeneration) interferes with some aspect of language function. Prosody (quality of rhythm and emphasis that adds meaning to speech) is usually influenced by both hemispheres but is sometimes affected by dysfunction of the nondominant hemisphere alone.

Aphasia is distinct from developmental disorders of language and from dysfunction of the motor pathways and muscles that produce speech (dysarthria). It is broadly divided into receptive and expressive aphasia.

- **Receptive (sensory, fluent, or Wernicke's) aphasia**: Patients cannot comprehend words or recognize auditory, visual, or tactile symbols. It is caused by a disorder of the posterosuperior temporal gyrus of the language-dominant hemisphere (Wernicke's area). Often, alexia (loss of the ability to read words) is also present.

- **Expressive (motor, nonfluent, or Broca's) aphasia**: The ability to create words is impaired, but comprehension and ability to conceptualize are relatively preserved. It is due to a disorder that affects the dominant left frontal or frontoparietal area, including Broca's area. It often causes agraphia (loss of the ability to write) and impairs oral reading.

There are other types of aphasia (see Table 172-1), which may overlap considerably. No aphasia classification system is ideal. Describing the types of deficits is often the most precise way to describe a particular aphasia.

Symptoms and Signs

**Wernicke's aphasia**: Patients speak normal words fluently, often including meaningless phonemes, but do not know their meaning or relationships. The result is a jumble of words or "word salad." Patients are typically unaware that their speech is incomprehensible to others. A right visual field cut commonly accompanies Wernicke's aphasia because the visual pathway is near the affected area.

**Broca's aphasia**: Patients can comprehend and conceptualize relatively well, but their ability to form words is impaired. Usually, the impairment affects speech production and writing (agraphia, dysgraphia), greatly frustrating patients' attempts to communicate. Broca's aphasia may include anomia (inability to name objects) and impaired prosody.

Diagnosis
• Exclusion of other communication problems

• Bedside and neuropsychologic testing

• Brain imaging

Verbal interaction can typically identify gross aphasias. However, the clinician should try to differentiate aphasias from communication problems that stem from severe dysarthria, impaired hearing, vision (eg, when assessing reading), or motor writing ability.

Initially, Wernicke's aphasia may be mistaken for delirium. However, Wernicke's aphasia is a pure language disturbance without other features of delirium (eg, fluctuating level of consciousness, hallucinations, inattention).

Testing to identify specific deficits should include assessment of the following:

• **Spontaneous speech**: Speech is assessed for fluency, number of words spoken, ability to initiate speech, presence of spontaneous errors, word-finding pauses, hesitations, and prosody.

• **Naming**: Patients are asked to name objects. Those who have difficulty naming often use circumlocutions (eg, "what you use to tell time" for "clock").

• **Repetition**: Patients are asked to repeat grammatically complex phrases (eg, "no ifs, ands, or buts").

• **Comprehension**: Patients are asked to point to objects named by the clinician, carry out one-step and multistep commands, and answer simple and complex yes-or-no questions.

• **Reading and writing**: Patients are asked to write spontaneously and to read aloud. Reading comprehension, spelling, and writing in response to dictation are assessed.

Formal cognitive testing by a neuropsychologist or speech and language therapist may detect finer levels of dysfunction and assist in planning treatment and assessing potential for recovery. Various formal tests for diagnosing aphasia (eg, Boston Diagnostic Aphasia Examination, Western Aphasia Battery, Boston Naming Test, Token Test, Action Naming Test) are available.

Brain imaging (eg, CT, MRI; with or without angiographic protocols) is required to characterize the lesion (eg, infarct, hemorrhage, mass). Further tests are done to determine the etiology of the lesion (eg, stroke, seizure disorder) as indicated (see pp. 1648 and 1690).

**Prognosis**

Recovery is influenced by cause, size and location of lesions, extent of language impairment, and, to a lesser degree, the age, education, and general health of the patient. Children < 8 yr often regain language function after severe damage to either hemisphere. After that age, most recovery occurs within the first 3 mo, but improvement continues to a variable degree up to a year.

**Treatment**

• Speech therapy

• Augmentative communication devices

Effectiveness of treatment is unclear, but most clinicians think that treatment by qualified speech therapists helps and that patients treated soon after onset improve the most. Patients who cannot recover basic language skills and caregivers of such patients are sometimes able to convey messages with augmentative communication devices (eg, a book or communication board that contains pictures or symbols of a patient's daily needs, computer-based devices).
Apraxia

Apraxia is inability to execute purposeful, previously learned motor tasks, despite physical ability and willingness, as a result of brain damage. Diagnosis is clinical, often including neuropsychologic testing, with brain imaging (eg, CT, MRI) to identify cause. Prognosis depends on the cause and extent of damage and patient age. There is no specific treatment, but physical and occupational therapy may modestly improve functioning and patient safety.

Apraxia results from brain damage (eg, by infarct, tumor, or trauma) or degeneration, usually in the parietal lobes or their connections, which retain memories of learned movement patterns. Less commonly, apraxia results from damage to other areas of the brain, such as the premotor cortex (the part of the frontal lobe anterior to the motor cortex), other parts of the frontal lobe, or the corpus callosum, or from diffuse damage related to degenerative dementias.

Symptoms and Signs

Patients cannot conceptualize or do learned complex motor tasks despite an ability to do the individual component movements. For example, patients with constructional apraxia may be unable to copy a simple geometric shape despite being able to see and recognize the stimulus, hold and use a pen, and understand the task. Typically, patients do not recognize their deficits.

Diagnosis

- Bedside and neuropsychologic testing
- Brain imaging

Tests include asking patients to do or imitate common learned tasks (eg, saluting, stopping or starting to walk, combing hair, striking and blowing out a match, opening a lock with a key, using a screwdriver or scissors, taking a deep breath and holding it). Strength and range of motion must be assessed to exclude motor weakness and musculoskeletal abnormalities as the cause of symptoms. Neuropsychologic testing or assessment by a physical or occupational therapist may help identify more subtle apraxias.

Caregivers should be asked about the patient's ability to do activities of daily living, especially those that involve household tools (eg, correct and safe use of eating utensils, toothbrush, kitchen utensils to prepare a meal, hammer, and scissors) and writing.

Brain imaging (eg, CT, MRI; with or without angiographic protocols) is required to diagnose and characterize central lesions (eg, infarct, hemorrhage, mass, focal atrophy).

Prognosis

In general, patients become dependent, requiring help with activities of daily living and at least some degree of supervision. Patients with stroke may have a stable course and even improve somewhat.

Treatment

- Physical and occupational therapy

There is no specific medical treatment. Drugs that slow the symptomatic progression of dementia do not appear beneficial. Physical and occupational therapy may modestly improve functioning but is more often useful for making the environment safer and for providing devices that help patients circumvent the primary deficit.
Chapter 173. Stroke

Introduction

(Cerebrovascular Accident)

Strokes are a heterogeneous group of disorders involving sudden, focal interruption of cerebral blood flow that causes neurologic deficit. Strokes can be ischemic (80%), typically resulting from thrombosis or embolism, or hemorrhagic (20%), resulting from vascular rupture (eg, subarachnoid or intracerebral hemorrhage). Stroke symptoms lasting < 1 h are termed a transient ischemic attack (TIA). Strokes damage brain tissue; TIAs often do not, and when damage occurs, it is less extensive than that due to strokes. In Western countries, stroke is the 3rd most common cause of death and the most common cause of neurologic disability.

Strokes involve the arteries of the brain (see Fig. 173-1), either the anterior circulation (branches of the internal carotid artery) or the posterior circulation (branches of the vertebral and basilar arteries).

Risk factors: Risk factors include the following:

• Prior stroke
• Older age
• Family history of stroke
• Alcoholism
• Male sex
• Hypertension
• Cigarette smoking
• Hypercholesterolemia
• Diabetes
• Use of certain drugs (eg, cocaine, amphetamines)

Certain risk factors predispose to a particular type of stroke (eg, hypercoagulability predisposes to thrombotic stroke, atrial fibrillation to embolic stroke, and intracranial aneurysms to subarachnoid hemorrhage).

Symptoms and Signs

Initial symptoms occur suddenly. Generally, they include numbness, weakness, or paralysis of the contralateral limbs and the face; aphasia;

[Fig. 173-1. Arteries of the brain.]

confusion; visual disturbances in one or both eyes (eg, transient monocular blindness); dizziness or loss of balance and coordination; and headache.

Neurologic deficits reflect the area of brain involved (see Table 173-1). Anterior circulation stroke typically causes unilateral symptoms. Posterior circulation stroke can cause unilateral or bilateral deficits and is more likely to affect consciousness, especially when the basilar artery is involved.
Other manifestations, rather than neurologic deficits, often suggest the type of stroke. For example, sudden, severe headache suggests subarachnoid hemorrhage. Impaired consciousness or coma, often accompanied by headache, nausea, and vomiting, suggests increased intracranial pressure (see p. 1815), which can occur 48 to 72 h after large ischemic strokes and earlier with many hemorrhagic strokes; fatal brain herniation may result (see p. 1656).

**Complications:** Stroke complications can include sleep problems, confusion, depression, incontinence, atelectasis, pneumonia, and swallowing dysfunction, which can lead to aspiration, dehydration, or undernutrition. Immobility can lead to thromboembolic disease, deconditioning, sarcopenia, UTIs, pressure ulcers, and contractures. Daily functioning (including the ability to walk, see, feel, remember, think, and speak) may be decreased.

**Evaluation**

Evaluation aims to establish whether stroke has occurred, whether it is ischemic or hemorrhagic, and whether immediate treatment is required.

Stroke is suspected in patients with any of the following:

- Sudden neurologic deficits compatible with brain damage in an arterial territory
- A particularly sudden, severe headache
- Sudden, unexplained coma
- Sudden impairment of consciousness

If stroke is suspected, immediate neuroimaging is required to differentiate hemorrhagic from ischemic stroke and to detect signs of increased intracranial pressure. CT is sensitive for intracranial blood but may be normal or show only subtle changes during the first hours of symptoms after anterior circulation ischemic stroke. CT also misses some small posterior circulation strokes and up to 3% of subarachnoid hemorrhages. MRI is sensitive for intracranial blood and may detect signs of ischemic stroke missed by CT, but CT can usually be done more rapidly. If CT does not confirm clinically suspected stroke, diffusion-weighted MRI can usually detect ischemic stroke (see p. 1648). If consciousness is impaired and lateralizing signs are absent or equivocal, further tests to check for other causes are done (see p. 1656).

After the stroke is identified as ischemic or hemorrhagic, tests are done to determine the cause. Patients are also evaluated for coexisting acute general disorders (eg, infection, dehydration, hypoxia, hyperglycemia, hypertension). Patients are asked about depression, which commonly occurs after stroke. A dysphagia team evaluates swallowing; sometimes a barium swallow study is necessary.

**Treatment**

- **Stabilization**

- **Supportive measures and treatment of complications**

Stabilization may need to precede complete evaluation. Comatose or obtunded patients (eg, Glasgow Coma Score \( \leq 8 \)) may require airway support (see p. 2279). If increased intracranial pressure is suspected, intracranial pressure monitoring (see p. 2246) and measures to reduce cerebral edema (see p. 3225) may be necessary. Specific acute treatments vary by type of stroke.

Providing supportive care, correcting coexisting abnormalities (eg, fever, hypoxia, dehydration,
hyperglycemia, sometimes hypertension), and preventing and treating complications are vital during the acute phase and convalescence (see Table 173-2); these measures clearly improve clinical outcomes. During convalescence, measures to prevent aspiration, deep venous thrombosis, UTIs, pressure ulcers, and undernutrition may be necessary. Passive exercises, particularly of paralyzed limbs, and breathing exercises are started early to prevent contractures, atelectasis, and pneumonia. Most patients require occupational and physical therapy (see p. 3462) to maximize functional recovery. Some need additional therapies (eg, speech therapy, feeding restrictions). Depression after stroke may require antidepressants; many patients benefit from counseling. For rehabilitation, an interdisciplinary approach is best. Modifying risk factors through lifestyle changes (eg, stopping cigarette smoking) and drug therapy (eg, for hypertension) can help delay or prevent subsequent strokes.

Table 173-2. Strategies to Prevent and Treat Stroke Complications

Ischemic Stroke

Ischemic stroke is sudden neurologic deficits that result from focal cerebral ischemia associated with permanent brain infarction (eg, positive diffusion-weighted MRI). Common causes are (from most to least common) nonthrombotic occlusion of small, deep cortical arteries (lacunar infarction); cardiogenic embolism; arterial thrombosis that decreases cerebral blood flow; and artery-to-artery embolism. Diagnosis is clinical, but CT or MRI is done to exclude hemorrhage and confirm the presence and extent of stroke. Thrombolytic therapy may be useful acutely in certain patients. Depending on the cause of stroke, carotid endarterectomy, antiplatelet drugs, or warfarin may help reduce risk of subsequent strokes.

Etiology

Ischemia usually results from thrombi or emboli. Even infarcts classified as lacunar based on clinical criteria (morphology, size, and location) often involve small thrombi or emboli.

Thrombosis: Atheromas, particularly if ulcerated, predispose to thrombi. Atheromas can occur in any major cerebral artery and are common at areas of turbulent flow, particularly at the carotid bifurcation. Partial or complete thrombotic occlusion occurs most often at the main trunk of the middle cerebral artery and its branches but is also common in the large arteries at the base of the brain, in deep perforating arteries, and in small cortical branches. The basilar artery and the segment of the internal carotid artery between the cavernous sinus and supraclinoid process are often occluded.

Less common causes of thrombosis include vascular inflammation secondary to disorders such as acute or chronic meningitis, vasculitic disorders, and syphilis; dissection of intracranial arteries or the aorta; hypercoagulability disorders (eg, antiphospholipid syndrome, hyperhomocysteinemia); hyperviscosity disorders (eg, polycythemia, thrombocytosis, hemoglobinopathies, plasma cell disorders); and rare disorders (eg, moyamoya disease, Binswanger's disease). Older oral contraceptive formulations increase risk of thrombosis.

Embolism: Emboli may lodge anywhere in the cerebral arterial tree. Emboli may originate as cardiac thrombi, especially in the following conditions:

- Atrial fibrillation
- Rheumatic heart disease (usually mitral stenosis)
- Post-MI
- Vegetations on heart valves in bacterial or marantic endocarditis
- Prosthetic heart valves

Other sources include clots that form after open-heart surgery and atheromas in neck arteries or in the
aortic arch. Rarely, emboli consist of fat (from fractured long bones), air (in decompression sickness), or venous clots that pass from the right to the left side of the heart through a patent foramen ovale with shunt (paradoxical emboli). Emboli may dislodge spontaneously or after invasive cardiovascular procedures (eg, catheterization). Rarely, thrombosis of the subclavian artery results in embolic stroke in the vertebral artery or its branches.

**Lacunar infarcts:** Ischemic stroke can also result from lacunar infarcts. These small (≤ 1.5 cm) infarcts result from nonatherothrombotic obstruction of small, perforating arteries that supply deep cortical structures; the usual cause is lipohyalinosis (degeneration of the media of small arteries and replacement by lipids and collagen). Whether emboli cause lacunar infarcts is controversial. Lacunar infarcts tend to occur in elderly patients with diabetes or poorly controlled hypertension.

**Other causes:** Less commonly, ischemic stroke results from vasospasm (eg, during migraine, after subarachnoid hemorrhage, after use of sympathomimetic drugs such as cocaine or amphetamines) or venous sinus thrombosis (eg, during intracranial infection, postoperatively, peripartum, secondary to a hypercoagulation disorder).

**Pathophysiology**

Inadequate blood flow in a single brain artery can often be compensated for by an efficient collateral system, particularly between the carotid and vertebral arteries via anastomoses at the circle of Willis and, to a lesser extent, between major arteries supplying the cerebral hemispheres. However, normal variations in the circle of Willis and in the caliber of various collateral vessels, atherosclerosis, and other acquired arterial lesions can interfere with collateral flow, increasing the chance that blockage of one artery will cause brain ischemia.

Some neurons die when perfusion is < 5% of normal for > 5 min; however, the extent of damage depends on the severity of ischemia. If it is mild, damage proceeds slowly; thus, even if perfusion is 40% of normal, 3 to 6 h may elapse before brain tissue is completely lost. However, if severe ischemia (ie, decrease in perfusion) persists > 15 to 30 min, all of the affected tissue dies (infarction). Damage occurs more rapidly during hyperthermia and more slowly during hypothermia. If tissues are ischemic but not yet irreversibly damaged, promptly restoring blood flow may reduce or reverse injury. For example, intervention may be able to salvage the moderately ischemic areas (penumbras) that often surround areas of severe ischemia (these areas exist because of collateral flow).

Mechanisms of ischemic injury include edema, microvascular thrombosis, programmed cell death (apoptosis), and infarction with cell necrosis. Inflammatory mediators (eg, IL-1B, tumor necrosis factor-α) contribute to edema and microvascular thrombosis. Edema, if severe or extensive, can increase intracranial pressure. Many factors may contribute to necrotic cell death; they include loss of ATP stores, loss of ionic homeostasis (including intracellular Ca accumulation), lipid peroxidative damage to cell membranes by free radicals (an iron-mediated process), excitatory neurotoxins (eg, glutamate), and intracellular acidosis due to accumulation of lactate.

**Symptoms and Signs**

Symptoms and signs depend on the part of brain affected. Patterns of neurologic deficits often suggest the affected artery (see Table 173-1), but correlation is often inexact.

Deficits may become maximal within several minutes of onset, typically in embolic stroke. Less often, deficits evolve slowly, usually over 24 to 48 h (called evolving stroke or stroke in evolution), typically in thrombotic stroke. In most evolving strokes, unilateral neurologic dysfunction (often beginning in one arm, then spreading ipsilaterally) extends without causing headache, pain, or fever. Progression is usually stepwise, interrupted by periods of stability. A stroke is considered submaximal when, after it is complete, there is residual function in the affected area, suggesting viable tissue at risk of damage.

Embolic strokes often occur during the day; headache may precede neurologic deficits. Thrombi tend to occur during the night and thus are first noticed on awakening. Lacunar infarcts may produce one of the classic lacunar syndromes (eg, pure motor hemiparesis, pure sensory hemianesthesia, ataxic
hemiparesis, dysarthria-clumsy hand syndrome); signs of cortical dysfunction (eg, aphasia) are absent. Multiple lacunar infarcts may result in multi-infarct dementia.

Deterioration during the first 48 to 72 h after onset of symptoms, particularly progressively impaired consciousness, results more often from cerebral edema than from extension of the infarct. Unless the infarct is large or extensive, function commonly improves within the first few days; further improvement occurs gradually for up to 1 yr.

**Diagnosis**

- Primarily clinical evaluation
- Neuroimaging and bedside glucose testing
- Evaluation to identify the cause

Diagnosis is suggested by sudden neurologic deficits referable to a specific arterial territory. Ischemic stroke must be distinguished from other causes of similar focal deficits (eg, hypoglycemia; postictal [Todd's] paralysis; hemorrhagic stroke; rarely, migraine). Headache, coma or stupor, and vomiting are more likely with hemorrhagic stroke.

Although diagnosis is clinical, neuroimaging and bedside glucose testing are mandatory. CT is done first to exclude intracerebral hemorrhage, subdural or epidural hematoma, and a rapidly growing, bleeding, or suddenly symptomatic tumor. CT evidence of even large anterior circulation ischemic stroke may be subtle during the first few hours; changes may include effacement of sulci or the insular cortical ribbon, loss of the gray-white junction between cortex and white matter, and a dense middle cerebral artery sign. After 24 h of ischemia, medium-sized to large infarcts are usually visible as hypodensities; small infarcts (eg, lacunar infarcts) may be visible only with MRI. Diffusion-weighted MRI (highly sensitive for early ischemia) can be done immediately after CT initial neuroimaging.

Distinction between lacunar, embolic, and thrombotic stroke based on history, examination, and neuroimaging is not always reliable, so tests to identify common or treatable causes and risk factors for all of these types of strokes are routinely done. These tests typically include carotid duplex ultrasonography, ECG, transesophageal echocardiography, and various blood tests (CBC, platelet count, PT/PTT, fasting blood glucose, lipid profile, homocysteine, ESR, and, for at-risk patients, syphilis serology). Troponin I level is measured to detect concomitant MI. Magnetic resonance or CT angiography is also often done. Other tests (eg, antiphospholipid antibodies) are done if certain disorders are suspected clinically.

**Prognosis**

Stroke severity and progression are often assessed using standardized measures such as the National Institutes of Health Stroke Scale (see Table 173-3); the score on this scale correlates with extent of functional impairment and prognosis. During the first days, progression and outcome can be difficult to predict. Older age, impaired consciousness, aphasia, and brain stem signs suggest a poor prognosis. Early improvement and younger age suggest a favorable prognosis.

About 50% of patients with moderate or severe hemiplegia and most with milder deficits have a clear sensorium and eventually can take care of their basic needs and walk adequately. Complete neurologic recovery occurs in about 10%. Use of the affected limb is usually limited, and most deficits that remain after 12 mo are permanent. Subsequent strokes often occur, and each tends to worsen neurologic function. About 20% of patients die in the hospital; mortality rate increases with age.

**Treatment**
• General stroke treatments
• Acute antihypertensive therapy only in certain circumstances
• Antiplatelet therapy
• Occasionally for acute treatment, tPA or thrombolysis-in-situ
• Sometimes anticoagulation
• Long-term control of risk factors
• Sometimes carotid endarterectomy

**Acute:** Guidelines for early management of stroke are available from the Stroke Council of the American Heart Association/American Stroke Association. Patients with acute ischemic strokes are usually hospitalized. Supportive measures (see p. 1646) may be needed during initial evaluation and stabilization.

Perfusion of an ischemic brain area may require a high BP because autoregulation is lost; thus, BP should not be decreased except in the following situations:

- BP is > 220 mm Hg systolic or > 120 mm Hg diastolic on 2 successive readings > 15 min apart.
- There are signs of other end-organ damage (eg, aortic dissection, acute MI, pulmonary edema, hypertensive encephalopathy, retinal hemorrhages, acute renal failure).
- Use of recombinant tissue plasminogen activator (tPA) is likely.

If indicated, nicardipine 2.5 mg/h IV is given initially; dose is increased by 2.5 mg/h q 5 min to a maximum of 15 mg/h as needed to decrease systolic BP by 10 to 15%. Alternatively, IV labetalol can be used.

Patients with presumed thrombi or emboli may be treated with tPA, thrombolysis-in-situ, antiplatelet drugs, and/or anticoagulants. Most patients are not candidates for thrombolytic therapy; they should be given an antiplatelet drug (usually aspirin 325 mg po) when they are admitted to the hospital. Contraindications to antiplatelet drugs include aspirin-or NSAID-induced asthma or urticaria, other hypersensitivity to aspirin or to tartrazine, acute GI bleeding, G6PD deficiency, and use of warfarin.

**Recombinant tPA** is used for patients with acute ischemic stroke of < 3 h duration and no contraindications to tPA (see *Table 174-4*). Although tPA can cause fatal or other symptomatic brain hemorrhage, patients treated with tPA strictly following protocol have a higher likelihood of functional neurologic recovery. Thus, only physicians experienced in stroke management should use tPA to treat patients with acute stroke; inexperienced physicians are more likely to violate protocols, resulting in more brain hemorrhages and deaths. tPA must be given within 3 h of symptom onset—a difficult requirement. Because the precise time of symptom onset may not be known, clinicians must start timing from the moment the patient was last observed to be well. Before treatment with tPA, brain hemorrhage must be excluded by CT, and systolic BP must be < 185 mm Hg and diastolic BP < 110 mm Hg; antihypertensive drugs may be given as above. Dose of tPA is 0.9 mg/kg IV (maximum dose 90 mg); 10% is given by rapid IV injection, and the remainder by constant infusion over 60 min. Vital signs are closely monitored for 24 h after treatment, and BP is maintained below the target levels listed above. Any bleeding complications are aggressively managed. Anticoagulants and antiplatelet drugs are not used within 24 h of treatment with tPA.

*Table 173-4. Exclusion Criteria for Use of Tissue Plasminogen Activator in Stroke*

**Thrombolysis-in-situ** (angiographically directed intra-arterial thrombolysis) of a thrombus or embolus can sometimes be used for major strokes if symptoms have begun > 3 h but < 6 h ago, particularly for
strokes due to large occlusions in the middle cerebral artery. Clots in the basilar artery may be intra-arterially lysed up to 12 h after stroke onset, sometimes even later depending on the clinical circumstances. This treatment, although standard of care in some large stroke centers, is often unavailable in other hospitals.

**Anticoagulation** with heparin or low molecular weight heparin is used for stroke caused by cerebral venous thrombosis and is sometimes used for emboli due to atrial fibrillation and when stroke due to presumed progressive thrombosis continues to evolve despite use of antiplatelet drugs and cannot be treated any other way (eg, with tPA or invasive methods). Warfarin is begun simultaneously with heparin. Before anticoagulation, hemorrhage must be excluded by CT. Constant weight-based heparin infusion (see Fig. 194-2 on p. 1916) is used to increase PTT to 1.5 to 2 times baseline values until warfarin has increased the INR to 2 to 3 (3 in hypercoagulable disorders). Because warfarin predisposes to bleeding and is continued after hospital discharge, its use should be restricted to patients likely to comply with dosage and monitoring requirements and not prone to falls.

**Long term: Supportive care** is continued during convalescence. Controlling general medical risk factors (especially hyperglycemia and fever) can limit brain damage after stroke, leading to better functional outcomes.

**Carotid endarterectomy** is indicated for patients with recent nondisabling, submaximal stroke attributed to an ipsilateral carotid obstruction of 70 to 99% of the arterial lumen or to an ulcerated plaque if life expectancy is at least 5 yr. In other symptomatic patients (eg, patients with TIA), endarterectomy with antiplatelet therapy is indicated for carotid obstruction of ≥ 60% with or without ulceration if life expectancy is at least 5 yr. The procedure should be done by surgeons who have a morbidity and mortality rate of < 3% with the procedure in the hospital where it will be done. If carotid stenosis is asymptomatic, endarterectomy is beneficial only when done by very experienced surgeons, and that benefit is likely to be small. For many patients, carotid stenting with an emboli-protection device (a type of filter) is as effective as surgery.

**Oral antiplatelet drugs** are used to prevent subsequent strokes (secondary prevention). Aspirin 81 or 325 mg once/day, clopidogrel 75 mg once/day, or the combination product aspirin 25 mg/extended-release dipyridamole 200 mg bid may be used. In patients taking warfarin, antiplatelet drugs additively increase risk of bleeding and are thus usually avoided; however, aspirin is occasionally used simultaneously with warfarin in certain high-risk patients. The combination of clopidogrel and aspirin is avoided because it has no advantage over aspirin alone in secondary stroke prevention and results in more bleeding complications.

**Transient Ischemic Attack**

A transient ischemic attack (TIA) is focal brain ischemia that causes sudden neurologic deficits and is not associated with permanent brain infarction (eg, negative results on diffusion-weighted MRI). Diagnosis is clinical. Carotid endarterectomy, antiplatelet drugs, and warfarin decrease risk of stroke after certain types of TIA.

TIA is similar to ischemic stroke except that symptoms last < 1 h; most TIAs last < 5 min. Infarction is very unlikely if deficits resolve within 1 h. Deficits that resolve spontaneously within 1 to 24 h have been shown on diffusion-weighted MRI and other studies to often be accompanied by infarction and are thus no longer considered TIAs. TIAs are most common among the middle-aged and elderly. TIAs markedly increase risk of stroke, beginning in the first 24 h.

**Etiology**

Most TIAs are caused by emboli, usually from carotid or vertebral arteries, although most of the causes of ischemic stroke (see p. 1647) can also result in TIAs. Uncommonly, TIAs result from impaired perfusion due to severe hypoxemia, reduced O2-carrying capacity of blood (eg, profound anemia, carbon monoxide poisoning), or increased blood viscosity (eg, severe polycythemia), particularly in brain arteries with preexisting stenosis. Systemic hypotension does not usually cause cerebral ischemia unless it is severe.
or arterial stenosis preexists because autoregulation maintains brain blood flow at near-normal levels over a wide range of systemic BPs.

In subclavian steal syndrome, a subclavian artery stenosed proximal to the origin of the vertebral artery "steals" blood from the vertebral artery (in which blood flow reverses) to supply the arm during exertion, causing signs of vertebrobasilar ischemia.

Occasionally, TIAs occur in children with a severe cardiovascular disorder that produces emboli or a very high Hct.

Symptoms and Signs

Neurologic deficits are similar to those of strokes (see Table 173-1). Transient monocular blindness (amaurosis fugax), which usually lasts < 5 min, may occur when the ophthalmic artery is affected. Symptoms begin suddenly, usually last 2 to 30 min, then resolve completely. Patients may have several TIAs daily or only 2 or 3 over several years. Symptoms are usually similar in successive carotid attacks but vary somewhat in successive vertebrobasilar attacks.

Diagnosis

• Resolution of stroke-like symptoms within 1 h

• Neuroimaging

• Evaluation to identify the cause

Diagnosis is made retrospectively when sudden neurologic deficits referable to ischemia in an arterial territory resolve within 1 h. Isolated peripheral facial nerve palsy, loss of consciousness, or impaired consciousness does not suggest TIA. TIAs must be distinguished from other causes of similar symptoms (eg, hypoglycemia, migraine aura, postictal [Todd's] paralysis). Because an infarct, a small hemorrhage, and even a mass lesion cannot be excluded clinically, neuroimaging is required. Usually, CT is the study most likely to be immediately available. However, CT may not identify infarcts for > 24 h. MRI usually detects evolving infarction within hours. Diffusion-weighted MRI is the most accurate imaging test to rule out an infarct in patients with presumed TIA but is not always available.

The cause of a TIA is sought as for that of ischemic strokes, including tests for carotid stenosis, cardiac sources of emboli, atrial fibrillation, and hematologic abnormalities and screening for stroke risk factors. Because risk of subsequent ischemic stroke is high and immediate, evaluation proceeds rapidly, usually on an inpatient basis. It is not clear which patients, if any, can be safely discharged from the emergency department.

Treatment

• Prevention of strokes

Treatment is aimed at preventing strokes; antiplatelet drugs are used (see p. 1651). Carotid endarterectomy or arterial angioplasty plus stenting can be useful for some patients, particularly those who have no neurologic deficits but who are at high risk of stroke. Warfarin is indicated if cardiac sources of emboli are present. Modifying stroke risk factors, when possible, may prevent stroke.

Intracerebral Hemorrhage

Intracerebral hemorrhage is focal bleeding from a blood vessel in the brain parenchyma. The cause is usually hypertension. Typical symptoms include focal neurologic deficits, often with abrupt onset of headache, nausea, and impairment of consciousness. Diagnosis is by CT or MRI. Treatment includes BP control, supportive measures, and, for some patients, surgical evacuation.
Most intracerebral hemorrhages occur in the basal ganglia, cerebral lobes, cerebellum, or pons. Intracerebral hemorrhage may also occur in other parts of the brain stem or in the midbrain.

**Etiology**

Intracerebral hemorrhage usually results from rupture of an arteriosclerotic small artery that has been weakened, primarily by chronic arterial hypertension. Such hemorrhages are usually large, single, and catastrophic. Use of cocaine or, occasionally, other sympathomimetic drugs can cause transient severe hypertension leading to hemorrhage. Less often, intracerebral hemorrhage results from congenital aneurysm, arteriovenous or other vascular malformation (see Sidebar 173-1), trauma (see p. 3220), mycotic aneurysm, brain infarct (hemorrhagic infarction), primary or metastatic brain tumor, excessive anticoagulation, blood dyscrasia, or a bleeding or vasculitic disorder.

Lobar intracerebral hemorrhages (hematomas in the cerebral lobes, outside the basal ganglia) usually result from angiopathy due to amyloid deposition in cerebral arteries (cerebral amyloid angiopathy), which affects primarily the elderly. Lobar hemorrhages may be multiple and recurrent.

**Pathophysiology**

Blood from an intracerebral hemorrhage accumulates as a mass that can dissect through and compress adjacent brain tissues, causing neuronal dysfunction. Large hematomas increase intracranial pressure. Pressure from supratentorial hematomas and the accompanying edema may cause transtentorial brain herniation (see Fig. 174-1 on p. 1657), compressing the brain stem and often causing secondary hemorrhages in the midbrain and pons. If the hemorrhage ruptures into the ventricular system (intraventricular hemorrhage), blood may cause acute hydrocephalus. Cerebellar hematomas can expand to block the 4th ventricle, also causing acute hydrocephalus, or they can dissect into the brain stem. Cerebellar hematomas that are > 3 cm in diameter may cause midline shift or herniation. Herniation, midbrain or pontine hemorrhage, intraventricular hemorrhage, acute hydrocephalus, or dissection into the brain stem can impair consciousness and cause coma and death.

**Symptoms and Signs**

Symptoms typically begin with sudden headache, often during activity. However, headache may be mild or absent in the elderly. Loss of consciousness is common, often within seconds or a few minutes. Nausea, vomiting, delirium, and focal or generalized seizures are also common. Neurologic deficits are usually sudden and progressive. Large hemorrhages, when located in the hemispheres, cause hemiparesis; when located in the posterior fossa, they cause cerebellar or brain stem deficits (eg, conjugate eye deviation or ophthalmoplegia, stertorous breathing, pinpoint pupils, coma). Large hemorrhages are fatal within a few days in about one half of patients. In survivors, consciousness returns and neurologic deficits gradually diminish to various degrees as the extravasated blood is resorbed. Some patients have surprisingly few neurologic deficits because hemorrhage is less destructive to brain tissue than infarction.

**Sidebar 173-1 Vascular Lesions in the Brain**

Common brain vascular lesions include arteriovenous malformations and aneurysms.

**Arteriovenous malformations (AVMs):** AVMs are tangled, dilated blood vessels in which arteries flow directly into veins. AVMs occur most often at the junction of cerebral arteries, usually within the parenchyma of the frontal-parietal region, frontal lobe, lateral cerebellum, or overlying occipital lobe. AVMs can bleed or directly compress brain tissue; seizures or ischemia may result.

Neuroimaging may detect them incidentally; contrast or noncontrast CT can usually detect AVMs > 1 cm, but the diagnosis is confirmed with MRI. Occasionally, a cranial bruit suggests an AVM. Conventional angiography is required for definitive diagnosis and determination of whether the lesion is operable.

Superficial AVMs > 3 cm in diameter are usually obliterated by a combination of microsurgery,
radiosurgery, and endovascular surgery. AVMs that are deep or < 3 cm in diameter are treated with stereotactic radiosurgery, endovascular therapy (eg, preresection embolization or thrombosis via an intra-arterial catheter), or coagulation with focused proton beams.

**Aneurysms:** Aneurysms are focal dilations in arteries. They occur in about 5% of people. Common contributing factors may include arteriosclerosis, hypertension, and hereditary connective tissue disorders (eg, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, autosomal dominant polycystic kidney syndrome). Occasionally, septic emboli cause mycotic aneurysms. Brain aneurysms are most often < 2.5 cm in diameter and saccular (noncircumferential); sometimes they have one or more small, thin-walled, outpouchings (berry aneurysm). Most aneurysms occur along the middle or anterior cerebral arteries or the communicating branches of the circle of Willis, particularly at arterial bifurcations. Mycotic aneurysms usually develop distal to the first bifurcation of the arterial branches of the circle of Willis.

Many aneurysms are asymptomatic, but a few cause symptoms by compressing adjacent structures. Ocular palsies, diplopia, squint, or orbital pain may indicate pressure on the 3rd, 4th, 5th, or 6th cranial nerves. Visual loss and a bitemporal field defect may indicate pressure on the optic chiasm. Aneurysms may bleed into the subarachnoid space, causing subarachnoid hemorrhage. Aneurysms occasionally cause sentinel (warning) headaches before rupture; subarachnoid bleeding may accompany sentinel headaches. Rupture causes a sudden severe headache called a thunderclap headache.

Neuroimaging may detect aneurysms incidentally.

Diagnosis requires angiography, CT angiography, or magnetic resonance angiography.

If < 7 mm, asymptomatic aneurysms in the anterior circulation rarely rupture and do not warrant the risks of immediate treatment. They can be monitored with serial imaging. If aneurysms are larger, are in the posterior circulation, or cause symptoms due to bleeding or to compression of neural structures, endovascular therapy, if feasible, is required.

Small hemorrhages may cause focal deficits without impairment of consciousness and with minimal or no headache and nausea. Small hemorrhages may mimic ischemic stroke.

**Diagnosis**

- **Neuroimaging**
- **Bedside glucose measurement**

Diagnosis is suggested by sudden onset of headache, focal neurologic deficits, and impaired consciousness, particularly in patients with risk factors. Intracerebral hemorrhage must be distinguished from ischemic stroke, subarachnoid hemorrhage, and other causes of acute neurologic deficits (eg, seizure, hypoglycemia).

Immediate CT or MRI and bedside blood glucose measurement are necessary. Neuroimaging is usually diagnostic. If neuroimaging shows no hemorrhage but subarachnoid hemorrhage is suspected clinically, lumbar puncture is necessary.

**Treatment**

- **Supportive measures**
- **Sometimes surgical evacuation (eg, for many cerebellar hematomas > 3 cm)**

Treatment includes supportive measures and control of general medical risk factors. Anticoagulants and antiplatelet drugs are contraindicated. If patients have used anticoagulants, the effects are reversed when possible by giving fresh frozen plasma, vitamin K, or platelet transfusions as indicated. Hypertension should be treated only if mean arterial pressure is > 130 mm Hg or systolic BP is > 185 mm Hg.
Nicardipine 2.5 mg/h IV is given initially; dose is increased by 2.5 mg/h q 5 min to a maximum of 15 mg/h as needed to decrease systolic BP by 10 to 15%.

Cerebellar hemisphere hematomas that are > 3 cm in diameter may cause midline shift or herniation, so surgical evacuation is often lifesaving. Early evacuation of large lobar cerebral hematomas may also be lifesaving, but rebleeding occurs frequently, sometimes increasing neurologic deficits. Early evacuation of deep cerebral hematomas is seldom indicated because surgical mortality is high and neurologic deficits are usually severe.

**Subarachnoid Hemorrhage**

Subarachnoid hemorrhage is sudden bleeding into the subarachnoid space. The most common cause of spontaneous bleeding is a ruptured aneurysm. Symptoms include sudden, severe headache, usually with loss or impairment of consciousness. Secondary vasospasm (causing focal brain ischemia), meningismus, and hydrocephalus (causing persistent headache and obtundation) are common. Diagnosis is by CT or MRI; if neuroimaging is normal, diagnosis is by CSF analysis. Treatment is with supportive measures and neurosurgery or endovascular measures, preferably in a referral center.

**Etiology**

Subarachnoid hemorrhage is bleeding between the arachnoid and pia mater. In general, head trauma is the most common cause, but traumatic subarachnoid hemorrhage is usually considered a separate disorder (see p. 3218). Spontaneous (primary) subarachnoid hemorrhage usually results from ruptured aneurysms. A congenital intracranial saccular or berry aneurysm is the cause in about 85% of patients. Bleeding may stop spontaneously. Aneurysmal hemorrhage may occur at any age but is most common from age 40 to 65. Less common causes are mycotic aneurysms, arteriovenous malformations, and bleeding disorders.

**Pathophysiology**

Blood in the subarachnoid space causes a chemical meningitis that commonly increases intracranial pressure for days or a few weeks. Secondary vasospasm may cause focal brain ischemia; about 25% of patients develop signs of a transient ischemic attack (TIA) or ischemic stroke. Brain edema is maximal and risk of vasospasm and subsequent infarction (called angry brain) is highest between 72 h and 10 days. Secondary acute hydrocephalus is also common. A 2nd rupture (rebleeding) sometimes occurs, most often within about 7 days.

**Symptoms and Signs**

Headache is usually severe, peaking within seconds. Loss of consciousness may follow, usually immediately but sometimes not for several hours. Severe neurologic deficits may develop and become irreversible within minutes or a few hours. Sensorium may be impaired, and patients may become restless. Seizures are possible. Usually, the neck is not stiff initially unless the cerebellar tonsils herniate. However, within 24 h, chemical meningitis causes moderate to marked meningismus, vomiting, and sometimes bilateral extensor plantar responses. Heart or respiratory rate is often abnormal. Fever, continued headaches, and confusion are common during the first 5 to 10 days. Secondary hydrocephalus may cause headache, obtundation, and motor deficits that persist for weeks. Rebleeding may cause recurrent or new symptoms.

**Diagnosis**

- Usually noncontrast CT and, if negative, lumbar puncture

Diagnosis is suggested by characteristic symptoms. Testing should proceed as rapidly as possible, before damage becomes irreversible. Noncontrast CT is > 90% sensitive. MRI is comparably sensitive but less likely to be immediately available. False-negative results occur if volume of blood is small. If subarachnoid hemorrhage is suspected clinically but not identified on neuroimaging or if neuroimaging is not
immediately available, lumbar puncture is done. Lumbar puncture is contraindicated if increased intracranial pressure is suspected because the sudden decrease in CSF pressure may lessen the tamponade of a clot on the ruptured aneurysm, causing further bleeding.

CSF findings suggesting subarachnoid hemorrhage include numerous RBCs, xanthochromia, and increased pressure. RBCs in CSF may also be caused by traumatic lumbar puncture. Traumatic lumbar puncture is suspected if the RBC count decreases in tubes of CSF drawn sequentially during the same lumbar puncture. About 6 h or more after a subarachnoid hemorrhage, RBCs become crenated and lyse, resulting in a xanthochromic CSF supernatant and visible crenated RBCs (noted during microscopic CSF examination); these findings usually indicate that subarachnoid hemorrhage preceded the lumbar puncture. If there is still doubt, hemorrhage should be assumed, or the lumbar puncture should be repeated in 8 to 12 h.

In patients with subarachnoid hemorrhage, conventional cerebral angiography is done as soon as possible after the initial bleeding episode; alternatives include magnetic resonance angiography and CT angiography. All 4 arteries (2 carotid and 2 vertebral arteries) should be injected because up to 20% of patients (mostly women) have multiple aneurysms.

On ECG, subarachnoid hemorrhage may cause ST-segment elevation or depression. It can cause syncope, mimicking MI. Other possible ECG abnormalities include prolongation of the QRS or QT intervals and peaking or deep, symmetric inversion of T waves.

**Prognosis**

About 35% of patients die after the first aneurysmal subarachnoid hemorrhage; another 15% die within a few weeks because of a subsequent rupture. After 6 mo, a 2nd rupture occurs at a rate of about 3%/yr. In general, prognosis is grave with an aneurysm, better with an arteriovenous malformation, and best when 4-vessel angiography does not detect a lesion, presumably because the bleeding source is small and has sealed itself. Among survivors, neurologic damage is common, even when treatment is optimal.

**Treatment**

- Treatment in referral center
- Nicardipine if mean arterial pressure is > 130 mm Hg
- Nimodipine to prevent vasospasm
- Occlusion of causative aneurysms

Patients with subarachnoid hemorrhage should be treated in referral centers whenever possible.

**Hypertension** should be treated only if mean arterial pressure is > 130 mm Hg; euvolemia is maintained, and IV nicardipine is titrated as for intracerebral hemorrhage (see p. 1652). Bed rest is mandatory. Restlessness and headache are treated symptomatically. Stool softeners are given to prevent constipation, which can lead to straining. Anticoagulants and antiplatelet drugs are contraindicated.

**Vasospasm** is prevented by giving nimodipine 60 mg po q 4 h for 21 days to prevent vasospasm, but BP needs to be maintained in the desirable range (usually considered to be a mean arterial pressure of 70 to 130 mm Hg and a systolic pressure of 120 to 185 mm Hg). If clinical signs of acute hydrocephalus occur, ventricular drainage should be considered.

**Aneurysms** are occluded to reduce risk of rebleeding. Detachable endovascular coils can be inserted during angiography to occlude the aneurysm. Alternatively, if the aneurysm is accessible, surgery to clip the aneurysm or bypass its blood flow can be done, especially for patients with an evacuable hematoma or acute hydrocephalus. If patients are arousable, most vascular neurosurgeons operate within the first 24 h to minimize risk of rebleeding and risks due to angry brain. If > 24 h have elapsed, some neurosurgeons delay surgery until 10 days have passed; this approach decreases risks due to angry
brain but increases risk of rebleeding and overall mortality.
Chapter 174. Coma and Impaired Consciousness

Introduction

Coma is unresponsiveness from which the patient cannot be aroused. Similar, but less severe disturbances of consciousness may also occur. The mechanism involves dysfunction of both cerebral hemispheres or of the reticular activating system (also known as the ascending arousal system). Causes may be structural or nonstructural (eg, toxic or metabolic disturbances). Damage may be focal or diffuse. Diagnosis is clinical; identification of cause usually requires laboratory tests and neuroimaging. Treatment is immediate stabilization and specific management of the cause. For long-term coma, adjunctive treatment includes passive range-of-motion exercises, enteral feedings, and measures to prevent pressure ulcers.

Decreased or impaired consciousness or alertness refers to decreased responsiveness to external stimuli. Severe impairment includes

• **Coma**: The patient usually cannot be aroused, and the eyes do not open in response to any stimulation.

• **Stupor**: The patient can be awakened only by vigorous physical stimulation.

Less severely impaired levels of consciousness are often labeled as lethargy or, if more severe, obtundation. However, differentiation between less severely impaired levels is often imprecise; the label is less important than a precise clinical description (eg, “the best level of response is partial limb withdrawal to nail bed pressure”). Delirium differs because cognitive disturbances (in attention, cognition, and level of consciousness) fluctuate more; also, delirium is usually reversible (see p. 1669).

Pathophysiology

Maintaining alertness requires intact function of the cerebral hemispheres and preservation of arousal mechanisms in the reticular activating system (RAS—also known as the ascending arousal system)—an extensive network of nuclei and interconnecting fibers in the upper pons, midbrain, and posterior diencephalon. Therefore, the mechanism of impaired consciousness must involve both cerebral hemispheres or dysfunction of the RAS.

To impair consciousness, cerebral dysfunction must be bilateral; unilateral cerebral hemisphere disorders are not sufficient, although they may cause severe neurologic deficits. However, rarely, a unilateral massive hemispheric focal lesion (eg, left middle cerebral artery stroke) impairs consciousness if the contralateral hemisphere is already compromised.

Usually, RAS dysfunction results from a condition that has diffuse effects, such as toxic or metabolic disturbances (eg, hypoglycemia, hypoxia, uremia, drug overdose). RAS dysfunction can also be caused by focal ischemia (eg, certain upper brain stem infarcts), hemorrhage, or direct, mechanical disruption.

Any condition that increases intracranial pressure may decrease cerebral perfusion pressure, resulting in secondary brain ischemia. Secondary brain ischemia may affect the RAS or both cerebral hemispheres, impairing consciousness.

When brain damage is extensive, brain herniation (see Fig. 174-1 and Table 174-1) contributes to neurologic deterioration because it directly compresses brain tissue, increases intracranial pressure, and may lead to hydrocephalus.

Impaired consciousness may progress to coma and ultimately to brain death (see p. 1667).

Etiology

Coma or impaired consciousness may result from structural disorders, which typically cause focal
damage, or nonstructural disorders, which typically cause diffuse damage (see Table 174-2). But causes are usually thought of as structural or diffuse.

Psychiatric disorders (eg, psychogenic unresponsiveness) can mimic impaired consciousness but are usually distinguished from true impaired consciousness by neurologic examination.

**Symptoms and Signs**

Consciousness is decreased to varying degrees. Repeated stimuli arouse patients only briefly or not at all.

Depending on the cause, other symptoms develop (see Table 174-3):

- **Eye abnormalities:** Pupils may be dilated, pinpoint, or unequal. One or both pupils may be fixed in midposition. Eye movement may be dysconjugate or absent (oculomotor paresis). Homonymous hemianopia may be present. Other abnormalities include absence of blinking in response to visual threat (almost touching the eye), as well as loss of the oculocephalic reflex (the eyes do not move in response to head rotation), the oculovestibular reflex (the eyes do not move in response to caloric stimulation), and corneal reflexes.

- **Autonomic dysfunction:** Patients may have abnormal breathing patterns (Cheyne-Stokes or Biot's respirations) or hypertension with bradycardia (Cushing's reflex). Abrupt respiratory and cardiac arrest may occur.

- **Motor dysfunction:** Abnormalities include flaccidity, hemiparesis, asterixis, multifocal myoclonus, decorticate posturing (elbow flexion and shoulder adduction with leg extension), and decerebrate posturing (limb extension and internal shoulder rotation).

- **Other symptoms:** If the brain stem is compromised, nausea, vomiting, meningismus, occipital headache, ataxia, and increasing somnolence can occur.

**Diagnosis**

- **History**
- **General physical examination**
- **Neurologic examination, including eye examination**
- **Laboratory tests (eg, pulse oximetry, bedside glucose measurement, blood and urine tests)**
- **Immediate neuroimaging**
- **Sometimes measurement of intracranial pressure**
- **If diagnosis is unclear, lumbar puncture or EEG**

Impaired consciousness is diagnosed if repeated stimuli arouse patients only briefly or not at all. If stimulation triggers primitive reflex movements (eg, decerebrate or decorticate posturing), impaired consciousness may be deepening into coma.
Diagnosis and initial stabilization (airway, breathing, and circulation) should occur simultaneously.

[Table 174-2. Common Causes of Coma or Impaired Consciousness]

[Table 174-3. Findings by Location*]

Glucose levels must be measured at bedside to identify low levels, which should be corrected immediately. If trauma is involved, the neck is immobilized until clinical history, physical examination, or imaging tests exclude an unstable injury and damage to the cervical spine.

**History:** Medical identification bracelets or the contents of a wallet or purse may provide clues (eg, hospital identification card, drugs). Relatives, paramedics, and police officers should be questioned about the environment in which the patient was found; containers that may have held food, alcohol, drugs, or poisons should be examined and saved for identification (eg, drug identification aided by a poison center) and possible chemical analysis. Relatives should be asked about the onset of the problem (eg, whether seizure, headache, vomiting, head trauma, or drug ingestion was observed), baseline mental status, recent infections, psychiatric problems and symptoms, drug history, substance use, previous illnesses, the last time the patient was normal, and any hunches they may have about what might be the cause (eg, possible occult overdose, possible occult head trauma due to recent intoxication). Medical records should be reviewed if available.

**General physical examination:** Physical examination should be focused and efficient and should include thorough examination of the head and face, skin, and extremities. Signs of head trauma include periorbital ecchymosis (raccoon eyes), ecchymosis behind the ear (Battle's sign), hemotympanum, instability of the maxilla, and CSF rhinorrhea and otorrhea. Scalp contusions and small bullet holes can be missed unless the head is carefully inspected. If unstable injury and cervical spine damage have been excluded, passive neck flexion is done; stiffness suggests subarachnoid hemorrhage or meningitis.

Fever, petechial or purpuric rash, hypotension, or severe extremity infections (eg, gangrene of one or more toes) may suggest sepsis or CNS infection. Needle marks may suggest drug overdose (eg, of opioids or insulin). A bitten tongue suggests seizure. Breath odor may suggest alcohol, other drug intoxication, or diabetic ketoacidosis.

**Neurologic examination:** The neurologic examination determines whether the brain stem is intact and where the lesion is located within the CNS (see p. 1587). The examination focuses on the following:

- Level of consciousness
- Eyes (see p. 1661)
- Motor function
- Deep tendon reflexes

Level of consciousness is evaluated by attempting to wake patients first with verbal commands, then with non-noxious stimuli, and finally with noxious stimuli (eg, pressure to the supraorbital ridge, nail bed, or sternum). The Glasgow Coma Scale (see Table 174-4) was developed to assess patients with head trauma. For head trauma, the score assigned by the scale is valuable prognostically. For coma or impaired consciousness of any cause, the scale is used because it is a relatively reliable, objective measure of the severity of unresponsiveness and can be used serially for monitoring. The scale assigns points based on responses to stimuli. Eye opening, facial grimacing, and purposeful withdrawal of limbs from a noxious stimulus indicate that consciousness is not greatly impaired. Asymmetric motor responses to pain or deep tendon reflexes may indicate a focal hemispheric lesion.

As impaired consciousness deepens into coma, noxious stimuli may trigger stereotypic reflex posturing. Decorticate posturing indicates hemispheric damage with preservation of motor centers in the upper
portion of the brain stem (eg, rubrospinal tract). Decerebrate posturing indicates that the upper brain stem motor centers, which facilitate flexion, have been damaged and that only the lower brain stem centers (eg, vestibulospinal tract, reticulospinal tract), which facilitate extension, are responding to sensory stimuli. Flaccidity without movement indicates that the lower brain stem is not affecting movement, regardless of whether the spinal cord is damaged. It is the worst possible motor response.

Asterixis and multifocal myoclonus suggest metabolic disorders such as uremia, hepatic encephalopathy, hypoxic encephalopathy, and drug toxicity.

Psychogenic unresponsiveness can be differentiated because, although voluntary motor response is typically absent, muscle tone and deep tendon reflexes remain normal, and all brain stem reflexes are preserved.

**Eye examination:** The following are evaluated:

- Pupillary responses
- Extraocular movements
- Fundi
- Other neuro-ophthalmic reflexes

Pupillary responses and extraocular movements provide information about brain stem function (see [Table 174-5](#)). One or both pupils usually become fixed early in coma due to structural lesions, but pupillary responses are often preserved until very late when coma is due to diffuse metabolic disorders (called toxic-metabolic encephalopathy), although responses may be sluggish.

[Table 174-4. Glasgow Coma Scale*]

The fundi should be examined for papilledema, hemorrhages, and exudates. Papilledema or hemorrhages may indicate increased intracranial pressure (ICP). Subhyaloid hemorrhage may indicate subarachnoid hemorrhage.

In an unresponsive patient, the oculocephalic reflex is tested by the doll's-eye maneuver: The eyes are observed while the head is passively rotated from side to side or flexed and extended. *This maneuver should not be attempted if cervical spine instability is suspected.*

[Table 174-5. Interpretation of Pupillary Response and Eye Movements]

- If the reflex is present, the maneuver causes the eyes to move in the opposite direction of head rotation, flexion, or extension, indicating that the oculovestibular pathways in the brain stem are intact. Thus, in a supine patient, the eyes continue to look straight up when the head is moved.

- If the reflex is absent, the eyes do not move and thus point in whatever direction the head is turned, indicating the oculovestibular pathways are disrupted. The reflex is also absent in most patients with psychogenic unresponsiveness.

If the patient is unconscious and the oculocephalic reflex is absent or the neck is immobilized, oculocephalic (cold caloric) testing is done. After integrity of the tympanic membrane is confirmed, the patient's head is elevated 30°, and with a syringe connected to a flexible catheter, the examiner irrigates the external auditory canal with 50 mL of ice water over a 30-sec period.

- If both eyes deviate toward the irrigated ear, the brain stem is functioning normally, suggesting mildly impaired consciousness.

- If nystagmus away from the irrigated ear also occurs, the patient is conscious and psychogenic unresponsiveness is likely. In conscious patients, 1 mL of ice water is often enough to induce ocular
deviation and nystagmus. Thus, if psychogenic unresponsiveness is suspected, a small amount of water should be used because cold caloric testing can induce severe vertigo, nausea, and vomiting in conscious patients.

• If the eyes do not move or movement is dysconjugate after irrigation, the integrity of the brain stem is uncertain and the coma is deeper. Prognosis may be less favorable.

Certain patterns of eye abnormalities and other findings may suggest brain herniation (see Fig. 174-1 and Table 174-1).

Respiratory patterns: The spontaneous respiratory rate and pattern should be documented unless emergency airway intervention is required. It may suggest a cause.

• Periodic cycling of breathing (Cheyne-Stokes or Biot's respirations—see p. 1827) may indicate dysfunction of both hemispheres or of the diencephalon.

• Hyperventilation (central neurogenic hyperventilation) with respiratory rates of > 40 breaths/min may indicate midbrain or upper pontine dysfunction.

• An inspiratory gasp with respiratory pauses of about 3 sec after full inspiration (apneustic breathing) typically indicates pontine or medullary lesions; this type of breathing often progresses to respiratory arrest.

Tests: Initially, pulse oximetry, fingerstick plasma glucose measurements, and cardiac monitoring are done. Blood tests should include a comprehensive metabolic panel (including at least serum electrolytes, BUN, creatinine, and Ca levels), CBC with differential and platelets, liver function tests, and ammonia level. ABGs are measured, and if carbon monoxide toxicity is suspected, carboxyhemoglobin level is measured. Blood and urine should be obtained for culture and routine toxicology screening; serum ethanol level is also measured. Additional toxicology tests (eg, additional toxicology screening, serum drug levels) are done based on clinical suspicion. ECG (12-lead) should be done.

If the cause is not immediately apparent, noncontrast head CT should be done as soon as possible to check for masses, hemorrhage, edema, and hydrocephalus. MRI can be done instead if immediately available. Contrast CT can be done if noncontrast CT is not diagnostic. MRI or contrast CT may detect isodense subdural hematomas, multiple metastases, sagittal sinus thrombosis, herpes encephalitis, or other causes missed by noncontrast CT. Chest x-ray should also be taken.

If coma is unexplained after neuroimaging and other tests, lumbar puncture is done to check opening pressure and exclude infection, subarachnoid hemorrhage, and other abnormalities. CSF analysis includes cell and differential counts, protein, glucose, Gram stain, cultures, and sometimes, based on clinical suspicion, specific tests (eg, cryptococcal antigen, Venereal Disease Research Laboratory [VDRL] tests, PCR for herpes simplex, visual or spectrophotometric determination of xanthochromia). In unconscious patients with or without focal neurologic deficits, cranial CT or MRI should be done before lumbar puncture to exclude an intracranial mass and obstructive hydrocephalus because if either is present, suddenly lowering CSF pressure by lumbar puncture could trigger brain herniation.

If increased ICP is suspected, pressure is measured. Hyperventilation should be considered under the care of an ICU specialist. Hyperventilation produces hypocapnia, which in turn decreases cerebral blood flow globally through vasoconstriction. Reduction in PCO₂ from 40 mm Hg to 30 mm Hg can reduce ICP about 30%. It is recommended to maintain PCO₂ at 25 mm Hg to 30 mm Hg as required with the initiation of other treatment modalities, but aggressive hypoventilation < 25 mm Hg should be avoided since this may reduce cerebral blood flow excessively and result in cerebral ischemia.

If pressure is increased, it is monitored continuously (see p. 2246). If diagnosis remains uncertain, EEG may be done. In most comatose patients, EEG shows slowing and reductions in wave amplitude that are nonspecific but often occur in toxic-metabolic encephalopathy. However, in the rare patient with nonconvulsive status epilepticus, EEG shows spikes, sharp waves, or
Prognosis

Prognosis depends on the cause, duration, and depth of the impairment of consciousness. Prognosis is usually considered poor. However, if unresponsiveness lasts < 6 h, prognosis is more favorable.

After trauma, a Glasgow Coma Scale score of 3 to 5 may indicate fatal brain damage, especially if pupils are fixed or oculovestibular reflexes are absent. If pupils are unreactive or the motor response to noxious stimuli is absent or is only a reflex response 3 days after cardiac arrest, patients have virtually no chance of a good neurologic recovery. After coma, the early return of speech (even if incomprehensible), spontaneous eye movements, or ability to follow commands is a favorable prognostic sign. If the cause is a reversible condition (eg, sedative overdose, some metabolic disorders such as uremia), patients may lose all brain stem reflexes and all motor response and yet recover fully.

Treatment

- Immediate stabilization (airway, breathing, circulation)
- Supportive measures, including, when necessary, control of ICP
- Admission to an ICU
- Treatment of underlying disorder

Airway, breathing, and circulation must be ensured immediately. Hypotension must be corrected (see p. 2297). Patients are admitted to the ICU so that respiratory and neurologic status can be monitored.

Because some patients in coma are undernourished and susceptible to Wernicke encephalopathy, thiamin 100 mg IV or IM should be given routinely. If plasma glucose is low, patients should be given 50 mL of 50% dextrose. If opioid overdose is suspected, naloxone 2 mg IV is given. If trauma is involved, the neck is immobilized until damage to the cervical spine is ruled out.

Endotracheal intubation: Patients with infrequent, shallow, or stertorous respirations, low O₂ saturation (determined by pulse oximetry or ABG measurements), impaired airway reflexes, or severe unresponsiveness (including most patients with a Glasgow Coma Scale score ≤ 8) require endotracheal intubation to prevent aspiration and ensure adequate ventilation. If increased ICP is suspected, intubation should be done via rapid sequence oral intubation (using a paralytic drug) rather than via nasotracheal intubation (see Ch. 225); nasotracheal intubation in a patient who is breathing spontaneously causes more coughing and gagging, thus increasing ICP, which is already increased because of intracranial abnormalities.

To minimize the increase in ICP that may occur when the airway is manipulated, some clinicians recommend giving lidocaine 1.5 mg/kg IV 1 to 2 min before giving the paralytic. Patients are sedated before the paralytic is given. Etomidate is a good choice in hypotensive or trauma patients because it has minimal effects on BP; IV dose is 0.3 mg/kg for adults (or 20 mg for an average-sized adult) and 0.2 to 0.3 mg/kg for children. Alternatively, if hypotension is absent and unlikely and if propofol is readily available, propofol 0.2 to 1.5 mg/kg may be used. Succinylcholine 1.5 mg/kg IV is typically used as a paralytic. However, use of paralytics is minimized and, whenever possible, avoided because they can mask neurologic findings and changes.

Pulse oximetry and ABGs (if possible, end-tidal CO₂) should be used to assess adequacy of oxygenation and ventilation.

ICP control: If ICP is increased, intracranial and cerebral perfusion pressure should be monitored (see p. 2246), and pressures should be controlled. The goal is to maintain ICP at ≤ 20 mm Hg and cerebral perfusion pressure at 50 to 70 mm Hg. Cerebral venous drainage can be enhanced (thus lowering ICP) by elevating the head of the bed to 30° and by keeping the patient's head in a midline position.
Control of increased ICP involves several strategies:

- **Sedation:** Sedatives may be necessary to control agitation, excessive muscular activity (e.g., due to delirium), or pain, which can increase ICP. Propofol is often used in adults (contraindicated in children) because onset and duration of action are quick; dose is 0.3 mg/kg/h by continuous IV infusion, titrated gradually up to 3 mg/kg/h as needed. An initial bolus is not used. The most common adverse effect is hypotension. Prolonged use at high doses can cause pancreatitis. Benzodiazepines (e.g., midazolam, lorazepam) can also be used. Because sedatives can mask neurologic findings and changes, their use should be minimized and, whenever possible, avoided. Antipsychotics should be avoided if possible because they can delay recovery.

- **Hyperventilation:** Hyperventilation causes hypocapnia, which causes vasoconstriction, thus decreasing cerebral blood flow globally. Reduction in PCO\(_2\) from 40 to 30 mm Hg can reduce ICP about 30%. Hyperventilation that reduces PCO\(_2\) to 28 to 33 mm Hg decreases ICP for only about 30 min and is used by some clinicians as a temporary measure until other treatments take effect. Aggressive hypoventilation to < 25 mm Hg should be avoided because it may reduce cerebral blood flow excessively and result in cerebral ischemia. Other measures may be used to control increased ICP (see p. 3225).

- **Hydration:** Isotonic fluids are used. Providing free water through IV fluids (e.g., 5% dextrose, 0.45% saline) can aggravate cerebral edema and should be avoided. Fluids may be restricted to some degree, but patients should be kept euovolemic. If patients have no signs of dehydration or fluid overload, IV fluids with normal saline can be started at 50 to 75 mL/h. The rate can be increased or decreased based on serum Na, osmolality, urine output, and signs of fluid retention (e.g., edema).

- **Diuretics:** Serum osmolality should be kept at 295 to 320 mOsm/kg. Osmotic diuretics (e.g., mannitol) may be given IV to lower ICP and maintain serum osmolality. They do not cross the blood–brain barrier. They pull water from brain tissue across an osmotic gradient into plasma, eventually leading to equilibrium. Effectiveness of these drugs decreases after a few hours. Thus, they should be reserved for patients whose condition is deteriorating or used preoperatively for patients with hematomas. Mannitol 20% solution is given 0.5 to 1 g/kg IV (2.5 to 5 mL/kg) over 15 to 30 min, then given as often as needed (usually q 6 to 8 h) in a dose ranging from 0.25 to 0.5 g/kg (1.25 to 2.5 mL/kg). Mannitol must be used cautiously in patients with severe coronary artery disease, heart failure, renal insufficiency, or pulmonary vascular congestion because mannitol rapidly expands intravascular volume. Because osmotic diuretics increase renal excretion of water relative to Na, prolonged use of mannitol may result in water depletion and hyponatremia. Furosemide 1 mg/kg IV can decrease total body water, particularly when transient hypervolemia associated with mannitol is to be avoided. Fluid and electrolyte balance should be monitored closely while osmotic diuretics are used. A 3% saline solution is being studied as another potential osmotic agent to control ICP.

- **BP control:** Systemic antihypertensives are needed only when hypertension is severe (> 180/95 mm Hg). How much BP is reduced depends on the clinical context. Systemic BP needs to be high enough to maintain cerebral perfusion pressure even when ICP increases. Hypertension can be managed by titrating a nicardipine drip (5 mg/h, increased by 2.5 mg q 5 min to a maximum of 15 mg/h) or by boluses of labetalol (10 mg IV over 1 to 2 min, repeated q 10 min to a maximum of 150 mg).

- **Corticosteroids:** These drugs are usually helpful for patients with a brain tumor or brain abscess, but they are ineffective for patients with head trauma, cerebral hemorrhage, ischemic stroke, or hypoxic brain damage after cardiac arrest. Corticosteroids increase plasma glucose; this increase may worsen the effects of cerebral ischemia. After an initial dose of dexamethasone 20 to 100 mg, 4 mg once/day appears to be effective while minimizing adverse effects.

If ICP continues to increase despite other measures to control it, the following may be used:

- **Pentobarbital coma:** Pentobarbital can reduce cerebral blood flow and metabolic demands. However, its use is controversial because the effect on clinical outcome is not consistently beneficial. Coma is induced by giving pentobarbital 10 mg/kg IV over 30 min, followed by 5 mg/kg/h for 3 h, then 1 mg/kg/h.
The dose may be adjusted to suppress bursts of EEG activity, which is continuously monitored.
Hypotension is common and is managed by giving fluids and, if necessary, vasopressors. Other
possible adverse effects include arrhythmias, myocardial depression, and impaired uptake or release of
 glutamate.

**Decompressive craniotomy:** Craniotomy with duraplasty can be done to provide room for brain
swelling. This procedure can prevent deaths, but overall functional outcome may not improve much. It
may be most useful for large cerebral infarcts with impending herniation, particularly in patients < 50.

**Long-term care:** Patients require meticulous long-term care. Stimulants and opioids should be avoided.
Enteral feeding is started with precautions to prevent aspiration (eg, elevation of the head of the bed); a
percutaneous endoscopic jejunostomy tube is placed if necessary. Early, vigilant attention to skin care,
including checking for breakdown especially at pressure points, is required to prevent pressure ulcers.
Topical ointments to prevent desiccation of the eyes are beneficial. Passive range-of-motion exercises
done by physical therapists and taping or dynamic flexion splitting of the extremities may prevent
contractures. Measures are also taken to prevent UTIs and deep venous thrombosis.

**Vegetative State**

A vegetative state is absence of responsiveness and awareness due to overwhelming
dysfunction of the cerebral hemispheres, with sufficient sparing of the diencephalon and brain
stem to preserve autonomic and motor reflexes and sleep-wake cycles. Patients may have
complex reflexes, including eye movements, yawning, and involuntary movements to noxious
stimuli but show no awareness of self or environment. Diagnosis is clinical. Treatment is
supportive. Prognosis with persistent deficits is bleak, and withdrawal of care should be
discussed with family members.

The vegetative state is a chronic condition that preserves the ability to maintain BP, respiration, and
cardiac function, but not cognitive function. Although medullary brainstem functions remain intact to
support cardiorespiratory functions, the presence of midbrain or pontine reflexes may be variable.

A vegetative state occurs when the reticular activating system (RAS) remains functional (making
wakefulness possible), but the cortex is severely damaged (eliminating cognitive function). The patient
has no awareness of self and interacts with the environment only via reflexes. Hypothalamic and brain
stem autonomic function are preserved and sufficient for survival if medical and nursing care is adequate.
A vegetative state is considered persistent if it lasts > 1 mo.

The most common causes are traumatic brain injury and diffuse cerebral hypoxia. However, any disorder
that results in brain damage can cause a vegetative state. Typically, a vegetative state occurs because
the function of the brain stem and diencephalon resumes after coma, but cortical function does not.

**Symptoms and Signs**

Patients show no evidence of awareness of self or environment and cannot interact with other people.
Purposeful responses to external stimuli are absent, as are language comprehension and expression.

Signs of an intact reticular formation (eg, eye opening) and an intact brain stem (eg, reactive pupils,
oculocephalic reflex) are present. Sleep-wake cycles occur but do not necessarily reflect a specific
circadian rhythm and are not associated with the environment. More complex brain stem reflexes,
including yawning, chewing, swallowing, and, uncommonly, guttural vocalizations, are also present.
Arousal and startle reflexes may be preserved; eg, loud sounds or blinking with bright lights may elicit eye
opening. Eyes may water and produce tears. Patients may appear to smile or frown. Spontaneous roving
eye movements—usually slow, of constant velocity, and without saccadic jerks—may be misinterpreted as
volitional tracking and can be misinterpreted by family members as evidence of awareness.

Patients cannot react to visual threat and cannot follow commands. The limbs may move, but the only
purposeful motor responses that occur are primitive (eg, grasping an object that contacts the hand). Pain
usually elicits a motor response (typically decorticate or decerebrate posturing) but no purposeful
avoidance. Patients have fecal and urinary incontinence. Cranial nerve and spinal reflexes are typically preserved.

**Diagnosis**

- Clinical criteria after sufficient observation
- Sometimes functional brain imaging

A vegetative state is suggested by characteristic findings (eg, no purposeful activity or comprehension) plus signs of an intact reticular formation. Diagnosis is based on clinical criteria. However, neuroimaging is indicated to rule out treatable disorders.

The vegetative state must be distinguished from the minimally conscious state, which results from less severe but sometimes widespread cerebral damage. Fragments of awareness may be observed in patients in a minimally conscious state; they may reach for objects or visually fixate or speak a word or gesture in response to a command. Both states can be permanent or temporary, and the physical examination may not reliably distinguish one from the other. Sufficient observation is needed. If observation is too brief, evidence of awareness may be overlooked, resulting in a false-positive diagnosis.

CT or MRI can differentiate an ischemic infarct, an intracerebral hemorrhage, and a mass lesion involving the cortex or the brainstem. MR angiography can be used to visualize the cerebral vasculature following the exclusion of a cerebral hemorrhage. Additionally, diffusion-weighted MRI is becoming the desired imaging modality to follow ongoing ischemic changes in the brain. PET and SPECT provide an alternative method of imaging that assesses cerebral function rather than brain anatomy. If the diagnosis of persistent vegetative state is in doubt, PET or SPECT should be done. EEG is useful in assessing cortical dysfunction and identifying the presence of occult seizure activity.

**Prognosis**

Prognosis varies somewhat by cause and duration of the vegetative state. Prognosis may be better if the cause is a reversible metabolic condition (eg, toxic encephalopathy) than if the cause is neuronal death due to extensive hypoxia and ischemia or another injury. Also, younger patients may recover more motor function than older patients but not more cognition, behavior, or speech.

Recovery from a vegetative state is unlikely after 1 mo if brain damage is nontraumatic and after 12 mo if brain damage is traumatic. Even if some recovery occurs after these intervals, most patients are severely disabled. Rarely, improvement occurs late; after 5 yr, about 3% of patients recover the ability to communicate and comprehend, but even fewer can live independently; no patients regain normal function.

Most patients in a persistent vegetative state die within 6 mo of the original brain damage. The cause is usually pulmonary infection, UTI, or multiple organ failure, or death may be sudden and of unknown cause. For most of the rest, life expectancy is about 2 to 5 yr; a few patients live for decades.

**Treatment**

- Supportive care

There is no specific treatment, but supportive care should include the following:

- Preventing systemic complications due to immobilization (eg, pneumonia, UTI, thromboembolic disease)
- Providing good nutrition
- Preventing pressure ulcers
• Providing physical therapy to prevent limb contractures

Decisions about life-sustaining care should involve social services, the hospital ethics committee, and family members. Maintaining patients, especially those without advanced directives to guide decisions about terminating treatment (see p. 3471), in a prolonged vegetative state raises ethical and other (eg, resource utilization) questions.

**Locked-In Syndrome**

Locked-in syndrome is a state of wakefulness and awareness with quadriplegia and paralysis of the lower cranial nerves, resulting in inability to show facial expression, move, speak, or communicate, except by coded eye movements.

Locked-in syndrome typically results from a pontine hemorrhage or infarct that causes quadriplegia and disrupts and damages the lower cranial nerves and the centers that control horizontal gaze. Other disorders that produce severe widespread motor paralysis (eg, Guillain-Barre syndrome) are a less common cause.

Patients have intact cognitive function and are awake, with eye opening and normal sleepwake cycles. They can hear and see. However, they cannot move their lower face, chew, swallow, speak, breathe, move their limbs, or move their eyes laterally. Vertical eye movement is possible; patients can open and close their eyes or blink a specific number of times to answer questions.

**Diagnosis**

• Clinical evaluation

Diagnosis is primarily clinical. Because patients lack the motor responses (eg, withdrawal from painful stimuli) usually used to measure responsiveness, they may be mistakenly thought to be unconscious. Thus, all patients who cannot move should have their comprehension tested through requesting eye blinking or vertical eye movements.

Tests are chosen for the same indications as persistent vegetative state (see p. 1666). Brain imaging with CT or MRI is done and helps identify the pontine abnormality. PET or SPECT may be done if the diagnosis is in doubt. In patients with locked-in syndrome, EEG shows normal sleep-wake patterns.

**Prognosis**

Prognosis is usually dire. However, locked-in syndrome due to transient ischemia or a small stroke in the vertebrobasilar artery distribution may resolve completely. When the cause is partly reversible (eg, Guillain-Barre syndrome), recovery can occur over months but is seldom complete. Favorable prognostic features include early recovery of lateral eye movements and of evoked potentials in response to magnetic stimulation of the motor cortex. Irreversible or progressive disorders (eg, cancers that involve the posterior fossa and the pons) are usually fatal.

**Treatment**

• Supportive care

There is no specific treatment, but supportive care should include the following:

• Preventing systemic complications due to immobilization (eg, pneumonia, UTI, thromboembolic disease)
• Providing good nutrition
• Preventing pressure ulcers
• Providing physical therapy to prevent limb contractures
Speech therapists may help establish a communication code using eye blinks or movements. Because cognitive function is intact, patients should make their own health care decisions if communication can be established.

**Brain Death**

Brain death is loss of function of the entire cerebrum and brain stem, resulting in coma, no spontaneous respiration, and loss of all brain stem reflexes. Spinal reflexes, including deep tendon, plantar flexion, and withdrawal reflexes, may remain. Recovery does not occur.

The concept of brain death developed because ventilators and drugs can perpetuate cardiopulmonary and other body functions despite complete cessation of all cerebral activity. The concept that brain death (ie, total cessation of integrated brain function, especially that of the brain stem) constitutes a person's death has been accepted legally and culturally in most of the world.

**Diagnosis**

- Serial determination of clinical criteria
- Apnea testing
- Sometimes EEG, brain vascular imaging, or both

For a physician to declare brain death, a known structural or metabolic cause of brain damage must be present, and use of potentially anesthetizing or paralyzing drugs, especially self-administered, must be ruled out. Hypothermia < 32°C must be corrected, and if status epilepticus is suspected, EEG should be done. Sequential testing over 6 to 24 h is necessary (see Table 174-6). Examination includes assessment of pupil reactivity, oculovestibular and oculocephalic reflexes, corneal reflexes, and apnea testing. EEG or tests of brain perfusion may be used to confirm absence of brain activity or brain blood flow and thus provide additional evidence to family members, but these tests are not required.

**Prognosis**

The diagnosis of brain death is equivalent to the person's death. No one who meets criteria for brain death recovers. After brain death is confirmed, all supporting cardiac and respiratory treatments are ended. Cessation of ventilatory support results in terminal arrhythmias. Spinal motor reflexes may occur during terminal apnea; they include arching of the back, neck turning, stiffening of the legs, and upper extremity flexion (the so-called Lazarus sign). Family members who wish to be present when the ventilator is shut off need to be warned of such reflex movements.
Chapter 175. Delirium and Dementia

Introduction

Delirium (sometimes called acute confusional state) and dementia are the most common causes of cognitive impairment, although affective disorders (eg, depression) can also disrupt cognition. Delirium and dementia are separate disorders but are sometimes difficult to distinguish. In both, cognition is disordered; however, dementia affects mainly memory, and delirium affects mainly attention.

Other specific characteristics help distinguish the 2 disorders (see Table 175-1). Delirium is typically caused by acute illness or drug toxicity (sometimes life threatening) and is often reversible. Dementia is typically caused by anatomic changes in the brain, has slower onset, and is generally irreversible. Delirium often develops in patients with dementia. Mistaking delirium for dementia in an elderly patient—a common clinical error—must be avoided, particularly when delirium is superimposed on chronic dementia. No laboratory test can definitively establish the cause of cognitive impairment; a thorough history and physical examination as well as knowledge of baseline function are essential.

Delirium

Delirium is an acute, transient, usually reversible, fluctuating disturbance in attention, cognition, and consciousness level. Causes include almost any disorder, intoxication, or drug. Diagnosis is clinical, with laboratory and usually imaging tests to identify the cause. Treatment is correction of the cause and supportive measures.

Delirium may occur at any age but is more common among the elderly. At least 10% of elderly patients who are admitted to the hospital have delirium; 15 to 50% experience delirium at some time during hospitalization. Delirium is also common among nursing home residents. When delirium occurs in younger people, it is usually due to drug use or a life-threatening systemic disorder. Delirium is sometimes called acute confusional state or toxic or metabolic encephalopathy.

Etiology

The most common causes are the following:

• Drugs, particularly anticholinergics, psychoactive drugs, and opioids
• Dehydration
• Infection

Many other conditions can cause delirium (see Table 175-2). In about 10 to 20% of patients, no cause is identified.

Predisposing factors include brain disorders (eg, dementia, stroke, Parkinson's disease), advanced age, sensory impairment, and multiple coexisting disorders. Precipitating factors include use of drugs (particularly ≥ 3 new drugs), infection, dehydration, immobility, undernutrition, and use of bladder catheters. Recent exposure to anesthesia also increases risk, especially if exposure is prolonged and if anticholinergics are given during surgery. Decreased sensory stimuli at night may trigger delirium in at-risk patients. For elderly patients in an ICU, risk of delirium (ICU psychosis) is particularly high.

Pathophysiology

Mechanisms are not fully understood but may involve reversible impairment of cerebral oxidative metabolism, multiple neurotransmitter abnormalities, and generation of cytokines. Stress of any kind
upregulates sympathetic tone and downregulates parasympathetic tone, impairing cholinergic function and thus contributing to delirium. The elderly are particularly vulnerable to reduced cholinergic transmission, increasing their risk of delirium. Regardless of cause, the cerebral hemispheres or arousal mechanisms of the thalamus and brain stem reticular activating system become impaired.

[Table 175-2. Causes of Delirium]

**Symptoms and Signs**

Delirium is characterized primarily by difficulty focusing, maintaining, or shifting attention (inattention). Consciousness level fluctuates; patients are disoriented to time and sometimes place or person. They may have hallucinations. Confusion regarding day-to-day events and daily routines is common, as are changes in personality and affect. Thinking becomes disorganized, and speech is often disordered, with prominent slurring, rapidity, neologisms, aphasic errors, or chaotic patterns.

Symptoms fluctuate over minutes to hours; they may lessen during the day and worsen at night.

Symptoms may include inappropriate behavior, fearfulness, and paranoia. Patients may become irritable, agitated, hyperactive, and hyperalert, or they may become quiet, withdrawn, and lethargic. Very elderly people with delirium tend to become quiet and withdrawn—changes that may be mistaken for depression. Some patients alternate between the two. Usually, patterns of sleeping and eating are grossly distorted. Because of the many cognitive disturbances, insight is poor, and judgment is impaired. Other symptoms and signs depend on the cause.

**Diagnosis**

- Mental status examination
- Standard diagnostic criteria to confirm delirium
- Thorough history
- Directed physical examination and selective testing to determine cause

Delirium, particularly in elderly patients, is often overlooked by clinicians. Clinicians should consider delirium in any elderly patient who presents with impairment in memory or attention.

**Mental status examination:** Patients with any sign of cognitive impairment require a formal mental status examination (see Sidebar 168-1 on p. 1588). Attention is assessed first. Simple tests include immediate repetition of the names of 3 objects, digit span (ability to repeat 7 digits forward and 5 backward), and naming the days of the week forward and backward. Inattention (patient does not register directions or other information) must be distinguished from poor short-term memory (patient registers information but rapidly forgets it). Further cognitive testing is futile for patients who cannot register information.

After initial assessment, standard diagnostic criteria, such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or Confusion Assessment Method (CAM) may be used. The following features are required for diagnosis: • Acute change in cognition that fluctuates during the day

- Inattention (eg, difficulty focusing or following what is said)

plus one of the following:

- Disturbance of consciousness (ie, less clarity) with DSM

  or

- An altered level of consciousness (eg, hyperalert, lethargic, stuporous, comatose) or disorganized
History: History is obtained by interviewing family members, caregivers, and friends. It can determine whether the change in mental status is recent and is distinct from any baseline dementia (see Table 175-1). The history helps distinguish a mental disorder from delirium. Mental disorders, unlike delirium, almost never cause inattention or fluctuating consciousness, and onset of mental disorders is nearly always subacute. Sundowning (behavioral deterioration during evening hours), which is common among institutionalized patients with dementia, may be difficult to differentiate; newly symptomatic deterioration should be presumed to be delirium until proved otherwise.

History should also include use of alcohol and illicit, OTC, and prescription drugs, focusing particularly on drugs with CNS effects and on new additions, discontinuations, or changes in dose, including overdosing.

Physical examination: Examination, particularly in patients who are not fully cooperative, should focus on the following:

• Vital signs
• Hydration status
• Potential foci for infection
• Skin, head and neck, and neurologic examination

Findings can suggest a cause. For example, fever, meningismus, or Kernig and Brudzinski signs suggest CNS infection. Tremor and myoclonus suggest uremia, liver failure, drug intoxication, or certain electrolyte disorders (eg, hypocalcemia, hypomagnesemia). Ophthalmoplegia and ataxia suggest Wernicke-Korsakoff syndrome (see p. 1523). Focal neurologic abnormalities (eg, cranial nerve palsies, motor or sensory deficits) or papilledema suggests a structural CNS disorder. Lesions, swelling, and other findings suggest head trauma.

Testing: Testing usually includes CT or MRI, tests for suspected infections (eg, CBC, blood cultures, chest x-ray, urinalysis), and measurement of electrolytes, BUN, creatinine, plasma glucose, and levels of any drugs suspected to be having toxic effects.

If the diagnosis is unclear, further testing may include pulse oximetry (or ABGs); liver function tests; measurement of serum calcium and albumin, thyroid-stimulating hormone (TSH), vitamin B12, ESR, and antinuclear antibody (ANA); and a test for syphilis (eg, rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test).

If the diagnosis is still unclear, testing may include CSF analysis (particularly to rule out meningitis, encephalitis, or subarachnoid hemorrhage), measurement of serum ammonia, and testing to check for heavy metals.

If nonconvulsive status epilepticus, a rare cause, is suspected (based on history, subtle motor twitches, automatisms, or presence of a steadier but less intense pattern of bewilderment and drowsiness), EEG should be done.

Prognosis

Morbidity and mortality rates are higher in patients who have delirium when they are hospitalized or who develop delirium during hospitalization.

Delirium due to certain conditions (eg, hypoglycemia, intoxication, infection, iatrogenic factors, drug toxicity, electrolyte imbalance) typically resolves rapidly with treatment. However, recovery may be slow (days to even weeks or months), especially in the elderly, resulting in longer hospital stays, increased risk and severity of complications, increased costs, and long-term disability. Some patients never fully recover from delirium. For up to 2 yr after delirium occurs, risk of cognitive and functional decline,
in institutionalization, and death is increased.

**Treatment**

- Correction of the cause and removal of aggravating factors
- Supportive care
- Management of agitation

Correcting the cause (eg, treating infection, giving fluids and electrolytes for dehydration) and removing aggravating factors (eg, stopping drugs) may result in resolution of delirium. Nutritional deficiencies (eg, of thiamin or vitamin B12) should be corrected, and good nutrition and hydration should be provided.

**General measures:**

The environment should be stable, quiet, and well-lit and include visual cues to orient the patient (eg, calendar, clocks, family photographs). Frequent reorientation and reassurance by hospital staff or family members may also help. Sensory deficits should be minimized (eg, by replacing hearing aid batteries, by encouraging patients who need eyeglasses or hearing aids to use them).

**Approach to treatment should be interdisciplinary (with a physician, physical and occupational therapists, nurses, and social workers); it should involve strategies to enhance mobility and range of motion, treat pain and discomfort, prevent skin breakdown, ameliorate incontinence, and minimize risk of aspiration.**

Agitation may threaten the well-being of the patient, a caregiver, or a staff member. Simplifying drug regimens and avoiding use of IV lines, bladder catheters, and physical restraints (particularly in the long-term care setting) as much as possible can help prevent exacerbation of agitation and reduce risk of injury. However, in certain circumstances, physical restraints may be needed to prevent patients from harming themselves or others. Restraints should be applied by a staff member trained in their use; they should be released at least every 2 h to prevent injury and discontinued as soon as possible. Use of hospital-employed assistants (sitters) as constant observers may help avoid the need for restraints.

Explaining the nature of delirium to family members can help them cope. They should be told that delirium is usually reversible but that cognitive deficits often take weeks or months to abate after resolution of the acute illness.

**Drugs:** Drugs, typically low-dose haloperidol (0.5 to 1.0 mg po, IV, or IM once, then repeated q 1 to 2 h as needed), may lessen agitation or psychotic symptoms; occasionally, much higher doses are necessary. However, drugs do not correct the underlying problem and may prolong or exacerbate delirium. Second-generation (atypical) antipsychotics (eg, risperidone 0.5 to 3 mg po q 12 h, olanzapine 2.5 to 15 mg po once/day) may be used instead because they have fewer extrapyramidal adverse effects; however, long-term use in patients with dementia may increase risk of stroke and death. These drugs are not typically given IV or IM.

Benzodiazepines (eg, lorazepam 0.5 to 1.0 mg po or IV once, then repeated q 1 to 2 h as needed) have a more rapid onset of action (5 min after parenteral administration) than antipsychotics but commonly worsen confusion and sedation in patients with delirium.

Overall, antipsychotics and benzodiazepines are equally effective for managing agitation in delirium, but antipsychotics have fewer adverse effects. Benzodiazepines are preferred for delirium attributed to sedative withdrawal and for patients intolerant of antipsychotics (eg, those with Parkinson's disease or Lewy body dementia). Dose of these drugs should be reduced as quickly as possible.

**Prevention**

Because delirium greatly worsens prognosis for hospitalized patients, prevention should be emphasized. Hospital staff members should be trained to take measures to maintain orientation, mobility, and cognition and to ensure sleep, good nutrition and hydration, and sufficient pain relief, particularly in elderly patients. Family members can be encouraged to help with these strategies. The number and doses of drugs...
Dementia

Dementia is chronic, global, usually irreversible deterioration of cognition. Diagnosis is clinical; laboratory and imaging tests are used to identify treatable causes. Treatment is supportive. Cholinesterase inhibitors can sometimes temporarily improve cognitive function.

Dementia may occur at any age but affects primarily the elderly (about 5% of those aged 65 to 74 and 40% of those > 85). It accounts for more than one half of nursing home admissions. At least 5 million people in the US have dementia.

Dementias can be classified in several ways:

- Alzheimer’s or non-Alzheimer’s type
- Cortical or subcortical
- Irreversible or potentially reversible
- Common or rare

Etiology

Dementias may result from primary diseases of the brain or other conditions (see Table 175-3).

The most common types of dementia are Alzheimer’s disease, vascular dementia, Lewy body dementia, frontotemporal dementias, and HIV-associated dementia. Dementia also occurs in patients with Parkinson's disease, Huntington's disease, progressive supranuclear palsy, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, other prion disorders, and neurosyphilis. Patients can have > 1 type (mixed dementia).

Some structural brain disorders (eg, normal-pressure hydrocephalus, subdural hematoma), metabolic disorders (eg, hypothyroidism, vitamin B12 deficiency), and toxins (eg, lead) cause a slow deterioration of cognition that may resolve with treatment. This impairment is sometimes called reversible dementia, but some experts restrict the term dementia to irreversible cognitive deterioration.

Depression may mimic dementia (and was formerly called pseudodementia); the 2 disorders often coexist. However, depression may be the first manifestation of dementia.

Changes in cognition, including memory, occur with aging, but they are not dementia. The elderly have a relative deficiency in recall, particularly in speed of recall, compared with recall during their youth. However, this change does not affect daily function. Mild cognitive impairment is more severe than age-associated memory impairment; memory is impaired compared with that ofagematched controls, but other cognitive domains and daily function are not affected. Up to 50% of patients with mild cognitive impairment develop dementia within 3 yr.

Any disorder may exacerbate cognitive deficits in patients with dementia. Delirium often occurs in patients with dementia. Drugs, particularly benzodiazepines and anticholinergics (eg, some tricyclic antidepressants, antihistamines, antipsychotics, benztropine), may temporarily cause or worsen symptoms of dementia, as may alcohol, even in moderate amounts. New or progressive renal or liver failure may reduce drug clearance and cause drug toxicity after years of taking a stable drug dose (eg, of propranolol).

Symptoms and Signs

Dementia impairs cognition globally. Onset is gradual, although family members may suddenly notice
deficits (eg, when function becomes impaired). Often, loss of short-term memory is the first sign. Although symptoms exist in a continuum, they can be divided into early, intermediate, and late. Personality changes and behavioral disturbances may develop early or late. Motor and other focal neurologic deficits occur at different stages, depending on the type of dementia; they occur early in vascular dementia and late in Alzheimer's disease. Incidence of seizures is somewhat increased during all stages. Psychosis—hallucinations, delusions, or paranoia—occurs in about 10% of patients with dementia, although a higher percentage may experience these symptoms temporarily.

[Table 175-3. Classification of Some Dementias]

**Early:** Recent memory is impaired; learning and retaining new information become difficult. Language problems (especially with word finding), mood swings, and personality changes develop. Patients may have progressive difficulty with independent activities of daily living (eg, balancing their checkbook, finding their way around, remembering where they put things). Abstract thinking, insight, or judgment may be impaired. Patients may respond to loss of independence and memory with irritability, hostility, and agitation.

Functional ability may be further limited by the following:

- **Agnosia:** Impaired ability to identify objects despite intact sensory function (see p. 1638)
- **Apraxia:** Impaired ability to do previously learned motor activities despite intact motor function (see p. 1642)
- **Aphasia:** Impaired ability to comprehend or use language (see p. 1640)

Although early dementia may not compromise sociability, family members may report strange behavior accompanied by emotional lability.

**Intermediate:** Patients become unable to learn and recall new information. Memory of remote events is reduced but not totally lost. Patients may require help with basic activities of daily living (eg, bathing, eating, dressing, toileting). Personality changes may progress. Patients may become irritable, anxious, self-centered, inflexible, or angry more easily, or they may become more passive, with a flat affect, depression, indecisiveness, lack of spontaneity, or general withdrawal from social situations. Behavior disorders may develop: Patients may wander or become suddenly and inappropriately agitated, hostile, uncooperative, or physically aggressive (see p. 1684).

By this stage, patients have lost all sense of time and place because they cannot effectively use normal environmental and social cues. Patients often get lost; they may be unable to find their own bedroom or bathroom. They remain ambulatory but are at risk of falls or accidents secondary to confusion. Altered sensation or perception may culminate in psychosis with hallucinations and paranoid and persecutory delusions. Sleep patterns are often disorganized.

**Late (severe):** Patients cannot walk, feed themselves, or do any other activities of daily living; they may become incontinent. Recent and remote memory is completely lost. Patients may be unable to swallow. They are at risk of undernutrition, pneumonia (especially due to aspiration), and pressure ulcers. Because they depend completely on others for care, placement in a long-term care facility often becomes necessary. Eventually, patients become mute.

Because such patients cannot relate any symptoms to a physician and because elderly patients often have no febrile or leukocytic response to infection, a physician must rely on experience and acumen whenever a patient appears ill. End-stage dementia results in coma and death, usually due to infection.

**Diagnosis**

- Differentiation of delirium from dementia, mainly by mental status examination
- Identification of treatable causes clinically and by laboratory testing and neuroimaging
• Sometimes formal neuropsychologic testing

Recommendations about diagnosis of dementia are available from the American Academy of Neurology.

Distinguishing type or cause of dementia can be difficult; definitive diagnosis often requires postmortem pathologic examination of brain tissue. Thus, clinical diagnosis focuses on distinguishing dementia from delirium and other disorders and identifying the cerebral areas affected and potentially reversible causes.

Dementia must be distinguished from the following:

• Delirium: Distinguishing between dementia and delirium is crucial (because delirium is usually reversible with prompt treatment) but can be difficult. Attention is assessed first. If a patient is inattentive, the diagnosis is likely to be delirium, although advanced dementia also severely impairs attention. Other features that suggest delirium rather than dementia (eg, duration of cognitive impairment—see Table 175-1) are determined by the history, physical examination, and tests for specific causes.

• Age-associated memory impairment: This impairment is not severe enough to affect daily function. If affected people are given enough time to learn new information, their intellectual performance is good.

• Mild cognitive impairment: Memory is impaired, but other cognitive domains and daily function are not affected.

• Dementia of depression: This cognitive disturbance resolves with treatment of depression. Depressed older patients may experience cognitive decline, but unlike patients with dementia, they tend to exaggerate their memory loss and rarely forget important current events or personal matters. Neurologic examinations are normal except for signs of psychomotor slowing. When tested, patients with depression make little effort to respond, but those with dementia often try hard but respond incorrectly. When depression and dementia coexist, treating depression does not fully restore cognition.

Clinical criteria: The best screening test for dementia is a short-term memory test (eg, registering 3 objects and recalling them after 5 min); patients with dementia forget simple information within 3 to 5 min. Another test assesses the ability to name objects within categories (eg, lists of animals, plants, or pieces of furniture). Patients with dementia struggle to name a few; those without dementia easily name many.

In addition to loss of short-term memory, diagnosis of dementia requires at least one of the following cognitive deficits:

• Aphasia

• Apraxia

• Agnosia

• Impaired ability to plan, organize, sequence, or think abstractly (executive dysfunction)

Each cognitive deficit must substantially impair function and represent a significant decline from a previous level of functioning. Also, the deficits must not occur only during delirium.

A formal mental status examination (see Sidebar 168-1 on p. 1588) should be done. The Mini-Mental Status Examination is often used. When delirium is absent, the presence of multiple deficits, particularly in patients with an average or a higher level of education, suggests dementia.

History and physical examination should then focus on signs of treatable disorders that cause cognitive impairment (eg, vitamin B₁₂ deficiency, neurosyphilis, hypothyroidism, depression—see Table 175-2).

Laboratory testing: Tests should include thyroid-stimulating hormone and vitamin B₁₂ levels. Routine CBC and liver function tests are sometimes recommended, but yield is very low. If clinical findings
suggest a specific disorder, other tests (eg, for HIV or syphilis) are indicated. Lumbar puncture is rarely needed but should be considered if a chronic infection or neurosyphilis is suspected. Other tests may be used to exclude causes of delirium.

**Neuroimaging:** CT or MRI should be done in the initial evaluation of dementia or after any sudden change in cognition or mental status. Neuroimaging can identify potentially reversible structural disorders (eg, normal-pressure hydrocephalus, brain tumors, subdural hematoma) and certain metabolic disorders (eg, Hallervorden-Spatz disease, Wilson's disease). Occasionally, EEG is useful (eg, to evaluate episodic lapses in attention or bizarre behavior). Functional MRI or single-photon emission CT can provide information about cerebral perfusion patterns and help with differential diagnosis (eg, in differentiating Alzheimer's disease from frontotemporal dementia and Lewy body dementia).

**Neuropsychologic testing:** If the diagnosis remains in doubt, patients should be referred for formal neuropsychologic testing, which evaluates mood as well as all mental functions and takes 1 to 3 h. It is done or supervised by a neuropsychologist. Such testing helps primarily in differentiating the following:

- Age-associated memory impairment, mild cognitive impairment, and dementia, particularly when cognition is only slightly impaired or when the patient or family members are anxious for reassurance
- Dementia and focal syndromes of cognitive impairment (eg, amnesia, aphasia, apraxia, visuospatial difficulties) when the distinction is not clinically evident

Testing may also help characterize specific deficits due to dementia.

**Prognosis**

Dementia is usually progressive. However, progression rate varies widely and depends on the cause. Dementia shortens life expectancy, but survival estimates vary.

**Treatment**

- Measures to ensure safety
- Provision of appropriate stimulation, activities, and cues for orientation
- Elimination of drugs with sedating or anticholinergic effects
- Possibly cholinesterase inhibitors
- Assistance for caregivers
- Arrangements for end-of-life care

Recommendations about treatment of dementia are available from the American Academy of Neurology. Measures to ensure patient safety and to provide an appropriate environment are essential to treatment, as is caregiver assistance. Several drugs are available.

**Patient safety:** Occupational and physical therapists can evaluate the home for safety; the goals are to prevent accidents (particularly falls), to manage behavior disorders, and to plan for change as dementia progresses.

How well patients function in various settings (ie, kitchen, automobile) should be evaluated using simulations. If patients have deficits and remain in the same environment, protective measures (eg, hiding knives, unplugging the stove, removing the car, confiscating car keys) may be required. Some states require physicians to notify the Department of Motor Vehicles of patients with dementia because, at some point, such patients can no longer drive safely. If patients wander, signal monitoring systems can be installed, or patients can be registered in the Safe Return program. Information is available from the Alzheimer's Association. Ultimately, assistance (eg, housekeepers, home health aides) or a change of...
Environment (living facilities without stairs, assisted-living facility, skilled nursing facility) may be indicated.

**Environmental measures:** Patients with mild to moderate dementia usually function best in familiar surroundings. Whether at home or in an institution, the environment should be designed to help preserve feelings of self-control and personal dignity by providing the following:

- Frequent reinforcement of orientation
- A bright, cheerful, familiar environment
- Minimal new stimulation
- Regular, low-stress activities

Large calendars and clocks and a routine for daily activities can help with orientation; medical staff members can wear large name tags and repeatedly introduce themselves. Changes in surroundings, routines, or people should be explained to patients precisely and simply, omitting nonessential procedures. Patients require time to adjust and become familiar with the changes. Telling patients about what is going to happen (eg, about a bath or feeding) may avert resistance or violent reactions. Frequent visits by staff members and familiar people encourage patients to remain social. The room should be reasonably bright and contain sensory stimuli (eg, radio, television, night-light) to help patients remain oriented and focus their attention. Quiet, dark, private rooms should be avoided.

Activities can help patients function better; those related to interests before dementia began are good choices. Activities should be enjoyable, provide some stimulation, but not involve too many choices or challenges. Exercise to reduce restlessness, improve balance, and maintain cardiovascular tone should be done daily. Exercise can also help improve sleep and manage behavior disorders. Occupational therapy and music therapy help maintain fine motor control and provide nonverbal stimulation. Group therapy (eg, reminiscence therapy, socialization activities) may help maintain conversational and interpersonal skills.

**Drugs:** Eliminating or limiting drugs with CNS activity often improves function. Sedating and anticholinergic drugs, which tend to worsen dementia, should be avoided.

The cholinesterase inhibitors donepezil, rivastigmine, and galantamine (see p. 1679) are somewhat effective in improving cognitive function in patients with Alzheimer's disease or Lewy body dementia and may be useful in other forms of dementia. These drugs inhibit acetylcholinesterase, increasing the acetylcholine level in the brain.

Memantine, an NMDA (N-methyl-D-aspartate) antagonist, may help slow progression of moderate to severe dementia and can be used with a cholinesterase inhibitor.

Other drugs (eg, antipsychotics) have been used to control behavior disorders (see p. 1686). Patients with dementia and signs of depression should be treated with nonanticholinergic antidepressants, preferably SSRIs.

**Caregiver assistance:** Immediate family members are largely responsible for care of a patient with dementia. Nurses and social workers can teach them and other caregivers how to best meet the patient's needs (eg, how to deal with daily care and handle financial issues); teaching should be ongoing. Other resources (eg, support groups, educational materials, Internet web sites) are available.

Caregivers may experience substantial stress. Stress may be caused by worry about protecting the patient and by frustration, exhaustion, anger, and resentment from having to do so much to care for someone. Health care practitioners should watch for early symptoms of caregiver stress and burnout and, when needed, suggest support services (eg, social worker, nutritionist, nurse, home health aide). If a patient with dementia has an unusual injury, the possibility of elder abuse should be investigated.
End-of-life issues: Because insight and judgment deteriorate in patients with dementia, appointment of a family member, guardian, or lawyer to oversee finances may be necessary. Early in dementia, before the patient is incapacitated, the patient's wishes about care should be clarified, and financial and legal arrangements (eg, durable power of attorney, durable power of attorney for health care) should be made. When these documents are signed, the patient's capacity should be evaluated, and evaluation results recorded (see also p. 3468). Decisions about artificial feeding and treatment of acute disorders are best made before the need develops. In advanced dementia, palliative measures may be more appropriate than highly aggressive interventions or hospital care.

Alzheimer's Disease

Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, β-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter.

Alzheimer's disease is the most common cause of dementia; it accounts for > 65% of dementias in the elderly. The disease is twice as common among women as among men, partly because women have a longer life expectancy. Alzheimer's disease affects about 4% of people aged 65 to 74 and 30% of those > 85. Prevalence in industrialized countries is expected to increase as the proportion of the elderly increases.

Etiology

Most cases are sporadic, with late onset (≥ 60 yr) and unclear etiology. However, about 5 to 15% are familial; one half of these cases have an early (presenile) onset (< 60 yr) and are typically related to specific genetic mutations.

At least 5 distinct genetic loci, located on chromosomes 1, 12, 14, 19, and 21, influence initiation and progression of Alzheimer's disease. Mutations in genes for the amyloid precursor protein, presenilin I, and presenilin II may lead to autosomal dominant forms of Alzheimer's disease, typically with presenile onset. In affected patients, the processing of amyloid precursor protein is altered, leading to deposition and fibrillar aggregation of β-amyloid. β-Amyloid may lead to neuronal death and formation of neurofibrillary tangles and senile plaques, which consist of degenerated axonal or dendritic processes, astrocytes, and glial cells around an amyloid core.

Other genetic determinants include the apolipoprotein (apo) E alleles (ε). Apo E proteins influence β-amyloid deposition, cytoskeletal integrity, and efficiency of neuronal repair. Risk of Alzheimer's disease is substantially increased in people with 2 ε4 alleles and may be decreased in those who have the ε2 allele. Variants in SORL1 may also be involved; they are more common among people with lateonset Alzheimer's disease. These variants may cause the gene to malfunction, possibly resulting in increased production of β-amyloid.

The relationship of other factors (eg, low hormone levels, metal exposure) and Alzheimer's disease is under study, but no definite causal links have been established.

Pathophysiology

Typically, extracellular β-amyloid deposits, intracellular neurofibrillary tangles (paired helical filaments), and senile plaques develop, and neurons are lost. Cerebrocortical atrophy is common, and use of cerebral glucose is reduced, as is perfusion in the parietal lobe, temporal cortices, and prefrontal cortex.

Other common abnormalities include increased brain and CSF concentrations of the tau protein (a component of neurofibrillary tangles and β-amyloid) and reduced levels of choline acetyltransferase and various neurotransmitters (eg, somatostatin).

Symptoms and Signs

Symptoms and signs of Alzheimer's disease are similar to those of other dementias, with early,
intermediate, and late stages (see p. 1673). Loss of short-term memory is often the first sign. Cognitive deficits tend to involve multiple functions. The disease progresses gradually but may plateau for periods of time. Behavior disorders (eg, wandering, agitation, yelling, persecutory ideation) are common (see p. 1684).

**Diagnosis**

- Similar to that of other dementias
- Formal mental status examination
- History and physical examination
- Laboratory testing
- Neuroimaging

Generally, diagnosis is similar to that of other dementias (see p. 1675). Clinical criteria (including a thorough history and standard neurologic examination) are 85% accurate in establishing the diagnosis and differentiating Alzheimer's disease from other forms of dementia, such as vascular dementia and Lewy body dementia.

Traditional diagnostic criteria for Alzheimer's disease include all of the following:

- Dementia established clinically and documented by a formal mental status examination
- Deficits in ≥ 2 areas of cognition
- Gradual onset and progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset after age 40, most often after age 65
- No systemic or brain disorders that could account for the progressive deficits in memory and cognition

However, deviations from these criteria do not exclude a diagnosis of Alzheimer's disease, particularly because patients may have mixed dementia.

**Differential diagnosis:** Distinguishing Alzheimer's disease from other dementias is difficult. Assessment tools (eg, Hachinski Ischemic Score—see Table 175-4) can help distinguish vascular dementia from Alzheimer's disease. Fluctuations in cognition, parkinsonian symptoms, well-formed visual hallucinations, and relative preservation of short-term memory suggest Lewy body dementia rather than Alzheimer's disease (see Table 175-5). Patients with Alzheimer's disease are often better-groomed and neater than patients with other dementias.

**Prognosis**

Although progression rate varies, cognitive decline is inevitable. Average survival from time of diagnosis is 7 yr, although this figure is debated. Average survival from the time patients can no longer walk is about 6 mo.

**Treatment**
• Generally, similar to that of other dementias

• Possibly cholinesterase inhibitors and memantine

General treatment is the same as that of all dementias (see p. 1676).

**Cholinesterase inhibitors** modestly improve cognitive function and memory in some patients. Four are available; generally, donepezil, rivastigmine, and galantamine are equally effective, but tacrine is rarely used because of its hepatotoxicity. Donepezil is a first-line drug because it has once/day dosing and is well-tolerated. The recommended dose is 5 mg once/day for 4 to 6 wk, then increased to 10 mg once/day. Treatment should be continued if functional improvement is apparent after several months, but otherwise it should be stopped. The most common adverse effects are GI (eg, nausea, diarrhea). Rarely, dizziness and cardiac arrhythmias occur. Adverse effects can be minimized by increasing the dose gradually (see Table 175-6).

**Memantine**, an N-methyl-D-aspartate receptor antagonist, appears to slow the progression of Alzheimer's disease. The dose is 5 mg po once/day, which is increased to 10 mg po bid over about 4 wk. For patients with renal insufficiency, the dose should be reduced or the drug should be avoided. Memantine can be used with a cholinesterase inhibitor.

Efficacy of high-dose vitamin E (1000 IU po once/day or bid), selegiline, NSAIDs, *Ginkgo biloba* extracts, and statins is unclear. Estrogen therapy does not appear useful in prevention or treatment and may be harmful.

**Prevention**

Preliminary, observational evidence suggests that risk of Alzheimer's disease may be decreased by the following:

• Continuing to do challenging mental activities (eg, learning new skills, doing crossword puzzles) well into old age

• Exercising

• Controlling hypertension

• Lowering cholesterol levels

• Consuming a diet rich in ω-3 fatty acids and low in saturated fats

• Drinking alcohol in modest amounts

[Table 175-6, Drugs for Alzheimer's Disease]

However, there is no convincing evidence that people who do not drink alcohol should start drinking to prevent Alzheimer's disease.

**Vascular Dementia**

**Vascular dementia** is acute or chronic cognitive deterioration due to diffuse or focal cerebral infarction that is most often related to cerebrovascular disease.

Vascular dementia is the 2nd most common cause of dementia among the elderly. It is more common among men and usually begins after age 70. It occurs more often in people who have vascular risk factors (eg, hypertension, diabetes mellitus, hyperlipidemia, smoking) and in those who have had several strokes. Many people have both vascular dementia and Alzheimer's disease.

Vascular dementia occurs when multiple small cerebral infarcts (or sometimes hemorrhages) cause
enough neuronal or axonal loss to impair brain function. Vascular dementias include the following:

- **Lacunar disease**: Small blood vessels are affected.
- **Multi-infarct dementia**: Medium-sized blood vessels are affected.
- **Strategic single-infarct dementia**: A single infarct occurs in a crucial area of the brain (e.g., angular gyrus, thalamus).
- **Binswanger's dementia (subcortical arteriosclerotic encephalopathy)**: This uncommon variant of small-vessel dementia is associated with severe, poorly controlled hypertension and systemic vascular disease. It involves multiple lacunar infarcts in deep hemispheric white and gray matter.

### Symptoms and Signs

Symptoms and signs are similar to those of other dementias (see p. 1673). However, because infarction is the cause, vascular dementia tends to progress in discrete steps; each episode is accompanied by intellectual decline, sometimes followed by modest recovery.

As the disease progresses, focal neurologic deficits often develop:

- Exaggeration of deep tendon reflexes
- Extensor plantar response
- Gait abnormalities
- Weakness of an extremity
- Hemiplegias
- Pseudobulbar palsy with pathologic laughing and crying
- Other signs of extrapyramidal dysfunction

However, because small-vessel ischemic damage tends to cause small, incremental deficits, the decline appears to be gradual.

Cognitive loss may be focal. For example, short-term memory may be less affected than in other dementias. Patients with partial aphasia may be more aware of their deficits; thus, depression may be more common than in other dementias.

### Diagnosis

- Generally similar to diagnosis of other dementias

Diagnosis is similar to that of other dementias (see p. 1675). If focal signs or evidence of cerebrovascular disease is present, a thorough evaluation for stroke should be done (see p. 1645).

CT and MRI may show bilateral multiple infarcts in the dominant hemisphere and limbic structures, multiple lacunar strokes, or periventricular white-matter lesions extending into the deep white matter. In Binswanger's dementia, imaging shows leukoencephalopathy in the cerebrum semiovale adjacent to the cortex, often with multiple lacunae affecting structures deep in the gray matter (e.g., basal ganglia, thalamic nuclei).

The Hachinski Ischemic Score is sometimes used to help differentiate vascular dementia from Alzheimer's disease (see Table 175-4).
Prognosis

The 5-yr mortality rate is 61%, which is higher than that for most forms of dementia, presumably because other atherosclerotic disorders coexist.

Treatment

• Generally similar to treatment of other dementias

Generally, treatment is the same as that of other dementias (see p. 1676). However, vascular dementia may be preventable, and its progression may be slowed by BP control, cholesterol-lowering therapy, regulation of plasma glucose (90 to 150 mg/dL), and smoking cessation.

The efficacy of cholinesterase inhibitors and memantine is uncertain. However, because many patients also have Alzheimer's disease, these drugs may have some benefit. Adjunctive drugs for depression, psychosis, and sleep disorders are useful.

Lewy Body Dementia

Lewy body dementia is chronic cognitive deterioration characterized by cellular inclusions called Lewy bodies in the cytoplasm of cortical neurons.

Lewy body dementia is the 3rd most common dementia. Age of onset is typically > 60.

Lewy bodies are spherical, eosinophilic, neuronal cytoplasmic inclusions composed of aggregates of α-synuclein, a synaptic protein. They occur in the cortex of some patients with primary Lewy body dementia. Neurotransmitter levels and neuronal pathways between the striatum and the neocortex are abnormal.

Lewy bodies also occur in the substantia nigra of patients with Parkinson's disease, and patients with Parkinson's disease may develop Lewy body dementia. Thus, some experts think that Parkinson's disease and Lewy body dementia may be part of a more generalized synucleopathy affecting the central and peripheral nervous systems (see p. 1765). Lewy bodies sometimes occur in patients with Alzheimer's disease, and patients with Lewy body dementia may have neuritic plaques and neurofibrillary tangles. Lewy body dementia, Parkinson's disease, and Alzheimer's disease overlap considerably. Further research is needed to clarify the relationships among them.

Symptoms and Signs

Initial cognitive deterioration resembles that of other dementias (see p. 1673). Extrapyramidal symptoms occur. However, unlike in Parkinson's disease, in Lewy body dementia, cognitive and extrapyramidal symptoms usually begin within 1 yr of each other. Also the extrapyramidal symptoms differ from those of Parkinson's disease: In Lewy body dementia, tremor does not occur early, rigidity of axial muscles with gait instability occurs early, and deficits tend to be symmetric. Repeated falls are common.

Fluctuating cognitive function is a relatively specific feature of Lewy body dementia. Periods of being alert, coherent, and oriented may alternate with periods of being confused and unresponsive to questions, usually over a period of days to weeks but sometimes during the same interview. Memory is impaired, but the impairment appears to result more from deficits in alertness and attention than in memory acquisition; thus, short-term recall is affected less than digit span memory (ability to repeat 7 digits forward and 5 backward). Patients may stare into space for long periods. Excessive daytime drowsiness is common. Visuospatial and visuoconstructional abilities (tested by block design, clock drawing, or figure copying) are affected more than other cognitive deficits. Thus, Lewy body dementia may be difficult to distinguish from delirium, and all patients presenting with these symptoms and signs should be evaluated for delirium.

Visual hallucinations are common and often threatening, unlike the benign hallucinations of Parkinson's...
disease. Auditory, olfactory, and tactile hallucinations are less common. Delusions occur in 50 to 65% of patients and are often complex and bizarre, compared with the simple persecutory ideation common in Alzheimer's disease.

Autonomic dysfunction is common, and unexplained syncope may result. Autonomic dysfunction may occur simultaneously with or after onset of cognitive deficits. Extreme sensitivity to antipsychotics is typical. Many patients have rapid eye movement (REM) sleep behavior disorder, a parasomnia characterized by vivid dreams without the usual physiologic paralysis of skeletal muscles during REM sleep. As a result, dreams may be acted out, sometimes injuring the bed partner.

Lewy body dementia progresses; prognosis is poor.

Diagnosis

**Clinical criteria**

**Neuroimaging to rule out other disorders**

Diagnosis is clinical, but sensitivity and specificity are poor.

Diagnosis is considered probable if 2 of 3 features—fluctuations in cognition, visual hallucinations, and parkinsonism—are present and possible if only one is present. Supportive evidence consists of repeated falls, syncope, and sensitivity to antipsychotics. Overlap of symptoms in Lewy body dementia and Parkinson's disease may complicate diagnosis. When motor deficits (eg, tremor, bradykinesia, rigidity) precede and are more severe than cognitive impairment, Parkinson's disease is usually diagnosed. When early cognitive impairment and behavioral disturbances predominate, Lewy body dementia is usually diagnosed.

CT and MRI show no characteristic changes but are helpful initially in ruling out other causes of dementia. Positron emission tomography with fluorine-18-labeled deoxyglucose and single-photon emission CT (SPECT) with $^{123}$-FP-CIT (N-3-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]tropane), a fluoroalkyl analog of cocaine, may help identify Lewy body dementia but are not routinely done. Definitive diagnosis requires autopsy samples of brain tissue.

Treatment

**Supportive care**

Treatment is generally supportive (see p. 1676). Rivastigmine 1.5 mg po bid, titrated upward as needed to 6 mg bid, may improve cognition. Other cholinesterase inhibitors may also be useful. In about one half of patients, extrapyramidal symptoms respond to antiparkinsonian drugs (see p. 1767), but psychiatric symptoms may worsen. If such drugs are needed, levodopa is preferred.

Traditional antipsychotics, even at very low doses, tend to acutely worsen extrapyramidal symptoms and are best avoided.

HIV-Associated Dementia

**HIV-associated dementia is chronic cognitive deterioration due to brain infection by HIV.**

HIV-associated dementia (AIDS dementia complex) may occur in the late stages of HIV infection. Unlike almost all other forms of dementia, it tends to occur in younger people. Purely HIV-associated dementia is caused by neuronal damage by the HIV virus. However, in patients with HIV infection, dementia may result from other infections, such as secondary infection with JC virus causing progressive multifocal leukoencephalopathy. Other opportunistic infections (eg, fungal, bacterial, viral, protozoan) may also contribute.

In purely HIV-associated dementia, subcortical pathologic changes result when infected macrophages or
microglial cells infiltrate into the deep gray matter (i.e., basal ganglia, thalamus) and white matter.

Prevalence of dementia in late-stage HIV infection ranges from 7 to 27%, but 30 to 40% may have milder forms. Incidence is inversely proportional to CD4+ count.

**Symptoms and Signs**

Symptoms and signs may be similar to those of other dementias (see p. 1673). Early manifestations include slowed thinking and expression, difficulty concentrating, and apathy; insight is preserved, and manifestations of depression are few. Motor movements are slowed; ataxia and weakness may be evident. Abnormal neurologic signs may include paraparesis, lower-extremity spasticity, ataxia, and extensor-plantar responses. Mania or psychosis is sometimes present.

**Diagnosis**

- Generally similar to initial diagnosis of other dementias
- Prompt evaluation, including MRI, when deterioration is acute

Generally, diagnosis of dementia in patients with HIV infection is similar to that of other dementias (see p. 1675). However, when patients present with an acute change in cognitive function, the cause must be identified as soon as possible.

CT or MRI should be done to check for signs of CNS infection (e.g., toxoplasmosis). MRI is more useful than CT because it can exclude other CNS causes of dementia (e.g., progressive multifocal leukoencephalopathy, cerebral lymphoma). Late-stage findings of HIV dementia may include diffuse nonenhancing white matter hyperintensities, cerebral atrophy, and ventricular enlargement. If no contraindication is identified by neuroimaging, lumbar puncture is done to rule out infection.

**Prognosis**

Patients with HIV infection and untreated dementia have a worse prognosis (average life expectancy of 6 mo) than those without dementia.

**Treatment**

- Highly active antiretroviral therapy

The primary treatment is highly active antiretroviral therapy, which increases CD4+ counts and improves cognitive function (see p. 1450). Supportive measures are similar to those for other dementias (see p. 1676).

**Frontotemporal Dementia**

**Frontotemporal dementia (FTD)** refers to sporadic and hereditary disorders that affect the frontal and temporal lobes, including Pick's disease.

FTD accounts for up to 10% of dementias. Age at onset is typically younger (age 55 to 65) than in Alzheimer's disease. FTDs affect men and women about equally. Pick's disease is a variant of FTD, which may be pathologically characterized by severe atrophy, neuronal loss, gliosis, and presence of abnormal neurons (Pick cells) containing inclusions (Pick bodies).

About one half of FTDs are inherited; most mutations involve chromosome 17q21-22 and result in abnormalities of the microtubule-binding tau protein; thus, FTDs are considered tauopathies. Some experts classify supranuclear palsy and corticobasal degeneration with FTDs because they share similar pathology and gene mutations affecting the tau protein. Symptoms, gene mutations, and pathologic changes may not correspond to each other. For example, the same mutation causes FTD symptoms in one family member but symptoms of corticobasal degeneration in another, and Pick's cells may be absent...
in patients with typical symptoms of Pick's disease.

**Symptoms and Signs**

Generally, FTD affects personality, behavior, and usually language function (syntax and fluency) more and memory less than does Alzheimer's disease. Abstract thinking and attention (maintaining and shifting) are impaired; responses are disorganized. Orientation is preserved, but retrieval of information may be impaired. Motor skills are generally preserved. Patients have difficulty sequencing tasks, although visual-spatial and constructional tasks are affected less.

Frontal release signs (grasp, root, suck, snout, and palmomental reflexes and glabellar sign—see p. 1593) appear late in the disease but also occur in other dementias. Some patients develop motor neuron disease with generalized muscle atrophy, weakness, fasciculations, bulbar symptoms (eg, dysphagia, dysphonia, difficulty chewing), and increased risk of aspiration pneumonia and early death.

**Frontal variant FTD:** Social behavior and personality change because the orbitobasal frontal lobe is affected. Patients become impulsive and lose their social inhibitions (eg, they may shoplift); they neglect personal hygiene. Some have Kluver-Bucy syndrome, which involves emotional blunting, hypersexual activity, hyperorality (eg, bulimia, sucking and smacking of lips), and visual agnosias. Impersistence (impaired concentration), inertia, and mental rigidity appear.

Behavior becomes repetitive and stereotyped (eg, patients may walk to the same location every day). Patients may pick up and manipulate random objects for no reason (called utilization behavior). Verbal output is reduced; echolalia, perseveration (inappropriate repetition of a response), and eventually mutism occur.

**Primary progressive aphasia:** Language function deteriorates because of asymmetric (worse on left) anterolateral temporal lobe atrophy; the hippocampus and memory are relatively spared. Most patients present with difficulty finding words. Attention (eg, digit span) may be severely impaired. Many patients have aphasia, with decreased fluency and difficulty comprehending language; hesitancy in speech production and dysarthria are also common. In some patients, aphasia is the only symptom for ≥ 10 yr; in others, global deficits develop within a few years.

Semantic dementia is a type of primary progressive aphasia. When the left side of the brain is affected most, the ability to comprehend words is progressively lost. Speech is fluent but lacks meaning; a generic or related term may be used instead of the specific name of an object. When the right side is affected most, patients have progressive anomia (inability to name objects) and prosopagnosia (inability to recognize familiar faces). They cannot remember topographic relationships. Some patients with semantic dementia also have Alzheimer's disease.

**Diagnosis**

- Generally similar to diagnosis of other dementias
- Additional clinical evaluation to differentiate from some other dementias

Diagnosis is suggested by typical clinical findings. As for other dementias, cognitive deficits are evaluated (see p. 1675). CT and MRI are done to determine location and extent of brain atrophy and to exclude other possible causes (eg, brain tumors, abscesses, stroke). FTDs are characterized by severely atrophic, sometimes paper-thin gyri in the temporal and frontal lobes. However, MRI or CT may not show these changes until late in FTD. Thus, FTDs and Alzheimer's disease can usually be differentiated more easily by clinical criteria. For example, primary progressive aphasia differs from Alzheimer's disease in that memory and visuospatial function are preserved and syntax and fluency are impaired.

**Prognosis**

FTDs usually progress gradually, but progression rate varies; if symptoms are limited to speech and language, progression to general dementia may be slower.
Treatment

There is no specific treatment. Treatment is generally supportive (see p. 1676).

Normal-Pressure Hydrocephalus

Normal-pressure hydrocephalus is characterized by gait disturbance, urinary incontinence, dementia, enlarged brain ventricles, and normal or slightly elevated CSF pressure.

Normal-pressure hydrocephalus is thought to result from a defect in CSF resorption in arachnoid granulations. This disorder accounts for up to 6% of dementias.

Symptoms and Signs

Most commonly, the gait disturbance is nonspecific unsteadiness and impaired balance, although a magnetic gait (the feet appear to stick to the floor) is considered the characteristic gait disturbance. Dementia may not occur until late in the disorder. The most common early symptoms of dementia are disturbances of executive function and attention; memory tends to become impaired later.

Diagnosis

• Clinical evaluation

• Neuroimaging

• Sometimes removal of CSF

The classic symptoms (gait disturbance, urinary incontinence, and dementia), even combined, are nonspecific for normal-pressure hydrocephalus, particularly in the elderly. For example, some forms of vascular dementia can cause dementia, gait disturbance, and, less commonly, urinary incontinence. Brain imaging may show ventricular enlargement disproportionate to cortical atrophy; this finding is nonspecific but may support the diagnosis of normal-pressure hydrocephalus.

Lumbar puncture with removal of 20 to 30 mL of CSF can be done as a diagnostic trial. Improvement in gait, continence, and cognition after removal helps confirm the diagnosis, but improvement may not be evident until several hours after removal.

Treatment

• Sometimes ventriculoperitoneal shunting

Ventriculoperitoneal shunting is useful for patients with acceptable surgical risks. Improvements after lumbar puncture to remove CSF, done during diagnosis, may predict the response to shunting. In several case series (but in no randomized trials), patients improved substantially, typically in gait, continence, and daily functioning, after shunting; improvement in cognition was less common.

Behavioral and Psychologic Symptoms of Dementia

Disruptive actions are common among patients with dementia and are the primary reason for up to 50% of nursing home admissions. Disruptive actions include wandering, restlessness, yelling, throwing, hitting, refusing treatment, incessantly questioning, disrupting work of staff members, insomnia, and crying. Behavioral and psychologic symptoms of dementia have not been well characterized, and their treatment is poorly understood.

Deciding what actions constitute a behavioral symptom is highly subjective. Tolerability (what actions caregivers can tolerate) depends partly on the patient's living arrangements, particularly safety. For example, wandering may be tolerable if a patient lives in a safe environment (with locks and alarms on all
doors and gates); however, if the patient lives in a nursing home or hospital, wandering may be intolerable because it disturbs other patients or interferes with the operation of the institution. Many behaviors (eg, wandering, repeatedly questioning, being uncooperative) are better tolerated during the day. Whether sundowning (exacerbation of disruptive behaviors at sundown or early evening) represents decreased tolerance by caregivers or true diurnal variation is unknown. In nursing homes, 12 to 14% of patients with dementia act disruptively more often during the evening than during the day.

**Etiology**

Behavioral and psychologic symptoms may result from functional changes related to dementia:

- Reduced inhibition of inappropriate behaviors (eg, patients may undress in public places)
- Misinterpretation of visual and auditory cues (eg, they may resist treatment, which they perceive as an assault)
- Impaired short-term memory (eg, they repeatedly ask for things already received)
- Reduced ability or inability to express needs (eg, they wander because they are lonely, frightened, or looking for something or someone)

Patients with dementia often adapt poorly to the regimentation of institutional living. Mealtimes, bedtimes, and toileting times are not individualized. For many elderly patients with dementia, behavioral and psychologic symptoms develop or worsen after they are moved to a more restrictive environment.

Physical problems (eg, pain, shortness of breath, urinary retention, constipation, physical abuse) can exacerbate behavioral and psychologic symptoms partly because patients may be unable to adequately communicate. Physical problems can lead to delirium, and delirium superimposed on chronic dementia may worsen the behavioral symptom.

**Evaluation**

- Characterization of behaviors (eg, by Cohen-Mansfield Agitation Inventory)
- Recording of specific behaviors
- Evaluation for coexisting depression and psychosis

The best approach is to characterize and classify the behavior, rather than to label all such behaviors agitation, a term with too many meanings to be useful. The Cohen-Mansfield Agitation Inventory is commonly used; it classifies behaviors as follows:

- Physically aggressive: For example, hitting, pushing, kicking, biting, scratching, or grabbing people or things
- Physically nonaggressive: For example, handling things inappropriately, hiding things, dressing or undressing inappropriately, pacing, repeating mannerisms or sentences, acting restless, or trying to go elsewhere
- Verbally aggressive: For example, cursing, making strange noises, screaming, or having temper outbursts
- Verbally nonaggressive: For example, complaining, whining, constantly requesting attention, not liking anything, interrupting with relevant or irrelevant remarks, or being negative or bossy

Specific behaviors, precipitating events (eg, feeding, toileting, drug administration, visits), and time the behavior started and resolved should be recorded; this information helps identify changes in pattern or intensity of a behavior and makes planning a management strategy easier. If behavior changes, a
physical examination should be done to exclude physical disorders and physical abuse, but environmental changes (eg, a different caregiver) should also be noted because they, rather than a patient-related factor, may be the reason.

Depression, common among patients with dementia, may affect behavior and must be identified. It may first manifest as an abrupt change in cognition, decreased appetite, deterioration in mood, a change in sleep pattern (often hypersomnolence), withdrawal, decreased activity level, crying spells, talk of death and dying, sudden development of irritability or psychosis, or other sudden changes in behavior. Often, depression is suspected first by family members.

Psychotic behavior must also be identified because management differs. Presence of delusions or hallucinations indicates psychosis. Delusions and hallucinations must be distinguished from disorientation, fearfulness, and misunderstanding, which are common among patients with dementia. Delusions without paranoia may be confused with disorientation, but delusions are usually fixed (eg, a nursing home is repeatedly called a prison), and disorientation varies (eg, a nursing home is called a prison, a restaurant, and a home). Hallucinations occur without external sensory stimuli; hallucinations should be distinguished from illusions, which involve misinterpreting external sensory stimuli (eg, cellular phones, pagers).

Treatment

• Environmental measures and caregiver support

• Drugs only when necessary

Management of behavioral and psychologic symptoms of dementia is controversial and has been inadequately studied. Supportive measures are preferred; however, drugs are commonly used.

Environmental measures: The environment should be safe and flexible enough to accommodate behaviors that are not dangerous. Signs to help patients find their way and doors equipped with locks or alarms can help ensure the safety of patients who wander. Flexible sleeping hours and organization of beds can help patients with sleeping problems. Measures used to treat dementia generally also help minimize behavioral symptoms:

• Providing cues about time and place

• Explaining care before giving it

• Encouraging physical activity (see p. 1676)

If an institution cannot provide an appropriate environment for a particular patient, transferring the patient to one that can may be preferable to drug treatment.

Caregiver support: Learning how dementia leads to behavioral and psychologic symptoms and how to respond to disruptive behavior can help family members and other caregivers provide care for and cope with the patient better.

Learning how to manage stress, which may be considerable, is essential. Stressed caregivers should be referred to support services (eg, social workers, caregiver support groups, home health aides) and should be told how to obtain respite care if such care is available.

Family members who are caregivers should be monitored for depression, which occurs in nearly half of them. Depression in caregivers should be treated promptly.

Drugs: Drugs that improve cognition may also help manage behavioral and psychologic symptoms in patients with dementia. However, drugs directed primarily at behavior are used only when other approaches are ineffective and when drugs are essential for safety. The need for continued treatment should be reassessed at least every month. Drugs should be selected to target the most intolerable
behaviors. Antidepressants, preferably SSRIs, should be prescribed only for patients with signs of depression.

Antipsychotics are often used even though their efficacy has been shown only in psychotic patients (see p. 1562). Other patients are unlikely to benefit and likely to experience adverse effects, particularly extrapyramidal symptoms. Tardive dyskinesia or tardive dystonia may develop; these conditions often do not resolve when the dose is reduced or the drug is stopped.

Choice of antipsychotic depends on relative toxicity. Of conventional antipsychotics, haloperidol is relatively non-sedating and has less potent anticholinergic effects but is most likely to cause extrapyramidal symptoms; thioridazine and thiothixene are less likely to cause extrapyramidal symptoms but are more sedating and have more anticholinergic effects than haloperidol. Second-generation (atypical) antipsychotics (eg, aripiprazole, olanzapine, quetiapine, risperidone) are minimally anticholinergic and cause fewer extrapyramidal symptoms than conventional antipsychotics; however, these drugs, used for an extended period, may be associated with an increased risk of hyperglycemia and all-cause mortality. Also, they may increase risk of stroke in elderly patients who have dementia-related psychosis.

If antipsychotics are used, they should be given in a low dose (eg, olanzapine 2.5 to 15 mg po once/day; risperidone 0.5 to 3 mg po q 12 h; haloperidol 0.5 to 1.0 mg po, IV, or IM) and for a short time.

Anticonvulsants, particularly valproate, may be useful in controlling impulsive behavioral outbursts.

Sedatives (eg, a short-acting benzodiazepine such as lorazepam 0.5 mg po q 12 h as needed) are sometimes used in the short term to alleviate event-related anxiety, but such treatment is not recommended for the long term.
Chapter 176. Seizure Disorders

**Introduction**

(See also Febrile Seizures on p. 2898, Infantile Spasms on p. 2899, and Neonatal Seizure Disorders on p. 2900.)

A seizure is an abnormal, unregulated electrical discharge that occurs within the brain's cortical gray matter and transiently interrupts normal brain function. A seizure typically causes altered awareness, abnormal sensations, focal involuntary movements, or convulsions (widespread violent involuntary contraction of voluntary muscles).

About 2% of adults have a seizure at some time during their life. Two thirds of these people never have another one.

**Definitions:** Terminology can be confusing.

**Epilepsy** (also called epileptic seizure disorder) is a chronic brain disorder characterized by recurrent (≥ 2), unprovoked seizures (ie, not related to reversible stressors). Epilepsy is often idiopathic, but various brain disorders, such as malformations, strokes, and tumors, can cause symptomatic epilepsy.

**Nonepileptic seizures** are provoked by a temporary disorder or stressor (eg, metabolic disorders, CNS infections, cardiovascular disorders, drug toxicity or withdrawal).

[Table 176-1. Causes of Seizures]

In children, fever can provoke a seizure (see p. 2898).

**Symptomatic seizures** are due to a known cause (eg, brain tumor, stroke). Symptomatic seizures are most common among neonates (see p. 2900) and the elderly.

**Psychogenic seizures** (pseudoseizures) are symptoms that simulate seizures in patients with psychiatric disorders but that do not involve an abnormal electrical discharge in the brain.

**Etiology**

Common causes of seizures (see Table 176-1) vary by age of onset:

- **Before age 2:** Developmental defects, birth injuries, and metabolic disorders
- **Ages 2 to 14:** Idiopathic seizure disorders
- **Adults:** Cerebral trauma, alcohol withdrawal, tumors, strokes, and unknown cause (in 50%)
- **The elderly:** Tumors and strokes

In reflex epilepsy, a rare disorder, seizures are triggered predictably by an external stimulus, such as repetitive sounds, flashing lights, video games, or even touching certain parts of the body.

**Classification**

Seizures are classified as generalized or partial.

**Generalized:** In generalized seizures, the aberrant electrical discharge diffusely involves the entire cortex of both hemispheres from the onset, and consciousness is usually lost. Generalized seizures result most often from metabolic disorders and sometimes from genetic disorders. Generalized seizures include the following:
• Infantile spasms
• Absence seizures
• Tonic-clonic seizures
• Atonic seizures
• Myoclonic seizures

Partial seizures: In partial seizures, the excess neuronal discharge occurs in one cerebral cortex, and most often results from structural abnormalities. Partial seizures may be

• Simple (no impairment of consciousness)
• Complex (reduced but not complete loss of consciousness)

Partial seizures may be followed by a generalized seizure (called secondary generalization), which causes loss of consciousness. Secondary generalization occurs when a partial seizure spreads and activates the entire cerebrum bilaterally. Activation may occur so rapidly that the initial partial seizure is not clinically apparent or is very brief.

Symptoms and Signs

Seizures may be preceded by an aura. Auras may consist of sensory, autonomic, or psychic sensations (eg, paresthesias, a rising epigastric sensation, abnormal smells, a sensation of fear, a deja vu sensation).

Most seizures end spontaneously in 1 to 2 min. Generalized seizures are often followed by a postictal state, characterized by deep sleep, headache, confusion, and muscle soreness; this state lasts from minutes to hours. Sometimes the postictal state includes Todd's paralysis (a transient neurologic deficit, usually weakness, of the limb contralateral to the seizure focus).

Most patients appear neurologically normal between seizures, although high doses of the drugs used to treat seizure disorders, particularly anticonvulsants, can reduce alertness. Any progressive mental deterioration is usually related to the neurologic disorder that caused the seizures rather than to the seizures themselves. Rarely, seizures are unremitting.

Partial seizures: There are several types of partial seizures.

Simple partial seizures cause motor, sensory, or psychomotor symptoms without loss of consciousness. Specific symptoms reflect the affected area of the brain (see Table 176-2). In jacksonian seizures, focal motor symptoms begin in one hand, then march up the arm. Other focal seizures affect the face first, then spread to an arm and sometimes a leg. Some partial motor seizures begin with an arm raising and the head turning toward the moving arm.

Table 176-2. Manifestations of Partial Seizures by Site

Epilepsia partialis continua, a rare disorder, causes focal motor seizures that usually involve the arm, hand, or one side of the face; seizures recur every few seconds or minutes for days to years at a time. In adults, the cause is usually a structural lesion (eg, stroke). In children, it is usually a focal cerebral cortical inflammatory process (eg, Rasmussen encephalitis), possibly caused by a chronic viral infection or autoimmune processes.

Complex partial seizures are often preceded by an aura. During the seizure, patients may stare. Consciousness is impaired, but patients have some awareness of the environment (eg, they purposefully withdraw from noxious stimuli). The following may also occur:
• Oral automatisms (involuntary chewing or lip smacking)
• Limb automatisms (e.g., automatic purposeless movements of the hands)
• Utterance of unintelligible sounds without understanding what they say
• Resistance to assistance
• Tonic or dystonic posturing of the extremity contralateral to the seizure focus
• Head and eye deviation, usually in a direction contralateral to the seizure focus
• Bicycling or pedaling movements of the legs if the seizure emanates from the medial frontal or orbitofrontal head regions

Motor symptoms subside after 1 to 2 min, but confusion and disorientation may continue for another 1 or 2 min. Postictal amnesia is common. Patients may lash out if restrained during the seizure or while recovering consciousness if the seizure generalizes. However, unprovoked aggressive behavior is unusual.

Left temporal lobe seizures may cause verbal memory abnormalities; right temporal lobe seizures may cause visual spatial memory abnormalities.

**Generalized seizures:** Consciousness is usually lost, and motor function is abnormal from the onset.

**Infantile spasms** (see p. 2899) are characterized by sudden flexion and adduction of the arms and forward flexion of the trunk. Seizures last a few seconds and recur many times a day. They occur only in the first 5 yr of life, then are replaced by other types of seizures. Developmental defects are usually present.

**Typical absence seizures** (formerly called petit mal seizures) consist of 10- to 30-sec loss of consciousness with eyelid fluttering; axial muscle tone may or may not be lost. Patients do not fall or convulse; they abruptly stop activity, then just as abruptly resume it, with no postictal symptoms or knowledge that a seizure has occurred. Absence seizures are genetic and occur predominantly in children. Without treatment, such seizures are likely to occur many times a day. Seizures often occur when patients are sitting quietly, can be precipitated by hyperventilation, and rarely occur during exercise. Neurologic and cognitive examination results are usually normal.

**Atypical absence seizures** usually occur as part of the Lennox-Gastaut syndrome, a severe form of epilepsy that begins before age 4 yr. They differ from typical absence seizures as follows:

• They last longer.
• Jerking or automatic movements are more pronounced.
• Loss of awareness is less complete.

Many patients have a history of damage to the nervous system, developmental delay, abnormal neurologic examination results, and other types of seizures. Atypical absence seizures usually continue into adulthood.

**Atonic seizures** occur most often in children, usually as part of Lennox-Gastaut syndrome. Atonic seizures are characterized by brief, complete loss of muscle tone and consciousness. Children fall or pitch to the ground, risking trauma, particularly head injury.

**Tonic seizures** occur most often during sleep, usually in children. The cause is usually the Lennox-Gastaut syndrome. Tonic (sustained) contraction of axial muscles may begin abruptly or gradually, then
spread to the proximal muscles of the limbs. Tonic seizures usually last 10 to 15 sec. In longer tonic seizures, a few, rapid clonic jerks may occur as the tonic phase ends.

**Tonic-clonic seizures** may be primarily or secondarily generalized. Primarily generalized seizures typically begin with an outcry; they continue with loss of consciousness and falling, followed by tonic contraction, then clonic (rapidly alternating contraction and relaxation) motion of muscles of the extremities, trunk, and head. Urinary and fecal incontinence, tongue biting, and frothing at the mouth sometimes occur. Seizures usually last 1 to 2 min. There is no aura. Secondarily generalized tonic-clonic seizures begin with a simple partial or complex partial seizure.

**Myoclonic seizures** are brief, lightning-like jerks of a limb, several limbs, or the trunk. They may be repetitive, leading to a tonic-clonic seizure. The jerks may be bilateral or unilateral. Unlike other seizures with bilateral motor movements, consciousness is not lost unless the myoclonic seizure progresses into a generalized tonic-clonic seizure.

**Juvenile myoclonic epilepsy** is an epilepsy syndrome characterized by myoclonic, tonic-clonic, and absence seizures. It typically appears during adolescence. Seizures begin with a few bilateral, synchronous myoclonic jerks, followed in 90% by generalized tonic-clonic seizures. They often occur when patients awaken in the morning, especially after sleep deprivation or alcohol use. Absence seizures may occur in one third of patients.

**Febrile seizures** occur, by definition, with fever and in the absence of intracranial infection; they are considered a type of provoked seizure. They affect about 4% of children aged 3 mo to 5 yr (see p. 2898). Benign febrile seizures are brief, solitary, and generalized tonic-clonic in appearance. Complicated febrile seizures are focal, last > 15 min, or recur ≥ 2 times in < 24 h. Overall, 2% of patients with febrile seizures develop a subsequent seizure disorder. However, incidence of seizure disorders and risk of recurrent febrile seizures are much greater among children with complicated febrile seizures, preexisting neurologic abnormalities, onset before age 1 yr, or a family history of seizure disorders.

**Status epilepticus:** Generalized convulsive status epilepticus involves at least one of the following:

- Tonic-clonic seizure activity lasting > 5 to 10 min
- ≥ 2 seizures between which patients do not fully regain consciousness

The previous definition of > 30-min duration was revised to encourage more prompt identification and treatment. Untreated generalized seizures lasting > 60 min may result in permanent brain damage; longer-lasting seizures may be fatal. Heart rate and temperature increase. Generalized convulsive status epilepticus has many causes, including rapid withdrawal of anticonvulsants and head trauma.

Complex partial status epilepticus and absence status epilepticus often manifest as prolonged episodes of mental status changes. EEG may be required for diagnosis.

**Diagnosis**

- Clinical evaluation
- For new-onset seizures, neuroimaging, laboratory testing, and usually EEG
- For known seizure disorder, usually anticonvulsant levels
- For new-onset or known seizure disorders, other testing as clinically indicated

Evaluation must determine whether the event was a seizure vs another cause of obtundation, a pseudoseizure, or syncope), then identify possible causes or precipitants. Patients with new-onset seizures are evaluated in an emergency department; they can sometimes be discharged after thorough evaluation. Those with a known seizure disorder may be evaluated in a physician's office.
**History:** Patients should be asked about unusual sensations, suggesting an aura and thus a seizure, and about typical seizure manifestations. However, other conditions, such as suddenly decreased brain circulation (eg, due to ventricular arrhythmia) can have similar manifestations, including loss of consciousness and some myoclonic jerks.

History should include information about the first and any subsequent seizures (eg, duration, frequency, sequential evolution, longest and shortest interval between seizures, aura, postictal state, precipitating factors). All patients should be asked about risk factors for seizures:

- Prior head trauma or CNS infection
- Known neurologic disorders
- Drug use or withdrawal, particularly of recreational drugs
- Alcohol withdrawal
- Nonadherence to anticonvulsants
- Family history of seizures or neurologic disorders

Patients should also be asked about rare triggers (eg, repetitive sounds, flashing lights, video games, touching certain parts of the body) and about sleep deprivation, which can lower the seizure threshold.

**Physical examination:** A bitten tongue, incontinence (eg, urine or feces in clothing), or, in patients who have lost consciousness, prolonged confusion suggest seizure.

In pseudoseizures, generalized muscular activity and lack of response to verbal stimuli may at first glance suggest generalized tonic-clonic seizures. However, pseudoseizures can usually be distinguished from true seizures by clinical characteristics:

- Pseudoseizures often last longer (several minutes or more).
- Postictal confusion tends to be absent.
- Typical tonic phase activity, followed by clonic phase, usually does not occur.
- The progression of muscular activity does not correspond to true seizure patterns (eg, jerks moving from one side to the other and back [nonphysiologic progression], exaggerated pelvic thrusting).
- Intensity may wax and wane.
- Vital signs, including temperature, usually remain normal.
- Patients often actively resist passive eye opening.

Physical examination rarely indicates the cause when seizures are idiopathic but may provide clues when seizures are symptomatic (see Table 176-3).

**Testing:** Testing is done routinely, but normal results do not necessarily exclude a seizure disorder. Thus, the diagnosis may ultimately be clinical. Testing depends on the status of seizures and results of the neurologic examination.

If patients have a known seizure disorder and examination results are normal or unchanged, little testing is required except for blood anticonvulsant levels, unless patients have symptoms or signs of a treatable disorder such as trauma, infection, or a metabolic
disorder. If seizures are new-onset or if examination results are abnormal for the first time, neuroimaging is required.

**Head CT** is usually done immediately to exclude a mass or hemorrhage. Some experts say that CT can be deferred and possibly avoided in children with typical febrile seizures whose neurologic status rapidly returns to normal.

**Follow-up MRI** is recommended when CT is negative. It provides better resolution of brain tumors and abscesses and can detect cortical dysplasias, cerebral venous thrombosis, and herpes encephalitis. An epilepsy-protocol MRI of the head uses high-resolution coronal T1 and T2 sequences, which can detect hippocampal atrophy or sclerosis. MRI can detect some common causes of seizures, such as malformations of cortical development in young children and mesial temporal sclerosis, traumatic gliosis, and small tumors in adults.

**EEG** is critical in the diagnosis of epileptic seizures, particularly of complex partial or absence status epilepticus, when EEG may be the most definitive indication of a seizure. EEG may detect epileptiform abnormalities (spikes, sharp waves, spike and slow-wave complexes, polyspike and slow-wave complexes). Epileptiform abnormalities may be bilateral and generalized in patients with generalized seizures and may be localized in patients with partial seizures. EEG findings may include the following:

- Epileptiform abnormalities in temporal lobe foci between seizures (interictal) in complex partial seizures originating in the temporal lobe
- Interictal symmetric bursts of 4- to 7-Hz epileptiform activity in primarily generalized tonic-clonic seizures
- Focal epileptiform discharges in secondarily generalized seizures
- Spikes and slow-wave discharges at a rate of 3/sec in typical absence seizures
- Slow spike and wave discharges usually at a rate of < 2.5/sec in atypical absence seizures
- Bilateral polyspike and wave abnormality at a rate of 4- to 6-Hz in juvenile myoclonic epilepsy

However, normal EEG cannot exclude the diagnosis of epileptic seizures, which must be made clinically. EEG is less likely to detect abnormalities if seizures are infrequent. The initial EEG may detect an epileptiform abnormality in only 30 to 55% of patients with a known epileptic seizure disorder. Serial EEG may detect epileptiform abnormalities in up to 80 to 90% of such patients. In general, serial EEG with extended recording times and with tests done during sleep deprivation greatly increases the chance of detecting epileptiform abnormalities in patients with epileptic seizures. Inpatient combined video-EEG monitoring, usually for 2 to 7 days, records EEG activity and clinical behavior simultaneously. It is the most sensitive EEG testing available and is thus useful in differentiating epileptic from nonepileptic seizures.

Testing is also done to check for other disorders:

- Laboratory tests (eg, plasma glucose, BUN, creatinine, Na, Ca, Mg, and P, liver function tests) are done if a metabolic disorder is suspected.
- Head CT is done if meningitis or CNS infection is suspected; if results are normal, a lumbar puncture is required.
- Drug screens may be done to check for unreported use of recreational drugs, although this practice is controversial because positive results do not indicate causality and test results can be inaccurate.

If seizures are refractory and surgical resection is being considered, advanced imaging tests may be done in epilepsy centers. Functional MRI can identify functioning cortex and guide surgical resection. If EEG
and MRI do not clearly identify the epileptic focus, magnetoencephalography (MEG) with EEG (called magnetic source imaging, or MSI) may localize the lesion, avoiding the need for invasive intraoperative mapping procedures. Single-photon emission CT (SPECT) during the peri-ictal period may detect increased perfusion in the seizure focus and help localize the area to be surgically removed. Because injection of contrast is required at the time of seizure, patients must be admitted for continuous EEG-video monitoring when SPECT is done during the peri-ictal period.

Neuropsychologic testing may help identify functional deficits before and after surgery and help predict social and psychologic prognosis and capacity for rehabilitation.

**Prognosis**

With treatment, seizures are eliminated in one third of patients with epileptic seizures, and frequency of seizures is reduced by > 50% in another third. About 60% of patients whose seizures are well-controlled by drugs can eventually stop the drugs and remain seizure-free.

Sudden unexplained death in epilepsy (SUDEP) is a rare complication of unknown cause.

**Treatment**

- Elimination of the cause if possible
- Avoidance of or precautions during situations when loss of consciousness could be life threatening
- Drugs to control seizures
- Surgery if ≥ 2 drugs do not control seizures

Optimal treatment is to eliminate the causes whenever possible. If the cause cannot be corrected or identified, anticonvulsants are often required, particularly after a 2nd seizure; usefulness of anticonvulsants after a single seizure is controversial, and risks and benefits should be discussed with the patient. Because the risk of a subsequent seizure is low, drugs may be withheld until a 2nd seizure occurs, particularly in children. In children, certain anticonvulsants cause important behavior and learning problems.

During a generalized tonic-clonic seizure, injury should be prevented by loosening clothing around the neck and placing a pillow under the head. Attempting to protect the tongue is futile and likely to damage the patient's teeth or the rescuer's fingers. Patients should be rolled onto their left side to prevent aspiration. These measures should be taught to the patient's family members and coworkers.

Because partial seizures can become generalized, patients are at risk of losing consciousness and thus should be advised to take certain precautions. Until seizures are controlled, patients should refrain from activities in which loss of consciousness could be life threatening (eg, driving, swimming, climbing, operating power tools, bathing in a bathtub). After seizures are completely controlled (typically for > 6 mo), many such activities can be resumed if appropriate safeguards (eg, lifeguards) are used, and patients should be encouraged to lead a normal life, including exercise and social activities. In a few states, physicians must report patients with seizures to the Department of Motor Vehicles. However, most states allow automobile driving after patients have been seizure-free for 6 mo to 1 yr.

Patients should be advised to avoid cocaine and some other illicit drugs (eg, phencyclidine, amphetamines), which can trigger seizures, and to avoid alcohol. Some drugs (eg, haloperidol, phenothiazines) may lower seizure threshold and should be avoided if possible.

Family members must be taught a commonsense approach toward the patient. Overprotection should be replaced with sympathetic support that lessens negative feelings (eg, of inferiority or self-consciousness); invalidism should be prevented. Institutional care is rarely advisable and should be reserved for severely cognitively impaired patients and for patients with seizures so frequent and violent despite drug treatment that they cannot be cared for elsewhere.
**Acute seizures and status epilepticus:** Most seizures remit spontaneously in several minutes or less and do not require emergency drug treatment. Status epilepticus and most seizures lasting > 5 min require drugs to terminate the seizures, with monitoring of respiratory status. Endotracheal intubation is necessary if there is any indication of airway compromise. IV access should be quickly obtained, and lorazepam 0.05 to 0.1 mg/kg IV is given at a rate of 2 mg/min. Larger doses are sometimes required. However, if seizures continue after about 8 mg is given, fosphenytoin 15 to 20 PE (phenytoin equivalents)/kg IV is given at a rate of 100 to 150 PE/min; phenytoin 15 to 20 mg/kg IV at a rate of 50 mg/min is a 2nd choice. Additional seizures require an additional 5 to 10 PE/kg of fosphenytoin or 5 to 10 mg/kg of phenytoin. If IV access cannot be obtained, options include IM fosphenytoin and sublingual or rectal benzodiazepines.

Seizures that persist after use of lorazepam and phenytoin define refractory status epilepticus. Recommendations for a 3rd anticonvulsant vary and include phenobarbital, propofol, midazolam, and valproate. Phenobarbital 15 to 20 mg/kg IV at 100 mg/min (3 mg/kg/min in children) is given; continued seizures require another 5 to 10 mg/kg. A loading dose of valproate 10 to 15 mg/kg IV is an alternative. At this point, if status epilepticus has not abated, intubation and general anesthesia are necessary. The optimal anesthetic to use is controversial, but many physicians use propofol 15 to 20 mg/kg at 100 mg/min or pentobarbital 5 to 8 mg/kg (loading dose) followed by infusion of 2 to 4 mg/kg/h until EEG manifestations of seizure activity have been suppressed. Inhalational anesthetics are rarely used. After initial treatment, the cause of status epilepticus must be identified and treated.

**Posttraumatic seizures:** Drugs are given to prevent seizures if head injury causes significant structural injury (eg, large contusions or hematomas, brain laceration, depressed skull fracture) or a Glasgow Coma Scale (GCS) score of < 10. These drugs reduce risk of seizures during the first week after injury but do not prevent permanent posttraumatic epilepsy months or years later. They should be stopped after 1 wk unless seizures occur. If seizures begin > 1 wk after head injury, long-term treatment with drugs is required.

**Principles of long-term treatment:** No single drug controls all types of seizures, and different patients require different drugs. Some patients require multiple drugs. Some general principles apply:

- A single drug, usually the 1st or 2nd one tried, controls epileptic seizures in about 60% of patients.

- If seizures are difficult to control from the outset (in 30 to 40% of patients), ≥ 2 drugs may eventually be required.

- If seizures are intractable (refractory to an adequate trial of ≥ 2 drugs), patients should be referred to an epilepsy center to determine whether they are candidates for surgery.

Some drugs (eg, phenytoin, valproate), given IV or orally, reach the targeted therapeutic range very rapidly. Others (eg, lamotrigine, topiramate) must be started at a relatively low dose and gradually increased over several weeks to the standard therapeutic dose, based on the patient's lean body mass. Dose should be tailored to the patient's tolerance of the drug. Some patients have symptoms of drug toxicity when blood drug levels are low; others tolerate high levels without symptoms. If seizures continue, the daily dose is increased by small increments. The appropriate dose of any drug is the lowest dose that stops all seizures and has the fewest adverse effects, regardless of blood drug level. Blood drug levels are only guidelines. Once drug response is known, following the clinical course is more useful than measuring blood levels.

If toxicity develops before seizures are controlled, the dose is reduced to the pretoxic level. Then, another drug is added at a low dose, which is gradually increased until seizures are controlled. Patients should be closely monitored because the 2 drugs can interact, interfering with either drug's rate of metabolic degradation. The initial, ineffective drug is then slowly tapered and eventually withdrawn completely. Use of multiple drugs should be avoided if possible because incidence of adverse effects, poor adherence, and drug interactions increases significantly. Adding a 2nd drug helps about 10% of patients, but incidence of adverse effects more than doubles. The blood level of anticonvulsants is altered by many other drugs, and vice versa. Physicians should be aware of all potential drug-drug interactions.
interactions before prescribing a new drug.

Once seizures are controlled, the drug should be continued without interruption until patients have been seizure-free for at least 2 yr. At that time, stopping the drug may be considered. Most of these drugs can be tapered by 10% every 2 wk. Relapse is more likely in patients who have had any of the following:

- A seizure disorder since childhood
- Need for > 1 drug to be seizure-free
- Previous seizures while taking an anticonvulsant
- Partial or myoclonic seizures
- Underlying static encephalopathy
- Abnormal EEG results within the last year

Of patients who relapse, about 60% do so within 1 yr, and 80% within 2 yr. Patients who have a relapse when they are not taking anticonvulsants should be treated indefinitely.

**Drug choice for long-term treatment:** The drugs preferred vary according to type of seizure (see Table 176-4). For more detailed drug-specific information, see Table 176-5.

For partial seizures and generalized tonic-clonic seizures, the newer anticonvulsants (eg, clonazepam, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zosinamide) are no more effective than the established drugs. However, the newer drugs tend to have fewer adverse effects and to be better tolerated.

Infantile spasms, atonic seizures, and myoclonic seizures are difficult to treat. Valproate is preferred, followed by clonazepam. For infantile spasms, corticosteroids for 8 to 10 wk are often effective. The optimal regimen is controversial. ACTH 20 to 60 units IM once/day may be used. A ketogenic diet (a very high fat diet that induces ketosis) may help but is difficult to maintain.

For juvenile myoclonic epilepsy, life-long treatment is usually recommended. Carbamazepine, oxcarbazepine, or gabapentin can exacerbate the seizures.

For febrile seizures, drugs are not recommended unless children have a subsequent seizure in the absence of febrile illness. Previously, many physicians gave phenobarbital or other anticonvulsants to children with complicated febrile seizures to prevent nonfebrile seizures from developing, but this treatment does not appear effective, and long-term use of phenobarbital reduces learning capacity.

For seizures due to alcohol withdrawal, drugs are not recommended. Instead, treating the withdrawal syndrome tends to prevent seizures. Treatment usually includes a benzodiazepine.

**Adverse drug effects:** All anticonvulsants may cause an allergic scarlatiniform or morbilliform rash, and none is completely safe during pregnancy (see p. 2648).

For patients taking carbamazepine, CBC should be monitored routinely for the first year of therapy. Decreases in WBC count and dose-dependent neutropenia (neutrophil count < 1000/μL) are common. Sometimes, if no other drug can be readily substituted, decreasing the dose can manage these effects. However, if the WBC count decreases rapidly, the drug should be stopped.
Patients taking valproate should have liver function tests every 3 mo for 1 yr; if serum transaminases or ammonia levels increase significantly (> 2 times the upper limit of normal), the drug should be stopped. An increase in ammonia up to 1.5 times the upper limit of normal can be tolerated safely.

Carbamazepine, phenytoin, and valproate are pregnancy category D drugs (ie, teratogenicity occurs in animal and human pregnancies). Risk of neural tube defects is somewhat greater with valproate than other commonly used anticonvulsants. The newer drugs are category C (ie, teratogenicity occurs in animals, but human risk is unknown).

Fetal antiepileptic drug syndrome (cleft lip, cleft palate, cardiac defects, microcephaly, growth retardation, developmental delay, abnormal facies, limb or digit hypoplasia) occurs in 4% of children of women who take anticonvulsants during pregnancy. Yet, because uncontrolled generalized seizures during pregnancy can lead to fetal injury and death, continued treatment with drugs is generally advisable (see p. 2648). The risk should be put in perspective: Alcohol is more toxic to the developing fetus than any anticonvulsant. Taking folate supplements before conception helps reduce risk of neural tube defects and should be recommended to all women who are of childbearing age and who take anticonvulsants.

Surgery: About 10 to 20% of patients have intractable seizures refractory to medical treatment and are potential surgical candidates. If seizures originate from a focal, resectable area in the brain, resection of the epileptic focus usually improves seizure control markedly. If the focus is in the anteromesial temporal lobe, resection eliminates seizures in about 60% of patients. After surgical resection, some patients remain seizure-free without taking anticonvulsants, but many still require the drugs, but in reduced doses and possibly as monotherapy. Because surgery requires extensive testing and monitoring, these patients are best treated in specialized epilepsy centers.

Vagus nerve stimulation: Intermittent electrical stimulation of the left vagus nerve with an implanted pacemaker-like device (vagus nerve stimulator) is used as an adjunct to drug therapy in patients who have intractable seizures and are not candidates for epilepsy surgery. This procedure reduces the number of partial seizures by ≥ 50% in about 40%. After the device is programmed, patients can activate it with a magnet to abort an imminent seizure. Adverse effects include deepening of the voice during stimulation, cough, and hoarseness. Complications are minimal. Duration of effectiveness is unclear.
Chapter 177. Sleep and Wakefulness Disorders

Introduction

(See also Sleep Apnea on p. 1903; for sleep problems in children, see p. 2750.)

Almost half of all people in the US report sleep-related problems. Disordered sleep can cause emotional disturbance, memory difficulty, poor motor skills, decreased work efficiency, and increased risk of traffic accidents. It can even contribute to cardiovascular disorders and mortality.

Approach to the Patient With a Sleep or Wakefulness Disorder

The most commonly reported sleep-related symptoms are insomnia and excessive daytime sleepiness (EDS).

• Insomnia is difficulty falling or staying asleep or a sensation of unrefreshing sleep.

• EDS is the tendency to fall asleep during normal waking hours.

Insomnia and EDS are not disorders themselves but are symptoms of various sleep-related disorders. Parasomnias are abnormal sleep-related events.

Pathophysiology

There are 2 states of sleep, each marked by characteristic physiologic changes:

• Nonrapid eye movement (NREM): NREM sleep constitutes about 75 to 80% of total sleep time in adults. It consists of 4 stages in increasing depth of sleep. Slow, rolling eye movements, which characterize quiet wakefulness and early stage 1 sleep, disappear in deeper sleep stages. Muscle activity decreases as well. Stages 3 and 4 are referred to as deep sleep because arousal threshold is high; people may perceive these stages as high-quality sleep.

• Rapid eye movement (REM): REM sleep follows each cycle of NREM sleep. It is characterized by low-voltage fast activity on the EEG and postural muscle atonia. Respiration rate and depth fluctuate dramatically. Most dreams occur during REM sleep.

Progression through the stages, typically followed by a brief interval of REM sleep, occurs cyclically 5 to 6 times a night (see Fig. 177-1).

Individual sleep requirements vary widely, ranging from 6 to 10 h/24 h. Infants sleep a large part of the day; with aging, total sleep time and deep sleep tend to decrease, and sleep becomes more interrupted. In the elderly, stages 3 and 4 may disappear. These changes may account for increasing EDS and fatigue with aging, but their clinical significance is unclear.

Etiology

Some disorders can cause either insomnia or EDS (sometimes both), and some cause one or the other (see Table 177-1).

Insomnia is most often caused by

• Inadequate sleep hygiene

• Psychiatric disorders, particularly mood, anxiety, and substance use disorders

• Miscellaneous medical disorders such as cardiopulmonary disorders, musculoskeletal conditions, and
chronoic pain

• Adjustment sleep disorder and psychophysiologic insomnia

EDS is most often caused by

• Insufficient sleep syndrome
• Obstructive sleep apnea syndrome
• Miscellaneous medical, neurologic, and psychiatric conditions
• Circadian rhythm disorders such as jet lag and shift work sleep disorders

Inadequate sleep hygiene refers to behaviors that are not conducive to sleep. They include consumption of caffeine or sympathomimetic or other stimulant drugs (typically near bedtime, but even in the afternoon for people who are particularly sensitive), exercise or excitement (eg, a thrilling TV show) late in the evening, and an irregular sleep-wake schedule. Patients who compensate for lost sleep by sleeping late or by napping further fragment their nocturnal sleep.

Adjustment insomnia results from acute emotional stressors (eg, job loss, hospitalization) that disrupt sleep.

Psychophysiologic insomnia is insomnia (regardless of cause) that persists well beyond resolution of precipitating factors, usually because patients feel anticipatory anxiety about the prospect of another sleepless night followed by another day of fatigue. Typically, patients spend hours in bed focusing on and brooding about their sleeplessness, and they have greater difficulty falling asleep in their own bedroom than falling asleep away from home.

[Fig. 177-1. Typical sleep pattern in young adults.]

Physical disorders that cause pain or discomfort (eg, arthritis, cancer, herniated disks), particularly those that worsen with movement, can cause transient awakenings and poor sleep quality. Nocturnal seizures can also interfere with sleep.

Most major mental disorders are associated with EDS and insomnia. About 80% of patients with major depression report EDS and insomnia; conversely, 40% of chronic insomniacs have a major mental disorder, most commonly a mood disorder.

Insufficient sleep syndrome involves not sleeping enough at night despite adequate opportunity to do so, typically because of various social or employment commitments.

Drug-related sleep disorders result from chronic use of or withdrawal from various drugs (see Table 177-2).

Circadian rhythm disorders result in misalignment between endogenous sleep-wake rhythms and environmental light-darkness cycle. The cause may be external (eg, jet lag, shift work) or internal (eg, delayed or advanced sleep phase syndrome).

Central sleep apnea consists of repeated episodes of breathing cessation or shallow breathing during sleep, lasting at least 10 sec, caused by diminished respiratory effort. The disorder typically manifests as insomnia or as disturbed and unrefreshing sleep.

Obstructive sleep apnea consists of episodes of partial or complete closure of the upper airway during sleep, leading to cessation of breathing for > 10 sec. Sometimes patients awaken, gasping. These episodes disrupt sleep and result in a feeling of unrefreshing sleep and EDS.

Narcolepsy is characterized by chronic EDS, often with cataplexy, sleep paralysis, and hypnagogic or
hypnopompic hallucinations. Cataplexy is momentary muscular weakness or paralysis without loss of consciousness that is evoked by sudden emotional reactions (eg, mirth, anger, fear, joy, surprise). Weakness may be confined to the limbs (eg, patients may drop the rod when a fish strikes their line) or may cause a limp fall during hearty laughter (as in “weak with laughter”) or sudden anger. Sleep paralysis is momentary inability to move when just falling asleep or immediately after awakening. Hypnagogic and hypnopompic phenomena are vivid auditory or visual illusions or hallucinations that occur when just falling asleep (hypnagogic) or, less often, immediately after awakening (hypnopompic).

**Periodic limb movement disorder** (PLMD) is characterized by repetitive (usually every 20 to 40 sec) twitching or kicking of the lower extremities during sleep. Patients usually complain of interrupted nocturnal sleep or EDS. They are typically unaware of the movements

[Table 177-1. Some Causes of Insomnia and Excessive Daytime Sleepiness]

and brief arousals that follow and have no abnormal sensations in the extremities.

**Restless legs syndrome** is characterized by an irresistible urge to move the legs and, less frequently, the arms, usually accompanied by paresthesias (eg, creeping or crawling sensations) in the limbs when reclining. To relieve symptoms, patients move the affected extremity by stretching, kicking, or walking. As a result, they have difficulty falling asleep, repeated nocturnal awakenings, or both.

**Evaluation**

**History:** **History of present illness** should include duration and age at onset of symptoms and any events (eg, a life or work change, new drug, new medical disorder) that coincided with onset. Symptoms during sleeping and waking hours should be noted. The quality and quantity of sleep are identified by determining bedtime, latency of sleep (time from bedtime to falling asleep), number and time of awakenings, final morning awakening and arising times, and frequency and duration of naps. Having patients keep a sleep log for several weeks is more accurate than questioning them. Bedtime events (eg, food or alcohol consumption, physical or mental activity) should be evaluated. Intake of and withdrawal from drugs, alcohol, caffeine, and nicotine as well as level and timing of physical activity should also be included.

If EDS is the problem, severity should be quantified based on the propensity for falling asleep in different situations (eg, resting comfortably vs when driving a car). The Epworth Sleepiness Scale (see Table 177-3) may be used; a cumulative score ≥ 10 represents abnormal daytime sleepiness.

**Review of systems** should check for symptoms of specific sleep disorders, including snoring, interrupted breathing patterns, other nocturnal respiratory disturbances (sleep apnea syndromes); depression, anxiety, mania, and hypomania (mental sleep disorders); restlessness in the legs, an irresistible desire to move them, and jerking leg movements (restless legs syndrome); and cataplexy, sleep paralysis, and hypnagogic phenomena (narcolepsy). Bed partners or other family members can best identify some of these symptoms.

**Past medical history** should check for known disorders that can interfere with sleep, including COPD, asthma, heart failure, hyperthyroidism, gastroesophageal reflux, neurologic disorders (particularly movement and degenerative disorders), and painful disorders (eg, RA). Risk factors for obstructive sleep apnea include obesity, heart disorders, hypertension, stroke, smoking, snoring, and nasal trauma. Drug history should include questions about use of any drugs associated with sleep disturbance (see Table 177-2).

**Physical examination:** The physical examination is useful mainly for identifying signs associated with obstructive sleep apnea syndrome. Signs include obesity with fat distributed around the neck or midriff;
large neck circumference (≥ 43.2 cm in males, ≥ 40.6 cm in females); mandibular hypoplasia and retrognathia; nasal obstruction; enlarged tonsils, tongue, uvula, or soft palate; decreased pharyngeal patency; increased obstruction of uvula and soft palate by the tongue; and redundant pharyngeal mucosa. The chest should be examined for expiratory wheezes and kyphoscoliosis. Signs of right ventricular failure should be noted. A thorough neurologic examination should be done.

**Red flags:** The following findings are of particular concern:

- Falling asleep while driving or other potentially dangerous situations
- Repeated sleep attacks (falling asleep without warning)
- Breathing interruptions or awakening with gasping reported by bed partner
- Unstable cardiac or pulmonary status
- Recent stroke
- Status cataplecticus (continuous cataplexy attacks)
- History of violent behaviors or injury to self or others during asleep
- Frequent sleepwalking or other out-of-bed behavior

**Interpretation of findings:** Inadequate sleep hygiene and situational stressors are usually apparent in the history. EDS that disappears when sleep time is increased (eg, on weekends or vacations) suggests inadequate sleep syndrome. EDS that occurs without insomnia and is accompanied by cataplexy, hypnagogic/hypnopompic hallucinations, or sleep paralysis suggests narcolepsy.

Difficulty falling asleep (initial insomnia) should be distinguished from difficulty maintaining sleep (sleep maintenance insomnia). Initial insomnia suggests delayed sleep phase syndrome, chronic psychophysiologic insomnia, or childhood phobias. Sleep maintenance insomnia suggests advanced sleep phase syndrome, major depression, central or obstructive sleep apnea, periodic limb movement disorder, or aging. In patients with significant snoring, frequent awakenings, and other risk factors, obstructive sleep apnea is quite likely.

**Testing:** Tests are usually done when the clinical diagnosis is in doubt or when response to initial presumptive treatment is inadequate. Patients with obvious problems (eg, poor sleep habits, transient stress, shift work) do not require testing.

**Polysomnography** is particularly useful when obstructive sleep apnea syndrome, narcolepsy, nocturnal seizures, or periodic limb movement disorder is suspected. It also helps clinicians evaluate violent and potentially injurious sleep-related behaviors. It monitors brain activity (via EEG), eye movements, heart rate, respirations, O₂ saturation, and muscle tone and activity during sleep. Video recording may be used to identify abnormal movements during sleep. Polysomnography is typically done in a sleep laboratory; equipment for home use has been devised but is not widely used.

The **multiple sleep latency test** assesses speed of sleep onset in 5 daytime nap opportunities 2 h apart during the patient's typical daytime. Patients lie in a darkened room and are asked to sleep. Onset and stage of sleep (including REM) are monitored by polysomnography. This test's main use is in the diagnosis of narcolepsy.

For the **maintenance of wakefulness test**, patients are asked to stay awake in a quiet room. This test is probably a more accurate measure of ability to remain awake in everyday situations.

Patients with EDS may require laboratory tests of renal, liver, and thyroid function.

**Treatment**
Specific conditions are treated. Good sleep hygiene (see Table 177-4) is important whatever the cause and is often the only treatment patients with mild problems need.

**Hypnotics:** General guidelines for use of hypnotics (see Table 177-5) aim at minimizing abuse, misuse, and addiction.

For commonly used hypnotics, see Table 177-6. All hypnotics except ramelteon act at the benzodiazepine recognition site on the γ-aminobutyric (GABA) receptor and augment the inhibitory effects of GABA. The drugs differ primarily in elimination half-life and onset of action. Drugs with a short half-life are used for sleep-onset insomnia. Drugs with a longer half-life are useful for both sleep-onset and sleep-maintenance insomnia; they have greater potential for daytime carryover effects, especially after prolonged use or in the elderly. Patients who experience daytime sedation, incoordination, or other daytime effects should avoid activities requiring alertness (eg, driving), and the dose should be reduced, the drug stopped, or, if needed, another drug used. Other adverse effects include amnesia, hallucinations, incoordination, and falls.

Hypnotics should be used cautiously in patients with pulmonary insufficiency. In the elderly, any hypnotic, even in small doses, can cause restlessness, excitement, or exacerbation of delirium and dementia. Rarely, hypnotics can cause complex sleep-related behaviors, such as sleepwalking and even sleep driving; use of higher-than-recommended doses and concurrent consumption of alcoholic beverages may increase risk of such behaviors. Rarely, severe allergic reactions occur.

Prolonged use is discouraged because tolerance can develop (see p. 1524) and because abrupt discontinuation can cause rebound insomnia or even anxiety, tremor, and seizures. These effects are more common with benzodiazepines (particularly triazolam) and less common with the nonbenzodiazepines. Difficulties can be minimized by using the lowest effective dose for brief periods and by tapering the dose before stopping the drug (see also p. 1525).

**Other sedatives:** Many drugs not specifically indicated for insomnia are used to induce and maintain sleep.

Many patients use alcohol to help them sleep, but alcohol is a poor choice because after prolonged use and at higher doses, it produces unrefreshing, disturbed sleep with frequent nocturnal awakenings, often increasing daytime sleepiness. Alcohol can further impair respiration during sleep in patients with obstructive sleep apnea syndrome.

OTC antihistamines (eg, doxylamine, diphenhydramine) can induce sleep. However, efficacy is unpredictable, and these drugs have adverse effects such as daytime sedation, confusion, and systemic anticholinergic effects, which are particularly worrisome in the elderly.

Low doses of some antidepressants at bedtime may improve sleep, eg, doxepin 25 to 50 mg, paroxetine 5 to 20 mg, trazodone 50 mg, trimipramine 75 to 200 mg. However, antidepressants should be used in these low doses mainly when standard hypnotics are not tolerated (rare) or in higher (antidepressant) doses when depression is present.

Melatonin is a hormone that is secreted by the pineal gland (and that occurs naturally in some foods). Darkness stimulates secretion, and light inhibits it. By binding with melatonin receptors in the suprachiasmatic nucleus, melatonin mediates circadian rhythm, especially during physiologic sleep onset. Oral melatonin (typically 0.5 to 5 mg at bedtime) may be effective for sleep problems due to delayed sleep phase syndrome. It must be taken at the appropriate time (when endogenous melatonin is normally
secreted, in early evening for most people); taken at the wrong time, it can aggravate sleep problems. Its efficacy is largely unproved, and its safety is in question because it appears to stimulate coronary artery changes in animals. Available preparations of melatonin are unregulated, so content and purity cannot be ensured, and the effects of long-term use are unknown. Its use should be supervised by a physician.

Key Points

- Poor sleep hygiene and situational disruptors (eg, shift work, emotional stressors) cause many cases of insomnia.
- Medical conditions (eg, sleep apnea syndromes, pain disorders) and psychiatric conditions (eg, mood disorders) must be considered.
- Sleep studies (eg, polysomnography) are usually done when sleep apnea syndrome, periodic limb movements, or other sleep disorders are suspected; the clinical diagnosis is in doubt; or when response to initial presumptive treatment is inadequate.
- Hypnotics and sedatives should be used with caution in the elderly.
- Good sleep hygiene may be the only treatment needed by patients with mild insomnia problems.

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders are caused by desynchronization between internal sleep-wake rhythms and the light-darkness cycle. Patients typically have insomnia, excessive daytime sleepiness, or both, which typically resolve as the body clock realigns itself. Diagnosis is clinical. Treatment depends on the cause.

In circadian rhythm disorders, endogenous sleep-wake rhythms (body clock) and the external light-darkness cycle become misaligned (desynchronized). The cause may be internal (eg, delayed or advanced sleep phase syndrome) or external (eg, jet lag, shift work).

If the cause is external, the timing of other circadian body rhythms, including temperature and hormone secretion, is altered; in addition to insomnia and sleepiness, these alterations may cause nausea, malaise, irritability, and depression. Risk of cardiovascular disorders may also be increased.

Repetitive circadian shifts (eg, due to frequent long-distance travel or rotating shift work) are particularly difficult to adapt to, especially when the shifts change in a counterclockwise direction. Counterclockwise shifts are those that shift awakening and sleeping times earlier (eg, when flying eastward or when rotating shifts from days to nights to evenings). Symptoms resolve over several days or, in some patients (eg, the elderly), over a few weeks or months, as rhythms realign. Because light is the strongest synchronizer of circadian rhythms, exposure to bright light (sunlight or artificial light of 5,000 to 10,000 lux intensity) after desired awakening time speeds readjustment. Melatonin given in the evening may be tried (see p. 1708).

Patients with circadian rhythm disorders often misuse alcohol, hypnotics, and stimulants.

Circadian rhythm disorders include the following.

Circadian rhythm sleep disorder, jet lag type (jet lag disorder): This syndrome is caused by rapid travel across > 2 time zones. Eastward travel (advancing the sleep cycle) causes more severe symptoms than westward travel (delaying sleep).

If possible, travelers should gradually shift their sleep-wake schedule before travel to approximate that of their destination and maximize exposure to daylight (particularly in the morning) in the new locale. Short-acting hypnotics or wake-promoting drugs (eg, modafinil) may be used for brief periods after arrival.
Circadian rhythm sleep disorder, shift work type (shift work disorder): Severity of symptoms is proportional to the frequency of shift changes, the magnitude of each change, and the frequency of counterclockwise (sleep advancing) changes. Fixed-shift work (i.e., fulltime night or evening) is preferable; rotating shifts should go clockwise (i.e., day to evening to night). However, even fixed-shift workers have difficulties because daytime noise and light interfere with sleep quality, and workers often shorten sleep times to participate in social or family events.

Shift workers should maximize their exposure to bright light (sunlight or, for night workers, especially constructed bright artificial lightboxes) at times when they should be awake and ensure that the bedroom is as dark and quiet as possible during sleep. Sleep masks and white-noise devices are helpful. When symptoms persist and interfere with functioning, judicious use of hypnotics with a short half-life and wake-promoting drugs is appropriate.

Circadian rhythm sleep disorder, altered sleep phase types: In these syndromes, patients have normal sleep quality and duration with a 24-h circadian rhythm cycle, but the cycle is out of synch with desired or necessary wake times. Less commonly, the cycle is not 24 h, and patients awaken and sleep earlier or later each day. If able to follow their natural cycle, patients have no symptoms.

• Delayed sleep phase syndrome: Patients consistently go to sleep and awaken late (e.g., 3 AM and 10 AM). This pattern is more common during adolescence. If required to awaken earlier for work or school, excessive daytime sleepiness results; patients often present because school performance is poor or they miss morning classes. They can be distinguished from people who stay up late by choice because they cannot fall asleep earlier even if they try. Mild phase delay (< 3 h) is treated by progressive earlier arising plus morning bright light therapy, perhaps with melatonin 1 h before the desired bedtime. An alternative method is to progressively delay bedtime and awakening time by 3 h/day until the correct sleep and awake times are reached.

• Advanced sleep phase syndrome: This syndrome (early to bed and early to rise) is more common among the elderly and responds to treatment with bright light in the evening and light-preventing goggles in the morning.

• Non-24-h sleep-wake syndrome: Much less common, this syndrome is characterized by a free-running sleep-wake rhythm. The sleep-wake cycle commonly remains constant in length but is > 24 h, resulting in a delay of sleep and wake times by 1 to 2 h each day. This disorder is more common among blind people.

Insomnia and Excessive Daytime Sleepiness

Many sleep disorders manifest with insomnia and usually excessive daytime sleepiness (EDS). Sleep disorders may be caused by factors inside the body (intrinsic) or outside the body (extrinsic).

Inadequate sleep hygiene: Sleep is impaired by certain behaviors. They include consumption of caffeine or sympathomimetic or other stimulant drugs (typically near bedtime, but even in the afternoon for people who are particularly sensitive), exercise or excitement (e.g., a thrilling TV show) late in the evening, and an irregular sleep-wake schedule. Patients who compensate for lost sleep by sleeping late or by napping further fragment nocturnal sleep.

Insomniacs should adhere to a regular awakening time and avoid naps regardless of the amount of nocturnal sleep.

Adequate sleep hygiene can improve sleep (see Table 177-4).

Adjustment insomnia: Acute emotional stressors (e.g., job loss, hospitalization) can cause insomnia. Symptoms typically remit shortly after the stressors abate; insomnia is usually transient and brief. Nevertheless, if daytime sleepiness and fatigue develop, especially if they interfere with daytime functioning, short-term treatment with hypnotics is warranted. Persistent anxiety may require specific treatment.
Psychophysiologic insomnia: Insomnia, regardless of cause, may persist well beyond resolution of precipitating factors, usually because patients feel anticipatory anxiety about the prospect of another sleepless night followed by another day of fatigue. Typically, patients spend hours in bed focusing on and brooding about their sleeplessness, and they have greater difficulty falling asleep in their own bedroom than falling asleep away from home.

Optimal treatment combines cognitive-behavioral strategies and hypnotics. Although cognitive-behavioral strategies are more difficult to implement and take longer, effects are longer lasting, up to 2 yr after treatment is ended. These strategies include sleep hygiene (particularly restriction of time in bed), education, relaxation training, stimulus control, and cognitive therapy.

Hypnotics are suitable for patients who need rapid relief and whose insomnia has had daytime effects, such as EDS and fatigue. These drugs must not be used indefinitely in most cases.

Physical sleep disorders: Physical disorders may interfere with sleep and cause insomnia and EDS. Disorders that cause pain or discomfort (eg, arthritis, cancer, herniated disks), particularly those that worsen with movement, cause transient awakenings and poor sleep quality. Nocturnal seizures can also interfere with sleep.

Treatment is directed at the underlying disorder and symptom relief (eg, with bedtime analgesics).

Mental sleep disorders: Most major mental disorders can cause insomnia and EDS. About 80% of patients with major depression report these symptoms. Conversely, 40% of chronic insomniacs have a major mental disorder, most commonly a mood disorder.

Patients with depression may have initial sleeplessness or sleep maintenance insomnia. Sometimes in the depressed phase of bipolar disorder and in seasonal affective disorder, sleep is uninterrupted, but patients complain of unrelenting daytime fatigue.

If depression is accompanied by sleeplessness, antidepressants that provide more sedation (eg, amitriptyline, doxepin, mirtazapine, paroxetine, trazodone) may be chosen. These drugs are used at regular, not low, doses to ensure correction of the depression. These drugs may cause EDS and other adverse effects, such as weight gain. Alternatively, any antidepressant may be used with a hypnotic.

If depression is accompanied by EDS, antidepressants with activating qualities (eg, bupropion, venlafaxine, certain SSRIs such as fluoxetine and sertraline) may be chosen.

Insufficient sleep syndrome (sleep deprivation): Patients with this syndrome do not sleep enough at night, despite adequate opportunity to do so, to stay alert when awake. The cause is usually various social or employment commitments. This syndrome is probably the most common cause of EDS, which disappears when sleep time is increased (eg, on weekends or vacations).

Drug-related sleep disorders: Drug-related sleep disorders: Insomnia and EDS can result from chronic use of CNS stimulants (eg, amphetamines, caffeine), hypnotics (eg, benzodiazepines), other sedatives, antineoplastic chemotherapy, anticonvulsants (eg, phenytoin), oral contraceptives, methyldopa, propranolol, alcohol, and thyroid hormone preparations (see Table 177-2). Commonly prescribed hypnotics can cause irritability and apathy and reduce mental alertness. Many psychoactive drugs can induce abnormal movements during sleep.

Insomnia can develop during withdrawal of CNS depressants (eg, barbiturates, opioids, sedatives), tricyclic antidepressants, monoamine oxidase inhibitors, or illicit drugs (eg, cocaine, heroin, marijuana, phencyclidine). Abrupt withdrawal of hypnotics or sedatives can cause nervousness, tremors, and seizures.

Narcolepsy

Narcolepsy is characterized by chronic excessive daytime sleepiness, often with sudden loss
of muscle tone (cataplexy). Other symptoms include sleep paralysis and hypnagogic and hypnopompic hallucinations. Diagnosis is by polysomnography and multiple sleep latency testing. Treatment is with modafinil, various stimulants, or Na oxybate for excessive daytime sleepiness and certain antidepressants for associated symptoms.

The cause is unknown. In Europe, Japan, and the US, incidence is 0.2 to 1.6/1000. Narcolepsy is equally common in both sexes.

Narcolepsy is strongly associated with specific HLA haplotypes, and children of patients with narcolepsy have a 40-fold increased risk, suggesting a genetic cause. However, concordance in twins is low (25%), suggesting a prominent role for environmental factors, which often trigger the disorder. The neuropeptide hypocretin-1 is deficient in CSF of narcoleptic animals and most human patients, suggesting that the cause may be HLA-associated autoimmune destruction of hypocretin-containing neurons in the lateral hypothalamus.

Narcolepsy features dysregulation of the timing and control of REM sleep. Therefore, REM sleep intrudes into wakefulness and into the transition from wakefulness to sleep. Many symptoms of narcolepsy result from postural muscle paralysis and vivid dreaming, which characterize REM.

Symptoms and Signs

The main symptoms are excessive daytime sleepiness (EDS), cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis; about 10% of patients have all 4. Nocturnal sleep is often also disturbed and some patients develop hypersomnia (prolonged sleep times). Symptoms usually begin in adolescents or young adults without prior illness, although onset can be precipitated by an illness, a stressor, or a period of sleep deprivation. Once established, narcolepsy persists throughout life; life span is unaffected.

EDS: EDS can occur anytime. Sleep episodes vary from few to many per day, and each may last minutes or hours. Patients can resist the desire to sleep only temporarily but can be roused as readily as from normal sleep. Sleep tends to occur during monotonous conditions (eg, reading, watching television, attending meetings) but may also occur during complex tasks (eg, driving, speaking, writing, eating). Patients may also experience sleep attacks—episodes of sleep that strike without warning. Patients may feel refreshed when they awaken yet fall asleep again in a few minutes. Nighttime sleep may be unsatisfying and interrupted by vivid, frightening dreams. Consequences include low productivity, breaches in interpersonal relationships, poor concentration, low motivation, depression, a dramatic reduction in quality of life, and potential for physical injury (particularly due to motor vehicle collisions).

Cataplexy: Momentary muscular weakness or paralysis occurs without loss of consciousness; it is evoked by sudden emotional reactions, such as mirth, anger, fear, joy, or, often, surprise. Weakness may be confined to the limbs (eg, patients may drop the rod when a fish strikes their line) or may cause a limp fall during hearty laughter (as in "weak with laughter") or sudden anger. These attacks resemble the loss of muscle tone that occurs during REM sleep. Cataplexy occurs in about three fourth of patients.

Sleep paralysis: Patients are momentarily unable to move as they are just falling asleep or immediately after they awaken. These occasional episodes may be very frightening. They resemble the motor inhibition that accompanies REM sleep. Sleep paralysis occurs in about one fourth of patients but also in some healthy children and, less commonly, in healthy adults.

Hypnagogic or hypnopompic hallucinations: Particularly vivid auditory or visual illusions or hallucinations may occur when just falling asleep (hypnagogic) or, less often, immediately after awakening (hypnopompic). They are difficult to distinguish from intense reverie and are somewhat similar to vivid dreams, which are normal in REM sleep. Hypnagogic hallucinations occur in about one third of patients, are common among healthy young children, and occasionally occur in healthy adults.

Diagnosis

- Polysomnography
Multiple sleep latency testing

A delay of 10 yr from onset to diagnosis is common. A history of cataplexy strongly suggests narcolepsy in patients with EDS. Nocturnal polysomnography, followed by multiple sleep latency testing, is diagnostic. Findings include the following:

- REM episodes during at least 2 of 5 daytime nap opportunities
- Average sleep latency (time to fall asleep) of ≤ 8 min, observed after a minimum of 6 h of nocturnal sleep
- No other diagnostic abnormalities on nocturnal polysomnography

The maintenance of wakefulness test does not help with diagnosis but does help monitor treatment efficacy.

Other disorders that can cause chronic EDS are usually suggested by the history and physical examination; brain imaging and blood and urine tests can confirm the diagnosis. These disorders include space-occupying lesions affecting the hypothalamus or upper brain stem, increased intracranial pressure, and certain forms of encephalitis. Hypothyroidism, hyperglycemia, hypoglycemia, anemia, uremia, hypercapnia, hypercalcaemia, hepatic failure, and seizure disorders can also cause EDS with or without hypersomnia. Acute, relatively brief EDS and hypersomnia commonly accompany acute systemic disorders such as influenza.

The Kleine-Levin syndrome, a very rare disorder in adolescent boys, causes episodic hypersomnia and hyperphagia. Etiology is unclear but may be an autoimmune response to an infection.

Treatment

- Modafinil
- Sometimes amphetamine derivatives or Na oxybate
- Certain REM-suppressant antidepressants

Some patients who have occasional episodes of sleep paralysis or hypnagogic and hypnopompic hallucinations, infrequent and partial cataplexy, and mild EDS need no treatment. For others, stimulant drugs and anticataplectic drugs are used. Patients should also get enough sleep at night and take brief naps (< 30 min) at the same time every day (typically afternoon).

Patients with mild to moderate EDS benefit from modafinil, a long-acting wake-promoting drug. Its mechanism of action is unclear. Typically, modafinil 100 to 200 mg po is given in the morning. Dose is increased to 400 mg as needed, but some patients require considerably more. If effects do not last into the evening, a small 2nd dose (eg, 100 mg) at noon or 1 PM may be used, although this dose sometimes interferes with nocturnal sleep. Adverse effects include nausea and headache, which are mitigated by lower initial doses and slower titration. Modafinil can lower the effectiveness of oral contraceptives. It has abuse potential, although this is low.

Patients who do not respond to modafinil are usually given amphetamine derivatives instead of or with modafinil. Methylphenidate 5 mg po bid to 20 mg po tid is especially useful for immediate management because modafinil's onset is delayed. Methamphetamine 5 to 20 mg po bid or dextroamphetamine 5 mg po bid to 20 mg po tid may be used; all are available in long-acting preparations and therefore can be dosed once/day in many patients. They can also be used on an as needed basis for patients already taking modafinil because onset is rapid and duration is relatively short. Adverse effects include agitation, hypertension, tachycardia, and mood changes (eg, manic reactions); abuse potential is high.

Pemoline, although less addictive than amphetamines, is not recommended because it may be
hepatotoxic and liver enzymes must be monitored every 2 wk.

Na oxybate can also be used to treat EDS and cataplexy. A dose of 2.25 g po is taken at bedtime while in bed, followed by the same dose 2.5 to 4 h later. The maximum dose is 9 g/night. Adverse effects include headache, nausea, dizziness, nasopharyngitis, somnolence, vomiting, urinary incontinence, and sometimes sleepwalking. Na oxybate is a schedule III drug and has potential for abuse and dependence. It is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency and should not be used in patients with respiratory disorders.

Tricyclic antidepressants (particularly clomipramine, imipramine, and protriptyline) and monoamine oxidase inhibitors are useful in treating cataplexy, sleep paralysis, and hypnagogic and hypnopompic hallucinations. Clomipramine 25 to 150 mg po once/day in the morning seems to be the most potent anticataplectic but should be taken only during the day to reduce nocturnal arousal. SSRIs can also be used.

**Idiopathic Hypersomnia**

Idiopathic hypersomnia is EDS with or without long sleep time; it is differentiated from narcolepsy by lack of cataplexy, hypnagogic hallucinations, and sleep paralysis.

Idiopathic hypersomnia is not well characterized. Cause is presumed to be CNS dysfunction.

In idiopathic hypersomnia with long sleep time, the history or sleep logs reveal nocturnal sleep > 10 h; in idiopathic hypersomnia without long sleep time it is > 6 h but < 10 h. In both cases, polysomnography shows no evidence of other sleep abnormalities. Multiple sleep latency testing shows short sleep latencies (< 8 min) with fewer than 2 REM periods.

Treatment is similar to that of narcolepsy, except that anticataplectic drugs are unnecessary.

**Parasomnias**

Parasomnias are undesirable behaviors that occur during entry into sleep, during sleep, or during arousal from sleep. Diagnosis is clinical. Treatment may include drugs and psychotherapy.

For many of these disorders, history and physical examination can confirm the diagnosis.

**Somnambulism:** Sitting, walking, or other complex behavior occurs during sleep, usually with the eyes open but without evidence of recognition. Somnambulism is most common during late childhood and adolescence and occurs after and during arousal from nonrapid eye movement (NREM) stage 3 or 4 sleep. Prior sleep deprivation and poor sleep hygiene increase the likelihood of these episodes, and risk is higher for 1st-degree relatives of patients with the disorder. Patients may mumble repetitiously, and some injure themselves on obstacles or stairs. There is no accompanying dream. Usually, patients do not remember the episode.

Treatment is directed at protecting patients from injury. It includes using electronic alarms to awaken patients when they leave the bed, using a low bed, and removing obstacles from the bedroom. Benzodiazepines, particularly clonazepam 0.5 to 2 mg po, at bedtime may help.

**Sleep (night) terrors:** During the night, patients have episodes of fear, screaming, and flailing, often with sleepwalking. Patients are difficult to awaken. Sleep terrors are more common among children and occur after arousal from NREM stages 3 or 4 sleep; thus, they do not represent nightmares. In adults, sleep terrors can be associated with mental difficulties or alcoholism. If daily activities are affected (eg, if school work deteriorates), intermediate- or long-acting oral benzodiazepines (eg, clonazepam 1 to 2 mg, diazepam 2 to 5 mg) at bedtime may help.

**Nightmares:** Children are more likely to have nightmares than adults. Nightmares occur during REM sleep, more commonly when fever is present or after alcohol has been ingested. Treatment is directed at
any underlying mental distress.

REM sleep behavior disorder: Verbalization (sometimes profane) and often violent movements (eg, waving the arms, punching, kicking) occur during REM sleep. These behaviors may represent acting out dreams by patients who, for unknown reasons, do not have the atonia normally present during REM sleep.

This disorder is more common among the elderly, particularly those with CNS degenerative disorders (eg, Parkinson’s or Alzheimer’s disease, vascular dementia, olivopontocerebellar degeneration, multiple system atrophy, progressive supranuclear palsy). It can also occur in patients who have narcolepsy and with use of norepinephrine reuptake inhibitors (eg, atomoxetine, reboxetine, venlafaxine). Cause is usually unknown.

Diagnosis may be suspected based on symptoms reported by patients or the bed partner. Polysomnography can usually confirm the diagnosis. It may detect excessive motor activity during REM; audiovisual monitoring may document abnormal body movements and vocalizations. A neurologic examination is done to rule out neurodegenerative disorders. If an abnormality is detected, CT or MRI may be done.

Treatment is with clonazepam 0.5 to 2 mg po at bedtime. Most patients need to take the drug indefinitely to prevent recurrences; potential for tolerance or abuse is low. Bed partners should be warned about the possibility of harm and may wish to sleep in another bed until symptoms resolve. Sharp objects should be removed from the bedside.

Sleep-related leg cramps:

Muscles of the calf or foot muscles often cramp during sleep in otherwise healthy middle-aged and elderly patients. Diagnosis is based on the history and lack of physical signs or disability.

Prevention includes stretching the affected muscles for several minutes before sleep. Stretching as soon as cramps occur relieves symptoms promptly and is preferable to drug treatment. Numerous drugs (eg, quinine, Ca and Mg supplements, diphenhydramine, benzodiazepines, mexiletine) have been used; none is likely to be effective, and adverse effects may be significant (particularly with quinine and mexiletine). Avoiding caffeine and other sympathetic stimulants may help.

Periodic Limb Movement Disorder and Restless Legs Syndrome

Periodic limb movement disorder (PLMD) and restless legs syndrome (RLS) are characterized by abnormal motions of and sometimes sensations in the lower or upper extremities, which may interfere with sleep.

PLMD and RLS are more common during middle and older age; > 80% of patients with RLS also have PLMD.

The mechanism is unclear but may involve abnormalities in dopamine neurotransmission in the CNS. The disorders can occur in isolation or during drug withdrawal, with use of stimulants or certain antidepressants, during pregnancy, or in patients with chronic renal or hepatic failure, iron deficiency, anemia, and other disorders. In primary RLS, heredity may be involved; more than one third of patients with primary RLS have a family history of it. Risk factors may include a sedentary lifestyle, smoking, and obesity.

Symptoms and Signs

PLMD is characterized by repetitive (usually every 20 to 40 sec) twitching or kicking of the lower or upper extremities during sleep. Patients usually complain of interrupted nocturnal sleep or excessive daytime sleepiness. They are typically unaware of the movements and brief arousals that follow and have no abnormal sensations in the extremities.
RLS is a sensorimotor disorder characterized by an irresistible urge to move the legs, usually accompanied by paresthesias (eg, creeping or crawling sensations) and sometimes pain in the upper or lower extremities, which are more prominent when patients are inactive or recline, and peak in severity around bedtime. To relieve symptoms, patients move the affected extremity by stretching, kicking, or walking. As a result, they have difficulty falling asleep, repeated nocturnal awakenings, or both.

**Diagnosis**

- For RLS, history alone
- For PLMD, history and polysomnography

Diagnosis may be suggested by the patient's or bed partner's history. Polysomnography is necessary to confirm the diagnosis of PLMD, which is usually apparent as repetitive bursts of electromyographic activity. Polysomnography may be also done after RLS is diagnosed to determine whether patients also have PLMD, but polysomnography is not necessary for diagnosis of RLS itself.

Patients with either disorder should be evaluated medically for disorders that can contribute (eg, with blood tests for anemia and iron deficiency and with hepatic and renal function tests).

**Treatment**

- Pramipexole or ropinirole

Numerous drugs (eg, dopaminergic drugs, benzodiazepines, anticonvulsants, vitamins and minerals) are used; only dopaminergic drugs are specific for RLS.

Dopaminergic drugs, although often effective, may have adverse effects such as augmentation (symptoms are felt earlier in the day), rebound (symptoms worsen after stopping the drug or after effects of the drug dissipate), nausea, orthostatic hypotension, and insomnia. Two D₂ and D₃ dopamine agonists, pramipexole and ropinirole, are effective and have few serious adverse effects. Pramipexole 0.125 mg po is given 2 h before onset of severe symptoms and increased, as needed, by 0.125 mg po q 2 nights until symptoms are relieved (maximum dose 0.5 mg). Ropinirole 0.25 mg po is given 1 to 3 h before symptoms occur and is increased, as needed, by 0.25 mg nightly (maximum dose 4 mg).

Benzodiazepines may improve sleep continuity but do not reduce limb movements; they should be used cautiously to avoid tolerance and daytime sleepiness. Gabapentin beginning with 300 mg at bedtime can help when RLS is accompanied by pain. Dose is increased by 300 mg weekly (maximum dose 2700 mg). Opioids may also work but are used as a last resort because of tolerance, adverse effects, and abuse potential. Ferritin levels should be obtained and, if low (< 50 μg/L), supplementation with ferrous sulfate 325 mg with 100 to 200 mg of vitamin C at bedtime is warranted. Patients should exercise good sleep hygiene.
Chapter 178. Headache

**Approach to the Patient With Headache**

Headache is pain in any part of the head, including the scalp, face (including the orbitotemporal area), and interior of the head. Headache is one of the most common reasons patients seek medical attention.

**Pathophysiology**

Headache is due to activation of pain-sensitive structures in or around the brain, skull, face, sinuses, or teeth.

**Etiology**

Headache may occur as a primary disorder or be secondary to another disorder. Primary headache disorders include migraine, cluster headache (including chronic paroxysmal hemicrania and hemicrania continua), and tension-type headache. Secondary headache has numerous causes (see Table 178-1).

Overall, the most common causes of headache are:

- Tension-type headache
- Migraine

Some causes of headache are common; others are important to recognize because they are dangerous, require specific treatment, or both (see Table 178-2).

**Evaluation**

Evaluation focuses on determining whether a secondary cause is present. If no cause is identified, it focuses on diagnosing primary headache disorders.

**History: History of present illness** includes questions about headache location, duration, severity, onset (eg, sudden, gradual), and quality (eg, throbbing, constant, intermittent, pressure-like). Exacerbating and remitting factors (eg, head position, time of day, sleep, light, sounds, physical activity, odors, chewing) are noted. If the patient has had previous or recurrent headaches, the previous diagnosis (if any) needs to be identified, and whether the current headache is similar or different needs to be determined. For recurrent headaches, age at onset, frequency of episodes, temporal pattern (including any relationship to phase of menstrual cycle), and response to treatments (including OTC treatments) are noted.

**Review of systems** should seek symptoms suggesting a cause, including:

- Vomiting: Migraine, increased intracranial pressure
- Fever: Infection (eg, encephalitis, meningitis, sinusitis)
- Red eye and/or visual symptoms (halos, blurring): Acute angle-closure glaucoma
- Visual field deficits, diplopia, or blurring vision: Ocular migraine, brain mass lesion, idiopathic intracranial hypertension
• Lacrimation and facial flushing: Cluster headache

• Rhinorrhea: Sinusitis

• Pulsatile tinnitus: Idiopathic intracranial hypertension

• Preceding aura: Migraine

• Focal neurologic deficit: Encephalitis, meningitis, intracerebral hemorrhage, subdural hematoma, tumor or other mass lesion

• Seizures: Encephalitis, tumor or other mass lesion

• Syncope at headache onset: Subarachnoid hemorrhage

• Myalgias and/or vision changes (in people > 55 yr): Giant cell arteritis

**Past medical history** should identify risk factors for headache, including exposure to drugs, substances (particularly caffeine), and toxins (see Table 178-1), recent lumbar puncture, immunosuppressive disorders or IV drug use (risk of infection); hypertension (risk of brain hemorrhage); cancer (risk of brain metastases); and dementia, trauma, coagulopathy, or use of anticoagulants or ethanol (risk of subdural hematoma).

Family and social history should include any family history of headaches, particularly because migraine headache may be undiagnosed in family members.

**Physical examination:** Vital signs, including temperature, are measured. General appearance (eg, whether restless or calm in a dark room) is noted. A general examination, with a focus on the head and neck, and a full neurologic examination are done.

The scalp is examined for areas of swelling and tenderness. The ipsilateral temporal artery is palpated, and both temporomandibular joints are palpated for tenderness and crepitance while the patient opens and closes the jaw.

The eyes and periorbital area are inspected for lacrimation, flushing, and conjunctival injection. Pupillary size and light responses, extraocular movements, and visual fields are assessed. The fundi are checked for spontaneous venous pulsations and papilledema. If patients have vision-related symptoms or eye abnormalities, visual acuity is measured. If the conjunctiva is red, the anterior chamber and cornea are examined with a slit lamp if possible, and intraocular pressure is measured.

The nares are inspected for purulence. The oropharynx is inspected for swellings, and the teeth are percussed for tenderness.

Neck is flexed to detect discomfort, stiffness, or both, indicating meningismus. The cervical spine is palpated for tenderness.

**Red flags:** The following findings are of particular concern:

• Neurologic symptoms or signs (eg, altered mental status, weakness, diplopia, papilledema, focal neurologic deficits)

• Immunosuppression or cancer

• Meningismus

• Onset of headache after age 50
• Thunderclap headache (severe headache that peaks within a few seconds)

• Symptoms of giant cell arteritis (eg, visual disturbances, jaw claudication, fever, weight loss, temporal artery tenderness, proximal myalgias)

• Systemic symptoms (eg, fever, weight loss)

• Progressively worsening headache

• Red eye and halos around lights

**Interpretation of findings:** If similar headaches recur in patients who appear well and have a normal examination, the cause is rarely ominous. Headaches that have recurred since childhood or young adulthood suggest a primary headache disorder. If headache type or pattern clearly changes in patients with a known primary headache disorder, secondary headache should be considered.

Most single symptoms of primary headache disorders other than aura are nonspecific. A combination of symptoms and signs is more characteristic (see Table 178-2).

Red flag findings suggest a cause (see Table 178-3).

**Testing:** Most patients can be diagnosed without testing. However, some serious disorders may require urgent or immediate testing. Some patients require tests as soon as possible. CT (or MRI) should be done in patients with any of the following findings:

• Thunderclap headache

• Altered mental status

• Meningismus

• Papilledema

• Signs of sepsis (eg, rash, shock)

• Acute focal neurologic deficit

• Severe hypertension (eg, systolic > 220 mm Hg or diastolic > 120 mm Hg on consecutive readings)

In addition, if meningitis, subarachnoid hemorrhage, or encephalitis is being considered,

[Table 178-3, Matching Red Flag Findings with a Cause for Headache]

Lumbar puncture and CSF analysis should be done, if not contraindicated by imaging results.

Tonometry should be done if findings suggest acute narrow-angle glaucoma (eg, visual halos, nausea, corneal edema, shallow anterior chamber).

Other testing should be done within hours or days, depending on the acuity and seriousness of findings and suspected causes.

Neuroimaging, usually MRI, should be done if patients have any of the following:

• Focal neurologic deficit of subacute or uncertain onset

• Age > 50 yr
• Weight loss
• Cancer
• HIV infection or AIDS
• Change in an established headache pattern
• Diplopia

ESR should be done if patients have visual symptoms, jaw or tongue claudication, temporal artery signs, or other findings suggesting giant cell arteritis.

CT of the paranasal sinuses is done to rule out complicated sinusitis if patients have a moderately severe systemic illness (eg, high fever, dehydration, prostration, tachycardia) and findings suggesting sinusitis (eg, frontal, positional headache, epistaxis, purulent rhinorrhea).

Lumbar puncture and CSF analysis are done if headache is progressive and findings suggest idiopathic intracranial hypertension (eg, transient obscuration of vision, diplopia, pulsatile intracranial tinnitus) or chronic meningitis (eg, lethargy, vomiting, focal neurologic deficits).

**Treatment**

Treatment of headache is directed at the cause.

**Geriatrics Essentials**

New-onset headache after age 50 should be considered a secondary disorder until proven otherwise.

**Key Points**

• Recurrent headaches that began at a young age in patients with a normal examination are usually benign.

• Immediate neuroimaging is recommended for patients with altered mental status, seizures, papilledema, focal neurologic deficits, or thunderclap headache.

• CSF analysis is required for patients with meningismus and usually, after neuroimaging, for immunosuppressed patients.

• Patients with thunderclap headache require CSF analysis even if CT and examination findings are normal.

**Cluster Headache**

Cluster headaches cause excruciating, unilateral periorbital or temporal pain, with ipsilateral autonomic symptoms (ptosis, lacrimation, rhinorrhea, nasal congestion). Diagnosis is clinical. Acute treatment is with parenteral triptans, dihydroergotamine, or O\textsubscript{2}. Prevention is with verapamil, lithium, topiramate, divalproex, or a combination.

Cluster headache affects primarily men, typically beginning at age 20 to 40; prevalence in the US is 0.4%. Usually, cluster headache is episodic; for 1 to 3 mo, patients experience ≥ 1 attack/day, followed by remission for months to years. Some patients have cluster headaches without remission.

Pathophysiology is unknown, but the periodicity suggests hypothalamic dysfunction. Alcohol intake triggers cluster headache during the attack period but not during remission.

**Symptoms and Signs**
Symptoms are distinctive. Attacks usually occur at the same time each day, often awakening patients from sleep. Pain is always unilateral in an orbitotemporal distribution. It is excruciating, peaking within minutes; it usually subsides spontaneously within 30 min to 1 h. Patients are agitated, restlessly pacing the floor, unlike migraine patients who prefer to lie quietly in a darkened room.

Autonomic features, including nasal congestion, rhinorrhea, lacrimation, facial flushing, and Horner's syndrome, are prominent and usually occur on the same side as the headache.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on the distinctive symptom pattern and exclusion of intracranial abnormalities.

Other unilateral primary headache syndromes with autonomic symptoms should be excluded:

- Chronic paroxysmal hemicrania: Attacks are more frequent (> 5/day) and much briefer (usually just minutes) than in cluster headache.

- Hemicrania continua: Moderately severe continuous unilateral head pain occurs with superimposed brief episodes of more intense pain.

These 2 painful disorders, unlike cluster headache (and migraine), respond dramatically to indomethacin, but not to other NSAIDs.

**Treatment**

- For aborting attacks, parenteral triptans, dihydroergotamine, or 100% O₂

- For long-term prophylaxis, verapamil, lithium, topiramate, divalproex, or a combination

Acute attacks of cluster headache can be aborted with either parenteral triptans or dihydroergotamine alone (see Table 178-4) and/or 100% O₂ inhalation given by nonrebreathing face mask.

All patients require preventive drugs because cluster headache is frequent, severe, and incapacitating. Prednisone (eg, 60 mg po once/day) or a greater occipital nerve block (with a local anesthetic and a corticosteroid) can provide prompt temporary prevention while preventive drugs with slower onset of action (eg, verapamil, lithium, topiramate, divalproex) are initiated.

**Idiopathic Intracranial Hypertension**

(Benign Intracranial Hypertension; Pseudotumor Cerebri)

Idiopathic intracranial hypertension causes increased intracranial pressure without a mass lesion or hydrocephalus, probably by obstructing venous drainage; CSF composition is normal.

Idiopathic intracranial hypertension typically occurs in women of childbearing age. Incidence is 1/100,000 in normal-weight women but 20/100,000 in obese women. Intracranial pressure is elevated (> 250 mm H₂O); the cause is unknown but probably involves obstruction of cerebral venous outflow.

**Symptoms and Signs**

Almost all patients have a daily or near daily generalized headache of fluctuating intensity, at times with nausea. They may also have transient obscuration of vision, diplopia (due to 6th cranial nerve dysfunction), and pulsatile intracranial tinnitus. Vision loss begins peripherally and may not be noticed by
patients until late in the course. Permanent vision loss is the most serious consequence.

Bilateral papilledema is common; a few patients have unilateral or no papilledema. In some asymptomatic patients, papilledema is discovered during routine ophthalmoscopic examination. Neurologic examination may detect partial 6th cranial nerve palsy but is otherwise unremarkable.

[Table 178-4. Drugs for Migraine and Cluster Headaches*]

Diagnosis

- MRI with magnetic resonance venography
- Lumbar puncture

Diagnosis is suspected clinically and established by brain imaging (preferably MRI with magnetic resonance venography) that shows normal results, followed by lumbar puncture showing elevated opening pressure and normal CSF composition. Use of certain drugs and certain disorders can produce a clinical picture resembling idiopathic intracranial hypertension (see Table 178-5).

Treatment

- Acetazolamide
- Often weight loss
- NSAIDs or drugs used for migraines

Treatment is aimed at reducing pressure and relieving symptoms. Acetazolamide 250 mg po qid is used as a diuretic. Obese patients are encouraged to lose weight, which may help reduce intracranial pressure. Serial lumbar punctures are controversial but are sometimes used. Any potential causes (disorders or drugs) are corrected or eliminated if possible. NSAIDs or drugs used for migraine may relieve headache.

[Table 178-5. Conditions Associated with Papilledema and Idiopathic Intracranial Hypertension]

If vision deteriorates despite treatment, optic nerve sheath fenestration, shunting (lumboperitoneal or ventriculoperitoneal), or endovascular venous stenting may be indicated. Bariatric surgery with sustained weight loss may cure the disorder in obese patients who were otherwise unable to lose weight.

Frequent ophthalmologic assessment (including quantitative visual fields) is required to monitor response to treatment; testing visual acuity is not sensitive enough to warn of impending vision loss.

Migraine

Migraine is an episodic primary headache disorder. Symptoms typically last 4 to 72 h and may be severe. Pain is often unilateral, throbbing, worse with exertion, and accompanied by symptoms such as nausea and sensitivity to light, sound, or odors. Auras occur in about 25% of patients, usually just before but sometimes after the headache. Diagnosis is clinical. Treatment is with triptans, dihydroergotamine, antiemetics, and analgesics. Preventive regimens include lifestyle modifications (eg, of sleeping habits or diet) and drugs (eg, β-blockers, amitriptyline, topiramate, divalproex).

Epidemiology

Migraine is the most common cause of recurrent moderate to severe headache; 1-year prevalence is 18% for women and 6% for men in the US. Migraine most commonly begins during puberty or young adulthood, waxing and waning in frequency and severity over the ensuing years; it often diminishes after
Pathophysiology

Migraine is thought to be a neurovascular pain syndrome with altered central neuronal processing (activation of brain stem nuclei, cortical hyperexcitability, and spreading cortical depression) and involvement of the trigeminovascular system (triggering neuropeptide release, which causes painful inflammation in cranial vessels and the dura mater).

Many potential migraine triggers have been identified; they include the following:

- Drinking red wine
- Skipping meals
- Excessive afferent stimuli (eg, flashing lights, strong odors)
- Weather changes
- Sleep deprivation
- Stress
- Hormonal factors

Head trauma, neck pain, or temporomandibular joint dysfunction sometimes triggers or exacerbates migraine.

Fluctuating estrogen levels are a potent migraine trigger. Many women have onset of migraine at menarche, severe attacks during menstruation (menstrual migraine), and worsening during menopause. For most women, migraines remit during pregnancy (but sometimes they worsen during the 1st or 2nd trimester). Oral contraceptives and other hormone therapy occasionally trigger or worsen migraine and have been associated with stroke in women who have migraine with aura.

A rare subtype of migraine called familial hemiplegic migraine is associated with genetic defects on chromosomes 1, 2, and 19. The role of genes in the more common forms of migraine is under study.

Symptoms and Signs

Often, attacks are heralded by a prodrome (a sensation that a migraine is beginning), which may include mood changes, loss of appetite, nausea, or a combination.

An aura precedes attacks in about 25% of patients. Auras are temporary neurologic disturbances that can affect sensation, balance, muscle coordination, speech, or vision; they last minutes to an hour. The aura may persist after headache onset. Most commonly, auras involve visual symptoms (fortification spectra—eg, binocular flashes, arcs of scintillating lights, bright zigzags, scotomata). Paresthesias and numbness (typically starting in one hand and marching to the ipsilateral arm and face), speech disturbances, and transient brain stem dysfunction (causing, eg, ataxia, confusion or even obtundation) are less common than visual auras. Some patients have an aura with little or no headache.

Headache varies from moderate to severe, and attacks last from 4 hours to several days, typically resolving with sleep. The pain is often unilateral but may be bilateral, most often in a frontotemporal distribution, and is typically described as pulsating or throbbing.

Migraine is more than a headache. Associated symptoms such as nausea (and occasionally vomiting), photophobia, sonophobia, and osmophobia are prominent. Patients report difficulty concentrating during attacks. Routine physical activity usually aggravates migraine headache; this effect, plus the photophobia and sonophobia, encourages most patients to lie in a dark, quiet room during attacks. Severe attacks can
be incapacitating, disrupting family and work life.

Attacks vary significantly in frequency and severity. Many patients have several types of headache, including milder attacks without nausea or photophobia; they may resemble tension-type headache but are a forme fruste of migraine.

**Chronic migraines:** Patients with episodic migraine can develop chronic migraine. These patients have headaches ≥ 15 days/mo. This headache disorder used to be called combination or mixed headache because it had features of migraine and tension-type headache. These headaches often develop in patients who overuse drugs for acute treatment of headaches.

**Other symptoms:** Other, rare forms of migraine can cause other symptoms. Basilar artery migraine causes combinations of vertigo, ataxia, visual field loss, sensory disturbances, focal weakness, and altered level of consciousness. Hemiplegic migraine, which may be sporadic or familial, causes unilateral weakness.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on characteristic symptoms and a normal physical examination, which includes a thorough neurologic examination.

Red flag findings include the following:

- Pain that reaches peak intensity within a few seconds or less (thunderclap headache)
- Onset after age 50
- Headaches that increase in intensity or frequency for weeks or longer
- History of cancer (brain metastases) or an immunosuppressive disorder (eg, HIV infection, AIDS)
- Fever, meningismus, altered mental status, or a combination
- Persistent focal neurologic deficits
- Papilledema
- A clear change in an established headache pattern

Patients with characteristic symptoms and no red flag findings do not require testing. Patients with red flag findings often require brain imaging and sometimes lumbar puncture.

Common diagnostic errors include the following:

- Not realizing that migraine often causes bilateral pain and is not always described as throbbing
- Misdiagnosing migraine as sinus headache or eyestrain because of autonomic and visual symptoms of migraine
- Assuming that any headache in patients known to have migraine represents another migraine attack—a thunderclap headache or a change in the previous headache pattern may indicate a new, potentially serious disorder
- Mistaking migraine with aura for a transient ischemic attack, especially when the aura occurs without headache, in older people
Several unusual disorders can mimic migraine with aura: dissection of the carotid or vertebral artery, cerebral vasculitis, moyamoya disease, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), and MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes) syndrome.

**Prognosis**

For some patients, migraine is an infrequent, tolerable inconvenience. For others, it is a devastating disorder resulting in frequent periods of incapacity, loss of productivity, and severely impaired quality of life.

**Treatment**

- Elimination of triggers
- For stress, behavioral interventions
- For mild headaches, acetaminophen or NSAIDs
- For severe attacks, triptans

A thorough explanation of the disorder helps patients understand that, although migraine cannot be cured, it can be controlled, enabling them to better participate in treatment.

Patients are urged to keep a written headache diary to document the number and timing of attacks, possible triggers, and response to treatment. Identified triggers are eliminated when possible. Behavioral interventions (biofeedback, stress management, psychotherapy) are used when stress is a major trigger or when analgesics are being overused. Treatment of acute migraine headache is based on frequency, duration, and severity of attacks.

**Mild to moderate attacks:** NSAIDs or acetaminophen is used. Analgesics containing opioids, caffeine, or butalbital are helpful for infrequent, mild attacks but are prone to being overused, sometimes leading to a type of daily headache syndrome called medication overuse headache. Opioids should be used as a last resort (rescue drug) for severe headache when other measures are ineffective.

An antiemetic alone may be used to relieve mild or moderate attacks.

**Severe attacks:** If mild attacks evolve into incapacitating migraine or if attacks are severe from the onset, triptans are used. Triptans are selective serotonin 1B,1D receptor agonists. They are not analgesic per se but specifically block the release of vasoactive neuropeptides that trigger migraine pain. Triptans are most effective when taken at the onset of attacks. They are available in oral, intranasal, and sc forms (see Table 178-4); sc forms are more effective but have more adverse effects. Overuse of triptans can also lead to medication overuse headache. When nausea is prominent, combining a triptan with an antiemetic at the onset of attacks is effective.

IV dihydroergotamine with a dopamine antagonist antiemetic (eg, metoclopramide 10 mg IV, prochlorperazine 5 to 10 mg IV) helps abort very severe, persistent attacks. Dihydroergotamine is also available in an sc form and as a nasal spray.

Triptans and dihydroergotamine can cause coronary artery constriction and are thus contraindicated in patients with coronary artery disease or uncontrolled hypertension; these drugs must be used with caution in elderly patients and in patients with vascular risk factors.

A good response to dihydroergotamine or a triptan should not be interpreted as diagnostic for migraine because these drugs may relieve headache due to subarachnoid hemorrhage and other structural abnormalities.

Prochlorperazine suppositories (25 mg) or tablets (10 mg) are an option for patients who cannot tolerate...
triptans and other vasoconstrictors.

**Chronic migraines:** The same drugs used to prevent episodic migraine are used to treat chronic migraine.

**Prevention**

Daily preventive therapy is warranted when frequent migraines interfere with activity despite acute treatment.

For patients who use analgesics frequently, particularly those with medication overuse headache, preventive drugs (see Table 178-4) should be combined with a program for stopping overused analgesics. Choice of drug can be guided by coexisting disorders, as for the following:

- A small bedtime dose of amitriptyline for patients with insomnia
- A β-blocker for patients with anxiety or coronary artery disease
- Topiramate, which can induce weight loss, for obese patients or for patients who wish to avoid weight gain
- Divalproex for patients with mania

**Post-Lumbar Puncture and Other Low-Pressure Headaches**

Low-pressure headaches result from reduction in CSF volume and pressure due to lumbar puncture or spontaneous or traumatic CSF leaks.

Removal of CSF by lumbar puncture (LP) reduces CSF volume and pressure, as do spontaneous or traumatic CSF leaks.

Headache after LP is common, usually occurring hours to a day or two afterward, and can be severe. Younger patients with a small body mass are at greatest risk. Using small, noncutting needles reduces risk. The amount of CSF removed and duration of recumbency after LP do not affect incidence.

Spontaneous CSF leaks may result when an arachnoid cyst along the spinal canal ruptures. Coughing or sneezing may cause the rupture. CSF may leak after certain head or facial injuries (eg, basilar skull fractures).

Headache results when head elevation while sitting or standing stretches the pain-sensitive basal meninges. Headaches are intense, postural, and often accompanied by neck pain, meningismus, and vomiting. Headache is alleviated only by lying completely flat.

**Diagnosis**

- Clinical evaluation

Post-LP headache is clinically obvious, and testing is rarely needed; other low-pressure headaches may require brain imaging. MRI with gadolinium often shows diffuse enhancement of the pachymeninges and, in severe cases, downward sagging of the brain. CSF pressure is typically low or unobtainable if patients have been upright for any length of time (gravity accelerates CSF loss).

**Treatment**

- Hydration and analgesics
- Sometimes an epidural blood patch
The first line of treatment is recumbency, hydration, an elastic abdominal binder, mild analgesics, and caffeine. If post-LP headache persists after a day of such treatment, an epidural blood patch (injection of a few mL of the patient's clotted venous blood into the lumbar epidural space) is usually effective. A blood patch may also be effective for spontaneous or traumatic CSF leaks, which rarely require surgical closure.

**Tension-Type Headache**

Tension-type headache causes mild generalized pain without the incapacity, nausea, or photophobia associated with migraine.

Tension-type headaches may be episodic or chronic. Episodic tension-type headaches occur < 15 days/mo. Episodic tension-type headache is very common; most patients obtain relief with OTC analgesics and do not seek medical attention. Tension-type headaches that occur ≥ 15 days/mo are considered chronic.

**Symptoms and Signs**

The pain is usually mild to moderate and often described as viselike. These headaches originate in the occipital or frontal region bilaterally and spread over the entire head. Unlike migraine headaches, tension-type headaches are not accompanied by nausea and vomiting and are not made worse by physical activity, light, sounds, or smells. Potential triggers for chronic tension-type headache include sleep disturbances, stress, temporomandibular joint dysfunction, neck pain, and eyestrain.

Many patients with frequent tension-type headache often have mild headaches with some but not all features of migraine; these headaches resemble tension-type headaches but are a forme fruste of migraine and respond to migraine specific drugs.

Episodic headaches may last 30 min to several days. They typically start several hours after waking and worsen as the day progresses. They rarely awaken patients from sleep.

Chronic headaches may vary in intensity throughout the day but are almost always present.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on characteristic symptoms and a normal physical examination, which includes a neurologic examination. Potential triggers for chronic tension-type headache should be identified and treated.

**Treatment**

- Analgesics

- Sometimes behavioral and psychologic intervention

Some drugs used to prevent migraine, particularly amitriptyline, can help prevent chronic tension-type headache.

For most mild to moderate tension-type headaches, OTC analgesics (eg, aspirin, acetaminophen) can provide relief. Massaging the affected area may help.

For severe headaches, prescription analgesics (eg, those that contain opioids) may be used.

Behavioral and psychologic interventions (eg, relaxation and stress management techniques) are often used and are effective, especially when combined with drug treatment.
Chapter 179. Brain Infections

Introduction

Inflammation of the brain (encephalitis) is usually secondary to viral infection. Other brain infections include brain abscesses, helminthic infections, prion diseases, and subdural empyema. Meningitis (inflammation of the brain and spinal cord—see p. 1734), cytomegalovirus infection (see p. 1416), and HIV infection (see p. 1438) can also affect the brain. Slow virus infections, such as progressive multifocal leukoencephalopathy (see p. 1731), caused by JC virus, or subacute sclerosing panencephalitis, caused by the measles virus, are characterized by a long incubation and a prolonged course. Slow virus infection involving the rubella virus is now very rare in the US.

Brain Abscess

A brain abscess is an intracerebral collection of pus. Symptoms may include headache, lethargy, fever, and focal neurologic deficits. Diagnosis is by contrast-enhanced MRI or CT and sometimes culture. Treatment is with antibiotics and usually surgical drainage.

An abscess forms when an area of cerebral inflammation becomes necrotic and encapsulated by glial cells and fibroblasts. Edema around the abscess may increase intracranial pressure.

Etiology

A brain abscess can result from

- Direct extension of cranial infections (eg, osteomyelitis, mastoiditis, sinusitis, subdural empyema)
- Penetrating head wounds (including neurosurgical procedures)
- Hematogenous spread (eg, in bacterial endocarditis, congenital heart disease with right-to-left shunt, or IV drug abuse)
- Unknown causes

The bacteria involved are usually anaerobic and sometimes mixed, often including anaerobic streptococci or Bacteroides. Staphylococci are common after cranial trauma, neurosurgery, or endocarditis. Enterobacteriaceae are common with ear infections. Fungi (eg, Aspergillus) and protozoa (eg, Toxoplasma gondii, particularly in HIV-infected patients) can cause abscesses.

Symptoms and Signs

Symptoms result from increased intracranial pressure and mass effect. Headache, nausea, vomiting, lethargy, seizures, personality changes, papilledema, and focal neurologic deficits develop over days to weeks. Fever, chills, and leukocytosis may develop before the infection is encapsulated, but they may be absent or subside over time.

Diagnosis

- MRI
- Sometimes CT-guided aspiration

When symptoms suggest an abscess, contrast-enhanced MRI or CT is done. An abscess appears as an edematous mass with ring enhancement, which may be difficult to distinguish from a tumor or occasionally infarction; CT-guided aspiration, culture, surgical excision, or a combination may be necessary. Lumbar puncture is not done because it may precipitate transtentorial herniation and because CSF findings are nonspecific (see
Treatment

- Antibiotics (initially cefotaxime or ceftriaxone, then as guided by culture and susceptibility testing)
- Usually surgical drainage
- Sometimes corticosteroids, anticonvulsants, or both

All patients receive antibiotics for ≥ 4 to 8 wk. Initial empiric antibiotics include cefotaxime 2 g IV q 4 h or ceftriaxone 2 g IV q 12 h; both are effective against streptococci, Enterobacteriaceae, and most anaerobes but not against Bacteroides fragilis, which requires metronidazole 15 mg/kg (loading dose), then 7.5 mg/kg IV q 6 h. If Staphylococcus aureus is suspected, vancomycin 1 g q 12 h is used until sensitivity to nafcillin (2 g q 4 h) is determined. Response to antibiotics is best monitored by serial CT or MRI.

Drainage, stereotactic or open, provides optimal therapy and is necessary for most abscesses that are solitary and surgically accessible, particularly those > 2 cm in diameter.

Patients with increased intracranial pressure may benefit from a short course of high-dose corticosteroids (dexamethasone 10 mg IV once, then 4 mg IV q 6 h for 3 or 4 days). Anticonvulsants are sometimes recommended to prevent seizures.

Encephalitis

Encephalitis is inflammation of the parenchyma of the brain, resulting from direct viral invasion. Acute disseminated encephalomyelitis is brain and spinal cord inflammation caused by a hypersensitivity reaction to a virus or another foreign protein. Both disorders can be caused by many viruses. Symptoms include fever, headache, and altered mental status, often accompanied by seizures or focal neurologic deficits. Diagnosis requires CSF analysis and neuroimaging. Treatment is supportive and, for certain causes, includes antiviral drugs.

Etiology

Encephalitis may be a primary manifestation or a secondary (postinfectious) immunologic complication of viral infection.

Primary viral infection: Viruses causing primary encephalitis directly invade the brain. These infections may be

- Epidemic (eg, due to arbovirus, poliovirus, echovirus, or coxsackievirus)
- Sporadic (eg, due to herpes simplex, rabies, varicella-zoster, or mumps virus)

Mosquito-borne arboviral encephalitides infect people during the spring, summer, and early fall when the weather is warm. Incidence in the US varies from 150 to > 4000 cases yearly, mostly in children. Most cases occur during epidemics. Among arboviruses, La Crosse virus (California virus) is identified as a cause primarily in the north central US. However, the virus is geographically widespread, and La Crosse encephalitis is probably underrecognized and accounts for most cases of arbovirus encephalitis in children. Mortality rate is probably < 1%. Until 1975, St. Louis encephalitis occurred every 10 yr, mostly in the central and eastern US; it is now rare. As of 2009, West Nile encephalitis has spread from the East Coast, where it first appeared in 1999, to all of the western states. Mortality rate is about 9%. Small epidemics of eastern equine encephalitis occur every 10 to 20 yr in the eastern US, mainly among young children and people > 55. Mortality rate is about 50 to 70%. For unknown reasons, western equine encephalitis has largely disappeared from the US since 1988.

In the US, the most common sporadic encephalitis is caused by herpes simplex virus (HSV); hundreds to
several thousand cases occur yearly. Most are due to HSV-1, but HSV-2 may be more common among immunocompromised patients. HSV encephalitis occurs at any time of the year, tends to affect patients < 20 or > 40 yr, and is often fatal if untreated.

Primary encephalitis can occur as a late consequence of a viral infection. The best known types are HIV encephalopathy (which causes dementia—see p. 1682), subacute sclerosing panencephalitis (which occurs years after a measles infection and is thought to represent reactivation of the original infection—see p. 1466), and progressive multifocal leukoencephalopathy (which is caused by reactivation of JC virus—see p. 1731).

**Immunologic reaction:** Encephalitis can occur as a secondary immunologic complication of certain viral infections or vaccinations. Inflammatory demyelination of the brain and spinal cord can occur 1 to 3 wk later (as acute disseminated encephalomyelitis); the immune system attacks one or more CNS antigens that resemble proteins of the infectious agent. The most common causes used to be measles, rubella, chickenpox, and mumps (all now uncommon because childhood vaccination is widespread); smallpox vaccine; and live-virus vaccines (eg, the older rabies vaccines prepared from sheep or goat brain). In the US, most cases now result from influenza A or B virus, enteroviruses, Epstein-Barr virus, hepatitis A or B virus, or HIV.

**Pathophysiology**

In acute encephalitis, cerebral edema and petechial hemorrhages occur throughout the hemispheres, brain stem, cerebellum, and, occasionally, spinal cord. Direct viral invasion of the brain usually damages neurons, sometimes producing visible inclusion bodies. Severe infection, particularly untreated HSV encephalitis, can cause brain hemorrhagic necrosis.

Acute disseminated encephalomyelitis is characterized by perivenous demyelination and absence of virus in the brain.

**Symptoms and Signs**

Symptoms include fever, headache, and altered mental status, often accompanied by seizures and focal neurologic deficits. A GI or respiratory prodrome may precede these symptoms. Meningeal signs are typically mild and less prominent than other manifestations. Status epilepticus, particularly convulsive status epilepticus, or coma suggests severe brain inflammation and a poor prognosis. Olfactory seizures, manifested as an aura of foul smells (rotten eggs, burnt meat), indicate temporal lobe involvement and suggest HSV encephalitis.

**Diagnosis**

- MRI
- CSF testing

Encephalitis is suspected in patients with unexplained alterations in mental status. Clinical presentation and differential diagnoses may suggest certain diagnostic tests, but MRI and CSF analysis (including PCR for HSV) are usually done, sometimes with other tests to identify the causative virus. Despite extensive testing, the cause of most cases of encephalitis remains unknown.

**MRI:** MRI is sensitive for early HSV encephalitis, showing edema in the orbitofrontal and temporal areas, which HSV typically infects. MRI shows demyelination in progressive multifocal leukoencephalopathy and may show basal ganglia and thalamic abnormalities in West Nile and eastern equine encephalitis. MRI can also exclude lesions that mimic viral encephalitis (eg, brain abscess, sagittal sinus thrombosis). CT is much less sensitive than MRI for HSV encephalitis but can help because it is rapidly available and can exclude disorders that make lumbar puncture risky (eg, mass lesions, hydrocephalus, cerebral edema).

**CSF testing:** If encephalitis is present, CSF is characterized by lymphocytic pleocytosis, normal glucose, mildly elevated protein, and an absence of pathogens using Gram stain and culture (similar to CSF in
aseptic meningitis). CSF abnormalities may not develop until 8 to 24 h after onset of symptoms. Hemorrhagic necrosis can introduce many RBCs and some neutrophils into CSF, elevate protein, and modestly lower glucose.

PCR testing of CSF for many viruses (eg, HSV-1, HSV-2, varicella-zoster virus, cytomegalovirus, West Nile virus, enteroviruses, JC virus) is becoming increasingly available. PCR for HSV in CSF is sensitive and specific. However, results may not be available rapidly and, despite advances in technology, false-negative and false-positive results may still occur due to a variety of causes, not all being technical failures (eg, the blood in a mildly traumatic CSF tap may inhibit the PCR amplification step).

CSF viral cultures grow enteroviruses but not most other viruses.

CSF viral IgM titers are often useful for diagnosing acute infection, especially West Nile encephalitis, for which they are more reliable than PCR. Paired acute and convalescent serologic tests of CSF and blood must be drawn several weeks apart; they can detect an increase in viral titers specific for certain viral infections.

Brain biopsy: Brain biopsy may be indicated for patients who are worsening, who are responding poorly to treatment with acyclovir or another antimicrobial, or who have a lesion that is still undiagnosed.

Prognosis

Mortality rate varies with cause, but severity of epidemics due to the same virus varies during different years. Permanent neurologic deficits are more likely to occur in infants.

Treatment

- Supportive care
- Acyclovir for HSV encephalitis

Supportive therapy includes treatment of fever, dehydration, electrolyte disorders, and seizures. Euvolemia should be maintained.

If HSV encephalitis is suspected, acyclovir 10 mg/kg IV q 8 h is started promptly and continued usually for 14 days. Acyclovir is relatively nontoxic but can cause liver function abnormalities, bone marrow suppression, and transient renal failure. Giving acyclovir IV slowly over 1 h helps prevent nephrotoxicity.

Helminthic Brain Infections

Parasitic helminthic worms infect the CNS of millions of people in developing countries. Infected people who visit or immigrate to nonendemic areas, including the US, may present there. Worms may cause meningitis, encephalitis, cerebral masses, hydrocephalus, stroke, and myelopathy.

Neurocysticercosis: (See also p. 1365.) Among about 20 helminths that can cause neurologic disorders, the pork tapeworm Taenia solium causes by far the most cases in the Western Hemisphere. The resulting disorder is neurocysticercosis. After a person eats food contaminated with the worm's eggs, larvae migrate to tissues, including the brain, spinal cord, and CSF pathways, and form cysts. Cyst diameter rarely exceeds 1 cm in neural parenchyma but may exceed 5 cm in CSF spaces. Brain parenchymal cysts cause few symptoms until death of the worms triggers local inflammation, gliosis, and edema, causing seizures (most commonly), cognitive or focal neurologic deficits, or personality changes. Larger cysts in CSF pathways may cause obstructive hydrocephalus. Cysts may rupture into CSF, inducing subacute eosinophilic meningitis. Mortality rate for symptomatic neurocysticercosis is up to 50%.

Neurocysticercosis is suspected in patients who come from developing countries and who have eosinophilic meningitis or unexplained seizures, cognitive or focal deficits, or personality changes. It is suggested by multiple calcified cystic lesions seen on CT or MRI; a contrast agent may enhance the lesions. Diagnosis requires serum and CSF serologic tests and occasionally cyst biopsy.
Albendazole (7.5 mg/kg po q 12 h for 8 to 30 days; maximum daily dose, 800 mg) is the antihelminthic drug of choice. Alternatively, praziquantel 20 to 33 mg/kg po tid may be given for 30 days. Dexamethasone 8 mg once/day IV or po for the first 2 to 4 days may lessen the acute inflammatory response as the worms die. Antihelminthic therapy can cause serious morbidity in patients with a large number of cysts and may not help patients with a single cyst. Treatment must be carefully individualized. Short- or long-term anticonvulsant treatment may be required. Surgical excision of cysts and ventricular shunts may also be required.

Other infections: In schistosomiasis (see p. 1358), necrotizing eosinophilic granulomas develop in the brain, causing seizures, increased intracranial pressure, and diffuse and focal neurologic deficits.

Large, solitary echinococcal cysts (see Echinococcosis on p. 1362) can cause focal deficits and, occasionally, seizures.

Coenurosis, caused by tapeworm larvae, usually produces grapelike cysts that may obstruct CSF outflow in the 4th ventricle.

Gnathostomiasis, a rare infection, results in necrotic tracts surrounded by inflammation along the nerve roots, spinal cord, and brain or in subarachnoid hemorrhage, causing low-grade fever, stiff neck, photophobia, headache, migratory neurologic deficits (occasionally affecting the 6th or 7th cranial nerve), and paralysis.

Prion Diseases

(Transmissible Spongiform Encephalopathies)

Prion diseases are progressive, fatal, and untreatable degenerative brain disorders. They include

• Creutzfeldt-Jakob disease (CJD), the prototypic example
• Gerstmann-Straussler-Scheinker disease (GSS)
• Fatal insomnia (FI)
• Variant CJD (vCJD)
• Kuru

Prion diseases usually occur sporadically, with a worldwide annual incidence of about 1/1 million.

Prion diseases result from misfolding of a normal cell-surface brain protein called prion protein (PrP), whose exact function is unknown. Misfolded prion proteins (or prions) induce previously normal PrP to misfold; they are markedly resistant to degradation (similar to β-amyloid, which they resemble), resulting in slow but inexorable intracellular accumulation and neuronal cell death. Accompanying pathologic changes include gliosis and characteristic histologic vacuolar (spongiform) changes, resulting in dementia and other neurologic deficits. Symptoms and signs develop months to years after exposure.

Prion diseases can be caused by spontaneous or hereditary defects of the PrP gene, contained in the short arm of chromosome 20. Some defects cause familial CJD, some cause GSS, and others cause FI. Small abnormalities in particular codons may determine the predominant symptoms and rate of disease progression.

Prion diseases can also be transmitted by infected tissue. Cannibalism caused the spread of kuru in New Guinea, and prions can be transmitted via organ transplants and rarely by blood transfusion. Prion diseases can be transmitted between species via the food chain (eg, in vCJD). Prion diseases occur in mink, elk, deer, domestic sheep and cattle, and other mammals. In several western US states and Canada, chronic wasting disease of elk and deer, a prion disease, is a concern; whether this disease can
be transmitted to people who hunt, butcher, or eat affected animals is unknown.

Prion diseases should be considered in all patients with dementia, especially if it progresses rapidly.

Treatment is symptomatic. Prions resist standard disinfection techniques and pose risks to surgeons, pathologists, and technicians who handle contaminated tissues and instruments.

**Creutzfeldt-Jakob Disease**

*Creutzfeldt-Jakob disease is a sporadic or familial prion disease. Bovine spongiform encephalopathy (mad cow disease) is a variant form. Symptoms include dementia, myoclonus, and other CNS deficits; death occurs in 1 to 2 yr. Transmission can be prevented by taking precautions when handling infected tissues and using bleach to clean contaminated instruments. Treatment is supportive.*

CJD typically affects people > 40 yr (median, about 60 yr). It occurs worldwide; incidence is higher among North African Jews. Most cases are sporadic, but 5 to 15% are familial, with autosomal dominant transmission. In the familial form, age at onset is earlier and duration of disease is longer. CJD can be transmitted iatrogenically (eg, after cadaveric corneal or dural transplants, use of stereotactic intracerebral electrodes, or use of growth hormone prepared from human pituitary glands).

**vCJD** is most common in the United Kingdom (UK); it develops at a younger average age (< 30 yr) than does sporadic CJD. In the early 1980s, because of relaxed regulations for processing animal by-products, tissue from sheep infected with scrapie, a prion disease, was introduced into cattle feed. Thousands of cattle developed bovine spongiform encephalopathy (BSE), called mad cow disease. Some people who ate meat from affected cattle developed vCJD.

Because the incubation period in BSE is long, a connection between BSE and contaminated feed was not recognized in the UK until BSE had become an epidemic, which was controlled by massive slaughter of cattle. In the UK, the annual number of cases of vCJD starting in 1995 peaked at 28 in 2000 and then steadily declined, with only 5 cases/yr reported between 2005 and 2007 and only 1 in 2008; as of December 2008, the total number of cases was 167. However, 2 of 3 cases linked to blood transfusion occurred in 2006. Whether there exists a latent pool of people who have received blood transfusions who are thus at risk for development of vCJD is unclear. Although vCJD has been restricted to the UK and Europe thus far, BSE has been reported in a small number of North American cattle.

**Symptoms and Signs**

About 70% of patients present with memory loss and confusion, which eventually occur in all patients; 15 to 20% present with incoordination and ataxia, which often develop early in the disease. Myoclonus provoked by noise or other sensory stimuli (startle myoclonus) often develops in the middle to late stages of disease. Although dementia, ataxia, and myoclonus are most characteristic, other neurologic abnormalities (eg, hallucinations, seizures, neuropathy, various movement disorders) can occur. Ocular disturbances (eg, visual field defects, diplopia, dimness or blurring of vision, visual agnosia) are common.

**Prognosis**

Death typically occurs after 6 to 12 mo, commonly due to pneumonia. Life expectancy in vCJD is longer (averaging 1.5 yr).

**Diagnosis**

• MRI

• Exclusion of other disorders

CJD should be considered in elderly patients with rapidly progressive dementia, especially if accompanied by myoclonus or ataxia; however, CNS vasculitis, hyperthyroidism, and bismuth intoxication...
must be excluded.

vCJD is considered in younger patients who have ingested processed beef in the UK; Wilson's disease should be excluded.

Diagnosis may be difficult, and diagnostic findings may develop only over time. MRI may show cerebral atrophy. Diffusion-weighted MRI frequently shows basal ganglia and cortical abnormalities. CSF is typically normal, but characteristic 14-3-3 protein is often detected. EEG may show characteristic periodic sharp waves. Brain biopsy is usually unnecessary.

Prevention

Because there is no effective treatment, prevention is essential. Workers handling fluids and tissues from patients suspected of having CJD must wear gloves and avoid mucous membrane exposure. Contaminated skin can be disinfected by 5 to 10 min of exposure to 4% Na hydroxide, followed by extensive washing with water. Steam autoclaving of materials at 132°C for 1 h or immersion in 4% Na hydroxide or 10% Na hypochlorite solution for 1 h is recommended. Standard methods of sterilization (eg, exposure to formalin) are ineffective. The US Department of Agriculture (USDA) currently carries out BSE surveillance for 2000 to 5000 cattle/mo. In 2004, a positive BSE case in the US caused testing to be expanded to an average 1000 cattle/day, but testing was subsequently reduced when ensuing years yielded only 2 positive cases.

Gerstmann-Straussler-Scheinker Disease

Gerstmann-Straussler-Scheinker disease is an autosomal dominant prion brain disease that begins during middle age.

GSS occurs worldwide and is similar to but about 100-fold less common than CJD. It develops at an earlier age (40 vs 60 yr), and average life expectancy is longer (5 yr vs 6 mo).

Patients have cerebellar dysfunction with unsteady gait, dysarthria, and nystagmus. Gaze palsies, deafness, dementia, parkinsonism, hyporeflexia, and extensor plantar responses are also common. Myoclonus is much less common than in CJD.

GSS should be considered in patients with characteristic symptoms and signs and a family history, particularly if they are ≤ 45 yr. Genetic testing can confirm the diagnosis.

Fatal Insomnia

Fatal insomnia is a typically hereditary prion disorder causing difficulty sleeping, motor dysfunction, and death.

FI, a very rare disease, usually results from an autosomal dominant mutation, but several sporadic cases have been identified. Average age at onset is 40 yr (ranging from the late 30s to the early 60s).

Common early symptoms include difficulty falling asleep and intermittent motor dysfunction (eg, myoclonus, spastic paresis). This stage can last for months but eventually progresses to severe insomnia, myoclonus, sympathetic hyperactivity (eg, hypertension, tachycardia, hyperthermia, sweating), and dementia. Death occurs in an average of 13 mo.

FI should be considered in patients with motor dysfunction, sleep disturbances, and a family history. Genetic testing can confirm the diagnosis.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of the JC virus. The disease usually occurs in patients with impaired cell-mediated immunity. It causes subacute and progressive CNS demyelination, multifocal neurologic deficits, and death, usually
within a year. Diagnosis is with contrast-enhanced CT or MRI plus CSF PCR. In AIDS patients, highly active antiretroviral therapy may slow down the progression, and patients taking immunosuppressants may improve when those drugs are withdrawn. Treatment is otherwise supportive.

Etiology

PML is caused by reactivation of the JC virus, a ubiquitous human papovavirus that is typically acquired during childhood and remains latent in the kidneys and possibly other sites (eg, mononuclear cells, CNS). The reactivated virus has a tropism for oligodendrocytes. Most patients have depressed cell-mediated immunity due to AIDS (the most common risk factor), reticuloendothelial system disorders (eg, leukemia, lymphoma), or other conditions (eg, Wiskott-Aldrich syndrome, organ transplantation). The risk in AIDS increases with increasing HIV viral load; prevalence of PML has decreased because of widespread use of more effective antiretrovirals. Rarely, PML occurs as a complication of immunomodulatory therapy (eg, natalizumab, rituximab).

Symptoms and Signs

Clumsiness may be the first symptom. Hemiparesis is the most common finding. Aphasia, dysarthria, and hemianopia are also common. Multifocal cortical damage produces cognitive impairment in two thirds of patients. Sensory, cerebellar, and brain stem deficits may be present. Headaches and convulsive seizures are rare and occur most often in patients with AIDS. Gradual, relentless progression culminates in death, usually 1 to 9 mo after symptoms begin.

Diagnosis

- MRI
- CSF testing for JC viral antigen

PML is suspected in patients with unexplained progressive brain dysfunction, particularly in those with depressed cell-mediated immunity. Provisional diagnosis is made by contrast-enhanced MRI, which shows single or multiple white matter lesions on T2-weighted images. A contrast agent enhances, usually faintly and peripherally, 5 to 15% of lesions. CT usually shows low-density, nonenhancing lesions but is significantly less sensitive than MRI.

CSF is analyzed for JC viral antigen using PCR; a positive result with compatible neuroimaging findings is nearly pathognomonic. Routine CSF analysis is usually normal.

Serologic tests are not helpful. Stereotaxic biopsy can provide a definitive diagnosis but is rarely warranted.

Treatment

- Supportive care

Treatment is supportive. Experimental use of drugs such as cidofovir and other antivirals has failed to provide benefit. However, highly active antiretroviral therapy (HAART) in AIDS patients has improved outcome in PML, increasing the 1-yr survival rate from 10% to 50%. Withdrawal of immunosuppressants may also result in clinical improvement.

However, using aggressive antiretroviral therapy (or stopping immunosuppressants) has been associated with immune reconstitution inflammatory syndrome (IRIS—see p. 1450), in which the recovering immune system produces an intense inflammatory response against the JC virus, thus worsening symptoms. If IRIS develops, imaging shows new contrast enhancement of the lesions and may show significant cerebral edema. Corticosteroids may be helpful.

Rabies
Rabies is a viral encephalitis transmitted by the saliva of infected bats and certain other infected mammals. Symptoms include depression and fever, followed by agitation, excessive salivation, and hydrophobia. Diagnosis is by serologic tests or biopsy. Vaccination is indicated for people at high risk of exposure. Postexposure prophylaxis involves wound care and passive and active immunoprophylaxis. The disorder is almost universally fatal. Treatment is supportive.

Rabies causes > 50,000 human deaths worldwide annually, mostly in Latin America, Africa, and Asia, where canine rabies is endemic. In the US, vaccination of domestic animals has reduced rabies cases in people to < 6/yr, mostly transmitted by infected bats. Infected raccoons, skunks, and foxes can also transmit rabies.

Rabid animals transmit the infection through their saliva, usually by biting. Rarely, the virus can enter through a skin abrasion or across mucous membranes of the eyes, nose, or mouth. The virus travels from the site of entry via peripheral nerves to the spinal cord (or to the brain stem when the face is bitten), then to the brain. It spreads from the CNS via peripheral nerves to other parts of the body. Involvement of the salivary glands and oral mucosa is responsible for transmissibility.

Symptoms and Signs

Pain or paresthesias may develop at the site of the bite. Rapidity of progression depends on the viral inoculum and proximity of the wound to the brain. The incubation period averages 1 to 2 mo but may be > 1 yr. Initial symptoms are nonspecific: fever, headache, and malaise. Within days, encephalitis (furious rabies; in 80%) or paralysis (dumb rabies; in 20%) develops. Encephalitis causes restlessness, confusion, agitation, bizarre behavior, hallucinations, and insomnia. Salivation is excessive, and attempts to drink cause painful spasms of the laryngeal and pharyngeal muscles (hydrophobia). In the paralytic form, ascending paralysis and quadriplegia develop without delirium and hydrophobia.

Diagnosis

• Skin biopsy

• Sometimes PCR testing of fluid or tissue samples

Rabies is suspected in patients with encephalitis or ascending paralysis and a history of an animal bite or exposure to bats; bat bites may be superficial and overlooked.

Direct fluorescence antibody testing of a biopsy specimen of skin from the nape of the neck is the diagnostic test of choice. Diagnosis can also be made by PCR of CSF, saliva, or tissue. Specimens tested for rabies antibodies include serum and CSF. CT, MRI, and EEG are normal or show nonspecific changes.

Treatment

• Supportive care

Treatment is only supportive and includes heavy sedation (eg, with ketamine and midazolam) and comfort measures. Death usually occurs 3 to 10 days after symptoms begin. Only a handful of patients have survived; all but one of them received immunoprophylaxis before onset of symptoms. There is evidence that giving rabies vaccine and immune globulin after clinical rabies develops may cause more rapid deterioration.

Experimental therapies with ribavirin, amantadine, interferon-alfa, and other drugs are sometimes tried in desperation.

Prevention
**Preexposure**: Rabid animals can often be recognized by their strange behavior; they may be agitated and vicious, weak, or paralyzed and may show no fear of people. Nocturnal animals (eg, bats, skunks, raccoons) may be out during the day. Bats may make unusual noises and have difficulty flying. An animal suspected of having rabies should not be approached. Local health authorities should be contacted to remove the animal.

Human diploid cell rabies vaccine (HDCV) is safe and recommended for preexposure prophylaxis for people at risk, including veterinarians, animal handlers, spelunkers, workers who handle the virus, and travelers to endemic areas. A total of three 1-mL doses are given IM, one each on days 0, 7, and between day 21 and 28.

**Postexposure**: Exposure is considered to be a bite that breaks the skin or any contact between mucous membrane or broken skin and animal saliva. If exposure occurs, prompt, meticulously executed prophylaxis almost always prevents human rabies. The wound is cleansed immediately and thoroughly with soap and water or benzalkonium chloride. Deep puncture wounds are flushed with soapy water using moderate pressure. Wounds are usually left open.

Postexposure prophylaxis (PEP) with rabies vaccine and rabies immune globulin (RIG) is given depending on the biting animal and circumstances (see Table 179-1). PEP is begun, and the animal's brain is tested for virus. Local or state health departments or the Centers for Disease Control and Prevention usually conduct testing and can advise on other treatment issues.

For PEP, RIG 20 IU/kg is infiltrated around the wound for passive immunization; if injection volume is too much for distal areas (eg, fingers, nose), some RIG may be given IM. This treatment is accompanied by HDCV for active immunization. HDCV is given in a series of five 1-mL IM injections (deltoid area is preferred), beginning on the day of exposure (day 0), in a limb other than the one used for RIG. Subsequent injections occur on days 3, 7, 14, and 28. The WHO also recommends a 6th injection on day 90. Rarely, a serious systemic or neuroparalytic reaction occurs; then, completion of vaccination is weighed against the patient's risk of developing rabies. Rabies antibody titer is measured to help assess risk of stopping vaccination.

PEP for a person previously vaccinated against rabies includes 1-mL IM injections of HDCV on days 0 and 3 but no RIG.

**Subdural Empyema**

Subdural empyema is a collection of pus between the dura mater and arachnoid. Symptoms include fever, lethargy, focal neurologic deficits, and seizures. Diagnosis is by contrast-enhanced CT or MRI. Treatment is with surgical drainage and antibiotics.

**Etiology**

Subdural empyema is usually a complication of sinusitis (especially frontal, ethmoidal, or sphenoidal), but it can follow ear infections, cranial trauma or surgery, or, rarely, bacteremia. Pathogens are similar to those that cause brain abscess (see p. 1726). In children < 5 yr, the usual cause is bacterial meningitis; because childhood meningitis is now uncommon, childhood subdural empyema is uncommon.

**Complications**: Cortical venous thrombosis and brain abscess are common complications, and subdural empyema can rapidly spread to involve an entire cerebral hemisphere.

**Symptoms and Signs**

Fever, headache, lethargy, focal neurologic deficits (suggesting widespread involvement of one cerebral
hemisphere), and seizures evolve over several days. Meningeal signs, vomiting, and papilledema are common. Without treatment, coma and death occur rapidly.

**Diagnosis**

- MRI

Diagnosis is by contrast-enhanced MRI or CT. Blood and surgical specimens are cultured aerobically and anaerobically. Lumbar puncture provides little useful information and may precipitate transtentorial herniation. If subdural empyema is suspected (eg, based on symptom duration of several days, focal deficits, or risk factors) in patients with meningeal signs, lumbar puncture is contraindicated until neuroimaging excludes a mass lesion. In infants, a subdural tap may be diagnostic and may relieve pressure.

**Treatment**

- Surgical drainage
- Antibiotics

Emergency surgical drainage of the empyema and any underlying sinusitis should be done. Pending culture results, antibiotic coverage is the same as that for brain abscess except in young children, who may require antibiotics for any accompanying meningitis (see [Table 180-2](#) on p. 1740 and [Table 180-3](#) on p. 1741). Anticonvulsants and measures to reduce intracranial pressure may be needed.
Chapter 180. Meningitis

Introduction

(For brain infections, see Ch. 179 on p. 1726.)

Meningitis is inflammation of the meninges of the brain or spinal cord.

Meningitis is often infectious and is one of the most common CNS infections. Inflammation involves both the meninges and brain parenchyma (meningoencephalitis). Meningitis may become evident over hours or days (acute) or a longer period (subacute or chronic).

The most common types of acute meningitis are

• Acute bacterial meningitis
• Aseptic meningitis

Acute bacterial meningitis is a severe illness characterized by purulent CSF. It is rapidly progressive and, without treatment, fatal.

Aseptic meningitis is milder and typically self-limited; it is usually caused by viruses.

Symptoms and Signs

Many cases of infectious meningitis begin with a vague prodrome of viral symptoms. The classic meningitis triad of fever, headache, and nuchal rigidity develops over hours or days. Passive flexion of the neck is restricted and painful, but rotation and extension are typically not as painful. In severe cases, attempts at neck flexion may induce flexion of the hip or knee (Brudzinski's sign), and there may be resistance to passive extension of the knee while the hip is flexed (Kernig's sign). Neck stiffness and Brudzinski's and Kernig's signs are termed meningeal signs or meningismus; they occur because tension on nerve roots passing through inflamed meninges causes irritation.

Although brain parenchyma is not typically involved early in meningitis, lethargy, confusion, seizures, and focal deficits will develop if bacterial meningitis is left untreated.

Diagnosis

• Blood DNA PCR for bacterial pathogens
• CSF analysis
• Sometimes CT before lumbar puncture

Acute meningitis is a medical emergency that requires rapid diagnosis and treatment. After IV access is secured, blood samples are drawn for culture, CBC, and PCR of bacterial pathogens if available. Treatment is started empirically.

Lumbar puncture is done to obtain CSF for Gram stain, culture, cell count and differential, glucose concentration, protein content and other specialized tests. These tests must be done in a timely manner. However, patients with signs compatible with a mass lesion (eg, focal deficits, papilledema, deterioration in consciousness, seizures) require head CT before lumbar puncture because there is a small possibility that lumbar puncture can cause cerebral herniation if a brain abscess or other mass lesion is present.

CSF findings aid in the diagnosis of meningitis (see Table 180-1). Presence of bacteria on Gram stain or growth of bacteria in culture is diagnostic of bacterial meningitis. Gram stain is positive about 80% of the time in bacterial meningitis and usually differentiates among the common causative pathogens. CSF lymphocytosis and absence of pathogens
suggest aseptic meningitis but may represent partially treated bacterial meningitis.

**Treatment**

If patients appear ill and have findings of meningitis, antibiotics (see p. 1739) are started as soon as blood cultures are drawn. If patients do not appear very ill and the diagnosis is less certain, antibiotics can await CSF results.

**Acute Bacterial Meningitis**

(For neonatal meningitis, see p. 2830.)

**Acute bacterial meningitis is a fulminant, often fatal pyogenic infection beginning in the meninges. Symptoms include headache, fever, and stiff neck. Without rapid treatment, obtundation and coma follow. Diagnosis is by CSF tests. Treatment requires antibiotics, often beginning empirically with a 3rd-or 4th-generation cephalosporin, vancomycin, and ampicillin; corticosteroids are usually given. Residual morbidity is common.**

**Etiology**

Many bacteria can cause meningitis, but the most common are

- Group B streptococci (during the first 2 mo of life)
- *Neisseria meningitidis* (meningococci)
- *Streptococcus pneumoniae* (pneumococci)

**Meningococci** exist in the nasopharynx of about 5% of people and spread by respiratory droplets and close contact. Only a small fraction of carriers develop meningitis; what makes them susceptible is unknown. Meningococcal meningitis occurs most often during the first year of life. It also tends to occur in epidemics among closed populations (eg, in military barracks, college dormitories, and boarding schools).

**Pneumococci** are the most common cause of meningitis in adults. Especially at risk are alcoholics and people with chronic otitis, sinusitis, mastoiditis, CSF leaks, recurrent meningitis, pneumococcal pneumonia, sickle cell disease, or asplenia. Incidence of pneumococcal meningitis is decreasing because of routine vaccination.

**Gram-negative organisms** (most often *Escherichia coli*, *Klebsiella* sp, or *Enterobacter* sp) can cause meningitis in infants; in immunocompromised patients; or after CNS surgery, CNS trauma, bacteremia (eg, due to GU manipulation), or hospital-acquired infections. *Pseudomonas* sp occasionally causes meningitis in immunocompromised or colonized patients. *Haemophilus influenzae* type b meningitis, now uncommon because of widespread vaccination, can occur in immunocompromised patients or after head trauma in unvaccinated people.

**Staphylococci** can cause meningitis after penetrating head wounds or neurosurgical procedures (often as part of a mixed infection) or after bacteremia (eg, due to endocarditis).

**Listeria** typically cause meningitis in the very young, the very old, and patients of any age who are immunocompromised because of chronic renal failure, hepatic disorders, or corticosteroid or cytotoxic therapy after organ transplantation.

Bacteria typically reach the meninges by hematogenous spread from sites of colonization in the nasopharynx or other foci of infection (eg, pneumonia). Why some bacteria are more prone to colonize CSF is not clear, but binding pili and encapsulation appear to play a role. Receptors for pili and other bacterial surface components in the choroid plexus facilitate penetration into CSF.

**Bacteria can also enter CSF by direct extension from nearby infections (eg, sinusitis, mastoiditis) or**
through exterior openings in normally closed CSF pathways (eg, due to meningomyelocele, spinal dermal sinus, penetrating injuries, or neurosurgical procedures).

**Pathophysiology**

Bacterial surface components, complement, and inflammatory cytokines (eg, tumor necrosis factor, IL-1) draw neutrophils into the CSF space. The neutrophils release metabolites that damage cell membranes including those of the vascular endothelium. The result is vasculitis and thrombophlebitis (which cause focal ischemia or infarction) and brain edema. Vasculitis also disrupts the blood-brain barrier, further increasing brain edema. The purulent exudate in the CSF blocks CSF reabsorption by the arachnoid villi, causing hydrocephalus. Brain edema and hydrocephalus increase intracranial pressure.

**Systemic complications** include

- Hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH)
- Disseminated intravascular coagulation (DIC)
- Septic shock

Occasionally, bilateral adrenal hemorrhagic infarction (Waterhouse-Friderichsen syndrome) results, particularly with meningococcal infection.

**Symptoms and Signs**

A respiratory illness or sore throat often precedes the more characteristic symptoms of fever, headache, stiff neck, and vomiting. Kernig's and Brudzinski's signs appear in about half of patients. Adults may become desperately ill within 24 h, and children even sooner. Seizures occur in about 30%. Cranial nerve abnormalities (eg, 3rd [oculomotor] or 7th [facial] cranial nerve palsy; occasionally, deafness) and other focal deficits occur in 10 to 20%. In patients > 2 yr, changes in consciousness progress through irritability, confusion, drowsiness, stupor, and coma. Opisthotonic posturing may occur.

Dehydration is common, and vascular collapse causes shock. Infection, particularly meningococcal, may be disseminated widely, to the joints, lungs, sinuses, and elsewhere. A petechial or purpuric rash commonly occurs in meningococcal meningitis. Examination of the head, ears, spine, and skin may reveal a source or route of infection. Spinal dimples, nevi, or tufts of hair suggest a spinal dermal sinus that communicates with the meninges and provides a portal for bacteria entry.

**Young children:** In children < 2 yr, meningeal signs may be absent. In those < 2 mo, symptoms and signs are often nonspecific, particularly in early disease. Fever, hypothermia, poor feeding, lethargy, vomiting, and irritability are common presenting symptoms. Seizures, a high-pitched cry, and bulging or tight fontanelles are possible but often occur late. Subdural effusions may develop after several days; typical signs are seizures, persistent fever, and enlarging head size.

**Elderly:** The elderly may also have nonspecific symptoms (eg, confusion with or occasionally without fever). Meningeal signs may be absent or mild. Arthritis may restrict neck motion, often in multiple directions, and should not be mistaken for meningismus.

**Patients with partially treated meningitis:** Patients seen early in the disease, before typical findings of meningitis appear, are sometimes diagnosed with otitis media or sinusitis and given oral antibiotics. Depending on the drug, the infection may be partially (but temporarily) suppressed. Patients may appear less ill and have milder meningeal signs and slower disease progression. This situation can significantly hamper recognition of meningitis.
Diagnosis

• CSF analysis

Acute bacterial meningitis is suspected in children < 2 yr with lethargy, progressive irritability, a high-pitched cry, a bulging fontanelle, meningeal signs, or hypothermia. Signs are often nonspecific, and threshold for suspecting meningitis must be low. Meningitis is suspected in patients > 2 yr with meningeal signs or unexplained alterations in consciousness, particularly in those with fever or risk factors.

Because acute bacterial meningitis, especially meningococcal, can be lethal within hours, it must be treated as soon as the diagnosis is suspected. Blood is drawn for culture, Gram stain, and bacterial DNA PCR if available. Prompt lumbar puncture with or without prior CT is required, but these procedures should not delay immediate treatment with corticosteroids and antibiotics.

CSF tests: CSF pressure may be elevated. Gram stain shows organisms in CSF in 80% of patients with acute bacterial meningitis. CSF contains a predominantly neutrophilic WBC count, usually between 1,000 μL and 10,000/μL. Glucose is usually < 40 mg/dL because of impaired CNS glucose transport and glucose consumption by neutrophils and bacteria. Protein is typically > 100 mg/dL. Cultures are positive in 90%; they may be falsely negative in patients who are partially treated. Latex agglutination tests can be used to detect antigens of meningococci, H. influenzae type b, pneumococci, group B streptococci, and E. coli K1 strains. However, these tests are not routinely done because they probably add little to other routine CSF tests. The limulus amebocyte lysate test can detect endotoxin in gram-negative meningitis. This test and the latex agglutination tests may be helpful when patients have received prior antibiotics (partial treatment), when patients are immunocompromised, or when other CSF tests do not identify the causative organism. Broad range bacterial PCR for 16S ribosomal DNA testing can be useful if CSF cultures detect no organisms. PCR testing is also available for meningococcus and pneumococcus.

Imaging tests: CT, when done, may be normal or show small ventricles, effacement of the sulci, and contrast enhancement over the convexities. MRI with gadolinium is more sensitive for subarachnoid inflammation. Scans should be scrutinized for evidence of brain abscess, sinusitis, mastoiditis, skull fracture, and congenital malformations. Evidence of venous infarctions or communicating hydrocephalus may appear after days or weeks.

Other tests: Peripheral blood tests include blood cultures (positive in 50%), cell count with differential, electrolytes, glucose, renal function, coagulation tests, and PCR for bacterial pathogens (where available). Serum Na is monitored for evidence of SIADH, and coagulation results are monitored for evidence of DIC. Urine and any nasopharyngeal or respiratory secretions and skin lesions are cultured.

Alternate diagnoses: Disorders that resemble bacterial meningitis can usually be differentiated by clinical presentation, neuroimaging, and routine CSF tests.

Viral meningitis can cause fever, headache, and stiff neck, but patients do not appear as ill, and CSF test results are different (see Table 180-1).

Viral encephalitis, especially herpes encephalitis, also causes fever, headache, confusion, seizure and coma, which can be confused with bacterial meningitis. MRI and CSF testing are helpful in distinguishing viral encephalitis from bacterial meningitis. Serum procalcitonin and C-reactive protein are elevated to a much greater degree with bacterial than with viral infections.

Subarachnoid hemorrhage causes severe headache and a stiff neck, but onset is explosive and fever is usually absent; CT shows hemorrhage, or the CSF contains RBCs or is xanthochromic.

Brain abscess can cause fever, headache, and impaired consciousness, but the neck is typically supple unless abscess contents have ruptured into the CSF space, causing a fulminant secondary meningitis.

Severe systemic infections (eg, sepsis, infective endocarditis) can impair cognition or consciousness by causing fever and compromising tissue perfusion; CSF is normal or contains a small number of WBCs, and the neck is supple.
Cerebellar tonsillar herniation can cause impaired consciousness (secondary to obstructive hydrocephalus) and neck stiffness but usually not fever, and it can be differentiated by CT or MRI.

Cerebral vasculitis (eg, due to SLE) and cerebral venous thrombosis can cause mild fever, headache, altered mental status, and mild to moderate meningeal inflammation, typically producing CSF test results similar to those of viral encephalitis.

Fungal meningitis or amebic (Naegleria) meningoencephalitis occasionally causes acute, fulminant meningitis with clinical findings and routine CSF test results similar to those of bacterial meningitis. Gram stain and routine cultures show no bacteria. In such cases, CSF is checked for cryptococcal polysaccharide antigen, Histoplasma polysaccharide antigen, and Coccidioides immitis complement fixation antibodies; CSF is also examined using India ink and cultured for fungi (see p. 1744). In amebic meningoencephalitis, ameboid movement can be detected in unspun wet mounts of CSF, and the amebas can be cultured.

TB meningitis is usually subacute or chronic but is occasionally acute; CSF characteristics are usually intermediate between those of acute bacterial and aseptic meningitis. Special stains (eg, acid-fast, immunofluorescent) and PCR are needed to identify TB.

Waterhouse-Friderichsen syndrome: This disorder should be suspected in any febrile patient who remains in shock despite adequate volume replacement and who has rapidly evolving purpura and evidence of DIC. With hemorrhagic necrosis of the adrenal glands, adrenocorticol insufficiency develops rapidly. A serum cortisol level < 13 μg/dL (in combination with an increased ACTH level) suggests glucocorticoid deficiency due to primary adrenal insufficiency. CT, MRI, or ultrasonography of the adrenal glands is done.

Prognosis

Immediate empirical treatment with corticosteroids, antibiotics, and supportive care have improved outcome and reduced mortality to < 10%. However, if meningitis is treated late or occurs in neonates, the elderly, or immunocompromised patients, death is common. A poor outcome is predicted by persistent leukopenia or development of Waterhouse-Friderichsen syndrome. Survivors occasionally have deafness, other cranial nerve deficits, cerebral infarction, recurrent seizures, or intellectual disability.

Treatment

• Corticosteroids

• Antibiotics (eg, ampicillin and ceftriaxone, with or without vancomycin)

If acute bacterial meningitis is suspected, corticosteroids and antibiotics are given as soon as blood cultures are drawn. If the diagnosis is unclear and the patient does not appear ill, antibiotics may be withheld pending CSF test results. Giving antibiotics before lumbar puncture slightly increases the probability of false-negative cultures, particularly with pneumococci, but does not affect other test results.

Corticosteroids: Dexamethasone 0.15 mg/kg IV q 6 h in children and 10 mg IV q 6 h in adults should be given with the first dose of antibiotics and continued for 4 days. Dexamethasone may prevent hearing loss and other neurologic sequelae by inhibiting release of proinflammatory cytokines triggered by antibiotic-induced bacterial lysis. Because corticosteroids impede vancomycin's penetration into CSF, vancomycin is given in a higher dose—15 to 20 mg/kg q 8 h.

In immunocompromised patients, the benefits of dexamethasone in reducing intracranial pressure must be weighed against the risk of worsening immunodeficiency.

Antibiotics: Choice of empiric antibiotics depends on the suspected pathogen and patient age (see Table 180-2; for antibiotic doses, see Table 180-3). Third-generation cephalosporins (eg, ceftriaxone, cefotaxime) are effective against...
pathogens common in patients of all ages. Cefepime, a 4th-generation cephalosporin, can be substituted for a 3rd-generation cephalosporin in children and can be useful for *Pseudomonas* infection. However, because cephalosporin-resistant pneumococci are becoming increasingly prevalent, vancomycin, with or without rifampin, is usually added. Meropenem is also effective against *Pseudomonas* and many gram-negative bacteria. Ampicillin is added to cover *Listeria* sp. Aminoglycosides penetrate the CNS poorly but are still used empirically to cover gram-negative bacteria in neonates (see p. 2831). When meningitis due to a gram-negative anaerobe is a consideration (eg, because of otitis, sinusitis, or mastoiditis), meropenem should be added. For meningitis patients with a recent neurosurgical procedure or with an intraventricular shunt, vancomycin, meropenem, plus metronidazole provide coverage against staphylococci, gram-negative bacteria, and anaerobes.

Because herpes encephalitis can resemble bacterial meningitis at presentation, acyclovir is usually included with the initial empirical therapy. Similarly, during tick season, doxycycline may be added to cover CNS infection with Rocky Mountain spotted fever.

**Reevaluation:** As the results of blood, CSF, and other tests become available and the pathogen and drug susceptibility are identified, antibiotics are adjusted accordingly.

If no pathogen is identified in the CSF, addition of antibiotics for TB should be considered, especially if CSF glucose levels are very low.

If no bacteria grow in culture or are otherwise identified after 24 to 48 h, corticosteroids are stopped; corticosteroids continued for > 1 day without appropriate antibiotic coverage could worsen the infection. When initial CSF tests are inconclusive, a repeat lumbar puncture in 8 to 24 h (or sooner if the patient deteriorates) may help. If clinical and CSF findings continue to suggest aseptic meningitis, antibiotics are withheld. If the patient's condition is serious, especially if antibiotics have been given (possibly causing falsely sterile cultures), antibiotics should be continued.

Lumbar puncture should be repeated 24 to 48 h after starting antibiotics to confirm CSF sterility and conversion to lymphocytic predominance. Generally, antibiotics are continued for ≥ 1 wk after fever subsides and CSF is nearly normal (complete normalization may take weeks). Drug doses are not reduced when clinical improvement occurs because drug penetration commonly decreases as meningeal inflammation decreases.

**Other measures:** Supportive therapy includes treatment of fever, dehydration, electrolyte disorders, seizures, and shock.

If Waterhouse-Friderichsen syndrome is suspected, high-dose hydrocortisone (eg, 100 to 200 mg IV q 4 to 6 h or as a continuous infusion after an initial bolus) is given; treatment should not be delayed pending measurement of hormone levels.

Cerebral edema can be minimized by avoiding overhydration. If brain herniation is suspected, hyperventilation (PaCO₂, 25 to 30 mm Hg acutely), mannitol (0.25 to 1.0 g/kg IV), and additional dexamethasone (4 mg IV q 4 h) can be used; barbiturate-induced coma may be considered. Monitoring intracranial pressure may be helpful. If ventricles are enlarged, intracranial pressure may be monitored and CSF drained, but outcome is usually poor.

If infants up to 1 yr of age have subdural effusion, daily subdural taps through the cranial sutures usually help. No more than 20 mL/day of CSF should be removed from one side to avoid sudden shifts in intracranial contents. If effusion persists after 3 to 4 wk of taps, surgical exploration for possible excision of a subdural membrane is indicated.

Patients with severe meningococcal meningitis may benefit from drotrecogin alfa (activated protein C),

**Table 180-2. Antibiotic Therapy for Acute Bacterial Meningitis**

**Table 180-3. Common IV Antibiotic Dosages for Bacterial Meningitis**

*Table 180-3. Common IV Antibiotic Dosages for Bacterial Meningitis*
which downregulates the inflammatory response. In patients with sepsis due to meningitis, intracranial bleeding occurs more frequently, with or without drotrecogin alfa treatment.

Prevention

Physical measures: Spread of meningitis is prevented by keeping patients in respiratory isolation (droplet precautions) for the first 24 h of therapy. Gloves, masks, and gowns are used.

Vaccinations: Certain types of bacterial meningitis can be prevented by vaccination.

A conjugated pneumococcal vaccine effective against 7 serotypes, including > 80% of organisms that cause meningitis, is recommended for all children (see p. 1177 and Table 268-10 on p. 2718).

Routine vaccination against *H. influenzae* type b is highly effective and begins at age 2 mo.

A quadrivalent meningococcal vaccine is given to children aged 2 to 10 yr with immunodeficiencies or functional asplenia, all children at age 11 to 12 yr (and older children, college students living in dormitories, and military recruits who have not had the vaccine previously), travelers to endemic areas, and laboratory personnel who routinely handle meningococcal specimens. Chemoprophylaxis is given to close contacts of patients with meningococcal meningitis. During an epidemic, the population at risk must be identified (eg, college students, a small town) and its size determined before proceeding to mass vaccination. The effort is expensive and requires public education and support, but it saves lives and reduces morbidity. NOTE: The meningococcal vaccine does not protect against serotype B meningococcal meningitis; this information should be kept in mind when a vaccinated patient presents with symptoms of meningitis.

Chemoprophylaxis: Anyone who has face-to-face contact with the patient (eg, family, medical staff members) should receive postexposure chemoprophylaxis.

For meningococcal meningitis, chemoprophylaxis consists of one of the following:

- Rifampin 600 mg (for children > 1 mo, 10 mg/kg; for children < 1 mo, 5 mg/kg) po q 12 h for 4 doses
- Ceftriaxone 250 mg (for children < 15 yr, 125 mg) IM for 1 dose
- In adults, a fluoroquinolone (ciprofloxacin or levofloxacin 500 mg or ofloxacin 400 mg) po for 1 dose

Chemoprophylaxis against *H. influenzae* type b is rifampin 20 mg/kg po once/day (maximum: 600 mg/day) for 4 days. There is no consensus on whether children < 2 yr require prophylaxis for exposure at day care.

Chemoprophylaxis is not usually needed for contacts of patients with pneumococcal meningitis.

Aseptic Meningitis

Aseptic meningitis is inflammation of the meninges with CSF lymphocytic pleocytosis and no cause apparent after routine CSF stains and cultures. Viruses are the most common cause. Other causes may be infectious or noninfectious. Symptoms include fever, headache, and meningeal signs. Viral aseptic meningitis is usually self-limited. Treatment is usually symptomatic.

Etiology

There are many causes (see Table 180-4), which are typically classified as

- Infectious (eg, viruses, rickettsiae, spirochetes, parasites)
Noninfectious (eg, intracranial tumors and cysts, drugs, systemic disorders)

**Viruses:** Enteroviruses, including echovirus, coxsackievirus, and enteroviruses 68 through 71, cause most cases of aseptic meningitis. They are transmitted through a fecaloral, food-borne route, entering the GI tract and spreading via the bloodstream.

The next most common causes of viral meningitis are herpes simplex virus type 2 (HSV-2), HIV, and the arthropod-borne viruses. Mumps virus is a common cause worldwide but has been minimized in the US by vaccination.

Mollaret's meningitis is a syndrome of self-limited, recurrent aseptic meningitis characterized by large atypical monocytes (once thought to be endothelial cells) in the CSF; it is caused by HSV-2 and associated with prior exposure to genital herpes; most patients are unaware of their exposure.

Viruses that cause encephalitis typically also cause a low-grade aseptic meningitis.

**Bacteria:** Bacteria may cause lymphocytic meningitis; they include spirochetes (in syphilis, Lyme disease, or leptospirosis) and rickettsiae (in typhus, Rocky Mountain spotted fever, or ehrlichiosis). CSF abnormalities may be transient or chronic.

Bacterial infections such as mastoiditis, sinusitis, brain abscess, and infective endocarditis can result in CSF with characteristics of aseptic meningitis because infection adjacent to the meninges can induce a sympathetic inflammatory response without bacteria being present.

**Noninfectious causes:** Meningeal inflammation may result from neoplastic infiltration, leakage of the contents of an intracranial cyst, intrathecal drugs, lead poisoning, and radiopaque agents. Infrequently, inflammation results from certain systemically administered drugs, presumably as a hypersensitivity reaction. The most common causative drugs are NSAIDs (especially ibuprofen), antimicrobials (especially sulfa drugs), and immune modulators (eg, IV immune globulins, OKT3 monoclonal antibodies, cyclosporine, vaccines).

**Symptoms and Signs**

Aseptic meningitis often follows a flu-like syndrome and usually causes fever and headache, but coryza is not prominent. Meningeal signs are less marked and slower to develop than in acute bacterial meningitis. Patients are usually not critically ill; systemic or nonspecific symptoms may predominate. Focal neurologic symptoms are absent. Patients with noninfectious meningeal inflammation are often afebrile.

**Diagnosis**

- CSF analysis
- Sometimes CT before lumbar puncture

The initial concern is whether patients presenting with headache, fever, and meningeal signs have acute bacterial meningitis requiring immediate antibiotic treatment. Viral or other aseptic meningitis should be considered when patients appear less acutely ill.

Head CT or MRI is done before lumbar puncture if a brain mass is suspected (eg, based on focal neurologic signs or papilledema). Idiopathic intracranial hypertension sometimes mimics aseptic meningitis.

**Differentiating bacterial meningitis from aseptic meningitis:** Because bacterial meningitis requires immediate treatment and aseptic meningitis usually does not, rapid identification of bacterial meningitis is important (and sometimes difficult).

**CSF findings** help make the distinction (see Table 180-1). CSF glucose is usually decreased and protein...
is elevated in bacterial meningitis but not in aseptic meningitis. CSF WBCs are predominantly lymphocytes in aseptic meningitis; even a few CSF neutrophils (which may, however, be present in early viral meningitis) should prompt consideration of early bacterial meningitis. However, several types of bacterial meningitis have CSF characteristics that are similar to those of aseptic meningitis; they include partially treated bacterial meningitis, *Listeria* meningitis (which may be difficult to detect using Gram stain and may produce CSF monocytosis, which is more characteristic of aseptic meningitis), and TB meningitis. Clues to TB meningitis are clinical findings, elevated CSF protein, and mildly decreased CSF glucose (see p. 1744). CSF pressure is somewhat variable; although it is typically normal or mildly elevated in aseptic meningitis and quite high in bacterial meningitis, it may be markedly elevated in aseptic meningitis.

**Blood tests** sometimes help. Serum levels of procalcitonin and C-reactive protein are much higher in bacterial infections than in viral ones.

**Diagnosis of specific cause:** In viral meningitis, PCR is the quickest way to identify the specific infectious agent, including enteroviruses, HSV-2, HIV, and cytomegalovirus. PCR is less reliable in West Nile virus infection, which is usually diagnosed based on IgM titers.

Tests are also done to diagnose nonviral causes of aseptic meningitis (eg, rickettsial infection, Lyme disease, syphilis). Drug-induced aseptic meningitis is a diagnosis of exclusion.

**Treatment**

• Supportive care

In most patients, the diagnosis is clear, and treatment requires only hydration, analgesics, and antipyretics. If listerial, partially treated, and early bacterial meningitis cannot be excluded, antibiotics effective against bacterial meningitis are given pending results of cultures or repeated CSF tests.

Drug-induced aseptic meningitis resolves when the causative drug is withdrawn.

Recurrent HSV-2 meningitis may be treated with acyclovir, famciclovir, or valacyclovir (see Table 151-2 on p. 1413).

### Subacute and Chronic Meningitis

Meningeal inflammation that lasts > 2 wk (subacute meningitis) or > 1 mo (chronic meningitis) may have infectious or noninfectious causes (eg, cancer). Diagnosis requires CSF analysis, usually after CT or MRI. Treatment is directed at the cause.

**Etiology**

Subacute or chronic meningitis may have infectious or noninfectious causes and may be an aseptic meningitis (see Table 180-4). Infectious causes include fungal infections (most commonly with *Cryptococcus neoformans*), TB, Lyme disease, AIDS, *Actinomyces* infections, and syphilis; noninfectious causes include sarcoidosis, vasculitis, Behcet's syndrome, and cancers such as lymphomas, leukemia, melanomas, certain carcinomas, and gliomas (particularly glioblastoma, ependymoma, and medulloblastoma). Other causes include chemical reactions to certain intrathecal injections.

Use of immunosuppressants and the AIDS epidemic have increased the incidence of fungal meningitis. *Cryptococcus* sp (see p. 1329) is the most common cause in patients with AIDS, Hodgkin lymphoma, or lymphosarcoma and in those taking high-dose, long-term corticosteroids. *Coccidioides, Candida, Actinomyces, Histoplasma*, and *Aspergillus* spp are less common causes (see Ch. 142).

**Symptoms and Signs**
Most manifestations are similar to those of acute meningitis but evolve over weeks. Fever may be minimal. Headache, backache, and cranial nerve or spinal nerve root deficits are common. Communicating hydrocephalus may develop and cause dementia. Intracranial pressure may remain elevated and cause headache, vomiting, and decreased alertness for days or weeks. Without treatment, death can occur within a few weeks or months (eg, with TB or tumor), or symptoms can continue for years (eg, with Lyme disease).

**Diagnosis**

- CT or MRI
- CSF analysis

The diagnosis is suspected if meningeal symptoms or signs develop over > 2 wk, with or without symptoms of cerebral dysfunction, particularly if a potential cause of meningitis (eg, active TB, cancer) exists.

The diagnosis requires CSF analysis. CT or MRI is done to exclude mass lesions that cause slowly evolving cerebral dysfunction (eg, tumors, abscesses, subdural effusions) and to determine whether lumbar puncture can be done safely. CSF pressure is often elevated but may be normal. CSF cell count is elevated with a lymphocytic predominance; glucose is slightly or moderately reduced but may be significantly decreased in TB or fungal meningitis. CSF protein is high (see Table 180-1).

Other CSF tests (eg, special stains, fungal and acid-fast bacillus culture) are determined by the patient's risk factors. For example, TB is suspected in patients who are alcoholic, HIV-positive, or from areas where TB is endemic (see p. 1302). Identification of TB by microscopy has a notoriously low yield and requires acid-fast staining or immunofluorescence and an exhaustive microscopic search of CSF sediment, ideally from a large volume of CSF (30 to 50 mL), which may require 2 or 3 lumbar punctures (typically 20 to 30 mL can be withdrawn at a time). Positive cultures are the gold standard for diagnosis but also require 30 to 50 mL of CSF, and results take 2 to 6 wk. Although results differ among laboratories, PCR has a yield of about 50% in TB meningitis and can provide a specific diagnosis within days. Measurement of CSF tubulostearic acid by gas-liquid chromatography is specific but technically complex and not widely used.

Fungi may be detected microscopically in wet mounts or, for Cryptococcus sp, in India ink preparations (see also p. 1329). CSF cultures grow Cryptococcus and Candida spp in a few days and less common fungi in weeks. CSF cryptococcal antigen is highly specific and sensitive.

Neurosyphilis is diagnosed using the CSF Venereal Disease Research Laboratories (VDRL) test (see p. 1478). In Lyme disease (see p. 1268), diagnosis can be made by testing for serum antibodies against Borrelia burgdorferi. If serology is negative but clinical signs of meningitis are found, testing for intrathecal antibodies can be useful for diagnosis.

Diagnosis of neoplastic meningitis requires detecting cancer cells in CSF; detection depends on adequate CSF volume, frequency of collection (malignant cells may shed periodically; multiple samples increase the yield), sampling site (cisternal CSF is more often positive), and prompt fixation to preserve cell morphology. For 95% sensitivity, 30 to 50 mL of CSF (typically requiring several lumbar punctures) is collected and delivered to the laboratory promptly. For suspected neurosarcoïdosis, ACE in CSF is measured; it is elevated in up to 24 to 50% of patients. For certain tumors, CSF tumor markers (eg, IL-10 for lymphoma; soluble CD27 for lymphoid cancers, such as acute lymphoblastic leukemia and non-Hodgkin lymphoma) can help with diagnosis or monitoring disease activity.

Some causes of subacute or chronic meningitis (eg, Behcet's syndrome) cannot be diagnosed by CSF analysis and must be diagnosed clinically.

**Treatment**

Treatment depends on the cause (see elsewhere in THE MANUAL).
Chapter 181. Neuro-Ophthalmologic and Cranial Nerve Disorders

**Introduction**

(See also [Horner's Syndrome](#) on p. 1618 and Chs. 47, 53, 69, and 168.)

Dysfunction of certain cranial nerves may affect the eye, pupil, optic nerve, or extraocular muscles and their nerves; thus, they can be considered cranial nerve disorders, neuroophthalmologic disorders, or both. Neuroophthalmologic disorders may also involve dysfunction of the central pathways that control and integrate ocular movement and vision. Cranial nerve disorders can also involve dysfunction of smell, vision, chewing, facial sensation or expression, taste, hearing, balance, swallowing, phonation, head turning and shoulder elevation, or tongue movements (see [Table 181-1](#)). One or more cranial nerves may be affected.

Causes and symptoms of neuro-ophthalmologic and cranial nerve disorders overlap. Both types of disorders can result from tumors, inflammation, trauma, systemic disorders, and degenerative or other processes, causing such symptoms as vision loss, diplopia, ptosis, pupillary abnormalities, periorcular pain, facial pain, or headache.

**Diagnosis**

Evaluation includes the following:

- Detailed questioning about symptoms
- Examination of the visual system (see also p. 537)
- Tests to detect nystagmus (see [Sidebar 46-1](#) on p. 414)
- Examination of the cranial nerves (see p. 1587)

Visual system examination includes ophthalmoscopy and testing of visual acuity, visual fields (see p. 539), pupils (see [Table 181-2](#)), and eye movements (ocular motility—see [Table 181-3](#)). As part of this testing, the 2nd, 3rd, 4th, and 6th cranial nerves are examined (see also p. 1587). Neuroimaging with CT or MRI is also usually required.

The following parts of the visual examination are of particular interest in diagnosing neuroophthalmologic and cranial nerve disorders:

**Pupils** are inspected for size, equality, and regularity. Normally, the pupils constrict promptly (within 1 sec) and equally during accommodation and during exposure to direct light and to light directed at the other pupil (consensual light reflex). Testing pupillary response to consensual light via a swinging flashlight test can determine whether a defect is present. Normally, the degree of pupillary constriction does not change as the flashlight is swung from eye to eye.

- If a relative afferent defect (deafferented pupil, afferent pupillary defect, or Marcus Gunn pupil) is present, the pupil paradoxically dilates when the flashlight swings to the side of the defect. A deafferented pupil constricts in response to consensual but not to direct light.

- If an efferent defect is present, the pupil responds sluggishly or does not respond to both direct and consensual light.

**Eye movements** are checked by having the patient hold the head steady while tracking the examiner's finger as it moves to the far right,
left, upward, downward, diagonally to either side, and inward toward the patient's nose (to assess accommodation). However, such examination may miss mild paresis of ocular movement sufficient to cause diplopia.

Diplopia may indicate a defect in bilateral coordination of eye movements (eg, in neural pathways) or in the 3rd (oculomotor), 4th (trochlear), or 6th (abducens) cranial nerve. If diplopia persists when one eye is closed (monocular diplopia), the cause is probably a nonneurologic eye disorder (see p. 550). If diplopia disappears when either eye is closed (binocular diplopia), the cause is probably a disorder of ocular motility. The 2 images are furthest apart when the patient looks in the direction served by the paretic eye muscle (eg, to the left when the left lateral rectus muscle is paretic). The eye that, when closed, eliminates the more peripheral image is paretic. Placing a red glass over one eye can help identify the paretic eye. When the red glass covers the paretic eye, the more peripheral image is red (see also p. 551).

**Table 181-2. Common Pupillary Abnormalities**

is paretic. The eye that, when closed, eliminates the more peripheral image is paretic. Placing a red glass over one eye can help identify the paretic eye. When the red glass covers the paretic eye, the more peripheral image is red (see also p. 551).

**Treatment**

Treatment of neuro-ophthalmologic and cranial disorders depends on the cause.

**Conjugate Gaze Palsies**

A conjugate gaze palsy is inability to move both eyes in a single horizontal (most commonly) or vertical direction.

Gaze palsies most commonly affect horizontal gaze; some affect upward gaze, and fewer affect downward gaze.

**Horizontal gaze palsies:** Conjugate horizontal gaze is controlled by neural input from the cerebral hemispheres, cerebellum, vestibular nuclei, and neck. Neural input from these sites converges at the horizontal gaze center (paramedian pontine reticular formation) and is integrated into a final command to the adjacent 6th cranial nerve nucleus, which controls the lateral rectus on the same side, and, via the medial longitudinal fasciculus (MLF), to the contralateral 3rd cranial nerve nucleus and the medial rectus it controls. Inhibitory signals to opposing eye muscles occur simultaneously.

**Table 181-3. Common Disturbances of Ocular Motility**

The most common and devastating impairment of horizontal gaze results from pontine lesions that affect the horizontal gaze center and the 6th cranial nerve nucleus. Strokes are a common cause, resulting in loss of horizontal gaze ipsilateral to the lesion. In palsies due to stroke, the eyes may not move in response to any stimulus (eg, voluntary or vestibular). Milder palsies may cause only nystagmus or inability to maintain fixation.

Another common cause is a lesion in the contralateral cerebral hemisphere rostral to the frontal gyrus. These lesions are typically caused by a stroke. The resulting palsy usually abates with time. Horizontal conjugate gaze mediated by brain stem reflexes (eg, in response to cold-water caloric stimulation) is preserved.

**Vertical gaze palsies:** Upward and downward gaze depends on input from fiber paths that ascend from the vestibular system through the MLF on both sides to the 3rd and 4th cranial nerve nuclei, the interstitial nucleus of Cajal, and the rostral interstitial nucleus of the MLF. A separate system descends, presumably from the cerebral hemispheres, through the midbrain pretectum to the 3rd and 4th cranial nerve nuclei. The rostral interstitial nucleus of the MLF integrates the neural input into a final command for vertical gaze.

Vertical gaze becomes more limited with aging.
Vertical gaze palsies commonly result from midbrain lesions, usually infarcts and tumors. Parinaud's syndrome (dorsal midbrain syndrome), a conjugate upward vertical gaze palsy, may result from a pineal tumor or, less commonly, a tumor or infarct of the midbrain pretectum. This syndrome is characterized by impaired upward gaze, lid retraction (Collier's sign), downward gaze preference (setting-sun sign), convergence-retraction nystagmus, and dilated pupils (about 6 mm) that respond poorly to light but better to accommodation (light-near dissociation).

**Downward gaze palsies:** Impaired downward gaze with preservation of upward gaze usually indicates progressive supranuclear palsy (see p. 1771); other causes are rare.

**Internuclear Ophthalmoplegia**

Internuclear ophthalmoplegia is characterized by paresis of eye adduction in horizontal gaze but not in convergence. It can be unilateral or bilateral.

During horizontal gaze, the medial longitudinal fasciculus (MLF) on each side of the brain stem enables abduction of one eye to be coordinated with adduction of the other. The MLF connects the following structures:

- 6th cranial nerve nucleus (which controls the lateral rectus, responsible for abduction)
- Adjacent horizontal gaze center (paramedian pontine reticular formation)
- Contralateral 3rd cranial nerve nucleus (which controls the medial rectus, responsible for adduction)

The MLF also connects the vestibular nuclei with the 3rd cranial nerve nuclei.

Internuclear ophthalmoplegia results from a lesion in the MLF. In young people, the disorder is commonly caused by multiple sclerosis and may be bilateral. In the elderly, internuclear ophthalmoplegia is typically caused by stroke and is unilateral. Occasionally, the cause is neurosyphilis, Lyme disease, tumor, or drug intoxication (e.g., with tricyclic antidepressants).

If a lesion in the MLF blocks signals from the horizontal gaze center to the 3rd cranial nerve, the eye on the affected side cannot adduct (or adducts weakly) past the midline. The affected eye adducts normally in convergence because convergence does not require signals from the horizontal gaze center. This finding distinguishes internuclear ophthalmoplegia from 3rd cranial nerve palsy, which impairs adduction in convergence (this palsy also differs because it causes limited vertical eye movement, ptosis, and pupillary abnormalities).

During horizontal gaze to the side opposite the affected eye, images are horizontally displaced, causing diplopia; nystagmus often occurs in the abducting eye. Sometimes vertical bilateral nystagmus occurs during attempted upward gaze.

Treatment is directed at the underlying disorder.

**One-and-a-half syndrome:** This uncommon syndrome occurs if a lesion affects the horizontal gaze center and the MLF on the same side. The eyes cannot move horizontally to either side except the eye on the side opposite the lesion can abduct; convergence is unaffected. Causes include multiple sclerosis, infarction, hemorrhage, and tumor.

With treatment (e.g., radiation therapy for a tumor, treatment of multiple sclerosis), improvement may occur but is often limited after infarction.

**Third Cranial Nerve Disorders**

Third cranial nerve disorders can impair ocular motility, pupillary function, or both. Symptoms and signs include diplopia, ptosis, and paresis of eye adduction and of upward and downward gaze. If the pupil is affected, it is dilated and light reflexes are impaired. If the pupil is affected or
patients are increasingly unresponsive, CT is done as soon as possible.

**Etiology**

Third cranial (oculomotor) nerve disorders that cause palsies and affect the pupil commonly result from aneurysms (especially of the posterior communicating artery) and transtentorial brain herniation (see Fig. 174-1 on p. 1657) and less commonly from meningitis affecting the brain stem (eg, TB meningitis). The most common cause of palsies that spare the pupil, particularly partial palsies, is ischemia of the 3rd cranial nerve (usually due to diabetes) or of the midbrain. Occasionally, a posterior communicating artery aneurysm causes complete oculomotor palsy and spares the pupil.

**Symptoms and Signs**

Diplopia and ptosis (drooping of the upper eyelid) occur. The affected eye may deviate slightly out and down in straight-ahead gaze; adduction is slow and may not proceed past the midline. Upward gaze is impaired. When downward gaze is attempted, the superior oblique muscle causes the eye to adduct slightly and rotate. The pupil may be normal or dilated; its response to direct or consensual light may be sluggish or absent (efferent defect). Mydriasis (pupil dilation) may be an early sign.

**Diagnosis**

- Clinical evaluation
- CT or MRI

Differential diagnosis includes midbrain lesions that disrupt the oculomotor fascicle (Claude's syndrome, Benedict's syndrome), leptomeningeal tumor or infection, cavernous sinus disease (giant carotid aneurysm, fistula, or thrombosis), intraorbital structural lesions (eg, orbital mucormycosis) that restrict ocular motility, ocular myopathies (eg, due to hyperthyroidism or mitochondrial disorders), and disorders of the neuromuscular junction (eg, due to myasthenia gravis or botulism). Differentiation may be clinical. Exophthalmos or enophthalmos, a history of severe orbital trauma, or an obviously inflamed orbit suggests an intraorbital structural disorder. Graves' orbitopathy (ophthalmopathy) should be considered in patients with bilateral ocular paresis, paresis of upward gaze or abduction, exophthalmos, lid retraction, lid lag during downward gaze (Graefe's sign), and a normal pupil.

CT or MRI is required. If a patient has a dilated pupil and a sudden, severe headache (suggesting ruptured aneurysm) or is increasingly unresponsive (suggesting herniation), CT is done immediately. If ruptured aneurysm is suspected and CT does not show blood or is not available rapidly, other tests, such as lumbar puncture, magnetic resonance angiography, CT angiography, or cerebral angiography, are indicated. Cavernous sinus disease and orbital mucormycosis require immediate MRI imaging for timely treatment.

**Fourth Cranial Nerve Palsy**

Fourth cranial nerve palsy impairs the superior oblique muscle, causing paresis of vertical gaze, mainly in adduction.

Fourth cranial (trochlear) nerve palsy is often idiopathic. Few causes have been identified. Causes include closed head injury (common), which may cause unilateral or bilateral palsies, and infarction due to small-vessel disease (eg, in diabetes). Rarely, this palsy results from aneurysms, tumors (eg, tentorial meningioma, pinealoma), or multiple sclerosis.

Because the superior oblique muscle is paretic, the eyes do not adduct normally. Patients see double images, one above and slightly to the side of the other; thus, going down stairs, which requires looking down and inward, is difficult. However, tilting the head to the side opposite the palsied muscle can compensate and eliminate the double images.

Examination may detect subtle impaired ocular motility, causing symptoms but not signs.
Oculomotor exercises or prism glasses may help restore concordant vision.

**Sixth Cranial Nerve Palsy**

Sixth cranial nerve palsy affects the lateral rectus muscle, impairing eye abduction. The eye may be slightly adducted when the patient looks straight ahead. The palsy may be secondary to nerve infarction, Wernicke's encephalopathy, trauma, infection, or increased intracranial pressure, or it may be idiopathic. Determining the cause requires MRI and often lumbar puncture and evaluation for vasculitis.

**Etiology**

Sixth cranial (abducens) nerve palsy may result from small-vessel disease, particularly in diabetics as part of a disorder called mononeuritis multiplex (multiple mononeuropathy). It may result from compression of the nerve by lesions in the cavernous sinus (eg, nasopharyngeal tumors), orbit, or base of the skull. The palsy may also result from increased intracranial pressure, head trauma, or both. Other causes include meningitis, meningeal carcinomatosis, Wernicke's encephalopathy, aneurysm, vasculitis, multiple sclerosis, pontine stroke, and, rarely, low CSF pressure headache (eg, after lumbar puncture). Children with respiratory infection may have recurrent palsy. However, the cause of an isolated 6th cranial nerve palsy is often not identified.

**Symptoms and Signs**

Symptoms include binocular horizontal diplopia when looking to the side of the paretic eye. Because the tonic action of the medial rectus muscle is unopposed, the eye is slightly adducted when the patient looks straight ahead. The eye abducts sluggishly, and even when abduction is maximal, the lateral sclera is exposed. With complete paralysis, the eye cannot abduct past midline.

Palsy resulting from nerve compression by a thrombus (eg, due to head trauma or stroke), tumor, or aneurysm in the cavernous sinus causes severe head pain, chemosis (conjunctival edema), anesthesia in the distribution of the 1st division of the 5th cranial nerve, optic nerve compression with vision loss, and paralysis of the 3rd, 4th, and 6th cranial nerves. Both sides are typically affected, although unevenly.

**Diagnosis**

- MRI
- If vasculitis is suspected, ESR, antinuclear antibodies, and rheumatoid factor

A 6th nerve palsy is usually obvious, but the cause is not. If retinal venous pulsations are seen during ophthalmoscopy, increased intracranial pressure is unlikely. CT is often done because it is often immediately available. However, MRI is the test of choice; MRI provides greater resolution of the orbits, cavernous sinus, posterior fossa, and cranial nerves. If imaging results are normal but meningitis or increased intracranial pressure is suspected, lumbar puncture is done.

If vasculitis is suspected clinically, evaluation begins with measurement of ESR, antinuclear antibodies, and rheumatoid factor. In children, if increased intracranial pressure is excluded, respiratory infection is considered.

**Treatment**

In many patients, 6th cranial nerve palsies resolve once the underlying disorder is treated. Idiopathic palsy usually abates within 2 mo.

**Trigeminal Neuralgia**

(Tic Douloureux)
Trigeminal neuralgia is severe paroxysmal, lancinating facial pain due to a disorder of the 5th cranial nerve. Diagnosis is clinical. Treatment is usually with carbamazepine or gabapentin; sometimes surgery is required.

Trigeminal neuralgia affects mainly adults, especially the elderly.

**Etiology**

Trigeminal neuralgia is usually caused by an intracranial artery (eg, anterior inferior cerebellar artery, ectatic basilar artery) or, less often, a venous loop that compresses the 5th cranial (trigeminal) nerve at its root entry zone into the brain stem. Other less common causes include compression by a tumor and occasionally a multiple sclerosis plaque at the root entry zone, but these are distinguished usually by accompanying sensory and other deficits. Other disorders that cause similar symptoms (eg, multiple sclerosis) are sometimes considered to be trigeminal neuralgia and sometimes not. Recognizing the cause is what is important.

The mechanism is unclear. One theory suggests that nerve compression causes local demyelination, which may result in ectopic impulse generation and/or disinhibition of central pain pathways involving the spinal trigeminal nucleus.

**Symptoms and Signs**

Pain occurs along the distribution of one or more sensory divisions of the trigeminal nerve, most often the maxillary. The pain is paroxysmal, lasting seconds up to 2 min, but attacks may recur rapidly. It is lancinating, excruciating, and sometimes incapacitating. Pain is often precipitated by stimulating a facial trigger point (eg, by chewing, brushing the teeth, or smiling). Sleeping on that side of the face is often intolerable.

**Diagnosis**

- Clinical evaluation

Symptoms are almost pathognomonic. Thus, some other disorders that cause facial pain can be differentiated clinically:

- Chronic paroxysmal hemicrania (Sjaastad syndrome) is differentiated by longer (5 to 8 min) attacks of pain and its dramatic response to indomethacin.

- Postherpetic pain is differentiated by its constant duration (without paroxysms), typical antecedent rash, scarring, and predilection for the ophthalmic division.

- Migraine, which may cause atypical facial pain, is differentiated by pain that is more prolonged and often throbbing.

Neurologic examination is normal in trigeminal neuralgia. Thus, neurologic deficits (usually loss of facial sensation) suggest that the trigeminal neuralgia-like pain is caused by another disorder (eg, tumor, stroke, multiple sclerosis plaque, vascular malformation, other lesions that compress the trigeminal nerve or disrupt its brain stem pathways.

**Treatment**

- Usually anticonvulsants

Carbamazepine 200 mg po tid or qid is usually effective for long periods; it is begun at 100 mg po bid, increasing the dose by 100 to 200 mg/day until pain is controlled (maximum daily dose 1200 mg). Hepatic enzymes and CBC should be checked after 2 wk, then every 3 to 6 mo. If carbamazepine is ineffective or has adverse effects, one of the following may be tried:
• Oxcarbazepine 150 to 300 mg po bid

• Gabapentin 300 to 600 mg po tid (300 mg po once on day 1, 300 mg po bid on day 2, 300 mg po tid on day 3, then increasing dose as needed to 600 mg po tid)

• Phenytoin 100 to 200 mg po bid (beginning with 100 mg po bid, then increasing as needed)

• Baclofen 10 to 30 mg po tid (beginning with 5 to 10 mg po tid, then increasing as needed by about 5 mg/day)

• Amitriptyline 25 to 150 mg po taken at bedtime (beginning with 25 mg, then increasing by 25-mg increments each week as needed)

Peripheral nerve block provides temporary relief.

If pain is severe despite these measures, neuroablative treatments are considered; however, efficacy may be temporary, and improvement may be followed by recurrent pain that is more severe than the preceding episodes. In a posterior fossa craniectomy, a small pad can be placed to separate the pulsating vascular loop from the trigeminal root. In radiosurgery, a gamma knife can be used to cut the proximal trigeminal nerve. Electrolytic or chemical lesions or balloon compression of the trigeminal (gasserian) ganglion can be made via a percutaneous stereotaxically positioned needle. Occasionally, the trigeminal nerve fibers between the gasserian ganglion and brain stem are cut. Sometimes, as a last resort to relieve intractable pain, the trigeminal nerve is destroyed.

Hemifacial Spasm

Hemifacial spasm refers to unilateral painless, synchronous contractions of facial muscles due to dysfunction of the 7th cranial (facial) nerve and/or its motor nucleus. Hemifacial spasm results from nerve compression by a pulsating blood vessel, similar to that in trigeminal neuralgia.

Diagnosis is clinical. Focal seizures, blepharospasm, and tics cause similar symptoms and should be considered.

Treatment is similar to that of trigeminal neuralgia except botulinum toxin (botulinum toxin type A or botulinum toxin type B) can also be used effectively.

Bell's Palsy

Bell's palsy is sudden, idiopathic, unilateral peripheral 7th cranial nerve palsy. Symptoms are hemifacial paresis of the upper and lower face. There are no specific tests for diagnosis. Treatment may include corticosteroids, antiviral drugs (eg, acyclovir), lubrication of the eye, and intermittent use of an eye patch.

Etiology

Cause is unknown, but the mechanism is presumably swelling of the 7th cranial (facial) nerve due to an immune or viral disorder. Recent evidence suggests herpes simplex virus infection. The nerve is compressed, resulting in ischemia and paresis, because the nerve passes through a narrow opening (internal acoustic meatus) in the temporal bone.

The orbicularis oculi and frontalis muscles are paretic when the lesion is distal to the 7th cranial nerve nucleus (ie, peripheral) but much less so when the lesion is proximal to the nucleus (ie, central). The effects differ because the orbicularis oculi and frontalis muscles are controlled by the 7th cranial nerve nuclei (central part of the facial nerve), which receive input from both left and right hemispheres. In contrast, the lower facial muscles (below the zygomatic arch) receive input from mainly the peripheral part of the facial nerve, distal to the 7th cranial nerve nuclei, which receives input from only one hemisphere. Thus, the muscles are paretic regardless of the location of the lesion along the 7th cranial nerve.
Symptoms and Signs

Pain behind the ear often precedes facial paresis. Paresis, often with complete paralysis, develops within hours and is usually maximal within 48 to 72 h. Patients may report a numb or heavy feeling in the face. The affected side becomes flat and expressionless; ability to wrinkle the forehead, blink, and grimace is limited or absent (see Plate 68). In severe cases, the palpebral fissure widens and the eye does not close, often irritating the conjunctiva and drying the cornea.

Sensory examination is normal, but the external auditory canal and a small patch behind the ear (over the mastoid) may be painful to the touch. If the nerve lesion is proximal to the geniculate ganglion, salivation, taste, and lacrimation may be impaired, and hyperacusis may be present.

Diagnosis

- Clinical evaluation
- Testing if indicated by clinical findings

There are no specific diagnostic tests. Thus, Bell's palsy is a diagnosis of exclusion. It can be distinguished from a central 7th cranial nerve lesion (eg, due to hemispheric stroke or tumor), which causes weakness primarily of the lower face; patients with central lesions can usually furrow their brow and close their eyes tightly. Other disorders that cause peripheral 7th cranial nerve palsies and must be excluded include the following:

- Geniculate herpes (Ramsay Hunt syndrome, which is due to herpes zoster)
- Middle ear or mastoid infections
- Sarcoidosis
- Lyme disease
- Petrous bone fractures
- Carcinomatous or leukemic nerve invasion
- Chronic meningitis
- Cerebellopontine angle or glomus jugulare tumors

Other disorders that cause peripheral 7th cranial nerve palsy typically develop more slowly than Bell's palsy and may have other distinguishing symptoms or signs.

In Bell's palsy, MRI may show contrast enhancement of the 7th cranial nerve at or near the geniculate ganglion. However, its enhancement may reflect other pathology, such as sarcoidosis or meningeal tumor. If the paralysis progresses over weeks to months, the likelihood of tumor (eg, most commonly schwannoma) compressing the 7th cranial nerve increases. MRI can also help exclude other structural disorders causing 7th cranial nerve palsy. CT, usually negative in Bell's palsy, is done if a fracture is suspected or if MRI is not immediately available and stroke is possible. Acute and convalescent serologic tests for Lyme disease are done if patients have been in a geographic area where ticks are endemic. For all patients, a chest x-ray is taken and serum ACE is measured to check for sarcoidosis. Viral titers are not helpful.

Prognosis

The extent of nerve damage determines outcome. If some function remains, full recovery typically occurs...
within several months. Nerve conduction studies and electromyography predict outcome. The likelihood of complete recovery after total paralysis is 90% if nerve branches in the face retain normal excitability to supramaximal electrical stimulation and is only about 20% if electrical excitability is absent.

Regrowth of nerve fibers may be misdirected, innervating lower facial muscles with periocular fibers and vice versa. The result is contraction of unexpected muscles during voluntary facial movements (synkinesia) or crocodile tears during salivation. Chronic disuse of the facial muscles may lead to contractures.

Treatment

• Possibly corticosteroids, antiviral drugs, or both

• Supportive measures

No treatment has proved effective for idiopathic Bell's palsy. Corticosteroids, if begun within 48 h after onset, may slightly reduce duration and degree of residual paralysis. Prednisone 60 to 80 mg po once/day is given for 1 wk, then decreased gradually over the 2nd wk. Antiviral drugs effective against herpes simplex virus (eg, valacyclovir 1 g po tid for 7 to 10 days, famciclovir 500 mg po tid for 5 to 10 days, acyclovir 400 mg po 5 times/day for 10 days) are also often given.

Corneal drying must be prevented by frequent use of natural tears, isotonic saline, or methylcellulose drops and by intermittent use of tape or a patch to help close the eye, particularly during sleep. Tarsorrhaphy is occasionally required.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is recurrent attacks of severe pain in the 9th cranial nerve distribution (posterior pharynx, tonsils, back of the tongue, middle ear). Diagnosis is clinical. Treatment is usually with carbamazepine or gabapentin.

Glossopharyngeal neuralgia sometimes results from nerve compression by an aberrant, pulsating artery similar to that in trigeminal neuralgia and hemifacial spasm. Rarely, the cause is a tumor in the cerebellopontine angle or the neck. Often, no cause is identified. The disorder is rare, more commonly affecting men, usually after age 40.

Symptoms and Signs

As in trigeminal neuralgia, paroxysmal attacks of unilateral brief, excruciating pain occur spontaneously or are precipitated by certain movements (eg, chewing, swallowing, talking, sneezing). The pain, lasting seconds to a few minutes, usually begins in the tonsillar region or at the base of the tongue and may radiate to the ipsilateral ear. Occasionally, increased vagus nerve activity causes sinus arrest with syncope; episodes may be very infrequent.

Diagnosis

• Clinical evaluation, often including response to anesthetics

• MRI

Diagnosis is clinical. Glossopharyngeal neuralgia is distinguished from trigeminal neuralgia by the location of the pain. Also, in glossopharyngeal neuralgia, swallowing or touching the tonsils with an applicator tends to precipitate pain, and applying lidocaine to the throat temporarily eliminates spontaneous or evoked pain. MRI is done to exclude tonsillar, pharyngeal, and cerebellopontine angle tumors and metastatic lesions in the anterior cervical triangle. Local nerve blocks done by an ENT physician can help distinguish between carotidynia, superior laryngeal neuralgia, and pain caused by tumors.
Treatment

• Usually anticonvulsants

Treatment is the same as that for trigeminal neuralgia (see p. 1754). If oral drugs are ineffective, topical cocaine applied to the pharynx may provide temporary relief, and surgery to decompress the nerve from a pulsating artery may be necessary. If pain is restricted to the pharynx, surgery can be restricted to the extracranial part of the nerve. If pain is widespread, surgery must involve the intracranial part of the nerve.
Chapter 182. Craniocervical Junction Abnormalities

Craniocervical junction abnormalities are congenital or acquired abnormalities of the occipital bone, foramen magnum, or first 2 cervical vertebrae that decrease the space for the lower brain stem and cervical cord. These abnormalities can result in neck pain; syringomyelia; cerebellar, lower cranial nerve, and spinal cord deficits; and vertebrobasilar ischemia. Diagnosis is by MRI or CT. Treatment often involves reduction, followed by stabilization via surgery or an external device.

Neural tissue is flexible and susceptible to compression. Craniocervical junction abnormalities can cause or contribute to cervical spinal cord or brain stem compression; some abnormalities and their clinical consequences include the following:

- Fusion of the atlas (C1) and occipital bone: Spinal cord compression if the anteroposterior diameter of the foramen magnum behind the odontoid process is < 19 mm
- Basilar invagination (upward bulging of the occipital condyles): A short neck and compression that can affect the cerebellum, brain stem, lower cranial nerves, and spinal cord
- Atlantoaxial subluxation or dislocation (displacement of the atlas anteriorly in relation to the axis): Acute or chronic spinal cord compression
- Klippel-Feil malformation (fusion of cervical vertebrae): Deformity and limited motion of the neck but usually no neurologic consequences
- Platybasia (flattening of the skull base so that the angle formed by the intersection of the clival and anterior fossa planes is > 135°), seen on lateral skull imaging: No symptoms or cerebellar or spinal cord deficits or normal-pressure hydrocephalus

Etiology

Craniocervical junction abnormalities can be congenital or acquired.

**Congenital:** Congenital abnormalities may be specific structural abnormalities or general or systemic disorders that affect skeletal growth and development. Many patients have multiple abnormalities.

**Structural abnormalities** include the following:

- Os odontoideum (anomalous bone that replaces all or part of the odontoid process)
- Atlas assimilation (congenital fusion of the atlas and occipital bone)
- Congenital Klippel-Feil malformation (eg, with Turner's or Noonan's syndrome), often associated with atlanto-occipital anomalies
- Atlas hypoplasia
- Chiari malformations (descent of the cerebellar tonsils or vermis into the cervical spinal canal, sometimes associated with platybasia—see p. 2992)

**General or systemic disorders** that affect skeletal growth and development and involve the craniocervical junction include the following:

- Achondroplasia (impair epiphyseal bone growth, resulting in shortened, malformed bones) sometimes causes the foramen magnum to narrow or fuse with the atlas and thus may compress the spinal cord or brain stem.
- Down syndrome, Morquio's syndrome (mucopolysaccharidosis IV), or osteogenesis imperfecta can
Acquired: Acquired causes include injuries and disorders.

- Injuries may involve bone, ligaments, or both and are usually caused by vehicle or bicycle accidents, falls, and particularly diving; some injuries are immediately fatal.

- RA (the most common disease cause) and Paget's disease of the cervical spine can cause atlantoaxial dislocation or subluxation, basilar invagination, or platybasia.

- Metastatic tumors that affect bone can cause atlantoaxial dislocation or subluxation.

- Slowly growing craniocervical junction tumors (eg, meningioma, chordoma) can impinge on the brain stem or spinal cord.

Symptoms and Signs

Symptoms and signs can occur after a minor neck injury or spontaneously and may vary in progression. Presentation varies by degree of compression and by structures affected. The most common manifestations are

- Neck pain, often with headache

- Symptoms and signs of spinal cord compression

Neck pain often spreads to the arms and may be accompanied by headache (commonly, occipital headache radiating to the skull vertex); it is attributed to compression of the C2 root and the greater occipital nerve and to local musculoskeletal dysfunction. Neck pain and headache usually worsen with head movement and can be precipitated by coughing or bending forward. If patients with Chiari malformation have hydrocephalus, being upright may aggravate the hydrocephalus and result in headaches.

Spinal cord compression involves the upper cervical cord. Deficits include spastic paresis in the arms, legs, or both, caused by compression of motor tracts. Joint position and vibration senses (posterior column function) are commonly impaired. Tingling down the back, often into the legs, with neck flexion (Lhermitte's sign) may occur. Uncommonly, pain and temperature senses (spinothalamic tract function) are impaired in a stocking-glove pattern.

Neck appearance, range of motion, or both can be affected by some abnormalities (eg, platybasia, basilar invagination, Klippel-Feil malformation). The neck may be short, webbed (with a skinfold running approximately from the sternocleidomastoid to the shoulder), or in an abnormal position (eg, torticollis in Klippel-Feil malformation). Range of motion may be limited.

Brain compression (eg, due to platybasia, basilar invagination, or craniocervical tumors) may cause brain stem, cranial nerve, and cerebellar deficits. Brain stem and cranial nerve deficits include sleep apnea, internuclear ophthalmoplegia (ipsilateral weakness of eye adduction plus contralateral horizontal nystagmus in the abducting eye with lateral gaze), downbeat nystagmus (fast component downward), hoarseness, dysarthria, and dysphagia. Cerebellar deficits usually impair coordination (see p. 1777).

Vertebrobasilar ischemia can be triggered by changing head position. Symptoms may include intermittent syncope, drop attacks, vertigo, confusion or altered consciousness, weakness, and visual disturbance.

Syringomyelia (cavity in the central part of the spinal cord—see p. 1812) is common in patients with Chiari malformation. It may cause segmental flaccid weakness and atrophy, which first appear or are most severe in the distal upper extremities; pain and temperature senses may be lost in a capelike distribution over the neck and proximal upper extremities, but light touch is preserved.
Diagnosis

- MRI or CT of the brain and upper spinal cord

A craniocervical abnormality is suspected when patients have pain in the neck or occiput plus neurologic deficits referable to the lower brain stem, upper cervical spinal cord, or cerebellum. Lower cervical spine disorders can usually be distinguished clinically (based on level of spinal cord dysfunction) and by neuroimaging.

**Neuroimaging:** If a craniocervical abnormality is suspected, MRI or CT of the upper spinal cord and brain, particularly the posterior fossa and craniocervical junction, is done. Acute or suddenly progressive deficits are an emergency, requiring immediate imaging. Sagittal MRI best identifies associated neural lesions (eg, hindbrain, cerebellar, spinal cord, and vascular abnormalities; syringomyelia) and soft-tissue lesions. CT shows bone structures more accurately than MRI and may be done more easily in an emergency.

If MRI and CT are unavailable, plain x-rays—lateral view of the skull showing the cervical spine, anteroposterior view, and oblique views of the cervical spine—are taken.

If MRI is unavailable or inconclusive and CT is inconclusive, CT myelography (CT after intrathecal injection of a radiopaque dye) is done. If MRI or CT suggests vascular abnormalities, magnetic resonance angiography or vertebral angiography is done.

Treatment

- Reduction and immobilization
- Sometimes surgical decompression, fixation, or both

If neural structures are compressed, treatment consists of reduction (traction or changes in head position to realign the craniocervical junction and thus relieve neural compression). After reduction, the head and neck are immobilized. **Acute or suddenly progressive spinal cord compression requires emergency reduction.**

For most patients, reduction involves skeletal traction with a crown halo ring and weight of up to about 4 kg. Reduction with traction may take 5 to 6 days. If reduction is achieved, the neck is immobilized in a halo vest for 8 to 12 wk; then x-rays must be taken to confirm stability.

If reduction does not relieve neural compression, surgical decompression, using a ventral or a dorsal approach, is necessary. If instability persists after decompression, posterior fixation (stabilization) is required. For some abnormalities (eg, due to RA), external immobilization alone is rarely successful; if it is unsuccessful, posterior fixation or anterior decompression and stabilization are required.

Several different methods of instrumentation (eg, plates or rods with screws) can be used for temporary stabilization until bones fuse and stability is permanent. In general, all unstable areas must be fused.

**Bone disease:** Radiation therapy and a hard cervical collar often help patients with metastatic bone tumors. Calcitonin, mithramycin, and bisphosphonates may help patients with Paget's disease.
Chapter 183. Movement and Cerebellar Disorders

Introduction

Voluntary movement requires interaction of the corticospinal (pyramidal) tracts, basal ganglia, and cerebellum (the center for motor coordination). The pyramidal tracts pass through the medullary pyramids to connect the cerebral cortex to lower motor centers of the brain stem and spinal cord. The basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra) form the extrapyramidal system. They are located deep in the forebrain and direct their output mainly rostrally through the thalamus to the cerebral cortex. Most neural lesions that cause movement disorders occur in the extrapyramidal system; thus, movement disorders are also called extrapyramidal disorders.

Classification

Movement disorders are classified as those with decreased or slow purposeful movements (hypokinesia) or those with excessive voluntary or abnormal involuntary movements (hyperkinesia). Although disorders of the cerebellum also impair gait and movement, they are classified separately (see p. 1777).

Hypokinesia: Most hypokinetic disorders are parkinsonian disorders, which are characterized by slow and decreased movement, muscular rigidity, resting tremor, and postural instability (see p. 1765).

Hyperkinesia: There are many hyperkinetic disorders (see Fig. 183-1 and Table 183-1). They can be subclassified as rhythmic or non-rhythmic.

Rhythmic disorders are primarily tremors—regular alternating or oscillatory movements, which can occur mainly at rest (as resting tremor) or during attempted movement (as intention tremor).

Nonrhythmic disorders are characterized as slow (eg, athetosis), sustained (eg, dystonias), or rapid. Rapid disorders are characterized as suppressible (eg, tics) or nonsuppressible (eg, hemiballismus, chorea, myoclonus). Athetosis and chorea often occur together as choreoathetosis. Chorea occurs in Huntington's disease (see p. 1763). Tic disorders include Tourette's syndrome (see p. 2902).

Chorea, Athetosis, and Hemiballismus

Chorea is nonrhythmic, jerky, rapid, nonsuppressible involuntary movements, mostly of distal muscles or the face; movements may merge imperceptibly into purposeful or semipurposeful acts that mask the involuntary movements. Athetosis is nonrhythmic, slow, writhing, sinuous movements predominantly in distal muscles, often alternating with postures of the proximal limbs to produce a continuous, flowing stream of movement. Hemiballismus is usually a unilateral, nonrhythmic, rapid, nonsuppressible, violent, flinging movement of the proximal arm.

Chorea and athetosis often occur together (as choreoathetosis). They are manifestations of overactivity in certain pathways of the basal ganglia. Huntington's disease (see p. 1763) is the most common degenerative disease causing chorea. Other causes include thyrotoxicosis, paraneoplastic syndromes, SLE affecting the CNS, other autoimmune disorders, and drugs (eg, antipsychotics). Rheumatic fever sometimes leads to Sydenham's chorea (see p. 2862). A tumor or infarct of the caudate nucleus can cause acute unilateral chorea (hemichorea). Chorea may occur as an isolated symptom in patients > 60 (as senile chorea); this chorea tends to be symmetric and does not cause dementia.

The cause is treated or corrected if possible. Sydenham's chorea and chorea due to infarcts of the caudate nucleus often lessen over time. Chorea due to thyrotoxicosis usually lessens when thyroid dysfunction is corrected. In Huntington's disease, drugs that suppress dopaminergic activity, such as antipsychotics (eg, risperidone), and dopamine-depleting drugs (eg, reserpine, tetrabenazine) can be used. However, improvement may be limited.
Chorea gravidarum occurs during pregnancy, often in patients who had rheumatic fever. Chorea usually begins during the 1st trimester and resolves spontaneously by or after delivery. Treatment is sedation with barbiturates; other sedatives may harm the fetus. Rarely, a similar disorder occurs in women taking oral contraceptives.

Hemiballismus is caused by a lesion, usually an infarct, around the contralateral subthalamic nucleus. Although disabling, hemiballismus is usually self-limited, lasting 6 to 8 wk. Treatment with antipsychotics is often effective.

Dystonias

Dystonias are sustained involuntary muscle contractions, often distorting body posture. Dystonias can be primary or secondary, and they can be generalized, focal, or segmental. Diagnosis is clinical. Treatment of generalized dystonia is often with a combination of anticholinergic drugs, muscle relaxants, and benzodiazepines. Treatment of focal or segmental dystonias is often with botulinum toxin; more generalized or refractory cases may benefit from surgery.

Dystonia may be primary (idiopathic) or secondary to degenerative or metabolic CNS disorders (eg, Wilson's disease, Hallervorden-Spatz disease, various lipidoses, multiple sclerosis, cerebral palsy, stroke, brain hypoxia) or drugs (most often phenothiazines, thioxanthenes, butyrophenones, and antiemetics).

Generalized dystonia (dystonia musculorum deformans): This rare dystonia is progressive and characterized by movements that result in sustained, often bizarre postures. It is often hereditary, usually as an autosomal dominant disorder with partial penetrance; asymptomatic siblings of patients often have a forme fruste of the disorder. The causative gene is usually DYT1, causing DYT1 dystonia.

Symptoms usually begin in childhood with inversion and plantar fixation of the foot while walking. The dystonia may affect only the trunk or a leg but sometimes affects the whole body. Patients with the most severe form may become twisted into grotesque fixed postures and ultimately confined to a wheelchair. Symptoms that begin during adulthood usually affect only the face or arms. Mental function is usually preserved.

Focal dystonias: These dystonias affect a single body part. They typically start in a person's 30s or 40s and affect women more often. Initially, spasms may be periodic, occurring randomly or during stress; they are triggered by certain movements of the affected body part and disappear during rest. Over days, weeks, or many years, spasms may progress; they may be triggered by movements of unaffected body parts and may continue during rest. Eventually, the affected body part remains distorted, sometimes in a painful position, resulting in severe disability. Symptoms vary depending on the specific muscles involved.

Occupational dystonia consists of focal dystonic spasms initiated by performing skilled acts (eg, writer's or typist's cramp, the yips in golfers).

Spasmodic dystonia consists of a strained, hoarse, or creaky voice due to abnormal involuntary contraction of laryngeal muscles.

Torticollis begins with a pulling sensation followed by sustained torsion and deviation of the head and neck. The cause is often unknown but, in some cases, is probably genetic. In early stages, it can be voluntarily overcome. Patients may discover sensory or tactile tricks that make the spasm stop, such as touching the face on the side contralateral to the deviation. Torticollis can also be caused by dopamine-blocking drugs (eg, haloperidol).

Segmental dystonias: These dystonias affect ≥ 2 contiguous body parts.
Meige's disease (blepharospasm-oromandibular dystonia) consists of involuntary blinking, jaw grinding, and grimacing, usually beginning in late middle age. It may mimic the buccal-lingual-facial movements of tardive dyskinesia.

**Diagnosis**

Diagnosis is clinical.

**Treatment**

- For generalized dystonia, anticholinergics, muscle relaxants, or both
- For focal dystonia, botulinum toxin

Treatment is often unsatisfactory. For generalized dystonia, a high-dose anticholinergic drug (trihexyphenidyl 2 to 10 mg po tid, benztropine 3 to 15 mg po once/day) is most commonly used, often with a muscle relaxant (usually baclofen), a benzodiazepine (eg, clonazepam), or both. Generalized dystonia that is severe or does not respond to drugs may be treated with deep brain stimulation of the globus pallidus interna, which requires surgery.

For focal or segmental dystonias or for generalized dystonia that severely affects specific body parts, the treatment of choice is purified botulinum toxin type A injected into the affected muscles by an experienced practitioner. Botulinum toxin weakens muscular contractions, but it does not alter the abnormal neural stimulus. Toxin injection is particularly effective for blepharospasm and torticollis. Dosage varies greatly. Treatments must be repeated every 3 to 6 mo.

**Fragile X-Associated Tremor/Ataxia Syndrome**

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a genetic disorder affecting mostly men and causing tremor, ataxia, and dementia.

FXTAS affects about 1/3000 men. A premutation (an increased number of CGG repeats) occurs in the fragile X mental retardation (FMR1) gene on the X chromosome; if the mutation is full, > 200 repeats occur, causing fragile X syndrome. People with the premutation are considered carriers. Daughters (but not sons) of men with the premutation inherit the premutation. Their children (grandchildren of men with the gene) have a 50% chance of inheriting the premutation, which can expand into a full mutation when passed from mother to child (and thus cause fragile X syndrome). FXTAS develops in about 30% of men with the premutation and in < 5% of women with the premutation. Risk of developing FXTAS increases with age.

**Symptoms and Signs**

Symptoms usually develop in older age; average age of onset in 60 yr. The more CGG repeats, the more severe are the symptoms.

Tremor that resembles essential tremor is a common early symptom, usually followed by ataxia within 2 yr. Other symptoms may include slow movements, stiffness, and decreased facial expression, similar to Parkinson's disease.

Cognitive impairment, including loss of short-term memory, slowed thought, and difficulty problem-solving, varies. These symptoms often progress to dementia. Depression, anxiety, impatience, hostility, and mood lability may develop.

Sensation and reflexes in the feet may be lost. Dysautonomia (eg, orthostatic hypotension) may occur. In later stages, bladder and bowel control may be lost. Life expectancy after motor symptoms is reported to range from about 5 to 25 yr.

In women with the premutation, symptoms are usually less severe, possibly because the presence of
another X chromosome is protective. Symptoms more often suggest multiple sclerosis or fibromyalgia than FXTAS. These women have an increased risk of early menopause, infertility, and ovarian dysfunction.

**Diagnosis**

- Genetic testing

Grandfathers of children who have fragile X syndrome should be asked whether they have neurologic symptoms associated with FXTAS. MRI can detect the characteristic brightness in the middle cerebellar peduncles, which is not always present in FXTAS but is rarely caused by other disorders. Diagnosis is confirmed by genetic testing.

**Treatment**

Tremor can often be relieved with many of the drugs used to control tremors due to Parkinson's disease (see p. 1767).

**Huntington's Disease**

(Huntington's Chorea; Chronic Progressive Chorea; Hereditary Chorea)

**Huntington's disease is an autosomal dominant disorder characterized by chorea and progressive cognitive deterioration, usually beginning in middle age. Diagnosis is by genetic testing. Treatment is supportive. First-degree relatives are encouraged to have genetic testing.**

Huntington's disease affects both sexes equally. The caudate nucleus atrophies, the inhibitory medium spiny neurons in the corpus striatum degenerate, and levels of the neurotransmitters γ-aminobutyric acid (GABA) and substance P decrease.

Huntington's disease results from a gene mutation causing abnormal repetition of the DNA sequence CAG that codes for the amino acid glutamine. The resulting gene product, a large protein called huntingtin, has an expanded stretch of polyglutamine residues, which leads to disease via unknown mechanisms. The more CAG repetitions, the earlier the disease begins and the more severe the effects. The number of repeats can increase with successive generations and, over time, lead to a more severe phenotype within a family tree.

**Symptoms and Signs**

Symptoms and signs develop insidiously, starting at about age 35 to 50 but can develop before adulthood. Dementia or psychiatric disturbances (eg, depression, apathy, irritability, anhedonia, antisocial behavior, full-blown bipolar or schizophreniform disorder) develop before or simultaneously with the movement disorder. Abnormal movements appear; they include myoclonic jerks or irregular movements of the extremities, a lilting gait (like a puppet's), facial grimacing, ataxia, and inability to sustain a motor act (motor impersistence) such as tongue protrusion.

The disorder progresses, making walking impossible, swallowing difficult, and dementia severe. Most patients eventually require institutionalization. Death usually occurs 13 to 15 yr after symptoms begin. The cause is usually pneumonia or coronary artery disease.

**Diagnosis**

- Clinical evaluation, confirmed by genetic testing
- MRI to rule out other causes

Diagnosis is based on typical symptoms and signs plus a positive family history and is confirmed by genetic testing. Neuroimaging is done to exclude other disorders; in advanced Huntington's disease, MRI and CT coronal views show boxcar ventricles (ie, squared-off edges due to atrophy of the caudate head).
Treatment

• Supportive measures

• Genetic counseling

Because the disease is progressive, end-of-life care should be discussed early (see p. 3480).

Treatment is supportive. Chorea and agitation may be partially suppressed by antipsychotics (eg, chlorpromazine 25 to 300 mg po tid, haloperidol 5 to 45 mg po bid); dose is increased until intolerable or undesirable adverse effects (eg, lethargy, parkinsonism) occur. Alternatively, tetrabenazine may be used. The dose is started at 12.5 mg po once/day; dosage is increased (to 12.5 mg bid in the 2nd wk, 12.5 mg tid in the 3rd wk, up to a total of 100 mg/day divided into 3 doses) until intolerable adverse effects (eg, sedation, akathisias, parkinsonism, depression) occur or chorea resolves.

Experimental therapies aim to reduce glutamatergic neurotransmission via the N-methyl-D-aspartate receptor and bolster mitochondrial energy production. Treatment to supplement GABA in the brain has been ineffective.

People who have 1st-degree relatives with the disease should have genetic testing and counseling (see also p. 2598) because people are likely to have children before symptoms appear. If such people are interested in testing, they are referred to centers that have expertise in dealing with the complex ethical and psychologic issues involved.

Myoclonus

Myoclonus is a brief, shocklike contraction of a muscle or group of muscles. Diagnosis is clinical and by selective testing. Treatment includes correction of reversible causes and sometimes oral drugs (eg, clonazepam, valproate).

Physiologic myoclonus may occur as a person falls asleep (nocturnal myoclonus). Myoclonus can result from other disorders and certain drugs (see Table 183-2). The most common causes are hypoxia, drug toxicity, and metabolic disturbances; other causes include degenerative disorders affecting the basal ganglia and some dementias.

[Table 183-2, Causes of Myoclonus]

Myoclonus may be focal, segmental (contiguous areas), multifocal (noncontiguous areas), or generalized.

Symptoms and Signs

Myoclonus can vary in amplitude, frequency, and distribution. Muscle jerks may be induced by a stimulus (eg, sudden noise, movement, light, visual threat). Myoclonus that occurs when patients are suddenly startled (startle myoclonus) may be an early symptom of Creutzfeldt-Jacob disease. Myoclonus due to severe closed head trauma or hypoxicischemic brain damage may worsen with purposeful movements (action myoclonus) or may occur spontaneously when movement is limited because of injury.

Myoclonus due to metabolic disturbances may be multifocal, asymmetric, and stimulus-induced; it usually involves facial or proximal limb muscles. If the disturbance persists, generalized myoclonic jerks and, ultimately, seizures may occur.

Diagnosis

Diagnosis is clinical. Testing is done based on clinically suspected causes.

Treatment
• Correction of metabolic disturbance

• Drug therapy to relieve symptoms

Treatment begins with correction of underlying metabolic disturbances.

For symptom relief, clonazepam 0.5 to 2 mg po tid is often effective. Valproate 250 to 500 mg po bid or levetiracetam 250 to 500 mg po once/day to bid may be effective; rarely, other anticonvulsants help. Doses of clonazepam or valproate may need to be lower in the elderly. Many forms of myoclonus respond to the serotonin precursor 5-hydroxytryptophan (initially, 25 mg po qid, increased to 150 to 250 mg po qid), which must be used with the oral decarboxylase inhibitor carbidopa (50 mg every morning and 25 mg at noon or 50 mg every evening and 25 mg at bedtime).

**Parkinson's Disease**

Parkinson's disease is an idiopathic, slowly progressive, degenerative CNS disorder characterized by resting tremor, muscular rigidity, slow and decreased movement, and postural instability. Diagnosis is clinical. Treatment is with levodopa plus carbidopa, other drugs, and, for refractory symptoms, surgery.

Parkinson's disease affects about 0.4% of people > 40 yr, 1% of people ≥ 65 yr, and 10% of people ≥ 80 yr. The mean age at onset is about 57 yr. Rarely, Parkinson's disease begins in childhood or adolescence (juvenile parkinsonism).

Parkinsonism refers to symptoms that are similar to those of Parkinson's disease but caused by another condition.

**Etiology**

Synuclein is a presynaptic neuronal and glial cell protein, which can form insoluble fibrils in Lewy bodies. Although there are rare cases of Parkinson's disease without Lewy bodies, the pathologic hallmark of Parkinson's disease remains synuclein-filled Lewy bodies in the nigrostriatal system. However, synucleinopathy can occur in many other parts of the nervous system, including the dorsal motor nucleus of the vagus nerve, basal nucleus of Meynert, hypothalamus, neocortex, olfactory bulb, sympathetic ganglia, and myenteric plexus of the GI tract. Lewy bodies appear in a temporal sequence, and many experts believe that Parkinson's disease is a relatively late development in a systemic synucleinopathy, which may also include Lewy body dementia. Patients with Parkinson's disease may also have Alzheimer's disease. Parkinson's disease, Lewy body dementia, and Alzheimer's disease share several features (see p. 1673); further research is needed to clarify their relationship to each other, including the relative contributions of synucleinopathy.

In Parkinson's disease, pigmented neurons of the substantia nigra, locus ceruleus, and other brain stem dopaminergic cell groups are lost. Loss of substantia nigra neurons, which project into the caudate nucleus and putamen, depletes dopamine in these areas.

A genetic predisposition is likely, at least in some cases. About 15 to 20% of patients have a family history of Parkinson's disease. Several abnormal genes have been identified. Inheritance is autosomal dominant for some genes and autosomal recessive for others.

**Symptoms and Signs**

In most patients, the disease begins insidiously.

A resting tremor of one hand is often the first symptom. The tremor is characterized as follows:

• Slow and coarse

• Maximal at rest, lessening during movement, and absent during sleep
• Amplitude increased by emotional tension or fatigue

• Often involving the wrist and fingers in movements similar to those used to manipulate small objects or pills (pill-rolling tremor)

Usually, the hands, arms, and legs are most affected, in that order. The jaw and tongue may also be affected, but not the voice. Tremor may become less prominent as the disease progresses.

**Rigidity** develops without tremor in many patients. When a clinician moves a rigid joint, sudden, rhythmic jerks due to variations in the intensity of the rigidity occur, producing a ratchet-like effect (cogwheel rigidity).

**Slow movements** (bradykinesia) are typical as rigidity progresses. Movement also becomes decreased (hypokinesia) and difficult to initiate (akinesia).

Rigidity and hypokinesia may contribute to muscular aches and sensations of fatigue. The face becomes masklike, with an open mouth, drooling, and reduced blinking. Early on, patients may appear depressed because facial expression is lacking and movements are decreased and slowed. Speech becomes hypophonic, with characteristic monotonous, slurring dysarthria. Hypokinesia and impaired control of distal musculature cause micrographia (writing in very small letters) and make activities of daily living increasingly difficult. Without warning, voluntary movement, including walking, may suddenly halt (called freezing).

**Postural instability** develops, resulting in gait abnormalities. Patients have difficulty starting to walk, turning, and stopping; the gait becomes shuffling with short steps, and the arms are held flexed to the waist and do not swing with the stride. Steps may inadvertently quicken, and patients may break into a run to keep from falling (festination). A tendency to fall forward (propulsion) or backward (retropulsion) when the center of gravity is displaced results from loss of postural reflexes. Posture becomes stooped.

**Dementia** can occur.

**Sleep disorders** are common. Insomnia may result from nocturia or from the inability to turn in bed. Rapid eye movement (REM) sleep behavior disorder may develop; in it, violent bursts of physical activity occur during REM sleep. Sleep deprivation may contribute to depression, exacerbate cognitive impairment, or cause excessive daytime sleepiness.

**Neurologic symptoms unrelated to parkinsonism** commonly develop because synucleinopathy occurs in other areas of the central, peripheral, and autonomic nervous systems. It may have the following effects:

• Almost universal sympathetic denervation of the heart, contributing to orthostatic hypotension

• Esophageal dysmotility, contributing to dysphagia and increased risk of aspiration

• Lower bowel dysmotility, contributing to constipation

• Urinary hesitancy and/or urgency (common)

• Anosmia (common)

**Seborrheic dermatitis** is also common.

**Postencephalitic parkinsonism** causes forced, sustained deviation of the head and eyes (oculogyric crises), other dystonias, autonomic instability, depression, and personality changes.

**Diagnosis**
Mainly by clinical evaluation

Diagnosis is clinical. Parkinson's disease is suspected in patients with characteristic unilateral resting tremor, decreased movement, or rigidity. The tremor disappears (or attenuates) during finger-to-nose coordination testing.

During the neurologic examination, patients cannot perform rapidly alternating or rapid successive movements well. Sensation and strength are usually normal. Reflexes are normal but may be difficult to elicit because of marked tremor or rigidity. Patients may not suppress eye closure when the frontal muscle is tapped between the eyes (glabellar reflex; if persistent, called Myerson's sign).

Slowed and decreased movement due to Parkinson's disease must be differentiated from decreased movement and spasticity due to lesions of the corticospinal tracts. Unlike Parkinson's disease, corticospinal tract lesions cause paresis (weakness or paralysis), preferentially in distal antigravity muscles; hyperreflexia; and extensor plantar responses (Babinski's sign). Spasticity due to corticospinal tract lesions increases muscle tone and deep tendon reflex responses; muscle tone increases in proportion to rate and degree of stretch placed on a muscle until resistance suddenly melts away (clasp-knife phenomenon). Rigidity in Parkinson's disease differs because resistance does not change through the entire range of motion (moving the limb is similar to bending a lead pipe).

Diagnosis is confirmed by the presence of other characteristic signs (eg, infrequent blinking, lack of facial expression, impaired postural reflexes, characteristic gait abnormalities). Tremor without other characteristic signs suggests early disease or another diagnosis. In the elderly, decreased spontaneous movements or a short-stepped gait may result from depression or dementia; such cases may be difficult to distinguish from Parkinson's disease.

To differentiate Parkinson's disease from secondary parkinsonism, clinicians note whether levodopa results in dramatic improvement, suggesting Parkinson's disease. Causes of parkinsonism can be identified by the following:

- Taking a thorough history, including occupational, drug, and family history
- Checking for neurologic deficits characteristic of disorders other than Parkinson's disease (such as neurodegenerative disorders)
- Neuroimaging when indicated

Treatment

- Carbidopa/levodopa (mainstay of treatment)
- Amantadine, monoamine oxidase type B (MAO-B) inhibitors, or anticholinergic drugs used first as monotherapy or late with levodopa
- Dopamine agonists at any stage
- Catechol O-methyltransferase (COMT) inhibitors sometimes used with levodopa
- Surgery if drugs are ineffective
- Exercise and adaptive measures

Many oral drugs are commonly used to relieve symptoms of Parkinson's disease (see Table 183-3). Traditionally, levodopa has been the first drug used. However, some experts believe that early use of levodopa hastens development of adverse effects and inconsistency of drug response; they prefer to delay levodopa, particularly in younger patients, if possible and to use MAO-B inhibitors, anticholinergic drugs, amantadine, or dopamine agonists first if drug treatment is necessary. Levodopa is then delayed until symptoms interfere with daily activities despite use of other treatments.
Doses are often reduced in the elderly. Drugs that cause or worsen symptoms, particularly antipsychotics, are avoided.

**Levodopa**: Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier into the basal ganglia, where it is decarboxylated to form dopamine. Coadministration of the peripheral decarboxylase inhibitor carbidopa prevents levodopa catabolism, thus lowering the levodopa dosage requirements and minimizing adverse effects. Levodopa is most effective at relieving bradykinesia and rigidity, although tremor is often substantially reduced. Mildly affected patients who take levodopa may return to nearly normal, and bedbound patients may become ambulatory.

Levodopa has central adverse effects; occasional hallucinations or delirium occurs, most often in the elderly and patients with dementia. The dose that causes dyskinesias tends to decrease as treatment continues. In some patients, the lowest dose that reduces parkinsonian symptoms also causes dyskinesias.

Dosage of carbidopa/levodopa is increased every 4 to 7 days as tolerated until maximum benefit is reached. Adverse effects may be minimized by increasing the dose gradually and by giving the drug with or after meals; however, high-protein meals may impair absorption of levodopa. If peripheral adverse effects predominate, increasing the amount of carbidopa may help. Most patients with Parkinson’s disease require 400 to 1000 mg/day of levodopa in divided doses every 2 to 5 h. A dissolvable immediate-release oral form of carbidopa/levodopa can be taken without water; this form is useful for patients who have difficulty swallowing. Doses are the same as for immediate-release carbidopa/levodopa.

Occasionally, levodopa must be used to maintain motor function despite levodopa-induced hallucinations or delirium. Psychosis can sometimes be treated with oral quetiapine or clozapine; these drugs aggravate parkinsonian symptoms much less than other antipsychotics (eg, risperidone, olanzapine) or not at all. Haloperidol should be avoided. Quetiapine can be started at 25 mg once/day or bid and increased in 25-mg increments every 1 to 3 days up to 800 mg/day as tolerated. Use of clozapine is limited because agranulocytosis occurs in 1% of patients. When clozapine is used, the dose is 12.5 to 50 mg once/day to 12.5 to 25 mg bid. CBC is done weekly for 6 mo and every 2 wk thereafter.

After 2 to 5 yr of treatment, most patients experience fluctuations in their response to levodopa (on-off effect). Whether dyskinesias and the on-off effect result from levodopa or the underlying disease is controversial. Eventually, the period of improvement after each dose shortens, and drug-induced dyskinesias result in swings from intense akinesia to uncontrollable hyperactivity. Traditionally, such swings are managed by keeping the levodopa dose as low as possible and using dosing intervals as short as every 1 to 2 h. Alternative methods include adjunctive use of dopamine agonists, controlled-release levodopa/carbidopa, COMT and/or MAO inhibitors, and amantadine.

**Amantadine**: This drug is useful as monotherapy for early, mild parkinsonism in 50% of patients and later can be used to augment levodopa’s effects. It may augment dopaminergic activity, anticholinergic effects, or both. If used as monotherapy, amantadine often loses its effectiveness after several months. Amantadine may ameliorate dyskinesias secondary to long-term use of levodopa.

**Dopamine agonists**: These drugs directly activate dopamine receptors in the basal ganglia. Oral drugs include bromocriptine, pramipexole, and ropinirole.

Oral dopamine agonists can be used as monotherapy but, as such, are rarely sufficient for more than a few years. They may be useful at all stages of the disease. Using these drugs early in treatment, with small doses of levodopa, may delay emergence of dyskinesias and on-off effects, possibly because dopamine agonists stimulate dopamine receptors longer than levodopa does. This type of stimulation is more physiologic and may better preserve the receptors. Dopamine agonists are particularly useful in later stages when response to levodopa decreases or on-off effects are prominent.

Rotigotine was recently withdrawn from the market because of problems with consistent drug delivery.

Adverse effects may limit use of dopamine agonists. Reducing the levodopa dose may minimize adverse
effects of dopamine agonists. Agonists can cause compulsive gambling, hypersexuality, or overeating in 1 to 2% of patients, requiring a change in drug or a reduction in dose. Bromocriptine is rarely used because cardiac valvular fibrosis and pleural fibrosis are concerns. Pergolide, another dopamine agonist, was recalled because it increases risk of cardiac valvular fibrosis.

Apomorphine is an injectable dopamine agonist used as rescue therapy when off effects are severe. Onset of action is rapid (5 to 10 min), and duration is short (60 to 90 min). Apomorphine 2 to 6 mg sc can be given up to 5 times/day as needed. A 2-mg test dose is given first to check for orthostatic hypotension. BP is checked in the standing and supine positions before treatment and 20, 40, and 60 min afterward. Other adverse effects are similar to those of other dopamine agonists. Nausea can be prevented by starting trimethobenzamide 300 mg po tid 3 days before apomorphine and continuing it for the first 2 mo of treatment.

Selective monoamine oxidase type B (MAO-B) inhibitors: Selegiline inhibits one of the 2 major enzymes that break down dopamine in the brain, thereby prolonging the action of each dose of levodopa. In some patients with mild on-off effects, selegiline helps prolong levodopa's effect. Used initially as monotherapy, selegiline can delay the initiation of levodopa by about 1 yr. Selegiline may slow progression of Parkinson's disease by potentiating residual brain dopamine in early disease or by reducing oxidative metabolism of brain dopamine. A dose of 5 mg po bid does not cause hypertensive crisis (sometimes triggered by consuming tyramine in foods, such as some cheeses, during MAO inhibitor therapy); this adverse effect is common with nonselective MAO inhibitors, which block A and B isoenzymes. Although virtually free of adverse effects, selegiline can potentiate levodopa-induced dyskinesias, mental and psychiatric adverse effects, and nausea, requiring reduction in the levodopa dose. Selegiline is also available in a formulation designed for buccal absorption (zydis-selegiline).

Rasagiline, an MAO-B inhibitor that is not metabolized to amphetamine, is effective and well-tolerated in early and late disease. Whether rasagiline's effects are purely symptomatic or also neuroprotective is unclear, but recent studies suggest rasagiline may alter disease progression.

Anticholinergic drugs: These drugs can be used as monotherapy in early disease and later to supplement levodopa. Commonly used anticholinergic drugs include benztropine and trihexyphenidyl. Antihistamines with anticholinergic effects (eg, diphenhydramine 25 to 50 mg po bid to qid, orphenadrine 50 mg po once/day to qid) are occasionally useful for treating tremor. Anticholinergic tricyclic antidepressants (eg, amitriptyline 10 to 150 mg po at bedtime), if used for depression, may be useful as an adjunct to levodopa. Doses of anticholinergic drugs are increased very slowly. Adverse effects are particularly troublesome in the elderly; if possible, they should not be given anticholinergic drugs.

Catechol O-methyltransferase (COMT) inhibitors: These drugs (eg, entacapone, tolcapone) inhibit the breakdown of dopamine and therefore appear to be useful adjuncts to levodopa. A combination of levodopa, carbidopa, and entacapone can be used. For each dose of levodopa taken, 200 mg of entacapone is given, to a maximum of 200 mg 8 times/day. Tolcapone, a potent COMT inhibitor, is less commonly used because of rare reports of liver toxicity.

Surgery: If drugs are ineffective and disease is advanced, surgery is considered. For patients with levodopa-induced dyskinesias or significant motor fluctuations, deep brain stimulation of the subthalamic nucleus or globus pallidus interna is often recommended. For patients with tremor only, stimulation of the ventralis intermediate nucleus of the thalamus is sometimes recommended; however, because most patients also have other symptoms, stimulation of the subthalamic nucleus, which relieves tremor as well as other symptoms, is usually preferable.

Physical measures: Maximizing activity is a goal. Patients should do daily activities to the extent possible. If they cannot, physical or occupational therapy, which may involve a regular exercise program, may help condition them physically. Therapists may teach patients adaptive strategies and help them make appropriate adaptations in the home (eg, installing grab bars to reduce the risk of falls).
Because the disease, antiparkinsonian drugs, and inactivity can lead to constipation, patients should consume a high-fiber diet, exercise when possible, and drink adequate amounts of fluids. Dietary supplements (eg, psyllium) and stimulant laxatives (eg, bisacodyl 10 to 20 mg po once/day) can help.

**Parkinsonism**

*Parkinsonism refers to symptoms that are similar to those of Parkinson's disease but caused by another condition.*

Parkinsonism results from drugs, disorders other than Parkinson's disease, or exogenous toxins (see Table 183-4). The mechanism is blockage of or interference with dopamine's action in the basal ganglia. The most common cause is ingestion of drugs that block dopamine receptors (eg, phenothiazine, thioxanthene, butyrophenone, antipsychotic drugs, reserpine).

(Table 183-4, Some Causes of Parkinsonism)

Parkinsonism causes the same symptoms as Parkinson's disease (eg, resting tremor, rigidity, bradykinesia, postural instability—see p. 1765).

**Diagnosis**

*Clinical evaluation, response to levodopa therapy, and, for differential diagnosis, sometimes neuroimaging*

To differentiate Parkinson's disease from secondary parkinsonism, clinicians note whether levodopa results in dramatic improvement, suggesting Parkinson's disease. Causes of parkinsonism can be identified by the following:

* A thorough history, including occupational, drug, and family history
* Evaluation for neurologic deficits characteristic of disorders other than Parkinson's disease (such as neurodegenerative disorders)
* Neuroimaging when indicated

**Treatment**

* Treatment of the cause*

The cause is corrected or treated if possible, sometimes resulting in amelioration or disappearance of symptoms. Drugs used to treat Parkinson's disease are often ineffective or have only transient benefit. But amantadine or an anticholinergic drug (eg, benztpoline) may ameliorate parkinsonism secondary to use of antipsychotic drugs.

Physical measures to maintain mobility and independence are useful (as for Parkinson's disease, see p. 1768). Good nutrition is essential.

**Progressive Supranuclear Palsy**

(Steele-Richardson-Olszewski Syndrome)

*Progressive supranuclear palsy is a rare, degenerative CNS disorder causing loss of voluntary eye movements, bradykinesia, muscular rigidity with progressive axial dystonia, pseudobulbar palsy, and dementia.*

The cause of progressive supranuclear palsy is unknown. Neurons in the basal ganglia and brain stem degenerate; neurofibrillary tangles containing an abnormally phosphorylated tau protein are also present.
Multiple lacunar strokes may occur in the basal ganglia and deep white matter.

**Symptoms and Signs**

Symptoms usually begin in late middle age. The first symptom may be difficulty looking up without extending the neck or difficulty climbing up and down stairs. Voluntary eye movements, particularly vertical, are difficult, but reflexive eye movements are unaffected. Movements are slowed, muscles become rigid, and axial dystonia develops. Patients tend to fall backward. Dysphagia and dysarthria with emotional lability (pseudobulbar palsy) is common; these deficits occur in a stepwise progression as occurs with multiple strokes. Dementia eventually occurs. Many patients become incapacitated within about 5 yr and die within about 10 yr.

**Diagnosis**

Diagnosis is clinical.

**Treatment**

- Supportive care

Treatment is unsatisfactory. Occasionally, levodopa, dopamine agonists and/or amantadine partially relieve rigidity.

Because the disorder is fatal, patients should be encouraged to prepare advance directives soon after the disorder is diagnosed. These directives should indicate what kind of medical care people want at the end of life (see p. 3471).

**Tremor**

Tremors are involuntary, rhythmic, alternating, or oscillatory movements of interrelated muscle groups. They typically involve the hands, head, facial structures, vocal cords, trunk, or legs. Tremors can be characterized by

- Frequency of oscillation (rapid or slow)
- Amplitude of movement (fine or coarse)
- Movements or postures that evoke them (eg, rest, action, certain positions)

**Pathophysiology**

Tremors are considered a movement disorder. Movement is controlled by interaction of the corticospinal (pyramidal) tracts, basal ganglia, and cerebellum. The basal ganglia consist of the caudate nucleus, putamen, globus pallidus, and substantia nigra, which together form the extrapyramidal system.

Most neural lesions that cause movement disorders occur in the extrapyramidal system; thus, movement disorders are also called extrapyramidal disorders. Neural dysfunction or lesions responsible for tremor may result from injury, ischemic or metabolic insult, or a neurodegenerative disorder. Sometimes tremor is an inherited condition (eg, essential tremor).

**Classification:** Tremor is classified primarily based on when it occurs:

- **Resting tremors** are maximal at rest and decrease with activity; they occur at a frequency of 3 to 6 cycles/sec (Hz).
- **Postural tremors** are maximal when a limb is maintained in a fixed position against gravity (eg, holding the arms out); they occur at a frequency of 5 to 18 Hz.
• **Intention tremors** are maximal during movement toward a target, as in finger-to-nose testing; they occur at a frequency of 3 to 10 Hz.

Tremor can also be classified based on whether it is within the range of normal (physiologic tremor), a primary disorder (essential tremor, Parkinson's disease), or a pathologic sign of CNS injury (eg, poststroke).

**Etiology**

**Physiologic tremor:** Physiologic tremor is the most common cause of tremor in otherwise healthy people; it is present normally but usually causes such small movements that it is noticeable only when enhanced by certain drugs or conditions (eg, anxiety; stress; fatigue; thyrotoxicosis; use of caffeine, phosphodiesterase inhibitors, β-adrenergic agonists, or corticosteroids).

**Nonphysiologic tremor:** There are many causes (see Table 183-5), but the most common are:

- Essential tremor
- Parkinson's disease
- Cerebral or cerebellar injury (eg, from a stroke or multiple sclerosis)
- Hereditary disorders involving the cerebellum (eg, spinocerebellar ataxia)

Drugs can cause or aggravate different types of tremor (see Table 183-6). Low doses of some sedatives (eg, alcohol) may relieve some tremors (eg, essential and physiologic tremor); higher doses may cause or exacerbate tremor.

**Evaluation**

Because the diagnosis of tremor is largely clinical, a meticulous history and physical examination are essential.

**History:** History of present illness should cover acuity of onset (eg, gradual, abrupt), age at onset, body parts affected, provoking factors (eg, movement, rest, standing), and alleviating or exacerbating factors (eg, alcohol, caffeine, stress, anxiety). If onset is abrupt, patients should be asked about potential triggering events (eg, recent trauma, use of a new drug).

**Review of systems** should seek symptoms of causative disorders, including double vision (multiple sclerosis), recent onset of motor weakness or dysarthria (stroke), headaches and fevers (brain abscess or tumor), muscle rigidity and slow movement (Parkinson's disease), weight loss and heat intolerance (hyperthyroidism), sensory deficits (peripheral neuropathy), and agitation and hallucinations (alcohol withdrawal).

**Past medical history** should cover conditions associated with tremor (see Table 183-5).

**Family history** should include questions about tremor in 1st-degree relatives. The drug profile should be reviewed for causative drugs (see Table 183-6), and patients should be asked specifically about caffeine intake and alcohol and recreational drug use (particularly recent discontinuation).

**Physical examination:** Vital signs should be reviewed for tachycardia, hypertension, or fever. General examination should note any cachexia, psychomotor agitation, and presence or absence of facial expressions. The thyroid should be palpated for nodules or thyromegaly, and any signs of exophthalmus.
or lid lag should be noted.

Focused examination of the tremor should note distribution and frequency of the tremor while the affected body parts are at rest and fully supported (eg, in the patient's lap), while the patient assumes certain postures (eg, holding the arms outstretched), and while the patient is walking or doing tasks with the affected body part. The examiner should note whether the tremor changes during mental distraction tasks (eg, serial subtraction of 7 from 100). The quality of the voice should be observed while the patient sustains a long note.

A complete and extensive neurologic examination is mandatory and should include cranial nerve evaluation, motor and sensory function testing, gait testing, assessment of deep tendon reflexes, and evaluation of cerebellar maneuvers (eg, finger-to-nose, shin-to-heel, rapid alternating hand movements). The examiner should test muscles for rigidity by moving the limbs through their range of motion.

**Red flags:** The following findings are of particular concern:

- Abrupt onset
- Onset in people < 50 and with no family history of tremor
- Other neurologic deficits (eg, change in mental status, motor weakness, cranial nerve palsy, ataxic gait, dysarthria)
- Tachycardia and agitation

**Interpretation of findings:** Clinical findings help suggest a cause (see also Table 183-5).

**Tremor type and onset** are useful clues. Resting tremors usually indicate Parkinson's disease, particularly when they are unilateral or when tremor is isolated to the chin, voice, or leg.

Intention tremors suggest a cerebellar disorder but may result from multiple sclerosis or Wilson's disease.

Postural tremor suggests physiologic or essential tremor if onset is gradual or a toxic or metabolic disorder if onset is sudden.

Severe essential tremor is often confused with Parkinson's disease but can usually be distinguished by specific characteristics (see Table 183-7). Occasionally, the 2 syndromes can overlap (mixed essential tremor-Parkinson's disease).

Sudden onset or stepwise progression suggests stroke, multiple sclerosis, or psychogenic etiology. Sudden onset after drug use suggests a drug cause. Onset of tremor with agitation, tachycardia, and hypertension within 24 to 72 h of hospitalization may suggest alcohol withdrawal.

**Gait** is observed. Gait abnormalities suggest multiple sclerosis, stroke, Parkinson's disease, or a cerebellar disorder. The gait is often normal in patients with essential tremor. It is characteristically narrow-based and shuffling in Parkinson's disease and wide-based and ataxic in cerebellar disorders. The gait may have histrionic or inconsistent qualities in patients with psychogenic tremor.

Complex tremor that decreases with mental distraction or whose frequency entrains to a volitional tapping rhythm in an unaffected body part (maintaining 2 different volitional movement frequencies simultaneously in 2 different body parts is difficult) suggests a psychogenic tremor.

**Testing:** In most patients, history and physical examination are sufficient to identify the likely etiology. However, MRI or CT of the brain should be done if

- Tremor onset is acute.
- Progression is rapid.
Neurologic signs suggest stroke, a demyelinating disorder, or a structural lesion.

[Table 183-7. Some Characteristics Differentiating Parkinson's Disease from Essential Tremor]

For certain patients (based on history and physical examination findings), thyroid-stimulating hormone (TSH) and thyroxine (T₄) are measured to check for hyperthyroidism, Ca and parathyroid hormone are measured to check for hyperparathyroidism, and glucose testing is done to rule out hypoglycemia.

In patients with toxic encephalopathy, the underlying condition is usually readily apparent, but measurement of BUN and ammonia levels can help confirm the diagnosis. Measurement of free metanephrines in plasma is indicated in patients with unexplained refractory hypertension; serum ceruloplasmin and urinary copper levels should be measured in patients who are < 40 and have tremor and no family history of benign tremor.

Although electromyography (EMG) can differentiate true tremor from other movement disorders (eg, myoclonus, clonus, epilepsia partialis continua), it is rarely required. However, EMG may help establish peripheral neuropathy as a potential cause of tremor if a neuropathy is clinically suspected.

Treatment

Physiologic tremors: No treatment is necessary unless symptoms are bothersome.

Physiologic tremors enhanced by alcohol withdrawal or thyrotoxicosis respond to treatment of the underlying condition.

Oral benzodiazepines (eg, diazepam 2 to 10 mg, lorazepam 1 to 2 mg, oxazepam 10 to 30 mg) given tid or qid may be useful for people with tremor and chronic anxiety, but continuous use should be avoided. Propranolol 20 to 80 mg po qid (and other β-blockers) is often effective for tremor enhanced by drugs or acute anxiety (eg, stage fright). Primidone 50 to 250 mg po tid may be tried if β-blockers are ineffective or poorly tolerated. For some patients, a small amount of alcohol is effective.

Essential tremors: Propranolol 20 to 80 mg po qid (or other β-blockers) is often effective, as is primidone 50 to 250 mg po tid.

Cerebellar tremors: No effective drug is available; physical measures (eg, weighting the affected limbs or teaching patients to brace the proximal limb during activity) sometimes help.

Parkinsonian tremors: The underlying disorder is treated, usually with anticholinergic drugs or other antiparkinson drugs such as amantadine, dopamine agonists, and levodopa.

Disabling tremor: For patients with severe, disabling, drug-refractory essential tremor, surgical management with stereotactic thalamotomy or chronic thalamic deep brain stimulation may be done. Similarly, in Parkinson’s disease, tremor substantially lessens after thalamic or subthalamic nucleus deep brain stimulation. Although these techniques are widely available, they should be used only after all drug treatment options have been tried.

Geriatrics Essentials

Many elderly patients attribute development of tremor to normal aging and may not seek medical attention. Although essential tremor is more prevalent among the elderly, a thorough history and physical examination are required to rule out other causes.

Comparatively lower doses of drugs may exacerbate tremor in the elderly, and adjusting doses of chronically used drugs (eg, amiodarone, metoclopramide, SSRIs, thyroxine) to the lowest effective dose should be considered. Similarly, elderly patients are more vulnerable to adverse effects of drugs used to treat tremor (eg, anticholinergic drugs); thus, drugs should be used cautiously in the elderly, usually at lower dosages than are otherwise considered optimal.
Tremor can significantly affect functional ability in the elderly, particularly if they have other physical or cognitive impairments. Physical and occupational therapy can provide simple coping strategies, and assistive devices may help maintain quality of life.

**Key Points**

- The most common causes of tremor include physiologic tremor, essential tremor, and Parkinson's disease.
- Tremor can be classified as resting, postural, or intention.
- History and physical examination can typically identify the etiology of tremor.
- Abrupt onset of tremor or tremor in patients who are < 50 and do not have a family history of benign tremor requires prompt, in-depth evaluation.

**Cerebellar Disorders**

Cerebellar disorders have numerous causes, including congenital malformations, hereditary ataxias, and acquired conditions. Symptoms vary with the cause but typically include ataxia (impaired muscle coordination). Diagnosis is clinical and often by imaging and sometimes genetic testing. Treatment is usually supportive unless the cause is acquired and reversible.

The cerebellum has 3 parts:

- **Archicerebellum (vestibulocerebellum):** It includes the flocculonodular lobe, which is located in the medial zone. It helps maintain equilibrium and coordinate eye, head, and neck movements; it is closely interconnected with the vestibular nuclei.

- **Midline vermis (paleocerebellum):** It helps coordinate trunk and leg movements. Vermis lesions result in abnormalities of stance and gait.

- **Lateral hemispheres (neocerebellum):** They control quick and finely coordinated limb movements, predominantly of the arms.

There is growing consensus that, in addition to coordination, the cerebellum controls some aspects of memory, learning, and cognition.

Ataxia is the archetypal sign of cerebellar dysfunction, but many other motor abnormalities may occur (see Table 183-8).

**Etiology**

**Congenital malformations:** Such malformations are almost always sporadic, often occurring as part of complex malformation syndromes (eg, Dandy-Walker malformation—see p. 2992) that affect other parts of the CNS. Malformations manifest early in life and are nonprogressive. Manifestations vary markedly depending on the structures involved; ataxia is usually present.

**Hereditary ataxias:** Hereditary ataxias may be autosomal recessive or autosomal dominant. Autosomal recessive ataxias include Friedreich's ataxia (the most prevalent), ataxia-telangiectasia, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, and cerebrotendinous xanthomatosis.

**Friedreich's ataxia** results from a gene mutation causing abnormal repetition of the DNA sequence GAA in the gene that codes for the mitochondrial protein frataxin. Decreased frataxin levels lead to mitochondrial iron overload and impaired mitochondrial function. Gait unsteadiness begins between ages 5 and 15; it is followed by upper-extremity ataxia, dysarthria, and paresis, particularly of the lower
extremities. Mental function often declines. Tremor, if present, is slight. Reflexes and vibration and position senses are lost. Talipes, scoliosis, and progressive cardiomyopathy are common.

Spinocerebellar ataxias (SCAs) are the main autosomal dominant ataxias. Classification of these ataxias has been revised many times recently as knowledge about genetics increases. Currently, at least 28 different gene loci are recognized; at least 10 involve expanded DNA sequence repeats. Some involve a repetition of the DNA sequence CAG that codes for the amino acid glutamine, similar to that in Huntington's disease. Manifestations vary. Some of the most common SCAs affect multiple areas in the central and peripheral nervous systems; neuropathy, pyramidal signs, and restless leg syndrome, as well as ataxia, are common. Some SCA usually cause only cerebellar ataxia. SCA3, formerly known as

(Table 183-8, Signs of Cerebellar Disorders]

Machado-Joseph disease, may be the most common dominantly inherited SCA. Symptoms include ataxia and possibly dystonia, facial twitching, ophthalmoplegia, and peculiar bulging eyes.

Acquired conditions: Acquired ataxias may result from nonhereditary neurodegenerative disorders (eg, multiple system atrophy—see p. 1618), systemic disorders, or toxin exposure, or they may be idiopathic. Systemic disorders include alcoholism (alcoholic cerebellar degeneration), celiac sprue, hypothyroidism, and vitamin E deficiency. Toxins include carbon monoxide, heavy metals, lithium, phenytoin, and certain solvents.

In children, primary brain tumors (medulloblastoma, cystic astrocytoma) may be the cause; the midline cerebellum is the most common site of such tumors. Rarely, in children, reversible diffuse cerebellar dysfunction follows viral infections.

Diagnosis

Diagnosis is clinical and includes a thorough family history and search for acquired systemic disorders. Neuroimaging, typically MRI, is done. Genetic testing is done if family history is suggestive.

Treatment

Some systemic disorders (eg, hypothyroidism, celiac sprue) and toxin exposure can be treated; occasionally, surgery for structural lesions (tumor, hydrocephalus) is beneficial. However, treatment is usually only supportive.
Chapter 184. Demyelinating Disorders

Introduction

Myelin sheaths cover many nerve fibers in the central and peripheral nervous system; they accelerate axonal transmission of neural impulses. Disorders that affect myelin interrupt nerve transmission; symptoms may reflect deficits in any part of the nervous system.

Myelin formed by oligodendroglia in the CNS differs chemically and immunologically from that formed by Schwann cells peripherally. Thus, some myelin disorders (eg, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, some other peripheral nerve polyneuropathies—see p. 1799) tend to affect primarily the peripheral nerves, and others affect primarily the CNS (see Table 184-1). The most commonly affected areas in the CNS are the brain, spinal cord, and optic nerves.

Demyelination is often secondary to an infectious, ischemic, metabolic, or hereditary disorder. In primary demyelinating disorders, cause is unknown, but an autoimmune mechanism is suspected because the disorder sometimes follows a viral infection or viral vaccination.

Demyelination tends to be segmental or patchy, affecting multiple areas simultaneously or sequentially. Remyelination often occurs, with repair, regeneration, and complete recovery of neural function. However, extensive myelin loss is usually followed by axonal degeneration and often cell body degeneration; both may be irreversible.

Demyelination should be considered in any patient with unexplained neurologic deficits. Primary demyelinating disorders are suggested by the following:

• Diffuse or multifocal deficits
• Sudden onset, particularly in young adults
• Onset within weeks of an infection or vaccination
• Deficits that wax and wane
• Symptoms suggesting a specific demyelinating disorder (eg, unexplained optic neuritis or internuclear ophthalmoplegia suggesting multiple sclerosis)

Specific tests and treatment depend on the specific disorder.

Multiple Sclerosis

Multiple sclerosis (MS) is characterized by disseminated patches of demyelination in the brain and spinal cord. Common symptoms include visual and oculomotor abnormalities, paresthesias, weakness, spasticity, urinary dysfunction, and mild cognitive impairment. Typically, neurologic deficits are multiple, with remissions and exacerbations gradually producing disability. Diagnosis is by history of remissions and exacerbations plus clinical signs, test results, lesions seen on MRI, or other criteria (depending on symptoms) to objectively demonstrate ≥ 2 separate neurologic abnormalities. Treatment includes corticosteroids for acute exacerbations, immunomodulatory drugs to prevent exacerbations, and supportive measures.

Table 184-1, Disorders that Can Cause CNS Demyelination]

MS is believed to involve an immunologic mechanism. One postulated cause is infection by a latent virus (possibly a human herpesvirus such as Epstein-Barr virus), which, when activated, triggers a secondary immune response. An increased incidence among certain families and presence of human leukocyte antigen (HLA) allotypes (HLA-DR2) suggests genetic susceptibility. MS is more common among people who spend their first 15 yr of life in temperate climates (1/2000) than in those who spend them in the
tropics (1/10,000). One explanation is that lower levels of vitamin D are associated with an increased risk of MS, and vitamin D levels correlate with the degree of sun exposure, which is lower in temperate climates. Cigarette smoking also appears to increase risk. Age at onset ranges from 15 to 60 yr, typically 20 to 40 yr; women are affected somewhat more often.

Neuromyelitis optica (Devic disease), previously considered a variant of MS, is now recognized as a separate disorder (see p. 1783).

Pathophysiology

Localized areas of demyelination (plaques) occur, with destruction of oligodendroglia, perivascular inflammation, and chemical changes in lipid and protein constituents of myelin in and around the plaques. Axonal damage is possible, but cell bodies and axons tend to be relatively preserved. Fibrous gliosis develops in plaques that are disseminated throughout the CNS, primarily in white matter, particularly in the lateral and posterior columns (especially in the cervical regions), optic nerves, and periventricular areas. Tracts in the midbrain, pons, and cerebellum are also affected. Gray matter in the cerebrum and spinal cord can be affected but to a much lesser degree.

Symptoms and Signs

MS is characterized by varied CNS deficits, with remissions and recurring exacerbations. Exacerbations average about 3/yr, but frequency varies greatly. Although MS may progress and regress unpredictably, there are typical patterns of progression:

• Relapsing-remitting pattern: Exacerbations alternate with remissions, when partial or full recovery occurs or symptoms are stable. Remissions may last months or years. Exacerbations can occur spontaneously or can be triggered by an infection such as influenza.

• Primary progressive pattern: The disease progresses gradually with no remissions, although there may be temporary plateaus during which the disease does not progress. Unlike in the relapsing-remitting pattern, there are no clear exacerbations.

• Secondary progressive pattern: This pattern begins with relapses alternating with remissions, followed by gradual progression of the disease.

• Progressive relapsing pattern: The disease progresses gradually, but progression is interrupted by sudden, clear relapses. This pattern is rare.

The most common initial symptoms are the following:

• Paresthesias in one or more extremities, in the trunk, or on one side of the face

• Weakness or clumsiness of a leg or hand

• Visual disturbances (eg, partial loss of vision and pain in one eye due to retrobulbar optic neuritis, diplopia due to ocular palsy, scotomas)

Other common early symptoms include slight stiffness or unusual fatigability of a limb, minor gait disturbances, difficulty with bladder control, vertigo, and mild affective disturbances; all usually indicate scattered CNS involvement and may be subtle. Excess heat (eg, warm weather, a hot bath, fever) may temporarily exacerbate symptoms and signs.

Mild cognitive impairment is common. Apathy, poor judgment, or inattention may occur. Affective disturbances, including emotional lability, euphoria, or, most commonly, depression, are common. Depression may be reactive or partly due to cerebral lesions of MS. A few patients have seizures.

Cranial nerves: Unilateral or asymmetric optic neuritis and bilateral internuclear ophthalmoplegia are typical. Optic neuritis causes loss of vision (ranging from scotomas to blindness), eye pain, and
sometimes abnormal visual fields, a swollen optic disk, or a partial or complete afferent pupillary defect (see p. 622).

Internuclear ophthalmoplegia results if there is a lesion in the medial longitudinal fasciculus connecting the 3rd, 4th, and 6th nerve nuclei. During horizontal gaze, adduction of one eye is decreased, with nystagmus of the other (abducting) eye; convergence is intact.

Rapid, small-amplitude eye oscillations in straight-ahead (primary) gaze (pendular nystagmus) are uncommon but characteristic of MS. Vertigo is common. Intermittent unilateral facial numbness or pain (resembling trigeminal neuralgia), palsy, or spasm may occur. Mild dysarthria may occur, caused by bulbar weakness, cerebellar damage, or disturbance of cortical control. Other cranial nerve deficits are unusual but may occur secondary to brain stem injury.

**Motor:** Weakness is common. It usually reflects corticospinal tract damage in the spinal cord, affects the lower extremities preferentially, and is bilateral and spastic. Deep tendon reflexes (eg, knee and ankle jerks) are usually increased, and an extensor plantar response (Babinski’s sign) and clonus are often present. Spastic paraparesis produces a stiff, imbalanced gait; in advanced cases, it may confine patients to a wheelchair. Painful flexor spasms in response to sensory stimuli (eg, bedclothes) may occur late. Cerebral or cervical spinal cord lesions may result in hemiparesis, which sometimes is the presenting symptom.

**Cerebellar:** In advanced MS, cerebellar ataxia plus spasticity may be severely disabling; other cerebellar manifestations include slurred speech, scanning speech (slow enunciation with a tendency to hesitate at the beginning of a word or syllable), and Charcot’s triad (intention tremor, scanning speech, and nystagmus).

**Sensory:** Paresthesias and partial loss of any type of sensation are common and often localized (eg, to one or both hands or legs). Various painful sensory disturbances (eg, burning or electric shocklike pains) can occur spontaneously or in response to touch, especially if the spinal cord is affected.

An example is Lhermitte’s sign, an electric shocklike pain that radiates down the spine or into the legs when the neck is flexed. Objective sensory changes tend to be transient and difficult to demonstrate.

**Spinal cord:** Involvement commonly causes bladder dysfunction (eg, urinary urgency or hesitancy, partial retention of urine, mild urinary incontinence). Constipation, erectile dysfunction in men, and genital anesthesia in women may occur. Frank urinary and fecal incontinence may occur in advanced MS.

Progressive myelopathy, a variant of MS, causes spinal cord motor weakness but no other deficits.

**Diagnosis**

- Clinical criteria
- Brain and spinal MRI
- Sometimes CSF IgG levels and evoked potentials

MS is suspected in patients with optic neuritis, internuclear ophthalmoplegia, or other symptoms that suggest MS, particularly if deficits are multifocal or intermittent. Most diagnostic criteria for MS require a history of exacerbations and remissions plus objective demonstration by examination or testing of ≥ 2 separate neurologic abnormalities. Brain and spinal MRI is done. MRI plus clinical findings may be diagnostic, but if they are inconclusive, additional testing may be necessary to objectively demonstrate separate neurologic abnormalities. Such testing usually begins with CSF analysis and, if necessary, includes evoked potentials.

**MRI** is the most sensitive imaging test for MS and can exclude other treatable disorders that may mimic MS, such as nonnemyelinating lesions at the junction of the spinal cord and medulla (eg, subarachnoid cyst, foramen magnum tumors). Gadolinium-contrast enhancement can distinguish actively inflamed from
older plaques. Alternatively, contrast-enhanced CT can be done. The sensitivity of MRI and CT is increased by giving twice the dose of contrast agent (which is standard practice) and delaying scanning (double-dose delayed scanning).

**CSF examination**, including opening pressure, cell count and differential, protein, glucose, Ig, oligoclonal bands, and usually myelin basic protein and albumin, is done. IgG is usually increased as a percentage of CSF components, such as protein (normally < 11%) or CSF albumin (normally < 27%). IgG levels correlate with disease severity. Oligoclonal bands can usually be detected by agarose electrophoresis of CSF. Myelin basic protein may be elevated during active demyelination. CSF lymphocyte count and protein content may be slightly increased.

**Other tests** include evoked potentials (delays in electrical responses to sensory stimulation—see p. 1597), which are often more sensitive for MS than symptoms or signs. Visual evoked responses are sensitive and particularly helpful in patients with no confirmed cranial lesions (eg, those with lesions only in the spinal cord). Somatosensory evoked potentials and brain stem auditory evoked potentials are sometimes also measured. Sometimes systemic disorders (eg, SLE) and infections (eg, Lyme disease) can mimic MS and should be excluded with specific blood tests. Blood tests to measure an IgG antibody specific for neuromyelitis optica (NMO-IgG) may be done to differentiate that disorder from MS.

**Prognosis**

The course is highly varied and unpredictable. In most patients, especially when MS begins with optic neuritis, remissions can last months to > 10 yr. However, some patients, particularly men with onset in middle age, have frequent exacerbations and are rapidly incapacitated. Cigarette smoking may accelerate the course. Life span is shortened only in very severe cases.

**Treatment**

- Corticosteroids for acute exacerbations
- Immunomodulators to prevent exacerbations
- Baclofen or tizanidine for spasticity
- Gabapentin or tricyclic antidepressants for pain
- Supportive care

Goals include shortening acute exacerbations, decreasing frequency of exacerbations, and relieving symptoms; maintaining the patient's ability to walk is particularly important.

**Disease-modifying drugs**: Acute exacerbations that cause objective deficits sufficient to impair function (eg, loss of vision, strength, or coordination) are treated with brief courses of corticosteroids (eg, prednisone 60 to 100 mg po once/day tapered over 2 to 3 wk, methylprednisolone 500 to 1000 mg IV once/day for 3 to 5 days). Some evidence indicates that IV corticosteroids shorten acute exacerbations, slow progression, and improve MRI measures of disease. Immunomodulatory therapy, such as interferons (IFNs) or glatiramer, decreases the frequency of acute exacerbations and delays eventual disability. Typical regimens include interferon beta-1b 8 million IU sc every other day, interferon beta-1a 6 million IU (30 μg) IM weekly, and interferon beta-1a 44 μg sc 3 times weekly. Common adverse effects of IFNs include flu-like symptoms and depression (which tend to decrease over time), development of neutralizing antibodies after months of therapy, and cytopenias. Glatiramer acetate 20 mg sc once/day may be used.

The immunosuppressant mitoxantrone, 12 mg/m² IV q 3 mo for 24 mo, may be helpful, particularly for progressive MS that is refractory to other treatments. Natalizumab, an anti-α₄ integrin antibody, inhibits passage of leukocytes across the blood-brain barrier; given as a monthly infusion, it reduces number of exacerbations and new brain lesions but may increase the risk of progressive multifocal leukoencephalopathy. If immunomodulatory drugs are ineffective, monthly IV immune globulin may help.
Immunosuppressants other than mitoxantrone (eg, methotrexate, azathioprine, mycophenolate, cyclophosphamide, cladribine) have been used for more severe, progressive MS but are controversial. Plasma exchange and hematopoietic stem cell transplantation may be somewhat useful for severe, intractable disease.

**Symptom control:** Other treatments can be used to control specific symptoms:

- Spasticity is treated with escalating doses of baclofen 10 to 20 mg po tid to qid or tizanidine 4 to 8 mg po tid. Gait training and range-of-motion exercises can help weak, spastic limbs.

- Painful paresthesias are usually treated with gabapentin 100 to 600 mg po tid; alternatives include tricyclic antidepressants (eg, amitriptyline 25 to 75 mg po at bedtime, desipramine 25 to 100 mg po at bedtime if amitriptyline has intolerable anticholinergic effects), carbamazepine 200 mg po tid, and opioids.

- Depression is treated with counseling and antidepressants.

- Bladder dysfunction is treated based on its underlying mechanism (see p. 2352).

- Fatigue can be treated with amantadine 100 mg po tid or modafinil 100 to 300 mg po once/day.

**Supportive care:** Encouragement and reassurance help. Regular exercise (eg, stationary biking, treadmill, swimming, stretching) is recommended, even for patients with advanced MS, because it conditions the heart and muscles, reduces spasticity, prevents contractures, and has psychologic benefits. Vitamin D supplements (800 to 1000 units daily) may decrease the risk of disease progression. Vitamin D also reduces the risk of osteoporosis, particularly in patients at increased risk because mobility is decreased or they take corticosteroids. Patients should maintain as normal and active a life as possible but should avoid overwork, fatigue, and exposure to excess heat. Cigarette smoking should be stopped. Vaccination does not appear to increase risk of exacerbations. Debilitated patients require measures to prevent pressure ulcers and UTIs; intermittent urinary self-catheterization may be necessary.

**Neuromyelitis Optica**

(Devic Disease)

Neuromyelitis optica affects only the eyes and spinal cord. It causes acute optic neuritis, sometimes bilateral, plus demyelination of the cervical or thoracic spinal cord. Neuromyelitis optica was previously considered to be a variant of multiple sclerosis (MS) but is now recognized as a different disorder.

Symptoms include visual loss, paraparesis or quadripleparesis, and incontinence.

**Diagnosis**

- Brain and spinal cord MRI

- Visual evoked potentials

Diagnosis usually includes brain and spinal cord MRI and visual evoked potentials. Blood tests to measure an IgG antibody specific for neuromyelitis optica (NMO-IgG) may be done to differentiate it from MS.

**Treatment**

- Corticosteroids and immunomodulatory or immunosuppressive treatments

There is no cure. However, treatment can prevent, slow, or decrease the severity of exacerbations. Methylprednisolone and azathioprine are often used. Plasma exchange may help people who do not
respond to corticosteroids. Rituximab, an anti-B-cell antibody, reduces IgG production and has been shown to be disease-stabilizing.

Treatment of symptoms is similar to that for MS (see above). Baclofen or tizanidine may relieve muscle spasms.
Chapter 185. Peripheral Nervous System and Motor Unit Disorders

Introduction

The peripheral nervous system refers to parts of the nervous system outside the brain and spinal cord. It includes the cranial nerves and spinal nerves from their origin to their end. The anterior horn cells, although technically part of the CNS, are sometimes discussed with the peripheral nervous system because they are part of the motor unit.

Motor neuron dysfunction results in muscle weakness or paralysis. Sensory neuron dysfunction results in abnormal or lost sensation. Some disorders are progressive and fatal.

Anatomy

A motor unit consists of an anterior horn cell, its motor axon, the muscle fibers it innervates, and the connection between them (neuromuscular junction). The anterior horn cells are located in the gray matter of the spinal cord and thus are technically part of the CNS. In contrast to the motor system, the cell bodies of the afferent sensory fibers lie outside the spinal cord, in dorsal root ganglia.

Nerve fibers outside the spinal cord join to form anterior (ventral) motor roots and posterior (dorsal) sensory root nerve roots. The ventral and dorsal roots combine to form a spinal nerve. Thirty of the 31 pairs of spinal nerves have dorsal and ventral roots; C1 has no sensory root (see Fig. 186-1 on p. 1805).

The spinal nerves exit the vertebral column via an intervertebral foramen. Because the spinal cord is shorter than the vertebral column, the more caudal the spinal nerve, the further the foramen is from the corresponding cord segment. Thus, in the lumbosacral region, nerve roots from lower cord segments descend within the spinal column in a near-vertical sheaf, forming the cauda equina. Just beyond the intervertebral foramen, spinal nerves branch into several parts.

Branches of the cervical and lumbosacral spinal nerves anastomose peripherally into plexuses, then branch into nerve trunks that terminate up to 1 m away in peripheral structures. The intercostal nerves are segmental.

The term peripheral nerve refers to the part of a spinal nerve distal to the root and plexus. Peripheral nerves are bundles of nerve fibers. They range in diameter from 0.3 to 22 μm. Schwann cells form a thin cytoplasmic tube around each fiber and further wrap larger fibers in a multilayered insulating membrane (myelin sheath).

Physiology

The myelin sheath enhances impulse conduction. The largest and most heavily myelinated fibers conduct quickly; they convey motor, touch, and proprioceptive impulses. The less myelinated and unmyelinated fibers conduct more slowly; they convey pain, temperature, and autonomic impulses. Because nerves are metabolically active tissues, they require nutrients, supplied by blood vessels called the vasa nervorum.

Etiology

Disorders can result from damage to or dysfunction of the cell body, myelin sheath, axons, or neuromuscular junction. Disorders can be genetic or acquired (due to toxic, metabolic, traumatic, infectious, or inflammatory conditions—see Table 185-1). Peripheral neuropathies may affect one nerve (mononeuropathy), several discrete nerves (multiple mononeuropathy, or mononeuritis multiplex), or multiple nerves diffusely (polyneuropathy). Some conditions involve a plexus (plexopathy) or nerve root (radiculopathy). More than one site can be affected; eg, in the most common variant of Guillain-Barre syndrome, multiple segments of cranial nerves, usually the 2 facial nerves, may be affected.

Pathophysiology
Because sensory and motor cell bodies are in different locations, a nerve cell body disorder typically affects either the sensory or motor component but rarely both.

**Damage:** Damage to the myelin sheath (demyelination—see p. 1779) slows nerve conduction. Demyelination affects mainly heavily myelinated fibers, causing large-fiber sensory dysfunction (buzzing and tingling sensations), motor weakness, and diminished reflexes. The hallmark of acquired demyelinating polyneuropathy is severe motor weakness with minimal atrophy.

Because the vasa nervorum do not reach the center of a nerve, centrally located fascicles are most vulnerable to vascular disorders (eg, vasculitis, ischemia). These disorders result in small-fiber sensory dysfunction (sharp pain and burning sensations), motor weakness proportional to atrophy, and less severe reflex abnormalities than in other nerve disorders. The distal two thirds of a limb is affected most. Initially, deficits tend to be asymmetric because the vasculitic or ischemic process is random. However, multiple infarcts may later coalesce, causing symmetric deficits (multiple mononeuropathy).

Toxic-metabolic or genetic disorders usually begin symmetrically. Immune-mediated processes may be symmetric or, early in rapidly evolving processes, asymmetric.

Damage to the axon transport system for cellular constituents, especially microtubules and microfilaments, causes significant axon dysfunction. First affected are the smaller fibers (because they have greater metabolic requirements) at the most distal part of the nerve. Then, axonal degeneration slowly ascends, producing

[Table 185-1. Causes of Peripheral Nervous System Disorders]

the characteristic distal-to-proximal pattern of symptoms (stocking-glove sensory loss, weakness).

**Recovery:** Damage to the myelin sheath (eg, by injury or Guillain-Barre syndrome) can often be repaired by surviving Schwann cells in about 6 to 12 wk.

After axonal damage, the fiber regrows within the Schwann cell tube at about 1 mm/day once the pathologic process ends. However, regrowth may be misdirected, causing aberrant innervation (eg, of fibers in the wrong muscle, of a touch receptor at the wrong site, or of a temperature instead of a touch receptor).

Regeneration is virtually impossible when the cell body dies and is unlikely when the axon is completely lost.

**Evaluation**

- Deficits defined by history and examination
- Attention to clinical clues to peripheral nervous system disorders
- Usually, nerve conduction velocity studies and electromyography

**Clinical evaluation:** History should focus on type of symptom, onset, progression, and location, as well as information about potential causes (eg, family history, toxic exposures, past medical disorders). Physical and neurologic examination should further define the type of deficit (eg, motor deficit, type of sensory deficit, combination). Sensation (using pinprick and light touch for small fibers and vibration for large fibers), proprioception, motor strength, and deep tendon reflexes are evaluated (see p. 1589). Cranial nerve as well as central and peripheral nerve function is evaluated. Whether motor weakness is proportional to the degree of atrophy is noted, as are type and distribution of reflex abnormalities. Autonomic function is evaluated (see p. 1615).

Physicians should suspect a peripheral nervous system disorder based on the pattern and type of neurologic deficits, especially if deficits are in the territories of nerve roots, spinal nerves, plexuses,
specific peripheral nerves, or a combination. These disorders are also suspected in patients with mixed sensory and motor deficits, with multiple foci, or with a focus that is incompatible with a single anatomic site in the CNS.

Physicians should also suspect peripheral nervous system disorders in patients with generalized or diffuse weakness but no sensory deficits; in these cases, peripheral nervous system disorders may be overlooked because they are not the most likely cause of such symptoms. Clues that a peripheral nervous system disorder may be the cause of generalized weakness include the following:

- Patterns of generalized weakness that suggest a specific cause (e.g., predominant ptosis and diplopia, which suggest early myasthenia gravis)
- Symptoms and signs other than weakness that suggest a specific disorder or group of disorders (e.g., cholinergic effects, which suggest organophosphate poisoning)
- Deficits in a stocking-glove distribution, which suggest diffuse axonal disorders or polyneuropathy
- Fasciculations
- Hypotonia
- Muscle wasting without hyperreflexia
- Weakness that is progressive, chronic, and unexplained

Clues that the cause may not be a peripheral nervous system disorder include hyperreflexia and hypertonia. These deficits suggest an upper motor neuron disorder as the cause of weakness. Hyporeflexia is consistent with peripheral nervous system deficits but is non-specific.

Although many exceptions are possible, certain clinical clues may also suggest possible causes of peripheral nervous system deficits (see Table 185-2).

Clinical assessment narrows diagnostic possibilities and guides further testing.

Testing: Usually, nerve conduction velocity studies and electromyography (collectively called electrodiagnostic testing) are done (see p. 1597). These tests help identify level of involvement (nerve, plexus, root) and distinguish demyelinating disorders (very slow conduction) from axonal disorders. Other testing depends on whether a CNS lesion must be ruled out.

Patients with weakness but no sensory deficits are evaluated for weakness.

Treatment

- Treatment of underlying disorder
- Supportive care, often by a multidisciplinary team

Treatment is directed at the underlying disorder when possible. Otherwise, treatment is supportive. A multidisciplinary team approach helps patients cope with progressive neurologic disability:

- Physical therapists may help patients maintain muscle function.
- Occupational therapists can recommend adaptive braces and walking devices to help with activities of daily living.
- Speech and language therapists may provide alternative communication devices.
• If pharyngeal weakness develops, nurses feed patients with extreme care.

• A gastroenterologist may recommend percutaneous endoscopic gastrostomy.

• If respiratory weakness develops, pulmonary specialists are needed to determine whether noninvasive respiratory support (eg, bilevel positive airway pressure) or tracheostomy with full ventilatory support should be used.

Table 185-2. Clinical Clues to Causes of Peripheral Nervous System* Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
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<tbody>
<tr>
<td>Eaton-Lambert syndrome</td>
<td>Due to impaired acetylcholine release from presynaptic nerve terminals (see p. 1055).</td>
</tr>
<tr>
<td>Botulism</td>
<td>Also due to impaired release of acetylcholine from presynaptic nerve terminals, botulism develops when toxin produced by Clostridium botulinum spores irreversibly binds to the terminal cholinergic nerve endings (see p. 1290). The result is severe weakness, sometimes with respiratory compromise. Other systemic symptoms may include mydriasis, dry mouth, constipation, urinary retention, and tachycardia due to unopposed sympathetic nervous system activity (anticholinergic syndrome). These systemic findings are absent in myasthenia gravis.</td>
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In botulism, electromyography (EMG) detects a mild decremental response to low-frequency (2- to 3-Hz) repetitive nerve stimulation but a pronounced incremental response after 10 sec of exercise or with rapid (50-Hz) repetitive nerve stimulation.

Disorders of Neuromuscular Transmission

Disorders of neuromuscular transmission affect the neuromuscular junction. They may involve

• Postsynaptic receptors (eg, in myasthenia gravis—see p. 1793)

• Presynaptic release of acetylcholine (eg, in botulism)

• Breakdown of acetylcholine within the synapse (eg, due to drugs or neurotoxic chemicals)

Common features of these disorders include fluctuating fatigue and muscle weakness with no sensory deficits.

Eaton-Lambert syndrome: This disorder is due to impaired acetylcholine release from presynaptic nerve terminals (see p. 1055).

Botulism: Also due to impaired release of acetylcholine from presynaptic nerve terminals, botulism develops when toxin produced by Clostridium botulinum spores irreversibly binds to the terminal cholinergic nerve endings (see p. 1290). The result is severe weakness, sometimes with respiratory compromise. Other systemic symptoms may include mydriasis, dry mouth, constipation, urinary retention, and tachycardia due to unopposed sympathetic nervous system activity (anticholinergic syndrome). These systemic findings are absent in myasthenia gravis.

In botulism, electromyography (EMG) detects a mild decremental response to low-frequency (2- to 3-Hz) repetitive nerve stimulation but a pronounced incremental response after 10 sec of exercise or with rapid (50-Hz) repetitive nerve stimulation.

Drugs or toxic chemicals: Cholinergic drugs, organophosphate insecticides, and most nerve gases block neuromuscular transmission by excessive acetylcholine action that depolarizes postsynaptic receptors. Miosis, bronchorrhea, and myasthenic-like weakness (cholinergic syndrome) result.

Aminoglycoside and polypeptide antibiotics decrease presynaptic acetylcholine release and sensitivity of the postsynaptic membrane to acetylcholine. At high serum levels, these antibiotics may increase neuromuscular block in patients with latent myasthenia gravis. Long-term penicillamine treatment may cause a reversible syndrome that clinically and electromyographically resembles myasthenia gravis. Excessive Mg po or IV (with blood levels approaching 8 to 9 mg/dL) can also induce severe weakness resembling a myasthenic syndrome.

Treatment consists of eliminating the drug or toxic chemical and providing necessary respiratory support and intensive nursing care. Atropine 0.4 to 0.6 mg po tid decreases bronchial secretions in patients with cholinergic excess. Higher doses (eg, 2 to 4 mg IV q 5 min) may be necessary for organophosphate insecticide or nerve gas poisoning.
Disorders With Neuromuscular Manifestations

Stiff-person syndrome: The syndrome affects the CNS but has neuromuscular manifestations. It often occurs in patients with type 1 diabetes. It may be autoimmune and can occur as a paraneoplastic syndrome (most often with breast, lung, or colon cancer or with Hodgkin lymphoma). Autoantibodies against several proteins involved in GABA (γ-aminobutyric acid)-glycine synapses are present, affecting primarily inhibitory neurons that originate in the anterior horn of the spinal cord.

Progressive stiffness develops insidiously in the trunk and abdomen and, to a lesser degree, in the legs and arms. Patients are otherwise normal, and examination detects only muscle hypertrophy and stiffness. EMG shows only the electrical activity of normal contraction.

Only symptomatic therapy is available. Diazepam is the only drug that consistently relieves muscle stiffness. Results of plasmapheresis are inconsistent.

Isaacs' syndrome: This syndrome, generally thought to be a channelopathy, sometimes occurs as a paraneoplastic syndrome. It may also occur in other disorders (eg, myasthenia gravis, thymoma, cancer, amyloidosis) or can be inherited. Cause is unknown. Abnormalities are thought to originate in a peripheral nerve because they are abolished by curare but usually persist after general anesthesia.

The limbs are most affected. The sine qua non is myokymia—continuous muscle twitching described as bag-of-worms movements. Other symptoms include carpopedal spasms, intermittent cramps, increased sweating, and pseudomyotonia (impaired relaxation after a strong muscle contraction but without the typical waxing-and-waning EMG abnormality of true myotonia). Carbamazepine or phenytoin may relieve these symptoms.

Guillain-Barre Syndrome

(Acute Idiopathic Polyneuritis; Acute Inflammatory Demyelinating Polyradiculoneuropathy)

Guillain-Barre syndrome is an acute, usually rapidly progressive inflammatory polyneuropathy characterized by muscular weakness and mild distal sensory loss. Cause is thought to be autoimmune. Diagnosis is clinical. Treatment includes plasmapheresis, γ-globulin, and, for severe cases, mechanical ventilation.

Guillain-Barre syndrome is the most common acquired inflammatory neuropathy. Although the cause is not fully understood, it is thought to be autoimmune. There are several variants. In some, demyelination predominates; others affect the axon.

In about two thirds of patients, the syndrome begins 5 days to 3 wk after a banal infectious disorder, surgery, or vaccination. Infection is the trigger in > 50% of patients; common pathogens include Campylobacter jejuni, enteric viruses, herpesviruses (including cytomegalovirus and Epstein-Barr virus), and Mycoplasma sp. A cluster of cases followed the swine flu vaccination program in 1975.

Symptoms and Signs

Flaccid weakness predominates in most patients; it is always more prominent than sensory abnormalities and may be most prominent proximally. Relatively symmetric weakness with paresthesias usually begins in the legs and progresses to the arms, but it occasionally begins in the arms or head. In 90% of patients, weakness is maximal at 3 wk. Deep tendon reflexes are lost. Sphincters are usually spared. Facial and oropharyngeal muscles are weak in > 50% of patients with severe disease. Dehydration and undernutrition may result. Respiratory paralysis severe enough to require endotracheal intubation and mechanical ventilation occurs in 5 to 10%.

A few patients (possibly with a variant form) have significant, life-threatening autonomic dysfunction causing BP fluctuations, inappropriate ADH secretion, cardiac arrhythmias, GI stasis, urinary retention, and pupillary changes. An unusual variant (Fisher variant) may cause only ophthalmoparesis, ataxia, and areflexia.
Diagnosis

- Clinical evaluation
- Electrodiagnostic testing
- CSF analysis

Diagnosis is primarily clinical. Similar acute weakness can result from myasthenia gravis, botulism, poliomyelitis (mainly outside the US), tick paralysis, West Nile virus infection, and metabolic neuropathies, but these disorders can usually be distinguished as follows:

- Myasthenia gravis is intermittent and worsened by exertion.
- Botulism may cause fixed dilated pupils (in 50%) and prominent cranial nerve dysfunction with normal sensation.
- Poliomyelitis usually occurs in epidemics.
- Tick paralysis causes ascending paralysis but spares sensation.
- West Nile virus causes headache, fever, and asymmetric flaccid paralysis but spares sensation.
- Metabolic neuropathies occur with a chronic metabolic disorder.

Tests for infectious disorders and immune dysfunction, including tests for hepatitis and HIV and serum protein electrophoresis, are done.

If Guillain-Barre syndrome is suspected, patients should be admitted to a hospital for electrodiagnostic testing, CSF analysis, and monitoring by measuring forced vital capacity every 6 to 8 h. Initial electrodiagnostic testing detects slow nerve conduction velocities and evidence of segmental demyelination in two thirds of patients; however, normal results do not exclude the diagnosis and should not delay treatment.

CSF analysis may detect albuminocytologic dissociation (increased protein but normal WBC count), but it may not appear for up to 1 wk and does not develop in 10% of patients.

Prognosis

This syndrome is fatal in < 2%. Most patients improve considerably over a period of months, but about 30% of adults and even more children have some residual weakness at 3 yr. Patients with residual defects may require retraining, orthopedic appliances, or surgery.

After initial improvement, 3 to 10% of patients develop chronic inflammatory demyelinating polyneuropathy (CIDP—see p. 1790).

Treatment

- Intensive supportive care
- Plasmapheresis or IV immune globulin

Guillain-Barre syndrome is a medical emergency, requiring constant monitoring and support of vital functions, typically in an ICU. Forced vital capacity should be measured frequently so that respiration can be assisted if necessary; if vital capacity is < 15 mL/kg, endotracheal intubation is indicated. Inability to lift the head off the pillow by flexing the neck is another danger sign; it frequently develops simultaneously with phrenic nerve (diaphragm) weakness.
If oral fluid intake is difficult, IV fluids are given as needed to maintain a urine volume of at least 1 to 1.5 L/day. Extremities should be protected from trauma and from the pressure of bed rest. Heat therapy helps relieve pain, making early physical therapy possible. Immobilization, which may cause ankylosis and contractures, should be avoided. Passive full-range joint movement should be started immediately, and active exercises should be initiated when acute symptoms subside. Heparin 5000 units sc bid helps prevent deep venous thrombosis in bedbound patients.

Given early, immune globulin (γ-globulin) 400 mg/kg IV once/day for 5 consecutive days is the treatment of choice; it has some benefit up to 1 mo from disease onset.

Plasmapheresis (see p. 1044) helps when done early in the syndrome; it is used if γ-globulin is ineffective. Plasmapheresis is relatively safe, shortens the disease course and hospital stay, and reduces mortality risk and incidence of permanent paralysis. Plasmapheresis removes any previously administered γ-globulin, negating its benefits.

Corticosteroids do not improve the outcome and should not be used.

**Chronic Inflammatory Demyelinating Polyneuropathy**

(Chronic Acquired Demyelinating Polyneuropathy; Chronic Relapsing Polyneuropathy)

**Chronic inflammatory demyelinating polyneuropathy (CIDP)** is an immune-mediated polyneuropathy characterized by symmetric weakness of proximal and distal muscles and by progression continuing > 2 mo.

Progression for > 2 mo differentiates CIDP from Guillain-Barre syndrome, which is monophasic and self-limited. CIDP develops in 3 to 10% of patients with Guillain-Barre syndrome.

**Diagnosis**

• CSF analysis and electrodiagnostic tests

Testing includes CSF analysis and electrodiagnostic tests. Results are similar to those in Guillain-Barre syndrome: CSF protein level is increased, and electrodiagnostic testing detects demyelination. Nerve biopsy, which can detect demyelination, is seldom needed.

**Treatment**

• Corticosteroids

• Sometimes plasmapheresis or IV immune globulin

Unlike Guillain-Barre syndrome, CIDP responds to corticosteroids. Azathioprine may be added to decrease corticosteroid dependence. However, in severe or rapidly progressive cases, plasmapheresis or IV immune globulin may be preferred. Immunosuppressants (eg, azathioprine) may be helpful. Treatment may be needed for a long time.

**Hereditary Neuropathies**

Hereditary neuropathies include a variety of congenital degenerative peripheral neuropathies.

Hereditary neuropathies are classified as sensorimotor, sensory, or motor (see Motor Neuron Disorders on p. 1791). Causes of secondary hereditary neuropathies include Refsum's disease, porphyria, and Fabry's disease.

**Sensorimotor neuropathies**: There are 3 main types (I, II, and III); all begin in childhood. Some less common types begin at birth and result in greater disability.
**Types I and II** (Charcot-Marie-Tooth disease, peroneal muscular atrophy) are the most common; they are usually autosomal dominant disorders. Type I results from a duplication (extra copy) of the peripheral myelin protein-22 gene (PMP22), located on the short arm of chromosome 17. These disorders are characterized by weakness and atrophy, primarily in peroneal and distal leg muscles. Patients may also have other degenerative disorders (eg, Friedreich's ataxia) or a family history of them. Patients with type I present in middle childhood with footdrop and slowly progressive distal muscle atrophy, causing stork leg deformity. Intrinsic muscle wasting in the hands begins later. Vibration, pain, and temperature sensation decreases in a stocking-glove pattern. Deep tendon reflexes are absent. High pedal arches or hammertoes may be the only signs in family members who are carriers. Nerve conduction velocities are slow, and distal latencies are prolonged. Segmental demyelination and remyelination occur. Enlarged peripheral nerves may be palpated. The disease progresses slowly and does not affect life span. Type II evolves more slowly; weakness usually develops later in life. Patients have relatively normal nerve conduction velocities but low amplitude sensory nerve action potentials and compound muscle action potentials. Biopsies detect axonal (wallerian) degeneration.

**Type III** (hypertrophic interstitial neuropathy, Dejerine-Sottas disease), a rare autosomal recessive disorder, begins in childhood with progressive weakness and sensory loss and absent deep tendon reflexes. Although initially it resembles Charcot-Marie-Tooth disease, the motor weakness progresses more quickly. Demyelination and remyelination occur, producing enlarged peripheral nerves and onion bulbs, detected by nerve biopsy.

**Sensory neuropathies:** Hereditary sensory neuropathies are rare. Loss of distal pain and temperature sensation is more prominent than loss of vibratory and position sense. The main complication is foot mutilation due to pain insensitivity, resulting in a high risk of infections and osteomyelitis.

**Diagnosis**

The characteristic distribution of motor weakness, foot deformities, and family history suggests the diagnosis, which should be confirmed by electrophysiologic testing. Genetic analysis is available, but there are no specific treatments.

**Treatment**

- Supportive care

Bracing helps correct footdrop; orthopedic surgery to stabilize the foot may help. Physical therapy (to strengthen muscles) and occupational therapy may help; vocational counseling may help prepare young patients to maintain vocational skills despite disease progression.

**Hereditary Motor Neuropathy With Liability to Pressure Palsies**

In hereditary motor neuropathy with liability to pressure palsies (HNPP), nerves become increasingly sensitive to pressure and stretch.

In HNPP, nerves lose their myelin sheath and do not conduct nerve impulses normally. Inheritance is usually autosomal dominant. The cause is loss of one copy of peripheral myelin protein-22 gene (PMP22), located on the short arm of chromosome 17. Two copies of the gene are needed for normal function. Incidence of HNPP is estimated to be 2 to 5/100,000.

Usually, symptoms start during adolescence or young adulthood, but they may start at any age. Peroneal nerve palsy with footdrop, ulnar nerve palsy, and carpal tunnel syndrome commonly develop. The pressure palsies can be mild or severe and last from minutes to months. Numbness and weakness occur in affected areas.

**Diagnosis**

HNPP should be suspected in patients with any of the following:
• Recurrent compression mononeuropathies

• Multiple mononeuropathy of unknown origin

• Symptoms suggesting recurrent demyelinating polyneuropathy

• A family history of carpal tunnel syndrome

Electrodiagnostic testing and genetic testing aid in diagnosis; rarely, biopsy is required.

**Treatment**

• Supportive care

Treatment involves avoiding or modifying activities that cause symptoms. Wrist splints and elbow pads can reduce pressure, prevent reinjury, and allow the nerve to repair the myelin over time. Surgery is rarely indicated.

**Motor Neuron Disorders**

Motor neuron disorders (MNDs) are characterized by steady, relentless, progressive degeneration of corticospinal tracts, anterior horn cells, bulbar motor nuclei, or a combination. Symptoms vary in severity and may include muscle weakness and atrophy, fasciculations, emotional lability, and respiratory muscle weakness. Diagnosis involves nerve conduction velocity studies, electromyography, and exclusion of other disorders via MRI and laboratory tests. Treatment is supportive.

MNDs may involve the CNS as well as the peripheral nervous system. Usually, etiology is unknown. Nomenclature and symptoms vary according to the part of the motor system most affected. Myopathies have similar features but are disorders of the muscle membrane, contractile apparatus, or organelles (see p. 3008).

MNDs can be classified as upper and lower; some disorders (eg, amyotrophic lateral sclerosis) have features of both. They are more common among men, most often during their 50s.

**Symptoms and Signs**

Upper MNDs (eg, primary lateral sclerosis) affect neurons of the motor cortex, which extend to the brain stem (corticobulbar tracts) or spinal cord (corticospinal tracts). Generally, symptoms consist of stiffness, clumsiness, and awkward movements, usually affecting first the mouth, throat, or both, then spreading to the limbs.

Lower MNDs affect the anterior horn cells or cranial nerve motor nuclei or their efferent axons to the skeletal muscles. In bulbar palsies, only the cranial nerve motor nuclei in the brain stem (bulbar nuclei) are affected. Patients usually present with facial weakness, dysphagia, and dysarthria. When anterior horn cells of spinal (not cranial) nerves are affected, as in spinal muscular atrophies (see p. 1803), symptoms usually include muscle weakness and atrophy, fasciculations (visible muscle twitches), and muscle cramps, initially in a hand, a foot, or the tongue. Poliomyelitis, an enteroviral infection that attacks anterior horn cells, and postpolio syndrome are also lower MNDs (see p. 1426).

Physical findings help differentiate upper from lower MNDs (see Table 185-3) and weakness due to lower MNDs from that due to myopathy (see Table 185-4).

**Amyotrophic lateral sclerosis (ALS):** ALS (Lou Gehrig disease, Charcot's syndrome) is the most common MND.
Most patients present with random, asymmetric symptoms, consisting of cramps, weakness, and muscle atrophy of the hands (most commonly) or feet. Weakness progresses to the forearms, shoulders, and lower limbs. Fasciculations, spasticity, hyperactive deep tendon reflexes, extensor plantar reflexes, clumsiness, stiffness of movement, weight loss, fatigue, and difficulty controlling facial expression and tongue movements soon follow. Other symptoms include hoarseness, dysphagia, slurred speech, increased saliva production, and a tendency to choke on liquids. Late in the disorder, a pseudobulbar affect occurs, with inappropriate, involuntary, and uncontrollable excesses of laughter or crying. Sensory systems, consciousness, cognition, voluntary eye movements, sexual function, and urinary and anal sphincters are usually spared.

Death is usually caused by failure of the respiratory muscles; 50% of patients die within 3 yr of onset, 20% live 5 yr, and 10% live 10 yr. Survival for > 30 yr is rare. In the bulbar variant, deterioration and death occur more rapidly.

**Progressive bulbar palsy:** The muscles innervated by cranial nerves and corticobulbar tracts are predominantly affected, causing progressive difficulty with chewing, swallowing, and talking; nasal voice; reduced gag reflex; fasciculations and weak movement of the facial muscles and tongue; and weak palatal movement. A pseudobulbar affect, with emotional lability may occur if the corticobulbar tract is affected. Commonly, the disorder spreads, affecting extrabulbar segments; then it is called bulbar-variant ALS.

*Table 185-3. Distinguishing Upper from Lower Motor Neuron Lesions*

*Table 185-4. Distinguishing the Cause of Muscle Weakness: Lower Motor Neuron Dysfunction vs Myopathy*

Patients with dysphagia have a very poor prognosis; respiratory complications due to aspiration frequently result in death within 1 to 3 yr.

**Progressive muscular atrophy:** In many cases, especially those with childhood onset, inheritance is autosomal recessive. Other cases are sporadic. The disorder can develop at any age. Anterior horn cell involvement occurs alone or is more prominent than corticospinal involvement, and progression tends to be more benign than that of other MNDs.

Fasciculations may be the earliest manifestation. Muscle wasting and marked weakness begin in the hands and progress to the arms, shoulders, and legs, eventually becoming generalized. Patients may survive ≥ 25 yr.

**Primary lateral sclerosis and progressive pseudobulbar palsy:** Muscle stiffness and signs of distal motor weakness gradually increase, affecting the limbs in primary lateral sclerosis and the lower cranial nerves in progressive pseudobulbar palsy. Fasciculations and muscle atrophy may follow many years later. These disorders usually take several years to result in total disability.

**Diagnosis**

- Electrodiagnostic tests
- MRI of brain and, if no cranial nerve involvement, cervical spine
- Laboratory tests to check for other, more treatable causes

Diagnosis is suggested by progressive, generalized motor weakness without significant sensory abnormalities. Other disorders that cause pure muscle weakness should be ruled out:

- Disorders of neuromuscular transmission
- Various myopathies (including noninflammatory and drug-induced)
• Spinal muscular atrophies (mostly in children)

• Polymyositis

• Dermatomyositis

• Thyroid and adrenal disorders

• Electrolyte abnormalities (eg, hypokalemia, hypercalcemia, hypophosphatemia)

• Various infections (eg, syphilis, Lyme disease, hepatitis C)

When cranial nerves are affected, a treatable cause is less likely. Upper and lower motor neuron signs plus weakness in facial muscles strongly suggest ALS.

Electrodiagnostic tests should be done to check for evidence of disorders of neuromuscular transmission or demyelination. Such evidence is not present in MNDs; nerve conduction velocities are usually normal until late in the disease. Needle electromyography (EMG) is the most useful test, showing fibrillations, positive waves, fasciculations, and sometimes giant motor units, even in unaffected limbs.

Brain MRI is required. When there is no clinical or EMG evidence of cranial nerve motor weakness, MRI of the cervical spine is indicated to exclude structural lesions.

Laboratory tests are done to check for other, treatable causes. Tests include CBC, electrolytes, creatine kinase, and thyroid function tests. Serum and urine protein electrophoresis with immunofixation for monoclonal antibodies is done to check for a paraprotein that is rarely associated with MNDs. Discovering an underlying paraproteinemia may indicate that the MND is paraneoplastic, and treatment of the paraproteinemia may ameliorate the MND. Antimyelin-associated glycoprotein (MAG) antibodies are associated with a demyelinating motor neuropathy, which may mimic ALS. A 24-h urine collection is done to check for heavy metals in patients who may have been exposed to them. Lumbar puncture should be done; elevated WBCs or protein levels in CSF strongly suggest an alternative diagnosis.

Serum Venereal Disease Research Laboratories (VDRL) tests, ESR, and measurement of certain antibodies (rheumatoid factor, Lyme titer, HIV, hepatitis C virus, antinuclear [ANA], anti-Hu [to check for anti-Hu paraneoplastic syndrome]) are indicated only if suggested by risk factors or history. Genetic testing (eg, for superoxide dismutase gene mutation or genetic abnormalities that cause spinal muscular atrophies) and enzyme measurements (eg, hexosaminidase A) should not be done unless patients are interested in genetic counseling; disorders detected by these tests have no known specific treatments.

Treatment

• Supportive care

• Riluzole for bulbar-variant ALS

There is no specific treatment. However, an antiglutamate drug, riluzole 50 mg po bid, prolongs life in patients with progressive bulbar palsy. A multidisciplinary team approach helps patients cope with progressive neurologic disability.

The following drugs may help reduce symptoms:

• For spasticity, baclofen

• For cramps, quinine or phenytoin

• To decrease saliva production, a strong anticholinergic drug (eg, glycopyrrrolate, amitriptyline, benztpirine, trihexyphenidyl, transdermal hyoscine, atropine)
For pseudobulbar affect, amitriptyline and fluvoxamine

In patients with progressive bulbar palsy, surgery to improve swallowing has had limited success.

**Myasthenia Gravis**

Myasthenia gravis involves episodic muscle weakness and easy fatigability caused by autoantibody- and cell-mediated destruction of acetylcholine receptors. It is more common among young women but may occur at any age. Symptoms worsen with muscle activity and lessen with rest. Diagnosis is by antibody testing to acetylcholine receptor (AChR), electromyography, and IV edrophonium challenge, which briefly lessens the weakness. Treatment includes anticholinesterase drugs, immunosuppressants, corticosteroids, plasmapheresis, and possibly thymectomy.

Myasthenia gravis develops most commonly in women aged 20 to 40. It results from an autoimmune attack on postsynaptic acetylcholine receptors, which disrupts neuromuscular transmission. The trigger for autoantibody production is unknown, but the disorder is associated with abnormalities of the thymus, thyrotoxicosis, and other autoimmune disorders. The role of the thymus in myasthenia is unclear, but 65% of patients have thymic hyperplasia, and 10% have a thymoma. About half of the thymomas are malignant. Precipitating factors include infection, surgery, and certain drugs (eg, aminoglycosides, quinine, Mg sulfate, procainamide, Ca channel blockers).

Some patients with generalized myasthenia have no antibodies to acetylcholine receptors (AChR) in serum. About half of these patients have antibodies to muscle-specific receptor tyrosine kinase (MuSK), a surface membrane enzyme that helps AChR molecules aggregate during development of the neuromuscular junction. Anti-MuSK antibodies do not occur in patients with AChR antibodies or with isolated ocular myasthenia. The clinical significance of anti-MuSK antibodies is still under study, but patients with them may be less responsive to anticholinesterase drugs and require more aggressive early immunotherapy than patients who have AChR antibodies.

**Uncommon forms:** Ocular myasthenia gravis involves only extraocular muscles. It represents about 15% of cases.

Congenital myasthenia is a rare autosomal recessive disorder that begins in childhood; it results from structural abnormalities in the postsynaptic receptor rather than an autoimmune disorder. Ophthalmoplegia is common.

Neonatal myasthenia affects 12% of infants born to women with myasthenia gravis. It is due to IgG antibodies that passively cross the placenta. It causes generalized muscle weakness, which resolves in days to weeks as antibody titers decline. Thus, treatment is usually supportive.

**Symptoms and Signs**

The most common symptoms are ptosis, diplopia, and muscle weakness after use of the affected muscle. Weakness resolves when the affected muscles are rested but recurs when they are used again. Ocular muscles are affected initially in 40% of patients and eventually in 85%. Only ocular muscles are affected in 15%. Hand grip may alternate between weak and normal (milkmaid's grip). Neck muscles may become weak. If generalized myasthenia is going to develop after ocular symptoms, it usually does so within the first 3 yr. Proximal limb weakness is common. Some patients present with bulbar symptoms (eg, altered voice, nasal regurgitation, choking, dysphagia). Sensation and deep tendon reflexes are normal. Manifestations fluctuate in intensity over hours to days.

**Myasthenic crisis,** a severe generalized quadriplegia or life-threatening respiratory muscle weakness, occurs in about 10% of patients. It is often due to a supervening infection that reactivates the immune system. Once respiratory insufficiency begins, respiratory failure may occur rapidly.

**Diagnosis**
• Bedside anticholinesterase test

• AChR antibody levels, electromyography, or both

Diagnosis is suggested by symptoms and signs and confirmed by tests. An anticholinesterase test, done at bedside and using the short-acting (< 5 min) drug edrophonium, is positive in most patients who have myasthenia with overt weakness. A muscle with obvious weakness is tested. Patients are asked to exercise the affected muscle until fatigue occurs (eg, to hold the eyes open until ptosis occurs or to count aloud until slurred speech develops); then, edrophonium 2 mg IV is given. If no adverse reaction (eg, bradycardia, atioventricular block) occurs within 30 sec, another 8 mg is given. Rapid (< 2 min) recovery of muscle function is a positive result. However, a positive result is not definitive for myasthenia gravis because such improvement may occur in other neuromuscular disorders. Also, results may be equivocal. During the test, weakness due to cholinergic crisis may worsen. Resuscitation equipment and atropine (as an antidote) must be available during the test.

Even if the anticholinesterase test is unequivocally positive, serum AChR antibody levels, electromyography (EMG), or both are required to confirm the diagnosis. AChR antibodies are present in 80 to 90% of patients with generalized myasthenia but in only 50% with the ocular form. Antibody levels do not correlate with disease severity. About half of patients without AChR antibodies test positive for anti-MuSK antibodies.

EMG using repetitive stimuli (2 to 3/sec) shows a significant decrease in amplitude of the compound muscle action potential response in 60% of patients. Single-fiber EMG can detect such a decrease in > 95%.

Once myasthenia is diagnosed, CT or MRI of the thorax should be done to check for a thymoma. Other tests should be done to screen for autoimmune disorders frequently associated with myasthenia gravis (eg, vitamin B12 deficiency, hyperthyroidism, RA, SLE).

Patients in myasthenic crisis should be evaluated for an infectious trigger. Bedside pulmonary function tests (eg, forced vital capacity) help detect impending respiratory failure.

Treatment

• Anticholinesterase drugs and plasmapheresis to relieve symptoms

• Corticosteroids, immunosuppressants, and thymectomy to lessen the autoimmune reaction

• Supportive care

In patients with congenital myasthenia, anticholinesterase drugs and immunomodulating treatments are not beneficial and should be avoided. Patients with respiratory failure require intubation and mechanical ventilation.

Symptomatic treatment: Anticholinesterase drugs are the mainstay of symptomatic treatment but do not alter the underlying disease process. Moreover, they rarely relieve all symptoms, and myasthenia may become refractory to these drugs. Pyridostigmine is begun at 30 to 60 mg po q 3 to 4 h and titrated up to a maximum of 180 mg/dose based on symptoms. When parenteral therapy is necessary (eg, because of dysphagia), neostigmine (1 mg = 60 mg of pyridostigmine) may be substituted. Anticholinesterase drugs can cause abdominal cramps and diarrhea, which are treated with oral atropine 0.4 to 0.6 mg (given with pyridostigmine) or propantheline 15 mg tid to qid.

Cholinergic crisis is muscular weakness caused by a dose of neostigmine or pyridostigmine that is too high. A mild crisis may be difficult to differentiate from worsening myasthenia. Severe cholinergic crisis can usually be differentiated because it, unlike myasthenia gravis, results in increased lacrimation and salivation, tachycardia, and diarrhea.

The approach to deterioration in patients who have been responding well to treatment is controversial.
Some experts believe an edrophonium test is useful because strength improves only during myasthenic crisis. Others recommend initiating respiratory support and stopping anticholinesterase drugs for several days.

**Immunomodulating treatment:** Immunosuppressants interrupt the autoimmune reaction and slow the disease course, but they do not relieve symptoms rapidly. After being given IV immune globulin 400 mg/kg once/day for 5 days, 70% of patients improve in 1 to 2 wk. Effects may last 1 to 2 mo.

Corticosteroids are necessary as maintenance therapy for many patients but have little immediate effect in myasthenic crisis. Over one half of patients worsen acutely after starting high-dose corticosteroids. Initially, prednisone 20 mg po once/day is given; dose is increased by 5 mg q 2 to 3 days up to 60 or 70 mg, which is then given every other day. Improvement may take several months; then, the dose should be reduced to the minimum necessary to control symptoms.

Azathioprine 2.5 to 3.5 mg/kg po once/day may be as effective as corticosteroids, although significant benefit may not occur for many months. Cyclosporine 2 to 2.5 mg/kg po bid may allow the corticosteroid dose to be reduced. These drugs require the usual precautions. Other drugs that may be beneficial include methotrexate, cyclophosphamide, and mycophenolate mofetil.

Thymectomy is an option for most patients with generalized myasthenia if they are < 60 yr and should be done in all patients with a thymoma. Subsequently, in 80%, remission occurs or the maintenance drug dose can be lowered.

Plasmapheresis may be useful during myasthenia crisis and, for patients unresponsive to drugs, before thymectomy.

**Nerve Root Disorders**

(Radiculopathies)

Nerve root disorders result in segmental radicular deficits (eg, pain or paresthesias in a dermatomal distribution, weakness of muscles innervated by the root). Diagnosis may require neuroimaging, electrodiagnostic studies, and systemic testing for underlying disorders. Treatment depends on the cause but includes symptomatic relief with NSAIDs and other analgesics.

Nerve root disorders (radiculopathies) are precipitated by chronic pressure on a root in or adjacent to the spinal column. The most common cause is a herniated intervertebral disk. Bone changes due to RA or osteoarthritis, especially in the cervical and lumbar areas, may also compress isolated nerve roots. Less commonly, carcinomatous meningitis causes patchy multiple root dysfunction. Rarely, mass spinal lesions (eg, epidural abscesses and tumors, spinal meningiomas, neurofibromas) may manifest with radicular symptoms instead of the usual spinal cord dysfunction (see p. 1805). Diabetes can cause a painful thoracic or extremity radiculopathy by causing ischemia of the nerve root. Infectious disorders, such as those due to fungi (eg, histoplasmosis) and spirochetes (eg, Lyme disease, syphilis), sometimes affect nerve roots. Herpes zoster infection usually causes a painful radiculopathy with dermatomal sensory loss and characteristic rash, but it may cause a motor radiculopathy with myotomic weakness and reflex loss. Cytomegalovirus-induced polyradiculitis is a complication of AIDS.

**Symptoms and Signs**

Radiculopathies tend to cause characteristic radicular syndromes of pain and segmental neurologic deficits based on the cord level of the affected root (see Table 185-5). Muscles innervated by the affected motor root become weak and atrophy; they also may be flaccid with fasciculations. Sensory root involvement causes sensory impairment in a dermatomal distribution. Corresponding segmental deep tendon reflexes may be diminished or absent. Electric shock-like pains may radiate along the affected nerve root's distribution.

Pain may be exacerbated by movements that transmit pressure to the nerve root through the
subarachnoid space (eg, moving the spine, coughing, sneezing, doing the Valsalva maneuver). Lesions of the cauda equina, which affect multiple lumbar and sacral roots, cause radicular symptoms in both legs and may impair sphincter and sexual function.

[Table 185-5, Symptoms of Common Radiculopathies by Cord Level]

Findings indicating spinal cord compression include a sensory level (an abrupt change in sensation below a horizontal line across the spine), flaccid paraparesis or quadriparesis, reflex abnormalities below the site of compression, early-onset hyporeflexia followed later by hyperreflexia, and sphincter dysfunction.

**Diagnosis**

- Neuroimaging
- Sometimes electrodiagnostic tests

Radicular symptoms require MRI or CT of the affected area. Myelography is sometimes used if multiple levels are affected. The area imaged depends on symptoms and signs; if the level is unclear, electrodiagnostic studies should be done to localize the affected root, but electrodiagnostic studies cannot identify the cause.

If imaging does not detect an anatomic abnormality, CSF analysis is done to check for infectious or inflammatory causes, and fasting plasma glucose is measured to check for diabetes.

**Treatment**

- Treatment of the cause and of pain

Specific causes are treated. Acute pain requires appropriate analgesics (eg, acetaminophen, NSAIDs, sometimes opioids). NSAIDs are particularly useful for disorders that involve inflammation. Muscle relaxants, sedatives, and topical treatments rarely provide additional benefit. Chronic pain can be difficult to manage (see p. 1630); acetaminophen and NSAIDs are often only partly effective, and chronic use of NSAIDs has substantial risks. Opioids have a high risk of addiction. Tricyclic antidepressants and anticonvulsants may be effective, as may physical therapy and consultation with a mental health practitioner. For a few patients, alternative medical treatments (eg, transdermal electrical nerve stimulation, spinal manipulation, acupuncture, medicinal herbs) may be tried if all other treatments are ineffective.

**Herniated Nucleus Pulposus**

(Herniated, Ruptured, or Prolapsed Intervertebral Disk)

Herniated nucleus pulposus is prolapse of an intervertebral disk through a tear in the surrounding annulus fibrosus. The tear causes pain; when the disk impinges on an adjacent nerve root, a segmental radiculopathy with paresthesias and weakness in the distribution of the affected root results. Diagnosis is by CT, MRI, or CT myelography. Treatment of mild cases is with analgesics as needed. Bed rest is rarely indicated. Patients with progressive or severe neurologic deficits, intractable pain, or sphincter dysfunction may require immediate or elective surgery (eg, diskectomy, laminectomy).

Spinal vertebrae are separated by cartilaginous disks consisting of an outer annulus fibrosus and an inner nucleus pulposus. When degenerative changes (with or without trauma) result in protrusion or rupture of the nucleus through the annulus fibrosus in the lumbosacral or cervical area, the nucleus is displaced posterolaterally or posteriorly into the extradural space. Radiculopathy occurs when the herniated nucleus compresses or irritates the nerve root. Posterior protrusion may compress the cord or cauda equina, especially in a congenitally narrow spinal canal (spinal stenosis). In the lumbar area, > 80% of disk ruptures affect L5 or S1 nerve roots; in the cervical area, C6 and C7 are most commonly affected. Herniated disks are common.
Symptoms and Signs

Herniated disks often cause no symptoms, or they may cause symptoms and signs in the distribution of affected nerve roots. Pain usually develops suddenly, and back pain is typically relieved by bed rest. In contrast, nerve root pain caused by an epidural tumor or abscess begins more insidiously, and back pain is worsened by bed rest.

In patients with lumbosacral herniation, straight-leg raises stretch the lower lumbar roots and exacerbate back or leg pain (bilateral if disk herniation is central); straightening the knee while sitting also causes pain.

Cervical herniation causes pain during neck flexion or tilting. Cervical cord compression, if chronic, manifests with spastic paresis of the lower limbs and, if acute, causes quadriplegia.

Cauda equina compression often results in urine retention or incontinence due to loss of sphincter function.

Diagnosis

- CT, MRI, or CT myelography

CT, MRI, or CT myelography can identify the cause and precise level of the lesion. Electrodiagnostic studies may help identify the involved root. Because asymptomatic herniated disk is common, the clinician must carefully correlate symptoms with MRI abnormalities before invasive procedures are considered.

Treatment

- Conservative treatment initially

- Invasive procedures if neurologic deficits are progressive or severe

- Immediate surgical evaluation if spinal cord is compressed

Because a herniated disk desiccates over time, symptoms tend to abate regardless of treatment. Up to 95% of patients recover without surgery within 3 mo. Treatment should be conservative, unless neurologic deficits are progressive or severe. Heavy or vigorous physical activity is restricted, but ambulation and light activity (eg, lifting objects < 2.5 to 5 kg [≈ 5 to 10 lb] using correct techniques) are permitted as tolerated; prolonged bed rest (including traction) is contraindicated. Acetaminophen, NSAIDs, or other analgesics should be used as needed to relieve pain. Physical therapy and home exercises can improve posture and strengthen back muscles and thus reduce spinal movements that further irritate or compress the nerve root.

If lumbar radiculopathies result in persistent or worsening neurologic deficits, particularly objective deficits (weakness, reflex deficits), or in severe, intractable nerve root pain or sensory deficits, invasive procedures should be considered. Microscopic discectomy and laminectomy with surgical removal of herniated material are usually the procedures of choice. Percutaneous approaches to remove bulging disk material are being evaluated. Dissolving herniated disk material with local injections of the enzyme chymopapain is not recommended. Lesions acutely compressing the spinal cord or cauda equina (eg, causing urine retention or incontinence) require immediate surgical evaluation (see p. 1810).

If cervical radiculopathies result in signs of spinal cord compression, surgical decompression is needed immediately; otherwise, it is done electively when nonsurgical treatments are ineffective.

Peripheral Neuropathy

Peripheral neuropathy is dysfunction of one or more peripheral nerves (the part of a spinal nerve distal to the root and plexus). It includes numerous syndromes characterized by varying
degrees of sensory disturbances, pain, muscle weakness and atrophy, diminished deep tendon reflexes, and vasomotor symptoms, alone or in any combination. Initial classification is based on history and physical examination. Electromyography and nerve conduction velocity studies help localize the lesion and determine whether the pathophysiology is primarily axonal (often metabolic) or demyelinating (often autoimmune). Treatment is aimed mainly at the cause.

Peripheral neuropathy may affect a single nerve (mononeuropathy), ≥ 2 discrete nerves in separate areas (multiple mononeuropathy), or many nerves simultaneously and often suggesting a diffuse process (polyneuropathy).

**Mononeuropathies**

Single and multiple mononeuropathies are characterized by sensory disturbances and weakness in the distribution of the affected nerve or nerves. Diagnosis is clinical but should be confirmed with electrodiagnostic tests. Treatment is directed at the cause, sometimes with splinting, NSAIDs, corticosteroid injections, and, for severe cases of nerve entrapment, surgery.

Trauma is the most common cause of acute mononeuropathy and may result as follows:

- Violent muscular activity or forcible over-extension of a joint may cause focal neuropathy, as may repeated small traumas (eg, tight gripping of small tools, excessive vibration from air hammers).

- Prolonged, uninterrupted pressure at bony prominences can cause pressure neuropathy, usually affecting superficial nerves (ulnar, radial, peroneal), particularly in thin people; such pressure may occur during sound sleep, intoxication, bicycle riding, or anesthesia.

- Compression of nerves in narrow passageways causes entrapment neuropathy (eg, in carpal tunnel syndrome).

- Nerve compression by a tumor, bony hyperostosis, a cast, crutches, or prolonged cramped postures (eg, during gardening) may cause compression paralysis.

Hemorrhage that compresses a nerve, exposure to cold or radiation, or direct tumor invasion may also cause neuropathy. Compression of a nerve may be transient (eg, caused by an activity) or fixed (eg, caused by a mass or anatomic abnormality).

**Multiple mononeuropathy** (mononeuritis multiplex) is usually secondary to connective tissue disorders (eg, polyarteritis nodosa, SLE, other types of vasculitis, Sjogren's syndrome, RA), sarcoidosis, metabolic disorders (eg, diabetes, amyloidosis), or infectious disorders (eg, Lyme disease, HIV infection, leprosy). However, diabetes usually causes sensorimotor distal polyneuropathy (see p. 1799).

**Symptoms and Signs**

Single and multiple mononeuropathies are characterized by pain, weakness, and paresthesias in the distribution of the affected nerve or nerves. Pure motor nerve involvement begins with painless weakness; pure sensory nerve involvement begins with sensory disturbances and no weakness. Multiple mononeuropathy is often asymmetric at its onset; nerves may be involved all at once or progressively. Extensive involvement of many nerves may simulate polyneuropathy.

**Ulnar nerve palsy** of the elbow is often caused by trauma to the nerve in the ulnar groove of the elbow by repeated leaning on the elbow or by asymmetric bone growth after a childhood fracture (tardy ulnar palsy). The ulnar nerve can also be compressed at the cubital tunnel. Compression at the level of the elbow can cause paresthesias and a sensory deficit in the 5th digit and medial half of the 4th digit; the thumb adductor, 5th digit abductor, and interosseus muscles are weak and may be atrophied. Severe chronic ulnar palsy causes a clawhand deformity. Sensory symptoms due to this syndrome are similar to those due to C8 root dysfunction secondary to cervical radiculopathy; however, radiculopathy normally affects the more proximal aspects of the C8 dermatome.
Carpal tunnel syndrome (see also p. 391) may be unilateral or bilateral. It results from compression of the median nerve in the volar aspect of the wrist between the transverse superficial carpal ligament and the flexor tendons of the forearm muscles. The compression causes paresthesias in the radial-palmar aspect of the hand and pain in the wrist and palm. Pain may be referred to the forearm and shoulder. Pain may be more severe at night. A sensory deficit in the palmar aspect of the first 3 fingers may follow, and the muscles that control thumb abduction and opposition may become weak and atrophied. Sensory symptoms due to this syndrome are similar to those due to C6 root dysfunction secondary to cervical radiculopathy.

Peroneal nerve palsy is usually caused by compression of the nerve against the lateral aspect of the fibular neck. It is most common among emaciated bedbound patients and thin people who habitually cross their legs. It causes footdrop (weakened dorsiflexion and eversion of the foot) and, occasionally, a sensory deficit in the anterolateral aspect of the lower leg and the dorsum of the foot or in the web space between the 1st and 2nd metatarsals.

Radial nerve palsy (Saturday night palsy) is caused by compression of the nerve against the humerus, as when the arm is draped over the back of a chair for a long time (eg, during intoxication or deep sleep). Typical symptoms include wristdrop (weakness of the wrist and finger extensors) and sensory loss in the dorsal aspect of the first dorsal interosseous muscle.

Diagnosis
• Clinical evaluation
• Electrodiagnostic testing if clinical diagnosis is inconclusive

Symptoms and examination findings may be nearly pathognomonic. Palpating muscles while they are contracting may detect weakness better than testing movement because during movement, other muscles may compensate for the weak one.

Electrodiagnostic tests are usually done to clarify the diagnosis, particularly when clinical findings are inconclusive for example:
• To distinguish sensory symptoms due to ulnar nerve palsy from C8 root dysfunction due to cervical radiculopathy
• To distinguish sensory symptoms due to carpal tunnel syndrome from C6 root dysfunction due to cervical radiculopathy

Electrodiagnostic tests also help localize the lesion, assess severity, and estimate prognosis.

Treatment
Underlying disorders are treated. Treatment of compression neuropathy depends on cause:
• Fixed compression (eg, by tumor) often must be relieved surgically.
• For transient compression, rest, heat, limited courses of NSAIDs in doses that reduce inflammation (eg, ibuprofen 800 mg tid), and avoidance or modification of the causative activity usually relieve symptoms.
• For carpal tunnel syndrome, corticosteroid injections are sometimes helpful.

Braces or splints are often used pending resolution to prevent contractures. Surgery should be considered when progression occurs despite conservative treatment.

Polyneuropathy
A polyneuropathy is a diffuse peripheral nerve disorder that is bilaterally symmetrical and thus
Some polyneuropathies (eg, due to lead toxicity, dapsone use, tick bite, porphyria, or Guillain-Barre syndrome) affect primarily motor fibers; others (eg, due to dorsal root ganglionitis of cancer, leprosy, AIDS, diabetes mellitus, or chronic pyridoxine intoxication) affect primarily sensory fibers. Some disorders (eg, Guillain-Barre syndrome, Lyme disease, diabetes, diphtheria) can also affect cranial nerves. Certain drugs and toxins can affect sensory or motor fibers or both (see Table 185-6).

Symptoms and Signs

Because pathophysiology and symptoms are related, polyneuropathies are often classified by area of dysfunction: myelin, vasa nervorum, or axon. They may be acquired or inherited (see p. 1790).

Myelin dysfunction: Myelin dysfunction polyneuropathies most often result from a parainfectious immune response triggered by an encapsulated bacterium (eg, Campylobacter sp), virus (eg, enteric or influenza viruses, HIV), or vaccine (eg, influenza vaccine). Presumably, antigens in these agents cross-react with antigens in the peripheral nervous system, causing an immune response (cellular, humoral, or both) that culminates in varying degrees of myelin dysfunction. In acute cases (eg, in Guillain-Barre syndrome—see p. 1788), rapidly progressive weakness and respiratory failure may develop. In chronic inflammatory demyelinating polyneuropathy (CIDP), symptoms may recur or progress over months and years.

Myelin dysfunction usually results in large-fiber sensory disturbances (paresthesias), significant muscle weakness greater than expected for degree of atrophy, and greatly diminished reflexes. Trunk musculature and cranial nerves may be involved. Demyelination typically occurs along the entire length of a nerve, causing proximal and distal symptoms. There may be side-to-side asymmetries, and the upper body may be affected before the lower body, or vice versa. Muscle bulk and tone are relatively preserved.

Vasa nervorum compromise: Chronic arteriosclerotic ischemia, vasculitis, and hypercoagulable states can compromise the vascular supply to nerves.

[Table 185-6. Toxic Causes of Neuropathies]

Usually, small-fiber sensory and motor dysfunction occurs first. Patients typically have painful, often burning sensory disturbances. Abnormalities tend to be asymmetric early in the disorder and rarely affect the proximal one third of the limb or trunk muscles. Cranial nerve involvement is rare, except in diabetes, which commonly affects the 3rd cranial (oculomotor) nerve. Later, if nerve lesions coalesce, symptoms and signs may appear symmetric. Dysautonomia and skin changes (eg, atrophic, shiny skin) sometimes occur. Muscle weakness tends to be proportional to atrophy, and reflexes are rarely lost completely.

Axonopathy: Axonopathies tend to be distal; they may be symmetric or asymmetric.

Symmetric axonopathies result most often from toxic-metabolic disorders. Common causes include the following:

• Diabetes mellitus

• Chronic renal insufficiency

• Adverse effects of chemotherapy drugs (eg, vinca alkaloids)

Axonopathy may result from nutritional deficiencies (most commonly, of thiamin or vitamin B₆, B₁₂, or E) or from excess intake of vitamin B₆ or alcohol. Less common metabolic causes include hypothyroidism, porphyria, sarcoidosis, and amyloidosis. Other causes include certain infections (eg, Lyme disease), drugs (eg, nitrous oxide), and exposure to certain chemicals (eg, Agent Orange, n-hexane) or heavy
drugs (eg, nitrous oxide), and exposure to certain chemicals (eg, Agent Orange, \(n\)-hexane) or heavy metals (eg, lead, arsenic, mercury). In a paraneoplastic syndrome associated with small-cell lung cancer, loss of dorsal root ganglia and their sensory axons results in subacute sensory neuropathy.

Primary axon dysfunction may begin with symptoms of large- or small-fiber dysfunction or both. Usually, the resulting neuropathy has a distal symmetric, stocking-glove distribution; it evenly affects the lower extremities before the upper extremities and progresses symmetrically from distal to proximal areas.

Asymmetric axonopathy can result from parainfectious or vascular disorders.

**Diagnosis**

- Electrodiagnostic testing
- Laboratory tests, determined by suspected type of neuropathy

Polyneuropathy is suspected in patients with diffuse or multifocal sensory deficits, weakness without hyperreflexia, or both. Clinical findings, particularly tempo of onset, aid in diagnosis and identification of the cause, as in the following:

- Asymmetric neuropathies suggest a disorder affecting the myelin sheath or vasa nervorum.
- Symmetric, distal neuropathies suggest toxic or metabolic causes.
- Slowly progressive, chronic neuropathies tend to be inherited or due to long-term toxic exposure or metabolic disorders.
- Acute neuropathies suggest an autoimmune response, vasculitis, or a postinfectious cause.
- Rash, skin ulcers, and Raynaud's syndrome in patients with an asymmetric axonal neuropathy suggest a hypercoagulable state or parainfectious or autoimmune vasculitis.
- Weight loss, fever, lymphadenopathy, and mass lesions may suggest a tumor or paraneoplastic syndrome.

**Electrodiagnostic tests:** Regardless of clinical findings, electromyography (EMG) and nerve conduction velocity studies are necessary to classify type of neuropathy. At a minimum, EMG of both lower extremities should be done to assess for asymmetry and full extent of axon loss. Because EMG and nerve conduction studies assess primarily large myelinated fibers in distal limb segments, EMG may be normal in patients with proximal myelin dysfunction (eg, early in Guillain-Barre syndrome) and in patients with primarily small-fiber dysfunction. In such cases, quantitative sensory or autonomic testing or both may be done depending on the presenting symptoms.

**Laboratory tests:** Baseline laboratory tests for all patients include CBC, electrolytes, renal function tests, rapid plasma reagin test, and measurement of fasting plasma glucose, \(\text{HbA}_1\text{C}\), vitamin \(\text{B}_12\), folate, and thyroid-stimulating hormone. Some clinicians include serum protein electrophoresis. The need for other tests is determined by polyneuropathy subtype. When EMG and clinical differentiation are inconclusive, tests for all subtypes may be necessary.

For acute myelin dysfunction neuropathies, the approach is the same as that for Guillain-Barre syndrome (see p. 1788); forced vital capacity is measured to check for incipient respiratory failure. In acute or chronic myelin dysfunction, tests for infectious disorders and immune dysfunction, including tests for hepatitis and HIV and serum protein electrophoresis, are done. A lumbar puncture should also be done; myelin dysfunction due to an autoimmune response often causes albuminocytologic dissociation: increased CSF protein (> 45 mg%) but normal WBC count (≤ 5/\(\mu\)L).

For vasa nervorum compromise or asymmetric axonal polyneuropathies, tests for hypercoagulable states and parainfectious or autoimmune vasculitis, particularly if suggested by clinical findings, should be done; the minimum is ESR, serum protein electrophoresis, and measurement of rheumatoid factor, antinuclear
antibodies, and serum CK. CK may be elevated when rapid onset of disease results in muscle injury. Coagulation studies (eg, protein C, protein S, antithrombin III, anticardiolipin antibody, and homocysteine levels) should be done only if personal or family history suggests a hypercoagulable state. Tests for sarcoidosis, hepatitis C, or Wegener's granulomatosis should be done only if symptoms and signs suggest one of these disorders. If no cause is identified, nerve and muscle biopsy should be done. An affected sural nerve is usually biopsied. A muscle adjacent to the biopsied sural nerve or a quadriceps, biceps brachii, or deltoid muscle may be biopsied. The muscle should be one with moderate weakness that has not been tested by EMG using a needle. An abnormality is more often detected when the contralateral muscle has EMG abnormalities, particularly when the neuropathy is somewhat symmetric. Nerve biopsies are useful in symmetric and asymmetric polyneuropathies but are particularly useful in asymmetric axonopathies.

If initial tests do not identify the cause of distal symmetric axonopathies, a 24-h urine collection is tested for heavy metals, and urine protein electrophoresis is done. If chronic heavy metal poisoning is suspected, testing of hairs from the pubis or axillary region may help.

Whether tests for other causes are needed depends on history and physical examination findings.

**Treatment**

- Treatment directed at the cause
- Supportive care

Treatment focuses on correcting the causes when possible; a causative drug or toxin can be eliminated, or a dietary deficiency corrected. Although these actions may halt progression and lessen symptoms, recovery is slow and may be incomplete. If the cause cannot be corrected, treatment focuses on minimizing disability and pain. Physical and occupational therapists can recommend useful assistive devices. Amitriptyline, gabapentin, mexiletine, and topical lidocaine may relieve neuropathic pain (eg, diabetic burning feet).

For myelin dysfunction polyneuropathies, immune system-modifying treatments are usually used:

- Plasmapheresis or IV immune globulin for acute myelin dysfunction
- Corticosteroids or antimetabolite drugs for chronic myelin dysfunction

**Plexus Disorders**

Disorders of the brachial or lumbosacral plexus cause a painful mixed sensorimotor disorder of the corresponding limb.

Because several nerve roots intertwine within the plexus (see Fig. 185-1), the symptom pattern does not fit the distribution of individual roots or nerves. Disorders of the rostral brachial plexus affect the shoulders, those of the caudal brachial plexus affect the hands, and those of the lumbosacral plexus affect the legs.

Plexus disorders (plexopathies) are usually due to physical compression or injury. In infants, traction during birth may cause plexopathy. In adults, the cause is usually trauma (typically, for the brachial plexus, a fall that forces the head away from the shoulder) or invasion by metastatic cancer (typically, breast or lung cancer for the brachial plexus and intestinal or GU tumors for the lumbosacral plexus). In patients receiving anticoagulants, a hematoma may compress the lumbosacral plexus. Neurofibromatosis (see p. 2903) occasionally involves a plexus. Other causes include postradiation fibrosis (eg, after radiation therapy for breast cancer) and diabetes.

Acute brachial neuritis (neuralgic amyotrophy, Parsonage-Turner syndrome) occurs primarily in men and typically in young adults, although it can occur at any age. Cause is unknown, but viral or immunologic inflammatory processes are suspected.
Symptoms and Signs

Manifestations include extremity pain and motor or sensory deficits that do not correspond to an isolated nerve root or peripheral nerve.

For acute brachial neuritis, symptoms include severe supraclavicular pain, weakness, and diminished reflexes, with minor sensory abnormalities in the distribution of the brachial plexus. Usually, weakness develops and reflexes decrease as pain resolves. Severe weakness develops within 3 to 10 days, then typically regresses over the next few months. The most commonly affected muscles are the serratus anterior (causing winging of the scapula), other muscles innervated by the upper trunk, and muscles innervated by the anterior interosseus nerve (in the forearm—patients may not be able to make an O with the thumb and index finger).

Diagnosis

- Electromyography and somatosensory evoked potentials
- Sometimes MRI

Diagnosis is suggested by clinical findings. Electromyography and somatosensory evoked potentials should be done to clarify the anatomic distribution (including possible nerve root involvement). MRI of the appropriate plexus and adjacent spine is indicated for all nontraumatic plexopathies that are not a typical case of brachial neuritis.

Treatment

- Treatment directed at the cause

Corticosteroids, although commonly prescribed, have no proven benefit. Surgery may be indicated for injuries, hematomas, and benign or metastatic tumors. Metastases should also be treated with radiation therapy, chemotherapy, or both. Glycemic control can benefit patients with diabetic plexopathy.

Spinal Muscular Atrophies

Spinal muscular atrophies include several types of hereditary disorders characterized by skeletal muscle wasting due to progressive degeneration of anterior horn cells in the spinal cord and of motor nuclei in the brain stem. Manifestations may begin in infancy or childhood. They vary by the specific type and may include hypotonia; hyporeflexia; difficulty sucking, swallowing, and breathing; unmet developmental milestones; and, in more severe types, very early death. Diagnosis is by genetic testing. Treatment is supportive.

Spinal muscular atrophies usually result from autosomal recessive mutations of a single gene locus on the short arm of chromosome 5, causing a homozygous deletion. They may involve the CNS and thus are not purely peripheral nervous system disorders. There are 4 main types.

Type I spinal muscular atrophy (Werdnig-Hoffmann disease) is present in utero and becomes symptomatic by about age 6 mo. Affected infants have hypotonia (often notable at birth), hyporeflexia, tongue fasciculations, and pronounced difficulty sucking, swallowing, and eventually breathing. Death, usually due to respiratory failure, occurs within the first yr in 95% and by age 4 yr in all.

In type II (intermediate) spinal muscular atrophy, symptoms usually manifest between age 3 and 15 mo; < 25% of affected children learn to sit, and none walk or crawl. Children have flaccid muscle weakness and fasciculations, which may be hard to see in young children. Deep tendon reflexes are absent. Dysphagia may be present. The disorder is often fatal in early life, frequently resulting from respiratory complications. However, progression can stop spontaneously, leaving children with...
permanent, nonprogressive weakness and a high risk of severe scoliosis and its complications.

**Type III spinal muscular atrophy (Wohlfart-Kugelberg-Welander disease)** usually manifests between age 15 mo and 19 yr. Findings are similar to those of type I, but progression is slower and life expectancy is longer; some patients have a normal life span. Some familial cases are secondary to specific enzyme defects (eg, hexosaminidase deficiency). Symmetric weakness and wasting progress from proximal to distal areas and are most evident in the legs, beginning in the quadriceps and hip flexors. Later, arms are affected. Life expectancy depends on whether respiratory complications develop.

**Type IV spinal muscular atrophy** can be recessive, dominant, or X-linked, with adult onset (age 30 to 60 yr) and slow progression of primarily proximal muscle weakness and wasting. Differentiating this disorder from amyotrophic lateral sclerosis that involves predominantly lower motor neurons may be difficult.

**Diagnosis**

- Electrodiagnostic testing
- Genetic testing

The diagnosis should be suspected in patients with unexplained muscle wasting and flaccid weakness, particularly in infants and children.

Electromyography (EMG) and nerve conduction velocity studies should be done; muscles innervated by cranial nerves should be included. Conduction is normal, but affected muscles, which are often clinically unaffected, are denervated.

Definitive diagnosis is by genetic testing, which detects the causative mutation in about 95% of patients. Muscle biopsy is done occasionally. Serum enzymes (eg, CK, aldolase) may be slightly increased. Amniocentesis, done if family history is positive, is often diagnostic.

**Treatment**

- Supportive care

There is no specific treatment. Physical therapy, braces, and special appliances can benefit patients with static or slowly progressive disease by preventing scoliosis and contractures. Adaptive devices available through physical and occupational therapists may improve children's independence and self-care by enabling them to feed themselves, write, or use a computer.

**Thoracic Outlet Compression Syndromes**

Thoracic outlet compression syndromes are a group of poorly defined disorders characterized by pain and paresthesias in a hand, the neck, a shoulder, or an arm. They appear to involve compression of the brachial plexus (and perhaps the subclavian vessels) as these structures traverse the thoracic outlet. Diagnostic techniques have not been established. Treatment includes physical therapy, analgesics, and, in severe cases, surgery.

Pathogenesis is often unknown but sometimes involves compression of the lower trunk of the brachial plexus (and perhaps the subclavian vessels) as these structures traverse the thoracic outlet below the scalene muscles and over the 1st rib, before they enter the axilla, but this involvement is unclear. Compression may be caused by a cervical rib, an abnormal 1st thoracic rib, abnormal insertion or position of the scalene muscles, or a malunited clavicle fracture. Thoracic outlet syndromes are more common among women and usually develop between age 35 and 55.

**Symptoms and Signs**

Pain and paresthesias usually begin in the neck or shoulder and extend to the medial aspect of the arm.
and hand and sometimes to the adjacent anterior chest wall. Many patients have mild to moderate sensory impairment in the C8 to T1 distribution on the painful side; a few have prominent vascular-autonomic changes in the hand (eg, cyanosis, swelling). In even fewer, the entire affected hand is weak.

Rare complications include Raynaud's syndrome and distal gangrene.

**Diagnosis**

- Clinical evaluation
- Sometimes electrodiagnostic tests, MRI, or both

Diagnosis is suggested by distribution of symptoms. Various maneuvers are alleged to demonstrate compression of vascular structures (eg, by extending the brachial plexus), but sensitivity and specificity are not established. Auscultating bruits at the clavicle or apex of the axilla or finding a cervical rib by x-ray can aid in diagnosis. Although angiography may detect kinking or partial obstruction of axillary arteries or veins, neither finding is incontrovertible evidence of disease. Other testing is controversial, but evaluation as for brachial plexopathy (eg, electrodiagnostic tests, MRI—see p. 1802) may be reasonable.

**Treatment**

- Physical therapy and analgesia
- In severe cases, surgery

Most patients without objective neurologic deficits respond to physical therapy, NSAIDs, and low-dose tricyclic antidepressants.

If cervical ribs or subclavian artery compression is identified, an experienced specialist should decide whether surgery is necessary. With few exceptions, surgery should be reserved for patients who have significant or progressive neurovascular deficits and who do not respond to conservative treatment.
Chapter 186. Spinal Cord Disorders

Introduction

Spinal cord disorders can cause permanent severe neurologic disability. For some patients, such disability can be avoided or minimized if evaluation and treatment are rapid. Spinal cord disorders usually result from conditions extrinsic to the cord—eg, compression due to spinal stenosis, herniated disk, tumor, abscess, or hematoma. Less commonly, disorders are intrinsic to the cord. Intrinsic insults include infarction, hemorrhage, transverse myelitis, arteriovenous malformation, HIV infection, poliovirus infection (see p. 1426), syphilis (which can cause tabes dorsalis—see p. 1478), trauma (see p. 3227), vitamin B12 deficiency (which causes subacute combined degeneration—see p. 38), decompression sickness (see p. 3287), lightning injury (which can cause keraunoparalysis—see p. 3250), radiation therapy (which can cause myelopathy), syrinx, or spinal cord tumor (see p. 1821). Spinal nerve roots outside of the spinal cord may also be damaged (see p. 1795).

Anatomy

The spinal cord extends caudally from the medulla at the foramen magnum and terminates at the upper lumbar vertebrae, where it forms the conus medullaris. In the lumbosacral region, nerve roots from lower cord segments descend within the spinal column in a nearly vertical sheaf, forming the cauda equina.

The white matter at the cord's periphery contains ascending and descending tracts of myelinated sensory and motor nerve fibers. The central H-shaped gray matter is composed of cell bodies and nonmyelinated fibers (see Fig. 186-1). The anterior (ventral) horns of the "H" contain lower motor neurons, which receive impulses from the motor cortex via the descending corticospinal tracts and, at the local level, from internuncial neurons and afferent fibers from muscle spindles. The axons of the lower motor neurons are the efferent fibers of the spinal nerves. The posterior (dorsal) horns contain sensory fibers that originate in cell bodies in the dorsal root ganglia. The gray matter also contains many internuncial neurons that carry motor, sensory, or reflex impulses from dorsal to ventral nerve roots, from one side of the cord to the other, or from one level of the cord to another. The spinothalamic tract transmits pain and temperature sensation contralaterally in the spinal cord; most other tracts transmit information ipsilaterally. The cord is divided into functional segments (levels) corresponding approximately to the attachments of the 31 pairs of spinal nerve roots.

Symptoms and Signs

Neurologic dysfunction due to spinal cord disorders occurs at the involved spinal cord segment (see Table 186-1) and at all segments below it. The exception is the central cord syndrome (see Table 186-2), which may spare segments below.

Spinal cord disorders cause various patterns of deficits depending on which nerve tracts within the cord or which spinal roots outside the cord are damaged. Disorders affecting spinal nerves, but not directly affecting the cord, cause sensory or motor abnormalities or both only in the areas supplied by the affected spinal nerves.

Spinal cord dysfunction causes paresis, loss of sensation, reflex changes, and autonomic dysfunction (eg, bowel, bladder, and erectile dysfunction; loss of sweating). Dysfunction may be partial (incomplete). Autonomic and reflex abnormalities are usually

[Table 186-1, Effects of Spinal Cord Dysfunction by Segmental Level]

[Table 186-2, Spinal Cord Syndromes]
the most objective signs of cord dysfunction; sensory abnormalities are the least objective.

Corticospinal tract lesions cause upper motor neuron dysfunction. Acute, severe lesions (eg, infarction, traumatic lesions) cause spinal shock with flaccid paresis (decreased muscle tone, hyporeflexia, and no extensor plantar responses). After days or weeks, upper motor neuron dysfunction evolves into spastic paresis (increased muscle tone, hyperreflexia, and clonus). Extensor plantar responses and autonomic dysfunction are present. Flaccid paresis that lasts more than a few weeks suggests lower motor neuron dysfunction (eg, due to Guillain-Barre syndrome).

Specific cord syndromes include transverse sensorimotor myelopathy, Brown-Sequard syndrome, central cord syndrome, anterior cord syndrome, and conus medullaris syndrome (see Table 186-2).

Cauda equina syndrome, which involves damage to nerve roots at the caudal end of the cord, is not a spinal cord syndrome. However, it mimics conus medullaris syndrome, causing distal leg paresis and sensory loss in and around the perineum and anus (saddle anesthesia), as well as bladder, bowel, and pudendal dysfunction (eg, urinary retention, urinary frequency, urinary or fecal incontinence, erectile dysfunction, loss of rectal tone, abnormal bulbocavernosus and anal wink reflexes).

Diagnosis

• MRI

Neurologic deficits at segmental levels suggest a spinal cord disorder. Similar deficits, especially if unilateral, may result from nerve root or peripheral nerve disorders, which can usually be differentiated clinically. Level and pattern of spinal cord dysfunction help determine presence and location of a spinal cord lesion but not always type of lesion.

MRI is the most accurate imaging test for spinal cord disorders; MRI shows spinal cord parenchyma, soft-tissue lesions (eg, abscesses, hematomas, tumors, abnormalities involving intervertebral disks), and bone lesions (eg, erosion, severe hypertrophic changes, collapse, fracture, subluxation, tumors). Myelography with a radiopaque dye followed by CT is used less often. It is not as accurate as MRI and is more invasive but may be more readily available. Plain x-rays may help detect bone lesions.

Acute Transverse Myelitis

Acute transverse myelitis is acute inflammation of gray and white matter in one or more adjacent spinal cord segments, usually thoracic. Causes include multiple sclerosis, infections, autoimmune or postinfectious inflammation, vasculitis, and certain drugs. Symptoms include bilateral motor, sensory, and sphincter deficits below the level of the lesion. Diagnosis is usually by MRI, CSF analysis, and blood tests. IV corticosteroids and plasma exchange may be helpful early. Otherwise, treatment is supportive measures and correction of any causes.

Acute transverse myelitis is most commonly due to multiple sclerosis but can occur with vasculitis, mycoplasmal infections, Lyme disease, syphilis, TB, or viral meningoencephalitis or in patients taking amphetamines, IV heroin, or antiparasitic or antifungal drugs. Transverse myelitis occurs with optic neuritis in a variant of multiple sclerosis called neuromyelitis optica (Devic disease—see p. 1783). The mechanism of transverse myelitis is often unknown, but some cases follow viral infection or vaccination, suggesting an autoimmune reaction. Inflammation tends to involve the spinal cord diffusely at one or more levels, affecting all spinal cord functions.

Symptoms and Signs

Pain in the neck, back, or head may occur. A bandlike tightness around the chest or abdomen, weakness, tingling, numbness of the feet and legs, and difficulty voiding develop over hours to a few days. Deficits may progress over several more days to a complete transverse sensorimotor myelopathy, causing paraplegia, loss of sensation below the lesion, urinary retention, and fecal incontinence. Occasionally, position and vibration sensation are spared, at least initially. The syndrome occasionally recurs in patients with multiple sclerosis, SLE, or antiphospholipid syndrome.
Diagnosis

- MRI and CSF analysis
- Other tests to identify treatable causes

Diagnosis is suggested by transverse sensorimotor myelopathy with segmental deficits. Guillain-Barre syndrome (see p. 1788) can be distinguished because it does not localize to a specific spinal segment. Diagnosis requires MRI and CSF analysis. MRI typically shows cord swelling and helps exclude other treatable causes of spinal cord dysfunction (eg, spinal cord compression). CSF usually contains monocytes, protein content is slightly increased, and IgG index is elevated (normal, ≤ 0.85). A new and specific antibody marker for neuromyelitis optica (NMO-IgG), which distinguishes neuromyelitis optica from multiple sclerosis, has been recently described.

Tests for treatable causes should include chest x-ray; PPD; serologic tests for mycoplasma, Lyme disease, and HIV; vitamin B₁₂ and folate levels; ESR; antinuclear antibodies; and CSF and blood Venereal Disease Research Laboratory (VDRL) tests. History may suggest a drug as a cause. Brain MRI is done; multiple sclerosis develops in 50% of patients who have multiple periventricular T2 bright lesions and in 5% who do not have them.

Prognosis

Generally, the more rapid the progression is, the worse the prognosis. Pain suggests more intense inflammation. About one third of patients recover, one third retain some weakness and urinary urgency, and one third are bedbound and incontinent. Multiple sclerosis eventually develops in about 10 to 20% of the patients in whom the cause is initially unknown.

Treatment

- Treatment of the cause
- Sometimes corticosteroids

Treatment is directed at the cause or associated disorder but is otherwise supportive. In idiopathic cases, high-dose corticosteroids are often given and sometimes followed by plasma exchange because the cause may be autoimmune. Efficacy of such a regimen is uncertain.

Arteriovenous Malformations

Arteriovenous malformations (AVMs) in or around the spinal cord can cause cord compression, ischemia, parenchymal hemorrhage, subarachnoid hemorrhage, or a combination. Symptoms may include gradually progressive, ascending, or waxing and waning segmental neurologic deficits; radicular pain; and sudden back pain with sudden segmental neurologic deficits. Diagnosis is by MRI. Treatment is with surgery or stereotactic radiosurgery and may include angiographic embolization.

AVMs are the most common spinal vascular malformations. Most are thoracolumbar, posterior, and outside the cord (extramedullary). The rest are cervical or upper thoracic and often inside the cord (intramedullary). AVMs may be small and localized or may affect up to half the cord. They may compress or even replace normal spinal cord parenchyma, or they may rupture, causing focal or generalized hemorrhage.

Symptoms and Signs

A cutaneous angioma sometimes overlies a spinal AVM. AVMs commonly compress nerve roots, causing pain that radiates down the distribution of a nerve root (radicular pain), or compress the spinal cord, causing segmental neurologic deficits that gradually progress or that wax and wane. Combined lower and
upper motor neuron deficits are common. AVMs may rupture into the spinal cord parenchyma, causing sudden, severe back pain and sudden segmental neurologic deficits. Rarely, high cervical AVMs rupture into the subarachnoid space, causing sudden and severe headache, nuchal rigidity, and impaired consciousness (see p. 1654).

Diagnosis

• Imaging

Spinal cord AVMs may be detected incidentally during imaging. AVMs are suspected clinically in patients with unexplained segmental neurologic deficits or subarachnoid hemorrhage, particularly those who have sudden, severe back pain or cutaneous midline angiomas. Diagnosis is by MRI, magnetic resonance angiography, selective arteriography, or, occasionally, myelography plus CT.

Treatment

Surgery is indicated if spinal cord function is threatened, but expertise in specialized microtechniques is required. Stereotactic radiosurgery is helpful if the AVM is small and located in a surgically inaccessible location. Angiographic embolization occludes feeder arteries and often precedes surgical removal or stereotactic radiosurgery.

Cervical Spondylosis and Spondylotic Cervical Myelopathy

Cervical spondylosis is osteoarthritis of the cervical spine causing stenosis of the canal and sometimes cervical myelopathy due to encroachment of bony osteoarthritic growths (osteophytes) on the lower cervical spinal cord, sometimes with involvement of lower cervical nerve roots (radiculomyelopathy).

Cervical spondylosis due to osteoarthritis is common. Occasionally, particularly when the spinal canal is congenitally narrow (< 10 mm), osteoarthritis leads to stenosis of the canal and bony impingement on the cord, causing compression and myelopathy (functional disturbance of the spinal cord). Hypertrophy of the ligamentum flavum can aggravate this effect. Osteophytes in the neural foramina, most commonly between C5 and C6 or C6 and C7, can cause radiculopathy (a nerve root disorder—see also p. 1795). Manifestations vary according to the neural structures involved but commonly include pain.

Symptoms and Signs

Cord compression commonly causes gradual spastic paresis, paresthesias, or both in the hands and feet and may cause hyperreflexia. Neurologic deficits may be asymmetric, nonsegmental, and aggravated by cough or Valsalva maneuvers. After trauma, people with cervical spondylosis may develop central cord syndrome. Eventually, muscle atrophy and flaccid paresis may develop in the upper extremities at the level of the lesion, with spasticity below the level of the lesion.

Nerve root compression commonly causes early radicular pain; later there may be weakness, hyporeflexia, and muscle atrophy.

Diagnosis

• MRI or CT

Cervical spondylosis is suspected when characteristic neurologic deficits occur in patients who are elderly, have osteoarthritis, or have radicular pain at the C5 or C6 levels. Diagnosis is by MRI or CT.

Treatment

• For radiculopathy only, NSAIDs and a soft cervical collar

• For cord involvement or refractory radiculopathy, cervical laminectomy
For patients with cord involvement, cervical laminectomy is usually needed; a posterior approach can relieve the compression but leaves anterior compressive osteophytes and may result in spinal instability and kyphosis. Thus, an anterior approach with spinal fusion is generally preferred. Patients with only radiculopathy may try nonsurgical treatment with NSAIDs and a soft cervical collar; if this approach is ineffective, surgical decompression may be required.

**Hereditary Spastic Paraparesis**

Hereditary spastic paraparesis is a group of rare hereditary disorders characterized by progressive, spinal, nonsegmental, spastic leg paresis, sometimes with intellectual disability, seizures, and other extraspinal deficits.

The genetic basis of hereditary spastic paraparesis varies and, for many forms, is unknown. In all forms, the descending corticospinal tracts and, to a lesser extent, the dorsal columns and spino-cerebellar tracts degenerate, sometimes with loss of anterior horn cells. Onset can be at any age, from the first year of life to old age, depending on the specific genetic form.

**Symptoms and Signs**

Symptoms and signs include spastic leg paresis, with progressive gait difficulty, hyperreflexia, clonus, and extensor plantar responses. Sensation and sphincter function are usually spared. The arms may also be affected. Deficits are not localized to a spinal cord segment. In some forms, patients also have extraspinal neurologic deficits (eg, spino-cerebellar and ocular symptoms, extrapyramidal symptoms, optic atrophy, retinal degeneration, intellectual disability, dementia, polyneuropathy).

**Diagnosis**

- Clinical evaluation

Hereditary spastic paraparesis is suggested by a family history and any signs of spastic paraparesis. Diagnosis is by exclusion of other causes and sometimes by genetic testing.

**Treatment**

- Drugs to relieve spasticity

Treatment for all forms is symptomatic. Baclofen 10 mg po bid, increased as needed up to 40 mg po bid, is given for spasticity. Alternatives include diazepam, clonazepam, dantrolene, botulinum toxin (botulinum toxin type A or botulinum toxin type B), and tizanidine.

**Spinal Cord Infarction**

(Ischemic Myelopathy)

Spinal cord infarction usually results from ischemia originating in an extravertebral artery. Symptoms include sudden and severe back pain, bilateral flaccid limb weakness, and loss of sensation, particularly pain and temperature. Diagnosis is by MRI. Treatment is generally supportive.

The primary vascular supply for the posterior third of the spinal cord is the posterior spinal arteries; for the anterior two thirds, it is the anterior spinal arteries. Each of the anterior spinal arteries has only a few feeder arteries in the upper cervical region and one large feeder (the artery of Adamkiewicz) in the lower thoracic region. The feeder arteries originate in the aorta.

Because collateral circulation for the anterior spinal artery is sparse in places, certain cord segments (eg, those around the 2nd to 4th thoracic segments) are especially vulnerable to ischemia. Injury to an extravertebral feeder artery or the aorta (eg, due to atherosclerosis, dissection, or clamping during
surgery) causes infarction more commonly than do intrinsic disorders of spinal arteries. Thrombosis is an uncommon cause, and polyarteritis nodosa is a rare cause.

**Symptoms and Signs**

Sudden pain in the back with tightness radiating circumferentially is followed by segmental bilateral flaccid weakness and sensory loss. Pain and temperature sensation are disproportionately impaired. The anterior spinal artery is typically affected, resulting in the anterior cord syndrome (see Table 186-2). Position and vibration sensation, conducted by the posterior columns, and often light touch are relatively spared. If the infarct is small and affects primarily tissue farthest away from an occluded artery (toward the center of the cord), central cord syndrome is also possible. Neurologic deficits may partially resolve after the first few days.

**Diagnosis**

- MRI

Infarction is suspected when severe back pain and characteristic deficits develop suddenly. Diagnosis is by MRI. Acute transverse myelitis, spinal cord compression, and demyelinating disorders may cause similar findings but are usually more gradual and are excluded by MRI and by CSF analysis.

**Treatment**

- Supportive care

Occasionally, the cause of infarction (eg, aortic dissection, polyarteritis nodosa) can be treated, but often the only possible treatment is supportive.

**Spinal Cord Compression**

(See also p. 3230 for treatment of spinal trauma.)

Various lesions can compress the spinal cord, causing segmental sensory, motor, reflex, and sphincter deficits. Diagnosis is by MRI. Treatment is directed at relieving compression.

Compression is caused far more commonly by lesions outside the spinal cord (extramedullary) than by lesions within it (intramedullary). Compression may be acute, subacute, or chronic.

**Acute compression** develops within minutes to hours. It is often due to trauma (eg, vertebral crush fracture with displacement of fracture fragments, disk herniation, metastatic tumor, severe bone or ligamentous injury causing hematoma, vertebral subluxation or dislocation). It is occasionally due to abscess and rarely due to spontaneous epidural hematoma. Acute compression may follow subacute and chronic compression, especially if the cause is abscess or tumor.

**Subacute compression** develops over days to weeks. It is usually caused by a metastatic extramedullary tumor, a subdural or an epidural abscess or hematoma, or a cervical or, rarely, thoracic herniated disk.

**Chronic compression** develops over months to years. It is commonly caused by bony protrusions into the cervical, thoracic, or lumbar spinal canal (eg, due to osteophytes or spondylosis, especially when the spinal canal is narrow, as occurs in spinal stenosis—see p. 384). Compression can be aggravated by a herniated disk and hypertrophy of the ligamentum flavum. Less common causes include arteriovenous malformations and slow-growing extramedullary tumors.

Atlantoaxial subluxation (see p. 385) and other craniocervical junction abnormalities (see p. 1757) may cause acute, subacute, or chronic spinal cord compression.
Lesions that compress the spinal cord may also compress nerve roots or, rarely, occlude the spinal cord's blood supply, causing infarction.

**Symptoms and Signs**

Acute or advanced spinal cord compression causes segmental deficits, paraparesis or quadriparesis, hyperreflexia, extensor plantar responses, loss of sphincter tone (with bowel and bladder dysfunction), and sensory deficits. Subacute or chronic compression may begin with local back pain, often radiating down the distribution of a nerve root (radicular pain), and sometimes hyperreflexia and loss of sensation. Sensory loss may begin in the sacral segments. Complete loss of function may follow suddenly and unpredictably, possibly resulting from secondary spinal cord infarction. Spinal percussion tenderness is prominent if the cause is metastatic carcinoma, abscess, or hematoma.

Intramedullary lesions tend to cause poorly localized burning pain rather than radicular pain and to spare sensation in sacral dermatomes. These lesions usually result in spastic paresis.

**Diagnosis**

- MRI or CT myelography

Spinal cord compression is suggested by spinal or radicular pain with reflex, motor, or sensory deficits, particularly at a segmental level. MRI is done immediately if available. If MRI is unavailable, CT myelography is done; a small amount of iohexol (a nonionic, low osmolar radiopaque dye) is introduced via a lumbar puncture and allowed to run cranially to check for complete CSF block. If a block is detected, a radiopaque dye is introduced via a cervical puncture to determine the rostral extension of the block. If traumatic bone abnormalities (eg, fracture, dislocation, subluxation) that require immediate spinal immobilization are suspected, plain spinal x-rays can be done. However, CT detects bone abnormalities better.

**Treatment**

- Relief of compression

Treatment is directed at relieving pressure on the cord. Incomplete or very recent complete loss of function may be reversible, but complete loss of function rarely is; thus, for acute compression, diagnosis and treatment must occur immediately.

If compression is due to a tumor, IV dexamethasone 100 mg is given immediately, followed by 25 mg q 6 h and immediate surgery or radiation therapy. Surgery is indicated in the following cases:

- Neurologic deficits worsen despite nonsurgical treatment.
- A biopsy is needed.
- The spine is unstable.
- Tumors recur after radiation therapy.
- An abscess or a compressive subdural or epidural hematoma is suspected.

**Spinal Epidural Abscess**

A spinal epidural abscess is an accumulation of pus in the epidural space that can mechanically compress the spinal cord.

Spinal epidural abscesses usually occur in the thoracic or lumbar regions. An underlying infection is often present; it may be remote (eg, endocarditis, furuncle, dental abscess) or contiguous (eg, vertebral osteomyelitis, pressure ulcer, retroperitoneal abscess). In about one third of cases, the cause cannot be
The most common causative organism is *Staphylococcus aureus*, followed by *Escherichia coli* and mixed anaerobes. Occasionally, the cause is a tuberculous abscess of the thoracic spine (Pott's disease). Rarely, a similar abscess occurs in the subdural space.

**Symptoms and Signs**

Symptoms begin with local or radicular back pain and percussion tenderness, which become severe. Fever is common. Spinal cord compression may develop; compression of lumbar spinal roots may cause cauda equina syndrome, with neurologic deficits resembling those of conus medullaris syndrome (eg, leg paresis, saddle anesthesia, bladder and bowel dysfunction). Deficits progress over hours to days.

**Diagnosis**

- **MRI**

The diagnosis is suggested by characteristic neurologic deficits and by back pain worsened by recumbency, particularly in patients who have a fever or have had a recent infection. Diagnosis is by MRI; myelography followed by CT can be used if MRI is not available. Samples from blood and infectious areas are cultured. Lumbar puncture is contraindicated because it may trigger cord herniation if the abscess causes complete obstruction of CSF. Plain x-rays are not routinely indicated but may show osteomyelitis in about one third of patients.

**Treatment**

- **Antibiotics**

- If abscess causes neurologic compromise, immediate drainage

Antibiotics with or without parenteral needle aspiration may be sufficient; however, abscesses causing neurologic compromise (eg, paresis, bowel or bladder dysfunction) are surgically drained immediately. Pus is gramstained and cultured. Pending culture results, antibiotics to cover staphylococcus and anaerobes are given as for brain abscess (see p. 1726). If the abscess developed after a neurosurgical procedure, an aminoglycoside is added to cover gram-negative bacteria.

**Spinal Subdural or Epidural Hematoma**

A spinal subdural or epidural hematoma is an accumulation of blood in the subdural or epidural space that can mechanically compress the spinal cord.

Spinal subdural or epidural hematoma (usually thoracic or lumbar) is rare but may result from back trauma, anticoagulant or thrombolytic therapy, or, in patients with bleeding diatheses, lumbar puncture.

**Symptoms and Signs**

Symptoms begin with local or radicular back pain and percussion tenderness; they are often severe. Spinal cord compression may develop; compression of lumbar spinal roots may cause cauda equina syndrome and lower extremity paresis. Deficits progress over minutes to hours.

**Diagnosis**

- **MRI**

Hematoma is suspected in patients with acute, nontraumatic spinal cord compression or sudden, unexplained lower extremity paresis, particularly if a possible cause (eg, trauma, bleeding diathesis) is present. Diagnosis is by MRI or, if MRI is not immediately available, by CT myelography.

**Treatment**
Drainage

Treatment is immediate surgical drainage. Patients taking coumarin anticoagulants are given phytomenadione (vitamin K₁) 2.5 to 10 mg sc and fresh frozen plasma as needed to normalize INR. Patients with thrombocytopenia are given platelets (see p. 1039).

Syrinx

A syrinx is a fluid-filled cavity within the spinal cord (syringomyelia) or brain stem (syringobulbia). Predisposing factors include craniocervical junction abnormalities, spinal cord trauma, and spinal cord tumors. Symptoms include flaccid weakness of the hands and arms and deficits in pain and temperature sensation in a capelike distribution over the back and neck; light touch and position and vibration sensation are not affected. Diagnosis is by MRI. Treatment includes correction of the cause and surgical procedures to drain the syrinx or otherwise open CSF flow.

Syrinxes usually result from lesions that partially obstruct CSF flow. At least one half of syrinxes occur in patients with congenital abnormalities of the craniocervical junction (eg, herniation of cerebellar tissue into the spinal canal, called Chiari malformation), brain (eg, encephalocele—see p. 2994), or spinal cord (eg, myelomeningocele—see p. 2995). For unknown reasons, these congenital abnormalities often expand during the teen or young adult years. A syrinx can also develop in patients who have a spinal cord tumor, scarring due to previous spinal trauma, or no known predisposing factors. About 30% of people with a spinal cord tumor eventually develop a syrinx.

Syringomyelia is a paramedian, usually irregular, longitudinal cavity. It commonly begins in the cervical area but may extend downward along the entire length of the spinal cord. Syringobulbia, which is rare, usually occurs as a slitlike gap within the lower brain stem and may disrupt or compress the lower cranial nerves or ascending sensory or descending motor pathways.

Symptoms and Signs

Symptoms usually begin insidiously between adolescence and age 45. Syringomyelia develops in the center of the spinal cord, causing a central cord syndrome (see Table 186-2). Pain and temperature sensory deficits occur early but may not be recognized for years. The first abnormality recognized may be a painless burn or cut. Syringomyelia typically causes weakness, atrophy, and often fasciculations and hyporeflexia of the hands and arms; a deficit in pain and temperature sensation in a capelike distribution over the shoulders, arms, and back is characteristic. Light touch and position and vibration sensation are not affected. Later, spastic leg weakness develops. Deficits may be asymmetric.

Syringobulbia may cause vertigo, nystagmus, unilateral or bilateral loss of facial sensation, lingual atrophy and weakness, dysarthria, dysphagia, hoarseness, and sometimes peripheral sensory or motor deficits due to medullary compression.

Diagnosis

• MRI of spinal cord and brain with gadolinium

A syrinx is suggested by an unexplained central cord syndrome or other characteristic neurologic deficits, particularly pain and temperature sensory deficits in a capelike distribution. MRI of the entire spinal cord and brain is done. Gadolinium enhancement is useful for detecting any associated tumor.

Treatment

• Sometimes surgical decompression

Underlying problems (eg, craniocervical junction abnormalities, postoperative scarring, spinal tumors) are corrected when possible. Surgical decompression of the foramen magnum and upper cervical cord is the only useful treatment, but surgery usually cannot reverse severe neurologic deterioration.
Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy

Tropical spastic paraparesis/HTLV-1-associated myelopathy is a slowly progressive viral immunemediated disorder of the spinal cord caused by the human T-lymphotropic virus 1 (HTLV-1). It causes spastic weakness of both legs. Diagnosis is by serologic and PCR tests of serum and CSF. Treatment includes supportive care and possibly immunosuppressive therapies.

The HTLV-1 retrovirus is transmitted via sexual contact, IV drug use, exposure to infected blood, or from mother to child, via breastfeeding. It is most common among prostitutes, IV drug users, hemodialysis patients, and people from endemic areas such as equatorial regions, southern Japan, and parts of South America. HTLV-2 may cause a similar disorder.

The virus resides in T cells in blood and CSF. CD4+ memory T cells, CD8+ cytotoxic T cells, and macrophages infiltrate the perivascular areas and parenchyma of the spinal cord; astrocytosis occurs. For several years after onset of neurologic symptoms, inflammation of spinal gray and white matter progresses, causing preferential degeneration of the lateral and posterior columns. Myelin and axons in the anterior columns are also lost.

Symptoms and Signs

Spastic weakness develops gradually in both legs, with extensor plantar responses and bilateral symmetric loss of position and vibratory sensation in the feet. Achilles tendon reflexes are often absent. Urinary incontinence and urgency are common. Symptoms usually progress over several years.

Diagnosis

• Serologic and PCR tests of serum and CSF

The disorder is suggested by typical neurologic deficits that are otherwise unexplained, particularly in patients with risk factors. Serum and CSF serologic tests, PCR tests, and spinal cord MRI are indicated. If CSF-to-serum ratio of HTLV-1 antibodies is > 1 or if PCR detects HTLV-1 antigen in CSF, the diagnosis is very likely. Protein and Ig levels in CSF may also be elevated, often with oligoclonal bands; lymphocytic pleocytosis occurs in up to 50% of patients. Spinal cord lesions often appear hyperintense on T2-weighted MRI.

Treatment

• Immunomodulatory or immunosuppressive therapies

No treatment has proved effective, but interferon alfa, IV immune globulin, and oral methylprednisolone may have some benefit. Treatment of spasticity is symptomatic (eg, with baclofen or tizanidine).
Chapter 187. Intracranial and Spinal Tumors

Introduction

Intracranial tumors may involve the brain or other structures (eg, cranial nerves, meninges). The tumors usually develop during early or middle adulthood but may develop at any age; they are becoming more common among the elderly. Brain tumors are found in about 2% of routine autopsies.

Some tumors are benign, but because the cranial vault allows no room for expansion, even these tumors can be serious.

Classification

Some primary intracranial tumors (eg, gliomas, medulloblastomas, ependymomas) originate in brain parenchyma; others (eg, meningiomas, acoustic neuromas, other schwannomas) originate in extraneural structures. Extracranial tumors may metastasize to any intracranial structure or to the skull. In the brain, metastases are about 10 times more common than primary tumors.

Type of tumor varies somewhat by site (see Table 187-1) and patient age (see Table 187-2).

Pathophysiology

Neurologic dysfunction may result from the following:

• Invasion and destruction of brain tissue by the tumor
• Direct compression of adjacent tissue by the tumor
• Increased intracranial pressure (because the tumor occupies space within the skull)
• Bleeding within or outside the tumor
• Cerebral edema
• Obstruction of dural venous sinuses (especially by bone or extradural metastatic tumors)
• Obstruction of CSF drainage (occurring early with 3rd-ventricle or posterior fossa tumors)
• Obstruction of CSF absorption (eg, when leukemia or carcinoma involves the meninges)
• Obstruction of arterial flow
• Rarely, paraneoplastic syndromes (see p. 1054)

A malignant tumor can develop new internal blood vessels, which can bleed or become occluded, resulting in necrosis and neurologic dysfunction that mimics stroke.

Benign tumors grow slowly. They may become quite large before causing symptoms, partly because often there is no cerebral edema. Malignant tumors grow rapidly but rarely spread beyond the CNS. Death results from local tumor growth and thus can result from benign as well as malignant tumors. Therefore, distinguishing between benign and malignant

[Table 187-1, Common Localizing Manifestations of Brain Tumors]

is prognostically less important for brain tumors than for other tumors.
Symptoms and Signs

Many symptoms result from increased intracranial pressure:

• Headache

• Deterioration in mental status

• Focal brain dysfunction

Headache is the most common symptom. Headache may be most intense when patients awake from deep non-REM sleep (usually several hours after falling asleep) because hypoventilation, which increases cerebral blood flow and thus intracranial pressure, is usually maximal during non-REM sleep. Headache is also progressive and may be worsened by recumbency or the Valsalva maneuver. When intracranial pressure is very high, the headache may be accompanied by vomiting, sometimes with little nausea preceding it. Papilledema develops in about 25% of patients with a brain tumor but may be absent even when intracranial pressure is increased. In infants and very young children, increased intracranial pressure may enlarge the head. If intracranial pressure increases sufficiently, brain herniation occurs (see Fig. 174-1 on p. 1657).

Deterioration in mental status is the 2nd most common symptom. Manifestations include drowsiness, lethargy, personality changes, disordered conduct, and impaired cognition, particularly with malignant brain tumors. Generalized seizures may occur, more often with primary than metastatic brain tumors. Impaired consciousness (see p. 1656) can result from herniation, brain stem dysfunction, or diffuse bilateral cortical dysfunction. Airway reflexes may be impaired.

Some symptoms result from focal brain dysfunction. Focal neurologic deficits, endocrine dysfunction, or focal seizures (sometimes with secondary generalization) may develop depending on the tumor's location (see Table 187-1). Focal deficits often suggest the tumor's location. However, sometimes focal deficits do not correspond to the tumor's location. Such deficits, called false localizing signs, include the following:

• Unilateral or bilateral lateral rectus palsy (with paresis of eye abduction) due to increased intracranial pressure compressing the 6th cranial nerve

• Ipsilateral hemiplegia due to compression of the contralateral cerebral peduncle against the tentorium (Kernohan's notch)

• Ipsilateral visual field defect due to ischemia in the contralateral occipital lobe

Some tumors cause meningeal inflammation, resulting in subacute or chronic meningitis (see p. 1734).

Diagnosis

• T1-weighted MRI with gadolinium or CT with contrast

Early-stage brain tumors are often misdiagnosed. A brain tumor should be considered in patients with any of the following:

• Progressive focal or global deficits of brain function

• New seizures

• Persistent, unexplained, recent-onset headaches, particularly if worsened by sleep
• Evidence of increased intracranial pressure (eg, papilledema, unexplained vomiting)

• Pituitary or hypothalamic endocrinopathy

Similar findings can result from other intracranial masses (eg, abscess, aneurysm, arteriovenous malformation, intracerebral hemorrhage, subdural hematoma, granuloma, parasitic cysts such as neurocysticercosis) or ischemic stroke.

A complete neurologic examination, neuroimaging, and chest x-rays (for a source of metastases) should be done. T1-weighted MRI with gadolinium is the study of choice. CT with contrast agent is an alternative. MRI usually detects low-grade astrocytomas and oligodendrogliomas earlier than CT and shows brain structures near bone (eg, the posterior fossa) more clearly. If whole-brain imaging does not show sufficient detail in the target area (eg, sella turcica, cerebellopontine angle, optic nerve), closely spaced images or other special views of the area are obtained. If neuroimaging is normal but increased intracranial pressure is suspected, idiopathic intracranial hypertension (see p. 1720) should be considered and lumbar puncture done.

Radiographic clues to the type of tumor, mainly location (see Table 187-1) and pattern of enhancement on MRI, may be inconclusive; brain biopsy, sometimes excisional biopsy, may be required. Specialized tests (eg, molecular and genetic tumor markers in blood and CSF) can help in some cases; eg, in patients with AIDS, Epstein-Barr virus titers in CSF typically increase as CNS lymphoma develops.

**Treatment**

• Airway protection

• Dexamethasone for increased intracranial pressure

• Mannitol for herniation

• Definitive therapy with excision, radiation therapy, chemotherapy, or a combination

Patients in a coma or with impaired airway reflexes require endotracheal intubation. Brain herniation due to tumors is treated with mannitol 25 to 100 g infused IV, a corticosteroid (eg, dexamethasone 16 mg IV, followed by 4 mg po or IV q 6 h), and endotracheal intubation. Mass lesions should be surgically decompressed as soon as possible.

Increased intracranial pressure due to tumors but without herniation is treated with corticosteroids (eg, dexamethasone as for herniation above or prednisone 30 to 40 mg po bid).

Treatment of the brain tumor depends on pathology and location (for acoustic neuroma, see p. 441). Surgical excision should be used for diagnosis (excisional biopsy) and symptom relief. It may cure benign tumors. For tumors infiltrating the brain parenchyma, treatment is multimodal. Radiation therapy is required, and chemotherapy appears to benefit some patients.

Treatment of metastatic tumors includes radiation therapy and sometimes stereotactic radiosurgery. For patients with a solitary metastasis, surgical excision of the tumor before radiation therapy improves outcome.

**End-of-life issues:** If brain tumors are expected to soon be fatal, end-of-life issues should be considered (see p. 3480).

**Radiation Therapy and Neurotoxicity**

Radiation therapy may be directed diffusely to the whole head for diffuse or multicentric tumors or locally for well-demarcated tumors. Localized brain radiation therapy may be conformal, targeting the tumor with the aim of sparing normal brain tissue, or stereotactic, involving brachytherapy, a gamma knife, or a linear
accelerator. In brachytherapy, radioactive stable iodine (\(^{125}\)I) or iridium-192 (\(^{192}\)Ir) is implanted in or near the tumor. Gliomas are treated with conformal radiation therapy; a gamma knife or linear accelerator is useful for metastases. Giving radiation daily tends to maximize efficacy and minimize neurotoxicity damage to normal CNS tissue (see p. 3255).

Degree of neurotoxicity depends on

- Cumulative radiation dose
- Individual dose size
- Duration of therapy
- Volume of tissue irradiated
- Individual susceptibility

Because susceptibility varies, prediction of radiation neurotoxicity is imprecise. Symptoms can develop in the first few days (acute) or months of treatment (early-delayed) or several months to years after treatment (late-delayed). Rarely, radiation causes gliomas, meningiomas, or peripheral nerve sheath tumors years after therapy.

**Acute radiation neurotoxicity**: Typically, acute neurotoxicity involves headache, nausea, vomiting, somnolence, and sometimes worsening focal neurologic signs in children and adults. It is particularly likely if intracranial pressure is high. Using corticosteroids to lower intracranial pressure can prevent or treat acute toxicity. Acute toxicity lessens with subsequent treatments.

**Early-delayed neurotoxicity**: In children or adults, early-delayed neurotoxicity can cause encephalopathy, which must be distinguished by MRI or CT from worsening or recurrent brain tumor. It occurs in children who have received prophylactic whole-brain radiation therapy for leukemia; they develop somnolence, which lessens spontaneously over several days to weeks, possibly more rapidly if corticosteroids are used.

After radiation therapy to the neck or upper thorax, early-delayed neurotoxicity can result in a myelopathy, characterized by Lhermitte's sign (an electric shock-like sensation radiating down the back and into the legs when the neck is flexed). The myelopathy resolves spontaneously.

**Late-delayed neurotoxicity**: After diffuse brain radiation therapy, many children and adults develop late-delayed neurotoxicity if they survive long enough. The most common cause in children is diffuse therapy given to prevent leukemia or to treat medulloblastoma. After diffuse therapy, the main symptom is progressive dementia; adults also develop an unsteady gait. MRI or CT shows cerebral atrophy.

After localized therapy, neurotoxicity more often involves focal neurologic deficits. MRI or CT shows a mass that may be enhanced by contrast agent and that may be difficult to distinguish from recurrence of the primary tumor. Excisional biopsy of the mass is diagnostic and often ameliorates symptoms.

Late-delayed myelopathy can develop after radiation therapy for extraspinal tumors (eg, due to Hodgkin lymphoma). It is characterized by progressive paresis and sensory loss, often as a Brown-Sequard syndrome (ipsilateral paresis and proprioceptive sensory loss, with contralateral loss of pain and temperature sensation). Most patients eventually become paraplegic.

**Gliomas**

Gliomas are primary tumors that originate in brain parenchyma. Symptoms and diagnosis are similar to those of other brain tumors. Treatment involves surgical excision, radiation therapy, and, for some tumors, chemotherapy. Excision rarely cures.
Gliomas include astrocytomas, oligodendrogliomas, medulloblastomas, and ependymomas. Many gliomas infiltrate brain tissue diffusely and irregularly.

**Astrocytomas** are the most common gliomas. They are classified, in ascending order of malignancy, as:

- Grade 1 or 2: Low-grade astrocytomas
- Grade 3: Anaplastic astrocytomas
- Grade 4: Glioblastomas, including glioblastoma multiforme, the most malignant

Low-grade or anaplastic astrocytomas tend to develop in younger patients and can evolve into glioblastomas (secondary glioblastomas). Glioblastomas contain chromosomally heterogeneous cells. They can develop de novo (primary glioblastomas), usually in middle-aged or elderly people. Primary and secondary glioblastomas have distinct genetic characteristics, which can change as the tumors evolve. Some astrocytomas contain oligodendroglioma cells; patients with these tumors (called oligoastrocytomas) have a better prognosis than those with pure astrocytomas.

**Oligodendrogliomas** are among the most benign gliomas. They affect mainly the cerebral cortex, particularly the frontal lobes. Some oligodendrogliomas are characterized by deletion of the p arm of chromosome 1 (1p deletion), deletion of the q arm of chromosome 19 (19q deletion), or both. These deletions predict longer survival and better response to radiation therapy and chemotherapy. Anaplastic oligodendrogliomas are a more malignant form of oligodendrogliomas and are managed accordingly.

**Medulloblastomas** and **ependymomas** usually develop near the 4th ventricle. Medulloblastomas develop mainly in children and young adults. Ependymomas, which are uncommon, develop mainly in children. Both types of tumors predispose to obstructive hydrocephalus.

Symptoms and signs vary by location (see Table 187-1). Diagnosis is the same as that of other brain tumors.

**Treatment**

- Surgical excision
- Radiation therapy
- Chemotherapy for some types

**Anaplastic astrocytomas and glioblastomas**: Treatment involves surgery, radiation therapy, and chemotherapy to reduce tumor mass. Excising as much tumor as possible is safe, prolongs survival, and improves neurologic function.

After surgery, patients receive a full tumor dose of radiation therapy (60 Gy over 6 wk); ideally, conformal radiation therapy, which targets the tumor and spares normal brain tissue, is used.

For glioblastomas, chemotherapy with temozolomide is now routinely given with radiation therapy. The dose is 75/mg/m²/day (including weekend days when radiation is skipped) for 42 days, then 150 mg/m² po once/day for 5 days/mo during the next month, followed by 200 mg/m² po once/day for 5 days/mo in subsequent months for a total of 6 to 12 mo. During treatment with temozolomide, trimethoprim/sulfamethoxazole 800 mg/160 mg is given 3 times/wk to prevent *Pneumocystis jirovecii* pneumonia.

Patients receiving chemotherapy require a CBC at varying intervals. Implantation of chemotherapy wafers during surgical resection may be appropriate for some patients.

Investigational therapies (eg, stereotactic radiosurgery, new chemotherapeutic drugs, gene or immune
therapy, radiation therapy plus temozolomide) should also be considered.

After conventional multimodal treatment, the survival rate for patients with anaplastic astrocytomas or glioblastomas is about 50% at 1 yr, 25% at 2 yr, and 10 to 15% at 5 yr. Prognosis is better in the following cases:

• Patients are < 45 yr
• Histology is anaplastic astrocytoma (rather than glioblastoma multiforme)
• Initial excision improves neurologic function and leaves minimal or no residual tumor

Low-grade astrocytomas: These tumors are excised if possible, followed by radiation therapy. When radiation therapy should begin is controversial. Early treatment may maximize efficacy but may cause brain damage earlier.

With treatment, 5-yr survival rate is about 40 to 50%.

Oligodendrogliomas: Treatment involves excision and radiation therapy, similar to low-grade astrocytomas. Chemotherapy is sometimes also used.

With treatment, 5-yr survival rate is about 50 to 60%.

Medulloblastomas: Treatment involves whole-brain radiation therapy using about 35 Gy, a posterior fossa boost using 15 Gy, and spinal cord radiation therapy using about 35 Gy. Chemotherapy may be given as adjunctive therapy and for recurrences. Several drugs are effective for certain patients; these drugs include nitrosoureas, procarbazine, vincristine alone or in combination, intrathecal methotrexate, combination chemotherapy (eg, mechlorethamine, vincristine [Oncovin], procarbazine, plus prednisone [MOPP]), cisplatin, and carboplatin. However, no regimen is consistently effective.

With treatment, survival rates are at least 50% at 5 yr and about 40% at 10 yr.

Ependymomas: Usually, surgery to excise the tumor and open CSF pathways is done, followed by radiation therapy. For histologically benign ependymomas, radiation therapy is directed at the tumor; for more malignant tumors with residual tumor after surgery, whole-brain radiation therapy is used. For tumors with evidence of dissemination, radiation therapy is directed at the whole brain and spinal cord.

How much of the tumor can be excised may predict survival best. With treatment, overall 5-yr survival rate is about 50%; however, for patients with no residual tumor, the 5-yr survival rate is > 70%.

Meningiomas

Meningiomas are benign tumors of the meninges that can compress adjacent brain tissue. Symptoms depend on the tumor's location. Diagnosis is by MRI with contrast agent. Treatment may include excision, stereotactic radiosurgery, and sometimes radiation therapy.

Meningiomas, particularly those < 2 cm in diameter, are among the most common intracranial tumors. Meningiomas are the only brain tumor more common among women. These tumors tend to occur between ages 40 and 60 but can occur during childhood. These benign tumors can develop wherever there is dura, most commonly over the convexities near the venous sinuses, along the base of the skull, in the posterior fossa, and rarely within ventricles. Multiple meningiomas may develop. Meningiomas compress but do not invade brain parenchyma. They can invade and distort adjacent bone. There are many histologic types; all follow a similar clinical course, and some become malignant.

Symptoms and Signs

Symptoms depend on which part of the brain is compressed and thus on the tumor's location (see Table 187-3). Midline tumors in the elderly can cause dementia with few other focal neurologic findings.
Diagnosis

• MRI

Diagnosis is similar to that of other brain tumors, usually by MRI with a paramagnetic contrast agent. Bone abnormalities (eg, brain atrophy, hyperostosis around the cerebral convexities, changes in the tuberculum sellae) may be seen incidentally on CT or plain x-rays.

Treatment

• For symptomatic or enlarging meningiomas, excision or radiation therapy

For asymptomatic small meningiomas, particularly in older adults, monitoring with serial neuroimaging is sufficient.

Symptomatic or enlarging meningiomas should be excised if possible. If they are large, encroach on blood vessels (usually surrounding Table 187-3, Symptoms of Meningiomas by Site) veins), or are close to critical brain areas (eg, brain stem), surgery may cause more damage than the tumor and is thus deferred.

Stereotactic radiosurgery is used for surgically inaccessible meningiomas and electively for other meningiomas. It is also used when tumor tissue remains after surgical excision or when patients are elderly.

If stereotactic radiosurgery is impossible or if a meningioma recurs, radiation therapy may be useful.

Pineal Region Tumors

Most pineal region tumors are germ cell tumors.

Common primary pineal region tumors include germ cell tumors: germinomas (most common), choriocarcinomas, yolk-sac tumors, and teratomas. Less common primary pineal tumors include pineocytomas and the rare malignant pineoblastomas.

Pineal region tumors tend to occur during childhood but can occur at any age.

These tumors may increase intracranial pressure by compressing the aqueduct of Sylvius. They may also cause paresis of upward gaze, ptosis, and loss of pupillary light and accommodation reflexes by compressing the pretectum rostral to the superior colliculi (Parinaud's syndrome). These tumors may cause precocious puberty, especially in boys, probably because the hypothalamus is compressed.

CSF β-human chorionic gonadotropin or α-fetoprotein may be elevated, depending on the tumor type. Elevated levels suggest the diagnosis; levels may be measured to monitor response to treatment.

Prognosis and treatment depend on tumor histology. Radiation therapy, chemotherapy, radiosurgery, and surgery are used alone or in combination. Germinomas are very sensitive to radiation therapy and are often cured.

Pituitary Tumors

Most pituitary tumors are adenomas. Symptoms include headache and endocrinopathies; endocrinopathies result when the tumor produces hormones or destroys hormone-producing tissue. Diagnosis is by MRI. Treatment includes correction of any endocrinopathy and surgery, radiation therapy, or dopaminergic agonists.
Most tumors of the pituitary and suprasellar region are pituitary adenomas. Rarely, pituitary tumors are carcinomas. Meningiomas, craniopharyngiomas, metastases, and dermoid cysts may also develop in the region of the sella turcica.

Adenomas may be secretory or nonsecretory. Secretory adenomas produce pituitary hormones; many secretory adenomas are < 10 mm in size (microadenomas). Secretory adenomas can be classified by histologic staining characteristics (eg, acidophilic, basophilic, chromophobe [nonstaining]). The hormone produced often correlates with these characteristics; eg, acidophilic adenomas overproduce growth hormone, and basophilic adenomas overproduce ACTH. The hormone most commonly overproduced is prolactin.

Any tumor that grows out of the pituitary can compress optic nerve tracts, including the chiasm. Tumors may also compress or destroy pituitary or hypothalamic tissue, impairing hormone production or secretion.

**Symptoms and Signs**

Headache may result from an enlarging pituitary adenoma, even when intracranial pressure is not increased. Visual manifestations such as bitemporal hemianopia, unilateral optic atrophy, and contralateral hemianopia may develop if a tumor compresses optic nerve tracts (see Fig. 69-1 on p. 620).

Many patients present with an endocrinopathy due to hormone deficiency or excess:

- Diabetes insipidus if less vasopressin is released because the hypothalamus is compressed
- Amenorrhea and galactorrhea in women and, less commonly, erectile dysfunction and gynecomastia in men if prolactin is overproduced
- Gigantism before puberty or acromegaly after puberty if growth hormone is overproduced
- Cushing's syndrome if ACTH is overproduced

Rarely, hemorrhage into a pituitary tumor causes pituitary apoplexy, with sudden headache, ophthalmoplegia, and visual loss.

**Diagnosis**

- MRI with 1-mm slices

Pituitary tumors are suspected in patients with unexplained headaches, characteristic visual abnormalities, or endocrinopathies. Neuroimaging with 1-mm thick slices is done. MRI is usually much more sensitive than CT, particularly for microadenomas.

**Treatment**

Endocrinopathies are treated.

Pituitary tumors that produce ACTH, growth hormone, or thyroid-stimulating hormone are surgically excised, usually using a transsphenoidal approach. Sometimes, particularly for surgically inaccessible or multifocal tumors, radiation therapy is required.

Adenomas that produce prolactin are treated with dopaminergic agonists (eg, bromocriptine, pergolide, cabergoline), which lower blood levels and often shrink the tumor. Surgery and radiation therapy are usually unnecessary.

**Primary Brain Lymphomas**
Primary brain lymphomas originate in neural tissue and are usually B-cell tumors. Diagnosis requires neuroimaging and sometimes CSF analysis (including Epstein-Barr titers) or brain biopsy. Treatment includes corticosteroids, chemotherapy, and radiation therapy.

Incidence of primary brain lymphomas is increasing, particularly among immunocompromised patients and the elderly. Lymphomas tend to infiltrate the brain diffusely, often as multicentric masses adjacent to the ventricles, but may occur as solitary brain masses. Lymphomas may also occur in the meninges, uvea, or vitreous humor. Most are B-cell tumors, often immunoblastic. The Epstein-Barr virus may contribute to development of lymphomas in immunocompromised patients. Most patients do not develop subsequent systemic lymphoma.

**Diagnosis**

- MRI
- Sometimes CSF analysis or biopsy

MRI can suggest the diagnosis. MRI may be unable to distinguish cerebral toxoplasmosis, which is common among patients with AIDS, from lymphoma.

If there are meningeal signs, CSF is examined; it may contain lymphoma cells. In immunocompromised patients, Epstein-Barr virus DNA may be detected in CSF. If CSF does not contain lymphoma cells or Epstein-Barr virus DNA, guided-needle or open biopsy is required. Because lymphoma is initially highly sensitive to corticosteroids, giving these drugs just before biopsy may cause the lesion to disappear, resulting in a false-negative biopsy.

**Treatment**

- Corticosteroids
- Chemotherapy
- Radiation therapy

Most primary brain lymphomas are difficult to cure because they infiltrate the brain diffusely. Usually, corticosteroids result in rapid improvement initially. Many chemotherapy regimens, particularly those containing methotrexate (delivered as high-dose IV infusions), are effective; with methotrexate, median survival may approach 4 yr. Methotrexate can also be delivered intrathecally, usually via an sc intraventricular device (Ommaya reservoir). The drug is sometimes infused into the carotid artery after general anesthesia is induced and 25% mannitol is given IV to open the bloodbrain barrier.

Chemotherapy regimens may be followed by radiation therapy, usually after 12 to 16 wk but sometimes delayed until the tumor recurs. The delay helps reduce radiation toxicity.

**Spinal Cord Tumors**

Spinal cord tumors may develop within the spinal cord parenchyma, directly destroying tissue, or outside the cord parenchyma, often compressing the cord or nerve roots. Symptoms include progressive back pain and neurologic deficits referable to the spinal cord or spinal nerve roots. Diagnosis is by MRI. Treatment may include corticosteroids, surgical excision, and radiation therapy.

Spinal cord tumors may be intramedullary (within the cord parenchyma) or extramedullary (outside the parenchyma).

**Intramedullary tumors**: The most common are gliomas (eg, ependymomas, low-grade astrocytomas). Intramedullary tumors infiltrate and destroy cord parenchyma; they may extend over multiple spinal cord segments or result in a syrinx (see p. 1812).
Extramedullary tumors: These tumors may be intradural or extradural. Most intradural tumors are benign, usually meningiomas and neurofibromas, which are the most common primary spinal tumors. Most extradural tumors are metastatic, usually from carcinomas of the lungs, breasts, prostate, kidneys, or thyroid or from lymphoma (eg, Hodgkin lymphoma, lymphosarcoma, reticulum cell sarcoma).

Intradural and extradural tumors cause neurologic damage by compressing the spinal cord or nerve roots. Most extradural tumors invade and destroy bone before compressing the cord.

Symptoms and Signs

Pain is an early symptom, especially for extradural tumors. It is progressive, unrelated to activity, and worsened by recumbency. Pain may occur in the back, radiate along the sensory distribution of a particular dermatome (radicular pain), or both. Usually, neurologic deficits referable to the spinal cord eventually develop. Common examples are spastic weakness, incontinence, and dysfunction of some or all of the sensory tracts at a particular segment of the spinal cord and below. Deficits are usually bilateral.

Many patients with extramedullary tumors present with pain, but some present with sensory deficits of the distal lower extremities, segmental neurologic deficits, symptoms of spinal cord compression, or a combination. Symptoms of spinal cord compression can worsen rapidly and result in paraplegia and loss of bowel and bladder control. Symptoms of nerve root compression are also common; they include pain and paresthesias followed by sensory loss, muscular weakness, and, if compression is chronic, muscle wasting, which occurs along the distribution of the affected roots.

Diagnosis

• MRI

Patients with segmental neurologic deficits or suspected spinal cord compression require emergency diagnosis and treatment.

The following suggest spinal tumors:

• Progressive, unexplained, or nocturnal back or radicular pain

• Segmental neurologic deficits

• Unexplained neurologic deficits referable to the spinal cord or nerve roots

• Unexplained back pain in patients with primary tumors of the lungs, breasts, prostate, kidneys, or thyroid or with lymphoma

Diagnosis is by MRI of the affected area of the spinal cord. CT with myelography is an alternative but is less accurate.

If MRI does not show a spinal cord tumor, clinicians consider other spinal masses (eg, abscesses, arteriovenous malformations—see p. 1808) and paravertebral tumors. Spinal x-rays, taken for other reasons, may show bone destruction, widening of the vertebral pedicles, or distortion of paraspinal tissues, especially if the tumor is metastatic.

Treatment

• Corticosteroids

• Excision, radiation therapy, or both

For patients with neurologic deficits, corticosteroids (eg, dexamethasone 50 mg IV, then 10 mg po qid) are begun immediately to reduce spinal cord edema and preserve function. Tumors compressing the spinal
cord are treated as soon as possible.

Some well-localized primary spinal cord tumors can be excised surgically. Deficits resolve in about half of these patients. If tumors cannot be surgically excised, radiation therapy is used, with or without surgical decompression. Compressive metastatic extradural tumors are usually surgically excised from the vertebral body, then treated with radiation therapy. Noncompressive metastatic extradural tumors may be treated with radiation therapy alone but may require excision if radiation therapy is ineffective.
Chapter 188. Approach to the Patient With Pulmonary Symptoms

Introduction

Key components in the evaluation of patients with pulmonary symptoms are the history, physical examination, and, in most cases, a chest x-ray. These components establish the need for subsequent testing, which may include pulmonary function testing and ABG analysis (see p. 1851), CT or other imaging test (see p. 1860), and bronchoscopy (see p. 1862).

History

The history can often establish whether symptoms of dyspnea, chest pain, wheezing, stridor, hemoptysis, and cough are likely to be pulmonary in origin. When more than one symptom occurs concurrently, the history should focus on which symptom is primary and whether constitutional symptoms, such as fever, weight loss, and night sweats, are also present. Other important information includes occupational and environmental exposures; family history, travel history, and contact history; previous illnesses and use of prescription, OTC, or illicit drugs; and previous test results (eg, tuberculin skin test, chest x-rays).

Physical Examination

Physical examination starts with assessment of general appearance. Discomfort and anxiety, body habitus, and the effect of talking or movement on symptoms (eg, inability to speak full sentences without pausing to breathe) all can be assessed while greeting the patient and taking a history and may provide useful information relevant to pulmonary status. Next, inspection, auscultation, and chest percussion and palpation are done.

Inspection: Inspection should focus on

- Signs of respiratory difficulty and hypoxemia (eg, restlessness, tachypnea, cyanosis, accessory muscle use)
- Signs of possible chronic pulmonary disease (eg, clubbing, pedal edema)
- Chest wall deformities
- Abnormal breathing patterns (eg, Cheyne-Stokes respiration, Kussmaul's respirations)
- Jugular venous distention

Signs of hypoxemia include cyanosis (bluish discoloration of the lips, face, or nail beds), which signifies low arterial O$_2$ saturation (< 85%); the absence of cyanosis does not exclude the presence of hypoxemia.

Signs of respiratory difficulty include tachypnea and use of accessory respiratory muscles (sternocleidomastoids, intercostals, scalene) to breathe. Patients with COPD sometimes brace their arms against their legs or the examination table while seated (ie, tripod position) in a subconscious effort to provide more leverage to accessory muscles and thereby enhance respiration. Intercostal retractions (inward movement of the rib inter-spaces) are common among infants and older patients with severe airflow limitation; paradoxical breathing (inward motion of the abdomen during inspiration) signifies respiratory muscle fatigue or weakness.

Signs of possible chronic pulmonary disease include clubbing, barrel chest (the increased anterior-posterior diameter of the chest present in some patients with emphysema), and pursed lip breathing. Clubbing is enlargement of the fingertips (or toes) due to proliferation of connective tissue between the fingernail and the bone. Diagnosis is based on an increase in the profile angle of the nail as it exits the finger (to > 176°) or on an increase in the phalangeal depth ratio (to > 1—see
"Sponginess" of the nail bed beneath the cuticle also suggests clubbing. Clubbing is most commonly observed in patients with lung cancer but is an important sign of chronic pulmonary disease, such as cystic fibrosis and idiopathic pulmonary fibrosis; it also occurs (but less commonly) in cyanotic heart disease, chronic infection (eg, infective endocarditis), stroke, inflammatory bowel disease, and cirrhosis. Clubbing occasionally occurs with osteoarthropathy and periostitis (primary or hereditary hypertrophic osteoarthropathy); in this instance, clubbing may be accompanied by skin changes, such as hypertrophied skin on the dorsa of the hands (pachydermoperiostosis), seborrhea, and coarse facial features. Digital clubbing can also occur as a benign hereditary abnormality that can be distinguished from pathologic clubbing by the absence of pulmonary symptoms or disease and by the presence of clubbing from an early age (by patient report).

Chest wall deformities, such as pectus excavatum and kyphoscoliosis, may restrict respirations and exacerbate symptoms of preexisting pulmonary disease.

Abnormal breathing patterns cause fluctuations in respiratory rate so respiratory rate should be assessed and counted for 1 min.

- **Cheyne-Stokes respiration** (periodic breathing) is a cyclic fluctuation of respiratory rate and depth. From periods of brief apnea, patients breathe progressively faster and deeper (hyperpnea), then slower and shallower until they become apneic and repeat the cycle. Cheyne-Stokes respiration is most often caused by heart failure, a neurologic disorder (eg, stroke, advanced dementia), or drugs. The pattern in heart failure has been attributed to delays in cerebral circulation; respiratory centers lag in recognition of systemic acidosis/hypoxia (causing hyperpnea) or alkalosis/hypocapnia (causing apnea).

- **Biot's respiration** is an uncommon variant of Cheyne-Stokes respiration in which irregular periods of apnea alternate with periods in which 4 or 5 deep, equal breaths are taken. It differs from Cheyne-Stokes respiration in that it is characterized by abrupt starts and stops and lacks periodicity. It results from injury to the CNS and occurs in such disorders as meningitis.

- **Kussmaul's respirations** are deep, regular respiration caused by metabolic acidosis.

Jugular venous distention, sometimes observed during inspection, indicates an increase in right atrial and right ventricular pressure. The elevated pressure is usually caused by left ventricular dysfunction, but it may also be due to a pulmonary disorder causing pulmonary hypertension (see p. 1984). The presence of jugular venous distension should prompt a search for other signs of cardiac disorder (eg, 3rd heart sound [S₃ gallop], dependent edema).

Auscultation: Auscultation is arguably the most important component of the physical examination. All fields of the chest should be listened to, including the flanks, to detect abnormalities associated with each lobe of the lung. Features to listen for include:

- Character and volume of breath sounds
- Presence or absence of vocal sounds
- Pleural friction rubs
- Ratio of inspiration to expiration (I:E ratio)

Cardiac auscultation (see p. 2020), conducted simultaneously with pulmonary auscultation, may reveal signs of pulmonary hypertension, such as a loud pulmonic 2nd heart sound (P₂), and of right heart failure, such as a right ventricular 4th heart sound (S₄) and tricuspid regurgitation.

The character and volume of breath sounds are useful in identifying pulmonary disorders. Vesicular
breath sounds are the normal sounds heard over most lung fields. Bronchial breath sounds are slightly louder, harsher, and higher pitched; they normally can be heard over the trachea and over areas of lung consolidation, such as occur with pneumonia.

Adventitious sounds are abnormal sounds, such as crackles, rhonchi, wheezes, and stridor.

- **Crackles** (previously called rales) are discontinuous adventitious breath sounds. Fine crackles are short high-pitched sounds; coarse crackles are longer-lasting low-pitched sounds. Crackles have been compared to the sound of crinkling plastic wrap and can be simulated by rubbing strands of hair together between 2 fingers near one's ear. They occur most commonly with atelectasis, alveolar filling processes (eg, pulmonary edema), and interstitial lung disease (eg, pulmonary fibrosis); they signify opening of collapsed alveoli.

- **Rhonchi** are low-pitched respiratory sounds that can be heard during inspiration or expiration. They occur in various conditions, including chronic bronchitis. The mechanism may relate to variations in obstruction as airways distend with inhalation and narrow with exhalation.

- **Wheezes** are whistling, musical breath sounds that are worse during expiration than inspiration. Wheezing can be a physical finding or a symptom and is usually associated with dyspnea.

- **Stridor** is a high-pitched, predominantly inspiratory sound formed by extrathoracic upper airway obstruction. It usually can be heard without a stethoscope. Stridor is usually louder than wheezing, is predominantly inspiratory, and is heard loudly over the larynx. It should trigger a concern for life-threatening upper airway obstruction.

- **Decreased breath sounds** signify poor air movement in airways, as occurs with asthma and COPD where bronchospasm or other mechanisms limit airflow. Breath sounds may also be decreased in the presence of a pleural effusion, pneumothorax, or obstructing endobronchial lesion.

Vocal sounds involve auscultation while patients vocalize.

- **Bronchophony** and **whispered pectoriloquy** occur when the patient's spoken or whispered voice is clearly transmitted through the chest wall. Voice transmission results from alveolar consolidation, as occurs with pneumonia.

- **Egophony** is said to occur when a patient says the letter "E" and the examiner hears the letter "A" on auscultation, again as occurs with pneumonia.

Friction rubs are grating or creaking sounds that fluctuate with the respiratory cycle and sound like skin rubbing against wet leather. They are a sign of pleural inflammation and are heard in patients with pleurisy or empyema and after thoracotomy.

I:E ratio is normally 1:2 but is prolonged to ≥ 1:3 when airflow is limited, such as in asthma and COPD, even in the absence of wheezing.

**Percussion and palpation:** Percussion is the primary physical maneuver used to detect the presence and level of pleural effusion. Finding areas of dullness during percussion signifies underlying fluid or, less commonly, consolidation.

Palpation includes tactile fremitus (vibration of the chest wall felt when a patient is asked to speak); it is decreased in pleural effusion and pneumothorax and increased in pulmonary consolidation (eg, lobar pneumonias). Point tenderness on palpation may signal underlying rib fracture or pleural inflammation.

In cor pulmonale (see p. 2132), a right ventricular impulse at the left lower sternal border may become evident and may be increased in amplitude and duration (right ventricular heave).

**Chest Pain**
Pulmonary, pleural, and chest wall disorders cause chest pain; examples are

- Pneumonia
- Pulmonary embolism
- Pleuritis
- Lung cancer
- Rib fractures

Cardiac, GI, and musculoskeletal disorders also cause chest pain. The evaluation of patients with chest pain is discussed on p. 2025.

**Cough**

Cough is an explosive expiratory maneuver that is reflexively or deliberately intended to clear the airways. It is the 5th most common symptom prompting physician visits.

Likely causes of cough (see Table 188-1) differ depending on whether the symptom is acute (< 3 wk) or chronic.

In acute cough, the most common causes are

- URI (including acute bronchitis)
- Postnasal drip
- COPD exacerbation
- Pneumonia

In chronic cough, the most common causes are

- Chronic bronchitis
- Postnasal drip
- Airway hyperresponsiveness after resolution of a viral or bacterial respiratory infection (ie, postinfection cough)
- Gastroesophageal reflux

The causes in children (see p. 2731) are similar to those in adults, but asthma and foreign body aspiration may be more common.

Very rarely, impacted cerumen or a foreign body in the external auditory canal triggers reflex cough through stimulation of the auricular branch of the vagus nerve. Psychogenic cough is even rarer and is a diagnosis of exclusion.

**Evaluation**

**History:** *History of present illness* should cover the duration and characteristics of the

[Table 188-1, Some Causes of Cough]

cough (eg, whether dry or productive of sputum or blood) and whether it is accompanied by dyspnea,
chest pain, or both.

**Review of systems** should seek symptoms of possible cause, including runny nose and sore throat (URI, postnasal drip); fever, chills, and pleuritic chest pain (pneumonia); night sweats and weight loss (tumor, TB); heartburn (gastroesophageal reflux); and difficulty swallowing or choking episodes while eating or drinking (aspiration).

**Past medical history** should note recent respiratory infections (ie, within previous 1 to 2 mo); history of allergies, asthma, COPD, and gastroesophageal reflux disease; risk factors for (or known) TB or HIV infection; and smoking history. Drug history should specifically include use of ACE inhibitors. Patients with chronic cough should be asked about exposure to potential respiratory irritants or allergens and travel to or residence in regions with endemic fungal illness.

**Physical examination:** Vital signs should be reviewed for the presence of tachypnea and fever.

General examination should look for signs of respiratory distress and chronic illness (eg, wasting, lethargy).

Examination of the nose and throat should focus on appearance of the nasal mucosa (eg, color, congestion) and presence of discharge (external or in posterior pharynx). Ears should be examined for triggers of reflex cough.

The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy.

A full lung examination is done, particularly including adequacy of air entry and exit; symmetry of breath sounds; and presence of crackles, wheezes, or both. Signs of consolidation (eg, egophony, dullness to percussion) should be sought.

**Red flags:** The following findings are of particular concern:

- Dyspnea
- Hemoptysis
- Weight loss
- Risk factors for TB or HIV infection

**Interpretation of findings:** Some findings point to particular diagnoses (see Table 188-1).

Other important findings are less specific. For example, the color (eg, yellow, green) and thickness of sputum do not help differentiate bacterial from other causes. Wheezing may occur with several causes. Hemoptysis in small amounts may occur with severe cough of many etiologies, although larger amounts of hemoptysis suggest bronchitis, bronchiectasis, TB, or primary lung cancer. Fever, night sweats, and weight loss may occur with many chronic infections as well as with cancer.

**Testing:** Patients with red flag findings of dyspnea or hemoptysis and patients in whom suspicion of pneumonia is high should have pulse oximetry and chest x-ray. Those with weight loss or risk factors should have chest x-ray and testing for TB and HIV infection.

For many patients without red flag findings, clinicians can base the diagnosis on history and physical examination findings and begin treatment without testing. For patients without a clear cause but no red flag findings, many clinicians empirically begin treatment for postnasal drip (eg, antihistamine and decongestant combinations, nasal corticosteroid sprays) or gastroesophageal reflux disease (eg, proton pump inhibitors, H₂ blockers). An adequate response to these interventions usually precludes the need for further evaluation.

Patients with chronic cough in whom presumptive treatment is ineffective should have a chest x-ray. If the
x-ray findings are unremarkable, many clinicians sequentially test for asthma (pulmonary function tests with methacholine challenge), sinus disease (sinus CT), and gastroesophageal reflux disease (esophageal pH monitoring). Sputum culture is helpful for patients with a possible indolent infection, such as pertussis, TB, or nontuberculous mycobacterial infection. Sputum cytology is noninvasive and should be done if cancer is suspected and the patient is producing sputum or having hemoptysis. Chest CT and possibly bronchoscopy should be done in patients in whom lung cancer or another bronchial tumor is suspected (eg, patients with a long smoking history, nonspecific constitutional signs) and in patients in whom empiric therapy has failed and who have inconclusive findings on preliminary testing.

**Treatment**

Treatment is management of the cause.

There is little evidence to support the use of cough suppressants or mucolytic agents. Coughing is an important mechanism for clearing secretions from the airways and can assist in recovery from respiratory infections. Therefore, although patients often expect or request cough suppressants, such treatment should be given with caution and reserved for patients with a URI and for patients receiving therapy for the underlying disorder for whom cough is still troubling.

Antitussives depress the medullary cough center (dextromethorphan and codeine) or anesthetize stretch receptors of vagal afferent fibers in bronchi and alveoli (benzonatate). Dextromethorphan, a congener of the opioid levorphanol, is effective as a tablet or syrup at a dose of 15 to 30 mg po 1 to 4 times/day for adults or 0.25 mg/kg po qid for children. Codeine has antitussive, analgesic, and sedative effects, but dependence is a potential problem, and nausea, vomiting, constipation, and tolerance are common adverse effects. Usual doses are 10 to 20 mg po q 4 to 6 h as needed for adults and 0.25 to 0.5 mg/kg po qid for children. Other opioids (hydrocodone, hydromorphone, methadone, morphine) have antitussive properties but are avoided because of high potential for dependence and abuse. Benzonatate, a congener of tetracaine that is available in liquid-filled capsules, is effective at a dose of 100 to 200 mg po tid.

**Expectorants** are thought to decrease viscosity and facilitate expectoration (coughing up) of secretions but are of limited benefit. Guaifenesin (200 to 400 mg po q 4 h in syrup or tablet form) is most commonly used because it has no serious adverse effects, but multiple expectorants exist, including bromhexine, ipecac, and saturated solution of K iodide (SSKI). Aerosolized expectorants such as N-acetylcysteine and DNase are generally reserved for hospital-based treatment of cough in patients with bronchiectasis or cystic fibrosis. Ensuring adequate hydration may facilitate expectoration, as may inhalation of steam, although neither technique has been rigorously tested.

**Topical treatments**, such as acacia, licorice, glycerin, honey, and wild cherry cough drops or syrups (demulcents), are locally and perhaps emotionally soothing, but their use is not supported by scientific evidence.

**Protussives**, which stimulate cough, are indicated for such disorders as cystic fibrosis and bronchiectasis, in which a productive cough is thought to be important for airway clearance and preservation of pulmonary function. DNase or hypertonic saline is given in conjunction with chest physical therapy and postural drainage to promote cough and expectoration. This approach is beneficial in cystic fibrosis but not in most other causes of chronic cough.

**Bronchodilators**, such as albuterol and ipratropium or inhaled corticosteroids, can be effective for cough after URI and in cough-variant asthma.

**Key Points**

- Danger signs include respiratory distress, chronic fever, weight loss, and hemoptysis.
- Clinical diagnosis is usually adequate.
- Occult gastroesophageal reflux disease should be remembered as a possible cause.
• Antitussives and expectorants should be used selectively.

**Dyspnea**

Dyspnea is unpleasant or uncomfortable breathing. It is experienced and described differently by patients depending on the cause.

**Pathophysiology**

Although dyspnea is a relatively common problem, the pathophysiology of the uncomfortable sensation of breathing is poorly understood. Unlike those for other types of noxious stimuli, there are no specialized dyspnea receptors, although recent MRI studies have identified a few specific areas in the midbrain that may mediate perception of dyspnea.

The experience of dyspnea likely results from a complex interaction between chemoreceptor stimulation, mechanical abnormalities in breathing, and the perception of those abnormalities by the CNS. Some authors have described the imbalance between neurologic stimulation and mechanical changes in the lungs and chest wall as neuromechanical uncoupling.

**Etiology**

Dyspnea has many pulmonary, cardiac, and other causes, which vary by acuity of onset (see Table 188-2).

The most common causes include

- Asthma
- Pneumonia
- COPD
- Myocardial ischemia
- Deconditioning

The most common cause of dyspnea in patients with chronic pulmonary or cardiac disorders is

- Exacerbation of their disease

However, such patients may also acutely develop another condition (eg, a patient with long-standing asthma may have an MI, a patient with chronic heart failure may develop pneumonia).

[Table 188-2, Some Causes of Dyspnea]

**Evaluation**

**History:** *History of present illness* should cover the duration, temporal onset (eg, abrupt, insidious), and provoking or exacerbating factors (eg, allergen exposure, cold, exertion, supine position). Severity can be determined by assessing the activity level required to cause dyspnea (ie, dyspnea at rest is more severe than dyspnea only with climbing stairs). For patients with baseline dyspnea, the physician should note how much dyspnea has changed from the patient's usual state.

**Review of systems** should seek symptoms of possible causes, including chest pain or pressure (pulmonary embolism [PE], myocardial ischemia, pneumonia); dependent edema, orthopnea, and paroxysmal nocturnal dyspnea (heart failure); fever, chills, cough, and sputum production (pneumonia); black, tarry stools or heavy menses (occult bleeding possibly causing anemia); and weight loss or night
Past medical history should cover disorders known to cause dyspnea, including asthma, COPD, and heart disease, as well as risk factors for the different etiologies:

- Smoking history—for cancer, COPD, and heart disease
- Family history, hypertension, and high cholesterol levels—for coronary artery disease
- Recent immobilization or surgery, recent long-distance travel, cancer or risk factors for or signs of occult cancer, prior or family history of clotting, pregnancy, oral contraceptive use, calf pain, leg swelling, and known deep venous thrombosis—for PE

Occupational exposures (eg, gases, smoke, asbestos) should be investigated.

**Physical examination:** Vital signs are reviewed for fever, tachycardia, and tachypnea.

Examination focuses on the cardiovascular and pulmonary systems.

A full lung examination is done, particularly including adequacy of air entry and exit, symmetry of breath sounds, and presence of crackles, rhonchi, stridor, and wheezes. Signs of consolidation (eg, egophony, dullness to percussion) should be sought. The cervical, supraclavicular, and inguinal areas should be inspected and palpated for lymphadenopathy.

Neck veins should be inspected for distention, and the legs and presacral area should be palpated for pitting edema (both suggesting heart failure).

Heart sounds should be auscultated with notation of any extra heart sounds, muffled heart sounds, or murmur. Testing for pulsus paradoxus (a > 12-mm Hg drop of systolic BP during inspiration) can be done by inflating a BP cuff to 20 mm Hg above the systolic pressure and then slowly deflating until the first Korotkoff sound is heard only during expiration. As the cuff is further deflated, the point at which the first Korotkoff sound is audible during both inspiration and expiration is recorded. If the difference between the first and second measurement is > 12 mm Hg, then pulsus paradoxus is present.

Conjunctiva should be examined for pallor. Rectal examination and stool guaiac testing should be done.

**Red flags:** The following findings are of particular concern:

- Dyspnea at rest during examination
- Decreased level of consciousness or agitation or confusion
- Accessory muscle use and poor air excursion
- Chest pain
- Crackles
- Weight loss
- Night sweats

**Interpretation of findings:** The history and physical examination often suggest a cause and guide further testing (see Table 188-2). Several findings are of note. Wheezing (see p. 1847) suggests asthma or COPD. Stridor (see p. 1844) suggests extrathoracic airway obstruction (eg, foreign body, epiglottitis, vocal cord dysfunction). Crackles suggest left heart failure, interstitial lung disease, or, if accompanied by signs of consolidation, pneumonia.
However, the symptoms and signs of life-threatening conditions such as myocardial ischemia and PE can be nonspecific. Furthermore, the severity of symptoms is not always proportional to the severity of the cause (eg, PE in a fit, healthy person may cause only mild dyspnea). Thus, a high degree of suspicion for these common conditions is prudent. It is often appropriate to rule out these conditions before attributing dyspnea to a less serious etiology.

A clinical prediction rule (see Table 194-2 on p. 1912) can help estimate the risk of PE. Note that a normal O\textsubscript{2} saturation does not exclude PE.

Hyperventilation syndrome is a diagnosis of exclusion. Because hypoxia may cause tachypnea and agitation, it is unwise to assume every rapidly breathing, anxious young person merely has hyperventilation syndrome.

Testing: Pulse oximetry should be done in all patients, and a chest x-ray should be done as well unless symptoms are clearly caused by a mild or moderate exacerbation of a known condition. For example, patients with asthma or heart failure do not require an x-ray for each flare-up, unless clinical findings suggest another cause or an unusually severe attack. Most adults should have an ECG to detect myocardial ischemia (and serum cardiac marker testing if suspicion is high) unless myocardial ischemia can be excluded clinically.

In patients with severe or deteriorating respiratory status, ABGs should be measured to more precisely quantify hypoxemia, measure PaCO\textsubscript{2}, diagnose any acid-base disorders stimulating hyperventilation, and calculate the alveolar-arterial gradient.

Patients who have no clear diagnosis after chest x-ray and ECG and are at moderate or high risk of having PE (from the clinical prediction rule—see Table 194-2 on p. 1912) should undergo ventilation/perfusion scanning or CT angiography. Patients who are at low risk may have D-dimer testing (to detect the presence of clot); a normal D-dimer level effectively rules out PE in a low-risk patient.

Chronic dyspnea may warrant additional tests, such as CT, pulmonary function tests, echocardiography, and bronchoscopy.

Treatment

Treatment is correction of the underlying disorder.

Hypoxemia is treated with supplemental O\textsubscript{2} as needed to maintain SaO\textsubscript{2} > 88% or PaO\textsubscript{2} > 55 mm Hg, because levels above these thresholds provide adequate O\textsubscript{2} delivery to tissues. Levels below these thresholds are on the steep portion of the O\textsubscript{2}-Hb dissociation curve, in which small declines in arterial O\textsubscript{2} tension result in large declines in Hb saturation. O\textsubscript{2} saturation should be maintained at > 93% if myocardial or cerebral ischemia is a concern.

Morphine 0.5 to 5 mg IV helps reduce anxiety and the discomfort of dyspnea in various conditions, including MI, PE, and the dyspnea that commonly accompanies terminal illness. However, opioids can be deleterious in patients with acute airflow limitation (eg, asthma, COPD) because they suppress the ventilatory drive and worsen respiratory acidemia.

Key Points

• Pulse oximetry is a key component of the examination.

• Low O\textsubscript{2} saturation (< 90%) indicates a significant problem, but normal saturation does not rule one out.

• Accessory muscle use, low O\textsubscript{2} saturation, or decreased level of consciousness requires emergency evaluation and hospitalization.
• Myocardial ischemia and PE are relatively common, but symptoms and signs can be nonspecific.

• Exacerbation of known conditions (eg, asthma, COPD, heart failure) is common, but patients may also develop new problems.

**Hyperventilation Syndrome**

**Hyperventilation syndrome is anxiety-related dyspnea and tachypnea often accompanied by systemic symptoms.**

Hyperventilation syndrome most commonly occurs among young women but can affect either sex at any age. It is sometimes precipitated by emotionally stressful events. Hyperventilation syndrome is separate from panic disorder (see p. 1496), although the 2 conditions overlap; about half of patients with panic disorder have hyperventilation syndrome and one quarter of patients with hyperventilation syndrome have panic disorder. It occurs in both acute and chronic forms. Chronic hyperventilation is more common; however, the acute form is easier to recognize.

**Symptoms and Signs**

Patients with acute hyperventilation syndrome present with dyspnea sometimes so severe that they liken it to suffocation. It is accompanied by agitation and a sense of terror or by symptoms of chest pain, paresthesias (peripheral and perioral), peripheral tetany (eg, stiffness of fingers or arms), and presyncope or syncope or sometimes by a combination of all of these findings. Tetany occurs because respiratory alkalosis causes both hypophosphatemia and hypocalcemia. On examination, patients may appear anxious, tachypneic, or both; lung examination is unremarkable.

Patients with chronic hyperventilation syndrome present far less dramatically and often escape detection; they sigh deeply and frequently and often have nonspecific somatic symptoms in the context of mood and anxiety disorders and emotional stress.

**Diagnosis**

• Testing to exclude other diagnoses (chest x-ray, ECG, pulse oximetry)

Hyperventilation syndrome is a diagnosis of exclusion; the challenge is to use tests and resources judiciously to distinguish this syndrome from more serious diagnoses. Basic testing includes pulse oximetry, chest x-ray, and ECG. Pulse oximetry in hyperventilation syndrome shows $O_2$ saturation at or close to 100%. Chest x-ray is normal. ECG is done to detect cardiac ischemia, although hyperventilation syndrome itself can cause ST-segment depressions, T-wave inversions, and prolonged QT intervals. ABGs are needed when other causes of hyperventilation are suspected, such as metabolic acidosis. Occasionally, acute hyperventilation syndrome is indistinguishable from acute pulmonary embolism, and tests for pulmonary embolism (eg, D-dimer, ventilation/perfusion scanning, CT angiography) may be necessary.

**Treatment**

• Supportive counseling

• Sometimes psychiatric or psychologic treatment

Treatment is reassurance. Some physicians advocate teaching the patient maximal exhalation and diaphragmatic breathing. Most patients require treatment for underlying mood or anxiety disorders; such treatment includes cognitive therapy, stress reduction techniques, drugs (eg, anxiolytics, antidepressants, lithium), or a combination of these techniques.
Hemoptysis is coughing up of blood from the respiratory tract. Massive hemoptysis is production of ≥ 600 mL of blood (about a full kidney basin’s worth) within 24 h.

Pathophysiology

Most of the lung's blood (95%) circulates through low-pressure pulmonary arteries and ends up in the pulmonary capillary bed, where gas is exchanged. About 5% of the blood supply circulates through high-pressure bronchial arteries, which originate at the aorta and supply major airways and supporting structures. In hemoptysis, the blood generally arises from this bronchial circulation, except when pulmonary arteries are damaged by trauma, by erosion of a granulomatous or calcified lymph node or tumor, or, rarely, by pulmonary arterial catheterization or when pulmonary capillaries are affected by inflammation.

Etiology

Blood-streaked sputum is common in many minor respiratory illnesses, such as URI and viral bronchitis. The differential diagnosis is broad (see Table 188-3).

In adults, 70 to 90% of cases are caused by

• Bronchitis
• Bronchiectasis
• TB
• Necrotizing pneumonia

Primary lung cancer is an important cause in smokers ≥ 40 yr, but metastatic cancer rarely causes hemoptysis. Cavitary Aspergillus infection is increasingly recognized as a cause but is not as common as cancer.

In children, common causes are

• Lower respiratory tract infection
• Foreign body aspiration

Massive hemoptysis: The most common causes have changed over time and vary by geographic region but include the following:

• Bronchogenic carcinoma
• Bronchiectasis
• Tuberculous and other pneumonias

Evaluation

History: History of present illness should cover the duration and temporal patterns (eg, abrupt onset, cyclical recurrence), provoking factors (eg, allergen exposure, cold, exertion, supine position), and approximate volume of hemoptysis (eg, streaking, teaspoon, cup). Patients may need specific prompting to differentiate between true hemoptysis, pseudohemoptysis (ie, bleeding originating in the nasopharynx that is subsequently coughed up), and hematemesis. A sensation of postnasal drip or any bleeding from the nares without coughing is suggestive of pseudohemoptysis. Concomitant nausea and vomiting with
black, brown, or coffee-ground-colored blood is characteristic of hematemesis. Frothy sputum, bright red blood, and (if massive) a sensation of choking are characteristic of true hemoptysis.

**Review of systems** should seek symptoms suggesting possible causes, including fever and sputum production (pneumonia); night sweats, weight loss, and fatigue (cancer, TB); chest pain and dyspnea (pneumonia, pulmonary embolism); leg pain and leg swelling (pulmonary embolism); hematuria (Goodpasture's syndrome); and bloody nasal discharge (Wegener's granulomatosis).

Patients should be asked about risk factors for causes. These risk factors include HIV infection, use of immunosuppressants (TB, fungal infection); exposure to TB; long smoking history (cancer); and recent immobilization or surgery, known cancer, prior or family history of clotting, pregnancy, use of estrogen-containing drugs, and recent long-distance travel (pulmonary embolism).

**Past medical history** should cover known conditions that can cause hemoptysis, including chronic lung disease (eg, COPD, bronchiectasis, TB, cystic fibrosis), cancer, bleeding disorders, heart failure, thoracic aortic aneurysm, and pulmonary-renal syndromes (eg, Goodpasture's syndrome, Wegener's granulomatosis). Exposure to TB is important, particularly in patients with HIV infection or another immunocompromised state.

[Table 188-3, Some Causes of Hemoptysis]

A history of frequent nosebleeds, easy bruising, or liver disease suggests possible coagulopathy. The drug profile should be reviewed for use of anticoagulants and antiplatelet drugs.

**Physical examination:** Vital signs are reviewed for fever, tachycardia, tachypnea, and low $O_2$ saturation. Constitutional signs (eg, cachexia) and level of patient distress (eg, accessory muscle use, pursed lip breathing, agitation, decreased level of consciousness) should also be noted.

A full lung examination is done, particularly including adequacy of air entry and exit, symmetry of breath sounds, and presence of crackles, rhonchi, stridor, and wheezing. Signs of consolidation (eg, egophony, dullness to percussion) should be sought. The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy (suggesting cancer or TB).

Neck veins should be inspected for distention, and the legs and presacral area should be palpated for pitting edema (suggesting heart failure). Heart sounds should be auscultated with notation of any extra heart sounds or murmur that might support a diagnosis of heart failure and elevated pulmonary pressure.

The abdominal examination should focus on signs of hepatic congestion or masses, which could suggest either cancer or hematemesis from potential esophageal varices.

The skin and mucous membranes should be examined for ecchymoses, petechiae, telangiectasia, gingivitis, or evidence of bleeding from the oral or nasal mucosa.

If the patient can reproduce hemoptysis during examination, the color and amount of blood should be noted.

**Red flags:** The following findings are of particular concern:

- Massive hemoptysis
- Back pain
- Presence of a pulmonary artery catheter
- Malaise, weight loss, fatigue
- Extensive smoking history
• Dyspnea at rest during examination or absent or decreased breath sounds

**Interpretation of findings:** The history and physical examination often suggest a diagnosis and guide further testing (see [Table 188-3](#)).

Despite the many possibilities, some generalities can be made. A previously healthy person with a normal examination and no risk factors (eg, for TB, pulmonary embolism) who presents with acute-onset cough and fever most likely has hemoptysis due to an acute respiratory illness; chronic disorders are much lower on the list of possibilities. However, if risk factors are present, those specific disorders must be strongly suspected. A clinical prediction rule (see [Table 194-2](#) on p. 1912) can help estimate the risk of pulmonary embolism. A normal O\textsubscript{2} saturation does not exclude pulmonary embolism.

Patients whose hemoptysis is due to a lung disorder (eg, COPD, cystic fibrosis, bronchiectasis) or heart disease (eg, heart failure) typically have a clear history of those disorders. Hemoptysis is not an initial manifestation.

Patients with known immunocompromise should be suspected of having TB or a fungal infection.

Patients with symptoms or signs of chronic illness but no known disorders should be suspected of having cancer or TB, although hemoptysis can be the initial manifestation of lung cancer in a patient who is otherwise asymptomatic.

Several specific findings are of note. Known renal failure or hematuria suggests a pulmonary-renal syndrome (eg, Goodpasture's syndrome, Wegener's granulomatosis). Patients with Wegener's granulomatosis may have nasal mucosal lesions. Visible telangiectasias suggest arteriovenous malformations. Patients with hemoptysis due to a bleeding disorder usually have cutaneous findings (petechiae, purpura, or both) or a history of anticoagulant or antiplatelet drug use. Recurrent hemoptysis coinciding with menses strongly suggests pulmonary endometriosis.

**Testing:** Patients with massive hemoptysis require treatment and stabilization, usually in an ICU, before testing. Patients with minor hemoptysis can undergo outpatient testing.

**Imaging** is always done. A chest x-ray is mandatory. Patients with normal results, a consistent history, and nonmassive hemoptysis can undergo empiric treatment for bronchitis. Patients with abnormal results and patients without a supporting history should undergo CT and bronchoscopy. CT may reveal pulmonary lesions that are not apparent on the chest x-ray and can help locate lesions in anticipation of bronchoscopy and biopsy. Ventilation/perfusion scanning or CT angiography can confirm the diagnosis of pulmonary embolism. CT and pulmonary angiography can also detect pulmonary arteriovenous fistulas.

**Fiberoptic inspection** of the pharynx, larynx, and airways may be indicated along with esophagogastric endoscopy when the etiology is obscure to distinguish hemoptysis from hematemesis and from nasopharyngeal or oropharyngeal bleeding.

**Laboratory testing** is also done. Patients usually should have a CBC, a platelet count, and measurement of PT and PTT. Anti-factor Xa testing can be used to detect supratherapeutic anticoagulation in patients receiving low mol wt heparin. Urinalysis should be done to look for signs of glomerulonephritis (hematuria, proteinuria, casts). TB skin testing and sputum culture should be done as the initial tests for active TB, but negative results do not preclude the need to induce sputum or do fiberoptic bronchoscopy to obtain samples for further acid-fast bacillus testing if an alternative diagnosis is not found.

**Cryptogenic hemoptysis:** The cause of hemoptysis remains unknown in 30 to 40% of patients, but the prognosis for patients with cryptogenic hemoptysis is generally favorable, usually with resolution of bleeding within 6 mo of evaluation.

**Treatment**

**Massive hemoptysis:** Initial treatment of massive hemoptysis has two objectives:
• Prevent aspiration of blood into the uninvolved lung (which can cause asphyxiation)

• Prevent exsanguination from ongoing bleeding

It can be difficult to protect the uninvolved lung because it is often initially unclear which side is bleeding. Once the bleeding side is identified, strategies include positioning the patient with the bleeding lung in a dependent position and selectively intubating and obstructing the bronchus going to the bleeding lung.

Prevention of exsanguination involves reversal of any bleeding diathesis and direct efforts to stop the bleeding. Clotting deficiencies can be reversed with fresh-frozen plasma and factor-specific or platelet transfusions. Laser therapy, cauterization, or direct injection with epinephrine or vasopressin can be done bronchoscopically.

Massive hemoptysis is one of the few indications for rigid (as opposed to flexible) bronchoscopy, which provides control of the airway, allows for a larger field of view than flexible bronchoscopy, allows better suctioning, and is more suited to therapeutic interventions, such as laser therapy.

Emboli zation of a pulmonary segment via bronchial artery catheterization is becoming the preferred method with which to stop massive hemoptysis, with reported success rates of up to 90%. Emergency surgery is indicated for massive hemoptysis not controlled by rigid bronchoscopy or embolization and is generally considered a last resort.

Once a diagnosis is made, further treatment is directed at the cause.

**Minor hemoptysis**: Treatment of minor hemoptysis is directed at the cause.

Early resection may be indicated for bronchial adenoma or carcinoma. Broncholithiasis (erosion of a calcified lymph node into an adjacent bronchus) may require pulmonary resection if the stone cannot be removed via rigid bronchoscopy. Bleeding secondary to heart failure or mitral stenosis usually responds to specific therapy for heart failure. In rare cases, emergency mitral valvulotomy is necessary for life-threatening hemoptysis due to mitral stenosis.

Bleeding from a pulmonary embolism is rarely massive and almost always stops spontaneously. If emboli recur and bleeding persists, anticoagulation may be contraindicated, and placement of an inferior vena cava filter is the treatment of choice.

Because bleeding from bronchiectatic areas usually results from infection, treatment of the infection with appropriate antibiotics and postural drainage is essential.

**Key Points**

• Hemoptysis needs to be distinguished from hematemesis and nasopharyngeal or oropharyngeal bleeding.

• Bronchitis, bronchiectasis, TB, and necrotizing pneumonia or lung abscess are the most common causes in adults.

• Lower respiratory tract infection and foreign body aspiration are the most common causes in children.

• Patients with massive hemoptysis require treatment and stabilization before testing.

• With massive hemoptysis, if the side of bleeding is known, patients should be positioned with the affected lung in the dependent position.

• Bronchial artery embolization is the preferred treatment for massive hemoptysis.
A solitary pulmonary nodule is defined as a discrete lesion < 3 cm in diameter that is completely surrounded by lung parenchyma (ie, does not touch the hilum, mediastinum, or pleura and is without associated atelectasis or pleural effusion (for evaluation of a mediastinal mass, see p. 1993).

Solitary pulmonary nodules are most often detected incidentally when a chest x-ray is taken for other reasons. Nonpulmonary soft-tissue densities caused by nipple shadows, warts, cutaneous nodules, and bone abnormalities are often confused for a nodule on chest x-ray.

**Etiology**

Although cancer is usually the primary concern, solitary pulmonary nodules have many causes (see Table 188-4). Of these, the most common vary by age and risk factors, but typically include

- Granulomas
- Pneumonia
- Bronchogenic cysts

**Evaluation**

The primary goal of evaluation is to detect cancer and active infection.

**Table 188-4. Some Causes of a Solitary Pulmonary Nodule**

**History**: History may reveal information that suggests malignant and nonmalignant causes of a solitary pulmonary nodule and includes

- Current or past cigarette smoking
- History of cancer or an autoimmune disorder
- Occupational risk factors for cancer (eg, exposure to asbestos, vinyl chloride, radon)
- Travel to areas with endemic mycosis or high prevalence of TB
- Risk factors for opportunistic infections (eg, HIV, immune deficiency)

Older age, cigarette smoking, and history of cancer all increase the probability of cancer and are used along with the nodule diameter to estimate likelihood ratios for cancer (see Table 188-5).

**Physical examination**: A thorough physical examination may uncover findings that suggest an etiology (eg, a breast lump or skin lesion suggestive of cancer) for a pulmonary nodule but cannot definitely establish the cause.

**Testing**: The goal of initial testing is to estimate the malignant potential of the solitary pulmonary nodule. The first step is a review of plain x-rays and then usually CT.

**Radiographic characteristics** help define the malignant potential of a solitary pulmonary nodule:

- **Growth rate** is determined by comparison with previous chest x-ray or CT, if available. A lesion that has not enlarged in ≥ 2 yr suggests a benign etiology. Tumors that have volume doubling times from 21 to 400 days are likely to be malignant. Small nodules (< 1 cm) should be monitored at 3 mo, 6 mo, and then yearly for 2 yr.

- **Calcification** suggests benign disease, particularly if it is central (tuberculoma, histoplasmoda),
concentric (healed histoplasmosis), or in a popcorn configuration (hamartoma).

- **Margins** that are spiculated or irregular (scalloped) are more indicative of cancer.

- **Diameter** < 1.5 cm strongly suggests a benign etiology; diameter > 5.3 cm strongly suggests cancer. However, nonmalignant exceptions include lung abscess, Wegener’s granulomatosis, and hydatid cyst.

These characteristics are sometimes evident on the original plain film but usually require CT. CT can also distinguish pulmonary from pleural radiopacities. CT has a sensitivity of 70% and a specificity of 60% for detecting cancer.

**PET** has an uncertain role in evaluation. It has a sensitivity > 90% and a specificity of about 78% for detecting cancer, but it is relatively new, and its role in evaluating pulmonary nodules is still being developed. False-negative PET scans can result from metabolically inactive tumors, and false-positive results can occur in various infectious and inflammatory conditions.

[Table 188-5, Estimating the Probability of Cancer in a Solitary Pulmonary Nodule]

**Cultures** may be useful when historical information suggests an infectious cause (eg, TB, coccidioidomycosis) as a possible diagnosis.

**Invasive testing** options include CT- or ultrasonography-guided transthoracic needle aspiration, fiberoptic bronchoscopy, and surgical biopsy. Although cancers can be diagnosed by biopsy, definitive treatment is resection, and so patients with a high likelihood of cancer with a resectable lesion should proceed to surgical resection. Transthoracic needle aspiration is best for peripheral lesions and is particularly useful if infectious etiologies are strongly considered because using the transthoracic approach, as opposed to bronchoscopy, avoids the possibility of contamination of the specimen with upper airway organisms. The main disadvantage of transthoracic needle aspiration is the risk of pneumothorax, which is about 10%. Fiberoptic bronchoscopy allows for endobronchial washing, brushing, needle aspiration, and transbronchial biopsy. Yield is higher for larger, more centrally located lesions, but very experienced operators using specially designed thin scopes can successfully biopsy peripheral lesions that are < 1 cm in diameter. In cases in which nodules are not accessible from these less invasive approaches, open surgical biopsy is necessary.

**Treatment**

- Sometimes surgery

- Sometimes observation

If the suspicion of cancer is very low, the lesions are very small (< 1 cm), or the patient refuses or is not a candidate for surgical intervention, observation is reasonable. Monitoring with follow-up at 3 mo, 6 mo, and then yearly for 2 yr is recommended. If the lesion has not grown for > 2 yr, it is likely benign.

When cancer is the most likely cause or when nonmalignant causes are unlikely, patients should undergo resection unless surgery is contraindicated due to poor pulmonary function, comorbidities, or withholding of consent.

**Stridor**

Stridor is a high-pitched, predominantly inspiratory sound. It is most commonly associated with acute disorders, such as foreign body aspiration but can be due to more chronic disorders, such as tracheomalacia.

**Pathophysiology**

Stridor is produced by the rapid, turbulent flow of air through a narrowed or partially obstructed segment of the extrathoracic upper airway. Involved areas include the pharynx, epiglottis, larynx, and the
Extrathoracic trachea.

**Etiology**

Most causes manifest acutely, but some patients present with chronic or recurrent symptoms (see Table 188-6).

Acute causes are usually infectious except for foreign body and allergy. Chronic causes are usually a congenital or acquired structural abnormality of the upper airway.

**Children:** The most common causes of acute stridor in children include

- Croup
- Foreign body aspiration

Epiglottitis has historically been a common cause of stridor in children, but its incidence has decreased since the introduction of the *Haemophilus influenzae* type B (HiB) vaccine. Various congenital airway disorders can manifest as recurrent stridor in neonates and infants.

**Adults:** Common causes in adults include

- Vocal cord dysfunction
- Postextubation laryngeal edema
- Vocal cord edema or paralysis
- Laryngeal tumors
- Allergic reactions

Vocal cord dysfunction often mimics asthma, so many patients with vocal cord dysfunction are incorrectly given drugs for asthma but do not respond. Epiglottitis may be becoming more common among adults, but adults with epiglottitis are less likely than children to have stridor.

[Table 188-6. Some Causes of Stridor]

**Evaluation**

**History:** History of present illness should first identify whether symptoms are acute or chronic. If acute, any symptoms of URI (runny nose, fever, sore throat) or allergy (itching, sneezing, facial swelling, rash, potential allergen exposure) are noted. Recent intubation or neck surgery should be clinically obvious. If chronic, the age at onset (eg, since birth, since infancy, only in adulthood) and duration are determined, as well as whether symptoms are continuous or intermittent. For intermittent symptoms, provoking or exacerbating factors (eg, position, allergen exposure, cold, anxiety, feeding, crying) are sought. Important associated symptoms in all cases include cough, pain, drooling, respiratory distress, cyanosis, and difficulty feeding.

**Review of systems** should seek symptoms suggesting causative disorders, including heartburn or other reflux symptoms (laryngospasm); night sweats, weight loss, and fatigue (cancer); and voice change, trouble swallowing, and recurrent aspiration (neurologic disorders).

**Past medical history** in children should cover perinatal history, particularly regarding need for endotracheal intubation, presence of known congenital anomalies, and vaccination history (particularly HiB). In adults, history of prior endotracheal intubation, tracheotomy, recurrent respiratory infections, and tobacco and alcohol use should be elicited.
Physical examination: The first step is to determine the presence and degree of respiratory distress by evaluating vital signs (including pulse oximetry) and doing a quick examination. Signs of severe distress include cyanosis, decreased level of consciousness, low $O_2$ saturation (eg, < 90%), air hunger, use of accessory inspiratory muscles, and difficulty speaking. Children with epiglottitis may sit upright with arms braced on the legs or examination table, lean forward, and hyperextend the neck with the jaw thrust forward and mouth open in an effort to enhance air exchange (tripod position). Moderate distress is indicated by tachypnea, use of accessory muscles or respiration, and intercostal retractions. If distress is severe, further examination is deferred until equipment and personnel are arranged for emergency management of the airway.

Oropharyngeal examination of a patient (particularly a child) with epiglottitis may provoke anxiety, leading to functional obstruction and loss of the airway. Thus, if epiglottitis is suspected, a tongue depressor or other instrument should not be placed in the mouth. When suspicion is low and patients are in no distress, they may undergo imaging; others should be sent to the operating room for direct laryngoscopy, which should be done by an otolaryngologist with the patient under anesthesia.

If the patient's vital signs and airway are stable and acute epiglottitis is not suspected, the oral cavity should be thoroughly examined for pooled secretions, hypertrophic tonsils, in-dwelling, erythema, or foreign bodies. The neck is palpated for masses and tracheal deviation. Careful auscultation of the nose, oropharynx, neck, and chest may help discern the location of the stridor. Infants should be examined with special attention to craniofacial morphology (looking for signs of congenital malformations), patency of the nares, and cutaneous abnormalities.

Red flags: The following findings are of particular concern:

- Drooling and agitation
- Tripod position
- Cyanosis or hypoxemia on pulse oximetry
- Decreased level of consciousness

Interpretation of findings: The distinction between acute and chronic stridor is important. Other clinical findings are also often helpful (see Table 188-6).

Acute manifestations are more likely to reflect an immediately life-threatening disorder. With these disorders, fever indicates infection. Fever plus barking cough suggests croup or, very rarely, tracheitis. Patients with croup typically have more prominent URI symptoms and less of a toxic appearance. Fever without cough, particularly if accompanied by toxic appearance, sore throat, difficulty swallowing, or respiratory distress, suggests epiglottitis and, in young children, the less common retropharyngeal abscess. Drooling and the tripod position are suggestive of epiglottitis, whereas retropharyngeal abscess may manifest with neck stiffness and inability to extend the neck.

Patients without fever or URI symptoms may have an acute allergic reaction or aspirated foreign body. Acute allergic reaction severe enough to cause stridor usually has other manifestations of airway edema (eg, oral or facial edema, wheezing) or anaphylaxis (itching, urticaria). Foreign body obstruction of the upper airway that causes stridor is always acute but may be occult in toddlers (older children and adults can communicate the event unless there is near-complete airway obstruction, which will manifest as such, not as stridor). Cough is often present with foreign body but rare with allergic reaction.

Chronic stridor that begins early in childhood and without a clear inciting factor suggests a congenital anomaly or an upper airway tumor. In adults, heavy smoking and alcohol use should raise suspicion of laryngeal cancer. Vocal cord paralysis usually has a clear precipitant, such as surgery or intubation, or is associated with other neurologic findings, such as muscle weakness. Patients with tracheomalacia frequently have cough productive of sputum and have a history of recurrent respiratory infections.

Testing: Testing should include pulse oximetry. In patients with minimal respiratory distress, soft-tissue
neck x-rays may help. An enlarged epiglottis or retropharyngeal space can be seen on the lateral view, and the subepiglottic narrowing of croup (steeple sign) may be seen on the anteroposterior view. X-rays may also identify foreign objects in the neck or chest.

In other cases, direct laryngoscopy can detect vocal cord abnormalities, structural abnormalities, and tumors. CT of the neck and chest should be done if there is concern about a structural abnormality, such as an upper airway tumor or tracheomalacia. Flow-volume loops can be useful in chronic and intermittent stridor to show the presence of an upper airway obstruction. Abnormal flow-volume loop findings generally require follow up with CT or laryngoscopy.

Treatment

Definitive treatment of stridor involves treating the underlying disorder. As a temporizing measure in patients with severe distress, a mixture of helium and O\textsubscript{2} (heliox) improves airflow and reduces stridor in disorders of the large airways, such as postextubation laryngeal edema, croup, and laryngeal tumors. The mechanism of action is thought to be reduced flow turbulence as a result of lower density of helium compared with O\textsubscript{2} and nitrogen.

Nebulized racemic epinephrine (0.5 to 0.75 mL of 2.25% racemic epinephrine added to 2.5 to 3 mL of normal saline) and dexamethasone (10 mg IV, then 4 mg IV q 6 h) may be helpful in patients in whom airway edema is the cause.

Endotracheal intubation should be used to secure the airway in patients with advanced respiratory distress, impending loss of airway, or decreased level of consciousness. When significant edema is present, endotracheal intubation can be difficult, and emergency surgical airway measures (eg, cricothyrotomy, tracheostomy) may be required.

Key Points

- Inspiratory stridor is often a medical emergency.
- Assessment of vital signs and degree of respiratory distress is the first step.
- In some cases, securing the airway may be necessary before or in parallel with the physical examination.
- Acute epiglottitis is uncommon in children who have received HiB vaccine.

Vocal Cord Dysfunction

Paradoxical or dysfunctional movement of the vocal cords is defined as adduction of the true vocal cords on inspiration and abduction on expiration; it causes inspiratory airway obstruction and stridor that is often mistaken for asthma. Vocal cord paralysis (unilateral and bilateral) is discussed on p. 484. The general evaluation of patients with stridor is discussed on p. 1846.

Vocal cord dysfunction occurs more commonly among women aged 20 to 40. Etiology is unclear, but it appears to be associated with anxiety, depression, posttraumatic stress disorder, and personality disorders. It is not considered a factitious disorder (ie, patients are not doing it consciously).

Symptoms are usually inspiratory stridor and less often expiratory wheezing. Other manifestations can include hoarseness, throat tightness, a choking sensation, and cough.

Diagnosis is made by observing inspiratory closure of the vocal cords with direct laryngoscopy. Sometimes a diagnosis of vocal cord dysfunction is entertained only after patients have been misdiagnosed as having asthma and then not responded to bronchodilators or corticosteroids.

Treatment involves educating the patient about the nature of the problem; counseling from a speech therapist on special breathing techniques, such as panting, which can relieve episodes of stridor and
Wheezing

Wheezing is a relatively high-pitched whistling noise produced by movement of air through narrowed or compressed small airways. It is a symptom as well as a physical finding.

**Pathophysiology**

Airflow through a narrowed or compressed segment of a small airway becomes turbulent, causing vibration of airway walls; this vibration produces the sound of wheezing.

Wheeze are more common during expiration because increased intrathoracic pressure during this phase narrows the airways. Wheezing during expiration alone indicates milder obstruction than wheezing during both inspiration and expiration, which suggests more severe airway narrowing.

By contrast, turbulent flow of air through a narrowed segment of the large, extrathoracic airways produces a whistling inspiratory noise (stridor—see p. 1844).

**Etiology**

Small airway narrowing may be caused by bronchoconstriction, mucosal edema, or external compression, or partial obstruction by a tumor, foreign body, or thick secretions.

Overall, the most common causes are

- Asthma
- COPD

But wheezing may occur in other disorders affecting the small airways, including heart failure (cardiac asthma), anaphylaxis, and toxic inhalation. Sometimes, healthy patients manifest wheezing during a bout of acute bronchitis. In children, bronchiolitis and foreign body aspiration are also causes (see Table 188-7).

**Evaluation**

When patients are in significant respiratory distress, evaluation and treatment proceed at the same time.

**History: History of present illness** should determine whether the wheezing is new or recurrent. If recurrent, patients are asked the previous diagnosis and whether current symptoms are different in nature or severity. Particularly when the diagnosis is unclear, the acuity of onset (eg, abrupt or gradual), temporal patterns (eg, persistent vs intermittent, seasonal variations), and provoking or exacerbating factors (eg, current URI, allergen exposure, cold air, exercise, feeding in infants) are noted. Important associated symptoms include shortness of breath, fever, cough, and sputum production.

**Review of systems** should seek symptoms and signs of causative disorders, including fever, sore throat, and rhinorhea (respiratory infection); orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema (heart failure); night sweats, weight loss, and fatigue (cancer); nasal congestion, itching eyes, sneezing, and rash (allergic reaction); and vomiting, heartburn, and swallowing difficulties (gastroesophageal reflux disease with aspiration).

**Past medical history** should ask about conditions known to cause wheezing, particularly asthma, COPD, and heart failure. Sometimes the patient’s drug list may be the only indication of such diagnoses (eg, inhaled bronchodilators and corticosteroids in COPD; diuretics and ACE inhibitors in heart failure).

Vocal cord dysfunction associated with psychiatric diagnoses is often resistant to these measures. Referral for psychiatric counseling is indicated in these cases.
Patients with known disease should be asked about indicators of disease severity, such as previous hospitalization, intubation, or ICU admission. Also, conditions that predispose to heart failure are identified, including atherosclerotic or congenital heart disease and hypertension. Smoking history and exposure to secondhand smoke should be noted.

**Physical examination:** Vital signs are reviewed for presence of fever, tachycardia, tachypnea, and low $O_2$ saturation.

Any signs of respiratory distress (eg, accessory muscle use, intercostal retractions, pursed lip breathing, agitation, cyanosis, decreased level of consciousness) should be immediately noted.

Examination focuses on the lungs, particularly adequacy of air entry and exit, symmetry of breath sounds, and localization of wheezing (diffuse vs localized; inspiratory, expiratory, or both). Any signs of consolidation (eg, egophony, dullness to percussion) or crackles should be noted.

The cardiac examination should focus on findings that might indicate heart failure, such as murmurs, a 3rd heart sound ($S_3$ gallop), and jugular venous distention.

The nose and throat examination should note appearance of the nasal mucosa (eg, color, congestion), swelling of the face or tongue, and signs of rhinitis, sinusitis, or nasal polyps.

The extremities are examined for clubbing and edema, and the skin is examined for signs of allergic reactions (eg, urticaria, rash) or atopy (eg, eczema). The patient's general appearance is noted for constitutional signs, such as the cachexia and barrel chest of severe COPD.

**Red flags:** The following findings are of particular concern:

- Accessory muscle use, clinical signs of tiring, or decreased level of consciousness
- Fixed inspiratory and expiratory wheezing
- Swelling of the face and tongue (angioedema)

**Interpretation of findings:** Recurrent wheezing in a patient with a known history of

[Table 188-7, Some Causes of Wheezing] disorders such as asthma, COPD, or heart failure is usually presumed to represent an exacerbation. In patients who have both lung and heart disease, manifestations may be similar (eg, neck vein distention and peripheral edema in cor pulmonale due to COPD and in heart failure), and testing is often required. When the cause is known asthma or COPD, a history of cough, postnasal drip, or exposure to allergens or to toxic or irritant gases (eg, cold air, dust, tobacco smoke, perfumes) may suggest a trigger.

Clinical findings help suggest a cause of wheezing in patients without a known history (see Table 188-7).

**Acute** (sudden-onset) wheezing in the absence of URI symptoms suggests an allergic reaction or impending anaphylaxis, especially if urticaria or angioedema is present. Fever and URI symptoms suggest infection: acute bronchitis in older children and adults and bronchiolitis in children < 2 yr. Crackles, distended neck veins, and peripheral edema suggest heart failure. Association of wheezing with feeding or vomiting in infants can be a result of gastroesophageal reflux.

Patients with asthma usually have paroxysmal or intermittent bouts of acute wheezing.

**Persistent,** localized wheezing suggests focal bronchial obstruction by a tumor or foreign body. Persistent wheezing manifesting very early in life suggests a congenital or structural abnormality. Persistent wheezing with sudden onset is consistent with foreign body aspiration, whereas the slowly progressive onset of wheezing may be a sign of extraluminal bronchial compression by a growing tumor or lymph node.
**Testing:** Testing seeks to assess severity, determine diagnosis, and identify complications.

- Pulse oximetry
- Chest x-ray (if diagnosis unclear)
- Sometimes ABG
- Sometimes pulmonary function testing

Severity is assessed by pulse oximetry and, in patients with respiratory distress or clinical signs of tiring, ABG testing. Patients known to have asthma usually have bedside peak flow measurements (or, when available, forced expiratory volume in 1 sec [FEV1]).

Patients with new-onset or undiagnosed persistent wheezing should have a chest x-ray. X-ray can be deferred in patients with asthma who are having a typical exacerbation and in patients having an obvious allergic reaction. Cardiomegaly, pleural effusion, and fluid in the major fissure suggest heart failure. Hyperinflation and hyperlucency suggest COPD. Segmental or subsegmental atelectasis or infiltrate suggests an obstructing endobronchial lesion. Radiopacity in the airways or focal areas of hyperinflation suggest a foreign body.

If the diagnosis is unclear in patients with recurrent wheezing, pulmonary function testing can confirm airflow limitation and quantify its reversibility and severity. Methacholine challenge testing and exercise testing can confirm airway hyperreactivity in patients for whom the diagnosis of asthma is in question.

**Treatment**

Definitive treatment of wheezing is treatment of underlying disorders.

Wheezing itself can be relieved with inhaled bronchodilators (eg, albuterol 2.5 mg nebulized solution or 180 mg metered dose inhalation). Long-term control of persistent asthmatic wheezing may require inhaled corticosteroids and leukotriene inhibitors.

Intravenous H₂ blockers (diphenhydramine), corticosteroids (methylprednisolone), and subcutaneous and inhaled racemic epinephrine are indicated in cases of anaphylaxis.

**Key Points**

- Asthma is the most common cause, but not all wheezing is asthma.
- Acute onset of wheezing in a patient without a lung disorder may be due to aspiration, allergic reaction, or heart failure.
- Reactive airway disease can be confirmed via spirometry.
- Inhaled bronchodilators are the mainstay of acute treatment.
Chapter 189. Tests of Pulmonary Function

Introduction

Pulmonary function tests provide measures of airflow, lung volumes, gas exchange, response to bronchodilators, and respiratory muscle function. Basic pulmonary function tests available in the ambulatory setting include spirometry and pulse oximetry; these tests provide physiologic measures of pulmonary function and can be used to quickly narrow a differential diagnosis and suggest a subsequent strategy of additional testing or therapy. More complicated testing includes measurement of lung volumes; lung, chest wall, and respiratory system compliance (which requires measurement of esophageal pressure); and complete cardiopulmonary exercise testing. These tests provide a more detailed description of physiologic abnormalities and the likely underlying pathology. The choice and sequence of testing are guided by information taken from the history and physical examination.

Airflow, Lung Volumes, and Flow-Volume Loop

Airflow and lung volume measurements can be used to differentiate obstructive from restrictive pulmonary disorders, to characterize severity, and to measure responses to therapy. Measurements are typically reported as absolute flows and volumes and as percentages of predicted values using data derived from large populations of people presumed to have normal lung function. Variables used to predict normal values include age, sex, ethnicity, and height.

Airflow: Quantitative measures of inspiratory and expiratory flow are obtained by forced spirometry. Nose clips are used to occlude the nares.

In assessments of expiratory flow, patients inhale as deeply as possible, seal the lips around a mouthpiece, and exhale as forcefully and completely as possible into an apparatus that records the exhaled volume (forced vital capacity [FVC]) and the volume exhaled in the first second (the forced expiratory volume in 1 sec [FEV₁]—see Fig. 189-1). Most currently used devices measure only airflow and integrate time to estimate the expired volume.

In assessments of inspiratory flow and volume, patients exhale as completely as possible, then forcibly inhale. These maneuvers provide several measures. The FVC is the maximal amount of air that the patient can forcibly exhale after taking a maximal inhalation. The FEV₁ is the most reproducible flow parameter and is especially useful in diagnosing and monitoring patients with obstructive pulmonary disorders (eg, asthma, COPD).

The forced expiratory flow averaged over the time during which 25 to 75% of the FVC is exhaled may be a more sensitive marker of mild, small airway airflow limitation than the FEV₁, but the reproducibility of this variable is poor. The peak expiratory flow (PEF) is the peak flow occurring during exhalation. This variable is used primarily for home monitoring of patients with asthma and for determining diurnal variations in airflow.

Interpretation of these measures depends on good patient effort, which is often improved by coaching during the actual maneuver. Acceptable spiro-grams demonstrate good test initiation (eg, a quick and forceful onset of exhalation), no coughing, smooth curves, and absence of early termination of expiration (eg, minimum exhalation time of 6 sec with no change in volume for the last 1 sec). Reproducible efforts agree within 5% or 100 mL with other efforts. Results not meeting these minimum acceptable criteria should be interpreted with caution.

Lung volume: Lung volumes (see Fig. 189-2) are measured by determining functional residual capacity (FRC) and with spirometry.
FRC is measured using gas dilution techniques or a plethysmograph (which is more accurate in patients who have airflow limitation and trapped gas).

**Gas dilution** techniques include

- Nitrogen washout
- Helium equilibration

With nitrogen washout, the patient exhales to FRC and then breathes from a spirometer containing 100% O₂. The test ends when the exhaled nitrogen concentration is zero. The collected volume of exhaled nitrogen is equal to 81% of the initial FRC.

With helium equilibration, the patient exhales to FRC and then is connected to a closed system containing known volumes of helium and O₂. Helium concentration is measured until it is the same on inhalation and exhalation, indicating it has equilibrated with the volume of gas in the lung, which can then be estimated from the change in helium concentration that has occurred.

Both of these techniques may underestimate FRC because they measure only the lung volume that communicates with the airways. In patients with severe airflow limitation, a considerable volume of trapped gas may communicate very poorly or not at all.

**Body plethysmography** uses Boyle’s law to measure the compressible gas volume within the thorax and is more accurate than gas dilution techniques. While sitting in an airtight box, the patient tries to inhale against a closed mouthpiece from FRC. As the chest wall expands, the pressure in the closed box rises. Knowing the pre-inspiratory box volume and the pressure in the box before and after the inspiratory effort allows for calculation of the change in box volume, which must equal the change in lung volume.

Knowing FRC allows the lungs to be divided into subvolumes that are either measured with spirometry or calculated (see **Fig. 189-2**). Normally the FRC represents about 40% of total lung capacity (TLC).

**Flow-volume loop:** In contrast to the spiro-gram, which displays airflow (in L) over time (in sec), the flow-volume loop (see **Fig. 189-3**) displays airflow (in L/sec) as it relates to lung volume (in L) during maximal inspiration from complete exhalation (residual volume [RV]) and during maximum expiration from complete inhalation (TLC). The principal advantage of the flow-volume loop is that it can show whether airflow is appropriate for a particular lung volume. For example, airflow is normally slower at low lung volumes. Because patients with pulmonary fibrosis have low lung volumes, airflow appears to be decreased if measured alone. However, when airflow is presented as a function of lung volume, it becomes apparent that airflow is actually higher than normal (as a result of the increased elastic recoil characteristic of fibrotic lungs).

**Patterns of Abnormalities**

Most common respiratory disorders can be categorized as obstructive or restrictive on the basis of airflow and lung volumes (see **Table 189-1**).

**Obstructive disorders:** Obstructive disorders are characterized by a reduction in airflow, particularly the FEV₁ and the FEV₁ expressed as a percentage of the FVC (FEV₁/FVC). The degree of reduction in
FEV\textsubscript{1} compared with predicted values determines the degree of the obstructive defect (see Table 189-2). Obstructive defects are caused by

- Increased resistance to flow due to abnormalities within the airway lumen (eg, tumors, secretions, mucosal thickening)
- Changes in the wall of the airway (eg, contraction of smooth muscle, edema)
- Decreased elastic recoil (eg, the parenchymal destruction that occurs in emphysema)

With decreased airflow, expiratory times are longer than usual, and air may become trapped in the lungs due to incomplete emptying, thereby increasing lung volumes (eg, TLC, RV).

[Table 189-2. Severity of Obstructive and Restrictive Lung Disorders*]

Improvement of FEV\textsubscript{1} and FEV\textsubscript{1}/FVC by ≥ 12% or 200 mL with the administration of a bronchodilator confirms the diagnosis of asthma or airway hyperresponsiveness. However, some patients with asthma can have normal pulmonary function and normal spirometric parameters between exacerbations. When suspicion of asthma remains high despite normal spirometry results, provocative testing with methacholine, a synthetic analog of acetylcholine that is a nonspecific bronchial irritant, is indicated to detect or exclude bronchoconstriction. In a methacholine challenge test, spirometric parameters are measured at baseline and after inhalation of increasing concentrations of methacholine. Laboratories have different definitions of airway hyperreactivity, but in general patients showing at least a 20% drop in FEV\textsubscript{1} from baseline (PC\textsubscript{20}) when the concentration of inhaled methacholine is < 1 mg/mL is considered diagnostic of increased bronchial reactivity, whereas a PC\textsubscript{20} > 16 mg/mL excludes the diagnosis. PC\textsubscript{20} values between 1 and 16 mg/mL are inconclusive.

Exercise testing may be used to detect exercise-induced bronchoconstriction but is less sensitive than methacholine challenge testing for detecting general airway hyperresponsiveness. The patient does a constant level of work on a treadmill or cycle ergometer for 6 to 8 min at an intensity selected to produce a heart rate of 80% of predicted maximum heart rate. The FEV\textsubscript{1} and FVC are measured before and after, exercise-induced bronchospasm reduces FEV\textsubscript{1} or FVC ≥ 15% after exercise. Eucapnic voluntary hyperventilation (EVH) may also be used to diagnose exercise-induced bronchoconstriction and is the method accepted by the International Olympic Committee. EVH involves hyperventilation of a gas mixture of 5% CO\textsubscript{2} and 21% O\textsubscript{2} at 85% of maximum voluntary ventilation for 6 min. FEV\textsubscript{1} is then measured at specified intervals after the test. As with other bronchial provocation tests, the drop in FEV\textsubscript{1} that is diagnostic of exercise-induced bronchospasm varies by laboratory.

Restrictive disorders: Restrictive disorders are characterized by a reduction in lung volume, specifically a TLC < 80% of the predicted value. The decrease in TLC determines the severity of restriction (see Table 189-2). The decrease in lung volumes causes a decrease in airflow (reduced FEV\textsubscript{1}—see Fig. 189-3B). However, airflow relative to lung volume is increased, so the FEV\textsubscript{1}/FVC ratio is normal or increased.

Restrictive defects are caused by the following:

- Loss in lung volume (eg, lobectomy)
- Abnormalities of structures surrounding the lung (eg, pleural disorder, kyphosis, obesity)
- Weakness of the inspiratory muscles of respiration (eg, neuromuscular disorders)
- Abnormalities of the lung parenchyma (eg, pulmonary fibrosis)

The feature common to all is a decrease in the compliance of the lungs, the chest wall, or both.
Measurement of Gas Exchange

Gas exchange is measured through several means, including diffusing capacity for carbon monoxide, pulse oximetry, and arterial blood gas sampling.

Diffusing Capacity for Carbon Monoxide

The diffusing capacity for carbon monoxide (DLCO) is a measure of the ability of gas to transfer from the alveoli across the alveolar epithelium and the capillary endothelium to the RBCs. The DLCO depends not only on the area and thickness of the blood-gas barrier but also on the volume of blood in the pulmonary capillaries. The distribution of alveolar volume and ventilation also affects the measurement.

DLCO is measured by sampling end-expiratory gas for carbon monoxide (CO) after patients inspire a small amount of CO, hold their breath, and exhale. Measured DLCO should be adjusted for alveolar volume (which is estimated from dilution of helium) and the patient's Hct. DLCO is reported as mL/min/mm Hg and as a percentage of a predicted value.

Conditions that decrease DLCO: Conditions that primarily affect the pulmonary vasculature, such as primary pulmonary hypertension and pulmonary embolism, decrease DLCO. Conditions that affect the lung diffusely, such as emphysema and pulmonary fibrosis, decrease both DLCO and alveolar ventilation ($V_A$). Reduced DLCO also occurs in patients with previous lung resection because total lung volume is smaller, but DLCO corrects to or even exceeds normal when adjusted for $V_A$ because increased additional vascular surface area is recruited in the remaining lung. Anemic patients have lower DLCO values that correct when adjusted for Hb.

Conditions that increase DLCO: DLCO may be higher than predicted in patients with heart failure, presumably because the increased pulmonary venous and arterial pressure recruits additional pulmonary microvessels. DLCO is also increased in patients with erythrocythemia, in part because of increased Hct and because of the vascular recruitment that occurs with increased pulmonary pressures due to increased viscosity. DLCO is increased in patients with alveolar hemorrhage because RBCs in the alveolar space can also bind CO. DLCO is also increased in patients with asthma. Although this increase is attributed to presumed vascular recruitment, recent data suggest it may also be due to growth factor-stimulated neovascularization.

Pulse Oximetry

Transcutaneous pulse oximetry estimates $O_2$ saturation ($SpO_2$) of capillary blood based on the absorption of light from light-emitting diodes positioned in a finger clip or adhesive strip probe. The estimates are generally very accurate and correlate to within 5% of measured arterial $O_2$ saturation ($SaO_2$). Results may be less accurate in patients with highly pigmented skin; patients wearing nail polish; and patients with arrhythmias, hypotension, or profound systemic vasoconstriction, in whom the amplitude of the signal may be dampened. Also, pulse oximetry is able to detect only oxyhemoglobin or reduced Hb but not other types of Hb (eg, carboxyhemoglobin, methemoglobin); those types are assumed to be oxyhemoglobin and falsely elevate the $SpO_2$ measurement.

Arterial Blood Gas Sampling

ABG sampling is done to obtain accurate measures of $PaO_2$, $PaCO_2$, and blood pH; these variables combined with the patient's temperature allow for calculation of $HCO_3$ level (which can also be measured directly from venous blood) and $SaO_2$. ABG sampling can also accurately measure carboxyhemoglobin and methemoglobin.

The radial artery is usually used. Because arterial puncture in rare cases leads to thrombosis and impaired perfusion of distal tissue, Allen's test is first done to ensure adequate collateral circulation. With this maneuver, the radial and ulnar pulses are simultaneously occluded until the hand becomes pale.
ulnar pulse is then released while the pressure on the radial pulse is maintained. A blush across the entire hand within 7 sec of release of the ulnar pulse suggests adequate flow through the ulnar artery.

Under sterile conditions, a 22- to 25-gauge needle attached to a heparinized syringe is inserted just proximal to the maximal impulse of the radial arterial pulse and advanced slightly distally into the artery until pulsatile blood is returned. Systolic BP often pushes back the syringe plunger. After 3 to 5 mL of blood is collected, the needle is quickly withdrawn, and firm pressure is applied to the puncture site to facilitate hemostasis. Simultaneously, the ABG specimen is placed on ice to reduce O₂ consumption and CO₂ production by WBCs and is sent to the laboratory.

**Oxygenation**

Hypoxemia is a decrease in PO₂ in arterial blood; hypoxia is a decrease in the PO₂ in the tissue. ABGs accurately assess the presence of hypoxemia, which is generally defined as a PaO₂ low enough to reduce the SaO₂ below 90% (i.e., PaO₂ < 60 mm Hg). Abnormalities in Hb (e.g., methemoglobin), higher temperatures, lower pH, and higher levels of 2,3-diphosphoglycerate reduce Hb O₂ saturation despite an adequate PaO₂, as indicated by the oxyhemoglobin dissociation curve (see **Fig. 189-4**).

Causes of hypoxemia can be classified based on whether the alveolar-arterial PO₂ gradient [(A-a)DO₂], defined as the difference between alveolar O₂ tension (PAO₂) and PaO₂, is elevated or normal. PAO₂ is calculated as follows:

\[
\text{PAO}_2 = \left[ \text{FI}_2 \times \left( \text{P}_{\text{atm}} - \text{P}_{\text{H}_2\text{O}} \right) \right] - \text{PaCO}_2/R
\]

where FI₂ is the fraction of inspired O₂ (e.g., 0.21 at room air), P_{atm} is the ambient barometric pressure (e.g., 760 mm Hg at sea level), PH₂O is the partial pressure of water vapor (e.g., usually 47 mm Hg), PaCO₂ is the measured partial pressure of arterial CO₂, and R is the respiratory quotient, which is assumed to be 0.8 in a resting patient eating a normal diet.

For patients at sea level and breathing room air, FI₂ = 0.21, and the (A-a)DO₂ can be simplified as follows:

\[
(A - a)\text{DO}_2 = 150 - \text{PaCO}_2/0.8 - \text{PaCO}_2
\]

where (A-a)DO₂ is typically < 20 but increases with age (because of age-related decline in pulmonary function) and with increasing FI₂ (because, although Hb becomes 100% saturated at a PaO₂ of about 150 mm Hg, O₂ is soluble in blood, and the O₂ content of plasma continues to increase at increasing FI₂). Estimations of normal (A-a)DO₂ values as < (2.5 + [FI₂ × age in years]) or as less than the absolute value of the FI₂ (e.g., < 21 on room air; < 30 on 30% FI₂) correct for these effects.

**Hypoxemia with increased (A-a)DO₂:** This situation is caused by

- Ventilation/perfusion (V/Q) mismatch
- Right-to-left shunting
- Severely impaired diffusing capacity

**V/Q mismatch** is one of the more common reasons for hypoxemia and contributes to the hypoxemia occurring with COPD and asthma. In normal lungs, regional perfusion closely matches regional ventilation...
because of the arteriolar vasoconstriction that occurs in response to alveolar hypoxia. In disease states, dysregulation leads to perfusion of alveolar units that are receiving less than complete ventilation (V/Q mismatch). As a result, systemic venous blood passes through the pulmonary capillaries without achieving normal levels of PaO$_2$. Supplemental O$_2$ can correct hypoxemia due to V/Q mismatch by increasing the PaO$_2$, although the increased (A-a)DO$_2$ persists.

**Right-to-left shunting** is an extreme example of V/Q mismatch. With shunting, deoxygenated pulmonary arterial blood arrives at the left side of the heart without having passed through ventilated lung segments. Shunting may occur through lung parenchyma, through abnormal connections between the pulmonary arterial and venous circulations, or through intracardiac communications (eg, patent foramen ovale). Hypoxemia due to right-to-left shunting does not respond to supplemental O$_2$.

**Impaired diffusing capacity** only rarely occurs in isolation; usually it is accompanied by significant V/Q mismatch. Because O$_2$ completely saturates Hb after only a fraction of the time that blood is in contact with alveolar gas, hypoxemia due to impaired diffusing capacity occurs only when cardiac output is increased (eg, with exercise), when barometric pressure is low (eg, at high altitudes), or when > 50% of the pulmonary parenchyma is destroyed. As with V/Q mismatch, the (A-a)DO$_2$ is increased, but PaO$_2$ can be increased by increasing the FIO$_2$. Hypoxemia due to impaired diffusing capacity responds to supplemental O$_2$.

**Hypoxemia with normal (A-a)DO$_2$:** This situation is caused by

- Hypoventilation
- Low partial pressures of inspired O$_2$ (PIO$_2$)

**Hypoventilation** (reduced alveolar ventilation) decreases the PAO$_2$ and increases the PaCO$_2$, there by decreasing PaO$_2$. In cases of pure hypoventilation, the (A-a)DO$_2$ is normal. Causes of hypoventilation include decreased respiratory rate or depth (eg, due to neuromuscular disorders, severe obesity, or drug overdose) or an increase in the fraction of dead space ventilation in patients already at their maximal ventilatory limit (eg, an exacerbation of severe COPD). Hypoventilatory hypoxemia responds to supplemental O$_2$.

**Decreased PIO$_2$** is a final uncommon cause of hypoxemia that in most cases occurs only at high altitude. Although FIO$_2$ does not change with altitude, ambient air pressure decreases exponentially; thus, PIO$_2$ decreases as well. For example, PIO$_2$ is only 43 mm Hg at the summit of Mt. Everest (altitude, 8848 m [29,028 ft]). The (A-a)DO$_2$ remains normal. Hypoxic stimulation of respiratory drive increases alveolar ventilation and decreases PaCO$_2$ level. This type of hypoxemia responds to supplemental O$_2$.

**Carbon Dioxide**

PCO$_2$ normally is maintained between 35 and 45 mm Hg. A dissociation curve similar to that for O$_2$ exists for CO$_2$ but is nearly linear over the physiologic range of PaCO$_2$. Abnormal PCO$_2$ is always linked to disorders of ventilation and is always associated with acid-base changes.

**Hypercapnia:** Hypercapnia is PCO$_2$ > 45 mm Hg. Causes of hypercapnia are the same as those of hypoventilation (see above). Disorders that increase CO$_2$ production (eg, hyperthyroidism, fever) when combined with an inability to increase ventilation also cause hypercapnia.

**Hypocapnia:** Hypocapnia is PCO$_2$ < 35 mm Hg. Hypocapnia is always caused by hyperventilation due to pulmonary (eg, pulmonary edema or embolism), cardiac (eg, heart failure), metabolic (eg, acidosis), drug-induced (eg, aspirin, progesterone), CNS (eg, infection, tumor, bleeding, increased intracranial pressure), or physiologic (eg, pain, pregnancy) disorders or conditions. Hypocapnia is thought to directly increase bronchoconstriction and lower the threshold for cerebral and myocardial ischemia, perhaps
through its effects on acid-base status.

**Carboxyhemoglobinemia**

CO binds to Hb with an affinity 210 times that of O\(_2\) and prevents O\(_2\) transport. Clinically toxic carboxyhemoglobin levels are most often the result of exposure to exhaust fumes or from smoke inhalation, although cigarette smokers have detectable levels. Patients with CO poisoning (see p. 3334) may present with nonspecific symptoms such as malaise, headache, and nausea. Because poisoning often occurs during colder months (because of indoor use of combustible fuel heaters), symptoms may be confused with a viral syndrome such as influenza. Clinicians must be alert to the possibility of CO poisoning and measure levels of carboxyhemoglobin when indicated; COHb can be directly measured from venous blood—an arterial sample is unnecessary.

Treatment is the administration of 100% O\(_2\) (which shortens the half-life of carboxyhemoglobin) and sometimes the use of a hyperbaric chamber.

**Methemoglobinemia**

Methemoglobin is Hb in which the iron is oxidized from its ferrous (Fe\(^{2+}\)) to its ferric (Fe\(^{3+}\)) state. Methemoglobin does not carry O\(_2\) and shifts the normal HbO\(_2\) dissociation curve to the left, thereby limiting the release of O\(_2\) to the tissues. Methemoglobinemia is caused by certain drugs (eg, dapsone, local anesthetics, nitrates, primaquine, sulfonamides) or, less commonly, by certain chemicals (eg, aniline dyes, benzene derivatives). Methemoglobin level can be directly measured by co-oximetry (which emits 4 wavelengths of light and is capable of detecting methemoglobin, COHb, Hb, and HbO\(_2\)) or may be estimated by the difference between the O\(_2\) saturation calculated from the measured PaO\(_2\) and the directly measured SaO\(_2\). Patients with methemoglobinemia most often have asymptomatic cyanosis. In severe cases, O\(_2\) delivery is reduced to such a degree that symptoms of tissue hypoxia result, such as confusion, angina, and myalgias. Stopping the causative drug or chemical exposure is often sufficient. Rarely, methylene blue (a reducing agent; a 1% solution is given 1 to 2 mg/kg slowly IV) or exchange transfusion is needed.

Tests of Respiratory Muscle Function

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) measurements may aid in evaluating respiratory muscle weakness.

**MIP** is the pressure generated during maximal inspiratory effort against a closed system. It is usually measured at residual volume (RV) because inspiratory muscle strength is inversely related to lung volume (in a curvilinear fashion).

**MEP** is measured during a similar maneuver at total lung capacity (TLC) because expiratory muscle strength is directly related to lung volume (again in a curvilinear fashion). The information available from these maneuvers is nonspecific, however, and cannot distinguish between insufficient effort, muscle weakness, and a neurologic disorder.

The **maximal voluntary ventilation** (MVV) is another measure of the neuromuscular and respiratory systems. The MVV is the total volume of air exhaled during 12 sec of rapid, deep breathing, which can be compared with a predicted MVV defined as the forced expiratory volume in 1 sec (FEV\(_1\)) × 35 or 40. A significant difference between the predicted and measured MVV may indicate insufficient neuromuscular reserve, abnormal respiratory mechanics, or an inadequate effort. Progressive reduction of tidal volumes during the test is consistent with neuromuscular abnormalities but also occurs with gas trapping as a result of disorders that cause airflow limitation.

The **sniff test** is sometimes used in suspected cases of diaphragmatic paralysis or paresis. During continuous fluoroscopic examination, the patient makes a quick, short, strong inspiratory effort ("sniff"). This maneuver minimizes the contribution of the other muscles of respiration (eg, intercostals).
weakened hemidiaphragm may have decreased excursion compared with the contralateral diaphragm or may move upward paradoxically. Occasionally, electromyographic interrogation of the diaphragm and phrenic nerve is done but is of uncertain diagnostic accuracy. Muscle and nerve biopsies may be helpful in selected cases.

**Exercise Testing**

The two most common forms of exercise testing used to evaluate pulmonary disorders are the 6-min walk test and full cardiopulmonary exercise testing.

**Six-minute walk test:** This simple test measures the maximal distance that patients can walk at their own pace in 6 min. The test assesses global functional capacity but does not provide specific information on the individual systems involved in exercise capacity (ie, cardiac, pulmonary, hematologic, musculoskeletal). Neither does it assess patient effort. This test is used for preoperative and postoperative evaluation of patients undergoing lung transplantation and lung volume reduction surgery, to monitor response to therapeutic interventions and pulmonary rehabilitation, and to predict mortality and morbidity in patients with cardiac and pulmonary vascular disorders.

**Cardiopulmonary exercise testing (CPET):** This computerized test provides a breath-by-breath analysis of respiratory gas exchange and cardiac function at rest and during a period of exercise, the intensity of which is increased incrementally until symptoms limit testing. Information on airflow, \( \text{O}_2 \) consumption, \( \text{CO}_2 \) production, and heart rate are collected and used for computation of other variables; ABGs may also be sampled. Exercise is done on a treadmill or on a bicycle ergometer; the ergometer may be preferable because work rate can be directly measured.

CPET primarily determines whether patients have normal or reduced maximal exercise capacity (\( \text{VO}_2\text{max} \)) and, if so, suggests probable causes. CPET is used to define which organ systems contribute to a patient's symptoms of exertional dyspnea and exercise intolerance and to what extent. The test is also more sensitive for detecting early or subclinical disease than are less comprehensive tests that are done at rest. Examples of applications include

- Assessment of exercise capacity for disability evaluation
- Preoperative assessment
- Determination of whether dyspnea symptoms result from cardiac or pulmonary problems in patients who have disorders of both organ systems
- Selection of candidates for cardiac transplantation
- Assessment of prognosis in selected disorders (eg, heart disease, pulmonary vascular disorders, and cystic fibrosis)

CPET can also help gauge responses to therapeutic interventions and guide prescription of exercise in rehabilitation programs. In following the response to therapy or disease progression, a steady-state CPET involving at least 6 min of constant work at 50 to 70% of the maximal work rate achieved during a maximal CPET may be more useful than an incremental, maximal CPET. Repeated evaluation at this work rate over time provides comparable data and is sensitive to improvement or decline in cardiopulmonary function.

Several variables are assessed during CPET, and no single one is diagnostic of a cause for exercise limitation. Instead, an integrative approach using clinical data, trends during exercise, and recognition of underlying patterns of physiologic responses is used.
Chapter 190. Diagnostic and Therapeutic Pulmonary Procedures

Introduction

Diagnostic tests besides pulmonary function testing (see p. 1851) include various types of chest imaging, electrocardiography, and ventilation/perfusion scanning. Diagnostic procedures include bronchoscopy, mediastinoscopy and mediastinotomy, pleural biopsy, thoracentesis, thoracoscopy and video-assisted thorascopic surgery, thoracotomy, transthoracic needle biopsy, and tube thoracostomy. Pulmonary artery catheterization is discussed elsewhere (see p. 2248). Therapeutic procedures include chest physiotherapy and pulmonary rehabilitation.

Chest Imaging

Imaging includes use of x-rays, MRI, nuclear scanning, and ultrasonography. There are no absolute contraindications to undergoing noninvasive imaging procedures.

X-Ray Techniques

X-ray techniques that are used to image the chest include plain x-rays, fluoroscopy, high-resolution and helical (spiral) CT, and CT angiography.

Chest x-ray: Plain chest x-rays and fluoroscopy are used to provide images of the lungs and surrounding structures.

Plain chest x-rays provide images of structures in and around the thorax and are most useful for identifying abnormalities in the heart, lung parenchyma, pleura, chest wall, diaphragm, mediastinum, and hilum. They are usually the initial test done to evaluate the lungs. The standard chest x-ray is taken from back to front (posteroanterior view) to minimize x-ray scatter that could artifactualy enlarge the cardiac silhouette and from the side of the thorax (lateral view). Lordotic or oblique views can be obtained to evaluate pulmonary nodules or to clarify abnormalities that may be due to superimposed structures, although chest CT provides more information and has largely superseded these views. Lateral decubitus views may be used to distinguish free-flowing from loculated pleural effusion, but again CT provides more information. End-expiratory views can be used to detect small pneumothoraces. Screening chest x-rays are often done but are almost never indicated; one exception is in asymptomatic patients with positive tuberculin skin test results, in whom a single posteroanterior chest x-ray without a lateral view is used to make decisions regarding treatment for pulmonary TB. Portable (usually anteroposterior) chest x-rays are almost always suboptimal and should be used only when patients are too ill to be transported to the radiology department.

Chest fluoroscopy is the use of a continuous x-ray beam to image movement. It is useful for detecting unilateral diaphragmatic paralysis. During a sniff test, in which the patient is instructed to forcibly inhale through the nose (or sniff), a paralyzed hemidiaphragm moves cranially (paradoxically) while the unaffected hemidiaphragm moves caudally.

Computed tomography: CT defines intrathoracic structures and abnormalities more clearly than does a chest x-ray. Conventional (planar) CT provides multiple 10-mm-thick cross-sectional images through the thorax. Its main advantage is wide availability. Disadvantages are motion artifact and limited detail from volume averaging of tissue within each 10-mm slice.

High-resolution CT (HRCT) provides 1-mm-thick cross-sectional images. HRCT is particularly helpful in evaluating interstitial lung diseases (eg, lymphangitic carcinomatosis, sarcoid, fibrosing alveolitis) and bronchiectasis.

Helical (spiral) CT provides multiplanar images of the entire chest as patients hold their breath for 8 to 10 sec while being moved continuously through the CT gantry. Helical CT is thought to be at least equivalent to conventional CT for most purposes. Its main advantages are speed, less radiation exposure, and an ability to construct 3-dimensional images. Software can also generate images of bronchial mucosa (virtual bronchoscopy). Its main disadvantages are less availability and the requirement for breath-
holding, which can be difficult for patients with symptomatic pulmonary disease.

**CT angiography** uses a bolus of IV contrast to highlight the pulmonary arteries, which is useful in diagnosis of pulmonary embolism. Dye load is comparable to conventional angiography, but the test is quicker and less invasive. Several studies have confirmed sufficient accuracy of CT angiography for the detection of pulmonary emboli, so it has largely replaced ventilation/perfusion (V/Q) scanning and conventional pulmonary angiography (except in patients unable to tolerate contrast).

**Magnetic Resonance Imaging**

MRI has a relatively limited role in pulmonary imaging but is preferred over CT in specific circumstances, such as assessment of superior sulcus tumors, possible cysts, and other lesions that abut the chest wall. In patients with suspected pulmonary embolism in whom IV contrast cannot be used, MRI can sometimes identify large proximal emboli but usually is limited in this disorder. The use of MRI to evaluate pulmonary hypertension is being studied, and this practice may become more common.

Advantages include absence of radiation exposure, excellent visualization of vascular structures, lack of artifact from bone, and excellent soft-tissue contrast. Disadvantages include respiratory and cardiac motion and the time it takes to do the procedure.

**Ultrasoundography**

Ultrasoundography is primarily used to facilitate procedures such as thoracentesis and central venous catheter insertion. Endobronchial ultrasonography is sometimes used in conjunction with fiberoptic bronchoscopy to help localize masses and enlarged lymph nodes. Ultrasonography is also useful for evaluating presence and size of pleural effusions.

**Nuclear Scanning**

Nuclear scanning techniques used to image the chest include ventilation/perfusion (V/Q) scanning and positron emission tomography (PET) scanning.

**V/Q scanning:** V/Q scanning uses inhaled radionuclides to detect ventilation and IV radionuclides to detect perfusion. Areas of ventilation without perfusion, perfusion without ventilation, or matched increases and decreases in both can be detected with 6 to 8 views of the lungs.

V/Q scanning is most commonly used for diagnosing pulmonary embolism but has largely been replaced by CT angiography. Split-function ventilation scanning, in which the degree of ventilation is quantified for each lobe, is used to predict the effect of lobar or lung resection on pulmonary function; post-surgical forced expiratory volume in 1 sec (FEV$_1$) is estimated as the percentage of uptake of ventilation tracer in the healthy fraction of the lungs multiplied by preoperative FEV$_1$ (in liters). A value of $< 0.8$ L (or $< 40\%$ of that predicted for the patient) indicates limited pulmonary reserve and a high likelihood of unacceptably high perioperative morbidity and mortality.

**PET scanning:** PET scanning uses radioactively labeled glucose (fluorodeoxyglucose) to measure metabolic activity in tissues. It is used in pulmonary disorders to determine whether lung nodules or mediastinal lymph nodes harbor tumor (metabolic staging) and whether cancer is recurrent in previously irradiated, scarred areas of the lung. PET is superior to CT for mediastinal staging because PET can identify tumor in normal-sized lymph nodes and at extrathoracic sites, thereby decreasing the need for invasive procedures such as mediastinoscopy and needle biopsy. Current spatial resolution of PET is 7 to 8 mm; thus, the test is not useful for lesions $< 1$ cm. PET reveals metastatic disease in up to 14% of patients in whom it would not otherwise be suspected. The sensitivity of PET (80 to 95%) is comparable to that of histologic tissue examination. False-positive results can occur with inflammatory lesions, such as granulomas; slowly growing tumors (eg, bronchoalveolar carcinoma, carcinoid tumor, some metastatic cancers) may cause false-negative results. Newer combined CT-PET scanners may become the most cost-effective technology for lung cancer diagnosis and staging.

**Electrocardiography**
Electrocardiography is a useful adjunct to other pulmonary tests because it provides information about the right side of the heart (see p. 2054) and therefore pulmonary disorders such as chronic pulmonary hypertension and pulmonary embolism.

**Chronic pulmonary hypertension** leading to chronic right atrial and ventricular hypertrophy and dilation may manifest as prominent P waves (P pulmonale) and ST-segment depression in leads II, III, and aVF; rightward shift in QRS axis; inferior shift of the P wave vector; and decreased progression of R waves in precordial leads.

**COPD** patients commonly have low voltage due to interposition of hyperexpanded lungs between the heart and ECG electrodes.

**Pulmonary embolism** (submassive or massive) may cause acute right ventricle overload or failure, which manifests as right axis deviation (R > S in V1), with S-wave deepening in lead I, Q-wave deepening in lead III, and ST-segment elevation and T-wave inversion in lead III and the precordial leads (S1Q3T3 pattern). Right bundle branch block also sometimes occurs.

**Bronchoscopy**

Bronchoscopy is introduction of an endoscope into the airways. Flexible fiberoptic bronchoscopy has replaced rigid bronchoscopy for virtually all diagnostic, and most therapeutic, indications.

**Rigid bronchoscopy** is now used only when a wider aperture and channels are required for better visualization and instrumentation such as when

- Investigating vigorous pulmonary hemorrhage (in which the rigid bronchoscope can better identify the bleeding source and, with its larger suction channel, can better suction the blood and prevent asphyxiation)
- Viewing and removing aspirated foreign bodies in young children
- Viewing obstructive endobronchial lesions (requiring laser debulking or stent placement)

**Flexible bronoscopes** are nearly all color video-compatible, facilitating airway visualization and documentation of findings.

Diagnostically, flexible fiberoptic bronchoscopy allows for

- Direct airway visualization down to, and including, subsegmental bronchi
- Sampling of respiratory secretions and cells via bronchial washings, brushings, and lavage of peripheral airways and alveoli
- Biopsy of endobronchial, parenchymal, and mediastinal structures

Therapeutic uses include suctioning of retained secretions, endobronchial stent placement, and balloon dilation of airway stenoses.

**Contraindications:** Absolute contraindications include

- Untreatable life-threatening arrhythmias
- Inability to adequately oxygenate the patient during the procedure
- Acute respiratory failure with hypercapnia (unless the patient is intubated and ventilated)

**Relative contraindications** include

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• Uncooperative patient
• Recent MI
• High-grade tracheal obstruction
• Unrectractable coagulopathy

Transbronchial biopsy should be done with caution in patients with uremia, superior vena cava obstruction, or pulmonary hypertension because of increased risk of bleeding. Inspection of the airways is safe in these patients, however.

Procedure: Bronchoscopy should be done only by a pulmonologist or trained surgeon in a monitored setting, typically a bronchoscopy suite, operating room, or ICU (for ventilated patients).

Patients should receive nothing by mouth for at least 4 h before bronchoscopy and have IV access, intermittent BP monitoring, continuous pulse oximetry, and cardiac monitoring. Supplemental O\textsubscript{2} should be available. Premedication with atropine 0.01 mg/kg IM or IV to decrease secretions and vagal tone is common, although this practice has been called into question by recent studies. Shortacting benzodiazepines, opioids, or both are generally given to patients before the procedure to decrease anxiety, discomfort, and cough.

The pharynx and vocal cords are anesthetized with nebulized or aerosolized lidocaine (1 or 2%, to a maximum of 250 to 300 mg for a 70-kg patient). The bronchoscope is lubricated with lidocaine jelly and passed through the nostril or through the mouth with use of an oral airway or bite block. After inspecting the nasopharynx and larynx, the clinician passes the bronchoscope through the vocal cords during inspiration, into the trachea and then further distally into the bronchi.

Several ancillary procedures can be done as needed, with or without fluoroscopic guidance:

• Bronchial washing: Saline is injected through the bronchoscope and subsequently aspirated from the airways.

• Bronchial brushing: A brush is advanced through the bronchoscope and used to abrade suspicious lesions to obtain cells.

• Bronchoalveolar lavage: 50 to 200 mL of sterile saline is infused into the distal bronchoalveolar tree and subsequently suctioned out, retrieving cells, protein, and microorganisms located at the alveolar level. Local areas of pulmonary edema created by lavage may cause transient hypoxemia.

• Transbronchial biopsy: Forceps are advanced through the bronchoscope and airway to obtain samples from one or more sites in the lung parenchyma. Transbronchial biopsy can be done without x-ray guidance, but evidence supports increased diagnostic yields and lower incidence of pneumothorax when fluoroscopic guidance is used.

• Transbronchial needle aspiration: A retractable needle is inserted through the bronchoscope and can be used to sample enlarged mediastinal lymph nodes or masses.

Patients are typically given supplemental O\textsubscript{2} and observed for 2 to 4 h after the procedure. Return of a gag reflex and maintenance of O\textsubscript{2} saturation when not receiving O\textsubscript{2} are the two primary indices of recovery. Standard practice is to obtain a posteroanterior chest x-ray after transbronchial lung biopsy to exclude pneumothorax.

Complications: Serious complications are uncommon; minor bleeding from a biopsy site and fever occur in 10 to 15% of patients. Premedication can cause oversedation with respiratory depression, hypotension, and cardiac arrhythmias. Rarely, topical anesthesia causes laryngospasm, bronchospasm,
seizures, methemoglobinemia with refractory cyanosis, or cardiac arrhythmias or arrest.

Bronchoscopy itself may cause minor laryngeal edema or injury with hoarseness, hypoxemia in patients with compromised gas exchange, arrhythmias (most commonly premature atrial contractions, ventricular premature beats, or bradycardia), and, very rarely, transmission of infection from suboptimally sterilized equipment. Mortality is 1 to 4/10,000 patients. The elderly and patients with serious comorbidities (severe COPD, coronary artery disease, pneumonia with hypoxemia, advanced cancers, mental dysfunction) are at greatest risk.

Transbronchial biopsy can cause pneumothorax (2 to 5%) and significant hemorrhage (1 to 1.5%); mortality increases to 12/10,000 patients, but doing the procedure can avoid the need for thoracotomy.

**Mediastinoscopy and Mediastinotomy**

Mediastinoscopy is introduction of an endoscope into the mediastinum. Mediastinotomy is surgical opening of the mediastinum. The two are complementary. Mediastinotomy gives direct access to aortopulmonary window lymph nodes, which are inaccessible by mediastinoscopy. Both procedures are done to evaluate or excise mediastinal lymphadenopathy or masses and to stage cancers (eg, lung cancer, esophageal cancer), although PET scanning is decreasing the need for these procedures for cancer staging.

**Contraindications:** Contraindications include the following:

- Superior vena cava syndrome
- Previous mediastinal irradiation
- Mediastinoscopy
- Median sternotomy
- Tracheostomy
- Aneurysm of the aortic arch

Mediastinoscopy and mediastinotomy are done by surgeons in an operating room using general anesthesia. For mediastinoscopy, the soft tissue of the neck is bluntly dissected down to the trachea and distally to the carina through an incision in the suprasternal notch. A mediastinoscope is inserted into the space allowing access to the paratracheal, tracheobronchial, azygous, and subcarinal nodes and to the superior posterior mediastinum. Anterior mediastinotomy (the Chamberlain procedure) is surgical entry to the mediastinum through an incision in the parasternal 2nd left intercostal space, allowing access to anterior mediastinal and aortopulmonary window lymph nodes, common sites of metastases for left upper lobe lung cancers.

**Complications:** Complications occur in < 1% of patients and include bleeding, infection, vocal cord paralysis due to recurrent laryngeal nerve damage, chylothorax from duct injury, and pneumothorax.

**Pleural Biopsy**

Pleural biopsy is done to determine the cause of an exudative pleural effusion when thoracentesis is not diagnostic. The yield of closed pleural biopsy is about twice as high for TB than it is for pleural cancers. Improved laboratory techniques, newer diagnostic tests for pleural fluid (eg, adenosine deaminase levels, interferon-γ, PCR studies for suspected TB), and more widespread availability of thoracoscopy have made the procedure less necessary.

Percutaneous pleural biopsy should be done only by a pulmonologist or surgeon trained in the procedure and should be done only in patients who are cooperative and have no coagulation abnormalities. Technique is essentially the same as that for thoracentesis and can be done at the bedside; no specific
additional patient preparation is necessary. At least 3 specimens obtained from one skin location, with 3, 6, and 9 o'clock positioning of the needle-cutting chamber, are needed for histology and culture.

Chest x-ray should be done after biopsy because of increased risk of complications, which are the same as those for thoracentesis but with higher incidence of pneumothorax and hemorrhage.

**Thoracentesis**

Thoracentesis is puncture through the chest wall for the purpose of aspirating pleural fluid. It is used to determine the etiology of a pleural effusion (diagnostic thoracentesis), to relieve dyspnea caused by pleural fluid (therapeutic thoracentesis), and, occasionally, to carry out pleurodesis.

**Contraindications:** No absolute contraindications to thoracentesis exist except refusal of or inability to consent to the procedure.

**Relative contraindications** include

- Uncertain fluid location by examination
- Minimal fluid volume
- Altered chest wall anatomy
- Pulmonary disease severe enough to make complications life threatening
- Bleeding diatheses or coagulopathy
- Uncontrolled coughing

**Procedure:** Thoracentesis can be safely done at the patient's bedside or in an outpatient setting. Presence and location of pleural fluid is verified by physical examination (chest percussion) or by imaging techniques. Ultrasonography, CT, or both may be useful if chest x-rays are equivocal, if prior thoracentesis attempts were unsuccessful, or if the fluid is loculated.

Thoracentesis is best done with the patient sitting upright and leaning slightly forward with arms supported. Recumbent or supine thoracentesis (eg, in a ventilated patient) is possible but best done with ultrasound or CT guidance. Only unstable patients and patients at high risk of decompensation due to complications require monitoring (eg, pulse oximetry, ECG).

Under sterile conditions, 1 to 2% lidocaine is injected with a 25-gauge needle to anesthetize the skin. A larger (20- or 22-gauge) needle with anesthetic is then inserted at the upper border of the rib one intercostal space below the fluid level in the midscapular line. The needle is advanced with periodic aspiration (to avoid inadvertent insertion into a blood vessel and intravascular injection), and anesthetic is injected at progressively deeper levels. The most painful level after the skin is the parietal pleura, which should be infiltrated the most. The needle is then advanced beyond the parietal pleura until pleural fluid is aspirated, at which point the depth of the needle should be noted. A large-bore (16- to 19-gauge) thoracentesis needle-catheter device is then attached to a 3-way stopcock, which is connected to a 30- to 50-mL syringe and tubing that drains into a container. The thoracentesis needle is passed through the skin and subcutaneous tissue along the upper border of the rib into the effusion at about the same depth noted during anesthesia. The catheter is inserted through the needle, and the needle is withdrawn to decrease the risk of pneumothorax.

Pleural fluid can then be aspirated and, with a turn of the stopcock, collected in tubes or bags for further evaluation. Fluid should be removed in stages not to exceed 1.5 L/day because hypotension and pulmonary edema may occur with removal of > 1.5 L of fluid at one sitting or with rapid evacuation of the pleural space using a vacuum or suction bottle. When large volumes of fluid must be removed, blood pressure should be monitored continuously.
It has been standard practice to obtain a chest x-ray after thoracentesis to rule out pneumothorax, document the extent of fluid removal, and view lung fields previously obscured by fluid, but evidence suggests that routine chest x-ray is not necessary in asymptomatic patients.

Coughing is common as the lung re-expands; it does not signify pneumothorax. If the pleural process is inflammatory, pleuritic pain, an audible pleural rub, or both may develop as fluid is removed because of approximation of inflamed visceral and parietal pleura. When substantial volumes of fluid are removed from the pleural space, the plunger on the syringe should be released periodically during aspiration. If the fluid in the syringe is drawn back into the pleural space when negative pressure on the syringe is decreased, pleural pressure may be too negative, and the lung may be restricted from re-expanding because of enveloping adhesions or tumor.

**Complications:** Complications include

- Pneumothorax
- Hemoptysis due to lung puncture
- Re-expansion pulmonary edema or hypotension after rapid removal of large volumes of fluid
- Hemothorax due to damage to intercostal vessels
- Puncture of the spleen or liver
- Vasovagal syncope

Bloody fluid that does not clot in a collecting tube indicates that blood in the pleural space was not iatrogenic, because free blood in the pleural space rapidly defibrinates.

**Thoracoscopy and Video-Assisted Thoracoscopic Surgery**

Thoracoscopy is introduction of an endoscope into the pleural space. Thoracoscopy can be used for visualization (pleuroscopy) or for surgical procedures. Surgical thoracoscopy is more commonly referred to as video-assisted thoracoscopic surgery (VATS). Pleuroscopy can be done with the patient under conscious sedation in an endoscopy suite, whereas VATS requires general anesthesia and is done in the operating room. Both procedures induce a pneumothorax to create a clear view.

Thoracoscopy is used to evaluate exudative effusions and various pleural and lung lesions when noninvasive testing is inconclusive. The diagnostic accuracy for malignant and tuberculous disease of the pleura is 95%. The procedure is also used for pleurodesis in patients with recurrent malignant effusions and to break up loculations in patients with empyema.

Indications for VATS include correction of spontaneous primary pneumothorax, bullectomy and lung volume reduction surgery in emphysema, wedge resection, and, in some medical centers, lobectomy and even pneumonectomy. Less common indications are excision of benign mediastinal masses; biopsy and staging of esophageal cancer; sympathectomy for severe hyperhidrosis or causalgia; and repair of traumatic injuries to the lung, pleura, and diaphragm.

**Contraindications:** Contraindications are the same as those for thoracentesis; adhesive obliteration of the pleural space is an absolute contraindication. Biopsy is contraindicated in patients with highly vascular cancers, severe pulmonary hypertension, and severe bullous lung disease.

**Procedure:** Although some pulmonologists do pleuroscopy, VATS is done by thoracic surgeons. Both procedures are similar to chest tube insertion; a trocar is inserted into an intercostal space through a skin incision, through which a thoracoscope is inserted. Additional incisions permit the use of video cameras and accessory instruments.

After thoracoscopy, a chest tube is usually required for 1 to 2 days.
**Complications:** Complications are similar to those of thoracentesis. Postprocedural fever is common (16%); pleural tears causing air leak, subcutaneous emphysema, or both are less common (2% each). Hemorrhage, lung perforation, and gas embolism are serious but rare.

**Thoracotomy**

Thoracotomy is surgical opening of the chest. It is done to evaluate and treat pulmonary problems when noninvasive procedures are nondiagnostic or unlikely to be definitive.

**Contraindications:** Contraindications are those general to surgery and include coagulopathy that cannot be corrected, acute cardiac ischemia, and instability or insufficiency of major organ systems.

**Procedure:** Three basic approaches are used.

• Limited anterior or lateral thoracotomy: A 6- to 8-cm intercostal incision is made to approach the anterior structures.

• Posterolateral thoracotomy: The posterolateral approach gives access to pleurae, hilum, mediastinum, and the entire lung.

• Sternal splitting incision (median sternotomy): When access to both lungs is desired, as in lung volume reduction surgery, a sternal splitting incision is used.

Patients undergoing limited thoracotomy require a chest tube for 1 to 2 days and in many cases can leave the hospital in 3 to 4 days. The principal indications for thoracotomy are lobectomy and pneumonectomy (eg, lung cancer surgery). Video-assisted thoracoscopic surgery has replaced thoracotomy for open pleural and lung biopsies.

**Complications:** Complications are greater than those for any other pulmonary biopsy procedure because of the risks of general anesthesia, surgical trauma, and a longer hospital stay with more postoperative discomfort. Hemorrhage, infection, pneumothorax, bronchopleural fistula, and reactions to anesthetics are the greatest hazards. Mortality for exploratory thoracotomy ranges from 0.5 to 1.8%.

**Transthoracic Needle Biopsy**

Transthoracic needle biopsy of thoracic or mediastinal structures uses a cutting needle to aspirate a core of tissue for histologic analysis. Transthoracic needle biopsy is done to evaluate peripheral lung nodules or masses; hilar, mediastinal, and pleural abnormalities; and undiagnosed infiltrates or pneumonias when bronchoscopy is contraindicated or nondiagnostic. When done with the use of CT guidance and with a skilled cytopathologist in attendance, transthoracic needle biopsy confirms the diagnosis of cancer with > 95% accuracy. Needle biopsy yields an accurate diagnosis in benign processes only 50 to 60% of the time.

**Contraindications:** Contraindications are similar to those of thoracentesis. Additional contraindications include the following:

• Mechanical ventilation

• Contralateral pneumonectomy

• Suspected vascular lesions

• Putrid lung abscess

• Hydatid cyst

• Pulmonary hypertension
• Bullous lung disease

• Intractable coughing

• Coagulopathy, platelet count < 50,000/μL, and other bleeding diatheses

**Procedure:** Transthoracic needle biopsy is usually done by an interventional radiologist, often with a cytopathologist present. Under sterile conditions, local anesthesia, and imaging guidance—usually CT but sometimes ultrasonography for pleural-based lesions—a biopsy needle is passed into the suspected lesion while patients hold their breath. Lesions are aspirated with or without saline; 2 or 3 samples are collected for cytologic and bacteriologic processing. After the procedure, fluoroscopy and chest x-rays are used to rule out pneumothorax and hemorrhage. Core needle biopsies are used to obtain a cylinder of tissue suitable for histologic examination.

**Complications:** Complications include pneumothorax (10 to 37%), hemoptysis (10 to 25%), parenchymal hemorrhage, air embolism, and subcutaneous emphysema.

**Tube Thoracostomy**

Tube thoracostomy is insertion of a tube into the pleural space. It is used to drain air or fluid from the chest (eg, for large or recurrent effusion refractory to thoracentesis, pneumothorax, complicated parapneumonic effusions, empyema, or hemothorax) and to do pleurodesis or fibrinolytic adhesiolysis.

**Procedure:** Chest tube insertion is best done by a physician trained in the procedure. Other physicians can handle emergency situations (eg, tension pneumothorax) using a needle and syringe. Tube insertion requires 1 or 2 hemostats or Kelly clamps, a silk suture, gauze dressing, and a chest tube. Recommended tube sizes are 16 to 24 French (F) for pneumothorax; 20 to 24 F for malignant pleural effusion; 28 to 36 F for bronchopleural fistula, complicated parapneumonic effusions, and empyema; and 32 to 40 F for hemothorax.

The insertion site and patient position depend on whether air or fluid is being drained. For pneumothorax, the tube is usually inserted in the 4th intercostal space and for other indications in the 5th or 6th intercostal space, in the midaxillary line with the ipsilateral arm abducted above the head.

No specific patient preparation is necessary except, in some cases, conscious sedation. Under sterile conditions, the skin, subcutaneous tissue, rib periosteum, and parietal pleura are locally anesthetized, more generously than for thoracentesis (see p. 1864). Proper location is confirmed by return of air or fluid in the anesthetic syringe. A purse-string suture can be placed but not yet tied around the site while the anesthetic takes effect. A 2-cm skin incision is made, and the intercostal soft tissue down to the pleura is then bluntly dissected by advancing a clamped hemostat or Kelly clamp and opening it; the pleura is then perforated with the clamped instrument and opened in the same way. A finger can be used to widen the tract and confirm entry into the pleural space. The chest tube, with a clamp grasping the tip, is inserted through the tract and directed inferoposteriorly for effusions, or apically for pneumothorax, until all of the tube’s holes are inside the chest wall. The pursestring suture is closed, the tube is sutured to the chest wall, and a sterile dressing with petroleum gauze to help seal the wound is placed over the site.

The tube is connected to water seal to prevent air from entering the chest through the tube and to allow drainage without suction (for effusions or empyema) or with suction (for pneumothorax). Posteroanterior and lateral chest x-rays are obtained after insertion to check the tube’s position.

The tube is removed when the condition for which it was placed resolves. In the case of pneumothorax, suction is stopped and the tube is placed on water seal for several hours to ensure that the air leak has stopped and that the lung remains expanded. At the moment of removal, the patient is asked to take a deep breath and then to forcibly exhale; the tube is removed during exhalation and the site is covered with petroleum gauze, a sequence that reduces the chance of pneumothorax during removal. For effusions or hemothorax, the tube is typically removed when the drainage is < 100 mL/day.
Complications: Complications include the following:

- Malpositioning of the tube in the lung parenchyma, in the lobar fissure, under the diaphragm, or subcutaneously
- Clotting, kinking, or dislodgement of the tube, requiring replacement
- Re-expansion pulmonary edema
- Subcutaneous emphysema
- Infection of residual pleural fluid or recurrent effusion
- Pulmonary or diaphragmatic laceration
- Rarely perforation of other structures

Chest Physiotherapy

Chest physiotherapy consists of external mechanical maneuvers, such as chest percussion, postural drainage, and vibration, to augment mobilization and clearance of airway secretions. It is indicated for patients in whom cough is insufficient to clear thick, tenacious, or loculated secretions. Examples include patients with cystic fibrosis, bronchiectasis, lung abscess, neuromuscular disorders, and pneumonias in dependent lung regions.

Contraindications: Contraindications all are relative and include the following:

- Discomfort caused by physical positions or manipulations
- Anticoagulation
- Rib or vertebral fractures or osteoporosis
- Recent hemoptysis

Procedure: Chest physiotherapy may be administered by a respiratory therapist, although the techniques can often be taught to family members of patients.

The most common procedure used is postural drainage and chest percussion, in which the patient is rotated to facilitate drainage of secretions from a specific lobe or segment while being clapped with cupped hands to loosen and mobilize retained secretions that can then be expectorated or drained. The procedure is somewhat uncomfortable and tiring for the patient. Alternatives to chest percussion by hand include use of mechanical vibrators and inflatable vests.

Other methods that help clear airways include using controlled patterns of breathing, positive expiratory pressure devices to maintain airway patency, and ultra-low-frequency airway oscillation devices to mobilize sputum. The methods of airway clearance are comparable, and methods should be selected based on individual patient needs and preferences.

Complications: Complications are unusual but include position-related hypoxia and aspiration of secretions in other lung regions.

Pulmonary Rehabilitation

Pulmonary rehabilitation is the use of exercise, education, and behavioral intervention to enhance quality of life. It is indicated for any condition in which respiratory symptoms restrict activity (eg, COPD, interstitial lung disease, neuromuscular disorders causing chest wall weakness) and for respiratory retraining after prolonged ventilator dependence.
For many patients with chronic respiratory disorders, medical therapy only partially allays the symptoms and complications of the disorder. A comprehensive program of pulmonary rehabilitation may lead to significant clinical improvement by reducing shortness of breath, increasing exercise tolerance, and, to a lesser extent, decreasing the number of hospitalizations. However, these programs do not improve survival. There are no complications from pulmonary rehabilitation beyond those expected from physical exertion and exercise.

**Contraindications:** Contraindications are relative and include comorbidities that could complicate attempts to increase a patient's level of exercise (e.g., untreated angina, left ventricular dysfunction). These comorbidities do not preclude application of other components of pulmonary rehabilitation programs, however.

**Procedure:** Pulmonary rehabilitation is best administered as part of an integrated program of exercise training, education, and psychosocial and behavioral intervention by a team of physicians, nurses, respiratory therapists, physical and occupational therapists, and psychologists or social workers.

**Exercise training** involves aerobic exercise and respiratory muscle and extremity strength training; lower extremity strength training may be particularly important for patients with COPD.

**Education** revolves around smoking cessation; teaching breathing strategies (such as pursed-lip breathing, in which exhalations are begun against closed lips to decrease respiratory rate, thereby decreasing gas trapping); principles of conserving physical energy; treatment options, including drug therapy; and advanced-care planning.

**Psychosocial interventions** involve counseling and feedback for the depression, anxieties, and fear that obstruct the patient's full participation in activities.
Chapter 191. Asthma

Introduction

Asthma is a disease of diffuse airway inflammation caused by a variety of triggering stimuli resulting in partially or completely reversible bronchoconstriction. Symptoms and signs include dyspnea, chest tightness, cough, and wheezing. The diagnosis is based on history, physical examination, and pulmonary function tests. Treatment involves controlling triggering factors and drug therapy, most commonly with inhaled β₂-agonists and inhaled corticosteroids. Prognosis is good with treatment.

Epidemiology

The prevalence of asthma has increased continuously since the 1970s, and it now affects an estimated 4 to 7% of people worldwide. More than 20 million people in the US are affected. Asthma is one of the most common chronic diseases of childhood, affecting more than 6 million children; it occurs more frequently in boys before puberty and in girls after puberty. It also occurs more frequently in blacks and Puerto Ricans. Despite its increasing prevalence, however, there has been a recent decline in mortality. About 4000 deaths occur from asthma annually in the US. However, the death rate is 5 times higher for blacks than for whites. Asthma is the leading cause of hospitalization for children and is the number one chronic condition causing elementary school absenteeism. In 2002, the total cost of asthma care was $14 billion.

Etiology

Development of asthma is multifactorial and depends on the interactions among multiple susceptibility genes and environmental factors.

Susceptibility genes are thought to include those for T-helper 1 and 2 (T_{H1} and T_{H2}) cells, IgE, cytokines (IL-3, -4, -5, -9, and -13), granulocyte-monocyte colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), and the ADAM33 gene, which may stimulate airway smooth muscle and fibroblast proliferation or regulate cytokine production.

Environmental factors may include the following:

• Allergen exposure
• Diet
• Perinatal factors

Evidence clearly implicates household allergens (eg, dust mite, cockroach, pets) and other environmental allergens in disease development in older children and adults. Diets low in vitamins C and E and in ω-3 fatty acids have been linked to asthma, as has obesity. Asthma has also been linked to perinatal factors, such as young maternal age, poor maternal nutrition, prematurity, low birthweight, and lack of breastfeeding.

On the other hand, endotoxin exposure early in life can induce tolerance and may be protective. Air pollution is not definitively linked to disease development, though it may trigger exacerbations. The role of childhood exposure to cigarette smoke is controversial, with some studies finding a contributory and some a protective effect.

Genetic and environmental components may interact by determining the balance between T_{H1} and T_{H2} cell lineages. Infants may be born with a predisposition toward proallergic and proinflammatory T_{H2} immune responses, characterized by growth and activation of eosinophils and IgE production. Early childhood exposure to bacterial and viral infections and endotoxins may shift the body to T_{H1} responses, which suppresses T_{H2} cells and induces tolerance. Trends in developed countries toward smaller
families with fewer children, cleaner indoor environments, and early use of vaccinations and antibiotics may deprive children of these T\textsubscript{H}2-suppressing, tolerance-inducing exposures and may partly explain the continuous increase in asthma prevalence in developed countries (the hygiene hypothesis).

**Reactive airways dysfunction syndrome (RADS):** Indoor exposures to nitrogen oxide and volatile organic compounds are implicated in the development of RADS, a persistent asthma-like syndrome in people with no history of asthma (see p. \textit{1979}). RADS appears to be distinct from asthma and may be, on occasion, a form of environmental lung disease. However, RADS and asthma have many clinical similarities (eg, wheezing, dyspnea, cough), and both may respond to corticosteroids.

**Pathophysiology**

Asthma involves

- Bronchoconstriction
- Airway edema and inflammation
- Airway hyperreactivity
- Airway remodeling

In patients with asthma, T\textsubscript{H}2 cells and other cell types—notably, eosinophils and mast cells, but also other CD4+ subtypes and neutrophils—form an extensive inflammatory infiltrate in the airway epithelium and smooth muscle, leading to airway remodeling (ie, desquamation, subepithelial fibrosis, angiogenesis, smooth muscle hypertrophy). Hypertrophy of smooth muscle narrows the airways and increases reactivity to allergens, infections, irritants, parasympathetic stimulation (which causes release of pro-inflammatory neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide), and other triggers of bronchoconstriction. Additional contributors to airway hyperreactivity include loss of inhibitors of bronchoconstriction (epithelium-derived relaxing factor, prostaglandin E\textsubscript{2} and loss of other substances called endopeptidases that metabolize endogenous bronchoconstrictors. Mucus plugging and peripheral blood eosinophilia are additional classic findings in asthma and may be epiphenomena of airway inflammation.

**Triggers:** Common triggers of an asthma attack include

- Environmental and occupational allergens (numerous)
- Infections
- Exercise
- Inhaled irritants
- Emotion
- Aspirin
- Gastroesophageal reflux

Infectious triggers in young children include respiratory syncytial virus, rhinovirus, and parainfluenza virus infection. In older children and adults, URIs (particularly with rhinovirus) and pneumonia are common infectious triggers. Exercise can be a trigger, especially in cold or dry environments. Inhaled irritants, such as air pollution, cigarette smoke, perfumes, and cleaning products, are often involved. Emotions such as anxiety, anger, and excitement sometimes trigger attacks. Aspirin is a trigger in up to 30% of older patients and in patients with more severe asthma. Aspirin-induced asthma is typically accompanied by nasal polyps with nasal and sinus congestion. Gastroesophageal reflux disease (GERD) is a common
exacerbating factor among some patients with asthma, possibly via esophageal acid-induced reflex bronchoconstriction or by microaspiration of acid. Allergic rhinitis often coexists with asthma; it is unclear whether the two are different manifestations of the same allergic process or whether rhinitis is a discrete asthma trigger.

**Response:** In the presence of triggers, there is reversible airway narrowing and uneven lung ventilation. Relative perfusion exceeds relative ventilation in lung regions distal to narrowed airways; thus, alveolar $O_2$ tensions fall and alveolar $CO_2$ tensions rise. Most patients can compensate by hyperventilating, but in severe exacerbations, diffuse bronchoconstriction causes severe gas trapping, and the respiratory muscles are put at a marked mechanical disadvantage so that the work of breathing increases. Under these conditions, hypoxemia worsens and Pa$CO_2$ rises. Respiratory and metabolic acidosis may result and, if left untreated, cause respiratory and cardiac arrest.

**Classification**

Unlike, eg, hypertension, in which one parameter (BP) defines the severity of the disorder and the efficacy of treatment, asthma causes a number of clinical and testing abnormalities. Also unlike most hypertension, asthma manifestations typically wax and wane. Thus, monitoring (and studying) asthma requires a consistent terminology and defined benchmarks.

**Severity** is the intrinsic intensity of the disease process (ie, how bad it is). Severity can usually be assessed directly only before treatment is started, because patients who have responded well to treatment by definition have few symptoms. Asthma severity is categorized as

- Intermittent
- Mild persistent
- Moderate persistent
- Severe persistent

The term status asthmaticus describes severe, intense, prolonged bronchospasm that is resistant to treatment.

**Control** is the degree to which symptoms, impairments, and risks are minimized by treatment. Control is the parameter assessed in patients receiving treatment. Good control is the goal of asthma management whatever the disease severity. Control is classified as

- Well controlled
- Not well controlled
- Very poorly controlled

Severity and control are assessed in terms of patient impairment and risk (see Table 191-1).

**Impairment** refers to the frequency and intensity of patients’ symptoms and functional limitations. Impairment is assessed by spirometry, mainly forced expiratory volume in 1 sec (FEV$_1$), and the ratio of FEV$_1$ to forced vital capacity (FVC), as well as clinical features such as

- How often symptoms are experienced
- How often the patient awakens at night
- How often the patient uses a short-acting β$_2$-agonist for symptom relief
• How often asthma interferes with normal activity

**Risk** refers to the likelihood of future exacerbations or decline in lung function and the risk of adverse drug effects. Risk is assessed by long-term trends in spirometry and clinical features such as

• Frequency of need for oral corticosteroids

• Need for hospitalization

• Need for ICU admission

• Need for intubation

It is important to remember that the severity category does not predict how serious an exacerbation a patient may have. For example, a patient who has mild asthma with long periods of no or mild symptoms and normal pulmonary function may have a severe, life-threatening exacerbation.

**Symptoms and Signs**

Patients with mild asthma are typically asymptomatic between exacerbations. Patients with more severe disease and those with exacerbations experience dyspnea, chest tightness, audible wheezing, and coughing. Coughing may be the only symptom in some patients (cough-variant asthma). Symptoms can follow a circadian rhythm and worsen during sleep, often around 4 AM. Many patients with more severe disease waken during the night (nocturnal asthma).

Signs include wheezing, pulsus paradoxus (ie, a fall of systolic BP > 10 mm Hg during inspiration—see p. 2018), tachypnea, tachycardia, and visible efforts to breathe (use of neck and suprasternal [accessory] muscles, upright posture, pursed lips, inability to speak). The expiratory phase of respiration is prolonged, with an inspiratory:expiratory ratio of at least 1:3. Wheezes can be present through both phases or just on expiration, but patients with severe bronchoconstriction may have no audible wheezing because of markedly limited airflow.

Patients with a severe exacerbation and impending respiratory failure typically have some combination of altered consciousness, cyanosis, pulsus paradoxus > 15 mm Hg, O₂ saturation (O₂sat) < 90%, PaCO₂ > 45 mm Hg, or hyperinflation. Rarely, pneumothorax or pneumomediastinum is seen on chest x-ray.

Symptoms and signs disappear between acute attacks, although soft wheezes may be audible during forced expiration at rest, or after exercise in some asymptomatic patients. Hyperinflation of the lungs may alter the chest wall in patients with long-standing uncontrolled asthma, causing a barrel-shaped thorax.

All symptoms and signs are nonspecific, are reversible with timely treatment, and typically are brought on by exposure to one or more triggers.

**Diagnosis**

• Clinical evaluation

• Pulmonary function testing

Diagnosis is based on history and physical examination and is confirmed with pulmonary function tests. Diagnosis of causes and the exclusion of other disorders that cause wheezing are also important. Asthma and COPD are sometimes easily confused; they cause similar symptoms and produce similar results on pulmonary function tests but differ in important biologic ways that are not always clinically apparent.

**Pulmonary function tests:** Patients suspected of having asthma should undergo pulmonary
function testing to confirm and quantify the severity and reversibility of airway obstruction. Pulmonary function data quality is effort-dependent and requires patient education before the test. If it is safe to do so, bronchodilators should be stopped before the test: 6 h for short-acting β₂-agonists, such as albuterol; 8 h for ipratropium; 12 to 36 h for theophylline; 24 h for long-acting β₂-agonists, such as salmeterol and formoterol; and 48 h for tiotropium.

Spirometry (see Ch. 189) should be done before and after inhalation of a short-acting bronchodilator. Signs of airflow limitation before bronchodilator inhalation include reduced FEV₁ and a reduced FEV₁/FVC ratio. The FVC may also be decreased because of gas trapping, such that lung volume measurements may show an increase in the residual volume, the functional residual capacity, or both. An improvement in FEV₁ of > 12% or an increase ≥ 10% of predicted FEV₁ in response to bronchodilator treatment confirms reversible airway obstruction, although absence of this finding should not preclude a therapeutic trial of bronchodilators. Spirometry should be repeated at least every 1 to 2 yr in patients with asthma to monitor disease progression.

Flow-volume loops should also be reviewed to diagnose vocal cord dysfunction, a common cause of upper airway obstruction that mimics asthma.

Provocative testing, in which inhaled methacholine (or alternatives, such as inhaled histamine, adenosine, or bradykinin, or exercise testing) is used to provoke bronchoconstriction, is indicated for patients suspected of having asthma who have normal findings on spirometry and flow-volume testing, and for patients suspected of having cough-variant asthma, provided there are no contraindications. Contraindications include FEV₁ < 1 L or < 50%, recent MI or stroke, and severe hypertension (systolic BP > 200 mm Hg; diastolic BP > 100 mm Hg). A decline in FEV₁ of > 20% on provocative testing supports the diagnosis of asthma. However, FEV₁ may decline in response to these drugs in other disorders, such as COPD.

Other tests: Other tests may be helpful in some circumstances:

• Diffusing capacity for carbon monoxide (DLCO)

• Chest x-ray

• Allergy testing

DLCO testing can help distinguish asthma from COPD. Values are normal or elevated in asthma and usually reduced in COPD, particularly in patients with emphysema.

A chest x-ray may help exclude some causes of asthma or alternative diagnoses, such as heart failure or pneumonia. The chest x-ray in asthma is usually normal but may show hyperinflation or segmental atelectasis, a sign of mucous plugging. Infiltrates, especially those that come and go and that are associated with findings of central bronchiectasis, suggest allergic bronchopulmonary aspergillosis (see p. 1887).

Allergy testing may be indicated for children whose history suggests allergic triggers (particularly for allergic rhinitis) because these children may benefit from immunotherapy. It should be considered for adults whose history indicates relief of symptoms with allergen avoidance and for those in whom a trial of therapeutic anti-IgE antibody therapy (see p. 1881) is being considered. Skin testing and measurement of allergen-specific IgE via radioallergosorbent testing (RAST) can identify specific allergic triggers (see p. 1115).

Elevated blood eosinophils (> 400 cells/µL) and nonspecific IgE (> 150 IU) are suggestive but not diagnostic of allergic asthma because they can be elevated in other conditions.
Sputum evaluation for eosinophils is not commonly done; finding large numbers of eosinophils is suggestive of asthma but is neither sensitive nor specific.

Peak expiratory flow (PEF) measurements with inexpensive handheld flow meters are recommended for home monitoring of disease severity and for guiding therapy.

**Evaluation of exacerbations**: Patients with asthma with an acute exacerbation should have certain tests:

- Pulse oximetry
- PEF or FEV$_1$ measurement

All 3 measures help establish the severity of an exacerbation and document treatment response. PEF values are interpreted in light of the patient's personal best, which may vary widely among patients who are equally well controlled. A 15 to 20% reduction from this baseline indicates a significant exacerbation. When baseline values are not known, the percent predicted value gives a general idea of airflow limitation but not the individual patient's degree of worsening.

Chest x-ray is not necessary for most exacerbations but should be done in patients with symptoms suggestive of pneumonia or pneumothorax.

ABG measurements should be taken in patients with marked respiratory distress or symptoms and signs of impending respiratory failure.

**Prognosis**

Asthma resolves in many children, but for as many as 1 in 4, wheezing persists into adulthood or relapse occurs in later years. Female sex, smoking, earlier age of onset, sensitization to household dust mites, and airway hyperresponsiveness are risk factors for persistence and relapse.

About 4000 deaths/yr in the US are attributable to asthma, most of which are preventable with treatment. Thus, the prognosis is good with adequate access and adherence to treatment. Risk factors for death include increasing requirements for oral corticosteroids before hospitalization, previous hospitalization for acute exacerbations, and lower peak flow measurements at presentation. Several studies show that use of inhaled corticosteroids decreases hospital admission and mortality rates.

Over time, the airways in some patients with asthma undergo permanent structural changes (remodeling) that prevent return to normal lung functioning. Early aggressive use of anti-inflammatory drugs may help prevent this remodeling.

**Treatment**

- Control of triggers
- Drug therapy
- Monitoring
- Patient education
- Treatment of acute exacerbations

Treatment objectives are to minimize impairment and risk, including preventing exacerbations and minimizing chronic symptoms, including nocturnal awakenings; to minimize the need for emergency department visits or hospitalizations; to maintain baseline (normal) pulmonary function and activity levels; and to avoid adverse treatment effects.
Control of triggering factors: Triggering factors in some patients may be controlled with use of synthetic fiber pillows and impermeable mattress covers and frequent washing of bed sheets, pillowcases, and blankets in hot water. Upholstered furniture, soft toys, carpets, and pets should be removed (dust mites, animal dander). Dehumidifiers should be used in basements and in other poorly aerated, damp rooms (molds). Steam treatment of homes diminishes dust mite allergens. House cleaning and extermination to eliminate cockroach exposure is especially important. Although control of triggering factors is more difficult in urban environments, the importance of these measures is not diminished. High-efficiency particulate air (HEPA) vacuums and filters may relieve symptoms, but beneficial effects on pulmonary function and on the need for drugs are unproved. Sulfite-sensitive patients should avoid red wine. Nonallergenic triggers, such as cigarette smoke, strong odors, irritant fumes, cold temperatures, high humidity, and exercise, should also be avoided or controlled when possible. Avoidance of viral URIs is also important. Patients with aspirin-induced asthma can use acetaminophen, choline magnesium salicylate, or selective cyclooxygenase-2 (COX-2) inhibitors in place of NSAIDs. Asthma is a relative contraindication to the use of nonselective β-blockers, including topical formulations, but cardioselective drugs (eg, metoprolol, atenolol) probably have no adverse effects.

Drug therapy: Major drug classes commonly used in the treatment of chronic asthma and asthma exacerbations include

• Bronchodilators (β2-agonists, anticholinergics)

• Corticosteroids

• Leukotriene modifiers

• Mast cell stabilizers

• Methylxanthines

Drugs in these classes (see Table 191-2) are inhaled or taken orally; inhaled drugs come in aerosolized and powdered forms. Use of aerosolized forms with a spacer or holding chamber facilitates deposition of the drug in the airways rather than the pharynx; patients are advised to wash and dry their spacers after each use to prevent bacterial contamination. In addition, use of aerosolized forms requires coordination between actuation of the inhaler (drug delivery) and inhalation; powdered forms reduce the need for coordination, because drug is delivered only when the patient inhales. In addition, powdered forms reduce the release of fluorocarbon propellants into the environment.

β2-Agonists relax bronchial smooth muscle, decrease mast cell degranulation and histamine release, inhibit microvascular leakage into the airways, and increase mucociliary clearance. β2-Agonists come in short- and long-acting preparations (see Table 191-2). Short-acting β2-agonists (eg, albuterol) 2 puffs inhaled q 4 h prn are the drug of choice for relieving acute bronchoconstriction and preventing exercise-induced asthma. They are not used for long-term maintenance. They take effect within minutes and are active for up to 6 to 8 h, depending on the drug. Tachycardia and tremor are the most common acute adverse effects of inhaled β2-agonists and are dose-related. Mild hypokalemia occurs uncommonly. Use of levalbuterol (a solution containing the R-isomer of albuterol) theoretically minimizes adverse effects, but its long-term efficacy and safety are unproved. Oral β2-agonists have more systemic effects and generally should be avoided.

Long-acting β2-agonists (eg, salmeterol) are active for up to 12 h and are used for moderate and severe asthma but should never be used as monotherapy. They interact synergistically with inhaled corticosteroids and permit lower dosing of corticosteroids. The safety of regular long-term use of β2-agonists is controversial. Long-acting β2-agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, salmeterol should be used only as additional therapy, not monotherapy, for patients whose condition is not adequately controlled with other asthma controllers (eg, low- to mediumdose inhaled corticosteroids) or whose disease severity clearly warrants additional
maintenance therapies. Daily use of β2-agonists, increased dosing or diminishing effects, or use of ≥ 1 canisters a month suggests inadequate control and the need to begin or intensify other therapies.

[Table 191-2, Drug Treatment of Chronic Asthma*]

**Anticholinergics** relax bronchial smooth muscle through competitive inhibition of muscarinic (M<sub>3</sub>) cholinergic receptors. Ipratropium may have an additive effect when combined with short-acting β<sub>2</sub>-agonists. Adverse effects include pupillary dilation, blurred vision, and dry mouth. Tiotropium is a 24-h inhaled anticholinergic that has not been adequately evaluated for asthma use.

**Corticosteroids** inhibit airway inflammation, reverse β-receptor down-regulation, and inhibit cytokine production and adhesion protein activation. They block the late response (but not the early response) to inhaled allergens. Routes of administration include oral, IV, and inhaled. In acute asthma exacerbation, early use of systemic corticosteroids often aborts the exacerbation, decreases the need for hospitalization, prevents relapse, and speeds recovery. Oral and IV routes are equally effective. Inhaled corticosteroids have no role in acute exacerbation but are indicated for long-term suppression, control, and reversal of inflammation and symptoms. They substantially reduce the need for maintenance oral corticosteroid therapy. Adverse local effects of inhaled corticosteroids include dysphonia and oral candidiasis, which can be prevented or minimized by having the patient use a spacer, gargle with water after corticosteroid inhalation, or both. Systemic effects are all dose-related, can occur with oral or inhaled forms, and occur mainly with inhaled doses > 800 μg/day. They include suppression of the adrenal-pituitary axis, osteoporosis, cataracts, skin atrophy, hyperphagia, and easy bruisability. Whether inhaled corticosteroids suppress growth in children is controversial: Most children reach their predicted adult height. Latent TB may be reactivated by systemic corticosteroid use.

**Mast cell stabilizers** inhibit histamine release from mast cells, reduce airway hyperresponsiveness, and block the early and late responses to allergens. They are given by inhalation prophylactically to patients with exercise-induced or allergen-induced asthma. They are ineffective once symptoms have occurred. They are the safest of all antiasthmatic drugs but the least effective.

**Leukotriene modifiers** are taken orally and can be used for long-term control and prevention of symptoms in patients with mild persistent to severe persistent asthma. The main adverse effect is liver enzyme elevation (which occurs with zileuton). Although rare, patients have developed a clinical syndrome resembling that of Churg-Strauss syndrome.

**Methylxanthines** relax bronchial smooth muscle (probably by inhibiting phosphodiesterase) and may improve myocardial and diaphragmatic contractility through unknown mechanisms. Methylxanthines appear to inhibit intracellular release of Ca<sup>2+</sup>, decrease microvascular leakage into the airway mucosa, and inhibit the late response to allergens. They decrease the infiltration of eosinophils into bronchial mucosa and of T lymphocytes into epithelium. Methylxanthines are used for long-term control as an adjunct to β<sub>2</sub>-agonists; extended-release theophylline helps manage nocturnal asthma. Theophylline is falling into disuse because of its many adverse effects and interactions compared with other drugs. Adverse effects include headache, vomiting, cardiac arrhythmias, and seizures. Methylxanthines have a narrow therapeutic index; multiple drugs (any metabolized by the cytochrome P-450 pathway, eg, macrolide antibiotics) and conditions (eg, fever, liver disease, heart failure) alter methylxanthine metabolism and elimination. Serum theophylline levels should be monitored periodically and maintained between 5 and 15 μg/mL (28 and 83 μmol/L).

Immunomodulators include omalizumab, an anti-IgE antibody developed for use in severely allergic patients with asthma who have elevated IgE levels. Omalizumab may decrease asthma exacerbations, decreases corticosteroid requirements, and relieves symptoms. Dosing is determined by a dosing chart based on the patient's weight and IgE levels. The drug is administered sc q 2 to 4 wk. Clinicians who administer omalizumab should be prepared to identify and treat anaphylaxis, which may occur.

**Other drugs** are used uncommonly in specific circumstances. Magnesium is often used in the emergency department, but it is not recommended in the management of chronic asthma. Immunotherapy may be indicated when symptoms are triggered by allergy, as suggested by history and confirmed by allergy
testing. Immunotherapy is generally more effective in children than adults. If symptoms are not significantly relieved after 24 mo, then therapy is stopped. If symptoms are relieved, therapy should continue for ≥ 3 yr, although the optimum duration is unknown. Other drugs that suppress the immune system are occasionally prescribed to reduce dependence on high-dose oral corticosteroids, but these drugs have a significant risk of toxicity. Low-dose methotrexate (5 to 15 mg once/wk) can lead to modest improvements in FEV$_1$ and modest decreases in daily oral corticosteroid use. Gold and cyclosporine are also modestly effective, but toxicity and need for monitoring limit their use. Other therapies for management of chronic asthma include nebulized lidocaine, nebulized heparin, colchicine, and high-dose IV immune globulin. Limited evidence supports the use of any of these therapies, and their benefits are unproved, so none are currently recommended for routine clinical use.

**Monitoring response to treatment:** Guidelines recommend office use of spirometry (FEV$_1$, FEV$_1$/FVC, FVC) to measure airflow limitation and assess impairment and risk. Outside the office, home PEF monitoring, in conjunction with patient symptom diaries and the use of an asthma action plan, is especially useful for charting disease progression and response to treatment in patients with moderate to severe persistent asthma. When asthma is quiescent, one PEF measurement in the morning suffices. Should PEF measurements fall to < 80% of the patient's personal best, then twice/day monitoring to assess circadian variation is useful. Circadian variation of > 20% indicates airway instability and the need to re-evaluate the therapeutic regimen.

**Patient education:** The importance of patient education cannot be overemphasized. Patients do better when they know more about asthma—what triggers an attack, what drug to use when, proper inhaler technique, how to use a spacer with a metered-dose inhaler (MDI), and the importance of early use of corticosteroids in exacerbations. Every patient should have a written action plan for day-to-day management, especially for management of acute attacks, that is based on the patient's best personal peak flow rather than on a predicted normal value. Such a plan leads to much better asthma control, largely attributable to improved adherence to therapies.

**Treatment of acute exacerbation:** The goal of asthma exacerbation treatment is to relieve symptoms and return patients to their best lung function. Treatment includes

- Inhaled bronchodilators (β$_2$-agonists and anticholinergics)

- Usually systemic corticosteroids

Patients having an attack are instructed to self-administer 2 to 4 puffs of inhaled albuterol or a similar short-acting β$_2$-agonist up to 3 times spaced 20 min apart for an acute exacerbation and to measure PEF if possible. When these short-acting rescue drugs are effective (symptoms are relieved and PEF returns to > 80% of baseline), the acute exacerbation may be managed in the outpatient setting. Patients who do not respond, have severe symptoms, or have a PEF persistently < 80% should follow a treatment management program outlined by the physician or should go to the emergency department (see Table 191-3 for specific dosing information).

Inhaled bronchodilators (β$_2$-agonists and anticholinergics) are the mainstay of asthma treatment in the emergency department. In adults and older children, albuterol given by an MDI and spacer is as effective as that given by nebulizer. Nebulized treatment is preferred for younger children because of difficulties coordinating MDIs and spacers; evidence suggests that bronchodilator response improves when the nebulizer is powered with helium-O$_2$ (heliox) rather than with O$_2$. Subcutaneous epinephrine 1:1000 solution or terbutaline is an alternative for children. Terbutaline may be preferable to epinephrine because of its lesser cardiovascular effects and longer duration of action, but it is no longer produced in large quantities and is expensive. Subcutaneous administration of β$_2$-agonists in adults raises concerns of adverse cardiostimulatory effects. However, clinically important adverse effects are few, and subcutaneous administration may benefit patients unresponsive to maximal inhaled therapy or patients unable to receive effective nebulized treatment (eg, those who cough excessively, have poor
ventilation, or are uncooperative). Nebulized ipratropium can be co-administered with nebulized albuterol for patients who do not respond optimally to albuterol alone; some evidence favors simultaneous high-dose $\beta_2$-agonist and ipratropium as first-line treatment, but no data favor continuous $\beta_2$-agonist nebulization over intermittent administration. Theophylline has very little role in treatment.

Systemic corticosteroids (prednisone, prednisolone, methylprednisolone) should be given for all but the mildest acute exacerbation; they are unnecessary for patients whose PEF normalizes after 1 or 2 bronchodilator doses. IV and oral routes of administration are probably equally effective. IV methylprednisolone can be given if an IV line is already in place and can be switched to oral dosing whenever necessary or convenient. Tapering usually starts after 7 to 10 days and should last 2 to 3 wk.

Antibiotics are indicated only when history, examination, or chest x-ray suggests underlying bacterial infection; most infections underlying asthma exacerbations are probably viral in origin. Supplemental $O_2$ is indicated for hypoxemia and should be given by nasal cannula or face mask at a flow rate or concentration sufficient to maintain $O_2$sat > 90%.

Reassurance is the best approach when anxiety is the cause of asthma exacerbation. Anxiolytics and morphine are relatively contraindicated because they are associated with increased mortality and the need for mechanical ventilation.

Hospitalization generally is required if patients have not returned to their baseline within 4 h of aggressive emergency department treatment. Criteria for hospitalization vary, but definite indications are failure to improve, worsening fatigue, relapse after repeated $\beta_2$-agonist therapy, and significant decrease in PaO$_2$ (< 50 mm Hg) or increase in PaCO$_2$ (> 40 mm Hg), indicating progression to respiratory failure.

Patients who continue to deteriorate despite aggressive treatment are candidates for noninvasive positive pressure ventilation or endotracheal intubation and invasive mechanical ventilation (see p. 2279). Patients requiring intubation may benefit from sedation, but neuromuscular blocking agents should be avoided because of possible interactions with corticosteroids that can cause prolonged neuromuscular weakness.

Generally, volume-cycled ventilation in assist-control mode is used because it provides constant alveolar ventilation when airway resistance is high and changing. The ventilator should be set to a relatively low frequency with a relatively high inspiratory flow rate (> 80 L/min) to prolong exhalation time, minimizing autopositive end-expiratory pressure (PEEP). Initial tidal volumes can be set to 6 to 10 mL/kg. High peak airway pressures can generally be ignored, because they result from high airway resistance and inspiratory flow rates and do not reflect the degree of lung distention caused by alveolar pressure. However, if plateau pressures exceed 30 to 35 cm H$_2$O, then tidal volume should be reduced to limit the risk of pneumothorax. When reduced tidal volumes are necessary, a moderate degree of hypercapnia is acceptable, but if arterial pH falls below 7.10, a slow NaHCO$_3$ infusion is indicated to maintain pH between 7.20 and 7.25. Once airflow obstruction is relieved and PaCO$_2$ and arterial pH normalize, patients can usually be quickly weaned from the ventilator.

Other therapies are reportedly effective for asthma exacerbation, but none have been thoroughly studied. Heliox is used to decrease the work of breathing and improve ventilation through a decrease in turbulent flow attributable to helium, a gas less dense than $O_2$. Despite the theoretical benefits of heliox, studies have reported conflicting results concerning its efficacy; lack of ready availability also limits its use. Magnesium sulfate relaxes smooth muscle, but efficacy in management of asthma exacerbation in the emergency department is debated. General anesthesia in patients with status asthmaticus causes bronchodilation by an unclear mechanism, perhaps by a direct relaxant effect on airway smooth muscle or attenuation of cholinergic tone.

**Treatment of chronic asthma:** Current asthma guidelines initiate treatment based on the severity classification. Continuing therapy is based on assessment of control (see Table 191-1). Therapy is increased in a stepwise fashion (see...
Until the best control of impairment and risk is achieved (step-up). Before therapy is stepped up, adherence, exposure to environmental factors (eg, trigger exposure), and presence of comorbid conditions (eg, obesity, allergic rhinitis, gastroesophageal reflux disease, COPD, obstructive sleep apnea, vocal cord dysfunction) are reviewed. These factors should be addressed before increasing drug therapy. Once asthma has been well controlled for at least 3 mo, drug therapy is reduced if possible to the minimum that maintains good control (step-down). For specific drugs and doses, see Table 191-2.

**Exercise-induced asthma:** Exercise-induced asthma can generally be prevented by inhalation of a short-acting β₂-agonist or mast cell stabilizer before starting the exercise. If β₂-agonists are not effective or if exercise-induced asthma is associated with severe symptoms, the patient has more severe asthma than is recognized and requires controller therapy.

**Aspirin-sensitive asthma:** The primary treatment for aspirin-sensitive asthma is avoidance of NSAIDs. Cyclooxygenase-2 (COX-2) inhibitors do not appear to be triggers. Leukotriene modifiers can blunt the response to NSAIDs. Alternatively, inpatient desensitization has been successful in a few patients.

**Future therapies:** Multiple therapies are being developed to target specific components of the inflammatory cascade. Therapies directed at IL-4, IL-13, tumor necrosis factor-α, other chemokines, and cytokines or their receptors are all under investigation or consideration as therapeutic targets.

**Special Populations**

**Infants, children, and adolescents:** Asthma is difficult to diagnose in infants; thus, under-recognition and undertreatment are common. Empiric trials of inhaled bronchodilators and anti-inflammatory drugs may be helpful for both. Drugs may be given by nebulizer or MDI with a holding chamber with or without a face mask. Infants and children < 5 yr requiring treatment > 2 times/wk should be given daily anti-inflammatory therapy with inhaled corticosteroids (preferred), leukotriene receptor antagonists, or cromolyn. Children > 5 yr and adolescents with asthma can be treated similarly to adults but should be encouraged to maintain physical activities, exercise, and sports participation. Predicted norms for pulmonary function tests in adolescents are closer to childhood (not adult) standards. Adolescents and mature younger children should participate in developing their own asthma management plans and establishing their own goals for therapy to improve adherence. The action plan should be understood by teachers and school nurses to ensure reliable and prompt access to rescue drugs. Cromolyn and nedocromil are often tried in this group but are not as beneficial as inhaled corticosteroids. Long-acting drugs prevent the embarrassment of having to take drugs at school.

**Pregnant women:** About one third of women with asthma who become pregnant notice relief of symptoms, one third notice worsening (at times to a severe degree), and one third notice no change. GERD may be an important contributor to symptomatic disease in pregnancy. Asthma control during pregnancy is crucial (see p. 2636), because poorly controlled maternal disease can result in increased prenatal mortality, premature delivery, and low birth weight. Asthma drugs have not been shown to have adverse fetal effects, but safety data are lacking.

**Elderly patients:** The elderly have a high prevalence of other obstructive lung disease (eg, COPD), so it is important to determine the magnitude of the reversible component of airflow obstruction (eg, by a 2- to 3-wk trial of inhaled corticosteroids or pulmonary function testing with bronchodilator challenge). The elderly may be more sensitive to adverse effects of β₂-agonists and inhaled corticosteroids. Patients requiring inhaled corticosteroids, particularly those with risk factors for osteoporosis, may benefit from measures to preserve bone density (eg, Ca and vitamin D supplements, bisphosphonates).

**Allergic Bronchopulmonary Aspergillosis**

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to *Aspergillus fumigatus* that occurs almost exclusively in patients with asthma or, less commonly, cystic
fibrosis. Immune responses to *Aspergillus* antigens cause airway obstruction and, if untreated, bronchiectasis and pulmonary fibrosis. Symptoms and signs are those of asthma with the addition of productive cough and, occasionally, fever and anorexia. Diagnosis is suspected based on history and imaging tests and confirmed by *Aspergillus* skin testing and measurement of IgE levels, circulating precipitins, and *A. fumigatus*-specific antibodies. Treatment is with corticosteroids and, in patients with refractory disease, itraconazole.

ABPA develops when airways of patients with asthma or cystic fibrosis become colonized with *Aspergillus* sp (ubiquitous fungi in the soil).

**Pathophysiology**

For unclear reasons, colonization in these patients prompts vigorous antibody (IgE and IgG) and cell-mediated immune responses (type I, III, and IV hypersensitivity reactions) to *Aspergillus* antigens, leading to frequent, recurrent asthma exacerbations. Over time, the immune reactions, combined with direct toxic effects of the fungus, lead to airway damage with dilatation and, ultimately, bronchiectasis and fibrosis. The disorder is characterized histologically by mucoid impaction of airways, eosinophilic pneumonia, infiltration of alveolar septa with plasma and mononuclear cells, and an increase in the number of bronchiolar mucous glands and goblet cells. Rarely, other fungi, such as *Penicillium*, *Candida*, *Curvularia*, *Helminthosporium*, and *Drechslera* spp, cause an identical syndrome called allergic bronchopulmonary mycosis in the absence of underlying asthma or cystic fibrosis.

*Aspergillus* is present intraluminally but is not invasive. Thus, ABPA must be distinguished from invasive aspergillosis, which occurs in immunocompromised patients; from aspergillomas, which are collections of *Aspergillus* in patients with established cavitary lesions or cystic airspaces; and from the rare *Aspergillus* pneumonia, which occurs in patients who take low doses of prednisone long term (eg, patients with COPD).

**Symptoms and Signs**

Symptoms are those of asthma or pulmonary cystic fibrosis exacerbation, with the addition of cough productive of dirty-green or brown plugs and, occasionally, hemoptysis. Fever, headache, and anorexia are common systemic symptoms in severe disease. Signs are those of airway obstruction, specifically, wheezing and prolonged expiration, which are indistinguishable from asthma exacerbation.

**Diagnosis**

- History of asthma
- Chest x-ray or high-resolution CT
- Skin prick test with *Aspergillus* antigen
- *Aspergillus* precipitins in blood
- IgE levels

The diagnosis is suspected in patients with asthma with recurrent asthma exacerbations, migratory or nonresolving infiltrates on chest x-ray (often due to atelectasis from mucoid plugging and bronchial obstruction), evidence of bronchiectasis on imaging studies (see p. 1941), sputum cultures positive for *A. fumigatus*, or notable peripheral eosinophilia.

Several criteria have been proposed for the diagnosis (see Table 191-5), but in practice 4 essential criteria are generally assessed. An immediate wheal-and-flare reaction to an initial skin prick test with *Aspergillus* antigen should prompt measurement of serum IgE and *Aspergillus* precipitins; up to 25% of patients with asthma without ABPA may have a positive skin test. An IgE level > 1000 ng/mL and positive precipitins suggest the diagnosis, which should be confirmed by
measurement of specific anti-Aspergillus immunoglobulins (up to 10% of healthy patients have circulating precipitins). A finding of A. fumigatus-specific IgG and IgE antibodies in concentrations at least twice those found in patients without ABPA establishes the diagnosis. Whenever test results diverge, such as with an IgE > 1000 ng/mL but negative A. fumigatus-specific immunoglobulins, testing should be repeated, the patient should be monitored over time to definitively establish or exclude the diagnosis.

Treatment

• Prednisone

• Sometimes antifungal drugs

[Table 191-5. Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis]

[Table 191-6. Stages of Allergic Bronchopulmonary Aspergillosis*]

Treatment is based on disease stage (see Table 191-6). Stage I is treated with prednisone 0.5 to 0.75 mg/kg once/day for 2 to 4 wk, then tapered over 4 to 6 mo. Chest x-ray, blood eosinophils, and IgE levels should be checked quarterly for improvement, defined as resolution of infiltrates, ≥ 50% decline in eosinophils, and 33% decline in IgE. Patients who achieve stage II disease require annual monitoring only. Stage II patients who relapse (Stage III) are given another trial of prednisone. Stage I or III patients who do not improve with prednisone (Stage IV) are candidates for antifungal treatment. Itraconazole 200 mg po bid for 4 to 6 mo with a 6-mo taper is recommended as a substitute for prednisone and as a corticosteroid-sparing drug. Itraconazole therapy requires checking drug levels and monitoring liver enzymes and triglyceride and potassium levels.

All patients should be optimally treated for their underlying asthma or cystic fibrosis. In addition, patients taking long-term corticosteroids should be monitored for complications, such as cataracts, hyperglycemia, and osteoporosis, and possibly prescribed treatments to prevent bone demineralization and Pneumocystis jirovecii lung infection.
Chapter 192. Chronic Obstructive Pulmonary Disease

Introduction

Chronic obstructive pulmonary disease (COPD) is partially reversible airflow limitation caused by an inflammatory response to inhaled toxins, often cigarette smoke. α1-Antitrypsin deficiency and various occupational exposures are less common causes in nonsmokers. Symptoms are productive cough and dyspnea that develop over years; common signs include decreased breath sounds, prolonged expiratory phase of respiration, and wheezing. Severe cases may be complicated by weight loss, pneumothorax, frequent acute decompensation episodes, right heart failure, and acute or chronic respiratory failure. Diagnosis is based on history, physical examination, chest x-ray, and pulmonary function tests. Treatment is with bronchodilators, corticosteroids, and, when necessary, O2 and antibiotics. About 50% of patients die within 10 yr of diagnosis.

COPD comprises

• Chronic obstructive bronchitis (clinically defined)

• Emphysema (pathologically or radiologically defined)

Many patients have features of both.

Chronic obstructive bronchitis is chronic bronchitis with airflow obstruction. Chronic bronchitis is defined as productive cough on most days of the week for at least 3 mo total duration in 2 successive years. Chronic bronchitis becomes chronic obstructive bronchitis if spirometric evidence of airflow obstruction develops. Chronic asthmatic bronchitis is a similar, overlapping condition characterized by chronic productive cough, wheezing, and partially reversible airflow obstruction; it occurs predominantly in smokers with a history of asthma. In some cases, the distinction between chronic obstructive bronchitis and chronic asthmatic bronchitis is unclear.

Emphysema is destruction of lung parenchyma leading to loss of elastic recoil and loss of alveolar septa and radial airway traction, which increases the tendency for airway collapse. Lung hyperinflation, airflow limitation, and air trapping follow. Airspaces enlarge and may eventually develop bullae.

Epidemiology

An estimated 24 million people in the US have airflow limitation, of whom about half have COPD. COPD is the 4th leading cause of death, resulting in 122,000 deaths in 2003—compared with 52,193 deaths in 1980. From 1980 to 2000, the COPD mortality rate increased 64% (from 40.7 to 66.9/100,000). Prevalence, incidence, and mortality rates increase with age. Prevalence is higher in men, but total mortality is similar in both sexes. Incidence and mortality are generally higher in whites, blue-collar workers, and people with fewer years of formal education, probably because these groups have a higher prevalence of smoking. COPD seems to aggregate in families independent of α1-antitrypsin (α1-antiprotease inhibitor) deficiency (see p. 1901).

COPD is increasing worldwide because of the increase in smoking in developing countries, the reduction in mortality due to infectious diseases, and the widespread use of biomass fuels. It caused an estimated 2.74 million deaths worldwide in the year 2000 and is projected to become one of the top 5 causes of disease burden globally by the year 2020.

Etiology

There are several causes of COPD:

• Smoking (and less often other inhalational exposures)
• Genetic factors

Inhalational exposure: Of all inhalational exposures, cigarette smoking is the primary risk factor in most countries, although only about 15% of smokers develop clinically apparent COPD; an exposure history of 40 or more pack-years is especially predictive. Smoke from burning biomass fuels for indoor cooking and heating is an important contributing factor in developing countries. Smokers with preexisting airway reactivity (defined by increased sensitivity to inhaled methacholine), even in the absence of clinical asthma, are at greater risk of developing COPD than are those without.

Low body weight, childhood respiratory disorders, and exposure to passive cigarette smoke, air pollution, and occupational dust (eg, mineral dust, cotton dust) or inhaled chemicals (eg, cadmium) contribute to the risk of COPD but are of minor importance compared with cigarette smoking.

Genetic factors: The best-defined causative genetic disorder is α₁-antitrypsin deficiency (see p. 1901), which is an important cause of emphysema in nonsmokers and influences susceptibility to disease in smokers.

Polymorphisms in microsomal epoxide hydrolase, vitamin D-binding protein, IL-1β, IL-1 receptor antagonist, phospholipase A₂, matrix metalloproteinase 9, and ADAM-33 genes are all associated with rapid decline in forced expiratory volume in 1 sec (FEV₁) in selected populations.

Pathophysiology

Various factors cause the airflow limitation and other complications of COPD.

Inflammation: Inhalational exposures can trigger an inflammatory response in airways and alveoli that leads to disease in genetically susceptible people. The process is thought to be mediated by an increase in protease activity and a decrease in antiprotease activity (see p. 1901). Lung proteases, such as neutrophil elastase, matrix metalloproteinases, and cathepsins, break down elastin and connective tissue in the normal process of tissue repair. Their activity is normally balanced by antiproteases, such as α₁-antitrypsin, airway epithelium-derived secretory leukoproteinase inhibitor, elafin, and matrix metalloproteinase tissue inhibitor. In patients with COPD, activated neutrophils and other inflammatory cells release proteases as part of the inflammatory process; protease activity exceeds antiprotease activity, and tissue destruction and mucus hypersecretion result. Neutrophil and macrophage activation also leads to accumulation of free radicals, superoxide anions, and hydrogen peroxide, which inhibit antiproteases and cause bronchoconstriction, mucosal edema, and mucous hypersecretion. Neutrophil-induced oxidative damage, release of profibrotic neuropeptides (eg, bombesin), and reduced levels of vascular endothelial growth factor may contribute to apoptotic destruction of lung parenchyma.

The inflammation in COPD increases with increasing disease severity, and, in severe (advanced) disease, inflammation does not resolve completely with smoking cessation. This inflammation does not seem to respond to corticosteroids.

Infection: Respiratory infection (which COPD patients are prone to), in conjunction with cigarette smoking, may amplify progression of lung destruction.

Bacteria, especially Haemophilus influenzae, colonize the normally sterile lower airways of about 30% of patients with COPD. In more severely affected patients (eg, those with previous hospitalizations), Pseudomonas aeruginosa colonization is common. Smoking and airflow obstruction may lead to impaired mucus clearance in lower airways, which predisposes to infection. Repeated bouts of infection increase the inflammatory burden that hastens disease progression. There is no evidence, however, that long-term use of antibiotics slows the progression of COPD.

Airflow limitation: The cardinal pathophysiologic feature of COPD is airflow limitation caused by airway obstruction, loss of elastic recoil, or both.

Airway obstruction is caused by inflammation-mediated mucus hypersecretion, mucus plugging, mucosal
edema, bronchospasm, peribronchial fibrosis, or a combination of these mechanisms. Alveolar attachments and alveolar septa are destroyed, contributing to loss of airway support and airway closure during expiration.

Enlarged alveolar spaces sometimes consolidate into bullae, defined as airspaces ≥ 1 cm in diameter. Bullae may be entirely empty or have strands of lung tissue traversing them in areas of locally severe emphysema; they occasionally occupy the entire hemithorax. These changes lead to loss of elastic recoil and lung hyperinflation.

Increased airway resistance increases the work of breathing, as does lung hyperinflation. Increased work of breathing may lead to alveolar hypoventilation with hypoxia and hypercapnia, although hypoxia is also caused by ventilation/perfusion (V/Q) mismatch.

**Complications:** In addition to airflow limitation and sometimes respiratory insufficiency, complications include

- Pulmonary hypertension
- Respiratory infection
- Weight loss and other comorbidities

Chronic hypoxemia increases pulmonary vascular tone, which, if diffuse, causes pulmonary hypertension (see p. 1984) and cor pulmonale (see p. 2132).

Viral or bacterial respiratory infections are common among patients with COPD and cause a large percentage of acute exacerbations. It is currently thought that acute bacterial infections are due to acquisition of new strains of bacteria rather than overgrowth of chronic colonizing bacteria.

Weight loss may occur, perhaps in response to decreased caloric intake and increased levels of circulating tumor necrosis factor (TNF-α).

Other coexisting or complicating disorders that adversely affect quality of life and survival include osteoporosis, depression, coronary artery disease, lung cancer, muscle atrophy, and gastroesophageal reflex. The extent to which these disorders are consequences of COPD, smoking, and the accompanying systemic inflammation is unclear.

**Symptoms and Signs**

COPD takes years to develop and progress. Most patients have smoked ≥ 20 cigarettes/day for > 20 yr. Productive cough usually is the initial symptom, developing among smokers in their 40s and 50s. Dyspnea that is progressive, persistent, exertional, or worse during respiratory infection appears when patients are in their late 50s or 60s. Symptoms usually progress quickly in patients who continue to smoke and in those who have a higher lifetime tobacco exposure. Morning headache develops in more advanced disease and signals nocturnal hypercapnia or hypoxemia.

**Acute exacerbations** occur sporadically during the course of COPD and are heralded by increased symptom severity. The specific cause of any exacerbation is almost always impossible to determine, but exacerbations are often attributed to viral URIs or acute bacterial bronchitis. As COPD progresses, acute exacerbations tend to become more frequent, averaging about 3 episodes/yr.

Signs of COPD include wheezing, increased expiratory phase of breathing, lung hyperinflation manifested as decreased heart and lung sounds, and increased anteroposterior diameter of the thorax (barrel chest). Patients with advanced emphysema lose weight and experience muscle wasting that has been attributed to immobility, hypoxia, or release of systemic inflammatory mediators, such as TNF-α. Signs of advanced disease include pursed-lip breathing, accessory muscle use, paradoxical inward movement of the lower intercostal interspaces during inspiration (Hoover's sign), and cyanosis. Signs of cor pulmonale include neck vein distention, splitting of the 2nd heart sound with an accentuated pulmonic component, tricuspid...
insufficiency murmur, and peripheral edema. Right ventricular heaves are uncommon in COPD because the lungs are hyperinflated.

Spontaneous pneumothorax may occur as a result of rupture of bullae and should be suspected in any patient with COPD whose pulmonary status abruptly worsens.

Diagnosis

• Chest x-ray

• Pulmonary function testing

Diagnosis is suggested by history, physical examination, and chest imaging and is confirmed by pulmonary function tests. Differential diagnosis includes asthma, heart failure, and bronchiectasis. COPD and asthma are sometimes easily confused. Asthma (see also p. 1868) and COPD are distinguished by numerous factors (see Table 192-1).

Systemic disorders that may have a component of airflow limitation may suggest COPD; they include HIV infection, abuse of IV drugs (particularly cocaine and amphetamines), sarcoidosis, Sjogren's syndrome, bronchiolitis obliterans, lymphangioleiomyomatosis, and eosinophilic granuloma.

Pulmonary function tests: Patients suspected of having COPD should undergo complete pulmonary function testing (see also p. 1851) to confirm airflow limitation, to quantify its severity and reversibility, and to distinguish COPD from other disorders. Pulmonary function testing is also useful for following disease progression and monitoring response to treatment. The primary diagnostic tests are

• \( \text{FEV}_1 \), which is the volume of air forcefully expired during the first second after taking a full breath

• Forced vital capacity (FVC), which is the total volume of air expired with maximal force

• Flow-volume loops, which are simultaneous spirometric recordings of airflow and volume during forced maximal expiration and inspiration

Reductions of \( \text{FEV}_1 \), FVC, and the ratio of \( \text{FEV}_1/\text{FVC} \) are the hallmark of airflow limitation. Flow-volume loops show a concave pattern in the expiratory tracing (see Fig. 189-3 on p. 1854). \( \text{FEV}_1 \) declines up to 60 mL/yr in smokers, compared with a less steep decline of 25 to 30 mL/yr in nonsmokers, beginning at about age 30. In middle-aged smokers who already have a low \( \text{FEV}_1 \), the decline occurs more rapidly. When the \( \text{FEV}_1 \) falls below about 1 L, patients develop dyspnea with activities of daily living (although dyspnea is more closely related to the degree of air trapping than to the degree of airflow limitation); when the \( \text{FEV}_1 \) falls below about 0.8 L, patients are at risk of hypoxemia, hypercapnia, and cor pulmonale. \( \text{FEV}_1 \) and FVC are easily measured with office spirometry and define severity of disease (see Table 192-2) because they correlate with symptoms and mortality. Normal reference values are determined by patient age, sex, and height.

Additional pulmonary function testing is necessary only in specific circumstances,

[Table 192-1. Factors that May Help Differentiate Asthma and COPD]

such as before lung volume reduction surgery (see p. 1898). Other test abnormalities may include increased total lung capacity, functional residual capacity, and residual volume, which can help distinguish COPD from restrictive pulmonary disease, in which these measures are diminished; decreased vital capacity; and decreased single-breath diffusing capacity for carbon monoxide (DLCO). Decreased DLCO is nonspecific and is reduced in other disorders that affect the pulmonary vascular bed, such as interstitial lung disease, but can help distinguish emphysema from asthma, in which DLCO is normal or elevated.
Imaging tests: The chest x-ray may have characteristic findings. Changes in emphysema can include lung hyperinflation manifested as a flat diaphragm (ie, increase in the angle formed by the sternum and anterior diaphragm on a lateral film from the normal value of 45° to > 90°), rapid tapering of hilar vessels, and bullae (ie, radiolucencies > 1 cm surrounded by arcuate, hairline shadows). Other typical findings include widening of the retrosternal airspace and a narrow cardiac shadow. Emphysematous changes occurring predominantly in the lung bases suggest α₁-antitrypsin deficiency (see p. 1901). The lungs may look normal or have increased lucency secondary to loss of parenchyma. Among patients with chronic obstructive bronchitis, chest x-rays may be normal or may show a bibasilar increase in bronchovascular markings as a result of bronchial wall thickening.

Prominent hila suggest large central pulmonary arteries that may signify pulmonary hypertension. Right ventricular enlargement that occurs in cor pulmonale may be masked by lung hyperinflation or may manifest as

[Table 192-2, Stages and Treatment of COPD]

encroachment of the heart shadow on the retrosternal space or by widening of the transverse cardiac shadow in comparison with previous chest x-rays.

CT may reveal abnormalities that are not apparent on the chest x-ray and may also suggest coexisting or complicating disorders, such as pneumonia, pneumoconiosis, or lung cancer. CT helps assess the extent and distribution of emphysema, estimated either by visual scoring or with analysis of the distribution of lung density. Indications for obtaining CT in patients with COPD include evaluation for lung volume reduction surgery, suspicion of coexisting or complicating disorders that are not clearly evident or excluded by chest x-ray, and suspicion of cancer.

Adjunctive tests: α₁-Antitrypsin levels should be measured in patients < 50 yr with symptomatic COPD and in nonsmokers of any age with COPD to detect α₁-antitrypsin deficiency (see p. 1901). Other indications of α₁-antitrypsin deficiency include a family history of premature COPD or infantile liver disease, lower-lobe distribution of emphysema, and COPD associated with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis. If levels of α₁-antitrypsin are low, the diagnosis should be confirmed by establishing the α₁-antitrypsin phenotype.

ECG, often done to exclude cardiac causes of dyspnea, typically shows diffusely low QRS voltage with a vertical heart axis caused by lung hyperinflation and increased P-wave voltage or rightward shifts of the P-wave vector caused by right atrial enlargement in patients with advanced emphysema. Findings of right ventricular hypertrophy include an R or R’ wave as tall as or taller than the S wave in lead V₁; an R wave smaller than the S wave in lead V₆; right-axis deviation > 110° without right bundle branch block; or some combination of these. Multifocal atrial tachycardia, an arrhythmia that can accompany COPD, manifests as a tachyarrhythmia with polymorphic P waves and variable PR intervals.

Echocardiography is occasionally useful for assessing right ventricular function and pulmonary hypertension, although air trapping makes it technically difficult in patients with COPD. Echocardiography is most often indicated when coexistent left ventricular or valvular heart disease is suspected.

CBC is of little diagnostic value in the evaluation of COPD but may show erythrocythemia (Hct > 48%) if the patient has chronic hypoxemia. Patients with anemia (for reasons other than COPD) have disproportionately severe dyspnea.

Evaluation of exacerbations: Patients with acute exacerbations usually have combinations of increased work of breathing, low O₂ saturation on pulse oximetry, diaphoresis, tachycardia, anxiety, and cyanosis. However, patients with exacerbations accompanied by retention of CO₂ may be lethargic or somnolent, a very different appearance. All patients requiring hospitalization for an acute exacerbation should undergo ABG sampling to quantify hypoxemia and hypercapnia. Hypercapnia may exist with hypoxemia.
Findings of PaO\textsubscript{2} < 50 mm Hg or PaCO\textsubscript{2} > 50 mm Hg in the setting of respiratory acidemia define acute respiratory failure (see p. 2279). However, some patients chronically manifest such levels of PaO\textsubscript{2} and PaCO\textsubscript{2} in the absence of acute respiratory failure.

A chest x-ray is often done to check for pneumonia or pneumothorax. Very rarely, infiltrates among patients receiving chronic systemic corticosteroids may represent Aspergillus pneumonia.

Yellow or green sputum is a reliable indicator of neutrophils in the sputum and suggests bacterial colonization or infection. Culture is usually done in hospitalized patients but is not usually necessary in outpatients. In samples from outpatients, Gram stain usually shows neutrophils with a mixture of organisms, often gram-positive diplococci (Streptococcus pneumoniae), gram-negative bacilli (H. influenzae), or both. Other oropharyngeal commensal organisms, such as Moraxella (Branhamella) catarrhalis, occasionally cause exacerbations. In hospitalized patients, cultures may show resistant gram-negative organisms (eg, Pseudomonas) or, rarely, Staphylococcus.

**Prognosis**

Severity of airway obstruction predicts survival in patients with COPD. The mortality rate in patients with an FEV\textsubscript{1} ≥ 50% of predicted is slightly greater than that of the general population. If the FEV\textsubscript{1} is 0.75 to 1.25 L, 5-yr survival is about 40 to 60%; if < 0.75 L, about 30 to 40%.

More accurate prediction of death risk is possible by simultaneously measuring body mass index (B), the degree of airflow obstruction (O, which is the FEV\textsubscript{1}), dyspnea (D, which is measured with a Modified Medical Research Council [MMRC] dyspnea scale), and exercise capacity (E, which is measured with a 6-min walking test); this is the BODE index. Also, heart disease, anemia, resting tachycardia, hypercapnia, and hypoxemia decrease survival, whereas a significant response to bronchodilators predicts improved survival. Risk factors for death in patients with acute exacerbation requiring hospitalization include older age, higher PaCO\textsubscript{2}, and use of maintenance oral corticosteroids.

Patients at high risk of imminent death are those with progressive unexplained weight loss or severe functional decline (eg, those who experience dyspnea with self-care, such as dressing, bathing, or eating). Mortality in COPD may result from intercurrent illnesses rather than from progression of the underlying disorder in patients who have stopped smoking. Death is generally caused by acute respiratory failure, pneumonia, lung cancer, heart disease, or pulmonary embolism.

**Treatment of Stable COPD**

- Inhaled bronchodilators, corticosteroids, or both

- Supportive care (eg, smoking cessation, O\textsubscript{2} therapy, pulmonary rehabilitation)

COPD management involves treatment of chronic stable disease and of exacerbations. Treatment of cor pulmonale, a common complication of long-standing, severe COPD, is discussed elsewhere (see p. 2133).

Treatment of chronic stable COPD aims to prevent exacerbations and improve lung and physical function through drug and O\textsubscript{2} therapy, smoking cessation, exercise, enhancement of nutrition, and pulmonary rehabilitation. Surgical treatment of COPD is indicated for selected patients.

**Drug therapy**: Recommended drug therapy is summarized in Table 192-2.

**Inhaled bronchodilators** are the mainstay of COPD management; drugs include

- β-agonists

- Anticholinergics (antimuscarinics)
These two classes are equally effective. Patients with mild (stage 1) disease are treated only when symptomatic. Those with stage 2 or higher COPD should be taking drugs from one or both of these classes regularly to improve pulmonary function and increase exercise capacity. The frequency of exacerbations can be reduced with the use of anticholinergics, inhaled corticosteroids, or long-acting β-agonists. However, there is no evidence that regular bronchodilator use slows deterioration of lung function. The initial choice among short-acting β-agonists, long-acting β-agonists, anticholinergics (which have a greater bronchodilating effect), and combination β-agonist and anticholinergic therapy is often a matter of tailoring cost and convenience to the patient's preferences and symptoms.

In treatment of chronic stable disease, administration by metered-dose inhaler or dry-powder inhaler is preferred over nebulized home treatment; home nebulizers are prone to contamination from incomplete cleaning and drying. Patients should be taught to exhale to functional residual capacity, inhale the aerosol slowly to total lung capacity, and hold the inhalation for 3 to 4 sec before exhaling. Spacers help ensure optimal delivery of drug to the distal airways and reduce the importance of coordinating activation of the inhaler with inhalation. Some spacers alert patients if they are inhaling too rapidly. Newer metered-dose inhalers that use hydrofluoroalkane (HFA) propellants require slightly different techniques than inhalers containing older environmentally damaging chlorinated fluorocarbon propellants; inhalers containing HFA require 2 to 3 priming doses if they are new or not recently used.

**β-Agonists** relax bronchial smooth muscle and increase mucociliary clearance. Albuterol aerosol, 2 puffs (90 to 100 μg/puff) inhaled from a metered-dose inhaler 4 to 6 times/day prn, is usually the drug of choice because of low cost. Long-acting β-agonists are preferable for patients with nocturnal symptoms or for those who find frequent dosing inconvenient. Options include salmeterol powder, 1 puff (50 μg) inhaled bid, and formoterol powder, 1 puff (12 μg) inhaled bid. The dry-powder formulations may be more effective for patients who have trouble coordinating use of a metered-dose inhaler. Patients should be taught the difference between short-acting and long-acting drugs, because long-acting drugs that are used as needed or more than twice/day increase the risk of cardiac arrhythmias. Adverse effects commonly result from use of any β-agonist and include tremor, anxiety, tachycardia, and mild, temporary hypokalemia.

**Anticholinergics** relax bronchial smooth muscle through competitive inhibition of muscarinic receptors (M1, M2, and M3). Ipratropium is most commonly used because of low cost and ready availability; dose is 2 to 4 puffs (18 μg/puff) from a metered-dose inhaler q 4 to 6 h. Ipratropium has a slower onset of action (within 30 min; peak effect in 1 to 2 h), so a β2-agonist is often prescribed with it in a single combination inhaler or as a separate as-needed rescue drug. Tiotropium, a long-acting quaternary anticholinergic inhaled as a powder formulation, is M1 and M3 selective and may therefore have an advantage over ipratropium, because M2 receptor blockade (as occurs with ipratropium) may limit bronchodilation. Dose is 1 puff (18 μg) once/day. Adverse effects of all anticholinergics are pupillary dilation, blurred vision, and dry mouth.

**Corticosteroids** are often part of treatment. Inhaled corticosteroids seem to reduce airway inflammation, reverse β-receptor down-regulation, and inhibit leukotriene and cytokine production. They do not alter the course of pulmonary function decline in patients with COPD who continue to smoke, but they do relieve symptoms and improve short-term pulmonary function in some patients, are additive to the effect of bronchodilators, and may diminish the frequency of COPD exacerbations. They are indicated for patients who have repeated exacerbations or symptoms despite optimal bronchodilator therapy. Dose depends on the drug; examples include fluticasone 500 to 1000 μg/day and beclomethasone 400 to 2000 μg/day. The long-term risks of inhaled corticosteroids in elderly people are not proved but probably include osteoporosis, cataract formation, and an increased risk of nonfatal pneumonia. Long-term users therefore should undergo periodic ophthalmologic and bone densitometry screening and should possibly receive supplemental calcium, vitamin D, and a bisphosphonate as indicated. Corticosteroid therapy should be stopped if no subjective or objective improvement results (eg, after a few months).

Combinations of a long-acting β-agonist (eg, salmeterol) and an inhaled corticosteroid (eg, fluticasone) are more effective than either drug alone in the treatment of chronic stable disease.
Oral or systemic corticosteroids should usually not be used to treat chronic stable COPD.

**Theophylline** plays only a small role in the treatment of chronic stable COPD now that safer, more effective drugs are available. Theophylline decreases smooth muscle spasm, enhances mucociliary clearance, improves right ventricular function, and decreases pulmonary vascular resistance and arterial pressure. Its mode of action is poorly understood but appears to differ from that of β2-agonists and anticholinergics. Its role in improving diaphragmatic function and dyspnea during exercise is controversial. Low-dose theophylline (300 to 400 mg/day) has anti-inflammatory properties and may enhance the effects of inhaled corticosteroids.

Theophylline can be used for patients who have not adequately responded to inhaled drugs and who have shown symptomatic benefit from a trial of the drug. Serum levels need not be monitored unless the patient does not respond to the drug, develops symptoms of toxicity, or is questionably adherent; slowly absorbed oral theophylline preparations, which require less frequent dosing, enhance adherence. Toxicity is common and includes sleeplessness and GI upset, even at low blood levels. More serious adverse effects, such as supraventricular and ventricular arrhythmias and seizures, tend to occur at blood levels > 20 mg/L. Hepatic metabolism of theophylline varies greatly and is influenced by genetic factors, age, cigarette smoking, hepatic dysfunction, and some drugs, such as macrolide and fluoroquinolone antibiotics and nonsedating histamine2 blockers.

**Oxygen therapy**: Long-term O2 therapy prolongs life in patients with COPD whose PaO2 is chronically < 55 mm Hg. Continual 24-h use is more effective than a 12-h nocturnal regimen. O2 therapy brings Hct toward normal levels; improves neuropsychologic factors, possibly by facilitating sleep; and ameliorates pulmonary hemodynamic abnormalities. O2 therapy also increases exercise tolerance in many patients.

O2 saturation should be measured during exercise and while at rest. Similarly, a sleep study should be considered for patients with advanced COPD who do not meet the criteria for long-term O2 therapy while they are awake (see Table 192-3) but whose clinical assessment suggests pulmonary hypertension in the absence of daytime hypoxemia. Nocturnal O2 may be prescribed if a sleep study shows episodic desaturation to ≤ 88%. Such treatment prevents progression of pulmonary hypertension, but its effects on survival are unknown.

O2 is administered by nasal cannula at a flow rate sufficient to achieve a PaO2 > 60 mm Hg (SaO2 > 90%), usually ≤ 3 L/min at rest. O2 is supplied by electrically driven O2 concentrators, liquid O2 systems, or cylinders of compressed gas. Concentrators, which limit mobility but are the least expensive, are preferable for patients who spend most of their time at home. Such patients require small O2 tanks for backup in case of an electrical failure and for portable use.

**[Table 192-3. Indications for Long-Term O2 Therapy in COPD]**

A liquid system is preferable for patients who spend much time out of their home. Portable canisters of liquid O2 are easier to carry and have more capacity than portable cylinders of compressed gas. Large compressed-air cylinders are the most expensive way of providing O2 and should be used only if no other source is available. All patients must be taught the dangers of smoking during O2 use.

Various O2-conserving devices can reduce the amount of O2 used by the patient, either by using a reservoir system or by permitting O2 flow only during inspiration. Systems with these devices correct hypoxemia as effectively as do continuous flow systems.

Some patients need supplemental O2 during air travel, because flight cabin pressure in commercial airliners is below sea level air pressure (often equivalent to 1830 to 2400 m [6000 to 8000 ft]). Eucapnic COPD patients who have a PaO2 > 68 mm Hg at sea level generally have an in-flight PaO2 > 50 mm Hg and do not require supplemental O2. All patients with COPD with a PaO2 ≤ 68 mm Hg at sea level, hypercapnia, significant anemia (Hct < 30), or a coexisting heart or cerebrovascular disorder should use
supplemental O2 during long flights and should notify the airline when making their reservation. Airlines can provide supplemental O2, and most require a minimum notice of 24 h, a physician’s statement of necessity, and an O2 prescription before the flight. Patients should bring their own nasal cannulas, because some airlines provide only face masks. Patients are not permitted to transport or use their own liquid O2, but many airlines now permit use of portable battery-operated O2 concentrators, which also provide a suitable O2 source on arrival.

**Smoking cessation:** Smoking cessation (see p. 3432) is both extremely difficult and extremely important; it slows but does not halt the rate of FEV1 decline (see Fig. 192-1). Simultaneous use of multiple strategies is most effective: establishment of a quit date, behavior modification techniques, group sessions, nicotine replacement therapy (by gum, transdermal patch, inhaler, lozenge, or nasal spray), varenicline or bupropion, and physician encouragement. Quit rates > 50% at 1 yr have not been demonstrated even with the most effective interventions, such as use of bupropion combined with nicotine replacement or use of varenicline alone.

**Vaccinations:** All patients with COPD should be given annual influenza vaccinations. If a patient is unable to receive a vaccination or if the prevailing influenza strain is not included in the annual vaccine formulation, prophylactic treatment (amantadine, rimantadine, oseltamivir, or zanamivir) is appropriate during community influenza outbreaks. Pneumococcal polysaccharide vaccine, although of unproven efficacy in COPD, has minimal adverse effects and should probably also be given.

**Nutrition:** COPD patients are at risk of weight loss and nutritional deficiencies because of a 15 to 25% increase in resting energy expenditure from breathing; a higher energy cost of daily activities; reduced caloric intake relative to need because of dyspnea; and the catabolic effect of inflammatory cytokines such as TNF-α. Generalized muscle strength and efficiency of O2 use are impaired. Patients with poorer nutritional status have a worse prognosis, so it is prudent to recommend a balanced diet with adequate caloric intake in conjunction with exercise to prevent or reverse undernutrition and muscle atrophy. However, excessive weight gain should be avoided, and obese patients should strive to gradually reduce body fat. Studies of nutritional supplementation alone have not shown improvement in pulmonary function or exercise capacity. Trials of anabolic steroids (eg, megestrol, oxandrolone), growth hormone supplementation, and TNF antagonists in reversing undernutrition and improving functional status and prognosis in COPD have been disappointing.

**Pulmonary rehabilitation:** Pulmonary rehabilitation programs serve as adjuncts to drug treatment to improve physical function; many hospitals and health care organizations offer formal multidisciplinary rehabilitation programs. Pulmonary rehabilitation includes exercise, education, and behavioral interventions. Treatment should be individualized; patients and family members are taught about COPD and medical treatments, and patients are encouraged to take as much responsibility for personal care as possible. The benefits of rehabilitation are greater independence and improved quality of life and exercise capacity. Pulmonary rehabilitation typically does not improve pulmonary function or increase longevity, however. A carefully integrated rehabilitation program helps patients with severe COPD accommodate to physiologic limitations while providing realistic expectations for improvement. Patients with severe disease require a minimum of 3 mo of rehabilitation to benefit and should continue with maintenance programs.

An exercise program can be helpful in the home, in the hospital, or in institutional settings. Graded exercise can ameliorate skeletal muscle deconditioning resulting from inactivity or prolonged hospitalization for respiratory failure. Specific training of respiratory muscles is less helpful than general aerobic conditioning.

A typical training program begins with slow walking on a treadmill or unloaded cycling on an ergometer for a few minutes. Duration and exercise load are progressively increased over 4 to 6 wk until the patient can exercise for 20 to 30 min nonstop with manageable dyspnea. Patients with very severe COPD can usually achieve an exercise regimen of walking for 30 min at 1 to 2 mph. Maintenance exercise should be done 3
to 4 times/wk to maintain fitness levels. $O_2$ saturation is monitored, and supplemental $O_2$ is provided as needed.

Upper extremity resistance training helps the patient in doing daily tasks (eg, bathing, dressing, house cleaning). The usual benefits of exercise are modest increases in lower extremity strength, endurance, and maximum $O_2$ consumption.

Patients should be taught ways to conserve energy during activities of daily living and to pace their activities. Difficulties in sexual function should be discussed and advice should be given on using energy-conserving techniques for sexual gratification.

**Surgery:** Surgical options for treatment of severe COPD include lung volume reduction and transplantation.

**Lung volume reduction surgery** consists of resecting nonfunctioning emphysematous areas. The procedure improves exercise tolerance and decreases 2-yr mortality in patients with severe, predominantly upper-lung emphysema who have low baseline exercise capacity after pulmonary rehabilitation. Other patients may experience symptom relief and improved exercise capacity after surgery, but mortality has been the same as or increased when compared with that for drug therapy. The effect on ABGs is variable and not predictable, but most patients who require $O_2$ before surgery continue to need it. Long-term effects of the procedure are unknown. Improvement is less than that with lung transplantation. The mechanism of improvement is believed to be enhanced lung recoil and improved diaphragmatic function. Operative mortality is about 5%. The best candidates for lung volume reduction surgery are patients with an FEV$_1$ 20 to 40% of predicted, a DLCO > 20% of predicted, significantly impaired exercise capacity, heterogeneous pulmonary disease on CT with an upper-lobe predominance, $PaCO_2$ < 50 mm Hg, and absence of severe pulmonary hypertension and coronary artery disease.

Rarely, patients have extremely large bullae that compress the functional lung. These patients can be helped by surgical resection of these bullae, with resulting relief of symptoms and improved pulmonary function. Generally, resection is most beneficial for patients with bullae affecting more than one third of a hemithorax and an FEV$_1$ about half of the predicted normal value. Improved pulmonary function is related to the amount of normal or minimally diseased lung tissue that was compressed by the resected bullae. Serial chest x-rays and CT scans are the most useful procedures for determining whether a patient's functional status is due to compression of viable lung by bullae or to generalized emphysema. A markedly reduced DLCO (< 40% predicted) indicates widespread emphysema and suggests a poorer outcome from surgical resection.

**Single-lung transplantation** has largely replaced double-lung transplantation in patients with COPD. Candidates for transplantation are patients < 60 to 65 yr with an FEV$_1$ < 25% predicted after bronchodilator therapy or with severe pulmonary hypertension. The goal of lung transplantation is to improve quality of life, because survival time is rarely increased. The 5-yr survival after transplantation for emphysema is 45 to 60%. Lifelong immunosuppression is required, with the attendant risk of opportunistic infections.

**Treatment of Acute COPD Exacerbation**

- $O_2$ supplementation
- Bronchodilators
- Corticosteroids
- Antibiotics
- Sometimes ventilatory assistance

The immediate objectives are to ensure adequate oxygenation and near-normal blood pH, reverse airway
The immediate objectives are to ensure adequate oxygenation and near-normal blood pH, reverse airway obstruction, and treat any cause.

The cause of an acute exacerbation is usually unknown, although some acute exacerbations result from bacterial or viral infections. Smoking, irritative inhalational exposure, and high levels of air pollution also contribute. Mild exacerbations can often be treated on an outpatient basis in patients with adequate home support. Elderly, frail patients and patients with comorbidities, a history of respiratory failure, or acute changes in ABG measurements are admitted to the hospital for observation and treatment. Patients with life-threatening exacerbations manifested by uncorrected moderate to severe acute hypoxemia, acute respiratory acidosis, new arrhythmias, or deteriorating respiratory function despite hospital treatment should be admitted to the ICU and their respiratory status monitored frequently.

**Oxygen:** Most patients require O\textsubscript{2} supplementation, even those who do not need it chronically. Hypercapnia may worsen in patients given O\textsubscript{2}. This worsening has traditionally been thought to result from an attenuation of hypoxic respiratory drive. However, increased V/Q mismatch probably is a more important factor. Before O\textsubscript{2} administration, pulmonary vasoconstriction minimizes V/Q mismatch by decreasing perfusion of the most poorly ventilated areas of the lungs. Increased V/Q mismatch occurs because O\textsubscript{2} administration attenuates this hypoxic pulmonary vasoconstriction. The Haldane effect may also contribute to worsening hypercapnia, although this theory is controversial. The Haldane effect is a decrease in Hb's affinity for CO\textsubscript{2}, which results in increased amounts of CO\textsubscript{2} dissolved in plasma. O\textsubscript{2} administration, even though it may worsen hypercapnia, is recommended; many patients with COPD have chronic as well as acute hypercapnia and thus severe CNS depression is unlikely unless PaCO\textsubscript{2} is > 85 mm Hg. The target level for PaO\textsubscript{2} is about 60 mm Hg; higher levels offer little advantage and increase the risk of hypercapnia. O\textsubscript{2} is given via Venturi mask so it can be closely regulated, and the patient is closely monitored. Patients whose condition deteriorates with O\textsubscript{2} therapy (eg, those with severe acidemia or CNS depression) require ventilatory assistance.

Many patients who require home O\textsubscript{2} for the first time when they are discharged from the hospital after an exacerbation improve within 30 days and no longer require O\textsubscript{2}. Thus, the need for home O\textsubscript{2} should be reassessed 60 to 90 days after discharge.

**Ventilatory assistance:** Noninvasive positive pressure ventilation (eg, pressure support or bilevel positive airway pressure ventilation by face mask—see p. 2282) is an alternative to full mechanical ventilation. Noninvasive ventilation appears to decrease the need for intubation, reduce hospital stay, and reduce mortality in patients with severe exacerbations (defined as a pH < 7.30 in hemodynamically stable patients not at immediate risk of respiratory arrest). Noninvasive ventilation appears to have no effect in patients with less severe exacerbation. However, it may be indicated for patients with less severe exacerbations whose ABGs worsen despite initial drug or O\textsubscript{2} therapy or who appear to be imminent candidates for full mechanical ventilation but who do not require intubation for control of the airway or sedation for agitation. Deterioration while receiving noninvasive ventilation necessitates invasive mechanical ventilation.

Deteriorating ABG values and mental status and progressive respiratory fatigue are indications for endotracheal intubation and mechanical ventilation. Ventilator settings, management strategies, and complications are discussed elsewhere (see p. 2281). Risk factors for ventilatory dependence include an FEV\textsubscript{1} < 0.5 L, stable ABGs with a PaO\textsubscript{2} < 50 mm Hg, or a PaCO\textsubscript{2} > 60 mm Hg, severe exercise limitation, and poor nutritional status. Therefore, a discussion of patients' wishes regarding intubation and mechanical ventilation should be initiated and documented (see p. 3471). However, overconcern about possible ventilator dependence should not delay management of acute respiratory failure; many patients who require mechanical ventilation can return to their pre-exacerbation level of health.

In patients who require prolonged intubation (eg, > 2 wk), a tracheostomy is indicated to facilitate comfort, communication, and eating. With a good multidisciplinary rehabilitation program, including nutritional and psychologic support (see p. 1867), many patients who require prolonged mechanical ventilation can be successfully liberated and can return to their former level of function. Specialized programs are available
for patients who remain ventilator-dependent after acute respiratory failure. Some patients can remain off the ventilator during the day. For patients with adequate home support, training of family members can permit some patients to be sent home with ventilators.

**Drug therapy:** β-Agonists and anticholinergics, with or without corticosteroids, should be started concurrently with \( \text{O}_2 \) therapy (regardless of how \( \text{O}_2 \) is administered) with the aim of reversing airway obstruction. Methylxanthines, once considered essential to treatment of acute COPD exacerbations, are no longer used; toxicities exceed benefits.

**Short-acting β-agonists** are the cornerstone of drug therapy for acute exacerbations. The most widely used drug is albuterol 2.5 mg by nebulizer or 2 to 4 puffs (100 μg/puff) by metered-dose inhaler q 2 to 6 h. Inhalation using a metered-dose inhaler causes rapid bronchodilation; there are no data indicating that doses taken with nebulizers are more effective than the same doses correctly taken with metered-dose inhalers. In life-threatening exacerbations, risks of the exacerbation usually exceed those of high-dose α-agonists; thus, β-agonists may be given continuously via nebulizer until improvement occurs.

**Ipratropium**, the most commonly used anticholinergic, is effective in acute COPD exacerbations and should be given concurrently or alternating with β-agonists. Dosage is 0.25 to 0.5 mg by nebulizer or 2 to 4 inhalations (17 to 18 μg of drug delivered per puff) by metered-dose inhaler q 4 to 6 h. Ipratropium generally provides bronchodilating effect similar to that of usual recommended doses of α-agonists. The role of the longer-acting anticholinergic tiotropium in treating acute exacerbations has not been defined.

**Corticosteroids** should be begun immediately for all but mild exacerbations. Options include prednisone 30 to 60 mg po once/day for 5 days or tapered over 7 to 14 days, or methylprednisolone 60 to 500 mg IV once/day for 3 days and then tapered over 7 to 14 days. These drugs are equivalent in their acute effects; inhaled corticosteroids have no role in the treatment of acute exacerbations.

**Antibiotics** are recommended for exacerbations in patients with purulent sputum. Some physicians give antibiotics empirically for change in sputum color or for nonspecific chest x-ray abnormalities. Routine cultures and Gram stains are not necessary before treatment unless an unusual or resistant organism is suspected (eg, in hospitalized, institutionalized, or immunosuppressed patients). Drugs directed against oral flora are indicated. Trimethoprim/sulfamethoxazole 160 mg/800 mg po bid, amoxicillin 250 to 500 mg po tid, tetracycline 250 mg po qid, and doxycycline 50 to 100 mg po bid given for 7 to 14 days are all effective and inexpensive. Choice of drug is dictated by local patterns of bacterial sensitivity and patient history. If the patient is seriously ill or if clinical evidence suggests that the infectious organisms are resistant, more expensive 2nd-line drugs can be used. These drugs include amoxicillin/clavulanate 250 to 500 mg po tid, fluoroquinolones (eg, ciprofloxacin, levofloxacin), 2nd-generation cephalosporins (eg, cefuroxime, cefaclor), and extended-spectrum macrolides (eg, azithromycin, clarithromycin). These drugs are effective against β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* but have not been shown to be more effective than first-line drugs for most patients. Patients can be taught to recognize a change in sputum from normal to purulent as a sign of impending exacerbation and to start a 10- to 14-day course of antibiotic therapy. Long-term antibiotic prophylaxis is recommended only for patients with underlying structural changes in the lung, such as bronchiectasis or infected bullae.

**Antitussives**, such as dextromethorphan and benzonatate, have little role.

**Opioids** (eg, codeine, hydrocodone, oxycodone) should be used judiciously for relief of symptoms (eg, severe coughing paroxysms, pain) insofar as these drugs may suppress a productive cough, impair mental status, and cause constipation.

**End-of-life care:** With very severe disease, particularly when death is imminent, exercise is unwarranted and activities of daily living are arranged to minimize energy expenditure. For example, patients may arrange to live on one floor of the house, have several small meals rather than fewer large meals, and avoid wearing shoes that must be tied. End-of-life care should be discussed, including whether to pursue mechanical ventilation, the use of palliative sedation, and appointment of a surrogate medical decision-maker in the event of the patient's incapacitation.

**α1-Antitrypsin Deficiency**
α₁-Antitrypsin deficiency is congenital lack of a primary lung antiprotease, α₁-antitrypsin, which leads to increased protease-mediated tissue destruction and emphysema in adults. Hepatic accumulation of abnormal α₁-antitrypsin can cause liver disease in both children and adults. Serum α₁-antitrypsin level < 11 μmol/L (< 80 mg/dL) confirms the diagnosis. Treatment is smoking cessation, bronchodilators, early treatment of infection, and, in selected cases, α₁-antitrypsin replacement. Severe liver disease may require transplantation. Prognosis is related mainly to degree of lung impairment.

Pathophysiology

α₁-Antitrypsin is a neutrophil elastase inhibitor (an antiprotease), the major function of which is to protect the lungs from protease-mediated tissue destruction. Most α₁-antitrypsin is synthesized by hepatocytes and monocytes and passively diffuses through the circulation into the lungs; some is secondarily produced by alveolar macrophages and epithelial cells. The protein conformation (and hence functionality) and quantity of circulating α₁-antitrypsin are determined by codominant expression of parental alleles; > 90 different alleles have been identified and described by protease inhibitor (PI*) phenotype.

Liver: Inheritance of some variant alleles causes a change in conformation of the α₁-antitrypsin molecule, leading to polymerization and retention within hepatocytes. The hepatic accumulation of aberrant α₁-antitrypsin molecules causes neonatal cholestatic jaundice in 10 to 20% of patients; the remaining patients are probably able to degrade the abnormal protein, although the exact protective mechanism is unclear. About 20% of cases of neonatal hepatic involvement result in development of cirrhosis in childhood. About 10% of patients without childhood liver disease develop cirrhosis as adults. Liver involvement increases the risk of liver cancer.

Lungs: In the lungs, α₁-antitrypsin deficiency increases neutrophil elastase activity, which facilitates tissue destruction leading to emphysema (especially in smokers, because cigarette smoke also increases protease activity). α₁-Antitrypsin deficiency accounts for 1 to 2% of all cases of COPD. α₁-Antitrypsin deficiency most commonly causes early emphysema; symptoms and signs of lung involvement occur earlier in smokers than in nonsmokers but in both cases are rare before age 25.

Other tissues: Other disorders possibly associated with α₁-antitrypsin allele variants include panniculitis (an inflammatory disorder of the subcutaneous tissue), life-threatening hemorrhage (through a mutation that converts α₁-antitrypsin from a neutrophil elastase to a coagulation factor inhibitor), aneurysms, ulcerative colitis, antineutrophilic cytoplasmic antibody (ANCA)-positive vasculitis, and glomerular disease.

Classification

The normal PI phenotype is PI*MM. More than 95% of people with severe α₁-antitrypsin deficiency and emphysema are homozygous for the Z allele (PI*ZZ) and have α₁-antitrypsin levels of about 30 to 40 mg/dL (5 to 6 μmol/L). Prevalence in the general population is 1/1500 to 1/5000. Most are whites of Northern European descent; the Z allele is rare in people of Asian descent and blacks. Though emphysema is common among PI*ZZ patients, many nonsmoking patients who are homozygous for PI*ZZ do not develop emphysema; patients who do typically have a family history of COPD. PI*ZZ smokers have a lower life expectancy than PI*ZZ nonsmokers, who have a lower life expectancy than PI*MM nonsmokers and smokers. Nonsmoking people who are PI*MZ heterozygous are more likely to experience more rapid decreases in forced expiratory volume in 1 sec (FEV₁) over time than do people in the general population.

Other rare phenotypes include PI*SZ and two types with nonexpressing alleles, PI*Z-null and PI*null-null (see Table 192-4). The null phenotype leads to undetectable serum levels of α₁-antitrypsin. Normal serum
levels of malfunctioning α1-antitrypsin may occur with rare mutations.

**Symptoms and Signs**

Neonates with hepatic involvement present with cholestatic jaundice and hepatomegaly during the first week of life; jaundice usually resolves by 2 to 4 mo of age. Cirrhosis may develop in childhood or adulthood (symptoms and signs of cirrhosis and hepatocellular carcinoma are discussed elsewhere in THE MANUAL). Adults with emphysema have symptoms and signs of COPD (see p. 1891), including dyspnea, cough, wheezing, and prolonged expiration. Severity of pulmonary disease varies greatly depending on phenotype, smoking status, and other factors. Pulmonary function is well preserved in some Pi*ZZ smokers and can be severely impaired in some Pi*ZZ nonsmokers. Pi*ZZ people identified in population surveys (ie, those without symptoms or pulmonary disease) tend to have better pulmonary function, whether they smoke or not, than do index people (those identified because they have pulmonary disease). Airflow obstruction occurs more frequently in men and in people with asthma, recurrent respiratory infections, occupational dust exposure, and a family history of pulmonary disease.

Panniculitis, an inflammatory disorder of subcutaneous soft tissue, manifests as indurated, tender, discolored plaques or nodules, typically on the lower abdomen, buttocks, and thighs (see p. 687).

**Diagnosis**

- Serum α1-antitrypsin level
- Genotyping

α1-Antitrypsin deficiency is suspected in the following:

- Smokers who develop emphysema before age 45
- Nonsmokers without occupational exposures who develop emphysema at any age
- Patients whose chest x-ray shows predominately lower lung emphysema
- Patients with a family history of emphysema or unexplained cirrhosis
- Patients with panniculitis
- Neonates with jaundice or liver enzyme elevations
- Patients with unexplained bronchiectasis or liver disease

Diagnosis is made by identifying serum α1-antitrypsin levels < 80 mg/dL (< 11 μmol/L) if measured by the radial immunodiffusion method or levels < 50 mg/dL (< 6.9 μmol/L) if measured by nephelometry. Patients with low levels should have confirmation by genotyping.

**Prognosis**

As a group, people with severe α1-antitrypsin deficiency who have never smoked have a normal life expectancy and only moderate impairment of pulmonary function. The most common cause of death in α1-antitrypsin deficiency is emphysema, followed by cirrhosis, often with hepatic carcinoma.

**Treatment**

- Supportive care
• For pulmonary disease, often α₁-antitrypsin replacement

Treatment of pulmonary disease is with purified human α₁-antitrypsin (60 mg/kg IV over 45 to 60 min given once/wk or 250 mg/kg over 4 to 6 h given once/mo [pooled only]), which can maintain the serum α₁-antitrypsin level above a target protective level of 80 mg/dL (35% of normal). Because emphysema causes permanent structural change, therapy cannot repair damaged lung structure or improve lung function but is given to halt progression. Treatment is expensive and is therefore reserved for nonsmoking patients in whom both alleles are abnormal and who have mild to moderately abnormal pulmonary function and confirmation of diagnosis by low serum α₁-antitrypsin levels. It is not indicated for patients who have severe disease or for patients in whom one or both alleles are normal.

Smoking cessation, use of bronchodilators, and early treatment of respiratory infections are particularly important for α₁-antitrypsin-deficient patients with emphysema. Experimental treatments, such as phenylbutyric acid that can reverse the misfolding of the abnormal α₁-antitrypsin proteins in the hepatocytes, thereby stimulating protein release, are being investigated. For severely impaired people < 60 yr, lung transplantation should be considered. Lung volume reduction in treating the emphysema of α₁-antitrypsin deficiency is controversial. Gene therapy is under study.

Treatment of liver disease is supportive. Enzyme replacement does not help because the disease is caused by abnormal processing rather than by enzyme deficiency. Liver transplantation may be used for patients with liver failure.

Treatment of panniculitis is not well defined. Corticosteroids, antimalarials, and tetracyclines have been used.
Chapter 193. Sleep Apnea

Introduction
Breathing disorders that occur during sleep include obstructive sleep apnea and central sleep apnea. Less severe forms include snoring and upper airway resistance syndrome. The term sleep-disordered breathing is used to encompass all such disorders. (See also Ch. 177.)

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) consists of episodes of partial or complete closure of the upper airway that occur during sleep and lead to breathing cessation (defined as a period of apnea > 10 sec). Symptoms include restlessness, snoring, recurrent awakening, morning headache, and excessive daytime sleepiness. Diagnosis is based on sleep history and polysomnography. Treatment is with nasal continuous positive airway pressure, oral appliances, and, in refractory cases, surgery. Prognosis is good with treatment. Most cases remain undiagnosed and untreated and are often associated with hypertension, heart failure, and injury or death due to motor vehicle crashes and other accidents resulting from hypersomnolence.

In at-risk patients, sleep destabilizes patency of the upper airway, leading to partial or complete obstruction of the nasopharynx, oropharynx, or both. When breathing is diminished but not absent, the condition is called obstructive sleep hypopnea.

The prevalence of OSA is 2 to 9% in adults; the condition is under-recognized and often undiagnosed even in symptomatic patients. OSA is up to 4 times more common among men and 7 times more common among people who are obese (ie, body mass index [BMI] > 30). Severe OSA (apnea-hypopnea index [AHI] > 30/h) increases the risk of death in middle-aged men.

Etiology
Anatomic risk factors include obesity, an oropharynx "crowded" by a short or retracted mandible, a prominent tongue base or tonsils, a rounded head shape and a short neck, a neck circumference > 43 cm, thick lateral pharyngeal walls, or lateral parapharyngeal fat pads. Other identified risk factors include postmenopausal status, aging, and alcohol or sedative use. A family history of sleep apnea is present in 25 to 40% of cases, perhaps reflective of intrinsic ventilatory drive or craniofacial structure. The likelihood of other family members having sleep apnea increases as more family members have it.

Many people with OSA have disorders such as hypertension, stroke, diabetes, gastroesophageal reflux disease, nocturnal angina, heart failure, acromegaly, and hypothyroidism. OSA can also be associated with cardiac arrhythmias (eg, atrial fibrillation).

Because obesity is a common risk factor for both OSA and obesity-hypoventilation syndrome (see p. 57), the two conditions may coexist.

Airway obstruction causes paroxysms of inspiratory effort, reductions in gas exchange, disruption of normal sleep architecture, and partial or complete arousals from sleep. Factors that may interact to cause the characteristic symptoms and signs include hypoxia, hypercapnia, and sleep fragmentation.

OSA is an extreme form of sleep-related upper airway resistance. Less severe forms that do not cause \( \text{O}_2 \) desaturation include snoring; pharyngeal airflow resistance causing noisy inspiration but without sleep arousals; and upper airway resistance syndrome, characterized by crescendo snoring terminated by respiratory effort-related arousals (RERAs). People with upper airway resistance syndrome are typically younger and less obese than those with OSA and they complain of daytime sleepiness more than do those with primary snoring. The symptoms, diagnostic evaluation, and treatment of snoring and upper airway resistance syndrome are otherwise the same as for OSA.

Symptoms and Signs
Although loud disruptive snoring is reported by 85% of OSA patients, most people who snore do not have OSA. Other symptoms of OSA may include choking, gasping, or snorting during sleep, restless and unrefreshing sleep, and difficulty staying asleep. Most patients are unaware of these symptoms (because they occur during sleep) but are informed of them by bed partners, roommates, or housemates.

When awake, patients may experience hypersomnolence, fatigue, and impaired concentration. The frequency of sleep complaints and the degree of daytime sleepiness do not correlate well with number of nocturnal arousals.

**Diagnosis**

- Symptom criteria
- Sleep studies

The diagnosis is suspected in patients with identifiable risk factors, symptoms, or both. Criteria for diagnosis consist of daytime symptoms, nighttime symptoms, and sleep monitoring that documents > 5 episodes of hypopnea and apnea per hour. Specifically, in regard to symptoms, there should be ≥ 1 of the following:

- Daytime sleepiness, unintentional sleep episodes, unrefreshing sleep, fatigue, or insomnia
- Awakening with breath holding, gasping, or choking
- Reports by a bed partner of loud snoring, breathing interruptions, or both in the patient's sleep

The patient and any bed partners, roommates, or housemates should be interviewed. The differential diagnosis of excessive daytime sleepiness is broad (see p. 1710) and includes

- Reduced quantity or quality of sleep due to poor sleep hygiene
- Sedation or mental status changes due to drugs, chronic diseases (including cardiovascular or respiratory diseases), metabolic disturbances, and accompanying therapies
- Depression
- Alcohol or drug abuse
- Narcolepsy
- Other primary sleep disorders (eg, periodic limb movement disorder, restless legs syndrome)

An extended sleep history should be taken in all patients who

- Are over the age of about 65
- Report daytime fatigue, sleepiness, or insomnia
- Are overweight (BMI > 30)
- Have poorly controlled hypertension (which may be caused or exacerbated by OSA), heart failure (which may cause OSA), stroke, or diabetes

Most patients who report only snoring, without other symptoms or cardiovascular risks, do not need an extensive evaluation for OSA.

The physical examination should include evaluation for nasal obstruction, tonsillar hypertrophy, and
pharyngeal structure and identification of clinical features of hypothyroidism and acromegaly.

The diagnosis is confirmed with polysomnography (see p. 1706), which includes continuous measurement of breathing effort by plethysmography, airflow at the nose and mouth using flow sensors, O₂ saturation by oximetry, sleep architecture by EEG, chin electromyography (looking for hypotonia), and electro-oculograms to assess the occurrence of rapid eye movements. Polysomnography records and helps classify stages of sleep and the occurrence and duration of apneic and hypopneic periods. The patient is also observed by video, and ECG monitoring is used to determine whether arrhythmias occur in conjunction with the apneic episodes. Other variables evaluated include limb muscle activity (to assess nonrespiratory causes of sleep arousal, such as restless legs syndrome and periodic limb movements disorder) and body position (apnea may occur only in the supine position).

The common summary measure used to describe respiratory disturbances during sleep is the AHI, which is the total number of episodes of apnea and hypopnea occurring during sleep divided by the hours of sleep time. AHI values can be computed for different sleep stages. The respiratory disturbance index (RDI) is a similar measure, describing the number of times per hour that blood O₂ saturation falls > 3% but also includes RERAs. If EEG monitoring is used, an arousal index (AI) can be computed, which is the number of arousals per hour of sleep. The AI may be correlated with AHI or RDI, but about 20% of apneas and desaturation episodes are not accompanied by arousals, or other causes of arousals are present. An AHI > 5 is required for the diagnosis of OSA; a value of > 15 indicates a moderate level of sleep apnea and a value > 30 indicates a severe level of apnea. Snoring loudly enough to be heard in the next room confers a 10-fold increase in the likelihood of having AHI > 5. The AI and RDI correlate only moderately with a patient's symptoms.

Ambulatory diagnostic tools are being used more often to diagnose OSA. Portable monitors can measure heart rate, pulse oximetry, effort, position, and nasal airflow to provide estimates of respiratory disturbances during self-reported sleep, thereby providing a value for AHI/RDI. Ambulatory diagnostic tools are often used in combination with tools that calculate patients' risk (the sensitivity and specificity of the test depend on pre-test probability). When ambulatory diagnosis is used, coexisting sleep disorders (e.g., restless legs syndrome) are not excluded. Follow-up polysomnography may still be needed.

Adjunctive testing may include upper airway imaging, measurement of thyroid-stimulating hormone, and other tests as appropriate to assess chronic medical conditions associated with OSA.

Prognosis

Prognosis is excellent if effective treatment is instituted.

Untreated or unrecognized OSA leads to cognitive impairment as a result of sleeplessness, which, in turn, can lead to serious injury or death caused by accidents, especially motor vehicle crashes. Sleepy patients should be warned of the risk of driving, operating heavy machinery, or engaging in other activities during which sleep attacks would be hazardous.

Adverse effects of hypersomnolence, such as loss of employment and sexual dysfunction, can affect families considerably.

Long-term cardiovascular sequelae of untreated OSA include poorly controlled hypertension and heart failure.

In addition, perioperative complications, including cardiac arrest, have been attributed to OSA, probably because anesthesia can cause airway obstruction after a mechanical airway is removed. Patients should therefore inform their anesthesiologist of the diagnosis before undergoing surgery and should expect to receive continuous positive airway pressure (CPAP) when they receive preoperative drugs and during recovery.

Treatment
- Control of risk factors

- CPAP or oral appliances

- Possibly airway surgery for anatomic encroachment or intractable disease

The aim of treatment is to reduce episodes of hypoxia and sleep fragmentation; treatment is tailored to the patient and to the degree of impairment. Cure is defined as a resolution of symptoms with AHI reduction below a threshold, usually 10/h.

Treatment is directed first at risk factors and then at OSA itself. Specific treatments for OSA include CPAP, oral appliances, and airway surgery.

**Control of risk factors:** Initial treatment aims at optimal control of modifiable risk factors, including obesity, alcohol and sedative use, hypothyroidism, acromegaly, and other chronic disorders. Although modest weight loss (15%) may result in clinically meaningful improvement, weight loss is extremely difficult for most people, especially those who are fatigued or sleepy. Bariatric surgery reverses symptoms and improves AHI in 85% of morbidly obese (BMI > 40) patients.

**CPAP:** Nasal CPAP is the treatment of choice for most patients with OSA and subjective daytime sleepiness; adherence is lower in patients who do not experience sleepiness. CPAP improves upper airway patency by applying positive pressure to the collapsible upper airway segment. Effective pressures typically range from 3 to 15 cm H$_2$O. Disease severity does not correlate with pressure requirements. If clinical improvement is not apparent, pressure can be titrated during monitoring with repeat polysomnography. Regardless of improvement in the AHI, CPAP will reduce cognitive impairment and BP. If CPAP is withdrawn, symptoms recur over several days, though short interruptions of therapy for acute medical conditions are usually well tolerated. Duration of therapy is indefinite.

Failures of nasal CPAP are common because of limited patient adherence. Adverse effects include dryness and nasal irritation, which can be alleviated in some cases with the use of warm humidified air, and discomfort resulting from a poorly fitting mask.

CPAP can be augmented with inspiratory assistance (bilevel positive airway pressure) for patients with obesity-hypoventilation syndrome (see p. 57).

**Oral appliances:** Oral appliances are designed to advance the mandible or, at the very least, prevent retrusion with sleep. Some are also designed to pull the tongue forward. Use of these appliances to treat both snoring and OSA is gaining acceptance. Comparisons of appliances to CPAP show equivalence in mild to moderate OSA, but results of costeffectiveness studies are not available.

**Airway surgery:** Surgical correction of upper airway obstruction caused by enlarged tonsils and nasal polyps should be considered. Surgery for macroglossia or micrognathia is also an option. Surgery is a first-line treatment if anatomic encroachment is identified; otherwise, surgery is a second-tier approach.

Uvulopalatopharyngoplasty (UPPP) is the most commonly used procedure. It involves resection of submucosal tissue from the tonsillar pillars to the arytenoepiglottic folds, including resection of the adenoids, to enlarge the upper airway. Equivalence with CPAP was shown in one study using CPAP as a bridge to surgery, but the interventions have not been directly compared. UPPP may not be successful in patients who are morbidly obese or who have anatomic narrowing of the airway. Moreover, recognition of sleep apnea after UPPP is obscured because of a lack of snoring. Such silent obstructions may be as severe as apneic episodes before surgical intervention.

Adjunctive surgical procedures include midline glossectomy, hyoid advancement, and mandibulomaxillary advancement. The latter is often offered as a 2nd-stage procedure if UPPP is not curative. Studies of multistage approaches across centers in unselected patients are not available.

Tracheostomy is the most effective therapeutic maneuver for OSA but is done as a last resort. It bypasses the site of obstruction and is indicated for patients most severely affected (eg, those with cor pulmonale).
Laser-assisted uvuloplasty, uvular splints, and radiofrequency tissue ablation have been promoted as treatments for loud snoring in patients without OSA. Although they may transiently decrease snoring loudness, efficacy declines over months to years.

**Adjunctive treatments:** Adjunctive treatments are commonly used but have no proven role as first-line treatment.

Modafinil can be used for residual sleepiness in OSA in patients who are effectively using CPAP.

Supplemental O₂ improves blood oxygenation, but a beneficial clinical effect cannot be predicted. Also, O₂ may provoke respiratory acidosis and morning headache in some patients.

A number of drugs have been used to stimulate ventilatory drive (eg, tricyclic antidepressants, theophylline) but cannot be routinely advocated because of limited efficacy, a low therapeutic index, or both.

Nasal dilatory devices and throat sprays sold OTC for snoring have not been studied sufficiently to prove benefits for OSA.

**Patient education and support:** An informed patient and family are better able to cope with a treatment strategy, including tracheostomy. Patient support groups provide helpful information and effectively support timely treatment and follow-up.

**Obstructive Sleep Apnea in Children**

Obstructive sleep apnea (OSA) is episodes of partial or complete closure of the upper airway that occur during sleep and lead to breathing cessation. Symptoms include snoring and sometimes restless sleep, nocturnal sweating, and morning headache. Complications may include growth disturbance, cor pulmonale, pulmonary hypertension, and learning or behavioral disturbances. Diagnosis is by polysomnography. Treatment is usually adenotonsillectomy.

The prevalence of OSA in children is about 2%. The condition is underdiagnosed and can lead to serious sequelae.

**Etiology**

Risk factors for OSA in children include the following:

- Enlarged tonsils or adenoids
- Certain dental abnormalities (eg, large overbite)
- Obesity
- Craniofacial abnormalities (eg, micrognathia, retrognathia, midfacial hypoplasia, excessively angled skull base)
- Certain drugs (eg, sedatives, opioids)
- Mucopolysaccharidoses
- Disorders causing hypotonia or hypertonia (eg, Down syndrome, cerebral palsy, muscular dystrophies)
- Possibly genetic factors

**Symptoms and Signs**
Almost all affected children snore. Other sleep symptoms may include restless sleep, sweating at night, and observed apnea. Daytime symptoms may include nasal obstruction, mouth breathing, morning headache, and problems concentrating. Children may have nocturnal enuresis. Excessive daytime sleepiness is less common than among adults with OSA.

Complications of OSA may include cor pulmonale, pulmonary hypertension, growth disturbance, and problems with learning and behavior.

Examination may reveal no abnormalities or may show anatomic facial, nasal, or oral abnormalities contributing to obstruction, increase in the pulmonic component of the 2nd heart sound, or growth disturbance.

Diagnosis

- Polysomnography with end-tidal CO₂ monitoring

OSA is considered in children with snoring or risk factors. If symptoms of OSA are present, diagnostic testing is done; clinical criteria are not accurate. Diagnosis is by overnight polysomnography in a sleep laboratory that includes end-tidal CO₂ monitoring. The accuracy of home polysomnography is under evaluation. Although criteria for OSA in adults do not apply to children, experts disagree on what criteria should be used to diagnose OSA in children. Outcome data are lacking. However, OSA is generally considered present if polysomnography shows the following:

- > 1 apneic or > 2 hypopneic events/h (an event lasts > 2 breaths)

- End-tidal CO₂ > 50 mm Hg for > 10% total sleep time together with paradoxical respiration or snoring in patients without lung disorders

Patients with OSA are evaluated for cardiopulmonary complications with ECG and chest x-ray.

Treatment

- Adenotonsillectomy or correction of congenital micrognathia

- CPAP as 2nd-line therapy

Children who are otherwise healthy are treated with adenotonsillectomy, which is usually effective. Adenoidectomy alone is often ineffective. The risk of perioperative airway obstruction is higher among children with OSA than among children without OSA who undergo adenotonsillectomy; thus, close monitoring is important.

For children who are not otherwise healthy, who have complex anatomic abnormalities or genetic conditions altering respiratory control, or who have cardiopulmonary complications, a physician experienced in management of OSA in children should be consulted. Adenotonsillectomy may be effective or may provide some relief. Depending on the anatomic abnormality causing OSA, an alternate surgical procedure may be indicated (eg, uvulopalatopharyngoplasty, tongue or midface surgeries).

CPAP can be used for children who are not candidates for corrective surgery or who continue to have OSA after adenotonsillar surgery. Weight loss can decrease OSA severity in obese children and has other health benefits but is rarely sufficient treatment for OSA as monotherapy. Nocturnal O₂ supplementation may help prevent hypoxemia until definitive treatment can be accomplished. Corticosteroids and antibiotics are not usually indicated.

Central Sleep Apnea

Central sleep apnea (CSA) is a heterogeneous group of conditions characterized by changes in ventilatory drive without airway obstruction. Most of these conditions cause asymptomati
changes in breathing pattern during sleep.

**Etiology**

Patients with CSA fall into 2 groups. One group presents with hypercapnia with decreased ventilatory drive. Causes include hypothyroidism and central lesions, such as brain stem infarctions, encephalitis, and Arnold-Chiari malformation. This type of CSA may also complicate neuromuscular diseases (eg, muscular dystrophy, amyotrophic lateral sclerosis, postpolio syndrome) and chest wall abnormalities (notably, kyphoscoliosis). The other group presents with eucapnia or hypocapnia with increased ventilatory drive but with sleep-induced apnea, periodic breathing, or both. Cheyne-Stokes breathing is a discrete pattern of this form of CSA thought to be caused by delays in circulation time that, in turn, cause a lag in recognition by respiratory centers of acidosis, hypoxia, or both (causing hyperpnea) and of alkalosis, hypocapnia, or both (causing apnea). High altitude is another cause of recurrent CSA manifesting with hypocapnia. Use of opioids can cause either hypercapneic or hypocapneic CSA.

Congenital central hypoventilation (a form of Ondine's curse) is a rare form of idiopathic CSA in neonates and may be associated with Hirschsprung's disease. A mutation in the \textit{PHOX2} gene is responsible for 80 to 90% of cases. This mutation produces variable phenotypes, and clinically evident cases are inherited in a dominant pattern.

**Symptoms and Signs**

CSA is usually asymptomatic and is detected by caretakers or bed partners who notice long respiratory pauses, shallow breaths, or restless sleep. Patients with hypercapnic forms may experience daytime somnolence, lethargy, and morning headache.

**Diagnosis**

Diagnosis is suspected on the basis of history and is confirmed by polysomnography. However, testing may not be necessary if CSA causes no symptoms or is clearly related to an identifiable disorder. To diagnose causes of CSA, brain or brain stem imaging may be indicated.

**Treatment**

* Supportive care

Primary treatment is optimal management of underlying conditions and avoidance of opioids and other sedatives. Secondary treatment of symptomatic patients can be a trial of supplemental O\textsubscript{2} or, in patients with hypercapnic CSA who have symptoms despite other treatments, noninvasive continuous or bi-level positive airway pressure. Acetazolamide is effective in CSA caused by high altitude. Phrenic nerve pacing is an option for children > 2 yr with congenital central hypoventilation syndrome.
Chapter 194. Pulmonary Embolism

Introduction

Pulmonary embolism (PE) is the occlusion of ≥ 1 pulmonary arteries by thrombi that originate elsewhere, typically in the large veins of the lower extremities or pelvis. Risk factors are conditions that impair venous return, conditions that cause endothelial injury or dysfunction, and underlying hypercoagulable states. Symptoms are nonspecific and include dyspnea, pleuritic chest pain, cough, and, in severe cases, syncope or cardiorespiratory arrest. Signs are also nonspecific and may include tachypnea, tachycardia, hypotension, and a loud pulmonic component of the 2nd heart sound. Diagnosis is based on a CT angiogram, ventilation/perfusion scan, or a pulmonary arteriogram. Treatment is with anticoagulants and, sometimes, clot dissolution with thrombolytics or surgical removal. Preventive measures include anticoagulants and sometimes insertion of an inferior vena caval filter.

PE affects an estimated 117 people per 100,000 person years, resulting in about 350,000 cases yearly, and causes up to 85,000 deaths/yr. PE affects mainly adults.

Etiology

Nearly all PEs arise from thrombi in the lower extremity or pelvic veins (deep venous thrombosis [DVT]—see p. 2224). Thrombi in either the lower extremity or pelvic veins may be occult. Risk of embolization is higher with thrombi proximal to the calf veins. Thromboemboli can also originate in upper extremity veins (associated with central venous catheters) or from right-sided cardiac chambers. Risk factors for DVT and PE are similar in children and adults and include conditions that impair venous return, conditions that cause endothelial injury or dysfunction, and underlying hypercoagulability disorders (see Table 194-1). Bed rest and confinement without walking, even for a few hours, are common precipitators.

Pathophysiology

Once DVT develops, clots may dislodge and travel through the venous system and right side of the heart to lodge in the pulmonary arteries, where they partially or completely occlude one or more vessels. The consequences depend on the size and number of emboli, the pulmonary reaction, the underlying condition of the lungs, and the ability of the body's intrinsic thrombolytic system to dissolve the clots.

Small emboli may have no acute physiologic effects; many begin to lyse immediately and resolve within hours or days. Larger emboli can cause a reflex increase in ventilation (tachypnea), hypoxemia due to ventilation/perfusion (V/Q) mismatch, shunting and low mixed venous O_2 content as a result of low cardiac output, atelectasis due to alveolar hypocapnia and abnormalities in surfactant, and an increase in pulmonary vascular resistance caused by mechanical obstruction and vasoconstriction. Endogenous lysis reduces most emboli, even those of moderate size, without treatment, and physiologic alterations decrease over hours or days. Some emboli resist lysis and may organize and persist. Occasionally, chronic residual obstruction leads to pulmonary hypertension (chronic thromboembolic pulmonary hypertension) that may develop over years and result in chronic right heart failure. When large emboli occlude major arteries, or when many small emboli occlude > 50% of the distal arterial system, right ventricular pressure increases, causing acute right ventricular failure, failure with shock (massive PE), or sudden death in severe cases. Risk factors for death include age > 70 yr, cancer, and COPD. The risk of death depends on the degree and rate of rise of right-sided pressures and on the patient's underlying cardiopulmonary status; higher pressures more commonly occur among patients with preexisting cardiopulmonary disease. Otherwise healthy patients may survive a PE that occludes > 50% of the pulmonary vascular bed.

Pulmonary infarction occurs in < 10% of patients diagnosed with PE. This low rate has been attributed to the dual blood supply to the lung (ie, bronchial and pulmonary).
PE can also arise from nonthrombotic sources (see Sidebar 194-1).

**Symptoms and Signs**

Most PEs are small, physiologically insignificant, and asymptomatic. Even when present, symptoms are nonspecific and vary in frequency and intensity, depending on the extent of pulmonary vascular occlusion and preexisting cardiopulmonary function.

Larger emboli cause acute dyspnea, pleuritic chest pain, or both. Dyspnea may be intermittent or occur only with exercise. Less common symptoms include cough and hemoptysis. The first symptom in an elderly patient may be altered mental status. Massive PE manifests with hypotension, tachycardia, syncope, or cardiac arrest.

The most common signs of PE are tachycardia and tachypnea. Less commonly, patients have hypotension, a loud 2nd heart sound ($S_2$) due to a loud pulmonic component ($P_2$), and crackles or wheezing. In the presence of right ventricular failure, distended internal jugular veins and a right ventricular heave may be evident, and right ventricular gallop (3rd and 4th heart sounds [$S_3$ and $S_4$]), with or without tricuspid regurgitation, may be audible. Fever can occur; DVT and PE are often overlooked causes of fever.

Pulmonary infarction is typically characterized by chest pain (mainly pleuritic), fever, and, occasionally, hemoptysis. Chronic thromboembolic pulmonary hypertension causes symptoms and signs of right heart failure, including exertional dyspnea, easy fatigue, and peripheral edema that develops over months to years.

**Diagnosis**

- High index of suspicion
- Assessment of pretest probability (based on clinical findings, pulse oximetry, and chest x-ray)
- Subsequent testing based on pre-test probability

Diagnosis is challenging, because symptoms and signs are nonspecific and diagnostic tests have imperfect diagnostic accuracy or are invasive. Most important is to include PE in the differential diagnosis when nonspecific symptoms, such as dyspnea, pleuritic chest pain, fever, hemoptysis, and cough, are encountered. Thus, PE should be considered in the differential diagnosis of patients suspected of having such conditions as cardiac ischemia, heart failure, COPD exacerbation, pneumothorax, pneumonia, sepsis, acute chest syndrome (in patients with sickle cell disease), and acute anxiety with hyperventilation. PE also should be considered in any elderly patient with tachypnea and altered mental status.

Initial evaluation should include pulse oximetry and chest x-ray. Some experts also recommend ECG, ABG, or both, sometimes to exclude other diagnoses (eg, acute MI). The chest x-ray usually is nonspecific but may show atelectasis, focal infiltrates, an elevated hemidiaphragm, or a pleural effusion. The classic findings of focal loss of vascular markings (Westermark's sign), a peripheral wedge-shaped density (Hampton's hump), or enlargement of the right descending pulmonary artery (Palla's sign) are suggestive but uncommon (ie, insensitive) and have an unknown specificity. Chest x-ray can also help exclude pneumonia.

Pulse oximetry provides a quick way to assess oxygenation; hypoxemia is one sign of PE, and it requires further evaluation. ABG measurement may show an increased alveolar to arterial oxygen (A-a) gradient (see p. 1856) or hypocapnia; one or both of these tests are moderately sensitive for PE but are not specific. ABG testing should be considered particularly for patients with dyspnea or tachypnea who do not have hypoxemia detected with pulse oximetry.

**Sidebar 194-1 Nonthrombotic Pulmonary Embolism**
PE caused by various nonthrombotic sources causes clinical syndromes that differ from those caused by thrombotic PE. Treatment of all includes supportive measures.

**Air embolism** is caused by introduction of large amounts of air into systemic veins or into the right side of the heart, which then move to the pulmonary arterial system. Pulmonary outflow tract obstruction may occur, which can be rapidly fatal. Causes include surgery, blunt trauma, defective or uncapped venous catheters, and errors occurring during the insertion or removal of central venous catheters. Treatment includes placement of patient in left lateral decubitus position, preferably in the Trendelenburg position (ie, head lower than feet), to trap air in the apex of the right ventricle and thus prevent brain embolism and supportive measures. Rapid decompression after underwater diving may cause microbubble formation in the pulmonary circulation, a different problem, which results in endothelial damage, hypoxemia, and diffuse infiltrates (see p. 3285).

**Fat embolism** is caused by introduction of fat or bone marrow particles into the systemic venous system and then into pulmonary arteries. Causes include fractures of long bones, orthopedic procedures, microvascular occlusion or necrosis of bone marrow in patients with sickle cell crisis, and, rarely, toxic modification of native or parenteral serum lipids. Fat embolism causes a pulmonary syndrome similar to acute respiratory distress syndrome (ARDS), with severe hypoxemia of rapid onset often accompanied by neurologic changes and a petechial rash. Early splinting of fractures of long bones and operative rather than external fixation are thought to help prevent fat embolism.

**Amniotic fluid embolism** is a rare syndrome caused by introduction of amniotic fluid into the maternal venous and then pulmonary arterial system. The syndrome occurs around the time of labor (see p. 2678) or, even less often, during prepartum uterine manipulations. Patients can have cardiac and respiratory distress due to anaphylaxis, vasoconstriction causing acute severe pulmonary hypertension, and direct pulmonary microvascular toxicity with hypoxemia and pulmonary infiltrates.

**Septic embolism** occurs when infected material embolizes to the lung. Causes include IV drug use, right-sided infective endocarditis, and septic thrombophlebitis. Septic embolism causes symptoms and signs of pneumonia or sepsis. Initially, nodular opacities appear on the chest x-ray; the appearance may progress to peripheral infiltrates, and emboli may cavitate (particularly emboli caused by *Staphylococcus aureus*). Treatment includes that of the underlying infection.

**Foreign body embolism** caused by introduction of particulate matter into the pulmonary arterial system, usually by IV injection of inorganic substances, such as talc by heroin users or elemental mercury by patients with mental disorders. Focal pulmonary infiltrates may result.

**Tumor embolism** is a rare complication of cancer (usually adenocarcinoma) in which neoplastic cells from an organ enter the systemic venous and pulmonary arterial system, where they lodge, proliferate, and obstruct flow. Patients typically present with dyspnea and pleuritic chest pain and signs of cor pulmonale that develop over weeks to months. Diagnosis, which is suggested by micronodules or diffuse pulmonary infiltrates on chest x-ray, can be confirmed by biopsy or occasionally by cytologic aspiration and histologic study of pulmonary capillary blood.

ECG most often shows tachycardia and various ST-T wave abnormalities, which are not specific for PE (see Fig. 194-1). An S₁Q₃T₃ or a new right bundle branch block may indicate the effect of abrupt rise in right ventricular pressure on right ventricular conduction; these findings are moderately specific but insensitive, occurring in only about 5% of patients. Right axis deviation (R > S in V₁) and P-pulmonale may be present. T-wave inversion in leads V₁ to V₄ also occurs.

**Clinical probability**: Clinical probability of PE can be assessed by combining ECG and chest x-ray findings with findings from the history and physical examination (see Table 194-2). Judgment of whether PE is more likely than an alternate diagnosis is somewhat subjective. PE should probably be considered more likely if ≥ 1 of its symptoms and signs, particularly dyspnea,
hemoptysis, tachycardia, or hypoxemia, cannot be explained clinically or by chest x-ray
results. Patients with a low clinical probability of PE may need only minimal additional
testing. Patients with an intermediate clinical probability are likely to need more additional
testing. Patients with a high probability may be candidates for immediate treatment pending confirmation with additional testing. Patients do not need any testing for PE if the clinical probability is very low and there are no objective cardiopulmonary abnormalities.

**Noninvasive testing:** Noninvasive testing typically can be obtained more quickly and carries less morbidity than invasive testing. Tests most useful for diagnosing or excluding PE are D-dimer testing, V/Q scanning, duplex ultrasonography, CT angiography (helical CT with IV contrast), and echocardiography.

There is no universally accepted algorithm for the best choice and sequence of tests, but one common approach is

- Screening with D-dimer testing
- Lower extremity ultrasonography (which exposes the patient to no ionizing radiation) when the D-dimer result is positive
- CT angiography (or V/Q scanning) if duplex ultrasonography is negative

Patients with a moderate to high probability of disease based on clinical criteria who have low- or intermediate-probability V/Q scans usually require pulmonary arteriography or CT angiography to make or exclude the diagnosis. Lower-extremity ultrasonography is not diagnostic for PE, but a study that reveals thrombus formation establishes the need for anticoagulation and obviates the need for further diagnostic testing. A negative result on ultrasonography does not negate the need for additional studies. D-Dimer measurements, ECG, ABG measurements, chest x-ray, and echocardiography are adjunctive tests; positive results of these tests lack sufficient specificity to be diagnostic alone.

**D-Dimer** is a by-product of intrinsic fibrinolysis; thus, elevated levels occur in the presence of a recent thrombus. However, elevated levels are not specific for venous thrombus because many patients without DVT or PE also have elevated levels. More importantly, absence of elevated levels suggests the absence of recent thrombus because the test is sensitive; > 95% of patients with DVT or PE have elevated levels. Thus, a low D-dimer level has a negative predictive value of > 95%, making such a result sufficiently reliable for excluding the diagnosis of PE in routine practice among patients with a low or moderate pre-test probability.

**V/Q scans** detect areas of lung that are ventilated but not perfused, as occurs in PE; results are reported as low, intermediate, or high probability of PE based on patterns of V/Q mismatch. A completely normal scan excludes PE with nearly 100% accuracy, but a low probability scan still carries a 15% likelihood of PE. Perfusion deficits may occur in many other lung conditions, including pleural effusion, chest mass, pulmonary hypertension, pneumonia, and COPD. With an intermediate probability scan, there is a 30 to 40% probability of PE; with a high probability scan, there is an 80 to 90% probability of PE.

**Duplex ultrasonography** is a safe, noninvasive, portable technique for detecting lower extremity (primarily femoral vein) thrombi. A clot can be detected by visualizing the lining of the vein, by showing incompressibility of the vein, or by showing reduced flow by Doppler ultrasonography. The test has a sensitivity of > 90% and a specificity of > 95% for thrombus. It cannot reliably detect a clot in calf or iliac veins. Absence of thrombi in the femoral veins does not exclude the possibility of thrombus from other sources, but patients with negative results on Doppler duplex ultrasonography have > 95% event-free survival, because thrombi from other sources are so much less common.

**CT angiography** is an alternative to V/Q scanning and pulmonary arteriography in most settings because
it is fast, available, and noninvasive and gives more information about other lung pathology. However, patients must be able to hold their breath for several seconds. The sensitivity of CT angiography is highest for PE in lobar and segmental vessels and lowest for emboli in smaller subsegmental vessels (about 30% of all PEs) and thus is less sensitive than perfusion scans. In studies done using older scanners, overall sensitivities range from 53 to 100%; values are at the lower end of the range for subsegmental vessels. Specificities range from 81 to 100%. A positive scan may be diagnostic of PE, but a negative scan does not necessarily exclude subsegmental disease, though the clinical significance of emboli in smaller subsegmental vessels remains to be determined. Newer multidetector scans are more sensitive (about 83%) and are specific (about 96%) overall. Magnetic resonance angiography (MRA) is an alternative to CT angiography for patients who cannot tolerate contrast agents and for pregnant patients.

**Echocardiography** as a diagnostic test for PE is controversial. Its sensitivity is > 80% for detecting right ventricular dysfunction (eg, dilation and hypokinesis, which occur when pulmonary artery pressure exceeds 40 mm Hg). Right ventricular dysfunction is a useful measure of hemodynamic severity in acute PE, but dysfunction is present in several disorders, including COPD, heart failure, and sleep apnea, and is therefore a nonspecific finding. Estimation of pulmonary artery systolic pressure using Doppler flow signals gives additional useful information about the severity of acute PE. Absence of right ventricular dysfunction or pulmonary hypertension makes the diagnosis of a large PE unlikely but does not exclude the diagnosis of a smaller one.

**Cardiac marker testing** is evolving as a useful means of stratifying mortality risk in patients with acute PE. Elevated troponin levels can signify right ventricular strain. Elevated brain natriuretic peptide (BNP) and pro-BNP levels are not helpful, but low levels appear to signify good prognosis. The clinical role of these tests remains to be determined, because they are not specific for right ventricular strain or for PE.

Patients with PE and no known risk factors should be considered for hypercoagulability testing (see p. 973), especially if they are < 35 yr, have recurrent PE, or have a positive family history.

**Invasive tests:** Pulmonary arteriography is indicated

- When the pre-test probability of PE is moderate or high and noninvasive tests are inconclusive
- When the need to make or exclude the diagnosis is urgent, such as in an acutely ill patient
- When anticoagulation is contraindicated
- When chronic thromboembolic pulmonary hypertension is suspected

Pulmonary arteriography is still the most accurate test for diagnosing PE, but it is needed much less often because of the sensitivity of ultrasonography and CT angiography. A pulmonary arteriogram that reveals intraluminal filling defects or abrupt cutoff of flow is positive. Findings suggestive but not diagnostic of PE include partial occlusion of pulmonary arterial branches with increased proximal and decreased distal caliber, oligemic zones, and persistence of dye in the proximal artery during the late (venous) phase of the pulmonary arteriogram. In lung segments with obstructed arteries, venous filling with contrast medium is delayed or absent.

**Prognosis**

An estimated 10% of patients with PE die within 1 h. Of those patients who survive the first hour, only about 30% are diagnosed and receive treatment; > 95% of these patients survive. Thus, most patients with PE are never diagnosed; it is in such patients that most mortality from PE occurs. The best prospects for reducing mortality lie in improving diagnosis, not in improving treatment. Patients with chronic thromboembolic disease represent a tiny fraction of patients with PE who survive. Anticoagulant therapy reduces the rate of recurrence of PE to about 5% in all patients.

**Treatment**
Anticoagulation

Inferior vena cava filter placement when anticoagulation contraindicated or ineffective

Clot elimination (eg, thrombolytic therapy, embolectomy) for massive emboli

Initial treatment of PE is $O_2$ for hypoxemia and IV 0.9% saline and vasopressors for hypotension and anticoagulation. All patients with strongly suspected or confirmed PE should be hospitalized and, ideally, should also be continually monitored for life-threatening cardiovascular complications in the first 24 to 48 h. Clot elimination should be considered in patients with massive PE at the time of diagnosis.

**Clot elimination:** Clot elimination by means of embolectomy or dissolution by IV thrombolytic therapy should be considered for hypotensive patients. It may also be indicated for patients with clinical, ECG, or echocardiographic evidence of right ventricular overload or failure, but data supporting use in these patients are scarce and not definitive, and controlled prospective studies are unlikely to be done.

Embolectomy is reserved for patients with PE who are hypotensive despite supportive measures (persistent systolic BP ≤ 90 mm Hg after fluid therapy and $O_2$ or if pressor therapy is required) or on the verge of cardiac or respiratory arrest. Surgical embolectomy appears to improve survival in patients with massive PE but is not widely available. Catheter-based embolectomy can be done by some interventional radiologists. The decision to proceed with embolectomy and the choice of technique depend on local resources and expertise.

**Thrombolytic therapy** with tissue plasminogen activator (tPA), streptokinase, or urokinase offers a noninvasive way to rapidly restore pulmonary blood flow but is controversial because long-term benefits do not clearly outweigh the risk of hemorrhage. In patients with submassive PE (ie, who are normotensive but have right ventricular dysfunction), thrombolytics speed the resolution of radiographic abnormalities and the return of hemodynamic function (heart rate and right ventricular function) and prevent cardiopulmonary deterioration but have not been shown to improve survival. Some experts recommend thrombolytics for patients with submassive PE suspected on the basis of echocardiographic evidence of proximal pulmonary artery (large) embolism or of right ventricular dysfunction due to either PE or preexisting disease. Others reserve thrombolytic therapy for patients with massive PE.

Absolute contraindications to thrombolytics include prior hemorrhagic stroke, ischemic stroke within 1 yr, active external or internal bleeding from any source, intracranial injury or surgery within 2 mo, intracranial tumor, GI bleeding within 6 mo, and CPR.

Relative contraindications include recent surgery (≤ 10 days), hemorrhagic diathesis (as in hepatic insufficiency), pregnancy, current use of anticoagulants and an INR > 2, punctures of large noncompressible veins (eg, subclavian or internal jugular veins), recent femoral artery catheterization (eg, ≤ 10 days), peptic ulcer disease or other conditions that increase the risk of bleeding, and severe hypertension (systolic BP > 180 or diastolic BP > 110 mm Hg).

Options for thrombolysis include streptokinase, urokinase, and alteplase (recombinant tPA). Standard IV regimens are streptokinase 250,000 units over 30 min followed by continuous infusion of 100,000 units/h for 24 h; urokinase 4400 units/kg over 10 min followed by 4400 units/kg/h for 12 h; or alteplase 100 mg continuous infusion over 2 h followed by an additional 40 mg over another 4 h (10 mg/h) if clinical presentation and repeat pulmonary angiogram suggest failure of clot lysis and initial dosing does not cause bleeding. Although no drug has proved superior to the others, streptokinase is now rarely used because of the risk of allergic and pyrogenic reactions and because administration requires constant infusion for > 24 h.

An initial loading dose of heparin should be given concurrently, but the activated PTT should be allowed to fall to 1.5 to 2.5 times the baseline value before beginning continuous heparin infusion. Direct delivery of thrombolytics to the clot via a pulmonary artery catheter is occasionally used for patients with massive PE or for those with relative contraindications to systemic thrombolytics, but this approach does not prevent systemic thrombolysis. Bleeding, if it occurs, can be reversed with cryoprecipitate or fresh frozen plasma. Accessible vascular access sites can be compressed.
Anticoagulation: Because embolization rarely involves an entire venous thrombus, anticoagulation is required acutely to prevent residual clot from extending and embolizing. Patients in whom anticoagulants are contraindicated or those who have thromboemboli despite therapeutic anticoagulation should have placement of a removable percutaneous inferior vena cava filter.

Heparin, either unfractionated or low molecular weight, is the mainstay of treatment of acute DVT and PE and should be given immediately on diagnosis or sooner if clinical suspicion is high and if the patient has cardiorespiratory compromise. Inadequate anticoagulation in the first 24 h is linked to increased risk of recurrent PE for up to 3 mo. Heparin accelerates the action of antithrombin III, an inhibitor of coagulation factors; unfractionated heparin also has antithrombin III-mediated anti-inflammatory properties, which may facilitate clot organization and reduce thrombophlebitis. Unfractionated heparin should be given as a bolus and infusion by protocol (see Fig. 194-2) to achieve an activated PTT 1.5 to 2.5 times that of normal control. Subcutaneous low molecular weight heparin (LMWH) is as effective as unfractionated heparin and may cause less thrombocytopenia (for dosing, see Table 194-3). Because of its long half-life, it is useful in outpatient treatment (usually restricted to patients with DVT without PE) and to facilitate earlier discharge of patients who have not achieved therapeutic anticoagulation with warfarin.

Adverse effects of all heparins include the following:

- Bleeding
- Thrombocytopenia
- Urticaria
- Thrombosis or anaphylaxis (rarely)

Long-term heparin administration may cause the following:

- Hypokalemia
- Liver enzyme elevations
- Osteoporosis

Before use, patients should be screened for GI bleeding by testing for occult blood in stool. During treatment, they should be monitored for bleeding with serial CBCs and tests for occult blood in stool. Bleeding caused by over-heparinization can be stopped with a maximum of 50 mg of protamine per 5000 units unfractionated heparin infused over 15 to 30 min (or 1 mg in 20 mL normal saline infused over 10 to 20 min for LMWH, though the precise dose is undefined because protamine only partially neutralizes LMWH inactivation of factor Xa). Treatment with heparin or LMWH is continued until full anticoagulation has been achieved with oral warfarin. The use of LMWH in long-term anticoagulation after acute PE has not been studied but will likely be limited by cost and ease of administration compared with oral warfarin.

Warfarin is the oral drug of choice for long-term anticoagulation in all patients except pregnant women and patients with new or worsening venous thromboembolism during warfarin treatment. Five to 10 mg po once/day should be started when the PTT has been consistently ≥ 1.5 to 2.0 times control values. The therapeutic goal with warfarin is usually an INR of 2 to 3.

Physicians prescribing warfarin should be wary of drug interactions (see Table 194-4), including interactions with nonprescription drugs and medicinal herbs. Patients with
temporary risk factors for DVT or PE (eg, fracture or surgery) can stop the drug after 3 to 6 mo. Patients
with permanent risk factors (eg, hypercoagulability), no known risk factors, or recurrent DVT or PE should
take warfarin for at least 6 mo and possibly for life unless complications of therapy intervene. In low-risk
patients, low-intensity warfarin (to maintain

**Table 194-3.** Some Low Molecular Weight Heparin* Options in Thromboembolic Disease

INR at 1.5 to 2.0) may be safe and effective for at least 2 to 4 yr, but this regimen requires further proof of
safety before it can be routinely recommended.

Bleeding is the most common complication of warfarin treatment; patients > 65 and those with
comorbidities (especially diabetes, recent MI, Hct < 30%, or creatinine > 1.5 mg/dL) and a history of
stroke or GI bleeding seem to be at greatest risk. Bleeding can be reversed with 2.5 to 10 mg of vitamin K
sc or po and, in an emergency, with fresh frozen plasma. Vitamin K may cause flushing, local pain, and,
rarely, anaphylaxis.

**Table 194-4.** Drug, Herbal Preparation, and Food Interactions with Warfarin

Prevention

Prevention of PE means prevention of DVT; the need depends on the patient's risks. Bedbound patients
and patients undergoing surgical, especially orthopedic, procedures especially benefit, and most of these
patients can be identified before a thrombus forms (see

**Table 194-5.** Risk of Deep Venous Thrombosis and Pulmonary Embolism in Surgical Patients)

Drugs: LDUH is given in doses of 5000 units sc 2 h preoperatively and q 8 to 12 h thereafter for 7 to 10
days or until the patient is fully ambulatory. Immobilized patients not

undergoing surgery should receive 5000 units sc q 12 h until they are ambulatory.

**Table 194-5.** Risk of Deep Venous Thrombosis and Pulmonary Embolism in Surgical Patients]

LMWH dosing depends on the drug and on whether the drug is being used for prevention or treatment;
enoxaparin, dalteparin, and tinzaparin are equally effective as LDUH for preventing DVT and PE.

Fondaparinux 2.5 mg sc once/day is as effective as LMWH for orthopedic surgery and in some other
settings. It is a selective factor Xa inhibitor.

Warfarin is usually effective and safe at a dose of 2 to 5 mg po once/day or at a dose adjusted to
maintain an INR of 2 to 3.

**Newer anticoagulants**, including hirudin, a subcutaneous direct thrombin inhibitor, and lepirudin, a
recombinant hirudin, have demonstrated efficacy in DVT and PE prevention but warrant further study to
determine their cost-effectiveness and safety relative to heparins and warfarin (also see Tables 194-3
and 194-6).

Aspirin is better than placebo but worse than all other available drugs for preventing DVT and PE.

**Devices:** Inferior vena cava filters, intermittent pneumatic compression, and graded elastic compression
stockings may be used in combination with drugs to prevent PE.

An **inferior vena cava filter** (IVCF) may help prevent PE in patients with lower extremity DVT, but IVCF
placement may risk long-term complications. Benefits outweigh risks if a 2nd PE is predicted to be life
threatening; however, risks outweigh benefits in most patients. A filter is most commonly
Table 194-6. Some Anticoagulation Options Other Than Heparin in Thromboembolic Disease

placed in patients with contraindications to anticoagulation, with recurrent DVT (or emboli) despite adequate anticoagulation, after embolectomy, and, occasionally, in those whose marginal cardiopulmonary function raises concern for their ability to tolerate additional small emboli. Because venous collaterals can develop, providing a pathway for emboli to circumvent the IVCF, patients with recurrent DVT or nonmodifiable risk factors for DVT may still require anticoagulation. An IVCF is placed in the inferior vena cava just below the renal veins via catheterization of an internal jugular or femoral vein. Some IVCFs are removable. Occasionally, a filter dislodges, may migrate up the venous bed, even to the heart, and needs to be removed or replaced. A filter can also become clotted, causing bilateral lower extremity venous congestion (including acute phlegmasia cerulea dolens), lower body ischemia, and acute renal failure. Filter clotting requires careful evaluation for complications and risks of intervention.

Intermittent pneumatic compression (IPC) provides rhythmic external compression to the legs or to the legs and thighs. It is more effective for preventing calf than proximal DVT and thus is considered inadequate after hip or knee surgery. IPC is contraindicated in obese patients and can theoretically trigger PE in immobilized patients who have developed occult DVT while not undergoing preventive treatment.

Graded elastic compression stockings have largely been abandoned in favor of external pneumatic leg compression.

Choice of prevention: For surgical procedures with a high incidence of venous thromboembolism, such as hip and lower extremity orthopedic surgery, LDUH q 8 h, LMWH, or adjusted-dose warfarin is recommended. For total knee replacement, risk reductions provided by LMWH and IPC are comparable but not optimal, so both should be used. The regimens for orthopedic surgery may be initiated preoperatively and should be continued for at least 7 days postoperatively. In selected patients at very high risk of both venous thromboembolism and bleeding, placement of an IVCF is an option for prophylaxis.

A high risk of venous thromboembolism also occurs in patients undergoing elective neurosurgery and those with acute spinal cord injury and multiple trauma. Although physical methods (IPC, elastic stockings) have been used in neurosurgical patients because of concern about intracranial bleeding, LMWH appears to be an acceptable alternative. The combination of IPC and LMWH may be more effective than either alone in high-risk patients. Limited data support the combination of IPC, elastic compression stockings, and LMWH in patients with spinal cord injury or in multiple trauma. For very high-risk patients, an IVCF may be considered.

The most common nonsurgical conditions in which DVT prophylaxis is indicated are acute MI and ischemic stroke. For MI patients, LDUH is effective; IPC, elastic compression stockings, or both may be used when anticoagulants are contraindicated. For stroke patients, LDUH or LMWH can be used; IPC, elastic compression stockings, or both may be beneficial.

Recommendations for some other nonsurgical conditions include LDUH for patients with heart failure; adjusted-dose warfarin (INR 1.3 to 1.9) for patients with metastatic breast cancer; and warfarin 1 mg/day for cancer patients with an indwelling central venous catheter.

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Chapter 194. Pulmonary Embolism
Chapter 195. Acute Bronchitis

Acute bronchitis is inflammation of the upper airways, commonly following a URI. The cause is usually a viral infection, though it is sometimes a bacterial infection; the pathogen is rarely identified. The most common symptom is cough, with or without fever, and possibly sputum production. In patients with COPD, hemoptysis, burning chest pain, and hypoxemia may also occur. Diagnosis is based on clinical findings. Treatment is supportive; antibiotics are necessary only for selected patients with chronic lung disease. Prognosis is excellent in patients without lung disease, but in patients with COPD, acute respiratory failure may result.

Acute bronchitis is frequently a component of a URI caused by rhinovirus, parainfluenza, influenza A or B, respiratory syncytial virus, coronavirus, or human metapneumovirus. Less common causes may be *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Chlamydia pneumoniae*. Patients at risk include those who smoke and those with COPD or other diseases that impair bronchial clearance mechanisms, such as cystic fibrosis or conditions leading to bronchiectasis (see p. 1939).

Symptoms and Signs

Symptoms are a nonproductive or minimally productive cough accompanied or preceded by URI symptoms. Subjective dyspnea results from chest pain or tightness with breathing, not from hypoxia, except in patients with underlying lung disease. Signs are often absent but may include scattered rhonchi and wheezing. Sputum may be clear, purulent, or, occasionally, bloody. Sputum characteristics do not correspond with a particular etiology (ie, viral vs bacterial). Mild fever may be present, but high or prolonged fever is unusual and suggests influenza or pneumonia.

On resolution, cough is the last symptom to subside and often takes several weeks or even longer to do so.

Diagnosis

- Clinical evaluation
- Sometimes chest x-ray

Diagnosis is based on clinical presentation. Chest x-ray is necessary only if findings suggest pneumonia (eg, abnormal vital signs, crackles, signs of consolidation, hypoxemia). Elderly patients are the occasional exception. They may require chest x-ray for productive cough and fever in the absence of auscultatory findings (particularly if there is a history of COPD or another lung disorder).

Sputum Gram stain and culture usually have no role.

Cough resolves within 2 wk in 75% of patients. Patients with persistent cough should undergo a chest x-ray. Evaluation for pertussis, with a culture from nasopharyngeal secretions, and noninfectious etiologies, such as postnasal drip, allergic rhinitis, and coughvariant asthma, may be needed.

Treatment

- Symptom relief (acetaminophen, hydration, possibly antitussives)
- Inhaled β-agonist or anticholinergic for wheezing
- Sometimes oral antibiotics for patients with COPD

Acute bronchitis in otherwise healthy patients is a major reason that antibiotics are overused. Nearly all patients require only symptomatic treatment, such as acetaminophen and hydration. Antitussives should be used only if the cough is interfering with sleep (see p. 1831). Patients with wheezing may benefit from an inhaled β2-agonist (eg, albuterol) or an anticholinergic (eg, ipratropium) for ≤ 7 days. If cough persists
for > 2 wk because of airway irritation, some patients benefit from a few days of inhaled corticosteroids. Oral antibiotics are typically not used except in patients with pertussis or in patients with COPD who have at least 2 of the following:

- Increased cough
- Increased dyspnea
- Increase in sputum purulence

Drugs include amoxicillin 500 mg po tid for 7 days, doxycycline 100 mg po bid for 7 days, azithromycin 500 mg po once/day for 4 days, or trimethoprim/sulfamethoxazole 160/800 mg po bid for 7 days.
Chapter 196. Pneumonia

Introduction

(See also Neonatal Pneumonia on p. 2832.)

Pneumonia is acute inflammation of the lungs caused by infection. Initial diagnosis is usually based on chest x-ray. Causes, symptoms, treatment, preventive measures, and prognosis differ depending on whether the infection is bacterial, viral, fungal, or parasitic; whether it is acquired in the community, hospital, or nursing home; and whether it develops in a patient who is immunocompetent or immunocompromised.

An estimated 2 to 3 million people in the US develop pneumonia each year, of whom about 45,000 die. Pneumonia is the most common fatal hospital-acquired infection and the most common overall cause of death in developing countries.

Bacteria are the most common cause of pneumonia in adults > 30 yr, *Streptococcus pneumoniae* infection being the most common pathogen in all age groups, settings, and geographic regions. However, pathogens of every sort, from viruses to parasites, cause pneumonia.

The airways and lungs are constantly exposed to pathogens in the external environment; the upper airways and oropharynx in particular are colonized with so-called normal flora rendered harmless by host defenses. Infection develops when pathogens that are inhaled or aspirated or reach the lungs via the bloodstream or contiguous spread overcome multiple host defenses.

Upper airway defenses include salivary IgA, proteases, and lysozymes; growth inhibitors produced by normal flora; and fibronectin, which coats the mucosa and inhibits adherence. Nonspecific lower airway defenses include cough, mucociliary clearance, and airway angulation preventing infection in airspaces. Specific lower airway defenses include various pathogen-specific immune mechanisms, including IgA and IgG opsonization, anti-inflammatory effects of surfactant, phagocytosis by alveolar macrophages, and T-cell-mediated immune responses. These mechanisms protect most people against infection. But numerous conditions alter normal flora (eg, systemic illness, undernutrition, hospital or nursing home exposure, antibiotic exposure) or impair these defenses (eg, cigarette smoking, nasogastric or endotracheal intubation). Pathogens that then reach airspaces can multiply and cause pneumonia.

Specific pathogens causing pneumonia cannot be found in < 50% of patients, even with extensive diagnostic investigation. But because pathogens and outcomes tend to be similar by setting and host risk factors, pneumonias can be categorized as

- Community-acquired
- Hospital-acquired (including ventilator-acquired and postoperative)
- Nursing home-acquired
- Occurring in immunocompromised people

These categorizations allow treatment to be selected empirically.

The term interstitial pneumonia refers to various unrelated conditions of varied and sometimes unknown causes characterized by inflammation and fibrosis of the pulmonary interstitium (see p. 1945).

Community-Acquired Pneumonia

Community-acquired pneumonia develops in people with limited or no contact with medical institutions or settings. The most commonly identified pathogens are *Streptococcus pneumoniae, Haemophilus influenzae*, and atypical organisms (ie, *Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella* sp). Symptoms and signs are fever, cough, pleuritic chest
Mycoplasma pneumoniae, Legionella sp. Symptoms and signs are fever, cough, pleuritic chest pain, dyspnea, tachypnea, and tachycardia. Diagnosis is based on clinical presentation and chest x-ray. Treatment is with empirically chosen antibiotics. Prognosis is excellent for relatively young or healthy patients, but many pneumonias, especially when caused by S. pneumoniae or influenza virus, are fatal in older, sicker patients.

**Etiology**

Many organisms cause community-acquired pneumonia, including bacteria, viruses, and fungi. Pathogens vary by patient age and other factors (see Tables 196-1 and 196-2), but the relative importance of each as a cause of community-acquired pneumonia is uncertain, because most patients do not undergo thorough testing, and because even with testing, specific agents are identified in < 50% of cases.

*S. pneumoniae, H. influenzae, C. pneumoniae,* and *M. pneumoniae* are the most common bacterial causes. Pneumonia caused by chlamydia and mycoplasma are often clinically indistinguishable from other pneumonias. Common viral agents include respiratory syncytial virus (RSV), adenovirus, influenza viruses, metapneumovirus, and parainfluenza viruses. Bacterial superinfection can make distinguishing viral from bacterial infection difficult.

*C. pneumoniae* accounts for 2 to 5% of community-acquired pneumonia and is the 2nd most common cause of lung infections in healthy people aged 5 to 35 yr. *C. pneumoniae* is commonly responsible for outbreaks of respiratory infection within families, in college dormitories, and in military training camps. It causes a relatively benign form of pneumonia that infrequently requires hospitalization. *Chlamydia psittaci* pneumonia (psittacosis) is rare and occurs in patients who own or are often exposed to birds.

A host of other organisms causes lung infection in immunocompetent patients, although the term community-acquired pneumonia is usually reserved for the more common bacterial and viral etiologies.

Q fever, tularemia, anthrax, and plague are uncommon bacterial syndromes in which pneumonia may be a prominent feature; the latter three should raise the suspicion of bioterrorism.

Adenovirus, Epstein-Barr virus, and coxsackievirus are common viruses that rarely cause pneumonia. Varicella virus and hantavirus cause lung infection as part of adult chickenpox and hantavirus pulmonary syndrome; a coronavirus causes severe acute respiratory syndrome (SARS—see p. 1411).

Common fungal pathogens include *Histoplasma capsulatum* (histoplasmosis) and *Coccidioides immitis* (coccidioidomycosis). Less common fungi include *Blastomyces dermatitidis* (blastomycosis) and *Paracoccidioides brasiliensis* (paracoccidioidomycosis). *Pneumocystis jirovecii* commonly causes pneumonia in patients who have HIV infection or are immunosuppressed.

Parasites causing lung infection in developed countries include *Toxocara canis* or *T. catis* (visceral larva migrans), *Dirofilaria immitis* (dirofilariasis), and *Paragonimus westermani* (paragonimiasis). (For a discussion of pulmonary TB or of specific microorganisms, see p. 1302.)

**Symptoms and Signs**

Symptoms include malaise, cough, dyspnea, and chest pain. Cough typically is productive in older children and adults and dry in infants, young children, and the elderly. Dyspnea usually is mild and exertional and is rarely present at rest. Chest pain is pleuritic and is adjacent to the infected area. Pneumonia may manifest as upper abdominal pain when lower lobe infection irritates the diaphragm. Symptoms become variable at the extremes of age. Infection in infants may manifest as nonspecific irritability and restlessness; in the elderly, as confusion and obtundation.
Signs include fever, tachypnea, tachycardia, crackles, bronchial breath sounds, egophony, and dullness to percussion. Signs of pleural effusion may also be present (see p. 1998). Nasal flaring, use of accessory muscles, and cyanosis are common among infants. Fever is frequently absent in the elderly.

Symptoms and signs were previously thought to differ by type of pathogen, but presentations overlap considerably. In addition, no single symptom or sign is sensitive or specific enough to predict the organism. Symptoms are even similar for noninfective lung diseases such as pulmonary embolism, pulmonary cancer, and other inflammatory lung diseases.

**Diagnosis**

- Chest x-ray
- Consideration of pulmonary embolism
- Sometimes identification of pathogen

Diagnosis is suspected on the basis of clinical presentation and is confirmed by chest x-ray (see Table 196-3). The most serious condition misdiagnosed as pneumonia is pulmonary embolism, which may be more likely in patients with minimal sputum production, no accompanying URI or systemic symptoms, and risk factors for thromboembolism (see Table 194-1 on p. 1908).

Chest x-ray almost always shows some degree of infiltrate; rarely, an infiltrate is absent in the first 24 to 48 h of illness. In general, no specific findings distinguish one type of infection from another, although multilobar infiltrates suggest *S. pneumoniae* or *Legionella pneumophila* infection and interstitial pneumonia suggests viral or mycoplasmal etiology.

Hospitalized patients (see p. 1929) should undergo WBC count and electrolytes, BUN, and creatinine testing to classify risk and hydration status. Two sets of blood cultures are often obtained to detect pneumococcal bacteremia and sepsis, because about 12% of all patients hospitalized with pneumonia have bacteremia; *S. pneumoniae* accounts for two thirds of these cases. Whether the results of blood cultures alter therapy commonly enough to warrant the expense is under study. Pulse oximetry or ABG should also be done.

**Pathogens:** Attempts to identify a pathogen are not routinely indicated; exceptions may be made for critically ill patients, patients in whom a drug-resistant or unusual organism is suspected (eg, TB, *P. jirovecii*), and patients who are deteriorating or not responding to treatment within 72 h.

The use of Gram stain and culture of sputum for diagnosis is of uncertain benefit, because specimens often are contaminated and because overall diagnostic yield is low. Samples can be obtained noninvasively by simple expectoration or after hypertonic saline nebulization for those unable to produce sputum. Alternatively, patients can undergo bronchoscopy or endotracheal suctioning, either of which can be easily done through an endotracheal tube in mechanically ventilated patients. Testing should include mycobacterial and fungal stains and cultures in patients whose condition is deteriorating and in those unresponsive to broad-spectrum antibiotics.

Additional tests are indicated in some circumstances. Patients at risk of *Legionella* pneumonia (eg, patients who smoke, have chronic pulmonary disease, are > 40, receive chemotherapy

[Table 196-2, Community-Acquired Pneumonia in Adults*]

therapy, or take immunosuppressants for organ transplantation) should undergo testing for urinary *Legionella* antigen, which remains present long after treatment is initiated, but the test detects only *L. pneumophila* serogroup 1 (70% of cases). A 4-fold rise in antibody titers to ≥ 1:128 (or a single titer of ≥ 1:256 in a convalescent patient) is also considered diagnostic. These tests are specific (95 to 100%) but are not very sensitive (40 to 60%); thus, a positive test indicates infection, but a negative test does not...
Infants and young children with possible RSV infection should undergo rapid antigen testing of specimens obtained with nasal or throat swabs. No other tests for viral pneumonias are done; viral culture and serologic tests are rarely clinically warranted.

PCR testing for mycoplasma and chlamydia species, although not widely available, holds promise as a highly sensitive and specific rapid diagnostic test and is likely to play a greater role as PCR technologies are refined.

**Prognosis**

Candidates for outpatient treatment usually improve over 24 to 72 h. Hospitalized patients may improve or deteriorate depending on comorbidities. Aspiration is a major risk factor for death, as are older age and number and type of comorbidities. Pneumonia caused by certain organisms may also increase the risk of death. Death may be caused by pneumonia itself, progression to sepsis syndrome affecting other organs, or exacerbation of comorbidities.

**Pneumococcal** infection accounts for about two thirds of fatal cases of community-acquired pneumonia in which an etiologic agent is known. The overall mortality rate in hospitalized patients is about 12%. Poor prognostic factors include age < 1 or > 60 yr; involvement of > 1 lobe; peripheral WBC count < 5000/µL; comorbidities (eg, heart failure, alcoholism, hepatic or renal insufficiency), immunosuppression (eg, agammaglobulinemia, anatomic or functional asplenia), infection with serotypes 3 and 8; and hematogenous spread with either positive blood cultures or extrapulmonary complications (usually arthritis, meningitis, endocarditis). Infants and children are at special risk of pneumococcal otitis media, bacteremia, and meningitis.

Mortality in **Legionella** infection is 10 to 20% among community-acquired cases and is higher among immunosuppressed or hospitalized patients. Patients who respond do so slowly, and x-ray abnormalities usually persist for ≥ 1 mo. Most patients require hospitalization, many require ventilator support, and 10 to 20% die despite appropriate antibiotic therapy.

Prognosis in **mycoplasma** pneumonia is excellent; nearly all patients recover.

**Chlamydophila pneumoniae** responds more slowly to treatment than mycoplasma pneumonia and tends to recur if therapy is stopped prematurely. Young adults with *C. pneumoniae* usually do well, but the elderly have a mortality rate of 5 to 10%.

**Treatment**

- Risk stratification
- Antibiotics
- Antivirals for influenza or varicella
- Supportive measures

A prediction rule may be used to estimate mortality risk. The rule has been used to identify those patients who can be safely treated as outpatients and those who require hospitalization because of high risk of complications (see Table 196-4). However, the rule was not developed to determine site of care. Thus, the rule should supplement, not replace, clinical judgment, because many unrepresented factors, such as likelihood of adherence, ability to care for self, and wishes to avoid hospitalization, should also influence triage decisions. Also, certain criteria that extend across a continuum of severity have dichotomous cutoffs; eg, a heart rate of 124 beats/min may indicate distress, but points are not assigned unless heart rate exceeds 140 beats/min.
rate is ≥ 125 beats/min. ICU admission is required for patients who need mechanical ventilation and for those with hypotension (systolic BP < 90 mm Hg) that is unresponsive to volume resuscitation. Other criteria that mandate consideration for ICU admission include respiratory rate > 30/min, PaO$_2$/fraction of inspired O$_2$ (FIO$_2$) < 250, multilobar pneumonia, diastolic BP < 60 mm Hg, confusion, and BUN > 19.6 mg/dL.

Appropriate treatment involves starting antibiotics as soon as possible, preferably ≤ 8 h after presentation. Supportive care includes fluids, antipyretics, analgesics, and, for patients with hypoxemia, O$_2$.

Because organisms are difficult to identify, antibiotics are selected based on likely pathogens and severity of illness. Consensus guidelines have been developed by many professional organizations; one widely used set is detailed in Table 196-2. Guidelines should be adapted to local susceptibility patterns, drug formularies, and individual patient circumstances. Importantly, none provide recommendations for treatment of viral pneumonia.

Ribavirin and RSV Ig have been used alone and in combination for RSV bronchiolitis in children, but their effectiveness is controversial, and neither is standard practice. Ribavirin is not used in adults with RSV infection.

[Table 196-4, Risk Stratification for Community-Acquired Pneumonia]

Oseltamivir 75 mg po bid or zanamivir 10 mg inhaled bid started within 48 h of symptom onset and given for 5 days reduces the duration and severity of symptoms in patients who develop influenza infection. Acyclovir 5 to 10 mg/kg IV q 8 h for adults or 250 to 500 mg/m$^2$ body surface area IV q 8 h for children is recommended for varicella lung infections. Some patients with viral pneumonia, especially those with influenza, develop superimposed bacterial infections and require antibiotics directed against S. pneumoniae, H. influenzae, and Staphylococcus aureus.

With empiric treatment, 90% of patients with bacterial pneumonia improve. Improvement is manifested by decreased cough and dyspnea, defervescence, relief of chest pain, and decline in WBC count. Failure to improve should trigger suspicion of an unusual organism, resistance to the antimicrobial used for treatment, empyema, coinfection or superinfection with a 2nd infectious agent, an obstructive endobronchial lesion, immunosuppression, metastatic focus of infection with reseeding (in the case of pneumococcal infection), or nonadherence to treatment (in the case of outpatients). If none of these can be proved, treatment failure is likely due to inadequate host defenses.

Most viral pneumonias resolve without specific treatment.

Chest physical therapy can be used to treat pneumonia; however, there is no clear evidence for its efficacy. Follow-up x-rays should be obtained 6 wk after treatment in patients > 35; persistence of an infiltrate at ≥ 6 wk raises suspicions of an underlying, possibly malignant endobronchial lesion or of TB.

Prevention

Some forms of community-acquired pneumonia are preventable with pneumococcal conjugate vaccine (for patients < 2 yr), H. influenzae type b (Hib) vaccine (for patients < 2 yr), pneumococcal pneumonia vaccine (for patients at high risk, such as those with underlying heart, lung, or immune system disorders), varicella vaccine (for patients < 18 mo and a later booster vaccine), and influenza vaccine (for patients age ≥ 65 and those at high risk—see Table 131-2 on p. 1174 and see Table 268-10 on p. 2718). Oseltamivir 75 mg po once/day or zanamivir 10 mg once/day can be given for 2 wk to prevent influenza (although resistance has recently been described for oseltamivir) for household contacts of patients with influenza and to high-risk patients not vaccinated against influenza during influenza epidemics. Pneumococcal pneumonia vaccination is recommended for all patients ≥ 65 (see p. 1177).

Hospital-Acquired Pneumonia
Hospital-acquired pneumonia (HAP) develops at least 48 h after hospital admission. The most common pathogens are gram-negative bacilli and *Staphylococcus aureus*; drug-resistant organisms are an important concern. Symptoms and signs are the same as those for community-acquired pneumonia, but in ventilated patients, pneumonia may also manifest as worsening oxygenation and increased tracheal secretions. Diagnosis is suspected on the basis of clinical presentation and chest x-ray and is confirmed by blood culture or bronchoscopic sampling of the lower respiratory tract. Treatment is with antibiotics. Overall prognosis is poor, due in part to comorbidities.

HAP includes ventilator-associated pneumonia (VAP), postoperative pneumonia, and pneumonia that develops in unventilated but otherwise moderately or critically ill hospitalized inpatients. It also includes the new category healthcare-associated pneumonia (HCAP), which refers to pneumonia acquired by patients in healthcare facilities such as chronic care facilities, dialysis centers, and infusion centers.

**Etiology**

The most common cause is microaspiration of bacteria that colonize the oropharynx and upper airways in seriously ill patients.

**Risk factors:** Endotracheal intubation with mechanical ventilation poses the greatest overall risk; VAP constitutes > 85% of all cases, with pneumonia occurring in 17 to 23% of ventilated patients. Endotracheal intubation breaches airway defenses, impairs cough and mucociliary clearance, and facilitates microaspiration of bacteria-laden secretions that pool above the inflated endotracheal tube cuff. In addition, bacteria form a biofilm on and within the endotracheal tube that protects them from antibiotics and host defenses.

In nonintubated patients, risk factors include previous antibiotic treatment, high gastric pH (due to stress ulcer prophylaxis or therapy), and coexisting cardiac, pulmonary, hepatic, or renal insufficiency. Major risk factors for postoperative pneumonia are age > 70, abdominal or thoracic surgery, and dependent functional status.

**Pathogens:** Pathogens and antibiotic resistance patterns vary significantly among institutions and can vary within institutions over short periods (eg, month to month). In general, the most important pathogen is *Pseudomonas aeruginosa*, which is especially common in pneumonias acquired in intensive care settings and in patients with cystic fibrosis, neutropenia, advanced AIDS, and bronchiectasis. Other important pathogens include enteric gram-negative bacteria (mainly *Enterobacter* sp, *Klebsiella pneumonieae*, *Escherichia coli*, *Serratia marcescens*, *Proteus* sp, and *Acinetobacter* sp) and both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*.

*S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are most commonly implicated when pneumonia develops within 4 to 7 days of hospitalization, whereas enteric gram-negative organisms become more common with increasing duration of intubation. Patients with HAP due to *S. aureus* or gram-negative bacilli tend to be elderly or have serious circumstances, such as needing a ventilator, undergoing chemotherapy for cancer, or having chronic pulmonary disease.

Prior antibiotic treatment greatly increases the likelihood of polymicrobial infection, resistant organisms, particularly methicillin-resistant *S. aureus*, and *Pseudomonas* infection. Infection with a resistant organism markedly worsens mortality and morbidity.

High-dose corticosteroids increase the risk of *Legionella* and *Pseudomonas* infections.

**Symptoms and Signs**

Symptoms and signs in nonintubated patients are generally the same as those for community-acquired pneumonia (see p. 1925). Pneumonia in critically ill, mechanically ventilated patients more typically causes fever and increased respiratory rate or heart rate or changes in respiratory parameters, such as an increase in purulent secretions or worsening hypoxemia.
Diagnosis

- Chest x-ray and clinical criteria (limited accuracy)
- Sometimes bronchoscopy, blood cultures

Diagnosis is imperfect. In practice, HAP is often suspected on the basis of the appearance of a new infiltrate on a chest x-ray that is taken for evaluation of new symptoms or signs or of leukocytosis. However, no symptom, sign, or x-ray finding is sensitive or specific for the diagnosis, because all can be caused by atelectasis, pulmonary embolism, or pulmonary edema and may be part of the clinical findings in acute respiratory distress syndrome. Alternative diagnoses should be sought, particularly in patients who have a pneumonia risk score < 6 (see Table 196-5).

Gram stain and culture of endotracheal aspirates are of uncertain benefit, because specimens are likely to be contaminated with bacteria that are colonizers as well as pathogens, and a positive culture may or may not indicate infection. Bronchoscopic sampling of lower airway secretions for quantitative culture seems to yield more reliable specimens, but the effect of this approach on outcomes is undetermined. Measurement of inflammatory mediators in bronchoalveolar lavage fluid may play a future role in diagnosis; eg, a concentration of soluble triggering receptor expressed on myeloid cells (a protein expressed and shed by immune cells during infection) > 5 pg/mL may help distinguish bacterial and fungal pneumonia from noninfectious causes of clinical and radiographic changes in ventilated patients. However, this approach requires further investigation. The only finding that reliably identifies both pneumonia and the responsible organism is a pleural fluid culture that is positive for a respiratory pathogen. Blood cultures are relatively specific if a respiratory pathogen is identified but are insensitive.

Prognosis

The mortality associated with HAP due to gram-negative infection is about 25 to 50% despite the availability of effective antibiotics. Whether death is due to underlying illness or to the pneumonia itself is uncertain. Women may be at greater risk of death. The mortality rate with S. aureus pneumonia is 10 to 40%, in part due to the serious circumstances with which it is associated.

Treatment

- Empirically chosen antibiotics active against resistant gram-negative and gram-positive organisms

If the diagnosis is suspected, treatment is with antibiotics that are chosen empirically based on local sensitivity patterns, specific patient risk factors, and the conditions noted in Table 196-2.

Indiscriminate use of antibiotics is a major contributor to development of antimicrobial resistance. Therefore, treatment may begin with initial use of broad-spectrum drugs, which are replaced by the most specific drug available for the pathogens identified by culture. Alternative strategies for limiting resistance that have not proved effective include stopping antibiotics after 72 h in patients whose pulmonary infection scores (see Table 196-5) improve to < 6 and regularly rotating empirically chosen antibiotics (eg, q 3 to 6 mo).

Multiple regimens exist, but all should include antibiotics that are effective against both resistant gram-negative and gram-positive organisms. Options include

- A carbapenem (imipenem/cilastatin 500 mg IV q 6 h or 1 g q 8 h or meropenem 1 g IV q 8 h), monobactam (aztreonam 1 to 2 g IV q 8 h), or piperacillin/tazobactam 4.5 g q 6 h
• Ceftazidime 2 g IV q 8 h or cefepime 1 to 2 g q 8 to 12 h

• These drugs are given alone or combined with vancomycin 15 mg/kg q 12 h

Linezolid 600 mg IV q 12 h may be used for some pulmonary infections involving methicillin-resistant S. aureus. Daptomycin should not be used for pulmonary infections.

**Prevention**

Most measures focus on preventing VAP. Semiupright or upright positioning reduces risk of aspiration and pneumonia compared with recumbent positioning and is the simplest and most effective preventive method. Noninvasive ventilation using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) prevents the breach in airway defense that occurs with endotracheal intubation and eliminates the need for intubation in some patients.

Continuous aspiration of subglottic secretions using a specially designed endotracheal tube attached to a suction device seems to reduce the risk of aspiration.

Selective decontamination of the oropharynx (using topical gentamicin, colistin, chlorhexidine, vancomycin cream, or a combination) or of the entire GI tract (using polymyxin, an aminoglycoside or quinolone, and either nystatin or amphotericin B) is controversial because of concerns about resistant strains and because decontamination, although it decreases incidence of HAP, has not been shown to decrease mortality.

Surveillance cultures and routinely changing ventilator circuits or endotracheal tubes have not been shown to decrease VAP.

Incentive spirometry is recommended to help prevent postoperative pneumonia.

**Nursing Home-Acquired Pneumonia**

Common nursing home-acquired pneumonia pathogens include gram-negative bacilli, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, anaerobes, and influenza viruses. Symptoms and signs are similar to those of pneumonia that occurs in other settings, except many elderly patients have less prominent changes in vital signs. Diagnosis is based on clinical presentation and chest x-ray, which is often not immediately available in nursing homes. Treatment is with antibiotics provided in the nursing home for less severe illness and in the hospital for more severe illness. Mortality is moderately high but may be due in part to comorbidities.

Nursing home-acquired pneumonia falls between community-acquired and hospital-acquired pneumonia in etiology and management. *Streptococcus pneumoniae* and gram-negative bacilli may be roughly equally responsible for most infections, though there is debate over whether gram-negative bacilli are pathogens or merely colonizers. *Haemophilus influenzae* and *Moraxella catarrhalis* are next most common; *Chlamydia*, *Mycoplasma*, and *Legionella* spp are rarely identified. Risk factors are common among debilitated nursing home residents; they include poor functional status, mood disorder, altered mental status, difficulty swallowing, immunosuppression, older age, use of tube feedings, influenza or other viral respiratory infections, conditions that predispose to bacteremia (eg, indwelling bladder catheter, pressure ulcers), and presence of a tracheostomy tube.

**Symptoms and Signs**

Symptoms often resemble those of community-acquired or hospital-acquired pneumonia but may be more subtle. Cough and altered mental status are common, as are nonspecific symptoms of anorexia, weakness, restlessness and agitation, falling, and incontinence. Subjective dyspnea occurs but is less common. Signs include diminished or absent responsiveness, fever, tachycardia, tachypnea, wheezes or crackles, and stertorous, wet breathing.
Diagnosis

• Clinical manifestations
• Chest x-ray
• Assessment of renal function and oxygenation

Diagnosis is based on clinical manifestations and chest x-ray. Because detection of physical changes may be delayed in a nursing home setting and because these patients are at greater risk of complications, evaluation for hypoxemia with pulse oximetry and for decreased intravascular volume with serum BUN and creatinine should also be done.

X-rays are often difficult to obtain in nursing home patients, so it may be necessary to transfer them to a hospital at least for initial evaluation. In some cases (eg, if clinical diagnosis is clear, if illness is mild, or if aggressive care is not the goal), treatment may be started without x-ray confirmation. It is thought that nursing home patients may initially lack a radiographic infiltrate, presumably because of the dehydration that commonly accompanies febrile pneumonia in the elderly or a blunted immune response, although the phenomenon is not proved to occur.

Prognosis

Mortality rate for patients requiring admission for treatment is 13 to 41%, whereas that for patients treated in the nursing home is 7 to 19%. Mortality rate exceeds 30% in patients with > 2 of the following findings:

• Respiratory rate > 30 breaths/min
• Heart rate > 125 beats/min
• Acute mental status change
• History of dementia

An alternative predictive index incorporates laboratory data (see Table 196-6). Physicians should follow all medical directives, because pneumonia is often a terminal event in debilitated nursing home patients.

Treatment

• Antibiotics given before hospitalization in patients being hospitalized

Few data are available to guide decisions about where treatment should take place. In general, patients should be hospitalized if they have ≥ 2 unstable vital signs and if the nursing home cannot administer acute care. Some nursing home patients are not candidates for aggressive treatment or hospital transfer under any circumstances. In patients who are to be hospitalized, one dose of antibiotics that are effective against *S. pneumoniae*, *H. influenzae*, and common gram-negative bacilli should be given before transfer; a common regimen is an oral antipneumococcal quinolone (eg, levofloxacin 750 mg once/day or moxifloxacin 400 mg once/day). Ceftriaxone, ertapenem, and ampicillin/sulbactam (each as monotherapy) are alternatives.

Pneumonia in Immunocompromised Patients

Pneumonia in immunocompromised patients is often caused by unusual pathogens. Symptoms and signs depend on the pathogen. Diagnosis is based on blood cultures and bronchoscopic sampling of respiratory secretions, sometimes with quantitative cultures. Treatment depends on the host defect and pathogen.

The potential pathogens in patients with compromised defenses are legion. Likely pathogens based on
the type of defect in host defenses are listed in Table 196-7. However, respiratory symptoms and changes on chest x-rays in immunocompromised patients may be due to various processes other than infection, such as pulmonary hemorrhage, pulmonary edema, radiation injury, pulmonary toxicity due to cytotoxic drugs, and tumor infiltrates.

[Table 196-6. Nursing Home-Acquired Pneumonia Risk Index]

[Table 196-7. Pneumonia in Immunocompromised Patients]

Symptoms and Signs

Symptoms and signs may be the same as those found with community-acquired or hospital-acquired pneumonia in immunocompetent patients, though immunocompromised patients may have no fever or respiratory signs and are less likely to have purulent sputum if they are neutropenic. In some patients, the only sign is fever.

Diagnosis

• Chest x-ray
• Assessment of oxygenation
• Induction or bronchoscopy to obtain sputum
• Blood cultures
• Pathogens predicted based on symptoms, x-ray changes, and type of immunodeficiency

An immunocompromised patient with respiratory symptoms, signs, or fever should undergo chest x-ray and assessment of oxygenation (usually by pulse oximetry). If an infiltrate is present, diagnostic studies should include sputum Gram stain and culture and blood cultures. Chest x-ray may be normal in *Pneumocystis jirovecii* pneumonia, but hypoxia is usually present. Optimally, a firm diagnosis is made with induced sputum, bronchoscopy, or both, especially in patients with chronic pneumonia, atypical presentation, severe defects in immune function, or failure to respond to broad-spectrum antibiotics.

Likely pathogens can often be predicted based on symptoms, x-ray changes, and the type of immunodeficiency. In patients with acute symptoms, likely diagnoses are bacterial infection, hemorrhage, pulmonary edema, a leukocyte agglutinin reaction, and pulmonary emboli. A subacute or chronic presentation is more suggestive of a fungal or mycobacterial infection, an opportunistic viral infection, *P. jirovecii* pneumonia, tumor, a cytotoxic drug reaction, or radiation injury.

X-rays showing localized consolidation usually indicate an infection involving bacteria, mycobacteria, fungi, or *Nocardia* sp. A diffuse interstitial pattern is more likely to represent a viral infection, *P. jirovecii* pneumonia, drug or radiation injury, or pulmonary edema. Diffuse nodular lesions suggest mycobacteria, *Nocardia* sp, fungi, or tumor. Cavitary disease suggests mycobacteria, *Nocardia* sp, fungi, or bacteria.

In organ or marrow transplantation recipients with bilateral interstitial pneumonia, the usual cause is cytomegalovirus, or the disease is idiopathic. A pleural-based consolidation is usually aspergillosis. In AIDS patients, bilateral pneumonia is usually *P. jirovecii* pneumonia. About 30% of patients with HIV infection have *P. jirovecii* pneumonia as the initial AIDS-defining diagnosis, and > 80% of AIDS patients have this infection at some time if prophylaxis is not given (see p. 1455). Patients with HIV infection become vulnerable to *P. jirovecii* pneumonia when the CD4⁺ helper cell count is < 200/µL.

Treatment

• Broad-spectrum antimicrobial therapy
In neutropenic patients, empiric treatment depends on the host defect, x-ray, and severity of illness. Generally, broad-spectrum drugs are needed to cover gram-negative bacilli, *Staphylococcus aureus*, and anaerobes, as for hospital-acquired pneumonia (see p. 1931). If patients with conditions other than HIV do not improve with 5 days of antibiotic therapy, antifungal therapy is frequently added empirically.

**Pneumocystis jirovecii** Pneumonia

*P. jirovecii* is a common cause of pneumonia in immunosuppressed patients, especially in those infected with HIV and in those receiving systemic corticosteroids. Symptoms include fever, dyspnea, and dry cough. Diagnosis requires demonstration of the organism in an induced sputum specimen or bronchoscopic brushing. Treatment is with antibiotics, usually trimethoprim/sulfamethoxazole or dapsone/trimethoprim, clindamycin/primaquine, atovaquone, or pentamidine. Patients with PaO\(_2\) < 70 mm Hg receive systemic corticosteroids. Prognosis is generally good with timely treatment.

*P. jirovecii* is a ubiquitous organism transmitted by aerosol route and causes no disease in immunocompetent patients. Patients with HIV infection and CD4+ counts < 200/\(\mu\)L, organ transplant recipients, patients who have hematologic cancers, and patients taking corticosteroids are at risk of developing *P. jirovecii* pneumonia. Most have fever, dyspnea, and a dry, nonproductive cough that evolves subacutely over several weeks (HIV infection) or acutely over several days (other causes of compromised cell-mediated immunity).

**Diagnosis**

- Chest x-ray
- Pulse oximetry
- Histopathologic confirmation

Patients should have chest x-ray and assessment of oxygenation by pulse oximetry. The chest x-ray characteristically shows diffuse, bilateral perihilar infiltrates, but 20 to 30% of patients have normal x-rays. However, hypoxemia is often present even when chest x-ray shows no infiltrate; this finding can be an important clue to diagnosis. When pulse oximetry is abnormal, ABGs are often obtained to show severity of hypoxemia (including an increase in the alveolar-arterial O\(_2\) gradient). If obtained, pulmonary function tests show altered diffusing capacity (although this is rarely done as a diagnostic test).

Confirmation of diagnosis requires histopathologic demonstration of the organism with methenamine silver, Giemsa, Wright-Giemsa, modified Grocott, Weigert-Gram, or monoclonal antibody stain. Sputum specimens are usually obtained by induced sputum or bronchoscopy. Sensitivity ranges from 30 to 80% for induced sputum and is > 95% for bronchoscopy with bronchoalveolar lavage.

**Prognosis**

Overall mortality for *P. jirovecii* pneumonia in hospitalized patients is 15 to 20%. Risk factors for death may include previous history of *P. jirovecii* pneumonia, older age, and, in HIV-infected patients, CD4+ cell count < 50/\(\mu\)L.

**Treatment**

- Trimethoprim/sulfamethoxazole
- Corticosteroids if PaO\(_2\) < 70 mm Hg

Treatment is with trimethoprim/sulfamethoxazole (TMP/SMX) 4 to 5 mg/kg IV or po tid for 14 to 21 days. Treatment can be started before diagnosis is confirmed because *P. jirovecii* cysts persist in the lungs for weeks. Adverse effects of treatment are more common among patients with AIDS and include rash,
neutropenia, hepatitis, and fever. Alternative regimens are pentamidine 4 mg/kg IV once/day; atovaquone 750 mg po bid; TMP 5 mg/kg po qid with dapsone 100 mg po once/day; or clindamycin 300 to 900 mg IV q 6 to 8 h with primaquine base 15 to 30 mg/day po, also for 21 days. The major limitation of pentamidine is the high frequency of toxic adverse effects, including renal failure, hypotension, and hypoglycemia. Adjunctive therapy with corticosteroids is recommended for patients with a PaO₂ < 70 mm Hg. The suggested regimen is prednisone 40 mg bid (or its equivalent) for the first 5 days, 40 mg once/day for the next 5 days (or 20 mg bid), and then 20 mg once/day for the duration of treatment.

Prevention

HIV-infected patients who have had *P. jirovecii* pneumonia or who have a CD4+ count < 200/μL should receive prophylaxis with TMP/SMX 80/400 mg once/day; if this regimen is not tolerated, dapsone 100 mg po once/day or aerosolized pentamidine 300 mg once/month can be used. These prophylactic regimens are also probably indicated for non-HIV-infected patients at risk of *P. jirovecii* pneumonia.

**Aspiration Pneumonitis and Pneumonia**

Aspiration pneumonitis and pneumonia are caused by inhaling toxic substances, usually gastric contents, into the lungs. Chemical pneumonitis, bacterial pneumonia, or airway obstruction can occur. Symptoms include cough and dyspnea. Diagnosis is based on clinical presentation and chest x-ray findings. Treatment and prognosis differ by aspirated substance.

Aspiration can cause lung inflammation (chemical pneumonitis), infection (bacterial pneumonia or abscess), or airway obstruction. However, most episodes of aspiration cause minor symptoms or pneumonitis rather than infection or obstruction, and some patients aspirate with no sequelaes. Drowning is discussed on p. 3279; airway obstruction is discussed on p. 2269.

Risk factors for aspiration include impaired cognition, impaired swallowing, vomiting, GI and respiratory devices and procedures (eg, nasogastric or endotracheal tube placement, dental work), and gastroesophageal reflux disease.

**Pathophysiology**

**Chemical pneumonitis**: Multiple substances are directly toxic to the lungs or stimulate an inflammatory response when aspirated; gastric acid is the most common such aspirated substance, but others include petroleum products (particularly of low viscosity, such as petroleum jelly) and laxative oils (such as mineral, castor, and paraffin oil), all of which cause lipoid pneumonia. Aspirated gasoline and kerosene also cause a chemical pneumonitis (see p. 3339).

**Gastric contents** cause damage mainly from gastric acid, although food and other ingested material (eg, activated charcoal as in treatment of overdose) are injurious in quantity. Gastric acid causes a chemical burn of the airways and lung leading to rapid bronchoconstriction, atelectasis, edema, and alveolar hemorrhage. Symptoms include acute dyspnea with cough that is sometimes productive of pink frothy sputum, tachypnea, tachycardia, fever, diffuse crackles, and wheezing. Chest x-ray shows diffuse infiltrates frequently but not exclusively in dependent segments, while pulse-oximetry and ABGs demonstrate hypoxemia. Treatment is supportive, often involving supplemental O₂ and mechanical ventilation. Antibiotics often are given to patients with witnessed or known gastric aspiration. The syndrome may resolve spontaneously, usually within a few days, or may progress to acute respiratory distress syndrome. Sometimes bacterial superinfection occurs.

**Oil or petroleum jelly** aspiration causes exogenous lipoid pneumonia, which is characterized histologically by chronic granulomatous inflammation with fibrosis. It is often asymptomatic and is detected incidentally on chest x-ray or may manifest with low-grade fever, gradual weight loss, and crackles. Chest x-ray findings vary; consolidation, cavitation, interstitial or nodular infiltrates, pleural effusion, and other changes may be slowly progressive. Treatment is avoidance of the toxic substance. Anecdotal reports suggest systemic corticosteroids may be beneficial.

**Aspiration pneumonia**: Healthy people commonly aspirate small amounts of oral secretions, but normal
Aspiration pneumonia: Healthy people commonly aspirate small amounts of oral secretions, but normal defense mechanisms usually clear the inoculum without sequelae. Aspiration of larger amounts, or aspiration in a patient with impaired pulmonary defenses, often causes pneumonia and/or abscess (see also Ch. 197). Elderly patients tend to aspirate because of conditions associated with aging that alter consciousness, such as sedative use and disorders (eg, neurologic disorders, weakness). Empyema (see p. 1998) also occasionally complicates aspiration.

Anaerobes often can be cultured from sputum, but it is unclear whether they are primary infecting organisms to which treatment should be directed or whether they are simply one of several organisms causing infection.

Symptoms and Signs

Symptoms and signs of pneumonia and abscess are similar and include chronic low-grade dyspnea, fever, weight loss, and cough productive of putrid, foul-tasting sputum. Patients may have signs of poor oral hygiene.

Diagnosis

• Chest x-ray

Chest x-ray shows an infiltrate, frequently but not exclusively, in the dependent lung segments, ie, the superior or posterior basal segments of a lower lobe or the posterior segment of an upper lobe.

Treatment

• Antibiotics, usually clindamycin

Abscess: Treatment of lung abscess is with clindamycin 450 to 900 mg IV q 8 h followed by 300 mg po qid once fever and clinical symptoms subside. An alternative is a combination of penicillin (either penicillin G 1 to 2 million units q 4 to 6 h or amoxicillin 0.5 to 1 g po tid) plus either metronidazole 500 mg po tid, amoxicillin/clavulanate 875/125 mg po tid, or imipenem. Treatment is continued for 6 wk to 3 mo.

Pneumonia: Treatment of aspiration pneumonia can be with clindamycin, but other antibiotics with lower risk of adverse effects may be effective, because it is not clear that all the anaerobes cultured from the infection require specific treatment. Duration of treatment is usually 1 to 2 wk.
Chapter 197. Lung Abscess

Introduction

Lung abscess is a necrotizing lung infection characterized by a pus-filled cavitory lesion. It is almost always caused by aspiration of oral secretions by patients who have impaired consciousness. Symptoms are persistent cough, fever, sweats, and weight loss. Diagnosis is based primarily on chest x-ray. Treatment usually is with clindamycin or combination β-lactam/β-lactamase inhibitors.

Etiology

Most lung abscesses develop after aspiration of oral secretions by patients with gingivitis or poor oral hygiene. Typically, patients have altered consciousness as a result of alcohol intoxication, illicit drugs, anesthesia, sedatives, or opioids. Older patients and those unable to handle their oral secretions, often because of neurologic disease, are also at risk.

A less common cause of lung abscess is necrotizing pneumonia that may develop from hematogenous seeding of the lungs due to suppurative thromboembolism (eg, septic embolism due to IV drug use) or right-sided endocarditis. In contrast to aspiration, these conditions typically cause multiple rather than isolated lung abscesses.

The most common pathogens of lung abscesses due to aspiration are anaerobic bacteria, but about half of all cases involve both anaerobic and aerobic organisms (see Table 197-1). The most common aerobic pathogens are streptococci and staphylococci—sometimes methicillin-resistant Staphylococcus aureus (MRSA). An unusual but very important acute and often lethal form of lung necrosis is caused by S. aureus with genes for Panton-Valentine leukocidin. Very serious and fulminant cases may be caused by MRSA (USA 300 strain), which has become a rare but very important cause of necrotizing pneumonia in young previously healthy adults and children. Occasionally, cases are due to gram-negative bacteria, especially Klebsiella. Immunocompromised patients with lung abscess may have infection with Nocardia, Mycobacteria sp, or fungi. Some people, especially those from developing countries, are at risk of abscess due to Mycobacterium tuberculosis, and rare cases are due to amebic infection (eg, with Entamoeba histolytica), paragonimiasis, or Burkholderia pseudomallei.

Introduction of these pathogens into the lungs first causes inflammation, which leads to tissue necrosis and then abscess formation. The abscess usually ruptures into a bronchus, and its contents are expectorated, leaving an air- and fluid-filled cavity. In about one third of cases, direct or indirect extension (via bronchopleural fistula) into the pleural cavity results in empyema.

Cavitary pulmonary lesions are not always caused by infection. Noninfectious causes include the following:

• Bullae with air-fluid level
• Bronchiectasis
• Lung cancer
• Lung infarction
• Nodular silicosis nodule with central necrosis
• Pulmonary embolism
• Pulmonary sequestration
• Sarcoidosis
Wegener’s granulomatosis

**Symptoms and Signs**

Symptoms of abscess due to anaerobic bacteria or mixed anaerobic and aerobic bacteria

**Table 197-1. Infectious Causes of Cavitary Lung Lesions**

are usually chronic (eg, over weeks or months) and include productive cough, fever, sweats, and weight loss. Severe prostration may occur. Sputum may be purulent or blood-streaked and classically smells or tastes foul. Symptoms of abscess due to aerobic bacteria develop more acutely and resemble bacterial pneumonia. Abscesses due to organisms other than anaerobes (eg, *Mycobacteria*, *Nocardia*) lack putrid respiratory secretions and may be more likely to occur in nondependent lung regions.

Signs of lung abscess, when present, are nonspecific and resemble those of pneumonia: decreased breath sounds indicating consolidation or effusion, temperature ≥ 38°C, crackles over the affected area, egophony, and dullness to percussion in the presence of effusion. Patients typically have signs of periodontal disease and a history of a predisposing cause of aspiration, such as dysphagia or a condition causing impaired consciousness.

**Diagnosis**

- Chest x-ray
- CT as needed
- Sputum cultures (unless anaerobic infection is very likely), including for fungi and mycobacteria
- Bronchoscopy as needed to exclude cancer

Lung abscess is suspected based on history in a patient who is aspiration-prone due to altered consciousness or dysphagia and is confirmed by chest x-ray. In an anaerobic infection due to aspiration, chest x-ray classically shows consolidation with a single cavity containing an air-fluid level in portions of the lung that would be dependent when the patient is recumbent (eg, the posterior segments of the upper lobes or the superior or lateral basal segments of the lower lobes). This pattern helps distinguish anaerobic abscess from other causes of cavitary pulmonary disease, because diffuse or embolic pulmonary disease often causes multiple cavitations, and TB typically involves the apices.

CT is not routinely needed but may be useful when the x-ray suggests a cavitating lesion or when an underlying pulmonary mass obstructing the drainage of a lung segment is suspected.

Bronchial carcinoma can lead to obstruction that causes pneumonia and abscess formation. This should be suspected in smokers, recent smokers, and patients with unexplained cavitary lesions and no fever. Bronchoscopy is sometimes done to exclude cancer or the presence of a foreign body or to detect unusual pathogens, such as fungi.

**Cultures:** Anaerobic bacteria are rarely identifiable on culture because uncontaminated specimens are difficult to obtain and because most laboratories do not culture anaerobes well or often. If sputum is putrid, then anaerobic infection is assumed to be the cause. However, if empyema is present, pleural fluid provides a good source for anaerobic culture.

When clinical findings make anaerobic infection less likely, aerobic, fungal, or mycobacterial infection should be suspected, and attempts should be made to identify a pathogen. Cultures of sputum, bronchoscopic aspirates, or both are helpful. MRSA is generally found in both the sputum and blood cultures.

**Treatment**
• IV antibiotics or, for less seriously affected patients, oral antibiotics

• Percutaneous drainage or surgery if empyema present or no response to antibiotics

Treatment is with antibiotics. Clindamycin 600 mg IV q 6 to 8 h is usually the drug of choice because it has excellent activity against streptococci and anaerobic organisms. The primary alternative is a combination β-lactam/β-lactamase inhibitor (eg, ampicillin/sulbactam 1 to 2 g IV q 6 h, ticarcillin/clavulanate 3 to 6 g IV q 6 h, piperacillin/tazobactam 3 g IV q 6 h). Metronidazole 500 mg q 8 h may be used but must be combined with penicillin 2 million units q 6 h IV. Less seriously ill patients may be given oral antibiotics such as clindamycin 300 mg po q 6 h or amoxicillin/clavulanate 875/125 mg po q 12 h. IV regimens can be converted to oral ones when the patient defervesces. For very serious infections involving MSRA, the best treatment is vancomycin or linezolid.

Optimal duration of treatment is unknown, but common practice is to treat until the chest x-ray shows complete resolution, which generally takes 3 to 6 wk or longer. In general, the larger the abscess, the longer it will take for x-rays to show resolution.

Most authorities do not recommend chest physical therapy and postural drainage because they may cause spillage of infection into other bronchi with extension of the infection or acute obstruction. If the patient is weak or paralyzed or has respiratory failure, tracheostomy and suctioning may be necessary. Rarely, bronchoscopic aspiration helps facilitate drainage. An accompanying empyema must be drained. Percutaneous or surgical drainage of lung abscesses is necessary in the roughly 10% of patients in whom lesions do not respond to antibiotics. Resistance to antibiotic treatment is most common with large cavities and with infections that complicate obstructions.

When surgery is necessary, lobectomy is the most common procedure; segmental resection may suffice for small lesions (< 6 cm diameter cavity). Pneumonectomy may be necessary for multiple abscesses or for pulmonary gangrene unresponsive to drug therapy.
Chapter 198. Bronchiectasis

Introduction

Bronchiectasis is dilation and destruction of larger bronchi caused by chronic infection and inflammation. Common causes are cystic fibrosis, immune defects, and recurrent infections, though some cases seem to be idiopathic. Symptoms are chronic cough and purulent sputum expectoration; some patients may also have fever and dyspnea. Diagnosis is based on history and imaging, usually involving high-resolution CT, though standard chest x-rays may be diagnostic. Treatment and prevention of acute exacerbations are with antibiotics, drainage of secretions, and management of complications, such as superinfection and hemoptysis. Treatment of underlying disorders is important whenever possible.

Etiology

Bronchiectasis may affect many areas of the lung (diffuse bronchiectasis), or it may appear in only one or two areas (focal bronchiectasis). Diffuse bronchiectasis develops in patients with genetic, immune, or anatomic defects that affect the airways. Cystic fibrosis is the most common cause. Immunodeficiencies may also cause diffuse disease, as may rare abnormalities in airway structure. Diffuse bronchiectasis is an uncommon complication of more common conditions, such as RA or Sjogren's syndrome. Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to Aspergillus sp (see p. 1887). It occurs primarily in people with asthma and less commonly in people with cystic fibrosis and can lead to bronchiectasis.

Focal bronchiectasis develops from untreated pneumonia or obstruction (eg, due to foreign bodies and tumors). Mycobacteria can cause focal bronchiectasis as well as colonize the lungs of patients with bronchiectasis due to other disorders (see Table 198-1). Some cases have no readily apparent cause.

Pathophysiology

All the causative conditions impair airway clearance mechanisms and host defenses, resulting in an inability to clear secretions, which, in turn, predisposes patients to chronic infection and inflammation. As a result of frequent infections, most commonly with Haemophilus influenzae (35%), Pseudomonas aeruginosa (31%), Moraxella catarrhalis (20%), Staphylococcus aureus (14%), and Streptococcus pneumoniae (13%), airways become inspissated with viscous mucous containing inflammatory mediators and pathogens and slowly become dilated, scarred, and distorted. Histologically, bronchial walls are thickened by edema, inflammation, and neovascularization. Destruction of surrounding interstitium and alveoli causes fibrosis, emphysema, or both.

Superinfection with multidrug-resistant organisms, including Mycobacterium tuberculosis, and mycobacteria other than M. tuberculosis can cause recurrent exacerbations and worsen airflow limitation on pulmonary function tests. Pulmonary hypertension and right-sided heart failure may ensue because functional lung tissue decreases.

Symptoms and Signs

Symptoms characteristically begin insidiously and gradually worsen over years. The major presenting symptom of bronchiectasis

[Table 198-1, Factors Predisposing to Bronchiectasis]

is chronic cough that almost always produces large volumes of thick, tenacious, purulent sputum. Dyspnea and wheezing are common. Hemoptysis, which can be massive, is due to neovascularization of the airways from the bronchial (as opposed to pulmonary) arteries. Acute exacerbations of disease due to new or worsened infection increase the extent of cough and the volume and purulence of sputum production. Low-grade fever may also be present.
Halitosis and abnormal breath sounds, including crackles, rhonchi, and wheezing, are typical signs of disease. Finger clubbing may also be present. In advanced cases, hypoxemia and signs of pulmonary hypertension (eg, shortness of breath, dizziness) and right-sided heart failure can occur.

**Diagnosis**

- History and physical examination
- Chest x-ray
- High-resolution CT for confirmation
- Pulmonary function tests for baseline function and progression of disease
- Specific tests for suspected causes

Diagnosis is based on a history, physical examination, and radiologic testing, beginning with a chest x-ray. Chronic bronchitis may mimic bronchiectasis clinically, but bronchiectasis is distinguished by more voluminous daily production of purulent sputum and by dilated airways on imaging studies.

**Imaging:** X-ray findings suggestive of bronchiectasis include scattered irregular opacities caused by mucous plugs, honeycombing, and rings and "tram lines" caused by thickened, dilated airways located perpendicular to the x-ray beam. Radiographic patterns may differ by underlying disease: Bronchiectasis due to cystic fibrosis develops predominantly in upper lobes, whereas that due to other causes is more diffuse or predominates in the lower lobes.

High-resolution CT is the test of choice for defining the extent of bronchiectasis. The test is nearly 100% sensitive and specific. CT typically shows thickening of airways characterized by tram-track parallel lines or ring shadows representing thickened bronchial walls when imaged in cross-section. Cysts (sometimes appearing as grapelike clusters), scattered mucous plugs, and airways that are dilated > 1.5 times the diameter of nearby blood vessels can also be seen. Dilated medium-sized bronchi may extend almost to the pleurae. Atelectasis, consolidation, and decreased vascularity are nonspecific findings. A differential diagnosis of dilated airways includes bronchitis and traction bronchiectasis that occurs when pulmonary fibrosis pulls airways open.

**Pulmonary function tests:** Pulmonary function tests can be helpful for documenting baseline function and for following the progression of disease over time. Bronchiectasis causes airflow limitation (reduced forced expiratory volume in 1 sec [FEV\(_1\)], forced vital capacity [FVC], and FEV\(_1\)/FVC); the FEV\(_1\) can improve in response to β-agonist bronchodilators. Lung volume measurements may be increased or decreased, and diffusing capacity for carbon monoxide (DLCO) may be decreased.

**Diagnosis of cause:** Tests to help diagnose a cause include sputum evaluation, including staining and cultures for bacterial, mycobacterial (*Mycobacterium avium* complex and *M. tuberculosis*), and fungal (*Aspergillus*) infection. Mycobacterial superinfection is diagnosed by repeatedly culturing mycobacteria other than TB in high colony counts and by finding granulomas on biopsy with concurrent radiologic evidence of disease. Additional tests may include the following:

- Sweat chloride testing to diagnose cystic fibrosis (which should be done even in older patients)
- Rheumatoid factor and other serologic tests to look for connective tissue diseases
- Immunoglobulin measurement (including IgG subclass determination), *Aspergillus* precipitins, IgE, and eosinophilia to rule out allergic bronchopulmonary aspergillosis
- α\(_1\)-Antitrypsin levels to document α\(_1\)-antitrypsin deficiency
When the clinical presentation suggests ciliary dyskinesia (by concurrent sinus disease and middle and lower lobe bronchiectasis with or without infertility), a nasal or bronchial epithelial sample should be obtained and examined by transmission electron microscopy for abnormal ciliary structure. A less invasive alternative is examination of sperm motility. The diagnosis of ciliary dyskinesia should be made cautiously by an experienced physician trained in specialized electron microscopic techniques because nonspecific structural defects can be present in up to 10% of cilia in healthy patients and in patients with pulmonary disease; infection can cause transient dyskinesia; and ciliary ultrastructure may be normal in patients with primary ciliary dyskinesia syndromes characterized by abnormal ciliary function.

Bronchoscopy is indicated when an anatomic or an obstructing object or lesion is suspected.

Prognosis

Overall, prognosis is thought to be good, with about 80% of patients having no further deterioration of lung function on the basis of bronchiectasis alone. However, cystic fibrosis patients have a median survival of 36 yr, and most patients continue to have intermittent acute exacerbations.

Treatment

• Prevention of exacerbations with antibiotics and regular vaccinations
• Measures to help clear secretions
• Antibiotics for acute exacerbations
• Sometimes surgical resection

There is no consensus on the best approach to prevent or limit acute exacerbations. Options include daily prophylactic oral antibiotics (eg, ciprofloxacin 500 mg bid) and, in patients who have cystic fibrosis and are colonized with *P. aeruginosa*, inhaled tobramycin (300 mg bid every other month). In patients with diffuse bronchiectasis due to other causes, aerosolized gentamicin (40 mg bid) may also be effective. Chronic therapy with azithromycin 500 mg po 3 times/wk has demonstrated efficacy in patients with cystic fibrosis; it is unclear whether macrolides are useful in other patients. The mechanism of this effect is not known and may not be due to antibiotic effect.

As with all patients with chronic pulmonary disease, annual vaccination against influenza and vaccination every 5 yr against pneumococcus is recommended.

Various techniques can facilitate clearance of secretions, including postural drainage and chest percussion, positive expiratory pressure devices, intrapulmonary percussive ventilators, pneumatic vests, and autogenic drainage (a breathing technique thought to help move secretions from peripheral to central airways). Nebulized drugs, including a mucolytic (rhDNase) or hypertonic (7%) saline, have clinical utility in patients with cystic fibrosis. Patients should be introduced to these techniques by a respiratory therapist and should use whichever technique is most effective for them because no evidence favors one technique.

Additional treatment depends on the cause. For cystic fibrosis, see p. 2881. Allergic bronchopulmonary aspergillosis is treated with corticosteroids and possibly with azole antifungals (see p. 1888). Patients with immunoglobulin or α1-antitrypsin deficiencies should receive replacement therapy.

**Acute exacerbations:** Acute exacerbations are treated with antibiotics and increased efforts to clear sputum from the airways with the use of bronchodilators and mucolytics. Inflammation may be treated with inhaled or oral corticosteroids. Antibiotic choice depends on whether patients have cystic fibrosis or non-cystic fibrosis bronchiectasis.

Antibiotics for non-cystic fibrosis bronchiectasis should initially cover *H. influenzae, P. aeruginosa, M. catarrhalis, S. aureus*, and *S. pneumoniae* (eg, ciprofloxacin 500 mg po bid or levofloxacin 500 mg po once/day for 7 to 14 days) and should be adjusted according to culture results.
Antibiotic selection for cystic fibrosis exacerbations is guided by sputum culture. Routine annual sputum cultures should be done on all patients with cystic fibrosis. During childhood, common infecting organisms are *S. aureus* and *H. influenzae* and quinolone antibiotics such as ciprofloxacin and levofloxacin may be used. In the later stages of cystic fibrosis, infections involve highly resistant strains of certain gram-negative organisms including *P. aeruginosa*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. In these patients, treatment is with multiple antibiotics (eg, tobramycin, aztreonam, ticarcillin/clavulanate, ceftazidime, cefepime). IV administration is frequently required.

**Complications:** Significant hemoptysis is usually treated with bronchial artery embolization, but surgical resection may be considered if pulmonary function is adequate.

Superinfection with mycobacterial organisms such as *M. avium* complex almost always requires multiple drug regimens that include clarithromycin 500 mg po bid or azithromycin 250 mg once/day; rifampin 600 mg po once/day or rifabutin 300 mg po once/day; and ethambutol 25 mg/kg po once/day for 2 mo followed by 15 mg/kg once/day. Drug therapy is modified based on culture and sensitivity results. All drugs should be taken until sputum cultures have been negative for 12 mo.

Surgical resection for localized bronchiectasis is rarely needed but is considered when medical therapy has been optimized and the symptoms are intolerable. In certain patients with diffuse bronchiectasis, lung transplantation is also an option. Five-year survival rates as high as 65 to 75% have been reported when a heart-lung or double lung transplantation is done. Pulmonary function usually improves within 6 mo, and the improvement may be sustained for at least 5 yr.
Chapter 199. Interstitial Lung Diseases

Introduction

(Diffuse Parenchymal Lung Diseases)

Interstitial lung diseases are a heterogeneous group of disorders characterized by alveolar septal thickening, fibroblast proliferation, collagen deposition, and, if the process remains unchecked, pulmonary fibrosis. Interstitial lung diseases can be classified using various criteria (eg, acute vs chronic, granulomatous vs nongranulomatous, known cause vs unknown cause, primary lung disease vs secondary to systemic disease).

Among the numerous possible causes are most connective tissue disorders and occupational lung exposures and many drugs (see Table 199-1 and also Ch. 201). A number of interstitial diseases of unknown etiology have characteristic histology, clinical features, or presentation [Table 199-1. Causes of Interstitial Lung Disease]

and thus are considered unique diseases, including eosinophilic pulmonary diseases, pulmonary Langerhans' cell granulomatosis (histiocytosis), lymphangioleiomyomatosis, pulmonary alveolar proteinosis, and sarcoidosis. In up to 30% of patients who have interstitial diseases with no clear cause, the processes are distinguished primarily by characteristic histopathologic features; these processes are termed the idiopathic interstitial pneumonias.

Idiopathic Interstitial Pneumonias

Idiopathic interstitial pneumonias (IIPs) are interstitial lung diseases of unknown etiology that share similar clinical and radiologic features and are distinguished primarily by the histopathologic patterns on lung biopsy. Classified into 6 histologic subtypes, all are characterized by varying degrees of inflammation and fibrosis and all cause dyspnea. Diagnosis is based on history, physical examination, imaging, pulmonary function tests, and lung biopsy. Treatment varies by subtype but typically involves corticosteroids, cytotoxic drugs, or both; treatment is frequently ineffective. Prognosis varies by subtype and ranges from excellent to nearly always fatal.

The 6 histologic subtypes of IIP in decreasing order of frequency are

- Usual interstitial pneumonia, known clinically as idiopathic pulmonary fibrosis
- Nonspecific interstitial pneumonia
- Cryptogenic organizing pneumonia
- Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
- Desquamative interstitial pneumonia
- Acute interstitial pneumonia

These subtypes are characterized by varying degrees of interstitial inflammation and fibrosis. All cause dyspnea; diffuse usually reticular opacities on chest x-ray; and inflammation, fibrosis, or both on biopsy. The subtypes are important to distinguish, however, because they have different clinical features (see Table 199-2) and respond differently to treatment. Lymphoid interstitial pneumonia, although still considered a subtype of IIP, is now thought to be part of the lymphoproliferative disease spectrum rather than a primary interstitial lung disease (see p. 1961).

Symptoms and Signs
Symptoms and signs are usually nonspecific. Cough and dyspnea on exertion are typical, with variable onset and progression. Common signs include tachypnea, reduced chest expansion, and bibasilar end-inspiratory dry crackles.

**Diagnosis**

- Chest x-ray
- High-resolution CT (HRCT)
- Pulmonary function tests
- Lung biopsy

IIP should be suspected in any patient with unexplained interstitial lung disease. Clinicians, radiologists, and pathologists should exchange information to determine the diagnosis in individual patients. Potential causes (see Table 199-1) are assessed systematically. For maximum diagnostic yield, history should address the following criteria:

- Symptom duration
- Family history of lung disease, especially lung fibrosis
- History of tobacco use (because some diseases occur mostly among current or former smokers)
- Current and prior drug use
- Detailed review of home and work environments, including those of family members. A chronologic listing of the patient's entire employment history, including specific duties and known exposures to dusts, gases, and chemicals, is obtained. The degree of exposure, duration of exposure, latency of exposure, and the use of protective devices is elicited.

Chest x-rays are always done as are pulmonary function tests (see p. 1851). HRCT, which distinguishes airspace from interstitial disease, provides better assessment of the extent and distribution of disease and is more likely to detect underlying or coexisting disease (eg, occult mediastinal adenopathy, cancer, emphysema). HRCT is best done with the patient prone to reduce dependent lung atelectasis.

The initial laboratory evaluation includes liver and renal function tests and CBC to check for anemia, polycythemia, and leukocytosis. Other tests are done for patients who have clinical features suggesting a connective tissue disorder, vasculitis, or environmental exposure. Such tests include ESR, antinuclear antibodies, rheumatoid factor, hypersensitivity panel (a collection of tests for antibodies to common antigens from microbial, fungal, and animal sources), antineutrophil cytoplasmic antibodies, and anti-basement membrane antibody.

Bronchoscopic transbronchial biopsy can exclude interstitial lung disease, establishing [Table 199-2, Key Features of Idiopathic Interstitial Pneumonias*]

a diagnosis of another disorder, but the biopsy does not yield enough tissue to diagnose one of the IIPs. Bronchoalveolar lavage helps narrow the differential diagnosis in some patients and can provide information about disease progression and response to therapy. The usefulness of this procedure in the initial clinical assessment and follow-up of most patients with these diseases has not been established, however.

Surgical lung biopsy is usually needed to confirm the diagnosis except when HRCT shows a pattern consistent with idiopathic pulmonary fibrosis. Biopsy of multiple sites with an open or video-assisted thoracoscopic surgery (VATS) procedure is required.
Treatment

Treatment may vary by disorder (see Table 199-3). Smoking cessation is always recommended to avoid accelerating disease progression. Corticosteroids are recommended for cryptogenic organizing pneumonia, lymphoid interstitial pneumonia, and nonspecific interstitial pneumonia. Lung transplantation may be recommended for end-stage disorders.

Idiopathic Pulmonary Fibrosis

(Cryptogenic Fibrosing Alveolitis)

Idiopathic pulmonary fibrosis (IPF), the most common form of IIP, causes progressive pulmonary fibrosis predominantly in male smokers. Symptoms and signs develop over months to years and include exertional dyspnea, cough, and fine (Velcro) crackles. Diagnosis is based on history, physical examination, chest x-ray, and pulmonary function tests and is confirmed with HRCT, lung biopsy, or both if necessary. No specific treatment has proved effective. Most patients deteriorate; median survival is < 3 yr from diagnosis.

IPF, identified histologically as usual interstitial pneumonia, accounts for about 50% of cases of IIP. IPF affects men and women in their 50s and 60s in a ratio of 2:1. Current or former cigarette smoking is most strongly associated with the disease. There is some genetic predisposition; familial clustering occurs in up to 3% of cases.

Etiology

Environmental, genetic, or other unknown factors are thought to initially trigger alveolar epithelial cell injury, but self-perpetuating and aberrant interstitial fibroblast and mesenchymal cell proliferation (with collagen deposition and fibrosis) are thought to account for development of clinical disease.

Pathophysiology

The key histologic findings are subpleural fibrosis with sites of fibroblast proliferation (fibroblast foci) and dense scarring, alternating with areas of normal lung tissue (heterogeneity). Scattered interstitial inflammation occurs with lymphocyte, plasma cell, and histiocyte infiltration. Cystic dilatation of peripheral alveoli (honeycombing) occurs in all patients and increases with advanced disease. A similar histologic pattern uncommonly occurs in cases of interstitial lung diseases of known etiology (see Table 199-2).

Symptoms and Signs

Symptoms and signs typically develop over 6 mo to several years and include dyspnea on exertion and nonproductive cough. Constitutional symptoms, such as low-grade fever and myalgias, are uncommon. The classic sign of IPF is fine, dry, bibasilar inspiratory crackles (Velcro crackles). Clubbing is present in about 50% of cases. The remainder of the examination is normal until disease is advanced, at which time signs of pulmonary hypertension and right ventricular systolic dysfunction may develop.

Diagnosis

- HRCT
- Pulmonary function tests
- Often surgical lung biopsy
Diagnosis is suspected in patients with subacute dyspnea, nonproductive cough, and Velcro crackles on chest examination. However, IPF is commonly overlooked initially because of clinical similarities to other more common diseases, such as bronchitis, asthma, and heart failure. Diagnosis requires HRCT, pulmonary function tests, and often surgical lung biopsy.

Chest x-ray typically shows diffuse reticular opacities in the lower and peripheral lung zones. Small cystic lesions (honeycombing) and dilated airways due to traction bronchiectasis are additional findings.

Pulmonary function tests typically reveal a restrictive pattern (see p. 1855). Diffusing capacity for carbon monoxide (DLCO) is also reduced. ABGs show hypoxemia, which is often exaggerated or elicited by exercise and low arterial CO\textsubscript{2} levels.

HRCT shows diffuse, patchy, subpleural, reticular opacities with irregularly thickened interlobular septa and intralobular lines; subpleural honeycombing; and traction bronchiectasis. Ground-glass opacities affecting > 30% of the lung suggest an alternative diagnosis.

Laboratory testing plays little role in diagnosis.

**Prognosis**

Most patients have moderate to advanced clinical disease at the time of diagnosis and deteriorate despite treatment. Normal PaO\textsubscript{2} at presentation and fewer fibroblastic foci on biopsy predict a better prognosis. Prognosis is worse with advanced age, poor pulmonary function at presentation (forced vital capacity [FVC] < 55% of predicted or DLCO < 35% of predicted), and severe dyspnea. Median survival is < 3 yr from time of diagnosis.

Causes of acute deterioration include infections, pulmonary embolism, pneumothorax, and heart failure. Also, acute exacerbations without an identifiable cause are common and have a high morbidity. Lung cancer occurs more frequently in patients with IPF, but cause of death is usually respiratory failure, respiratory infection, or heart failure with ischemia and arrhythmia. Because of the poor prognosis of IPF, discussions with the patient and family about advance care planning and end-of-life care are important at the early stages of diagnosis and management (see p. 3471).

**Treatment**

- Supportive care

- Possibly corticosteroids and immunosuppressants

- Sometimes lung transplantation

No specific treatment has proved effective. Supportive therapy consists of O\textsubscript{2} for hypoxemia, pulmonary rehabilitation, and antibiotics for pneumonias. Smoking must be stopped. Joining a support group may help reduce the stress of the illness. Treatment of IPF with corticosteroids and cytotoxic agents is of unproven benefit and causes substantial morbidity; thus, combined therapy should not be routinely prescribed. Drugs such as N-acetylcysteine, bosentan, pirfenidone, warfarin, and etanercept show promise, but there is insufficient evidence to recommend their general use.

Lung transplantation is successful for otherwise healthy IPF patients < 55 yr with end-stage pulmonary disease (< 40% of all IPF patients). Otherwise healthy IPF patients should be evaluated for lung transplantation at the time of diagnosis.

**Nonspecific Interstitial Pneumonia**

Nonspecific interstitial pneumonia is an idiopathic interstitial pneumonia that occurs mainly in women, nonsmokers, and patients < 50 yr.
Idiopathic nonspecific interstitial pneumonia is the second most common idiopathic interstitial pneumonia. Most patients are between the ages of 40 and 50 and have no known cause or association. However, a similar pathologic process can occur in patients with a connective tissue disorder (in particular, systemic sclerosis or polymyositis/dermatomyositis), in some forms of drug-induced lung injury, and in patients with hypersensitivity pneumonitis.

Clinical presentation is similar to that of IPF. Cough and dyspnea are present for months to years. Constitutional symptoms are unusual, although a low-grade fever and malaise are possible.

**Diagnosis**

- HRCT
- Pulmonary function tests
- Biopsy

The diagnosis should be considered in patients with unexplained subacute or chronic cough and dyspnea. Diagnosis usually requires chest x-ray, HRCT, pulmonary function tests, and biopsy. In contrast to idiopathic pulmonary fibrosis, antinuclear antibodies and rheumatoid factor may be positive in low titer.

Pulmonary function tests usually show a restrictive pattern. Hypoxemia is often present at rest and is even more prominent with exercise.

Chest x-ray primarily shows lower-zone reticular opacities. Bilateral patchy opacities are also possible. HRCT findings include bilateral patchy ground-glass attenuation, bilateral areas of consolidation, irregular lines, and bronchial dilatation. Ground-glass attenuation is the predominant finding in most cases and is the sole abnormality in about one third of cases. More than half of patients have an increased percentage of lymphocytes in bronchoalveolar lavage fluid.

The main histologic feature of nonspecific interstitial pneumonia is homogenous inflammation and fibrosis, as opposed to the heterogeneity in usual interstitial pneumonia. The changes are temporally uniform, but the process may be patchy, with intervening areas of unaffected lung. Honeycomb areas are rare.

**Treatment**

- Corticosteroids

Most patients respond to corticosteroids. Relapse may occur. The disease progresses in a small percentage of patients and these die 5 to 10 yr after diagnosis. The estimated overall 10-yr mortality is < 15 to 20%.

**Cryptogenic Organizing Pneumonia**

*(Bronchiolitis Obliterans Organizing Pneumonia)*

Cryptogenic organizing pneumonia (COP) is an idiopathic condition in which granulation tissue obstructs alveolar ducts and alveolar spaces with chronic inflammation occurring in adjacent alveoli.

COP affects men and women equally, usually in their 40s or 50s. Cigarette smoking does not seem to be a risk factor.

About one half of patients recall having a community-acquired pneumonia-like syndrome (ie, a nonresolving flu-like illness characterized by cough, fever, malaise, fatigue, and weight loss) at the onset of the illness. Progressive cough and exertional dyspnea are what usually prompt the patient to seek medical attention. Chest examination demonstrates Velcro crackles.
Diagnosis

• HRCT

• Pulmonary function tests

• Often biopsy

Diagnosis requires imaging tests, pulmonary function tests, and, if the diagnosis is not clear from these tests, biopsy. Chest x-ray shows bilateral, diffuse, peripherally distributed alveolar opacities with normal lung volumes; a peripheral distribution similar to chronic eosinophilic pneumonia may occur. Rarely, alveolar opacities are unilateral. Recurrent and migratory pulmonary opacities are common. Rarely, irregular linear or nodular interstitial opacities or honeycombing are visible at presentation. HRCT of the lung shows patchy airspace consolidation (present in 90% of patients), ground-glass opacities, small nodular opacities, and bronchial wall thickening and dilatation. The patchy opacities are more common in the periphery of the lung, often in the lower lung zone. CT may show much more extensive disease than is expected from review of the chest x-ray.

Pulmonary function tests usually show a restrictive defect, although an obstructive defect (ratio of forced expiratory volume in 1 sec to forced vital capacity \[\text{FEV}_1/\text{FVC} \leq 70\%\]) is found in 21% of patients, and pulmonary function is occasionally normal. Hypoxemia during rest and exercise is common.

Routine laboratory test results are nonspecific. Leukocytosis without an increase in eosinophils occurs in about one half of patients. The initial ESR often is elevated.

Lung biopsy shows excessive proliferation of granulation tissue within small airways and alveolar ducts, with chronic inflammation in the surrounding alveoli. Foci of organizing pneumonia are nonspecific and can occur secondary to other pathologic processes, including infections, Wegener's granulomatosis, lymphoma, hypersensitivity pneumonitis, and eosinophilic pneumonia.

Treatment

• Corticosteroids

Clinical recovery follows treatment with corticosteroids in two thirds of patients, often within 2 wk. Relapses occur in up to 50% of patients, but these patients are responsive to additional courses of corticosteroids. Recovery after treatment is common when COP appears on HRCT as parenchymal consolidation, ground-glass opacity, or nodules. In contrast, recovery is less common when COP appears on HRCT as linear and reticular opacities.

Respiratory Bronchiolitis-Associated Interstitial Lung Disease

Respiratory bronchiolitis-associated interstitial lung disease (RBILD) is a syndrome of small airway inflammation and interstitial lung disease occurring in smokers.

Most smokers develop a subclinical bronchiolitis characterized by mild or moderate inflammation of the small airways. The few patients who develop more severe inflammation with clinically significant interstitial disease are said to have RBILD. Male-to-female ratio is 2:1. RBILD is characterized histologically by submucosal inflammation of the membranous and respiratory bronchioles manifested by the presence of tan-brown pigmented macrophages (resulting from increased iron content, as occurs in smokers), mucus stasis, and metaplastic cuboidal epithelium in bronchioles and alveoli. Alveolar septal scarring always occurs. Similar findings, however, occur in some hypersensitivity reactions, occupational lung exposures (usually due to mineral dusts), viral infections, and drug reactions. RBILD also resembles desquamative interstitial pneumonia histologically, but in RBILD inflammation is patchier and less extensive. The similarity of the 2 conditions has led to the suggestion that they are different manifestations of the same disease caused by cigarette smoking.
Symptoms of cough and breathlessness with exertion resemble those of other interstitial lung diseases, especially idiopathic pulmonary fibrosis, but are milder. Crackles on examination are the only physical finding.

**Diagnosis**

- Chest x-ray, CT
- Pulmonary function tests

Diagnosis is considered in patients being evaluated for interstitial lung disease. Diagnostic testing includes imaging tests, pulmonary function tests, and biopsy. Chest x-ray findings include the following:

- Diffuse, fine reticular or nodular opacities
- Bronchial wall thickening
- Prominent peribronchovascular interstitium
- Small regular and irregular opacities
- Small peripheral ring shadows

HRCT often shows attenuation nodules and patchy areas of hazy ground-glass opacities. A mixed obstructive-restrictive pattern is common on pulmonary function tests, although results may be normal or show an isolated increase in residual volume. ABG measurements show mild hypoxemia. Routine laboratory tests are not helpful.

**Treatment**

- Smoking cessation

Treatment is smoking cessation and avoidance of even passive cigarette smoke exposure, which may prevent improvement or lead to recurrence of the illness. There is only anecdotal evidence of the efficacy of corticosteroids. The natural clinical course of the disease is unknown, but prognosis is good with smoking cessation.

**Desquamative Interstitial Pneumonia**

Desquamative interstitial pneumonia is chronic lung inflammation characterized by mononuclear cell infiltration of the airspaces; it occurs almost exclusively in current or former cigarette smokers.

Over 90% of patients with desquamative interstitial pneumonia are smokers, who tend to develop the disease in their 30s or 40s. The disease tends to affect the lung parenchyma uniformly. The alveolar walls are lined with plump cuboidal pneumocytes; there is moderate infiltration of the alveolar septum by lymphocytes, plasma cells, and, occasionally, eosinophils. Alveolar septal fibrosis, if present, is mild. The most striking feature is the presence of numerous pigmented macrophages within distal airspaces, mistaken as desquamated pneumocytes when the disease was first described. Honeycombing is rare. Similar but much less extensive findings occur in RBILD, leading to the suggestion that desquamative interstitial pneumonia and RBILD are different manifestations of the same disease caused by cigarette smoking.

**Diagnosis**

- Chest x-ray, CT

Chest x-ray abnormalities include bibasilar hazy opacities without honeycombing; findings may be normal.
in up to 20% of cases. HRCT shows multifocal or diffuse, basilar, subpleural ground-glass opacities. Irregular linear and reticular opacities are common but are not usually the dominant features. Honeycombing may be visible, occurs in the minority of patients, and is usually limited.

Treatment

- Smoking cessation
- Sometimes corticosteroids or cytotoxic drugs

Smoking cessation results in clinical improvement in an estimated 75% of patients. Patients who do not improve may respond to corticosteroids or cytotoxic drugs. Prognosis is good, with about 70% survival at 10 yr.

Acute Interstitial Pneumonia

(Accelerated Interstitial Pneumonia; Hamman-Rich Syndrome)

Acute interstitial pneumonia (AIP) is an idiopathic version of acute respiratory distress syndrome (ARDS—see p. 2284).

AIP equally affects apparently healthy men and women usually > 40 yr.

AIP is defined histologically by organizing diffuse alveolar damage, a nonspecific pattern that occurs in other causes of lung injury unrelated to IIP. The hallmark of organizing diffuse alveolar damage is diffuse, marked alveolar septal edema with inflammatory cell infiltration; fibroblast proliferation; occasional hyaline membranes; and thickening of the alveolar walls. Septa are lined with atypical, hyperplastic type II pneumocytes, and airspaces are collapsed. Thrombi develop in small arteries but are nonspecific.

Symptoms consist of the abrupt onset of fever, cough, and shortness of breath, which in most patients increase in severity over 7 to 14 days, progressing to respiratory failure.

Diagnosis is suspected in patients with symptoms, signs, and chest x-ray findings of ARDS (eg, diffuse bilateral airspace opacification). Diagnosis is supported by HRCT but usually requires biopsy. HRCT shows bilateral patchy symmetric areas of ground-glass attenuation and sometimes bilateral areas of airspace consolidation in a predominantly subpleural distribution. Mild honeycombing, usually affecting < 10% of the lung, may be present. Routine laboratory tests are nonspecific and generally not helpful.

Diagnosis is confirmed by surgical lung biopsy showing diffuse alveolar damage in the absence of known causes of ARDS and diffuse alveolar damage (eg, sepsis, drugs, toxins, radiation, viral infection). Biopsy is often required to distinguish AIP from diffuse alveolar hemorrhage syndrome, acute eosinophilic pneumonia, and cryptogenic organizing pneumonia.

Treatment is supportive and usually requires mechanical ventilation. Corticosteroid therapy is generally used, but efficacy has not been established.

Mortality is > 60%; most patients die within 6 mo of presentation, and death is usually due to respiratory failure. Patients who survive the initial acute episode may recover complete pulmonary function, although the disease may recur.

Drug-Induced Pulmonary Disease

Drug-induced pulmonary disease is not a single disorder, but rather a common clinical problem in which a patient without previous pulmonary disease develops respiratory symptoms, chest x-ray changes, deterioration of pulmonary function, histologic changes, or several of these findings in association with drug therapy. Over 150 drugs or categories of drugs have been reported to cause pulmonary disease; the mechanism is rarely known, but many drugs are thought to provoke a hypersensitivity response. Some drugs (eg, nitrofurantoin) can cause different injury patterns in different patients.
Depending on the drug, drug-induced syndromes can cause interstitial fibrosis, organizing pneumonia, asthma, noncardiogenic pulmonary edema, pleural effusions, pulmonary eosinophilia, pulmonary hemorrhage, or veno-occlusive disease (see Table 199-4).

Diagnosis is based on observation of responses to withdrawal from and, if practical, reintroduction to the suspected drug.

Treatment is stopping the drug. A screening pulmonary function test is commonly done in patients about to begin or already taking drugs with pulmonary toxicities, but the benefits of screening for prediction or early detection of toxicity are unproved.

Eosinophilic Pulmonary Diseases

Eosinophilic pulmonary diseases are a heterogeneous group of disorders characterized by the accumulation of eosinophils in alveolar spaces, the interstitium, or both. Peripheral blood eosinophilia is also common. Known causes of eosinophilic pulmonary disease include

- Infections (especially helminthic infections)
- Drug-induced pneumonitis (eg, antibiotics, phenytoin, L-tryptophan)
- Inhaled toxins (eg, cocaine)
- Systemic disorders (eg, Churg-Strauss syndrome)
- Allergic bronchopulmonary aspergillosis

Often the cause is unknown.

Diagnosis is based on demonstration of opacities on chest x-ray and identification of eosinophilia (> 450/μL) in peripheral blood, bronchoalveolar lavage fluid, or lung biopsy tissue. However, pulmonary eosinophilia may occur in the absence of peripheral eosinophilia.

Table 199-4, Substances with Toxic Pulmonary Effects

Pulmonary opacities on chest x-ray associated with blood eosinophilia are sometimes called PIE (pulmonary infiltrates with eosinophilia) syndrome.

Eosinophils are primarily tissue-dwelling and are several hundred-fold more abundant in tissues than in blood. Consequently, blood eosinophil numbers do not necessarily indicate the extent of eosinophilic involvement in affected tissues. Eosinophils are most numerous in tissues with a mucosal epithelial interface with the environment, such as the respiratory, GI, and lower GU tracts. Eosinophils are not present in the lungs of healthy people, so their presence in tissue or bronchoalveolar lavage fluid (> 5% of differential count) identifies a pathologic process.

Eosinophils are exquisitely sensitive to corticosteroids and completely disappear from the bloodstream within a few hours after administration of corticosteroids. This rapid disappearance from the blood may obscure the diagnosis in patients who receive corticosteroids before the diagnostic assessment is instituted.

The two primary eosinophilic pulmonary diseases of unknown etiology are chronic and acute eosinophilic pneumonia. Hypereosinophilic syndrome, a systemic disease affecting multiple organs, is discussed elsewhere (see p. 990).

Chronic Eosinophilic Pneumonia
Chronic eosinophilic pneumonia (CEP) is a disorder of unknown etiology characterized by an abnormal, chronic accumulation of eosinophils in the lung.

CEP is not truly chronic; rather it is an acute or subacute illness that recurs (thus, a better name might be recurrent eosinophilic pneumonia). The prevalence and incidence of CEP are unknown. Etiology is suspected to be an allergic diathesis. Most patients are nonsmokers.

Symptoms and Signs

Patients often present with fulminant illness characterized by cough, fever, progressive breathlessness, wheezing, and night sweats. The clinical presentation may suggest a community-acquired pneumonia. Asthma accompanies or precedes the illness in > 50% of cases. Those with recurrent symptoms may have weight loss.

Diagnosis

- Chest x-ray
- Exclusion of infectious causes of pneumonia

Diagnosis is suspected in patients with characteristic symptoms and typical radiographic appearance. Diagnosis also requires CBC, ESR, sometimes iron studies, and exclusion of infectious causes by appropriate cultures (see p. 3471). Peripheral blood eosinophilia, a very high ESR, iron deficiency anemia, and thrombocytosis are all frequently present. Chest x-ray findings of bilateral peripheral or pleural-based opacities, most commonly in the middle and upper lung zones, is described as the photographic negative of pulmonary edema and is virtually pathognomonic (although present in < 25% of patients). A similar pattern is present on CT in virtually all cases. Bronchoalveolar lavage and biopsy are almost always done. Eosinophilia > 40% in bronchoalveolar lavage fluid is suggestive of CEP; serial bronchoalveolar lavage examinations may help document the course of disease. Biopsy shows interstitial and alveolar eosinophils and histiocytes, including multinucleated giant cells, and organizing pneumonia. Fibrosis is minimal.

Treatment

- Systemic corticosteroids
- Sometimes maintenance therapy with inhaled corticosteroids, oral corticosteroids, or both

Patients with CEP are uniformly responsive to IV or oral corticosteroids; failure to respond suggests another diagnosis. Initial treatment is prednisone 40 to 60 mg once/day. Clinical improvement is often striking and rapid, often occurring within 48 h. Complete resolution of symptoms and x-ray abnormalities occurs within 14 days in most patients and by 1 mo in almost all. Symptoms and plain chest x-rays are both reliable and efficient guides to therapy. Although CT is more sensitive for the detection of radiographic abnormalities, there is no benefit gained by repeating it. Peripheral eosinophil counts, ESR, and IgE levels can also be used to follow the clinical course during treatment. However, not all patients have abnormal laboratory test results.

Symptomatic or radiographic relapse occurs in 50 to 80% of cases either after cessation of therapy or, less commonly, with tapering of the corticosteroid dose. Relapse can occur months to years after the initial episode. Thus, corticosteroid therapy is occasionally continued indefinitely. Inhaled corticosteroids (eg, fluticasone or beclomethasone 500 to 750 μg bid) appear to be effective, especially in reducing the maintenance dose of oral corticosteroid.

Relapse does not appear to indicate treatment failure, a worse prognosis, or greater morbidity. Patients continue to respond to corticosteroids as during the initial episode. Fixed airflow obstruction can occur in some patients who recover, but the abnormalities are usually of borderline clinical significance.

CEP occasionally leads to physiologically important restrictive lung function abnormalities as a result of...
irreversible fibrosis, but abnormalities are usually mild enough that CEP is an extremely unusual cause of morbidity or death.

**Acute Eosinophilic Pneumonia**

**Acute eosinophilic pneumonia (AEP) is a disorder of unknown etiology characterized by rapid eosinophilic infiltration of the lung interstitium.**

In contrast to CEP, AEP is an acute illness that occurs once and does not recur. Incidence and prevalence are unknown. AEP can occur at any age but most often affects patients between 20 and 40 yr, with a male-to-female ratio of 21:1. The cause is unknown, but AEP may be an acute hypersensitivity reaction to an unidentified inhaled antigen in an otherwise healthy person. Cigarette or other smoke exposure may be involved.

**Symptoms and Signs**

AEP causes an acute febrile illness of short duration (usually < 7 days). Symptoms are nonproductive cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain. Signs include tachypnea, fever (often > 38.5° C), and bibasilar inspiratory crackles and, occasionally, rhonchi on forced exhalation. Patients with AEP frequently present with acute respiratory failure requiring mechanical ventilation. Rarely, distributive (hyperdynamic) shock can occur.

**Diagnosis**

- HRCT
- Usually CBC, pleural fluid analysis, and pulmonary function testing
- Bronchoscopy

The diagnosis is suspected in patients with symptoms of acute pneumonia that progresses to respiratory failure and does not respond to antibiotics. Diagnosis is based on findings from routine testing and is confirmed by bronchoscopy. AEP is a diagnosis of exclusion and requires the absence of known causes of eosinophilic pneumonia (eg, drug- and toxininduced, helminthic and fungal infection-related, Churg-Strauss syndrome, idiopathic hypereosinophilic syndrome, tumors). The CBC in most patients demonstrates markedly elevated eosinophil counts. ESR and IgE levels are high but are nonspecific.

The chest x-ray initially may show only subtle reticular or ground-glass opacities, often with Kerley B lines. Isolated alveolar (about 25% of cases) or reticular (about 25% of cases) opacities may also be observed. The pattern is unlike that occurring in chronic eosinophilic pneumonia, in which the opacities are localized to the lung periphery. Small pleural effusions occur in two thirds of patients and are frequently bilateral.

HRCT is always abnormal with bilateral, random, patchy ground-glass or reticular opacities.

Pleural fluid examination shows marked eosinophilia with high pH. Pulmonary function tests often show a restrictive process with reduced diffusing capacity for carbon monoxide (DLCO).

Bronchoscopy should be done for lavage and, occasionally, biopsy. Bronchoalveolar lavage fluid often shows a high number and percentage (> 25%) of eosinophils. The most common histopathologic features on biopsy include eosinophilic infiltration with acute and organizing diffuse alveolar damage, but few patients have undergone lung biopsy.

**Treatment**

- Systemic corticosteroids

Some patients improve spontaneously. Most are treated with prednisone 40 to 60 mg po once/day.
patients with respiratory failure, methylprednisolone 60 to 125 mg IV q 6 h is preferred. The prognosis is excellent; response to corticosteroids and complete recovery without recurrence is almost universal. Pleural effusions resolve more slowly than parenchymal opacities.

**Loffler's Syndrome**

Loffler's syndrome is characterized by absent or mild respiratory symptoms (most often dry cough), fleeting migratory pulmonary opacities, and peripheral blood eosinophilia. Parasitic infections, especially *Ascaris lumbricoides*, may be the cause, but an identifiable etiologic agent is not found in up to one third of patients. The disease usually resolves within 1 mo. Treatment is symptomatic and consists of corticosteroids.

**Hypersensitivity Pneumonitis**

*(Extrinsic Allergic Alveolitis)*

Hypersensitivity pneumonitis is a syndrome of cough, dyspnea, and fatigue caused by sensitization and subsequent hypersensitivity to environmental (frequently occupational) antigens. Acute, subacute, and chronic forms exist; all are characterized by acute interstitial inflammation and development of granulomas and fibrosis with long-term exposure. Diagnosis is based on a combination of history, physical examination, imaging tests, bronchoalveolar lavage, and biopsy. Short-term treatment is with corticosteroids; long-term treatment is antigen avoidance.

**Etiology**

Over 300 antigens have been identified as triggers for hypersensitivity pneumonitis, although farming, birds, and water contamination account for about 75% of cases. Antigens are commonly categorized by type and occupation (see Table 199-5); farmer's lung, caused by inhalation of hay dust containing thermophilic actinomycetes, is the prototype. Substantial overlap exists between hypersensitivity pneumonitis and chronic bronchitis in farmers, in whom chronic bronchitis is far more common, occurs independently of smoking status, is linked to thermophilic actinomycete exposure, and leads to findings similar to those of hypersensitivity pneumonitis on diagnostic testing.

[Table 199-5, Examples of Hypersensitivity Pneumonitis]

**Pathophysiology**

The disorder seems to represent a type IV hypersensitivity reaction, in which repeated exposure to antigen in genetically susceptible people leads to acute neutrophilic and mononuclear alveolitis, followed by interstitial lymphocytic infiltration and granulomatous reaction. Fibrosis with bronchiolar obliteration occurs with continued exposure.

Circulating precipitins (antibodies sensitized to antigen) seem not to have a primary etiologic role, and clinical history of allergy (such as asthma and seasonal allergies) is not a predisposing factor. Cigarette smoking seems to delay or prevent development, perhaps through down-regulation of the lung's immune response to inhaled antigens. However, smoking may exacerbate the disease once established.

Hypersensitivity pneumonitis has clinical similarities to other disorders that have different pathophysiologies. Organic dust toxic syndrome (pulmonary mycotoxicosis, grain fever), for example, is a syndrome consisting of fever, chills, myalgias, and dyspnea that does not require prior sensitization and is thought to be caused by inhalation of toxins produced by fungi or other contaminants of organic dust. Silo filler's disease may lead to respiratory failure, acute respiratory distress syndrome (ARDS), and bronchiolitis obliterans or bronchiolitis but is caused by inhalation of toxic nitrogen oxides produced by freshly fermented corn or alfalfa silage. Occupational asthma causes dyspnea in people previously sensitized to an inhaled antigen, but features such as airflow obstruction, airway eosinophilia, and differences in triggering antigens distinguish it from hypersensitivity pneumonitis (see p. 1979).
Symptoms and Signs

Symptoms and signs tend to depend on whether onset is acute, subacute, or chronic. Only a small proportion of exposed people develop symptoms and in most cases only after weeks to months of exposure and sensitization.

Acute disease occurs in previously sensitized people with acute high-level antigen exposure and manifests as fever, chills, cough, bilateral vice-like chest tightness (as can occur in asthma), and dyspnea 4 to 8 h after exposure. Anorexia, nausea, and vomiting may also be present. Physical examination shows tachypnea, diffuse fine-to-medium inspiratory crackles, and, in almost all cases, absence of wheezing.

Chronic disease occurs in people with chronic low-level antigen exposure (such as owners of birds) and manifests as onset over months to years of exertional dyspnea, productive cough, fatigue, and weight loss. There are few physical findings; clubbing uncommonly occurs and fever is absent. In advanced cases, pulmonary fibrosis causes symptoms and signs of right heart failure, respiratory failure, or both.

Subacute disease falls between the acute and chronic forms and manifests either as cough, dyspnea, fatigue, and anorexia that develops over days to weeks or as acute superimposed on chronic symptoms.

Diagnosis

- Specific clinical criteria
- Chest x-ray and high-resolution CT (HRCT)
- Pulmonary function tests
- Bronchoalveolar lavage
- Histologic examination and serologic tests

Diagnosis requires a high index of suspicion in patients at risk and with compatible symptoms and a compatible occupational, avocational, or domestic exposure history. Chest x-ray, HRCT, and pulmonary function tests are done routinely. Bronchoalveolar lavage and biopsy may be necessary if results are inconclusive. Diagnosis is categorized as definite, probable, subclinical, or sensitization based on specific criteria (see Table 199-6). The differential diagnosis is broad and includes environmental pulmonary diseases (see Ch. 201), sarcoidosis, bronchiolitis obliterans, connective tissue-associated pulmonary disease, and other interstitial lung diseases.

[Table 199-6. Diagnostic Criteria for Hypersensitivity Pneumonitis]

Clues in the history include

- Recurring atypical pneumonias
- Symptom onset after moving to a new job or home
- A hot tub, a sauna, a swimming pool, or other sources of standing water or water damage in the home or regular exposure to them elsewhere
- Having birds as pets
- Exacerbation and relief of symptoms in and away from specific settings

Examination often is not useful in making the diagnosis, although abnormal lung sounds and clubbing may be present.
**Imaging tests:** Imaging tests are typically done for patients with appropriate history, symptoms, and signs.

Chest x-ray is neither sensitive nor specific for detecting disease and is frequently normal in patients with acute and subacute forms. It may show reticular or nodular opacities, usually when symptoms are present. Chest x-rays of patients with chronic disease are more likely to show reticular or nodular opacities in the upper lobes with reduced lung volumes and honeycombing, similar to that of idiopathic pulmonary fibrosis.

HRCT is far more likely to show abnormalities and is considered standard for evaluating parenchymal changes in hypersensitivity pneumonitis. The most typical HRCT finding is the presence of profuse, poorly defined centrilobular micronodules. These micronodules may be present in patients with acute, subacute, or chronic disease and, in the correct clinical context, strongly suggest hypersensitivity pneumonitis. Occasionally, ground-glass opacification (attenuation) is the predominant or only finding. It is usually diffuse but sometimes spares the periphery of the secondary lobule. Focal areas of hyperlucency, similar to those present in obliterative bronchiolitis, may be a prominent feature in some patients (eg, mosaic attenuation with air trapping on expiratory HRCT). In chronic hypersensitivity pneumonitis, there are findings of lung fibrosis (eg, lobar volume loss, linear or reticular opacities, or honeycombing). Some nonsmoking patients with chronic hypersensitivity pneumonitis have findings of upper lobe emphysema. Mediastinal lymphadenopathy is uncommon, thereby distinguishing hypersensitivity pneumonitis from sarcoidosis.

**Pulmonary function tests:** These should be done as part of the standard evaluation of suspected cases of hypersensitivity pneumonitis. The syndrome can cause obstructive, restrictive, or a mixed pattern of airway changes. Advanced disease most commonly causes a restrictive defect (decreased lung volumes), a decreased diffusing capacity for carbon monoxide (DLCO), and hypoxemia. Airway obstruction is unusual in acute disease but may develop in chronic disease.

**Bronchoalveolar lavage:** Results are rarely specific for the diagnosis but are often a component of the diagnostic assessment for chronic respiratory symptoms and pulmonary function abnormalities. A lymphocytosis in lavage fluid (> 60%) with CD4+/CD8+ ratio < 1.0 (the normal ratio ± standard error of the mean = 2.3 ± 0.2) is characteristic of the disorder; by contrast, lymphocytosis with CD4+ predominance (ratio > 1.0) is more characteristic of sarcoidosis. Other findings may include mast cells > 1% (after acute exposure) and increased neutrophils and eosinophils.

Lymphocyte transformation testing is an in vitro test of sensitization and is particularly useful in detecting sensitization to metals. The test can be done on peripheral blood but is better done on bronchial lavage fluid. In this test, the patient's lymphocytes are exposed to potential antigens. If the lymphocytes transform into blasts and proliferate, they (and hence the patient) were previously sensitized to that antigen.

**Lung biopsy:** Biopsy is indicated when noninvasive testing is inconclusive. Transbronchial biopsy done through a bronchoscope is sufficient as long as multiple specimens are taken from areas of active disease and multiple sequential sections of tissue are examined histologically. Findings vary but include lymphocytic alveolitis, noncaseating granulomas, and granulomatosis. Interstitial fibrosis may be present but is usually mild in the absence of advanced radiographic changes.

**Other tests:** Additional testing is indicated when additional support for the diagnosis is required or to detect other causes of interstitial lung disease. Circulating precipitins (specific precipitating antibodies to the suspected antigen) are suggestive of an exposure that may be the cause of the illness. When combined with other criteria, they can be helpful diagnostically and avoid the need for biopsy. However, in isolation, presence of circulating precipitins is neither sensitive nor specific. Identification of a specific precipitating antigen may require detailed aerobiologic or microbiologic assessment or both of the workplace by industrial hygiene specialists, but workplace assessments usually are guided by known sources of inciting antigens (eg, *Bacillus subtilis* in detergent factories). Skin tests are not helpful, and eosinophilia is absent. Tests helpful in detecting other disorders include serologic tests and cultures (for psittacosis and other pneumonias) and autoantibodies (for collagen-vascular disease). Elevated
eosinophils may suggest chronic eosinophilic pneumonias. Hilar and paratracheal lymph node enlargement is more characteristic of sarcoidosis.

Prognosis

Pathologic changes are completely reversible if detected early and if antigen exposure is eliminated. Acute disease is self-limiting with antigen avoidance; symptoms usually lessen within hours. Chronic disease has a more complicated prognosis: fibrosis is usually irreversible but may not progress if the patient is no longer exposed to the antigen.

Treatment

• Corticosteroids

Treatment of acute or subacute hypersensitivity pneumonitis is with corticosteroids, usually prednisone 60 mg po once/day for 1 to 2 wk, then tapered over the next 2 to 4 wk to 20 mg once/day, followed by weekly decrements of 2.5 mg until the drug is stopped. This regimen relieves initial symptoms but does not appear to alter long-term outcome.

Prevention

The most important aspect of long-term management is avoidance of exposure to antigens. A complete change of environment is rarely realistic, especially for farmers and other workers, in which case dust control measures (such as wetting down compost before disturbing it) or using air filters or protective masks may be effective. Fungicides may be used to prevent the growth of antigenic microorganisms (eg, in hay or on sugar cane), but the long-term safety of this approach is unknown. Extensive cleaning of wet ventilation systems, removal of moist carpets, and maintenance of low humidity are also effective in some settings. Patients must be told, however, that these measures may be inadequate in the presence of continued exposure.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is nonmalignant growth of smooth muscle cells throughout the lung, pulmonary blood vessels, lymphatics, and pleurae. It is rare and occurs exclusively in young women. The cause is unknown. Symptoms are dyspnea, cough, chest pain, and hemoptysis; spontaneous pneumothorax is common. Diagnosis is suspected on the basis of symptoms and chest x-ray and is confirmed by high-resolution CT. Prognosis is uncertain, but the disorder is slowly progressive and over years often leads to respiratory failure and death. Primary treatment is lung transplantation.

LAM is not an interstitial lung disease, but patients are occasionally misdiagnosed as having interstitial lung disease (and also asthma or COPD).

LAM is a rare disease exclusive to women, typically affecting those between 20 and 40 yr. Whites are at greatest risk. LAM affects < 1 in 1 million people. It is characterized by nonmalignant proliferation of atypical smooth muscle cells throughout the chest, including lung parenchyma, vasculature, lymphatics, and pleurae, leading to distortion of lung architecture, cystic emphysema, and progressive deterioration of lung function.

Etiology

The cause of LAM is unknown. The tempting hypothesis that female sex hormones play a role in pathogenesis remains unproved. The disease usually arises spontaneously, but LAM bears many similarities to the pulmonary findings of tuberous sclerosis (TS—see p. 2905); LAM occurs in some patients with TS and is thought by some to be a forme fruste of TS. Mutations in the tuberous sclerosis complex-2 gene (TSC-2) have been described in LAM cells and angiomyolipomas (benign renal hamartomas made of smooth muscle, blood vessels, and adipose). Also, angiomyolipomas occur in up to 50% of patients with LAM. These observations suggest 1 of 2 possibilities: (1) somatic mosaicism for
TSC-2 mutations within the lungs and kidneys result in foci of disease superimposed against a background of normal cells within these tissues (although multiple discrete sites of disease might be expected) or (2) LAM represents dissemination of angiomyolipoma tissue to the lung in a fashion analogous to the syndrome of benign metastasizing leiomyoma.

Symptoms and Signs

Initial symptoms are dyspnea and, less commonly, cough, chest pain, and hemoptysis. There are few signs of disease, but some women have crackles and rhonchi. Many patients present with spontaneous pneumothorax. They may also present with manifestations of lymphatic obstruction, including chylothorax, chylous ascites, and chyluria. Symptoms are thought to worsen during pregnancy. Angiomyolipomas, although usually asymptomatic, can cause bleeding if they grow large (eg, > 4 cm), which usually presents as hematuria or flank pain.

Diagnosis

- Chest x-ray and high-resolution CT (HRCT)
- Lung biopsy if HRCT is nondiagnostic

Diagnosis is suspected in young women with dyspnea plus interstitial changes with normal or increased lung volumes on chest x-ray, spontaneous pneumothorax, or chylous effusion. HRCT is done in all patients suspected of having the disorder; findings of multiple, small, diffusely distributed cysts are generally pathognomonic for LAM.

Biopsy is indicated only when HRCT findings are nondiagnostic. Findings of an abnormal proliferation of smooth muscle cells (LAM cells) associated with cystic changes on histologic examination confirm disease.

Pulmonary function tests support the diagnosis and are especially useful for monitoring. Typical findings are of an obstructive or mixed obstructive and restrictive pattern. The lungs are usually hyperinflated with an increase in the total lung capacity (TLC) and thoracic gas volume. Gas trapping (an increase in residual volume [RV] and RV/TLC ratio) is commonly present. The PaO₂ and diffusing capacity for carbon monoxide (DLCO) are commonly reduced. Exercise performance is decreased in most patients.

Prognosis

Prognosis is unclear because the disorder is so rare and because the clinical course of patients with LAM is variable. In general, the disease is slowly progressive, leading eventually to respiratory failure and death, but the time to death varies widely among reports. Median survival is likely > 8 yr from diagnosis. Lung function declines 2 to 3 times faster than it does in healthy people. Women should be advised that progression may accelerate during pregnancy.

Treatment

- Lung transplantation

Standard treatment is lung transplantation, but the disorder can recur in transplanted lungs. Alternative treatments, such as hormonal manipulation with progestins, tamoxifen, and oophorectomy, are largely ineffective. Pneumothoraces may be difficult to manage because they are often recurrent, bilateral, and less responsive to standard measures. Recurrent pneumothorax requires pleural abrasion, talc or chemical pleurodesis, or pleurectomy. Embolization to prevent bleeding should be considered for angiomyolipomas > 4 cm.

Air travel is well-tolerated by most patients but may be contraindicated in those with

- New or worsening respiratory symptoms
Prior pneumothorax or hemoptysis

Evidence of extensive subpleural bullous or cystic changes on HRCT

Patients can receive education and psychologic support from the LAM Foundation in the US.

**Lymphoid Interstitial Pneumonia**

*(Lymphocytic Interstitial Pneumonitis)*

Lymphoid interstitial pneumonia (LIP) is lymphocytic infiltration of the alveolar interstitium and air spaces. The cause is unknown. It most often occurs in children with HIV infection and in people of any age with an autoimmune disorder. Symptoms and signs are cough, progressive dyspnea, and crackles. Diagnosis is based on history, physical examination, imaging tests, pulmonary function tests, and lung biopsy. Treatment is with corticosteroids, cytotoxic drugs, or both, although efficacy is unknown. Five-year survival is 50 to 66%.

LIP is a rare disorder characterized by infiltration of alveoli and alveolar septa with small lymphocytes and varying numbers of plasma cells. Noncaseating, poorly formed granulomas may be present but are usually rare and inconspicuous.

LIP is the most common cause of pulmonary disease after *Pneumocystis* infection in HIV-positive children and is the AIDS-defining illness in up to one half of HIV-positive children. LIP affects < 1% of adults with or without HIV infection. Women and girls are affected more commonly.

The cause is postulated to be an autoimmune disease or a nonspecific response to infection with Epstein-Barr virus, HIV, or other viruses. Evidence of an autoimmune etiology includes its frequent association with Sjogren's syndrome (25% of cases of LIP) and other diseases (eg, SLE, RA, Hashimoto's thyroiditis—14% of cases). Evidence of an indirect viral etiology includes frequent association with immunodeficient states (HIV/AIDS, combined variable immunodeficiency, agammaglobulinemia—14% of cases) and findings of Epstein-Barr virus DNA and HIV RNA in lung tissue of LIP patients. According to this theory, LIP is an extreme manifestation of the normal ability of lymphoid tissue in the lung to respond to inhaled and circulating antigens.

**Symptoms and Signs**

In adults, LIP causes symptoms of progressive dyspnea and cough. These manifestations progress over months or, in some cases, years and appear at a mean age of 54. Weight loss, fever, arthralgias, and night sweats occur but are less common.

In children, LIP causes bronchospasm, cough, or respiratory distress and failure to thrive, usually at age 2 or 3 yr.

Examination may reveal crackles. Findings such as hepatosplenomegaly, arthritis, and lymphadenopathy are uncommon and suggest an accompanying or alternative diagnosis.

**Diagnosis**

- High-resolution CT (HRCT)
- Pulmonary function tests
- For confirmation, biopsy (or sometimes serum protein abnormality in children)

Diagnosis is usually suspected in at-risk patients with compatible symptoms. Imaging tests, pulmonary function tests, and sometimes lung biopsy are done.

Chest x-ray shows bibasilar linear reticular or nodular opacities, a nonspecific finding that is present in a
number of pulmonary infections. Alveolar opacities, cystic dilatation of peripheral alveoli (honeycombing), or both may be present in more advanced disease. HRCT of the chest is done and helps establish the extent of disease, define the hilar anatomy, and identify pleural involvement. The HRCT findings of LIP are variable; however, their lymphatic distribution, along the peribronchovascular interstitium, interlobular septa, and presence within the visceral pleura distinguish LIP from usual interstitial pneumonia. Characteristic findings are centrilobular and subpleural nodules, thickened bronchovascular bundles, ground-glass opacities, and, rarely, diffuse cystic structures.

Pulmonary function tests show restrictive defects with reduced lung volumes and diffusing capacity for carbon monoxide (DLCO) and preserved airflow. Marked hypoxemia may occur. Bronchoalveolar lavage should be done to rule out infection and may reveal an increased number of lymphocytes.

About 80% of patients have a serum protein abnormality, most commonly a polyclonal gammopathy and, especially in children, hypogammaglobulinemia, the significance of which is unknown. These elements are sufficient to confirm the diagnosis in HIV-positive children. In adults, diagnosis requires lung biopsy with demonstration of expansion of the alveolar septae with lymphocytic and other immune cell (plasma cell, immunoblastic, and histiocytic) infiltrates. Infiltrates appear occasionally along bronchi and vessels but most commonly along alveolar septa. Immunohistochemical staining and flow cytometry must be done on the tissue to distinguish LIP from primary lymphomas. In LIP, the infiltrate is polyclonal (both T and B cells), whereas other lymphomas produce monoclonal infiltrates. Other common findings include germinal centers and multinucleated giant cells with noncaseating granulomas.

**Prognosis**

The natural history and prognosis of LIP are poorly understood. Good prognosis may correlate with more severe radiographic abnormalities, which may indicate a more vigorous immune response. Spontaneous resolution, resolution after treatment with corticosteroids or other immunosuppressive drugs, progression to lymphoma, or development of pulmonary fibrosis with respiratory insufficiency may ensue. Five-year survival is 50 to 66%. Common causes of death are infection, development of malignant lymphoma (5%), and progressive fibrosis.

**Treatment**

Treatment is with corticosteroids, cytotoxic drugs, or both, but, as with many other causes of interstitial lung diseases, the efficacy of this approach is unknown.

**Pulmonary Alveolar Proteinosis**

Pulmonary alveolar proteinosis is accumulation of surfactant in alveoli. Etiology is almost always unknown. Symptoms are dyspnea, fatigue, and malaise. Diagnosis is based on bronchoalveolar lavage, although characteristic x-ray and laboratory test abnormalities occur. Treatment is with whole lung lavage. Five-year survival is about 80% with treatment.

**Etiology**

Pulmonary alveolar proteinosis is most often idiopathic and occurs in otherwise healthy men and women between 30 and 50 yr. Rare secondary forms occur in patients with acute silicosis, *Pneumocystis jirovecii* infection, hematologic cancers, or immunosuppression by drugs and in patients with significant inhalation exposures to aluminum, titanium, cement, and cellulose dusts. Rare congenital forms causing neonatal respiratory failure also exist. It is unclear whether idiopathic and secondary cases share a common pathophysiology.

**Pathophysiology**

Impaired alveolar macrophage processing of surfactant due to abnormal granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling is thought to contribute to the disorder, perhaps due to reduced or absent function of the common β chain of the GM-CSF/IL-13/IL-5 receptor on mononuclear cells (present in some children but not in adults with the disorder). Anti-GM-CSF antibodies have also been found in
most patients. Toxic lung injury is suspected but not proved in secondary inhalation causes. Alveoli are filled with acellular lipoprotein surfactant that stains periodic acid-Schiff (PAS) positive. Alveolar and interstitial cells remain normal. Posterobasal lung segments are mostly affected. The pleura and mediastinum are unaffected.

**Symptoms and Signs**

Most patients present with progressive exertional dyspnea and weight loss, fatigue, malaise, or low-grade fever. Cough, occasionally producing chunky or gummy sputum, occurs but is less common. Clubbing and cyanosis are uncommon. Inspiratory crackles are rare because alveoli are fluid-filled; when crackles are present, they suggest infection.

**Diagnosis**

- Bronchoalveolar lavage
- Sometimes biopsy

Pulmonary alveolar proteinosis is usually first suspected when a chest x-ray is taken for nonspecific respiratory symptoms. The x-ray shows bilateral mid- and lower-lung field opacities in a butterfly distribution with normal hila.

Bronchoalveolar lavage is done. Lavage fluid is milky or opaque, stains PAS-positive, and is characterized by scattered surfactant-engorged macrophages, an increase in T lymphocytes, and high levels of surfactant apoprotein-A. Thoracoscopic or open lung biopsy is done when bronchoscopy is contraindicated or when specimens from lavage fluid are nondiagnostic. Tests typically done before treatment begins include high-resolution CT (HRCT), pulmonary function tests, ABGs, and laboratory tests.

HRCT shows ground-glass opacification, thickened intralobular structures, and interlobular septa in typical polygonal shapes (crazypaving). This finding is not specific, however, as it may also occur in patients with lipoid pneumonia, bronchoalveolar cell carcinoma, and *Pneumocystis jirovecii* pneumonia.

Pulmonary function tests show reduction in diffusing capacity for carbon monoxide (DLCO) that is disproportionate to the decreases in vital capacity, residual volume, functional residual capacity, and total lung capacity.

Laboratory test abnormalities include polycythemia, hypergammaglobulinemia, increased serum LDH levels, and increased serum surfactant proteins A and D. All abnormalities are suggestive but nondiagnostic. ABGs may show hypoxemia with mild to moderate exercise or at rest if disease is more severe.

**Prognosis**

Without treatment, pulmonary alveolar proteinosis remits spontaneously in up to 10% of patients. A single whole lung lavage is curative in up to 40%; other patients require lavage every 6 to 12 mo for many years. Five-year survival is about 80%; the most common cause of death is respiratory failure, typically occurring within the first year after diagnosis. Secondary pulmonary infections with bacteria (eg, *Mycobacteria, Nocardia*) and other organisms (*Aspergillus, Cryptococcus*, and other opportunistic fungi) occasionally develop because of impaired macrophage function; these infections require treatment.

**Treatment**

- Whole lung lavage

Treatment is unnecessary for patients without symptoms or for those with only mild symptoms. Whole lung lavage is done in patients with troubling dyspnea by using general anesthesia and a double-lumen
endotracheal tube. Lavage of one lung is done up to 15 times with 1 to 2 L saline while the other lung is ventilated. The process is then reversed. Lung transplantation is not done because the disorder recurs in the transplanted lung.

Systemic corticosteroids play no role in management and may increase the risk of secondary infection. The role of GM-CSF (IV or sc) in management remains to be determined. An open-label study showed clinical improvement in 57% of the patients studied.

**Pulmonary Langerhans' Cell Histiocytosis**

(Eosinophilic Granuloma; Pulmonary Granulomatosis X; Pulmonary Langerhans' Cell Granulomatosis; Histiocytosis X)

Pulmonary Langerhans' cell histiocytosis (PLCH) is proliferation of monoclonal Langerhans' cells in lung interstitium and airspaces. Etiology is unknown, but cigarette smoking plays a primary role. Symptoms are dyspnea, cough, fatigue, and pleuritic chest pain. Diagnosis is based on history and imaging tests and sometimes on bronchoalveolar lavage and biopsy findings. Treatment is smoking cessation. Corticosteroids are given in many cases, but efficacy is unknown. Lung transplantation is curative when combined with smoking cessation. Five-year survival is about 74%. Patients are at increased risk of cancer.

PLCH is a disease in which monoclonal CD1a-positive Langerhans' cells (a type of histiocyte) infiltrate the bronchioles and alveolar interstitium, accompanied by lymphocytes, plasma cells, neutrophils, and eosinophils. PLCH is one manifestation of Langerhans' cell histiocytosis (see p. 993), which can affect organs in isolation (most notably the lungs, skin, bones, pituitary, and lymph nodes) or simultaneously. PLCH occurs in isolation ≥ 85% of the time.

The etiology of PLCH is unknown, but the disease occurs almost exclusively in whites 20 to 40 yr of age who smoke. Men and women are affected equally. Women develop disease later, but any differences in disease presentation by sex may represent differences in smoking behavior. Pathophysiology may involve recruitment and proliferation of Langerhans' cells in response to cytokines and growth factors secreted by alveolar macrophages in response to cigarette smoke.

**Symptoms and Signs**

Typical symptoms and signs of PLCH are dyspnea, nonproductive cough, fatigue, fever, weight loss, and pleuritic chest pain, and 10 to 25% of patients have sudden, spontaneous pneumothorax. About 15% of patients are asymptomatic, with disease noted incidentally on a chest x-ray taken for another reason. Bone pain due to bone cysts (18%), rash (13%), and polyuria due to diabetes insipidus (5%) are the most common manifestations of extrapulmonary involvement and occur in up to 15% of patients, rarely being the presenting symptoms of PLCH. There are few signs of PLCH; the physical examination results are usually normal.

**Diagnosis**

- High-resolution CT (HRCT)
- Pulmonary function tests
- Sometimes bronchoscopy and biopsy

PLCH is suspected based on history and chest x-ray and is confirmed by HRCT and bronchoscopy with biopsy and bronchoalveolar lavage.

Chest x-ray classically shows bilaterally symmetric nodular opacities in the middle and upper lung fields with cystic changes and normal or increased lung volumes. The lung bases are often spared. Appearance may mimic COPD or lymphangioleiomyomatosis (see p. 1960). Confirmation on HRCT of middle and upper lobe cysts (often with bizarre shapes) and/or nodules with interstitial thickening is considered.
diagnostic of PLCH. Pulmonary function test findings are normal, restrictive, obstructive, or mixed depending on when the test is done during the course of the disease. Most commonly, the diffusing capacity for carbon monoxide (DLCO) is reduced and exercise is impaired.

Bronchoscopy and biopsy are indicated when imaging and pulmonary function tests are inconclusive. Finding > 5% of CD1a cells in bronchoalveolar lavage fluid is highly suggestive of the disease. Biopsy shows proliferation of Langerhans’ cells with occasional clustering of eosinophils (the origin of the outdated term eosinophilic granuloma) in the midst of cellular and fibrotic nodules that may take on a stellate configuration. Immunohistochemical staining is positive for CD1a, S-100 protein, and HLA-DR antigens.

Treatment

- Smoking cessation
- Possibly corticosteroids and cytotoxic drugs or lung transplantation

The main treatment is smoking cessation, which leads to symptom resolution in up to one third of patients. Empiric use of corticosteroids and cytotoxic drugs is common practice even though their effectiveness is unproved. Lung transplantation is an option for otherwise healthy patients with accelerating respiratory insufficiency, but the disorder may recur in the transplanted lung if the patient continues or resumes smoking.

Spontaneous resolution of symptoms occurs in some patients with minimally symptomatic disease; 5-yr survival is about 75%, and median survival is 12 yr. However, some patients develop slowly progressive disease, for which the clinical markers include continued smoking, age extremes, multiorgan involvement, persistent constitutional symptoms, numerous cysts on chest x-ray, reduced DLCO, low forced expiratory volume in 1 sec (FEV₁)/forced vital capacity (FVC) ratio (< 66%), high residual volume (RV)/total lung capacity (TLC) ratio (> 33%), and need for prolonged corticosteroid use. Cause of death is respiratory insufficiency or cancer. Lung cancer risk is increased because of cigarette smoking.
Chapter 200. Sarcoidosis

Introduction

Sarcoidosis is a disorder resulting in noncaseating granulomas in one or more organs and tissues; etiology is unknown. The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ. Pulmonary symptoms range from none (limited disease) to exertional dyspnea and, rarely, lung or other organ failure (advanced disease). Diagnosis usually is first suspected because of pulmonary involvement and is confirmed by chest x-ray, biopsy, and exclusion of other causes of granulomatous inflammation. First-line treatment is corticosteroids. Prognosis is excellent for limited disease but poor for more advanced disease.

Sarcoidosis affects mostly people aged 20 to 40 but occasionally affects children and older adults. Worldwide, prevalence is greatest in black Americans and northern Europeans, especially Scandinavians. Disease presentation varies widely by racial and ethnic background, with black Americans and Puerto Ricans having more frequent extrathoracic manifestations. Sarcoidosis is slightly more prevalent in women. The incidence increases in winter and early spring for unknown reasons.

Lofgren's syndrome: Lofgren's syndrome is a type of acute sarcoidosis that manifests as a triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It has distinct features, including fever, malaise, joint disease, and sometimes uveitis and parotitis. It is more common among Scandinavian and Irish women.

Lofgren's syndrome is often self-limited. Patients usually respond to NSAIDs. Rate of relapse is low.

Etiology

Sarcoidosis is thought to be due to an inflammatory response to environmental exposure in a genetically susceptible person. Proposed triggers include

- Viral, bacterial, and mycobacterial infections
- Inhalation of various agents: inorganic (e.g., aluminum, zirconium, talc) or organic (e.g., pine tree pollen, clay)

Pathophysiology

The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T lymphocytes and macrophages, release of cytokines and chemokines, and organization of responding cells into granulomas. Clusters of disease in families and communities suggest a genetic predisposition, shared exposures, or, less likely, person-to-person transmission.

The result of the inflammatory process is formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis. Granulomas are collections of mononuclear cells and macrophages that are differentiated into epithelioid and multinucleated giant cells, surrounded by lymphocytes, plasma cells, mast cells, fibroblasts, and collagen. Granulomas occur most commonly in the lungs and lymph nodes but can involve the liver, spleen, eyes (see p. 609), sinuses, skin, bones, joints, skeletal muscle, kidneys, reproductive organs, heart, salivary glands, and nervous system. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions.

Symptoms and Signs

Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness. Accordingly, frequent reassessment for new symptoms in different organs is needed. Most cases are probably asymptomatic and thus go undetected. Pulmonary disease occurs in > 90% of adult patients.

Symptoms and signs may include dyspnea, cough, chest discomfort, and crackles. Fatigue, malaise,
weakness, anorexia, weight loss, and low-grade fever are also common; sarcoidosis is an unusual cause of fever of unknown origin. Nontender lymphadenopathy is often the only sign. Systemic involvement causes various symptoms (see Table 200-1), which vary by race, sex, and age. Blacks are more likely than whites to have involvement of the eye, liver, bone marrow, peripheral lymph nodes, and skin; erythema nodosum is an exception. Women are more likely to have erythema nodosum and eye or nervous system involvement. Men and older patients are more likely to be hypercalcemic.

In children < 4 yr, arthritis, rash, and uveitis are the most common manifestations. Sarcoidosis may be confused with juvenile RA in this age group.

**Diagnosis**

- Chest imaging
- Biopsy
- Exclusion of other granulomatous disorders

[Table 200-1. Systemic Involvement in Sarcoidosis]

Sarcoidosis is most often suspected when hilar adenopathy is incidentally detected on chest x-ray. These changes are the most common abnormality, and the x-ray appearance is roughly predictive of the likelihood of spontaneous remission (see Table 200-2) in patients with pulmonary involvement. Therefore, if sarcoidosis is suspected, a chest x-ray should be the first test if it has not already been done.

A normal chest x-ray generally excludes the diagnosis; however, high-resolution CT may be indicated if sarcoidosis is strongly suspected because CT is more sensitive for detecting hilar and mediastinal lymphadenopathy. CT findings in more advanced stages (II to IV) include thickening of the bronchovascular bundles and bronchial walls; beading of the interlobular septa; ground-glass opacification; parenchymal nodules, cysts, or cavities; and traction bronchiectasis.

When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on biopsy and exclusion of alternative causes of granulomatous disease (see Table 200-3).

[Table 200-2. Staging Sarcoidosis]

The diagnostic evaluation, therefore, requires the following:

- Selection of a biopsy site
- Exclusion of other causes of granulomatous disease
- Assessment of the severity and extent of disease to determine whether therapy is indicated

**Sites for biopsy:** Appropriate biopsy sites may be obvious from physical examination and initial assessment; peripheral lymph nodes, skin lesions, and conjunctivae are all easily accessible. However, bronchoscopic transbronchial biopsy is the diagnostic procedure of choice in patients with intrathoracic involvement because sensitivity is as high as 90% when an experienced clinician does the procedure. Video-assisted thoracoscopy can provide access to lung tissue when bronchoscopic transbronchial biopsy is nondiagnostic. Mediastinoscopy is sometimes done when hilar or mediastinal lymphadenopathy exists in the absence of pulmonary infiltrates, especially if lymphoma is in the differential diagnosis. However, even in patients with only mediastinal adenopathy on x-ray or CT, transbronchial biopsies are often diagnostic. Open lung biopsy provides another way to obtain tissue but requires general anesthesia and is now rarely necessary. Clinical and x-ray findings may be accurate enough for diagnosis in stage I disease or in stage II disease when biopsy is not possible.
Exclusion of other diagnoses: Exclusion of other diagnoses is critical, especially when symptoms and x-ray signs are minimal, because many other disorders and processes can cause granulomatous inflammation (see Table 200-3). Biopsy tissue should be cultured for fungi and mycobacteria. Exposure history to occupational (silicates, beryllium), environmental (moldy hay, birds, and other antigenic triggers of hypersensitivity pneumonitis), and infectious (TB, coccidioidomycosis, histoplasmosis) antigens should be explored. PPD skin testing should be done early in the assessment along with anergy controls.

Disease severity assessment: Severity is assessed with

- Pulmonary function tests
- Exercise pulse oximetry

Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DLCO) in advanced disease. Airflow obstruction also occurs and may suggest involvement of the bronchial mucosae. Pulse oximetry is often normal when measured at rest but may show effort desaturation with more extensive lung involvement. ABG analysis at rest and during exercise is more sensitive than pulse oximetry.

Recommended screening tests for extrapulmonary disease include

- ECG
- Slit-lamp ophthalmologic examination
- Routine blood tests to evaluate renal and hepatic function
- Serum Ca levels

Echocardiography, neuroimaging, lumbar puncture, bone x-rays or MRI, and electromyography may be appropriate when symptoms suggest cardiac, neurologic, or rheumatologic disorders. Abdominal CT with radiopaque dye is not routinely recommended but can provide evidence of hepatic or splenic involvement (eg, enlargement, hypolucent lesions).

Laboratory testing plays an adjunctive role in establishing the diagnosis and extent of organ involvement. CBC may show anemia, eosinophilia, or leukopenia. Serum Ca may be elevated because vitamin D analogs are produced by activated macrophages. BUN, creatinine, and liver function test results may be elevated in renal and hepatic sarcoidosis. Total protein may be elevated because of hypergammaglobulinemia. Elevated ESR is common but nonspecific. Measurement of Ca in a urine specimen collected over 24 h is recommended to exclude hypercalciuria, even in patients with normal serum Ca levels. Elevated serum ACE levels also suggest sarcoidosis but are nonspecific and may be low in patients taking ACE inhibitors or elevated in patients with various other conditions (eg, hyperthyroidism, Gaucher's disease, silicosis, mycobacterial disease, hypersensitivity pneumonitis). However, ACE levels may be useful for monitoring disease activity and therapeutic response in patients with confirmed sarcoidosis. Increased ACE levels in CSF may be useful for diagnosing CNS sarcoidosis.

Other adjunctive tests include bronchoalveolar lavage (BAL) and gallium scanning. BAL is used to help exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes > 10%), a CD4+/CD8+ ratio of > 3.5 in the lavage fluid cell differential, or both suggest the diagnosis in the proper clinical context. However, absence of these findings does not exclude sarcoidosis.

Whole-body gallium scanning may provide useful supportive evidence in the absence of tissue confirmation. Symmetric increased uptake in mediastinal and hilar nodes (lambda sign) and in lacrimal,
parotid, and salivary glands (panda sign) are patterns highly suggestive of sarcoidosis. A negative result in patients taking prednisone is unreliable.

**Prognosis**

Although spontaneous improvement is common, the manifestations of the disorder and its severity are highly variable, and many patients require corticosteroids some time during the course of their disease. Thus, serial monitoring for evidence of relapse is imperative. In about 90% of patients who have spontaneous remission, remission occurs within the first 2 yr after diagnosis; < 10% of these patients have relapses after 2 yr. Patients who do not experience remission within 2 yr are likely to have chronic disease.

Sarcoidosis is thought to be chronic in up to 30% of patients, and 10 to 20% experience permanent sequelae. The disease is fatal in 1 to 5% of patients, typically due to respiratory failure caused by pulmonary fibrosis, and less often due to pulmonary hemorrhage caused by aspergilloma. However, in Japan, infiltrative cardiomyopathy causing heart failure and arrhythmias is the most common cause of death.

Prognosis is worse for patients with extrapulmonary sarcoidosis and for blacks. Recovery occurs in 89% of whites and 76% of blacks with no extrathoracic disease and in 70% of whites and 46% of blacks with extrathoracic disease.

**Good prognostic signs** include

- Erythema nodosum
- Acute arthritis

**Poor prognostic signs** include

- Uveitis
- Lupus pernio
- Chronic hypercalcemia
- Neurosarcoidosis
- Nephrocalcinosis
- Myocardial disease
- Extensive pulmonary involvement

Little difference is demonstrable in long-term outcome between treated and untreated patients, and relapse is common when treatment ends.

**Treatment**

- Sometimes corticosteroids
- Rarely immunosuppressants

Because sarcoidosis often spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial x-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (eg, routine renal and liver function testing). Patients who require treatment regardless of stage include those with the following:
• Worsening symptoms
• Limitation of activity
• Markedly abnormal or deteriorating lung function
• Worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension)
• Heart, nervous system, or eye involvement
• Renal or hepatic insufficiency or failure
• Disfiguring skin or joint disease

Treatment is with corticosteroids. A standard protocol is prednisone 0.3 to 1 mg/kg po once/day depending on symptoms and severity of findings. Alternate-day regimens are also used; eg, prednisone 40 to 60 mg po once every other day. Although patients rarely require > 40 mg/day, higher doses may be needed to reduce complications in patients with ocular, myocardial, or neurologic disease. Response usually occurs within 2 to 4 wk, so symptoms and results of chest x-ray and pulmonary function tests may be reassessed between 4 and 12 wk. Chronic, insidious cases may respond more slowly. Corticosteroids are tapered to a maintenance dose (eg, prednisone ≤ 10 mg every other day if possible) after evidence of response and are continued for a minimum of 12 mo if improvement occurs. The optimal duration of treatment is unknown. Premature taper can result in relapse. The drug is slowly stopped if response is absent or equivocal. Corticosteroids can ultimately be stopped in most patients, but because relapse occurs up to 50% of the time, monitoring should be repeated, usually every 3 to 6 mo. Corticosteroid treatment should be resumed for recurrence of symptoms and signs, including dyspnea, arthralgia, fever, hepatic insufficiency, cardiac arrhythmia, CNS involvement, hypercalcemia, ocular disease uncontrolled by local drugs, and disfiguring skin lesions.

Data on use of inhaled corticosteroids for pulmonary sarcoidosis are not definitive, but some evidence suggests that this route of administration can relieve cough in patients with endobronchial involvement. Topical corticosteroids may be useful in some cases of dermatologic and ocular disease.

About 10% of patients requiring therapy are unresponsive to tolerable doses of a corticosteroid and should be given a 6-mo trial of methotrexate starting at 2.5 mg po once/wk and increasing in increments of 2.5 mg/wk to a total of 10 to 15 mg/wk as tolerated to keep the WBC count > 3000/μL. Initially, methotrexate and corticosteroids are both given; over 8 wk, the corticosteroid dose can be tapered and, in many cases, stopped. The maximal response to methotrexate, however, may take 6 to 12 mo. In such cases, prednisone must be tapered more slowly. Serial blood counts and liver enzyme tests should be done every 1 to 2 wk initially and then every 4 to 6 wk once a stable dose is achieved. Folate (1 mg po once/day) is recommended for patients treated with methotrexate.

Other drugs reported to be effective in small numbers of patients who are corticosteroid-resistant or who experience complicating adverse effects include azathioprine, cyclophosphamide, chlorambucil, chloroquine or hydroxychloroquine, thalidomide, pentoxifylline, and infliximab.

Hydroxychloroquine 200 mg po bid to tid can be as effective as corticosteroids for treating hypercalcemia or disfiguring skin sarcoidosis. Although immunosuppressants are often more effective in refractory cases, relapse is common after cessation.

No available drugs have consistently prevented pulmonary fibrosis.

Lung transplantation is an option for patients with end-stage pulmonary involvement, although disease may recur in the transplanted organ.
Chapter 201. Environmental Pulmonary Diseases

Introduction

Environmental pulmonary diseases result from inhalation of dusts, allergens, chemicals, gases, and environmental pollutants. The lungs are continually exposed to the external environment and are susceptible to a host of environmental diseases. Pathologic processes can involve any part of the lungs, including the airways (e.g., in occupational asthma, reactive airways dysfunction syndrome, or toxic inhalations), interstitium (e.g., or pneumoconioses in hypersensitivity pneumonitis), and pleura (e.g., in asbestos-related diseases).

Prevention of occupational and environmental pulmonary diseases centers on reducing exposure (primary prevention). Exposure can be limited by the use of

- Administrative controls (e.g., limiting the number of people exposed to hazardous conditions)
- Engineering controls (e.g., enclosures, ventilation systems, safe clean-up procedures)
- Product substitution (e.g., using safer, less toxic materials)
- Respiratory protection devices (e.g., respirator, dust mask, gas mask)

Many clinicians erroneously assume that a patient who has used a respirator or another respiratory protection device has been well protected. Although respirators do afford a degree of protection, especially when fresh air is provided by tank or air hose, the benefit is limited and idiosyncratic. When recommending use of a respirator, clinicians should consider several factors. Workers with cardiovascular disease may be unable to carry out jobs that require strenuous work, especially if they must wear a self-contained breathing apparatus (tank). Respirators that are tight-fitting and that require the wearer to draw air through filter cartridges can increase the work of breathing, which can be especially difficult for patients with asthma, COPD, or interstitial lung diseases.

Medical surveillance is a form of secondary prevention. Workers can be offered medical tests that identify disorders early when treatment might help reduce long-term consequences.

Air Pollution-Related Illness

The major components of air pollution in developed countries are nitrogen dioxide (from combustion of fossil fuels), ozone (from the effect of sunlight on nitrogen dioxide and hydrocarbons), and suspended solid or liquid particles. Indoors, passive smoking is an additional source, as is burning of biomass fuel in developing countries (e.g., for cooking and heating).

High levels of air pollution can adversely affect lung function and trigger asthma and COPD exacerbations. People living in areas with high traffic, especially when stagnant air is created by thermal inversions, are at particular risk. All of the so-called criteria air pollutants (oxides of nitrogen, oxides of sulfur, ozone, carbon monoxide, lead, particulates), except carbon monoxide and lead, cause airway hyperreactivity. Long-term exposure may increase respiratory infections and symptoms in the general population, especially in children.

Ozone, which is the major component of smog, is a strong respiratory irritant and oxidant. Ozone levels tend to be highest in the summer and in the late morning and early afternoon. Short-term exposures can cause dyspnea, chest pain, and airways reactivity. Children who regularly participate in outdoor sports during days on which ozone pollution is high are more likely to develop asthma. Long-term exposure to ozone produces a small, permanent decrease in lung function.

Oxides of sulfur, resulting from combustion of fossil fuels that are high in sulfur content, can create acid aerosols with high solubility, which are likely to be deposited in the upper airways. Sulfur oxides can induce airway inflammation, possibly increasing the risk of chronic bronchitis as well as inducing bronchoconstriction.
Particulate air pollution is a complex mixture, derived from fossil fuel combustion (especially diesel). The particles can have both local and systemic inflammatory effects, suggesting an explanation for their impact on both pulmonary and cardiovascular health. So-called PM2.5 (particulate matter < 2.5 μm diameter) produce a greater inflammatory response per mass than do larger particles. Data suggest that particulate air pollution increases death rates from all causes, especially cardiovascular and respiratory illness.

Air pollution data have raised concerns regarding the potential health effects of even smaller particles, so-called nanoparticles, but clinical evidence of disorders related to exposure to nanoparticles has yet to be reported.

Asbestos-Related Disorders

Asbestos-related disorders are caused by inhalation of asbestos fibers. The disorders include asbestosis, lung carcinoma, nonmalignant pleural plaque formation and thickening, benign pleural effusions, and mesothelioma. Asbestosis and mesothelioma both cause progressive dyspnea, as do extensive effusions and plaques. Diagnosis is based on history and chest x-ray or CT findings and, in the case of cancer, tissue biopsy. Treatment is supportive, except for cancer, which may require surgery, chemotherapy, or both.

Asbestos is a family of naturally occurring silicates whose heat-resistant and structural properties made it useful for inclusion in construction and shipbuilding materials, automobile brakes, and some textiles. Chrysotile (a serpentine fiber), crocidolite, and amosite (amphibole, or straight fibers) are the 3 main types of asbestos that cause disease. Asbestos can affect the lung, the pleura, or both.

Asbestosis

Asbestosis is a form of interstitial pulmonary fibrosis caused by asbestos exposure.

Asbestosis is a much more common consequence of asbestos exposure than cancer. Shipbuilders, textile and construction workers, home remodelers, workers who do asbestos abatement, and miners who are exposed to asbestos fibers are among the many workers at risk. Secondhand exposure may occur among family members of exposed workers and among people who live close to mines.

Pathophysiology

Alveolar macrophages attempting to engulf inhaled fibers release cytokines and growth factors that stimulate inflammation, oxidative injury, collagen deposition, and ultimately fibrosis. Asbestos fibers may also be directly toxic to lung tissue. Risk of disease is generally related to duration and intensity of exposure and type, length, and thickness of inhaled fibers.

Symptoms and Signs

Asbestosis is initially asymptomatic but can cause progressive dyspnea, nonproductive cough, and fatigue. The disorder progresses in > 10% of patients even after cessation of exposure. Advanced asbestosis may cause clubbing, dry bibasilar crackles, and, in severe cases, symptoms and signs of right ventricular failure (cor pulmonale).

Diagnosis

- Chest x-ray, preferably chest CT
- Pulmonary function tests
- Sometimes bronchoalveolar lavage or lung biopsy

Diagnosis is based on history of exposure and chest x-ray or chest CT. Chest x-ray shows linear reticular
Opacities signifying fibrosis, usually in the peripheral lower lobes. Opacities are often bilateral and are often accompanied by pleural changes (see p. 1974). Honeycombing signifies more advanced disease, which may involve the mid and lower lung fields. As with silicosis, severity is graded on the International Labor Organization scale (International Classification of Radiographs of Pneumoconioses) based on size, shape, location, and profusion of opacities. In contrast to silicosis, asbestosis produces reticular opacities with a lower lobe predominance. Hilar and mediastinal adenopathy and nodular opacities are uncharacteristic and suggest a different diagnosis. Chest x-ray is insensitive; thin-section chest CT is useful when asbestosis is a likely diagnosis. CT is also superior to chest x-ray in identifying pleural abnormalities.

Pulmonary function tests, which may show reduced lung volumes and diffusing capacity for carbon monoxide (DLCO), are nonspecific but help characterize changes in lung function over time. Pulse oximetry measured at rest and with exertion is nonspecific but sensitive for detecting asbestos-induced impairment.

Bronchoalveolar lavage or lung biopsy is indicated only when noninvasive measures fail to provide conclusive diagnosis; demonstration of asbestos fibers indicates asbestosis in people with pulmonary fibrosis, although such fibers can occasionally be found in lungs of exposed people without disease and may not be present in specimens from patients with asbestosis. Thus, demonstration of asbestos fibers may be helpful but is not necessary for diagnosis.

**Prognosis**

Prognosis varies; many patients have no or mild symptoms and do well, whereas some develop progressive dyspnea and a few develop respiratory failure, right ventricular failure, and cancer.

Lung cancer (usually non-small cell lung carcinoma) develops in patients with asbestosis at 8 to 10 times the rate of those without asbestosis and is especially common among workers exposed to amphibole fibers, although all forms of inhaled asbestos have been associated with an elevated cancer risk. Asbestos and smoking have a synergistic effect on lung cancer risk (see p. 2005).

**Treatment**

- Supportive care

No specific treatment exists. Early detection of hypoxemia and right ventricular failure leads to use of supplemental O₂ and treatment of heart failure. Pulmonary rehabilitation can be helpful for patients with impairment.

**Prevention**

Preventive measures include eliminating exposure, asbestos abatement in occupational and nonoccupational settings, smoking cessation, and pneumococcal and influenza vaccination. Smoking cessation is particularly important in light of the multiplicative risk of lung cancer in patients who have both tobacco smoke and asbestos exposures.

**Mesothelioma**

Pleural mesothelioma is the only known pleural cancer and is caused by asbestos exposure in nearly all cases.

Asbestos workers have up to a 10% lifetime risk of developing the disorder, with an average latency of 30 yr. Risk is independent of smoking. Mesothelioma can spread locally, or it can metastasize to the hilar and mediastinal lymph nodes, pericardium, diaphragm, peritoneum, liver, adrenals, or kidneys and, rarely, the tunica vaginalis of the testis.

**Symptoms and Signs**
Patients most often present with dyspnea and nonpleuritic chest pain. Constitutional symptoms are uncommon at presentation. Invasion of the chest wall and other adjacent structures may cause severe pain, hoarseness, dysphagia, Horner’s syndrome, brachial plexopathy, or ascites.

**Diagnosis**

- Chest x-ray
- Pleural fluid cytology or pleural biopsy
- Sometimes video-assisted thorascopic surgery (VATS) or thoracotomy
- Staging with chest CT, mediastinoscopy, and MRI or sometimes with PET and bronchoscopy

The pleural form of mesothelioma, which represents > 90% of all cases (the other 10% include pericardial and peritoneal mesotheliomas), appears on x-ray as diffuse unilateral or bilateral pleural thickening that appears to encase the lungs, usually producing blunting of the costophrenic angles. Pleural effusions are present in 95% of cases and are typically unilateral, large, and hemorrhagic. Diagnosis is based on pleural fluid cytology or pleural biopsy. If diagnosis is uncertain after these procedures, biopsy by VATS or thoracotomy is done.

Staging is done with chest CT, mediastinoscopy, and MRI. Sensitivity and specificity of MRI and CT are comparable, although MRI is helpful in determining tumor extension into the spine or spinal cord. PET may have better sensitivity and specificity for distinguishing benign from malignant pleural thickening. Bronchoscopy should be done to exclude coexisting endobronchial lung cancers. Increased levels of hyaluronidase in pleural fluid are suggestive but not diagnostic of mesothelioma. Soluble mesothelin-related proteins released into the serum by mesothelial cells are being studied as possible tumor markers for disease detection and monitoring, but the false-positive rate may limit their effectiveness.

**Prognosis**

Mesothelioma remains an incurable cancer, and long-term survival is uncommon. Surgery to remove the pleura, ipsilateral lung, phrenic nerve, hemidiaphragm, and pericardium combined with chemotherapy or radiation therapy may be considered, although it does not substantially change prognosis or survival time. No treatment substantially prolongs survival. Survival from time of diagnosis averages 8 to 15 mo, depending on the location and cell type. A few patients, usually younger patients with shorter duration of symptoms, have a more favorable prognosis, sometimes surviving for several years after diagnosis.

**Treatment**

- Supportive care
- Pleurodesis or pleurectomy for pleural effusions and relief of dyspnea
- Analgesia with opioids and sometimes radiation therapy
- Chemotherapy for tumor shrinkage and symptom relief
- Experimental therapies

Complete surgical resection usually is not feasible. Combination pemetrexed (an antifolate antimetabolite) and cisplatin shows promise but warrants further study.

The major focus of treatment is supportive care and relief of pain and dyspnea. Given the diffuse nature of the disorder, radiation therapy is usually unsuitable except to treat localized pain or needle-tract metastases. It is not generally used for treatment of nerve root pain. Pleurodesis or pleurectomy can be used to help reduce dyspnea caused by pleural effusions. Adequate analgesia is important but difficult to
achieve. Usually, opioids, both transdermal and delivered via indwelling epidural catheters, are used. Chemotherapy using cisplatin and gemcitabine relieves symptoms in most cases and sometimes decreases tumor size. Multimodality therapies are advocated by some authorities. Intrapleural injection of granulocyte-macrophage colony-stimulating factor or interferon-γ 1b, IV ranpirnase (a ribonuclease), and gene therapies are under study.

Other Asbestos-Related Pleural Disease

Pleural disease, a hallmark of asbestos exposure, includes formation of pleural plaques, calcification, thickening, rounded atelectasis, adhesions, effusion, and mesothelioma (see p. 1973).

Pleural disease causes effusion but few symptoms. All pleural changes are diagnosed by chest x-ray or CT, though chest CT is more sensitive than chest x-ray for detecting pleural disorders. Treatment is rarely needed except for cancer.

Discrete plaques, which occur in up to 60% of workers exposed to asbestos, typically affect the bilateral parietal pleurae between the 5th and 9th ribs and adjacent to the diaphragm. Plaque calcification is common and can lead to misdiagnosis of severe pulmonary disease when radiographically superimposed on lung fields. CT can distinguish pleural from parenchymal disease in this setting. Fat stripes may be mistaken for pleural plaques on chest x-ray. CT can distinguish pleural disease from fat.

Diffuse thickening affects visceral as well as parietal pleurae. It may be an extension of pulmonary fibrosis from parenchyma to the pleurae or a nonspecific reaction to pleural effusion. With or without calcification, pleural thickening can cause a restrictive defect.

Rounded atelectasis is a benign manifestation of pleural thickening in which invagination of pleura into the parenchyma can entrap lung tissue, causing atelectasis. On chest x-ray and CT, it typically appears as a curvilinear cicatricial mass, often in the lower lung zones, and can be confused with a pulmonary cancer.

Pleural effusions occur but are less common than the other pleural changes they accompany. These benign effusions are usually bilateral, exudative, and often hemorrhagic. They typically resolve spontaneously (see p. 1995).

Beryllium Disease

(Berylliosis)

Acute beryllium disease and chronic beryllium disease are caused by inhalation of dust or fumes from beryllium compounds and products. Acute beryllium disease is now rare; chronic beryllium disease is characterized by formation of granulomas throughout the body, especially in the lungs, intrathoracic lymph nodes, and skin. Chronic beryllium disease causes progressive dyspnea, cough, and fatigue. Diagnosis is by history, beryllium lymphocyte proliferation test, and biopsy. Treatment is with corticosteroids.

Etiology

Beryllium exposure is a common but under-recognized cause of illness in many industries, including beryllium mining and extraction, alloy production, metal alloy machining, electronics, telecommunications, nuclear weapon manufacture, defense, aircraft, automotive, aerospace, and metal scrap, computer, and electronics recycling. Because small amounts of beryllium are toxic and are added to many copper, aluminum, nickel, and magnesium alloys, workers are often unaware of their exposure and its risks.

Pathophysiology

Acute beryllium disease is a chemical pneumonitis causing diffuse parenchymal inflammatory infiltrates and nonspecific intra-alveolar edema. Other tissues (eg, skin and conjunctivae) may be affected. Acute
Chronic beryllium disease remains a common illness in industries that use beryllium and beryllium alloy. It differs from most pneumoconioses in that it is a cell-mediated hypersensitivity disease. Beryllium is presented to CD4+ T lymphocytes by antigen-presenting cells, principally in HLA-DP molecules. T lymphocytes in the blood, lungs, or other organs, in turn, recognize the beryllium, proliferate, and form T-lymphocyte clones. These clones then release proinflammatory cytokines, such as tumor necrosis factor-α, IL-2, and interferon-γ. These cytokines amplify the immune response, resulting in formation of mononuclear cell infiltrates and noncaseating granulomas in target organs where beryllium has deposited. On average, about 2% to 6% of beryllium-exposed people develop beryllium sensitization (defined by positive blood lymphocyte proliferation to beryllium salts in vitro), with most progressing to disease. In certain high-risk groups, such as beryllium metal and alloy machinists, chronic beryllium disease prevalence is > 17%. Workers with bystander exposures, such as secretaries and security guards, also develop sensitization and disease but at lower rates. The typical pathologic consequence is a diffuse pulmonary, hilar, and mediastinal lymph node granulomatous reaction that is histologically indistinguishable from sarcoidosis. Early granuloma formation with mononuclear and giant cells can also occur. Many lymphocytes are found when cells are washed from the lungs (bronchoalveolar lavage [BAL]) during bronchoscopy. These T lymphocytes proliferate when exposed to beryllium in vitro, much as the blood cells do (a test called beryllium lymphocyte proliferation test [BeLPT]).

**Symptoms and Signs**

Patients with chronic beryllium disease often have dyspnea, cough, weight loss, and a variable chest x-ray pattern, typically showing nodular opacities in the mid and upper lung zones, frequently with hilar and mediastinal adenopathy. Patients complain of insidious and progressive exertional dyspnea, cough, chest pain, weight loss, night sweats, and fatigue. Symptoms may develop within months of first exposure or > 40 yr after exposure has ceased. Some people remain asymptomatic.

**Diagnosis**

- Beryllium lymphocyte proliferation test (using blood or bronchoalveolar lavage cells)
- Chest x-ray or CT

Diagnosis depends on a history of exposure, the appropriate clinical manifestations, and an abnormal blood or BAL BeLPT or both. BAL BeLPT is highly sensitive and specific, helping to distinguish chronic beryllium disease from sarcoidosis and other forms of diffuse pulmonary disease. Chest x-ray may be normal or show diffuse infiltrates that can be nodular, reticular, or have a hazy ground-glass appearance, often with hilar adenopathy resembling the pattern seen in sarcoidosis. A miliary pattern also occurs. High-resolution CT is more sensitive than x-ray, although cases of biopsy-proven disease occur even in people with normal imaging tests.

**Prognosis**

Acute beryllium disease can be fatal, but prognosis is usually excellent unless progression to chronic beryllium disease occurs. Chronic beryllium disease often results in progressive loss of respiratory function. Early abnormalities include air flow obstruction and decreased oxygenation on ABG at rest and during exercise testing. Decreased diffusing capacity for carbon monoxide (DLCO) and restriction appear later. Pulmonary hypertension and right ventricular failure develop in about 10% of cases, with death due to cor pulmonale. Beryllium sensitization progresses to chronic beryllium disease at a rate of about 6%/yr after initial detection through workplace medical surveillance programs. Subcutaneous granulomatous nodules caused by inoculation with beryllium splinters or dust usually persist until excised.

**Treatment**

- Corticosteroids
In acute beryllium disease, sometimes mechanical ventilation

In chronic beryllium disease, sometimes supplemental O₂, pulmonary rehabilitation, and treatment for right ventricular failure

In end-stage chronic beryllium disease, sometimes lung transplantation

In acute disease, the lungs often become edematous and hemorrhagic. Mechanical ventilation is necessary in severely affected patients.

Some patients with chronic beryllium disease never require treatment because the disease progresses relatively slowly. When needed, treatment is with corticosteroids, which decrease symptoms and improve oxygenation. Treatment is generally started only in patients with significant symptoms and evidence of abnormal gas exchange or evidence of an accelerated decline in lung function or oxygenation. In symptomatic patients with abnormal pulmonary function, prednisone 40 to 60 mg po once/day or every other day is given for 3 to 6 mo. Then, measures of pulmonary physiology and gas exchange are repeated to document a response to therapy, and the dose is gradually tapered to the lowest dose that maintains symptomatic and objective improvement (usually about 10 to 15 mg once/day or every other day). Lifelong treatment with corticosteroids is usually required. There is anecdotal evidence that the addition of methotrexate (10 to 25 mg po once/wk) reduces the need for corticosteroids as it does in sarcoidosis.

Spontaneous remission of chronic beryllium disease is rare. In patients with end-stage disease, lung transplantation can be lifesaving. Other supportive measures, such as supplemental O₂ therapy, pulmonary rehabilitation, and drugs for treatment of right ventricular failure, are used as needed.

Prevention

Industrial dust suppression is the basis for preventing beryllium exposure. Exposures must be reduced to levels that are as low as reasonably achievable—preferably more than 50-fold below current Occupational Safety and Health Administration (OSHA) standards—to reduce the risk of sensitization and chronic beryllium disease. Medical surveillance, using blood BeLPT and chest x-ray, is recommended for all exposed workers, including those with indirect contact. Both acute and chronic disease must be promptly recognized and affected workers removed from further beryllium exposure.

Building-Related Illnesses

Building-related illnesses (BRIs) are a heterogeneous group of disorders whose etiology is linked to the environment of modern airtight buildings. Such buildings are characterized by sealed windows and dependence on heating, ventilation, and air conditioning systems for circulation of air. Most cases occur in nonindustrial office buildings, but cases can occur in apartment buildings, single-family homes, schools, museums, and libraries.

BRIs can be specific or nonspecific.

Specific BRIs: Specific BRIs are those for which a link between building-related exposure and illness is proved. Examples include

- *Legionella* infection (see p. 1253)
- Occupational asthma (see p. 1979)
- Hypersensitivity pneumonitis (see p. 1956)
- Inhalational fever

Inhalational fever is a febrile reaction caused by exposure to organic aerosols or dusts. Names used to describe this type of BRI include humidifier fever, grain fever, swine confinement fever, and mycotoxicosis.
depending on the causative agent. Metal fumes and polymer fumes can also cause febrile illness. The term organic dust toxic syndrome (ODTS) has been used to encompass the subacute febrile and respiratory reaction to organic dust that is typically highly contaminated with bacterial endotoxin. Toxic pneumonitis is a commonly used but less specific term.

**Humidifier fever** occurs in nonindustrial buildings as a consequence of humidifiers or other types of ventilation units serving as a reservoir for the growth of bacteria or fungi and as a method of aerosolizing these contaminants. The disorder usually manifests as low-grade fever, malaise, cough, and dyspnea. Improvement after removal from exposure (eg, weekend away from the office building) is often one of the first indications of etiology. Humidifier fever has an acute onset and is self-limiting (usually 2 to 3 days). Physical signs may be absent or subtle. Clusters of cases are common.

Unlike immunologically mediated conditions (eg, hypersensitivity pneumonitis, building-related asthma), inhalational fevers do not require a period of sensitization. The disorder can occur after initial exposure. Acute episodes do not generally require treatment apart from antipyretics and removal from the contaminated environment. If symptoms persist, evaluation may be required to rule out infection, hypersensitivity pneumonitis, or other conditions. Biologic sampling to detect airborne microbials in the work environment can be costly and time consuming but is sometimes necessary to document the source of contaminated air. Inhalational fevers of all types are usually prevented by good maintenance of ventilation systems.

**Nonspecific BRIs:** Nonspecific BRIs are those for which a link between building-related exposure and illness is more difficult to prove. The term sick building syndrome has been used to refer to illnesses that occur in clusters within a building and that cause often nonspecific symptoms, including

- Itchy, irritated, dry or watery eyes
- Rhinorrhea or nasal congestion
- Throat soreness or tightness
- Dry itchy skin or unexplained rashes
- Headache, lethargy, or difficulty concentrating

Some building-related factors appear to account for symptoms in some instances. These factors include higher building temperature, higher humidity, and poor ventilation, typically with a failure to incorporate sufficient fresh air from outdoors. Patient factors, including female sex, history of atopy, increased attention to body sensations, worry about the meaning of symptoms, anxiety, depression, and occasionally mass hysteria, also seem to underlie experience of symptoms.

**Byssinosis**

**Byssinosis is a form of reactive airways disease characterized by bronchoconstriction in cotton, flax, and hemp workers.** The etiologic agent is unknown. Symptoms are chest tightness and dyspnea that worsen on the first day of the work week and subside as the week progresses. Diagnosis is based on history and pulmonary function test findings. Treatment includes avoidance of exposure and use of asthma drugs.

**Etiology**

Byssinosis occurs almost entirely in workers who contact unprocessed, raw cotton, especially those who are exposed to open bales or who work in cotton spinning or in the card room. Byssinosis can occur after acute exposure but usually occurs in workers with a history of chronic exposure. Evidence suggests that some agent in the cotton bract leads to bronchoconstriction. Although bacterial endotoxin is a likely cause, the absence of similar symptoms in other settings in which workers are exposed to endotoxin leaves some uncertainty. Prolonged exposure to cotton dust was once thought to cause emphysema, a theory now disproved. Chronic bronchitis symptoms are common among people exposed to cotton dust.
Symptoms and Signs

Symptoms are chest tightness and dyspnea that lessen with repeated exposure. Symptoms develop on the first day of work after a weekend or vacation and diminish or disappear by the end of the week. With repeated exposure over a period of years, chest tightness tends to return and persist through midweek and occasionally to the end of the week or as long as the person continues to work. This typical temporal pattern distinguishes byssinosis from asthma.

Signs of acute exposure are tachypnea and wheezing. Patients with more chronic exposure may have crackles.

Diagnosis

Diagnosis is based on history and pulmonary function tests that show typical airflow obstruction and a reduction in ventilatory capacity, especially if measured at the start and end of a first work shift. Hyperresponsiveness to methacholine is also often observed. Surveillance measures, including symptom reporting and spirometry in textile workers, can aid in early detection.

Treatment

Treatment includes avoidance or reduction of exposure and use of asthma drugs.

Coal Workers’ Pneumoconiosis

(Anthracosis; Black Lung Disease; Coal Miner's Pneumoconiosis)

Coal workers' pneumoconiosis (CWP) is caused by inhalation of coal dust. Deposition of dust produces dust-laden macrophages around bronchioles (coal macules), occasionally causing focal bronchiolar emphysema. CWP usually causes no symptoms but can progress to progressive massive fibrosis (PMF) with impaired lung function. Diagnosis is based on history and chest x-ray findings. Treatment is generally supportive.

Etiology

CWP is caused by chronic inhalation of dust from high-carbon coal (anthracite and bituminous) and rarely graphite, typically over ≥ 20 yr. Inhalation of silica contained in coal may also contribute to clinical disease.

Pathophysiology

Alveolar macrophages engulf the dust, release cytokines that stimulate inflammation, and collect in lung interstitium around bronchioles and alveoli (coal macules). Coal nodules develop as collagen accumulates, and focal emphysema develops as bronchiole walls weaken and dilate. Fibrosis can occur but is usually limited to areas adjacent to coal macules. Distortion of lung architecture, airflow obstruction, and functional impairment are usually mild but can be highly destructive in some patients.

Two forms of CWP are described:

• Simple, with individual coal macules

• Complicated, with coalescence of macules and PMF

Patients with simple CWP develop PMF at a rate of about 1 to 2%. In PMF, nodules coalesce to form black, rubbery parenchymal masses usually in the upper posterior fields. The masses may encroach on and destroy vascular supply and airways or may cavitate. PMF can develop and progress even after exposure to coal dust has ceased. Despite the similarity of coal-induced PMF and conglomerate silicosis, the development of PMF in coal workers is unrelated to the silica content of the coal.
Complications: An association between CWP and features of rheumatoid arthritis (RA) is well-described. It is unclear whether CWP predisposes miners to developing RA, whether RA takes on a unique form in patients with CWP, or whether RA alters the response of miners to coal dust. Multiple rounded nodules in the lung appearing over a relatively short time (Caplan's syndrome) represent an immunopathologic response related to rheumatoid diathesis. Histologically, they resemble rheumatoid nodules but have a peripheral region of more acute inflammation. Patients with CWP are at a slightly increased risk of developing active TB and non-TB mycobacterial infections. Weak associations have been reported between CWP and progressive systemic sclerosis and stomach cancer.

Symptoms and Signs

CWP does not usually cause symptoms. Most chronic pulmonary symptoms in coal miners are caused by other conditions, such as industrial bronchitis due to coal dust or coincident emphysema due to smoking. Cough can be chronic and problematic in patients even after they leave the workplace, even in those who do not smoke.

PMF causes progressive dyspnea. Occasionally, patients cough up black sputum (melanoptysis), which occurs when PMF lesions rupture into the airways. PMF often progresses to pulmonary hypertension with right ventricular and respiratory failure.

Diagnosis

- History of exposure to coal dust
- Chest CT or chest x-ray

Diagnosis is based on a history of exposure and chest x-ray or chest CT appearance. In patients with CWP, x-ray or CT reveals diffuse, small, rounded opacities or nodules. The finding of at least one opacity > 10 mm suggests PMF. The specificity of the chest x-ray for PMF is low because up to one third of the lesions identified as being PMF turn out to be cancers, scars, or other disorders. Chest CT is more sensitive than chest x-ray for detecting coalescing nodules, early PMF, and cavitation.

Pulmonary function tests are nondiagnostic but are useful for characterizing lung function in patients in whom obstructive, restrictive, or mixed defects may develop. Because abnormalities of gas exchange occur in some patients with extensive simple CWP and in those with complicated CWP, baseline and periodic measures of diffusing capacity for carbon monoxide (DLCO) and ABG at rest and during exercise are recommended.

Because patients with CWP often have had exposure to both silica dust and coal dust, surveillance for TB is usually done. Patients with CWP should have annual tuberculin skin testing. In those with positive test results, sputum culture and cytology, CT, and bronchoscopy may be needed to confirm TB.

Treatment

- Sometimes supplemental O₂ and pulmonary rehabilitation
- Restriction from further exposure

Treatment is rarely necessary in simple CWP, although smoking cessation and TB surveillance are recommended. Patients with pulmonary hypertension, hypoxemia, or both are given supplemental O₂ therapy. Pulmonary rehabilitation can help more severely affected workers carry out activities of daily living. Workers with CWP, especially those with PMF, should be restricted from further exposure, especially to high concentrations of dust. TB is treated in accordance with current recommendations (see p. 1306).

Prevention
Preventive measures include eliminating exposure, stopping smoking, and giving pneumococcal and influenza vaccinations. CWP can be prevented by suppressing coal dust at the coal face. Despite long-standing regulations, exposures continue to occur in the mining trade. Respiratory masks provide only limited protection.

**Occupational Asthma**

**Occupational asthma** is reversible airway obstruction that develops after months to years of sensitization to an allergen encountered in the workplace. Symptoms are dyspnea, wheezing, cough, and, occasionally, upper respiratory allergic symptoms. Diagnosis is based on occupational history, including assessment of job activities, allergens in the work environment, and a temporal association between work and symptoms. Allergen skin testing and provocative inhalational challenge may be used in specialized centers but are usually unnecessary. Treatment involves removing the person from the work environment and using asthma drugs as needed.

Occupational asthma is development of asthma in a worker who has no previous history of asthma. Symptoms typically develop over months to years because of sensitization to an allergen encountered in the workplace. Once sensitized, the worker invariably responds to much lower concentrations of the allergen than that which initiated the response. Occupational asthma differs from occupationally aggravated asthma, which is an exacerbation or worsening of asthma in workers with preexisting asthma by single or repeated workplace exposures to pulmonary irritants such as dusts and fumes. Occupationally aggravated asthma, which is more common than occupational asthma, generally subsides with reduction of exposure and appropriate asthma treatment. It has a better prognosis and does not require the same level of clinical investigation of specific triggering allergens.

Several other airway diseases caused by inhalational workplace exposures can be distinguished from occupational and occupationally aggravated asthma.

In **reactive airways dysfunction syndrome** (RADS), which is nonallergenic, people with no history of asthma develop persistent, reversible airway obstruction after acute overexposure to irritant dust, fumes, or gas. Airway inflammation persists even after removal of the acute irritant, and the syndrome is indistinguishable from asthma.

In **reactive upper airways syndrome**, upper airway (ie, nasal, pharyngeal) mucosal symptoms develop after acute or repeated exposure to airways irritants.

In **irritant-associated vocal cord dysfunction**, which mimics asthma, abnormal apposition and closure of the vocal cords, especially during inspiration, occur after acute irritant inhalation.

In **industrial bronchitis** (irritant-induced chronic bronchitis), bronchial inflammation causes cough after acute or chronic irritant inhalation.

In **bronchiolitis obliterans**, bronchiolar damage occurs after acute inhalation of gases (eg, anhydrous ammonia). The 2 major forms are proliferative and constrictive. The constrictive form is more common and may or may not be associated with other forms of diffuse lung injury. Recently, cases of bronchiolitis obliterans have been reported in workers exposed to the chemical diacetyl during the manufacture of butter-flavored microwave popcorn. So-called popcorn workers' lung may occur in workers exposed to other flavorings and possibly in some consumers exposed to this chemical.

**Etiology**

Occupational asthma is caused by both immune- and non-immune-mediated mechanisms. Immune mechanisms involve IgE- and non-IgE-mediated hypersensitivity to workplace allergens. Hundreds of occupational allergens exist, ranging from low molecular weight chemicals to large proteins. Examples include grain dust, proteolytic enzymes used in detergent manufacturing, red cedar wood, isocyanates, formalin (rarely), antibiotics (eg, ampicillin, spiramycin), epoxy resins, and tea.
Non-immune-mediated inflammatory mechanisms cause direct irritation of the respiratory epithelium and upper airway mucosae.

**Symptoms and Signs**

Symptoms include shortness of breath, chest tightness, wheezing, and cough, often with upper respiratory symptoms such as sneezing, rhinorrhea, and tearing. Upper airway and conjunctival symptoms may precede the typical asthmatic symptoms by months or years. Symptoms may develop during work hours after specific dust or vapor exposure but often do not become apparent until several hours after leaving work, thereby making the association with occupational exposure less obvious. Nocturnal wheezing may be the only symptom. Often, symptoms disappear on weekends or during vacations, although with ongoing exposure temporal exacerbations and relief become less apparent.

**Diagnosis**

- Occupational history of allergen exposure
- Immunologic testing
- Sometimes inhalation challenge test

Diagnosis depends on recognizing the link between workplace allergens and asthma. Diagnosis is suspected on the basis of an occupational history of allergen exposure. A materials safety data sheet can be used to identify potential allergens, and substances listed can be used to direct immunologic testing (eg, skin prick, puddle, or patch testing) of suspected antigens to demonstrate that an agent in the workplace is affecting a person. An increase in bronchial hyperresponsiveness after exposure to the suspected antigen is also helpful in making the diagnosis.

In difficult cases, a carefully controlled inhalation challenge test done in the laboratory confirms the cause of the airway obstruction. Such procedures should be done only at centers experienced in inhalation challenge testing and capable of monitoring and treating the sometimes severe reactions that can occur. Pulmonary function tests or peak expiratory flow measurements that show decreasing airflow during work are further evidence that occupational exposure is causative. Methacholine challenge tests can be used to establish the degree of airway hyperreactivity. Sensitivity to methacholine may decrease after exposure to the occupational allergen has ceased.

Differentiation from idiopathic asthma is generally based on the pattern of symptoms, demonstration that allergens are present in the workplace, and the relationship between exposure to allergens and symptoms and physiologic worsening.

**Treatment**

Treatment is the same as that for idiopathic asthma, including inhaled bronchodilators and corticosteroids (see p. 1873). Treatment should also include removal of the patient from ongoing exposure to the causative agent.

**Prevention**

Dust suppression is essential. However, elimination of all instances of sensitization and clinical disease may not be possible. Once sensitized, patients with occupational asthma may react to extremely low levels of airborne allergen. Patients who return to environments in which the allergen persists generally have a poorer prognosis, with more respiratory symptoms, more abnormal lung physiology, a greater need for drugs, and more frequent and severe exacerbations. Whenever possible, a symptomatic person should be removed from a setting known to cause symptoms. If exposure continues, symptoms tend to persist. Occupational asthma can sometimes be cured if it is diagnosed early and exposure ceases.

**Silicosis**
Silicosis is caused by inhalation of unbound (free) crystalline silica dust and is characterized by nodular pulmonary fibrosis. Chronic silicosis initially causes no symptoms or only mild dyspnea but over years can advance to involve most of the lung and cause dyspnea, hypoxemia, pulmonary hypertension, and respiratory impairment. Diagnosis is based on history and chest x-ray findings. No effective treatment exists except supportive care and, for severe cases, lung transplantation.

Etiology

Silicosis, the oldest known occupational pulmonary disease, is caused by inhalation of tiny particles of silicon dioxide in the form of unbound (free) crystalline silica (usually quartz) or, less commonly, by inhalation of silicates, minerals containing silicon dioxide bound to other elements, such as talc. Workers at greatest risk are those who move or blast rock and sand (miners, quarry workers, stonecutters) or who use silica-containing rock or sand abrasives (sandblasters; glass makers; foundry, gemstone, and ceramic workers; potters). Coal miners are at risk of mixed silicosis and coal workers' pneumoconiosis (see p. 1977).

Factors that influence the likelihood of development of silicosis include

- Duration and intensity of exposure
- Form of silicon (exposure to the crystalline form poses greater risk than the bound form)
- Surface characteristics (exposure to the uncoated form poses greater risk than the coated form)
- Rapidity of inhalation after the dust is fractured and becomes airborne (exposure immediately after fracturing poses greater risk than delayed exposure)

Pathophysiology

Alveolar macrophages engulf inhaled free silica particles and enter lymphatics and interstitial tissue. The macrophages cause release of cytokines (tumor necrosis factor-α, IL-1), growth factors (tumor growth factor-β), and oxidants, stimulating parenchymal inflammation, collagen synthesis, and, ultimately, fibrosis.

When the macrophages die, they release the silica into interstitial tissue around the small bronchioles, causing formation of the pathognomonic silicotic nodule. These nodules initially contain macrophages, lymphocytes, mast cells, fibroblasts with disorganized patches of collagen, and scattered birefringent particles that are best seen by polarized light microscopy. As they mature, the centers of the nodules become dense balls of fibrotic scar with a classic onion-skin appearance and are surrounded by an outer layer of inflammatory cells. In low-intensity or short-term exposures, these nodules remain discrete and do not compromise lung function (simple chronic silicosis). But with higher-intensity or more prolonged exposures (complicated chronic silicosis), these nodules coalesce and cause progressive fibrosis and reduction of lung volumes (total lung capacity, ventilatory capacity) on pulmonary function tests, or they coalesce, sometimes forming large conglomerate masses (called progressive massive fibrosis).

Chronic silicosis is the most common form of the disorder and generally develops only after exposure over decades.

Acute silicosis and the rarer accelerated silicosis are caused by intense silica dust exposure over short periods (several months or years). Mononuclear cells infiltrate alveolar septa, and alveolar spaces fill with a proteinaceous material that stains periodic acid-Schiff (PAS) positive and is similar to that found in pulmonary alveolar proteinosis (silicoproteinosis—see p. 1962). The occupational history of acute exposure is needed to distinguish silicoproteinosis from the idiopathic variety.

Conglomerate (complicated) silicosis is the advanced form of chronic or accelerated silicosis and is characterized by widespread masses of fibrosis, typically in the upper lung zones.

Complications: Patients with silicosis are at risk of other disorders:
TB
Lung cancer
Progressive systemic sclerosis (scleroderma)
Possibly RA

All patients with silicosis are at about a 30-fold increased risk of pulmonary TB or nontubercular mycobacterial disease and are more likely to develop both pulmonary and extrapulmonary manifestations. Increased risk may result from impaired macrophage function and an increased risk of activation of latent infection. People exposed to silica but without silicosis have 3 times the risk of developing TB compared with the nonexposed general population.

Other complications include spontaneous pneumothorax, broncholithiasis, and tracheobronchial obstruction. Emphysema is a common finding in areas immediately peripheral to conglomerate nodules and in areas of progressive massive fibrosis.

Symptoms and Signs

Chronic silicosis is often asymptomatic, but many patients eventually develop dyspnea during exertion that progresses to dyspnea at rest. Productive cough, when present, may be due to silicosis, coexisting chronic occupational (industrial) bronchitis, or smoking. Breath sounds diminish as the disorder progresses, and pulmonary consolidation, pulmonary hypertension, and respiratory failure with or without right ventricular failure may develop in advanced disease.

Patients with accelerated silicosis experience the same symptoms as those with chronic silicosis, but symptoms develop over a shorter period.

Acute silicosis patients experience rapid progression of dyspnea, weight loss, and fatigue with diffuse bilateral crackles. Respiratory failure often develops within 2 yr.

Conglomerate silicosis causes severe, chronic respiratory symptoms.

Diagnosis

Occupational history of silica exposure
Chest CT or chest x-ray
Sometimes tissue biopsy for confirmation
Adjunctive tests for distinguishing silicosis from other disorders

Imaging: Silicosis is usually recognized on the basis of chest x-ray or CT appearance in patients with a history of exposure. CT is more sensitive than x-ray, especially when helical CT and high-resolution techniques are used. In most cases, chest CT is preferable because it is more sensitive for detecting silicosis as well as the transition from simple to conglomerate silicosis. Chest CT can also better distinguish asbestosis from silicosis, although this differentiation can usually be made on the basis of chest x-ray and exposure history. In patients who develop RA, 3- to 5-mm pulmonary rheumatoid nodules are visible on chest x-ray or CT.

Chronic silicosis produces multiple 1- to 3-mm rounded opacities or nodules recognized on chest x-ray or CT, usually in upper lung fields. Severity is graded on a standardized scale developed by the International Labor Organization, in which specially trained readers examine the chest x-ray for size and shape of opacities, concentration of opacities (profusion), and pleural changes. An equivalent scale does not exist for CT appearance. Calcified hilar and mediastinal lymph nodes are common and occasionally
Numerous disorders resemble chronic silicosis on x-ray; they include welders' siderosis, hemosiderosis, sarcoidosis, chronic beryllium disease, hypersensitivity pneumonitis, coal workers' pneumoconiosis, miliary TB, fungal pulmonary diseases, and metastatic cancer. Eggshell calcifications in hilar and mediastinal lymph nodes may help distinguish silicosis from other pulmonary disorders but are not a pathognomonic finding and are not commonly present.

**Accelerated silicosis** resembles chronic silicosis on x-ray but develops more rapidly.

**Acute silicosis** is recognized by rapid progression of symptoms. X-ray findings include diffuse alveolar bibasilar opacities representing fluid-filled alveoli. On CT, areas of ground-glass density consisting of reticular infiltration and areas of patchy increased attenuation and inhomogeneity occur. These areas are best observed on thin-section, spiral CT views. The multiple rounded opacities of chronic and accelerated silicosis are not characteristic of acute silicosis.

**Conglomerate silicosis** is recognizable by confluent opacities > 10 mm in diameter against a background of chronic silicosis findings.

**Adjunctive tests:** Tuberculin skin testing, sputum culture and cytology, PET, and bronchoscopy all may assist in distinguishing silicosis from disseminated TB or cancer.

Pulmonary function tests and measures of gas exchange (diffusing capacity for carbon monoxide [DLCO], ABGs) are not diagnostic but help monitor progression. Early chronic silicosis may manifest with reduced lung volumes that are at the lower end of the predicted range and with normal functional residual capacity and residual volume. In conglomerate silicosis, pulmonary function tests reveal decreased lung volumes, decreased DLCO, and airway obstruction. ABGs show hypoxemia usually without CO2 retention. Measurement of gas exchange during exercise, using pulse oximetry or preferably an indwelling arterial catheter, is one of the most sensitive measures of pulmonary impairment.

Antinuclear antibodies and elevated rheumatoid factor are detectable in some patients and are suggestive but not diagnostic of a coexisting connective tissue disorder (eg, scleroderma, RA).

**Treatment**

- Sometimes whole lung lavage
- Sometimes oral corticosteroids
- Rarely lung transplantation
- Empiric use of bronchodilators and inhaled corticosteroids for obstruction
- Removal from further exposure

Whole lung lavage may be useful in some cases of acute silicosis. Whole lung lavage can reduce the total mineral dust load in the lungs of patients with chronic silicosis. Some studies have shown short-term reduction in symptoms after lavage, but controlled trials have not been done. Anecdotal evidence supports the use of oral corticosteroids in acute and accelerated silicosis. Lung transplantation is a last resort.

Patients with airway obstruction may be treated empirically with bronchodilators and inhaled corticosteroids. Patients should be monitored and treated for hypoxemia to forestall pulmonary hypertension. Pulmonary rehabilitation may help patients carry out activities of daily living. Workers who develop silicosis should be removed from further exposure.
Management of TB is the same as for other patients with TB except that longer courses are usually recommended because relapse is more common in patients with silicotuberculosis.

**Prevention**

The most effective preventive interventions occur at an industrial rather than clinical level and include dust suppression, process isolation, ventilation, and use of non-silicacontaining abrasives. Respiratory masks provide imperfect protection and, although helpful, are not an adequate solution. Surveillance of exposed workers with respiratory questionnaires, spirometry, and chest x-rays is recommended. Frequency of surveillance depends to some degree on the expected intensity of the exposure. Other preventive measures include smoking cessation and pneumococcal and influenza vaccination.

Physicians must be alert to the risk of TB and nontuberculous mycobacterial infections in silica-exposed patients, especially miners. People exposed to silica should have annual tuberculin testing. Those with a positive skin test should have sputum culture for TB. In some cases, CT and bronchoscopy may be needed to confirm TB. Patients with a positive tuberculin test and negative TB cultures should be given isoniazid chemoprophylaxis in keeping with standard guidelines for tuberculin reactors.

**Irritant Gas Inhalation Injury**

Irritant gases are those which, when inhaled, dissolve in the water of the respiratory tract mucosa and cause an inflammatory response, usually from the release of acidic or alkaline radicals. Irritant gas exposures predominantly affect the airways, causing tracheitis, bronchitis, and bronchiolitis. Other inhaled agents may be directly toxic (eg, cyanide, carbon monoxide) or cause harm simply by displacing O₂ and producing asphyxia (eg, methane, carbon dioxide).

The effect of inhaling irritant gases depends on the extent and duration of exposure and on the specific agent. Chlorine, phosgene, sulfur dioxide, hydrogen chloride or sulfide, nitrogen dioxide, ozone, and ammonia are among the most important irritant gases. Hydrogen sulfide is also a potent cellular toxin, blocking the cytochrome system and inhibiting cellular respiration. A common exposure involves mixing household ammonia with cleansers containing bleach; the irritant gas chloramine is released.

**Acute Exposure**

Acute exposure to high concentrations of toxic gas over a short time is characteristic of industrial accidents resulting from a faulty valve or pump in a gas tank or occurring during gas transport. Many people may be exposed and affected. The release of methyl isocyanate from a chemical plant in Bhopal, India in 1984 killed > 2000 people.

Respiratory damage is related to the concentration of the gas and its solubility.

More water-soluble gases (eg, chlorine, ammonia, sulfur dioxide, hydrogen chloride) dissolve in the upper airway and immediately cause mucous membrane irritation, which may alert people to the need to escape the exposure. Permanent damage to the upper respiratory tract, distal airways, and lung parenchyma occurs only if escape from the gas source is impeded.

Less soluble gases (eg, nitrogen dioxide, phosgene, ozone) may not dissolve until they are well into the respiratory tract, often reaching the lower airways. These agents are less likely to produce early warning signs (phosgene in low concentrations has a pleasant odor), are more likely to cause severe bronchiolitis, and often have a lag of ≥ 12 h before symptoms of pulmonary edema develop.

**Complications:** The most serious immediate complication is ARDS, which usually occurs within 24 h. Patients with significant lower airway involvement may develop bacterial infection.

Ten to 14 days after acute exposure to some agents (eg, ammonia, nitrogen oxides, sulfur dioxide, mercury), some patients develop bronchiolitis obliterans progressing to ARDS. Bronchiolitis obliterans with organized pneumonia can ensue when granulation tissue accumulates in the terminal airways and...
alveolar ducts during the body’s reparative process. A minority of these patients develop late pulmonary fibrosis.

Symptoms and Signs

Soluble irritant gases cause severe burning and other manifestations of irritation of the eyes, nose, throat, trachea, and major bronchi. Marked cough, hemoptysis, wheezing, retching, and dyspnea are common. The upper airway may be obstructed by edema, secretions, or laryngospasm. Severity is generally doserelated. Nonsoluble gases cause fewer immediate symptoms but can cause dyspnea or cough.

Patients who develop ARDS have worsening dyspnea and increasing O₂ requirements.

Diagnosis

• History of exposure

• Chest x-ray

Diagnosis is usually obvious from the history. Patients should have a chest x-ray and pulse oximetry. Chest x-ray findings of patchy or confluent alveolar consolidation usually indicate pulmonary edema.

CT is used to evaluate patients with late-developing symptoms. Those with bronchiolitis obliterans that progresses to respiratory failure manifest a pattern of bronchiolar thickening and a patchy mosaic of hyperinflation.

Prognosis

Most people recover fully, but some have persistent lung injury with reversible airway obstruction (reactive airways dysfunction syndrome) or pulmonary fibrosis; smokers may be at greater risk.

Treatment

• Removal from exposure and 24-h observation

• Bronchodilators and supplemental O₂

• Sometimes inhaled racemic epinephrine, endotracheal intubation, and mechanical ventilation

Management does not differ by specific inhaled agent but rather by symptoms. Patients should be moved into fresh air and given supplemental O₂. Treatment is directed toward ensuring adequate oxygenation and alveolar ventilation. Bronchodilators and O₂ therapy may suffice in less severe cases. Severe airflow obstruction is managed with inhaled racemic epinephrine, endotracheal intubation or tracheostomy, and mechanical ventilation. The efficacy of corticosteroid therapy (eg, prednisone 45 to 60 mg once/day for 1 to 2 wk) is unproved, but it is frequently used.

Because of the risk of ARDS, any patient with respiratory tract symptoms after toxic inhalation should be observed for 24 h.

After the acute phase has been managed, physicians must remain alert to the development of reactive airways dysfunction syndrome, bronchiolitis obliterans with or without organized pneumonia, pulmonary fibrosis, and delayed-onset ARDS.

Prevention

Care in handling gases and chemicals is the most important preventive measure. The availability of adequate respiratory protection (eg, gas masks with a self-contained air supply) for rescuers is also very
important; rescuers without protective gear who rush in to extricate a victim often succumb themselves.

**Chronic Exposure**

Low-level continuous or intermittent exposure to irritant gases or chemical vapors may lead to chronic bronchitis, although the role of such exposure is especially difficult to substantiate in smokers.

Chronic inhalational exposure to some agents (eg, bis[chloromethyl]ether, certain metals) causes lung and other cancers (eg, liver angiosarcomas after vinyl chloride monomer exposure).
Chapter 202. Pulmonary Hypertension

Introduction

Pulmonary hypertension is increased pressure in the pulmonary circulation. It has many secondary causes; some cases are idiopathic. In pulmonary hypertension, pulmonary vessels become constricted, hypertrophied, and fibrosed. Severe pulmonary hypertension leads to right ventricular overload and failure. Symptoms are fatigue, exertional dyspnea, and, occasionally, chest discomfort and syncope. Diagnosis is made by measuring pulmonary artery pressure. Treatment is with vasodilators and diuretics. In some advanced cases, lung transplantation is an option. Prognosis is poor overall if a treatable secondary cause is not found.

Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥ 25 mm Hg at rest or ≥ 35 mm Hg during exercise.

Etiology

Many conditions and drugs cause pulmonary hypertension. A small number of cases occur sporadically, unrelated to any identifiable disorder; these cases are termed idiopathic pulmonary arterial hypertension. The most common overall causes of pulmonary hypertension include

- Left heart failure, including diastolic dysfunction
- Parenchymal lung disease with hypoxia
- Miscellaneous: Sleep apnea, connective tissue disorders, and pulmonary embolism

Pulmonary hypertension is currently classified into 5 groups (see Table 202-1) based on a number of pathologic, physiologic, and clinical factors. In the first group (pulmonary arterial hypertension), the primary disorder affects the small pulmonary arterioles.

Pathophysiology

Pathophysiologic mechanisms that cause pulmonary hypertension include increased pulmonary vascular resistance and increased pulmonary venous pressure. Pulmonary vascular resistance can be caused by obliteration of the pulmonary vascular bed or hypoxic vasoconstriction. Pulmonary hypertension is characterized by variable vasoconstriction, smooth muscle hypertrophy, and vascular wall remodeling. Vasoconstriction is thought to be due in part to enhanced activity of thromboxane and endothelin-1 (both vasoconstrictors) and reduced activity of prostacyclin and nitric oxide (both vasodilators). The increased pulmonary vascular pressure that results from vascular obstruction further injures the endothelium. Injury activates coagulation at the intimal surface, which may worsen the hypertension. Thrombotic coagulopathy due to increased activity of plasminogen activator inhibitor type 1 and fibrinopeptide A and decreased tissue plasminogen activator activity may also contribute. Focal coagulation at the endothelial surface should not be confused with chronic thromboembolic pulmonary hypertension, in which pulmonary hypertension is caused by organized pulmonary emboli.

In most patients, pulmonary hypertension eventually leads to right ventricular hypertrophy followed by dilation and right ventricular failure.

Symptoms and Signs

Progressive exertional dyspnea and easy fatigability occur in almost all patients. Atypical chest discomfort and exertional light-headedness or presyncope may accompany dyspnea. These symptoms are due primarily to insufficient cardiac output. Raynaud's syndrome occurs in about 10% of patients with
idiopathic pulmonary arterial hypertension; the majority are women. Hemoptysis is rare but may be fatal. Hoarseness due to recurrent laryngeal nerve compression by an enlarged pulmonary artery (ie, Ortner syndrome) also occurs rarely.

In advanced disease, signs may include right ventricular heave, widely split 2nd heart sound (S₂), an accentuated pulmonic component (P₂) of S₂, a pulmonary ejection click, a right ventricular 3rd heart sound (S₃), tricuspid murmur, and jugular vein distention. Liver congestion and peripheral edema are common late manifestations.

**Diagnosis**

- Exertional dyspnea
- Initial confirmation: Chest x-ray, spirometry, ECG, echocardiography, and CBC
- Identification of underlying disorder: Ventilation-perfusion scan or CT angiography, pulmonary function testing, polysomnography, HIV testing, liver function testing, and antinuclear antibodies
- Determination of severity: Right heart catheterization

Pulmonary hypertension is suspected in patients with significant exertional dyspnea who are otherwise relatively healthy and have no history or signs of other diseases known to cause pulmonary symptoms.

Patients initially undergo chest x-ray, spirometry, and ECG to identify more common causes of dyspnea, followed by Doppler echocardiography to assess right ventricular and pulmonary artery pressures as well as to detect structural heart disease that might be causing pulmonary hypertension. CBC is obtained to document the presence or absence of polycythemia, anemia, and thrombocytopenia.

The most common x-ray finding in pulmonary hypertension is enlarged hilar vessels that rapidly prune into the periphery and a right ventricle that fills the anterior airspace on lateral view. Spirometry and lung volumes may be normal or detect mild restriction, and diffusing capacity for carbon monoxide (DLCO) is usually reduced. Common ECG findings include right axis deviation, R > S in V₁, S₁Q₃T₃, and peaked P waves.

Additional tests are obtained as indicated to diagnose secondary causes that are not apparent clinically. These tests include

- Ventilation-perfusion scanning or CT angiography to detect thromboembolic disease
- Pulmonary function tests to identify obstructive or restrictive lung disease
- Serum serologic tests to gather evidence for or against rheumatologic disease

Chronic thromboembolic pulmonary hypertension is suggested by CT or lung scan findings and is confirmed by arteriography. CT angiography is useful to evaluate proximal clot and fibrotic encroachment of the vascular lumen. Other tests, such as HIV testing, liver function tests, and polysomnography, are done in the appropriate clinical context.

When the initial evaluation detects no conditions known to be associated with pulmonary hypertension, pulmonary artery catheterization is necessary to measure right atrial and ventricular, pulmonary artery, and pulmonary artery occlusion pressures; cardiac output; and left ventricular diastolic pressure. Right-sided O₂ saturation should be measured to exclude atrial septal defect. Although finding a mean pulmonary arterial pressure of > 25 mm Hg in the absence of an underlying disorder identifies pulmonary hypertension, most patients with pulmonary arterial hypertension present with substantially higher pressure (eg, mean of 60 mm Hg). Vasodilating drugs, such as inhaled nitric oxide, IV epoprostenol, or adenosine, are often administered during catheterization. Decreasing right-sided pressures in response to these drugs may help in the choice of drugs for treatment. Lung biopsy, once widely done, is neither
needed nor recommended because of its associated high morbidity and mortality.

Once pulmonary hypertension is diagnosed, the patient's family history should be reviewed to detect possible genetic transmission (eg, premature deaths in otherwise healthy members of the extended family). In familial pulmonary arterial hypertension, genetic counseling is needed to advise mutation carriers of the risk of disease (about 20%) and to advocate serial screening with echocardiography. Testing for mutations in the *BMPR2* gene in idiopathic pulmonary arterial hypertension may have a future role.

**Prognosis**

Untreated patients have a median survival of 2.5 yr. Cause of death is usually sudden death in the context of right ventricular failure. Five-year survival for epoprostenol-treated patients is 54%, whereas that for the small minority of patients who respond to Ca channel blockers is > 90%. Signs predictive of poor survival include low cardiac output, higher pulmonary artery and right atrial pressures, lack of response to vasodilators, heart failure, hypoxemia, and reduced overall physical functioning. Patients with the connective tissue disorder systemic sclerosis are at high risk of pulmonary arterial hypertension and have a poor prognosis.

**Treatment**

- **Avoidance of activities that may exacerbate the condition** (eg, cigarette smoking, use of sympathomimetics)

- **Idiopathic and familial pulmonary arterial hypertension**: Ca channel blockers; IV epoprostenol; inhaled, oral, or sc prostacyclin analogs; oral endothelin-receptor antagonists; and/or oral phosphodiesterase inhibitors

- **Secondary pulmonary arterial hypertension**: Treatment of the underlying disorder

- **Rarely lung transplantation**

- **Adjunctive therapy**: Supplemental O\textsubscript{2}, diuretics, and/or anticoagulants

Patients are encouraged to avoid activities or circumstances that may exacerbate their condition. Examples include cigarette smoking, exposure to high altitudes, and drugs that lead to vasoconstriction, such as sympathomimetics.

**Pulmonary arterial hypertension, group 1**: Treatment is rapidly evolving. Oral Ca channel blockers reduce pulmonary arterial pressure or pulmonary vascular resistance in about 5% of patients. No differences in efficacy exist among Ca channel blocker types, though most specialists avoid verapamil because of its negative inotropic effects. Response to Ca channel blockers is a favorable prognostic sign, and patients who respond should continue this treatment. Patients who do not respond at the time of diagnosis are given other drugs.

IV epoprostenol, a prostacyclin analog, improves function and lengthens survival even in patients who are unresponsive to a vasodilator during catheterization. Epoprostenol is currently the most effective therapy for pulmonary arterial hypertension. Disadvantages are the need for continuous central catheter infusion and frequent, troubling adverse effects, including flushing, diarrhea, and bacteremia associated with the indwelling central catheter. Prostacyclin analogs that are inhaled (iloprost) or given sc or IV (treprostinil) are available.

Two oral endothelin-receptor antagonists, bosentan and ambrisentan, are available in the US; these drugs are useful in some patients, generally those with milder disease at diagnosis. Oral sildenafil is also effective.

Lung transplantation offers the only hope of cure but has high morbidity because of rejection, infection, and bronchiolitis obliterans. The 5-yr survival rate is 60%. Lung transplantation is reserved for patients
with New York Heart Association class IV disease (defined as dyspnea associated with minimal activity, leading to bed to chair limitations) in whom all therapies have failed and who meet other health criteria to be a transplant candidate.

Many patients require adjunctive therapies to treat heart failure, including diuretics, and most should receive warfarin unless there is a contraindication.

**Pulmonary hypertension, groups 2 to 5:** Primary treatment involves management of the underlying disorder. Patients with left-sided heart disease may need surgery for valvular disease. Patients with lung disorders and hypoxia benefit from supplemental $\text{O}_2$ as well as treatment of the primary disorder. Patients with severe pulmonary hypertension secondary to chronic thromboembolic disease should be considered for pulmonary thromboendarterectomy. During cardiopulmonary bypass, an organized endothelialized thrombus is dissected along the pulmonary trunk in a procedure more complex than acute surgical embolectomy. This procedure cures pulmonary hypertension in a substantial percentage of patients and restores cardiopulmonary function; operative mortality is < 10% in patients treated in centers that have extensive experience.

**Portopulmonary Hypertension**

**Portopulmonary hypertension is pulmonary arterial hypertension associated with portal hypertension without other secondary causes.**

Pulmonary hypertension occurs in patients with various conditions that involve portal hypertension with or without cirrhosis. Portopulmonary hypertension occurs less commonly than the hepatopulmonary syndrome in patients with chronic liver disease (3.5 vs 12%).

Presenting symptoms are dyspnea and fatigue. Chest pain and hemoptysis can also occur. Patients have physical findings and ECG abnormalities consistent with pulmonary hypertension and may develop evidence of cor pulmonale (elevated jugular venous pulse, edema). Tricuspid regurgitation is common.

The diagnosis is suspected based on echocardiography findings and confirmed by right heart catheterization.

Treatment is the same as that of pulmonary arterial hypertension except that hepatotoxic drugs should be avoided. Some patients benefit from vasodilator therapy. The underlying liver disease is a major determinant of outcome. Portopulmonary hypertension is a relative contraindication to liver transplantation because of increased morbidity and mortality from the procedure. However, in some patients who receive a transplant, particularly those with mild pulmonary hypertension, pulmonary hypertension regresses. Some centers consider transplantation in patients who have mean pulmonary arterial pressures < 35 mm Hg after a trial of vasodilator therapy.

**Hepatopulmonary Syndrome**

**Hepatopulmonary syndrome is hypoxemia caused by pulmonary microvascular vasodilation in patients with portal hypertension; dyspnea and hypoxemia are worse in the upright position.**

The hepatopulmonary syndrome results from the formation of microscopic intrapulmonary arteriovenous dilations in patients with chronic liver disease. The mechanism is unknown but is thought to be due to increased hepatic production or decreased hepatic clearance of vasodilators, possibly nitric oxide. The vascular dilations cause overperfusion relative to ventilation, leading to hypoxemia. Because the lesions frequently are more numerous at the lung bases, the hepatopulmonary syndrome causes platypnea (dyspnea) and orthodeoxia (hypoxemia), which occur in the seated or upright position and are relieved by recumbency. Most patients also have characteristic findings of chronic liver disease, such as spider angiomas. About 20% of patients present with pulmonary symptoms alone.

**Diagnosis**

- Pulse oximetry
Hepatopulmonary syndrome should be suspected in a patient with known liver disease who reports dyspnea (particularly platypnea). Patients with clinically significant symptoms should have pulse oximetry. If the syndrome is advanced, ABGs should be measured with the patient breathing room air and 100% O\textsubscript{2} to determine shunt fraction.

A useful diagnostic test is contrast echocardiography. Intravenous microbubbles from agitated saline that are normally trapped in the pulmonary capillaries rapidly (ie, within 7 heartbeats) traverse the lung and appear in the left atrium. Similarly, IV technetium-99m-labeled albumin may traverse the lungs and appear in the kidneys and brain. Pulmonary angiography may reveal a diffusely fine or blotchy vascular configuration. Angiography is generally not needed unless thromboembolism is suspected.

**Treatment**

- **Supplemental O\textsubscript{2}**

The main treatment is supplemental O\textsubscript{2} for symptoms. Other therapies, such as somatostatin to inhibit vasodilation, are of modest benefit in only some patients. Coil embolization is virtually impossible because of the number and size of the lesions. Inhaled nitric oxide synthesis inhibitors may be a future treatment option. Hepatopulmonary syndrome may regress after liver transplantation or if the underlying liver disease subsides. Prognosis is poor without treatment (survival < 2 yr).
Chapter 203. Diffuse Alveolar Hemorrhage and Pulmonary-Renal Syndromes

Introduction

Some alveolar hemorrhage syndromes are associated with glomerulonephritis; then, the disorder is called pulmonary-renal syndrome (see p. 1990).

Diffuse Alveolar Hemorrhage Syndrome

Diffuse alveolar hemorrhage syndrome is persistent or recurrent pulmonary hemorrhage. There are numerous causes, but autoimmune disorders are the most common. Most patients present with dyspnea, cough, hemoptysis, and new alveolar infiltrates. Diagnostic tests are directed at the suspected cause. Treatment is with immunosuppressants for patients with autoimmune causes and respiratory support if needed.

Diffuse alveolar hemorrhage syndrome is not a specific entity but is a syndrome that suggests a differential diagnosis and a specific sequence of testing.

Pathophysiology

Diffuse alveolar hemorrhage syndrome results from widespread damage of the pulmonary small vessels, leading to blood collection within the alveoli, thereby disrupting O₂ and CO₂ exchange. The specific pathophysiology and manifestations vary depending on cause. For example, isolated pauci-immune pulmonary capillaritis is a small-vessel vasculitis limited to the lung; its only manifestation is alveolar hemorrhage affecting people aged 18 to 35 yr. Idiopathic pulmonary hemosiderosis is diffuse alveolar hemorrhage syndrome with no detectable underlying disorder; it occurs mainly in children < 10 yr and is thought to be due to a defect in the alveolar capillary endothelium, possibly due to autoimmune injury.

Etiology

Many disorders can cause alveolar hemorrhage; they include

• Autoimmune disorders (eg, systemic vasculitides, Goodpasture's syndrome, antiphospholipid antibody syndrome)

• Pulmonary infections (eg, invasive aspergillosis, hantavirus infection)

• Toxic exposures (eg, trimellitic anhydride, isocyanates, crack cocaine, certain pesticides)

• Drug reactions (eg, propylthiouracil, diphenylhydantoïn, amiodarone, methotrexate, nitrofurantoin, bleomycin, montelukast, infliximab)

• Cardiac disorders (eg, mitral stenosis)

• Coagulation disorders caused by diseases or anticoagulant drugs

• Isolated pauci-immune pulmonary capillaritis

• Idiopathic pulmonary hemosiderosis

• Bone marrow or solid organ transplantation

Symptoms and Signs

Symptoms and signs of milder diffuse alveolar hemorrhage syndrome are dyspnea, cough, and fever; however, many patients present with acute respiratory failure, sometimes leading to death. Hemoptysis is common but may be absent in up to one third of patients. Children with idiopathic pulmonary
hemosiderosis may have failure to thrive.

There are no specific physical examination findings.

Other manifestations depend on the underlying disorder (e.g., diastolic murmur in patients with mitral stenosis).

**Diagnosis**

- Chest x-ray
- Sometimes bronchoscopy
- Serologic and other tests to diagnose the cause

Diagnosis is suggested by dyspnea, cough, and hemoptysis accompanied by chest x-ray findings of diffuse bilateral alveolar infiltrates. Bronchoscopy with bronchoalveolar lavage (BAL) may be done to confirm the diagnosis when manifestations are atypical or an airway source of hemorrhage has not been excluded. Specimens show blood with numerous erythrocytes and siderophages; lavage fluid typically remains hemorrhagic even after sequential sampling.

**Evaluation of the cause:** Further testing for the cause should be done. Urinalysis is indicated to exclude glomerulonephritis; serum BUN and creatinine also should be done. Other routine tests include CBC, coagulation studies, platelet counts, and serologic tests (antinuclear antibody, anti-double-stranded DNA (anti-dsDNA), antiglomerular basement membrane [anti-GBM] antibodies, antineutrophil cytoplasmic antibodies [ANCA], antiphospholipid antibody) to look for underlying disorders; perinuclear-ANCA (p-ANCA) titers are elevated in some cases of isolated pauciimmune pulmonary capillaritis. Diagnosis of idiopathic pulmonary hemosiderosis involves demonstration of iron deficiency anemia and hemosiderin-laden macrophages in BAL fluid or lung biopsy specimens when there is no evidence of small-vessel vasculitis (pulmonary capillaritis) or of other diagnoses.

Other tests depend on clinical context. Pulmonary function tests may be done to document lung function. They may show increased diffusing capacity for carbon monoxide (DLCO) due to increased uptake of carbon monoxide by intralveolar Hb; however, this finding, which is consistent with hemorrhage, does not assist with establishing a diagnosis. Echocardiography may be indicated to exclude mitral stenosis. BAL is done when diffuse alveolar hemorrhage is suspected. Lung or kidney biopsy is frequently needed when a cause remains unclear or the progression of disease is too rapid to await the results of serologic testing.

**Prognosis**

Patients can require mechanical ventilation and even die as a result of hemorrhage-associated respiratory failure. Recurrent alveolar hemorrhage causes pulmonary hemosiderosis and fibrosis, both of which develop when ferritin aggregates within alveoli and exerts toxic effects. COPD occurs in some patients with recurrent diffuse alveolar hemorrhage secondary to microscopic polyarteritis.

**Treatment**

- Corticosteroids
- Sometimes cyclophosphamide or plasmapheresis
- Supportive measures

Treatment involves correcting the cause. Corticosteroids and possibly cyclophosphamide are used to treat vasculitides, connective tissue disorders, and Goodpasture's syndrome. Plasmapheresis may be used to treat Goodpasture's syndrome. Corticosteroids are also used to treat idiopathic pulmonary hemosiderosis; immunosuppressants are added for nonresponders. Several studies have reported
successful use of recombinant activated human factor VII in treating alveolar hemorrhage.

Other possible management measures include supplemental O\textsubscript{2}, bronchodilators, reversal of any coagulopathy, intubation with bronchial tamponade, protective strategies for the less involved lung, and mechanical ventilation.

**Pulmonary-Renal Syndrome**

Pulmonary-renal syndrome (PRS) is diffuse alveolar hemorrhage and glomerulonephritis occurring simultaneously. Cause is almost always an autoimmune disorder. Diagnosis is by serologic tests and sometimes lung and renal biopsy. Treatment typically includes immunosuppression with corticosteroids and cytotoxic drugs.

PRS is not a specific entity but is a syndrome that suggests a differential diagnosis and a specific sequence of testing.

Pulmonary pathology is small-vessel vasculitis involving arterioles, venules, and, frequently, alveolar capillaries. Renal pathology is small-vessel vasculitis resulting in a form of focal proliferative glomerulonephritis.

**Etiology**

PRS is almost always a manifestation of an underlying autoimmune disorder. Goodpasture's syndrome is the prototype cause, but PRS can also be caused by SLE, Wegener's granulomatosis, microscopic polyangiitis, and, less commonly, by other vasculitides and connective tissue disorders (see Table 203-1).

PRS is less commonly a manifestation of IgA-mediated disorders, such as IgA nephropathy or Henoch-Schönlein purpura, and of immune complex-mediated renal disease, such as essential mixed cryoglobulinemia. Rarely, rapidly progressive glomerulonephritis alone can cause PRS through a mechanism involving renal failure, volume overload, and pulmonary edema with hemoptyis.

**Symptoms and Signs**

Symptoms and signs typically include dyspnea, cough, fever, and hemoptyis in combination with peripheral edema and hematuria or other signs of glomerulonephritis.

**Diagnosis**

- Serologic testing
- Sometimes lung and renal biopsies

PRS is suspected in patients with hemoptyis not obviously attributable to other causes (eg, pneumonia, carcinoma, bronchiectasis), particularly when hemoptyis is accompanied by diffuse parenchymal infiltrates and findings suggesting renal disease.

Initial testing includes urinalysis for evidence of hematuria and red cell casts (suggesting [Table 203-1, Causes of Pulmonary-Renal Syndrome] glomerulonephritis), serum creatinine for renal function assessment, and CBC for evidence of anemia. Chest x-ray is done if not yet obtained.

Serum antibody testing may help distinguish some causes, as in the following:

- Antiglomerular basement membrane antibodies: Goodpasture's syndrome
Definitive diagnosis requires lung biopsy with findings of small-vessel vasculitis and renal biopsy with findings of glomerulonephritis with or without antibody deposition.

Pulmonary function tests and bronchoalveolar lavage are not diagnostic of PRS but can be used to help confirm diffuse alveolar hemorrhage in patients with glomerulonephritis and pulmonary infiltrates but without hemoptysis. Lavage fluid that remains hemorrhagic after sequential sampling establishes diffuse alveolar hemorrhage, especially in the context of falling Hct.

Treatment

- Corticosteroids
- Sometimes cyclophosphamide

Immunosuppression is the cornerstone of treatment. Standard induction-remission regimens include pulse IV methylprednisolone (500 to 1000 mg IV once/day for 3 to 5 days). As life-threatening features subside, the corticosteroid dose can be reduced; 1 mg/kg prednisone (or equivalent) po once/day is given for the first month, then tapered over the next 3 to 4 mo. Cyclophosphamide should be added to corticosteroid therapy in critically ill patients with generalized disease, at a dose of 0.5 to 1 g/m$^2$ IV given as a pulse once/mo or orally (1 to 2 mg/kg once/day).

Transition to maintenance therapy may occur 6 to 12 mo after the initiation of induction therapy or after clinical remission. Maintenance therapy includes low-dose corticosteroids coupled with cytotoxic agents. However, relapse may occur despite ongoing therapy.

Goodpasture's Syndrome

(Anti-GBM Antibody Disease)

Goodpasture's syndrome, a subtype of PRS, is an autoimmune syndrome of alveolar hemorrhage and glomerulonephritis caused by circulating anti-glomerular basement membrane (anti-GBM) antibodies. Goodpasture's syndrome most often develops in genetically susceptible people who smoke cigarettes, but hydrocarbon exposure and viral respiratory infections are additional possible triggers. Symptoms are dyspnea, cough, fatigue, hemoptysis, and hematuria. Goodpasture's syndrome is suspected in patients with hemoptysis or hematuria and is confirmed by the presence of anti-GBM antibodies in the blood or in a renal biopsy specimen. Prognosis is good when treatment is begun before onset of respiratory or renal failure. Treatment includes plasmapheresis, corticosteroids, and immunosuppressants, such as cyclophosphamide.

Pathophysiology

Goodpasture's syndrome is the combination of glomerulonephritis with alveolar hemorrhage and anti-GBM antibodies. Goodpasture's syndrome most often manifests as diffuse alveolar hemorrhage and glomerulonephritis together but can occasionally cause glomerulonephritis (10 to 20%) or pulmonary disease (10%) alone. Men are affected more often than women.

Anti-GBM antibodies are directed against the noncollagenous (NC-1) domain of the $\alpha_3$ chain of type IV collagen, which occurs in highest concentration in the basement membranes of renal and pulmonary capillaries. Environmental exposures—cigarette smoking, viral URI, and hydrocarbon solvent inhalation most commonly and pneumonia less commonly—expose alveolar capillary antigens to circulating antibody.
in genetically susceptible people, most notably those with HLA-DRw15, -DR4, and -DRB1 alleles. Circulating anti-GBM antibodies bind to basement membranes, fix complement, and trigger a cell-mediated inflammatory response, causing glomerulonephritis, pulmonary capillaritis, or both.

**Symptoms and Signs**

Hemoptysis is the most prominent symptom; however, hemoptysis may not occur in patients with hemorrhage, and patients may present with only chest x-ray infiltrates or with infiltrates and respiratory distress, respiratory failure, or both. Dyspnea, cough, fatigue, fever, and weight loss are common. Up to 40% of patients have gross hematuria, although pulmonary hemorrhage may precede renal manifestations by weeks to years.

Signs vary over time and range from clear lungs on auscultation to crackles and rhonchi. Some patients have peripheral edema due to renal failure and pallor due to anemia.

**Diagnosis**

- Serum anti-GBM antibody tests
- Sometimes renal biopsy

Definitive diagnosis of Goodpasture's syndrome requires demonstration of serum anti-GBM antibodies by indirect immunofluorescence testing or, when available, direct enzyme-linked immunosorbent assay (ELISA) with recombinant or human NC-1 α3. However, ANCA testing is positive (in a peripheral pattern) in only 25% of patients with Goodpasture's syndrome.

Renal biopsy is indicated in patients with glomerulonephritis (hematuria, proteinuria, red cell casts detected with urinalysis, renal insufficiency, or a combination of these findings). A rapidly progressive focal segmental necrotizing glomerulonephritis with crescent formation is found in biopsy specimens in patients with Goodpasture's syndrome and all other causes of PRS. Immunofluorescence staining of renal or lung tissue classically shows linear IgG deposition along the glomerular or alveolar capillaries. IgG deposition also occurs in the kidneys of patients with diabetes or with fibrillary glomerulonephritis (a rare disorder causing PRS), but GBM binding of antibodies in these disorders is nonspecific and does not occur in linear patterns.

**Prognosis**

Goodpasture's syndrome is often rapidly progressive and can be fatal if prompt recognition and treatment are delayed; prognosis is good when treatment begins before onset of respiratory or renal failure. Long-term morbidity is related to the degree of renal impairment at presentation; patients requiring dialysis at presentation and those with > 50% crescents in the biopsy specimen (who often will require dialysis) usually survive for < 2 yr unless kidney transplantation is done. Hemoptysis may be a good prognostic sign because it leads to earlier detection; the minority of patients who are ANCA-positive respond better to treatment. Relapse occurs in a small number and is linked to continued tobacco use and respiratory infection. In patients with end-stage renal disease who receive kidney transplantation, disease can recur in the graft.

**Treatment**

- Plasmapheresis
- Corticosteroids and cyclophosphamide

Immediate survival in patients with pulmonary hemorrhage and respiratory failure is linked to airway control; endotracheal intubation and mechanical ventilation are recommended for patients with borderline ABGs and impending respiratory failure. Patients with significant renal impairment may require dialysis or kidney transplantation.
Treatment is daily or every-other-day plasmapheresis for 2 to 3 wk using 4-L exchanges to remove anti-GBM antibodies, combined with a corticosteroid (usually methylprednisolone 1 g IV over 20 min once/day or every other day for 3 doses followed by prednisone (1 mg/kg po once/day for 3 wk, then titrated down to 20 mg po once/day for 6 to 12 mo) and cyclophosphamide (2 mg/kg po or IV once/day for 6 to 12 mo) to prevent formation of new antibodies. Therapy can be tapered when pulmonary and renal function stop improving.
Chapter 204. Mediastinal and Pleural Disorders

Introduction

Mediastinal and pleural disorders include masses, mediastinitis, pleural effusion, pleural fibrosis and calcification, pneumomediastinum, pneumothorax, and viral pleuritis.

Mediastinal Masses

Mediastinal masses are caused by a variety of cysts and tumors; likely causes differ by patient age and by location of the mass (anterior, middle, or posterior mediastinum). The masses may be asymptomatic (in adults) or cause obstructive respiratory symptoms (in children). Testing involves CT with biopsy and adjunctive tests as needed. Treatment differs by cause.

Etiology

Mediastinal masses are divided into those that occur in the anterior, middle, and posterior mediastinum. The anterior mediastinum extends from the sternum to the pericardium and brachiocephalic vessels posteriorly. The middle mediastinum lies between the anterior and posterior mediastinum. The posterior mediastinum is bounded by the pericardium and trachea anteriorly and the vertebral column posteriorly.

Adults: In adults, thymomas and lymphomas (both Hodgkin and non-Hodgkin) are the most common anterior lesions, lymph node enlargement and vascular masses are the most common middle lesions, and neurogenic tumors and esophageal abnormalities are the most common posterior lesions. For other causes, see Fig. 204-1.

Children: In children, the most common mediastinal masses are neurogenic tumors and cysts. For other causes, see Table 204-1.

Symptoms and Signs

Many mediastinal masses are asymptomatic. In general, malignant lesions and masses in children are much more likely to cause symptoms. The most common symptoms are chest pain and weight loss. Lymphomas may manifest with fever and weight loss. In children, mediastinal masses are more likely to cause tracheobronchial compression and stridor or symptoms of recurrent bronchitis or pneumonia.

Symptoms and signs also depend on location. Large anterior mediastinal masses may cause dyspnea when patients are supine. Lesions in the middle mediastinum may compress blood vessels or airways, causing the superior vena cava syndrome or airway obstruction. Lesions in the posterior mediastinum may encroach on the esophagus, causing dysphagia or odynophagia.

Diagnosis

- Chest x-ray
- CT
- Sometimes tissue examination

Mediastinal masses are most often incidentally discovered on chest x-ray or other imaging tests during an
examination for chest symptoms. Additional diagnostic testing, usually imaging and biopsy, is indicated to determine etiology.

CT with IV contrast is the most valuable imaging technique. With thoracic CT, normal variants and benign tumors, such as fat- and fluid-filled cysts, can be distinguished from other processes. A definitive diagnosis can be obtained for many mediastinal masses with needle aspiration or needle biopsy. Fine-needle aspiration techniques usually suffice for carcinomatous lesions, but a cutting-needle biopsy should be done whenever lymphoma, thymoma, or a neural mass is suspected. If ectopic thyroid tissue is considered, thyroid-stimulating hormone is measured.

**Treatment**

Treatment depends on etiology. Some benign lesions, such as pericardial cysts, can be observed. Most malignant tumors should be removed surgically, but some, such as lymphomas, are best treated with chemotherapy. Granulomatous disease should be treated with the appropriate antimicrobial drug.

**Mediastinitis**

Mediastinitis is inflammation of the mediastinum. Acute mediastinitis usually results from esophageal perforation or median sternotomy. Symptoms include severe chest pain, dyspnea, and fever. The diagnosis is confirmed by chest x-ray or CT. Treatment is with antibiotics (eg, clindamycin plus ceftriaxone) and sometimes surgery.

The 2 most common causes of acute mediastinitis are esophageal perforation and median sternotomy.

Esophageal perforation may complicate esophagoscopy or insertion of a Sengstaken-Blakemore or Minnesota tube (for esophageal variceal bleeding). Rarely, it results from forceful vomiting (Boerhaave's syndrome). Another possible cause is swallowing caustic substances (eg, lye, certain button batteries). Certain pills or esophageal ulcers (eg, in AIDS patients with esophagitis) can contribute.

Patients with esophageal perforation become acutely ill within hours, with severe chest pain and dyspnea due to mediastinal inflammation. Diagnosis is usually obvious from clinical presentation and a history of instrumentation or of another risk factor. The diagnosis should also be considered in patients who are very ill, have chest pain, and may have a risk factor that they cannot describe (eg, in intoxicated patients who may have vomited forcefully but do not remember and in preverbal children who may have ingested a button battery). The diagnosis is confirmed by chest x-ray or CT showing air in the mediastinum.

Treatment is with parenteral antibiotics selected to be effective against oral and GI flora (eg, clindamycin 450 mg IV q 6 h plus ceftriaxone 2 g once/day, for at least 2 wk). Patients who have severe mediastinitis with pleural effusion or pneumothorax require emergency exploration of the mediastinum with primary repair of the esophageal tear and drainage of the pleural space and mediastinum.

**Median sternotomy:** This procedure is complicated by mediastinitis in about 1% of cases. Patients most commonly present with wound drainage or sepsis. Diagnosis is based on finding infected fluid obtained by a needle aspiration through the sternum. Treatment consists of immediate surgical drainage, debridement, and parenteral broad-spectrum antibiotics. Mortality approaches 50% in some series.

**Chronic fibrosing mediastinitis:** This condition is usually due to TB or histoplasmosis but can be due to sarcoidosis, silicosis, or other fungal diseases. An intense fibrotic process develops, leading to compression of mediastinal structures that can cause the superior vena cava syndrome, tracheal narrowing, or obstruction of the pulmonary arteries or veins.

Diagnosis is based on CT. If the cause is TB, anti-TB therapy is indicated. Otherwise, no known treatment is beneficial, but insertion of vascular or airway stents can be considered.

**Pleural Effusion**

Pleural effusions are accumulations of fluid within the pleural space. They have multiple causes...
and usually are classified as transudates or exudates. Detection is by physical examination and chest x-ray; thoracentesis and pleural fluid analysis are often required to determine cause. Asymptomatic transudates require no treatment. Symptomatic transudates and almost all exudates require thoracentesis, chest tube drainage, pleurodesis, pleurectomy, or a combination.

Normally, 10 to 20 mL of pleural fluid, similar in composition to plasma but lower in protein (< 1.5 g/dL), is spread thinly over visceral and parietal pleurae, facilitating movement between the lung and chest wall. The fluid enters the pleural space from systemic capillaries in the parietal pleurae and exits via parietal pleural stomas and lymphatics. Pleural fluid accumulates when too much fluid enters or too little exits the pleural space.

Etiology

Pleural effusions are usually categorized as transudates or exudates based on laboratory characteristics of the fluid (see Table 204-2). Whether unilateral or bilateral, a transudate can usually be treated without extensive evaluation, whereas the cause of an exudate requires investigation. There are numerous causes (see Table 204-3).

Transudative effusions are caused by some combination of increased hydrostatic pressure and decreased plasma oncotic pressure. Heart failure is the most common cause, followed by cirrhosis with ascites and hypoalbuminemia, usually due to the nephrotic syndrome.

Exudative effusions are caused by local processes leading to increased capillary permeability resulting in exudation of fluid, protein, cells, and other serum constituents. Causes are numerous; the most common are pneumonia, cancer, pulmonary embolism, viral infection, and TB. Yellow nail syndrome is a rare disorder causing chronic exudative pleural effusions, lymphedema, and dystrophic yellow nails—all thought to be the result of impaired lymphatic drainage.

Chylous effusion (chylothorax) is a milky white effusion high in triglycerides caused by traumatic or neoplastic (most often lymphomatous) damage to the thoracic duct. Chylous effusion also occurs with the superior vena cava syndrome.

Chyliform (cholesterol or pseudochylous) effusions resemble chylous effusions but are low in triglycerides and high in cholesterol. Chyliform effusions are thought to be due to release of cholesterol from lysed RBCs and neutrophils in long-standing effusions when absorption is blocked by the thickened pleura.

Hemothorax is bloody fluid (pleural fluid Hct > 50% peripheral Hct) in the pleural space due to trauma or, rarely, as a result of coagulopathy or after rupture of a major blood vessel, such as the aorta or pulmonary artery.

Empyema is pus in the pleural space. It can occur as a complication of pneumonia, thoracotomy, abscesses (lung, hepatic, or subdiaphragmatic), or penetrating trauma with secondary infection. Empyema necessitatis is soft-tissue extension of empyema leading to chest wall infection and external drainage.

Trapped lung is a lung encased by a fibrous peel caused by empyema or tumor. Because the lung cannot expand, the pleural pressure becomes more negative than normal, increasing transudation of fluid from parietal pleural capillaries. The fluid characteristically is borderline between a transudate and an exudate; ie, the biochemical values are within 15% of the cutoff levels for Light's criteria (see Table 204-2).
Iatrogenic effusions can be caused by migration or misplacement of a feeding tube into the trachea or perforation of the superior vena cava by a central venous catheter, leading to infusion of tube feedings or IV solution into the pleural space.

Effusions with no obvious cause are often due to occult pulmonary emboli, TB, or cancer. Etiology is unknown for about 15% of effusions even after extensive study; many of these effusions are thought to be due to viral infection.

Symptoms and Signs

Some pleural effusions are asymptomatic and are discovered incidentally during physical examination or on chest x-ray. Many cause dyspnea, pleuritic chest pain, or both. Pleuritic chest pain, a vague discomfort or sharp pain that worsens during inspiration, indicates inflammation of the parietal pleura. Pain is usually felt over the inflamed site, but referred pain is possible. The posterior and peripheral portions of the diaphragmatic pleura are supplied by the lower 6 intercostal nerves, and irritation there may cause pain in the lower chest wall or abdomen that may simulate intra-abdominal disease. Irritation of the central portion of the diaphragmatic pleura, innervated by the phrenic nerves, causes pain referred to the neck and shoulder.

Physical examination reveals absent tactile fremitus, dullness to percussion, and decreased breath sounds on the side of the effusion. These findings can also be caused by pleural thickening. With large-volume effusions, respiration is usually rapid and shallow. A pleural friction rub, although infrequent, is the classic physical sign. The friction rub varies from a few intermittent sounds that may simulate crackles to a fully developed harsh grating, creaking, or leathery sound synchronous with respiration, heard during inspiration and expiration. Friction sounds adjacent to the heart (pleuroperticardial rub) may vary with the heartbeat and may be confused with the friction rub of pericarditis. Pericardial rub is best heard over the left border of the sternum in the 3rd and 4th intercostal spaces, is characteristically a to-and-fro sound synchronous with the heartbeat, and is not influenced significantly by respiration. Sensitivity and specificity of the physical examination for detecting effusion are probably low.

Diagnosis

• Chest x-ray

• Pleural fluid analysis

• Sometimes helical CT or other tests

Pleural effusion is suspected in patients with pleuritic pain, unexplained dyspnea, or suggestive signs. Diagnostic tests are indicated to document the presence of pleural fluid and to determine its cause (see Fig. 204-2).

Presence of effusion: Chest x-ray is the first test done to confirm the presence of pleural fluid. The lateral upright chest x-ray should be examined when a pleural effusion is suspected. In an upright x-ray, 75 mL of fluid blunts the posterior costophrenic angle. Blunting of the lateral costophrenic angle usually requires about 175 mL but may take as much as 500 mL. Larger pleural effusions opacify portions of the hemithorax and may cause mediastinal shift; effusions > 4 L may cause complete opacification of the hemithorax and mediastinal shift to the contralateral side.

Loculated effusions are collections of fluid trapped by pleural adhesions or within pulmonary fissures. Lateral decubitus x-rays, chest CT, or ultrasonography should be done if it is unclear whether an x-ray density represents fluid or parenchymal infiltrates or whether suspected fluid is loculated or free-flowing; [Fig. 204-2. Diagnosis of pleural effusion.]

these tests are more sensitive than upright x-rays and can detect fluid volumes < 10 mL. Loculated effusions, particularly those in the horizontal or oblique fissure, can be confused with a solid pulmonary mass (pseudotumor). They may change shape and size with changes in the patient's position and amount
of pleural fluid.

CT is not routinely indicated but is valuable for evaluating the underlying lung parenchyma for infiltrates or masses when the lung is obscured by the effusion or when the detail on chest x-rays is insufficient and for distinguishing loculated fluid from a solid mass.

**Cause of effusion:** Thoracentesis (see p. 1864) should be done in almost all patients who have pleural fluid that is ≥ 10 mm in thickness on CT, ultrasonography, or lateral decubitus x-ray and that is new or of uncertain etiology. In general, the only patients who do not require thoracentesis are those who have heart failure with symmetric pleural effusions and no chest pain or fever; in these patients, diuresis can be tried, and thoracentesis avoided unless effusions persist for ≥ 3 days.

Despite common practice, chest x-ray need not be repeated after thoracentesis unless patients develop symptoms suggesting pneumothorax (dyspnea or chest pain) or unless there is reason to suspect that air may have entered the pleural space during the procedure. Thoracentesis and subsequent pleural fluid analysis often are not necessary for pleural effusions that are chronic, have a known cause, and cause no symptoms.

Ultrasonography is helpful for identifying the site for thoracentesis when the amount of pleural fluid is small, the fluid is loculated, or blind thoracentesis is unsuccessful.

Pleural fluid analysis is done to diagnose the cause of pleural effusion. Analysis begins with visual inspection, which can

- Distinguish bloody and chylous (or chyliform) from other effusions
- Identify purulent effusions strongly suggestive of empyema
- Identify viscous fluid, which is characteristic of some mesotheliomas

Fluid should always be sent for total protein, LDH, cell count and cell differential, Gram stain, and aerobic and anaerobic bacterial cultures. Other tests (glucose, cytology, TB fluid markers [adenosine deaminase or interferon-γ], amylase, mycobacterial and fungal stains and cultures) are used in appropriate clinical settings.

Fluid chemistries help distinguish transudates from exudates; multiple criteria exist, but not one perfectly discriminates between the 2 types. When Light's criteria are used (see Table 204-2), serum LDH and total protein levels should be measured as close as possible to the time of thoracentesis for comparison with pleural fluid. Light's criteria correctly identify almost all exudates but misidentify about 20% of transudates as exudates. If transudative effusion is suspected (eg, due to heart failure or cirrhosis) and none of the biochemical measurements are > 15% above the cutoff levels for Light's criteria, the difference between serum and the pleural fluid protein is measured. If the difference is > 3.1 g/dL, the patient probably has a transudative effusion.

If the diagnosis remains unclear after pleural fluid analysis, helical CT is indicated to look for pulmonary emboli, pulmonary infiltrates, or mediastinal lesions. Findings of pulmonary emboli indicate the need for long-term anticoagulation; parenchymal infiltrates, the need for bronchoscopy; and mediastinal lesions, the need for transthoracic needle aspiration or mediastinoscopy. However, helical CT requires patients to hold their breath for ≥ 24 sec, and not all patients can comply. If helical CT is unrevealing, observation is the best course unless the patient has a history of cancer, weight loss, persistent fever, or other findings suggesting cancer or TB, in which case thoracoscopy may be indicated. Needle biopsy of the pleura can be done when thoracoscopy is unavailable. When thoracoscopy is unrevealing, an open thoracotomy must sometimes be done. Most patients with exudative effusions should have a PPD placed with a control on the other arm, but TB can neither be diagnosed if the PPD result is positive nor definitively excluded if it is negative, so pleural biopsy is generally needed.

**Treatment**
• Treatment of symptoms and underlying disorder

• Drainage of some symptomatic effusions

• Other treatments for parapneumonic and malignant effusions

The effusion itself generally does not require treatment if it is asymptomatic when the underlying disorder is treated because many effusions resorb spontaneously, especially those due to uncomplicated pneumonias, pulmonary embolism, or surgery. Pleuritic pain can usually be managed with NSAIDs or other oral analgesics. At times, a short course of oral opioids is required.

Thoracentesis is sufficient treatment for many symptomatic effusions and can be repeated for effusions that reaccumulate. Removal of fluid can be continued until the patient develops chest tightness, chest pain, or severe coughing.

Effusions that are chronic, recurrent, and causing symptoms can be treated with pleurodesis or by intermittent drainage with an indwelling catheter (see p. 2003). Effusions caused by pneumonia and cancer may require additional specific measures.

Parapneumonic effusion and empyema: In patients with adverse prognostic factors (pH < 7.20, glucose < 60 mg/dL, positive Gram stain or culture, loculations), the effusion should be completely drained via thoracentesis or tube thoracostomy. If complete drainage is impossible, a thrombolytic (fibrinolytic) drug (eg, urokinase 100,000 units or tissue plasminogen activator 10 mg in 100 mL saline solution) can be administered intrapleurally, but the effectiveness of this intervention is unproved. If attempts at drainage are unsuccessful, thoracostomy should be done to lyse adhesions and remove fibrous tissue coating the lung to allow the lung to expand. If thoracoscopy is unsuccessful, thoracotomy with surgical decortication (eg, removal of scar, clot, or fibrous membrane surrounding the lung) is necessary.

Malignant pleural effusion: If dyspnea caused by malignant pleural effusion is relieved by thoracentesis but fluid reaccumulates (with dyspnea), chronic (intermittent) drainage or pleurodesis is indicated. Asymptomatic effusions and effusions causing dyspnea unrelieved by thoracentesis do not require additional procedures.

Indwelling catheter drainage is the preferred approach for ambulatory patients because hospitalization is not necessary for catheter insertion and the pleural fluid can be drained intermittently into vacuum bottles. Pleurodesis is done by instilling a sclerosing agent into the pleural space to fuse the visceral and parietal pleura and eliminate the space. The most effective and commonly used sclerosing agents are t alc, doxycycline, and bleomycin delivered via chest tube or thoracotomy. Pleurodesis is contraindicated if the mediastinum has shifted toward the side of the effusion or if the lung does not expand after a chest tube is inserted.

Shunting of pleural fluid to the peritoneum (pleuroperitoneal shunt) is useful for patients with malignant effusion in whom pleurodesis is unsuccessful and in patients who have trapped lung.

Pleural Fibrosis and Calcification

Pleural fibrosis and calcification are usually benign sequelae of pleural inflammation or asbestos exposure.

Pleural fibrosis and calcification can be either postinflammatory or asbestos related. These disorders are suspected and diagnosed based on imaging studies.

Postinflammatory: Pleural inflammation commonly causes acute pleural thickening due to fibrosis. In most cases, the thickening resolves almost completely. Some patients are left with minor degrees of pleural thickening, which usually causes no symptoms or impairment of lung function. Occasionally, the lung becomes encased with a thick, fibrous pleural peel that limits expansion, pulls the mediastinum toward the side of disease, and impairs pulmonary function. Chest x-ray shows asymmetry of the lungs.
with thickened pleura (trapped lung). Differentiating localized pleural thickening from loculated pleural fluid may be difficult on x-ray, but this differentiation is easily made with CT.

Pleural fibrosis after inflammation can, on occasion, calcify. Calcification produces a dense image on the chest x-ray and almost always involves the visceral pleura. Postinflammatory calcifications are invariably unilateral.

**Asbestos-related:** Exposure to asbestos can lead to focal, plaquelike pleural fibrosis, at times with calcification, occurring up to ≥ 20 yr after the initial exposure. Diagnosis is usually by chest-x-ray. The diameter of the plaques can vary from several millimeters to 10 cm. Any pleural or pericardial surface can be affected, but asbestos-related pleural plaques are usually in the lower two thirds of the thorax and are bilateral. Calcification most often affects the parietal and diaphragmatic pleura and spares the costophrenic sulci and apices. Calcification may be the only evidence of exposure. Dense pleural fibrosis surrounding the entire lung and >1 cm in thickness can also follow asbestos exposure.

**Pneumomediastinum**

**Pneumomediastinum is air in mediastinal interstices.**

The 3 main causes of pneumomediastinum are alveolar rupture with dissection of air into the mediastinum, esophageal perforation, and esophageal or bowel rupture with dissection of air from the neck or the abdomen into the mediastinum.

The primary symptom is substernal chest pain which can, on occasion, be severe. Physical examination may show subcutaneous emphysema, usually in the suprasternal notch, along with a crunching or clicking noise synchronous with the heartbeat; this noise is best heard over the heart when the patient is in the left lateral decubitus position (Hamman's sign).

The diagnosis is confirmed by chest x-ray, which shows air in the mediastinum.

Treatment usually is not necessary, although tension pneumomediastinum with compression of mediastinal structures (rare) can be relieved with needle aspiration, leaving the needle open to the atmosphere as is done with tension pneumothorax. Hospital admission is required if pneumomediastinum is secondary to esophageal or bowel rupture but not necessarily if secondary to alveolar rupture.

**Pneumothorax**

**Pneumothorax is air in the pleural space causing partial or complete lung collapse.**

Pneumothorax can occur spontaneously or result from trauma or medical procedures. Diagnosis is based on clinical criteria and chest x-ray. Most pneumothoraces require transcatheter aspiration or tube thoracostomy.

Intrapleural pressure is normally negative (less than atmospheric pressure) because of inward lung and outward chest wall recoil. In pneumothorax, air enters the pleural space from outside the chest or from the lung itself via mediastinal tissue planes or direct pleural perforation. Intrapleural pressure increases, and lung volume decreases.

**Etiology**

**Primary spontaneous pneumothorax** occurs in patients without underlying pulmonary disease, classically in tall, thin young men in their teens and 20s. It is thought to be due to spontaneous rupture of subpleural apical blebs or bullae that result from smoking or that are inherited. It generally occurs at rest, although some cases occur during activities involving reaching or stretching. Primary spontaneous pneumothorax also occurs during diving and high-altitude flying because of unequally transmitted pressure changes in the lung.

**Secondary spontaneous pneumothorax** occurs in patients with underlying pulmonary disease. It most often results from rupture of a bleb or bulla in patients with severe COPD (forced expiratory volume in 1
sec [FEV₁] < 1 L), HIV-related *Pneumocystis jirovecii* infection, cystic fibrosis, or any underlying pulmonary parenchymal disease (see Table 204-4). Secondary spontaneous pneumothorax is more serious than primary spontaneous pneumothorax because it occurs in patients whose underlying lung disease decreases their pulmonary reserve. Catamenial pneumothorax is a rare form of secondary spontaneous pneumothorax that occurs within 48 h of the onset of menstruation in premenopausal women and sometimes in postmenopausal women taking estrogen. The cause is intrathoracic endometriosis, possibly due to migration of peritoneal endometrial tissue through diaphragmatic defects or embolization through pelvic veins.

| Table 204-4: Causes of Secondary Spontaneous Pneumothorax |

**Traumatic pneumothorax** is a common complication of penetrating or blunt chest injuries.

**Tension pneumothorax** is a pneumothorax causing a progressive rise in intrapleural pressure to levels that become positive throughout the respiratory cycle and collapse the lung, shift the mediastinum, and impair venous return to the heart. Air continues to get into the pleural space but cannot exit. Without appropriate treatment, the impaired venous return can cause systemic hypotension and respiratory and cardiac arrest (pulseless electrical activity) within minutes. Tension pneumothorax most commonly occurs in patients receiving positive-pressure ventilation (with mechanical ventilation or particularly during resuscitation). Rarely, it is a complication of traumatic pneumothorax, when a chest wound acts as a one-way valve that traps increasing volumes of air in the pleural space during inspiration.

**Iatrogenic pneumothorax** is caused by medical interventions, including transthoracic needle aspiration, thoracentesis, central venous catheter placement, mechanical ventilation, and cardiopulmonary resuscitation.

**Symptoms and Signs**

Small pneumothoraces are occasionally asymptomatic. Symptoms of pneumothoraces include dyspnea and pleuritic chest pain. Dyspnea may be sudden or gradual in onset depending on the rate of development and size of the pneumothorax. Pain can simulate pericarditis, pneumonia, pleuritis, pulmonary embolism, musculoskeletal injury (when referred to the shoulder), or an intra-abdominal process (when referred to the abdomen). Pain can also simulate cardiac ischemia, although typically the pain of cardiac ischemia is not pleuritic.

Physical findings classically consist of absent tactile fremitus, hyperresonance to percussion, and decreased breath sounds on the affected side. If the pneumothorax is large, the affected side may be enlarged with the trachea visibly shifted to the opposite side. With tension pneumothorax, hypotension can occur.

**Diagnosis**

- **Upright inspiratory chest x-ray**

The diagnosis is suspected in stable patients with dyspnea or pleuritic chest pain and is confirmed with upright inspiratory chest x-ray. Radiolucent air and the absence of lung markings juxtaposed between a shrunken lobe or lung and the parietal pleura are diagnostic of pneumothorax. Tracheal deviation and mediastinal shift occur with large pneumothoraces.

The size of a pneumothorax is defined as the percentage of the hemithorax that is vacant. This percentage is estimated by taking 1 minus the ratio of the cubes of the width of the lung and hemithorax. For example, if the width of the hemithorax is 10 cm and the width of the lung is 5 cm, the ratio is \(5^3/10^3 = 0.125\). Thus, the size of the pneumothorax is about 1 minus 0.125, or 87.5%. If adhesions are present between the lung and the chest wall, the lung does not collapse symmetrically, the pneumothorax may appear atypical or loculated, and the calculation is not accurate.

Small pneumothoraces (eg, < 10%) are sometimes overlooked on chest x-ray. Conditions that mimic
pneumothorax radiographically include emphysematous bullae, skinfolds, folded bed sheets, and overlap of stomach or bowel markings on lung fields.

Tension pneumothorax is suspected in patients with sudden, unexplained hypotension and dyspnea or some risk factor, particularly positive pressure ventilation. If such a patient also has signs of pneumothorax, such as decreased breath sounds and hyperresonance to percussion, tension pneumothorax should be assumed.

**Treatment**

- Immediate needle decompression for tension pneumothoraces
- Observation and follow-up x-ray for small, asymptomatic primary spontaneous pneumothoraces
- Catheter aspiration for large or symptomatic primary spontaneous pneumothoraces
- Tube thoracostomy for secondary and traumatic pneumothoraces

Patients should receive supplemental O$_2$ until chest x-ray results are available because O$_2$ accelerates pleural reabsorption of air. Treatment then depends on the type, size, and effects of pneumothorax. Primary spontaneous pneumothorax that is < 20% and that does not cause respiratory or cardiac symptoms can be safely observed without treatment if follow-up chest x-rays obtained at about 6 and 48 h show no progression. Larger or symptomatic primary spontaneous pneumothoraces should be evacuated by catheter aspiration. Tube thoracostomy is an alternative.

Catheter aspiration is accomplished by insertion of a small-bore (about 7 to 9 French) IV or pigtail catheter into the chest in the 2nd intercostal space at the midclavicular line. The catheter is attached to a 3-way stopcock and syringe. Air is withdrawn from the pleural space through the stopcock into the syringe and expelled into the room. The process is repeated until the lung re-expands or until 4 L of air are removed. If the lung expands, the catheter can be removed or kept in place attached to a one-way Heimlich valve (thus permitting ambulation), and the patient need not be hospitalized. If the lung does not expand, a chest tube should be inserted, and the patient should be hospitalized. Primary spontaneous pneumothoraces can also be managed initially with a chest tube attached to a water seal without or with suction. Patients with primary spontaneous pneumothoraces should also undergo smoking cessation counseling.

Secondary and traumatic pneumothoraces are generally treated with tube thoracostomy. (see p. 1866). Symptomatic patients with iatrogenic pneumothoraces are best managed initially with aspiration.

**Tension pneumothorax is a medical emergency, and time should not be wasted confirming the diagnosis with a chest x-ray.** It should be treated immediately by inserting a 14- or 16-gauge needle with a catheter through the chest wall in the 2nd intercostal space at the midclavicular line. The sound of high-pressure air escaping confirms diagnosis. The catheter can be left open to air or attached to a Heimlich valve. Emergency decompression must be followed immediately by tube thoracostomy, after which the catheter is removed.

**Complications**

The 3 main problems encountered when treating pneumothorax are air leaks, failure of the lung to expand, and re-expansion pulmonary edema.

Air leaks are usually due to the primary defect—ie, continued leakage of air from the lung into the pleural space—but can be due to air leaking around the chest tube insertion site if the site is not properly sutured and sealed. Air leaks are more common in secondary than in primary spontaneous pneumothorax. Most resolve spontaneously in < 1 wk.

Failure of the lung to re-expand is usually due to a persistent air leak, an endobronchial obstruction, a trapped lung, or a malpositioned chest tube. Thoracoscopy or thoracotomy should be considered if an air
leak or an incompletely expanded lung persists beyond 1 wk.

Re-expansion pulmonary edema occurs when the lung is rapidly expanded, as occurs when a chest tube is connected to negative pressure after the lung has been collapsed for > 2 days. Treatment is supportive, with O₂, diuretics, and cardiopulmonary support as needed.

Prevention

Recurrence approaches 50% in the 3 yr after initial spontaneous pneumothorax. The best preventive procedure is video-assisted thoracic surgery (VATS) in which blebs are stapled and pleurodesis is done with pleural abrasion, parietal pleurectomy, or talc insufflation; in some medical centers, thoracotomy is still used. These procedures are recommended when catheter aspiration fails with spontaneous pneumothorax, when pneumothorax recurs, or when patients have secondary spontaneous pneumothorax. Recurrence after these procedures is < 5%. If thoracoscopy cannot be done or is contraindicated, chemical pleurodesis through a chest tube may be done (see p. 2001); this procedure, though much less invasive, reduces the recurrence rate to only about 25%.

Viral Pleuritis

Viral pleuritis is a viral infection of the pleurae.

Viral pleuritis is most commonly caused by infection with coxsackie B virus. Occasionally, echovirus causes a rare condition known as epidemic or Bornholm's pleurodynia, manifesting as pleuritis, fever, and chest muscle spasms. The condition occurs in the late summer and affects adolescents and young adults.

The primary symptom of viral pleuritis is pleuritic pain; pleural friction rub may be a sign (see p. 1998).

Diagnosis is suspected in patients with pleuritic chest pain with or without systemic symptoms of viral infection. Chest x-ray is usually done. Other causes of pleuritic chest pain, such as pulmonary emboli and pneumonia, need to be considered and sometimes ruled out with testing.

Treatment is symptomatic, with oral NSAIDs or a short course of oral opioids if needed.
Chapter 205. Tumors of the Lungs

Introduction

Lung tumors may be primary or metastatic from other sites in the body. Primary tumors of the lung may be malignant (see Table 205-1) or benign (see Table 205-2). The most common lung tumor is lung carcinoma, also called bronchogenic carcinoma or lung cancer.

Lung Carcinoma

Lung carcinoma is the leading cause of cancer-related death worldwide. About 85% of cases are related to cigarette smoking. Symptoms can include cough, chest discomfort or pain, weight loss, and, less commonly, hemoptysis; however, many patients present with metastatic disease without any clinical symptoms. The diagnosis is typically made by chest x-ray or CT scan and confirmed by biopsy. Depending on the stage of the disease, treatment includes surgery, chemotherapy, radiation therapy, or a combination. Despite advances in treatment, the prognosis remains poor, with only 15% of patients surviving > 5 yr from time of diagnosis. For patients with stage IV (metastatic) disease, the 5-yr overall survival rate is < 1%. Improving survival requires focusing attention on smoking cessation, early detection, and research into the genetic profile of lung tumors and developing novel forms of therapy.

Epidemiology

In 2007, an estimated 213,380 new cases of lung cancer were diagnosed in the US, and about 160,390 people died from the disease. The incidence of lung cancer has been rising in women but appears to be leveling off in men.

Etiology

Cigarette smoking is the most important cause of lung cancer, accounting for about 85% of cases. The risk of cancer differs by age, smoking intensity, and smoking duration; the risk of cancer declines after smoking cessation, but it never returns to baseline. About 15% of people who develop lung cancer have never smoked. In these people, the exact reason lung cancer develops is unknown. Recent studies have reported that some never-smoking people with lung cancer have genetic mutations in the epidermal growth factor gene (EGFR). Although an environmental association has not clearly been established, it is theorized that exposure to radon gas, a breakdown product of naturally occurring radium and uranium, may be an environmental risk factor. Other possible risk factors include exposure to secondhand smoke and exposure to carcinogens, such as asbestos, radiation, arsenic, chromates, nickel, chloromethyl ethers, mustard gas, or coke-oven emissions, encountered or breathed in at work.

The risk of lung cancer increases with combined exposure to occupational carcinogens, toxins, and cigarette smoking. It is suspected that COPD and pulmonary fibrosis (α1-antitrypsin deficiency) may increase susceptibility to lung cancer. Also, active smokers who take β-carotene supplements have an increased risk of developing lung cancer. Air pollution and cigar smoke contain carcinogens; these substances have not been shown to cause lung cancer, although they may be associated with an increased risk. People whose lungs are scarred by other lung diseases (eg, TB) are at an increased risk of lung cancer.

Respiratory epithelial cells require prolonged exposure to cancer-promoting agents and accumulation of multiple genetic mutations before becoming neoplastic (an effect called field carcinogenesis). Over time, mutations in genes that stimulate cell growth (K-ras, MYC) cause abnormalities in growth factor receptor signaling (EGFR, HER2/neu), inhibit apoptosis (BCL-2), and contribute to proliferation of abnormal cells.
In addition, mutations that inhibit tumor-suppressor genes (p53, APC) can lead to cancer.

**Classification**

Lung cancer is classified into 2 major categories:

- Small cell lung cancer (SCLC)
- Non-small cell lung cancer (NSCLC)

SCLC is highly aggressive and almost always occurs in smokers. It is rapidly growing, and roughly 60% of patients have widespread metastatic disease at the time of diagnosis.

The clinical behavior of NSCLC is more variable and depends on histologic type, but about 40% of patients have metastatic disease outside of the chest at the time of diagnosis.

Other features of the 2 categories (eg, location, risks, treatment, complications) also vary (see Table 205-3).

**Symptoms and Signs**

About 25% of lung cancers are asymptomatic and are detected incidentally with chest imaging. Symptoms and signs can result from local tumor progression, regional spread, or distant metastases. Paraneoplastic syndromes and constitutional symptoms may occur at any stage of the disease. Although symptoms are not specific to the classification or histology of the cancer, certain complications may be more likely with different types (see Table 205-3).

**Local tumor:** The local tumor can cause cough and, less commonly, dyspnea due to airway obstruction, postobstructive atelectasis, and lymphangitic spread. Fever may occur with postobstructive pneumonia. Up to half of patients report vague or localized chest pain. Hemoptysis is less common, and blood loss is minimal, except in rare instances when the tumor erodes into a major artery, causing massive hemorrhage and death by exsanguination and asphyxiation.

**Regional spread:** Regional spread of the tumor may cause pleuritic chest pain or dyspnea due to development of a pleural effusion, hoarseness due to tumor encroachment on the recurrent laryngeal nerve, and dyspnea and hypoxia caused by diaphragmatic paralysis due to involvement of the phrenic nerve.

Superior vena cava (SVC) syndrome results from compression or invasion of the SVC and can cause headache or a sensation of head fullness, facial or upper-extremity swelling, supine breathlessness, and flushing (plethora). Physical signs of SVC syndrome include facial and upper-extremity edema, dilated neck and subcutaneous veins in the face and upper trunk, and facial and truncal plethora.

Apical tumors, usually NSCLC, can invade the brachial plexus, pleura, or ribs, causing shoulder and upper-extremity pain and atrophy of the ipsilateral hand (Pancoast's tumor). Horner's syndrome (ptosis, miosis, enophthalmos, and anhidrosis) results when the paravertebral sympathetic chain or cervical stellate ganglion is involved. Spread of the tumor to the pericardium may be asymptomatic or lead to constrictive pericarditis or cardiac tamponade (see p. 2201). Rarely, esophageal compression causes dysphagia.

**Metastases:** Metastases eventually cause symptoms that vary by location. Metastases to the liver cause pain, GI symptoms, and ultimately hepatic insufficiency. Metastases to the brain cause behavioral changes, confusion, aphasia, seizures, paresis or paralysis, nausea and vomiting, and ultimately coma.
and death. Bone metastases can lead to severe pain and pathologic fractures. Although lung cancer commonly metastasizes to the adrenal glands, it rarely leads to adrenal insufficiency.

Paraneoplastic syndromes: Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastases (see p. 1054). Common paraneoplastic syndromes in patients with lung cancer include hypercalcemia (in patients with squamous cell carcinoma, which results because the tumor produces parathyroid hormone-related protein), syndrome of inappropriate antidiuretic hormone secretion (SIADH), finger clubbing with or without hypertrophic pulmonary osteoarthropathy, hypercoagulability with migratory superficial thrombophlebitis (Trousseau’s syndrome), myasthenia (Eaton-Lambert syndrome), and various neurologic syndromes, including neuropathies, encephalopathies, encephalitides, myelopathies, and cerebellar disease. Mechanisms for neuromuscular syndromes involve tumor expression of autoantigens with production of autoantibodies, but the cause of most other syndromes is unknown.

Diagnosis

- Chest x-ray
- CT or combined PET-CT
- Cytopathology examination of pleural fluid or sputum
- Usually bronchoscopy-guided biopsy and fine-needle aspiration
- Sometimes open lung biopsy

Chest x-ray is often the initial imaging test. It may show clearly defined abnormalities, such as a single mass or multifocal masses or a solitary pulmonary nodule (see p. 1841), an enlarged hilum, widened mediastinum, tracheobronchial narrowing, atelectasis, nonresolving parenchymal infiltrates, cavitary lesions, or unexplained pleural thickening or effusion. These findings are suggestive but not diagnostic of lung cancer and require follow-up with CT or combined PET-CT and cytopathologic confirmation.

CT demonstrates many characteristic anatomic patterns and appearances that may confirm the diagnosis. CT also can guide needle biopsy of accessible lesions and is useful for staging. If a lesion found on a plain x-ray is highly likely to be lung cancer, PET-CT may be done. This study combines anatomic imaging from CT with functional imaging from PET. The PET images can help differentiate inflammatory and malignant processes.

The method used to obtain cells or tissue for confirmation depends on the accessibility of tissue and the location of lesions. Sputum or pleural fluid cytology is the least invasive method. In patients with productive cough, sputum specimens obtained on awakening may contain high concentrations of malignant cells, but yield for this method is < 50% overall. Pleural fluid is another convenient source of cells; a malignant effusion is a poor prognostic sign (see Table 205-4). In general, false-negative cytology readings can be minimized by obtaining as large a volume of sputum or fluid as possible early in the day and sending the sample to the pathology laboratory immediately to minimize delays in processing, which lead to cell breakdown.

A percutaneous biopsy is the next least invasive procedure. It is more useful for metastatic sites (supraclavicular or other peripheral lymph nodes, pleura, liver, adrenals) than for lung lesions because of the 20 to 25% risk of pneumothorax and the risk of false-negative results.

Bronchoscopy is the procedure most often used for diagnosing lung cancer. In theory, the procedure of choice for obtaining tissue is the one that is least invasive. In practice, bronchoscopy is often done in addition to or instead of less invasive procedures because diagnostic yields are greater and because bronchoscopy is important for staging. A combination of washings, brushings, biopsies, and fine-needle aspirations of visible endobronchial lesions and of paratracheal, subcarinal, mediastinal, and hilar lymph nodes often yields a tissue diagnosis.
Mediastinoscopy is the gold standard test for evaluating mediastinal lymph nodes but is a higher-risk procedure, which is usually used before surgery to confirm or exclude the presence of tumor in enlarged mediastinal lymph nodes.

Open lung biopsy, done via open thoracotomy or using video assistance (see p. 1865), is indicated when less invasive methods do not provide a diagnosis in patients whose clinical characteristics and radiographic features strongly suggest that the tumor is resectable.

**Screening:** No screening studies are universally accepted for healthy patients who do not have lung cancer. Clinical trials have evaluated screening chest x-rays in high-risk patients (smokers) to try to detect lung cancers at earlier stages, but mortality did not decline. Screening CT is being evaluated because it is more sensitive, but CT produces more false-positive results, which increase the number of unnecessary invasive diagnostic procedures needed to verify the CT findings. Such procedures are costly and risk additional complications. A strategy of yearly CT screening of smokers with follow-up PET or high-resolution CT (HRCT) to evaluate indeterminate lesions is currently being studied. So far, this strategy does not seem to lessen mortality and cannot be recommended as routine practice. The future of screening may lie in a combination of molecular analysis for genetic markers (eg, K-ras, p53, EGFR), sputum cytometry, and detection of cancer-related volatile organic compounds (eg, alkane, benzene) in exhaled breath.

[Table 205-4: Proposed International Staging System for Lung Cancer*]

**Staging**

SCLC has 2 stages: limited and extensive. Limited-stage SCLC is cancer confined to one hemithorax (including ipsilateral lymph nodes) that can be encompassed within one tolerable radiation therapy port, unless there is a pleural or pericardial effusion. Extensive-stage disease is cancer outside a single hemithorax or the presence of malignant cells detected in pleural or pericardial effusions. Less than one third of patients with SCLC present with limited-stage disease; the remainder of patients often have extensive distant metastases.

NSCLC has 4 stages: I through IV. Staging is based on tumor size, tumor and lymph node location, and the presence or absence of distant metastases (see Table 205-4).

Tests for initial evaluation and staging: All lung cancer patients need whole-body imaging. Different combinations of tests can be done. Some tests are done routinely, and others are done depending on whether the results would affect treatment decisions:

- PET or integrated PET-CT
- CT from neck to pelvis (done if PET-CT is not available)
- MRI of chest (for tumors near apex or diaphragm to evaluate vascular supply)
- Biopsy of questionable nodes (if PET is indeterminate)
- Bone scan (done with CT if PET-CT is not available)
- Head CT or brain MRI

Measurement of serum Ca and alkaline phosphatase; evaluation of liver function, immune system, and kidney function; platelets; Hb; and electrolytes are needed to assist with treatment decisions.

If PET-CT is not available, thin-section CT scanning from the neck to the upper abdomen (to detect cervical and supraclavicular and hepatic and adrenal metastases) is one of the first staging tests for both SCLC and NSCLC. However, CT often cannot distinguish postinflammatory changes from malignant intrathoracic lymph node enlargement or benign lesions from malignant hepatic or adrenal lesions (distinctions that determine stage). Thus, other tests are usually done when abnormalities are present in
PET is a reasonably accurate, noninvasive test used to identify malignant mediastinal lymph nodes and other distant metastases (metabolic staging). Integrated PET-CT, in which PET and CT images are combined into a single image by scanners in a single gantry, is more accurate for NSCLC staging than CT or PET alone or than visual correlation of the 2 tests. The use of PET and integrated PET-CT is limited by cost, availability, and specificity (ie, the test is quite sensitive and has an excellent negative predictive value, but its positive predictive value is not as high). When PET results are indeterminate, bronchoscopy, mediastinoscopy, or video-assisted thoracoscopic surgery (VATS) can be used to biopsy questionable mediastinal lymph nodes. Without PET, hepatic or adrenal lesions must be evaluated by needle biopsy.

MRI of the chest is slightly more accurate than high-chest HRCT for staging apical tumors and cancers close to the diaphragm and provides evaluation of the vasculature surrounding the tumors.

Blood tests are usually done. Ca and alkaline phosphatase levels, if elevated, suggest possible bone metastases. Other blood tests, such as CBC, serum albumin levels, AST, ALT, total bilirubin, electrolytes, and creatinine levels, have no role in staging but provide important prognostic information about the patient's ability to tolerate treatment and may detect paraneoplastic syndromes.

All patients with suspected lung cancer should undergo brain imaging. Brain imaging is especially necessary in patients with headache or neurologic abnormalities. Patients with bone pain or elevated serum Ca or alkaline phosphatase levels should undergo a PET-CT or radionuclide bone scanning if PET-CT is not available.

**Prognosis**

The overall prognosis for lung cancer is poor. The median survival time for limited-stage SCLC is 20 mo, with a 5-yr survival rate of 20%. Patients with extensive-stage SCLC do especially poorly, with a 5-yr survival rate of < 1%.

The 5-yr survival rate of patients with NSCLC varies by stage, from 60 to 70% for patients with stage I disease to < 1% for patients with stage IV disease. On average, untreated patients with metastatic NSCLC survive 6 mo, whereas the median survival for treated patients is about 9 mo. Recently, patient survival has improved in both early and later stage NSCLC. Evidence shows improved survival in early-stage disease when platinum-based chemotherapy regimens are used after surgical resection. In addition, targeted therapies have improved survival in patients with stage IV disease. However, given the disappointing results in patients with metastatic disease, efforts at reducing mortality have increasingly focused on early detection and active interventions to prevent disease. Basing therapy on molecular signatures within the tumors has been the focus of laboratory and translational research.

**Treatment**

- Surgery (depending on cell type and stage)
- Chemotherapy
- Radiation therapy

Treatment varies by cell type and by stage of disease. Many patient factors not related to the tumor affect treatment choice. Poor cardiopulmonary reserve, undernutrition, frailty or poor physical performance status, comorbidities (including cytopenias), and psychiatric or cognitive illness all may lead to a decision for palliative rather than curative treatment or for no treatment at all, even though a cure with aggressive therapy might technically be possible.

Radiation therapy has the risk of radiation pneumonitis when large areas of the lung are exposed to high doses of radiation over time. Radiation pneumonitis can occur up to 3 mo after treatment is completed. Cough, dyspnea, low-grade fever, or pleuritic chest pain may signal the condition, as may crackles or a pleural friction rub detected during chest auscultation. Chest x-ray findings may be nonspecific; CT may show a nonspecific infiltrate without an obvious mass. The diagnosis is often one of exclusion. Radiation
Pneumonitis can be treated with a corticosteroid taper over several weeks and bronchodilators for symptom relief.

Multiple chemotherapy regimens exist for treatment of lung cancer. In addition to standard chemotherapy drugs, several biologic agents that specifically target lung tumors are under investigation. EGFR tyrosine kinase inhibitors may be used in patients who have not responded to platinum-based or docetaxel therapy. Bevacizumab, a vascular endothelial growth factor inhibitor, is now used in combination with standard chemotherapy regimens in certain patients. Many other biologic agents are under investigation; some specifically target cancer cell signal transduction pathways or the angiogenesis pathways that supply O₂ and nutrition to growing tumor cells.

Radiofrequency ablation, in which high-frequency electrical current is used to destroy tumor cells, is a newer technique that can sometimes be used in patients who have small, early-stage tumors or small tumors that have recurred in a previously irradiated chest. This procedure may preserve more lung function than open surgery does and, because it is less invasive, may be appropriate for patients who are not candidates for open surgery.

**SCLC:** Typically, SCLC of any stage is initially responsive to treatment, but responses are usually short-lived. Chemotherapy, with or without radiation therapy, is given depending on the stage of disease. In many patients, chemotherapy prolongs survival and improves quality of life enough to warrant its use. Surgery generally plays no role in treatment of SCLC, although it may be curative in the rare patient who has a small focal tumor without spread (such as a solitary pulmonary nodule) and who had surgical resection before the tumor was identified as SCLC.

Chemotherapy regimens of etoposide and a platinum compound (either cisplatin or carboplatin) are commonly used, as are other drugs, such as irinotecan, topotecan, vinca alkaloids (vinblastine, vincristine, vinorelbine), alkylating agents (cyclophosphamide, ifosfamide), doxorubicin, taxanes (docetaxel, paclitaxel), and gemcitabine. In limited-stage disease, radiation therapy further improves response; the very definition of limited-stage disease as disease confined to a hemithorax is based on the significant improvement in survival observed with radiation therapy. The use of cranial radiation to prevent brain metastases is also advocated in certain cases of limited- and extensive-stage disease; micrometastases are common in SCLC, and chemotherapy has less ability to cross the blood-brain barrier.

In extensive-stage disease, treatment is based on chemotherapy rather than radiation therapy, although radiation therapy is often used as palliative treatment for metastases to bone or brain. In patients with an excellent response to chemotherapy, prophylactic brain irradiation is sometimes used, as in limited-stage SCLC to prevent growth of SCLC in the brain. It is unclear whether replacing etoposide with topoisomerase inhibitors (irinotecan or topotecan) improves survival. These drugs alone or in combination with other drugs are also commonly used in refractory disease and in cancer of either stage that has recurred.

In general, patients with recurrent SCLC have a poor prognosis, although patients who maintain a good performance status should be offered a clinical trial.

**NSCLC:** Treatment for NSCLC typically involves assessment of eligibility for surgery followed by choice of surgery, chemotherapy, radiation therapy, or a combination of modalities as appropriate, depending on tumor type and stage.

For stage I and II disease, the standard approach is surgical resection with either lobectomy or pneumonectomy combined with mediastinal lymph node sampling or complete lymph node dissection. Lesser resections, including segmentectomy and wedge resection, are considered for patients with poor pulmonary reserve. Surgery is curative in about 55 to 75% of patients with stage I and in 35 to 55% of patients with stage II disease.

Surgery is done only if NSCLC patients will have adequate pulmonary reserve once a lobe or lung is resected. Patients with preoperative forced expiratory volume in 1 sec (FEV₁) > 2 L generally tolerate...
pneumonectomy. Those with FEV₁ < 2 L should have a quantitative xenon radionuclide perfusion scan to determine the proportion of function the patient can expect to lose from resection. Postoperative FEV₁ can be predicted by multiplying percent perfusion of the nonresected lung by the preoperative FEV₁. A predicted FEV₁ > 800 mL or > 40% of the predicted normal FEV₁ suggests adequate postoperative lung function, although studies of lung volume reduction surgery in COPD patients suggest that patients with FEV₁ < 800 mL can tolerate resection if the cancer is located in poorly functional, bullous (generally apical) lung regions. Patients undergoing resection at hospitals that do more resections have fewer complications and are more likely to survive than those who undergo surgery at hospitals that do fewer lung cancer procedures.

Adjuvant chemotherapy after surgery is now standard practice for patients with stage II or stage III disease, possibly also for patients with stage IB disease with tumors > 4 cm. Clinical trials have shown an increase in 5-yr survival rates with the use of adjuvant chemotherapy. However, the decision for adjuvant chemotherapy should depend on the patient’s comorbidities and risk assessment. The role of neoadjuvant chemotherapy in early-stage NSCLC is under investigation.

Stage III disease is treated with either chemotherapy, radiation therapy, surgery, or a combination; the sequence and choice of treatment depend on the location of the patient’s disease and comorbidities. In general, concurrent chemotherapy and radiation therapy are considered standard treatment for unresectable clinically staged IIIA disease, but survival remains poor (median survival, 10 to 14 mo). Patients with stage IIIB disease plus contralateral mediastinal nodal disease or supraclavicular nodal disease are offered either either radiation therapy or chemotherapy or both. Patients with locally advanced tumors invading the heart, great vessels, mediastinum, or spine usually receive radiation therapy. In some patients (with T4 N0 M0 tumors), surgical resection with either neoadjuvant or adjuvant combined chemotherapy and radiation therapy may be feasible. The 5-yr survival rate for patients with treated stage IIIB disease is 5%.

In stage IV disease, palliation of symptoms is the goal. Chemotherapy and radiation therapy may be used to reduce tumor burden, treat symptoms, and improve quality of life. However, median survival is only 9 mo, and < 25% of patients survive 1 yr. Surgical palliative procedures may be required and may include thoracentesis and pleurodesis of recurrent effusions, placement of indwelling pleural drainage catheters, bronchoscopic fulguration of tumors involving the trachea and mainstem bronchi, placement of stents to prevent airway occlusion, and, in some cases, spinal stabilization for impending spinal cord compression.

Recurrent disease: Treatment options for disease that recurs after treatment vary by location and include repeat chemotherapy for local recurrence, radiation therapy for metastases, and brachytherapy for endobronchial disease when additional external radiation cannot be tolerated. Rarely, surgical resection of a solitary metastasis or for palliative purposes is considered. The treatment of a locally recurrent NSCLC follows the same guidelines as for primary tumor stages I to III. If surgery was used initially, radiation therapy is the main modality. If the recurrence manifests as distant metastases, patients are treated as stage IV with a focus on palliation.

Complications: Asymptomatic malignant pleural effusions require no treatment. Initial treatment of a symptomatic effusion is with thoracentesis; symptomatic effusions that recur despite multiple thoracenteses are drained through a chest tube. Infusion of talc (or occasionally, tetracycline or bleomycin) into the pleural space (a procedure called pleurodesis) scars the pleura, eliminates the pleural space, and is effective in > 90% of cases (see p. 1995).

Treatment of SVC syndrome is the same as treatment of lung cancer, with chemotherapy (SCLC), radiation therapy (NSCLC), or both (NSCLC). Corticosteroids are commonly used but are of unproven benefit.

Treatment of Horner’s syndrome caused by apical tumors is with surgery with or without preoperative radiation or with radiation therapy with or without adjuvant chemotherapy.

Treatment of paraneoplastic syndromes varies by syndrome (see p. 1054).
End-of-life care: Because many patients with lung cancer die, the need for end-of-life care should be anticipated (see p. 3480). Symptoms of breathlessness can be treated with supplemental oxygen and bronchodilators. Pain, anxiety, nausea, and anorexia are especially common and can be treated with parenteral morphine; oral, transdermal, or parenteral opioids; and antiemetics. The care provided by hospice programs is extremely well-accepted by patients and families, yet this intervention is markedly underused.

Prevention

No active interventions to prevent lung cancer have proved to be effective except for smoking cessation (see p. 3432). Remediation of high radon levels in private residences removes known cancer-promoting radiation, but a reduction in lung cancer incidence is unproved. Increasing dietary intake of fruits and vegetables high in retinoids and β-carotene appears to have no effect on lung cancer incidence. Vitamin supplementation is either unproved (vitamin E) or harmful (β-carotene) in smokers. Preliminary evidence hinting that NSAIDs and vitamin E supplementation may protect former smokers from lung cancer requires confirmation. New molecular approaches targeting cell signaling and cell cycle pathways and tumor-associated antigens are under investigation.

Airway Tumors

The airway can be affected by primary tracheobronchial tumors, primary tumors that are adjacent to and invade the airway, or cancers that metastasize to the airway.

Primary tracheal tumors are rare (0.1/100,000 people). They are often malignant and found at a locally advanced stage. The most common malignant tracheal tumors include adenoid cystic carcinoma, squamous cell carcinoma, carcinoid, and mucoepidermoid carcinomas. The most common benign airway tumor is a squamous papilloma, although pleomorphic adenomas and granular cell and benign cartilaginous tumors also occur.

Symptoms and Signs

Patients often present with dyspnea, cough, wheezing, hemoptysis, and stridor. Hemoptysis may occur with a squamous cell carcinoma and can potentially lead to earlier diagnosis, whereas wheezing or stridor occurs more often with the adenoid cystic variant. Dysphagia and hoarseness can also be present initially and usually indicate advanced disease.

Diagnosis

• Bronchoscopic biopsy

Symptoms of airway narrowing can herald life-threatening airway obstruction and require immediate hospitalization and evaluation with bronchoscopy. Bronchoscopy can both stabilize the airways and allow specimens to be obtained for diagnosis. If cancer is found, more extensive testing for metastases is done (see p. 2007).

Prognosis

Prognosis depends on the histology. Squamous cell carcinomas tend to metastasize to regional lymph nodes and directly invade mediastinal structures, leading to high local and regional recurrence rates. Even with definitive surgical resection, the 5-yr survival is only 20 to 40%. Adenoid cystic carcinomas are typically indolent but tend to metastasize to the lungs and to spread perineurally, leading to high recurrence rates after resection. However, these patients have a higher 5-yr survival of 60 to 75% because of the slow rate of growth.

Treatment

• Surgery
• Sometimes radiation therapy
• Obstruction reduction techniques

Primary airway tumors should be treated definitively with surgical resection if possible. Tracheal, laryngotracheal, or carinal resections are the most common procedures. Up to 50% of the length of the trachea can be safely resected with primary re-anastomosis. If a lung or thyroid cancer invades the airway, surgery is sometimes still feasible if assessment indicates sufficient tissue is available for airway reconstruction. Adjuvant radiation therapy is recommended if adequate surgical margins cannot be obtained.

Most primary airway tumors are not resectable because of metastasis, locally advanced stage, or patient comorbidities. In cases of endoluminal tumors, a therapeutic bronchoscopy can mechanically core-out the tumor. Other techniques to eliminate obstruction include laser vaporization, photodynamic therapy, cryotherapy, and endobronchial brachytherapy. Tumors that compress the trachea are treated with airway stenting, radiation therapy, or both.

**Bronchial Carcinoid**

Bronchial carcinoids are rare, slow-growing neuroendocrine tumors arising from bronchial mucosa; they affect patients in their 40s to 60s.

Half of patients are asymptomatic, and half present with symptoms of airway obstruction, including dyspnea, wheezing, and cough, which often leads to a misdiagnosis of asthma. Recurrent pneumonia, hemoptysis, and chest pain are also common. Paraneoplastic syndromes, including Cushing’s syndrome due to ectopic ACTH, acromegaly due to ectopic growth hormone-releasing factor, and Zollinger-Ellison syndrome due to ectopic gastrin production, are more common than carcinoid syndrome (see p. 908), which occurs in < 3% of patients with the tumor. A left-sided heart murmur (mitral stenosis or regurgitation) occurs rarely due to serotonin-induced valvular damage (as opposed to the right-sided valvular lesions of GI carcinoid).

Diagnosis is based on bronchoscopic biopsy, but evaluation often initially involves chest CT, which reveals tumor calcifications in up to one third of patients. Indium-111-labeled octreotide scans are useful for determining regional and metastatic spread. Increased urinary serotonin and 5-hydroxyindoleacetic acid levels support the diagnosis, but these substances are not commonly elevated.

Treatment is with surgical removal with or without adjuvant therapy. Prognosis depends on tumor type. Five-year survival for typical (well-differentiated) carcinoids is > 90%; for atypical tumors, it is 50 to 70%.

**Chest Wall Tumors**

Chest wall tumors are benign or malignant tumors that can interfere with pulmonary function.

Primary chest wall tumors account for 5% of all thoracic tumors and 1 to 2% of all primary tumors. Almost half are benign; the most common are osteochondroma, chondroma, and fibrous dysplasia. A wide range of malignant chest wall tumors exist. Over half are metastases from distant organs or direct invasions from adjacent structures (breast, lung, pleura, mediastinum). The most common malignant primary tumors arising from the chest wall are sarcomas; about 45% originate from soft tissue, and 55% from cartilaginous or bone tissue. Chondrosarcomas are the most common primary bone chest wall sarcoma and arise in the anterior tract of ribs and less commonly from the sternum, scapula, or clavicle. Other bone tumors include osteosarcoma and small-cell malignant tumors (Ewing’s sarcoma, Askin’s tumor). The most common soft-tissue primary malignant tumors are fibrosarcomas (desmoids, neurofibrosarcomas) and malignant fibrous histiocytomas. Other primary tumors include chondroblastomas, osteoblastomas, melanomas, lymphomas, rhabdomyosarcomas, lymphangiosarcomas, multiple myeloma, and plasmacytomas.

**Symptoms and Signs**
Soft-tissue chest wall tumors often manifest as a localized mass without other symptoms. Some patients have fever. Patients usually do not experience pain until the tumor is more advanced. In contrast, primary cartilaginous and bone tumors are often painful.

**Diagnosis**

Patients with chest wall tumors require chest x-ray, CT, MRI, and sometimes PET-CT to determine the original site and extent of the tumor and its status (primary chest wall tumor or a metastasis). Biopsy and histologic evaluation confirm the diagnosis.

**Prognosis**

Prognosis varies by cancer type, cell differentiation, and stage; firm conclusions are limited by the low incidence of any given tumor. Sarcomas have been the most well studied, and primary chest wall sarcomas have a reported 5-yr survival of 17%. Survival is better with early-stage disease.

**Treatment**

- Surgery
- Sometimes combination chemotherapy, radiation therapy, and surgery

Most chest wall tumors are treated with surgical resection and reconstruction. Reconstruction often uses a combination of myocutaneous flaps and prosthetic materials. The presence of a malignant pleural effusion is a contraindication for surgical resection. Also, in cases of multiple myeloma or isolated plasmacytoma, chemotherapy and radiation should be the primary therapy. Small-cell malignant tumors such as Ewing's sarcoma and Askin's tumor should be treated with a multimodality approach combining chemotherapy, radiation therapy, and surgery. In cases of chest wall metastasis from distant tumors, a palliative chest wall resection is recommended only when nonsurgical options do not alleviate symptoms.
Introduction

Symptoms or the physical examination may suggest a cardiovascular disorder. For confirmation, selected noninvasive and invasive tests are usually done (see Ch. 207).

History

A thorough history is fundamental; it cannot be replaced by testing. The history must include a thorough systems review because many symptoms apparently occurring in other systems (eg, dyspnea, indigestion) are often caused by cardiac disease. A family history is taken because many cardiac disorders (eg, coronary artery disease, systemic hypertension, bicuspid aortic valve, hypertrophic cardiomyopathy, mitral valve prolapse) have a heritable basis.

Serious cardiac symptoms include chest pain or discomfort, dyspnea (see p. 1832), weakness, fatigue, palpitations, light-headedness, sense of an impending faint, syncope, and edema. These symptoms commonly occur in more than one cardiac disorder and in noncardiac disorders.

Physical Examination

Complete examination of all systems is essential to detect peripheral and systemic effects of cardiac disorders and evidence of noncardiac disorders that might affect the heart. Examination includes the following:

• Vital sign measurement
• Pulse palpation and auscultation
• Vein observation
• Chest inspection, percussion, auscultation, and palpation
• Cardiac percussion, palpation, and auscultation
• Lung examination (see p. 1827)
• Extremity and abdomen examination

Vital Signs

BP is measured in both arms and, for suspected congenital cardiac disorders or peripheral vascular disorders, in both legs. The bladder of an appropriately sized cuff encircles 80% of the limb's circumference, and the bladder's width is 40% of the circumference. The first sound heard as the Hg column falls is systolic pressure; disappearance of the sound is diastolic pressure (5th-phase Korotkoff sound). Up to a 15 mm Hg pressure differential between the right and left arms is normal; a greater differential suggests a vascular abnormality (eg, dissecting thoracic aorta) or a peripheral vascular disorder. Leg pressure is usually 20 mm Hg higher than arm pressure. Ankle-brachial index (ratio of ankle to arm systolic BP) is normally > 1. A Doppler probe may be used to measure the ankle BP if the pedal pulses are not easily palpable.

Heart rate and rhythm are assessed by palpatting the carotid or radial pulse or by cardiac auscultation if arrhythmia is suspected; some heartbeats during arrhythmias may be audible but do not generate a palpable pulse.
Respiratory rate, if abnormal, may indicate cardiac decompensation or a primary lung disorder. The rate increases in patients with heart failure or anxiety and decreases or becomes intermittent in the moribund. Shallow, rapid respirations may indicate pleuritic pain.

Temperature may be elevated by acute rheumatic fever or cardiac infection (eg, endocarditis). After MI, low grade fever is very common. Other causes are sought only if fever persists > 72 h.

Orthostatic changes: BP and heart rate are measured with the patient supine, seated, and standing; a 1-min interval is needed between each change in position. A difference of ≤ 10 mm Hg is normal; the difference tends to be a little greater in the elderly due to loss of vascular elasticity.

Pulsus paradoxus: Normally during inspiration, systolic arterial BP can decrease as much as 10 mm Hg, and pulse rate increases to compensate. A greater decrease in systolic BP or weakening of the pulse during inspiration is considered pulsus paradoxus. Pulsus paradoxus occurs in

- Cardiac tamponade (commonly)
- Constrictive pericarditis, severe asthma, and COPD (occasionally)
- Restrictive cardiomyopathy, severe pulmonary embolism, and hypovolemic shock (rarely)

BP decreases during inspiration because negative intrathoracic pressure increases venous return and hence right ventricular (RV) filling; as a result, the interventricular septum bulges slightly into the left ventricular (LV) outflow tract, decreasing cardiac output and thus BP. This mechanism (and the drop in systolic BP) is exaggerated in disorders that cause high negative intrathoracic pressure (eg, asthma) or that restrict RV filling (eg, cardiac tamponade, cardiomyopathy) or outflow (eg, pulmonary embolism).

Pulsus paradoxus is quantified by inflating a BP cuff to just above systolic BP and deflating it very slowly (eg, ≤ 2 mm Hg/heartbeat). The pressure is noted when Korotkoff sounds are first heard (at first, only during expiration) and when Korotkoff sounds are heard continuously. The difference between the pressures is the "amount" of pulsus paradoxus.

Pulses

Peripheral pulses: Major peripheral pulses in the arms and legs are palpated for symmetry and volume (intensity); elasticity of the arterial wall is noted. Absence of pulses may suggest an arterial disorder (eg, atherosclerosis) or systemic embolism. Peripheral pulses may be difficult to feel in obese or muscular people. The pulse has a rapid upstroke, then collapses in disorders with a rapid runoff of arterial blood (eg, arteriovenous communication, aortic regurgitation). The pulse is rapid and bounding in thyrotoxicosis and hypermetabolic states; it is slow and sluggish in myxedema. If pulses are asymmetric, auscultation over peripheral vessels may detect a bruit due to stenosis.

Carotid pulses: Observation, palpation, and auscultation of both carotid pulses may suggest a specific disorder (see Table 206-1).

Table 206-1. Carotid Pulse Amplitude and Associated Disorders

Auscultation over the carotid arteries can distinguish murmurs from bruits. Murmurs originate in the heart or great vessels and are usually louder over the upper precordium and diminish toward the neck. Bruits are higher-pitched, are heard only over the arteries, and seem more superficial. An arterial bruit must be distinguished from a venous hum. Unlike an arterial bruit, a venous hum is usually continuous, heard best with the patient sitting or standing, and is eliminated by compression of the ipsilateral internal jugular vein.

Veins
Peripheral veins: The peripheral veins are observed for varicosities, arteriovenous malformations (AVMs) and shunts, and overlying inflammation and tenderness due to thrombophlebitis. An AVM or a shunt produces a continuous murmur (heard on auscultation) and often a palpable thrill (because resistance is always lower in the vein than in the artery during systole and diastole).

Neck veins: The neck veins are examined to estimate venous wave height and waveform. Height is proportional to right atrial pressure, and waveform reflects events in the cardiac cycle; both are best observed in the internal jugular vein.

The jugular veins are usually examined with the patient reclining at 45°. The top of the venous column is normally just below the clavicles (upper limit of normal: 4 cm above the sternal notch in a vertical plane). The venous column is elevated in heart failure, volume overload, cardiac tamponade, constrictive pericarditis, tricuspid stenosis, superior vena cava obstruction, or reduced compliance of the RV. If such conditions are severe, the venous column can extend to jaw level, and its top can be detected only when the patient sits upright or stands. The venous column is low in hypovolemia.

Normally, the venous column can be briefly elevated by firm hand pressure on the abdomen (hepatojugular or abdominojugular reflux); the column falls back in a few seconds (maximum 3 respiratory cycles or 15 sec) despite continued abdominal pressure (because a compliant RV increases its stroke volume via the Frank-Starling mechanism). However, the column remains elevated (> 3 cm) during abdominal pressure in disorders that cause a dilated and poorly compliant RV or in obstruction of RV filling by tricuspid stenosis or right atrial tumor.

Normally, the venous column falls slightly during inspiration as lowered intrathoracic pressure draws blood from the periphery into the vena cava. A rise in the venous column during inspiration (Kussmaul's sign) occurs typically in chronic constrictive pericarditis, right ventricular MI, and COPD, and usually in heart failure and tricuspid stenosis.

Jugular vein waves (see Fig. 206-1) can usually be discerned clinically but are better seen on the screen during central venous pressure monitoring.

[Fig. 206-1. Normal jugular vein waves.]

The a waves are increased in pulmonary hypertension and tricuspid valve stenosis. Giant a waves (Cannon waves) are seen in atrioventricular dissociation when the atrium contracts while the tricuspid valve is closed. The a waves disappear in atrial fibrillation and are accentuated when RV compliance is poor (eg, in pulmonary hypertension or pulmonic stenosis). The v waves are very prominent in tricuspid regurgitation. The x descent is steep in cardiac tamponade. When RV compliance is poor, the y descent is very abrupt because the elevated column of venous blood rushes into the RV when the tricuspid valve opens, only to be stopped abruptly by the rigid RV wall (in restrictive myopathy) or the pericardium (in constrictive pericarditis).

Chest Inspection and Palpation

Chest contour and any visible cardiac impulses are inspected. The precordium is palpated for pulsations (determining apical impulse and thus cardiac situs) and thrills.

Inspection: Chest deformities, such as shield chest and pectus carinatum (a prominent birdlike sternum), may be associated with hereditary disorders involving congenital cardiac defects (eg, Turner's syndrome). Rarely, a localized upper chest bulge indicates aortic aneurysm due to syphilis. Pectus excavatum (depressed sternum) with a narrow anteroposterior chest diameter and an abnormally straight thoracic spine may suggest myxomatous degeneration of valves or chordae (particularly mitral) or Marfan syndrome.

Palpation: A central precordial heave is a palpable lifting sensation under the sternum and anterior chest wall to the left of the sternum; it suggests severe RV hypertrophy (RVH). Occasionally, in congenital
disorders that cause severe RVH, the precordium visibly bulges asymmetrically to the left of the sternum.

A sustained thrust at the apex (easily differentiated from the less focal, somewhat diffuse precordial heave of RVH) suggests LV hypertrophy (LVH). Abnormal focal systolic impulses in the precordium can sometimes be felt in patients with a dyskinetic ventricular aneurysm. An abnormal diffuse systolic impulse lifts the precordium in patients with severe mitral regurgitation. The lift occurs because the left atrium expands, causing anterior cardiac displacement. A diffuse and inferolaterally displaced apical impulse is found when the LV is dilated and hypertrophied (eg, in mitral regurgitation).

Location of thrills (palpable buzzing sensation present with particularly loud murmurs) suggests the cause (see Table 206-2).

A sharp impulse at the 2nd intercostal space to the left of the sternum may result from exaggerated pulmonic valve closure in pulmonary hypertension. A similar early systolic impulse at the cardiac apex may represent closure of a stenotic mitral valve; opening of the stenotic valve sometimes can be felt at the beginning of diastole. These findings coincide with an augmented 1st heart sound and an opening snap of mitral stenosis, heard on auscultation.

Cardiac Auscultation

Auscultation of the heart requires excellent hearing and the ability to distinguish subtle differences in pitch and timing. Hearing-impaired health care practitioners can use amplified stethoscopes. High-pitched sounds are best heard with the diaphragm of the stethoscope. Low-pitched sounds are best heard with the bell. Very little pressure should be exerted when using the bell. Excessive pressure converts the underlying skin into a diaphragm and eliminates very low-pitched sounds.

The entire precordium is examined systematically, typically beginning over the apical impulse with the patient in the left lateral decubitus position. The patient rolls supine, and auscultation continues at the lower left sternal border, proceeds cephalad with auscultation of each interspace, then caudad from the right upper sternal border. The clinician also listens over the left axilla and above the clavicles. The patient sits upright for auscultation of the back, then leans forward to aid auscultation of aortic and pulmonic diastolic murmurs or pericardial friction rub.

Major auscultatory findings include

- Heart sounds
- Murmurs
- Rubs

**Heart sounds** are brief, transient sounds produced by valve opening and closure; they are divided into systolic and diastolic sounds.

**Murmurs** are produced by blood flow turbulence and are more prolonged than heart sounds; they may be systolic, diastolic, or continuous. They are graded by intensity (see Table 206-3) and are described by their location and when they occur within the cardiac cycle.

**Rubs** are high-pitched, scratchy sounds often with 2 or 3 separate components; during tachycardia, the sound may be almost continuous.

The clinician focuses attention sequentially on each phase of the cardiac cycle, noting each heart sound and murmur. Intensity, pitch, duration, and timing of the sounds and the intervals between them are analyzed, often providing an accurate diagnosis. A diagram of the major auscultatory and palpatory
findings of the precordium should be routinely drawn in the patient's chart each time the patient's cardiovascular system is examined (see Fig. 206-2). With such diagrams, findings from each examination can be compared.

**Systolic heart sounds:** Systolic sounds include the following:

- 1st heart sound (S₁)
- Clicks

[Table 206-3. Heart Murmur Intensity]

S₁ and the 2nd heart sound (S₂, a diastolic heart sound) are normal components of the cardiac cycle, the familiar "lub-dub" sounds.

S₁ occurs just after the beginning of systole and is predominantly due to mitral closure but may also include tricuspid closure components. It is often split and has a high pitch. S₁ is loud in mitral stenosis. It may be soft or absent in mitral regurgitation due to valve leaflet sclerosis and rigidity but is often distinctly heard in mitral regurgitation due to myxomatous degeneration of the mitral apparatus or due to ventricular myocardial abnormality (eg, papillary muscle dysfunction, ventricular dilation).

Clicks occur only during systole; they are distinguished from S₁ and S₂ by their higher pitch and briefer duration. Some clicks occur at different times during systole as hemodynamics change. Clicks may be single or multiple.

Clicks in congenital aortic or pulmonic stenosis are thought to result from abnormal ventricular wall tension. These clicks occur early in systole (very near S₁) and are not affected by hemodynamic changes. Similar clicks occur in severe pulmonary hypertension. Clicks in mitral or tricuspid valve prolapse, typically occurring in mid to late systole, are thought to result from abnormal tension on redundant and elongated chordae tendineae or valve leaflets.

Clicks due to myxomatous degeneration of valves may occur any time during systole but move toward S₁ during maneuvers that transiently decrease ventricular filling volume (eg, standing, Valsalva maneuver). If ventricular filling volume is increased (eg, by lying supine), clicks move toward S₂, particularly in mitral valve prolapse. For unknown reasons, characteristics of the clicks may vary greatly between examinations, and clicks may come and go.

[Fig. 206-2. Diagram of physical findings in a patient with aortic stenosis and mitral regurgitation.]

**Diastolic heart sounds:** Diastolic sounds include the following:

- 2nd, 3rd, and 4th heart sounds (S₂, S₃, and S₄)
- Diastolic knocks
- Mitral valve sounds

Unlike systolic sounds, diastolic sounds are low-pitched; they are softer in intensity and longer in duration. Except for S₂, these sounds are always abnormal in adults.

S₂ occurs at the beginning of diastole, due to aortic and pulmonic valve closure. Aortic valve closure normally precedes pulmonic valve closure unless the former is late or the latter is early. Aortic valve closure is late in left bundle branch block or aortic stenosis; pulmonic valve closure is early in some forms of preexcitation phenomena. Delayed pulmonic valve closure may result from increased blood flow through the RV (eg, in atrial septal defect of the common secundum variety) or complete right bundle branch block. Increased RV flow in atrial septal defect also abolishes the normal respiratory variation in
aortic and pulmonic valve closure, producing a fixed split S\textsubscript{2}. Left-to-right shunts with normal RV volume flow (eg, in membranous ventricular septal defects) do not cause fixed splitting. A single S\textsubscript{2} may occur when the aortic valve is regurgitant, severely stenotic, or atretic (in truncus arteriosus when there is a common valve).

S\textsubscript{3} occurs in early diastole, when the ventricle is dilated and noncompliant. It occurs during passive diastolic ventricular filling and indicates serious ventricular dysfunction in adults; in children, it can be normal. RV S\textsubscript{3} is heard best (sometimes only) during inspiration (because negative intrathoracic pressure augments RV filling volume) with the patient supine. LV S\textsubscript{3} is best heard during expiration (because the heart is nearer the chest wall) with the patient in the left lateral decubitus position.

S\textsubscript{4} is produced by augmented ventricular filling, caused by atrial contraction, near the end of diastole. It is similar to S\textsubscript{3} and heard best or only with the bell of the stethoscope. During inspiration, RV S\textsubscript{4} increases and LV S\textsubscript{4} decreases. S\textsubscript{4} is heard much more often than S\textsubscript{3} and indicates a lesser degree of ventricular dysfunction, usually diastolic. S\textsubscript{4} is absent in atrial fibrillation (because the atria do not contract) but is almost always present in active myocardial ischemia or soon after MI. S\textsubscript{3} with or without S\textsubscript{4}, is usual in significant systolic LV dysfunction; S\textsubscript{4} without S\textsubscript{3} is usual in diastolic LV dysfunction.

A summation gallop occurs when S\textsubscript{3} and S\textsubscript{4} are present in a patient with tachycardia, which shortens diastole so that the 2 sounds merge. Loud S\textsubscript{3} and S\textsubscript{4} may be palpable at the apex when the patient is in the left lateral decubitus position.

A diastolic knock occurs at the same time as S\textsubscript{3}, in early diastole. It is not accompanied by S\textsubscript{4} and is a louder, thudding sound, which indicates abrupt arrest of ventricular filling by a noncompliant, constricting pericardium.

An opening snap may occur in early diastole in mitral stenosis or, rarely, in tricuspid stenosis. Mitral opening snap is very high pitched, brief, and heard best with the diaphragm of the stethoscope. The more severe mitral stenosis is (ie, the higher the left atrial pressure), the closer the opening snap is to the pulmonic component of S\textsubscript{2}. Intensity is related to the compliance of the valve leaflets: The snap sounds loud when leaflets remain elastic, but it gradually softens and ultimately disappears as sclerosis, fibrosis, and calcification of the valve develop. Mitral opening snap, although sometimes heard at the apex, is often heard best or only at the lower left sternal border.

[Table 206-4. Etiology of Murmurs by Timing]

**Approach to murmurs:** Timing of the murmur in the cardiac cycle correlates with the cause (see Table 206-4); auscultatory findings correlate with specific heart valve disorders. Various maneuvers (eg, inspiration, Valsalva, handgrip, squatting, amyl nitrate inhalation) can modify cardiac physiology slightly, making differentiation of causes of heart murmur possible (see Table 206-5).

All patients with heart murmurs are evaluated by chest x-ray and ECG. Most require echocardiography to confirm the diagnosis, determine severity, and track severity over time. Usually, a cardiac consultation is obtained if significant disease is suspected.

**Systolic murmurs:** Systolic murmurs may be normal or abnormal. They may be early, mid, or late systolic, or holosystolic (pansystolic). Systolic murmurs may be divided into ejection, regurgitant, and shunt murmurs.

**Ejection murmurs** are due to turbulent forward flow through narrowed or irregular valves or outflow tracts (eg, due to aortic or pulmonic stenosis). They are typically mid systolic and have a crescendo-diminuendo character that usually becomes louder and longer as flow becomes more obstructed. The greater the stenosis and turbulence, the longer the crescendo phase and the shorter the diminuendo
Systolic ejection murmurs may occur without hemodynamically significant outflow tract obstruction and thus do not necessarily indicate a disorder. In normal infants and children, flow is often mildly turbulent, producing soft ejection murmurs. The elderly often have ejection murmurs due to valve and vessel sclerosis. During pregnancy, many women have soft ejection murmurs at the 2nd intercostal space to the left or right of the sternum. The murmurs occur because a physiologic increase in blood volume and cardiac output increases flow velocity through normal structures. The murmurs may be greatly exaggerated if severe anemia complicates the pregnancy.

Regurgitant murmurs represent retrograde or abnormal flow (eg, due to mitral regurgitation, tricuspid regurgitation, or ventricular septal defects) into chambers that are at lower resistance. They are typically holosystolic and tend to be louder with high-velocity, low-volume regurgitation or shunts and softer with high-volume regurgitation or shunts. Late systolic murmurs, which may or may not be preceded by a click, are typical of mitral valve prolapse or papillary muscle dysfunction. Various maneuvers are usually required for more accurate diagnosis of timing and type of murmur (see Table 206-5).

Shunt murmurs may originate at the site of the shunt (eg, patent ductus arteriosus, ventricular septal defects) or result from altered hemodynamics remote from the shunt (eg, pulmonic systolic flow murmur due to an atrial septal defect with left-to-right shunt).

Diastolic murmurs: Diastolic murmurs are always abnormal; most are early or mid diastolic, but they may be late diastolic (presystolic). Early diastolic murmurs are typically due to aortic or pulmonic regurgitation. Mid diastolic (or early to mid diastolic) murmurs are typically due to mitral or tricuspid stenosis. A late diastolic murmur may be due to rheumatic mitral stenosis in a patient in sinus rhythm.

A mitral or tricuspid murmur due to an atrial tumor or thrombus may be evanescent and may vary with position and from one examination to the next because the position of the intracardiac mass changes.

Continuous murmurs: Continuous murmurs occur throughout the cardiac cycle. They are always abnormal, indicating a constant shunt flow throughout systole and diastole. They may be due to various cardiac defects (see Table 206-4). Some defects produce a thrill; many are associated with signs of RVH and LVH. As pulmonary artery resistance increases in shunt lesions, the diastolic component gradually decreases. When pulmonary and systemic resistance equalize, the murmur may disappear.

Patent ductus arteriosus murmurs are loudest at the 2nd intercostal space just below the medial end of the left clavicle. Aorticopulmonary window murmurs are central and heard at the 3rd intercostal space level. Murmurs of systemic arteriovenous fistulas are best heard directly over the lesions; those of pulmonic arteriovenous fistulas and pulmonary artery branch stenosis are more diffuse and heard throughout the chest.

During pregnancy, a continuous venous hum from breast vessels (mammary souffle) may be mistaken for a continuous cardiac murmur.

Pericardial friction rub: A pericardial friction rub is caused by movement of inflammatory adhesions between visceral and parietal pericardial layers. It is a high-pitched or squeaking sound; it may be systolic, diastolic and systolic, or triphasic (when atrial contraction accentuates the diastolic component during late diastole). The rub sounds like pieces of leather squeaking as they are rubbed together. Rubs are best heard with the patient leaning forward or on hands and knees with breath held in expiration.

Extremity and Abdominal Examination

The extremities and abdomen are examined for signs of fluid overload, which may occur with heart failure.
as well as noncardiac disorders (eg, renal, hepatic, lymphatic).

**Extremities:** In the extremities (primarily the legs), fluid overload is manifest as edema (see p. 2031), which is swelling of soft tissues due to increased interstitial fluid. Edema may be visible on inspection, but modest amounts of edema in very obese or muscular people may be difficult to recognize visually. Thus, extremities are palpated for presence and degree of pitting (visible and palpable depressions caused by pressure from the examiner's fingers, which displaces the interstitial fluid). The area of edema is examined for extent, symmetry (ie, comparing both extremities), warmth, erythema, and tenderness. With significant fluid overload, edema may also be present over the sacrum, genitals, or both.

Tenderness, erythema, or both, particularly when unilateral, suggests an inflammatory cause (eg, cellulitis or thrombophlebitis). Nonpitting edema is more suggestive of lymphatic or vascular obstruction than fluid overload.

**Abdomen:** In the abdomen, significant fluid overload manifests as ascites (see p. 206). Marked ascites causes visible abdominal distention, which is tense and nontender to palpation, with shifting dullness on abdominal percussion and a fluid wave. The liver may be distended and slightly tender, with a hepatojugular reflux (see p. 2019) present.

**Chest Pain**

Chest pain is a very common complaint. Many patients are well aware that it is a warning of potential life-threatening disorders and seek evaluation for minimal symptoms. Other patients, including many with serious disease, minimize or ignore its warnings. Pain perception (both character and severity) varies greatly between individuals as well as between men and women. However described, chest pain should never be dismissed without an explanation of its cause.

**Pathophysiology**

The heart, lungs, esophagus, and great vessels provide afferent visceral input through the same thoracic autonomic ganglia. A painful stimulus in these organs is typically perceived as originating in the chest, but because afferent nerve fibers overlap in the dorsal ganglia, thoracic pain may be felt (as referred pain) anywhere between the umbilicus and the ear, including the upper extremities.

Painful stimuli from thoracic organs can cause discomfort described as pressure, tearing, gas with the urge to eructate, indigestion, burning, aching, stabbing, and sometimes sharp needle-like pain. When the sensation is visceral in origin, many patients deny they are having pain and insist it is merely "discomfort."

**Etiology**

Many disorders cause chest pain or discomfort. These disorders may involve the cardiovascular, GI, pulmonary, neurologic, or musculoskeletal systems (see Table 206-6).

Some disorders are immediately life threatening:

- **Acute coronary syndromes (acute MI/unstable angina)**
- **Thoracic aortic dissection**
- **Tension pneumothorax**
- **Esophageal rupture**
- **Pulmonary embolism (PE)**

Other causes range from serious, potential threats to life to causes that are simply uncomfortable. Often, no cause can be confirmed even after full evaluation.
Overall, the most common causes are

- Chest wall disorders (ie, those involving muscle, rib, or cartilage)
- Pleural disorders
- GI disorders (eg, esophageal reflux or spasm, ulcer disease, cholelithiasis)
- Idiopathic
- Acute coronary syndromes

**Evaluation**

**History:** History of present illness should note the location, duration, character, and quality of the pain. The patient should be asked about any precipitating events (eg, straining or overuse of chest muscles), as well as any triggering and relieving factors. Specific factors to note include whether pain is present during exertion or at rest, presence of psychologic stress, whether pain occurs during respiration or coughing, difficulty swallowing, relationship to meals, and positions that relieve or exacerbate pain (eg, lying flat, leaning forward). Previous similar episodes and their circumstances should be noted with attention to the similarity or lack thereof. Important associated symptoms to seek include

[Table 206-6. Some Causes of Chest Pain]

dyspnea, palpitations, syncope, diaphoresis, nausea or vomiting, cough, fever, and chills.

**Review of systems** should seek symptoms of possible causes, including leg pain, swelling, or both (deep venous thrombosis [DVT] and therefore possible PE) and chronic weakness, malaise, and weight loss (cancer).

**Past medical history** should document known causes, particularly cardiovascular and GI disorders, and any cardiac investigations or procedures (eg, stress testing, catheterization). Risk factors for coronary artery disease (CAD—eg, hypertension, hyperlipidemia, diabetes, cerebrovascular disease, tobacco use) or PE (eg, lower extremity injury, recent surgery, immobilization, known cancer, pregnancy) should also be noted.

Drug history should note use of drugs that can trigger coronary artery spasm (eg, cocaine, triptans, phosphodiesterase inhibitors) or GI disease (particularly alcohol, NSAIDs).

Family history should note history of MI (particularly at an early age) and hyperlipidemia.

**Physical examination:** Vital signs and weight are measured, and body mass index (BMI) is calculated. Pulses are palpated in both arms and both legs, BP is measured in both arms, and pulsus paradoxus is measured.

General appearance is noted (eg, pallor, diaphoresis, cyanosis, anxiety).

Neck is inspected for venous distention and hepatojugular reflux, and the venous wave forms are noted. The neck is palpated for carotid pulses, lymphadenopathy, or thyroid abnormality. The carotid arteries are auscultated for bruit.

Lungs are percussed and auscultated for presence and symmetry of breath sounds, signs of congestion (dry or wet rales, rhonchi), consolidation (pectoriloquy), pleural friction rubs, and effusion (decreased breath sounds, dullness to percussion).

The cardiac examination notes the intensity and timing of the 1st heart sound (S1) and 2nd heart sound (S2), the respiratory movement of the pulmonic component of S2, clicks and snap of the mitral apparatus,
pericardial friction rubs, murmurs, and gallops. When murmurs are detected, the timing, duration, pitch, shape, and intensity and the response to changes of position, handgrip, and the Valsalva maneuver should be noted. When gallops are detected, differentiation should be made between the 4th heart sound (S₄), which is often present with diastolic dysfunction or myocardial ischemia, and the 3rd heart sound (S₃), which is present with systolic dysfunction.

The chest is inspected for skin lesions of trauma or herpes zoster infection and palpated for crepitance (suggesting subcutaneous air) and tenderness. The abdomen is palpated for tenderness, organomegaly, and masses or tenderness, particularly in the epigastric and right upper quadrant regions.

The legs are examined for arterial pulses, adequacy of perfusion, edema, varicose veins, and signs of DVT (eg, swelling, erythema, and tenderness).

Red flags: Certain findings raise suspicion of a more serious etiology of chest pain:

- Abnormal vital signs (tachycardia, bradycardia, tachypnea, hypotension)
- Signs of hypoperfusion (eg, confusion, ashen color, diaphoresis)
- Shortness of breath
- Asymmetric breath sounds or pulses
- New heart murmurs
- Pulsus paradoxus > 10 mm Hg

Interpretation of findings: Symptoms and signs of thoracic disorders vary greatly, and those of serious and nonserious conditions often overlap. Although red flag findings indicate a high likelihood of serious disease, and many disorders have “classic” manifestations (see Table 206-6), many patients who have serious illness do not present with these classic symptoms and signs. For example, patients with myocardial ischemia may complain only of indigestion or have a very tender chest wall on palpation. A high index of suspicion is important when evaluating patients with chest pain. Nonetheless, some distinctions and generalizations are possible.

Duration of pain can provide clues to the severity of the disorder. Long-standing pain (ie, for weeks or months) is not a manifestation of a disorder that is immediately life threatening. Such pain is often musculoskeletal in origin, although GI origin or a cancer should be considered, particularly in patients who are elderly. Similarly, brief (< 5 sec), sharp, intermittent pains rarely result from serious disorders. Serious disorders typically manifest pain lasting minutes to hours, although episodes may be recurrent (eg, unstable angina may cause several bouts of pain over 1 or more days).

Patient age is helpful in evaluating chest pain. Chest pain in children and young adults (< 30 yr) is less likely to result from myocardial ischemia, although MI can occur in people in their 20s. Musculoskeletal and pulmonary disorders are more common causes in these age groups.

Exacerbation and relief of symptoms also are helpful in evaluating chest pain. Although angina can be felt anywhere between the ear and the umbilicus (and often not in the chest), it is typically consistently related to physical or emotional stress, ie, patients do not experience angina from climbing one flight of stairs one day and tolerate 3 flights the next day. Nocturnal angina is characteristic of heart failure or coronary artery spasm.

Pain from many disorders, both serious and minor, can be exacerbated by respiration, movement, or palpation of the chest. These findings are not specific for origin in the chest wall; about 15% of patients with acute MI have chest tenderness on palpation.

Nitroglycerin may relieve pain of both myocardial ischemia and noncardiac smooth muscle spasm (eg, esophageal or biliary disorders); its efficacy or lack thereof should not be used for diagnosis.
**Associated findings** may also suggest a cause. Fever is nonspecific but, if accompanied by cough, suggests a pulmonary cause. Patients with Raynaud's syndrome or migraine headaches sometimes have coronary spasm.

The presence or absence of risk factors for CAD (eg, hypertension, hypercholesterolemia, smoking, obesity, diabetes, positive family history) alters the probability of underlying CAD but does not help diagnose the cause of a given episode of acute chest pain. Patients with those factors may well have another cause of chest pain, and patients without them may have an acute coronary syndrome. However, known CAD in a patient with chest pain raises the likelihood of that diagnosis as the cause (particularly if the patient describes the symptoms as "like my angina" or "like my last heart attack").

**Testing:** For adults with acute chest pain, immediate life threats must be ruled out. Most patients should initially have pulse oximetry, ECG, and chest x-ray. If symptoms suggest an acute coronary syndrome or if no other cause is clear (particularly in at-risk patients), troponin and CK levels are measured. If a PE is considered possible, D-dimer testing is done. Expeditious evaluation is essential because if MI or other acute coronary syndrome is present, the patient should be sent immediately to the heart catheterization laboratory (when available); the therapeutic window for primary percutaneous coronary intervention is 90 min and that for thrombolysis is only slightly longer.

Some abnormal findings on these tests confirm a diagnosis (eg, acute MI, pneumothorax, pneumonia). Other abnormalities suggest a diagnosis or at least the need to pursue further investigation (eg, abnormal aortic contour suggests need for testing for thoracic aortic dissection). Thus, if these initial test results are normal, thoracic aortic dissection, tension pneumothorax, and esophageal rupture are highly unlikely. However, in acute coronary syndromes, ECG may not change for several hours or sometimes not at all, and in PE, oxygenation may be normal. Thus, other studies may need to be obtained based on findings from the history and physical examination (see Table 206-6).

Because a single normal set of cardiac markers does not rule out a cardiac cause, patients whose symptoms suggest an acute coronary syndrome should have serial measurement of cardiac markers (troponin and CK-MB fraction) and ECGs. Some clinicians follow these tests (acutely or within several days) with a stress ECG or a stress imaging test. Drug treatment is begun while awaiting results from the 2nd set of markers unless there is a clear contraindication. A diagnostic trial of sublingual nitroglycerin or an oral liquid antacid does not adequately differentiate myocardial ischemia from gastroesophageal reflux disease or gastritis. Either drug may relieve symptoms of either disorder. Troponin will be elevated in all acute coronary syndromes except new-onset angina and often in other disorders that damage the myocardium (eg, myocarditis, pericarditis, aortic dissection involving coronary artery flow, PE, heart failure, severe sepsis). CK may be elevated from damage to any muscle tissue, but CK-MB elevation is specific to damage to the myocardium. ST-segment abnormality on the ECG may be nonspecific or due to antecedent disorders, so comparison with previous ECGs is important.

The likelihood of PE is affected by a number of factors (see Table 194-2 on p. 1912), which can be used in an algorithm to derive an approach to testing.

In patients with chronic chest pain, immediate threats to life are unlikely. Most clinicians initially obtain a chest x-ray and do other tests based on symptoms and signs.

**Treatment**

Specific identified disorders are treated. If etiology is not clearly benign, patients are usually admitted to the hospital or an observation unit for cardiac monitoring and more extensive evaluation. Symptoms are treated with acetaminophen or opioids as needed (see p. 1623), pending a diagnosis. Pain relief following opioid treatment should not diminish the urgency of ruling out serious and life-threatening disease.

**Geriatrics Essentials**

The probability of serious and life-threatening disease increases with age. Many elderly patients recover more slowly than younger patients but survive for significant time if properly diagnosed and treated. Drug
doses are usually lower, and rapidity of dose escalation is slower. Chronic disorders (eg, decreased renal function) are often present and may complicate diagnosis and treatment.

**Key Points**

- Immediate life threats must be ruled out first.

- Some serious disorders, particularly coronary ischemia and PE, often do not have a classic presentation.

- Most patients should have pulse oximetry, ECG, cardiac markers, and chest x-ray.

- Evaluation must be prompt so that patients with ST-elevation MI can be in the heart catheterization laboratory (or have thrombolysis) within the 90-min standard.

- If PE is highly likely, antithrombin drugs should be given while the diagnosis is pursued; another embolus in a patient who is not receiving anticoagulants may be fatal.

**Edema**

Edema is swelling of soft tissues due to increased interstitial fluid. The fluid is predominantly water, but protein and cell-rich fluid can accumulate if there is infection or lymphatic obstruction.

Edema may be generalized or local (eg, limited to a single extremity or part of an extremity). It sometimes appears abruptly; patients complain that an extremity suddenly swells. More often, edema develops insidiously, beginning with weight gain, puffy eyes at awakening in the morning, and tight shoes at the end of the day. Slowly developing edema may become massive before patients seek medical care.

Edema itself causes few symptoms other than occasionally a feeling of tightness or fullness; other symptoms are usually related to the underlying disorder. Patients with edema due to heart failure (a common cause) often have dyspnea during exertion, orthopnea, and paroxysmal nocturnal dyspnea. Patients with edema due to deep venous thrombosis (DVT) often have pain.

Edema due to extracellular fluid volume expansion is often dependent. Thus, in ambulatory patients, edema is in the feet and lower legs; patients requiring bed rest develop edema in the buttocks, genitals, and posterior thighs. Women who lie on only one side may develop edema in the dependent breast. Lymphatic obstruction causes edema distal to the site of obstruction.

**Pathophysiology**

Edema results from increased movement of fluid from the intravascular to the interstitial space or decreased movement of water from the interstitium into the capillaries or lymphatic vessels. The mechanism involves one or more of the following:

- Increased capillary hydrostatic pressure
- Decreased plasma oncotic pressure
- Increased capillary permeability
- Obstruction of the lymphatic system

As fluid shifts into the interstitial space, intravascular volume is depleted. Intravascular volume depletion activates the renin-angiotensin-aldosterone-ADH system, resulting in renal Na retention. By increasing osmolality, renal Na retention triggers water retention by the kidneys and helps maintain plasma volume. Increased renal Na retention also may be a primary cause of fluid overload and hence edema. Excessive exogenous Na intake may also contribute.
Less often, edema results from decreased movement of fluid out of the interstitial space into the capillaries due to lack of adequate plasma oncotic pressure as in nephrotic syndrome, protein-losing enteropathy, or starvation.

Increased capillary permeability occurs in infections or as the result of toxin or inflammatory damage to the capillary walls.

The lymphatic system is responsible for removing protein and WBCs (along with some water) from the interstitium. Lymphatic obstruction allows these substances to accumulate in the interstitium.

**Etiology**

**Generalized edema** is most commonly caused by

- Heart failure
- Liver failure
- Kidney disorders (especially nephrotic syndrome)

**Localized edema** is most commonly caused by

- DVT or another venous obstruction (eg, by tumor)
- Infection
- Angioedema
- Lymphatic obstruction

Chronic venous insufficiency may involve one or both legs.

Common causes are listed by primary mechanism in Table 206-7.

**Evaluation**

**History:** **History of present illness** should include location and duration of edema and presence and degree of pain or discomfort.

(Table 206-7, Some Causes of Edema)

Female patients should be asked whether they are pregnant and whether edema seems related to menstrual periods. Having patients with chronic edema keep a log of weight gain or loss is valuable.

**Review of systems** should include symptoms of causative disorders, including dyspnea during exertion, orthopnea, and paroxysmal nocturnal dyspnea (heart failure); alcohol or hepatotoxin exposure, jaundice, and easy bruising (a liver disorder); malaise and anorexia (cancer or a liver or kidney disorder); and immobilization, extremity injury, or recent surgery (DVT).

**Past medical history** should include any disorders known to cause edema, including heart, liver, and kidney disorders and cancer (including any related surgery or radiation therapy). The history should also include predisposing conditions for these causes, including streptococcal infection, recent viral infection (eg, hepatitis), chronic alcohol abuse, and hypercoagulable disorders. Drug history should include specific questions about drugs known to cause edema (see Table 206-7). Patients are asked about the amount of Na used in cooking and at the table.

**Physical examination:** The area of edema is identified and examined for extent, warmth, erythema, and
tenderness; symmetry or lack of it is noted. Presence and degree of pitting (visible and palpable depressions caused by pressure from the examiner's fingers on the edematous area, which displaces the interstitial fluid) are noted.

In the general examination, the skin is inspected for jaundice, bruising, and spider angiomas (suggesting a liver disorder).

Lungs are examined for dullness to percussion, reduced or exaggerated breath sounds, crackles, rhonchi, and pleural friction rub.

The internal jugular vein height, waveform, and reflux are noted.

The heart is palpated for thrills, thrust, parasternal lift, and asynchronous abnormal systolic bulge. Auscultation for 3rd (S₃) or 4th (S₄) heart sounds, murmurs, and pericardial rub or knock is done; all suggest cardiac origin.

The abdomen is inspected, palpated, and percussed for ascites, hepatomegaly, and splenomegaly to check for a liver disorder or heart failure. The kidneys are palpated, and the bladder is percussed. An abnormal abdominal mass, if present, should be palpated.

**Red flags:** Certain findings raise suspicion of a more serious etiology of edema:

- Sudden onset
- Significant pain
- Shortness of breath
- History of a heart disorder or an abnormal cardiac examination
- Hemoptysis, dyspnea, or pleural friction rub
- Hepatomegaly, jaundice, ascites, splenomegaly, or hematemesis
- Unilateral leg swelling with tenderness

**Interpretation of findings:** Potential acute life threats, which typically manifest with sudden onset of focal edema, must be identified. Such a presentation suggests acute DVT, soft-tissue infection, or angioedema. Acute DVT may lead to pulmonary embolism (PE), which can be fatal. Soft-tissue infections range from minor to life threatening, depending on the infecting organism and the patient's health. Acute angioedema sometimes progresses to involve the airway, with serious consequences.

Dyspnea may occur with edema due to heart failure, DVT if PE has occurred, acute respiratory distress syndrome, or angioedema that involves the airways.

Generalized, slowly developing edema suggests a chronic heart, kidney, or liver disorder. Although these disorders can also be life threatening, complications tend to take much longer to develop.

These factors and other clinical features help suggest the cause (see Table 206-7).

**Testing:** For most patients with generalized edema, testing should include CBC, serum electrolytes, BUN, creatinine, liver function tests, serum protein, and urinalysis (particularly noting the presence of protein and microscopic hematuria). Other tests should be done based on the suspected cause (see Table 206-7)—eg, brain natriuretic peptide (BNP) for suspected heart failure or D-dimer for suspected PE.

Patients with isolated lower-extremity swelling should usually have venous obstruction excluded by ultrasonography.
Treatment

Specific causes are treated.

Patients with Na retention often benefit from restriction of dietary Na. Patients with heart failure should eliminate salt in cooking and at the table and avoid prepared foods with added salt. Patients with advanced cirrhosis or nephrotic syndrome often require more severe Na restriction (≤ 1 g/day). K salts are often substituted for Na salts to make Na restriction tolerable; however, care should be taken, especially in patients receiving K-sparing diuretics, ACE inhibitors, or angiotensin receptor blockers and in those with a kidney disorder because potentially fatal hyperkalemia can result.

People with conditions involving Na retention may also benefit from loop or thiazide diuretics. However, diuretics should not be prescribed only to improve the appearance caused by edema. When diuretics are used, K wasting can be dangerous in some patients; K-sparing diuretics (eg, amiloride, triamterene, spironolactone, eplerenone) inhibit Na reabsorption in the distal nephron and collecting duct. When used alone, they modestly increase Na excretion. Both triamterene and amiloride have been combined with a thiazide to prevent K wasting. An ACE inhibitor-thiazide combination also reduces K wasting.

Geriatrics Essentials

In the elderly, use of drugs that treat causes of edema requires special caution, such as the following:

- Starting doses low and evaluating patients thoroughly when the dose is changed
- Monitoring for orthostatic hypotension if diuretics, ACE inhibitors, angiotensin receptor blockers, or β-blockers are used
- Evaluating for bradycardia or heart block if digoxin, rate-limiting Ca channel blockers, or β-blockers are used
- Frequently testing for hypokalemia or hyperkalemia
- Not stopping Ca channel blockers because of pedal edema, which is benign

Logging daily weight helps in monitoring clinical improvement or deterioration immensely.

Key Points

- Edema may result from a generalized or local process.
- Main causes of generalized edema are chronic heart, liver, and kidney disorders.
- Sudden onset should trigger prompt evaluation.
- Edema may occur anywhere in the body, including the brain.
- Not all edema is harmful; consequences depend mainly on the cause.

Orthostatic Hypotension

Orthostatic (postural) hypotension is an excessive fall in BP when an upright position is assumed. The consensus definition is a drop of > 20 mm Hg systolic, 10 mm Hg diastolic, or both. Symptoms of faintness, light-headedness, dizziness, confusion, or blurred vision occur within seconds to a few minutes of standing and resolve rapidly on lying down. Some patients experience falls, syncope (see p. 2041), or even generalized seizures. Exercise or a heavy meal may exacerbate symptoms. Most other associated symptoms and signs relate to the cause. Orthostatic hypotension is a manifestation of abnormal BP regulation due to various conditions, not a specific disorder.
Postural orthostatic tachycardia syndrome (POTS): POTS (also called postural autonomic tachycardia or chronic or idiopathic orthostatic intolerance) is a syndrome of orthostatic intolerance in younger patients. Various symptoms (eg, fatigue, light-headedness, exercise intolerance, cognitive impairment) and tachycardia occur with standing; however, there is little or no fall in BP. The reason for symptoms is unclear.

Pathophysiology

Normally, the gravitational stress of suddenly standing causes blood (1/2 to 1 L) to pool in the capacitance veins of the legs and trunk. The subsequent transient decrease in venous return reduces cardiac output and thus BP. In response, baroreceptors in the aortic arch and carotid bodies activate autonomic reflexes to rapidly return BP to normal. The sympathetic system increases heart rate and contractility and increases vasomotor tone of the capacitance vessels. Simultaneous parasympathetic (vagal) inhibition also increases heart rate. In most people, changes in BP and heart rate with standing are minimal and transient, and symptoms do not occur.

With continued standing, activation of the renin-angiotensin-aldosterone system and ADH secretion cause Na and water retention and increase circulating blood volume.

Etiology

Homeostatic mechanisms may be inadequate to restore low BP if afferent, central, or efferent portions of the autonomic reflex arc are impaired by disorders or drugs, if myocardial contractility or vascular responsiveness is depressed, if hypovolemia is present, or if hormonal responses are faulty (see Table 206-8).

Causes differ depending on whether symptoms are acute or chronic.

The most common causes of acute orthostatic hypotension include

• Hypovolemia
• Drugs
• Prolonged bed rest
• Adrenal insufficiency

The most common causes of chronic orthostatic hypotension include

• Age-related changes in BP regulation
• Drugs
• Autonomic dysfunction

Postprandial orthostatic hypotension is also common. It may be caused by the insulin response to high-carbohydrate meals and blood pooling in the GI tract; this condition is worsened by alcohol intake.

Evaluation

Orthostatic hypotension is diagnosed when a marked fall in measured BP and symptoms suggesting hypotension are provoked by standing and relieved by lying down. A cause must be sought.

History: History of present illness should identify the duration and severity (eg, whether associated with syncope or falls) of symptoms. The patient is asked about known triggers (eg, drugs, bed rest, fluid loss) and the relationship of symptoms to meals.
Review of symptoms seeks symptoms of causative disorders, particularly symptoms of autonomic insufficiency such as visual impairment (due to mydriasis and loss of accommodation), incontinence or urinary retention, constipation, heat intolerance (due to impaired sweating), and erectile dysfunction. Other important symptoms include tremor, rigidity, and difficulty walking (Parkinson's disease, multiple system atrophy); weakness and fatigue (adrenal insufficiency, anemia); and black, tarry stool (GI hemorrhage). Other symptoms of neurologic and cardiovascular disorders and cancer are noted.

Table 206-8. Causes of Orthostatic Hypotension

Past medical history should identify known potential causes, including diabetes, Parkinson's disease, and cancer (ie, causing a paraneoplastic syndrome). The drug profile should be reviewed for offending prescription drugs (see Table 206-8) particularly antihypertensives and nitrates. A family history of orthostatic symptoms suggests possible familial dysautonomia.

Physical examination: BP and heart rate are measured after 5 min supine and at 1 and 3 min after standing; patients unable to stand may be assessed while sitting upright. Hypotension without a compensatory increase in heart rate (< 10 beats/min) suggests autonomic impairment. Marked increase (to > 100 beats/min or by > 30 beats/min) suggests hypovolemia or, if symptoms develop without hypotension, POTS.

The skin and mucosae are inspected for signs of dehydration and for pigment changes suggestive of Addison's disease (eg, hyperpigmented areas, vitiligo). A rectal examination is done to detect GI bleeding.

During the neurologic examination, GU and rectal reflexes are tested to evaluate autonomic function; assessment includes the cremasteric reflex (normally, stroking the thigh results in retraction of the testes), anal wink reflex (normally, stroking perianal skin results in contraction of the anal sphincter), and bulbocavernosus reflex (normally, squeezing the glans penis or clitoris results in contraction of the anal sphincter). Signs of peripheral neuropathy (eg, abnormalities of strength, sensation, and deep tendon reflexes) are assessed.

Red flags: Certain findings suggest a more serious etiology:

- Bloody or heme-positive stool
- Abnormal neurologic examination

Interpretation of findings: In patients with acute symptoms, the most common causes—drugs, bed rest, and volume depletion—are often apparent clinically.

In patients with chronic symptoms, an important goal is to detect any neurologic disorder causing autonomic dysfunction. Patients with movement abnormalities may have Parkinson's disease or multiple system atrophy. Patients with findings of peripheral neuropathy may have an apparent cause (eg, diabetes, alcoholism), but a paraneoplastic syndrome due to an occult cancer and amyloidosis must be considered. Patients who have only peripheral autonomic symptoms may have pure autonomic failure.

Testing: ECG and serum electrolytes and glucose are routinely checked. However, these and other tests are usually of little benefit unless suggested by specific symptoms.

Autonomic function can be evaluated with bedside cardiac monitoring. When the autonomic system is intact, heart rate increases in response to inspiration. The heart is monitored as the patient breathes slowly and deeply (about a 5-sec inspiration and a 7-sec expiration) for 1 min. The longest interbeat (R-R) interval during expiration is normally at least 1.15 times the minimum R-R interval during inspiration; a shorter interval suggests autonomic dysfunction. A similar variation in R-R interval should exist between rest and a 10- to 15-sec Valsalva maneuver. Patients with abnormal R-R intervals or with autonomic symptoms or signs require further evaluation for diabetes, Parkinson's disease, and possibly multiple system atrophy (see p. 1618) and pure autonomic failure (see p. 1619); the last may require plasma norepinephrine or ADH (vasopressin) measurements with the patient supine and upright.
The dose of a suspected drug may be reduced or the drug stopped to confirm the drug as the cause.

**Tilt table testing** (see p. 2065) may be done when autonomic dysfunction is suspected; it gives more consistent results than supine and upright BP assessment and eliminates augmentation of venous return by leg muscle contraction. The patient may remain upright for 30 to 45 min of BP assessment.

**Treatment**

Patients requiring prolonged bed rest should sit up each day and exercise in bed when possible. Patients should rise slowly from a recumbent or sitting position, consume adequate fluids, limit or avoid alcohol, and exercise regularly when feasible. Regular modest-intensity exercise promotes overall vascular tone and reduces venous pooling. Elderly patients should avoid prolonged standing. Sleeping with the head of the bed raised may relieve symptoms by promoting Na retention and reducing nocturnal diuresis.

Postprandial hypotension can often be prevented by reducing the size and carbohydrate content of meals, minimizing alcohol intake, and avoiding sudden standing after meals.

Waist-high fitted elastic hose may increase venous return, cardiac output, and BP after standing. In severe cases, inflatable aviator-type antigravity suits, although often poorly tolerated, may be needed to produce adequate leg and abdominal counterpressure.

Increasing Na intake may expand intravascular volume and lessen symptoms. In the absence of heart failure or hypertension, Na intake can be increased 5 to 10 g above the usual dietary level by liberally salting food or taking NaCl tablets. This approach risks heart failure, particularly in elderly patients and patients with impaired myocardial function; development of dependent edema without heart failure does not contraindicate continuing this approach.

Fludrocortisone, a mineralocorticoid, causes Na retention, which expands plasma volume, and often lessens symptoms but is effective only when Na intake is adequate. Dosage is 0.1 mg po at bedtime, increased weekly to 1 mg or until peripheral edema occurs. This drug may also improve the peripheral vasoconstrictor response to sympathetic stimulation. Supine hypertension, heart failure, and hypokalemia may occur; K supplements may be needed.

Midodrine, a peripheral α-agonist that is both an arterial and venous constrictor, is often effective. Dosage is 2.5 mg to 10 mg po tid. Adverse effects include paresthesias and itching (probably secondary to piloerection). This drug is not recommended for patients with coronary artery or peripheral arterial disease.

NSAIDs (eg, indomethacin 25 to 50 mg po tid) may inhibit prostaglandin-induced vasodilation, increasing peripheral vascular resistance. However, NSAIDs may cause GI symptoms and unwanted vasopressor reactions (reported with concurrent use of indomethacin and sympathomimetic drugs).

L-Dihydroxyphenylserine, a norepinephrine precursor, may be beneficial for autonomic dysfunction (reported in limited trials).

Propranolol or other β-blockers may enhance the beneficial effects of Na and mineralocorticoid therapy. β-Blockade with propranolol leads to unopposed α-adrenergic peripheral vascular vasoconstriction, preventing the vasodilation that occurs when some patients stand.

**Geriatrics Essentials**

Orthostatic hypotension occurs in about 20% of the elderly; it is more common among people with coexisting disorders, especially hypertension, and among residents of long-term care facilities. Many falls may result from unrecognized orthostatic hypotension.

The increased incidence in the elderly is due to decreased baroreceptor responsiveness plus decreased arterial compliance. Decreased baroreceptor responsiveness delays cardioacceleration and peripheral
vasoconstriction in response to standing. Paradoxically, hypertension may contribute to poor baroreceptor sensitivity, increasing vulnerability to orthostatic hypotension. The elderly also have decreased resting parasympathetic tone, so that cardioacceleration due to reflex vagal withdrawal is lessened.

**Key Points**

- Orthostatic hypotension typically involves volume depletion or autonomic dysfunction.
- Some degree of autonomic dysfunction is common in the elderly, but neurologic disorders must be ruled out.
- Bedside tests of autonomic function and often tilt table testing are done.
- Treatment involves physical measures to reduce venous pooling, increased Na intake, and sometimes fludrocortisone or midodrine.

**Palpitations**

Palpitations are the perception of cardiac activity. They are often described as a fluttering, racing, or skipping sensation. They are common; some patients find them unpleasant and alarming. Palpitations can occur in the absence of heart disease or can result from life-threatening heart disorders. The key to diagnosis and treatment is to "capture" the rhythm on ECG and make careful observations during the palpitations.

**Pathophysiology**

The mechanisms responsible for the sensation of palpitations are unknown. Ordinarily, sinus rhythm at a normal rate is not perceived, and palpitations thus usually reflect changes in cardiac rate, rhythm, or contractility. In all cases, it is the abnormal movement of the heart within the chest that is felt. In cases of isolated extrasystoles, the patient may actually perceive the augmented post-extrasystolic beat as the "skipped" beat rather than the premature beat itself, probably because the extrasystole blocks the next sinus beat and allows longer ventricular filling and thus a higher stroke volume.

The clinical perception of cardiac phenomena is highly variable. Some patients are aware of virtually every premature ventricular beat, but others are unaware of even complex atrial or ventricular tachyarrhythmias. Awareness is heightened in sedentary, anxious, or depressed patients and reduced in active, happy patients. In some cases, palpitations are perceived in the absence of any abnormal cardiac activity.

**Etiology**

Some patients simply have heightened awareness of normal cardiac activity, particularly when exercise, febrile illness, or anxiety increases heart rate. However, in most cases, palpitations result from arrhythmia. Arrhythmias range from benign to life threatening.

The **most common arrhythmias** include

- Premature atrial contractions (PACs)
- Premature ventricular contractions (PVCs)

Both of these arrhythmias usually are harmless.

Other common arrhythmias include

- Paroxysmal supraventricular tachycardia (PSVT)
- Atrioventricular nodal reentrant tachycardia
• Atrial fibrillation or flutter
• Ventricular tachycardia
• Bradyarrhythmias and heart block

Causes of arrhythmias: Some arrhythmias (eg, PACs, PVCs, PSVT) often occur spontaneously in patients without serious underlying disorders, but others are often caused by a serious cardiac disorder.

Serious cardiac causes include myocardial ischemia or other myocardial disorders, congenital heart disease, valvular heart disease, and conduction system disturbances (eg, disturbances that cause bradycardia or heart block). Patients with orthostatic hypotension commonly sense palpitations caused by sinus tachycardia on standing.

Noncardiac disorders that increase myocardial contractility (eg, thyrotoxicosis, pheochromocytoma, anxiety) may cause palpitations.

Some drugs, including digitalis, caffeine, alcohol, nicotine, and sympathomimetics (eg, albuterol, amphetamines, cocaine, dobutamine, epinephrine, ephedrine, isoproterenol, norepinephrine, and theophylline), frequently cause palpitations.

Metabolic disturbances, including anemia, hypoxia, hypovolemia, and electrolyte abnormalities (eg, diuretic-induced hypokalemia), can trigger or exacerbate palpitations.

Consequences: Many arrhythmias that cause palpitations have no adverse physiologic consequences of their own (ie, independent of the underlying disorder). However, bradyarrhythmias, tachyarrhythmias, and heart blocks can be unpredictable and may adversely affect cardiac output and cause hypotension or death. Ventricular tachycardia sometimes degenerates to ventricular fibrillation.

Evaluation
A complete history and physical examination are essential. Observations by other medical personnel or reliable observers should be sought.

History: History of present illness should cover the frequency and duration of palpitations and provoking or exacerbating factors (eg, emotional distress, activity, change in position, intake of caffeine or other drugs). Important associated symptoms include syncope, light-headedness, tunnel vision, dyspnea, and chest pain. Asking the patient to tap out the rate and cadence of palpitations is better than a verbal description and often allows a definitive diagnosis, as in the "missed beat" of atrial or ventricular extrasystoles or the rapid total irregularity of atrial fibrillation.

Review of systems should cover symptoms of causative disorders, including heat intolerance, weight loss, and tremor (hyperthyroidism); chest pain and dyspnea on exertion (cardiac ischemia); and fatigue, weakness, heavy vaginal bleeding, and dark tar-like stools (anemia).

Past medical history should identify known potential causes, including documented arrhythmias and heart or thyroid disorders. Family history should note occurrences of syncope or sudden death at an early age.

The drug profile should be reviewed for offending prescription drugs (eg, antiarrhythmics, digitalis, β-agonists, theophylline, and rate-limiting drugs); OTC drugs (eg, cold and sinus medications, dietary supplements containing stimulants), including alternative medicines; and illicit drugs (eg, cocaine, methamphetamine). Caffeine (eg, coffee, tea, numerous soft drinks and energy drinks), alcohol, and tobacco use should be determined.

Physical examination: The general examination should note whether an anxious demeanor or psychomotor agitation is present. Vital signs are reviewed for fever, hypertension, hypotension,
tachycardia, bradycardia, tachypnea, and low O2 saturation. Orthostatic changes in BP and heart rate should be measured.

Examination of the head and neck should note any abnormality or dyssynchrony of the jugular pulse waves compared with the carotid pulse or auscultated heart rhythm and findings of hyperthyroidism, such as thyroid enlargement or tenderness and exophthalmos. The conjunctivae, palmar creases, and buccal mucosa should be inspected for pallor.

Cardiac auscultation should note the rate and regularity of the rhythm as well as any murmurs or extra heart sounds that might indicate underlying valvular or structural heart disease.

Neurologic examination should note whether resting tremors or brisk reflexes are present (suggesting excess sympathetic stimulation). An abnormal neurologic finding suggests that seizures rather than a cardiac disorder may be the cause if syncope is one of the symptoms.

**Red flags:** Certain findings suggest a more serious etiology:

- Light-headedness or syncope (particularly if injury occurs from syncope)
- Chest pain
- New onset of irregularly irregular heart rhythm
- Heart rate >120 beats/min or < 45 beats/min while at rest
- Significant underlying heart disease
- Family history of sudden death

**Interpretation of findings:** History (see **Table 206-9**) and, to a lesser extent, physical examination provide clues to the diagnosis.

Palpation of the arterial pulse and cardiac auscultation may reveal a rhythm disturbance. However, the examination is not always diagnostic of a specific rhythm, except when it identifies the unique irregular irregularity of some cases of rapid atrial fibrillation, the regular irregularity of coupled atrial or ventricular extrasystoles, the regular tachycardia at 150 beats/min of atrial flutter (in adults, this rate is rare with any other arrhythmia), and the regular bradycardia of < 35 beats/min of complete atrioventricular block. Careful examination of the jugular venous pulse waves simultaneously with cardiac auscultation and palpation of the carotid artery allows diagnosis of most arrhythmias if an ECG is not available, because the jugular waves will show the atrial rhythm while the auscultated sounds or the pulse in the carotids are the product of ventricular contraction.

**Table 206-9. Suggestive Historical Findings with Palpitations**

Thyroid enlargement or tenderness with exophthalmos suggests thyrotoxicosis. Marked hypertension and regular tachycardia suggest pheochromocytoma.

**Testing:** Testing typically is done.

- ECG, sometimes with ambulatory monitoring
- Laboratory testing
- Sometimes imaging studies, stress testing, or both

ECG is done, but unless the recording is done while symptoms are occurring, it may not provide a diagnosis. Many cardiac arrhythmias are intermittent and show no fixed ECG abnormalities; exceptions include...
• Wolff-Parkinson-White syndrome

• Long QT syndrome

• Arrhythmogenic right ventricular dysplasia cardiomyopathy

• Brugada syndrome and its variants

If no diagnosis is apparent and symptoms are frequent, Holter monitoring for 24 to 48 h is useful; for intermittent symptoms, an event recorder worn for longer periods and activated by the patient when symptoms are felt is better. These tests are used mainly when a sustained arrhythmia is suspected, rather than when symptoms suggest only occasional skipped beats. Patients with very infrequent symptoms that clinicians suspect represent a serious arrhythmia may have a device implanted beneath the skin of the upper chest. This device continuously records the rhythm and can be interrogated by an external machine that allows the cardiac rhythm to be printed.

Laboratory testing is needed in all patients. All patients should have measurement of CBC, serum electrolytes including Mg and Ca, and C-reactive protein (indicating inflammation that may be affecting the heart or coronary arteries). Cardiac markers (eg, troponin and CK) should be measured in patients with ongoing arrhythmias, chest discomfort, or other symptoms suggesting active or recent coronary ischemia, myocarditis, or pericarditis.

Thyroid function tests are indicated when atrial fibrillation is newly diagnosed or there are symptoms of hyperthyroidism. Patients with paroxysms of high BP should be evaluated for pheochromocytoma.

Sometimes tilt-table testing is done in patients with postural syncope.

Imaging is often needed. Patients with findings suggesting cardiac dysfunction or structural heart disease require echocardiography and sometimes cardiac MRI. Patients with symptoms on exertion require stress testing sometimes with stress echocardiography, nuclear scanning, or PET.

Treatment

Precipitating drugs and substances are stopped. If dangerous or debilitating arrhythmias are caused by a necessary therapeutic drug, a different drug should be tried.

For isolated PACs and PVCs in patients without structural heart disease, simple reassurance is appropriate. For otherwise healthy patients in whom these phenomena are disabling, a β-blocker can be given provided efforts are made to avoid reinforcing the perception by anxious patients that they have a serious disorder.

Identified rhythm disturbances and underlying disorders are investigated and treated (see Table 206-10).

Geriatrics Essentials

Elderly patients are at particular risk of adverse effects of antiarrhythmics; reasons include lower GFR and concomitant use of other drugs. When drug treatment is needed, lower doses should be used to start. Subclinical conduction abnormalities may be present (recognized on ECG or other studies), which might worsen with use of antiarrhythmics; such patients may require a pacemaker to allow the use of antiarrhythmics.

Key Points

• Palpitations are a frequent but relatively nonspecific symptom.

• Palpitations are not a reliable indicator of a significant arrhythmia, but palpitations in a patient with
structural heart disease or an abnormal ECG may be a sign of a serious problem and warrant investigation.

• An ECG or other recording done during symptoms is essential; a normal ECG in a symptom-free interval does not rule out significant disease.

• Most antiarrhythmics themselves can cause arrhythmias.

• If in doubt about a rapid tachyarrhythmia in a patient in hemodynamic distress, use electrocardioversion first and ask questions later.

Syncope

Syncope is a sudden, brief loss of consciousness (LOC) with loss of postural tone followed by spontaneous revival. The patient

[Table 206-10. Some Treatments for Arrhythmias]

is motionless and limp and usually has cool extremities, a weak pulse, and shallow breathing.

Near syncope is light-headedness and a sense of an impending faint without LOC. It is usually classified and discussed with syncope because the causes are the same.

Seizures can cause sudden LOC but are not considered syncope. However, seizures must be considered in patients presenting for apparent syncope because history may be unclear or unavailable, and some seizures do not cause tonic-clonic convulsions. Furthermore, a brief (< 5 sec) seizure sometimes occurs with true syncope.

Diagnosis depends on a careful history, eyewitness accounts, or fortuitous examination during the event.

Pathophysiology

Most syncope results from insufficient cerebral blood flow. Some cases involve adequate flow but with insufficient cerebral substrate (O₂, glucose, or both).

Insufficient cerebral blood flow: Most deficiencies in cerebral blood flow result from decreased cardiac output (CO).

Decreased CO can be caused by

• Cardiac disorders that obstruct outflow

• Cardiac disorders of systolic dysfunction

• Cardiac disorders of diastolic dysfunction

• Arrhythmias (too fast or too slow)

• Conditions that decrease venous return

Outflow obstruction can be exacerbated by exercise, vasodilation, and hypovolemia (particularly in aortic stenosis and hypertrophic cardiomyopathy), which may precipitate syncope.

Arrhythmias cause syncope when the heart rate is too fast to allow adequate ventricular filling (eg, > 150 to 180 beats/min) or too slow to provide adequate output (eg, < 30 to 35 beats/min).

Venous return can be decreased by hemorrhage, increased intrathoracic pressure, increased vagal tone (which can also decrease heart rate), and loss of sympathetic tone (eg, from drugs, carotid sinus
pressure, autonomic dysfunction). Syncope involving these mechanisms (except for hemorrhage) is often termed vasovagal or neurocardiogenic and is common and benign.

Orthostatic hypotension, a common benign cause of syncope, results from failure of normal mechanisms (eg, sinus tachycardia, vasoconstriction, or both) to compensate for the temporary decrease in venous return that occurs with standing (see p. 2035).

Cerebrovascular disorders (eg, strokes, transient ischemic attacks) rarely cause syncope because most of them do not involve the centrencephalic structures that must be affected to produce LOC. However, basilar artery ischemia, due to transient ischemic attack or migraine, may cause syncope. Rarely, patients with severe cervical arthritis or spondylosis develop vertebrobasilar insufficiency with syncope when the head is moved in certain positions.

Insufficient cerebral substrate: The CNS requires O2 and glucose to function. Even with normal cerebral blood flow, a significant deficit of either will cause LOC. In practice, hypoglycemia is the primary cause because hypoxia rarely develops in a manner causing abrupt LOC (other than in flying or diving incidents). LOC due to hypoglycemia is seldom as abrupt as in syncope or seizures because warning symptoms occur (except in patients taking β-blockers); however, the onset may be unclear to the examiner unless the event was witnessed.

Etiology

Causes are usually classified by the mechanism (see Table 206-11).

The most common causes are

• Vasovagal
• Idiopathic

Many cases never have a firm diagnosis but lead to no apparent harm. A smaller number of cases have a serious cause, usually cardiac.

Evaluation

Evaluation should be done as soon as possible after the event. The more remote the syncopeal event, the more difficult the diagnosis. Information from witnesses is quite helpful and best obtained as soon as possible.

History: History of present illness should ascertain events leading up to the syncope, including the patient's activity (eg, exercising, arguing, in a potentially emotional situation), position (eg, lying or standing), and, if standing, for how long. Important associated symptoms immediately before or after the event include whether there was a sense of impending LOC, nausea, sweating, blurred or tunnel vision, tingling of lips or fingertips, chest pain, or palpitations. Witnesses, if any, should be sought and asked to describe events, particularly the presence and duration of any seizure activity.

Review of systems should ask about any areas of pain or injury, episodes of dizziness or near syncope on arising, and episodes of palpitations or chest pain with exertion. Patients should be asked about symptoms suggesting possible causes, including bloody or tarry stools, heavy menses (anemia); vomiting, diarrhea, or excess urination (dehydration or electrolyte abnormalities); and risk factors for pulmonary embolism (recent surgery or immobilization, known cancer, previous clots or hypercoagulable state).

Past medical history should ask about previous syncopal events, known cardiovascular disease, and known seizure disorders. Drugs used should be identified (particularly antihypertensives, diuretics, vasodilators, and antiarrhythmics—see Table 206-12). Family history should note presence at a young age of heart disease or sudden death in any family member.
Physical examination: Vital signs are essential. Heart rate and BP are measured with the patient supine and after 2 min of standing. Pulse is palpated for irregularity.

General examination notes patient's mental status, including any confusion or hesitancy suggesting a postictal state and any signs of injury (eg, bruising, swelling, tenderness, tongue bite).

The heart is auscultated for murmurs; if present, any change in the murmur with a Valsalva maneuver, standing, or squatting is noted.

Careful evaluation of the jugular venous waves (see Fig. 206-1) while palpating the carotid or auscultating the heart may allow diagnosis of an arrhythmia if an ECG is not available.

Some clinicians carefully apply unilateral carotid sinus pressure during ECG monitoring with the patient supine to detect bradycardia or heart block, suggesting carotid sinus hypersensitivity. Carotid sinus pressure should not be applied if a carotid bruit is present.

Abdomen is palpated for tenderness, and a rectal examination is done to check for gross or occult blood.

A full neurologic examination is done to identify any focal abnormalities, which suggest a CNS cause (eg, seizure disorder).

Red flags: Certain findings suggest a more serious etiology:

- Syncope during exertion
- Multiple recurrences within a short time
- Heart murmur or other findings suggesting structural heart disease (eg, chest pain)

[Table 206-11, Some Causes of Syncope]

- Older age
- Significant injury during syncope
- Family history of sudden unexpected death

Interpretation of findings: Although the cause is often benign, it is important to identify the occasional life-threatening cause (eg, tachyarrhythmia, heart block) because sudden death is a risk. Clinical findings (see Table 206-11) help suggest a cause in 40 to 50% of cases. A few generalizations are useful.

Benign causes often lead to syncope. Syncope precipitated by unpleasant physical or emotional stimuli (eg, pain, fright), usually occurring in the upright position and often preceded by vagally mediated warning symptoms (eg, nausea, weakness, yawning, apprehension, blurred vision, diaphoresis), suggests vasovagal syncope.

Syncope that occurs most often when assuming an upright position (particularly in elderly patients after prolonged bed rest or in patients taking drugs in certain classes) suggests orthostatic syncope. Syncope that occurs after standing for long periods without moving is usually due to venous pooling.

LOC that is abrupt in onset; is associated with muscular jerking or convulsions, incontinence, or tongue biting; and is followed by postictal confusion or somnolence suggests a seizure.

Red flag findings suggest a dangerous cause.

Syncope with exertion suggests cardiac outflow obstruction. Such patients sometimes also have chest pain, palpitations, or both. Cardiac findings may help identify a cause. A harsh, late-peaking, basal
murmur radiating to the carotid arteries suggests aortic stenosis; a systolic

[Table 206-12. Some Drug Causes of Syncope]

murmur that increases with the Valsalva maneuver and disappears with squatting suggests hypertrophic cardiomyopathy. A systolic click followed by a blowing systolic murmur that moves closer to the 1st heart sound on standing suggests mitral valve prolapse (suggesting the cause is an arrhythmia).

Syncope that begins and ends suddenly and spontaneously is typical of cardiac causes, most commonly an arrhythmia. Because vasovagal and orthostatic mechanisms do not cause syncope in the recumbent position, syncope while lying down also suggests an arrhythmia.

If the patient is injured during the episode of syncope, the likelihood of a cardiac cause or seizure is somewhat greater, and therefore the event is of greater concern. The warning signs and slower LOC that accompany benign vasovagal syncope somewhat reduce the likelihood of injury.

**Testing:** Testing typically is done.

- ECG
- Pulse oximetry
- Sometimes echocardiography
- Sometimes tilt table testing
- Blood tests only if clinically indicated
- CNS imaging rarely indicated

In general, if syncope results in an injury or is recurrent (particularly within a brief period), more intensive evaluation is warranted.

Patients with suspected arrhythmia, myocarditis, or ischemia should be evaluated as in-patients. Others may be evaluated as outpatients.

**ECG** is done for all patients. The ECG may reveal arrhythmia, a conduction abnormality, ventricular hypertrophy, pre-excitation, QT prolongation, pacemaker malfunction, myocardial ischemia, or MI. If there are no clinical clues, measuring cardiac markers and obtaining serial ECGs to rule out MI in older patients plus ECG monitoring for at least 24 h are prudent. Any detected arrhythmia must be associated with altered consciousness in order to be implicated as the cause, but most patients do not experience syncope during monitoring. On the other hand, the presence of symptoms in the absence of rhythm disturbance helps rule out a cardiac cause. An event recorder may be useful if warning symptoms precede syncope. A signal-averaged ECG may identify predisposition to ventricular arrhythmias in patients with ischemic heart disease or in post-MI patients.

**Pulse oximetry** should be done during or immediately after an episode to identify hypoxemia (which may indicate pulmonary embolism). If hypoxemia is present, a CT scan or lung scan is indicated to rule out pulmonary embolism.

**Laboratory tests** are done based on clinical suspicion; reflexively obtained laboratory panels are of little use. However, all females of childbearing age should have a pregnancy test. Hct is measured if anemia is suspected. Electrolytes are measured only if an abnormality is clinically suspected (eg, by symptoms or drug use). Cardiac markers (eg, serum troponin, CK-MB) are measured if acute MI is suspected.

**Echocardiography** is indicated for patients with exercise-induced syncope, cardiac murmurs, or suspected intracardiac tumors (eg, those with positional syncope).
Tilt table testing is done if history and physical examination indicate vasodepressor or other reflex-induced syncope. It is also used to evaluate exercise-induced syncope if echocardiography or exercise stress testing is negative.

Stress testing (exercise or pharmacologic) is done when intermittent myocardial ischemia is suspected. It is often done for patients with exercise-induced symptoms.

Invasive electrophysiologic testing is considered if noninvasive testing does not identify arrhythmia in patients with unexplained recurrent syncope; a negative response defines a low-risk subgroup with a high rate of remission of syncope. The use of electrophysiologic testing is controversial in other patients. Exercise testing is less valuable unless physical activity precipitated syncope.

EEG is warranted if a seizure disorder is suspected.

CT and MRI of the head and brain are indicated only if signs and symptoms suggest a focal CNS disorder.

Treatment

In witnessed syncope, pulses are checked immediately. If the patient is pulseless, CPR is begun and cardiac resuscitation is done. If pulses are present, severe bradycardia is treated with atropine or external transthoracic pacing. Isoproterenol can be used to maintain adequate heart rate while a temporary pacemaker is placed.

Tachyarrhythmias are treated (see also p. 2146); a direct-current synchronized shock is quicker and safer for unstable patients. Inadequate venous return is treated by keeping the patient supine, raising the legs, and giving IV normal saline. Tamponade is relieved by pericardiocentesis. Tension pneumothorax requires insertion of a plural cannula and drainage. Anaphylaxis is treated with parenteral epinephrine.

Placing the patient in a horizontal position with legs elevated typically ends the syncopal episode if life-threatening disorders are ruled out. If the patient sits upright too rapidly, syncope may recur; propping the patient upright or transporting the patient in an upright position may prolong cerebral hypoperfusion and prevent recovery.

Specific treatment depends on the cause and its pathophysiology.

Geriatrics Essentials

The most common cause of syncope in the elderly is postural hypotension due to a combination of factors. Factors include rigid, noncompliant arteries, reduced skeletal muscle pumping of venous return due to physical inactivity, and degeneration of the sinoatrial node and conduction system due to progressive structural heart disease.

In the elderly, syncope often has more than one cause. For example, the combination of taking several heart and BP drugs and standing in a hot church during a long or emotional service may lead to syncope even though no single factor might cause syncope.

Key Points

• Syncope results from global CNS dysfunction, usually from insufficient cerebral blood flow.

• Most syncpe results from benign causes.

• Some less common causes involve cardiac arrhythmia or outflow obstruction and are serious or potentially fatal.

• Vasovagal syncope usually has an apparent trigger, warning symptoms, and a few minutes of postrecovery symptoms.
• Syncope from cardiac arrhythmias typically occurs abruptly and with quick recovery.

• Seizures have a prolonged (eg, hours) recovery period.

• If a benign etiology is not clear, driving and use of machinery should be prohibited until the etiology is determined and treated—the next manifestation of an unrecognized cardiac cause may be fatal.
Chapter 207. Cardiovascular Tests and Procedures

Introduction

Many noninvasive and invasive tests can delineate cardiac structure and function (see Table 207-1). Also, treatments can be administered during certain invasive diagnostic tests (eg, percutaneous coronary intervention during cardiac catheterization, radiofrequency ablation during electrophysiologic testing).

Cardiac Catheterization

Cardiac catheterization is the passage of a catheter through peripheral arteries or veins into cardiac chambers and coronary arteries. Cardiac catheterization can be used to do various tests, including angiography, intravascular ultrasonography, measurement of cardiac output (CO), detection and quantification of shunts, endomyocardial biopsy, and measurements of myocardial metabolism. These tests define coronary artery anatomy, cardiac anatomy, and cardiac function to establish diagnoses and help select treatment. Cardiac catheterization is also the basis for several therapeutic interventions.

Procedure

Patients must be npo for 4 to 6 h before cardiac catheterization. Most patients do not require overnight hospitalization.

Left heart catheterization is most commonly used to assess coronary artery anatomy; it is also useful for assessing aortic BP and systemic vascular resistance, aortic and mitral valve function, and left ventricular (LV) pressure and function. The procedure is done by percutaneous femoral, radial, or brachial artery puncture, with a catheter passed into the coronary artery ostia or across the aortic valve into the LV. Catheterization of the left atrium (LA) and LV is occasionally done using transseptal perforation during right heart catheterization.

Right heart catheterization is most commonly used to assess right atrial (RA), right ventricular (RV), and pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP)—see Fig. 207-1 and p. 2245; PAOP approximates LA and LV end-diastolic pressure. In seriously ill patients, PAOP helps assess volume status and, with simultaneous measurements of CO, can help guide therapy. Right heart catheterization is also useful for assessing pulmonary vascular resistance, tricuspid or pulmonic valve function, and RV pressure; RV pressure may help in the diagnosis of cardiomyopathy, constrictive pericarditis, and cardiac tamponade when noninvasive testing is nondiagnostic. The procedure is done by femoral, subclavian, internal jugular, or antecubital vein puncture. A catheter is passed into the RA, through the tricuspid valve, into the RV, and across the pulmonary valve into the pulmonary artery (see p. 2244). Selective catheterization of the coronary sinus can also be done.

Specific Tests During Cardiac Catheterization

Angiography: Injection of radiopaque dye into coronary or pulmonary arteries, the aorta, and cardiac chambers is useful in certain circumstances. Digital subtraction angiography is used for nonmoving arteries and for chamber cineangiography.

Coronary angiography via left heart catheterization is used to evaluate coronary artery anatomy in various clinical situations, as in patients with suspected coronary atherosclerotic or congenital disease, valvular disorders before valvular replacement, or unexplained heart failure.

Pulmonary angiography via right heart catheterization is used to diagnose pulmonary embolism. Intraluminal filling defects or arterial cutoffs are diagnostic. Radiopaque dye is usually selectively injected into one or both pulmonary arteries and their segments. Computed tomographic pulmonary angiography
(CTPA) has largely replaced right heart catheterization for diagnosis of pulmonary embolism.

Aortic angiography via left heart catheterization is used to assess aortic regurgitation, coarctation, patent ductus arteriosus, and dissection.

Ventriculography is used to visualize ventricular wall motion and ventricular outflow tracts, including subvalvular, valvular, and supravalvular regions. After LV mass and volume are determined from single planar or biplanar ventricular angiograms, end-systolic and end-diastolic volumes and ejection fraction can be calculated.

**Intravascular ultrasonography:** Miniature ultrasound transducers on the end of coronary artery catheters can produce images of coronary vessel lumina and walls and delineate blood flow. This technique is being increasingly used at the same time as coronary angiography.

**Tests for cardiac shunts:** Measuring blood O\(_2\) content at successive levels in the heart and great vessels can help determine the presence, direction, and volume of central shunts. The maximal normal difference in O\(_2\) content is 0.5 mL/dL between the pulmonary artery and RV, 0.9 mL/dL between the RV and RA, and 1.9 mL/dL between the RA and superior vena cava. If the blood O\(_2\) content in a chamber exceeds that of the more proximal chamber by more than these values, a left-to-right shunt at that level is probable. Right-to-left shunts are strongly suspected when LA, LV, or arterial O\(_2\) saturation is low (≤ 92%) and does not improve when pure O\(_2\) (fractional inspirational O\(_2\) = 1.0) is given. Left heart or arterial desaturation plus increased O\(_2\) content in blood samples drawn beyond the shunt site on the right side of circulation suggests a bidirectional shunt.

**Measurement of cardiac output and flow:** CO is the volume of blood ejected by the heart per minute (normal at rest: 4 to 8 L/min). Techniques used to calculate CO include the Fick, indicator-dilution, and thermodilution techniques (see Table 207-2).

With the Fick technique, CO is proportional to O\(_2\) consumption divided by arteriovenous O\(_2\) difference.

Dilution techniques rely on the assumption that after an indicator is injected into the circulation, it appears and disappears proportionately to CO.

Usually, CO is expressed in relation to BSA as the cardiac index (CI) in L/min/m\(^2\) (ie, CI = CO/BSA—see Table 207-3). BSA is calculated using DuBois’ height (ht)-weight (wt) equation:

\[
\text{BSA in m}^2 = (\text{wt in kg})^{0.425} \times (\text{ht in cm})^{0.725} \times 0.007184
\]

**Endomyocardial biopsy:** This procedure helps assess transplant rejection and myocardial disorders due to infection or infiltrative diseases. The biopsy catheter (bioprome) can be passed into either ventricle, usually the right. Three to 5 samples of myocardial tissue are removed from the septal endocardium. The main complication, cardiac perforation, occurs in 0.3 to 0.5% of patients; it may cause hemopericardium leading to cardiac tamponade.

**Coronary artery flow measurements:** Coronary angiography shows the presence and degree of stenosis but not the functional significance of the lesion (ie, how much blood flows across the stenosis). Extremely thin guidewires are available with pressure sensors or Doppler flow sensors. Data from these sensors can be used to estimate blood flow, which is expressed as fractional flow reserve (FFR). FFR is the ratio of maximal flow through the stenotic area to normal maximal flow; an FFR of < 0.75 to 0.8 is considered abnormal. These flow estimates correlate well with the need for intervention and long-term outcome; lesions with good FFR do not seem to benefit from stenting. These flow measurements are
most useful with intermediate lesions (40 to 70% stenosis) and with multiple lesions (to identify those that are clinically most significant).

**[Table 207-2, Cardiac Output Equations]**

**[Table 207-3, Normal Values for Cardiac Index and Related Measurements]**

### Contraindications

**Relative contraindications** to cardiac catheterization include

- Renal insufficiency
- Coagulopathy
- Fever
- Systemic infection
- Uncontrolled arrhythmia or hypertension
- Uncompensated heart failure
- Radiopaque dye allergies in patients who have not been appropriately premedicated (see p. 3404)

### Complications

Injection of radiopaque dye produces a transient sense of warmth throughout the body in many patients. Tachycardia, a slight fall in systemic pressure, an increase in CO, nausea, vomiting, and coughing may occur. Serious complications (eg, cardiac arrest, anaphylactic reactions, shock, seizures, cyanosis, renal toxicity) are rare. Rarely, bradycardia occurs when a large amount of dye is injected; asking the patient to cough often restores normal rhythm. Patients with a high Hct are susceptible to thrombosis; the Hct should be < 65% before angiography is done. Allergic reactions may include urticaria and conjunctivitis, which usually respond to diphenhydramine 50 mg IV. Bronchospasm, laryngeal edema, and dyspnea are rare reactions; they are treated with salbutamol or epinephrine. Anaphylactic shock is treated with epinephrine and other supportive measures. If the catheter tip contacts the ventricular endocardium, ventricular arrhythmias commonly occur, but ventricular fibrillation is rare. If it occurs, direct current (DC) cardioversion is administered immediately (see p. 2260). Radiopaque dyes, all hypertonic, are excreted by the kidneys and may worsen renal insufficiency. For patients at risk, infusion of normal saline IV, and perhaps premedication with acetylcysteine, reduces this risk.

Mortality rate is 0.1 to 0.2%. MI (0.1%) and stroke (0.1%) may result in significant morbidity. Incidence of stroke is higher in patients > 80 yr. Dissection of a coronary artery can complicate angiography. Local vascular injury at the peripheral insertion site of catheterization can cause hemorrhage or formation of pseudoaneurysms or arteriovenous fistulas.

### Coronary Artery Bypass Grafting

Coronary artery bypass grafting (CABG—see also p. 2098) involves bypassing native coronary arteries with high-grade stenosis or occlusion not amenable to angioplasty with stenting. Indications are changing as percutaneous interventions (see p. 2059) are being increasingly used.

### Traditional CABG Procedure

The procedure involves thoracotomy via a midline (median) sternotomy. A heart-lung machine is used to establish cardiopulmonary bypass (CPB), allowing the heart to be stopped and emptied of blood to maximize operative exposure and facilitate vessel anastomosis; stopping the heart also markedly decreases myocardial O₂ demand. Before initiation of CPB, the patient is given a very high dose of
heparin to prevent clotting in the bypass circuit. Then the aorta is cross-clamped and the heart is stopped by injection of a cardioplegic solution (crystalloid or more commonly blood-based) that also contains substances that help myocardial cells tolerate ischemia and reperfusion. The cardioplegic solution and the heart are sometimes cooled slightly to enhance tolerance of ischemia; the patient's body is cooled via the CPB machine for similar reasons.

The left internal mammary artery is typically used as a pedicled graft to the left anterior descending coronary artery. Other grafts consist of segments of saphenous vein removed from the leg. Occasionally, the right internal mammary artery or radial artery from the non-dominant arm can be used.

On completion of the vascular anastomoses, the aorta is unclamped, allowing the coronary arteries to be perfused by oxygenated blood, which typically restores cardiac activity. Heparin anticoagulation is reversed by giving protamine. Despite cardioprotective measures, stopping the heart is not without consequences. During reperfusion, myocardial dysfunction is common and can lead to bradycardia, arrhythmias (eg, ventricular fibrillation), and low cardiac output; these events are treated by standard measures, such as pacing, defibrillation, and inotropic drugs.

Typically, hospital stays are 4 to 5 days unless prolonged by complications.

**Complications:** Complications and disadvantages of traditional CABG involve mainly

- **Sternotomy**
- **CPB**

Median sternotomy is surprisingly well tolerated; however, healing takes 4 to 6 wk. Also, wound infections occasionally cause mediastinitis or sternal osteomyelitis, which can be vexing to treat.

CPB causes several complications, including

- **Bleeding**
- **Organ dysfunction**
- **Neuropsychiatric effects**
- **Stroke**

Post-CPB bleeding is a common problem caused by various factors, including hemodilution, heparin use, platelet dysfunction due to exposure to the bypass pump, consumptive coagulopathy, and induced hypothermia. Also, the CPB machine evokes a systemic inflammatory response (probably due to exposure of blood components to the foreign material of the bypass circuit); this response can cause organ dysfunction in any system (eg, pulmonary, renal, brain, GI). Aortic cannulation, cross-clamping, and release can trigger release of emboli, causing stroke in about 1.5%; microemboli may contribute to post-CPB neuropsychiatric effects, which appear in about 5 to 10%.

Other common complications of CABG include focal and global myocardial ischemia and dysrhythmias. Perioperative MI occurs in about 1% of patients. Atrial fibrillation occurs in 15 to 40% of patients, typically 2 to 4 days after surgery. Nonsustained ventricular tachycardia may occur in up to 50% of patients.

**Mortality** depends mainly on patients' underlying health; operator and institutional experience (ie, number of annual procedures) also is important. In an experienced program, periprocedural mortality in otherwise healthy patients is typically < 1 to 3%.

**Alternative CABG Procedures**

Newer techniques seek to limit the complications of traditional CABG by
Avoiding CPB (off-pump CABG)

Avoiding median sternotomy (minimally invasive CABG)

Both

CPB can be avoided in select patients by using new techniques that allow the surgeon to revascularize the beating heart. Various devices and methods stabilize a portion of the myocardium, holding the operative site relatively motionless. Off-pump procedures are more commonly done through small parasternal or intercostal incisions (minimally invasive CABG), sometimes with endoscopy or even robotic assistance, but they may be done through a traditional median sternotomy, which provides better operative exposure.

Allowing the heart to beat means that the myocardium requires more O$_2$ than when CPB is used. Thus, the heart is sensitive to the interruption of blood flow necessitated while the vascular anastomosis is done; this interruption can cause ischemia or infarction in the myocardium supplied by the affected vessel. Some surgeons place a temporary coronary artery shunt to provide distal perfusion.

The minimally invasive technique is somewhat more difficult to do and may not be suitable when multiple bypass grafts, particularly those involving vessels behind the heart, are required. Transfusion requirements, length of stay, and costs are typically less with off-pump CABG, but in some studies, the rate of the more serious complications of death, MI, and stroke are similar to that of CABG using CPB. Thus, the theoretic advantages of avoiding CPB do not seem to have been fully realized.

Minimally invasive CABG is usually done off-pump but may be done using CPB. In such cases, CPB is done endovascularly using special catheters inserted into the arterial and venous systems; the aorta is occluded by a balloon at the end of the aortic catheter rather than an external clamp. Although avoiding median sternotomy complications, this technique otherwise has similar rates of mortality and major perioperative complications as conventional techniques.

Echocardiography

Echocardiography uses ultrasound waves to produce an image of the heart and great vessels. It helps assess heart wall thickness (eg, in hypertrophy or atrophy) and motion and provides information about ischemia and infarction. It can be used to assess diastolic filling patterns of the left ventricle, which can help in the diagnosis of left ventricular hypertrophy, hypertrophic or restrictive cardiomyopathy, severe heart failure, constrictive pericarditis, and severe aortic regurgitation.

Techniques: There are 2 techniques for doing echocardiography:

- Transthoracic
- Transesophageal

In transthoracic echocardiography (TTE), the most common technique, a transducer is placed along the left or right sternal border, at the cardiac apex, at the suprasternal notch (to allow visualization of the aortic valve, left ventricular outflow tract, and descending aorta), or over the subxiphoid region. TTE provides 2- or 3-dimensional tomographic images of most major cardiac structures.

In transesophageal echocardiography (TEE), a transducer on the tip of an endoscope allows visualization of the heart via the esophagus. TEE is used to assess cardiac disorders when transthoracic study is technically difficult, as in obese patients and in patients with COPD. It reveals better detail of small abnormal structures (eg, endocarditic vegetations or patent foramen ovale) and posterior cardiac structures (eg, left atrium, left atrial appendage, interatrial septum) because they are closer to the esophagus than to the anterior chest wall. TEE can also produce images of the ascending aorta, which arises behind the 3rd costal cartilage; of structures < 3 mm (eg, thrombi, vegetations); and of prosthetic valves.
Methodology: Two-dimensional (cross-sectional) echocardiography is most commonly used; contrast and spectral Doppler echocardiography provide additional information.

Contrast echocardiography is 2-dimensional TTE done while agitated saline is rapidly injected into the cardiac circulation. Agitated saline develops microbubbles, which produce a cloud of echoes in the right cardiac chambers and which, if a septal defect is present, appear on the left side of the heart. Usually, the microbubbles do not traverse the pulmonary capillary bed; however, one agent, sonicated albumin microbubbles, can do so and can enter left heart structures after IV injection.

Spectral Doppler echocardiography can record velocity, direction, and type of blood flow. This technique is useful for detecting abnormal blood flow (eg, due to regurgitant lesions) or velocity (eg, due to stenotic lesions). Spectral Doppler echocardiography does not provide spatial information about the size or shape of the heart or its structures.

Color Doppler echocardiography combines 2-dimensional and spectral Doppler echocardiography to provide information about the size and shape of the heart and its structures as well as the velocity of and direction of blood flow around the valves and outflow tracts. Color is used to code blood flow information; by convention, red is toward and blue away from the transducer.

Tissue Doppler imaging uses Doppler techniques to measure the velocity of myocardial tissue contraction (rather than of blood flow). These data can be used to calculate myocardial strain (percentage change in length between contraction and relaxation) and myocardial strain rate (rate of change in length). Strain and strain rate measurements can help assess systolic and diastolic function and identify ischemia during stress testing.

Stress echocardiography: TTE is an alternative to radionuclide imaging to identify myocardial ischemia during and after exercise or pharmacologic stress. Stress echocardiography shows regional wall motion abnormalities that result from an imbalance in blood flow in epicardial coronary vessels during stress. Computer programs can provide side-by-side assessment of ventricular contraction during systole and diastole at rest and under stress. Exercise and pharmacologic protocols are the same as those used in radionuclide stress testing. Stress echocardiography and radionuclide stress testing detect ischemia equally well. The choice between tests is often based on availability, the provider's experience, and cost.

Electrocardiography

The standard ECG provides 12 different vector views of the heart's electrical activity as reflected by electrical potential differences between positive and negative electrodes placed on the limbs and chest wall. Six of these views are vertical (using frontal leads I, II, and III and limb leads aVR, aVL, and aVF), and 6 are horizontal (using precordial leads V₁, V₂, V₃, V₄, V₅, and V₆). The 12-lead ECG is crucial for establishing many cardiac diagnoses, especially arrhythmias and myocardial ischemia (see Table 207-4). It can also identify atrial enlargement, ventricular hypertrophy (see Table 207-5), and conditions that predispose to syncope or sudden death (eg, Wolff-Parkinson-White syndrome, long QT syndrome, Brugada syndrome).

Standard ECG Components

By convention, the ECG tracing is divided into the P wave, PR interval, QRS complex, QT interval, ST segment, T wave, and U wave (see Fig. 207-2).

P wave: The P wave represents atrial depolarization. It is upright in most leads except aVR. It may be biphasic in leads II and V₁; the initial component represents right atrial activity, and the 2nd component represents left atrial activity.

An increase in amplitude of either or both components occurs with atrial enlargement. Right atrial enlargement produces a P wave > 2 mm in leads II, III, and aVF (P pulmonale); left atrial enlargement produces a P wave that is broad and double-peaked in lead II (P mitrale). Normally, the P axis is between 0° and 75°.
**PR interval:** The PR interval is the time between onset of atrial depolarization and onset of ventricular depolarization. Normally, it is 0.10 to 0.20 sec; prolongation defines 1st-degree atrioventricular block.

**QRS complex:** The QRS complex represents ventricular depolarization. The Q wave is the initial downward deflection; normal Q waves last < 0.05 sec in all leads except V_{1-3}, in which any Q wave is considered abnormal, indicating past or current infarction. The R wave is the first upward deflection; criteria for normal height or size are not absolute, but taller R waves may be caused by ventricular hypertrophy. A 2nd upward deflection in a QRS complex is designated R’. The S wave is the 2nd downward deflection if there is a Q wave and the first downward deflection if not. The QRS complex may be R alone, QS (no R), QR (no S), RS (no Q), or RSR’, depending on the ECG lead, vector, and presence of heart disorders.

Normally, the QRS interval is 0.07 to 0.10 sec. An interval of 0.10 to 0.11 sec is considered incomplete bundle branch block or a nonspecific intraventricular conduction delay, depending on QRS morphology; ≥ 0.12 sec is considered complete bundle branch block or an intraventricular conduction delay. Normally, the QRS axis is 90° to -30°. An axis of -30° to -90° is considered left axis deviation and occurs in left anterior fascicular block (-60°) and inferior MI. An axis of 90° to 180° is considered right axis deviation; it occurs in any condition that increases pulmonary pressures and causes right ventricular hypertrophy (cor pulmonale, acute pulmonary embolism, pulmonary hypertension), and it sometimes occurs in right bundle branch block or left posterior fascicular block.

**QT interval:** The QT interval is the time between onset of ventricular depolarization and end of ventricular repolarization. The QT interval must be corrected for heart rate using the formula:

\[
QT_c = \frac{QT}{\sqrt{RR}}
\]

where QT_c is the corrected QT interval; R-R interval is the time between 2 QRS complexes. All intervals are recorded in seconds. QT_c prolongation is strongly implicated in development of torsades de pointe ventricular tachycardia (see p. 2176). QT_c is often difficult to calculate because the end of the T wave is often unclear or followed by a U wave with which it merges.

**ST segment:** The ST segment represents completed ventricular myocardial depolarization. Normally, it is horizontal along the baseline of the PR (or TP) intervals or slightly off baseline.

**ST segment elevation** can be caused by

- Early repolarization
- Left ventricular hypertrophy
- Myocardial ischemia and infarction
- Left ventricular aneurysm
- Pericarditis
- Hyperkalemia
• Hypothermia

• Pulmonary embolism

**ST segment depression** can be caused by

• Hypokalemia

• Digoxin

• Subendocardial ischemia

• Reciprocal changes in acute MI

**T wave**: The T wave reflects ventricular repolarization. It usually takes the same direction as the QRS complex (concordance); opposite polarity (discordance) may indicate past or current infarction. The T wave is usually smooth and rounded but may be of low amplitude in hypokalemia and hypomagnesemia and may be tall and peaked in hyperkalemia, hypocalcemia, and left ventricular hypertrophy.

**U wave**: The U wave appears commonly in patients who have hypokalemia, hypomagnesemia, or ischemia. It is often present in healthy people.

**Specialized ECG Tests**

A standard 12-lead ECG represents only a single brief period of cardiac activity; enhanced techniques can provide additional information.

**Additional precordial leads**: Additional precordial leads are used to help diagnose right ventricular and posterior wall MI.

Right-sided leads are placed across the right side of the chest to mirror standard left-sided leads. They are labeled V1R to V6R; sometimes only V4R is used, because it is the most sensitive for right ventricular MI.

Additional left-sided leads can be placed in the 5th intercostal space, with V7 at the posterior axillary line, V8 at the midscapular line, and V9 at the left border of the spine. These leads are rarely used but may help diagnose a true posterior MI.

**Esophageal lead**: An esophageal lead is much closer to the atria than surface leads; it is an option when the presence of P waves on a standard recording is uncertain and when detecting atrial electrical activity is important, as when atrial or ventricular origin of wide-complex tachycardia must be differentiated or when atrioventricular dissociation is suspected. An esophageal lead may also be used to monitor intraoperative myocardial ischemia or to detect atrial activity during cardioplegia. The lead is placed by having the patient swallow an electrode, which is then connected to a standard ECG machine, often in the lead II port.

**Signal averaging**: Signal-averaging of QRS waveforms creates a digital composite of several hundred cardiac cycles to detect high-frequency, low-amplitude potentials and microcurrents at the terminal part of the QRS complex. These findings represent areas of slow conduction through abnormal myocardium, indicating increased risk of reentrant ventricular tachycardia. Signal-averaged ECG is still largely a research technique but is occasionally used to assess risk of sudden cardiac death (eg, in post-MI patients without evidence of conduction delay, patients with myocardial ischemia and unexplained syncope, and those with nonischemic cardiomyopathy) and to assess efficacy of surgery to correct the arrhythmia. This technique may also be useful for assessing the proarrhythmic effects of antiarrhythmic
drugs and for detecting rejection of heart transplants. Signal averaging of P waves is being studied as a way to identify patients at risk of atrial fibrillation.

**Continuous ST-segment monitoring:** This type of monitoring is used for early detection of ischemia and serious arrhythmias. Monitoring can be automated (dedicated electronic monitoring units are available) or done clinically using serial ECGs. Applications include emergency department monitoring of patients with crescendo angina, evaluation after percutaneous intervention, intraoperative monitoring, and postoperative care.

**QT dispersion:** QT dispersion (the difference between the longest and shortest QT intervals on a 12-lead ECG) has been proposed as a measure of myocardial repolarization heterogeneity. Increased dispersion suggests electrically heterogeneous myocardium caused by ischemia or fibrosis, with increased risk of reentrant arrhythmias and sudden death. QT dispersion predicts mortality risk but is not widely measured because measurement error is common, values in patients with and without disease overlap substantially, there is no reference standard, and other validated risk predictors are available.

**Heart rate variability:** This measurement reflects the balance between sympathetic and parasympathetic (vagal) input to the heart. Decreased variability suggests decreased vagal input and increased sympathetic input, which predict increased risk of arrhythmias and mortality. The most common measure of variability is the mean of the standard deviations of all normal R-R intervals in a 24-h ECG recording. Heart rate variability is used primarily in research, but evidence suggests that it provides useful information about left ventricular dysfunction after MI, heart failure, and hypertrophic cardiomyopathy. Most Holter monitors have software that measures and analyzes heart rate variability.

**Holter monitor:** Holter monitoring is continuous monitoring and recording of the ECG, BP, or both for 24 or 48 h. It is useful for evaluating intermittent arrhythmias and, secondarily, for detecting hypertension. The Holter monitor is portable, enabling patients to participate in normal daily activities; it may also be used for sedentary hospitalized patients if automated monitoring is unavailable. Patients are asked to record symptoms and activities so that they may be correlated with events on the monitor. The Holter monitor does not automatically analyze the ECG data; a physician does so at a later date.

**Event recorder:** Event recorders are worn for up to 30 days and can detect infrequent rhythm disturbances that 24-h Holter monitoring may miss. The recorder does not operate continuously but is activated by the patient when symptoms occur. A memory loop enables information to be stored for seconds or minutes before and after activation. The patient can transmit ECG data by telephone to be read by a physician. If patients have serious events (eg, syncope) at intervals of > 30 days, an event recorder may be placed subcutaneously; it can be activated by a small magnet. Battery life for subcutaneous recorders is 14 mo.

**Electrophysiologic Studies**

In electrophysiologic studies, recording and stimulating electrodes are inserted via right- or left-sided cardiac catheterization into all 4 cardiac chambers. Atria are paced from the right or left atrium, ventricles are paced from the right ventricular apex or right ventricular outflow tract, and cardiac conduction is recorded. Programmed stimulation techniques may be used to trigger and terminate a reentrant arrhythmia.

Electrophysiologic studies are indicated primarily for evaluation and treatment of arrhythmias that are difficult to capture, serious, or sustained. These studies may be used to make a primary diagnosis, to evaluate the efficacy of antiarrhythmic drugs, or to map arrhythmia foci before radiofrequency catheter ablation (see p. 2161). Various mapping techniques are available.

**Cardiac Imaging Tests**

Standard imaging tests include echocardiography (see p. 2053), chest x-ray, CT, MRI, and various radionuclide techniques (see p. 2061). Standard CT and MRI have limited application because the heart constantly beats, but faster CT and MR techniques can provide useful cardiac images; sometimes patients are given a drug (eg, a β-blocker) to slow the heart rate during imaging. In addition, by
synchronizing image recording (or reconstruction) with the ECG (ECG gating), information from several cardiac cycles can be used to create single images of selected points in the cardiac cycle. CT gating that uses the ECG to trigger the x-ray beam at the desired portion of the cardiac cycle gives less x-ray exposure than gating that simply reconstructs information from only the desired portion of the cardiac cycle (gated reconstruction) and does not interrupt the x-ray beam.

**Chest x-rays:** Chest x-rays are often useful as a starting point in a cardiac diagnosis. Posteroanterior and lateral views provide a gross view of atrial and ventricular size and shape and pulmonary vasculature, but additional tests are almost always required for precise characterization of cardiac structure and function.

**CT:** Spiral (helical) CT may be used to evaluate pericarditis, congenital cardiac disorders (especially abnormal arteriovenous connections), disorders of the great vessels (eg, aortic aneurysm, aortic dissection), cardiac tumors, acute pulmonary embolism, chronic pulmonary thromboembolic disease, and arrhythmogenic right ventricular dysplasia. However, CT requires a radiopaque dye, which may limit its use in patients with renal impairment.

**Electron beam CT,** formerly called ultrafast CT or cine CT, unlike conventional CT, does not use a moving x-ray source and target. Instead, the direction of the x-ray beam is guided by a magnetic field and detected by an array of stationary detectors. Because mechanical motion is not required, images can be acquired in a fraction of a second (and targeted to a specific point in the cardiac cycle). Electron beam CT is used primarily to detect and quantify coronary artery calcification, an early sign of atherosclerosis. However, spatial resolution is poor and the equipment cannot be used for noncardiac disorders, so newer standard CT techniques are becoming preferred for cardiac use.

**Multidetector CT (MDCT),** with ≥ 64 detectors, has a very rapid scan time; some advanced machines may generate an image from a single heartbeat, although typical acquisition times are 30 sec. Dual-source CT uses 2 x-ray sources and 2 multidetector arrays on a single gantry, which cuts scan time in half. Both of these modalities appear able to identify coronary calcifications and flow-limiting (ie, > 50% stenosis) coronary artery obstruction. Typically, an IV contrast agent is used, although nonenhanced scans can detect coronary artery calcification.

MDCT is currently used mainly for patients with indeterminate stress imaging test results as a noninvasive alternative to coronary angiography. However, radiation dose is significant, about 15 mSv (vs 0.1 mSv for a chest x-ray and 7 mSv for coronary angiography). The presence of high-density calcified plaques creates imaging artifacts that interfere with interpretation.

**MRI:** Standard MRI is useful for evaluating areas around the heart, particularly the mediastinum and great vessels (eg, for studying aneurysms, dissections, and stenoses). With ECG-gated data acquisition, image resolution can approach that of CT or echocardiography, clearly delineating myocardial wall thickness and motion, chamber volumes, intraluminal masses or clot, and valve planes. Sequential MRI after injecting a paramagnetic contrast agent (gadolinium-diethylenetriamine pentaacetic acid [Gd-DTPA]) produces higher resolution of myocardial perfusion patterns than does radionuclide imaging. However, patients with impaired renal function can develop nephrogenic systemic fibrosis, a potentially life-threatening disorder, after use of gadolinium contrast. Using contrast, 3-dimensional information on infarct size and location can be obtained, and blood flow velocities in cardiac chambers can be measured. MRI can assess tissue viability by assessing the contractile response to inotropic stimulation with dobutamine or by using a contrast agent (eg, Gd-DTPA, which is excluded from cells with intact membranes).

**Magnetic resonance angiography (MRA)** is used to assess blood volumes of interest (eg, blood vessels in the chest or abdomen); all blood flow can be assessed simultaneously. MRA can be used to detect aneurysms, stenosis, or occlusions in the carotid, coronary, renal, or peripheral arteries. Use of this technique to detect deep venous thrombosis is being studied.

**PET:** PET can demonstrate myocardial perfusion and metabolism.

Perfusion agents include carbon-11 (¹¹C) CO₂, oxygen-15 (¹⁵O) water, nitrogen-13 (¹³N) ammonia, and
rubidium-82 (\(^{82}\text{Rb}\)). Only \(^{82}\text{Rb}\) does not require an on-site cyclotron.

Metabolic agents include fluorine-18 (\(^{18}\text{F}\))-labeled deoxyglucose (FDG) and \(^{11}\text{C}\) acetate. FDG detects the enhancement of glucose metabolism under ischemic conditions, and can thus distinguish ischemic but still viable myocardium from scar tissue. Sensitivity is greater than with myocardial perfusion imaging, possibly making FDG imaging useful for selecting patients for revascularization and for avoiding such procedures when only scar tissue is present. This use may justify the greater expense of PET. Half-life of \(^{18}\text{F}\) is long enough (110 min) that FDG can often be produced off-site. Techniques that enable FDG imaging to be used with conventional single-photon emission CT (SPECT) cameras may make this type of imaging widely available.

Uptake of \(^{11}\text{C}\) acetate appears to reflect overall \(\text{O}_2\) metabolism by myocytes. Uptake does not depend on such potentially variable factors as blood glucose levels, which can affect FDG distribution. \(^{11}\text{C}\) acetate imaging may better predict postintervention recovery of myocardial function than FDG imaging. However, because of a 20-min half-life, \(^{11}\text{C}\) must be produced by an on-site cyclotron.

### Percutaneous Coronary Interventions

Percutaneous coronary interventions (PCI) include percutaneous transluminal coronary angioplasty (PTCA) with or without stenting. Primary indications are treatment of angina pectoris (stable or unstable), myocardial ischemia, and acute MI (particularly in patients with developing or established cardiogenic shock). Primary PTCA and stent placement within 90 min of onset of pain is the optimal treatment of transmural ST-segment-elevation MI. Elective PCI may be appropriate for post-MI patients who have recurrent or inducible angina before hospital discharge and for patients who have angina and remain symptomatic despite medical treatment. Percutaneous transluminal angioplasty (PTA) is used to treat peripheral arterial disease (see p. 2220).

#### Procedure:
PTCA is done via percutaneous femoral, radial, or brachial artery puncture. A guiding catheter is inserted into a large peripheral artery and threaded to the appropriate coronary ostium. A balloon-tipped catheter, guided by fluoroscopy or intravascular ultrasonography, is aligned within the stenosis, then inflated to disrupt the atherosclerotic plaque and dilate the artery. Angiography is repeated after the procedure to document any changes. The procedure is commonly done in 2 or 3 vessels as needed.

#### Stents:
Stents are most useful for

- Short lesions in large native coronary arteries not previously treated with PTCA
- Focal lesions in saphenous vein grafts
- Treatment of abrupt closure during PTCA

The role of stenting in acute MI, ostial or left main disease, chronic total occlusions, and bifurcation lesions is still evolving.

#### Types of stents:
Bare metal stents (BMS) are made of nickel-titanium alloy. Drug eluting stents (DES) have drugs (eg, sirolimus, paclitaxel) bonded to the metal that limit neointimal proliferation to reduce the risk of restenosis. In intracoronary brachytherapy, the site of stenosis is exposed to radiation in the form of small pellets embedded in a nylon ribbon temporarily (eg, 30 min) placed in the coronary artery prior to stenting. This technique appears to decrease the risk of early restenosis, but it is unclear whether later stenosis is slightly increased; trials are ongoing. Radioactive stents have not proven effective at limiting restenosis.

#### Anticoagulation:
Various anticoagulation regimens are used during and after angioplasty to reduce the incidence of thrombosis at the site of balloon dilation. Clopidogrel and glycoprotein Ib/IIa inhibitors are the standard of care for patients with unstable non-ST-segment elevation MI. Clopidogrel (often in
combination with aspirin) is continued for 9 to 12 mo after PCI. Ca channel blockers and nitrates may also reduce risk of coronary spasm.

Contraindications

Absolute contraindications include

- Lack of cardiac surgical support
- Significant obstruction of the left main coronary artery without a nonobstructed bypass graft to the left anterior descending or left circumflex arteries

Relative contraindications include

- Coagulopathy
- Hypercoagulable states
- Diffusely diseased vessels without focal stenoses
- A single diseased vessel providing all perfusion to the myocardium
- Total occlusion of a coronary artery
- Stenosis < 50%

Complications

The main complications of balloon angioplasty and stenting are

- Thrombosis
- Restenosis

Thrombosis causes complete blockage and may occur at any time—acutely (immediately during or after the procedure), subacutely (within 30 days), or late (> 30 days). Stent thrombosis may be due to inadequate stent expansion or apposition at the time of the procedure, discontinuation of dual antiplatelet therapy (eg, from nonadherence, need for noncardiac surgery), or both.

Restenosis is typically due to collagen deposition and thus does not occur until several weeks after the procedure or later; it may cause partial or, less commonly, complete vessel blockage.

With balloon angioplasty, risk of acute thrombosis is about 5 to 10%, risk of subacute restenosis is about 5%, and the overall restenosis rate is about 30 to 45%. Use of stents has almost eliminated the need for emergency coronary artery bypass grafting following PCI. With stenting, the rate of acute and subacute thrombosis or restenosis is < 1%. With BMS, risk of late restenosis is decreased to 20 to 30%. Use of a DES lowers late restenosis risk to about 5 to 10%. However, using a DES increases risk of late stent thrombosis, about 0.6%/yr up to 3 yr.

Complications besides restenosis are similar to those of coronary angiography, although risk of death, MI, and stroke is greater. Of all angiographic procedures, PCI has the highest risk of contrast nephropathy; this risk can be reduced by preprocedural hydration and possibly by use of a nonionic contrast agent, acetylcysteine, or hemofiltration in patients with preexisting renal insufficiency. Stenting, in addition to the above, has complications of bleeding secondary to aggressive adjunctive anticoagulation, side branch occlusion, and stent embolism.

Radionuclide Imaging
Radionuclide imaging uses a special detector (gamma camera) to create an image following injection of radioactive material. This test is done to evaluate coronary artery disease (CAD), valvular or congenital cardiac disorders, cardiomyopathy, and other cardiac disorders. Radionuclide imaging exposes patients to less radiation than do comparable x-ray studies. However, because the radioactive material is retained in the patient briefly, sophisticated radiation alarms (eg, in airports) may be triggered by the patient for several days after such testing.

**Single-photon emission computed tomography (SPECT):** Planar techniques, which produce a 2-dimensional image, are rarely used; SPECT, which uses a rotating camera system and tomographic reconstruction to produce a 3-dimensional image, is more common in the US. With multthead SPECT systems, imaging can often be completed in ≤ 10 min. Visual comparison of stress and delayed images can be supplemented by quantitative displays. With SPECT, inferior and posterior abnormalities and small areas of infarction and the vessels responsible for infarction can be identified. The mass of infarcted and viable myocardium can be quantified, helping determine prognosis.

**Myocardial Perfusion Imaging**

In myocardial perfusion imaging, IV radionuclides are taken up by cardiac tissues in rough proportion to perfusion; thus, areas of decreased uptake represent areas of relative or absolute ischemia. For this reason, myocardial perfusion imaging is used with stress testing to evaluate patients with chest pain of uncertain origin, to determine the functional significance of coronary artery stenosis or collateral vessels seen on angiography, and to evaluate the success of reperfusion interventions (eg, coronary artery bypass grafting [CABG], percutaneous intervention, thrombolysis). After acute MI, myocardial perfusion imaging can help estimate prognosis because it can show extent of the perfusion abnormality due to acute MI, extent of scarring due to previous infarcts, and residual peri-infarct or other areas of reversible ischemia.

Radioactive thallium-201 ($^{201}$Tl), which acts as a K analog, was the original tracer used in stress testing. It is injected at peak stress and imaged with SPECT, followed 4 h later by injection of one half the original dose during rest and by repeat SPECT. The goal of this protocol is to evaluate reversible perfusion defects that may warrant intervention. After stress testing, the perfusion imbalance between normal coronary arteries and those distal to a stenosis appears as a relative decrease in $^{201}$Tl uptake in the areas perfused by the stenosed arteries. Sensitivity of stress testing with $^{201}$Tl for CAD is similar whether imaging is done after exercise or pharmacologic stress.

Because the imaging characteristics of $^{201}$Tl are not ideal for the gamma camera, several technetium-$^{99m}$Tc myocardial perfusion markers have been developed: sestamibi (commonly used), tetrofosmin, and teboroxime (see [Table 207-6](#)). Protocols

**[Table 207-6. Technetium-99M Myocardial Perfusion Markers]**

include 2-day stress-rest, 1-day rest-stress, and 1-day stress-rest. Some protocols use dual isotopes ($^{201}$Tl and $^{99m}$Tc), although this approach is expensive. With either of these markers, sensitivity is about 90%, and specificity is about 71%.

For 2-day protocols, imaging at rest may be omitted if the initial stress test shows no evidence of abnormal perfusion. When higher doses of $^{99m}$Tc (> 30 mCi) are used, first-transit function studies (with ventriculography) may be used with perfusion imaging.

Other radionuclides include iodine-123 ($^{123}$I)-labeled fatty acids, which produces cold spots where myocardium is ischemic; gallium citrate-67 ($^{67}$Ga), which accumulates in sites of active inflammation (eg, in acute inflammatory cardiomyopathy); and $^{123}$I metaiodobenzylguanidine, a neurotransmitter analog taken up and stored in neurons of the sympathetic nervous system and used in research to evaluate heart failure, diabetes, certain arrhythmias, and arrhythmogenic right ventricular dysplasia.
Attenuation of myocardial activity by overlying soft tissue may cause false-positive results. Attenuation by breast tissue in women is especially common. Attenuation by the diaphragm and abdominal contents may produce spurious inferior wall defects in both sexes but is more common among men. Attenuation is more likely with $^{99m}$Tc than with $^{201}$Tl.

Infarct Avid Imaging

Infarct avid imaging uses radiolabeled markers that accumulate in areas of damaged myocardium, such as $^{99m}$Tc pyrophosphate and antimyosin (indium-111 $^{[111]}$In]-labeled antibodies to cardiac myosin). Images usually become positive 12 to 24 h after acute MI and remain positive for about 1 wk; they may remain positive if myocardial necrosis continues post-MI or if aneurysms develop. This technique is rarely used now because other diagnostic tests for MI (eg, biomarkers) are more readily available and less expensive and because it provides no prognostic information other than infarct size.

Radionuclide Ventriculography

Radionuclide ventriculography is used to evaluate ventricular function. It is useful for measuring resting and exercise ejection fraction in CAD, valvular heart disease, and congenital heart disease. Some clinicians prefer it for serial assessment of ventricular function in patients taking cardiotoxic cancer chemotherapy (eg, anthracyclines). However, radionuclide ventriculography has been largely replaced by echocardiography, which is less expensive, does not require radiation exposure, and theoretically can measure ejection fractions as accurately.

$^{99m}$Tc-labeled RBCs are injected into the ventricles. Left ventricular (LV) and right ventricular (RV) function can be evaluated by first-transit studies (a type of beat-to-beat evaluation) or by gated (ECG-synchronized) blood pool imaging done over several minutes (multiple-gated acquisition [MUGA]). Either study can be done during rest or after exercise. First-transit studies are rapid and relatively easy, but MUGA provides better images and is more widely used.

In first-transit studies, 8 to 10 cardiac cycles are imaged as the marker mixes with blood and passes through the central circulation. First-transit studies are ideal for assessing RV function and intracardiac shunts.

In MUGA, imaging is synchronized with the R wave of the ECG. Multiple images are taken of short, sequential portions of each cardiac cycle for 5 to 10 min. Computer analysis generates an average blood pool configuration for each portion of the cardiac cycle and synthesizes the configurations into a continuous cinematic loop resembling a beating heart.

MUGA can quantitate numerous indexes of ventricular function, including regional wall motion, ejection fraction (EF); ratio of stroke volume to end-diastolic volume, ejection and filling rates, LV volume, and indexes of relative volume overload (eg, LV:RV stroke volume ratios). EF is used most commonly.

MUGA during rest has virtually no risk. It is used for serially evaluating RV and LV function in various disorders (eg, valvular heart disorders); for monitoring patients taking potentially cardiotoxic drugs (eg, doxorubicin); and for assessing the effects of angioplasty, CABG, thrombolysis, and other procedures in patients with CAD or MI. Arrhythmias are a relative contraindication because there may be few normal cardiac cycles.

LV: MUGA is useful for detecting LV aneurysms; sensitivity and specificity are > 90% for typical anterior or anteropapical true aneurysms. Conventional gated blood pool imaging shows inferoposterior LV aneurysms less well than it shows anterior and lateral aneurysms; additional views are required. Gated SPECT imaging takes longer (about 20 to 25 min with a multihead camera) than a single planar gated view (5 to 10 min) but shows all portions of the ventricles.

RV: MUGA is used to assess RV function in patients who have a lung disorder or an inferior LV infarct that may involve the RV. Normally, RVEF (40 to 55% with most techniques) is lower than LVEF. RVEF is
subnormal in many patients with pulmonary hypertension and in patients with RV infarction or cardiomyopathy affecting the RV. Idiopathic cardiomyopathy is usually characterized by biventricular dysfunction, unlike typical CAD, which usually causes more LV than RV dysfunction.

Valves: MUGA can be used with rest-stress protocols to assess valvular disorders that result in LV volume overload. In aortic regurgitation, a reduction in resting EF or no increase in EF with exercise is a sign of deteriorating cardiac function and may indicate a need for valvular repair. MUGA also can be used to calculate the regurgitant fraction in regurgitation of any valve. Normally, the stroke volume of the 2 ventricles is equal. However, in patients with left-sided valvular regurgitation, LV stroke volume exceeds that of the RV by an amount proportional to the regurgitant fraction. Thus, if the RV is normal, the regurgitant fraction of the LV can be calculated from the LV:RV stroke volume ratio.

Shunts: With MUGA and commercially available computer programs, size of a congenital shunt can be quantified by the stroke volume ratio or, during the first transit of the marker, by the ratio of abnormal early pulmonary recirculation of radioactivity to total pulmonary radioactivity.

Stress Testing

In stress testing, the heart is monitored by ECG and often imaging studies during an induced episode of increased cardiac demand so that ischemic areas potentially at risk of infarction can be identified. Heart rate is increased to 85% of age-predicted maximum (target heart rate) or until symptoms develop, whichever occurs first.

Stress testing is used for diagnosis of coronary artery disease (CAD) and for risk stratification and monitoring of patients with known CAD. In patients with CAD, a blood supply that is adequate at rest may be inadequate when cardiac demands are increased by exercise or other forms of stress. Stress testing is less invasive and less expensive than cardiac catheterization, and it detects pathophysiologic abnormalities of blood flow; however, it is less accurate for diagnosis in patients with a low pretest likelihood of CAD. It can define the functional significance of abnormalities in coronary artery anatomy identified with coronary angiography during catheterization. Because coronary artery plaques that are not significantly stenotic (ie, do not result in ischemia during stress testing) may nonetheless rupture and cause an acute coronary syndrome, a normal stress test result does not guarantee future freedom from MI.

Risks of stress testing include infarction and sudden death, which occur in about 1/5000 patients tested. Stress testing has several contraindications (see Table 207-7). Patients must be npo for 4 to 6 h before the test.

Stress Methodology

Cardiac demand can be increased by exercise or drugs.

[Table 207-7, Contraindications to Exercise Stress Testing]

Exercise stress testing: Exercise is preferred to drugs for increasing cardiac demand because it more closely replicates ischemia-inducing stressors. Usually, a patient walks on a conventional treadmill, following the Bruce protocol or a similar exercise schedule, until the target heart rate is reached or symptoms occur. The Bruce protocol increases treadmill speed and slope incrementally at roughly 3-min intervals.

Pharmacologic stress testing: Pharmacologic stress testing is usually used when patients cannot walk on a treadmill long enough to reach their target heart rate because of deconditioning, musculoskeletal disorders, obesity, peripheral arterial disease, or other disorders. Drugs used include IV dipyridamole, adenosine, and dobutamine.

Dipyridamole augments endogenous adenosine, causing coronary artery vasodilation. It increases myocardial blood flow in normal coronary arteries but not in arteries distal to a stenosis, creating a "steal" phenomenon from stenosed arteries and an imbalance in perfusion. Dipyridamole-induced ischemia or
other adverse effects (eg, nausea, vomiting, headache, bronchospasm) occur in about 10% of patients, but these effects can be reversed by IV aminophylline. Severe reactions occur in < 1% of patients. Contraindications include asthma, acute phase MI, unstable angina pectoris, critical aortic stenosis, and systemic hypotension (systolic BP < 90 mm Hg).

Adenosine has the same effect as dipyridamole but must be given in a continuous IV infusion because it is rapidly degraded in the plasma. Adverse effects include transient flushing and chest pain, which can be reversed by terminating the infusion.

Dobutamine is an inotrope, chronotrope, and vasodilator used mainly when dipyridamole and adenosine are contraindicated (eg, in patients with asthma or 2nd-degree atrioventricular block) and when echocardiography is used to image the heart. Dobutamine must be used with caution in patients who have severe hypertension or arrhythmia, left ventricular outflow tract obstruction, multiple previous MIs, or acute MI.

Xanthine compounds (eg, aminophylline, theophylline, caffeine) may produce a false-negative result during stress testing with dipyridamole, so such substances (including tea and coffee) should be avoided for 24 h before testing.

**Diagnostic Methodology**

Several imaging tests can detect ischemia after exercise or pharmacologic stress:

- ECG
- Radionuclide perfusion imaging
- Echocardiography

**ECG** is always used with stress testing to diagnose CAD and help determine prognosis. ECG is most useful in patients with intermediate likelihood of CAD based on age and sex and with a normal ECG at rest. Diagnosis involves assessment of ST-segment response (a measure of global subendocardial ischemia), BP response, and the patient's symptoms. Average sensitivity is 67%; average specificity is 72%. Sensitivity and specificity are lower in women partly because incidence of CAD is lower in young and middle-aged women. Prognosis worsens with depth of ST depression.

**Radionuclide myocardial perfusion imaging** (see p. 2061) is more sensitive (85 to 90%) and specific (70 to 80%) than ECG stress testing; combining findings from both tests increases sensitivity for CAD. Myocardial perfusion imaging is particularly useful for patients with baseline ECG abnormalities that may interfere with interpretation of ECG changes during a stress test (eg, patients with bundle branch block, those with fixed-rate pacemakers, those taking digitalis). It is also useful for groups with a high probability of false-positive results on exercise ECGs (eg, premenopausal women, patients with mitral valve prolapse). This imaging test can help determine the functional significance of coronary artery stenosis, identified by coronary angiography, when surgeons are choosing lesions to bypass or dilate via percutaneous transluminal coronary angioplasty.

**Echocardiography** is useful when information about more than just perfusion is needed; echocardiography detects wall motion abnormalities that are a sign of regional ischemia and, using Doppler techniques, helps evaluate valvular disorders that may contribute to or result from ischemia or valvular disorders unrelated to ischemia but which deserve concomitant evaluation (see p. 2053). The echocardiogram is typically obtained immediately before and after an exercise treadmill test or during dobutamine infusion. Echocardiography is relatively portable, does not use ionizing radiation, has a rapid acquisition time, and is inexpensive, but it is difficult to carry out in obese patients and in patients with COPD and lung hyperinflation. Done by experts, stress echocardiography has a predictive value similar to that of stress myocardial radionuclide perfusion testing.

**Radionuclide ventriculography** is occasionally used with exercise stress testing instead of echocardiography to assess exercise ejection fraction (EF), the best prognostic indicator in patients with
CAD. Normally, EF is ≥ 5 percentage points higher during exercise than at rest. Ventricular dysfunction (eg, due to valvular heart disorders, cardiomyopathy, or CAD) can decrease exercise EF below baseline or prevent it from increasing. In patients with CAD, the 8-yr survival rate is 80% with an exercise EF of 40 to 49%, 75% with an exercise EF of 30 to 39%, and 40% with an exercise EF of < 30%.

**Tilt Table Testing**

Tilt table testing is used to evaluate syncope in younger, apparently healthy patients and, when cardiac and other tests have not provided a diagnosis, in elderly patients. Tilt table testing produces maximal venous pooling, which can trigger vasovagal (neurocardiogenic) syncope and reproduce the symptoms and signs that accompany it (nausea, light-headedness, pallor, hypotension, bradycardia).

After an overnight fast, a patient is placed on a motorized table with a foot board at one end and is held in place by a single strap over the stomach; an IV line is inserted. After the patient remains supine for 15 min, the table is tilted nearly upright to 60 to 80° for 45 min. If vasovagal symptoms develop, vasovagal syncope is confirmed. If they do not occur, a drug (eg, isoproterenol) may be given to induce them. Sensitivity varies from 30 to 80% depending on the protocol used. The false-positive rate is 10 to 15%.

With vasovagal syncope, heart rate and BP usually decrease. Some patients have only a decrease in heart rate (cardioinhibitory); others have only a decrease in BP (vasodepressor). Other responses include a gradual decrease in systolic and diastolic BP with little change in heart rate (dysautonomic pattern), significant increase in heart rate (> 30 beats/min) with little change in BP (postural orthostatic tachycardia syndrome), and report of syncope with no hemodynamic changes (psychogenic syncope).

Relative contraindications include severe aortic or mitral stenosis, hypertrophic cardiomyopathy, and severe coronary artery disease (CAD). In particular, isoproterenol should not be used in patients with hypertrophic cardiomyopathy or severe CAD.
Chapter 208. Arterial Hypertension

Introduction

Hypertension is sustained elevation of resting systolic BP (≥ 140 mm Hg), diastolic BP (≥ 90 mm Hg), or both. Hypertension with no known cause (primary; formerly, essential hypertension) is most common. Hypertension with an identified cause (secondary hypertension) is usually due to a renal disorder. Usually, no symptoms develop unless hypertension is severe or long-standing. Diagnosis is by sphygmomanometry. Tests may be done to determine cause, assess damage, and identify other cardiovascular risk factors. Treatment involves lifestyle changes and drugs, including diuretics, β-blockers, ACE inhibitors, angiotensin II receptor blockers, and Ca channel blockers.

In the US, about 65 million people have hypertension. Only about 70% of these people are aware that they have hypertension, only 59% are being treated, and only 34% have adequately controlled BP. In adults, hypertension occurs more often in blacks (32%) than in whites (23%) or Mexican Americans (23%), and morbidity and mortality are greater in blacks.

BP increases with age. About two thirds of people > 65 have hypertension, and people with a normal BP at age 55 have a 90% lifetime risk of developing hypertension. Because hypertension becomes so common with age, the age-related increase in BP may seem innocuous, but higher BP increases morbidity and mortality risk. Hypertension may develop during pregnancy (see pp. 2645 and 2670).

Etiology

Hypertension may be primary (85 to 95% of cases) or secondary.

Primary hypertension: Hemodynamics and physiologic components (eg, plasma volume, activity of the renin-angiotensin system) vary, indicating that primary hypertension is unlikely to have a single cause. Even if one factor is initially responsible, multiple factors are probably involved in sustaining elevated BP (the mosaic theory). In afferent systemic arterioles, malfunction of ion pumps on sarclemmal membranes of smooth muscle cells may lead to chronically increased vascular tone. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors (eg, dietary Na, obesity, stress) seem to affect only genetically susceptible people.

Secondary hypertension: Causes include renal parenchymal disease (eg, chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders, obstructive uropathy), renovascular disease (see p. 2077), pheochromocytoma, Cushing's syndrome, primary aldosteronism, congenital adrenal hyperplasia, hyperthyroidism, myxedema, and coarctation of the aorta. Excessive alcohol intake and use of oral contraceptives are common causes of curable hypertension. Use of sympathomimetics, NSAIDs, corticosteroids, cocaine, or licorice commonly contributes to hypertension.

Pathophysiology

Because BP equals cardiac output (CO) × total peripheral vascular resistance (TPR), pathogenic mechanisms must involve increased CO, increased TPR, or both.

In most patients, CO is normal or slightly increased, and TPR is increased. This pattern is typical of primary hypertension and hypertension due to pheochromocytoma, primary aldosteronism, renovascular disease, and renal parenchymal disease.

In other patients, CO is increased (possibly because of vasoconstriction in large veins), and TPR is inappropriately normal for the level of CO. Later in the disorder, TPR increases and CO returns to normal, probably because of autoregulation. Some disorders that increase CO (thyrotoxicosis, arteriovenous fistula, aortic regurgitation), particularly when stroke volume is increased, cause isolated systolic hypertension. Some elderly patients have isolated systolic hypertension with normal or low CO, probably due to inelasticity of the aorta and its major branches. Patients with high, fixed diastolic pressures often have decreased CO.
Plasma volume tends to decrease as BP increases; rarely, plasma volume remains normal or increases. Plasma volume tends to be high in hypertension due to primary aldosteronism or renal parenchymal disease and may be quite low in hypertension due to pheochromocytoma. Renal blood flow gradually decreases as diastolic BP increases and arteriolar sclerosis begins. GFR remains normal until late in the disorder; as a result, the filtration fraction is increased. Coronary, cerebral, and muscle blood flow is maintained unless severe atherosclerosis coexists in these vascular beds.

**Abnormal Na transport:** In many cases of hypertension, Na transport across the cell wall is abnormal, because the Na-K pump (Na\(^+\), K\(^+\)-ATPase) is defective or inhibited or because permeability to Na\(^+\) is increased. The result is increased intracellular Na, which makes the cell more sensitive to sympathetic stimulation. Ca follows Na, so accumulation of intracellular Ca may be responsible for the increased sensitivity. Because Na\(^+\), K\(^+\)-ATPase may pump norepinephrine back into sympathetic neurons (thus inactivating this neurotransmitter), inhibition of this mechanism could also enhance the effect of norepinephrine, increasing BP. Defects in Na transport may occur in normotensive children of hypertensive parents.

**Sympathetic nervous system:** Sympathetic stimulation increases BP, usually more in patients with prehypertension (systolic BP 120 to 139 mm Hg, diastolic BP 80 to 89 mm Hg) or hypertension (systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or both) than in normotensive patients. Whether this hyperresponsiveness resides in the sympathetic nervous system or in the myocardium and vascular smooth muscle is unknown. A high resting pulse rate, which may result from increased sympathetic nervous activity, is a well-known predictor of hypertension. In some hypertensive patients, circulating plasma catecholamine levels during rest are higher than normal.

**Renin-angiotensin-aldosterone system:** This system helps regulate blood volume and therefore BP. Renin, an enzyme formed in the juxtaglomerular apparatus, catalyzes conversion of angiotensinogen to angiotensin I. This inactive product is cleaved by ACE, mainly in the lungs but also in the kidneys and brain, to angiotensin II, a potent vasoconstrictor that also stimulates autonomic centers in the brain to increase sympathetic discharge and stimulates release of aldosterone and ADH. Aldosterone and ADH cause Na and water retention, elevating BP. Aldosterone also enhances K excretion; low plasma K (< 3.5 mEq/L) increases vasoconstriction through closure of K channels. Angiotensin III, present in the circulation, stimulates aldosterone release as actively as angiotensin II but has much less pressor activity. Because chymase enzymes also convert angiotensin I to angiotensin II, drugs that inhibit ACE do not fully suppress angiotensin II production.

Renin secretion is controlled by at least 4 mechanisms, which are not mutually exclusive: (1) A renal vascular receptor responds to changes in tension in the afferent arteriolar wall; (2) a macula densa receptor detects changes in the delivery rate or concentration of NaCl in the distal tubule; (3) circulating angiotensin has a negative feedback effect on renin secretion; and (4) via the renal nerve, the sympathetic nervous system stimulates renin secretion mediated by β-receptors.

Angiotensin is generally acknowledged to be responsible for renovascular hypertension, at least in the early phase, but the role of the renin-angiotensin-aldosterone system in primary hypertension is not established. However, in black and elderly patients with hypertension, renin levels tend to be low. The elderly also tend to have low angiotensin II levels.

Hypertension due to chronic renal parenchymal disease (renoprival hypertension) results from the combination of a renin-dependent mechanism and a volume-dependent mechanism. In most cases, increased renin activity is not evident in peripheral blood. Hypertension is typically moderate and sensitive to Na and water balance.

**Vasodilator deficiency:** Deficiency of a vasodilator (eg, bradykinin, nitric oxide) rather than excess of a vasoconstrictor (eg, angiotensin, norepinephrine) may cause hypertension. If the kidneys do not produce adequate amounts of vasodilators (because of renal parenchymal disease or bilateral nephrectomy), BP can increase. Vasodilators and vasoconstrictors (mainly endothelin) are also produced in endothelial cells. Therefore, endothelial dysfunction greatly affects BP.
Pathology and complications: No pathologic changes occur early in hypertension. Severe or prolonged hypertension damages target organs (primarily the cardiovascular system, brain, and kidneys), increasing risk of coronary artery disease (CAD), MI, stroke (particularly hemorrhagic), and renal failure. The mechanism involves development of generalized arteriolosclerosis and acceleration of atherogenesis (see p. 2081). Arteriolosclerosis is characterized by medial hypertrophy, hyperplasia, and hyalinization; it is particularly apparent in small arterioles, notably in the eyes and the kidneys. In the kidneys, the changes narrow the arteriolar lumen, increasing TPR; thus, hypertension leads to more hypertension. Furthermore, once arteries are narrowed, any slight additional shortening of already hypertrophied smooth muscle reduces the lumen to a greater extent than in normal-diameter arteries. These effects may explain why the longer hypertension has existed, the less likely specific treatment (eg, renovascular surgery) for secondary causes is to restore BP to normal.

Because of increased afterload, the left ventricle gradually hypertrophies, causing diastolic dysfunction. The ventricle eventually dilates, causing dilated cardiomyopathy and heart failure (HF) due to systolic dysfunction. Thoracic aortic dissection is typically a consequence of hypertension; almost all patients with abdominal aortic aneurysms have hypertension.

Symptoms and Signs

Hypertension is usually asymptomatic until complications develop in target organs. Dizziness, flushed facies, headache, fatigue, epistaxis, and nervousness are not caused by uncomplicated hypertension. Severe hypertension (hypertensive emergencies—see p. 2078) can cause severe cardiovascular, neurologic, renal, and retinal symptoms (eg, symptomatic coronary atherosclerosis, HF, hypertensive encephalopathy, renal failure).

A 4th heart sound is one of the earliest signs of hypertensive heart disease.

Retinal changes may include arteriolar narrowing, hemorrhages, exudates, and, in patients with encephalopathy, papilledema (see p. 616). Changes are classified (according to the Keith, Wagener, and Barker classification) into 4 groups with increasingly worse prognosis: constriction of arterioles only (grade 1), constriction and sclerosis of arterioles (grade 2), hemorrhages and exudates in addition to vascular changes (grade 3), and papilledema (grade 4).

Diagnosis

- Multiple measurements of BP to confirm
- Urinalysis and urinary albumin:creatinine ratio; if abnormal, consider renal ultrasonography
- Blood tests: Fasting lipids, creatinine, K
- Renal ultrasonography if creatinine increased
- Evaluate for aldosteronism if K decreased
- ECG: If left ventricular hypertrophy, consider echocardiography
- Sometimes thyroid-stimulating hormone measurement
- Evaluate for pheochromocytoma if BP elevation sudden and labile or severe

Hypertension is diagnosed and classified by sphygomanometry. History, physical examination, and other tests help identify etiology and determine whether target organs are damaged.

BP must be measured twice—first with the patient supine or seated, then after the patient has been standing for ≥ 2 min—on 3 separate days. The average of these measurements is used for diagnosis. BP is classified as normal, prehypertension, or stage 1 (mild) or stage 2 hypertension (see
Normal BP is much lower for infants and children. Ideally, BP is measured after the patient rests > 5 min and at different times of day. A BP cuff is applied to the upper arm. An appropriately sized cuff covers two thirds of the biceps; the bladder is long enough to encircle > 80% of the arm, and bladder width equals at least 40% of the arm's circumference. Thus, obese patients require large cuffs. The health care practitioner inflates the cuff above the expected systolic pressure and gradually releases the air while listening over the brachial artery. The pressure at which the first heartbeat is heard as the pressure falls is systolic BP. Disappearance of the sound marks diastolic BP. The same principles are followed to measure BP in a forearm (radial artery) and thigh (popliteal artery). Sphygmomanometers that contain mercury are most accurate. Mechanical devices should be calibrated periodically; automated readers are often inaccurate.

BP is measured in both arms; if BP in one arm is much higher, the higher value is used. BP is also measured in a thigh (with a much larger cuff) to rule out coarctation of the aorta, particularly in patients with diminished or delayed femoral pulses; with coarctation, BP is significantly lower in the legs. If BP is in the low-hypertensive range or is markedly labile, more BP measurements are desirable. BP measurements may be sporadically high before hypertension becomes sustained; this phenomenon probably accounts for "white coat hypertension," in which BP is elevated when measured in the physician's office but normal when measured at home or by ambulatory BP monitoring. However, extreme BP elevation alternating with normal readings is unusual and possibly suggests pheochromocytoma or unacknowledged drug use.

### Table 208-1

#### History:
The history includes the known duration of hypertension and previously recorded levels; any history or symptoms of CAD, HF, or other relevant coexisting disorders (eg, stroke, renal dysfunction, peripheral arterial disease, dyslipidemia, diabetes, gout); and a family history of any of these disorders.

#### Social history:
Includes exercise levels and use of tobacco, alcohol, and stimulant drugs (prescribed and illicit). A dietary history focuses on intake of salt and stimulants (eg, tea, coffee, caffeine-containing sodas, energy drinks).

#### Physical examination:
The physical examination includes measurement of height, weight, and waist circumference; funduscopic examination (see p. 616) for retinopathy; auscultation for bruits in the neck and abdomen; and a full cardiac, respiratory, and neurologic examination. The abdomen is palpated for kidney enlargement and abdominal masses. Peripheral arterial pulses are evaluated; diminished or delayed femoral pulses suggest aortic coarctation, particularly in patients < 30.

#### Testing:
The more severe the hypertension and the younger the patient, the more extensive is the evaluation. Generally, when hypertension is newly diagnosed, routine testing to detect target-organ damage and cardiovascular risk factors is done. Tests include urinalysis, spot urine albumin:creatinine ratio, blood tests (creatinine, K, Na, fasting plasma glucose, lipid profile), and ECG. Thyroid-stimulating hormone is often measured. Ambulatory BP monitoring, renal radionuclide imaging, chest x-ray, screening tests for pheochromocytoma, and renin-Na profiling are not routinely necessary. Peripheral plasma renin activity is not helpful in diagnosis or drug selection.

Depending on results of initial tests and examination, other tests may be needed. If urinalysis detects albuminuria (proteinuria), cylindruria, or microhematuria or if serum creatinine is elevated (≥ 1.4 mg/dL in men; ≥ 1.2 mg/dL in women), renal ultrasonography to evaluate kidney size may provide useful information. Patients with hypokalemia unrelated to diuretic use are evaluated for primary aldosteronism (see p. 799) and high salt intake.

On ECG, a broad, notched P-wave indicates atrial hypertrophy and, although nonspecific, may be one of the earliest signs of hypertensive heart disease. Left ventricular hypertrophy, indicated by a sustained apical thrust and abnormal QRS voltage with or without evidence of ischemia, may occur later. If either of these findings is present, echocardiography is often done. In patients with an abnormal lipid profile or symptoms of CAD, tests for other cardiovascular risk factors (eg, C-reactive protein) may be useful.

If coarctation of the aorta is suspected, chest x-ray, echocardiography, CT, or MRI helps confirm the
Patients with labile, significantly elevated BP and symptoms such as headache, palpitations, tachycardia, excessive perspiration, tremor, and pallor are screened for pheochromocytoma (eg, by measuring plasma free metanephrines—see p. 802).

Patients with symptoms suggesting Cushing's syndrome, a connective tissue disorder, eclampsia, acute porphyria, hyperthyroidism, myxedema, acromegaly, or CNS disorders are evaluated (see elsewhere in THE MANUAL).

**Prognosis**

The higher the BP and the more severe the retinal changes and other evidence of target-organ involvement, the worse is the prognosis. Systolic BP predicts fatal and nonfatal cardiovascular events better than diastolic BP. Without treatment, 1-yr survival is < 10% in patients with retinal sclerosis, cotton-wool exudates, arteriolar narrowing, and hemorrhage (grade 3 retinopathy), and < 5% in patients with the same changes plus papilledema (grade 4 retinopathy). CAD is the most common cause of death among treated hypertensive patients. Ischemic or hemorrhagic stroke is a common consequence of inadequately treated hypertension. However, effective control of hypertension prevents most complications and prolongs life.

**General Treatment**

- Weight loss and exercise
- Smoking cessation
- Diet: Increased fruits and vegetables, decreased salt, limited alcohol
- Drugs if BP is initially high (> 160/100 mm Hg) or unresponsive to lifestyle modifications

Primary hypertension has no cure, but some causes of secondary hypertension can be corrected. In all cases, control of BP can significantly limit adverse consequences. Despite the theoretical efficacy of treatment, BP is lowered to the desired level in only one third of hypertensive patients in the US.

For all patients, treatment aims to reduce BP to < 140/90 mm Hg; for those with a kidney disorder or diabetes, the goal is < 130/80 mm Hg or as near this level as tolerated. Even the elderly and frail elderly can tolerate a diastolic BP as low as 60 to 65 mm Hg well and without an increase in cardiovascular events. Ideally, patients or family members measure BP at home, provided they have been trained to do so, they are closely monitored, and the sphygmomanometer is regularly calibrated. Treatment of hypertension during pregnancy requires special considerations because some antihypertensive drugs can harm the fetus (see p. 2646).

**Lifestyle modifications:** Recommendations include regular aerobic physical activity at least 30 min/day most days of the week; weight loss to a body mass index of 18.5 to 24.9; smoking cessation; a diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat content; dietary sodium [Na\(^+\)] of < 2.4 g/day (< 6 g NaCl); and alcohol consumption of ≤ 1 oz/day in men and ≤ 0.5 oz/day in women. In stage 1 (mild) hypertension with no signs of target-organ damage, lifestyle changes may make drugs unnecessary. Patients with uncomplicated hypertension do not need to restrict their activities as long as BP is controlled. Dietary modifications can also help control diabetes, obesity, and dyslipidemias. Patients with prehypertension are encouraged to follow these lifestyle recommendations.

**Drugs:** If systolic BP remains > 140 mm Hg or diastolic BP remains > 90 mm Hg after 6 mo of lifestyle modifications, antihypertensive drugs are required. Unless hypertension is severe, drugs are usually started at low doses. Drugs are initiated simultaneously with lifestyle changes for all patients with prehypertension or hypertension plus diabetes, a kidney disorder, target-organ damage, or cardiovascular risk factors and for those with an initial BP of > 160/100 mm Hg. Signs of hypertensive emergencies require immediate BP reduction with parenteral antihypertensives.
For most hypertensive patients, one drug, usually a thiazide-type diuretic, is given initially. Depending on
the patient's characteristics and coexisting disorders, other drugs can be used initially or added to the
thiazide. Low-dose aspirin (81 mg once/day) appears to reduce incidence of cardiac events in
hypertensive patients and is recommended when tolerated and not contraindicated; some evidence
suggests it is better to take the aspirin in the evening rather than in the morning—this timing appears to
increase efficacy of antihypertensive drugs.

Some antihypertensives are contraindicated in certain disorders (eg, β-blockers in asthma) or are
indicated particularly for certain disorders (eg, β-blockers or Ca channel blockers for angina pectoris, ACE
inhibitors or angiotensin II receptor blockers for diabetes or proteinuria—see
Tables 208-2 and
208-3). When a single drug is used, black men may respond best to a Ca channel blocker (eg, diltiazem).
Thiazide-type diuretics appear to be particularly effective in people > 60 and in blacks.

If the initial drug is ineffective or has intolerable adverse effects, another drug can be substituted. If the
initial drug is only partly effective but well tolerated, the dose can be increased or a second drug with a
different mechanism added.

If initial systolic BP is > 160 mm Hg, 2 drugs are often used. Options include combining a diuretic with a β
-blocker, an ACE inhibitor, or an angiotensin II receptor blocker and combining a Ca channel blocker with
an ACE inhibitor or an angiotensin II receptor blocker. An appropriate combination and dose are
determined; many are available as single tablets, which improve compliance (see
Table 208-4). For severe or refractory hypertension, 3 or 4 drugs may be necessary.

Achieving adequate control often requires several evaluations and changes in drug therapy. Reluctance
to titrate or add drugs until BP is at an acceptable level must be overcome. Lack of patient adherence,
particularly because lifelong treatment is required, can interfere with adequate BP control. Education, with
empathy and support, is essential for success.

**Drugs for Hypertension**

**Diuretics:** Main classes (see
Table 208-5) are thiazide-type diuretics, loop diuretics, and K-sparing diuretics. Loop diuretics are used to
treat hypertension only in patients who have lost > 50% of kidney function; these diuretics are given twice
daily. Diuretics modestly reduce plasma volume and reduce vascular resistance, possibly via shifts in Na
from intracellular to extracellular loci. These drugs are the least expensive initial therapy, and the dose
needed is small, especially for the elderly (eg, for most people > 60 hydrochlorothiazide 12.5 mg is
sufficient). Thiazide-type diuretics are most commonly used. In addition to other antihypertensive effects,
they cause vasodilation as long as intravascular volume is normal. All thiazides are equally effective in
equivalent doses.

All diuretics except the K-sparing distal tubular diuretics cause significant K loss, so serum K is measured
every 1 mo until the

[Table 208-2, Choice of Antihypertensive Drug Class]

[Table 208-3, Antihypertensives for High-Risk Patients]

level stabilizes. Unless serum K is normalized, K channels in the arterial walls close and the resulting
vasoconstriction makes achieving the BP goal difficult. Patients with K levels < 3.5 mEq/L are given K
supplements. Supplements may be continued long-term at a lower dose, or a K-sparing diuretic (eg, daily
spironolactone 25 to 100 mg, triamterene 50 to 150 mg, amiloride 5 to 10 mg) may be added.
Supplements or addition of a K-sparing diuretic is also recommended for any patients who are also taking
digitals, have a known heart disorder, have an abnormal ECG, have ectopy or arrhythmias, or develop
ectopy or arrhythmias while taking a diuretic. Although the K-sparing diuretics do not cause hypokalemia,
hyperuricemia, or hyperglycemia, they are not as effective as thiazide-type diuretics in controlling
hypertension and thus are not used for initial treatment. K-sparing diuretics or supplements are not
needed when an ACE inhibitor or angiotensin II receptor blocker is used because these drugs increase serum K.

In most patients with diabetes, thiazide-type diuretics do not affect control of diabetes. Uncommonly, diuretics precipitate or worsen type 2 diabetes in patients with metabolic syndrome.

Thiazide-type diuretics can increase serum cholesterol slightly (mostly low-density lipoprotein) and also increase triglyceride levels, although these effects may not persist > 1 yr. Furthermore, levels seem to increase in only a few patients. The increase is apparent within 4 wk of treatment and can be ameliorated by a low-fat diet. The possibility of a slight increase in lipid levels does not contraindicate diuretics in hyperlipidemic patients.

A hereditary predisposition probably explains the few cases of gout due to diuretic-induced hyperuricemia. Diuretic-induced hyperuricemia without gout does not require treatment or discontinuation of the diuretic.

**β-Blockers:** These drugs (see Table 208-6) slow heart rate and reduce myocardial contractility, thus reducing BP. All β-blockers are similar in antihypertensive efficacy. In patients with diabetes, chronic peripheral arterial disease, or COPD, a cardioselective β-blocker (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol) may be preferable, although cardioslectivity is only relative and decreases as dose increases. Even cardioselective β-blockers are contraindicated in patients with asthma or in patients with COPD with a prominent bronchospastic component.

β-Blockers are particularly useful in patients who have angina, who have had an MI, or who have HF, although atenolol may worsen prognosis in patients with CAD. These drugs are no longer considered problematic for the elderly.

β-Blockers with intrinsic sympathomimetic activity (eg, acebutolol, carteolol, penbutolol, pindolol) do not adversely affect serum lipids; they are less likely to cause severe bradycardia.

β-Blockers have CNS adverse effects (sleep disturbances, fatigue, lethargy) and exacerbate depression. Nadolol affects the CNS the least and may be best when CNS effects must be avoided. β-Blockers are contraindicated in patients with 2nd- or 3rd-degree atrioventricular block, asthma, or sick sinus syndrome.

**Ca channel blockers:** Dihydropyridines (see Table 208-7) are potent peripheral vasodilators and reduce BP by decreasing TPR; they sometimes cause reflexive tachycardia. The nondihydropyridines verapamil and diltiazem slow the heart rate, decrease atrioventricular conduction, and decrease myocardial contractility. These drugs should not be prescribed for patients with 2nd- or 3rd-degree atrioventricular block or with left ventricular failure.

Long-acting nifedipine, verapamil, or diltiazem is used to treat hypertension, but short-acting nifedipine and diltiazem are associated with a high rate of MI and are not recommended.

A Ca channel blocker is preferred to a β-blocker in patients with angina pectoris and a bronchospastic disorder, with coronary spasms, or with Raynaud's syndrome.

**ACE inhibitors:** These drugs (see Table 208-8) reduce BP by interfering with the conversion of angiotensin I to angiotensin II and by inhibiting the degradation of bradykinin, thereby decreasing peripheral vascular resistance without causing reflex tachycardia. These drugs reduce BP in many hypertensive patients, regardless of plasma renin activity. Because these drugs provide renal protection, they are the drugs of choice for patients with diabetes and may be preferred for blacks.
A dry, irritating cough is the most common adverse effect, but angioedema is the most serious and, if it affects the oropharynx, can be fatal. Angioedema is most common among blacks and smokers. ACE inhibitors may increase serum K and creatinine levels, especially in patients with chronic renal failure and those taking K-sparing diuretics, K supplements, or NSAIDs. ACE inhibitors are the least likely of the antihypertensives to cause erectile dysfunction. ACE inhibitors are contraindicated during pregnancy. In patients with a renal disorder, serum creatinine and K levels are monitored at least every 3 mo. Patients who have stage 3 nephropathy (estimated GFR of < 60 mL/min to > 30 mL/min) and are given ACE inhibitors can usually tolerate up to a 30 to 35% increase in serum creatinine above baseline. ACE inhibitors can cause acute renal failure in patients who are hypovolemic or who have severe HF, severe bilateral renal artery stenosis, or severe stenosis in the artery to a solitary kidney.

Thiazide-type diuretics enhance the antihypertensive activity of ACE inhibitors more than that of other classes of antihypertensives. Spironolactone and eplerenone also appear to enhance the effect of ACE inhibitors.

**Angiotensin II receptor blockers:** These drugs (see Table 208-8) block angiotensin II receptors and therefore interfere with the renin-angiotensin system. Angiotensin II receptor blockers and ACE inhibitors are equally effective as antihypertensives. Angiotensin II receptor blockers may provide added benefits via tissue ACE blockade. The 2 classes have the same beneficial effects in patients with left ventricular failure or with nephropathy due to type 1 diabetes. An angiotensin II receptor blocker used with an ACE inhibitor or a β-blocker reduces the hospitalization rate for patients with HF. Angiotensin II receptor blockers may be safely started in people < 60 with initial serum creatinine of ≤ 3 mg/dL.

Incidence of adverse events is low; angioedema occurs but much less frequently than with ACE inhibitors. Precautions for use of angiotensin II receptor blockers in patients with renovascular hypertension, hypovolemia, and severe HF are the same as those for ACE inhibitors. Angiotensin II receptor blockers are contraindicated during pregnancy.

**Direct renin inhibitor:** Aliskiren, a direct renin inhibitor, is used in the management of hypertension. Dosage is 150 to 300 mg po once/day, with a starting dose of 150 mg. Clinical trials are ongoing to assess its efficacy for slowing diabetic nephropathy and reducing mortality in HF.

**Adrenergic modifiers:** This class (see Table 208-9) includes central α2-agonists, postsynaptic α1-blockers, and peripheral-acting adrenergic blockers.

α2-Agonists (eg, methyldopa, clonidine, guanabenz, guanfacine) stimulate α2-adrenergic receptors in the brain stem and reduce sympathetic nervous activity, lowering BP. Because they have a central action, they are more likely than other antihypertensives to cause drowsiness, lethargy, and depression; they are no longer widely used. Clonidine can be applied transdermally once/wk as a patch; thus, it may be useful for nonadherent patients (eg, those with dementia).

Postsynaptic α1-blockers (eg, prazosin, terazosin, doxazosin) are no longer used for primary treatment of hypertension because evidence suggests no reduction in mortality. Also, doxazosin used alone or with antihypertensives other than diuretics increases risk of HF.

Peripheral-acting adrenergic blockers (eg, reserpine, guanethidine, guanadrel) deplete tissue stores of
norepinephrine. Reserpine also depletes the brain of norepinephrine and serotonin. Guanethidine and guanadrel block sympathetic transmission at the neuroeffector junction. Guanethidine, in particular, is potent but difficult to titrate, so it is rarely used. Guanadrel is shorter acting and has fewer adverse effects. These 3 adrenergic blockers are not routinely recommended for initial therapy; they are used as 3rd or 4th drugs if required.

**Direct vasodilators:** These drugs (including minoxidil and hydralazine—see Table 208-10) work directly on vessels, independently of the autonomic nervous system. Minoxidil is more potent than hydralazine but has more adverse effects, including Na and water retention and hypertrichosis, which is poorly tolerated by women. Minoxidil should be reserved for severe, refractory hypertension. Hydralazine is used during pregnancy (eg, for preeclampsia) and as an adjunct antihypertensive. Long-term, high-dose (> 300 mg/day) hydralazine has been associated with a drug-induced lupus syndrome, which resolves when the drug is stopped.

[Table 208-9: Adrenergic Modifiers for Hypertension]

[Table 208-10: Direct Vasodilators for Hypertension]

**Renovascular Hypertension**

Renovascular hypertension is BP elevation due to partial or complete occlusion of one or more renal arteries or their branches. It is usually asymptomatic unless long-standing. A bruit can be heard over one or both renal arteries in < 50% of patients. Diagnosis is by physical examination and renal imaging with duplex ultrasonography, radionuclide imaging, or magnetic resonance angiography. Angiography is done before definitive treatment with surgery or angioplasty.

Renovascular disease is one of the most common causes of curable hypertension but accounts for < 2% of all cases of hypertension. Stenosis or occlusion of one or both main renal arteries, an accessory renal artery, or any of their branches can cause hypertension by stimulating release of renin from juxtaglomerular cells of the affected kidney. The area of the arterial lumen must be decreased by ≥ 70% before stenosis is likely to cause hypertension. For unknown reasons, renovascular hypertension is much less common among blacks than among whites.

Overall, about two thirds of cases are caused by atherosclerosis and one third by fibromuscular dysplasia. Atherosclerosis is more common among men > 50 and affects mainly the proximal one third of the renal artery. Fibromuscular dysplasia is more common among younger patients (usually women) and usually affects the distal two third of the main renal artery and the branches of the renal arteries. Rarer causes include emboli, trauma, inadvertent ligation during surgery, and extrinsic compression of the renal pedicle by tumors.

Renovascular hypertension is characterized by high cardiac output and high peripheral resistance.

**Symptoms and Signs**

Renovascular hypertension is usually asymptomatic. A systolic-diastolic bruit in the epigastrium, usually transmitted to one or both upper quadrants and sometimes to the back, is almost pathognomonic, but it is present in only about 50% of patients with fibromuscular dysplasia and is rare in patients with renal atherosclerosis.

Renovascular hypertension should be suspected if diastolic hypertension develops abruptly in a patient < 30 or > 50; if new or previously stable hypertension rapidly worsens within 6 mo; or if hypertension is initially very severe, associated with worsening renal function, or highly refractory to drug treatment. A history of trauma to the back or flank or acute pain in this region with or without hematuria suggests renovascular hypertension (possibly due to arterial injury), but these historical findings are rare. Asymmetric renal size (discovered incidentally during imaging tests) and recurrent episodes of unexplained acute pulmonary edema or heart failure also suggest it.

**Diagnosis**
• Initial identification with ultrasonography, magnetic resonance angiography, or radionuclide imaging

• Confirmation with renal angiography (also may be therapeutic)

If renovascular hypertension is suspected, ultrasonography, magnetic resonance angiography (MRA), or radionuclide imaging may be done to identify patients who should have renal angiography, the definitive test.

Duplex Doppler ultrasonography can assess renal blood flow and is a reliable noninvasive method for identifying significant stenosis (eg, > 60%) in the main renal arteries. Sensitivity and specificity approach 90% when experienced technicians do the test. It is less accurate in patients with branch stenosis.

MRA is a more accurate and specific noninvasive test to assess the renal arteries.

Radionuclide imaging is often done before and after an oral dose of captopril 50 mg. The ACE inhibitor causes the affected artery to narrow, decreasing perfusion on the scintiscan. Narrowing also causes an increase in serum renin, which is measured before and after captopril administration. This test may be less reliable in blacks and in patients with decreased renal function.

Renal angiography is done if MRA indicates a lesion amenable to angioplasty or stenting or if other screening tests are positive. Digital subtraction angiography with selective injection of the renal arteries can also confirm the diagnosis, but angioplasty or stent placement cannot be done in the same procedure.

Measurements of renal vein renin activity are sometimes misleading and, unless surgery is being considered, are not necessary. However, in unilateral disease, a renal vein renin activity ratio of > 1.5 (affected to unaffected side) usually predicts a good outcome with revascularization. The test is done when patients are depleted of Na, stimulating the release of renin.

**Treatment**

• Angioplasty sometimes with stent placement

• Rarely bypass graft

If the renal vein renin activity ratio is > 1.5:1, opening the obstructed renal artery using angioplasty with or without a stent usually relieves hypertension. Even when the ratio is lower, revascularization or removal of the affected kidney often cures hypertension.

Percutaneous transluminal angioplasty (PTA) is recommended for most patients, including younger patients with fibromuscular dysplasia of the renal artery. Placement of a stent reduces the risk of restenosis; antiplatelet drugs (aspirin, clopidogrel) are given afterward. Saphenous vein bypass grafting is recommended only when extensive disease in the renal artery branches makes PTA technically unfeasible. Sometimes complete surgical revascularization requires microvascular techniques that can only be done ex vivo with autotransplantation of the kidney. Cure rate is 90% in appropriately selected patients; surgical mortality rate is < 1%. Medical treatment is always preferable to nephrectomy in young patients whose kidneys cannot be revascularized for technical reasons.

Atherosclerotic lesions respond less well to surgery and angioplasty than do lesions due to fibromuscular dysplasia, presumably because patients are older and vascular disease is more extensive. Hypertension may persist, and surgical complications are more common. Surgical mortality rate is higher than that in young patients with fibromuscular dysplasia. Restenosis occurs within 2 yr after PTA in up to 50% of patients with renovascular atherosclerosis, especially when the lesion is located at the ostium of the renal artery, and, with stenting, in about 25%.

Without treatment, the prognosis is similar to that for patients with untreated primary hypertension. Medical treatment is inadequate without intervention to alleviate the stenosis, but aggressive medical
treatment in adherent patients usually ameliorates and sometimes controls hypertension.

**Hypertensive Emergencies**

A hypertensive emergency is severe hypertension with signs of damage to target organs (primarily the brain, cardiovascular system, and kidneys). Diagnosis is by BP measurement, ECG, urinalysis, and serum BUN and creatinine measurements. Treatment is immediate BP reduction with IV drugs (eg, nitroprusside, β-blockers, hydralazine).

Target-organ damage includes hypertensive encephalopathy, preeclampsia and eclampsia, acute left ventricular failure with pulmonary edema, myocardial ischemia, acute aortic dissection, and renal failure. Damage is rapidly progressive and often fatal.

Hypertensive encephalopathy may involve a failure of cerebral autoregulation of blood flow. Normally, as BP increases, cerebral vessels constrict to maintain constant cerebral perfusion. Above a mean arterial pressure (MAP) of about 160 mm Hg (lower for normotensive people whose BP suddenly increases), the cerebral vessels begin to dilate rather than remain constricted. As a result, the very high BP is transmitted directly to the capillary bed with transudation and exudation of plasma into the brain, causing cerebral edema, including papilledema. Pathophysiology of other target-organ manifestations is discussed elsewhere in THE MANUAL.

Although many patients with stroke and intracranial hemorrhage present with elevated BP, elevated BP is often a consequence rather than a cause of the condition. Whether rapidly lowering BP is beneficial in these conditions is unclear; it may even be harmful.

**Hypertensive urgencies:** Very high blood pressure (eg, diastolic pressure > 120 to 130 mm Hg) without target-organ damage (except perhaps grades 1 to 3 retinopathy—see p. 2067) may be considered a hypertensive urgency. BP at these levels often worries the physician; however, acute complications are unlikely, so immediate BP reduction is not required. However, patients should be started on a 2-drug oral combination (see p. 2070), and close evaluation (with evaluation of treatment efficacy) should be continued on an outpatient basis.

**Symptoms and Signs**

BP is elevated, often markedly (diastolic pressure > 120 mm Hg). CNS symptoms include rapidly changing neurologic abnormalities (eg, confusion, transient cortical blindness, hemiparesis, hemisensory defects, seizures). Cardiovascular symptoms include chest pain and dyspnea. Renal involvement may be asymptomatic, although severe azotemia due to advanced renal failure may cause lethargy or nausea.

Physical examination focuses on target organs, with neurologic examination, funduscopy, and cardiovascular examination. Global cerebral deficits (eg, confusion, obtundation, coma), with or without focal deficits, suggest encephalopathy; normal mental status with focal deficits suggests stroke. Severe retinopathy (sclerosis, cotton-wool spots, arteriolar narrowing, hemorrhage, papilledema) is usually present with hypertensive encephalopathy, and some degree of retinopathy is present in many other hypertensive emergencies. Jugular venous distention, basilar lung crackles, and a 3rd heart sound suggest pulmonary edema. Asymmetry of pulses between arms suggests aortic dissection.

**Diagnosis**

- Very high BP

- Identify target-organ involvement: ECG, urinalysis, BUN, creatinine; if neurologic findings, head CT

Testing typically includes ECG, urinalysis, and serum BUN and creatinine. Patients with neurologic findings require head CT to diagnose intracranial bleeding, edema, or infarction. Patients with chest pain or dyspnea require chest x-ray. ECG abnormalities suggesting target-organ damage include signs of left ventricular hypertrophy or acute ischemia. Urinalysis abnormalities typical of renal involvement include RBCs, RBC casts, and proteinuria.
Diagnosis is based on the presence of a very high BP and findings of target-organ involvement.

**Treatment**

- Admit to ICU
- Short-acting IV drug: nitrate, fenoldopam, nicardipine, or labetalol
- Goal: 20 to 25% reduction MAP in 1 to 2 h

Hypertensive emergencies are treated in an ICU; BP is progressively (although not abruptly) reduced using a short-acting, titratable IV drug. Choice of drug and speed and degree of reduction vary somewhat with the target organ involved, but generally a 20 to 25% reduction in MAP over an hour or so is appropriate, with further titration based on symptoms. Achieving "normal" BP urgently is not necessary. Typical first-line drugs include nitroprusside, fenoldopam, nicardipine, and labetalol (see [Table 208-11](#)). Nitroglycerin alone is less potent.

Oral drugs are not indicated because onset is variable and the drugs are difficult to titrate. Although short-acting oral nifedipine reduces BP rapidly, it may lead to acute cardiovascular and cerebrovascular events (sometimes fatal) and is therefore not recommended.

Nitroprusside is a venous and arterial dilator, reducing preload and afterload; thus, it is the most useful for hypertensive patients with heart failure. It is also used for hypertensive encephalopathy and, with β-blockers, for aortic dissection. Starting dose is 0.25 to 1.0 μg/kg/min titrated in increments of 0.5 μg/kg to a maximum of 8 to 10 μg/kg/min; maximum dose is given for ≤ 10 min to minimize risk of cyanide toxicity. The drug is rapidly broken down into cyanide and nitric oxide (the active moiety). Cyanide is detoxified to thiocyanate. However, administration of > 2 μg/kg/min can lead to cyanide accumulation with toxicity to the CNS and heart; manifestations include agitation, seizures, cardiac instability, and an anion gap metabolic acidosis. Prolonged administration (> 1 wk or, in patients with renal insufficiency, 3 to 6 days) leads to accumulation of thiocyanate, with lethargy, tremor, abdominal pain, and vomiting. Other adverse effects include transitory elevation of hair follicles (cutis anserina) if BP is reduced too rapidly. Thiocyanate levels should be monitored daily after 3 consecutive days of therapy, and the drug should be stopped if the serum thiocyanate level is > 12 mg/dL (> 2 mmol/L). Because the drug is broken down by ultraviolet light, the IV bag and tubing are wrapped in an opaque covering.

Fenoldopam is a peripheral dopamine-1 agonist that causes systemic and renal vasodilation and natriuresis. Onset is rapid and half-life is brief, making it an effective alternative to nitroprusside, with the added benefit that it does not cross the blood-brain barrier. Initial dosage is 0.1 μg/kg/min IV infusion, titrated upward by 0.1 μg/kg q 15 min to a maximum of 1.6 μg/kg/min.

Nitroglycerin is a vasodilator that affects veins more than arterioles. It can be used to manage hypertension during and after coronary artery bypass graft surgery, acute MI, unstable angina pectoris, and acute pulmonary edema. IV nitroglycerin is preferable to nitroprusside for patients with severe coronary artery disease because nitroglycerin increases coronary flow, whereas nitroprusside tends to decrease coronary flow to ischemic areas, possibly because of a "steal" mechanism. Starting dose is 10 to 20 μg/min titrated upward by 10 μg/min q 5 min to maximum antihypertensive effect. For long-term BP control, nitroglycerin must be used with other drugs. The most common adverse effect is headache (in about 2%); others include tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, and palpitations.

Nicardipine, a dihydropyridine Ca channel blocker with less negative inotropic effects than nifedipine, acts primarily as a vasodilator. It is most often used for postoperative hypertension and during pregnancy. Dosage is 5 mg/h IV, increased q 15 min to a maximum of 15 mg/h. It may cause flushing, headache, and tachycardia; it can decrease GFR in patients with renal insufficiency.

[Table 208-11, Parenteral Drugs for Hypertensive Emergencies]
Labetalol is a β-blocker with some α₁-blocking effects, thus causing vasodilation without the typical accompanying reflex tachycardia. It can be given as a constant infusion or as frequent boluses; use of boluses has not been shown to cause significant hypotension. Labetalol is used during pregnancy, for intracranial disorders requiring BP control, and after MI. Infusion is 0.5 to 2 mg/min, titrated upward to a maximum of 4 to 5 mg/min. Boluses begin with 20 mg IV followed every 10 min by 40 mg, then 80 mg (up to 3 doses) to a maximum total of 300 mg. Adverse effects are minimal, but because of its β-blocking activity, labetalol should not be used for hypertensive emergencies in patients with asthma. Low doses may be used for left ventricular failure if nitroglycerin is given simultaneously.
Chapter 209. Arteriosclerosis

Introduction

Arteriosclerosis is a general term for several disorders that cause thickening and loss of elasticity in the arterial wall. Atherosclerosis, the most common form, is also the most serious because it causes coronary artery disease and cerebrovascular disease. Nonatheromatous forms of arteriosclerosis include arteriolosclerosis and Monckeberg's arteriosclerosis.

Atherosclerosis

Atherosclerosis is patchy intimal plaques (atheromas) in medium-sized and large arteries; the plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue. Risk factors include dyslipidemia, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension. Symptoms develop when growth or rupture of the plaque reduces or obstructs blood flow; symptoms vary by artery affected. Diagnosis is clinical and confirmed by angiography, ultrasonography, or other imaging tests. Treatment includes risk factor and dietary modification, physical activity, antiplatelet drugs, and antiatherogenic drugs.

Atherosclerosis can affect all large and medium-sized arteries, including the coronary, carotid, and cerebral arteries; the aorta; its branches; and major arteries of the extremities. It is the leading cause of morbidity and mortality in the US and in most developed countries. In recent years, age-related mortality attributable to atherosclerosis has been decreasing, but in 2005, cardiovascular disease, primarily coronary and cerebrovascular atherosclerosis still caused almost 870,000 deaths in the US (more than cancer and almost 9 times more than injuries). Atherosclerosis is rapidly increasing in prevalence in developing countries, and as people in developed countries live longer, incidence will increase. By 2020, atherosclerosis is expected to be the leading cause of death worldwide.

Pathophysiology

The hallmark of atherosclerosis is the atherosclerotic plaque, which contains lipids (intracellular and extracellular cholesterol and phospholipids), inflammatory cells (eg, macrophages, T cells), smooth muscle cells, connective tissue (eg, collagen, glycosaminoglycans, elastic fibers), thrombi, and Ca deposits. All stages of atherosclerosis—from initiation and growth to complication of the plaque—are considered an inflammatory response to injury. Endothelial injury is thought to have a primary role.

Atherosclerosis preferentially affects certain areas of the arterial tree. Nonlaminar or turbulent blood flow (eg, at branch points in the arterial tree) leads to endothelial dysfunction and inhibits endothelial production of nitric oxide, a potent vasodilator and anti-inflammatory molecule. Such blood flow also stimulates endothelial cells to produce adhesion molecules, which recruit and bind inflammatory cells. Risk factors for atherosclerosis (eg, dyslipidemia, diabetes, cigarette smoking, hypertension), oxidative stressors (eg, superoxide radicals), angiotensin II, and systemic infection and inflammation also inhibit nitric oxide production and stimulate production of adhesion molecules, proinflammatory cytokines, chemotactic proteins, and vasoconstrictors; exact mechanisms are unknown. The net effect is endothelial binding of monocytes and T cells, migration of these cells to the subendothelial space, and initiation and perpetuation of a local vascular inflammatory response. Monocytes in the subendothelium transform into macrophages. Lipids in the blood, particularly low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), also bind to endothelial cells and are oxidized in the subendothelium. Uptake of oxidized lipids and macrophage transformation into lipid-laden foam cells result in the typical early atherosclerotic lesions called fatty streaks. Degraded erythrocyte membranes that result from rupture of vasa vasorum and intraplaque hemorrhage may be an important additional source of lipids within plaques.

Macrophages elaborate proinflammatory cytokines that recruit smooth muscle cell migration from the media and that further attract and stimulate growth of macrophages. Various factors promote smooth muscle cell replication and increase production of dense extracellular matrix. The result is a subendothelial fibrous plaque with a fibrous cap, made of intimal smooth muscle cells surrounded by connective tissue and intracellular and extracellular lipids. A process similar to bone formation causes
calcification within the plaque.

Atherosclerotic plaques may be stable or unstable. Stable plaques regress, remain static, or grow slowly over several decades until they may cause stenosis or occlusion. Unstable plaques are vulnerable to spontaneous erosion, fissure, or rupture, causing acute thrombosis, occlusion, and infarction long before they cause stenosis. Most clinical events result from unstable plaques, which do not appear severe on angiography; thus, plaque stabilization may be a way to reduce morbidity and mortality.

The strength of the fibrous cap and its resistance to rupture depend on the relative balance of collagen deposition and degradation. Plaque rupture involves secretion of metalloproteinases, cathepsins, and collagenases by activated macrophages in the plaque. These enzymes digest the fibrous cap, particularly at the edges, causing the cap to thin and ultimately rupture. T cells in the plaque contribute by secreting cytokines. Cytokines inhibit smooth muscle cells from synthesizing and depositing collagen, which normally reinforces the plaque.

Once the plaque ruptures, plaque contents are exposed to circulating blood, triggering thrombosis; macrophages also stimulate thrombosis because they contain tissue factor, which promotes thrombin generation in vivo. One of 5 outcomes may occur:

- The resultant thrombus may organize and be incorporated into the plaque, changing the plaque's shape and causing its rapid growth.
- The thrombus may rapidly occlude the vascular lumen and precipitate an acute ischemic event.
- The thrombus may embolize.
- The plaque may fill with blood, balloon out, and immediately occlude the artery.
- Plaque contents (rather than thrombus) may embolize, occluding vessels downstream.

Plaque stability depends on multiple factors, including plaque composition (relative proportion of lipids, inflammatory cells, smooth muscle cells, connective tissue, and thrombus), wall stress (cap fatigue), size and location of the core, and configuration of the plaque in relation to blood flow. By contributing to rapid growth and lipid deposition, intraplaque hemorrhage may play an important role in transforming stable into unstable plaques. In general, unstable coronary artery plaques have a high macrophage content, a thick lipid core, and a thin fibrous cap; they narrow the vessel lumen by < 50% and tend to rupture unpredictably. Unstable carotid artery plaques have the same composition but typically cause problems through severe stenosis and occlusion or deposition of platelet thrombi, which embolize rather than rupture. Low-risk plaques have a thicker cap and contain fewer lipids; they often narrow the vessel lumen by > 50% and may produce predictable exercise-induced stable angina.

Clinical consequences of plaque rupture in coronary arteries depend not only on plaque anatomy but also on relative balance of procoagulant and anticoagulant activity in the blood and on the vulnerability of the myocardium to arrhythmias.

A link between infection and atherosclerosis has been observed, specifically an association between serologic evidence of certain infections (eg, *Chlamydia pneumoniae*, cytomegalovirus) and coronary artery disease (CAD). Putative mechanisms include indirect effects of chronic inflammation in the bloodstream, cross-reactive antibodies, and inflammatory effects of infectious pathogens on the arterial wall.

**Risk Factors**

There are numerous risk factors (see Table 209-1). Certain factors tend to cluster as the metabolic syndrome, which is becoming increasingly prevalent. This syndrome includes abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, a prothrombotic state, and a proinflammatory state in sedentary patients (see p. 64). Insulin resistance is not synonymous with the metabolic syndrome but may be key in its etiology.
Dyslipidemia (high total, high LDL, or low high-density lipoprotein [HDL] cholesterol), hypertension, and diabetes promote atherosclerosis by amplifying or augmenting endothelial dysfunction and inflammatory pathways in vascular endothelium.

In dyslipidemia, subendothelial uptake and oxidation of LDL increases; oxidized lipids stimulate production of adhesion molecules and inflammatory cytokines and may be antigenic, inciting a T cell-mediated immune response and inflammation in the arterial wall. HDL protects against atherosclerosis via reverse cholesterol transport (see p. 889); it may also protect by transporting antioxidant enzymes, which can break down and neutralize oxidized lipids. The role of hypertriglyceridemia in atherogenesis is complex, although it may have a small independent effect.

Hypertension may lead to vascular inflammation via angiotensin II-mediated mechanisms. Angiotensin II stimulates endothelial cells, vascular smooth muscle cells, and macrophages to produce proatherogenic mediators, including proinflammatory cytokines, superoxide anions, prothrombotic factors, growth factors, and lectin-like oxidized LDL receptors.

Diabetes leads to the formation of advanced glycation end products, which increase the production of proinflammatory cytokines from endothelial cells. Oxidative stress and reactive O₂ radicals, generated in diabetes, directly injure the endothelium and promote atherogenesis.

Tobacco smoke contains nicotine and other chemicals that are toxic to vascular endothelium. Smoking, including passive smoking, increases platelet reactivity (possibly promoting platelet thrombosis) and plasma fibrinogen levels and Hct (increasing blood viscosity). Smoking increases LDL and decreases HDL; it also promotes vasoconstriction, which is particularly dangerous in arteries already narrowed by atherosclerosis. HDL increases by about 6 to 8 mg/dL (0.16 to 0.21 mmol/L) within 1 mo of smoking cessation.

Hyperhomocysteinemia increases risk of atherosclerosis, although not as much as the above risk factors. It may result from folate deficiency or a genetic metabolic defect. The pathophysiologic mechanism is unknown but may involve direct endothelial injury, stimulation of monocyte and T-cell recruitment, LDL uptake by macrophages, and smooth muscle cell proliferation.

Lipoprotein(a) is a modified form of LDL that has a cysteine-rich region homologous with the fibrin-binding domain of plasminogen. High levels of lipoprotein(a) may compete with fibrin to bind with plasminogen and thus interfere with thrombolysis, predisposing to atherothrombosis.

A high level of small, dense LDL, characteristic of diabetes, is highly atherogenic. Mechanisms may include increased susceptibility to oxidation and nonspecific endothelial binding (see p. 890).

A high C-reactive protein (CRP) level does not reliably predict extent of atherosclerosis but can predict increased likelihood of ischemic events. In the absence of other inflammatory disorders, it may indicate increased risk of atherosclerotic plaque rupture, ongoing ulceration or thrombosis, or increased activity of lymphocytes and macrophages. CRP may have a direct role in atherogenesis through multiple mechanisms, including downregulation of nitric oxide synthesis and upregulation of angiotensin type I receptors, chemoattractant proteins, and adhesion molecules.

*C. pneumoniae* infection or other infections (eg, viral, *Helicobacter pylori*) may cause endothelial dysfunction through direct infection, exposure to endotoxin, or stimulation of systemic or subendothelial inflammation.

Renal insufficiency promotes development of atherosclerosis via several pathways, including worsening hypertension and insulin resistance; decreased apolipoprotein A-I levels; and increased lipoprotein(a), homocysteine, fibrinogen, and CRP levels.
Prothrombotic states (see p. 973) increase likelihood of atherothrombosis.

5-Lipoxygenase polymorphisms (deletion or addition of alleles) may promote atherosclerosis by increasing leukotriene production within plaques, which causes vascular permeability and monocyte-macrophage migration, thus increasing subendothelial inflammation and dysfunction.

**Documented vascular disease:** The presence of atherosclerotic disease in one vascular territory increases the likelihood of disease in other vascular territories. Patients with non-coronary atherosclerotic vascular disease have cardiac event rates comparable to those of patients with known CAD, and they are now considered to have a CAD risk equivalent and should be treated as aggressively.

**Symptoms and Signs**

Atherosclerosis is initially asymptomatic, often for decades. Symptoms and signs develop when lesions impede blood flow. Transient ischemic symptoms (eg, stable exertional angina, transient ischemic attacks, intermittent claudication) may develop when stable plaques grow and reduce the arterial lumen by > 70%. Symptoms of unstable angina or infarction, ischemic stroke, or rest pain in the limbs may develop when unstable plaques rupture and acutely occlude a major artery, with superimposition of thrombosis or embolism. Atherosclerosis may also cause sudden death without preceding stable or unstable angina pectoris.

Atherosclerotic involvement of the arterial wall can lead to aneurysms and arterial dissection, which can manifest as pain, a pulsatile mass, absent pulses, or sudden death.

**Diagnosis**

**Approach depends on the presence or absence of symptoms.**

**Symptomatic patients:** Patients with symptoms and signs of ischemia are evaluated for the amount and location of vascular occlusion by various invasive and noninvasive tests, depending on the organ involved (see elsewhere in THE MANUAL). Such patients also should be evaluated for atherosclerosis risk factors by using

- History and physical examination
- Fasting lipid profile
- Plasma glucose and glycosylated hemoglobin (HbA<sub>1c</sub>) levels

Patients with documented disease at one site (eg, peripheral arteries) should be evaluated for disease at other sites (eg, coronary and carotid arteries).

Because not all atherosclerotic plaques have similar risk, various imaging technologies are being studied as a way to identify plaques especially vulnerable to rupture. Most technologies are catheter-based; they include intravascular ultrasonography (which uses an ultrasound transducer on the tip of a catheter to produce images of the arterial lumen and wall), angioscopy, plaque thermography (to detect the increased temperature in plaques with active inflammation), optical coherence tomography (which uses infrared laser light for imaging), and elastography (to identify soft, lipid-rich plaques). Immunoscintigraphy is a noninvasive alternative using radioactive tracers that localize in vulnerable plaque.

Some clinicians measure serum markers of inflammation. CRP levels > 3 mg/dL (> 3000 μg/L) are highly predictive of cardiovascular events. High levels of lipoprotein-associated phospholipase A2 appear to predict cardiovascular events in patients with a normal or low LDL level.

**Asymptomatic patients (screening):** In patients with risk factors for atherosclerosis but no symptoms or signs of ischemia, the role of additional testing beyond the fasting lipid profile is unclear. Although imaging studies such as electron beam or multidetector row CT, MRI, and ultrasonography (see p. 3402) can detect atherosclerotic plaque, they probably do not improve prediction of ischemic events over
assessment of risk factors or established prediction tools (eg, Framingham risk index—see Table 100-6 on p. 899; see Table 100-7 on p. 900) and are not routinely recommended.

Urinary microalbuminuria (> 30 mg albumin/24 h) is a marker for renal disorders and their progression, as well as a strong predictor of cardiovascular and noncardiovascular morbidity and mortality; however, the direct relationship between microalbuminuria and atherosclerosis has not been established.

**Treatment**

- **Lifestyle changes** (diet, smoking, physical activity)
- **Drug treatment of diagnosed risk factors**
- **Antiplatelet drugs**
- **Possibly statins, ACE inhibitors, β-blockers**

Treatment involves aggressive modification of risk factors to slow progression and induce regression of existing plaques. Recent evidence suggests that LDL should be < 70 mg/dL (< 1.81 mmol/L) in patients with disease or at high risk of cardiovascular events. Lifestyle changes include diet modification, smoking cessation, and regular participation in physical activity. Drugs to treat dyslipidemia, hypertension, and diabetes are often required. These lifestyle changes and drugs directly or indirectly improve endothelial function, reduce inflammation, and improve clinical outcome. The statins can decrease atherosclerosis-related morbidity and mortality even when serum cholesterol is normal or slightly high. Antiplatelet drugs help all atherosclerotic patients. Patients with CAD may benefit additionally from ACE inhibitors and β-blockers.

**Diet:** Several changes are beneficial:

- **Less saturated fat**
- **No trans fats**
- **More fruits and vegetables**
- **More fiber**
- **Moderate (if any) alcohol**

Substantial decreases in saturated fat and simple carbohydrate intake and increases in fruit, vegetable, and fiber intake are recommended. These dietary changes are a prerequisite for lipid control and weight reduction and are essential for all patients. Calorie intake should be limited to keep weight within the normal range.

Small decreases in fat intake do not appear to lessen or stabilize atherosclerosis. Effective change requires limiting fat intake to 20 g/day, consisting of 6 to 10 g of polyunsaturated fat with ω-6 (linoleic acid) and ω-3 (eicosapentaenoic acid, docosahexaenoic acid) fatty acids in equal proportion, ≤ 2 g of saturated fat, and the rest as monounsaturated fat. Trans fats, which are highly atherogenic, should be avoided.

Increasing carbohydrates to compensate for decreasing saturated fats in the diet increases plasma triglyceride levels and reduces HDL levels. Thus, any caloric deficiency should be made up with proteins and unsaturated fats rather than simple carbohydrates. Excessive sugar intake should be avoided, although sugar intake has not been directly related to cardiovascular risk. Instead, consumption of complex carbohydrates (eg, vegetables, whole grains) is encouraged.

Fruits and vegetables (5 daily servings) seem to decrease risk of coronary atherosclerosis, but whether
this effect is due to phytochemicals or to a proportional decrease in saturated fat intake and increase in fiber and vitamin intake is unclear. Phytochemicals called flavonoids (in red and purple grapes, red wine, black teas, and dark beers) appear especially protective; high concentrations in red wine may help explain why incidence of coronary atherosclerosis in the French is relatively low, even though they use more tobacco and consume more fat than Americans do. But no clinical data indicate that eating flavonoid-rich foods or using supplements instead of foods prevents atherosclerosis.

Increased fiber intake decreases total cholesterol and may have a beneficial effect on glucose and insulin levels. Daily intake of at least 5 to 10 g of soluble fiber (eg, oat bran, beans, soy products, psyllium) is recommended; this amount decreases LDL by about 5%. Insoluble fiber (eg, cellulose, lignin) does not appear to affect cholesterol but may confer additional health benefits (eg, reduced risk of colon cancer, possibly by stimulating bowel movement or reducing contact time with dietary carcinogens). However, excessive fiber interferes with the absorption of certain minerals and vitamins. In general, foods rich in phytochemicals and vitamins are also rich in fiber.

Alcohol increases HDL and has poorly defined antithrombotic, antioxidant, and anti-inflammatory properties. These effects appear to be the same for wine, beer, and hard liquor, and occur at moderate levels of consumption; about 30 mL (1 oz) 5 to 6 times/wk protects against coronary atherosclerosis. However, at higher doses, alcohol can cause significant health problems. Thus, the relationship between alcohol and total mortality rate is J-shaped; mortality rate is lowest for men who consume < 14 drinks/wk and women who consume < 9 drinks/wk.

There is little evidence that dietary supplementation with vitamins, phytochemicals, and trace minerals reduces risk of atherosclerosis. The one exception is fish oil supplements (see p. 903). Although alternative medicines and health foods are becoming more popular, and some may have minor effects on blood pressure or cholesterol, these treatments are not always proven safe or effective and may have negative interactions with proven drugs. Levels of coenzyme Q10, which is necessary for the basic functioning of cells, tend to decrease with age and may be low in patients with certain heart and other chronic diseases; thus, coenzyme Q10 supplementation has been used or recommended, but its therapeutic benefit remains controversial.

**Physical activity:** Regular physical activity (eg, 30 to 45 min of walking, running, swimming, or cycling 3 to 5 times/wk) reduces incidence of some risk factors (hypertension, dyslipidemia, diabetes), CAD (eg, MI), and death attributable to atherosclerosis in patients with and without previous ischemic events. Whether the association is causal or merely indicates that healthier people are more likely to exercise regularly is unclear. Optimal intensity, duration, frequency, and type of exercise have not been established, but most evidence suggests an inverse linear relationship between aerobic physical activity and risk. Walking regularly increases the distance patients with peripheral vascular disease can walk without pain.

An exercise program that involves aerobic exercise has a clear role in preventing atherosclerosis and promoting weight loss (see p. 3292). Before starting a new exercise program, the elderly and people who have risk factors for atherosclerosis or who have had recent ischemic events should probably be evaluated by a physician. Evaluation includes history, physical examination, and assessment of risk factor control.

**Antiplatelet drugs:** Oral antiplatelet drugs are essential because most complications result from plaque fissure or rupture with platelet activation and thrombosis. The following are used:

- Aspirin
- Sometimes clopidogrel

Aspirin is most widely used but, despite its proven benefits, remains underused. It is indicated for secondary prevention and recommended for primary prevention of coronary atherosclerosis in patients at high risk (eg, patients with diabetes with or without atherosclerosis, patients with ≥ 20% risk of cardiac events within 10 yr). Optimal dose and duration are unknown, but 75 to 325 mg po once/day indefinitely is commonly used for primary and secondary prevention because it is effective while minimizing risk of
bleeding. In about 10 to 20% of patients taking aspirin for secondary prevention, ischemic events recur. The reason may be aspirin resistance; assays to detect lack of thromboxane suppression (indicated by elevated urinary 11-dehydro thromboxane B₂) are being studied for clinical use. Some evidence suggests that ibuprofen can interfere with aspirin’s antithrombotic effect, so other NSAIDs are recommended for patients taking aspirin for prevention. However, all NSAIDs, some more than others, including COX-2 selective inhibitors (eg, rofecoxib), appear to increase cardiovascular risks.

Clopidogrel (usually 75 mg/day) is substituted for aspirin when ischemic events recur in patients taking aspirin and in patients intolerant of aspirin. Clopidogrel in combination with aspirin is effective in treating acute ST-segment and non-ST-segment elevation MI (see p. 2101); the combination is also given for 9 to 12 mo after percutaneous intervention (PCI) to reduce risk of recurrent ischemic events.

Ticlopidine is no longer widely used because it causes severe neutropenia in 1% of users and has severe GI adverse effects.

Other drugs: ACE inhibitors, angiotensin II receptor blockers, statins, and thiazolidinediones (eg, rosiglitazone, pioglitazone) have anti-inflammatory properties that reduce risk of atherosclerosis independent of their effects on BP, lipids, and glucose. ACE inhibitors inhibit the contributions of angiotensin to endothelial dysfunction and inflammation. Statins enhance endothelial nitric oxide production, stabilize atherosclerotic plaques, reduce lipid accumulation in the arterial wall, and induce regression of plaques. Thiazolidinediones may control expression of proinflammatory genes, although recent studies suggest that they may increase the risk of coronary events. Routine use of statins for primary prevention of ischemic events is controversial. However, several well-controlled studies support their use in high-risk patients (eg, diabetics with normal BP and lipid levels and patients with multiple risk factors, including hyperlipidemia and/or hypertension). Statins are sometimes recommended for patients with normal LDL and high CRP; few data now support this practice, but it is under study.

Folate (folic acid) 0.8 mg po bid has been previously used to treat hyperhomocysteinemia but does not appear to reduce the risk of acute coronary events. Vitamins B₆ and B₁₂ also lower homocysteine levels, but current data do not justify their use alone or in combination with folate. Macrolide and other antibiotics are being studied to determine whether treating chronic occult C. pneumoniae infections can suppress inflammation and alter the course and manifestations of atherosclerosis.

Nonatheromatous Arteriosclerosis

Nonatheromatous arteriosclerosis is age-related fibrosis in the aorta and its major branches.

Nonatheromatous arteriosclerosis causes intimal thickening and weakens and disrupts the elastic lamellae. The smooth muscle (media) layer atrophies, and the lumen of the affected artery widens (becomes ectatic), predisposing to aneurysm or dissection. Hypertension is a major factor in development of aortic arteriosclerosis and aneurysm. Intimal injury, ectasia, and ulceration may lead to thrombosis, embolism, or complete arterial occlusion.

Arteriolsclerosis affects distal arteries in patients with diabetes or hypertension. Hyaline arteriolsclerosis affects small arteries and arterioles in patients with diabetes; typically, hyaline thickening occurs, the arteriolar wall degenerates, and the lumen narrows, causing diffuse ischemia, especially in the kidneys. Hyperplastic arteriolsclerosis occurs more often in patients with hypertension; typically, laminated, concentric thickening and luminal narrowing occur, sometimes with fibrinoid deposits and vessel wall necrosis (necrotizing arteriolitis). Hypertension promotes these changes, and arteriolsclerosis, by increasing arteriolar rigidity and increasing peripheral resistance, may help sustain the hypertension.

Monckeberg's arteriosclerosis (medial calcific sclerosis) affects patients > 50; age-related medial degeneration occurs with focal calcification and even bone formation within the arterial wall. Segments of the artery may become a rigid calcified tube without luminal narrowing. The diagnosis is usually obvious by plain x-ray. This disorder is clinically important only because it can greatly reduce arterial compressibility, causing extremely but falsely elevated BP readings.
**Chapter 210. Coronary Artery Disease**

**Introduction**

Coronary artery disease (CAD) involves impairment of blood flow through the coronary arteries, most commonly by atheromas. Clinical presentations include silent ischemia, angina pectoris, acute coronary syndromes (unstable angina, MI), and sudden cardiac death. Diagnosis is by symptoms, ECG, stress testing, and sometimes coronary angiography. Prevention consists of modifying reversible risk factors (eg, hypercholesterolemia, hypertension, physical inactivity, obesity, and smoking). Treatment includes drugs and procedures to reduce ischemia and restore or improve coronary blood flow.

In developed countries, CAD is the leading cause of death in both sexes, accounting for about one third of all deaths. Mortality rate among white men is about 1/10,000 at ages 25 to 34 and nearly 1/100 at ages 55 to 64. Mortality rate among white men aged 35 to 44 is 6.1 times that among age-matched white women. For unknown reasons, the sex difference is less marked in nonwhites. Mortality rate among women increases after menopause and, by age 75, equals or even exceeds that of men.

**Etiology**

Usually, CAD is due to subintimal deposition of atheromas in large and medium-sized coronary arteries (atherosclerosis—see p. 2081). Less often, CAD is due to coronary spasm. Rare causes include coronary artery embolism, dissection, aneurysm (eg, in Kawasaki disease), and vasculitis (eg, in SLE, syphilis).

**Pathophysiology**

Coronary atherosclerosis is often irregularly distributed in different vessels but typically occurs at points of turbulence (eg, vessel bifurcations). As the atheromatous plaque grows, the arterial lumen progressively narrows, resulting in ischemia (often causing angina pectoris). The degree of stenosis required to produce ischemia varies with $O_2$ demand.

Occasionally, an atheromatous plaque ruptures or splits. Reasons are unclear but probably relate to plaque morphology, plaque Ca content, and plaque softening due to an inflammatory process. Rupture exposes collagen and other thrombogenic material, which activates platelets and the coagulation cascade, resulting in an acute thrombus, which interrupts coronary blood flow and causes some degree of myocardial ischemia. The consequences of acute ischemia, collectively referred to as acute coronary syndromes (ACS), depend on the location and degree of obstruction and range from unstable angina to transmural infarction.

**Coronary artery spasm** is a transient, focal increase in vascular tone, markedly narrowing the lumen and reducing blood flow; symptomatic ischemia (variant angina—see p. 2098) may result. Marked narrowing can trigger thrombus formation, causing infarction or life-threatening arrhythmia. Spasm can occur in arteries with or without atheroma. In arteries without atheroma, basal coronary artery tone is probably increased, and response to vasoconstricting stimuli is probably exaggerated. The exact mechanism is unclear but may involve abnormalities of nitric oxide production or an imbalance between endothelium-derived contracting and relaxing factors. In arteries with atheroma, the atheroma may cause local hypercontractility; proposed mechanisms include loss of sensitivity to intrinsic vasodilators (eg, acetylcholine) and increased production of vasoconstrictors (eg, angiotensin II, endothelin, leukotrienes, serotonin, thromboxane) in the area of the atheroma. Recurrent spasm may damage the intima, leading to atheroma formation. Use of vasoconstricting drugs (eg, cocaine, nicotine) and emotional stress also can trigger coronary spasm.

**Risk Factors**

Risk factors for CAD are the same as those for atherosclerosis: high blood levels of low-density lipoprotein (LDL) cholesterol and lipoprotein a, low blood levels of high-density lipoprotein (HDL) cholesterol, diabetes mellitus (particularly type 2), smoking, obesity, and physical inactivity. Smoking may
be a stronger predictor of MI in women (especially those < 45). Genetic factors play a role, and several systemic disorders (eg, hypertension, hypothyroidism) and metabolic disorders (eg, hyperhomocysteinemia) contribute to risk. A high level of apoprotein B (apo B) is an important risk factor; it may identify increased risk when total cholesterol or LDL level is normal.

High blood levels of C-reactive protein indicate plaque instability and inflammation and may be a stronger predictor of risk of ischemic events than high levels of LDL. High blood levels of triglycerides and insulin (reflecting insulin resistance) may be risk factors, but data are less clear. CAD risk is increased by smoking; a diet high in fat and calories and low in phytochemicals (found in fruits and vegetables), fiber, and vitamins C and E; a diet relatively low in ω-3 (n-3) polyunsaturated fatty acids (PUFAs), at least in some people; and poor stress management.

Anatomy

The right and left coronary arteries arise from the right and left coronary sinuses in the root of the aorta just above the aortic valve orifice. The coronary arteries divide into large and medium-sized arteries that run along the heart's surface (epicardial coronary arteries) and subsequently send smaller arterioles into the myocardium. The left coronary artery begins as the left main artery and quickly divides into the left anterior descending (LAD) and circumflex arteries. The LAD artery usually follows the anterior interventricular groove and, in some people, continues over the apex. This artery supplies the anterior septum (including the proximal conduction system) and the anterior free wall of the left ventricle (LV). The circumflex artery, which is usually smaller than the LAD artery, supplies the lateral LV free wall. Most people have right dominance: The right coronary artery passes along the atrioventricular (AV) groove over the right side of the heart; it supplies the sinus node (in 55%), right ventricle, and usually the AV node and inferior myocardial wall. About 10 to 15% of people have left dominance: The circumflex artery is larger and continues along the posterior AV groove to supply the posterior wall and AV node.

Treatment

• Percutaneous coronary intervention

• For acute thrombosis, sometimes fibrinolytic drugs

• Coronary artery bypass grafting

Treatment generally aims to reduce cardiac workload, improve coronary artery blood flow, and, over the long term, halt and reverse the atherosclerotic process. Coronary blood flow can be improved by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). An acute coronary thrombosis may sometimes be dissolved by fibrinolytic drugs (see p. 2110).

PCI: At first, PCI was done with balloon angioplasty alone. However, roughly 50% of patients developed restenosis within 6 mo, and 1 in 3 ultimately required repeat angioplasty or CABG. Insertion of a bare-metal stent following angioplasty reduced the rate of restenosis, but many patients still required repeat treatment. Drug-eluting stents, which secrete an antiproliferative drug (eg, sirolimus, paclitaxel) over a period of several weeks, have reduced the rate of restenosis to about 10%. Now, most PCI is done with stents, and about three fourths of all stents used in the US are drug-eluting stents. With the recent controversy over drug-eluting stents and abrupt restenosis, use of the new drug-eluting stents appears to be decreasing in most centers. Patients with acute stenoses (ie, with unstable angina or acute MI) seem to do better with bare-metal stents. Patients without significant infarct or complications may quickly return to work and usual activities, but strenuous activities should be avoided for 6 wk.

In-stent thrombosis occurs because of the inherent thrombogenicity of metallic stents. Most cases occur within the first 24 to 48 h. However, late stent thrombosis, occurring after 30 days and as late as ≥ 1 yr, can occur with both bare-metal and drug-eluting stents, especially after cessation of antiplatelet therapy. Progressive endothelialization of the bare-metal stent occurs within the first few months and reduces the risk of thrombosis. However, the antiproliferative drugs secreted by drug-eluting stents inhibit this process and prolong the risk of thrombosis. Thus, patients who undergo stent placement are treated with various antiplatelet drugs and anticoagulants (see p. 2109). The current standard regimen for patients with a
bare-metal or drug-eluting stent consists of aspirin given indefinitely, either clopidogrel or prasugrel for at least 12 mo, and intraprocedural anticoagulation with heparin or a similar agent (eg, bivalirudin, particularly those at high risk of bleeding). Glycoprotein IIb/IIIa inhibitors are no longer routinely used in stable patients (ie, no comorbidities, no acute coronary syndrome) having elective stent placement. Although controversial, they may be beneficial in some patients with an acute coronary syndrome but should not be considered routine. It is unclear whether it is beneficial to give glycoprotein IIb/IIIa inhibitors before arrival in the cardiac catheterization laboratory. After stent insertion, a HMG-CoA reductase inhibitor (statin) is added if one is not already being used.

Overall risk of PCI is comparable with that for CABG. Mortality rate is 1 to 3%; MI rate is 3 to 5%. In < 3%, intimal dissection causes obstruction requiring emergency CABG.

CABG: CABG uses sections of autologous veins (eg, saphenous) or, preferably, arteries (eg, internal mammary, radial) to bypass diseased segments. At 1 yr, about 85% of venous bypass grafts are patent, but after 10 yr, as many as 97% of internal mammary artery grafts are patent. Arteries also hypertrophy to accommodate increased flow.

CABG is typically done during cardiopulmonary bypass with the heart stopped; a bypass machine pumps and oxygenates blood. Risks of the procedure include stroke and MI. For patients with a normal-sized heart, no history of MI, good ventricular function, and no additional risk factors, risk is < 5% for perioperative MI, 2 to 3% for stroke, and ≤ 1% for mortality; risk increases with age and presence of underlying disease. Operative mortality rate is 3 to 5 times higher for a second bypass than for the first; thus, timing of the first bypass should be optimal.

After cardiopulmonary bypass, about 25 to 30% of patients develop cognitive dysfunction, possibly caused by microemboli originating in the bypass machine. Dysfunction ranges from mild to severe and may persist for weeks to years. To minimize this risk, some centers use a beating heart technique (ie, no cardiopulmonary bypass), in which a device mechanically stabilizes the part of the heart upon which the surgeon is working.

CAD may progress despite bypass surgery. Postoperatively, the rate of proximal obstruction of bypassed vessels increases. Vein grafts become obstructed early if thrombi form and later (several years) if atherosclerosis causes slow degeneration of the intima and media. Aspirin prolongs vein graft patency. Continued smoking has a profound adverse effect on patency.

Prevention

Prevention of CAD involves modifying atherosclerosis risk factors (see p. 2084): smoking cessation, weight loss, a healthful diet, regular exercise, modification of serum lipid levels, and control of hypertension and diabetes. Antihypertensives should be used to achieve a goal blood pressure of < 130/80 mm Hg. Modification of serum lipid levels (particularly with statins) may slow or even partially reverse the progression of CAD. LDL targets are < 100 mg/dL (< 2.59 mmol/L) for patients with known CAD or 70 to 80 mg/dL (1.81 to 2.07 mmol/L) for those with a history of an ischemic event. Nicotinic acid or a fibrate should be added for patients with an HDL < 40 mg/dL (< 1.03 mmol/L).

Angina Pectoris

Angina pectoris is a clinical syndrome of precordial discomfort or pressure due to transient myocardial ischemia without infarction. It is typically precipitated by exertion or psychologic stress and relieved by rest or sublingual nitroglycerin. Diagnosis is by symptoms, ECG, and myocardial imaging. Treatment may include nitrates, β-blockers, Ca channel blockers, and coronary angioplasty or coronary artery bypass graft surgery.

Etiology

Angina pectoris occurs when cardiac workload and resultant myocardial O₂ demand exceed the ability of coronary arteries to supply an adequate amount of oxygenated blood, as can occur when the arteries are narrowed. Narrowing usually results from atherosclerosis but may result from coronary artery spasm or,
rarely, coronary artery embolism. Acute coronary thrombosis can cause angina if obstruction is partial or transient, but it usually causes MI.

Because myocardial O$_2$ demand is determined mainly by heart rate, systolic wall tension, and contractility, narrowing of a coronary artery typically results in angina that occurs during exertion and is relieved by rest.

In addition to exertion, cardiac workload can be increased by disorders such as hypertension, aortic stenosis, aortic regurgitation, or hypertrophic cardiomyopathy. In such cases, angina can result whether atherosclerosis is present or not. These disorders can also decrease relative myocardial perfusion because myocardial mass is increased (causing decreased diastolic flow).

A decreased O$_2$ supply, as in severe anemia or hypoxia, can precipitate or aggravate angina.

Pathophysiology

In stable angina, the relationship between workload or demand and ischemia is usually relatively predictable. However, atherosclerotic arterial narrowing is not entirely fixed; it varies with the normal fluctuations in arterial tone that occur in all people. Thus, more people have angina in the morning, when arterial tone is relatively high. Also, abnormal endothelial function may contribute to variations in arterial tone; eg, in endothelium damaged by atheromas, stress of a catecholamine surge causes vasoconstriction rather than dilation (normal response).

As the myocardium becomes ischemic, coronary sinus blood pH falls, cellular K is lost, lactate accumulates, ECG abnormalities appear, and ventricular function deteriorates. Left ventricular (LV) diastolic pressure usually increases during angina, sometimes inducing pulmonary congestion and dyspnea. The exact mechanism by which ischemia causes discomfort is unclear but may involve nerve stimulation by hypoxic metabolites.

Symptoms and Signs

Angina may be a vague, barely troublesome ache or may rapidly become a severe, intense precordial crushing sensation. It is rarely described as pain. Discomfort is most commonly felt beneath the sternum, although location varies. Discomfort may radiate to the left shoulder and down the inside of the left arm, even to the fingers; straight through to the back; into the throat, jaws, and teeth; and, occasionally, down the inside of the right arm. It may also be felt in the upper abdomen. The discomfort of angina is never above the ears or below the umbilicus.

Some patients have atypical angina (eg, bloating, gas, abdominal distress), often ascribing symptoms to indigestion; belching may even seem to relieve the symptoms. Others have dyspnea due to the sharp, reversible increase in LV filling pressure that often accompanies ischemia. Frequently, the patient's description is imprecise, and whether the problem is angina, dyspnea, or both may be difficult to determine. Because ischemic symptoms require a minute or more to resolve, brief, fleeting sensations rarely represent angina.

Between and even during attacks of angina, physical findings may be normal. However, during the attack, heart rate may increase modestly, BP is often elevated, heart sounds become more distant, and the apical impulse is more diffuse. The 2nd heart sound may become paradoxical because LV ejection is more prolonged during an ischemic attack. A 4th heart sound is common, and a 3rd heart sound may develop. A mid or late systolic apical murmur shrill—or blowing but not especially loud—may occur if ischemia causes localized papillary muscle dysfunction, causing mitral regurgitation.

Angina pectoris is typically triggered by exertion or strong emotion, usually persists no more than a few minutes, and subsides with rest. Response to exertion is usually predictable, but in some patients, exercise that is tolerated one day may precipitate angina the next because of variations in arterial tone. Symptoms are exaggerated when exertion follows a meal or occurs in cold weather; walking into the wind or first contact with cold air after leaving a warm room may precipitate an attack. Symptom severity is often classified by the degree of exertion resulting in angina (see
Attacks may vary from several a day to symptom-free intervals of weeks, months, or years. They may increase in frequency (called crescendo angina) to a fatal outcome or gradually decrease or disappear if adequate collateral coronary circulation develops, if the ischemic area infarcts, or if heart failure or intermittent claudication supervenes and limits activity.

Nocturnal angina may occur if a dream causes striking changes in respiration, pulse rate, and BP. Nocturnal angina may also be a sign of recurrent LV failure, an equivalent of nocturnal dyspnea. The recumbent position increases venous return, stretching the myocardium and increasing wall stress, which increases \( O_2 \) demand.

Angina may occur spontaneously during rest (called angina decubitus). It is usually accompanied by a modestly increased heart rate and a sometimes markedly higher BP, which increase \( O_2 \) demand. These increases may be the cause of rest angina or the result of ischemia induced by plaque rupture and thrombus formation. If angina is not relieved, unmet myocardial \( O_2 \) demand increases further, making MI more likely.

**Unstable angina:** Because angina characteristics are usually predictable for a given patient, any changes (ie, rest angina, new-onset angina, increasing angina) should be considered serious. Such changes are termed unstable angina and require prompt evaluation and treatment.

Unstable angina is classified based on severity and clinical situation (see Table 210-2). Also considered are whether unstable angina occurs during treatment for chronic stable angina and whether transient changes in ST-T waves occur during angina. If angina has occurred within 48 h and no contributory extracardiac condition is present, troponin levels may be measured to help estimate prognosis; troponin-negative indicates a better prognosis than troponin-positive.

**Diagnosis**

- Typical symptoms
- ECG
- Stress testing with ECG or imaging (echocardiographic or nuclear)
- Coronary angiography for significant symptoms or positive stress test

Diagnosis is suspected if chest discomfort is typical and is precipitated by exertion and relieved by rest. Patients whose chest discomfort lasts > 20 min or occurs during rest or who have syncope or heart failure are evaluated for an acute coronary syndrome (see p. 2099). Chest discomfort may also be caused by GI disorders (eg, reflux, esophageal spasm, indigestion, cholelithiasis), costochondritis, anxiety, panic attacks, hyperventilation, and other cardiac disorders (eg, pericarditis, mitral valve prolapse, supraventricular tachycardia, atrial fibrillation), even when coronary blood flow is not compromised (see p. 2025).

**ECG:** If typical exertional symptoms are present, ECG is indicated. Because angina resolves quickly with rest, ECG rarely can be done during an attack except during stress testing. If done during an attack, ECG is likely to show reversible ischemic changes: T wave discordant to the QRS vector, ST-segment depression (typically), ST-segment elevation, decreased R-wave height, intraventricular or bundle branch conduction disturbances, and arrhythmia (usually ventricular extrasystoles). Between attacks, the ECG (and usually LV function) at rest is normal.

[Table 210-2. Braunwald Classification of Unstable Angina*]
in about 30% of patients with a typical history of angina pectoris, even those with extensive 3-vessel disease. In the remaining 70%, the ECG shows evidence of previous infarction, hypertrophy, or nonspecific ST-segment and T-wave (ST-T) abnormalities. An abnormal resting ECG alone does not establish or refute the diagnosis.

**Stress testing:** More specific tests include stress testing with ECG or with myocardial imaging (eg, echocardiography, radionuclide imaging) and coronary angiography. Further testing is needed to confirm the diagnosis, evaluate disease severity, determine appropriate exercise levels for the patient, and help predict prognosis.

Noninvasive tests are considered first. For coronary artery disease (CAD), the most accurate are stress echocardiography and myocardial perfusion imaging with single-photon emission CT (SPECT) or PET. However, these tests are more expensive than simple stress testing with ECG.

If a patient has a normal resting ECG and can exercise, exercise stress testing with ECG is done. In men with chest discomfort suggesting angina, stress ECG testing has a specificity of 70%; sensitivity is 90%. Sensitivity is similar in women, but specificity is lower, particularly in women < 55 (< 70%). However, women are more likely than men to have an abnormal resting ECG when CAD is present (32% vs 23%). Although sensitivity is reasonably high, exercise ECG can miss severe CAD (even left main or 3-vessel disease). In patients with atypical symptoms, a negative stress ECG usually rules out angina pectoris and CAD; a positive result may or may not represent coronary ischemia and indicates need for further testing.

When the resting ECG is abnormal, false-positive ST-segment shifts are common on the stress ECG, so patients should have stress testing with myocardial imaging. Exercise or pharmacologic stress (eg, with dobutamine or dipyridamole infusion) may be used. The choice of imaging technique depends on institutional availability and expertise. Imaging tests can help assess LV function and response to stress; identify areas of ischemia, infarction, and viable tissue; and determine the site and extent of myocardium at risk. Stress echocardiography can also detect ischemia-induced mitral regurgitation.

**Angiography:** Coronary angiography (see also p. 2049) is the standard for diagnosing CAD but is not always necessary to confirm the diagnosis. It is indicated primarily to locate and assess severity of coronary artery lesions when revascularization (percutaneous intervention [PCI] or coronary artery bypass grafting [CABG]) is being considered. Angiography may also be indicated when knowledge of coronary anatomy is necessary to advise about work or lifestyle needs (eg, discontinuing job or sports activities). Obstruction is assumed to be physiologically significant when the luminal diameter is reduced > 70%. This reduction correlates well with the presence of angina pectoris unless spasm or thrombosis is superimposed.

Intravascular ultrasonography provides images of coronary artery structure. An ultrasound probe on the tip of a catheter is inserted in the coronary arteries during angiography. This test can provide more information about coronary anatomy than other tests; it is indicated when the nature of lesions is unclear or when apparent disease severity does not match symptom severity. Used with angioplasty, it can help ensure optimal placement of stents.

**Imaging:** Electron beam CT can detect the amount of Ca present in coronary artery plaque. The Ca score (from 1 to 100) is roughly proportional to the risk of subsequent coronary events. However, because Ca may be present in the absence of significant stenosis, the score does not correlate well with the need for angioplasty or CABG. Thus, the American Heart Association recommends that screening with electron beam CT should be done only for select groups of patients and is most valuable when combined with historical and clinical data to estimate risk of death or nonfatal MI. These groups may include asymptomatic patients with an intermediate Framingham 10-yr risk estimate of 10 to 20% and symptomatic patients with equivocal stress test results.

Multidetector row CT (MDRCT) coronary angiography can accurately identify coronary stenosis and has a number of advantages. The test is noninvasive, can exclude coronary stenosis with high accuracy, can establish stent or bypass graft patency, can visualize cardiac and coronary venous anatomy, and can assess calcified and noncalcified plaque burden. However, radiation exposure is significant, and the test is not suitable for patients with a heart rate of > 65 beats/min, those with irregular heart beats, and
pregnant women. Patients must also be able to hold their breath for 15 to 20 sec, 3 to 4 times during the study.

Evolving indications for MDRCT coronary angiography include

- Asymptomatic high-risk patients or patients with atypical or typical angina who have inconclusive exercise stress test results, cannot undergo exercise stress testing, or need to undergo major noncardiac surgery

- Patients in whom invasive coronary angiography was unable to locate a major coronary artery or graft

Cardiac MRI has become invaluable in evaluating many cardiac and great vessel abnormalities. It may be used to evaluate CAD by several techniques, which enable direct visualization of coronary stenosis, assessment of flow in the coronary arteries, evaluation of myocardial perfusion and metabolism, evaluation of wall motion abnormalities during stress, and assessment of infarcted myocardium vs viable myocardium.

Current indications for cardiac MRI include evaluation of cardiac structure and function, assessment of myocardial viability, and possibly diagnosis and risk assessment of patients with either known or suspected CAD.

**Prognosis**

The main adverse outcomes are unstable angina, MI, and sudden death due to arrhythmias. Annual mortality rate is about 1.4% in patients with angina, no history of MI, a normal resting ECG, and normal BP. However, women with CAD tend to have a worse prognosis. Mortality rate is about 7.5% when systolic hypertension is present, 8.4% when the ECG is abnormal, and 12% when both are present. Type 2 diabetes about doubles the mortality rate for each scenario.

Prognosis worsens with increasing age, increasingly severe anginal symptoms, presence of anatomic lesions, and poor ventricular function. Lesions in the left main coronary artery or proximal left anterior descending artery indicate particularly high risk. Although prognosis correlates with number and severity of coronary arteries affected, prognosis is surprisingly good for patients with stable angina, even those with 3-vessel disease, if ventricular function is normal.

**Treatment**

- Modification of risk factors (smoking, BP, lipids)
- Antiplatelet drugs (aspirin plus clopidogrel)
- β-Blockers
- Nitroglycerin and Ca channel blockers for symptom control
- Revascularization if symptoms persist despite medical therapy
- ACE inhibitors and statins

Reversible risk factors are modified as much as possible (see also p. 2084). Smokers should stop smoking; ≥ 2 yr after stopping smoking, risk of MI is reduced to that of people who never smoked. Hypertension is treated diligently because even mild hypertension increases cardiac workload. Weight loss alone often reduces the severity of angina. Sometimes treatment of mild LV failure markedly lessens angina. Paradoxically, digitalis occasionally intensifies angina, presumably because increased myocardial contractility increases O₂ demand, arterial tone is increased, or both. Aggressive reduction of total and LDL cholesterol (via diet plus drugs as necessary) slows the progression of CAD, may cause some lesions to regress (see p. 896), and improves endothelial function and thus arterial response to stress. An exercise program emphasizing walking often improves the sense of well-being, reduces CAD risk, and
improves exercise tolerance.

**Drugs:** The main goals are to relieve acute symptoms, prevent or reduce ischemia (see Table 210-3), and prevent future ischemic events. For an acute attack, sublingual nitroglycerin is the most effective drug.

To prevent ischemia, all patients diagnosed with CAD or at high risk of developing CAD should take an antiplatelet drug daily. β-Blockers, unless contraindicated or not tolerated, are given to most patients. For some patients, prevention of symptoms requires Ca channel blockers or long-acting nitrates.

**Antiplatelet drugs** inhibit platelet aggregation. Aspirin binds irreversibly to platelets and inhibits cyclooxygenase and platelet aggregation. Clopidogrel blocks adenosine diphosphate-induced platelet aggregation. Either drug can reduce risk of ischemic events (MI, sudden death), but the drugs are most effective when given together. Patients unable to tolerate one should receive the other drug alone.

**β-Blockers** limit symptoms and prevent infarction and sudden death better than other drugs. β-Blockers block sympathetic stimulation of the heart and reduce systolic BP, heart rate, contractility, and cardiac output, thus decreasing myocardial O₂ demand and increasing exercise tolerance. They also increase the threshold for ventricular fibrillation. Most patients tolerate these drugs well. Many β-blockers are available and effective. Dose is titrated upward as needed until limited by bradycardia or adverse effects. Patients who cannot tolerate β-blockers are given a Ca channel blocker with negative chronotropic effects (eg, diltiazem, verapamil). Those at risk of β-blocker intolerance (eg, those with asthma) may be tried on a cardioselective β-blocker (eg, carvedilol), perhaps with pulmonary function testing before and after drug administration to detect drug-induced bronchospasm.

**Nitroglycerin** is a potent smooth-muscle relaxant and vasodilator. Its main sites of action are in the peripheral vascular tree, especially in the venous or capacitance system, and in coronary blood vessels. Even severely atherosclerotic vessels may dilate in areas without atheroma. Nitroglycerin lowers systolic BP and dilates systemic veins, thus reducing myocardial wall tension, a major determinant of myocardial O₂ need. Sublingual nitroglycerin is given for an acute attack or for prevention before exertion. Dramatic relief usually occurs within 1.5 to 3 min, is complete by about 5 min, and lasts up to 30 min. The dose may be repeated every 4 to 5 min up to 3 times if relief is incomplete. Patients should always carry nitroglycerin tablets or aerosol spray to use promptly at the onset of an angina attack. Patients should store tablets in a tightly sealed, light-resistant glass container, so that potency is not lost. Because the drug deteriorates quickly, small amounts should be obtained frequently.

**Long-acting nitrates** (oral or transdermal) are used if symptoms persist after the β-blocker dose is maximized. If angina occurs at predictable times, a nitrate is given to cover those times. Oral nitrates include isosorbide dinitrate and mononitrate (the active metabolite of the dinitrate). They are effective within 1 to 2 h; their effect lasts 4 to 6 h. Sustained-release formulations of isosorbide mononitrate appear to be effective throughout the day. For transdermal use, cutaneous nitroglycerin patches have largely replaced nitroglycerin ointments primarily because ointments are inconvenient and messy. Patches slowly release the drug for a prolonged effect; exercise capacity improves 4 h after patch application and wanes in 18 to 24 h. Nitrate tolerance may occur, especially when plasma concentrations are kept constant. Because MI risk is highest in early morning, an afternoon or early evening respite period from nitrates is reasonable unless a patient commonly has angina at that time. For nitroglycerin, an 8- to 10-h respite period seems sufficient. Isosorbide may require a 12-h respite period. If given once/day, sustained-release isosorbide mononitrate does not appear to elicit tolerance.

**Ca channel blockers** may be used if symptoms persist despite use of nitrates or if nitrates are not tolerated. Ca channel blockers are particularly useful if hypertension or coronary spasm is also present. Different types of Ca channel blockers have different effects. Dihydropyridines (eg, nifedipine, amlodipine, felodipine) have no chronotropic effects and vary substantially in their negative inotropic effects. Shorter-acting dihydropyridines may cause reflex tachycardia and are associated with increased mortality in CAD patients; they should not be used to treat stable angina.

[Table 210-3, Drugs for Coronary Artery Disease]
Longer-acting formulations of dihydropyridines have fewer tachycardic effects; they are most commonly used with a β-blocker. In this group, amlodipine has the weakest negative inotropic effects; it may be used in patients with LV systolic dysfunction. Diltiazem and verapamil, other types of Ca channel blockers, have negative chronotropic and inotropic effects. They can be used alone in patients with β-blocker intolerance or asthma and normal LV systolic function but may increase cardiovascular mortality in patients with LV systolic dysfunction.

**Revascularization:** Revascularization, either with PCI (eg, angioplasty, stenting) or CABG should be considered if angina persists despite drug therapy and worsens quality of life or if anatomic lesions (noted during angiography) put a patient at high risk of mortality. The choice between PCI and CABG depends on extent and location of anatomic lesions, the experience of the surgeon and medical center, and, to some extent, patient preference.

PCI is usually preferred for 1- or 2-vessel disease with suitable anatomic lesions. Lesions that are long or near bifurcation points are often not amenable to PCI. However, as stent technology improves, PCI is being used for more complicated cases.

CABG is very effective in selected patients with angina. The ideal candidate has severe angina pectoris and localized disease, or diabetes mellitus. About 85% of patients have complete or dramatic symptom relief. Exercise stress testing shows positive correlation between graft patency and improved exercise tolerance, but exercise tolerance sometimes remains improved despite graft closure.

CABG improves survival for patients with left main disease, those with 3-vessel disease and poor LV function, and some patients with 2-vessel disease. However, for patients with mild or moderate angina (class I or II) or 3-vessel disease and good ventricular function, CABG appears to only marginally improve survival. For patients with 1-vessel disease, outcomes with drug therapy, PCI, and CABG are similar; exceptions are left main disease and proximal left anterior descending disease, for which revascularization appears advantageous.

**Variant Angina**

**Variant angina is angina pectoris secondary to epicardial coronary artery spasm (Prinzmetal’s angina).**

Most patients with variant angina have significant fixed proximal obstruction of at least one major coronary artery. Spasm usually occurs within 1 cm of the obstruction (often accompanied by ventricular arrhythmia).

Symptoms are anginal discomfort occurring mainly during rest, often at night, and only rarely and inconsistently during exertion (unless significant coronary artery obstruction is also present). Attacks tend to occur regularly at certain times of day.

Diagnosis is suspected if ST-segment elevation occurs during the attack. Between anginal attacks, the ECG may be normal or show a stable abnormal pattern. Confirmation is by provocative testing with ergonovine or acetylcholine, which may precipitate coronary artery spasm, identified by significant ST-segment elevation or by observation of a reversible spasm during cardiac catheterization. Testing is done most commonly in a cardiac catheterization laboratory and occasionally in a coronary care unit.

Average survival at 5 yr is 89 to 97%, but mortality risk is greater for patients with both variant angina and atherosclerotic coronary artery obstruction. Usually, sublingual nitroglycerin promptly relieves variant angina. Ca channel blockers may effectively prevent symptoms. Theoretically, β-blockers may exacerbate spasm by allowing unopposed α-adrenergic vasoconstriction, but this effect has not been proved clinically. Oral drugs most commonly used are sustained-release diltiazem 120 to 540 mg once/day, sustained-release verapamil 120 to 480 mg once/day (dose must be reduced in patients with renal or hepatic dysfunction), or amlodipine 15 to 20 mg once/day (dose must be reduced in elderly patients and patients with hepatic dysfunction). In refractory cases, amiodarone may be useful. Although these drugs relieve symptoms, they do not appear to alter prognosis.
Syndrome X

Syndrome X is cardiac microvascular dysfunction or constriction causing angina (microvascular angina).

Some patients with typical angina that is relieved by rest or nitroglycerin have normal coronary arteriograms (eg, no atherosclerosis, embolism, or inducible arterial spasm). Some of these patients have ischemia detected during stress testing; others do not. In some patients, the cause of ischemia seems to be reflex intramyocardial coronary constriction and reduced coronary flow reserve. Other patients have microvascular dysfunction within the myocardium: The abnormal vessels do not dilate in response to exercise or other cardiovascular stressors; sensitivity to cardiac pain may also be increased. Prognosis is good, although symptoms of ischemia may recur for years. In many patients, β-blockers relieve symptoms. This disorder should not be confused with variant angina due to epicardial coronary spasm or with another disorder called syndrome X, which refers to the metabolic syndrome (see p. 64).

Silent Ischemia

Patients with CAD (particularly diabetics) may have ischemia without symptoms. Ischemia is evidenced by transient asymptomatic ST-T abnormalities seen during 24-h Holter monitoring. Radionuclide studies can sometimes document asymptomatic myocardial ischemia during physical or mental stress (eg, mental arithmetic). Silent ischemia and angina pectoris may coexist, occurring at different times. Prognosis depends on severity of CAD.

Acute Coronary Syndromes

(Unstable Angina; Acute MI)

Acute coronary syndromes (ACS) result from acute obstruction of a coronary artery. Consequences depend on degree and location of obstruction and range from unstable angina to non-ST-segment elevation MI (NSTEMI), ST-segment elevation MI (STEMI), and sudden cardiac death. Symptoms are similar in each of these syndromes (except sudden death) and include chest discomfort with or without dyspnea, nausea, and diaphoresis. Diagnosis is by ECG and the presence or absence of serologic markers. Treatment is antiplatelet drugs, anticoagulants, nitrates, β-blockers, and, for STEMI, emergency reperfusion via fibrinolytic drugs, percutaneous intervention, or, occasionally, coronary artery bypass graft surgery.

In the US, about 1.5 million MIs occur annually. MI results in death for 400,000 to 500,000 people, with about half dying before they reach the hospital (see Cardiac Arrest on p. 2255).

Etiology

These syndromes usually occur when an acute thrombus forms in an atherosclerotic coronary artery. Atheromatous plaque sometimes becomes unstable or inflamed, causing it to rupture or split, exposing thrombogenic material, which activates platelets and the coagulation cascade and produces an acute thrombus. Platelet activation involves a conformational change in membrane glycoprotein (GP) IIb/IIIa receptors, allowing cross-linking (and thus aggregation) of platelets. Even atheromas causing minimal obstruction can rupture and result in thrombosis; in > 50% of cases, stenosis is < 40%. The resultant thrombus abruptly interferes with blood flow to parts of the myocardium. Spontaneous thrombolysis occurs in about two thirds of patients; 24 h later, thrombotic obstruction is found in only about 30%. However, in virtually all cases, obstruction lasts long enough to cause tissue necrosis.

Rarely, these syndromes are caused by arterial embolism (eg, in mitral or aortic stenosis, infective endocarditis, or marantic endocarditis). Cocaine use and other causes of coronary spasm can sometimes result in MI. Spasm-induced MI may occur in normal or atherosclerotic coronary arteries.

Pathophysiology

Initial consequences vary with size, location, and duration of obstruction and range from transient
ischemia to infarction. Measurement of newer, more sensitive markers indicates that some cell necrosis probably occurs even in mild forms; thus, ischemic events occur on a continuum, and classification into subgroups, although useful, is somewhat arbitrary. Sequelae of the acute event depend primarily on the mass and type of cardiac tissue infarcted.

**Myocardial dysfunction**: Ischemic (but not infarcted) tissue has impaired contractility, resulting in hypokinetic or akinetic segments; these segments may expand or bulge during systole (called paradoxical motion). The size of the affected area determines effects, which range from minimal to mild heart failure to cardiogenic shock. Some degree of heart failure occurs in about two thirds of hospitalized patients with acute MI. It is termed ischemic cardiomyopathy if low cardiac output and heart failure persist. Ischemia involving the papillary muscle may lead to mitral valve regurgitation.

**MI**: MI is myocardial necrosis resulting from abrupt reduction in coronary blood flow to part of the myocardium. Infarcted tissue is permanently dysfunctional; however, there is a zone of potentially reversible ischemia adjacent to infarcted tissue.

MI affects predominantly the left ventricle (LV), but damage may extend into the right ventricle (RV) or the atria. RV infarction usually results from obstruction of the right coronary or a dominant left circumflex artery; it is characterized by high RV filling pressure, often with severe tricuspid regurgitation and reduced cardiac output. An inferoposterior infarction causes some degree of RV dysfunction in about half of patients and causes hemodynamic abnormality in 10 to 15%. RV dysfunction should be considered in any patient who has inferoposterior infarction and elevated jugular venous pressure with hypotension or shock. RV infarction complicating LV infarction may significantly increase mortality risk.

Anterior infarcts tend to be larger and result in a worse prognosis than inferoposterior infarcts. They are usually due to left coronary artery obstruction, especially in the anterior descending artery; inferoposterior infarcts reflect right coronary or dominant left circumflex artery obstruction.

Transmural infarcts involve the whole thickness of myocardium from epicardium to endocardium and are usually characterized by abnormal Q waves on ECG. Nontransmural or subendocardial infarcts do not extend through the ventricular wall and cause only ST-segment and T-wave (ST-T) abnormalities. Subendocardial infarcts usually involve the inner one third of myocardium, where wall tension is highest and myocardial blood flow is most vulnerable to circulatory changes. These infarcts may follow prolonged hypotension. Because the transmural depth of necrosis cannot be precisely determined clinically, infarcts are usually classified by the presence or absence of ST-segment elevation or Q waves on the ECG. Volume of myocardium destroyed can be roughly estimated by the extent and duration of CK elevation.

**Electrical dysfunction**: Ischemic and necrotic cells are incapable of normal electrical activity, resulting in various ECG changes (predominantly ST-T abnormalities), arrhythmias, and conduction disturbances. ST-T abnormalities of ischemia include ST-segment depression (often downsloping from the J point), T-wave inversion, ST-segment elevation (often referred to as injury current), and peaked T waves in the hyperacute phase of infarction. Conduction disturbances can reflect damage to the sinus node, the atrioventricular (AV) node, or specialized conduction tissues. Most changes are transient; some are permanent.

**Classification**

Classification is based on ECG changes and presence or absence of cardiac markers in blood. Distinguishing NSTEMI and STEMI is useful because prognosis and treatment are different.

**Unstable angina** (acute coronary insufficiency, preinfarction angina, intermediate syndrome) is defined as:

- Rest angina that is prolonged (usually > 20 min)

- New-onset angina of at least class III severity in the Canadian Cardiovascular Society (CCS) classification (see Table 210-1)
• Increasing angina, i.e., previously diagnosed angina that has become distinctly more frequent, more severe, longer in duration, or lower in threshold (e.g., increased by ≥ 1 CCS class or to at least CCS class III)

Also, ECG changes such as ST-segment depression, ST-segment elevation, or T-wave inversion may occur during unstable angina but are transient. Of cardiac markers, CK is not elevated but troponin I or T may be slightly increased. Unstable angina is clinically unstable and often a prelude to MI or arrhythmias or, less commonly, to sudden death.

Non-ST-segment elevation MI (NSTEMI, subendocardial MI) is myocardial necrosis (evidenced by cardiac markers in blood; troponin I or T and CK will be elevated) without acute ST-segment elevation or Q waves. ECG changes such as ST-segment depression, T-wave inversion, or both may be present.

ST-segment elevation MI (STEMI, transmural MI) is myocardial necrosis with ECG changes showing ST-segment elevation that is not quickly reversed by nitroglycerin or showing new left bundle branch block. Q waves may be present. Both troponin and CK are elevated.

Symptoms and Signs

Symptoms of ACS depend somewhat on the extent and location of obstruction and are quite variable. Except when infarction is massive, recognizing the amount of ischemia by symptoms alone is difficult.

After the acute event, many complications can occur. They usually involve electrical dysfunction (e.g., conduction defects, arrhythmias), myocardial dysfunction (e.g., heart failure, interventricular septum or free wall rupture, ventricular aneurysm, pseudoaneurysm, mural thrombus formation, cardiogenic shock), or valvular dysfunction (typically mitral regurgitation). Electrical dysfunction can be significant in any form of ACS, but usually, large parts of myocardium must be ischemic to cause significant myocardial dysfunction. Other complications of ACS include recurrent ischemia and pericarditis. Pericarditis that occurs 2 to 10 wk after an MI is known as post-MI syndrome or Dressler’s syndrome.

Unstable angina: Symptoms are those of angina pectoris (see p. 2090), except that the pain or discomfort of unstable angina usually is more intense, lasts longer, is precipitated by less exertion, occurs spontaneously at rest (as angina decubitus), is progressive (crescendo) in nature, or involves any combination of these features.

NSTEMI and STEMI: Symptoms of NSTEMI and STEMI are the same. Days to weeks before the event, about two thirds of patients experience prodromal symptoms, including unstable or crescendo angina, shortness of breath, and fatigue. Usually, the first symptom of infarction is deep, substernal, visceral pain described as aching or pressure, often radiating to the back, jaw, left arm, right arm, shoulders, or all of these areas. The pain is similar to angina pectoris but is usually more severe and long-lasting; more often accompanied by dyspnea, diaphoresis, nausea, and vomiting; and relieved little or only temporarily by rest or nitroglycerin. However, discomfort may be mild; about 20% of acute MIs are silent (i.e., asymptomatic or causing vague symptoms not recognized as illness by the patient), more commonly in diabetics. Some patients present with syncope. Patients often interpret their discomfort as indigestion, particularly because spontaneous relief may be falsely attributed to belching or antacid consumption. Women are more likely to present with atypical chest discomfort. Elderly patients may report dyspnea more than ischemic-type chest pain. In severe ischemic episodes, the patient often has significant pain and feels restless and apprehensive. Nausea and vomiting may occur, especially with inferior MI. Dyspnea and weakness due to LV failure, pulmonary edema, shock, or significant arrhythmia may dominate.

Skin may be pale, cool, and diaphoretic. Peripheral or central cyanosis may be present. Pulse may be thready, and BP is variable, although many patients initially have some degree of hypertension during pain.

Heart sounds are usually somewhat distant; a 4th heart sound is almost universally present. A soft systolic blowing apical murmur (reflecting papillary muscle dysfunction) may occur. During initial examination, a friction rub or more striking murmurs suggest a preexisting heart disorder or another
diagnosis. Detection of a friction rub within a few hours after onset of MI symptoms suggests acute pericarditis rather than MI. However, friction rubs, usually evanescent, are common on days 2 and 3 post-STEMI. The chest wall is tender when palpated in about 15% of patients.

In RV infarction, signs include elevated RV filling pressure, distended jugular veins (often with Kussmaul's sign—see p. 2019), clear lung fields, and hypotension.

**Diagnosis**

- Serial ECGs
- Serial cardiac markers
- Immediate coronary angiography for patients with STEMI or complications (eg, persistent chest pain, markedly elevated cardiac markers, unstable arrhythmias)
- Delayed angiography (24 to 48 h) for patients with NSTEMI or unstable angina

[Fig. 210-1. Acute anterior left ventricular infarction (tracing obtained within a few hours of onset of illness).]

[Fig. 210-2. Acute anterior left ventricular infarction (after the first 24 h).]

[Fig. 210-3. Acute anterior left ventricular infarction (several days later).]

[Fig. 210-4. Acute inferior (diaphragmatic) left ventricular infarction (tracing obtained within a few hours of onset of illness).]

[Fig. 210-5. Acute inferior (diaphragmatic) left ventricular infarction (after the first 24 h).]

[Fig. 210-6. Acute inferior (diaphragmatic) left ventricular infarction (several days later).]

ACS should be considered in men > 30 yr and women > 40 yr (younger in patients with diabetes) whose main symptom is chest pain or discomfort. Pain must be differentiated from the pain of pneumonia, pulmonary embolism, pericarditis, rib fracture, costochondral separation, esophageal spasm, acute aortic dissection, renal calculus, splenic infarction, or various abdominal disorders. In patients with previously diagnosed hiatus hernia, peptic ulcer, or a gallbladder disorder, the clinician must be wary of attributing new symptoms to these disorders.

The approach is the same when any ACS is suspected: initial and serial ECG and serial cardiac marker measurements, which distinguish among unstable angina, NSTEMI, and STEMI. Every emergency department should have a triage system to immediately identify patients with chest pain for rapid assessment and ECG. Pulse oximetry and chest x-ray (particularly to look for mediastinal widening, which suggests aortic dissection) is also done.

**ECG:** ECG is the most important test and should be done within 10 min of presentation. It is the center of the decision pathway because fibrinolytics benefit patients with STEMI but may increase risk for those with NSTEMI. Also, urgent cardiac catheterization is indicated for patients with acute STEMI but not for those with NSTEMI.

For STEMI, initial ECG is usually diagnostic, showing ST-segment elevation ≥ 1 mm in 2 or more
contiguous leads sub-tending the damaged area (see Figs. 210-1, 210-2, 210-3, 210-4, 210-5, and 210-6).

Pathologic Q waves are not necessary for the diagnosis. The ECG must be read carefully because ST-segment elevation may be subtle, particularly in the inferior leads (II, III, aVF); sometimes the reader's attention is mistakenly focused on leads with ST-segment depression. If symptoms are characteristic, ST-segment elevation on ECG has a specificity of 90% and a sensitivity of 45% for diagnosing MI. Serial tracings (obtained every 8 h for 1 day, then daily) showing a gradual evolution toward a stable, more normal pattern or development of abnormal Q waves over a few days tends to confirm the diagnosis.

Because nontransmural (non-Q-wave) infarcts are usually in the subendocardial or midmyocardial layers, they do not produce diagnostic Q waves or distinct ST-segment elevation on the ECG. Instead, they commonly produce only varying degrees of ST-T abnormalities that are less striking, variable, or nonspecific and sometimes difficult to interpret (NSTEMI). If such abnormalities resolve (or worsen) on repeat ECGs, ischemia is very likely. However, when repeat ECGs are unchanged, acute MI is unlikely and, if still suspected clinically, requires other evidence to make the diagnosis. A normal ECG taken when a patient is pain free does not rule out unstable angina; a normal ECG taken during pain, although it does not rule out angina, suggests that the pain is not ischemic.

If RV infarction is suspected, a 15-lead ECG is usually recorded; additional leads are placed at V4R, and, to detect posterior infarction, V8 and V9.

ECG diagnosis of MI is more difficult when a left bundle branch block configuration is present because it resembles STEMI changes. ST-segment elevation concordant with the QRS complex strongly suggests MI as does > 5-mm ST-segment elevation in at least 2 precordial leads. But generally, any patient with suggestive symptoms and new-onset (or not known to be old) left bundle branch block is treated as for STEMI.

Cardiac markers: Cardiac markers are cardiac enzymes (eg, CK-MB) and cell contents (eg, troponin I, troponin T, myoglobin) that are released into the bloodstream after myocardial cell necrosis. The markers appear at different times after injury and decrease at different rates (see Fig. 210-7).

Usually, several different markers are measured at regular intervals, typically every 6 to 8 h for 1 day. Newer bedside tests, which are more convenient, can be just as sensitive when done at shorter intervals (eg, time 0, 1, 3, and 6 h after presentation).

Troponins are most specific for MI but can also be elevated by ischemia without infarction; elevated levels (actual number varies with assay used) are considered diagnostic. Borderline elevated troponin levels in patients with unstable angina indicate increased risk of adverse events and thus the need for further evaluation and treatment. False-positives sometimes occur in heart failure and renal failure. CK-MB is slightly less specific. False-positives occur in renal failure, hypothyroidism, and skeletal muscle injury. Myoglobin is not specific for MI but, because it increases earlier than other markers, may be an early warning sign to assist in triage of patients with nondiagnostic ECGs.

Coronary angiography: Coronary angiography most often combines diagnosis with percutaneous coronary intervention (PCI, ie, angioplasty, stenting). Angiography is obtained urgently for patients with STEMI, patients with persistent chest pain despite maximal medical therapy, and patients with complications (eg, markedly elevated cardiac markers, presence of cardiogenic shock, acute mitral regurgitation, ventricular septal defect, unstable arrhythmias). Patients with uncomplicated NSTEMI or unstable angina whose symptoms have resolved typically undergo angiography within the first 24 to 48 h of hospitalization to detect lesions that may require treatment.

After initial evaluation and therapy, coronary angiography may be used in patients with evidence of
ongoing ischemia (ECG findings or symptoms), hemodynamic instability, recurrent ventricular tachyarrhythmias, and other abnormalities that suggest recurrence of ischemic events. Some experts also recommend that angiography be done before hospital discharge in STEMI patients with inducible ischemia on stress imaging or an ejection fraction < 40%.

**Other tests:** Routine laboratory tests are nondiagnostic but, if obtained, show non-specific abnormalities compatible with tissue necrosis (eg, increased ESR, moderately elevated WBC count with a shift to the left). A fasting lipid profile should be obtained within the first 24 h for all patients hospitalized with ACS.

Myocardial imaging (see also p. 2058) is not needed to make the diagnosis if cardiac markers or ECG is positive. However, in patients with MI, bedside echocardiography is invaluable for detecting mechanical complications. Before or shortly after discharge, patients with symptoms suggesting an ACS but nondiagnostic ECGs and normal cardiac markers should have a stress imaging test (radionuclide or echocardiographic imaging with pharmacologic or exercise stress). Imaging abnormalities in such patients indicate increased risk of complications in the next 3 to 6 mo.

Right heart catheterization using a balloon-tipped pulmonary artery catheter (see p. 2244) can be used to measure right heart, pulmonary artery, and pulmonary artery occlusion pressures and cardiac output. This test is usually done only if patients have significant complications (eg, severe heart failure, hypoxia, hypotension).

**Prognosis**

**Unstable angina:** About 30% of patients with unstable angina have an MI within 3 mo of onset; sudden death is less common. Marked ECG changes with chest pain indicate higher risk of subsequent MI or death.

**NSTEMI and STEMI:** Overall mortality rate is about 30%, with 50 to 60% of these patients dying before reaching the hospital (typically due to ventricular fibrillation). Inhospital mortality rate is about 10% (typically due to cardiogenic shock) but varies significantly with severity of LV failure (see Table 210-4).

Most patients who die of cardiogenic shock have an infarct or a combination of scar and new infarct affecting ≥ 50% of LV mass. Five clinical characteristics predict 90% of the mortality in patients who present with STEMI (see Table 210-5): older age (31% of total mortality), lower systolic BP (24%), Killip class > 1 (15%), faster heart rate (12%), and anterior location (6%). Mortality rate of diabetics and women tends to be higher.

Mortality rate of patients who survive initial hospitalization is 8 to 10% in the year after acute MI. Most fatalities occur in the first 3 to 4 mo. Persistent ventricular arrhythmia, heart failure, poor ventricular function, and recurrent ischemia indicate high risk. Many authorities recommend stress ECG before hospital discharge or within 6 wk. Good exercise performance without ECG abnormalities is associated with a favorable prognosis; further evaluation is usually not required. Poor exercise performance is associated with a poor prognosis.

Cardiac performance after recovery depends largely on how much functioning myocardium survives the acute attack. Scars from previous infarcts add to the acute damage. When > 50% of LV mass is damaged, prolonged survival is unusual.

**General Treatment**

* Monitoring and O₂

* Bed rest initially, with early ambulation
• Low-salt, low-fat diet

• Stool softeners and anxiolytics as needed

Treatment is designed to relieve distress, interrupt thrombosis, reverse ischemia, limit infarct size, reduce cardiac workload, and prevent and treat complications. An ACS is a medical emergency; outcome is greatly influenced by rapid diagnosis and treatment.

Treatment occurs simultaneously with diagnosis. A reliable IV route must be established, O₂ given (typically 2 L by nasal cannula), and continuous single-lead ECG monitoring started. Prehospital interventions by ambulance personnel (including ECG, chewed aspirin (325 mg), early thrombolysis when indicated and possible, and triage to the appropriate hospital) can reduce risk of mortality and complications. Early diagnostic data and response to treatment can help determine the need for and timing of revascularization (see p. 2111).

Bedside cardiac marker tests can help identify low-risk patients with a suspected ACS (eg, those with initially negative cardiac markers and nondiagnostic ECGs), who can be managed in 24-h observation units or chest pain centers. Higher-risk patients should be admitted to a monitored inpatient unit or coronary care unit (CCU). Several validated tools can help stratify risk. Thrombolysis in MI (TIMI) risk scores may be the most widely used (see Tables 210-5 and 210-6).

Patients with suspected NSTEMI and intermediate or high risk should be admitted to an inpatient care unit. Those with STEMI should be admitted to a CCU.

Only heart rate and rhythm recorded by single-lead ECG are consistently useful for routine, continuous monitoring. However, some clinicians recommend routine multilead monitoring with continuous ST-segment recording to identify transient, recurrent ST-segment elevations or depressions. Such findings, even in patients without symptoms, suggest ischemia and identify higher-risk patients who may require more aggressive evaluation and treatment.

Qualified nurses can interpret the ECG for arrhythmia and initiate protocols for its treatment. All staff members should know how to do CPR.

[Table 210-5, Mortality Risk at 30 Days in Stemi]

Contributing disorders (eg, anemia, heart failure) are aggressively treated.

The care unit should be a quiet, calm, restful area. Single rooms are preferred; privacy consistent with monitoring should be ensured. Usually, visitors and telephone calls are restricted to family members during the first few days. A wall clock, a calendar, and an outside window help orient the patient and prevent a sense of isolation, as can access to a radio, television, and newspaper.

Bed rest is mandatory for the first 24 h. On day 1, patients without complications (eg, hemodynamic instability, ongoing ischemia), including those in whom reperfusion with fibrinolytics or PCI is successful, can sit in a chair, begin passive exercises, and use a

[Table 210-6, Risk of Adverse Events* at 14 Days in Nstemi]

commode. Walking to the bathroom and doing nonstressful paperwork is allowed shortly thereafter. Recent studies have shown that patients with successful, uncomplicated primary PCI for acute MI may be ambulated quickly and be safely discharged in 3 to 4 days. If reperfusion is not successful or complications are present, patients require longer bed rest, but they (particularly elderly patients) are mobilized as soon as possible. Prolonged bed rest results in rapid physical deconditioning, with development of orthostatic hypotension, decreased work capacity, increased heart rate during exertion, and increased risk of deep venous thrombosis. Prolonged bed rest also intensifies feelings of depression.
and helplessness.

Anxiety, mood changes, and denial are common. A mild tranquilizer (usually a benzodiazepine) is often given, but many experts believe such drugs are rarely needed.

Reactive depression is common by the 3rd day of illness and is almost universal at some time during recovery. After the acute phase of illness, the most important tasks are often management of depression, rehabilitation, and institution of long-term preventive programs. Overemphasis on bed rest, inactivity, and the seriousness of the disorder reinforces anxiety and depressive tendencies, so patients are encouraged to sit up, get out of bed, and engage in appropriate activities as soon as possible. The effects of the disorder, prognosis, and individualized rehabilitation program should be explained to the patient.

Maintaining normal bowel function with stool softeners (eg, docusate) to prevent straining is important. Urinary retention is common among elderly patients, especially after several days of bed rest or if atropine was given. A catheter may be required but can usually be removed when the patient can stand or sit to void.

Because smoking is prohibited, a hospital stay should be used to encourage smoking cessation. All caregivers should devote considerable effort to making smoking cessation permanent.

Although acutely ill patients have little appetite, tasty food in modest amounts is good for morale. Patients are usually offered a soft diet of 1500 to 1800 kcal/day with Na reduction to 2 to 3 g. Na reduction is not required after the first 2 or 3 days if there is no evidence of heart failure. Patients are given a diet low in cholesterol and saturated fats, which is used to teach healthy eating.

For diabetic patients with STEMI, intensive glucose control is no longer recommended; guidelines call for an insulin-based regimen to achieve and maintain glucose levels < 180 mg/dL while avoiding hypoglycemia.

Because the chest pain of MI usually subsides within 12 to 24 h, any chest pain that remains or recurs later is investigated. It may indicate such complications as recurrent ischemia, pericarditis, pulmonary embolism, pneumonia, gastritis, or ulcer.

**Drugs**

- Aspirin, clopidogrel, or both (prasugrel is an alternative to clopidogrel if fibrinolytic therapy has not been given)

- β-Blocker

- GP Ib/IIa inhibitor considered for certain patients undergoing PCI and for some others at high risk (eg, with markedly elevated cardiac markers, TIMI risk score ≥ 4, persistent symptoms)

- A heparin (unfractionated or low molecular weight heparin) or bivalirudin (particularly in STEMI patients at high risk of bleeding)

- IV nitroglycerin (unless low-risk, uncomplicated MI)

- Fibrinolytics for select patients with STEMI when timely PCI unavailable

- ACE inhibitor (as early as possible) and a statin

Antiplatelet and antithrombotic drugs, which stop clots from forming, are used routinely. Anti-ischemic drugs (eg, β-blockers, IV nitroglycerin) are frequently added, particularly when chest pain or hypertension is present (see Table 210-3). Fibrinolytics should be used if not contraindicated for STEMI if primary PCI is not immediately available but worsen outcome for unstable angina and NSTEMI.

Chest pain can be treated with morphine or nitroglycerin. Morphine 2 to 4 mg IV, repeated q 15 min as
needed, is highly effective but can depress respiration, can reduce myocardial contractility, and is a potent venous vasodilator. Hypotension and bradycardia secondary to morphine can usually be overcome by prompt elevation of the lower extremities. Nitroglycerin is initially given sublingually, followed by continuous IV drip if needed.

BP is normal or slightly elevated in most patients on arrival at the emergency department; BP gradually falls over the next several hours. Continued hypertension requires treatment with antihypertensives, preferably IV nitroglycerin, to lower BP and reduce cardiac workload. Severe hypotension or other signs of shock are ominous and must be treated aggressively with IV fluids and sometimes vasopressors (see p. 2296).

Antiplatelet drugs: Aspirin, clopidogrel, ticlopidine, and GP IIb/IIIa inhibitors are examples. All patients are given aspirin 160 to 325 mg (not enteric-coated), if not contraindicated, at presentation and 81 mg once/day indefinitely thereafter. Chewing the first dose before swallowing quickens absorption. Aspirin reduces short- and long-term mortality risk. If aspirin cannot be taken, clopidogrel 75 mg once/day or ticlopidine 250 mg bid may be used. Clopidogrel has largely replaced ticlopidine for routine use because neutropenia is a risk with ticlopidine and the WBC count must be monitored regularly. Patients with unstable angina or NSTEMI in whom intervention is not possible or recommended are given both aspirin and clopidogrel for at least 1 mo. The optimal duration of double antiplatelet therapy for these patients is the subject of ongoing investigation.

In patients undergoing PCI, a clopidogrel loading dose (300 to 600 mg po once) improves outcomes, particularly when administered 24 h in advance. However, delaying PCI for 24 h is not appropriate for many patients. Further, such a loading dose increases risk of perioperative bleeding in patients who require coronary artery bypass grafting (CABG) because their coronary anatomy proves unfavorable for PCI. Thus, many clinicians administer a clopidogrel loading dose only in the catheterization laboratory once coronary anatomy and lesions have been proven to be amenable to PCI.

For patients receiving a stent for revascularization, aspirin is continued indefinitely, and clopidogrel should be used for at least 1 mo in patients with a bare-metal stent. Patients with a drug-eluting stent have a prolonged risk of thrombosis and may benefit from 12 mo of clopidogrel treatment, although the recommended duration is still unclear.

GP IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide) are potent antiplatelet drugs that must be given IV. Although there is some controversy, evidence indicates that patients with ACS undergoing PCI may benefit from a GP IIb/IIIa inhibitor; results appear to be better if the drug is initiated at least 6 h before PCI and continued for 18 to 24 h thereafter. If PCI is not being done, some clinicians give a GP IIb/IIIa inhibitor to all high-risk patients (eg, those with markedly elevated cardiac markers, a TIMI risk score ≥ 4, or persistent symptoms despite adequate drug therapy). The GP IIb/IIIa inhibitor is continued for 24 to 36 h, and angiography is done before the infusion period is over. GP IIb/IIIa inhibitors are not recommended for patients receiving fibrinolytics. Abciximab, tirofiban, and eptifibatide appear to have equivalent efficacy, and the choice of drug should depend on other factors (eg, cost, availability, familiarity).

Anticoagulant drugs: Either a low molecular weight heparin (LMWH), unfractionated heparin, or bivalirudin is given routinely to patients with ACS unless contraindicated (eg, by active bleeding or planned use of streptokinase or anistreplase). Choice of agent is somewhat involved.

Unfractionated heparin is more complicated to use because it requires frequent (q 6 h) dosing adjustments to achieve an activated PTT (aPTT) 1.5 to 2 times the control value. In patients undergoing angiography, further dosing adjustment is done to achieve an activated clotting time (ACT) of 200 to 250 sec if the patient is treated with a GP IIb/IIIa inhibitor and 250 to 300 sec if a GP IIb/IIIa inhibitor is not being given. However, the effects of unfractionated heparin are shorter and can be reversed (with prompt discontinuation of heparin infusion and with administration of protamine sulfate) if bleeding develops following catheterization.

The LMWHs have better bioavailability, are given by simple weight-based dose without monitoring aPTT and dose titration, and have lower risk of heparin-induced thrombocytopenia. They also may produce an incremental benefit in outcomes relative to unfractionated heparin in patients with ACS. Of the LMWHs,
enoxaparin appears to be superior to dalteparin or nadroparin. However, enoxaparin may pose a higher bleeding risk in patients with STEMI who are > 75, and its effects are not completely reversible with protamine.

Thus, taking all into account, many published guidelines recommend LMWH (eg, enoxaparin) over unfractionated heparin in patients with unstable angina or NSTEMI and in patients < 75 with STEMI who are not undergoing PCI. By contrast, unfractionated heparin is recommended when emergency PCI is done (eg, patients with acute STEMI who proceed to the catheterization laboratory), when CABG is indicated within the next 24 h, and when patients are at high risk of bleeding complications (eg, history of GI bleeding within the last 6 mo) or have creatinine clearance < 30 mL/min. Ongoing studies should help clarify the choice between LMWH and unfractionated heparin.

Bivalirudin is an acceptable anticoagulant for patients undergoing primary PCI who are at high risk of bleeding and is recommended for those with a known or suspected history of heparin-induced thrombocytopenia. For patients with unstable angina or NSTEMI, dose is an initial bolus of 0.1 mg/kg IV followed by a drip of 0.25 mg/kg/h. For patients with STEMI, initial dose is 0.75 mg/kg IV followed by 1.75 mg/kg/h.

For patients undergoing PCI, postprocedure heparin is no longer recommended unless patients are at high risk of thromboembolic events (eg, those with large anterior MI, known LV thrombus, atrial fibrillation), because postprocedure ischemic events have decreased with the use of stents and antiplatelet drugs. For patients not undergoing PCI, heparin is continued for 48 h (or longer if symptoms persist).

The difficulties with the heparins (including bleeding complications, the possibility of heparin-induced thrombocytopenia, and, with unfractionated heparin, the need for dosing adjustments) have led to the search for better anticoagulants. The direct thrombin inhibitors, bivalirudin and argatroban, may have a lower incidence of serious bleeding and improved outcomes, particularly in patients with renal insufficiency (hirudin, another direct thrombin inhibitor, appears to cause more bleeding than the other drugs). The factor Xa inhibitor, fondaparinux, reduces mortality and reinfarction in patients with NSTEMI who undergo PCI without increasing bleeding but may result in worse outcomes than unfractionated heparin in patients with STEMI. Although routine use of these alternative anticoagulants is thus not currently recommended, they should be used in place of unfractionated heparin or LMWH in patients with a known or suspected history of heparin-induced thrombocytopenia.

Patients at high risk of systemic emboli also require long-term therapy with oral warfarin. Conversion to warfarin should begin 48 h after symptom resolution or PCI.

**β-Blockers:** These drugs are recommended unless contraindicated (eg, by bradycardia, heart block, hypotension, or asthma), especially for high-risk patients. β-Blockers reduce heart rate, arterial pressure, and contractility, thereby reducing cardiac workload and O₂ demand. IV β-blockers given within the first few hours improve prognosis by reducing infarct size, recurrence rate, incidence of ventricular fibrillation, and mortality risk. Infarct size largely determines cardiac performance after recovery.

Heart rate and BP must be carefully monitored during treatment with β-blockers. Dosage is reduced if bradycardia or hypotension develops. Excessive adverse effects may be reversed by infusion of the β-adrenergic agonist isoproterenol 1 to 5 μg/min.

**Nitrates:** A short-acting nitrate, nitroglycerin, is used to reduce cardiac workload in selected patients. Nitroglycerin dilates veins, arteries, and arterioles, reducing LV preload and afterload. As a result, myocardial O₂ demand is reduced, lessening ischemia. IV nitroglycerin is recommended during the first 24 to 48 h for patients with heart failure, large anterior MI, persistent chest discomfort, or hypertension. BP can be reduced by 10 to 20 mm Hg but not to < 80 to 90 mm Hg systolic. Longer use may benefit patients with recurrent chest pain or persistent pulmonary congestion. In high-risk patients, nitroglycerin given in the first few hours reduces infarct size and short-term and possibly long-term mortality risk. Nitroglycerin is not routinely given to low-risk patients with uncomplicated MI.

**Fibrinolytics:** Tenecteplase (TNK), alteplase (rTPA), reteplase (rPA), streptokinase, and anistreplase
(anisoylated plasminogen activator complex—APSAC), all given IV, are plasminogen activators. They convert single chain plasminogen to double-chain plasminogen, which has fibrinolytic activity. They have different characteristics and dosing regimens (see Table 210-7) and are appropriate only for selected patients with STEMI (see p. 2113).

Tenecteplase and reteplase are recommended most often because of their simplicity of administration; tenecteplase is given as a single bolus over 5 sec and reteplase as a double bolus 30 min apart. Administration time and drug errors are reduced compared with other fibrinolytics. Tenecteplase, like alteplase, has an intermediate risk of intracranial hemorrhage, has a higher rate of recanalization than other fibrinolytics, and is expensive. Reteplase has the highest risk of intracranial hemorrhage and a recanalization rate similar to that of tenecteplase, and it is expensive.

Streptokinase may induce allergic reactions, especially if it has been used previously, and must be given by infusion over 30 to 60 min; however, it has a low incidence of intracerebral hemorrhage and is relatively inexpensive. Anistreplase, related to streptokinase, is similarly allergenic and slightly more expensive but can be given as a single bolus. Neither drug requires concomitant heparin use. For both, recanalization rate is lower than that with other plasminogen activators. Because of the possibility of allergic reactions, patients who previously received streptokinase or anistreplase are not given that drug.

[Table 210-7. IV Fibrinolytic Drugs Available in the US]

Alteplase is given in an accelerated or front-loaded dosage over 90 min. Alteplase with concomitant IV heparin improves patency, is nonallergenic, has a higher recanalization rate than other fibrinolytics, and is expensive.

**Other drugs:** ACE inhibitors appear to reduce mortality risk in MI patients, especially in those with anterior infarction, heart failure, or tachycardia. The greatest benefit occurs in the highest-risk patients early during convalescence. ACE inhibitors are given > 24 h after thrombolysis stabilization and, because of continued beneficial effect, may be prescribed long-term.

Angiotensin II receptor blockers may be an effective alternative for patients who cannot tolerate ACE inhibitors (eg, because of cough). Currently, they are not first-line treatment after MI. Contraindications include hypotension, renal failure, bilateral renal artery stenosis, and known allergy.

HMG-CoA reductase inhibitors (statins) have long been used for prevention of coronary artery disease and ACS, but there is now increasing evidence that they also have short-term benefits, such as stabilizing plaque, reversing endothelial dysfunction, decreasing thrombogenicity, and reducing inflammation. Thus, all patients without contraindications to therapy should receive a statin as early as possible following ACS. LDL levels of 70 to 80 mg/dL (1.81 to 2.07 mmol/L) are the recommended ultimate target.

**Revascularization Modalities and Indications**

Revascularization is the restoration of blood supply to ischemic myocardium in an effort to limit ongoing damage, reduce ventricular irritability, and improve short-term and long-term outcomes. Modes of revascularization include thrombolysis with fibrinolytic drugs, PCI with or without stent placement, and CABG.

The use, timing, and modality of revascularization depend on which ACS is present, timing of presentation, extent and location of anatomic lesions, and availability of personnel and facilities (see Fig. 210-8).

**Unstable angina and NSTEMI:** Immediate reperfusion is not as urgent in patients with uncomplicated NSTEMI (in whom a completely occluded infarct-related artery at presentation is uncommon) or in those with unstable angina who respond to medical therapy. Such
patients typically undergo angiography within the first 24 to 48 h of hospitalization to identify coronary lesions requiring PCI or CABG. A noninterventional approach and a trial of medical management are used for those in whom angiography demonstrates only a small area of myocardium at risk, lesion morphology not amenable to PCI, anatomically insignificant disease (< 50% coronary stenosis), or significant left main disease in patients who are candidates for CABG. Further, angiography or PCI should be deferred in favor of medical management for patients with a high risk of procedure-related morbidity or mortality.

By contrast, patients with persistent chest pain despite maximal medical therapy or complications (eg, markedly elevated cardiac markers, presence of cardiogenic shock, acute mitral regurgitation, ventricular septal defect, unstable arrhythmias) should proceed directly to the cardiac catheterization laboratory to identify coronary lesions requiring PCI or CABG.

As in patients with stable angina, CABG is generally preferred over PCI for patients with left main or left main equivalent disease, for those with 3- or 2-vessel disease involving the left anterior descending artery, and for those with left ventricular dysfunction or diabetes. CABG must also be considered when PCI is unsuccessful, cannot be used (eg, in lesions that are long or near bifurcation points), or causes acute coronary artery dissection.

Fibrinolytics are not indicated for unstable angina or NSTEMI. Risk outweighs potential benefit.

**STEMI:** Emergency PCI is the preferred treatment of STEMI when available in a timely fashion (door to balloon-inflation time < 90 min) by an experienced operator. Indications for urgent PCI later in the course of STEMI include hemodynamic instability, malignant arrhythmias requiring transvenous pacing or repeated cardioversion, and age > 75. If the lesions necessitate CABG, there is about 4 to 12% mortality and a 20 to 43% morbidity rate.

If there is likely to be a significant delay in availability of PCI, thrombolysis should be done for STEMI patients meeting criteria (see Table 210-8). Reperfusion using fibrinolytics is most effective if given in the first few minutes to hours after onset of MI. The earlier a fibrinolytic is begun, the better. The goal is a door-to-needle time of 30 to 60 min. Greatest benefit occurs within 3 h, but the drugs may be effective up to 12 h. Used with aspirin, fibrinolytics reduce hospital mortality rate by 30 to 50% and improve ventricular function. Although controversial, prehospital use of fibrinolytics by trained paramedics can significantly reduce time to treatment and should be considered in situations in which PCI within 90 min is not possible, particularly in patients presenting within 3 h of symptom onset.

Regardless, most patients who undergo thrombolysis will ultimately require transfer to a PCI-capable facility for elective angiography and PCI as necessary prior to discharge. PCI should be considered after fibrinolytics if chest pain or ST-segment elevation persists ≥ 60 min after initiation of fibrinolytics or if pain and ST-segment elevation recur, but only if PCI can be initiated < 90 min after onset of recurrence. If PCI is unavailable, fibrinolytics can be repeated.

Characteristics and selection of fibrinolytic drugs are discussed on p. 2110.

**Complications**

Electrical dysfunction occurs in > 90% of MI patients (see also p. 2142). Electrical dysfunction that commonly causes mortality in the first 72 h includes tachycardia (from any focus) rapid enough to reduce cardiac output and lower BP, Mobitz type II block (2nd degree) or complete (3rd degree) AV block, ventricular tachycardia (VT), and ventricular fibrillation (VF). Asystole is uncommon, except as a terminal manifestation of progressive LV failure and shock. Patients with disturbances of cardiac rhythm are checked for hypoxia and electrolyte abnormalities, which can be causative or contributory.

**Sinus node disturbances:** If the artery supplying the sinus node is affected, sinus node disturbances can occur; they are more likely if there is a preexisting sinus node disorder (common among the elderly). Sinus bradycardia, the most common sinus node disturbance, is usually not treated unless there is hypotension or the heart rate is < 50 beats/min. A lower heart rate, if not extreme, means reduced cardiac
workload and possibly reduced infarct size. For bradycardia with hypotension (which may reduce myocardial perfusion), atropine sulfate 0.5 to 1 mg IV is used; it can be repeated after several minutes if response is inadequate. Several small doses are best because high doses may induce tachycardia. Occasionally, a temporary transvenous pacemaker must be inserted.

Persistent sinus tachycardia is usually ominous, often reflecting LV failure and low cardiac output. Without heart failure or another evident cause, this arrhythmia may respond to a \( \beta \)-blocker, given po or IV depending on degree of urgency.

**Atrial arrhythmias:** Atrial arrhythmias (atrial ectopic beats, atrial fibrillation [AF], and, less commonly, atrial flutter) occur in about 10% of MI patients and may reflect LV failure or right atrial infarction. Paroxysmal atrial tachycardia is uncommon and usually occurs in patients who have had previous episodes of it. Atrial ectopy is usually benign but if frequency increases, causes, particularly heart failure, are sought. Frequent atrial ectopic beats may respond to a \( \beta \)-blocker.

**AF** is usually transient if it occurs within the first 24 h. Risk factors include age > 70, heart failure, previous history of MI, large anterior infarction, atrial infarction, pericarditis, hypokalemia, hypomagnesemia, a chronic lung disorder, and hypoxia. Fibrinolytics reduce incidence. Recurrent paroxysmal AF is a poor prognostic sign and increases risk of systemic emboli.

For AF, heparin is usually used because systemic emboli are a risk (see p. 2165). IV \( \beta \)-blockers (eg, atenolol 2.5 to 5.0 mg over 2 min to total dose of 10 mg in 10 to 15 min, metoprolol 2 to 5 mg q 2 to 5 min to a total dose of 15 mg in 10 to 15 min) slow the ventricular rate. Heart rate and BP are closely monitored. Treatment is withheld when ventricular rate decreases satisfactorily or systolic BP is < 100 mm Hg. IV digoxin, which is not as effective as \( \beta \)-blockers, is used cautiously and only in patients with AF and LV systolic dysfunction. Usually, digoxin takes at least 2 h to effectively slow heart rate and may rarely aggravate ischemia in patients with recent ACS. For patients without evident LV systolic dysfunction or conduction delay manifested by a wide QRS complex, IV verapamil or IV diltiazem may be considered. Diltiazem may be given as an IV infusion to control heart rate for long periods.

If AF compromises circulatory status (eg, causing LV failure, hypotension, or chest pain), urgent electrical cardioversion is done. If AF returns after cardioversion, IV amiodarone should be considered.

For atrial flutter, rate is controlled as for AF, but heparin is not required. Low-energy direct current (DC) cardioversion will terminate atrial flutter.

**Conduction defects:** Mobitz type I block (Wenckebach block, progressive prolongation of PR interval) is relatively common with an inferior-diaphragmatic infarction; it is usually self-limited and rarely progresses to higher grade block. Mobitz type II block (dropped beats) usually indicates massive anterior MI, as does complete heart block with wide QRS complexes (atrial impulses do not reach the ventricle); both are uncommon. Frequency of complete (3rd degree) AV block depends on site of infarction. Complete AV block occurs in 5 to 10% of patients with inferior infarction and is usually transient. It occurs in < 5% with uncomplicated anterior infarction but in up to 26% of those with right bundle branch block and left posterior hemiblock.

Mobitz type I block usually does not warrant treatment. For true Mobitz type II block with dropped beats or for AV block with slow, wide QRS complexes, temporary transvenous pacing is the treatment of choice. External pacing can be used until a temporary transvenous pacemaker can be placed. Although isoproterenol infusion may restore rhythm and rate temporarily, it is not used because it increases \( O_2 \) demand and risk of rhythm abnormalities. Atropine 0.5 mg IV q 3 to 5 min to a total dose of 2.5 mg may be useful for narrow-complex AV block with a slow ventricular rate but is not recommended for new wide-complex AV block.

**Ventricular arrhythmias:** These arrhythmias are common and may result from hypoxia, electrolyte imbalance (hypokalemia, possibly hypomagnesemia), or sympathetic overactivity in ischemic cells adjacent to infarcted tissue (which is not electrically active). Treatable causes of ventricular arrhythmias are sought and corrected. Serum K should be kept above 4.0 mEq/L. IV KCl is recommended; usually, 10 mEq/h can be infused, but for severe hypokalemia (K < 2.5 mEq/L), 20 to 40 mEq/h can be infused.
through a central venous line. Ventricular ectopic beats, which are common after MI, do not warrant specific treatment. Nonsustained VT (ie, < 30 sec) and even sustained slow VT (accelerated idioventricular rhythm) without hemodynamic instability do not usually require treatment in the first 24 to 48 h. Polymorphic VT, sustained (≥ 30 sec) monomorphic VT, or any VT with symptoms of instability (eg, heart failure, hypotension, chest pain) is treated with synchronized cardioversion. VT without hemodynamic instability may be treated with IV lidocaine, procainamide, or amiodarone. Some clinicians also treat complex ventricular arrhythmias with Mg sulfate 2 g IV over 5 min whether or not serum Mg is low. VT may occur months after MI. Late VT is more likely to occur in patients with transmural infarction and to be sustained.

VF occurs in 5 to 12% of patients during the first 24 h after MI, usually within 6 h. Late VF usually indicates continued or recurrent myocardial ischemia and, when accompanied by hemodynamic deterioration, is a poor prognostic sign. VF is treated with immediate unsynchronized cardioversion (see p. 2262).

An IV β-blocker early in MI followed by continued oral β-blockers reduces the incidence of ventricular arrhythmias (including VF) and mortality in patients who do not have heart failure or hypotension. Prophylaxis with other drugs (eg, lidocaine) increases mortality risk and is not recommended.

After the acute phase, the presence of complex ventricular arrhythmias or nonsustained VT, especially with significant LV systolic dysfunction, increases mortality risk. An implantable cardioverter-defibrillator (ICD) should be considered. Programmed endocardial stimulation can help select the most effective antiarrhythmics or determine the need for an ICD. Before treatment with an antiarrhythmic or ICD, coronary angiography and other tests are done to look for recurrent myocardial ischemia, which may require PCI or CABG.

Heart failure: Patients with large infarctions (determined by ECG or serum markers) and those with mechanical complications, hypertension, or diastolic dysfunction are more likely to develop heart failure. Clinical findings depend on infarct size, elevation of LV filling pressure, and degree of reduction in cardiac output. Dyspnea, inspiratory rales at the lung bases, and hypoxemia are common.

Treatment depends on severity. For mild cases, a loop diuretic (eg, furosemide 20 to 40 mg IV once/day or bid) to reduce ventricular filling pressure is often sufficient. For severe cases, vasodilators (eg, IV nitroglycerin) are often used to reduce preload and afterload; during treatment, pulmonary artery occlusion pressure is often measured via right heart (Swan-Ganz) catheterization. ACE inhibitors are used as long as systolic BP remains > 100 mm Hg. A short-acting ACE inhibitor given in low doses (eg, captopril 3.125 to 6.25 mg po q 4 to 6 h, increasing doses as tolerated) is best for initial treatment. Once the maximum dose is reached (maximum for captopril, 50 mg tid), a longer-acting ACE inhibitor (eg, fosinopril, lisinopril, ramipril) is substituted for the long-term. If heart failure remains in New York Heart Association class II or worse (see Table 211-2 on p. 2124), an aldosterone inhibitor (eg, eplerenone, spironolactone) should be added. For severe heart failure, an intraarterial counterpulsation balloon pump may provide temporary hemodynamic support. When revascularization or surgical repair is not feasible, heart transplantation is considered. Long-term LV or biventricular implantable assist devices may be used as a bridge to transplantation; if transplantation is impossible, the LV assist device is occasionally used as permanent treatment. Occasionally, use of such a device results in recovery and can be removed in 3 to 6 mo.

If heart failure causes hypoxemia, O₂ is given by nasal prongs (to maintain PaO₂ at about 100 mg Hg). It may help oxygenate myocardium and limit the ischemic zone.

Papillary muscle disorders: Functional papillary muscle insufficiency occurs in about 35% of patients during the first few hours of infarction. Papillary muscle ischemia causes incomplete coaptation of the mitral valve leaflets, which is transient in most patients. But in some patients, papillary muscle or free wall scarring causes permanent mitral regurgitation. Functional papillary muscle insufficiency is characterized by an apical late systolic murmur and typically resolves without treatment.
Papillary muscle rupture occurs most often after an inferoposterior infarct due to right coronary artery occlusion. It produces acute, severe mitral regurgitation. Papillary muscle rupture is characterized by the sudden appearance of a loud apical holosystolic murmur and thrill, usually with pulmonary edema. Occasionally, when severe regurgitation is silent but suspected clinically, echocardiography is done. Mitral valve repair or replacement is effective.

**Myocardial rupture:** Interventricular septum or free wall rupture occurs in 1% of patients with acute MI. It causes 15% of hospital mortality.

Interventricular septum rupture, although rare, is 8 to 10 times more common than papillary muscle rupture. Intraventricular septum rupture is characterized by the sudden appearance of a loud systolic murmur and thrill medial to the apex along the left sternal border in the 3rd or 4th intercostal space, accompanied by hypotension with or without signs of LV failure. Diagnosis may be confirmed using a balloon-tipped catheter and comparing blood O₂ saturation or PO₂ of right atrial, RV, and pulmonary artery samples. A significant increase in RV PO₂ is diagnostic, as is Doppler echocardiography, which may demonstrate the actual shunt of blood across the ventricular septum. Treatment is surgery, which should be delayed for up to 6 wk after MI so that infarcted myocardium can heal maximally; if hemodynamic instability persists, earlier surgery is indicated despite a high mortality risk.

Free wall rupture increases in incidence with age and is more common among women. It is characterized by sudden loss of arterial pressure with momentary persistence of sinus rhythm and often by signs of cardiac tamponade. Surgery is rarely successful. Rupture of a free wall is almost always fatal.

**Ventricular aneurysm:** A localized bulge in the ventricular wall, usually the LV wall, can occur at the site of a large infarction. Ventricular aneurysms are common, especially with a large transmural infarct (usually anterior). Aneurysms may develop in a few days, weeks, or months. They are unlikely to rupture but may lead to recurrent ventricular arrhythmias, low cardiac output, and mural thrombosis with systemic embolism. A ventricular aneurysm may be suspected when paradoxical precordial movements are seen or felt. ECG shows persistent ST-segment elevation, and chest x-ray shows a characteristic bulge of the cardiac shadow. Echocardiography is done to confirm the diagnosis and determine whether a thrombus is present. Surgical excision may be indicated when LV failure or arrhythmia persists. Use of ACE inhibitors during acute MI modifies LV remodeling and may reduce the incidence of aneurysm.

Pseudoaneurysm is incomplete rupture of the free LV wall; it is limited by the pericardium. Pseudoaneurysms almost always contain a thrombus and often rupture completely. They are repaired surgically.

**Hypotension and cardiogenic shock:** Hypotension may be due to decreased ventricular filling or loss of contractile force secondary to massive MI. Marked hypotension (eg, systolic BP < 90 mm Hg) with tachycardia and symptoms of end-organ hypoperfusion (reduced urine output, mental confusion, diaphoresis, cold extremities) is termed cardiogenic shock (see also p. 2294). Pulmonary congestion develops rapidly in cardiogenic shock.

Decreased LV filling is most often caused by reduced venous return secondary to hypovolemia, especially in patients receiving intensive loop diuretic therapy, but it may reflect RV infarction. Marked pulmonary congestion suggests loss of LV contractile force (LV failure) as the cause. Treatment depends on the cause. In some patients, determining the cause requires use of a pulmonary artery catheter to measure intracardiac pressures. If pulmonary artery occlusion pressure is < 18 mm Hg, decreased filling, usually due to hypovolemia, is likely; if pressure is > 18 mm Hg, LV failure is likely. For hypotension due to hypovolemia, cautious fluid replacement with 0.9% saline is usually possible without left heart overload (excessive rise in left atrial pressure). However, sometimes LV function is so compromised that adequate fluid replacement sharply increases pulmonary artery occlusion pressure to levels associated with pulmonary edema (> 25 mm Hg). If left atrial pressure is high, hypotension is probably due to LV failure, and if diuretics are ineffective, inotropic therapy or circulatory support may be required.

In cardiogenic shock, an α- or β-agonist may be temporarily effective. Dopamine, a catecholamine with α and β1 effects, is given at 0.5 to 1 μg/kg/min, increased until response is satisfactory or dose is about 10 μg/kg/min. Higher doses induce vasoconstriction and atrial and ventricular arrhythmias. Dobutamine, a β-
agonist, may be given IV at 2.5 to 10 μg/kg/min or in higher doses. It often causes or exacerbates hypotension; it is most effective when hypotension is secondary to low cardiac output with increased peripheral vascular resistance. Dopamine may be more effective than dobutamine when a vasopressor effect is also required. In refractory cases, dobutamine and dopamine may be combined. An intraaortic counterpulsation balloon pump can often temporarily support the patient. Definitive treatment for postinfarction cardiogenic shock is revascularization by thrombolysis of the clot, angioplasty, or emergency CABG. Revascularization usually greatly improves ventricular function. PCI or CABG may be considered for persistent ischemia, refractory ventricular arrhythmia, hemodynamic instability, or shock if coronary anatomy is suitable.

**RV ischemia or infarction:** RV infarction rarely occurs in isolation; it usually accompanies inferior LV infarction, and the first sign may be hypotension developing in a previously stable patient. Right-sided ECG leads may show ST-segment changes. Volume loading with 1 to 2 L of 0.9% saline is often effective. Dobutamine may help. Nitrates and diuretics are not used; they reduce preload (and hence cardiac output), causing severe hypotension. Increased right-sided filling pressure should be maintained by IV fluid infusion.

**Recurrent ischemia:** Any chest pain that remains or recurs 12 to 24 h post-MI may represent recurrent ischemia. Post-MI ischemic pain indicates that more myocardium is at risk of infarction. Usually, recurrent ischemia can be identified by reversible ST-T changes on the ECG; BP may be elevated. However, because recurrent ischemia may be silent (ECG changes without pain) in up to one third of patients, serial ECGs are routinely obtained every 8 h for 1 day and then daily. Recurrent ischemia is treated similarly to unstable angina. Sublingual or IV nitroglycerin is usually effective. Coronary angiography and PCI or CABG should be considered to salvage ischemic myocardium.

**Mural thrombosis:** Mural thrombosis occurs in about 20% of patients with acute MI. Systemic embolism occurs in about 10% of patients with LV thrombosis; risk is highest in the first 10 days but persists at least 3 mo. Risk is highest (about 60%) for patients with large anterior infarctions (especially involving the distal septum and apex), a dilated and diffusely hypokinetic LV, or chronic AF. Anticoagulants are given to reduce risk of emboli. If not contraindicated, full-dose IV heparin followed by warfarin for 3 to 6 mo is given to maintain INR between 2 and 3. Anticoagulants are continued indefinitely when a dilated diffusely hypokinetic LV, LV aneurysm, or chronic AF is present. Aspirin may also be given indefinitely.

**Pericarditis:** Pericarditis (see p. 2201) results from extension of myocardial necrosis through the wall to the epicardium; it develops in about one third of patients with acute transmural MI. A friction rub usually begins 24 to 96 h after MI onset. Earlier onset of the friction rub is unusual, although hemorrhagic pericarditis occasionally complicates the early phase of MI. Acute tamponade is rare. Pericarditis is diagnosed by ECG, which shows diffuse ST-segment elevation and sometimes PR-interval depression. Echocardiography is frequently done, but results are usually normal. Occasionally, small pericardial effusions and even unsuspected tamponade are detected. Aspirin or another NSAID usually relieves symptoms. High doses or prolonged use of NSAIDs or corticosteroids may impair infarct healing and should be avoided. Anticoagulation is not contraindicated in early peri-infarction pericarditis but is contraindicated in later post-MI (Dressler's) syndrome.

**Post-MI syndrome (Dressler's syndrome):** Post-MI syndrome develops in a few patients several days to weeks or even months after acute MI; incidence appears to have decreased in recent years. It is characterized by fever, pericarditis with a friction rub, pericardial effusion, pleurisy, pleural effusions, pulmonary infiltrates, and joint pain. This syndrome is caused by an autoimmune reaction to material from necrotic myocytes. It may recur. Differentiating post-MI syndrome from extension or recurrence of infarction may be difficult. However, in post-MI syndrome, cardiac markers do not increase significantly, and ECG changes are nonspecific. NSAIDs are usually effective, but the syndrome can recur several times. In severe cases, a short, intensive course of another NSAID or a corticosteroid may be necessary. High doses of an NSAID or a corticosteroid are not used for more than a few days because they may interfere with early ventricular healing after an acute MI.

**Rehabilitation and Postdischarge Treatment**

- Functional evaluation
• Changes in lifestyle: Regular exercise, diet modification, weight loss, smoking cessation

• Drugs: Continuation of aspirin, β-blockers, ACE inhibitors, and statins

**Functional evaluation:** Patients who did not have coronary angiography during admission, have no high-risk features (eg, heart failure, recurrent angina, VT or VF after 24 h, mechanical complications such as new murmurs, shock), and have an ejection fraction > 40% whether or not they received fibrinolytics usually should have stress testing of some sort before or shortly after discharge (see Table 210-9).

**Activity:** Physical activity is gradually increased during the first 3 to 6 wk after discharge. Resumption of sexual activity, often of great concern to the patient, and other moderate physical activities may be encouraged. If good cardiac function is maintained 6 wk after acute MI, most patients can return to all their normal activities. A regular exercise program consistent with lifestyle, age, and cardiac status reduces risk of ischemic events and enhances general well-being.

**Risk factors:** The acute illness and treatment of ACS should be used to strongly motivate the patient to modify risk factors. Evaluating the patient's physical and emotional status and discussing them with the patient, advising about lifestyle (eg, smoking, diet, work and play habits, exercise), and aggressively managing risk factors may improve prognosis.

**Drugs:** Several drugs clearly reduce mortality risk post-MI and are used unless contraindicated or not tolerated.

Aspirin reduces mortality and reinfarction rates in post-MI patients by 15 to 30%. Enteric-coated aspirin 81 mg once/day is recommended long-term. Data suggest that warfarin with or without aspirin reduces mortality and reinfarction rates.

β-Blockers are considered standard therapy. Most available β-blockers (eg, acebutolol, atenolol, metoprolol, propranolol, timolol) reduce post-MI mortality rate by about 25% for at least 7 yr.

ACE inhibitors are given to all post-MI patients. These drugs may provide long-term cardioprotection by improving endothelial function. If an ACE inhibitor is not tolerated because of cough or rash (but not angioedema or renal dysfunction), an angiotensin II receptor blocker may be substituted.

Statins are prescribed. Reducing cholesterol levels after MI reduces rates of recurrent ischemic events and mortality in patients with elevated or normal cholesterol levels. Statins appear to benefit post-MI patients regardless of their initial cholesterol level. Post-MI patients whose primary problem is a low HDL level or an elevated triglyceride level may benefit from a fibrate, but evidence of benefit is less clear. A lipid-lowering drug should be continued indefinitely, unless significant adverse effects occur, and dose should be increased to achieve an LDL level of 70 to 80 mg/dL (1.81 to 2.07 mmol/L).
Chapter 211. Heart Failure

Introduction

(Congestive Heart Failure) (For heart failure in children, see p. 2947.)

Heart failure (HF) is a syndrome of ventricular dysfunction. Left ventricular failure causes shortness of breath and fatigue, and right ventricular failure causes peripheral and abdominal fluid accumulation; the ventricles can be involved together or separately. Diagnosis is initially clinical, supported by chest x-ray, echocardiography, and levels of plasma natriuretic peptides. Treatment includes diuretics, ACE inhibitors, angiotensin II receptor blockers, β-blockers, aldosterone antagonists, digitalis, specialized implantable pacemakers, and correction of the underlying disorder.

HF affects about 5 million people in the US; > 500,000 new cases occur each year.

Physiology

Cardiac contractility (force and velocity of contraction), ventricular performance, and myocardial O₂ requirements are determined by preload, afterload, substrate availability (e.g., O₂, fatty acids, glucose), heart rate and rhythm, and amount of viable myocardium. Cardiac output (CO) is the product of stroke volume and heart rate; it is also affected by venous return, peripheral vascular tone, and neurohumoral factors.

Preload is the loading condition of the heart at the end of its relaxation phase (diastole) just before contraction (systole). Preload represents the degree of end-diastolic fiber stretch and end-diastolic volume, which is influenced by ventricular diastolic pressure and the composition of the myocardial wall. Typically, left ventricular (LV) end-diastolic pressure, especially if higher than normal, is a reasonable measure of preload. LV dilation, hypertrophy, and changes in myocardial distensibility (compliance) modify preload.

Afterload is the force resisting myocardial fiber contraction at the start of systole; it is determined by chamber pressure, volume, and wall thickness at the time the aortic valve opens. Clinically, systemic systolic BP at or shortly after the aortic valve opens represents peak systolic wall stress and approximates afterload.

The Frank-Starling principle describes the relationship between preload and cardiac performance. It states that, normally, systolic contractile performance (represented by stroke volume or CO) is proportional to preload within the normal physiologic range (see Fig. 211-1). Contractility is difficult to measure without cardiac catheterization but is reasonably reflected by the ejection fraction (EF), which is the percentage of end-diastolic volume ejected with each contraction (LV stroke volume/end-diastolic volume); contractility can generally be adequately assessed noninvasively with echocardiography.

Cardiac reserve is the ability of the heart to increase its performance above resting levels in response to emotional or physical stress; body O₂ consumption may increase from 250 to ≥ 1500 mL/min during maximal exertion. Mechanisms include increasing heart rate, systolic and diastolic volume, stroke volume, and tissue extraction of O₂ (the difference between O₂ content in arterial blood and mixed venous or pulmonary artery blood). In well-trained young adults during maximal exercise, heart rate may increase from 55 to 70 beats/min at rest to 180 beats/min, and CO may increase from 6 to ≥ 25 L/min. At rest, arterial blood contains about 18 mL O₂/dL of blood, and mixed venous or pulmonary artery blood contains about 14 mL/dL. O₂ extraction is thus about 4 mL/dL, but when demand is increased, it may increase to 12 to 14 mL/dL. This mechanism also helps compensate for reduced tissue blood flow in HF.

[Fig. 211-1. Frank-Starling principle.]
Pathophysiology

In HF, the heart may not provide tissues with adequate blood for metabolic needs, and cardiac-related elevation of pulmonary or systemic venous pressures may result in organ congestion. This condition can result from abnormalities of systolic or diastolic function or, commonly, both. Although a primary abnormality may be a change in myocyte function, there are also changes in collagen turnover of the extracellular matrix. Cardiac structural defects (eg, congenital defects, valvular disorders), rhythm abnormalities (including persistently high heart rate), and high metabolic demands (eg, from thyrotoxicosis) also can cause HF.

Systolic dysfunction: In systolic dysfunction, the ventricle contracts poorly and empties inadequately, leading initially to increased diastolic volume and pressure and decreased EF. Many defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, with abnormalities in intracellular Ca modulation and cAMP production.

Predominant systolic dysfunction is common in HF due to MI, myocarditis, and dilated cardiomyopathy. Systolic dysfunction may affect primarily the LV or the right ventricle (RV); LV failure often leads to RV failure.

Diastolic dysfunction: In diastolic dysfunction (also called HF with preserved systolic function or HF with preserved/normal EF), ventricular filling is impaired, resulting in reduced ventricular end-diastolic volume, increased end-diastolic pressure, or both. Contractility and hence EF remain normal; EF may even increase as the poorly filled LV empties more completely to maintain CO. Markedly reduced LV filling can cause low CO and systemic symptoms. Elevated left atrial pressures can cause pulmonary hypertension and pulmonary congestion.

Diastolic dysfunction usually results from impaired ventricular relaxation (an active process), increased ventricular stiffness, valvular disease, or constrictive pericarditis. Acute myocardial ischemia is also a cause of diastolic dysfunction. Resistance to filling increases with age, probably reflecting myocyte loss and increased interstitial collagen deposition; thus, diastolic dysfunction is particularly common among the elderly. Diastolic dysfunction predominates in hypertrophic cardiomyopathy, disorders with ventricular hypertrophy (eg, hypertension, significant aortic stenosis), and amyloid infiltration of the myocardium. LV filling and function may also be impaired if marked increases in RV pressure shift the interventricular septum to the left.

Diastolic dysfunction is increasingly being recognized as a cause of HF. Estimates vary, but about 50% of patients with HF have diastolic dysfunction and a normal EF; the prevalence increases with age.

LV failure: In failure due to LV dysfunction, CO decreases and pulmonary venous pressure increases. When pulmonary capillary pressure exceeds the oncotic pressure of plasma proteins (about 24 mm Hg), fluid extravasates from the capillaries into the interstitial space and alveoli, reducing pulmonary compliance and increasing the work of breathing. Lymphatic drainage increases but cannot compensate for the increase in pulmonary fluid. Marked fluid accumulation in alveoli (pulmonary edema) significantly alters ventilation-perfusion (V/Q) relationships: Deoxygenated pulmonary arterial blood passes through poorly ventilated alveoli, decreasing systemic arterial oxygenation (PaO₂) and causing dyspnea. However, dyspnea may occur before V/Q abnormalities, probably because of elevated pulmonary venous pressure and increased work of breathing; the precise mechanism is unclear. In severe or chronic LV failure, pleural effusions characteristically develop in the right hemithorax and later bilaterally, further aggravating dyspnea. Minute ventilation increases; thus, PaCO₂ decreases and blood pH increases (respiratory alkalosis). Marked interstitial edema of the small airways may interfere with ventilation, elevating PaCO₂—a sign of impending respiratory failure.

RV failure: In failure due to RV dysfunction, systemic venous pressure increases, causing fluid extravasation and consequent edema, primarily in dependent tissues (feet and ankles of ambulatory patients) and abdominal viscera. The liver is affected most, but the stomach and intestine also become congested; fluid accumulation in the peritoneal cavity (ascites) can occur. RV failure commonly causes moderate hepatic dysfunction, with usually modest increases in conjugated and unconjugated bilirubin,
PT, and hepatic enzymes (eg, alkaline phosphatase, AST, ALT). The impaired liver breaks down less aldosterone, further contributing to fluid accumulation. Chronic venous congestion in the viscera can cause anorexia, malabsorption of nutrients and drugs, protein-losing enteropathy (characterized by diarrhea and marked hypoalbuminemia), chronic GI blood loss, and rarely ischemic bowel infarction.

**Cardiac response:** If ventricular function is impaired, a higher preload is required to maintain CO. As a result, the ventricles are remodeled over time: The LV becomes less ovoid and more spherical, dilates, and hypertrophies; the RV dilates and may hypertrophy. Initially compensatory, these changes eventually increase diastolic stiffness and wall tension (ie, diastolic dysfunction develops), compromising cardiac performance, especially during physical stress. Increased wall stress raises O_2_ demand and accelerates apoptosis (programmed cell death) of myocardial cells. Dilation of the ventricles can also cause mitral or tricuspid valve regurgitation with further increases in end-diastolic volumes.

**Hemodynamic responses:** With reduced CO, tissue O_2_ delivery is maintained by increasing O_2_ extraction and sometimes shifting the oxyhemoglobin dissociation curve (see Fig. 189-4 on p. 1857) to the right to favor O_2_ release.

Reduced CO with lower systemic BP activates arterial baroreflexes, increasing sympathetic tone and decreasing parasympathetic tone. As a result, heart rate and myocardial contractility increase, arterioles in selected vascular beds constrict, venoconstriction occurs, and Na and water are retained. These changes compensate for reduced ventricular performance and help maintain hemodynamic homeostasis in the early stages of HF. However, these compensatory changes increase cardiac work, preload, and afterload; reduce coronary and renal perfusion; cause fluid accumulation resulting in congestion; increase K excretion; and may cause myocyte necrosis and arrhythmias.

**Renal responses:** As cardiac function deteriorates, renal blood flow and GFR decrease, and blood flow within the kidneys is redistributed. The filtration fraction and filtered Na decrease, but tubular resorption increases, leading to Na and water retention. Blood flow is further redistributed away from the kidneys during exercise, but renal blood flow improves during rest, possibly contributing to nocturia.

Decreased perfusion of the kidneys (and possibly decreased arterial systolic stretch secondary to declining ventricular function) activates the renin-angiotensin-aldosterone system (see also p. 2066), increasing Na and water retention and renal and peripheral vascular tone. These effects are amplified by the intense sympathetic activation accompanying HF.

The renin-angiotensin-aldosterone-vasopressin (antiuretic hormone [ADH]) system causes a cascade of potentially deleterious long-term effects. Angiotensin II worsens HF by causing vasoconstriction, including efferent renal vasoconstriction, and by increasing aldosterone production, which not only enhances Na reabsorption in the distal nephron but also causes myocardial and vascular collagen deposition and fibrosis. Angiotensin II increases norepinephrine release, stimulates release of ADH, and triggers apoptosis. Angiotensin II may be involved in vascular and myocardial hypertrophy; thus contributing to the remodeling of the heart and peripheral vasculature, potentially worsening HF. Aldosterone can be synthesized in the heart and vasculature independently of angiotensin II (perhaps mediated by corticotropin, nitric oxide, free radicals, and other stimuli) and may have deleterious effects in these organs.

HF that causes progressive renal dysfunction (including that renal dysfunction caused by drugs used to treat HF) contributes to worsening HF and has been termed the cardiorenal syndrome.

**Neurohumoral responses:** In conditions of stress, neurohumoral responses help increase heart function and maintain BP and organ perfusion, but chronic activation of these responses is detrimental to the normal balance between myocardial-stimulating and vasoconstricting hormones and between myocardial-relaxing and vasodilating hormones.

The heart contains many neurohumoral receptors (α_1_, β_1_, β_2_, β_3_, angiotensin II type 1 [AT_1_] and type 2 [AT_2_], muscarinic, endothelin, serotonin, adenosine, cytokine); the role of these receptors is not yet fully defined. In patients with HF, β_1_ receptors (which constitute 70% of cardiac β receptors) are down-
regulated, probably in response to intense sympathetic activation. The result of down-regulation is impaired myocyte contractility and increased heart rate.

Plasma norepinephrine levels are increased, largely reflecting sympathetic nerve stimulation because plasma epinephrine levels are not increased. Detrimental effects include vasoconstriction with increased preload and afterload, direct myocardial damage including apoptosis, reduced renal blood flow, and activation of other neurohumoral systems, including the renin-angiotensin-aldosterone-ADH system.

ADH is released in response to a fall in BP via various neurohormonal stimuli. Increased ADH decreases renal excretion of free water, possibly contributing to hyponatremia in HF. ADH levels in HF with normal BP vary.

Atrial natriuretic peptide is released in response to increased atrial volume and pressure; brain (B-type) natriuretic peptide (BNP) is released from the ventricle in response to ventricular stretching. These peptides enhance renal excretion of Na, but in patients with HF, the effect is blunted by decreased renal perfusion pressure, receptor downregulation, and perhaps enhanced enzymatic degradation.

Because endothelial dysfunction occurs in HF, fewer endogenous vasodilators (eg, nitric oxide, prostaglandins) are produced, and more endogenous vasoconstrictors (eg, endothelin) are produced, thus increasing afterload.

The failing heart and other organs produce tumor necrosis factor (TNF)-α. This cytokine increases catabolism and is possibly responsible for cardiac cachexia (loss of lean tissue ≥ 10%), which may accompany severely symptomatic HF, and for other detrimental changes. The failing heart also undergoes metabolic changes with increased free fatty acid utilization and decreased glucose utilization; these changes may become therapeutic targets.

Changes with aging: Age-related changes in the heart and cardiovascular system lower the threshold for expression of HF. Interstitial collagen within the myocardium increases, the myocardium stiffens, and myocardial relaxation is prolonged. These changes lead to a significant reduction in diastolic LV function, even in healthy elderly people. Modest decline in systolic function also occurs with aging. An age-related decrease in myocardial and vascular responsiveness to β-adrenergic stimulation further impairs the ability of the cardiovascular system to respond to increased work demands.

As a result of these changes, peak exercise capacity decreases significantly (about 8%/decade after age 30), and CO at peak exercise decreases more modestly. This decline can be slowed by regular physical exercise. Thus, elderly patients are more prone than are younger ones to develop HF symptoms in response to the stress of systemic disorders or relatively modest cardiovascular insults. Stressors include infections (particularly pneumonia), hyperthyroidism, anemia, hypertension, myocardial ischemia, hypoxia, hyperthermia, renal failure, perioperative IV fluid loads, nonadherence to drug regimens or to low-salt diets, and use of certain drugs (including NSAIDs, β-blockers, and certain Ca channel blockers).

Etiology

Both cardiac and systemic factors can impair cardiac performance and cause or aggravate HF (see Table 211-1).

Classification

The traditional distinction of left and right ventricular failure is somewhat misleading because the heart is an integrated pump, and changes in one chamber ultimately affect the whole heart. However, these terms indicate the major site of pathology leading to HF and can be useful for initial evaluation and treatment. Other common descriptive terms include acute or chronic; congestive; high output or low output; systolic or diastolic; dilated or nondilated; and ischemic, hypertensive, or idiopathic dilated cardiomyopathy.

LV failure characteristically develops in ischemic heart disease, hypertension, mitral or aortic valvular regurgitation, aortic stenosis, most forms of cardiomyopathy, and congenital heart disorders (eg, ventricular septal defect or patent ductus arteriosus with large shunts).
**RV failure** is most commonly caused by previous LV failure (which increases pulmonary venous pressure and leads to pulmonary arterial hypertension, thus overloading the RV) or by a severe lung disorder (when it is called cor pulmonale—see p. 2132). Other causes are multiple pulmonary emboli, RV infarction, primary pulmonary hypertension, tricuspid regurgitation or stenosis, mitral stenosis, pulmonary artery or valve stenosis, pulmonary venous occlusive disease, or congenital disorders such as Ebstein's anomaly or Eisenmenger's syndrome. Some conditions mimic RV failure, except cardiac function may be normal; they include volume overload and increased systemic venous pressure in polycythemia or overtransfusion, acute renal failure with retention of Na and water, obstruction of either vena cava, and hypoproteinemia from any cause resulting in low plasma oncotic pressure and peripheral edema.

**Biventricular failure** results from disorders that affect the whole myocardium (eg, viral myocarditis, amyloidosis, Chagas' disease) or long-standing LV failure causing RV failure.

**High-output HF** results from a persistently high CO, which may eventually result in an inability of a normal heart to maintain adequate output. Conditions that may increase CO include severe anemia, beriberi, thyrotoxicosis, advanced Paget's disease, arteriovenous fistula, and persistent tachycardia. CO is high in various forms of cirrhosis, but much of the observed fluid retention is due to hepatic mechanisms.

**Cardiomyopathy** is a general term reflecting disease of the myocardium. Most commonly, the term refers to a primary disorder of the ventricular myocardium that is not caused by congenital anatomic defects; valvular, systemic, or pulmonary vascular disorders; isolated pericardial, nodal, or conduction system disorders; or epicardial coronary artery disease (CAD). The term is sometimes used to reflect etiology (eg, ischemic vs hypertensive cardiomyopathy). Cardiomyopathy does not always lead to symptomatic HF. It is often idiopathic and is classified as dilated congestive, hypertrophic, infiltrative-restrictive, or apical-ballooning cardiomyopathy.

**Symptoms and Signs**

Manifestations differ depending on the extent to which the LV and RV are initially affected. Clinical severity varies significantly and is usually classified according to the New York Heart Association system (see Table 211-2); the examples of ordinary activity may be modified for elderly, debilitated patients. Severe LV failure may cause pulmonary edema (see p. 2131) or cardiogenic shock (see p. 2294).

**History:** In LV failure, the most common symptoms are dyspnea, reflecting pulmonary congestion, and fatigue, reflecting low CO. Dyspnea usually occurs during exertion and is relieved by rest. As HF worsens, dyspnea can occur during rest and at night, sometimes causing nocturnal cough. Dyspnea occurring immediately or soon after lying flat and relieved promptly by sitting up (orthopnea) is common as HF advances. In paroxysmal nocturnal dyspnea (PND), dyspnea awakens patients several hours after they lie down and is relieved only after they sit up for 15 to 20 min. In severe HF, periodic cycling of breathing (Cheyne-Stokes respiration—see p. 1827)—a brief period of increased breathing [hyperpnea] followed by a brief period of no breathing [apnea]—can occur during the day or night; the sudden hyperpneic phase may awaken the patient from sleep. This breathing differs from PND in that the hyperpneic phase is short, lasting only a few seconds and resolving in < 1 min. PND is associated with pulmonary congestion, and Cheyne-Stokes respiration with low CO. Sleep-related breathing disorders, such as sleep apnea (see p. 1903), are common in HF and may aggravate HF. Severely reduced cerebral blood flow and hypoxemia can cause chronic irritability and impair mental performance.

In RV failure, the most common symptoms are ankle swelling and fatigue. Sometimes patients feel a sensation of fullness in the abdomen or neck. Hepatic congestion can cause right upper quadrant abdominal discomfort, and stomach and intestinal congestion can cause anorexia and abdominal bloating.
Less specific HF symptoms include cool peripheries, postural light-headedness, nocturia, and decreased daytime micturition. Skeletal muscle wasting can occur in severe biventricular failure and may reflect some disuse but also increased catabolism associated with increased cytokine production. Significant weight loss (cardiac cachexia) is an ominous sign associated with high mortality.

In the elderly, presenting complaints may be atypical, such as confusion, delirium, falls, sudden functional decline, nocturnal urinary incontinence, or sleep disturbance. Coexisting cognitive impairment and depression may also influence assessment and therapeutic interventions and may be worsened by the HF.

**Examination:** General examination may detect signs of systemic disorders that cause or aggravate HF (eg, anemia, hyperthyroidism, alcoholism, hemochromatosis).

In LV failure, tachycardia and tachypnea may occur. Patients with severe LV failure may appear visibly dyspneic or cyanotic, hypotensive, and confused or agitated because of hypoxia and poor cerebral perfusion. Some of these less specific symptoms (eg, confusion) are more common in the elderly.

Central cyanosis (affecting all of the body, including warm areas such as the tongue and mucous membranes) reflects severe hypoxemia.

**[Table 211-2, New York Heart Association (Nyha) Classification of Heart Failure]**

Peripheral cyanosis of the lips, fingers, and toes reflects low blood flow with increased \(O_2\) extraction. If vigorous massage improves nail bed color, cyanosis may be peripheral; increasing local blood flow does not improve color if cyanosis is central.

Cardiac findings in LV systolic dysfunction include a diffuse, sustained, and laterally displaced apical impulse; audible and occasionally palpable 3rd (\(S_3\)) and 4th (\(S_4\)) heart sounds, and an accentuated pulmonic component (\(P_2\)) of the 2nd heart sound (\(S_2\)). A pansystolic murmur of mitral regurgitation at the apex may occur. Pulmonary findings include inspiratory basilar crackles that do not clear with coughing and, if pleural effusion is present, dullness to percussion and diminished breath sounds at lung bases.

Signs of RV failure include nontender peripheral pitting edema (digital pressure leaves visible and palpable imprints, sometimes quite deep) in the feet and ankles; an enlarged and sometimes pulsatile liver palpable below the right costal margin; abdominal swelling and ascites; and visible elevation of the jugular venous pressure, sometimes with large \(a\) or \(v\) waves that are visible even when the patient is seated or standing (see **Fig. 206-1** on p. 2020). In severe cases, peripheral edema can extend to the thighs or even the sacrum, scrotum, lower abdominal wall, and occasionally even higher. Severe edema in multiple areas is termed anasarca. Edema may be asymmetric if patients lie predominantly on one side.

With hepatic congestion, the liver may be palpably enlarged or tender, and hepatojugular or abdominal-jugular reflux may be detected (see p. 2019). Precordial palpation may detect the left parasternal lift of RV enlargement, and auscultation may detect the murmur of tricuspid regurgitation or the RV \(S_3\) along the left sternal border; both findings are augmented upon inspiration.

**Diagnosis**

- Sometimes only clinical evaluation
- Chest x-ray
- Echocardiography
- Sometimes BNP or N-terminal-proBNP (NT-proBNP) levels
ECG and other tests for etiology as needed

Clinical findings (eg, exertional dyspnea or fatigue, orthopnea, edema, tachycardia, pulmonary crackles, S3, jugular venous distention) suggest HF but are not apparent early. Similar symptoms may result from COPD or recurrent pneumonia or may be erroneously attributed to obesity or old age. Suspicion for HF should be high in patients with a history of MI, hypertension, or valvular disorders or murmurs and should be moderate in any elderly or diabetic patient.

Chest x-ray, ECG, and an objective test of cardiac function, typically echocardiography, should be done. Blood tests, except for BNP levels, are not used for diagnosis but are useful for identifying cause and systemic effects.

**Chest x-ray:** Chest x-ray findings suggesting HF include an enlarged cardiac silhouette, pleural effusion, fluid in the major fissure, and horizontal lines in the periphery of lower posterior lung fields (Kerley B lines). These findings reflect chronic elevation of left atrial pressure and chronic thickening of the intralobular septa due to edema. Upper lobe pulmonary venous congestion and interstitial or alveolar edema may also be present. Careful examination of the cardiac silhouette on a lateral projection can identify specific ventricular and atrial chamber enlargement. The x-ray may also suggest alternative diagnoses (eg, COPD, pneumonia, interstitial pulmonary fibrosis, lung cancer).

**ECG:** ECG findings are not diagnostic, but an abnormal ECG, especially showing previous MI, LV hypertrophy, left bundle branch block, or tachyarrhythmia (eg, rapid atrial fibrillation), increases suspicion for HF and may help identify the cause. An entirely normal ECG is uncommon in chronic HF.

**Imaging:** Echocardiography can help evaluate chamber dimensions, valve function, EF, wall motion abnormalities, LV hypertrophy, and pericardial effusion. Intracardiac thrombi, tumors, and calcifications within the heart valves, mitral annulus, and aortic wall abnormalities can be detected. Localized or segmental wall motion abnormalities strongly suggest underlying CAD but can also be present with patchy myocarditis. Doppler or color Doppler echocardiography accurately detects valvular disorders and shunts. Doppler studies of mitral and pulmonary venous inflow often help identify and quantify LV diastolic dysfunction; tissue Doppler imaging is more accurate. Measuring LVEF can distinguish between predominant diastolic dysfunction (EF > 0.50) and systolic dysfunction (EF < 0.40). It is important to re-emphasize that HF can occur with a normal LVEF. Three-dimensional echocardiography may become important but currently is available only in specialized centers.

Radionuclide imaging also can help assess systolic and diastolic function, previous MI, and inducible ischemia or myocardial hibernation. Cardiac MRI provides accurate images of cardiac structures and is becoming more widely available. In many centers, multimode imaging (eg, stress MIBI [thallium and sestamibi stress tests] plus CT angiography) is becoming common, although there is growing concern about the radiation dose with CT angiography.

**Blood tests:** Serum BNP levels are high in HF; this finding may help when clinical findings are unclear or other diagnoses (eg, COPD) need to be excluded. It may be particularly useful for patients with a history of both pulmonary and cardiac disorders. NT-proBNP, an inactive moiety created when proBNP is cleaved, can be used similarly.

Recommended blood tests include CBC, creatinine, BUN, electrolytes (including Mg and Ca), glucose, albumin, and liver function tests. Thyroid function tests are recommended for patients with atrial fibrillation and for selected, especially elderly, patients.

**Other tests:** Coronary angiography is indicated when CAD is suspected or the etiology of HF is uncertain. Cardiac catheterization with intracardiac pressure measurements may be helpful in the diagnosis of restrictive cardiomyopathies and constrictive pericarditis.

Endocardial biopsy is sometimes done when an infiltrative cardiomyopathy is strongly suspected but cannot be confirmed with noninvasive imaging (eg, cardiac MRI).
Prognosis

Generally, patients with HF have a poor prognosis unless the cause is correctable. Mortality rate at 1 yr from first hospitalization for HF is about 30%. In chronic HF, mortality depends on severity of symptoms and ventricular dysfunction and can range from 10 to 40%/yr. Specific factors that suggest a poor prognosis include hypotension, low EF, presence of CAD, troponin release, elevation of BUN, reduced GFR, hyponatremia, and poor functional capacity (eg, as tested by a 6-min walk test).

HF usually involves gradual deterioration, interrupted by bouts of severe decompensation, and ultimately death, although the time course is being lengthened with modern therapies. However, death can also be sudden and unexpected, without prior worsening of symptoms.

End-of-life care: All patients and family members should be taught about disease progression. For some patients, improving quality of life is as important as increasing quantity of life. Thus, it is important to determine patients' wishes about resuscitation (eg, endotracheal intubation, CPR) if their condition deteriorates, especially when HF is already severe. All patients should be reassured that symptoms will be relieved, and they should be encouraged to seek medical attention early if their symptoms change significantly. Involvement of pharmacists, nurses, social workers, and clergy, who may be part of an interdisciplinary team or disease management program already in place, is particularly important in end-of-life care.

Treatment

• Diet and lifestyle changes
• Treatment of cause
• Drugs (numerous classes)
• Sometimes device therapy (eg, implantable cardioverter-defibrillator, biventricular pacing)
• Multidisciplinary care

Immediate inpatient treatment is required for patients with acute or worsening HF due to certain disorders (eg, acute MI, atrial fibrillation with a very rapid ventricular rate, severe hypertension, acute valvular regurgitation), as well as for patients with pulmonary edema (see p. 2131), severe symptoms, new-onset HF, or HF unresponsive to outpatient treatment. Patients with mild exacerbations of previously diagnosed HF can be treated at home.

The primary goal is to diagnose and to correct or treat the disorder that led to HF.

Short-term goals include relieving symptoms; improving hemodynamics; avoiding hypokalemia, renal dysfunction, and symptomatic hypotension; and correcting neurohumoral activation.

Long-term goals include correcting hypertension, preventing MI and atherosclerosis, improving cardiac function, reducing hospitalizations, and improving survival and quality of life. Treatment involves dietary and lifestyle changes, drugs (see p. 2128), devices, and sometimes percutaneous coronary interventions or surgery.

Treatment is tailored to the patient, considering causes, symptoms, and response to drugs, including adverse effects. Treatment of systolic and diastolic dysfunction has become more similar, although there are more evidence-based therapies for systolic HF.

General management: General measures, especially patient and caregiver education and diet and lifestyle modifications, are important for all HF patients.

• Education
• Na restriction

• Appropriate weight and fitness levels

• Correction of underlying conditions

Patient and caregiver education are critical to long-term success. The patient and family should be involved in treatment choices. They should be taught the importance of drug adherence, warning signs of decompensation, and how to link cause with effect (eg, increased salt in the diet with weight gain or symptoms).

Many centers (eg, specialized outpatient clinics) have integrated health care practitioners from different disciplines (eg, HF nurses, pharmacists, social workers, rehabilitation specialists) into multidisciplinary teams or outpatient HF management programs. These approaches can improve outcomes and reduce hospitalizations and are most effective in the sickest patients.

Dietary Na restriction helps limit fluid retention. All patients should eliminate salt in cooking and at the table and avoid salted foods; the most severely ill should limit Na to < 2 g/day by consuming only low-Na foods. Monitoring daily morning weight helps detect Na and water accumulation early. If weight increases > 2 kg over a few days, patients may be able to adjust their diuretic dose themselves, but if weight gain continues or symptoms occur, patients should seek medical attention. Intensive case management, particularly by monitoring drug adherence and frequency of unscheduled visits to the physician or emergency department and hospitalizations, can identify when intervention is needed. Specialized HF nurses are valuable in education, follow-up, and dosage adjustment according to predefined protocols.

Patients with atherosclerosis or diabetes should strictly follow a diet appropriate for their disorder. Obesity may cause and always aggravates the symptoms of HF; patients should attain a body mass index (BMI) of 21 to 25.

Regular light activity (eg, walking), tailored to symptoms, is generally encouraged. Activity prevents skeletal muscle deconditioning, which worsens functional status; whether this measure improves survival is under study. Rest is appropriate during acute exacerbations. The role of formal exercise rehabilitation programs is being studied; initial results appear favorable.

If hypertension, severe anemia, hemochromatosis, uncontrolled diabetes, thyrotoxicosis, beriberi, alcoholism, Chagas' disease, or toxoplasmosis is successfully treated, patients may dramatically improve. Significant myocardial ischemia should be treated aggressively; treatment may include revascularization by percutaneous coronary intervention (see p. 2059) or bypass surgery (see p. 2052). Management of extensive ventricular infiltration (eg, in amyloidosis) remains unsatisfactory.

Arrhythmias (see also p. 2142): It is important to identify and treat the cause of an arrhythmia.

• Electrolytes are normalized.

• Atrial and ventricular rate are controlled.

• Sometimes antiarrhythmic drugs are given.

Sinus tachycardia, a common compensatory change in HF, usually subsides when HF treatment is effective. If it does not, associated causes (eg, hyperthyroidism, pulmonary emboli, fever, anemia) should be sought. If it persists despite correction of causes, a β-blocker, given in gradually increasing doses, should be considered.

Atrial fibrillation with an uncontrolled ventricular rate must be treated; the target resting ventricular rate is typically < 80 beats/min. β-Blockers are the treatment of choice, although rate-limiting Ca channel blockers may be used cautiously if systolic function is preserved. Adding digoxin or low-dose amiodarone may help some patients. Routine conversion to and maintenance of sinus rhythm has not been shown to be superior to rate control alone in a recent large clinical trial. If rapid atrial fibrillation does not respond to
drugs, permanent pacemaker insertion with complete or partial ablation of the atrioventricular node may be considered in selected patients.

Isolated ventricular premature beats, which are common in HF, do not require specific treatment. However, optimization of HF treatments and correction of electrolyte abnormalities (especially K and Mg) reduce the risk of ventricular arrhythmias. Sustained ventricular tachycardia that persists despite correction of cause (eg, low K or Mg, ischemia) and optimal medical treatment of HF may require an antiarrhythmic drug. Amiodarone and β-blockers are the drugs of choice because other antiarrhythmics have adverse proarrhythmic effects when LV systolic dysfunction is present. Because amiodarone increases digoxin levels, the digoxin dose should be decreased by half. Because long-term use of amiodarone can cause adverse effects, a low-dose (200 to 300 mg po once/day) is used when possible; blood tests for liver function and thyroid-stimulating hormone are done every 6 mo, and if chest x-ray is abnormal or dyspnea worsens significantly, chest x-ray and pulmonary function tests are done yearly to check for pulmonary fibrosis. For sustained ventricular arrhythmias, amiodarone may be required; to reduce risk of sudden death, a loading dose of 400 to 800 mg po bid is given for 1 to 3 wk until rhythm control is adequate, then dose is decreased over 1 mo to a maintenance dose of 400 mg po once/day.

Device therapy: Use of an implantable cardioverter-defibrillator (ICD) or biventricular pacing is appropriate for some patients.

An ICD is recommended for patients with an otherwise good life expectancy if they have symptomatic sustained ventricular tachycardia (especially if it causes syncope), ventricular fibrillation, or an LVEF persistently < 0.30 while receiving good medical therapy.

Biventricular pacing (cardiac resynchronization therapy [CRT]) may relieve symptoms and reduce HF hospitalizations for patients who have HF, LVEF < 0.35, and a widened QRS complex (> 0.12 sec). Better ways of detecting ventricular dyssynchrony may help identify patients most likely to respond to CRT. CRT devices are effective but expensive, and patients must be appropriately selected.

Ultrafiltration (venovenous filtration) can be useful in selected hospitalized patients with severe volume overload if they have not responded well to diuretic therapy and have rising serum creatinine (cardiorenal syndrome). Long-term benefits are still unclear.

An intra-aortic counterpulsation balloon pump is helpful in selected patients who have a good chance of recovery (eg, acute HF following MI). LV assist devices are implantable pumps that augment LV output. They were initially used only as a short-term intervention to maintain patients with severe HF awaiting transplant but are sometimes now used for extended periods (1 to 2 yr) in patients who are not transplant candidates. However, although survival can be prolonged, few patients are able to recover sufficiently to tolerate device removal.

Surgery: Surgery may be appropriate when certain underlying disorders are present. Usually, surgery in HF patients should be done in a specialized center. Surgical closure of congenital or acquired intracardiac shunts can be curative. Coronary artery bypass grafting to reduce ischemia may help some patients with ischemic cardiomyopathy and is currently being studied in a large clinical trial of HF patients with ischemic systolic dysfunction. If HF is primarily due to a valvular disorder, valve repair or replacement is considered (see Ch. 214). Patients with primary mitral regurgitation are more likely to benefit than patients with mitral regurgitation secondary to LV dilation, in whom myocardial function is likely to continue to be poor postoperatively. Surgery is preferably done before myocardial dilation and damage become irreversible.

Heart transplantation (see p. 1131) is the treatment of choice for patients < 60 who have severe, refractory HF and no other life-threatening conditions and who are highly adherent to management recommendations. Some older patients with otherwise excellent health may be considered. Survival is 82% at 1 yr and 75% at 3 yr; however, mortality rate while waiting for a donor is 12 to 15%. Human organ donation remains low. LV assist devices can be a bridge to transplantation or recovery in carefully selected patients.

Experimental therapies: Artificial hearts are not yet a viable alternative. Stem cell transplantation is in
early-stage trials. Surgical options studied include implantation of restraining devices to reduce progressive dilation and a modified aneurysmectomy called surgical ventricular restoration, but neither showed clinical benefit.

Dynamic cardiomyoplasty, endocardial laser therapy, and excision of segments of dilated myocardium are no longer recommended.

**Persistent HF:** After treatment, symptoms often persist. Reasons include persistence of the underlying disorder (eg, hypertension, ischemia, valvular regurgitation) despite treatment; suboptimal treatment of HF; drug nonadherence; excess intake of dietary Na or alcohol; and presence of an undiagnosed thyroid disorder, anemia, or supervening arrhythmia (eg, atrial fibrillation with rapid ventricular response, intermittent ventricular tachycardia). Also, drugs used to treat other disorders may interfere with HF treatment. NSAIDs, thiazolidinediones (eg, pioglitazone) for diabetes, and short-acting dihydropyridine or nondihydropyridine Ca channel blockers can worsen HF and should be avoided unless no alternative exists; patients who must take such drugs should be followed closely.

**Drugs**

- **Symptom relief:** Diuretics, nitrates, or digoxin
- **Long-term management and improved survival:** ACE inhibitors, β-blockers, aldosterone receptor blockers, or angiotensin II receptor blockers (ARBs)

All these drug classes have been studied in systolic dysfunction, but fewer have been adequately studied in diastolic dysfunction. However, ACE inhibitors, ARBs, and β-blockers are generally used to treat diastolic HF. In patients with severe diastolic dysfunction, diuretics and nitrates should be used in lower doses because these patients do not tolerate reduced BP or plasma volume well. In patients with hypertrophic cardiomyopathy (see p. 2138), digoxin is not effective and may be harmful. All patients should be given clear and explicit information about their drugs, including the importance of timely prescription renewal and adherence to therapy, how to recognize adverse effects, and when to contact their physician. Research is seeking plasma biomarkers that may predict which patients might respond best to which drug or drug combination.

**Diuretics:** Diuretics (see Table 208-5 on p. 2073) are given to all patients with symptomatic systolic dysfunction and current or previous volume overload; dose is adjusted to the lowest dose that stabilizes weight and relieves symptoms. Loop diuretics are preferred. Furosemide is used most often, starting at 20 to 40 mg po once/day, increased to 120 mg once/day (or 60 mg bid) if needed based on response and renal function. Bumetanide is an alternative. In refractory cases, furosemide 40 to 160 mg IV, ethacrynic acid 50 to 100 mg IV, bumetanide 0.5 to 2 mg po or 0.5 to 1.0 mg IV, or metolazone 2.5 to 10 mg po may have an additive effect. IV infusion of furosemide (5 to 10 mg/h) may be helpful in selected patients with severe edema. Loop diuretics (particularly when used with metolazone) may cause hypovolemia with hypotension, hyponatremia, hypomagnesemia, and severe hypokalemia. The dose of diuretic required acutely can usually be gradually reduced when HF improves, and the diuretic may be stopped if other drugs improve heart function and clear HF symptoms. Using larger than required doses of diuretics lowers CO, impairs renal function, causes hypokalemia, and increases mortality. Serum electrolytes are monitored, initially daily (when diuretics are given IV) and subsequently as needed, particularly after a dose increase.

A K-sparing diuretic, either spironolactone or eplerenone (which are aldosterone receptor blockers), can be added to offset the K-losing effects of higher-dose loop diuretics. Hyperkalemia may result, especially when ACE inhibitors or ARBs are also taken, so electrolytes must still be monitored, especially during a dehydrating illness that could cause renal dysfunction. These drugs may have particular benefit in chronic RV failure, in which hepatic congestion results in elevated aldosterone levels as its metabolism is reduced.

Thiazide diuretics are not normally used as a single agent unless hypertension is present but may be added to furosemide for added diuresis.
Reliable patients are taught to take additional diuretic doses as needed when weight or peripheral edema increases. They should seek medical attention promptly if weight gain persists.

Experimental ADH blockers increase water excretion and serum Na levels and may cause less hypokalemia and renal dysfunction. Their clinical role remains to be defined.

**ACE inhibitors:** All patients with systolic dysfunction are given oral ACE inhibitors unless contraindicated (eg, by plasma creatinine > 2.8 mg/dL [> 250 μmol/L], bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, or previous angioedema due to ACE inhibitors).

ACE inhibitors reduce production of angiotensin II and breakdown of bradykinin, mediators that affect the sympathetic nervous system, endothelial function, vascular tone, and myocardial performance. Hemodynamic effects include arterial and venous vasodilation, sustained decreases in LV filling pressure during rest and exercise, decreased systemic vascular resistance, and favorable effects on ventricular remodeling. ACE inhibitors prolong survival and reduce HF hospitalizations. For patients with atherosclerosis and a vascular disorder, these drugs reduce MI and stroke risk. For patients with diabetes, they delay onset of nephropathy. Thus, ACE inhibitors may be used in patients with diastolic dysfunction and any of these disorders.

The starting dose typically should be low (usually one fourth to one half of the target dose depending on BP and renal function); the dose is gradually adjusted upward over 8 wk as tolerated, then continued indefinitely. Usual target doses of representative drugs include enalapril 10 to 20 mg bid, lisinopril 20 to 30 mg once/day, ramipril 5 mg bid, and captopril 50 mg tid.

If the hypotensive effect (more marked in patients with hyponatremia or volume depletion) is troublesome, it can often be minimized by separating administration of other BP-lowering drugs or reducing the dose of concomitant diuretics. ACE inhibitors often cause mild to moderate reversible serum creatinine elevation due to vasodilation of the efferent glomerular arteriole. An initial 20 to 30% increase in creatinine is no reason to stop the drug but does require slower increases in dose, reduction in diuretic dose, or avoidance of NSAIDs. Because aldosterone's effect is reduced, K retention may result, especially in patients receiving K supplements. Cough occurs in 5 to 15% of patients, probably because bradykinin accumulates, but other causes of cough should also be considered. Occasionally, rash or dysgeusia occurs. Angioedema is rare but can be life threatening and is a contraindication to this class of drugs. Alternatively, ARBs can be used, although rarely cross-reactivity is reported. Both are contraindicated in pregnancy.

Serum electrolytes and renal function should be measured before an ACE inhibitor is started, at 1 mo, and after each significant increase in dose or change in clinical condition. If dehydration or poor renal function due to acute illness develops, the ACE inhibitor dose may need to be reduced or the drug may be temporarily withheld.

**ARBs:** These drugs are not demonstrably superior to ACE inhibitors but are less likely to cause cough and angioedema; they may be used when these adverse effects prohibit ACE inhibitor use. ACE inhibitors and ARBs are equally effective post MI; however, their equivalence is less clear in chronic HF, and the best dose is still under study. Usual oral target doses are valsartan 160 mg bid, candesartan 32 mg once/day, and losartan 50 to 100 mg once/day. Introduction, upward titration, and monitoring of ARBs and ACE inhibitors are similar. Like ACE inhibitors, ARBs can cause reversible renal dysfunction, and the dose may need to be reduced or withheld temporarily during an acute dehydrating illness.

Adding an ARB to a regimen of an ACE inhibitor, β-blocker, and diuretic should be considered for HF patients with persistent symptoms and repeated hospitalizations. Such combination therapy requires increased monitoring of BP, serum electrolytes, and renal function.

**Aldosterone receptor blockers:** Because aldosterone can be produced independently of the renin-angiotensin system, its adverse effects are not inhibited completely even by maximal use of ACE inhibitors and ARBs. Thus, the aldosterone receptor blockers spironolactone, 25 to 50 mg po once/day, and eplerenone, 10 mg po once/day (does not cause gynecomastia in males), can reduce mortality, including from sudden death, in patients with LVEF < 30% and severe chronic HF or acute HF.
complicating acute MI. K supplements should be stopped. Serum K and creatinine should be checked every 1 to 2 wk for the first 4 to 6 wk and after dose changes; dose is lowered if K is between 5.5 and 6.0 mEq/L and stopped if K is > 6.0 mEq/L, if creatinine increases above 2.5 mg/dL (220 μmol/L), or if ECG changes of hyperkalemia are present. These drugs are usually not used in patients receiving both an ACE inhibitor and an ARB because of the high risk of hyperkalemia and renal dysfunction.

**β-Blockers:** β-Blockers, unless otherwise contraindicated (by asthma, 2nd- or 3rd-degree atrioventricular block, or previous intolerance), are an important addition to ACE inhibitors for chronic systolic dysfunction in most patients, including the elderly, and for diastolic dysfunction in hypertension and hypertrophic cardiomyopathy. They are best started when the patient has no evidence of pulmonary congestion. Some of these drugs improve LVEF, survival, and other major cardiovascular outcomes in patients with chronic systolic dysfunction, including those with severe symptoms. β-Blockers are particularly useful for diastolic dysfunction because they reduce heart rate, prolonging diastolic filling time, and possibly improve ventricular relaxation.

The starting dose should be low (one fourth of the target daily dose), then dose is gradually increased over 8 wk as tolerated. The acute negative inotropic effects of β-blockade may cause cardiac depression and fluid retention. In such cases, a temporary increase in diuretic dose and slower upward titration of the β-blocker dose is warranted. Tolerance may improve over time, and efforts should be made to reach target doses. Usual oral target doses are carvedilol 25 mg bid (50 mg bid for patients ≥ 85 kg), bisoprolol 10 mg once/day, and metoprolol 50 to 75 mg bid (tartrate) or 200 mg once/day (succinate extended-release). Carvedilol, a 3rd-generation nonselective β-blocker, is also a vasodilator with α-blocking and antioxidant effects; it is the preferred and most widely studied β-blocker but is more expensive in many countries. Some β-blockers (eg, bucindolol, xamoterol) do not appear beneficial and may be harmful.

During a severe, acute decompensation, β-blockers should not be started until patients are stabilized and have little evidence of fluid retention. For patients already taking a β-blocker, the dose may be temporarily reduced or, in severe decompensation, temporarily withheld but restarted and titrated again when patients are stable. For milder decompensations, the β-blocker dose should be continued with a temporary increase in diuretic dose.

After initial treatment, heart rate and myocardial O_2_ consumption decrease, and stroke volume and filling pressure are unchanged. With the slower heart rate, diastolic function improves. Ventricular filling returns to a more normal pattern (increasing in early diastole), which appears less restrictive. Improved myocardial function is measurable in some patients after 6 to 12 mo but may take longer; EF and CO increase, and LV filling pressure decreases. Exercise capacity improves.

**Vasodilators:** Hydralazine plus isosorbide dinitrate may help patients truly intolerant of ACE inhibitors or ARBs (usually because of significant renal dysfunction), although long-term benefit of this combination is limited. In African-American patients, this combination may also provide some additional benefits when added to standard therapy. As vasodilators, these drugs improve hemodynamics, reduce valvular regurgitation, and increase exercise capacity without causing significant renal impairment. Hydralazine is started at 25 mg po qid and increased every 3 to 5 days to a target total dose of 300 mg/day, although many patients cannot tolerate > 200 mg/day because of hypotension. Isosorbide dinitrate is started at 20 mg po tid (with a 12-h nitrate-free interval) and increased to a target of 40 to 50 mg tid. Whether lower doses (frequently used in clinical practice) provide long-term benefit is unknown. In general, vasodilators have been replaced by ACE inhibitors, which are easier to use, are usually better tolerated, and have greater proven benefit.

Nitrates alone can relieve HF symptoms; patients can be taught to use sublingual nitroglycerin spray as needed for acute dyspnea and a transdermal patch for nocturnal dyspnea. Nitrates are safe, effective, and well tolerated and are particularly helpful in patients with HF and angina. Adverse effects include hypotension and headache.

Other vasodilators such as Ca channel blockers are not used to treat systolic dysfunction. Short-acting dihydropyridines (eg, nifedipine) and nondihydropyridines (eg, diltiazem, verapamil) may be deleterious. However, amlodipine and felodipine are well tolerated and may be useful for patients with HF and associated angina or hypertension. Both drugs may cause peripheral edema; rarely, amlodipine causes
pulmonary edema. Felodipine should not be taken with grapefruit juice, which significantly increases plasma levels and adverse effects by inhibiting cytochrome P-450 metabolism. In patients with diastolic dysfunction, Ca channel blockers may be used as needed to treat hypertension or ischemia or to control ventricular rate in atrial fibrillation. Verapamil may be used in hypertrophic cardiomyopathy.

**Digitalis preparations:** These drugs inhibit the Na-K pump (Na^+-, K^+-ATPase). As a result, they cause weak positive inotropism, reduce sympathetic activity, block the atrioventricular node (slowing the ventricular rate in atrial fibrillation or prolonging the PR interval in sinus rhythm), reduce vasoconstriction, and improve renal blood flow. Digoxin is the most commonly prescribed digitalis preparation. It is excreted by the kidneys; elimination half-life is 36 to 40 h in patients with normal renal function.

Digoxin has no proven survival benefit but, when used with diuretics and an ACE inhibitor, may help control symptoms and reduce the likelihood of hospitalization. Digoxin is most effective in patients with large LV end-diastolic volumes and an S3. Acute withdrawal of digoxin may increase the hospitalization rate and worsen symptoms. In patients with normal renal function, digoxin, 0.125 to 0.375 mg po once/day depending on age, sex, and body size, achieves full digitalization in about 1 wk (5 half-lives). More rapid digitalization can be achieved with digoxin 0.5 mg IV over 15 min followed by 0.25 mg IV at 8 and 16 h or with 0.5 mg po followed by 0.25 mg po at 8, 16, and 24 h. Prescription patterns vary widely by physician and by country, but in general, doses are lower than those used in the past, and a trough (8- to 12-h post-dose) digoxin level of 1 ng/mL is acceptable.

Toxicity is a concern, especially in patients with renal dysfunction and perhaps in women. These patients may need a lower oral dose, as may elderly patients, patients with a low lean body mass, and patients also taking amiodarone; patients > 80 kg may need a higher dose. Digoxin (and all digitalis glycosides) has a narrow therapeutic window. The most important toxic effects are life-threatening arrhythmias (eg, ventricular fibrillation, ventricular tachycardia, complete atrioventricular block). Bidirectional ventricular tachycardia, nonparoxysmal junctional tachycardia in the presence of atrial fibrillation, and hyperkalemia are serious signs of digitalis toxicity. Nausea, vomiting, anorexia, diarrhea, confusion, amblyopia, and, rarely, xerophthalmia may occur. If hypokalemia or hypomagnesemia (often due to diuretic use) is present, lower doses and serum levels can still cause toxicity. Electrolyte levels should be monitored in patients taking diuretics and digoxin, so that abnormalities can be prevented if possible; K-sparing diuretics may be helpful.

When digitalis toxicity occurs, the drug should be stopped; electrolyte abnormalities should be corrected (IV if abnormalities are severe and toxicity is acute). Patients with severe toxicity are admitted to a monitored unit, and digoxin immune Fab (ovine antidigoxin antibody fragments) is given if arrhythmias are present or if significant overingestion is accompanied by a serum K of > 5 mEq/L. This drug is also useful for glycoside toxicity due to plant ingestion. Dose is based on the steady-state serum digoxin level or total amount ingested. Ventricular arrhythmias are treated with lidocaine or phenytoin. Atrioventricular block with a slow ventricular rate may require a temporary transvenous pacemaker. Isoproterenol is contraindicated because it increases risk of ventricular arrhythmia.

**Other drugs:** Various positive inotropic drugs have been evaluated in HF but, except for digoxin, they increase mortality risk. Regular outpatient IV infusions of inotropes (eg, dobutamine) increase mortality and are not recommended. Drugs under study include Ca sensitizers (eg, levosimendan), cytokine blockers, endothelin blockers, matrix metalloproteinase (MMP) inhibitors, and immune modulators.

**Pulmonary Edema**

Pulmonary edema is acute, severe left ventricular failure with pulmonary venous hypertension and alveolar flooding. Findings are severe dyspnea, diaphoresis, wheezing, and sometimes blood-tinged frothy sputum. Diagnosis is clinical and by chest x-ray. Treatment is with O2, IV nitrates, diuretics, and sometimes morphine and short-term IV positive inotropes, endotracheal intubation, and mechanical ventilation.

If left ventricular (LV) filling pressure increases suddenly, plasma fluid moves rapidly from pulmonary capillaries into interstitial spaces and alveoli, causing pulmonary edema. Although precipitating causes
vary by age and country, about one half of cases result from acute coronary ischemia; some from
decompensation of significant underlying heart failure (HF), including diastolic dysfunction HF due to
hypertension; and the rest from arrhythmia, an acute valvular disorder, or acute volume overload often
due to IV fluids. Drug or dietary nonadherence is often involved.

Symptoms and Signs

Patients present with extreme dyspnea, restlessness, and anxiety with a sense of suffocation. Cough
producing blood-tinged sputum, pallor, cyanosis, and marked diaphoresis are common; some patients
froth at the mouth. Frank hemoptysis is uncommon. The pulse is rapid and low volume, and BP is
variable. Marked hypertension indicates significant cardiac reserve; hypotension with systolic BP < 100
mg Hg is ominous. Inspiratory fine crackles are widely dispersed anteriorly and posteriorly over both lung
fields. Marked wheezing (cardiac asthma) may occur. Noisy respiratory efforts often make cardiac
auscultation difficult; a summation gallop—merger of 3rd (S₃) and 4th (S₄) heart sounds—may be
present. Signs of right ventricular (RV) failure (eg, neck vein distention, peripheral edema) may be
present.

Diagnosis

• Clinical evaluation showing severe dyspnea and pulmonary crackles

• Chest x-ray

• Sometimes serum brain natriuretic peptide (BNP) or N-terminal-pro BNP (NT-pro-BNP)

• ECG, cardiac markers, and other tests for etiology as needed

A COPD exacerbation can mimic pulmonary edema due to LV failure or even that due to biventricular
failure if cor pulmonale (see below) is present. Pulmonary edema may be the presenting symptom in
patients without a history of cardiac disorders, but COPD patients with such severe symptoms usually
have a history of COPD, although they may be too dyspneic to relate it.

A chest x-ray, done immediately, is usually diagnostic, showing marked interstitial edema. Bedside
measurement of serum BNP levels (elevated in pulmonary edema; normal in COPD exacerbation) is
helpful if the diagnosis is in doubt. ECG, pulse oximetry, and blood tests (cardiac markers, electrolytes,
BUN, creatinine, and, for severely ill patients, ABGs) are done. An echocardiogram may be helpful to
determine the cause of the pulmonary edema (eg, MI, valvular dysfunction, hypertensive heart disease,
dilated cardiomyopathy) and may influence the choice of therapies. Hypoxemia can be severe. CO₂
retention is a late, ominous sign of secondary hypoventilation.

Treatment

• O₂

• Furosemide

• Nitrates

• IV morphine

• Ventilatory assistance as needed

• Treatment of cause

Initial treatment includes 100% O₂ by nonrebreather mask; upright position; furosemide 0.5 to 1.0 mg/kg
IV; nitroglycerin 0.4 mg sublingually q 5 min, followed by an IV drip at 10 to 20 μg/min, titrated upward at
10 μg/min q 5 min as needed to a maximum 300 μg/min if systolic BP is > 100 mm Hg; and morphine 1 to
Specific additional treatment depends on etiology:

- For acute MI or another acute coronary syndrome, thrombolysis or direct percutaneous coronary angioplasty with or without a stent
- For severe hypertension, an IV vasodilator
- For supraventricular or ventricular tachycardia, direct-current cardioversion
- For rapid atrial fibrillation, to slow the ventricular rate, an IV β-blocker, IV digoxin, or cautious use of an IV Ca channel blocker (cardioversion is preferred)

Other treatments, such as IV BNP (nesiritide) and new inotropic drugs (levosimendan), remain under study to elucidate safety profiles and efficacy. Because fluid status before onset of pulmonary edema is usually normal in patients with acute MI, diuretics are less useful than in patients with chronic HF and may precipitate hypotension. If systolic BP falls < 100 mm Hg or shock develops, IV dobutamine and an intra-aortic balloon pump (counterpulsation) may be required (see p. 2297).

Once patients are stabilized, long-term HF treatment is as described on p. 2126.

**Cor Pulmonale**

Cor pulmonale is right ventricular enlargement secondary to a lung disorder that causes pulmonary artery hypertension. Right ventricular failure follows. Findings include peripheral edema, neck vein distention, hepatomegaly, and a parasternal lift. Diagnosis is clinical and by echocardiography. Treatment is directed at the cause.

Cor pulmonale results from a disorder of the lung or its vasculature; it does not refer to right ventricular (RV) enlargement secondary to left ventricular (LV) failure, a congenital heart disorder (eg, ventricular septal defect), or an acquired valvular disorder. Cor pulmonale is usually chronic but may be acute and reversible. Primary pulmonary hypertension (ie, not caused by a pulmonary or cardiac disorder) is discussed elsewhere (see p. 2065).

**Pathophysiology**

Lung disorders cause pulmonary hypertension by several mechanisms:

- Loss of capillary beds (eg, due to bullous changes in COPD or thrombosis in pulmonary embolism)
- Vasoconstriction caused by hypoxia, hypercapnia, or both
- Increased alveolar pressure (eg, in COPD, during mechanical ventilation)
- Medial hypertrophy in arterioles (often a response to pulmonary hypertension due to other mechanisms)

Pulmonary hypertension increases afterload on the RV, resulting in a cascade of events that is similar to what occurs in LV failure, including elevated end-diastolic and central venous pressure and ventricular hypertrophy and dilation. Demands on the RV may be intensified by increased blood viscosity due to hypoxia-induced polycythemia. Rarely, RV failure affects the LV if a dysfunctional septum bulges into the LV, interfering with filling and thus causing diastolic dysfunction.

**Etiology**

Acute cor pulmonale has few causes. Chronic cor pulmonale is usually caused by COPD, but there are
several less common causes (see Table 211-3). In patients with COPD, an acute exacerbation or pulmonary infection may trigger RV overload. In chronic cor pulmonale, risk of venous thromboembolism is increased.

Symptoms and Signs

Initially, cor pulmonale is asymptomatic, although patients usually have significant symptoms due to the underlying lung disorder (eg, dyspnea, exertional fatigue). Later, as RV pressures increase, physical signs commonly include a left parasternal systolic lift, a loud pulmonic component of the 2nd heart sound (S₂), and murmurs of functional tricuspid and pulmonic insufficiency. Later, an RV gallop rhythm (3rd [S₃] and 4th [S₄] heart sounds) augmented during inspiration, distended jugular veins (with a dominant a wave unless tricuspid regurgitation is present), hepatomegaly, and lower-extremity edema may occur.

Table 211-3. Causes of Cor Pulmonale

Diagnosis

- Clinical suspicion
- Echocardiography

Cor pulmonale should be suspected in all patients with one of its causes. Chest x-rays show RV and proximal pulmonary artery enlargement with distal arterial attenuation. ECG evidence of RV hypertrophy (eg, right axis deviation, QR wave in lead V₁, and dominant R wave in leads V₁ to V₃) correlates well with degree of pulmonary hypertension. However, because pulmonary hyperinflation and bullae in COPD cause realignment of the heart, physical examination, x-rays, and ECG may be relatively insensitive. Echocardiography or radionuclide imaging is done to evaluate LV and RV function; echocardiography can assess RV systolic pressure but is often technically limited by the lung disorder. Right heart catheterization may be required for confirmation.

Treatment

- Treatment of cause

Treatment is difficult; it focuses on the cause (see elsewhere in THE MANUAL), particularly alleviation or moderation of hypoxia. Early identification and treatment are important before structural changes become irreversible.

If peripheral edema is present, diuretics may seem appropriate, but they are helpful only if LV failure and pulmonary fluid overload are also present; they may be harmful because small decreases in preload often worsen cor pulmonale. Pulmonary vasodilators (eg, hydralazine, Ca channel blockers, nitrous oxide, prostacyclin, phosphodiesterase inhibitors), although beneficial in primary pulmonary hypertension, are not effective. Bosentan, an endothelin receptor blocker, also may benefit patients with primary pulmonary hypertension, but its use is not well studied in cor pulmonale. Digoxin is effective only if patients have concomitant LV dysfunction; caution is required because patients with COPD are sensitive to digoxin's effects. Phlebotomy during hypoxic cor pulmonale has been suggested, but the benefits of decreasing blood viscosity are not likely to offset the harm of reducing O₂-carrying capacity unless significant polycythemia is present. For patients with chronic cor pulmonale, long-term anticoagulants reduce risk of venous thromboembolism.
Chapter 212. Cardiomyopathies

Introduction

A cardiomyopathy is a primary disorder of the heart muscle. It is distinct from structural cardiac disorders such as coronary artery disease, valvular disorders, and congenital heart disorders. Cardiomyopathies are divided into 3 main types: dilated, hypertrophic, and restrictive (see Fig. 212-1) based on the pathologic features. The term ischemic cardiomyopathy refers to the dilated, poorly contracting myocardium that sometimes occurs in patients with severe coronary artery disease (with or without areas of infarction). Although it does not describe a primary myocardial disorder, the term remains in common use.

Manifestations of cardiomyopathies are usually those of heart failure and vary depending on whether there is systolic dysfunction, diastolic dysfunction, or both (see p. 2119). Some cardiomyopathies may also cause chest pain, syncope, or sudden death.

Evaluation typically includes ECG and echocardiography and sometimes MRI. Some patients require endomyocardial biopsy (transvenous right ventricular or retrograde left ventricular). Other tests are done as needed to determine the cause. Treatment depends on the specific type and cause of cardiomyopathy (see Table 212-1).

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is myocardial dysfunction causing heart failure in which ventricular dilation and systolic dysfunction predominate. Symptoms include dyspnea, fatigue, and peripheral edema. Diagnosis is clinical and by chest x-ray and echocardiography. Treatment is directed at the cause; if progressive and severe, heart transplantation may be needed.

Pathophysiology

In some patients, DCM is believed to start with acute myocarditis (probably viral in most cases), followed by a variable latent phase, a phase with diffuse necrosis of myocardial myocytes (due to an autoimmune reaction to virus-altered myocytes), and chronic fibrosis. Regardless of the cause, the myocardium dilates, thins, and hypertrophies in compensation (see Fig. 212-1), often leading to functional mitral or tricuspid regurgitation and atrial dilation.

The disorder affects both ventricles in most patients, only the left ventricle (LV) in a few (unless with an ischemic etiology), and only the right ventricle (RV) rarely.

Mural thrombi frequently form once chamber dilation is significant, especially during the acute myocarditis phase. Cardiac arrhythmias often complicate the acute myocarditis and late chronic dilated phases as may atrioventricular (AV) block. Atrial fibrillation commonly occurs as the left atrium dilates.

Etiology

DCM has many known and probably many unidentified causes (see Table 212-2). The most common cause in temperate zones is diffuse coronary artery disease (CAD) with diffuse ischemic myopathy. More than 20 viruses can cause DCM; in temperate zones, coxsackievirus B is most common. In Central and South America, Chagas’ disease due to Trypanosoma cruzi is the most common infectious cause. DCM is becoming increasingly common among patients with HIV infection. Other causes include toxoplasmosis, thyrotoxicosis, and beriberi. Many toxic substances, particularly alcohol, various organic solvents, and certain chemotherapeutic drugs (eg, doxorubicin, trastuzumab), damage the heart.

Stress and other hyperadrenergic states can trigger acute DCM that is typically reversible (as is that caused by prolonged episodes of tachycardia). An example is acute apical ballooning cardiomyopathy (takotsubo cardiomyopathy); in this disorder, only the apex of the LV is affected, causing regional wall...
dysfunction and sometimes focal dilation (ballooning).

Genetic factors play a role in 20 to 35% of cases; several genes and loci have been implicated.

Symptoms and Signs

Onset is usually gradual except in acute myocarditis, acute apical ballooning cardiomyopathy, and tachyarrhythmia-induced myopathy. Symptoms depend on which ventricle is affected. LV dysfunction causes exertional dyspnea and fatigue due to elevated LV diastolic pressure and low cardiac output. RV failure causes peripheral edema and neck vein distention. Infrequently the RV is predominantly affected in younger patients, and atrial arrhythmias and sudden death due to malignant ventricular tachyarrhythmias are typical. About 25% of all patients with DCM have atypical chest pain.

[Fig. 212-1. Forms of cardiomyopathy.]

[Table 212-1. Diagnosis and Treatment of Cardiomyopathies]

Diagnosis

• Chest x-ray

• ECG

• Echocardiography

• Testing for cause as indicated

Diagnosis is by history, physical examination, and exclusion of other common causes of ventricular failure (eg, systemic hypertension, primary valvular disorders, MI—see Table 212-1). Thus, chest x-ray, ECG, and echocardiography are required. If acute symptoms or chest pain is present, serum cardiac markers are measured; although typically indicative of coronary ischemia, troponin levels can be elevated in heart failure, especially if renal function is decreased. Specific causes suspected clinically are diagnosed (see elsewhere in THE MANUAL). If no specific cause is clinically apparent, serum ferritin and iron-binding capacity and thyroid-stimulating hormone levels are measured and serologic tests for Toxoplasma, T. cruzi, coxsackievirus, and echovirus may be done in appropriate cases.

Chest x-ray shows cardiomegaly, usually of all chambers. Pleural effusion, particularly on the right, often accompanies increased pulmonary venous pressure and interstitial edema.

The ECG may show sinus tachycardia and nonspecific ST-segment depression with low voltage or inverted T waves. Sometimes pathologic Q waves are present in the precordial leads, simulating previous MI. Left bundle branch block is common.

Echocardiography shows dilated, hypokinetic cardiac chambers and rules out primary valvular disorders. Segmental wall motion abnormalities, typical of MI, can also occur in DCM because the process may be patchy. Echocardiography may also show a mural thrombus. MRI is not routinely done but may be useful when detailed imaging of myocardial structure or function is needed. In cardiomyopathy, MRI may show abnormal myocardial tissue texture.

Coronary angiography is required when the diagnosis is in doubt after noninvasive tests, particularly for patients with chest pain or several cardiovascular risk factors or for elderly patients, who are more likely to have CAD. However, nonobstructive coronary artery lesions detected by angiography may not be the cause of DCM. Either ventricle can be biopsied during catheterization, but biopsy is not usually done because the yield can be low, the disease process can be patchy, and results may not change treatment.
Prognosis

Prognosis generally is poor, although prognosis has improved with current management regimens (eg, use of β-blockers): About 20% die in the first year and then about 10%/yr thereafter; about 40 to 50% of deaths are sudden, due to a malignant arrhythmia or an embolic event. Prognosis is better if compensatory hypertrophy preserves ventricular wall thickness and is worse if ventricular walls thin markedly and the ventricle dilates.

Treatment

• Cause (if any) treated

• Measures for heart failure

• Anticoagulants in some patients

• Possibly implantable cardioverter-defibrillator, biventricular pacing, or transplantation

Treatable primary causes (eg, toxoplasmosis, hemochromatosis, thyrotoxicosis, beriberi) are corrected. Otherwise, treatment is the same as for heart failure (see p. 2126): ACE inhibitors, β-blockers, aldosterone receptor blockers, angiotensin II receptor blockers, diuretics, digoxin, and nitrates. Corticosteroids, azathioprine, and equine antithymocyte globulin are no longer used; although they may shorten the acute phase of certain inflammatory myocarditic myopathies (eg, acute postviral or sarcoid myocarditis), they do not improve long-term outcome. Antivirals are not helpful.

Because mural thrombi may form, prophylactic oral anticoagulants (see p. 2228) are often given to help prevent systemic or pulmonary emboli, and a large randomized trial is underway to test whether this approach is effective. Patients with a previous cerebrovascular embolism, those with acute severe myocarditis, and some with severe LV dilation should receive anticoagulants.

Aggressive treatment of heart failure reduces risk of arrhythmia, but significant cardiac arrhythmias may be treated with antiarrhythmic drugs. Permanent pacemakers may be required if AV block occurs during the chronic dilated phase. However, AV block during acute myocarditis often resolves, so permanent pacemakers are usually not needed. If patients have a widened QRS interval with a low LV ejection fraction and severe symptoms despite optimized medical treatment, biventricular pacing should be considered. An implantable cardioverter-defibrillator may be used to prevent sudden arrhythmia-induced death.

Because prognosis may be poor, patients with DCM may become candidates for heart transplantation. Selection criteria include absence of associated systemic disorders and psychologic disorders and high, irreversible pulmonary vascular resistance; because donor hearts are scarce, younger patients (usually <60) are given higher priority.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a congenital or acquired disorder characterized by marked ventricular hypertrophy with diastolic dysfunction but without increased afterload (eg, from valvular aortic stenosis, coarctation of the aorta, systemic hypertension). Symptoms include dyspnea, chest pain, syncope, and sudden death. A systolic murmur, increased by Valsalva maneuver, is typically present in the hypertrophic obstructive type. Diagnosis is by echocardiography. Treatment is with β-blockers, verapamil, disopyramide, and sometimes chemical reduction or surgical removal of outflow tract obstruction.

HCM is a common cause of sudden death in young athletes (see p. 2236). It may cause unexplained syncope and may not be diagnosed before autopsy.
Most cases of HCM are inherited. At least 50 different mutations that are inherited in an autosomally dominant pattern have been identified; spontaneous mutations are common. Perhaps 1 in 500 people is affected; phenotypic expression varies markedly.

Pathophysiology

The myocardium is abnormal with cellular and myofibrillar disarray, although this finding is not specific for HCM. In the most common form, the upper interventricular septum below the aortic valve is markedly hypertrophied and thickened, with little or no hypertrophy of the left ventricular (LV) posterior wall; this pattern is called asymmetric septal hypertrophy. During systole, the septum thickens, and sometimes the anterior leaflet of the mitral valve, already abnormally oriented because of the abnormally shaped ventricle, is sucked toward the septum by a Venturi effect of high velocity blood flow, further obstructing the outflow tract and decreasing cardiac output. The resulting disorder may be termed hypertrophic obstructive cardiomyopathy. Less commonly, midventricular hypertrophy leads to an intracavitary gradient at the papillary muscle level. In both forms, the distal LV may ultimately thin and dilate. Apical hypertrophy can also occur but does not obstruct outflow, although it may obliterate the apical portion of the LV during systole. Sometimes the hypertrophy is diffuse and symmetrical.

Contractility is grossly normal, resulting in a normal ejection fraction (EF). Later, EF is elevated because the ventricle has a small volume and empties nearly completely to maintain cardiac output.

Hypertrophy results in a stiff, noncompliant chamber (usually the LV) that resists diastolic filling, elevating end-diastolic pressure and thus increasing pulmonary venous pressure. As resistance to filling increases, cardiac output decreases, an effect worsened by any outflow tract gradient present. Because tachycardia allows less time for filling, symptoms tend to appear mainly during exercise or tachyarrhythmias.

Coronary blood flow may be impaired, causing angina pectoris, syncope, or arrhythmias in the absence of epicardial coronary artery disease (CAD). Flow may be impaired because capillary density relative to myocyte size is inadequate (capillary/myocyte imbalance) or lumen diameter of intramyocardial coronary arteries is narrowed by intimal and medial hyperplasia and hypertrophy. Also, exercise lowers peripheral vascular resistance and aortic root diastolic pressure, thus reducing coronary perfusion pressure.

In some cases, myocytes gradually die, probably because capillary/myocyte imbalance causes chronic diffuse ischemia. As myocytes die, they are replaced by diffuse fibrosis. Then, the hypertrophied ventricle with diastolic dysfunction gradually dilates and systolic dysfunction also develops.

Infective endocarditis can complicate HCM because of the mitral valve abnormality and because of rapid blood flow through the outflow tract during early systole. Atrioventricular block is sometimes a late complication.

Symptoms and Signs

Typically, symptoms appear between ages 20 and 40 and are exertional. They include dyspnea, chest pain (usually resembling typical angina—see p. 2090), palpitations, and syncope. Because systolic function is preserved, fatigability is seldom reported.

Syncope usually occurs without warning during exertion either because outflow obstruction worsens with the increased contractility or because of nonsustained ventricular or atrial arrhythmia. Syncope is a marker of increased risk of sudden death, which is thought to result from ventricular tachycardia or fibrillation.

BP and heart rate are usually normal, and signs of increased venous pressure are rare. When the outflow tract is obstructed, the carotid pulse has a brisk upstroke, bifid peak, and rapid downstroke. The apex beat may have a sustained thrust due to LV hypertrophy. A4th heart sound (S4) is often present and is associated with a forceful atrial contraction against a poorly compliant LV in late diastole.

Septal hypertrophy produces a systolic ejection-type murmur that does not radiate to the neck and may
be heard at the left sternal edge in the 3rd or 4th intercostal space. A mitral regurgitation murmur due to distortion of the mitral apparatus may be heard at the apex. When the right ventricular outflow tract is narrowed, a systolic ejection murmur is sometimes heard in the 2nd interspace at the left sternal border. The LV outflow ejection murmur of HCM can be increased by a Valsalva maneuver (which reduces venous return and LV diastolic volume), by measures to lower aortic pressure (eg, nitroglycerin), or by a postextrasystolic contraction (which increases the outflow tract pressure gradient). Handgrip increases aortic pressure, thereby reducing the murmur’s intensity.

**Diagnosis**

- Clinical suspicion (syncope and murmur)
- Echocardiography

Diagnosis is suspected based on a typical murmur and symptoms. Unexplained syncope in young athletes should always raise suspicion. HCM must be distinguished from aortic stenosis and CAD, which cause similar symptoms. ECG and 2-dimensional echocardiography (the best noninvasive confirmatory test) are done. Chest x-ray is often taken but is usually normal because the ventricles are not dilated (although the left atrium may be enlarged). Patients with syncope or sustained arrhythmias should be evaluated as inpatients. Exercise testing and 24-h ambulatory monitoring may be helpful for patients considered at high risk, although identifying such patients is difficult.

The ECG usually shows voltage criteria for LV hypertrophy (eg, S wave in lead V1 plus R wave in lead V5 or V6 > 35 mm). Very deep septal Q waves in leads I, aVL, V5, and V6 are often present with asymmetric septal hypertrophy; HCM sometimes produces a QRS complex in V1 and V2, simulating previous septal infarction. T waves are usually abnormal; the most common finding is deep symmetric T-wave inversion in leads I, aVL, V5, and V6. ST-segment depression in the same leads is common (particularly in the apical obliterative form). The P wave is often broad and notched in leads II, III, and aVF, with a biphasic P wave in leads V1 and V2, indicating left atrial hypertrophy. Incidence of preexcitation phenomenon of the Wolff-Parkinson-White syndrome type, which may cause palpitations, is increased. Bundle branch block is common.

Two-dimensional Doppler echocardiography can differentiate the forms of cardiomyopathy (see Fig. 212-1) and quantify the degree of outflow tract obstruction, including pressure gradient and area of the stenotic segment. These measurements are particularly useful for monitoring the effect of medical or surgical treatment. Midsystolic closure of the aortic valve sometimes occurs when outflow tract obstruction is severe.

Cardiac catheterization is usually done only when invasive therapy is considered. Usually, no significant stenoses are present in the coronary arteries, but elderly patients may have coexisting CAD.

**Prognosis**

Overall, annual mortality is 1 to 3% for adults but is higher for children. Mortality rate is inversely proportional to the age at which symptoms appear and is highest in patients who have frequent nonsustained ventricular tachycardia or syncope or have been resuscitated after sudden cardiac arrest. Prognosis is worse for young patients with a family history of sudden death and for patients > 45 yr with angina or exertional dyspnea. Death is usually sudden, and sudden death is the most common sequelae; chronic heart failure occurs less often. Genetic counseling is appropriate for patients with asymmetric septal hypertrophy, which appears to accelerate during puberty.

**Treatment**

- β-Blockers
- Rate-limiting and negative inotropic Ca channel blockers
Avoidance of nitrates, diuretics, and ACE inhibitors

Possibly implantable cardioverter-defibrillator and sometimes surgery or ablative procedures

Treatment is directed primarily at abnormal diastolic compliance. β-Blockers and rate-limiting Ca channel blockers with a lower arterial dilation capacity (usually verapamil), alone or combined, are the mainstays. By decreasing myocardial contractility, these drugs dilate the heart. By slowing the heart rate, they prolong the diastolic filling period. Both effects decrease outflow obstruction, thus improving ventricular diastolic function. In severe cases, disopyramide may be added for its negative inotropic effect.

Drugs that reduce preload (eg, nitrates, diuretics, ACE inhibitors, angiotensin II receptor blockers) decrease chamber size and worsen symptoms and signs. Vasodilators increase the outflow tract gradient and cause a reflex tachycardia that further worsens ventricular diastolic function. Inotropic drugs (eg, digitalis glycosides, catecholamines) worsen outflow tract obstruction, do not relieve the high end-diastolic pressure, and may induce arrhythmias.

If syncope or sudden cardiac arrest has occurred or if ventricular arrhythmia is confirmed by ECG or 24-h ambulatory monitoring, an implantable cardioverter-defibrillator or antiarrhythmics should be considered. Competitive sports should be avoided because many sudden deaths occur during increased exertion.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is characterized by noncompliant ventricular walls that resist diastolic filling; one or both ventricles, most commonly the left, may be affected. Symptoms include fatigue and exertional dyspnea. Diagnosis is by echocardiography and cardiac catheterization. Treatment is often unsatisfactory and is best directed at the cause. Surgery is sometimes useful.

RCM is the least prevalent form of cardiomyopathy. It is classified as

- Nonobliterative (myocardial infiltration by an abnormal substance)
- Obliterative (fibrosis of the endocardium and subendocardium)

Either type may be diffuse or nondiffuse (when the disorder affects only one ventricle or part of one ventricle unevenly).

Etiology

The cause is usually unknown; identified causes are listed in Table 212-3. Some disorders that cause RCM also affect other tissues (eg, amyloidosis, hemochromatosis). Some myocardial infiltrative disorders also affect other cardiac tissue. Rarely, amyloidosis affects coronary arteries. Sarcoidosis and Fabry’s disease may also affect nodal conduction tissue. Loffler’s syndrome (a subcategory of hypereosinophilic syndrome with primary cardiac involvement), which occurs in the tropics, begins as an acute arteritis with eosinophilia, followed by thrombus formation on the endocardium, chordae, and atrioventricular (AV) valves, progressing to fibrosis. Endocardial fibroelastosis, which occurs in temperate zones, affects only the left ventricle.

Pathophysiology

Endocardial thickening or myocardial infiltration (sometimes with death of myocytes, papillary muscle
infiltration, compensatory myocardial hypertrophy, and fibrosis) may occur in one, typically the left, or both ventricles. As a result, the mitral or tricuspid valves may malfunction, leading to regurgitation. Functional AV valve regurgitation may result from myocardial infiltration or endocardial thickening. If nodal and conduction tissues are affected, the sinoatrial node malfunctions, sometimes causing various grades of AV block.

[Table 212-3. Causes of Restrictive Cardiomyopathy]

The main hemodynamic consequence is diastolic dysfunction (see p. 2120) with a rigid, noncompliant ventricle, impaired diastolic filling, and high filling pressure, leading to pulmonary venous hypertension. Systolic function may deteriorate if compensatory hypertrophy of infiltrated or fibrosed ventricles is inadequate. Mural thrombi can form, resulting in systemic emboli.

Symptoms and Signs

Symptoms are exertional dyspnea, orthopnea, and, when the right ventricle is affected, peripheral edema. Fatigue results from a fixed cardiac output due to resistance to ventricular filling. Atrial and ventricular arrhythmias and AV block are common; angina and syncope are uncommon. Symptoms and signs closely mimic those of constrictive pericarditis (see p. 2203).

Physical examination detects a quiet precordium, a low-volume and rapid carotid pulse, pulmonary crackles, and pronounced neck vein distention with a rapid y descent (see Fig. 206-1 on p. 2020). A 4th heart sound (S4) is almost always present; a 3rd heart sound (S3) may occur and must be differentiated from the precordial knock of constrictive pericarditis. In some cases, a murmur of functional mitral or tricuspid regurgitation results because myocardial or endocardial infiltration or fibrosis changes chordae or ventricular geometry. Pulsus paradoxus does not occur.

Diagnosis

• Echocardiography

• Testing for cause

ECG, chest x-ray, and echocardiography are required. The ECG is usually nonspecifically abnormal, showing ST-segment and T-wave abnormalities and sometimes low voltage. Pathologic Q waves, not due to previous MI, sometimes occur. Left ventricular hypertrophy due to compensatory myocardial hypertrophy sometimes occurs. On chest x-ray, the heart size is often normal or small but can be enlarged in late-stage amyloidosis or hemochromatosis.

Echocardiography shows normal systolic function. Common findings include dilated atria and myocardial hypertrophy. RCM due to amyloidosis has an unusually bright echo pattern from the myocardium. Echocardiography helps differentiate constrictive pericarditis with its thickened pericardium, but paradoxical septal motion can occur in either disorder. If the diagnosis is still in doubt, CT may be more sensitive in showing whether the pericardium is normal, and MRI can show abnormal myocardial texture in disorders with myocardial infiltration (eg, by amyloid or iron).

Cardiac catheterization and myocardial biopsy are not often necessary. If done, catheterization detects high atrial pressure in RCM, with a prominent y descent and an early diastolic dip followed by a high diastolic plateau in the ventricular pressure curve. In contrast to constrictive pericarditis findings, diastolic pressure is usually a few mm Hg higher in the left ventricle than in the right. Angiography detects normal-sized ventricular cavities with normal or decreased systolic shortening. AV valve regurgitation may be present. Biopsy can detect endocardial fibrosis and thickening, myocardial infiltration by iron or amyloid, and chronic myocardial fibrosis. Coronary angiography is normal, except when amyloidosis affects epicardial coronary arteries. Occasionally, cardiac catheterization is not diagnostic, and rarely, thoracotomy is required to explore the pericardium.

Tests for the most common causes of RCM (eg, rectal biopsy for amyloidosis, iron tests or liver biopsy for
hemochromatosis) should be done.

**Prognosis**

Prognosis is poor (see Table 212-1) because the diagnosis is often made at a late stage. No treatment is available for most patients; symptomatic, supportive care can be provided.

**Treatment**

- Cause treated
- Diuretics considered

Diuretics may be used for patients with edema or pulmonary vascular congestion but must be given cautiously because they can lower preload; the noncompliant ventricles depend on preload to maintain cardiac output. Digitalis does little to alter hemodynamic abnormalities and may cause serious arrhythmias in cardiomyopathy due to amyloidosis, in which extreme digitalis sensitivity is common. If heart rate is elevated, β-blockers or rate-limiting Ca channel blockers may be used cautiously in low doses. Afterload reducers (eg, nitrates) may cause profound hypotension and usually are not useful.

If the diagnosis is made at an early stage, specific treatment of hemochromatosis, sarcoidosis, and Loffler's syndrome may help.

Transplantation is not recommended because the disorder may recur in the transplanted heart.
Chapter 213. Arrhythmias and Conduction Disorders

Introduction

The normal heart beats in a regular, coordinated way because electrical impulses generated and spread by myocytes with unique electrical properties trigger a sequence of organized myocardial contractions. Arrhythmias and conduction disorders are caused by abnormalities in the generation or conduction of these electrical impulses or both.

Any heart disorder, including congenital abnormalities of structure (eg, accessory atrioventricular connection) or function (eg, hereditary ion channelopathies), can disturb rhythm. Systemic factors that can cause or contribute to a rhythm disturbance include electrolyte abnormalities (particularly low K or Mg), hypoxia, hormonal imbalances (eg, hypothyroidism, hyperthyroidism), and drugs and toxins (eg, alcohol, caffeine).

Anatomy

At the junction of the superior vena cava and high lateral right atrium is a cluster of cells that generates the initial electrical impulse of each normal heart beat, called the sinoatrial (SA) or sinus node. Electrical discharge of these pacemaker cells stimulates adjacent cells, leading to stimulation of successive regions of the heart in an orderly sequence. Impulses are transmitted through the atria to the atrioventricular (AV) node via preferentially conducting internodal tracts and unspecialized atrial myocytes. The AV node is located on the right side of the interatrial septum. It has a slow conduction velocity and thus delays impulse transmission. AV nodal transmission time is heart-rate-dependent and is modulated by autonomic tone and circulating catecholamines to maximize cardiac output at any given atrial rate.

The atria are electrically insulated from the ventricles by the annulus fibrosus except in the anteroseptal region. There, the bundle of His, the continuation of the AV node, enters the top of the interventricular septum, where it bifurcates into the left and right bundle branches, which terminate in Purkinje fibers. The right bundle branch conducts impulses to the anterior and apical endocardial regions of the right ventricle. The left bundle branch fans out over the left side of the interventricular septum. Its anterior portion (left anterior hemifascicle) and its posterior portion (left posterior hemifascicle) stimulate the left side of the interventricular septum, which is the first part of the ventricles to be electrically activated. Thus, the interventricular septum depolarizes left to right, followed by near-simultaneous activation of both ventricles from the endocardial surface through the ventricular walls to the epicardial surface.

Physiology

An understanding of normal cardiac physiology is essential before rhythm disturbances can be understood.

Electrophysiology: The passage of ions across the myocyte cell membrane is regulated through specific ion channels that cause cyclical depolarization and repolarization of the cell, called an action potential. The action potential of a working myocyte begins when the cell is depolarized from its diastolic -90 mV transmembrane potential to a potential of about -50 mV. At this threshold potential, voltage-dependent fast Na channels open, causing rapid depolarization mediated by Na influx down its steep concentration gradient. The fast Na channel is rapidly inactivated and Na influx stops, but other time- and voltage-dependent ion channels open, allowing Ca to enter through slow Ca channels (a depolarizing event) and K to leave through K channels (a repolarizing event). At first, these 2 processes are balanced, maintaining a positive transmembrane potential and prolonging the plateau phase of the action potential. During this phase, Ca entering the cell is responsible for electromechanical coupling and myocyte contraction. Eventually, Ca influx ceases, and K efflux increases, causing rapid repolarization of the cell back to the -90 mV resting transmembrane potential. While depolarized, the cell is resistant (refractory) to a subsequent depolarizing event. Initially, a subsequent depolarization is not possible (absolute refractory period), and after partial but incomplete repolarization, a subsequent depolarization is possible but occurs slowly (relative refractory period).

There are 2 general types of cardiac tissue:
• Fast-channel tissues

• Slow-channel tissues

**Fast-channel tissues** (working atrial and ventricular myocytes, His-Purkinje system) have a high density of fast Na channels and action potentials characterized by little or no spontaneous diastolic depolarization (and thus very slow rates of pacemaker activity), very rapid initial depolarization rates (and thus rapid conduction velocity), and loss of refractoriness coincident with repolarization (and thus short refractory periods and the ability to conduct repetitive impulses at high frequencies).

**Slow-channel tissues** (SA and AV nodes) have a low density of fast Na channels and action potentials characterized by more rapid spontaneous diastolic depolarization (and thus more rapid rates of pacemaker activity), slow initial depolarization rates (and thus slow conduction velocity), and loss of refractoriness that is delayed after repolarization (and thus long refractory periods and the inability to conduct repetitive impulses at high frequencies).

Normally, the SA node has the most rapid rate of spontaneous diastolic depolarization, so its cells produce spontaneous action potentials at a higher frequency than other tissues. Thus, the SA node is the dominant automatic tissue (pacemaker) in a normal heart. If the SA node does not produce impulses, tissue with the next highest automaticity rate, typically the AV node, functions as the pacemaker. Sympathetic stimulation increases the discharge frequency of pacemaker tissue, and parasympathetic stimulation decreases it.

**Normal rhythm:** The resting sinus heart rate in adults is usually 60 to 100 beats/min. Slower rates (sinus bradycardia) occur in young people, particularly athletes (see p. 2238), and during sleep. Faster rates (sinus tachycardia) occur with exercise, illness, or emotion through sympathetic neural and circulating catecholamine drive. Normally, a marked diurnal variation in heart rate occurs, with lowest rates just before early morning awakening. A slight increase in rate during inspiration with a decrease in rate during expiration (respiratory sinus arrhythmia) is also normal; it is mediated by oscillations in vagal tone and is particularly common among healthy young people. The oscillations lessen but do not entirely disappear with age. Absolute regularity of the sinus rhythm rate is pathologic and occurs in patients with autonomic denervation (eg, in advanced diabetes) or with severe heart failure.

Most cardiac electrical activity is represented on the ECG (see Fig. 207-1 on p. 2050), although SA node, AV node, and His-Purkinje depolarization does not involve enough tissue to be detected. The P wave represents atrial depolarization. The QRS complex represents ventricular depolarization, and the T wave represents ventricular repolarization.

The PR interval (from the beginning of the P wave to the beginning of the QRS complex) is the time from the beginning of atrial activation to the beginning of ventricular activation. Much of this interval reflects slowing of impulse transmission in the AV node. The R-R interval (time between 2 QRS complexes) represents the ventricular rate. The QT interval (from the beginning of the QRS complex to the end of the T wave) represents the duration of ventricular depolarization. Normal values for the QT interval are slightly longer in women; they are also longer with a slower heart rate. The QT interval is corrected (QTc) for influence of heart rate. The most common formula (all intervals in sec) is:

\[
QTc = \frac{QT}{\sqrt{RR}}
\]

**Pathophysiology**

Rhythm disturbances result from abnormalities of impulse formation, impulse conduction, or both. Bradyarrhythmias result from decreased intrinsic pacemaker function or blocks in conduction, principally within the AV node or the His-Purkinje system. Most tachyarrhythmias are caused by reentry; some result from enhanced normal automaticity or from abnormal mechanisms of automaticity.

**Reentry** is the circular propagation of an impulse around 2 interconnected pathways with different
conduction characteristics and refractory periods (see Fig. 213-1).

Under certain conditions, typically precipitated by a premature beat, reentry can produce continuous circulation of an activation wavefront, causing a tachyarrhythmia (see Fig. 213-2). Normally, reentry is prevented by tissue refractoriness following stimulation. However, 3 conditions favor reentry: shortening of tissue refractoriness (eg, by sympathetic stimulation), lengthening of the conduction pathway (eg, by hypertrophy or abnormal conduction pathways), and slowing of impulse conduction (eg, by ischemia).

Symptoms and Signs

Arrhythmia and conduction disturbances may be asymptomatic or cause palpitations (sensation of skipped beats or rapid or forceful beats—see p. 2038), symptoms of hemo-dynamic compromise (eg, dyspnea, chest discomfort, presyncope, syncope), or cardiac arrest. Occasionally, polyuria results from release of atrial natriuretic peptide during prolonged supraventricular tachycardias (SVTs).

Palpation of pulse and cardiac auscultation can determine ventricular rate and its regularity or irregularity. Examination of the jugular venous pulse waves may help in the diagnosis of AV blocks and atrial tachyarrhythmias. For example, in complete AV block, the atria intermittently contract when the AV valves are closed, producing large a (cannon) waves in the jugular venous pulse (see p. 2020). Other physical findings of arrhythmias are few.

Diagnosis

• ECG

History and physical examination may detect an arrhythmia and suggest possible causes, but diagnosis requires a 12-lead ECG or, less reliably, a rhythm strip, preferably obtained during symptoms to establish the relationship between symptoms and rhythm.

The ECG is approached systematically; calipers measure intervals and identify subtle irregularities. The key diagnostic features are rate of atrial activation, rate and regularity of ventricular activation, and the relationship between the two. Irregular activation signals are classified as regularly irregular or irregularly irregular (no detectible pattern). Regular irregularity is intermittent irregularity in an otherwise regular rhythm (eg, premature beats) or a predictable pattern of irregularity (eg, recurrent relationships between groups of beats).

A narrow QRS complex (< 0.12 sec) indicates a supraventricular origin (above the His bundle bifurcation). A wide QRS complex (≥ 0.12 sec) indicates a ventricular origin (below the His bundle bifurcation) or a supraventricular rhythm conducted with an intraventricular conduction defect or with ventricular preexcitation in the Wolff-Parkinson-White syndrome.

Bradyarrhythmias: ECG diagnosis of bradyarrhythmias depends on the presence or absence of P waves, morphology of the P waves, and the relationship between P waves and QRS complexes.

A bradyarrhythmia with no relationship between P waves and QRS complexes indicates AV dissociation; the escape rhythm can be junctional (narrow QRS complex) or ventricular (wide QRS complex).

A regular QRS rhythm with a 1:1 relationship between P waves and QRS complexes indicates absence of AV block. P waves preceding QRS complexes indicate sinus bradycardia (if P waves are normal) or sinus arrest with an escape atrial bradycardia (if P waves are abnormal). P waves after QRS complexes indicate sinus arrest with a junctional or ventricular escape rhythm and retrograde atrial activation. A ventricular escape rhythm results in a wide QRS complex; a junctional escape
rhythm usually has a narrow QRS (or a wide QRS with bundle branch block or preexcitation).

When the QRS rhythm is irregular, P waves usually outnumber QRS complexes; some P waves produce QRS complexes, but some do not (indicating 2nd-degree AV block—see p. 2163). An irregular QRS rhythm with a 1:1 relationship between P waves and the following QRS complexes usually indicates sinus arrhythmia with gradual acceleration and deceleration of the sinus rate (if P waves are normal). Pauses in an otherwise regular QRS rhythm may be caused by blocked P waves (an abnormal P wave can usually be discerned just after the preceding T wave or distorting the morphology of the preceding T wave), sinus arrest, or sinus exit block (see p. 2161), as well as by 2nd-degree AV block.

**Tachyarrhythmias**: Tachyarrhythmias may be divided into 4 groups, defined by being visibly regular vs irregular and by having a narrow vs wide QRS complex.

**Irregular, narrow QRS complex** tachyarrhythmias include atrial fibrillation (AF), atrial flutter or true atrial tachycardia with variable AV conduction, and multifocal atrial tachycardia. Differentiation is based on atrial ECG signals, which are best seen in the longer pauses between QRS complexes. Atrial ECG signals that are continuous, irregular in timing and morphology, and very rapid (>300/min) without discrete P waves indicate AF. Discrete P waves that vary from beat to beat with at least 3 different morphologies suggest multifocal atrial tachycardia. Regular, discrete, uniform atrial signals without intervening isoelectric periods suggest atrial flutter.

**Irregular, wide QRS complex** tachyarrhythmias include the above 4 atrial tachyarrhythmias, conducted with either bundle branch block or ventricular preexcitation, and polymorphic ventricular tachycardia (VT). Differentiation is based on atrial ECG signals and the presence in polymorphic VT of a very rapid rate (>250/min).

**Regular, narrow QRS complex** tachyarrhythmias include sinus tachycardia, atrial flutter or true atrial tachycardia with a consistent AV conduction ratio, and paroxysmal SVTs (AV nodal reentrant SVT, orthodromic reciprocating AV tachycardia in the presence of an accessory AV connection, and SA nodal reentrant SVT). Vagal maneuvers or pharmacologic AV nodal blockade can help distinguish among these tachycardias. With these maneuvers, sinus tachycardia is not terminated, but it slows or AV block develops, disclosing normal P waves. Similarly, atrial flutter and true atrial tachycardia are usually not terminated, but AV block discloses flutter waves or abnormal P waves. The most common forms of paroxysmal SVT (AV nodal reentry and orthodromic reciprocating tachycardia) must terminate if AV block occurs.

**Regular, wide QRS complex** tachyarrhythmias include those listed for a regular, narrow QRS complex tachyarrhythmia, each with bundle branch block or ventricular pre-excitation, and monomorphic VT. Vagal maneuvers can help distinguish among them. ECG criteria to distinguish between VT and SVT with an intraventricular conduction defect have been proposed (see Table 213-1). When in doubt, the rhythm is assumed to be VT because some drugs for SVTs can worsen the clinical state if the rhythm is VT; however, the reverse is not true.

**Treatment**

• Treatment of cause

• Sometimes antiarrhythmic drugs, implantable cardioverter-defibrillators, and pacemakers

The need for treatment varies; it is guided by symptoms and risks of the arrhythmia. Asymptomatic arrhythmias without serious risks do not require treatment even if they worsen. Symptomatic arrhythmias may require treatment to improve quality of life. Potentially life-

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**Table 213-1. Modified Brugada Criteria for Ventricular Tachycardia**
threatening arrhythmias require treatment.

Treatment is directed at causes. If necessary, direct antiarrhythmic therapy, including anti-arrhythmic
drugs, cardioversion-defibrillation, pacemakers, or a combination, is used. Patients with arrhythmias that
have caused or are likely to cause symptoms of hemodynamic compromise may have to be restricted
from driving until response to treatment has been assessed.

**Drugs for Arrhythmias**

Most antiarrhythmic drugs are grouped into 4 main classes (Vaughan Williams classification) based on
their dominant cellular electrophysiologic effect (see Table 213-2). Digoxin and adenosine are not included in the Vaughan Williams classification. Digoxin shortens atrial and ventricular refractory periods and is vagotonic, thereby prolonging AV nodal
conduction and AV nodal refractory periods. Adenosine slows or blocks AV nodal conduction and can
terminate tachyarrhythmias that rely upon AV nodal conduction for their perpetuation.

**Class I:** Na channel blockers (membrane-stabilizing drugs) block fast Na channels, slowing conduction in
fast-channel tissues (working atrial and ventricular myocytes, His-Purkinje system). In the ECG, this effect
may be reflected as widening of the P wave, widening of the QRS complex, prolongation of the PR
interval, or a combination.

Class I drugs are subdivided based on the kinetics of the Na channel effects. Class Ib drugs have fast
kinetics, class Ic drugs have slow kinetics, and class la drugs have intermediate kinetics. The kinetics of
Na channel blockade determine the heart rates at which their electrophysiologic effects become manifest.
Because class Ib drugs have fast kinetics, they express their electrophysiologic effects only at fast heart
rates. Thus, an ECG obtained during normal rhythm at normal rates usually shows no evidence of fast-
channel tissue conduction slowing. Class Ib drugs are not very potent antiarrhythmics and have minimal
effects on atrial tissue. Because class Ic drugs have slow kinetics, they express their electrophysiologic
effects at all heart rates. Thus, an ECG obtained during normal rhythm at normal heart rates usually
shows fast-channel tissue conduction slowing. Class Ic drugs are more potent antiarrhythmics. Because
class la drugs have intermediate kinetics, their fast-channel tissue conduction slowing effects may or may
not be evident on an ECG obtained during normal rhythm at normal rates. Class Ia drugs also block
repolarizing K channels, prolonging the refractory periods of fast-channel tissues. On the ECG, this effect
is reflected as QT-interval prolongation even at normal rates. Class Ib drugs and class Ic drugs do not
block K channels directly.

The primary indications are SVTs for class Ia and Ic drugs and VTs for all class I drugs. The most
worrisome adverse effect is proarrhythmia, a drug-related arrhythmia worse than the arrhythmia being
treated. Class Ia drugs may cause torsades de pointes VT; class Ia and class Ic drugs may organize and
slow atrial tachyarrhythmias enough to permit 1:1 AV conduction with marked acceleration of the
ventricular response rate. All class I drugs may worsen VTs. They also tend to depress ventricular
contractility. Because these adverse effects are more likely to occur in patients with a structural heart
disorder, class I drugs are not generally recommended for such patients. Thus, these drugs are usually
used only in patients who do not have a structural heart disorder or in patients who have a structural
heart disorder but who have no other therapeutic alternatives.

**Class II:** Class II drugs are β-blockers, which affect predominantly slow-channel tissues (SA and AV
nodes), where they decrease rate of automaticity, slow conduction velocity, and prolong refractoriness.
Thus, heart rate is slowed, the PR interval is lengthened, and the AV node transmits rapid atrial
depolarizations at a lower frequency. Class II drugs are used primarily to treat SVTs, including sinus
tachycardia, AV nodal reentry, AF, and atrial flutter. These drugs are also used to treat VTs to raise the
threshold for ventricular fibrillation (VF) and reduce the ventricular proarrhythmic effects of β-
adrenoceptor stimulation. β-Blockers are generally well tolerated; adverse effects include lassitude, sleep
disturbance, and GI upset. These drugs are contraindicated in patients with asthma.

**Class III:** Class III drugs are primarily K channel blockers, which prolong action potential duration and
refractoriness in slow-and fast-channel tissues. Thus, the capacity of all cardiac tissues to transmit
impulses at high frequencies is reduced, but conduction velocity is not significantly affected. Because the
action potential is prolonged, rate of automaticity is reduced. The predominant effect on the ECG is QT-
interval prolongation. These drugs are used to treat SVTs and VTs. Class III drugs have a risk of
ventricular proarrhythmia, particularly torsades de pointes VT.

Class IV: Class IV drugs are the nondihydropyridine Ca channel blockers, which depress Ca-dependent
action potentials in slow channel tissues and thus decrease the rate of automaticity, slow conduction
velocity, and prolong refractoriness. Heart rate is slowed, the PR interval is lengthened, and the AV node
transmits rapid atrial depolarizations at a lower frequency. These drugs are used primarily to treat SVTs.

Devices and Procedures

Direct-current (DC) cardioversion-defibrillation: A transthoracic DC shock of sufficient magnitude
depolarizes the entire myocardium, rendering the entire heart momentarily refractory to repeat
depolarization. Thereafter, the most rapid intrinsic pacemaker, usually the SA node, reassumes control of
heart rhythm. Thus, DC cardioversion-defibrillation very effectively terminates tachyarrhythmias that result
from reentry. However, it is less effective for terminating tachyarrhythmias that result from automaticity
because the return rhythm is likely to be the automatic tachyarrhythmia. For tachyarrhythmias other than
VF, the DC shock must be synchronized to the QRS complex (called DC cardioversion) because a shock
that falls during the vulnerable period (near the peak of the T wave) can induce VF. In VF, synchronization
of a shock to the QRS complex is neither necessary nor possible. A DC shock applied without
synchronization to a QRS complex is DC defibrillation.

When DC cardioversion is elective, patients should fast for 6 to 8 h to avoid the possibility of aspiration.
Because the procedure is frightening and painful, brief general anesthesia or IV analgesia and sedation
(eg, fentanyl 1 \(\mu\)g/kg, then midazolam 1 to 2 mg q 2 min to a maximum of 5 mg) is necessary. Equipment
and personnel to maintain the airways must be present.

The electrodes (pads or paddles) used for cardioversion may be placed anteroposteriorly (along the left
sternal border over the 3rd and 4th intercostal spaces and in the left infrascapular region) or
anterolaterally (between the clavicle and the 2nd intercostal space along the right sternal border and over
the 5th and 6th intercostal spaces at the apex of the heart). After synchronization to the QRS complex is
confirmed on the monitor, a shock is given. The most appropriate energy level varies with the
tachyarrhythmia being treated. Cardioversion efficacy increases with use of biphasic shocks, in which the
current polarity is reversed part way through the shock waveform. Complications are usually minor and
include atrial and ventricular premature beats and muscle soreness. Less commonly, but more likely if
patients have marginal left ventricular function or multiple shocks are used, cardioversion precipitates
myocyte damage and electromechanical dissociation.

DC cardioversion-defibrillation can also be applied directly to the heart during a thoracotomy or through
use of an intracardiac electrode catheter; then, much lower energy levels are required.

Pacemakers: Pacemakers sense electrical events and respond when necessary by delivering electrical
stimuli to the heart. Permanent pacemaker leads are placed via thoracotomy or transvenously, but some
temporary emergency pacemaker leads can be placed on the chest wall.

Indications are numerous (see Table 213-3) but generally involve symptomatic bradycardia or high-grade AV block. Some
tachyarrhythmias may be terminated by over-drive pacing with a brief period of pacing at a faster rate; the
pacemaker is then slowed to the desired rate. Nevertheless, ventricular tachyarrhythmias are better
treated with devices that can cardiovert and defibrillate as well as pace (implantable cardioverter
defibrillators).

Types of pacemakers are designated by 3 to 5 letters (see Table 213-4), representing which cardiac chambers are paced, which chambers are sensed, how the
pacemaker responds to a sensed event (inhibits or triggers pacing), whether it can increase heart rate during exercise (rate-modulating), and whether pacing is multisite (in both atria, both ventricles, or more than one pacing lead in a single chamber). For example, a VVIR pacemaker paces (V) and senses (V) events in the ventricle, inhibits pacing in response to sensed event (I), and can increase its rate during exercise (R).

VVI and DDD pacemakers are the devices most commonly used. They offer equivalent survival benefits. Compared with VVI pacemakers, physiologic pacemakers (AAI, DDD, VDD) appear to reduce risk of AF and heart failure and slightly improve quality of life.

Advances in pacemaker design include lower-energy circuitry, new battery designs, and corticosteroid-eluting leads (which reduce pacing threshold), all of which increase pacemaker longevity. Mode switching refers to an automatic change in the mode of pacing in response to sensed events (eg, from DDDR to VVIR during AF).

Pacemakers may malfunction by oversensing or undersensing events, failing to pace or

Table 213-3. Indications for Permanent Pacemakers

Table 213-4. Pacemaker Codes

capture, or pacing at an abnormal rate. Tachycardias are an especially common complication. Rate-modulating pacemakers may increase stimuli in response to vibration, muscle activity, or voltage induced by magnetic fields during MRI. In pacemaker-mediated tachycardia, a normally functioning dual-chamber pacemaker senses a ventricular premature or paced beat transmitted to the atrium through the AV node or a retrograde-conducting accessory pathway, which triggers ventricular stimulation in a rapid, repeating cycle.

Additional complications associated with normally functioning devices include crosstalk inhibition, in which sensing of the atrial pacing impulse by the ventricular channel of a dual-chamber pacemaker leads to inhibition of ventricular pacing, and pacemaker syndrome, in which AV asynchrony induced by ventricular pacing causes fluctuating, vague cerebral (eg, light-headedness), cervical (eg, neck pulsations), or respiratory (eg, dyspnea) symptoms. Pacemaker syndrome is managed by restoring AV synchrony by atrial pacing (AAI), single-lead atrial sensing ventricular pacing (VDD), or dual-chamber pacing (DDD), most commonly the latter.

Environmental interference comes from electromagnetic sources such as surgical electrocautery and MRI, although MRI may be safe when the pacemaker generator and leads are not inside the magnet. Cellular telephones and electronic security devices are a potential source of interference; telephones should not be placed close to the device but are not a problem when used normally for talking. Walking through metal detectors does not cause pacemaker malfunction as long as patients do not linger.

Complications during implantation are uncommon but may include myocardial perforation, bleeding, and pneumothorax. Postoperative complications include infection, lead migration, and impulse generator migration.

Implantable cardioverter-defibrillators (ICDs): ICDs cardiovert or defibrillate the heart in response to VT or VF. Contemporary tiered-therapy ICDs also provide antibradycardia pacing and antitachycardia pacing (to terminate responsive atrial or ventricular tachycardias) and store intracardiac electrograms. ICDs are implanted subcutaneously or subpectorally, with electrodes inserted transvenously into the right ventricle and sometimes also the right atrium. A biventricular ICD has a left ventricular epicardial lead placed.

ICDs are the preferred treatment for patients who have had an episode of VF or hemodynamically significant VT not due to reversible or transient conditions (eg, electrolyte disturbance, antiarrhythmic drug proarrhythmia, acute MI). ICDs may also be indicated for patients with VT or VF inducible during an electrophysiologic study and for patients with idiopathic or ischemic cardiomyopathy, a left ventricular ejection fraction of < 35%, and a high risk of VT or VF. Other indications are less clear (see
Because ICDs treat rather than prevent VT or VF, patients prone to these arrhythmias may require an ICD and antiarrhythmic drugs to reduce the number of episodes and need for uncomfortable shocks; this approach also prolongs the life of the ICD.

Impulse generators for ICDs typically last about 5 yr. ICDs may malfunction by delivering inappropriate pacing or shocks in response to sinus rhythm or SVTs or by not delivering appropriate pacing or shocks when needed. Causes include lead or impulse generator migration, undersensing and an increase in pacing threshold due to epicardial fibrosis at the site of prior shocks, and battery depletion.

In patients who report that the ICD has discharged but that no associated symptoms of syncope, dyspnea, chest pain or persistent palpitations occurred, follow up with the electro-physiologist within the week is appropriate. The ICD can then be electronically interrogated to determine the reason for discharge. If such associated symptoms were present, or the patient received multiple shocks, emergency department referral is indicated to look for a treatable cause (eg, coronary ischemia, electrolyte abnormality) or device malfunction.

**Radiofrequency (RF) ablation:** If a tachyarrhythmia depends on a specific pathway or ectopic site of automaticity, the site can be ablated by low-voltage, high-frequency (300 to 750 MHz) electrical energy, applied through an electrode catheter. This energy heats and necroses an area < 1 cm in diameter and up to 1 cm deep. Before energy can be applied, the target site or sites must be mapped during an electrophysiologic study (see p. 2058).

Success rate is > 90% for reentrant tachycardias (via the AV node or an accessory pathway), focal atrial tachycardia and flutter, and focal idiopathic VTs (right ventricular outflow tract, left septal, or bundle branch reentrant VT). Because AF often originates or is maintained by an arrhythmogenic site in the pulmonary veins, this site can be ablated directly or, more commonly, electrically isolated by ablations at the pulmonary vein-left atrial junction or in the left atrium. Alternatively, in patients with refractory AF and rapid ventricular rates, the AV node may be ablated after permanent pacemaker implantation. RF ablation is sometimes successful in patients with VT refractory to drugs and with ischemic heart disease.

RF ablation is safe; mortality is < 1/2000. Complications include valvular damage, pulmonary vein stenosis or occlusion (if used to treat atrial fibrillation), stroke or other embolism, cardiac perforation, tamponade (1%), and unintended AV node ablation.

**Surgery:** Surgery to remove a focus of a tachyarrhythmia is becoming less necessary as the less invasive RF ablation techniques evolve. But it is still indicated when an arrhythmia is refractory to RF ablation or when another indication requires a cardiac surgical procedure, most commonly when patients with AF require valve replacement or repair or when patients with VT require revascularization or resection of a left ventricular aneurysm.

**Sinus Node Dysfunction**

(Sick Sinus Syndrome)

**Sinus node dysfunction** refers to a number of conditions causing physiologically inappropriate atrial rates. Symptoms may be minimal or include weakness, palpitations, and syncope. Diagnosis is by ECG. Symptomatic patients require a pacemaker.

Sinus node dysfunction includes inappropriate sinus bradycardia, alternating bradycardia and atrial tachyarrhythmias (bradycardiatacycardia syndrome), sinus pause or arrest, and sinoatrial (SA) exit block. Sinus node dysfunction affects mainly the elderly, especially those with another cardiac disorder or diabetes.
Sinus pause is temporary cessation of sinus node activity, seen on ECG as disappearance of P waves for seconds to minutes. The pause usually triggers escape activity in lower pacemakers (eg, atrial or junctional), preserving heart rate and function, but long pauses cause dizziness and syncope.

In SA exit block, the SA node depolarizes, but conduction of impulses to atrial tissue is impaired. In 1st-degree SA block, the SA node impulse is merely slowed, and ECG is normal. In type I 2nd-degree SA (SA Wenckebach) block, impulse conduction slows before blocking, seen on the ECG as a P-P interval that decreases progressively until the P wave drops altogether, creating a pause and the appearance of grouped beats; the duration of the pause is less than 2 P-P cycles. In type II 2nd-degree SA block, conduction of impulses is blocked without slowing beforehand, producing a pause that is a multiple (usually twice) of the P-P interval and the appearance of grouped beats. In 3rd-degree SA block, conduction is blocked; P waves are absent, giving the appearance of sinus arrest.

The most common cause of sinus node dysfunction is idiopathic SA node fibrosis, which may be accompanied by degeneration of lower elements of the conducting system. Other causes include drugs, excessive vagal tone, and many ischemic, inflammatory, and infiltrative disorders.

**Symptoms and Signs**

Many patients are asymptomatic, but depending on the heart rate, all the symptoms of bradycardias and tachycardias can occur (see p. 2144).

**Diagnosis**

A slow, irregular pulse suggests the diagnosis, which is confirmed by ECG, rhythm strip, or continuous 24-h ECG recording. Some patients present with atrial fibrillation (AF), and the underlying sinus node dysfunction manifests only after conversion to sinus rhythm.

**Prognosis**

Prognosis is mixed; without treatment, mortality is about 2%/yr, primarily resulting from an underlying structural heart disorder. Each year, about 5% of patients develop AF with its risks of heart failure and stroke.

**Treatment**

• Pacemaker

Treatment is pacemaker implantation. Risk of AF is greatly reduced when a physiologic (atrial or atrial and ventricular) pacemaker rather than a ventricular pacemaker is used. Newer dual chamber pacemakers that minimize ventricular pacing may further reduce risk of AF. Antiarrhythmic drugs may prevent paroxysmal tachyarrhythmias after pacemaker insertion. Theophylline and hydralazine are options to increase heart rate in healthy, younger patients who have bradycardia without syncope.

**Ectopic Supraventricular Rhythms**

Various rhythms result from supraventricular foci (usually in the atria); many are asymptomatic and require no treatment.

**Atrial premature beats:** Atrial premature beats (APBs), or premature atrial contractions (PACs), are common episodic impulses. They may occur in normal hearts with or without precipitating factors (eg, coffee, tea, alcohol, pseudoephedrine) or may be a sign of a cardiopulmonary disorder. They are common in patients with COPD. They occasionally cause palpitations. Diagnosis is by ECG (see Fig. 213-3).

APBs may be normally, aberrantly, or not conducted and are usually followed by a non-compensatory pause. aberrantly conducted APBs (usually with right bundle branch block morphology) must be
Atrial escape beats are ectopic atrial beats that emerge after long sinus pauses or sinus arrest. They may be single or multiple; escape beats from a single focus may produce a continuous rhythm (called ectopic atrial rhythm). Heart rate is typically slower, P wave morphology is typically different, and PR interval is slightly shorter than in sinus rhythm.

**Wandering atrial pacemaker:** Wandering atrial pacemaker (multifocal atrial rhythm) is an irregularly irregular rhythm caused by the random discharge of multiple ectopic atrial foci. By definition, heart rate is ≤ 100 beats/min. This arrhythmia most typically occurs in patients who have a pulmonary disorder and are hypoxic, acidotic, theophylline-intoxicated, or a combination. On ECG, P-wave morphology differs from beat to beat, and there are ≥ 3 distinct P-wave morphologies. The presence of P waves distinguishes wandering atrial pacemaker from atrial fibrillation.

**Multifocal atrial tachycardia:** Multifocal atrial tachycardia (chaotic atrial tachycardia) is an irregularly irregular rhythm caused by the random discharge of multiple ectopic atrial foci. By definition, heart rate is > 100 beats/min. Except for the rate, features are the same as those of wandering atrial pacemaker. Symptoms, when they occur, are those of rapid tachycardia. Treatment is directed at the underlying pulmonary disorder.

**Atrial tachycardia:** Atrial tachycardia is a regular rhythm caused by the consistent, rapid atrial activation from a single atrial focus. Heart rate is usually 150 to 200 beats/min; however, with a very rapid atrial rate, nodal dysfunction, or digitalis toxicity, atrioventricular (AV) block may be present, and ventricular rate may be slower. Mechanisms include enhanced atrial automaticity and intra-atrial reentry. Atrial tachycardia is the least common form (5%) of supraventricular tachycardia and usually occurs in patients with a structural heart disorder. Other causes include atrial irritation (eg, pericarditis), drugs (eg, digoxin), alcohol, and toxic gas inhalation. Symptoms are those of other tachycardias. Diagnosis is by ECG; P waves, which differ in morphology from normal sinus P waves, precede QRS complexes but may be hidden within the preceding T wave (see Fig. 213-4).

Vagal maneuvers may be used to slow the heart rate, allowing visualization of P waves when they are hidden, but these maneuvers do not usually terminate the arrhythmia (demonstrating that the AV node is not an obligate part of the arrhythmia circuit). Treatment involves managing causes and slowing ventricular response rate using a β-blocker or Ca channel blocker. An episode may be terminated by direct-current cardioversion. Pharmacologic approaches to termination and prevention of atrial tachycardia include antiarrhythmic drugs in class Ia, Ic, or III. If these noninvasive measures are ineffective, alternatives include overdrive pacing and radiofrequency ablation.

**Nonparoxysmal junctional tachycardia:** Nonparoxysmal junctional tachycardia is caused by abnormal automaticity in the AV node or adjacent tissue, which typically follows open heart surgery, acute inferior MI, myocarditis, or digitalis toxicity. Heart rate is 60 to 120 beats/min; thus, symptoms are usually absent. ECG shows regular, normal-appearing QRS complexes without identifiable P waves or with retrograde P waves (inverted in the inferior leads) that occur shortly before (< 0.1 sec) or after the QRS complex. The rhythm is distinguished from paroxysmal supraventricular tachycardia by the lower heart rate and gradual onset and offset. Treatment is directed at causes.

**Atrioventricular Block**

Atrioventricular (AV) block is partial or complete interruption of impulse transmission from the atria to the ventricles. The most common cause is idiopathic fibrosis and sclerosis of the conduction system. Diagnosis is by ECG; symptoms and treatment depend on degree of block, but treatment, when necessary, usually involves pacing.
AV block is caused by idiopathic fibrosis and sclerosis of the conduction system in about 50% of patients and by ischemic heart disease in 40%; the rest are due to drugs (eg, β-blockers, Ca channel blockers, digoxin, amiodarone); increased vagal tone; valvulopathy; or congenital heart, genetic, or other disorders.

**First-degree AV block:** All normal P waves are followed by QRS complexes, but the PR interval is longer than normal (> 0.20 sec—see Fig. 213-5).

First-degree AV block may be physiologic in younger patients with high vagal tone and in well-trained athletes. First-degree AV block is rarely symptomatic and no treatment is required, but further investigation may be indicated when it accompanies another heart disorder or appears to be caused by drugs.

**Second-degree AV block:** Some normal P waves are followed by QRS complexes, but some are not. Three types exist:

In Mobitz type I 2nd-degree AV block, the PR interval progressively lengthens with each beat until the atrial impulse is not conducted and the QRS complex is dropped (Wenckebach phenomenon); AV nodal conduction resumes with the next beat, and the sequence is repeated (see Fig. 213-6).

Mobitz type I 2nd-degree AV block may be physiologic in younger and more athletic patients. The block occurs at the AV node in about 75% of patients with a narrow QRS complex and at infranodal sites (His bundle, bundle branches, or fascicles) in the rest. If the block becomes complete, a reliable junctional escape rhythm typically develops. Treatment is therefore unnecessary unless the block causes symptomatic bradycardia and transient or reversible causes have been excluded. Treatment is pacemaker insertion, which may also benefit asymptomatic patients with Mobitz type I 2nd-degree AV block at infranodal sites detected by electrophysiologic studies done for other reasons.

In Mobitz type II 2nd-degree AV block, the PR interval remains constant. Beats are intermittently nonconducted and QRS complexes dropped, usually in a repeating cycle of every 3rd (3:1 block) or 4th (4:1 block) P wave (see Fig. 213-7).

Mobitz type II 2nd-degree AV block is always pathologic; the block occurs at the His bundle in 20% of patients and in the bundle branches in the rest. Patients may be asymptomatic or experience light-headedness, presyncope, and syncope, depending on the ratio of conducted to blocked beats. Patients are at risk of developing symptomatic high-grade or complete AV block, in which the escape rhythm is likely to be ventricular and thus too slow and unreliable to maintain systemic perfusion; therefore, a pacemaker is indicated.

In high-grade 2nd-degree AV block, every 2nd (or more) P wave is blocked (see Fig. 213-8).

The distinction between Mobitz type I and Mobitz type II block is difficult to make because

In high-grade 2nd-degree AV block, every 2nd (or more) P wave is blocked (see Fig. 213-8).

The distinction between Mobitz type I and Mobitz type II block is difficult to make because

[Fig. 213-8, Second-degree atrioventricular block (high grade).]

[Fig. 213-9, Third-degree atrioventricular block.]
2 P waves are never conducted in a row. Risk of complete AV block is difficult to predict, and a pacemaker is indicated.

Patients with any form of 2nd-degree AV block and a structural heart disorder should be considered candidates for permanent pacing unless there is a transient or reversible cause.

**Third-degree AV block**: Heart block is complete (see Fig. 213-9).

There is no electrical communication between the atria and ventricles and no relationship between P waves and QRS complexes (AV dissociation). Cardiac function is maintained by an escape junctional or ventricular pacemaker. Escape rhythms originating above the bifurcation of the His bundle produce narrow QRS complexes, relatively rapid (> 40 beats/min) and reliable heart rates, and mild symptoms (eg, fatigue, postural light-headedness, effort intolerance). Escape rhythms originating below the bifurcation produce wider QRS complexes, slower and unreliable heart rates, and more severe symptoms (eg, presyncope, syncope, heart failure). Signs include those of AV dissociation, such as cannon a waves, BP fluctuations, and changes in loudness of the 1st heart sound (S1). Risk of asystole-related syncope and sudden death is greater if low escape rhythms are present.

Most patients require a pacemaker (see Table 213-4). If the block is caused by anti-arrhythmic drugs, stopping the drug may be effective, although temporary pacing may be needed. A block caused by acute inferior MI usually reflects AV nodal dysfunction and may respond to atropine or resolve spontaneously over several days. A block caused by anterior MI usually reflects extensive myocardial necrosis involving the His-Purkinje system and requires immediate transvenous pacemaker insertion with interim external pacing as necessary. Spontaneous resolution may occur but warrants evaluation of AV nodal and infranodal conduction (eg, electrophysiologic study, exercise testing, 24-h ECG).

Most patients with congenital 3rd-degree AV block have a junctional escape rhythm that maintains a reasonable rate, but they require a permanent pacemaker before they reach middle age. Less commonly, patients with congenital AV block have a slow escape rhythm and require a permanent pacemaker at a young age, perhaps even during infancy.

**Atrial Fibrillation**

Atrial fibrillation (AF) is a rapid, irregularly irregular atrial rhythm. Symptoms include palpitations and sometimes weakness, dyspnea, and presyncope. Atrial thrombi often form, causing a significant risk of embolic stroke. Diagnosis is by ECG. Treatment involves rate control with drugs, prevention of thromboembolism with anticoagulation, and sometimes conversion to sinus rhythm by drugs or cardioversion.

AF has been attributed to multiple wave-lets with chaotic reentry within the atria. However, in many cases, firing of an ectopic focus within venous structures adjacent to the atria (usually the pulmonary veins) is responsible for initiation and perhaps maintenance of AF. In AF, the atria do not contract, and the atrioventricular (AV) conduction system is bombarded with many electrical stimuli, causing inconsistent impulse transmission and an irregularly irregular ventricular rate, which is usually in the tachycardia rate range.

AF is one of the most common arrhythmias, affecting about 2.3 million adults in the US. Men and whites are more likely to have AF than women and blacks. Prevalence increases with age; almost 10% of people > 80 yr are affected. It tends to occur in patients with a heart disorder, sometimes precipitating heart failure because cardiac output decreases. The absent atrial contractions predispose to thrombus formation; annual risk of cerebrovascular embolic events is about 7%. Risk of stroke is higher in patients with a rheumatic valvular disorder, hyperthyroidism, hypertension, diabetes, left ventricular systolic dysfunction, or previous thromboembolic events. Systemic emboli can also cause malfunction or necrosis of other organs (eg, heart, kidneys, GI tract, eyes) or a limb.

**Etiology**

The most common causes are hypertension, ischemic or nonischemic cardiomyopathy, mitral or tricuspid
valvular disorders, hyperthyroidism, and binge alcohol drinking (holiday heart). Less common causes include pulmonary embolism, atrial septal and other congenital heart defects, COPD, myocarditis, and pericarditis. AF without an identifiable cause in patients < 60 yr is called lone AF.

**Classification**

Acute AF is new-onset AF lasting < 48 h.

Paroxysmal AF is recurrent AF that typically lasts < 48 h and that converts spontaneously to normal sinus rhythm.

Persistent AF lasts > 1 wk and requires treatment to convert to normal sinus rhythm.

Permanent AF cannot be converted to sinus rhythm. The longer AF is present, the less likely is spontaneous conversion and the more difficult is cardioversion because of atrial remodeling (rapid atrial rate-induced changes in atrial electrophysiology that are dominated by a decrease in atrial refractoriness and may also include increase in spatial dispersion of atrial refractoriness slowed atrial conduction velocity, or both).

**Symptoms and Signs**

AF is often asymptomatic, but many patients have palpitations, vague chest discomfort, or symptoms of heart failure (eg, weakness, light-headedness, dyspnea), particularly when the ventricular rate is very rapid (often 140 to 160 beats/min). Patients may also present with symptoms and signs of acute stroke or of other organ damage due to systemic emboli.

The pulse is irregularly irregular with loss of a waves in the jugular venous pulse. A pulse deficit (the apical ventricular rate is faster than the rate palpated at the wrist) may be present because left ventricular stroke volume is not always sufficient to produce a peripheral pressure wave at fast ventricular rates.

**Diagnosis**

- ECG
- Echocardiography
- Thyroid function tests

Diagnosis is by ECG. Findings include absence of P waves, f (fibrillatory) waves between QRS complexes (irregular in timing, irregular in morphology; baseline undulations at rates > 300/min not always apparent in all leads), and irregularly irregular R-R intervals (see Fig. 213-10).

Other irregular rhythms may resemble AF on ECG but can be distinguished by the presence of discrete P or flutter waves, which can sometimes be made more visible with vagal maneuvers. Muscle tremor or electrical interference may resemble f waves, but the underlying rhythm is regular. AF may also cause a phenomenon that mimics ventricular extrasystoles or ventricular tachycardia (Ashman phenomenon). This phenomenon typically occurs when a short R-R interval follows a long R-R interval; the longer interval lengthens the refractory period of the infra-Hisian conduction system, and subsequent QRS complexes are conducted aberrantly, typically with right bundle branch morphology.

Echocardiography and thyroid function tests are important in the initial evaluation. Echocardiography is done to assess structural heart defects (eg, left atrial enlargement, left ventricular wall motion abnormalities suggesting past or present ischemia, valvular disorders, cardiomyopathy) and to identify additional risk factors for stroke (eg, atrial blood stasis or thrombus, complex aortic plaque). Atrial thrombi are more likely in the atrial appendages, where they are best detected by transesophageal rather than transthoracic echocardiography.
Treatment

- Rate control with drugs or AV node radio-frequency ablation
- Sometimes rhythm control with cardioversion, drugs, or AF substrate ablation
- Prevention of thromboembolism

If a significant underlying disorder is suspected, patients with new-onset AF may benefit from hospitalization, but those with recurrent episodes do not require hospitalization unless other symptoms suggest the need for it. Once causes have been managed, treatment of AF focuses on ventricular rate control, rhythm control, and prevention of thromboembolism.

Ventricular rate control: Patients with AF of any duration require rate control (typically to < 80 beats/min at rest) to control symptoms and prevent tachycardia-induced cardiomyopathy.

For acute paroxysms of rapid rate (eg, 140 to 160 beats/min), IV AV node blockers are used (for doses, see Table 213-2). CAUTION: AV node blockers should not be used in patients with Wolff-Parkinson-White syndrome when an accessory AV pathway is involved (indicated by wide QRS duration): these drugs increase frequency of conduction via the bypass tract, possibly causing ventricular fibrillation. β-Blockers (eg, metoprolol, esmolol) are preferred if excess catecholamines are suspected (eg, in thyroid disorders, exercise-triggered cases). Nondihydropyridine Ca channel blockers (eg, verapamil, diltiazem) are also effective. Digoxin is the least effective but may be preferred if heart failure is present. These drugs may be used orally for long-term rate control. When β-blockers, nondihydropyridine Ca channel blockers, and digoxin—separately or in combination—are ineffective, amiodarone may be required.

Rhythm control: In patients with heart failure or other hemodynamic compromise directly attributable to new-onset AF, restoration of normal sinus rhythm is indicated to improve cardiac output. In other cases, conversion of AF to normal sinus rhythm is optimal, but the antiarrhythmic drugs that are capable of doing so (class Ia, lc, III) have a risk of adverse effects and may increase mortality. Conversion to sinus rhythm does not necessarily eliminate the need for chronic anticoagulation.

For acute conversion, synchronized cardioversion or drugs can be used. Before conversion is attempted, the ventricular rate should be controlled to < 120 beats/min, and, if AF has been present > 48 h, patients should be given anticoagulants (conversion, regardless of method used, increases risk of thromboembolism). Anticoagulation with warfarin (see p. 2168) should be maintained for > 3 wk before conversion when possible and continued indefinitely because AF may recur. Alternatively, the patient can be anticoagulated with heparin, and transesophageal echocardiography done; if there is no intra-atrial clot, cardioversion can be done immediately.

Synchronized cardioversion (100 joules, followed by 200 and 360 joules as needed) converts AF to normal sinus rhythm in 75 to 90% of patients, although recurrence rate is high. Efficacy and maintenance of sinus rhythm after the procedure is improved with use of class Ia, lc, or III drugs 24 to 48 h before the procedure. Cardioversion is more effective in patients with shorter duration of AF, lone AF, or AF with a reversible cause; it is less effective when the left atrium is enlarged (> 5 cm), atrial appendage flow is low, or a significant underlying structural heart disorder is present.

Drugs for conversion to sinus rhythm include class Ia (procainamide, quinidine, disopyramide), lc (flecainide, propafenone), and III (amiodarone, dofetilide, ibutilide, sotalol) antiarrhythmics (see Table 213-2). All are effective in about 50 to 60% of patients, but adverse effects differ. These drugs should not be used until rate has been controlled by a β-blocker or nondihydropyridine Ca channel blocker. These converting drugs are also used for long-term maintenance of sinus rhythm (with or without previous cardioversion). Choice depends on patient tolerance. However, for paroxysmal AF that occurs only or almost only at rest or during sleep when vagal tone is high, drugs with vagolytic effects (eg, disopyramide) may be particularly effective. Exercise-induced AF may be better prevented with a β-
For certain patients with recurrent paroxysmal AF who also can identify its onset by symptoms, some clinicians provide a single oral loading dose of flecainide (300 mg for patients ≥ 70 kg otherwise 200 mg) or propafenone (600 mg for patients ≥ 70 kg, otherwise 450 mg) that patients carry and self-administer when palpitations develop ("pill-in-the-pocket" approach). This approach must be limited to patients who have no sinoatrial or AV node dysfunction, bundle branch block, QT prolongation, Brugada syndrome, or structural heart disease. Its hazard (estimated at 1%) is the possibility of converting AF to a slowish atrial flutter that conducts 1:1 in the 200 to 240 beat/min range.

ACE inhibitors, angiotensin II receptor blockers, and aldosterone blockers may attenuate the myocardial fibrosis that provides a substrate for AF in patients with heart failure, but the role of these drugs in routine AF treatment has yet to be defined.

Ablation procedures: For patients who do not respond to or cannot take rate-controlling drugs, radiofrequency ablation of the AV node may be done to produce complete heart block; insertion of a permanent pacemaker is then necessary. Ablation of only one AV nodal pathway (AV node modification) reduces the number of atrial impulses reaching the ventricles and eliminates the need for a pacemaker, but this approach is considered less effective than complete ablation and is rarely used.

Ablation procedures that isolate the pulmonary veins from the left atrium can prevent AF without producing AV block. In comparison to other ablation procedures, pulmonary vein isolation has a lower success rate (60 to 80%) and a higher complication rate (1 to 5%). Accordingly, this procedure is often reserved for the best candidates—younger patients with drug-resistant AF who have no significant structural heart disease.

Prevention of thromboembolism: Measures to prevent thromboembolism are necessary at the time of cardioversion and during long-term treatment of most patients.

Warfarin titrated to an INR of 2 to 3 should be given for ≥ 3 wk before elective cardioversion of lone AF present for > 48 h and continued for 4 wk after successful cardioversion. Anticoagulants should be continued indefinitely for patients with recurrent paroxysmal, persistent, or permanent AF in the presence of risk factors for thromboembolism. Healthy patients with a single episode of lone AF are given anticoagulants for 4 wk.

Aspirin is less effective than warfarin but is used for patients with no risk factors for thromboembolism or those with contraindications to warfarin. Direct thrombin inhibitors that do not require INR monitoring may be equivalent to warfarin for stroke prevention in high-risk patients, but they require further study before being recommended for mainstream use. The left atrial appendage may be surgically ligated or closed with a transcatheter device when warfarin and antiplatelet drugs are absolutely contraindicated.

Atrial Flutter

Atrial flutter is a rapid regular atrial rhythm due to an atrial macro-reentrant circuit. Symptoms are mainly palpitations. Atrial thrombi may form and embolize. Diagnosis is by ECG. Treatment involves rate control with drugs, prevention of thromboembolism with anticoagulants, and often conversion to sinus rhythm with drugs or cardioversion.

Atrial flutter is much less common than atrial fibrillation, but its causes and hemodynamic consequences are similar. Many patients with atrial flutter also have periods of atrial fibrillation.

Classical atrial flutter is due to a large reentrant circuit involving most of the right atrium. The atria depolarize at a rate of 250 to 350/min (typically 300/min). Because the atrioventricular (AV) node cannot usually conduct at this rate, typically half of the impulses get through (2:1 block), resulting in a regular ventricular rate of 150 beats/min. Sometimes the block varies from moment to moment, causing an irregular ventricular rhythm. Less commonly, a fixed 3:1, 4:1, or 5:1 block may be present.

The probability of a thromboembolic event, once considered rare in atrial flutter, is now thought to be...
about half of that in atrial fibrillation.

**Symptoms and Signs**

Symptoms depend primarily on ventricular rate and the nature of any underlying heart disorder. If ventricular rate is < 120 beats/min and regular, there are likely to be few or no symptoms. Faster rates and variable AV conduction usually cause palpitations, and decreased cardiac output may cause symptoms of hemodynamic compromise (eg, chest discomfort, dyspnea, weakness, syncope). Close inspection of the jugular venous pulse reveals flutter a waves.

**Diagnosis**

- ECG

The diagnosis is by ECG, which shows continuous and regular atrial activation with a sawtooth pattern, most obvious in leads II, III, and aVF (see Fig. 213-11).

Carotid sinus massage can increase AV block and better expose the typical flutter waves. A similar response may follow pharmacologic AV nodal blockade (eg, with adenosine), but such therapy does not terminate atrial flutter.

**Treatment**

- Rate control with drugs
- Rhythm control with cardioversion, drugs, or ablation
- Prevention of thromboembolism

As for atrial fibrillation, treatment focuses on ventricular rate control, rhythm control, and prevention of thromboembolism. However, pharmacologic rate control is more difficult to achieve in atrial flutter than in atrial fibrillation. Thus for most patients, electrical conversion (using synchronized cardioversion or overdrive pacing) is the treatment of choice for an initial episode and is mandatory with 1:1 AV conduction or hemodynamic compromise. Typically, low-energy (50 joules) conversion is effective. Anticoagulation, as in atrial fibrillation, is necessary before cardioversion.

If drugs are used to restore sinus rhythm, rate must first be controlled with β-blockers or nondihydropyridine Ca channel blockers (eg, verapamil, diltiazem). Many of the antiarrhythmics that can restore sinus rhythm (especially class Ia and Ic) can slow atrial flutter, shorten AV nodal refractoriness (by their vagolytic effects), or do both enough to allow 1:1 conduction with paradoxical increase in ventricular rate and hemodynamic compromise. These drugs may be used for long-term maintenance as required to prevent recurrence.

An antitachycardia pacing system is an alternative to long-term use of antiarrhythmics in selected patients. Also, ablation procedures designed to interrupt the atrial reentrant circuit may effectively prevent atrial flutter, particularly classic atrial flutter.

Patients with chronic or recurrent atrial flutter require warfarin (to maintain an INR of 2 to 3) or aspirin therapy long-term. The choice between the 2 therapies is based on the same considerations as for atrial fibrillation.

[Fig. 213-11. Atrial flutter with variable atrioventricular block.]

**Reentrant Supraventricular Tachycardias**

Reentrant supraventricular tachycardias involve reentrant pathways with a component above the bifurcation of the His bundle. Patients have sudden episodes of palpitations that begin and
terminate abruptly; some have dyspnea or chest discomfort. Diagnosis is clinical and by ECG. Treatment is with vagotonic maneuvers and, if they are ineffective, with IV adenosine or nondihydropyridine Ca channel blockers for narrow QRS rhythms, procainamide or amiodarone for wide QRS rhythms, or synchronized cardioversion for all cases.

Pathophysiology

The reentry pathway (see Fig. 213-1) in supraventricular tachycardia (SVT) is within the atrioventricular (AV) node in about 50%, involves an accessory bypass tract in 40%, and is within the atria or sinoatrial (SA) node in 10%.

AV nodal reentrant tachycardia occurs most often in otherwise healthy patients. It is most commonly triggered by an atrial premature beat.

Accessory pathway reentrant tachycardia involves tracts of conducting tissue that partially or totally bypass normal AV connections (bypass tracts). They run most commonly from the atria directly to the ventricles and less commonly from the atrium to a portion of the conduction system or from a portion of the conduction system to the ventricle. They can be triggered by atrial premature beats or ventricular premature beats.

Wolff-Parkinson-White (WPW) syndrome: WPW (preexcitation) syndrome is the most common accessory pathway SVT, occurring in about 1 to 3/1000 people. WPW syndrome is mainly idiopathic, although it is more common among patients with hypertrophic or other forms of cardiomyopathy, transposition of the great vessels, or Epstein's anomaly.

In classic (or manifest) WPW syndrome, antegrade conduction occurs over both the accessory pathway and the normal conducting system during sinus rhythm. The accessory pathway, being faster, depolarizes some of the ventricle early, resulting in a short PR interval and a slurred upstroke to the QRS complex (delta wave—see Fig. 213-12).

The delta wave prolongs QRS duration to > 0.1 sec, although the overall configuration, apart from the delta wave, may appear normal. Depending on the orientation of the delta wave, a pseudoinfarction pattern Q-wave may be present. Because the early depolarized parts of the ventricle also repolarize early, the T-wave vector may be abnormal.

In concealed WPW syndrome, the accessory pathway does not conduct in an antegrade direction; consequently, the above ECG abnormalities do not appear. However, it conducts in a retrograde direction and thus can participate in reentrant tachycardia.

In the most common form of reentrant tachycardia (called orthodromic reciprocating tachycardia), the circuit uses the normal AV conduction pathway to activate the ventricles, returning to the atrium via the accessory AV connection. The resultant QRS complex is thus narrow (unless bundle branch block coexists) and without a delta wave. Orthodromic reciprocating tachycardia is typically a short RP tachycardia with the retrograde P wave in the ST segment.

Rarely, the reentrant circuit revolves in the opposite direction, from the atrium to the ventricle via the accessory AV connection, and returns from the ventricle in the retrograde direction up the normal AV conduction system (called antidromic reciprocating tachycardia). The QRS complex is wide because the ventricles are activated abnormally. In patients with 2 accessory AV connections (not uncommon), a reciprocating tachycardia using one accessory connection in the antegrade direction and the other in the retrograde direction may occur.

Tachycardias in WPW syndrome may begin as or degenerate into atrial fibrillation (AF), which can be very dangerous (see p. 2172). Enlarged atria due to hypertrophic and other forms of cardiomyopathy makes
patients with WPW syndrome more prone to AF.

Symptoms and Signs

Most patients present during young adulthood or middle age. They typically have episodes of sudden-onset, sudden-offset, rapid, regular palpitations often associated with symptoms of hemodynamic compromise (eg, dyspnea, chest discomfort, light-headedness). Attacks may last only a few seconds or persist for several hours (rarely, > 12 h).

Infants present with episodic breathlessness, lethargy, feeding problems, or rapid precordial pulsations. If the episode of tachycardia is protracted, they may present with heart failure.

Examination is usually unremarkable except for a heart rate of 160 to 240 beats/min.

Diagnosis

• ECG

Diagnosis is by ECG showing rapid, regular tachycardia. Previous tracings, if available, are reviewed for signs of manifest WPW syndrome.

P waves vary. In most cases of AV node re-entry, retrograde P waves are in the terminal portion of the QRS complex (often producing a pseudo-R’ deflection in lead V1); about one third occur just after the QRS complex, and very few occur before. P waves always follow the QRS complex in orthodromic reciprocating tachycardia of WPW syndrome.

QRS complex is narrow except with coexisting bundle branch block, antidromic tachycardia, or dual accessory connection reciprocating tachycardia. Wide-complex tachycardia must be distinguished from ventricular tachycardia (see Table 213-5 and Figs. 213-12 and 213-13).

Treatment

• Vagotonic maneuvers

• Adenosine

• Verapamil or diltiazem if narrow QRS complex

• For frequent recurrence, radiofrequency ablation

Many episodes stop spontaneously before treatment. Vagotonic maneuvers (eg, Valsalva maneuver, unilateral carotid sinus massage, ice water facial immersion, swallowing of ice-cold water), particularly if used early, may terminate the tachyarrhythmia; some patients use these maneuvers at home.

If these maneuvers are ineffective and the QRS complex is narrow (indicating orthodromic conduction), AV node blockers are used;

[Fig. 213-13. Narrow QRS tachycardia: Orthodromic reciprocating tachycardia using an accessory pathway in Wolff-Parkinson-White syndrome.]

blocking conduction through the AV node for one beat interrupts the reentrant cycle. Adenosine is the first choice. Dose is 6 mg by rapid IV bolus (0.05 to 0.1 mg/kg in children), followed by a 20-mL saline bolus. If this dosage is ineffective, 2 subsequent 12-mg doses are given q 5 min. Adenosine sometimes causes a brief (2- to 3-sec) period of cardiac standstill, which may distress patient and physician. Verapamil 5 mg IV or diltiazem 0.25 to 0.35 mg/kg IV are alternatives.

For a regular, wide QRS complex tachycardia known to be an antidromic reciprocating tachycardia not
involving double accessory pathways (which must be identified by the history; they cannot be established acutely), AV nodal blockers may also be effective. However, if the mechanism of the tachycardia is unknown, ventricular tachycardia has not been excluded, and AV nodal blockers should be avoided because they may worsen ventricular tachycardias. In such cases (or those in which drugs are ineffective), IV procainamide or amiodarone can be used. Alternatively, synchronized cardioversion with 50 joules (0.5 to 2 joules/kg for children) is quick and safe and may be preferred to these more toxic drugs.

When episodes of AV nodal reentrant tachycardia are frequent or bothersome, options include long-term antiarrhythmics or transvenous catheter radiofrequency ablation. Generally, ablation is recommended, but if it is not acceptable, drug prophylaxis usually begins with digoxin and proceeds, as required, to β-blockers, nondihydropyridine Ca channel blockers, or both, then to one or more class la, class lc, or class III antiarrhythmics.

Atrial Fibrillation and Wolff-Parkinson-White Syndrome

Atrial fibrillation (AF) is a medical emergency in the setting of antegrade conduction over an accessory pathway in Wolff-Parkinson-White (WPW) syndrome.

In manifest WPW syndrome, antegrade conduction occurs over the accessory pathway. If AF develops, the normal rate-limiting effects of the atrioventricular (AV) node are bypassed, and the resultant excessive ventricular rates (sometimes 200 to 240 beats/min) may lead to ventricular fibrillation (see Fig. 213-14) and sudden death. Patients with concealed WPW syndrome are not at risk because in them, antegrade conduction does not occur over the accessory connection.

[Fig. 213-14. Atrial fibrillation in Wolff-Parkinson-White syndrome.]

The treatment of choice is direct-current cardioversion. The usual rate-slowning drugs used in AF are not effective, and digoxin and the nondihydropyridine Ca channel blockers (eg, verapamil, diltiazem) are contraindicated because they may increase the ventricular rate and cause ventricular fibrillation. If cardioversion is impossible, drugs that prolong the refractory period of the accessory connection should be used. IV procainamide or amiodarone is preferred, but any class la, class lc, or class III antiarrhythmic can be used.

Bundle Branch and Fascicular Block

Bundle branch block is partial or complete interruption of impulse conduction in a bundle branch; fascicular block is similar interruption in a hemifascicle of the bundle. The 2 disorders often coexist. There are usually no symptoms, but presence of either suggests a heart disorder. Diagnosis is by ECG. No specific treatment is indicated.

Conduction blocks can be caused by many heart disorders, including intrinsic degeneration without another associated heart disorder.

Right bundle branch block (RBBB—see Fig. 213-15) can occur in apparently normal people. It may also occur with anterior MI, indicating substantial myocardial injury. New appearance of RBBB should prompt a search for underlying cardiac pathology, but often, none is found. Transient RBBB may occur after pulmonary embolism. Although RBBB distorts the QRS complex, it does not significantly interfere with ECG diagnosis of MI.

Left bundle branch block (LBBB—see Fig. 213-16) is associated with a structural heart disorder more often than is RBBB. LBBB usually precludes use of ECG for diagnosis of MI.

Fascicular block involves the anterior or posterior fascicle of the left bundle branch. Interruption of the left anterior fascicle causes left anterior hemiblock characterized by modest QRS prolongation (< 120 msec) and a frontal plane QRS axis more negative than -30° (left axis deviation). Left posterior hemiblock is associated with a frontal plane QRS axis more positive than +120°. The associations between hemiblocks
and a structural heart disorder are the same as for LBBB.

Hemiblocks may coexist with other conduction disturbances: RBBB and left anterior or posterior hemiblock (bifascicular block); and left anterior or posterior hemiblock, RBBB, and 1st-degree atrioventricular (AV) block (incorrectly called trifascicular block; 1st-degree block is usually AV nodal in origin). Trifascicular block refers to RBBB with alternating left anterior and left posterior hemiblock or alternating LBBB and RBBB. Presence of bifascicular or trifascicular block after MI implies extensive cardiac damage. Bifascicular blocks require no direct treatment unless intermittent 2nd- or 3rd-degree AV block is present. True trifascicular blocks require immediate, then permanent pacing.

Nonspecific intraventricular conduction defects are diagnosed when the QRS complex is

[Fig. 213-15. Right bundle branch block.]

[Fig. 213-16. Left bundle branch block.]

prolonged (> 120 msec), but the QRS pattern is not typical of LBBB or RBBB. The conduction delay may occur beyond the Purkinje fibers and result from slow cell-to-cell myocyte conduction. No specific treatment is indicated.

**Ventricular Premature Beats**

Ventricular premature beats (VPBs) are single ventricular impulses caused by reentry within the ventricle or abnormal automaticity of ventricular cells. They are extremely common in healthy patients and in patients with a heart disorder. VPBs may be asymptomatic or cause palpitations. Diagnosis is by ECG. Treatment is usually not required.

VPBs, also called premature ventricular contractions (PVCs), may occur erratically or at predictable intervals (eg, every 3rd [trigeminy] or 2nd [bigeminy] beat). VPBs may increase with stimulants (eg, anxiety, stress, alcohol, caffeine, sympathomimetic drugs), hypoxia, or electrolyte abnormalities.

VPBs may be experienced as missed or skipped beats; the VPB itself is not sensed but rather the following augmented sinus beat. When VPBs are very frequent, particularly when they represent every 2nd heart beat, mild hemodynamic symptoms are possible because the sinus rate has been effectively halved. Existing ejection murmurs may be accentuated because of increased cardiac filling and augmented contractility after the compensatory pause.

**Diagnosis**

• ECG

Diagnosis is by ECG showing a wide QRS complex without a preceding P wave, typically followed by a fully compensatory pause.

**Prognosis**

VPBs are not significant in patients without a heart disorder, and no treatment is required beyond avoiding obvious triggers. β-Blockers are offered only if symptoms are intolerable. Other antiarrhythmics that suppress VPBs increase risk of more serious arrhythmias.

**Treatment**

• β-Blockers for patients with symptomatic heart failure and after MI

In patients with a structural heart disorder (eg, aortic stenosis, post MI), treatment is controversial even though frequent VPBs (> 10/h) correlate with increased mortality, because no studies have shown that pharmacologic suppression reduces mortality. In post-MI patients, mortality rate is higher with class I antiarrhythmics than with placebo. This finding probably reflects adverse effects of the antiarrhythmics. β-
Blockers are beneficial in symptomatic heart failure and post MI. If VPBs increase during exercise in a patient with coronary artery disease, evaluation for percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery should be considered.

**Ventricular Tachycardia**

Ventricular tachycardia (VT) is ≥ 3 consecutive ventricular beats at a rate ≥ 120 beats/min. Symptoms depend on duration and vary from none to palpitations to hemodynamic collapse and death. Diagnosis is by ECG. Treatment of more than brief episodes is with cardioversion or antiarrhythmics depending on symptoms. If necessary, long-term treatment is with an implantable cardioverter defibrillator.

Some experts use a cutoff rate of ≥ 100 beats/min for VT. Repetitive ventricular rhythms at slower rates are called accelerated idioventricular rhythms or slow VT; they are usually benign and are not treated unless associated with hemodynamic symptoms.

Most patients with VT have a significant heart disorder, particularly prior MI or a cardiomyopathy. Electrolyte abnormalities (particularly hypokalemia or hypomagnesemia), acidemia, hypoxemia, and adverse drug effects contribute. The long QT syndrome (congenital or acquired) is associated with a particular form of VT, torsades de pointes.

VT may be monomorphic or polymorphic and nonsustained or sustained. Monomorphic VT results from a single abnormal focus or reentrant pathway and has regular, identical-appearing QRS complexes. Polymorphic VT results from several different foci or pathways and is thus irregular, with varying QRS complexes. Nonsustained VT lasts < 30 sec; sustained VT lasts ≥ 30 sec or is terminated sooner because of hemodynamic collapse. VT frequently deteriorates to ventricular fibrillation and thus cardiac arrest (see p. 2255).

**Symptoms and Signs**

VT of short duration or slow rate may be asymptomatic. Sustained VT is almost always symptomatic, causing palpitations, symptoms of hemodynamic compromise, or sudden cardiac death.

**Diagnosis**

- ECG

Diagnosis is by ECG (see Fig. 213-17). Any wide QRS complex tachycardia (QRS ≥ 0.12 sec) should be considered VT until proved otherwise. Diagnosis is supported by ECG findings of dissociated P-wave activity, fusion or capture beats, uniformity of QRS vectors in the V leads (concordance) with discordant T-wave vector (opposite QRS vectors), and a frontal-plane QRS axis in the northwest quadrant. Differential diagnosis includes supraventricular tachycardia conducted with bundle branch block or via an accessory pathway (see Table 213-1). However, because some patients tolerate VT surprisingly well, concluding that a well-tolerated wide

[Fig. 213-17. Broad QRS ventricular tachycardia.]

QRS complex tachycardia must be of supraventricular origin is a mistake. Using drugs appropriate for supraventricular tachycardia (eg, verapamil, diltiazem) in patients with VT may cause hemodynamic collapse and death.

**Treatment**

- **Acute:** Sometimes synchronized direct-current cardioversion, sometimes lidocaine

- **Long-term:** Usually an implantable cardioverter-defibrillator
**Acute:** Treatment depends on symptoms and duration of VT. Hypotensive VT requires synchronized direct-current cardioversion with ≥ 100 joules. Stable sustained VT can be treated with IV drugs, usually lidocaine (see Table 213-2), which acts quickly but is frequently ineffective. If lidocaine is ineffective, IV procainamide may be given, but it may take up to 1 h to work. Failure of IV procainamide is an indication for cardioversion.

Nonsustained VT does not require immediate treatment unless the runs are frequent or long enough to cause symptoms. In such cases, antiarrhythmics are used as for sustained VT.

**Long-term:** The primary goal is preventing sudden death, rather than simply suppressing the arrhythmia. It is best accomplished by use of an implantable cardioverter-defibrillator (ICD—see p. 2159). However, the decision about whom to treat is complex and depends on the estimated probability of life-threatening VTs and the severity of underlying heart disorders (see Table 213-2).

Long-term treatment is not required when the index episode of VT resulted from a transient cause (eg, during the 48 h after onset of MI) or a reversible cause (acid-base disturbances, electrolyte abnormalities, proarrhythmic drug effect).

In the absence of a transient or reversible cause, patients who have had an episode of sustained VT typically require an ICD. Most patients with sustained VT and a significant structural heart disorder should also receive a β-blocker. If an ICD cannot be used, amiodarone may be the preferred antiarrhythmic for prevention of sudden death.

Because nonsustained VT is a marker for increased risk of sudden death in patients with a structural heart disorder, such patients (particularly those with an ejection fraction < 0.35) require further evaluation. Such patients should receive an ICD.

When prevention of VTs is important (usually in patients who have an ICD and are having frequent episodes of VT), antiarrhythmics or transcatheter radiofrequency or surgical ablation of the arrhythmogenic substrate is required. Any class Ia, Ib, Ic, II, or III drug can be used. Because β-blockers are safe, they are the first choice unless contraindicated. If an additional drug is required, sotalol is commonly used, then amiodarone.

Transcatheter radiofrequency ablation is used most commonly in patients who have VT with well-defined syndromes (eg, right ventricular outflow tract VT or left septal VT [Belhassen VT, verapamil-sensitive VT]) and otherwise healthy hearts.

**Long QT Syndrome and Torsades de Pointes Ventricular Tachycardia**

**Torsades de pointes** is a specific form of polymorphic VT in patients with a long QT interval. It is characterized by rapid, irregular QRS complexes, which appear to be twisting around the ECG baseline. This arrhythmia may cease spontaneously or degenerate into ventricular fibrillation. It causes significant hemodynamic compromise and often death. Diagnosis is by ECG. Treatment is with IV Mg, measures to shorten the QT interval, and often direct-current cardioversion.

The long QT interval responsible for torsades de pointes can be congenital or drug-induced. QT-interval prolongation predisposes to arrhythmia by prolonging repolarization, which induces early after-depolarizations and spatial dispersion of refractoriness.

**Congenital:** At least 10 distinct forms of congenital long QT syndrome have been described. Most cases fall into the first 3 subgroups:

- Long QT syndrome type 1 (LQT1), caused by a loss of function mutation of gene *KCNQ1*, which encodes an adrenergic-sensitive cardiac K current (IKs)

- Long QT syndrome type 2 (LQT2), caused by a loss of function mutation of gene *HERG*, which encodes another cardiac K channel (IKr)
• Long QT syndrome type 3 (LQT3), caused by a mutation in gene SCN5A, which disrupts fast inactivation of the cardiac Na channel (I_{Na})

These forms are inherited as autosomal dominant disorders with incomplete penetrance and, in the past, were referred to as Romano-Ward syndrome. In rare patients with 2 abnormal copies of the genetic abnormality (particularly LQT1), the disorder is associated with congenital deafness and, in the past, was referred to as the Jervell and Lange-Nielsen syndrome. Patients with long QT syndrome are prone to recurrent syncope secondary to torsade de pointes and to sudden death secondary to torsade de pointes degenerating into ventricular fibrillation.

**Drug-induced:** More commonly, torsades de pointes results from a drug, usually a class Ia, Ic, or III antiarrhythmic. Other drugs that can induce torsades de pointes include tricyclic antidepressants, phenothiazines, and certain antivirals and antifungals (see www.torsades.org for an up-to-date list).

**Symptoms and Signs**

Patients often present with syncope because the underlying rate (200 to 250 beats/min) is nonperfusing. Palpitations are common among conscious patients. Sometimes the long QT interval is detected after resuscitation.

**Diagnosis**

• ECG

Diagnosis is by ECG showing an undulating QRS axis, with the polarity of complexes shifting around the baseline (see **Fig. 213-18**). ECG between episodes shows a long QT interval after correction for heart rate (QTc). Normal values average about 0.44 sec, although they vary among individuals and by sex. A family history may suggest a congenital syndrome.

**Treatment**

• Usually unsynchronized direct-current cardioversion

• Sometimes magnesium sulfate (MgSO_{4}) IV

An acute episode prolonged enough to cause hemodynamic compromise is treated with unsynchronized cardioversion, beginning with 100 joules. Nevertheless, early recurrence is the rule. Patients often respond to Mg: MgSO_{4} 2 g IV over 1 to 2 min. If this treatment is unsuccessful, a 2nd bolus is given in 5 to 10 min, and an Mg infusion of 3 to 20 mg/min may be started in patients without renal insufficiency. Lidocaine (class Ib) shortens the QT interval and may be effective especially for drug-induced torsades de pointes. Class la, lc, and III antiarrhythmics are avoided.

If a drug is the cause, it is stopped, but until drug clearance is complete, patients with frequent or long runs of torsades de pointes require treatment to shorten the QT interval. Because increasing the heart rate shortens the QT interval, temporary pacing, IV isoproterenol, or both are often effective. Long-term treatment is required for patients with a congenital long QT-interval syndrome. Treatment choices include β-blockers, permanent pacing, ICD, or a combination. Family members should be evaluated by ECG.

Patients with congenital long QT syndrome should clearly avoid drugs that prolong the QT interval, and patients with exercise-related symptoms (usually LQT1 or LQT2) should avoid strenuous exercise. Treatment options include β-blockers, pacing to maintain faster heart rates (which shortens the QT interval), and the ICD, alone or in combinations. Current guidelines recommend the ICD for patients resuscitated from cardiac arrest and those with syncope despite β-blocker treatment.
**Brugada Syndrome**

Brugada syndrome is an inherited disorder of cardiac electrophysiology causing an increased risk of syncope and sudden death.

Several different mutations are involved, most affecting the SCN5A gene that encodes the α-subunit of the voltage-dependent cardiac Na channel. Typically, patients have no structural heart disease. Nevertheless, relationships with other genetic and acquired structural heart diseases are increasingly being recognized, as are overlap syndromes with LQT3 and with arrhythmogenic right ventricular dysplasia (ARVD).

In some patients, Brugada syndrome has no clinical expression. However, in many patients it leads to syncope or sudden cardiac death due to polymorphic ventricular tachycardia and ventricular fibrillation. Events occur more often at night and are not usually related to exercise. Events may also be brought on by fever and by treatment with certain drugs including Na channel blockers, β-blockers, tricyclic antidepressants, lithium, and cocaine.

Initial diagnosis is based on a characteristic ECG pattern (type 1 Brugada ECG pattern—see Fig. 213-19) with prominent ST elevation in V1 and V2 (sometimes involving V3) that causes the QRS complex in these leads to resemble right bundle branch block. The ST segment is coved and descends to an inverted T-wave. Lesser degrees of these patterns (type 2 and type 3 Brugada ECG patterns) are not considered diagnostic. The type 2 and type 3 patterns may change to a type 1 pattern spontaneously, with fever, or in response to drugs. The latter is the basis of a challenge diagnostic test usually using ajmaline or procainamide. Diagnosis should be considered in patients with unexplained cardiac arrest or syncope or a family history of such. Role of electrophysiologic testing is currently unclear and is the subject of ongoing study.

Patients presenting with syncope and patients resuscitated from arrest should receive an implantable cardioverter-defibrillator. Best treatment of patients diagnosed based on ECG changes and family history is unclear, although they do have increased risk of sudden death.

**Ventricular Fibrillation**

Ventricular fibrillation (VF) causes uncoordinated quivering of the ventricle with no useful contractions. It causes immediate syncope and death within minutes. Treatment is with cardiopulmonary resuscitation, including immediate defibrillation.

VF is due to multiple wavelet reentrant electrical activity and is manifested on ECG by ultrarapid baseline undulations that are irregular in timing and morphology (see Fig. 213-14).

VF is the presenting rhythm for about 70% of patients in cardiac arrest and is thus the terminal event in many disorders. Overall, most patients with VF have an underlying heart disorder (typically ischemic, but also hypertrophic or dilated cardiomyopathies, arrhythmogenic right ventricular dysplasia [ARVD], or Brugada syndrome). Risk of VF in any disorder is increased by electrolyte abnormalities, acidosis, hypoxemia, or ischemia.

VF is much less common among infants and children, in whom asystole is the more common presentation of cardiac arrest.

Treatment is with cardiopulmonary resuscitation, including defibrillation (see p. 2260). The success rate for immediate (within 3 min) defibrillation is about 95%, provided that overwhelming pump failure does not preexist. When it does, even immediate defibrillation is only 30% successful, and most resuscitated patients die of pump failure before hospital discharge.
Patients who have VF without a reversible or transient cause are at high risk of future VF events and of sudden death. Most of these patients require an implantable cardioverterdefibrillator; many require concomitant antiarrhythmics to reduce the frequency of subsequent episodes of ventricular tachycardia and VF.
Chapter 214. Valvular Disorders

Introduction

Any heart valve can become stenotic or insufficient, causing hemodynamic changes long before symptoms. Most often, valvular stenosis or insufficiency occurs in isolation in individual valves, but multiple valvular disorders may coexist and a single valve may be both stenosed and insufficient.

Treatment depends on severity of disease but usually involves catheter-based valvuloplasty (eg, percutaneous balloon commissurotomy, valvotomy) or surgery (eg, surgical commissurotomy, valve repair, valve replacement). Two kinds of valve prosthesis are used: bioprosthetic (porcine) and mechanical (manufactured).

Traditionally, a mechanical valve has been used in patients < 65 and in older patients with a long life expectancy, because bioprosthetic valves deteriorate over 10 to 12 yr. Patients with a mechanical valve or bioprosthetic mitral valve require lifelong anticoagulation to an INR of 2.5 to 3.5 (to prevent thromboembolism) and antibiotics before some medical or dental procedures (to prevent endocarditis). An aortic bioprosthetic valve, which does not require anticoagulation beyond the immediate postoperative period, has been used in patients > 65, younger patients with a life expectancy < 10 yr, and those with some right-sided lesions. However, newer bioprosthetic valves may be more durable than 1st-generation valves; thus, patient preference regarding valve type can now be considered.

Women of childbearing age who require valve replacement and plan to become pregnant must balance the increased risk of teratogenicity from warfarin with mechanical valves against that of accelerated valve deterioration with bioprosthetic valves. These risks can be reduced by use of heparin instead of warfarin in the first 12 wk and last 2 wk of the pregnancy, but management is difficult and careful discussion is required before surgery.

Endocarditis prophylaxis is rarely indicated for patients with valvular heart disorders (see p. 2199).

Aortic Regurgitation

Aortic regurgitation (AR) is incompetency of the aortic valve causing flow from the aorta into the left ventricle during diastole. Causes include idiopathic valvular degeneration, rheumatic fever, endocarditis, myxomatous degeneration, congenital bicuspid aortic valve, aortic root dilation or dissection, and connective tissue or rheumatologic disorders. Symptoms include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and chest pain. Signs include widened pulse pressure and an early diastolic murmur. Diagnosis is by physical examination and echocardiography. Surgical treatment is aortic valve replacement.

Etiology

AR may be acute or chronic. The primary causes of acute AR are infective endocarditis and dissection of the ascending aorta. Mild chronic AR in adults is most often caused by a bicuspid or fenestrated aortic valve (2% of men and 1% of women), especially when severe diastolic hypertension (pressure ≥ 110 mm Hg) is present. Moderate to severe chronic AR in adults is most often caused by idiopathic degeneration of the aortic valves or root, rheumatic fever, infective endocarditis, myxomatous degeneration, or trauma. In children, the most common cause is a ventricular septal defect with aortic valve prolapse. Rarely, AR is caused by seronegative spondyloarthopathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis), RA, SLE, arthritis associated with ulcerative colitis, luetic (syphilitic) aortitis, osteogenesis imperfecta, thoracic aortic aneurysm, aortic dissection, supravalvular aortic stenosis, Takayasu's arteritis, rupture of a sinus of Valsalva, acromegaly, and temporal (giant cell) arteritis. AR due to myxomatous degeneration may develop in patients with Marfan syndrome or EhlersDanlos syndrome.

Pathophysiology

In chronic AR, left ventricular (LV) volume and LV stroke volume gradually increase because the LV
receives aortic blood regurgitated in diastole in addition to blood from the pulmonary veins and left atrium. LV hypertrophy compensates for the increase in LV volume over years, but decompensation eventually develops. These changes may ultimately cause arrhythmias, LV impairment, and heart failure (HF).

**Symptoms and Signs**

Acute AR causes symptoms of HF and cardiogenic shock. Chronic AR is typically asymptomatic for years; progressive exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and palpitations develop insidiously. Symptoms of HF correlate poorly with objective measures of LV function. Chest pain (angina pectoris) affects only about 5% of patients who do not have coexisting coronary artery disease (CAD) and, when it occurs, is especially common at night. Patients may present with endocarditis (eg, fever, anemia, weight loss, embolic phenomena) because the abnormal aortic valve is predisposed to bacterial seeding.

Signs vary by severity. As chronic disease progresses, systolic BP increases while diastolic BP decreases, creating a widened pulse pressure. With time, the LV impulse may become enlarged, sustained, increased in amplitude, and displaced downward and laterally, with systolic depression of the entire left parasternal area, giving a rocking motion to the left chest.

A systolic apical or carotid thrill may become palpable in later stages of AR; it is caused by large forward stroke volumes and low aortic diastolic pressure.

Auscultatory findings include a normal 1st heart sound (S$_1$) and a nonsplit, loud, sharp or slapping 2nd heart sound (S$_2$) caused by increased elastic aortic recoil. The murmur of AR is often unimpressive. The murmur is blowing, high-pitched, diastolic, and decrescendo, beginning soon after the aortic component of S$_2$ (A$_2$); it is loudest at the 3rd or 4th left parasternal intercostal space. The murmur is heard best with the diaphragm of the stethoscope when the patient is leaning forward, with breath held at end-expiration. It increases in volume in response to maneuvers that increase afterload (eg, squatting, isometric handgrip). If AR is slight, the murmur may occur only in early diastole. If LV diastolic pressure is very high, the murmur is short because aortic and LV diastolic pressures equalize earlier in diastole.

Other abnormal sounds include a forward ejection and backward regurgitant flow (to-and-fro) murmur, an ejection click soon after the S$_1$, and an aortic ejection flow murmur. A diastolic murmur heard near the axilla or mid left thorax (Cole-Cecil murmur) is caused by fusion of the aortic murmur with the 3rd heart sound (S$_3$), which is due to simultaneous filling of LV from the left atrium and AR. A mid-to-late diastolic rumble heard at the apex (Austin Flint murmur) may result from rapid regurgitant flow into the LV, causing mitral valve leaflet vibration at the peak of atrial flow; this murmur mimics the diastolic murmur of mitral stenosis.

Other signs are unusual; sensitivity and specificity are low or unknown. Visible signs include head bobbing (Muset's sign) and pulsation of the fingernail capillaries (Quincke's sign, best seen with slight pressure) or uvula (Muller's sign). Palpable signs include a large-volume pulse with rapid rise and fall (slapping, water-hammer, or collapsing pulse) and pulsation of the carotid arteries (Corrigan's sign), retinal arteries (Becker's sign), liver (Rosenbach's sign), or spleen (Gerhard's sign). BP findings may include popliteal systolic pressure ≥ 60 mm Hg higher than brachial pressure (Hill's sign) and a fall in diastolic BP of > 15 mm Hg with arm elevation (Mayne's sign). Auscultatory signs include a sharp sound heard over the femoral pulse (pistol-shot sound, or Traube's sign) and a femoral systolic bruit distal and a diastolic bruit proximal to arterial compression (Duroziez's murmur).

**Diagnosis**

• **Echocardiography**

Diagnosis is suspected based on history and physical examination and confirmed by echocardiography. Doppler echocardiography is the test of choice to detect and quantify the magnitude of regurgitant blood flow. Two-dimensional echocardiography can quantify aortic root size and anatomy and LV function. An end-systolic LV volume > 60 mL/m$^2$, endsystolic LV diameter > 50 mm, and LV ejection fraction (LVEF) <
50% suggest decompensation. Echocardiography can also assess severity of pulmonary hypertension secondary to LV failure, detect vegetations or pericardial effusions (eg, in aortic dissection), and provide information about prognosis.

Radionuclide imaging may be used to determine LVEF if echocardiographic results are borderline abnormal or if echocardiography is technically difficult.

An ECG and chest x-ray should be obtained. ECG may show repolarization abnormalities with or without QRS voltage criteria of LV hypertrophy, left atrial enlargement, and T-wave inversion with ST-segment depression in precordial leads. Chest x-ray may show cardiomegaly and a prominent aortic root in patients with chronic progressive AR. If AR is severe, signs of pulmonary edema and HF may also be present. Exercise testing may help assess functional capacity and symptoms in patients with documented AR and equivocal symptoms.

Coronary angiography should be done before surgery, even if no angina is present, because about 20% of patients with severe AR have significant CAD, which may need concomitant coronary artery bypass graft surgery.

Prognosis

With treatment, the 10-yr survival for patients with mild to moderate AR is 80 to 95%. With appropriately timed valve replacement (ie, before HF and using criteria below), long-term prognosis for patients with moderate to severe AR is good. However, the prognosis for those with severe AR and HF is considerably poorer.

Treatment

• Aortic valve replacement

• Sometimes vasodilators, diuretics, and nitrates

Treatment of acute AR is aortic valve replacement. Treatment of chronic AR varies by symptoms and degree of LV dysfunction. Patients with symptoms precipitated by normal daily activity or during exercise testing require aortic valve replacement; patients who prefer to avoid surgery may be treated with vasodilators (eg, long-acting nifedipine 30 to 90 mg po once/day or ACE inhibitors). Also, diuretics or nitrates to reduce preload may be beneficial for severe AR. Asymptomatic patients with LVEF < 55%, an end-systolic diameter ≥ 55 mm (55 rule), or an end-diastolic diameter > 75 mm also require surgery; oral drugs are a 2nd-best option for this group. Additional surgical criteria have been proposed, including fractional shortening < 25 to 29%, end-diastolic radius to myocardial wall thickness ratio > 4.0, and cardiac index < 2.2 to 2.5 L/min/m².

Patients who do not meet these criteria should be reevaluated by physical examination, echocardiography, and possibly rest-exercise radionuclide cineangiography to measure LV contractility every 6 to 12 mo.

Antibiotic prophylaxis against endocarditis is no longer recommended except for patients who have had valve replacement (see Table 215-4).

Aortic Stenosis

Aortic stenosis (AS) is narrowing of the aortic valve obstructing blood flow from the left ventricle to the ascending aorta during systole. Causes include a congenital bicuspid valve, idiopathic degenerative sclerosis with calcification, and rheumatic fever. Progressive untreated AS ultimately results in one or more of the classic triad of syncope, angina, and exertional dyspnea; heart failure and arrhythmias may develop. A carotid pulse with small amplitude and delayed upstroke and a crescendo-decrescendo ejection murmur are characteristic. Diagnosis is by physical examination and echocardiography. Asymptomatic AS often requires no
treatment. For progressive severe or symptomatic AS in children, balloon valvotomy is used; adults require valve replacement.

Etiology

Aortic sclerosis, a degenerative aortic valve disease with thickening of aortic valve structures by fibrosis and calcification initially without causing significant obstruction, is the most common cause of AS in elderly patients. Over years, aortic sclerosis progresses to stenosis in as many as 15% of patients. Aortic sclerosis resembles atherosclerosis, with deposition of lipoproteins, active inflammation, and calcification of the valves; risk factors are similar (see p. 2082).

The most common cause of AS in patients < 70 yr is a congenital bicuspid aortic valve. Congenital AS occurs in 3 to 5/1000 live births and affects more males.

In developing countries, rheumatic fever is the most common cause in all age groups. Supravalvular AS caused by a discrete, congenital membrane or hypoplastic constriction just above the sinuses of Valsalva is uncommon. A sporadic form of supravalvular AS is associated with a characteristic facies (high and broad forehead, hypertelorism, strabismus, upturned nose, long philtrum, wide mouth, dental abnormalities, puffy cheeks, micrognathia, low-set ears). When associated with idiopathic hypercalcemia of infancy, this form is known as Williams syndrome. Subvalvular AS caused by a congenital membrane or fibrous ring just beneath the aortic valve is uncommon.

Pathophysiology

Aortic regurgitation may accompany AS, and about 60% of patients > 60 yr with significant AS also have mitral annular calcification, which may lead to significant mitral regurgitation.

The left ventricle (LV) gradually hypertrophies in response to AS. Significant LV hypertrophy causes diastolic dysfunction and, with progression, may lead to decreased contractility, ischemia, or fibrosis, any of which may cause systolic dysfunction and heart failure (HF). LV chamber enlargement is a late finding unless there is coexisting MI. Patients with AS have a higher incidence of GI bleeding (called Heyde’s syndrome) because the high shear stress of stenotic valves makes multimeric von Willebrand’s factor more susceptible to cleavage by a plasma metalloprotease and may increase platelet clearance. GI bleeding may also be due to angiodysplasia.

Symptoms and Signs

Congenital AS is usually asymptomatic until at least age 10 or 20 yr, when symptoms may begin to develop insidiously. In all forms, progressive untreated AS ultimately results in exertional syncope, angina, and dyspnea (SAD triad). Other symptoms and signs may include those of HF and arrhythmias, including ventricular fibrillation leading to sudden death.

Exertional syncope occurs because cardiac output cannot increase enough to meet the demands of physical activity. Nonexertional syncope may result from altered baroreceptor responses or ventricular tachycardia. Exertional angina pectoris affects about two thirds of patients; about one half have significant coronary artery atherosclerosis, and one half have normal coronary arteries but have ischemia induced by LV hypertrophy, altered coronary flow dynamics, or both.

There are no visible signs of AS. Palpable signs include carotid and peripheral pulses that are reduced in amplitude and slow rising (pulsus parvus, mollus et tardus) and an apical impulse that is sustained (thrusts with the 1st heart sound [S1] and relaxes with the 2nd heart sound [S2]) because of LV hypertrophy. The LV impulse may become displaced when systolic dysfunction develops. A palpable 4th heart sound (S4), felt best at the apex, and a systolic thrill, corresponding with the murmur of AS and felt best at the left upper sternal border, are occasionally present in severe cases. Systolic BP may be high with mild or moderate AS and falls as AS becomes more severe.

On auscultation, S1 is normal and S2 is single because aortic valve closing is delayed and merges with...
the pulmonic (P₂) component of S₂. The aortic component may also be soft. Paradoxical splitting of S₂ may be heard. An S₄ may be audible. An ejection click may also be audible early after S₁ in patients with congenital bicuspid AS when valve leaflets are stiff but not completely immobile. The click does not change with dynamic maneuvers.

The hallmark finding is a crescendo-decrescendo ejection murmur, heard best with the diaphragm of the stethoscope at the right and left upper sternal border when a patient who is sitting upright leans forward. The murmur typically radiates to the right clavicle and both carotid arteries (left often louder than right) and has a harsh or grating quality. But in elderly patients, vibration of the un-fused cusps of calcified aortic valve leaflets may transmit a louder, more high-pitched, "cooing" or musical sound to the cardiac apex, with softening or absence of the murmur parasternally (Gallavardin's phenomenon), thereby mimicking mitral regurgitation. The murmur is soft when stenosis is less severe, grows louder as stenosis progresses, and becomes longer and peaks in volume later in systole (i.e., crescendo phase becomes longer and decrescendo phase becomes shorter) as stenosis becomes more severe. As LV contractility decreases in critical AS, the murmur becomes softer and shorter. The intensity of the murmur may therefore be misleading in these circumstances.

The murmur of AS typically increases with maneuvers that increase LV volume and contractility (e.g., leg-raising, squatting, Valsalva release, after a ventricular premature beat) and decreases with maneuvers that decrease LV volume (Valsalva maneuver) or increase afterload (isometric handgrip). These dynamic maneuvers have the opposite effect on the murmur of hypertrophic cardiomyopathy, which can otherwise resemble that of AS. The murmur of mitral regurgitation due to prolapse of the posterior leaflet may also mimic AS.

### Diagnosis

**Echocardiography**

Diagnosis is suspected clinically and confirmed by echocardiography. Two-dimensional transthoracic echocardiography is used to identify a stenotic aortic valve and possible causes, to quantify LV hypertrophy and degree of diastolic or systolic dysfunction, and to detect coexisting valvular heart disorders (aortic regurgitation, mitral valve disorders) and complications (e.g., endocarditis). Doppler echocardiography is used to quantify degree of stenosis by measuring aortic valve area, jet velocity, and transvalvular systolic pressure gradient.

A valve area of 0.5 to 1.0 cm² or a mean gradient > 45 to 50 mm Hg represents severe stenosis. The gradient may be overestimated in aortic regurgitation and underestimated in LV systolic dysfunction. The rate of progression of AS from mild to severe is quite variable and does not necessarily proceed in a linear fashion.

Cardiac catheterization is necessary to determine whether coronary artery disease (CAD) is the cause of angina and, occasionally, to resolve differences between clinical and echocardiographic findings.

An ECG and chest x-ray are obtained. ECG typically shows changes of LV hypertrophy with or without an ischemic ST- and T-wave pattern. Chest x-ray findings may include calcification of the aortic cusps (seen on the lateral projection or on fluoroscopy) and evidence of HF. Heart size may be normal or only mildly enlarged.

### Prognosis

AS may progress slowly or quickly and thus requires regular follow-up to detect progression, particularly in sedentary elderly patients. In such patients, flow may become significantly compromised without triggering symptoms.

Overall, about 3 to 6% of asymptomatic patients with normal systolic function develop symptoms or LV ejection fraction depression every year. However, surgery is usually delayed until symptoms develop because the risk of surgery outweighs the survival benefit in asymptomatic patients. Surgery should not
be delayed once symptoms develop. Mean survival in untreated symptomatic patients is about 2 to 3 yr. Aortic valve replacement relieves symptoms and improves survival. Risk with surgery increases for patients who require simultaneous coronary artery bypass graft (CABG) and for those with depressed systolic LV function.

About 50% of deaths occur suddenly. While awaiting surgery, patients with severe AS should be advised to restrict physical exertion.

**Treatment**

- Sometimes aortic valve replacement

Asymptomatic patients with a maximum gradient ≤ 25 mm Hg and a valve area > 1.0 cm² have a low mortality and low overall risk of requiring surgery in the next 2 yr; annual evaluation for symptom progression, including echocardiography to determine gradient and valve area, is appropriate.

Asymptomatic patients with gradients of 25 to 50 mm Hg or valve area < 1.0 cm² are at higher risk of developing symptoms in the next 2 yr, but generally elective valve replacement is not required in the absence of symptoms. Valve replacement is indicated for patients who have moderate or severe AS and primarily require CABG. Surgery may be indicated for patients who become hypotensive during exercise treadmill testing and for those with LV ejection fraction < 50%. Patients with ventricular arrhythmias and severe LV hypertrophy are also often referred for surgery, but benefits are less clear. Recommendations for patients without any of these qualifying conditions include more frequent monitoring for progression of symptoms, LV hypertrophy, gradients, and valve area with medical management as needed. It is unclear whether statins reduce the progression of AS. Other drugs may be detrimental, especially those that can cause hypotension. Small studies suggest that perhexilene maleate may decrease symptoms. Nitroprusside has been used as a temporizing measure to reduce afterload in patients with decompensated HF in the hours before valve replacement, but because this drug can have the same effect as rapid-acting nitrates, it must be used cautiously and monitoring is required.

Symptomatic patients should undergo valve replacement or balloon valvotomy. Valve replacement is indicated for virtually all who can tolerate surgery. In younger patients, the patient's own pulmonic valve can be used, providing good durability; a bioprosthesis is then used to replace the pulmonic valve (Ross procedure). Most often, the aortic valve is replaced with a mechanical or bio-prosthetic valve. Preoperative evaluation for CAD is indicated so that CABG and valve replacement, if indicated, can be done during the same procedure.

Balloon valvotomy is used primarily in children and very young adults with congenital AS. In older patients who are unfit for surgery, balloon valvuloplasty can provide temporary relief of symptoms, perhaps for 6 to 12 mo, and can be repeated in selected patients. Minimally invasive percutaneous valve replacement is being used as an alternative procedure in very elderly or frail patients.

**Mitral Valve Prolapse**

Mitral valve prolapse (MVP) is a billowing of mitral valve leaflets into the left atrium during systole. The most common cause is idiopathic myxomatous degeneration. MVP is usually benign, but complications include mitral regurgitation, endocarditis, valve rupture, and possibly thromboembolism. MVP is usually asymptomatic in the absence of important regurgitation, although there are reports that some patients experience chest pain, dyspnea, dizziness, and palpitations. Signs include a crisp mid-systolic click, followed by a late systolic murmur if regurgitation is present. Diagnosis is by physical examination and echocardiography. Prognosis is excellent in the absence of significant regurgitation, but chordal rupture and endocarditis may occur. No specific treatment is necessary unless mitral regurgitation is present.

MVP is common; prevalence is 1 to 3% in otherwise normal populations, depending on the echocardiographic criteria used. Women and men are affected equally; onset usually follows the adolescent growth spurt.
Etiology

MVP is most often caused by myxomatous degeneration of the mitral valve and chordae tendineae. Degeneration is usually idiopathic, although it may be inherited in an autosomal dominant or, rarely, in an X-linked recessive fashion. Myxomatous degeneration may also be caused by connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome, adult polycystic kidney disease, osteogenesis imperfecta, pseudoxanthoma elasticum, SLE, polyarteritis nodosa) and muscular dystrophies. MVP is more common among patients with Graves' disease, hypomastia, von Willebrand's syndrome, sickle cell disease, and rheumatic heart disease. Myxomatous degeneration may also affect the aortic or tricuspid valve, resulting in aortic or tricuspid prolapse. Tricuspid regurgitation is uncommon.

Mitral regurgitation (MR) may occur in patients with apparently normal mitral valve leaflets (ie, nonmyxomatous) if papillary muscle dysfunction is present or the mitral annulus is dilated (eg, in dilated cardiomyopathy). In hypertrophic cardiomyopathy with outflow obstruction, MR occurs due to interference with the closure of the mitral leaflets (which may also be abnormal). Transient MVP may occur when intravascular volume decreases significantly, as occurs in severe dehydration or sometimes during pregnancy (when the woman is recumbent and the gravid uterus compresses the inferior vena cava, reducing venous return).

MR is the most common complication of MVP. MR may be acute (due to ruptured chordae tendineae or flail mitral valve leaflets) or chronic; sequelae of chronic MR include heart failure and atrial fibrillation (AF) with thromboembolism. Whether MVP causes stroke independent of MR and AF is unclear. In addition, MR increases the risk of infective endocarditis.

Symptoms and Signs

Most patients are asymptomatic. Some experience nonspecific symptoms (eg, chest pain, dyspnea, palpitations, dizziness, near syncope, migraines, anxiety), thought to be due to poorly defined associated abnormalities in adrenergic signaling and sensitivity rather than to mitral valve pathology. In about one third of patients, emotional stress precipitates palpitations, which may be a symptom of benign arrhythmias (atrial premature beats, paroxysmal atrial tachycardia, ventricular premature beats, complex ventricular ectopy).

Occasionally, patients present with MR. Rarely, patients present with endocarditis (eg, fever, weight loss, thromboembolic phenomena) or stroke. Sudden death occurs in < 1%, most often resulting from ruptured chordae tendineae and flail mitral valve leaflets. Death due to a fatal arrhythmia is rare.

Typically, MVP causes no visible or palpable cardiac signs. MVP alone causes a crisp mid-systolic click heard best with the diaphragm of the stethoscope over the left apex when the patient is in the left lateral decubitus position. MVP with MR causes a click with a late-systolic MR murmur. The click becomes audible or moves closer to the 1st heart sound (S1) and becomes louder with maneuvers that decrease left ventricle (LV) size (eg, sitting, standing, Valsalva maneuver); the same maneuvers cause an MR murmur to appear or become louder and last longer. These effects occur because decreasing LV size causes papillary muscles and chordae tendineae to pull together more centrally beneath the valve, resulting in quicker, more forceful prolapse with earlier, more severe regurgitation. Conversely, squatting or isometric handgrip delays the S1 click and shortens the MR murmur. The systolic click may be confused with the click of congenital aortic stenosis, which can be distinguished because it occurs very early in systole and does not move with postural or LV volume changes. Other findings include a systolic honk or whoop, thought to be caused by valvular leaflet vibration; these findings are usually transient and may vary with respiratory phase. An early diastolic opening snap caused by return of the prolapsed valve to its normal position is rarely heard.

Other physical findings associated with but not diagnostic of MVP include hypomastia, pectus excavatum, straight back syndrome, and a narrow anteroposterior chest diameter.

Diagnosis
Echocardiography

Diagnosis is suggested clinically and confirmed by 2-dimensional echocardiography. Holosystolic displacement of ≥ 3 mm or late systolic displacement of ≥ 2 mm identifies 95% of patients with MVP; the percentage is slightly higher if echocardiography is done while the patient is standing. Thickened, redundant mitral valve leaflets and displacement of ≥ 5 mm are thought to indicate more extensive myxomatous degeneration and greater risk of endocarditis and MR.

Holter monitoring and 12-lead ECG may be useful for documenting arrhythmias in patients with palpitations.

Prognosis

MVP is usually benign, but severe myxomatous degeneration of the valve can lead to MR. In patients with severe MR, incidence of LV or left atrium enlargement, arrhythmias (eg, AF), infective endocarditis, stroke, need for valve replacement, and death is about 2 to 4%/yr.

Treatment

- Usually none
- Sometimes β-blockers

MVP does not usually require treatment. β-Blockers may be used to relieve symptoms of excess sympathetic tone (eg, palpitations, migraines, dizziness) and to reduce risk of tachyarrhythmias, although no data support this practice. A typical regimen is atenolol 25 to 50 mg po once/day or propranolol 20 to 40 mg po bid. AF may require additional treatment (see p. 2166).

Treatment of MR depends on severity and associated left atrial and LV changes.

Antibiotic prophylaxis against endocarditis is no longer recommended. Anticoagulants to prevent thromboembolism are recommended only for patients with AF or prior transient ischemic attack or stroke.

Mitral Regurgitation

Mitral regurgitation (MR) is incompetency of the mitral valve causing flow from the left ventricle (LV) into the left atrium during systole. Common causes include mitral valve prolapse, ischemic papillary muscle dysfunction, rheumatic fever, and annular dilation secondary to LV systolic dysfunction and dilation. Complications include progressive heart failure, arrhythmias, and endocarditis. Symptoms and signs include palpitations, dyspnea, and a holosystolic apical murmur. Diagnosis is by physical examination and echocardiography. Prognosis depends on LV function and severity and duration of MR. Patients with mild, asymptomatic MR may be monitored, but progressive or symptomatic MR requires mitral valve repair or replacement.

Etiology

MR may be acute or chronic. Causes of acute MR include ischemic papillary muscle dysfunction or rupture; infective endocarditis; acute rheumatic fever; spontaneous, traumatic, or ischemic tears or rupture of the mitral valve leaflets or subvalvular apparatus; acute dilation of the LV due to myocarditis or ischemia; and mechanical failure of a prosthetic mitral valve.

Common causes of chronic MR include those of acute MR plus myxomatous degeneration of the mitral leaflets or chordae tendineae, mitral valve prolapse (MVP), mitral annular enlargement, and nonischemic papillary muscle dysfunction (eg, due to LV enlargement). Uncommon causes of chronic MR include a congenital endocardial cushion defect with a cleft anterior leaflet, SLE, acromegaly, myxoma involving the valve or chordae, and calcification of the mitral annulus (mainly in elderly women).

In infants, the most likely causes of MR are papillary muscle dysfunction, endocardial fibroelastosis, acute
myocarditis, cleft mitral valve with or without an endocardial cushion defect, and myxomatous
degeneration of the mitral valve. MR may coexist with mitral stenosis when thickened valvular leaflets do
not close.

Pathophysiology

Acute MR may cause acute pulmonary edema and biventricular failure with cardiogenic shock or sudden
cardiac death. Complications of chronic MR include gradual enlargement of the left atrium (LA); LV
enlargement and hypertrophy, which initially compensates for regurgitant flow (preserving forward stroke
volume) but eventually decompensates (reducing forward stroke volume); atrial fibrillation (AF), which
may be further complicated by thromboembolism; and infective endocarditis.

Symptoms and Signs

Acute MR causes the same symptoms and signs as acute heart failure and cardiogenic shock (see p.
2116). Most patients with chronic MR are initially asymptomatic and develop symptoms insidiously as the
LA enlarges, pulmonary artery and venous pressure increases, and LV remodeling occurs. Symptoms
include dyspnea, fatigue (due to heart failure), orthopnea, and palpitations (often due to AF). Rarely,
patients present with endocarditis (eg, fever, weight loss, embolic phenomena).

Signs develop only when MR becomes moderate to severe. Inspection and palpation may detect a brisk
apical impulse and sustained left parasternal movement due to systolic expansion of an enlarged LA. An
LV impulse that is sustained, enlarged, and displaced downward and to the left suggests LV hypertrophy
and dilation. A diffuse precordial lift occurs with severe MR because the LA enlarges, causing anterior
cardiac displacement, and pulmonary hypertension causes right ventricular hypertrophy. A regurgitant
murmur (or thrill) may also be palpable in severe cases.

On auscultation, the 1st heart sound (S1) may be soft (or occasionally loud). A 3rd heart sound (S3) at
the apex reflects a dilated LV and important MR.

The cardinal sign of MR is a holosystolic (pansystolic) murmur, heard best at the apex with the diaphragm
of the stethoscope when the patient is in the left lateral decubitus position. In mild MR, the systolic
murmur may be abbreviated or occur late in systole. The murmur begins with S1 in conditions causing
leaflet incompetency throughout systole, but it often begins after S1 (eg, when chamber dilation during
systole distorts the valve apparatus or when myocardial ischemia or fibrosis alters dynamics). When the
murmur begins after S1, it always continues to the 2nd heart sound (S2). The murmur radiates toward the
left axilla; intensity may remain the same or vary. If intensity varies, the murmur tends to crescendo in
volume up to S2. MR murmurs increase in intensity with handgrip or squatting because peripheral
vascular resistance to ventricular ejection increases, augmenting regurgitation into the LA; murmurs
decrease in intensity with standing or the Valsalva maneuver. A short rumbling mid-diastolic inflow murmur
due to torrential mitral diastolic flow may be heard following an S3. In patients with posterior leaflet
prolapse, the murmur may be coarse and radiate to the upper sternum, mimicking aortic stenosis.

MR murmurs may be confused with tricuspid regurgitation, which can be distinguished because its
murmur is augmented during inspiration.

Diagnosis

• Echocardiography

Diagnosis is suspected clinically and confirmed by echocardiography. Doppler echocardiography is used
to detect regurgitant flow and help quantify its severity; 2-dimensional or 3-dimensional echocardiography
is used to determine the cause of MR and to detect pulmonary hypertension.

If endocarditis or valvular thrombi are suspected, transesophageal echocardiography (TEE) can provide a
more detailed view of the mitral valve and LA. TEE is also indicated when mitral valve repair instead of
replacement is being considered to confirm the anatomy in more detail.
An ECG and chest x-ray are usually obtained initially. ECG may show LA enlargement and LV hypertrophy with or without ischemia. Sinus rhythm is usually present when MR is acute because the atria have not had time to stretch and remodel.

Chest x-ray in acute MR may show pulmonary edema; abnormalities in cardiac silhouette are not evident unless an underlying chronic disorder is also present. Chest x-ray in chronic MR may show LA and LV enlargement. It may also show pulmonary vascular congestion and pulmonary edema with heart failure. Cardiac catheterization is done before surgery, mainly to determine whether coronary artery disease (CAD) is present. A prominent systolic c-v wave is seen on pulmonary artery occlusion pressure (pulmonary capillary wedge pressure) tracings during ventricular systole. Ventriculography can be used to quantify MR. Cardiac MRI can accurately measure regurgitant fraction and determine the underlying cause of dilated myopathy with MR.

**Prognosis**

Prognosis varies by acuity and cause of MR. Once MR becomes severe, about 10% of asymptomatic patients become symptomatic per year thereafter. About 10% of patients with chronic MR caused by MVP require surgical intervention.

**Treatment**

- Mitral valve repair or replacement

Acute MR requires emergency mitral valve repair or replacement; patients with ischemic papillary muscle rupture may also require coronary revascularization. Pending surgery, nitroprusside or nitroglycerin infusion may be used to reduce afterload, thus improving forward stroke volume and reducing ventricular and regurgitant volume.

Definitive treatment of chronic MR is also mitral valve repair or replacement, but patients with asymptomatic or mild chronic MR and no pulmonary hypertension or AF may do well with periodic monitoring. ACE inhibitors or angiotensin II receptor blockers are used to decrease left ventricular preload and afterload. They are used in patients with moderate mitral insufficiency to delay dilation of the LV. Loop diuretics such as furosemide are helpful in patients with exertional or nocturnal dyspnea. Digoxin may reduce symptoms in patients with AF or those in whom valve surgery is not appropriate. The ideal timing for surgery is uncertain, but intervention before ventricular decompensation (defined as echocardiographic end-diastolic dimension > 70 mm, end-systolic dimension > 45 mm, and ejection fraction < 60%) improves outcomes and decreases the chance of worsening LV function. After decompensation, ventricular function becomes dependent on the afterload reduction of MR, and in about 50% of decompensated patients, valve replacement causes a markedly depressed ejection fraction. For patients with moderate MR and significant CAD, perioperative mortality rate is 1.5% with bypass surgery alone and 25% with concomitant valve replacement. If technically feasible, valve repair instead of replacement is preferred; perioperative mortality rate is 2 to 4% (compared with 5 to 10% for replacement), and long-term prognosis is good (80 to 94% survival rate at 5 to 10 yr, compared with 40 to 60% for replacement).

New percutaneous procedures that tailor the mitral leaflets have been used in elderly and high-risk patients, and percutaneous placement of artificial valves is under trial.

Antibiotic prophylaxis is no longer recommended except for patients who have had valve replacement (see Table 215-4).

Anticoagulants are used to prevent thromboemboli (see p. 1920) in patients with heart failure or AF. Although severe MR without mitral stenosis or AF is less likely to be complicated by atrial thrombosis, most cardiologists still recommend anticoagulants.

**Mitral Stenosis**
Mitral stenosis (MS) is narrowing of the mitral orifice that impedes blood flow from the left atrium to the left ventricle. The (almost) invariable cause is rheumatic fever. Common complications are pulmonary hypertension, atrial fibrillation, and thromboembolism. Symptoms are those of heart failure; signs include an opening snap and a diastolic murmur. Diagnosis is by physical examination and echocardiography. Prognosis is good. Medical treatment includes diuretics, β-blockers or rate-limiting Ca channel blockers, and anticoagulants. Effective treatment for more severe disease consists of balloon valvotomy, surgical commissurotomy, or valve replacement.

In MS, mitral valve leaflets become thickened and immobile and the mitral orifice becomes narrowed due to fusion of the commissures. The chordae are usually thickened, matted, and shortened to a variable degree, contributing to the reduced mobility of the leaflets. The most common cause is rheumatic fever (see p. 2861), even though many patients do not recall the disorder. Less common causes include bacterial endocarditis, SLE, atrial myxoma, RA, malignant carcinoid syndrome with an atrial right-to-left shunt, and methysergide. Occasionally, MS is congenital. If the valve cannot close completely, mitral regurgitation (MR) may coexist with MS. Patients with MS due to rheumatic fever may also have lesions of the aortic or tricuspid valve or both.

The normal area of the mitral valve orifice is 4 to 5 cm$^2$. An area of 1 to 1.5 cm$^2$ reflects moderate MS and often causes exertional symptoms. An area < 1 cm$^2$ represents severe stenosis and may cause symptoms during rest. However, the relationship between the area of the valve orifice and symptoms is not always reliable. Left atrial (LA) size and pressure increase progressively to compensate for MS; pulmonary venous and capillary pressures also increase and may cause secondary pulmonary hypertension, leading to right ventricular (RV) heart failure and tricuspid and pulmonic regurgitation. Rate of progression varies.

LA enlargement predisposes to atrial fibrillation (AF), a risk factor for thromboembolism. The faster heart rate and loss of atrial contraction with onset of AF often leads to sudden worsening of symptoms.

**Symptoms and Signs**

Symptoms correlate poorly with disease severity because the disease often progresses insidiously and patients reduce their activity without being aware of it. Many patients are asymptomatic until they become pregnant or AF develops. Initial symptoms are usually those of heart failure (eg, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue). They typically do not appear until 15 to 40 yr after an episode of rheumatic fever, but in developing countries, much younger children may become symptomatic because streptococcal infections may not be treated with antibiotics and recurrent infections are common. Paroxysmal or chronic AF exacerbates existing diastolic dysfunction, precipitating pulmonary edema and acute dyspnea when ventricular rate is poorly controlled. AF may also cause palpitations; in up to 15% of unanticoagulated patients, it causes systemic embolism with symptoms of stroke or other organ ischemia.

Less common symptoms include hemoptysis due to rupture of small pulmonary vessels and pulmonary edema, particularly during pregnancy when blood volume increases; hoarseness due to compression of the left recurrent laryngeal nerve by a dilated LA or pulmonary artery (Ortner's syndrome); and symptoms of pulmonary hypertension (see p. 1986) and RV failure (see p. 2120).

Inspection and palpation may detect palpable 1st and 2nd heart sounds (S$_1$ and S$_2$). S$_1$ is best palpated at the apex, and S$_2$ at the upper left sternal border. The pulmonic component of S$_2$ (P$_2$) is responsible for the impulse and results from pulmonary hypertension. An RV impulse (heave) palpable at the left sternal border may accompany jugular venous distention when pulmonary hypertension is present and RV diastolic dysfunction develops.

Auscultatory findings include a loud S$_1$ caused by the leaflets of a stenotic mitral valve closing abruptly (M$_1$), like a sail on "coming about"; it is heard best at the apex. A normally split S$_2$ with an exaggerated P$_2$ due to pulmonary hypertension is also heard. Most prominent is an early diastolic opening snap as the leaflets billow into the left ventricle (LV), which is loudest close to left lower sternal border; it is followed by a low-pitched decrescendo-crescendo rumbling diastolic murmur, heard best with the bell of the
stethoscope at the apex (or over the palpable apex beat) at end-expiration when the patient is in the left lateral decubitus position. The opening snap may be soft or absent if the mitral valve is calcified; the snap moves closer to S₂ (increasing duration of the murmur) as MS becomes more severe and LA pressure increases. The diastolic murmur increases after a Valsalva maneuver (when blood pours into the LA), after exercise, and in response to squatting and handgrip. The murmur may be softer or absent when an enlarged RV displaces the LV posteriorly and when other disorders (pulmonary hypertension, right-sided valve abnormalities, AF with fast ventricular rate) decrease blood flow across the mitral valve. The presystolic crescendo is caused by increased flow with atrial contraction. However, the closing mitral valve leaflets during LV contraction may also contribute to this finding but only at the end of short diastoles when LA pressure is still high.

Diastolic murmurs that may coexist with the MS murmur are the early diastolic murmur of coexisting aortic regurgitation (AR), which may be conducted to the apex; the Austin Flint murmur (a low-pitched mid-diastolic murmur heard at the apex due to AR); Graham Steell’s murmur (a soft decrescendo diastolic murmur heard best along the left sternal border and caused by pulmonic regurgitation secondary to severe pulmonary hypertension); a diastolic flow murmur in the presence of severe MR; and (rarely) an obstructing left atrial myxoma or ball thrombus.

MS may cause signs of cor pulmonale (see p. 2132). The classic mitral facies, a plum-colored malar flush, occurs only when cardiac output is low and pulmonary hypertension is severe; cause is cutaneous vasodilation and chronic hypoxemia.

Occasionally, the initial symptoms and signs of MS are those of an embolic event such as stroke. Endocarditis is rare in MS unless MR is also present.

Diagnosis

- Echocardiography

Diagnosis is suspected clinically and confirmed by echocardiography. Two-dimensional echocardiography provides information about the degree of valvular calcification and stenosis and LA size. Doppler echocardiography provides information about the transvalvular gradient and pulmonary artery pressure. Transesophageal echocardiography can be used to detect or exclude small LA thrombi, especially those in the LA appendage, which usually cannot be seen transthoracically.

An ECG and chest x-ray are usually obtained. The ECG may show LA enlargement, manifest as a P wave lasting > 0.12 msec with prominent negative deflection of its terminal component (duration: > 0.04 msec; amplitude: > 0.10 mV) in V₁; broad, notched P waves in lead II; or both. Low voltage in V₁, right axis QRS deviation, and tall R waves in V₁ suggest RV hypertrophy.

Chest x-ray usually shows straightening of the left cardiac border due to a dilated LA appendage, and widening of the carina. With barium in the esophagus, the lateral chest x-ray will show the dilated LA displacing the esophagus posteriorly. The main pulmonary artery (trunk) may be prominent; the descending right pulmonary artery diameter is ≥ 16 mm if pulmonary hypertension is significant. The upper lobe pulmonary veins may be dilated. A double shadow of an enlarged LA may be seen along the right cardiac border. Horizontal lines in the lower posterior lung fields (Kerley B lines) indicate interstitial edema associated with high LA pressure.

Cardiac catheterization, indicated only for perioperative assessment of coronary artery disease (CAD) before surgical repair, can confirm elevated LA and pulmonary artery pressures, mitral gradient and valve area.

Prognosis

The natural history of MS varies, but the interval between onset of symptoms and severe disability is about 7 to 9 yr. Outcome is affected by the patient’s preprocedural age and functional status, pulmonary hypertension, and degree of MR. Symptomatic results of balloon valvotomy and surgical commissurotomy
are equivalent in patients with noncalcified valves. However, after a variable period of time, function deteriorates in most patients due to restenosis, and valve replacement may become necessary. Risk factors for death are AF and pulmonary hypertension. Cause of death is most commonly heart failure or pulmonary or cerebrovascular embolism.

Treatment

- Diuretics and sometimes β-blockers or Ca channel blockers
- Valvotomy, commissurotomy, or valve replacement

Asymptomatic patients require no treatment.

Mildly symptomatic patients usually respond to diuretics and, if sinus tachycardia or AF is present, to β-blockers or Ca channel blockers, which can control ventricular rate. Anticoagulants are indicated to prevent thromboembolism. All patients should be encouraged to continue at least low levels of physical exercise despite exertional dyspnea.

More severely symptomatic patients and patients with evidence of pulmonary hypertension require valvotomy, commissurotomy, or valve replacement.

Percutaneous balloon valvotomy is the procedure of choice for younger patients and for patients without heavily calcified valves, subvalvular distortion, LA thrombi, or significant MR. In this fluoroscopic- and echocardiographic-guided procedure, a transvenous catheter with an inflatable distal balloon is passed transseptally from the right atrium to the LA and inflated to separate fused mitral valve leaflets. Outcomes are equivalent to those of more invasive procedures. Complications are uncommon but include MR, embolism, and tamponade.

Patients with severe subvalvular disease, valvular calcification, or LA thrombi may be candidates for surgical commissurotomy, in which fused mitral valve leaflets are separated using a dilator passed through the LV (closed commissurotomy) via a thoracotomy, or by direct vision (open commissurotomy) via a sternotomy. Choice of procedure is based on surgeon's experience and the morphology of the valve, although closed valvotomy is now done less frequently in Western countries.

Valve replacement is confined to patients with severe morphologic changes that make the valve unsuitable for balloon or surgical valvotomy.

Antibiotic prophylaxis against endocarditis is no longer recommended except for patients who have had valve replacement (see Table 215-4 on p. 2200).

Pulmonic Regurgitation

Pulmonic (pulmonary) regurgitation (PR) is incompetency of the pulmonic valve causing blood flow from the pulmonary artery into the right ventricle during diastole. The most common cause is pulmonary hypertension. PR is usually asymptomatic. Signs include a decrescendo diastolic murmur. Diagnosis is by echocardiography. Usually, no specific treatment is necessary except for management of conditions causing pulmonary hypertension.

Secondary pulmonary hypertension (see Table 202-1 on p. 1985) is by far the most common cause of PR. Less common causes are infective endocarditis, surgical repair of tetralogy of Fallot, idiopathic pulmonary artery dilation, and congenital valvular heart disease. Carcinoid syndrome, rheumatic fever and catheter-induced trauma are rare causes. Severe PR is rare and most often results from an isolated congenital defect involving dilation of the pulmonary artery and pulmonary valve annulus.

PR may contribute to development of right ventricular (RV) dilatation and eventually RV dysfunction-induced heart failure (HF), but in most cases, pulmonary hypertension contributes to this complication much more significantly. Rarely, acute RV dysfunction-induced HF develops when endocarditis causes
acute PR.

**Symptoms and Signs**

PR is usually asymptomatic. A few patients develop symptoms and signs of RV dysfunction-induced HF (see p. 2122).

Palpable signs are attributable to pulmonary hypertension and RV hypertrophy. They include a palpable pulmonic component (P₂) of the 2nd heart sound (S₂) at the left upper sternal border and a sustained RV impulse that is increased in amplitude at the left middle and lower sternal border.

On auscultation, the 1st heart sound (S₁) is normal. The S₂ may be split or single. When split, P₂ may be loud and audible shortly after the aortic component of S₂ (A₂) because of pulmonary hypertension, or P₂ may be delayed because of increased RV stroke volume. S₂ may be single because of prompt pulmonic valve closing with a merged A₂-P₂ or, rarely, because of congenital absence of the pulmonic valve. An RV 3rd heart sound (S₃), 4th heart sound (S₄), or both may be audible with RV dysfunction-induced HF or RV hypertrophy; these sounds can be distinguished from left ventricular heart sounds because they are located at the left parasternal 4th intercostal space and because they grow louder with inspiration.

The murmur of PR due to pulmonary hypertension is a high-pitched, early diastolic decrescendo murmur that begins with P₂ and ends before S₁ and that radiates toward the mid-right sternal edge (Graham Steell's murmur); it is heard best at the left upper sternal border with the diaphragm of the stethoscope while the patient holds the breath at end-expiration and sits upright. The murmur of PR without pulmonary hypertension is shorter, lower-pitched (rougher in quality), and begins after P₂. Both murmurs may resemble the murmur of aortic regurgitation but can be distinguished by inspiration (which makes the PR murmur louder) and by Valsalva release. After Valsalva release, the PR murmur immediately becomes loud (because of immediate venous return to the right side of the heart), but the aortic regurgitation murmur requires 4 or 5 beats to do so. Also, a soft PR murmur may sometimes become even softer during inspiration because this murmur is usually best heard at the 2nd left intercostal space, where inspiration pushes the stethoscope away from the heart.

**Diagnosis**

- Echocardiography

PR is usually incidentally detected during a physical examination or Doppler echocardiography done for other reasons. An ECG and chest x-ray are obtained. Either may show signs of RV hypertrophy; chest x-ray typically shows evidence of conditions underlying pulmonary hypertension.

**Treatment**

- Treatment of cause
- Rarely valve replacement

Treatment is management of the condition causing PR. Pulmonic valve replacement is an option if symptoms and signs of RV dysfunction-induced HF develop, but outcomes and risks are unclear because the need for replacement is so infrequent.

**Pulmonic Stenosis**

Pulmonic stenosis (PS) is narrowing of the pulmonary outflow tract causing obstruction of blood flow from the right ventricle to the pulmonary artery during systole. Most cases are congenital; many remain asymptomatic until adulthood. Signs include a crescendo-decrescendo ejection murmur. Diagnosis is by echocardiography. Symptomatic patients and those with large gradients require balloon valvuloplasty.
**Etiology**

PS is most often congenital and affects predominantly children; stenosis may be valvular or just below the valve in the outflow tract (infundibular). It commonly is a component of tetralogy of Fallot. Less common causes are Noonan's syndrome (a familial syndrome similar to Turner's syndrome but with no chromosomal defect) and carcinoid syndrome in adults.

**Symptoms and Signs**

Many children remain asymptomatic for years and do not present to a physician until adulthood. Even then many patients remain asymptomatic. When symptoms develop, they resemble those of aortic stenosis (syncope, angina, dyspnea). Visible and palpable signs reflect the effects of right ventricular (RV) hypertrophy and include a prominent jugular venous a wave (due to forceful atrial contraction against a hypertrophied RV), an RV precordial lift or heave, and a left parasternal systolic thrill at the 2nd intercostal space.

On auscultation, the 1st heart sound (S₁) is normal and the 2nd heart sound (S₂) splitting is widened because of prolonged pulmonic ejection (pulmonic component of S₂ [P₂] is delayed). In RV failure and hypertrophy, the 3rd and 4th heart sounds (S₃ and S₄) are rarely audible at the left parasternal 4th intercostal space. A click in congenital PS is thought to result from abnormal ventricular wall tension. The click occurs early in systole (very near S₁) and is not affected by hemodynamic changes. A harsh crescendodecrescendo ejection murmur is audible and is heard best at the left parasternal 2nd (valvular stenosis) or 4th (infundibular stenosis) intercostal space with the diaphragm of the stethoscope when the patient leans forward. Unlike the aortic stenosis murmur, a PS murmur does not radiate, and the crescendo component lengthens as stenosis progresses. The murmur grows louder immediately with Valsalva release and with inspiration; the patient may need to be standing for this effect to be heard.

**Diagnosis**

- Echocardiography

Diagnosis is confirmed by Doppler echocardiography, which can characterize the stenosis as mild (≤ 40 mm Hg peak gradient), moderate (41 to 79 mm Hg), or severe (≥ 80 mm Hg). ECG is often part of the evaluation; it may be normal or show RV hypertrophy or right bundle branch block. Right heart catheterization is indicated only when 2 levels of obstruction are suspected (valvular and infundibular), when clinical and echocardiographic findings differ, or before intervention is done.

**Treatment**

- Sometimes balloon valvuloplasty

Prognosis without treatment is generally good and improves with appropriate intervention. Treatment is balloon valvuloplasty, indicated for symptomatic patients and asymptomatic patients with normal systolic function and a peak gradient > 40 to 50 mm Hg.

**Tricuspid Regurgitation**

Tricuspid regurgitation (TR) is insufficiency of the tricuspid valve causing blood flow from the right ventricle to the right atrium during systole. The most common cause is dilation of the right ventricle. Symptoms and signs are usually absent, but severe TR can cause neck pulsations, a holosystolic murmur, and right ventricular-induced heart failure or atrial fibrillation. Diagnosis is by physical examination and echocardiography. TR is usually benign and does not require treatment, but some patients require annuloplasty or valve repair or replacement.

**Etiology**

TR is most commonly caused by dilation of the right ventricle (RV) with malfunction of a normal valve, as
occurs in pulmonary hypertension, RV dysfunction-induced heart failure (HF), and pulmonary outflow tract obstruction. TR results less commonly from infective endocarditis in IV drug abusers, carcinoid syndrome, chest or abdominal injury, rheumatic fever, idiopathic myxomatous degeneration, ischemic papillary muscle dysfunction, congenital defects (eg, cleft tricuspid valve, endocardial cushion defects), Ebstein's anomaly (downward displacement of a distorted tricuspid cusp into the RV), Marfan syndrome, and use of certain drugs (eg, ergotamine, fenfluramine, phentermine).

Long-standing severe TR may lead to RV dysfunction-induced HF and atrial fibrillation (AF).

**Symptoms and Signs**

TR usually causes no symptoms, but some patients experience neck pulsations due to elevated jugular pressures. Acute or severe TR may cause symptoms of RV dysfunction-induced HF. Patients may also develop symptoms of AF or atrial flutter.

Pedal edema or ascites can occur in severe TR.

The only visible sign of moderate to severe TR is jugular venous distention, with a prominent merged c-v wave and a steep y descent. In severe TR, a right jugular venous thrill may be palpable, as may systolic hepatic pulsation and an RV impulse at the left lower sternal border. On auscultation, the 1st heart sound (S1) may be normal or barely audible if a TR murmur is present; the 2nd heart sound (S2) may be split (with a loud pulmonic component [P2] in pulmonary hypertension) or single because of prompt pulmonic valve closing with merger of P2 and the aortic component (A2). An RV 3rd heart sound (S3) may be audible near the sternum with RV dysfunction-induced HF.

The murmur of TR is a holosystolic murmur heard best at the left middle or lower sternal border or at the epigastrium with the bell of the stethoscope when the patient is sitting upright or standing. The murmur may be high-pitched if TR is trivial and due to pulmonary hypertension, or it may be medium-pitched if TR is severe and has other causes. Sometimes the murmur is not present at all and the diagnosis is best made by the appearance of the jugular venous wave pattern and the presence of hepatic systolic pulsations. The murmur varies with respiration, becoming louder with inspiration (Carvallo's sign).

**Diagnosis**

- Echocardiography

Mild TR is most often detected on echocardiography done for other reasons. More moderate or severe TR may be suggested by history and physical examination and confirmed by Doppler echocardiography.

An ECG and chest x-ray are also often obtained. ECG is usually normal but, in advanced cases, may show tall peaked P waves caused by right atrial enlargement, a tall R or QR wave in V1 characteristic of RV hypertrophy, or AF. Chest x-ray is usually normal but, in advanced cases with RV hypertrophy or RV dysfunction-induced HF, may show an enlarged superior vena cava, an enlarged right atrial or RV silhouette (behind the upper sternum in the lateral projection), or pleural effusion.

Cardiac catheterization is rarely indicated for evaluation of TR. When catheterization is indicated (eg, to evaluate coronary anatomy), findings include a prominent right atrial c-v wave during ventricular systole.

**Prognosis**

Few reliable data about prognosis exist because so few patients develop severe TR in isolation.

**Treatment**

- Treatment of cause

- Sometimes valve repair or replacement
TR is usually well tolerated and often does not require surgical treatment. Medical treatment of causes (e.g., HF, endocarditis) is indicated. The tricuspid valve may be repaired during surgery for left-sided heart lesions, such as mitral stenosis or regurgitation. Surgery may also be indicated for TR alone when RV impairment or cirrhosis threatens.

Surgical options include annuloplasty, valve repair, and valve replacement. Annuloplasty, in which the tricuspid valve annulus is sutured to a prosthetic ring or a tailored reduction in annulus circumferential size is done, is indicated when TR is due to annular dilation. Valve repair or replacement is indicated when TR is due to primary valve abnormalities or when annuloplasty is not technically feasible. Tricuspid valve replacement is indicated when TR is due to carcinoid syndrome or Ebstein's anomaly. A bioprosthetic valve is used to reduce the risk of thromboembolism associated with the low pressures of the right heart; in the right heart, unlike the left heart, bioprosthetic valves last > 10 yr.

If endocarditis has damaged the tricuspid valve and cannot be cured with antibiotics, the valve may be totally excised and not replaced until 6 to 9 mo later; this procedure is well tolerated.

Tricuspid Stenosis

Tricuspid stenosis (TS) is narrowing of the tricuspid orifice that obstructs blood flow from the right atrium to the right ventricle. Almost all cases result from rheumatic fever. Symptoms include a fluttering discomfort in the neck, fatigue, cold skin, and right upper quadrant abdominal discomfort. Jugular pulsations are prominent, and a presystolic murmur is often heard at the left sternal edge in the 4th intercostal space and is increased during inspiration. Diagnosis is by echocardiography. TS is usually benign, requiring no specific treatment, but symptomatic patients may benefit from surgery.

TS is almost always due to rheumatic fever; tricuspid regurgitation is almost always also present, as is a mitral valve disorder (usually mitral stenosis). Rare causes of TS include SLE, right atrial (RA) myxoma, congenital malformations, and metastatic tumors. The RA becomes hypertrophied and distended, and sequelae of right heart disease-induced heart failure develop but without right ventricular (RV) dysfunction; the RV remains underfilled and small. Uncommonly, atrial fibrillation occurs.

Symptoms and Signs

The only symptoms of severe TS are fluttering discomfort in the neck (due to giant waves in the jugular pulse), fatigue and cold skin (due to low cardiac output), and right upper quadrant abdominal discomfort (due to an enlarged liver).

The primary visible sign is a giant flickering wave with gradual descent in the jugular veins. Jugular venous distention may occur, increasing with inspiration (Kussmaul's sign). The face may become dusky and scalp veins may dilate when the patient is recumbent (suffusion sign). Hepatic congestion and peripheral edema may occur.

On auscultation, TS may produce a soft opening snap and a mid-diastolic rumble with presystolic accentuation. The murmur becomes louder and longer with maneuvers that increase venous return (exercise, inspiration, leg-raising, Muller's maneuver) and softer and shorter with maneuvers that decrease venous return (standing, Valsalva maneuver).

Findings of TS often coexist with those of mitral stenosis and are less prominent. The murmurs can be distinguished clinically (see Table 214-1).

Diagnosis

- Echocardiography

Diagnosis is suspected based on history and physical examination and confirmed by Doppler
echocardiography showing a pressure gradient across the tricuspid valve. Two-dimensional echocardiography shows thickened leaflets with reduced movement and RA enlargement. An ECG and chest x-ray are often obtained. ECG may show RA enlargement out of proportion to RV hypertrophy and tall, peaked P waves in inferior leads and V1. Chest x-ray may show a dilated superior vena cava and RA enlargement, indicated by an enlarged right heart border. Liver enzymes are elevated because of passive hepatic congestion.

Cardiac catheterization (see p. 2048) is rarely indicated for evaluation of TS. When catheterization is indicated (eg, to evaluate coronary anatomy), findings include elevated RA pressure with a slow fall in early diastole and a diastolic pressure gradient across the tricuspid valve.

**Treatment**

- Diuretics and aldosterone antagonists
- Rarely valve repair or replacement

Evidence to guide treatment is scarce. For all symptomatic patients, treatment should include a low-salt diet, diuretics, and aldosterone antagonists. Patients with hepatic congestion leading to cirrhosis or severe systemic venous congestion and effort limitation may benefit from interventions such as balloon valvotomy or valve repair or replacement. Comparative outcomes are unstudied.
Chapter 215. Endocarditis

Introduction

Endocarditis usually refers to infection of the endocardium (ie, infective endocarditis). The term can also include noninfective endocarditis, in which sterile platelet and fibrin thrombi form on cardiac valves and adjacent endocardium. Noninfective endocarditis sometimes leads to infective endocarditis. Both can result in embolization and impaired cardiac function.

Infective Endocarditis

Infective endocarditis is infection of the endocardium, usually with bacteria (commonly, streptococci and staphylococci) or fungi. It causes fever, heart murmurs, petechiae, anemia, embolic phenomena, and endocardial vegetations. Vegetations may result in valvular incompetence or obstruction, myocardial abscess, or mycotic aneurysm. Diagnosis requires demonstration of microorganisms in blood and usually echocardiography. Treatment consists of prolonged antimicrobial treatment and sometimes surgery.

Endocarditis can occur at any age. Men are affected about twice as often. IV drug abusers and immunocompromised patients are at highest risk.

Etiology

The normal heart is relatively resistant to infection. Bacteria and fungi do not easily adhere to the endocardial surface, and constant blood flow helps prevent them from settling on endocardial structures. Thus, 2 factors are generally required for endocarditis: a predisposing abnormality of the endocardium and microorganisms in the bloodstream (bacteremia). Rarely, massive bacteremia or particularly virulent microorganisms cause endocarditis on normal valves.

Endocardial factors: Endocarditis usually involves the heart valves. Major predisposing factors are congenital heart defects, rheumatic valvular disease, bicuspid or calcific aortic valves, mitral valve prolapse, and hypertrophic cardiomyopathy. Prosthetic valves are a particular risk. Occasionally, mural thrombi, ventricular-septal defects, and patent ductus arteriosus sites become infected. The actual nidus for infection is usually a sterile fibrin-platelet vegetation formed when damaged endothelial cells release tissue factor.

Infective endocarditis occurs most often on the left side (eg, mitral or aortic valve). About 10 to 20% of cases are right-sided (tricuspid or pulmonic valve). IV drug abusers have a much higher incidence of right-sided endocarditis (about 30 to 70%).

Microorganisms: Microorganisms that infect the endocardium may originate from distant infected sites (eg, cutaneous abscess, inflamed or infected gums, UTI) or have obvious portals of entry such as a central venous catheter or a drug injection site. Almost any implanted foreign material (eg, ventricular or peritoneal shunt, prosthetic device) is at risk of bacterial colonization, thus becoming a source of bacteremia and hence endocarditis. Endocarditis also may result from asymptomatic bacteremia, such as typically occurs during invasive dental, medical, or surgical procedures. Even toothbrushing and chewing can cause bacteremia (usually due to viridans streptococci) in patients with gingivitis.

Causative microorganisms vary by site of infection, source of bacteremia, and host risk factors (eg, IV drug abuse), but overall, streptococci and Staphylococcus aureus cause 80 to 90% of cases. Enterococci, gram-negative bacilli, HACEK organisms (Haemophilus sp, Actinobacillus actinomycetemcomitans, Cardio-bacterium hominis, Eikenella corroden, and Kingella kingae—see p. 1252), and fungi cause most of the rest. Why streptococci and staphylococci frequently adhere to vegetations and why gram-negative aerobic bacilli seldom adhere are unclear. However, the ability of S. aureus to adhere to fibronectin may play a role, as may dextran production by viridans streptococci.

After colonizing vegetations, microorganisms are covered by a layer of fibrin and platelets, which prevents...
Pathophysiology

Endocarditis has local and systemic consequences.

**Local consequences:** Local consequences include formation of myocardial abscesses with tissue destruction and sometimes conduction system abnormalities (usually with low septal abscesses). Severe valvular regurgitation may develop suddenly, causing heart failure and death (usually due to mitral or aortic valve lesions). Aortitis may result from contiguous spread of infection. Prosthetic valve infections are particularly likely to involve valve ring abscesses, obstructing vegetations, myocardial abscesses, and mycotic aneurysms manifested by valve obstruction, dehiscence, and conduction disturbances.

**Systemic consequences:** Systemic consequences are primarily due to embolization of infected material from the heart valve and, primarily in chronic infection, immune-mediated phenomena. Right-sided lesions typically produce septic pulmonary emboli, which may result in pulmonary infarction, pneumonia, or empyema. Left-sided lesions may embolize to any tissue, particularly the kidneys, spleen, and CNS. Mycotic aneurysms can form in any major artery. Cutaneous and retinal emboli are common. Diffuse glomerulonephritis may result from immune complex deposition.

Classification

Infective endocarditis may have an indolent, subacute course or a more acute, fulminant course with greater potential for rapid decompensation.

**Subacute bacterial endocarditis (SBE),** although aggressive, usually develops insidiously and progresses slowly (ie, over weeks to months). Often, no source of infection or portal of entry is evident. SBE is caused most commonly by streptococci (especially viridans, microaerophilic, anaerobic, and nonenterococcal group D streptococci and enterococci) and less commonly by *S. aureus, Staphylococcus epidermidis, Gemella morbillorum, Abiotrophia defectiva, Granulicatella* sp, and fastidious *Haemophilus* sp. SBE often develops on abnormal valves after asymptomatic bacteremia due to periodontal, GI, or GU infections.

**Acute bacterial endocarditis (ABE)** usually develops abruptly and progresses rapidly (ie, over days). A source of infection or portal of entry is often evident. When bacteria are virulent or bacterial exposure is massive, ABE can affect normal valves. It is usually caused by *S. aureus, group A hemolytic streptococci, pneumococci,* or gonococci.

**Prosthetic valvular endocarditis (PVE)** develops in 2 to 3% of patients within 1 yr after valve replacement and in 0.5%/yr thereafter. It is more common after aortic than after mitral valve replacement and affects mechanical and bioprosthetic valves equally. Early-onset infections (< 2 mo after surgery) are caused mainly by contamination during surgery with antimicrobial-resistant bacteria (eg, *S. epidermidis, diphtheroids, coliform bacilli, Candida* sp, *Aspergillus* sp). Late-onset infections are caused mainly by contamination with low-virulence organisms during surgery or by transient asymptomatic bacteremias, most often with streptococci; *S. epidermidis; diphtheroids; and the fastidious gram-negative bacilli, Haemophilus* sp, *Actinobacillus actinomycetemcomitans,* and *Cardiobacterium hominis.*

Symptoms and Signs

Symptoms and signs vary based on the classification but are nonspecific.

**SBE:** Initially, symptoms are vague: low-grade fever (< 39° C), night sweats, fatigability, malaise, and weight loss. Chills and arthralgias may occur. Symptoms and signs of valvular insufficiency may be a first clue. Initially, ≤ 15% of patients have fever or a murmur, but eventually almost all develop both. Physical examination may be normal or include pallor, fever, change in a preexisting murmur or development of a new regurgitant murmur, and tachycardia.

Retinal emboli can cause round or oval hemorrhagic retinal lesions with small white centers (Roth's
Cutaneous manifestations include petechiae (on the upper trunk, conjunctivae, mucous membranes, and distal extremities), painful erythematous subcutaneous nodules on the tips of digits (Osler's nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), and splinter hemorrhages under the nails. About 35% of patients have CNS effects, including transient ischemic attacks, stroke, toxic encephalopathy, and, if a mycotic CNS aneurysm ruptures, brain abscess and subarachnoid hemorrhage. Renal emboli may cause flank pain and, rarely, gross hematuria. Splenic emboli may cause left upper quadrant pain. Prolonged infection may cause splenomegaly or clubbing of fingers and toes.

**ABE and PVE:** Symptoms and signs are similar to those of SBE, but the course is more rapid. Fever is almost always present initially, and patients appear toxic; sometimes septic shock develops. Heart murmur is present initially in about 50 to 80% and eventually in > 90%. Rarely, purulent meningitis occurs.

**Right-sided endocarditis:** Septic pulmonary emboli may cause cough, pleuritic chest pain, and sometimes hemoptysis. A murmur of tricuspid regurgitation is typical.

**Diagnosis**

- Blood cultures
- Echocardiography
- Clinical criteria

Because symptoms and signs are nonspecific, vary greatly, and may develop insidiously, diagnosis requires a high index of suspicion. Endocarditis should be suspected in patients with fever and no obvious source of infection, particularly if a heart murmur is present. Suspicion of endocarditis should be very high if blood cultures are positive in patients who have a history of a heart valve disorder, who have had certain recent invasive procedures, or who abuse IV drugs. Patients with documented bacteremia should be examined thoroughly and repeatedly for new valvular murmurs and signs of emboli.

If endocarditis is suspected, 3 blood cultures (20 mL each) should be obtained within 24 h (if presentation suggests ABE, 2 cultures within the first 1 to 2 h). When endocarditis is present and no prior antibiotic therapy was given, all 3 blood cultures usually are positive because the bacteremia is continuous; at least one culture is positive in 99%. Premature use of empiric antibiotic therapy should be avoided in patients with acquired or congenital valvular or shunt lesions to avoid culture-negative endocarditis. If prior antimicrobial therapy was given, blood cultures should still be obtained, but they may be negative.

Echocardiography, typically transthoracic (TTE) rather than transesophageal (TEE), should be done. Although TEE is somewhat more accurate (ie, capable of revealing vegetations too small to be seen on TTE), it is invasive and more costly. TEE should be done when endocarditis is suspected in patients with prosthetic valves, when TTE is nondiagnostic, and when diagnosis of infective endocarditis has been established clinically.

Other than positive blood cultures, there are no specific laboratory findings. Established infections often cause a normocytic-normochromic anemia, elevated WBC count, increased ESR, increased lgs, circulating immune complexes, and rheumatoid factor, but these findings are not diagnostically helpful. Urinalysis often shows microscopic hematuria and, occasionally, RBC casts, pyuria, or bacteriuria.

Identification of the organism and its antimicrobial susceptibility is vital to guide treatment. Blood cultures may require 3 to 4 wk incubation for certain organisms; however, some proprietary, automated culture monitoring systems can identify positive cultures within a week. Other organisms (eg, Aspergillus sp) may not produce positive cultures. Some organisms (eg, Coxiella burnetii, Bartonella sp, Chlamydia psittaci, Brucella sp) require serodiagnosis; others (eg, Legionella pneumophila) require special culture media or PCR (eg, Tropheryma whippelii). Negative blood culture results may indicate suppression due to prior antimicrobial therapy, infection with organisms that do not grow in standard culture media, or another diagnosis (eg, non-infective endocarditis, atrial myxoma with embolic phenomena, vasculitis).
Infective endocarditis is definitively diagnosed when microorganisms are seen histologically in (or cultured from) endocardial vegetations obtained during cardiac surgery, embolectomy, or autopsy. Because vegetations are not usually available for examination, clinical criteria for establishing a diagnosis (with a sensitivity and specificity > 90%) have been developed (see Table 215-1).

**Prognosis**

Untreated, infective endocarditis is always fatal. Even with treatment, death is more likely and the prognosis is generally poorer for older people and people who have infection with resistant organisms, an underlying disorder, or a long delay in treatment. The prognosis is also poorer for people with aortic or multiple valve involvement, large vegetations, polymicrobial bacteremia, prosthetic valve infections, mycotic aneurysms, valve ring abscess, and major embolic events. The mortality rate for viridans streptococcal endocarditis without major complications is < 10% but is virtually 100% for *Aspergillus* endocarditis after prosthetic valve surgery.

The prognosis is better with right-sided than left-sided endocarditis because tricuspid valve dysfunction is tolerated better, systemic emboli are absent, and right-sided *S. aureus* endocarditis responds better to antimicrobial therapy.

**Treatment**

- IV antibiotics (based on the organism and its susceptibility)
- Sometimes valve debridement, repair, or replacement

Treatment consists of a prolonged course of antimicrobial therapy. Surgery may be needed for mechanical complications or resistant organisms. Typically, antimicrobials are given IV. Because they must be given for 2 to 8 wk, home IV therapy is often used.

Any apparent source of bacteremia must be managed: necrotic tissue debrided, abscesses drained, and foreign material and infected devices removed. Existing IV catheters (particularly central venous ones) should be changed. If endocarditis persists in a patient with a newly inserted central venous catheter, that catheter should also be removed. Organisms within biofilms adherent to catheters and other devices may not respond to antimicrobial therapy, leading to treatment failure or relapse. If continuous infusions are used instead of intermittent boluses, infusions should not be interrupted for long periods.

**Antibiotic regimens:** Drugs and dosages depend on the microorganism and its antimicrobial susceptibility (for typical regimens, see Table 215-2). Initial therapy before organism identification (but after adequate blood cultures have been obtained) should be broad spectrum to cover all likely organisms. Typically, patients with native valves and no IV drug abuse receive ampicillin 500 mg/h continuous IV infusion plus nafcillin 2 g IV q 4 h plus gentamicin 1 mg/kg IV q 8 h. Patients with a prosthetic valve receive vancomycin 15 mg/kg IV q 12 h plus gentamicin 1 mg/kg q 8 h plus rifampin 300 po q 8 h. IV drug abusers receive nafcillin 2 g IV q 4 h. In all regimens, penicillin-allergic patients require substitution of vancomycin 15 mg/kg IV q 12 h.

IV drug abusers frequently do not adhere to treatment, abuse IV access lines, and tend to leave the hospital too soon. For such patients, short-course IV or (less preferably) oral therapy may be used. For right-sided endocarditis caused by methicillin-sensitive *S. aureus*, nafcillin 2 g IV q 4 h plus gentamicin 1 mg/kg IV q 8 h for 2 wk is effective, as is a 4-wk oral regimen of ciprofloxacin 750 mg po bid plus rifampin 300 mg po bid. Left-sided endocarditis does not respond to 2-wk courses.

**Cardiac valve surgery:** Surgery (debridement, valve repair or replacement) is frequently required for abscess, persistent infection despite antimicrobial therapy (ie, persistent positive blood cultures or
recurrent emboli), or severe valvular regurgitation.

Timing of surgery requires experienced clinical judgment. If heart failure caused by a correctable lesion is worsening (particularly when the organism is S. aureus, a gram-negative bacillus, or a fungus), surgery may be required after only 24 to 72 h of antimicrobial therapy. In patients with prosthetic valves, surgery may be required when TEE shows

[Table 215-2, Antibiotic Regimens for Endocarditis]

valve dehiscence on a paravalvular abscess, when valve dysfunction precipitates heart failure, when recurrent emboli are detected, or when the infection is caused by an antimicrobial-resistant organism.

Response to treatment: After starting therapy, patients with penicillin-susceptible streptococcal endocarditis usually feel better, and fever is reduced within 3 to 7 days. Fever may continue for reasons other than persistent infection (eg, drug allergy, phlebitis, infarction due to emboli). Patients with staphylococcal endocarditis tend to respond more slowly. Diminution of vegetation size can be followed by serial echocardiography.

Relapse usually occurs within 4 wk. Antibiotic retreatment may be effective, but surgery may also be required. In patients without prosthetic valves, recrudescence of endocarditis after 6 wk usually results from a new infection rather than a relapse. Even after successful antimicrobial therapy, sterile emboli and valve rupture may occur up to 1 yr later.

Prevention

Preventive dental examination and therapy before surgery to repair heart valves or congenital heart lesions is recommended.

Patients: The American Heart Association (AHA) recommends antimicrobial prophylaxis for patients at high risk of an adverse outcome from infective endocarditis (see AHA guidelines). Such patients include those with

* Prosthetic heart valves
* Previous infective endocarditis
* Certain congenital heart diseases (CHD): Unrepaired cyanotic CHD (including palliative shunts and conduits), completely repaired CHD during the first 6 mo after surgery if prosthetic material or device was used, repaired CHD that has residual defects at or adjacent to the site of repair
* Heart transplant recipients with valvulopathy

Procedures: Most procedures for which prophylaxis is required for high-risk patients are oral-dental procedures that manipulate the gingiva or the periapical region of teeth or perforate the oral mucosa. Other procedures include those respiratory tract procedures in which mucosa is incised, and GI, GU, or musculo-skeletal procedures that involve an area with an established infection (see Table 215-3).

Antibiotic regimens: For most patients and procedures, a single dose shortly before the procedure is effective.

For oral-dental and respiratory procedures, a drug effective against viridans group streptococci is used (see Table 215-4).

For GI, GU, and musculoskeletal procedures on areas involving infected tissue, antibiotics should be selected based on the known organism and its sensitivities. If infection is present but the infecting organism has not been identified, antibiotics for GI and GU prophylaxis should be effective against
enterococci (eg, amoxicillin or ampicillin, and vancomycin for patients who are allergic to penicillin). Antibiotics for skin and musculoskeletal

[Table 215-3. Procedures Requiring Antimicrobial Endocarditis Prophylaxis in High-Risk Patients]

[Table 215-4. Recommended Endocarditis Prophylaxis During Oral-Dental or Respiratory Tract Procedures*]

prophylaxis should be effective against staphylococci and β-hemolytic streptococci (eg, a cephalosporin or vancomycin or clindamycin if infection with methicillin-resistant staphylococci is possible).

**Noninfective Endocarditis**

Noninfective endocarditis (nonbacterial thrombotic endocarditis) refers to formation of sterile platelet and fibrin thrombi on cardiac valves and adjacent endocardium in response to trauma, circulating immune complexes, vasculitis, or a hypercoagulable state. Symptoms are those of systemic arterial embolism. Diagnosis is by echocardiography and negative blood cultures. Treatment consists of anticoagulants.

**Etiology**

Vegetations are caused by physical trauma, not infection. They may be clinically undetectable or become a nidus for infection (leading to infective endocarditis), produce emboli, or impair valvular function.

Catheters passed through the right side of the heart may injure the tricuspid and pulmonic valves, resulting in platelet and fibrin attachment at the site of injury. In disorders such as SLE, circulating immune complexes may result in friable platelet and fibrin vegetations along a valve leaflet closure (Libman-Sacks lesions). These lesions do not usually cause significant valvular obstruction or regurgitation. Antiphospholipid syndrome (lupus anticoagulants, recurrent venous thrombosis, stroke, spontaneous abortions, livido reticularis) also can lead to sterile endocardial vegetations and systemic emboli. Rarely, Wegener's granulomatosis leads to noninfective endocarditis.

**Marantic endocarditis:** In patients with chronic wasting diseases, disseminated intravascular coagulation, mucin-producing metastatic carcinomas (of lung, stomach, or pancreas), or chronic infections (eg, TB, pneumonia, osteomyelitis), large thrombotic vegetations may form on valves and produce significant emboli to the brain, kidneys, spleen, mesentery, extremities, and coronary arteries. These vegetations tend to form on congenitally abnormal cardiac valves or those damaged by rheumatic fever.

**Symptoms and Signs**

Vegetations themselves do not cause symptoms. Symptoms result from embolization and depend on the organ affected (eg, brain, kidneys, spleen). Fever and a heart murmur are sometimes present.

**Diagnosis**

- Blood cultures
- Echocardiography

Noninfective endocarditis should be suspected when chronically ill patients develop symptoms suggesting arterial embolism. Serial blood cultures (see p. 2195) and echocardiography should be done. Negative blood cultures and valvular vegetations (but not atrial myxoma) suggest the diagnosis. Examination of embolic fragments after embolectomy can help make the diagnosis. Differentiation from culture-negative infective endocarditis may be difficult but is important. An anticoagulant is often needed in noninfective endocarditis but is contraindicated in infective endocarditis.

**Prognosis**
Prognosis is generally poor, more because of the seriousness of predisposing disorders than the cardiac lesion.

**Treatment**

• Anticoagulation

Treatment consists of anticoagulation with heparin or warfarin, although results of such treatment have not been evaluated. Predisposing disorders should be treated whenever possible.
Chapter 216. Pericarditis

Introduction

Pericarditis is inflammation of the pericardium, often with fluid accumulation. Pericarditis may be caused by many disorders (eg, infection, MI, trauma, tumors, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced. Diagnosis is based on symptoms, a friction rub, ECG changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram. Finding the cause requires further evaluation. Treatment depends on the cause, but general measures include analgesics, anti-inflammatory drugs, and sometimes surgery.

Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.

Anatomy

The pericardium has 2 layers. The visceral pericardium is a single layer of mesothelial cells that is attached to the myocardium, folds back (reflects) on itself over the origin of the great vessels, and joins with a tough, fibrous layer to envelop the heart as the parietal pericardium. The sac created by these layers contains a small amount of fluid (< 25 to 50 mL), composed mostly of an ultrafiltrate of plasma. The pericardium limits distention of the cardiac chambers and increases the heart's efficiency.

The pericardium is richly innervated with sympathetic and somatic afferents. Stretch-sensitive mechanoreceptors sense changes in cardiac volume and tension and may be responsible for transmitting pericardial pain. The phrenic nerves are embedded in the parietal pericardium and are vulnerable to injury during surgery on the pericardium.

Pathophysiology

Pericarditis may be

• Acute

• Chronic

Acute pericarditis develops quickly, causing an inflammatory reaction. Chronic pericarditis (defined as persisting > 6 mo) develops more slowly; its prominent feature is effusion. Acute disease may become chronic. Adverse hemodynamic effects and rhythm disturbance are rare, although cardiac tamponade is possible. Occasionally, pericarditis causes a marked thickening and stiffening of the pericardium (constrictive pericarditis). Pericarditis can lead to inflammation of the epicardial myocardium.

Pericardial effusion is accumulation of fluid in the pericardium. The fluid may be serous fluid (sometimes with fibrin strands), serosanguineous fluid, blood, pus, or chyle.

Cardiac tamponade occurs when a large pericardial effusion impairs cardiac filling, leading to low cardiac output and sometimes shock and death. If fluid (usually blood) accumulates rapidly, even small amounts (eg, 150 mL) may cause tamponade because the pericardium cannot stretch quickly enough to accommodate it. Slow accumulation of up to 1500 mL may not cause tamponade. Loculated effusion may cause localized tamponade on the right or left side of the heart.

Constrictive pericarditis, which is uncommon, results from marked inflammatory, fibrotic thickening of the pericardium. Sometimes the visceral and parietal layers adhere to each other or to the myocardium. The fibrotic tissue often contains Ca deposits. The stiff, thickened pericardium markedly impairs ventricular filling, decreasing stroke volume and cardiac output. Significant pericardial fluid accumulation is rare. Rhythm disturbance is common. The diastolic pressures in the ventricles, atria, and venous beds become virtually the same. Systemic venous congestion occurs, causing considerable transudation of fluid from systemic capillaries, with dependent edema and, later, ascites. Chronic elevation of systemic venous and hepatic venous pressure may lead to cardiac cirrhosis. Constriction of the left atrium, the left
Etiology

Acute pericarditis may result from infection, autoimmune and inflammatory disorders, uremia, trauma, MI, or certain drugs (see Table 216-1). Infectious pericarditis is most often viral. Purulent bacterial pericarditis is uncommon but may follow infective endocarditis, pneumonia, septicemia, penetrating trauma, or cardiac surgery. Often, the cause cannot be identified (called nonspecific or idiopathic pericarditis), but many of these cases are probably viral. Overall, the most common causes are viral and idiopathic. Acute MI causes 10 to 15% of cases of acute pericarditis. Post-MI syndrome (Dressler's syndrome) is a less common cause now, occurring mainly when reperfusion with percutaneous transluminal coronary angioplasty (PTCA) or thrombolytic drugs is ineffective in patients with transmural infarction. Pericarditis occurs after pericardiotomy (called postpericardiotomy syndrome) in 5 to 30% of cardiac operations.

Chronic pericardial effusion or constrictive pericarditis may follow almost any disorder that causes acute pericarditis, as well as TB, a tumor, irradiation, rheumatoid disease, and cardiac surgery. Sometimes no cause of chronic pericarditis is identified. Pericarditis with large effusion (serous, serosanguineous, or bloody) is most commonly caused by metastatic tumors, most often by lung or breast carcinoma, sarcoma, melanoma, leukemia, or lymphoma.

Fibrosis of the pericardium may follow purulent pericarditis or myocardial infection (myocarditis—a common cause in young people) or accompany a connective tissue disorder. In elderly patients, common causes are malignant tumors, MI, and TB. Hemopericardium (accumulation of blood within the pericardium) may lead to pericarditis or pericardial fibrosis; common causes include chest trauma, iatrogenic injury (eg, from cardiac catheterization, pacemaker insertion, or central venous line placement), and rupture of a thoracic aortic aneurysm.

Symptoms and Signs

Some patients present with symptoms and signs of inflammation (acute pericarditis); others present with those of fluid accumulation (pericardial effusion). Symptoms and signs vary depending on the severity of inflammation and the amount and rate of fluid accumulation. Even a large amount of pericardial fluid may be asymptomatic if it develops slowly (eg, over months).

**Acute pericarditis**: Acute pericarditis tends to cause chest pain and a pericardial rub, sometimes with dyspnea. The first evidence can be tamponade, with hypotension, shock, or pulmonary edema.

Because the innervation of the pericardium and myocardium is the same, the chest pain of pericarditis is sometimes similar to that of myocardial inflammation or ischemia: Dull or sharp precordial or substernal pain may radiate to the neck, trapezius ridge (especially the left), or shoulders. Pain ranges from mild to severe. Unlike ischemic chest pain, pain due to pericarditis is usually aggravated by thoracic motion, cough, breathing, or swallowing food; it may be relieved by sitting up and leaning forward. Tachypnea and nonproductive cough may be present; fever, chills, and weakness are common. In 15 to 25% of patients with idiopathic pericarditis, symptoms recur intermittently for months or years.

The most important physical finding is a triphasic or a systolic and diastolic precordial friction rub. However, the rub is often intermittent and evanescent; it may be present only during systole or, less frequently, only during diastole. If no rub is heard with the patient seated and leaning forward, auscultation may be attempted by listening with the diaphragm of the stethoscope while the patient is on all fours. Sometimes, a pleural component to the rub is noted during breathing, which is due to inflammation of the pleura adjacent to the pericardium. Considerable amounts of pericardial fluid may muffle heart sounds, increase the area of cardiac dullness, and change the size and shape of the cardiac silhouette.

**Pericardial effusion**: Pericardial effusion is often painless, but when it occurs with acute pericarditis,
pain may be present. Typically, heart sounds are muffled. A pericardial rub may be heard. With large effusions, compression of the base of the left lung can decrease breath sounds (heard near the left scapula) and cause crackles. Arterial pulse, jugular venous pulse, and BP are normal unless intrapericardial pressure increases substantially, causing tamponade.

In the post-MI syndrome, pericardial effusion can occur with fever, friction rub, pleurisy, pleural effusions, and joint pain. This syndrome usually occurs within 10 days to 2 mo after MI. It is usually mild but may be severe. Occasionally, the heart ruptures post-MI, causing hemopericardium and tamponade, usually 1 to 10 days post-MI and more commonly in women.

**Cardiac tamponade:** The clinical findings are similar to those of cardiogenic shock: decreased cardiac output, low systemic arterial pressure, tachycardia, and dyspnea. Neck veins are markedly dilated. Severe cardiac tamponade is nearly always accompanied by a fall of > 10 mm Hg in systolic BP during inspiration (pulsus paradoxus—see p. 2018). In advanced cases, pulse may disappear during inspiration. (However, pulsus paradoxus can also occur in COPD, bronchial asthma, pulmonary embolism, right ventricular infarction, and noncardiogenic shock.) Heart sounds are muffled unless the effusion is small.

**Constrictive pericarditis:** Fibrosis or calcification rarely causes symptoms unless constrictive pericarditis develops. The only early abnormalities may be elevated ventricular diastolic, atrial, pulmonary, and systemic venous pressures. Symptoms and signs of peripheral venous congestion (eg, peripheral edema, neck vein distention, hepatomegaly) may appear with an early diastolic sound (pericardial knock), often best heard during inspiration. This sound is due to abrupt slowing of diastolic ventricular filling by the rigid pericardium. Ventricular systolic function (based on ejection fraction) is usually preserved. Prolonged elevation of pulmonary venous pressure results in dyspnea (particularly during exertion) and orthopnea. Fatigue may be severe. Distention of neck veins with a rise in venous pressure during inspiration (Kussmaul's sign) is present; it is absent in tamponade. Pulsus paradoxus is rare and is usually less severe than in tamponade. Lungs are not congested unless severe left ventricular constriction develops.

**Diagnosis**

- ECG and chest x-ray
- Echocardiography
- Tests to identify cause (eg, pericardial fluid aspiration, pericardial biopsy)

**Acute pericarditis:** If acute pericarditis is suspected, hospitalization is sometimes required for initial evaluation. ECG and chest x-ray are done. If symptoms or signs of elevated right-sided pressure, tamponade, or an enlarged cardiac silhouette are present, echocardiography to check for effusion and cardiac filling abnormalities is also done. Blood tests may detect leukocytosis and an elevated ESR, but these findings are nonspecific.

The diagnosis is based on the presence of typical clinical findings and ECG abnormalities. Serial ECGs may be needed to show abnormalities.

The ECG in acute pericarditis may show abnormalities confined to ST segments and T waves, usually in most leads (see Fig. 216-1). The ST segments in 2 or 3 of the standard leads become elevated but subsequently return to baseline. Unlike MI, acute pericarditis does not cause reciprocal depression in ST segments (except in leads aVR and V1), and there are no pathologic Q waves. The PR segment may be depressed. After several days or longer, T waves may become flattened and then inverted throughout the ECG, except in lead aVR; T wave-inversion occurs after the ST segment has returned to baseline and thus differs from the pattern of acute ischemia or MI.

Because the pain of pericarditis may resemble that of acute MI or pulmonary infarction, additional tests (eg, serum cardiac marker measurement, lung scan) may be required if the history and ECG findings are atypical for pericarditis. Troponin is almost always elevated in acute pericarditis due to epicardial
inflammation so it cannot discriminate between acute infarction and pulmonary embolism. The CK level is usually normal in acute pericarditis unless myocarditis is also present.

Postpericardiotomy and post-MI syndromes may be difficult to identify and must be distinguished from recent MI, pulmonary embolism, and pericardial infection after surgery. Pain, friction rub, and fever appearing 2 wk to several months after surgery and a rapid response to aspirin, NSAIDs, or corticosteroids aid diagnosis.

Pericardial effusion: Diagnosis is suggested by clinical findings but often is suspected only after finding an enlarged cardiac silhouette on chest x-ray. On ECG, QRS voltage is often decreased, and sinus rhythm remains in about 90% of patients. With large, chronic effusions, the ECG may show electrical alternans (ie, P, QRS, or T wave amplitude increases and decreases on alternate beats). Electrical alternans is associated with variation in cardiac position (swinging heart). Echocardiography has a high degree of sensitivity and specificity for detecting pericardial fluid.

Patients with a normal ECG, small (< 0.5 L) effusion, and no suspicious findings from the history and examination may be observed with serial examination and echocardiography. Other patients must be evaluated further to determine etiology.

Constrictive pericarditis: Diagnosis may be suspected based on ECG, chest x-ray, and Doppler echocardiography findings, but cardiac catheterization and CT (or MRI) are usually required. Because ventricular filling is restricted, ventricular pressure tracings show a sudden dip followed by a plateau (resembling a square root sign) in early diastole. Rarely, right heart biopsy is needed to exclude restrictive cardiomyopathy.

ECG changes are nonspecific. QRS voltage is usually low. T waves are usually non-specifically abnormal. Atrial fibrillation occurs in about one third of patients; atrial flutter is less common.

Lateral chest x-rays often show pericardial calcification best, but the finding is nonspecific.

The changes on echocardiogram are also nonspecific. When the right and left ventricular filling pressures are equally elevated, Doppler echocardiography helps distinguish constrictive pericarditis from restrictive cardiomyopathy. During inspiration, mitral diastolic flow velocity usually falls > 25% in constrictive pericarditis but < 15% in restrictive cardiomyopathy. In constrictive pericarditis, inspiratory tricuspid flow velocity increases more than it normally does, but it does not do so in restrictive cardiomyopathy. Determining tissue velocities at the mitral annulus may be helpful when excessively high left atrial pressure blunts respiratory variation in transvalvular velocities.

If clinical and echocardiographic findings suggest constrictive pericarditis, right heart cardiac catheterization is done. It helps confirm and quantify the abnormal hemodynamics that define constrictive pericarditis: Mean pulmonary artery occlusion pressure (pulmonary capillary wedge pressure), pulmonary artery diastolic pressure, right ventricular end-diastolic pressure, and mean right atrial pressure are all at about 10 to 30 mm Hg. The pulmonary artery and right ventricular systolic pressures are normal or modestly elevated, so that pulse pressures are small. In the atrial pressure curve, x and y descents are typically accentuated; in the ventricular pressure curve, a diastolic dip occurs at the time of rapid ventricular filling. These changes almost always occur with significant constrictive pericarditis.

Right ventricular systolic pressure of > 50 mm Hg often occurs in restrictive cardiomyopathy but less often in constrictive pericarditis. When the pulmonary artery occlusion pressure equals the right atrial mean pressure and an early diastolic dip in the ventricular pressure curve occurs with large x and y waves in the right atrial curve, either disorder may be present.

CT or MRI can identify pericardial thickening > 5 mm. Such thickening with typical hemodynamic changes can confirm a diagnosis of constrictive pericarditis. When no pericardial thickening or fluid is seen, the diagnosis of restrictive cardiomyopathy is favored but not proved; a normal pericardial thickness does not
exclude the diagnosis of constrictive pericarditis.

**Cardiac tamponade:** Low voltage and electrical alternans on the ECG suggest cardiac tamponade, but these findings lack sensitivity and specificity. When tamponade is suspected, echocardiography is done unless even a brief delay might be life threatening. Then pericardiocentesis is done immediately for diagnosis and treatment. On an echocardiogram, respiratory variation of transvalvular and venous flows and compression or collapse of right cardiac chambers in the presence of a pericardial effusion support the diagnosis.

If tamponade is suspected, right heart (Swan-Ganz) catheterization may be done. In cardiac tamponade, there is no early diastolic dip in the ventricular pressure record. In the atrial pressure curve, x descent is preserved and y descent is lost. In contrast, in severe congestive states due to dilated cardiomyopathy, pulmonary artery occlusion or left ventricular diastolic pressure usually exceeds right atrial mean pressure and right ventricular diastolic pressure by ≥ 4 mm Hg.

**Diagnosis of cause:** After pericarditis is diagnosed, tests to determine etiology and the effect on cardiac function are done. In a young, previously healthy adult who presents with a viral infection and pericarditis, an extensive evaluation is usually unnecessary. Differentiating viral from idiopathic pericarditis is difficult, expensive, and generally of little practical importance.

A biopsy of pericardial tissue or aspiration of pericardial fluid may be needed to establish a diagnosis. Acid-fast stains and cultures of pericardial fluid help identify infectious causes. Samples are examined for malignant cells. However, complete drainage of a newly identified pericardial effusion is usually unnecessary for diagnosis. Persistent (usually > 3 mo) or progressive effusion, particularly when the etiology is uncertain, also warrants pericardiocentesis.

The choice between needle pericardiocentesis and surgical drainage depends on institutional resources and physician experience, the etiology of the effusion, the need for diagnostic tissue samples, and the prognosis of the patient. Needle pericardiocentesis is often best when the etiology is known or the presence of tamponade is in question. Surgical drainage is best when the presence of tamponade is certain but the etiology is unclear.

Laboratory tests of pericardial fluid other than culture and cytology are usually nonspecific. But specific diagnoses are sometimes possible using newer visual, cytologic, and immunologic analysis of fluid obtained via pericardioscopic-guided biopsy.

Cardiac catheterization may be useful for evaluating pericarditis and identifying the cause of reduced cardiac function.

CT or MRI can help identify metastases, although echocardiography is usually sufficient.

Other tests include CBC, acute-phase reactants, routine chemistries, cultures, autoimmune tests, and, when appropriate, tests for HIV, histoplasmosis complement fixation (in endemic areas), streptozyme, and neutralizing antibodies for coxsackievirus, influenza virus, and echovirus. Anti-DNA and anti-RNA antibody tests may be useful. A PPD skin test is done.

**Treatment**

* Varies by cause

* NSAIDs and sometimes colchicine or corticosteroids for pain and inflammation

* Pericardiocentesis for tamponade and some large effusions

* Sometimes intrapericardial drugs (eg, triamcinolone)

* Sometimes pericardial resection for constrictive pericarditis
Hospitalization to watch for complications is often advisable. Possible causative drugs (eg, anticoagulants, procainamide, phenytoin) are stopped. For cardiac tamponade, immediate pericardiocentesis (see Fig. 216-2) is done; removal of even a small volume of fluid may be lifesaving.

Pain can usually be controlled with aspirin 325 to 650 mg po q 4 to 6 h or other NSAIDs (eg, ibuprofen 600 to 800 mg po q 6 to 8 h); duration of therapy varies, and patients should be treated until an effusion, if present, has resolved. Colchicine 1 mg/day (for 3 mo), added to NSAIDs or given alone, is effective for the initial episode of pericarditis and helps prevent recurrences. The intensity of therapy is dictated by the patient's distress. Severe pain may require opioids and corticosteroids (eg, prednisone 60 to 80 mg po once/day for 1 wk, followed by rapid tapering of the dose). Corticosteroids are particularly useful in acute pericarditis due to uremia or a connective tissue disorder, but tuberculous and pyogenic pericarditis should be excluded before corticosteroid therapy is initiated. Intrapericardial instillation of triamcinolone (300 mg/m^2) avoids systemic adverse effects and is highly effective. Anticoagulants are usually contraindicated in acute pericarditis because they may cause intrapericardial bleeding and even fatal tamponade; however, they can be given in early pericarditis complicating acute MI. Uncommonly, pericardial resection is required.

Infections are treated with specific antimicrobials. Complete drainage is often necessary.

In postpericardiotomy syndrome, post-MI syndrome, or idiopathic pericarditis, antibiotics are not indicated. An NSAID at full doses may control pain and effusion. When required to control pain, fever, and effusion, prednisone 20 to 60 mg po once/day may be given for 3 to 4 days. If the response is satisfactory, the dose is gradually reduced, and the drug may be stopped in 7 to 14 days. But sometimes many months of treatment are needed.

For pericarditis due to rheumatic fever, another connective tissue disorder, or tumor, therapy is directed at the underlying process.

For pericardial effusion due to trauma, surgery is sometimes required to repair the injury and evacuate blood from the pericardium.

Pericarditis due to uremia may respond to increased frequency of hemodialysis, aspiration, or systemic or intrapericardial adrenal corticosteroids. Intrapericardial triamcinolone may be useful.

Chronic effusions are best treated by treating the cause, if known. Recurrent or persistent symptomatic effusions may be treated with balloon pericardiotomy or a surgical pericardial window. Recurrent effusion due to malignant tumor invasion may be treated with sclerosing drugs. Asymptomatic effusions of unknown cause may require only observation.

Congestion in chronic constrictive pericarditis may be alleviated with bed rest, salt restriction, and diuretics. Digoxin is indicated only if atrial arrhythmias or ventricular systolic dysfunction is present. Symptomatic constrictive pericarditis usually requires pericardial resection. However, patients with mild symptoms, heavy calcification, or extensive myocardial damage may be poor surgical candidates. The mortality rate for pericardial resection may approach 40% in New York Heart Association (NYHA) functional class IV patients. Patients who have constrictive pericarditis due to irradiation or a connective tissue disorder are especially likely to have severe myocardial damage and may not benefit from pericardial resection.
Chapter 217. Diseases of the Aorta and Its Branches

Introduction

The aorta originates at the left ventricle above the aortic valve (aortic root), travels upward (ascending thoracic aorta) to the first branch of the aorta (brachiocephalic or innominate artery), arches up and behind the heart (aortic arch), then turns downward distal to the left subclavian artery (descending aorta) through the thorax (thoracic aorta) and abdomen (abdominal aorta). The abdominal aorta ends by dividing into the 2 common iliac arteries.

Aneurysms

Aneurysms are abnormal dilations of arteries caused by weakening of the arterial wall. Common causes include hypertension, atherosclerosis, infection, trauma, and hereditary or acquired connective tissue disorders. Aneurysms are usually asymptomatic but can cause pain and lead to ischemia, thromboembolism, spontaneous dissection, and rupture, which may be fatal. Diagnosis is by imaging tests (eg, ultrasonography, CT angiography, magnetic resonance angiography, aortography). Treatment of unruptured aneurysms is with risk factor modification (eg, strict BP control) plus surveillance imaging or with open or endovascular stent-graft surgery, depending on size and location of the aneurysm and presence of symptoms. Treatment of ruptured aneurysms is immediate repair by either an open surgical synthetic graft or an endovascular stent-graft.

Aneurysms, defined as a ≥ 50% increase in arterial diameter compared with normal segments, result from localized weakening of an arterial wall. True aneurysms involve all 3 layers of the artery (intima, media, and adventitia). A pseudoaneurysm (false aneurysm) is a communication between the arterial lumen and overlying connective tissue resulting from arterial rupture; a blood-filled cavity forms outside the vessel wall and seals the leak as it thromboses. Aneurysms are classified as fusiform (circumferential widening of the artery) or saccular (localized outpouchings of the artery wall). Thrombi that develop in layers (laminated thrombi) may line the walls of either type and are a sign that blood flow beyond the aneurysm is normal or near normal.

Aneurysms may occur in any artery. Abdominal and thoracic aortic aneurysms are most common and significant; aneurysms of the major branches (subclavian and splanchnic arteries) are much less common. Aneurysms of the cerebrovascular system are discussed in Sidebar 173-1 on p. 1653.

Abdominal Aortic Aneurysms

Abdominal aortic aneurysms (AAAs) account for three fourths of aortic aneurysms and affect 0.5 to 3.2% of the population. Prevalence is 3 times greater in men. AAAs typically begin below the renal arteries but may include renal arterial ostia; about 50% involve the iliac arteries. Generally, aortic diameter ≥ 3 cm constitutes an AAA. Most AAAs are fusiform; some are saccular. Many are lined with laminated thrombi. AAAs involve all layers of the aorta and do not involve dissection; however, a thoracic aortic dissection may extend to the distal abdominal aorta.

Etiology

The most common cause is weakening of the arterial wall, usually associated with atherosclerosis. Other causes include trauma, vasculitis, cystic medial necrosis, and post-surgical anastomotic disruption. Uncommonly, syphilis and localized bacterial or fungal infection, typically due to sepsis or infective endocarditis, weaken the arterial wall and cause infected (mycotic) aneurysms.

Smoking is the strongest risk factor. Other risk factors include hypertension, older age (peak incidence at age 70 to 80), family history (in 15 to 25%), race (more common in whites than in blacks), and male sex.

Symptoms and Signs

Most AAAs are asymptomatic; symptoms and signs, when they do occur, may not be specific. As AAAs
expand, they may cause pain, which is steady, deep, boring, visceral, and felt most prominently in the lumbosacral region; patients may be aware of an abnormally prominent abdominal pulsation. Rapidly enlarging aneurysms that are about to rupture are frequently tender, but most aneurysms grow slowly without symptoms.

The aneurysm may or may not be palpable as a pulsatile mass, depending on its size and patient habitus. The probability that a patient with a pulsatile palpable mass has an aneurysm > 3 cm is about 40% (positive predictive value). A systolic bruit may be audible over the aneurysm.

If an AAA ruptures, patients who do not die immediately typically present with abdominal or back pain, hypotension, and tachycardia. They may have a history of recent upper abdominal trauma, often minimal, or isometric straining (eg, lifting a heavy object).

Patients with an occult AAA sometimes present with symptoms of complications (eg, extremity pain due to embolization of mural thrombi) or of the cause (eg, fever, malaise, or weight loss due to infection or vasculitis). Uncommonly, large AAAs cause disseminated intravascular coagulation, perhaps because large areas of abnormal endothelial surface trigger rapid thrombosis and consumption of coagulation factors.

**Diagnosis**

- Often incidental
- Confirmation by ultrasonography or CT
- Sometimes CT angiography or magnetic resonance angiography

Most AAAs are diagnosed incidentally when they are detected during physical examination or when abdominal ultrasonography, CT, or MRI is done for other reasons. An AAA should be considered in elderly patients who present with acute abdominal or back pain whether a palpable pulsatile mass is present or not.

When symptoms or physical examination findings suggest AAA, abdominal ultrasonography or CT is usually the test of choice. Symptomatic patients should have immediate testing to make the diagnosis before catastrophic rupture. For hemodynamically unstable patients with presumed rupture, ultrasonography provides bedside results more rapidly, but intestinal gas and distention may limit its accuracy. Laboratory tests, including CBC, electrolytes, BUN, creatinine, PT, PTT, blood type and cross-match, are done in preparation for possible surgery.

If rupture is not suspected, CT angiography (CTA) or magnetic resonance angiography (MRA) can more precisely characterize aneurysm size and anatomy. If thrombi line the aneurysm wall, CTA may underestimate true size; noncontrast CT may provide a more accurate estimate. Aortography is essential if renal artery or aortoiliac disease is suspected or if correction with endovascular stent-grafts (endografts) is being considered.

Plain abdominal x-rays are neither sensitive nor specific; however, if obtained for other purposes, aortic calcification may outline the aneurysm wall. If a mycotic aneurysm is suspected, bacterial and fungal blood cultures should be done.

**Treatment**

- Surgery or endovascular stent grafting

Some AAAs enlarge at a steady rate (2 to 3 mm/yr), some enlarge exponentially, and, for unknown reasons, about 20% remain the same size indefinitely. The need for treatment is related to size, which is linked to risk of rupture (see Table 217-1).
Ruptured AAAs require immediate open surgery or endovascular stent grafting. Without treatment, mortality rate approaches 100%. With open surgical treatment, mortality rate is about 50%; mortality with endovascular stent grafting is generally lower (20 to 30%). The mortality remains high because many patients have coexisting coronary, cerebrovascular, and peripheral atherosclerosis. Patients who present in hemorrhagic shock require fluid resuscitation (see p. 2297) and blood transfusions, but mean arterial pressure should not be elevated to > 70 to 80 mm Hg because bleeding may increase. Preoperative control of hypertension is important.

Elective surgical repair is recommended for aneurysms > 5 to 5.5 cm (when risk of rupture increases to > 5 to 10%/yr), unless coexisting medical conditions contraindicate surgery. Additional indications for elective surgery include increase in aneurysm size by > 0.5 cm within 6 mo regardless of size, chronic abdominal pain, thromboembolic complications, and an iliac or femoral artery aneurysm that causes lower-limb ischemia. Before elective repair, clinical recognition of coronary artery disease (CAD) is essential (see Table 207-1 on p. 2049) because many patients with an AAA have generalized atherosclerosis and surgical repair poses a major risk of cardiovascular events. Aggressive medical treatment and risk factor control are essential, and revascularization should be considered only in patients with unstable CAD. Routine preoperative coronary angioplasty or bypass surgery has not been shown to be necessary in most patients who can be prepared with good medical management before aneurysm repair.

Surgical repair consists of replacing the aneurysmal portion of the abdominal aorta with a synthetic graft. If the iliac arteries are involved, the graft must be extended to include them. If the aneurysm extends above the renal arteries, the renal arteries must be reimplanted into the graft, or bypass grafts must be created.

Placement of an endovascular stent-graft within the aneurysmal lumen via the femoral artery is a less invasive alternative and is indicated when risk of perioperative complications is high. This procedure excludes the aneurysm from systemic blood flow and reduces risk of rupture. The aneurysm eventually thrombosizes, and 50% of aneurysms decrease in diameter. Short-term results are good, but long-term results are unknown. Complications include angulation, kinking, thrombosis, migration of the stent-graft, and endoleak (persistent flow of blood into the aneurysm sac after endovascular stent-graft placement). Thus, follow-ups must be more frequent after endovascular stent-graft placement than after a traditional repair. If no complications occur, imaging tests are recommended at 1 mo, 6 mo, 12 mo, and every year thereafter. Complex anatomy (eg, short aneurysm neck below renal arteries, severe arterial tortuosity) makes endovascular stent grafting difficult in 30 to 40% of patients.

Repair of aneurysms < 5 cm does not appear to improve survival. These aneurysms should be monitored with ultrasonography every 6 to 12 mo for expansion that warrants treatment. Control of atherosclerotic risk factors, especially smoking cessation and use of antihypertensives as appropriate, is important. If a small or moderate-sized aneurysm becomes > 5.5 cm and if risk of perioperative complications is lower than estimated risk of rupture, AAA repair is indicated; risk of rupture vs that of perioperative complications should be discussed frankly with the patient.

Treatment of a mycotic aneurysm consists of vigorous antimicrobial therapy directed at the pathogen, followed by excision of the aneurysm. Early diagnosis and treatment improve outcome.

**Thoracic Aortic Aneurysms**

Thoracic aortic aneurysms (TAAs) account for one fourth of aortic aneurysms. Men and women are affected equally. About 40% of TAAs occur in the ascending thoracic aorta (between the aortic valve and brachiocephalic, or innominate, artery), 10% occur in the aortic arch (including the brachiocephalic, carotid, and subclavian arteries), 35% occur in the descending thoracic aorta (distal to the left subclavian artery), and 15% occur in the upper abdomen (as thoracoabdominal aneurysms).

**Etiology**
Most TAAs result from atherosclerosis. Risk factors for both include prolonged hypertension, dyslipidemia, and smoking; additional risk factors for TAAs include presence of aneurysms elsewhere and older age (peak incidence at age 65 to 70).

Congenital connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome) cause cystic medial necrosis, a degenerative change that leads to TAAs complicated by aortic dissection (see p. 2212) and by widening of the proximal aorta and aortic valve (annuloaortic ectasia), which causes aortic regurgitation. Marfan syndrome causes 50% of cases of annuloaortic ectasia, but cystic medial necrosis and its complications can occur in young people even if no congenital connective tissue disorder is present.

Infected (mycotic) TAAs result from hematogenous spread of systemic or local infections (eg, sepsis, pneumonia), lymphangitic spread (eg, in TB), or direct extension (eg, in osteomyelitis or pericarditis). Bacterial endocarditis and tertiary syphilis are uncommon causes. TAAs occur in some connective tissue disorders (eg, temporal arteritis, Takayasu's arteritis, Wegener's granulomatosis).

Blunt chest trauma causes pseudoaneurysms (extramural hematomas due to blood that has leaked through the torn aortic wall).

TAAs may dissect, compress or erode into adjacent structures, lead to thromboembolism, leak, or rupture.

**Symptoms and Signs**

Most TAAs are asymptomatic until complications (eg, thromboembolism, rupture, aortic regurgitation, dissection) develop. However, compression of adjacent structures can cause chest or back pain, cough, wheezing, dysphagia, hoarseness (due to recurrent laryngeal or vagus nerve compression), chest pain (due to coronary artery compression), and superior vena cava syndrome. Erosion of aneurysms into the lungs causes hemoptysis or pneumonitis; erosion into the esophagus (aortoesophageal fistula) causes massive hematemesis. Dissection manifests with tearing pain, often radiating to the back. Thromboembolism may cause stroke, abdominal pain (due to mesenteric embolism), or extremity pain. Patients who do not immediately die of a ruptured TAA present with severe chest or back pain and hypotension or shock; exsanguination most commonly occurs into the pleural or pericardial space.

Additional signs include Horner syndrome due to compression of sympathetic ganglia, palpable downward pull of the trachea with each cardiac contraction (tracheal tug), and tracheal deviation. Visible or palpable chest wall pulsations, occasionally more prominent than the left ventricular apical impulse, are unusual but may occur.

Syphilitic aneurysms of the aortic root classically lead to aortic regurgitation and inflammatory stenosis of the coronary artery ostia, which may manifest as chest pain due to myocardial ischemia. Syphilitic aneurysms do not dissect.

**Diagnosis**

- Incidental x-ray finding
- Confirmation by CTA, MRA, or transesophageal echocardiography (TEE)

TAAs are usually first suspected when a chest x-ray incidentally shows a widened mediastinum or enlargement of the aortic knob. These findings or symptoms and signs suggesting an aneurysm should be followed up with a 3-dimensional imaging test. CTA can delineate aneurysm size and proximal or distant extent, detect leakage, and identify coincident pathology. MRA may provide similar detail. TEE can delineate size and extent and detect leakage of aneurysms of the ascending but not descending aorta; TEE is especially useful for detecting aortic dissection. Contrast angiography provides the best image of the arterial lumen but no information on extraluminal structures, is invasive, and has a significant risk of renal and extremity atheroembolism and contrast nephropathy. Choice of imaging test is based on availability and local experience; however, if rupture is suspected, TEE or CTA, depending on availability, is done immediately.
Aortic root dilation or unexplained ascending aorta aneurysms warrant serologic testing for syphilis. If a mycotic aneurysm is suspected, bacterial and fungal blood cultures are done.

**Prognosis**

TAAs enlarge an average of 3 to 5 mm/yr; risk factors for rapid enlargement include larger size of aneurysm, location in the descending aorta, and presence of mural thrombi. Median diameter at aneurysm rupture is 6 cm for ascending aneurysms and 7 cm for descending aneurysms, but rupture of smaller aneurysms may occur in patients with Marfan syndrome. Survival rate of patients with untreated large TAAs is 65% at 1 yr and 20% at 5 yr.

**Treatment**

- Endovascular stent grafting or open surgical repair
- Control of hypertension

Treatment is endovascular stent grafting when anatomically possible and open surgical repair for more complex aneurysms. Immediate control of hypertension is essential.

Ruptured TAAs, if untreated, are universally fatal; they require immediate intervention, as do leaking aneurysms and those that cause acute dissection or acute valvular regurgitation. Surgery involves a median sternotomy (for ascending and aortic arch aneurysms) or left thoracotomy (for descending and thoracoabdominal aneurysms) and subsequent excision of the aneurysm and replacement with a synthetic graft. Transcatheter-placed endovascular stent-grafts (endografts) for descending TAAs are being used more frequently as a less invasive alternative to open surgery. With emergency surgery, 1-mo mortality rate is about 40 to 50%. In patients who survive, incidence of serious complications (eg, renal failure, respiratory failure, severe neurologic damage) is high.

Elective surgery is indicated for large aneurysms (diameter > 5 to 6 cm in the ascending aorta, > 6 to 7 cm in the descending aorta, and, for patients with Marfan syndrome, > 5 cm in any location) and also for those that rapidly enlarge (> 1 cm/yr). Elective surgery is also indicated for symptomatic, traumatic, or syphilitic aneurysms. For syphilitic aneurysms, benzathine penicillin 2.4 million units once/wk IM is given for 3 wk afterward. For patients allergic to penicillin, tetracycline or erythromycin 500 mg po qid for 30 days is acceptable.

Although surgical repair of an intact TAA improves outcome, mortality rate may still exceed 5 to 10% at 30 days and is 40 to 50% at 10 yr. Risk of death increases greatly if aneurysms are complicated (eg, in the aortic arch or thoracoabdominal aorta) or if patients have CAD, are older, are symptomatic, or have preexisting renal insufficiency. Perioperative complications (eg, stroke, spinal injury, renal failure) occur in about 10 to 20%.

Asymptomatic aneurysms that do not meet criteria for elective surgical or endovascular repair are treated with aggressive BP control using a β-blocker and other antihypertensives if necessary. Smoking cessation is essential. Patients require frequent follow-ups to check for symptoms and serial CT every 6 to 12 mo.

**Aortic Branch Aneurysms**

Aneurysms may occur in any major aortic branch; such aneurysms are much less common than abdominal or thoracic aortic aneurysms. Risk factors include atherosclerosis, hypertension, cigarette smoking, and older age. Localized infection can cause mycotic aneurysms.

Subclavian artery aneurysms are sometimes associated with cervical ribs or thoracic outlet syndrome.

Splanchnic artery aneurysms are uncommon. About 60% occur in the splenic artery, 20% in the hepatic artery, and 5.5% in the superior mesenteric artery. Splenic artery aneurysms occur in more women than men.
men (4:1). Causes include medial fibromuscular dysplasia, portal hypertension, multiple pregnancies, penetrating or blunt abdominal trauma, pancreatitis, and infection. Hepatic artery aneurysms occur in more men than women (2:1). They may result from previous abdominal trauma, illicit IV drug use, medial degeneration of the arterial wall, or periarterial inflammation. Renal artery aneurysms may dissect or rupture, causing acute occlusion (see p. 2430).

**Symptoms and Signs**

Symptoms vary. Subclavian aneurysms can cause local pain, a pulsating sensation, venous thrombosis or edema (due to compression of adjacent veins), distal ischemic symptoms, transient ischemic attacks, stroke, or hoarseness or impaired motor and sensory function (due to compression of the recurrent laryngeal nerve or brachial plexus). Superior mesenteric aneurysms may cause abdominal pain and ischemic colitis.

Regardless of location, mycotic or inflammatory aneurysms may cause local pain and sequelae of systemic infection (eg, fever, malaise, weight loss).

**Diagnosis**

- Ultrasonography or CT

Most aortic branch aneurysms are not diagnosed before rupture, although calcified asymptomatic or occult aneurysms may be seen on x-rays or other imaging tests done for other reasons. Ultrasonography or CT is typically used to detect or confirm aortic branch aneurysms. Angiography can be used as needed to evaluate distal symptoms thought to be due to the aneurysm or embolism.

**Treatment**

- Open repair or sometimes endovascular stent grafting

Treatment is surgical removal and replacement with a graft. Endovascular repair is an option for some patients. The decision to repair asymptomatic aneurysms is based on risk of rupture, extent and location of the aneurysm, and perioperative risk.

Surgery for subclavian artery aneurysms may involve removal of a cervical rib (if present) before repair and replacement.

For splanchnic aneurysms, risk of rupture and death is as high as 10% and is particularly high for women of childbearing age and for patients with hepatic aneurysms (> 35%). Elective repair of splanchnic aneurysms is therefore indicated for women of childbearing age, for symptomatic aneurysms in other age groups, and for hepatic aneurysms. For splenic aneurysms, repair may consist of ligation without arterial reconstruction or aneurysm exclusion and vascular reconstruction. Depending on location of the aneurysm, splenectomy may be necessary.

Treatment of mycotic aneurysms is aggressive antibiotic therapy directed at the specific pathogen. Generally, these aneurysms must also be surgically repaired.

**Aortic Dissection**

Aortic dissection is the surging of blood through a tear in the aortic intima with separation of the intima and media and creation of a false lumen. The intimal tear may be a primary event or secondary to hemorrhage within the media. The dissection may occur anywhere along the aorta and extend proximally or distally into other arteries. Hypertension is an important contributor. Symptoms and signs include abrupt onset of tearing chest or back pain, and dissection may result in aortic regurgitation and compromised circulation in branch arteries. Diagnosis is by imaging tests (eg, transesophageal echocardiography, CT angiography, MRI, contrast aortography). Treatment always involves aggressive BP control and serial imaging to monitor progression of dissection; surgical repair of the aorta and placement of a synthetic graft are
needed for ascending aortic dissection and for certain descending aortic dissections. Endovascular stent-grafts are used for certain patients, especially when dissection involves the descending thoracic aorta. One fifth of patients die before reaching the hospital, and up to one third die of operative or perioperative complications.

Evidence of dissection is found in 1 to 3% of all autopsies. African-Americans, men, the elderly, and people with hypertension are especially at risk. Peak incidence occurs at age 50 to 65 or, for patients with congenital connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome), at age 20 to 40.

Aortic dissections are classified anatomically. The DeBakey classification system is most widely used.

- Type I (50% of dissections): These dissections start in the ascending aorta and extend at least to the aortic arch and sometimes beyond.
- Type II (35%): These dissections start in and are confined to the ascending aorta.
- Type III (15%): These dissections start in the descending thoracic aorta just beyond the origin of the left subclavian artery and extend distally or, less commonly, proximally.

The Stanford system is simpler.

- Type A: These dissections involve the ascending aorta.
- Type B: These dissections are confined to the descending thoracic aorta.

Although dissection may originate anywhere along the aorta, it occurs most commonly at the proximal ascending aorta (within 5 cm of the aortic valve) or the descending thoracic aorta (just beyond the origin of the left subclavian artery). Rarely, dissection is confined to individual arteries (eg, coronary or carotid arteries), typically in pregnant or postpartum women.

**Etiology**

Aortic dissection always occurs in the setting of preexisting degeneration of the aortic media. Causes include connective tissue disorders and injury (see Table 217-2).

Atherosclerotic risk factors, notably hypertension, contribute in more than two thirds of patients. After rupture of the intima, which is a primary event in some patients and secondary to hemorrhage within the media in others, blood flows into the media, creating a false channel that extends distally or, less commonly, proximally along the artery.

**Pathophysiology**

Dissections may communicate back with the true aortic lumen through intimal rupture at a distal site, maintaining systemic blood flow. But serious consequences are common:

- Compromise of the blood supply of tributary arteries (including coronary arteries)
- Aortic valvular dilation and regurgitation
- Heart failure
- Fatal rupture of the aorta through the adventitia into the pericardium, right atrium, or left pleural space

Acute dissections and those present < 2 wk are most likely to cause these complications. Risk decreases at ≥ 2 wk if evidence indicates thrombosis of the false lumen and loss of communication between the true and false lumina.
Variants of aortic dissection include separation of the intima and media by intramural hematoma without a clear intimal tear or flap, intimal tear and bulge without hematoma or false lumen, and dissection or hematoma caused by ulceration of atherosclerotic plaque. These variants are thought to be precursors of classic aortic dissection.

**Symptoms and Signs**

Typically, excruciating precordial or inter-scapular pain, often described as tearing or ripping, occurs abruptly. The pain frequently migrates from the original location as the dissection extends along the aorta. Up to 20% of patients present with syncope due to severe pain, aortic baroreceptor activation, extracranial cerebral artery obstruction, or cardiac tamponade.

Occasionally, patients present with symptoms of stroke, MI, intestinal infarction, paraparesis or paraplegia due to interruption of the blood supply to the spinal cord, or ischemic limb due to acute distal arterial occlusion.

About 20% of patients have partial or complete deficits of major arterial pulses, which may wax and wane. Limb BPs may differ, sometimes by > 30 mm Hg; this finding suggests a poor prognosis. A murmur of aortic regurgitation is heard in about 50% of patients with proximal dissection. Peripheral signs of aortic regurgitation may be present. Rarely, heart failure results from severe acute aortic regurgitation. Leakage of blood or inflammatory serous fluid into the left pleural space may lead to signs of pleural effusion; occlusion of a limb artery may cause signs of peripheral ischemia or neuropathy. Renal artery occlusion may cause oliguria or anuria. Cardiac tamponade may cause pulsus paradoxus and jugular venous distention.

[Table 217-2. Conditions Contributing to Aortic Dissection]

**Diagnosis**

- Transesophageal echocardiography (TEE), CT angiography (CTA), or magnetic resonance angiography (MRA)

Aortic dissection must be considered in any patient with chest pain, thoracic back pain, unexplained syncope or abdominal pain, stroke, or acute-onset heart failure, especially when pulses or BPs in the limbs are unequal. Such patients require a chest x-ray; in 60 to 90%, the mediastinal shadow is widened, usually with a localized bulge signifying the site of origin. Left pleural effusion is common.

If chest x-ray suggests dissection, TEE, CTA, or MRA is done immediately after the patient is stabilized. Findings of an intimal flap and double lumina confirm dissection.

Multiplanar TEE is 97 to 99% sensitive and, with M-mode echocardiography, is nearly 100% specific. It can be done at the bedside in < 20 min and does not require contrast agents. If TEE is unavailable, CTA is recommended; it has a positive predictive value of 100% and a negative predictive value of 86%.

MRA has nearly 100% sensitivity and specificity for aortic dissection. But it is time-consuming and ill-suited for emergencies. It is probably best used for stable patients with sub-acute or chronic chest pain when dissection is suspected.

Contrast aortography is an option if surgery is being considered. In addition to identifying the origin and extent of dissection, severity of aortic regurgitation, and extent of involvement of the aorta's major branches, aortography helps determine whether simultaneous coronary artery bypass surgery is needed. Echocardiography should also be done to check for aortic regurgitation and thus determine whether the aortic valve should be repaired or replaced concomitantly.

ECG is nearly universally done. However, findings range from normal to markedly abnormal (in acute coronary artery occlusion or aortic regurgitation), so the test is not diagnostically helpful. Assays for soluble elastin compounds and smooth-muscle myosin heavy-chain protein are being studied; they look promising but are not routinely available. Serum CK-MB and troponin may help distinguish aortic
dissection from MI, except when dissection causes MI.

Routine laboratory tests may detect slight leukocytosis and anemia if blood has leaked from the aorta. Increased LDH may be a non-specific sign of celiac or mesenteric arterial trunk involvement.

A cardiothoracic surgeon should be consulted early during the diagnostic evaluation.

Prognosis

About 20% of patients with aortic dissection die before reaching the hospital. Without treatment, mortality rate is 1 to 3%/h during the first 24 h, 30% at 1 wk, 80% at 2 wk, and 90% at 1 yr.

Hospital mortality rate for treated patients is about 30% for proximal dissection and 10% for distal. For treated patients who survive the acute episode, survival rate is about 60% at 5 yr and 40% at 10 yr. About one third of late deaths are due to complications of the dissection; the rest are due to other disorders.

Treatment

- β-Blockers and other drugs to control BP
- Surgery

Patients who do not immediately die of aortic dissection should be admitted to an ICU with intra-arterial BP monitoring; an in-dwelling urethral catheter is used to monitor urine output. Blood should be typed and cross-matched for 4 to 6 units of packed RBCs when surgery is likely. Hemodynamically unstable patients should be intubated.

Drugs to decrease arterial pressure, arterial shear stress, ventricular contractility, and pain are started immediately to maintain systolic BP at ≤ 110 mm Hg or the lowest level compatible with adequate cerebral, coronary, and renal perfusion. A β-blocker is usually used first. Options include metoprolol 5 mg IV up to 4 doses 15 min apart, esmolol 50 to 200 μg/kg/min in a constant IV infusion, and labetalol (an α- and β-adrenergic blocker) 1 to 2 mg/min in a constant IV infusion or 5 to 20 mg IV initial bolus with additional doses of 20 to 40 mg given q 10 to 20 min until BP is controlled or a total of 300 mg has been given, followed by additional 20- to 40-mg doses q 4 to 8 h prn. Alternatives to β-blockers include Ca channel blockers (eg, verapamil 0.05 to 0.1 mg/kg IV bolus or diltiazem 0.25 mg/kg [up to 25 mg] IV bolus or 5 to 10 mg/h by continuous infusion).

If systolic BP remains > 110 mm Hg despite use of β-blockers, nitroprusside in a constant IV infusion can be started at 0.2 to 0.3 μg/kg/min and titrated upward (often to 200 to 300 μg/min) as necessary to control BP. Nitroprusside should not be given without a β-blocker or Ca channel blocker, because reflex sympathetic activation in response to vasodilation can increase ventricular inotropy and aortic shear stress, worsening the dissection.

A trial of drug therapy alone is appropriate for uncomplicated, stable dissection confined to the descending aorta (type B) and for stable, isolated dissection of the aortic arch. Surgery is virtually always indicated if dissection involves the proximal aorta. Surgery is also indicated for limb or visceral ischemia, uncontrolled hypertension, continued aortic enlargement, extension of the dissection, and evidence of aortic rupture, regardless of dissection type. Surgery may also be best for acute distal dissections in patients with Marfan syndrome.

The goal of surgery is to obliterate entry into the false channel and reconstitute the aorta with a synthetic graft. If present, significant aortic regurgitation must be treated by resuspending the aortic leaflets or replacing the valve. Surgical outcomes are best with early, aggressive intervention; mortality rate ranges from 7 to 36%. Predictors of poor outcome include hypotension, renal failure, age > 70, abrupt onset of chest pain, pulse deficit, and ST-segment elevation on ECG.

Stent-grafts that seal entry to the false lumen and improve patency of the true lumen, balloon fenestration (in which an opening is made in the dissection flap that separates the true and false lumina), or both may
be less invasive alternatives for patients with type B dissection if peripheral ischemic complications develop.

All patients, including those treated by surgery or endovascular methods, are given long-term antihypertensive drug therapy, usually including β-blockers, Ca channel blockers, and ACE inhibitors. Almost any combination of antihypertensives is acceptable; exceptions are those that act mainly by vasodilation (eg, hydralazine, minoxidil) and β-blockers that have intrinsic sympathomimetic action (eg, acebutolol, pindolol). Avoidance of strenuous physical activity is often recommended. MRI may be done before discharge and repeated at 6 mo and 1 yr, then every 1 to 2 yr.

The most important late complications include redissection, formation of localized aneurysms in the weakened aorta, and progressive aortic regurgitation. These complications may require surgical or endovascular repair.

**Aortitis**

**Aortitis is inflammation of the aorta, sometimes causing aneurysm or occlusion.**

Aortitis is caused by several connective tissue disorders (eg, Takayasu's arteritis, temporal arteritis, ankylosing spondylitis, relapsing polychondritis) and infections (eg, bacterial endocarditis, syphilis, Rocky Mountain spotted fever, fungal infections). It is also a feature of Cogan's syndrome (inflammatory keratitis, vestibular and auditory dysfunction, and aortitis).

Inflammation usually involves all layers of the aorta (intima, media, adventitia) and may lead to occlusion of the aorta or its branches or weakening of the arterial wall, resulting in aneurysms. Pathogenesis, symptoms and signs, diagnosis, and treatment differ by etiology.

**Abdominal Aortic Branch Occlusion**

Various branches of the aorta can be occluded by atherosclerosis, fibromuscular dysplasia, or other conditions, causing symptoms and signs of ischemia or infarction. Diagnosis is by imaging tests. Treatment is with embolectomy, angioplasty, or sometimes surgical bypass grafting.

Acute occlusion of branches of the abdominal aorta may result from embolism, atherothrombosis, or dissection; chronic occlusion may result from atherosclerosis, fibromuscular dysplasia, or external compression by mass lesions. Common sites of occlusion include

- Superior mesenteric arteries
- Celiac axis
- Renal arteries
- Aortic bifurcation

Chronic occlusion of the celiac axis is more common among women for unclear reasons.

**Symptoms and Signs**

Clinical manifestations (eg, pain, organ failure, necrosis) result from ischemia or infarction and vary depending on artery involved and acuity.

Acute mesenteric occlusion (see p. 109) causes intestinal ischemia and infarction, resulting in severe, diffuse abdominal pain typically out of proportion to the minimal physical findings. Acute occlusion of the celiac axis may cause liver or spleen infarction.
Chronic mesenteric vascular insufficiency rarely causes symptoms unless both the superior mesenteric artery and celiac axis are substantially narrowed or occluded, because collateral circulation between the major splanchnic trunks is extensive. Symptoms of chronic mesenteric vascular insufficiency typically occur postprandially (as intestinal angina) because digestion requires increased mesenteric blood flow; pain begins about 30 min to 1 h after eating and is steady, severe, and usually periumbilical and may be relieved by sublingual nitroglycerin. Patients become fearful of eating; weight loss, often extreme, is common. Rarely, malabsorption develops and contributes to weight loss. Patients may have an abdominal bruin, nausea, vomiting, diarrhea or constipation, and dark stools.

Acute renal artery embolism causes sudden flank pain, followed by hematuria (see p. 2430). Chronic occlusion may be asymptomatic or result in new or hard-to-control hypertension and other sequelae of renal insufficiency or failure.

Acute occlusion of the aortic bifurcation or distal branches can cause sudden onset of pain at rest, pallor, paralysis, absence of peripheral pulses, and coldness in the legs (see p. 2221). Chronic occlusion can cause intermittent claudication in the legs and buttocks and erectile dysfunction (Leriche syndrome). Femoral pulses are absent. A limb may be jeopardized.

Diagnosis

- Imaging tests

Diagnosis is based primarily on history and physical examination and is confirmed by duplex ultrasonography, CT angiography, magnetic resonance angiography, or traditional angiography.

Treatment

- Embolectomy or percutaneous angioplasty for acute occlusion
- Surgery or angioplasty for chronic occlusion

Acute occlusion is a surgical emergency requiring embolectomy or percutaneous transluminal angioplasty (PTA) with or without stent placement. Chronic occlusion, if symptomatic, may require surgery or angioplasty. Risk factor modification and antiplatelet drugs may help.

Acute mesenteric occlusion (eg, in the superior mesenteric artery), which causes significant morbidity and mortality, requires prompt revascularization. Prognosis is poor if the intestine is not revascularized within 4 to 6 h.

For chronic occlusion of the superior mesenteric artery and celiac axis, dietary modifications may temporarily relieve symptoms. If symptoms are severe, surgical bypass from the aorta to the splanchnic arteries distal to the occlusion usually results in revascularization. Long-term patency of the grafts exceeds 90%. In appropriately selected patients (particularly among older patients who may be poor candidates for surgery), revascularization by PTA with or without stent placement may be successful. Symptoms may resolve rapidly, and weight may be regained.

Acute renal artery occlusion requires embolectomy; sometimes PTA can be done. Initial treatment of chronic occlusion involves antihypertensives. If BP is not controlled adequately or if renal function deteriorates, PTA with stent placement or, when PTA is impossible, open surgical bypass or endarterectomy can improve blood flow.

Occlusion of the aortic bifurcation requires urgent embolectomy, usually done transfemorally. If chronic occlusion of the aortic bifurcation causes claudication, an aortoiliac or aortofemoral graft can be used to surgically bypass the occlusion. PTA is an alternative for selected patients.
Chapter 218. Peripheral Arterial Disorders

Introduction

Peripheral arterial disorders include acrocyanosis, erythromelalgia, fibromuscular dysplasia, peripheral arterial aneurysms, peripheral arterial disease (caused by atherosclerosis), Raynaud's syndrome, and thromboangiitis obliterans.

Acrocyanosis

Acrocyanosis is persistent, painless, symmetric cyanosis of the hands, feet, or face caused by vasospasm of the small vessels of the skin in response to cold.

Acrocyanosis usually occurs in women and is not associated with occlusive arterial disease. The digits and hands or feet are persistently cold and bluish, sweat profusely, and may swell. In acrocyanosis, unlike Raynaud's syndrome, cyanosis persists and is not easily reversed, trophic changes and ulcers do not occur, and pain is absent. Pulses are normal.

Treatment, other than reassurance and avoidance of cold, is usually unnecessary. Vasodilators may be tried but are usually ineffective.

Erythromelalgia

Erythromelalgia is distressing paroxysmal vaso-dilation of small arteries in the feet and hands and, less commonly, in the face, ears, or knees; it causes burning pain, increased skin temperature, and redness.

This rare disorder may be primary (cause unknown) or secondary to myeloproliferative disorders (eg, polycythemia vera, thrombocythemia), hypertension, venous insufficiency, diabetes mellitus, SLE, RA, lichen sclerosus, gout, spinal cord disorders, or multiple sclerosis. Less commonly, the disorder is related to the use of some drugs (eg, nifedipine, bromocriptine). A rare hereditary form of erythromelalgia starts at birth or during childhood.

Burning pain, heat, and redness in the feet or hands last a few minutes to several hours. In most patients, symptoms are triggered by warmth (temperatures of 29 to 32° C) and are typically relieved by immersion in ice water. Trophic changes do not occur. Symptoms may remain mild for years or become severe enough to cause total disability. Generalized vasomotor dysfunction is common, and Raynaud's syndrome may occur.

Diagnosis is clinical. Testing is done to detect causes. Because erythromelalgia may precede a myeloproliferative disorder by several years, repeated blood counts may be indicated. Differential diagnosis includes posttraumatic reflex dystrophies, shoulder-hand syndrome, peripheral neuropathy, causalgia, Fabry's disease, and bacterial cellulitis.

Treatment is warmth avoidance, rest, elevation of the extremity, and application of cold. For primary erythromelalgia, gabapentin may be of benefit. For secondary erythromelalgia, the underlying disorder is treated; aspirin may be helpful when a myeloproliferative disorder is involved.

Fibromuscular Dysplasia

Fibromuscular dysplasia includes a heterogenous group of nonatherosclerotic, noninflammatory arterial changes, causing some degree of vascular stenosis, occlusion, or aneurysm.

Fibromuscular dysplasia usually occurs in women aged 40 to 60. The cause is unknown. However, there may be a genetic component, and smoking may be a risk factor. Fibromuscular dysplasia is more common among people with certain connective tissue disorders (eg, Ehlers-Danlos syndrome type 4, cystic medial necrosis, hereditary nephritis, neurofibromatosis).
Medial dysplasia, the most common type, is characterized by alternating regions of thick and thin fibromuscular ridges containing collagen along the media. In perimedial dysplasia, extensive collagen deposition occurs in the outer half of the media. Fibromuscular dysplasia may affect the renal arteries (60 to 75%), carotid and intracranial arteries (25 to 30%), intra-abdominal arteries (9%), or external iliac arteries (5%).

Fibromuscular dysplasia is usually asymptomatic regardless of location. Symptoms, when they occur, vary by location:

- Claudication in the thighs and calves, femoral bruits, and decreased femoral pulses when leg arteries are affected
- Secondary hypertension when renal arteries are affected
- Transient ischemic attack or stroke symptoms when carotid arteries are affected
- Aneurysmal symptoms when intracranial arteries are affected
- Rarely, mesenteric ischemic symptoms when intra-abdominal arteries are affected

Ultrasonography may suggest the diagnosis, but definitive diagnosis is made by angiography showing a beaded appearance (in medial or perimedial dysplasia) or a concentric band or long, smooth narrowing (in other forms).

Treatment varies by location. It may involve percutaneous transluminal angioplasty, bypass surgery, or aneurysm repair. Smoking cessation is important. Control of other risk factors for atherosclerosis (hypertension, dyslipidemia, diabetes) helps prevent accelerated development of flow-limiting arterial stenoses.

Peripheral Arterial Aneurysms

Peripheral arterial aneurysms are abnormal dilations of the peripheral arteries caused by weakening of the arterial wall (see also p. 2207).

About 70% of peripheral arterial aneurysms are popliteal aneurysms; 20% are iliofemoral aneurysms. Aneurysms at these locations frequently accompany abdominal aortic aneurysms, and > 50% are bilateral. Rupture is relatively infrequent, but these aneurysms may lead to thromboembolism. They occur in men much more often than women (> 20:1); mean age at presentation is 65. Aneurysms in arm arteries are relatively rare; they may cause limb ischemia, distal embolism, and stroke.

Infectious (mycotic) aneurysms may occur in any artery but are most common in the femoral. They are usually due to salmonellae, staphylococci, or Treponema pallidum (which causes syphilitic aneurysm).

Common causes include atherosclerosis, popliteal artery entrapment, and septic emboli (which cause mycotic aneurysms).

Peripheral arterial aneurysms are usually asymptomatic at the time of detection. Thrombosis or embolism (or rarely, aneurysm rupture) causes extremities to be painful, cold, pale, paresthetic, or pulseless. Infectious aneurysms may cause local pain, fever, malaise, and weight loss.

Diagnosis is by ultrasonography, magnetic resonance angiography, or CT. Popliteal aneurysms may be suspected when physical examination detects an enlarged, pulsatile artery; the diagnosis is confirmed by imaging tests.

Risk of rupture of extremity aneurysms is low (< 5% for popliteal and 1 to 14% for iliofemoral aneurysms). For leg artery aneurysms, surgical repair is therefore often elective. It is indicated when the arteries are twice normal size or when the patient is symptomatic. However, surgical repair is indicated for all arm
artery aneurysms because serious complications (eg, thromboembolism) are a greater risk. The affected segment of artery is excised and replaced with a graft. Limb salvage rate after surgical repair is 90 to 98% for asymptomatic patients and 70 to 80% for symptomatic patients.

In certain patients, an endovascular-covered stent-graft is another option for repair.

**Peripheral Arterial Disease**

(Peripheral Vascular Disease)

Peripheral arterial disease (PAD) is atherosclerosis of the extremities (virtually always lower) causing ischemia. Mild PAD may be asymptomatic or cause intermittent claudication; severe PAD may cause rest pain with skin atrophy, hair loss, cyanosis, ischemic ulcers, and gangrene. Diagnosis is by history, physical examination, and measurement of the ankle-brachial index. Treatment of mild PAD includes risk factor modification, exercise, antiplatelet drugs, and cilostazol or possibly pentoxifylline as needed for symptoms. Severe PAD usually requires angioplasty or surgical bypass and may require amputation. Prognosis is generally good with treatment, although mortality rate is relatively high because coronary artery or cerebrovascular disease often coexists.

**Etiology**

PAD affects about 12% of people in the US; men are affected more commonly. Risk factors are the same as those for atherosclerosis: hypertension, diabetes, dyslipidemia (high low-density lipoprotein [LDL] cholesterol, low high-density lipoprotein [HDL] cholesterol), cigarette smoking (including passive smoking) or other forms of tobacco use, diabetes, and a family history of atherosclerosis. Obesity, male sex, and a high homocysteine level are also risk factors.

Atherosclerosis is a systemic disorder; 50 to 75% of patients with PAD also have clinically significant coronary artery disease (CAD) or cerebrovascular disease. However, CAD may be silent because PAD may prevent patients from exerting themselves enough to trigger angina.

**Symptoms and Signs**

Typically, PAD causes intermittent claudication, which is a painful, aching, cramping, uncomfortable, or tired feeling in the legs that occurs during walking and is relieved by rest. Claudication usually occurs in the calves but can occur in the feet, thighs, hips, buttocks, or, rarely, arms. Claudication is a manifestation of exercise-induced reversible ischemia, similar to angina pectoris. As PAD progresses, the distance that can be walked without symptoms may decrease, and patients with severe PAD may experience pain during rest, reflecting irreversible ischemia. Rest pain is usually worse distally, is aggravated by leg elevation (often causing pain at night), and lessens when the leg is below heart level. The pain may be burning, tightening, or aching, although this finding is nonspecific. About 20% of patients with PAD are asymptomatic, sometimes because they are not active enough to trigger leg ischemia. Some patients have atypical symptoms (eg, nonspecific exercise intolerance, hip or other joint pain).

Mild PAD often causes no signs. Moderate to severe PAD commonly causes diminished or absent peripheral (popliteal, tibialis posterior, dorsalis pedis) pulses; Doppler ultra-sonography can often detect blood flow when pulses cannot be palpated.

When below heart level, the foot may appear dusky red (called dependent rubor). In some patients, elevating the foot causes loss of color and worsens ischemic pain; when the foot is lowered, venous filling is prolonged (> 15 sec). Edema is usually not present unless the patient has kept the leg immobile and in a dependent position to relieve pain. Patients with chronic PAD may have thin, pale (atrophic) skin with hair thinning or loss. Distal legs and feet may feel cool. The affected leg may sweat excessively and become cyanotic, probably because of sympathetic nerve overactivity.

As ischemia worsens, ulcers may appear (typically on the toes or heel, occasionally on the leg or foot), especially after local trauma. The ulcers tend to be surrounded by black, necrotic tissue (dry gangrene).
They are usually painful, but people with peripheral neuropathy due to diabetes or alcoholism may not feel them. Infection of ischemic ulcers (wet gangrene) occurs readily, causing rapidly progressive cellulitis.

The level of arterial occlusion influences location of symptoms. Aortoiliac PAD may cause buttock, thigh, or calf claudication; hip pain; and, in men, erectile dysfunction (Leriche syndrome). In femoropopliteal PAD, claudication typically occurs in the calf; pulses below the femoral artery are weak or absent. In PAD of more distal arteries, femoropopliteal pulses may be present, but foot pulses are absent.

Arterial occlusive disease occasionally affects the arms, especially the left proximal subclavian artery, causing arm fatigue with exercise and occasionally embolization to the hands.

**Diagnosis**

- Ankle-brachial BP index
- Ultrasonography
- Angiography before surgery

PAD is suspected clinically but is under-recognized because many patients have atypical symptoms or are not active enough to have symptoms. Spinal stenosis may also cause leg pain during walking but can be distinguished because the pain (called pseudo-claudication) requires sitting, not just rest, for relief, and distal pulses remain intact.

Diagnosis is confirmed by noninvasive testing. First, bilateral arm and ankle systolic BP is measured; because ankle pulses may be difficult to palpate, a Doppler probe may be placed over the dorsalis pedis or posterior tibial arteries. Doppler ultrasonography is often used, because pressure gradients and pulse volume waveforms can help distinguish isolated aortoiliac PAD from femoropopliteal PAD and below-the-knee PAD.

A low (≤ 0.90) ankle-brachial index (ratio of ankle to arm systolic BP) indicates PAD, which can be classified as mild (0.71 to 0.90), moderate (0.41 to 0.70), or severe (≤ 0.40). If the index is normal (0.91 to 1.30) but suspicion of PAD remains high, the index is determined after exercise stress testing. A high index (> 1.30) may indicate noncompressible leg vessels (as occurs in Monckeberg's arteriosclerosis with calcification of the arterial wall). If the index is > 1.30 but suspicion of PAD remains high, additional tests (eg, Doppler ultrasonography, measurement of BP in the first toe using toe cuffs) are done to check for arterial stenoses or occlusions. Ischemic lesions are unlikely to heal when systolic BP is < 55 mm Hg in patients without diabetes or < 70 mm Hg in patients with diabetes; below-the-knee amputations usually heal if BP is ≥ 70 mm Hg. Peripheral arterial insufficiency can also be assessed by transcutaneous oximetry (TcO₂). A TcO₂ level < 40 mm Hg is predictive of poor healing, and a value < 20 mm Hg is consistent with critical limb ischemia.

Angiography provides details of the location and extent of arterial stenoses or occlusion; it is a prerequisite for surgical correction or percutaneous transluminal angioplasty (PTA). It is not a substitute for noninvasive testing because it provides no information about the functional significance of abnormal findings. Magnetic resonance angiography and CT angiography are noninvasive tests that may eventually supplant contrast angiography.

**Treatment**

- Risk factor modification
- Exercise
- Antiplatelet drugs
- Sometimes pentoxifylline or cilostazol for claudication
• PTA or surgery for severe disease

All patients require aggressive risk factor modification, including smoking cessation and control of diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia. β-Blockers are safe unless PAD is very severe.

Exercise—35 to 50 min of treadmill or track walking in an exercise-rest-exercise pattern 3 to 4 times/wk—is an important but underused treatment. It can increase symptom-free walking distance and improve quality of life. Mechanisms probably include increased collateral circulation, improved endothelial function with microvascular vasodilation, decreased blood viscosity, improved RBC filterability, decreased ischemia-induced inflammation, and improved O₂ extraction.

Patients are advised to keep the legs below heart level. For pain relief at night, the head of the bed can be elevated about 10 to 15 cm (4 to 6 inches) to improve blood flow to the feet.

Patients are also advised to avoid cold and drugs that cause vasoconstriction (eg, pseudoephedrine, contained in many sinus and cold remedies).

Preventive foot care is crucial, especially for patients with diabetes. It includes daily foot inspection for injuries and lesions; treatment of calluses and corns by a podiatrist; daily washing of the feet in lukewarm water with mild soap, followed by gentle, thorough drying; and avoidance of thermal, chemical, and mechanical injury, especially that due to poorly fitting footwear. For foot ulcer management, see also p. 740.

Antiplatelet drugs may modestly lessen symptoms and improve walking distance; more importantly, these drugs modify atherogenesis and help prevent acute coronary syndromes (see p. 2109) and transient ischemic attacks (see p. 1651). Options include aspirin 81 to 162 mg once/day, aspirin 25 mg plus dipyridamole 200 mg po once/day, and clopidogrel 75 mg po once/day or ticlopidine 250 mg po bid with or without aspirin. Aspirin is typically used alone first, followed by addition or substitution of other drugs if PAD progresses.

For relief of claudication, pentoxifylline 400 mg po tid with meals or cilostazol 100 mg po bid may be used to relieve intermittent claudication by improving blood flow and enhancing tissue oxygenation in affected areas; however, these drugs are no substitute for risk factor modification and exercise. Use of pentoxifylline is controversial because evidence of its effectiveness is mixed. A trial of ≥ 2 mo may be warranted, because adverse effects are uncommon and mild. The most common adverse effects of cilostazol are headache and diarrhea. Cilostazol is contraindicated by severe heart failure.

Other drugs that may relieve claudication are being studied; they include L-arginine (the precursor of endothelium-dependent vasodilator), nitric oxide, vasodilator prostaglandins, and angiogenic growth factors (eg, vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF]). Gene therapy for PAD is also being studied. In patients with severe limb ischemia, long-term parenteral use of vasodilator prostaglandins may decrease pain and facilitate ulcer healing, and intramuscular gene transfer of DNA encoding VEGF may promote collateral blood vessel growth.

**Percutaneous transluminal intervention:** PTA with or without stent insertion is the primary nonsurgical method for dilating vascular occlusions. PTA with stent insertion may keep the artery open better than balloon compression alone, with a lower rate of reclosure. Stents work best in large arteries with high flow (iliac and renal); they are less useful for smaller arteries and for long occlusions.

Indications for PTA are similar to those for surgery: intermittent claudication that inhibits daily activities, rest pain, and gangrene. Suitable lesions are flow-limiting, short iliac stenoses (< 3 cm) and short, single or multiple stenoses of the superficial femoropopliteal segment. Complete occlusions (up to 10 or 12 cm long) of the superficial femoral artery can be successfully dilated, but results are better for occlusions ≤ 5 cm. PTA is also useful for localized iliac stenosis proximal to a bypass of the femoropopliteal artery.

PTA is less useful for diffuse disease, long occlusions, and eccentric calcified plaques. Such lesions are particularly common in patients with diabetes, often affecting small arteries.
Complications of PTA include thrombosis at the site of dilation, distal embolization, intimal dissection with occlusion by a flap, and complications related to heparin use.

With appropriate patient selection (based on complete and adequate angiography), the initial success rate approaches 85 to 95% for iliac arteries and 50 to 70% for thigh and calf arteries. Recurrence rates are relatively high (25 to 35% at ≤ 3 yr); repeat PTA may be successful.

**Surgery:** Surgery is indicated for patients who can safely tolerate a major vascular procedure and whose severe symptoms do not respond to noninvasive treatments. The goal is to relieve symptoms, heal ulcers, and avoid amputation. Because many patients have underlying CAD, which places them at risk of acute coronary syndromes during surgical procedures for PAD, patients usually undergo cardiac evaluation prior to surgery.

Thromboendarterectomy (surgical removal of an occlusive lesion) is used for short, localized lesions in the aortoiliac, common femoral, or deep femoral arteries.

Revascularization (eg, femoropopliteal bypass grafting) uses synthetic or natural materials (often the saphenous or another vein) to bypass occlusive lesions. Revascularization helps prevent limb amputation and relieve claudication.

In patients who cannot undergo major vascular surgery, sympathectomy may be effective when a distal occlusion causes severe ischemic pain. Chemical sympathetic blocks are as effective as surgical sympathectomy, so the latter is rarely done.

Amputation is a procedure of last resort, indicated for uncontrolled infection, unrelenting rest pain, and progressive gangrene. Amputation should be as distal as possible, preserving the knee for optimal use with a prosthesis.

**External compression therapy:** External pneumatic compression of the lower limb to increase distal blood flow is an option for limb salvage in patients who have severe PAD and are not candidates for surgery. Theoretically, it controls edema and improves arterial flow, venous return, and tissue oxygenation, but data supporting its use are lacking. Pneumatic cuffs or stockings are placed on the lower leg and inflated rhythmically during diastole, systole, or part of both periods for 1 to 2 h several times/wk.

**Acute Peripheral Arterial Occlusion**

Peripheral arteries may be acutely occluded by a thrombus, an embolus, aortic dissection, or acute compartment syndrome.

Acute peripheral arterial occlusion may result from rupture and thrombosis of an atherosclerotic plaque, an embolus from the heart or thoracic or abdominal aorta, an aortic dissection, or acute compartment syndrome (see p. 3213).

Symptoms and signs are sudden onset in an extremity of the 5 P’s: severe pain, polar sensation (coldness), paresthesias (or anesthesias), pallor, and pulselessness. The occlusion can be roughly localized to the arterial bifurcation just distal to the last palpable pulse (eg, at the common femoral bifurcation when the femoral pulse is palpable; at the popliteal bifurcation when the popliteal pulse is palpable). Severe cases may cause loss of motor function. After 6 to 8 h, muscles may be tender when palpated.

Diagnosis is clinical. Immediate angiography is required to confirm location of the occlusion, identify collateral flow, and guide therapy.

Treatment consists of embolectomy (catheter or surgical), thrombolysis, or bypass surgery. The decision to do surgical thromboembolectomy vs thrombolysis is based on the severity of ischemia, the extent or location of the thrombus, and the general medical condition of the patient.
A thrombolytic (fibrinolytic) drug, especially when given by regional catheter infusion, is most effective for patients with acute arterial occlusions of < 2 wk and intact motor and sensory limb function. Tissue plasminogen activator and urokinase are most commonly used. A catheter is threaded to the occluded area, and the thrombolytic drug is given at a rate appropriate for the patient’s size and the extent of thrombosis. Treatment is usually continued for 4 to 24 h, depending on severity of ischemia and signs of thrombolysis (relief of symptoms and return of pulses or improved blood flow shown by Doppler ultrasonography). About 20 to 30% of patients with acute arterial occlusion require amputation within the first 30 days.

**Raynaud’s Syndrome**

Raynaud’s syndrome is vasospasm of parts of the hand in response to cold or emotional stress, causing reversible discomfort and color changes (pallor, cyanosis, erythema, or a combination) in one or more digits. Occasionally, other acral parts (eg, nose, tongue) are affected. The disorder may be primary or secondary. Diagnosis is clinical; testing focuses on distinguishing primary from secondary disease. Treatment of uncomplicated cases includes avoidance of cold, biofeedback, smoking cessation, and, as needed, vasodilating Ca channel blockers (eg, nifedipine) or prazosin.

Overall prevalence is about 3 to 5%; women are affected more than men, and younger people are affected more than older people. Raynaud’s syndrome is probably due to an exaggerated α2-adrenergic response that triggers vasospasm; the mechanism is not defined.

Primary Raynaud’s syndrome is much more common (> 80% of cases) than secondary; it occurs without symptoms or signs of other disorders. In the remaining 20% of patients with Raynaud’s symptoms, a causative underlying disease (eg, systemic sclerosis) will be evident at initial presentation or diagnosed subsequently.

Secondary Raynaud’s syndrome accompanies various disorders and conditions, mostly connective tissue disorders (see Table 218-1).

Nicotine commonly contributes to it but is often overlooked. Raynaud’s syndrome may accompany migraine headaches, variant angina, and pulmonary hypertension, suggesting that these disorders share a common vasospastic mechanism.

**Symptoms and Signs**

Sensations of coldness, burning pain, paresthesias, or intermittent color changes of one or more digits are precipitated by exposure to cold, emotional stress, or vibration. All can be reversed by removing the stimulus. Re-warming the hands accelerates restoration of normal color and sensation.

Color changes are clearly demarcated across the digit. They may be triphasic (pallor, followed by cyanosis and after warming by erythema due to reactive hyperemia), biphasic (cyanosis, erythema), or uniphasic (pallor or cyanosis only). Changes are often symmetric. Raynaud’s syndrome does not occur proximal to the metacarpophalangeal joints; it most commonly affects the middle 3 fingers and rarely affects the thumb. Vasospasm may last minutes to hours but is rarely severe enough to cause tissue loss.

[Table 218-1. Causes of Secondary Raynaud’s Syndrome]

Raynaud’s syndrome secondary to a connective tissue disorder may progress to painful digital gangrene; Raynaud’s syndrome secondary to systemic sclerosis tends to cause extremely painful, infected ulcers on the fingertips.

**Diagnosis**

• Clinical criteria
Examination and testing for underlying disorder

Raynaud's syndrome itself is diagnosed clinically. Acrocyanosis (see p. 2216) also causes color change of the digits in response to cold but differs from Raynaud's in that it is persistent, not easily reversed, and does not cause trophic changes, ulcers, or pain.

Primary and secondary forms are distinguished clinically, supported by vascular laboratory studies and blood testing. Vascular laboratory testing includes digital pulse wave forms and pressures. The primary blood testing is the panel for collagen vascular diseases.

Clinical findings: A thorough history and physical examination directed at identifying a causative disorder are helpful but rarely diagnostic.

Findings suggesting primary Raynaud's syndrome are the following:

- Age at onset < 40 (in two thirds of cases)
- Mild symmetric attacks affecting both hands
- No tissue necrosis or gangrene
- No history or physical findings suggesting another cause

Findings suggesting secondary Raynaud's syndrome are the following:

- Age at onset > 30
- Severe painful attacks that may be asymmetric and unilateral
- Ischemic lesions
- History and findings suggesting an accompanying disorder

Laboratory testing: Blood tests (eg, measurement of ESR, antinuclear antibodies, rheumatoid factor, anticentromere antibody, anti-SCL-70 antibody) are done to detect accompanying disorders.

Treatment

- Trigger avoidance
- Smoking cessation
- Ca channel blockers or prazosin

Treatment of the primary form involves avoidance of cold, smoking cessation, and, if stress is a triggering factor, relaxation techniques (eg, biofeedback) or counseling. Drugs are used more often than behavioral treatments because of convenience. Vasodilating Ca channel blockers (extended-release nifedipine 60 to 90 mg po once/day, amlopidine 5 to 20 mg po once/day, felodipine 2.5 to 10 mg po bid, or isradipine 2.5 to 5 mg po bid) are most effective, followed by prazosin 1 to 5 mg po once/day or bid. Topical nitroglycerine paste, pentoxifylline 400 mg po bid or tid with meals, or both may be effective, but no evidence supports routine use. β-Blockers, clonidine, and ergot preparations are contraindicated because they cause vasoconstriction and may trigger or worsen symptoms.

Treatment of the secondary form focuses on the underlying disorder. Ca channel blockers or prazosin is also indicated. Antibiotics, analgesics, and, occasionally, surgical debridement may be necessary for ischemic ulcers. Low-dose aspirin may prevent thrombosis but theoretically may worsen vasospasm via prostaglandin inhibition. IV prostaglandins (alprostadil, epoprostenol, iloprost) appear to be effective and may be an option for patients with ischemic digits. However, these drugs are not yet widely available, and
their role is yet to be defined. Cervical or local sympathectomy is controversial; it is reserved for patients with progressive disability unresponsive to all other measures, including treatment of underlying disorders. Sympathectomy often abolishes the symptoms, but relief may last only 1 to 2 yr.

**Thromboangiitis Obliterans**

(Buerger’s Disease)

Thromboangiitis obliterans is inflammatory thrombosis of small and medium-sized arteries and some superficial veins, causing arterial ischemia in distal extremities and superficial thrombophlebitis. Tobacco use is the primary risk factor. Symptoms and signs include claudication, nonhealing foot ulcers, rest pain, and gangrene. Diagnosis is by clinical findings, noninvasive vascular testing, angiography, and exclusion of other causes. Treatment is cessation of tobacco use. Prognosis is excellent when tobacco use is stopped, but when it is not, the disorder inevitably progresses, often requiring amputation.

Thromboangiitis obliterans occurs almost exclusively in tobacco users (nearly all of them smokers) and predominantly affects men aged 20 to 40; it rarely occurs in women. It occurs more commonly in people with HLA-A9 and HLA-B5 genotypes. Prevalence is highest in Asia and the Far and Middle East.

Thromboangiitis obliterans produces segmental inflammation in small and medium-sized arteries and, frequently, in superficial veins of the extremities. In acute thromboangiitis obliterans, occlusive thrombi accompany neutrophilic and lymphocytic infiltration of the intima; endothelial cells proliferate, but the internal elastic lamina remains intact. In an intermediate phase, thrombi organize and recanalize incompletely; the media is preserved but may be infiltrated with fibroblasts. In older lesions, periarterial fibrosis may occur, sometimes affecting the adjacent vein and nerve.

The cause is unknown, although cigarette smoking is a primary risk factor. The mechanism may involve delayed hypersensitivity or toxic angiitis. According to another theory, thromboangiitis obliterans may be an autoimmune disorder caused by cell-mediated sensitivity to types I and III human collagen, which are constituents of blood vessels.

**Symptoms and Signs**

Symptoms and signs are those of arterial ischemia and superficial thrombophlebitis. Some patients have a history of migratory phlebitis, usually in the superficial veins of a foot or leg.

Onset is gradual, starting in the most distal vessels of the upper and lower extremities with coldness, numbness, tingling, or burning. These symptoms may develop before objective evidence of disease. Raynaud’s syndrome is common. Intermittent claudication occurs in the affected extremity (usually in the arch of the foot or in the leg; rarely in the hand, arm, or thigh) and may progress to rest pain. Frequently, if pain is severe and persistent, the affected leg feels cold, sweats excessively, and becomes cyanotic, probably because of sympathetic nerve overactivity. Later, ischemic ulcers develop in most patients and may progress to gangrene.

Pulses are impaired or absent in one or more pedal arteries and often at the wrist. In young men who smoke and have extremity ulcers, a positive Allen’s test (the hand remains pale after the examiner simultaneously compresses the radial and ulnar arteries, then alternately releases them) suggests the disorder. Pallor with elevation and rubor with dependency frequently occur in affected hands, feet, or digits. Ischemic ulceration and gangrene, usually of one or more digits, may occur early in the disorder but not acutely. Noninvasive tests show greatly decreased blood flow and pressure in the affected toes, feet, and fingers.

**Diagnosis**

- Other causes of ischemia excluded by testing
- Angiography
History and physical examination suggest the diagnosis. It is confirmed when the ankle-brachial index (ratio of ankle to arm systolic BP) for legs or segmental pressures for arms indicates distal ischemia, when echocardiography excludes cardiac emboli, when blood tests (eg, measurement of antinuclear antibody, rheumatoid factor, complement, anticentromere antibody, anti-SCL-70 antibody) exclude vasculitis, when tests for antiphospholipid antibodies exclude antiphospholipid antibody syndrome (although these levels may be slightly elevated in thromboangiitis obliterans), and when angiography shows characteristic findings (segmental occlusions of the distal arteries in the hands and feet, tortuous, corkscrew collateral vessels around occlusions, and no atherosclerosis).

**Treatment**

- Smoking cessation
- Local measures
- Sometimes drug therapy

Treatment is cessation of tobacco use (see p. 3432). Continuing to use tobacco inevitably leads to disease progression and severe ischemia, often requiring amputation.

Other measures include avoiding cold; avoiding drugs that can cause vasoconstriction; and avoiding thermal, chemical, and mechanical injury, especially that due to poorly fitting footwear. For patients in the first phase of smoking cessation, iloprost 0.5 to 3 ng/kg/min IV infusion over 6 h may help prevent amputation. Pentoxifylline, Ca channel blockers, and thromboxane inhibitors may be tried empirically, but no data support their use. Use of antiendothelial cell antibody measurements to follow the course of disease is being studied. When these options fail, lumbar sympathetic chemical ablation or surgical sympathectomy can alleviate ischemic pain and enhance ulcer healing in about 70% of patients with an ankle-brachial pressure index ≥ 0.35 and no diabetes mellitus.
Chapter 219. Peripheral Venous and Lymphatic Disorders

Introduction

Venous and lymphatic disorders usually involve impairment of flow, abnormal vessel dilation, or both.

Deep Venous Thrombosis

Deep venous thrombosis (DVT) is clotting of blood in a deep vein of an extremity (usually calf or thigh) or the pelvis. DVT is the primary cause of pulmonary embolism. DVT results from conditions that impair venous return, lead to endothelial injury or dysfunction, or cause hypercoagulability. DVT may be asymptomatic or cause pain and swelling in an extremity. Diagnosis is by history, physical examination, and duplex ultrasonography, with D-dimer or other testing as necessary. Treatment is with anticoagulants. Prognosis is generally good with prompt, adequate treatment. Common long-term complications include venous insufficiency with or without postphlebitic syndrome.

DVT occurs most commonly in the lower extremities, or pelvis (see Fig. 219-1). It can also develop in deep veins of the upper extremities (4 to 13% of DVT cases).

Lower extremity DVT is much more likely to cause pulmonary embolism (PE), possibly because of the higher clot burden. The superficial femoral and popliteal veins in the thighs and the posterior tibial veins in the calves are most commonly affected. Calf vein DVT is less likely to be a source of large emboli but can cause repeated showers of small emboli or propagate to the proximal thigh veins and from there cause PE. About 50% of patients with DVT have occult PE, and at least 30% with PE have demonstrable DVT.

Etiology

Many factors can contribute to DVT (see Table 219-1). Cancer is a risk factor for DVT, particularly in elderly patients and in patients with recurrent thrombosis. The association is strongest for mucin-secreting endothelial cell tumors. Occult cancers may be present in patients with apparently idiopathic DVT, but extensive workup of patients for tumors is not recommended.

Pathophysiology

Lower extremity DVT most often results from impaired venous return (eg, in immobilized patients), endothelial injury or dysfunction (eg, after leg fractures), or hypercoagulability.

Upper extremity DVT most often results from endothelial injury due to central venous catheters, pacemakers, or injection drug use. Upper extremity DVT occasionally occurs as part of superior vena cava (SVC) syndrome or results from a hypercoagulable state or subclavian vein compression at the thoracic outlet. The compression may be due to a normal or an accessory first rib or fibrous band (thoracic outlet syndrome) or occur during strenuous arm activity (effort thrombosis, or Paget Schroetter syndrome, which accounts for 1 to 4% of upper extremity DVT cases).

DVT usually begins in venous valve cusps. Thrombi consist of thrombin, fibrin, and RBCs with relatively few platelets (red thrombi); without treatment, thrombi may propagate proximally or travel to the lungs.

Complications: Common complications include chronic venous insufficiency and postphlebitic syndrome, as well as PE.

Much less commonly, acute DVT leads to phlegmasia alba dolens or phlegmasia cerulea dolens, both of which, unless promptly diagnosed and treated, can result in venous gangrene.
In **phlegmasia alba dolens**, a rare complication of DVT during pregnancy, the leg turns milky white. Pathophysiology is unclear, but edema may increase soft-tissue pressure beyond capillary perfusion pressures, resulting in tissue ischemia and wet gangrene.

In **phlegmasia cerulea dolens**, massive iliofemoral venous thrombosis causes near-total venous occlusion; the leg becomes ischemic, extremely painful, and cyanotic. Pathophysiology may involve complete stasis of venous and arterial blood flow in the lower extremity because venous return is occluded or massive edema cuts off arterial blood flow. Venous gangrene may result.

Rarely, venous clots can become infected. Jugular vein supplicative thrombophlebitis (Lemierre syndrome), a bacterial (usually anaerobic) infection of the internal jugular vein and surrounding soft tissues, may follow tonsillitis and is often complicated by bacteremia and sepsis. In septic pelvic thrombophlebitis, pelvic thromboses develop postpartum and become infected, causing intermittent fever. Suppurative (septic) thrombophlebitis, a bacterial infection of a superficial peripheral vein, is infection and clotting usually caused by venous catheterization.

**Symptoms and Signs**

DVT may occur in ambulatory patients or as a complication of surgery or major medical illness. Among high-risk hospitalized patients, most deep vein thrombi occur in the small calf veins, are asymptomatic, and are never detected.

When present, symptoms and signs (eg, vague aching pain, tenderness along the distribution of the veins, edema, erythema) are nonspecific, vary in frequency and severity, and are similar in arms and legs. Dilated collateral superficial veins may become visible or palpable. Calf discomfort elicited by ankle dorsiflexion with the knee extended (Homans' sign) occasionally occurs with distal leg DVT but is neither sensitive nor specific. Tenderness, swelling of the whole leg, > 3 cm difference in circumference between calves, pitting edema, and collateral superficial veins may be most specific; DVT is likely with a combination of ≥ 3 in the absence of another likely diagnosis (see **Table 219-2**).

Low-grade fever may be present; DVT may be the cause of fever without an obvious source, especially in postoperative patients. If PE occurs, symptoms may include shortness of breath and pleuritic chest pain (see p. 1909).

Common causes of asymmetric leg swelling that mimic DVT are soft-tissue trauma, cellulitis, pelvic venous or lymphatic obstruction, and popliteal bursitis (Baker's cyst) that obstructs venous return. Abdominal or pelvic tumors that obstruct venous or lymphatic return are less common causes. Use of drugs that cause dependent edema (eg, dihydropyridine Ca channel blockers, estrogen, high-dose opioids), venous hypertension (usually due to right heart failure), and hypoalbuminemia cause symmetric bilateral leg swelling; swelling may be asymmetric if venous insufficiency coexists and is worse in one leg.

Common causes of calf pain that mimic acute DVT include venous insufficiency and postphlebitic syndrome; cellulitis that causes painful erythema of the calf; ruptured popliteal (Baker's) cyst (pseudo-DVT), which causes calf swelling, pain, and sometimes bruising in the region of the medial malleolus; and partial or complete tears of the calf muscles or tendons.

**Diagnosis**

- Ultrasonography
- Sometimes D-dimer testing
History and physical examination help determine probability of DVT before testing (see Table 219-2). Diagnosis is typically by ultrasonography with Doppler flow studies (duplex ultrasonography). The need for additional tests (eg, D-dimer testing) and their choice and sequence depend on pretest probability and sometimes ultrasonography results. No single testing protocol is best; one approach is described in Fig. 219-2.

**Ultrasonography:** Ultrasonography identifies thrombi by directly visualizing the venous lining and by demonstrating abnormal vein compressibility or, with Doppler flow studies, impaired venous flow. The test is > 90% sensitive and > 95% specific for femoral and popliteal vein thrombosis but is less accurate for iliac or calf vein thrombosis.

**D-Dimer:** D-Dimer is a byproduct of fibrinolysis; elevated levels suggest recent presence and lysis of thrombi. D-dimer assays vary in sensitivity and specificity; however, most are sensitive and not specific. Only the most accurate tests should be used. For example, a highly sensitive test is enzyme-linked immunosorbent assay (ELISA), which has a sensitivity of about 95%.

If pretest probability of DVT is low, DVT can be safely excluded in patients with a normal D-dimer level on a sensitive test. Thus, a negative D-dimer test can identify patients who have a low probability of DVT and do not require ultrasonography. However, a positive test result is nonspecific; because levels can be elevated by other conditions (eg, liver disease, trauma, pregnancy, positive rheumatoid factor, inflammation, recent surgery, cancer), further testing is necessary.

If pretest probability of DVT is moderate or high, D-dimer testing can be done at the same time as duplex ultrasonography. A positive ultrasound result confirms the diagnosis regardless of the D-dimer level. If ultrasonography does not reveal evidence of DVT, a normal D-dimer level helps exclude DVT. Patients with an elevated D-dimer level should have repeat ultrasonography in a few days or possibly immediate venography depending on clinical suspicion. Newer latex qualitative assays are highly specific (up to about 99%) but should not yet be used to confirm DVT without ultrasonography.

**Venography:** Contrast venography was the definitive test for the diagnosis of DVT but has been largely replaced by ultrasonography, which is noninvasive, more readily available, and almost equally accurate for detecting DVT. Venography may be indicated when ultrasonography results are normal but pretest suspicion for DVT is high. The complication rate is 2%, mostly because of contrast dye allergy.

**Other testing:** Noninvasive alternatives to contrast venography are being studied. They include magnetic resonance venography and direct MRI of thrombi using T1-weighted gradient-echo sequencing and a water-excitation radiofrequency pulse; theoretically, the latter test can provide simultaneous views of thrombi in deep veins and subsegmental pulmonary arteries (for diagnosis of PE).

If symptoms and signs suggest PE, additional imaging (eg, ventilation/perfusion [V/Q] scanning or helical CT) is required.

**Determination of cause:** Patients with confirmed DVT and an obvious cause (eg, immobilization, surgical procedure, leg trauma) need no further testing. Testing to detect hypercoagulability is controversial but is sometimes done in patients who have idiopathic recurrent DVT, in patients who have a personal or family history of other thromboses, and in young patients with no obvious predisposing factors. Some evidence suggests that presence of hypercoagulability does not predict DVT recurrence as well as clinical risk factors.

Screening patients with DVT for cancer has a low yield. Selective testing guided by complete history and physical examination aimed at detecting cancer is probably adequate.

**Prognosis**

Without adequate treatment, lower extremity DVT has a 3% risk of fatal PE; death due to upper extremity
DVT is very rare. Risk of recurrent DVT is lowest for patients with transient risk factors (eg, surgery, trauma, temporary immobility) and greatest for patients with persistent risk factors (eg, heart failure, cancer), idiopathic DVT, or incomplete resolution of past DVT (residual thrombus). A normal D-dimer level obtained after warfarin is stopped may help predict a relatively low risk of DVT or PE recurrence. Risk of venous insufficiency is impossible to predict. Risk factors for post-phlebitic syndrome include proximal thrombosis, recurrent ipsilateral DVT, and body mass index (BMI) $\geq 22$ kg/m$^2$.

**Treatment**

- **Anticoagulation**

Treatment is aimed primarily at PE prevention (see also p. 1920) and secondarily at symptom relief and prevention of DVT recurrence, chronic venous insufficiency, and post-phlebitic syndrome. Treatment of lower and upper extremity DVT is generally the same.

All patients with DVT are given anticoagulants, initially an injectable heparin (unfractionated or low molecular weight), followed by warfarin started within 24 to 48 h. Inadequate anticoagulation in the first 24 h may increase risk of recurrence or PE. Acute DVT can be treated on an outpatient basis unless severe symptoms require parenteral analgesics, other disorders preclude safe outpatient discharge, or other factors (eg, functional, socioeconomic) might prevent the patient from adhering to prescribed treatments. General supportive measures include pain control with analgesics other than aspirin and NSAIDs (because of their antiplatelet effects) and, during periods of inactivity, elevation of legs (supported by a pillow or other soft surface to avoid venous compression). Patients may be as physically active as they can tolerate; there is no evidence that early activity increases risk of clot dislodgement and PE.

**Anticoagulants:** The anticoagulants most often used are the following:

- Low molecular weight heparins (LMWHs)
- Unfractionated heparin (UFH)
- Fondaparinux
- Warfarin

LMWHs (eg, enoxaparin, dalteparin, tinzaparin—see Table 194-3 on p. 1917) are the initial treatment of choice because they can be given on an outpatient basis. LMWHs are as effective as UFH for reducing DVT recurrence, thrombus extension, and risk of death due to PE. Like UFH, LMWHs catalyze the action of antithrombin (which inhibits coagulation factor proteases), leading to inactivation of coagulation factor Xa and, to a lesser degree, factor IIa. LMWHs also have some antithrombin-mediated anti-inflammatory properties, which facilitate clot organization and resolution of symptoms and inflammation.

LMWHs are typically given sc in a standard weight-based dose (eg, enoxaparin 1.5 mg/kg sc once/day or 1 mg/kg sc q 12 h or dalteparin 200 units/kg sc once/day). Patients with renal insufficiency may be treated with UFH or with reduced doses of LMWH. Monitoring is not reliable because LMWHs do not significantly prolong the results of global tests of coagulation. Furthermore, they have a predictable dose response, and there is no clear relationship between LMWH overdose and bleeding. Treatment is continued until full anticoagulation is achieved with warfarin. However, evidence suggests that LMWH is effective for long-term DVT treatment in high-risk patients, such as those with cancer. Thus, LMWH may become an acceptable alternative to warfarin for some patients, although warfarin is likely to be the treatment of choice for most patients because of its low cost and oral route of administration.

UFH may be used instead of LMWH for hospitalized patients and for patients who have renal insufficiency or failure (creatinine clearance 10 to 30 mL/min) because UFH is not cleared by the kidneys. UFH is given as a bolus and infusion (see Fig. 194-2 on p. 1916) to achieve full anticoagulation, (eg, activated PTT [aPTT] 1.5 to 2.5 times that of the reference range). UFH 333 units/kg initial bolus, then 250 units/kg sc q 12 h can be substituted for IV
Complications of heparin include bleeding, thrombocytopenia (less common with LMWHs), urticaria, and, rarely, thrombosis and anaphylaxis. Long-term use of UFH causes hypokalemia, liver enzyme elevations, and osteoporosis. Rarely, UFH given sc causes skin necrosis. Inpatients and possibly outpatients should be screened for bleeding with serial CBCs and tests for occult blood in stool. Bleeding due to overheparinization can be stopped with protamine sulfate. The dose is 1 mg protamine for each milligram of LMWH given as 1 mg in 20 mL of normal saline infused slowly over 10 to 20 min. If a 2nd dose is required, it should be at one half the first dose. However, the precise dose is undefined because protamine only partially neutralizes LMWH inactivation of factor Xa. With all infusions, the patient should be observed for hypotension and a reaction similar to an anaphylactic reaction. Because UFH given IV has a half-life of 30 to 60 min, protamine is not given to patients receiving UFH (eg, if UFH was given > 60 min beforehand) or is given at a dose based on the amount of heparin estimated to be remaining in plasma, based on the half-life of UFH.

Fondaparinux, a selective factor Xa inhibitor, may be used as an alternative to UFH or LMWH for the initial treatment of DVT or PE. It is given in a fixed dose of 7.5 mg sc once/day (10 mg for patients > 100 kg, 5 mg for patients < 50 kg). It has the advantage of fixed dosing and is less likely to cause thrombocytopenia.

Vitamin K antagonists, including warfarin, are the drugs of choice for long-term anticoagulation for all patients except pregnant women (who should continue to take heparin) and patients who have had new or worsening venous thromboembolism during warfarin treatment (who may be candidates for an inferior vena cava filter). Warfarin 5 to 10 mg can be started immediately with heparin. The elderly and patients with a liver disorder typically require lower warfarin doses. Therapeutic goal is an INR of 2.0 to 3.0. INR is monitored weekly for the first 1 to 2 mo of warfarin treatment and monthly thereafter; the dose is increased or decreased by 0.5 to 3 mg to maintain the INR within this range. Patients taking warfarin should be informed of possible drug interactions, including interactions with foods and nonprescription medicinal herbs (see Table 194-4 on p. 1917).

Patients with transient risk factors for DVT (eg, immobilization, surgery) can stop taking warfarin after 3 to 6 mo. Patients with non-modifiable risk factors (eg, hypercoagulability), spontaneous DVT with no known risk factors, or recurrent DVT should take warfarin for at least 6 mo and probably for life unless complications occur.

Bleeding is the most common complication. Risk factors for severe bleeding (defined as life-threatening hemorrhage or loss of ≥ 2 units of blood in ≤ 7 days) include age ≥ 65; history of prior GI bleeding or stroke; recent MI; and coexisting anemia (Hct < 30%), renal insufficiency (serum creatinine > 1.5 mg/dL), or diabetes. Anticoagulation can be reversed with vitamin K; the dose is 1 to 4 mg po if INR is 5 to 9, 5 mg po if INR is > 9, and 10 mg IV (given slowly to avoid anaphylaxis) if hemorrhage occurs. If hemorrhage is severe, a transfusion of coagulation factors, fresh frozen plasma, or prothrombin complex concentrate should also be given. Overanticoagulation (INR > 3 or 4) without bleeding can be managed by omitting several warfarin doses and more frequent INR monitoring, then giving warfarin at a lower dose. Rarely, warfarin causes skin necrosis in patients with protein C or S deficiency or factor V Leiden mutations.

Other anticoagulants, such as direct thrombin inhibitors (DTIs, eg, hirudin given sc; lepirudin, bivalirudin, desirudin, argatroban, given parenterally; dabigatran given po) and oral factor Xa inhibitors (eg, rivaroxaban and apixaban) are being evaluated for the treatment of DVT (see Table 194-6 on p. 1921).

Inferior vena cava filter (IVCF): An IVCF may help prevent PE in patients with lower extremity DVT and contraindications to anticoagulants or with recurrent DVT (or emboli) despite adequate anticoagulation. An IVCF is placed in the inferior vena cava just below the renal veins via catheterization of an internal jugular or femoral vein. Some IVCFs are removable and can be used temporarily (eg, until contraindications to anticoagulation subside or resolve). IVCFs reduce risk of acute and subacute thrombotic complications but can have longer-term complications (eg, venous collaterals can develop,
providing a pathway for emboli to circumvent the IVCF). Also, IVCFs can dislodge or become obstructed by clot. Thus, patients with recurrent DVT or nonmodifiable risk factors for DVT may still require anticoagulation. A clotted filter may cause bilateral lower extremity venous congestion (including acute phlegmasia cerulea dolens), lower body ischemia, and acute renal failure. Treatment for a dislodged filter is removal, using angiographic, or, if necessary, surgical methods. Despite widespread use of IVCFs, efficacy in preventing PE is unstudied and unproved.

**Thrombolytic (fibrinolytic) drugs**: Streptokinase, urokinase, and alteplase lyse clots and appear to more effectively prevent post-phlebitic syndrome than heparin alone, but risk of bleeding is higher. Their use is under study. Thrombolytics may be indicated for large proximal thrombi, especially those in the iliofemoral veins, and for phlegmasia alba or cerulea dolens. Local perfusion with an indwelling catheter may be preferable to IV administration.

**Surgery**: Surgery is rarely needed. However, thrombectomy, fasciotomy, or both are mandatory for phlegmasia alba or cerulea dolens unresponsive to thrombolytics to try to prevent limb-threatening gangrene.

**Prevention**

- **Prevention of immobility**
- **Assessment of risk**
- **Anticoagulation (eg, LMWH, fondaparinux, adjusted-dose warfarin)**
- **Intermittent pneumatic compression**
- **IVCF**

Patients at low risk of DVT (eg, those who are undergoing minor surgery but have no clinical risk factors for DVT; those who must be temporarily inactive for long periods, as during an airplane flight) should be encouraged to walk or otherwise move their legs periodically; no medical treatment is needed. Dorsiflexion 10 times/h is probably sufficient.

Patients at higher risk of DVT (eg, those undergoing minor surgery if they have clinical risk factors for DVT; those undergoing major surgery, especially orthopedic surgery, even without risk factors; bedbound patients with major medical illnesses) require additional preventive treatment (see Table 194-5 on p. 1920). Most of these patients can be identified and should receive thrombosis prophylaxis.

After surgery, elevating the legs and avoiding sitting in chairs (which, by placing the legs in a dependent position, impedes venous return) can help. Additional treatment may involve low-dose UFH, LMWH, warfarin, newer anticoagulants such as fondaparinux, compression devices or stockings, or a combination, depending on patient's risk level, type of surgery (if applicable), projected duration of preventive treatment, contraindications, adverse effects, relative cost, ease of use, and local practice. Low-dose UFH 5000 units sc is given 2 h before surgery and q 8 to 12 h thereafter for 7 to 10 days or until patients are fully ambulatory. Bedbound patients who are not undergoing surgery are given 5000 units sc q 12 h until risk factors are reversed.

LMWHs are more effective than low-dose UFH for preventing DVT and PE, but widespread use is limited by cost. For example, enoxaparin 30 mg sc q 12 h, dalteparin 2500 units once/day, and tinzaparin 3500 units once/day are equally effective. Fondaparinux, 2.5 mg once/day, is equal to or more effective than LMWH depending on the surgical setting (eg, orthopedic surgery).

Warfarin, using a target INR of 2.0 to 3.0, is proven to be effective in orthopedic surgery.

Newer anticoagulants (eg, hirudin, lepirudin) are effective for preventing DVT and PE, but their cost-effectiveness and safety compared with heparin and warfarin require further study. Aspirin is better than
placebo but worse than all other available drugs for preventing DVT and PE and is not recommended as the sole method of prevention (see Table 194-5 on p. 1920).

Intermittent pneumatic compression (IPC) uses a pump to cyclically inflate and deflate hollow plastic legging, providing external compression to the lower legs and sometimes thighs. IPC may be used instead of or with anticoagulants before and during surgery. IPC is recommended after knee surgery. IPC is probably more effective for preventing calf than proximal DVT. IPC is usually contraindicated in obese patients and can theoretically trigger PE in immobilized patients who, without preventive treatment, develop occult DVT.

The benefit of graded compression stockings is questionable except for low-risk surgical patients. However, combining stockings with other preventive measures may be more protective than any single approach.

For elective neurosurgery, spinal cord injury, or multiple trauma, low-dose UFH (q 8 h), LMWH, or adjusted-dose warfarin is recommended. For hip and other lower extremity orthopedic surgery, LMWH, fondaparinux, or adjusted-dose warfarin is recommended. For patients undergoing total knee replacement and some other high-risk patients, IPC is also beneficial. For orthopedic surgery, preventive treatment may be started before or after surgery and continued for at least 14 days. Fondaparinux 2.5 mg once/day is more effective than LMWH for orthopedic surgery. For neurosurgery patients, physical measures (IPC, elastic stockings) have been used because intracranial bleeding is a concern; however, LMWH appears to be an acceptable alternative. Limited data support the combination of IPC, elastic stockings, and LMWH in patients with spinal cord injury or multiple trauma.

For patients who are at very high risk of venous thromboembolism and bleeding and are taking anticoagulants, IVCF placement is an option.

Preventive treatment is also indicated for patients who have a major medical illnesses requiring bed rest (eg, MI, ischemic stroke). Low-dose UFH is effective in patients who are not already receiving IV heparin or thrombolytics; IPC, elastic stockings, or both may be used when anticoagulants are contraindicated. After a stroke, low-dose UFH or LMWH can be used; IPC, elastic stockings, or both may be beneficial. Other recommendations include low-dose UFH for patients with heart failure, warfarin (target INR 2.0 to 3.0) for those with metastatic breast cancer, and warfarin 1 mg once/day for those with cancer and an indwelling central venous catheter. Fondaparinux 2.5 mg once/day is also recommended in patients with major medical illnesses.

In patients with symptomatic DVT, primary prevention of venous insufficiency and postphlebitic syndrome is recommended; knee-high compression stockings providing 30 to 40 mm Hg pressure are used.

**Chronic Venous Insufficiency and Postphlebitic Syndrome**

Chronic venous insufficiency is impaired venous return, sometimes causing lower extremity discomfort, edema, and skin changes. Postphlebitic (postthrombotic) syndrome is symptomatic chronic venous insufficiency after deep venous thrombosis (DVT). Causes of chronic venous insufficiency are disorders that result in venous hypertension, usually through venous damage or incompetence of venous valves, as occurs (for example) after DVT. Diagnosis is by history, physical examination, and duplex ultrasonography. Treatment is compression, wound care, and, rarely, surgery. Prevention requires adequate treatment of DVT and compression stockings.

Chronic venous insufficiency affects up to 5% of people in the US. Postphlebitic syndrome may affect one fifth to two thirds of patients with DVT, usually within 1 to 2 yr after acute DVT.

**Etiology**

Venous return from the lower extremities relies on contraction of calf muscles to push blood from intramuscular (soleal) sinusoids and gastrocnemius veins into and through deep veins. Venous valves direct blood proximally to the heart. Chronic venous insufficiency occurs when venous obstruction (eg, in DVT), venous valvular insufficiency, or decreased contraction of muscles surrounding the veins (eg, due
to immobility) decrease forward venous flow and increase venous pressure (venous hypertension). Fluid accumulation in the lower extremities (eg, in right heart failure) can also contribute by causing venous hypertension. Prolonged venous hypertension causes tissue edema, inflammation, and hypoxia, leading to symptoms. Pressure may be transmitted to superficial veins if valves in perforator veins, which connect deep and superficial veins, are ineffective.

DVT is the most common identifiable risk factor for chronic venous insufficiency, followed by trauma, age, and obesity. Idiopathic cases are often attributed to a history of occult DVT.

Symptomatic chronic venous insufficiency that follows DVT is referred to as postphlebitic (or postthrombotic) syndrome. Risk factors for postphlebitic syndrome in patients with DVT include proximal thrombosis, recurrent ipsilateral DVT, and body mass index (BMI) ≥ 22 kg/m². Age, female sex, and estrogen therapy are also associated with the syndrome but are probably nonspecific. Use of compression stockings after DVT decreases risk.

Symptoms and Signs

Clinically evident chronic venous insufficiency may not cause any symptoms but always causes signs; postphlebitic syndrome always causes symptoms. Both disorders are a concern because their symptoms can mimic those of acute DVT and both can lead to substantial reductions in physical activity and quality of life.

Symptoms include a sense of fullness, heaviness, aching, cramps, pain, tiredness, and paresthesias in the legs; these symptoms worsen with standing or walking and are relieved by rest and elevation. Pruritus may accompany skin changes. Signs occur along a continuum: no changes to varicose veins (rare) to stasis dermatitis on the lower legs and at the ankles, with or without ulceration (see Table 219-3). The calf may be painful when compressed.

Venous stasis dermatitis consists of reddish brown hyperpigmentation, induration, venous ectasia, lipodermatosclerosis (fibrosing subcutaneous panniculitis), and venous stasis ulcers.

Venous stasis ulcers may develop spontaneously or after affected skin is scratched or injured. They typically occur around the medial malleolus, tend to be shallow and moist, and may be malodorous (especially when poorly cared for) or painful. They do not penetrate the deep fascia. In contrast, ulcers due to peripheral arterial disease eventually expose tendons or bone.

Leg edema tends to be unilateral or asymmetric; bilateral symmetric edema is more likely to result from a systemic disorder (eg, heart failure, hypoalbuminemia) or certain drugs (eg, Ca channel blockers).

In general, unless the lower extremities are adequately cared for, patients with any manifestation of chronic venous insufficiency or postphlebitic syndrome are at risk of progression to more advanced forms.

[Table 219-3. Clinical Classification of Chronic Venous Insufficiency]

Diagnosis

• Clinical diagnosis

• Ultrasonography to exclude DVT

Diagnosis is usually based on history and physical examination. A clinical scoring system that ranks 5 symptoms (pain, cramps, heaviness, pruritus, paresthesia) and 6 signs (edema, hyperpigmentation, induration, venous ectasia, blanching hyperemia, pain with calf compression) on a scale of 0 (absent or minimal) to 3 (severe) is increasingly recognized as a standard diagnostic tool of disease severity. Scores of 5 to 14 on 2 visits separated by ≥ 6 mo indicate mild-to-moderate disease, and scores of ≥ 15 indicate severe disease.

Lower-extremity duplex ultrasonography helps exclude DVT. Absence of edema and a reduced ankle-
brachial index suggest peripheral arterial disease rather than chronic venous insufficiency and postphlebitic syndrome.

**Treatment**

- Elevation

- Compression

- Topical treatments

Treatment involves leg elevation; compression using bandages, stockings, and pneumatic devices; topical wound care; and surgery, depending on the disorder's severity. Some experts believe that weight loss, regular exercise, and reduction of dietary sodium may benefit patients with bilateral chronic venous insufficiency. However, all interventions may be difficult to implement.

Elevating the leg above the level of the right atrium decreases venous hypertension and edema, is appropriate for all patients, and should be done a minimum of 3 times/day for ≥ 30 min. However, most patients cannot adhere to this schedule during the day.

Compression is effective for treatment and prevention of the effects of chronic venous insufficiency and postphlebitic syndrome and is indicated for all patients. Elastic bandages are used initially until edema and ulcers resolve and leg size stabilizes; commercial compression stockings are then used. Stockings that provide 20 to 30 mm Hg of distal circumferential pressure are indicated for smaller varicose veins and mild chronic venous insufficiency; 30 to 40 mm Hg is indicated for larger varicose veins and moderate disease; and 40 to > 60 mm Hg is indicated for severe disease. Stockings should be put on when patients awaken, before leg edema worsens with activity, and should exert maximal pressure at the ankles and gradually less pressure proximally. Adherence to this treatment varies; many younger or more active patients consider stockings irritating, restricting, or cosmetically undesirable; elderly patients may have difficulty putting them on.

Intermittent pneumatic compression (IPC) uses a pump to cyclically inflate and deflate hollow plastic leggings. IPC provides external compression, squeezing blood and fluid out of the lower legs. It effectively treats severe post-phlebitic syndrome and venous stasis ulcers but may be no more effective than compression stockings alone and is much less practical for patients to adhere to on an ongoing basis.

Topical wound care is important in venous stasis ulcer management (see p. 740 for full discussion). When an Unna boot (zinc oxide-impregnated bandages) is properly applied, covered by compression bandages, and changed weekly, almost all ulcers heal. Occlusive interactive dressings (eg, hydrocolloids such as aluminum chloride) provide a moist environment for wound healing and promote growth of new tissue; they may be used for ulcers with light to moderate exudate, but they probably add little to simple Unna bandaging and are expensive. Passive dressings are absorptive, making them most appropriate for heavier exudate.

Drugs have no role in routine treatment of chronic venous insufficiency, although many patients are given aspirin, topical corticosteroids, diuretics for edema, or antibiotics. Surgery (eg, venous ligation, stripping, valve reconstruction) is also generally ineffective. Grafting autologous skin or skin created from epidermal keratinocytes or dermal fibroblasts may be an option for patients with stasis ulcers when all other measures are ineffective, but the graft will reulcerate unless underlying venous hypertension is managed.

**Prevention**

Primary prevention involves adequate anticoagulation after DVT and use of compression stockings for up to 2 yr after DVT or lower extremity venous trauma. Lifestyle changes (eg, weight loss, regular exercise, reduction of dietary sodium) can decrease risk by decreasing lower extremity venous pressure.

**Superficial Venous Thrombosis**
Superficial venous thrombosis is a blood clot in a superficial vein of the upper or lower extremities or, less commonly, in one or more veins of the chest or breast (Mondor's disease).

Superficial venous thrombosis in the upper extremity most commonly results from IV infusions or catheterization; varicose veins seem to be the main risk factor for the lower extremity, especially among women. Superficial venous thrombi rarely cause serious complications and rarely become emboli.

Typically, patients present with pain, tenderness, or an indurated cord along a palpable superficial vein. The overlying skin is usually warm and erythematous. Migratory superficial venous thrombosis, which develops, resolves, and recurs in normal veins of the arms, legs, and torso at various times, is a possible harbinger of pancreatic cancer and other adenocarcinomas (Trouseau's syndrome).

Diagnosis is based on history and physical examination. Patients with superficial phlebitis above the knee have an increased risk of deep venous thrombosis and should probably have ultrasonography. Treatment traditionally involves warm compresses and NSAIDs, but local thrombectomy with a local anesthetic is very effective. In patients with extensive superficial phlebitis, heparin is often beneficial.

**Varicose Veins**

Varicose veins are dilated superficial veins in the lower extremities. Usually, no cause is obvious. Varicose veins are typically asymptomatic but may cause a sense of fullness, pressure, and pain or hyperesthesia in the legs. Diagnosis is by physical examination. Treatment may include compression, wound care, sclerotherapy, and surgery.

Varicose veins may occur alone or with chronic venous insufficiency.

Etiology is usually unknown, but varicose veins may result from primary venous valvular insufficiency with reflux or from primary dilation of the vein wall due to structural weakness. In some people, varicose veins result from chronic venous insufficiency and venous hypertension. Most people have no obvious risk factors. Varicose veins are common within families, suggesting a genetic component. Varicose veins are more common among women because estrogen affects venous structure, pregnancy increases pelvic and leg venous pressures, or both. Rarely, varicose veins are part of Klippel-Trenaunay-Weber syndrome, which includes congenital arteriovenous fistulas and diffuse cutaneous capillary angiomas.

**Symptoms and Signs**

Varicose veins may initially be tense and palpable but are not necessarily visible. Later, they may progressively enlarge, protrude, and become obvious; they can cause a sense of fullness, fatigue, pressure, and superficial pain or hyperesthesia in the legs. Varicose veins are most visible when the patient stands. For unclear reasons, stasis dermatitis and venous stasis ulcers are uncommon. When skin changes (eg, induration, pigmentation, eczema) occur, they typically affect the medial malleolar region. Ulcers may develop after minimal trauma to an affected area; they are usually small, superficial, and painful. Varicose veins occasionally thrombose, causing pain. Superficial varicose veins may cause thin venous bullae in the skin, which may rupture and bleed after minimal trauma. Very rarely, such bleeding, if undetected during sleep, is fatal.

**Diagnosis**

• Clinical evaluation

Diagnosis is usually obvious from the physical examination. Trendelenburg's test (comparing venous filling before and after release of a thigh tourniquet) is no longer commonly used to identify retrograde blood flow past incompetent saphenous valves. Duplex ultra-sonography is an accurate test, but it is not clear whether it is routinely necessary. Ultra-sonography can be done to assess the function of the deep veins prior to surgery.

**Treatment**
Compression stockings

Sometimes sclerotherapy or surgery

Treatment aims to relieve symptoms, improve the leg's appearance, and, in some cases, prevent complications. Treatment includes compression stockings and local wound care as needed.

Injection therapy (sclerotherapy) and surgery are indicated for prevention of recurrent variceal thrombosis and for skin changes; these procedures are also commonly used for cosmetic reasons. Sclerotherapy uses an irritant (eg, Na tetradecyl sulfate) to induce a thrombophlebitic reaction that fibroses and occludes the vein; however, many varicose veins recannulate. Surgery involves ligation or stripping of the long and sometimes the short saphenous veins. These procedures provide good short-term symptom relief, but long-term efficacy is poor (ie, patients often develop recurrent varicose veins). Laser therapy is being used experimentally by some surgeons.

Regardless of treatment, new varicose veins develop, and treatment often must be maintained indefinitely.

**Idiopathic Telangiectasias**

*Idiopathic telangiectasias are fine, dilated intracutaneous veins that are not clinically significant but may be extensive and unsightly.*

Telangiectasias are usually asymptomatic. However, some patients report a burning sensation or pain, and many people consider even the smallest telangiectasias cosmetically unacceptable.

Telangiectasias can usually be eliminated by intracapillary injections of 0.3% solution of Na tetradecyl sulfate through a fine-bore needle. Hypertonic saline 23.4% is sometimes used but causes fairly severe, temporary, localized pain; therefore, large areas of spider veins (multiple telangiectasias) may require several treatments. Pigmentation may develop but usually subsides, often completely. Skin ulceration may result if the injection is extravascular or too large. Laser treatment is effective, but large areas require several treatments. Small telangiectasias may persist or recur after initial treatment.

**Arteriovenous Fistula**

*An arteriovenous fistula is an abnormal communication between an artery and a vein.*

An arteriovenous fistula may be congenital (usually affecting smaller vessels) or acquired as a result of trauma (eg, a bullet or stab wound) or erosion of an arterial aneurysm into an adjacent vein.

The fistula may cause symptoms and signs of arterial insufficiency (eg, ulceration due to reduced arterial flow or ischemia) or chronic venous insufficiency due to high-pressure arterial flow in the affected veins (eg, peripheral edema, varicose veins, stasis pigmentation). Emboli (eg, causing ulceration) may pass from the venous to the arterial circulation, although pressure differences make this unlikely. If the fistula is near the surface, a mass can be felt, and the affected area is usually swollen and warm with distended, often pulsating superficial veins. A thrill can be palpated over the fistula, and a continuous loud, to-and-fro (machinery) murmur with accentuation during systole can be heard during auscultation. Rarely, if a significant portion of cardiac output is diverted through the fistula to the right heart, high-output heart failure develops.

Congenital fistulas need no treatment unless significant complications develop (eg, leg lengthening in a growing child). When necessary, percutaneous vascular techniques can be used to place coils or plugs into the vessels to occlude the fistula. Treatment is seldom completely successful, but complications are often controlled. Acquired fistulas usually have a single large connection and can be effectively treated by surgery.

**Lymphedema**
Lymphedema is edema of a limb due to lymphatic hypoplasia (primary) or to obstruction or disruption (secondary) of lymphatic vessels. Symptoms and signs are brawny, fibrous, nonpitting edema in one or more limbs. Diagnosis is by physical examination. Treatment consists of exercise, pressure gradient dressings, massage, and sometimes surgery. Cure is unusual, but treatment may lessen symptoms, slow progression, and prevent complications. Patients are at risk of cellulitis, lymphangitis, and, rarely, lymphangiosarcoma.

Etiology

Lymphedema may be primary (due to lymphatic hypoplasia) or secondary (due to obstruction or disruption of lymphatic vessels).

Primary lymphedemas: Primary lymphedemas are inherited and uncommon. They vary in phenotype and patient age at presentation.

Congenital lymphedema appears before age 2 and is due to lymphatic aplasia or hypoplasia. Milroy's disease is an autosomal dominant familial form of congenital lymphedema attributed to vascular endothelial growth factor receptor-3 (VEGFR-3) gene mutations and sometimes associated with cholestatic jaundice and edema or diarrhea due to a protein-losing enteropathy caused by intestinal lymphangiectasia.

Lymphedema praecox appears between ages 2 and 35, typically in women at the onset of menses or pregnancy. Meige's disease is an autosomal dominant familial form of lymphedema praecox attributed to mutations in a transcription factor gene (FOXC2) and associated with extra eyelashes (distichiasis); cleft palate; and leg, arm, and sometimes facial edema.

Lymphedema tarda occurs after age 35. Familial and sporadic forms exist; the genetic basis of both is unknown. Clinical findings are similar to those of lymphedema praecox but may be less severe.

Lymphedema is prominent in some other genetic syndromes, including Turner's syndrome; yellow nail syndrome, characterized by pleural effusions and yellow nails; and Hennekam syndrome, a rare congenital syndrome of intestinal and other lymphangiectases, facial anomalies, and intellectual disability.

Secondary lymphedema: Secondary lymphedema is far more common than primary. It is most commonly caused by surgery (especially lymph node dissection, typically for breast cancer), radiation therapy (especially axillary or inguinal), trauma, lymphatic obstruction by a tumor, and, in developing countries, lymphatic filariasis. Mild lymphedema may also result from leakage of lymph into interstitial tissues in patients with chronic venous insufficiency.

Symptoms and Signs

Symptoms of secondary lymphedema include aching discomfort and a sensation of heaviness or fullness.

The cardinal sign is soft-tissue edema, graded in 3 stages:

- In stage 1, the edema is pitting, and the affected area often returns to normal by morning.
- In stage 2, the edema is nonpitting, and chronic soft-tissue inflammation causes early fibrosis.
- In stage 3, the edema is brawny and irreversible, largely because of soft-tissue fibrosis.

The swelling is most often unilateral and may worsen when the weather is warm, before menstruation occurs, and after the limb remains for a long time in a dependent position. It can affect any part of the limb (isolated proximal or distal) or the entire extremity; it can restrict range of motion when swelling is periarticular. Disability and emotional distress can be significant, especially when lymphedema results from medical or surgical treatment.

Skin changes are common and include hyperkeratosis, hyperpigmentation, verrucae, papillomas, and
fungal infections.

**Complications:** Lymphangitis (see p. 700) may develop, most often when bacteria enter through skin cracks between the toes as a result of fungal infections or through cuts to the hand. Lymphangitis is almost always streptococcal, causing erysipelas; sometimes it is staphylococcal. The affected limb becomes red and feels hot; red streaks may extend proximally from the point of entry, and lymphadenopathy may develop. Rarely, the skin breaks down. Rarely, long-standing lymphedema leads to lymphangiosarcoma (Stewart-Treves syndrome), usually in postmastectomy patients and in patients with filariasis.

**Diagnosis**

- Clinical diagnosis
- CT or MRI if cause not apparent

Primary lymphedema is usually obvious, based on characteristic soft-tissue edema throughout the body and other information from the history and physical examination. Diagnosis of secondary lymphedema is usually obvious from physical examination. Additional tests are indicated when secondary lymphedema is suspected unless the diagnosis and cause are obvious. CT and MRI can identify sites of lymphatic obstruction; radionuclide lymphoscintigraphy can identify lymphatic hypoplasia or sluggish flow. Progression can be monitored by measuring limb circumference, measuring water volume displaced by the submerged limb, or using skin or soft-tissue tonometry; these tests have not been validated. In developing countries, tests for lymphatic filariasis should be done (see p. 1346). If lymphedema seems much greater than expected (eg, on the basis of lymph node dissection) or appears after a delay in a woman treated for breast cancer, cancer recurrence should be considered.

**Prognosis**

Cure is unusual once lymphedema occurs. Meticulous treatment and possibly preventive measures can lessen symptoms, slow or halt disease progression, and prevent complications.

**Treatment**

- Sometimes surgical reconstruction for primary lymphedema
- Mobilizing fluid (eg, by elevation and compression, massage, pressure bandages, intermittent pneumatic compression)

Treatment of primary lymphedema may include surgical soft-tissue reduction (removal of subcutaneous fat and fibrous tissue) and reconstruction if quality of life is significantly reduced.

Treatment of secondary lymphedema involves managing its cause. For lymphedema itself, several interventions to mobilize fluid (complex decongestive therapy) can be used. They include manual lymphatic drainage, in which the limb is elevated and compressed ("milked") toward the heart; gradient pressure bandages or sleeves; limb exercises; and limb massage, including intermittent pneumatic compression. Surgical soft-tissue reduction, lymphatic reanastomoses, and formation of drainage channels are sometimes tried but have not been rigorously studied.

Preventive measures include avoiding heat, vigorous exercise, and constrictive garments (including blood pressure cuffs) around the affected limb. Skin and nail care require meticulous attention; vaccination, phlebotomy, and IV catheterization in the affected limb should be avoided.

Cellulitis and lymphangitis are treated with β-lactamase-resistant antibiotics that are effective against gram-positive organisms (eg, oxacillin, cloxacillin, dicloxacillin).
Chapter 220. Sports and the Heart

Introduction

Exercise and athletic training are of significant overall cardiovascular benefit, but occasionally they have adverse consequences.

Sudden Cardiac Death in Athletes

An estimated 1/200,000 apparently healthy young athletes develops abrupt-onset ventricular tachycardia or fibrillation and dies suddenly during exercise. Males are affected 10 times more often than females. Basketball and football players in the US and soccer players in Europe may be at highest risk.

In young athletes, sudden cardiac death has many causes (see Table 220-1) but the most common is

- Undetected hypertrophic cardiomyopathy

Athletes with thin, compliant chest walls are at risk of commotio cordis (sudden ventricular tachycardia or fibrillation after a blow to the precordium) even when no cardiovascular disorder is present. The blow may involve a moderate-force projectile (eg, baseball, hockey puck, lacrosse ball) or impact

[Table 220-1. Causes of Sudden Cardiovascular Death in Young Athletes*]

with another player during a vulnerable phase of myocardial repolarization. Other causes include inherited arrhythmia syndromes (eg, long QT syndrome, Brugada syndrome). Some young athletes die of aortic aneurysm rupture (in Marfan syndrome).

In older athletes, sudden cardiac death is typically caused by

- Coronary artery disease

Occasionally, hypertrophic cardiomyopathy, mitral valve prolapse, or acquired valvular disease is involved.

In other conditions underlying sudden death in athletes (eg, asthma, heatstroke, illicit or performance-enhancing drug-related complications), ventricular tachycardia or fibrillation is a terminal, not a primary event.

Symptoms and signs are those of cardiovascular collapse; diagnosis is obvious. Immediate treatment with advanced cardiac life support is successful in < 20%; the percentage may increase as distribution of community-based, automated external defibrillators expands. For survivors, treatment is management of the underlying condition. In some cases, an implanted cardioverter-defibrillator may ultimately be required.

Screening

Athletes are commonly screened to identify risk before participation in sports, and they are reevaluated every 2 yr (if high school age) or every 4 yr (if college age or older).

Screening recommendations for all children, adolescents, and college-age young adults include

- Medical, family, and drug history (including use of performance-enhancing drugs and drugs that predispose to long QT syndrome)
- Physical examination (including BP and supine and standing cardiac auscultation)
- Selected testing based on findings on history and physical examination
Screening for older adults also includes incremental symptom-limited exercise testing.

Athletes with a family history or symptoms or signs of hypertrophic cardiomyopathy (see p. 2138), long QT syndrome (see p. 2176), or Marfan syndrome (see p. 2908) require further evaluation, typically with ECG, echocardiography, or both. Confirmation of any of these disorders may preclude sports participation. Athletes with presyncope or syncope should also be evaluated for anomalous coronary arteries (eg, by cardiac catheterization). If ECG reveals Mobitz type II heart block, complete heart block, true right bundle branch block, or left bundle branch block, a search for cardiac disease is required. Athletes should be counseled against use of illicit and performance-enhancing drugs.

History and examination are neither sensitive nor specific; false-negative and false-positive findings are common because prevalence of cardiac disorders in an apparently healthy population is very low. Use of screening ECG or echocardiography would improve disease detection but would produce even more false-positive diagnoses and is impractical at a population level.

Genetic testing for hypertrophic cardiomyopathy or long QT syndrome is not recommended or even feasible for the screening of athletes.

**Athlete's Heart**

Athlete's heart is a constellation of structural and functional changes that occur in the heart of people who train for > 1 h most days. The changes are asymptomatic; signs include bradycardia, a systolic murmur, and extra heart sounds. ECG abnormalities are common. Diagnosis is clinical or by echocardiography. No treatment is necessary. Athlete's heart is significant because it must be distinguished from serious cardiac disorders.

Intensive, prolonged endurance and strength training causes many physiologic adaptations. Volume and pressure loads in the left ventricle (LV) increase, which, over time, increase LV muscle mass, wall thickness, and chamber size. Maximal stroke volume and cardiac output increase, contributing to a lower resting heart rate and longer diastolic filling time. Lower heart rate results primarily from increased vagal tone, but decreased sympathetic activation and other nonautonomic factors that decrease intrinsic sinus node activity may play a role. Bradycardia decreases myocardial O\textsubscript{2} demand; at the same time, increases in total Hb and blood volume enhance O\textsubscript{2} transport. Despite these changes, systolic function and diastolic function remain normal. Structural changes in women are typically less than those in men of the same age, body size, and training.

**Symptoms and Signs**

There are no symptoms. Signs vary but may include bradycardia; an LV impulse that is laterally displaced, enlarged, and increased in amplitude; a systolic ejection (flow) murmur at the left lower sternal border; a 3rd heart sound (S\textsubscript{3}) due to early, rapid diastolic ventricular filling; a 4th heart sound (S\textsubscript{4}), heard best during resting bradycardia because diastolic filling time is increased; and hyperdynamic carotid pulses. These signs reflect structural cardiac changes that are adaptive for intense exercise.

**Diagnosis**

- Clinical evaluation
- Usually ECG
- Sometimes echocardiography
- Rarely stress testing

Findings are typically detected during routine screening or during evaluation of unrelated symptoms. Most athletes do not require extensive testing, although ECG is often warranted. If symptoms suggest a cardiac disorder (eg, palpitations, chest pain), ECG, echocardiography, and exercise stress testing are done.
Athlete's heart is a diagnosis of exclusion; it must be distinguished from disorders that cause similar findings but are life threatening (eg, hypertrophic or dilated cardiomyopathies, ischemic heart disease, arrhythmogenic right ventricular dysplasia).

**ECG:** Numerous changes in rhythm and ECG morphology can occur; they correlate poorly with level of training and cardiovascular performance. The most common ECG finding is

- Sinus bradycardia

Rarely, heart rate is < 40 beats/min. Sinus arrhythmia often accompanies the slow heart rate. Resting bradycardia may also predispose to

- Atrial or ventricular ectopy (including couplets and bursts of nonsustained ventricular tachycardia); pauses after ectopic beats do not exceed 4 sec

- Wandering supraventricular pacemaker

- Atrial fibrillation

Other ECG findings that may occur include

- First-degree atrioventricular (AV) block (in up to one third of athletes)

- Second degree AV block (mainly type I); this finding occurs during rest and disappears with exercise

- High voltage QRS with inferolateral T-wave changes (reflecting LV hypertrophy)

- Deep anterolateral T-wave inversion

- Incomplete right bundle branch block

However, 3rd-degree AV block is abnormal and should be investigated thoroughly.

These ECG and rhythm changes have not been associated with adverse clinical events, suggesting that various arrhythmias are not abnormal in athletes. The arrhythmias are usually abolished or substantially reduced after a relatively brief period of deconditioning.

**Echocardiography:** Echocardiography can usually distinguish athlete's heart from cardiomyopathies (see Table 220-2), but the distinction is not always clear because there is a continuum from physiologic to pathologic cardiac enlargement. The zone of overlap between the athlete's heart and cardiomyopathy is left ventricular septal thickness between 13 to 15 mm in men and 11 to 13 mm in women. In this overlap area, the presence of mitral valve systolic anterior motion strongly suggests hypertrophic cardiomyopathy. In general, echocardiographic changes correlate poorly with level of training and cardiovascular performance. Trace mitral regurgitation and tricuspid regurgitation are commonly detected.

**Stress testing:** During exercise stress testing, heart rate remains lower than normal at submaximal stress and increases appropriately and comparably to nonathletes at maximal stress; it rapidly recovers after exercise. BP response is normal: Systolic BP increases, diastolic BP falls, and mean BP stays relatively constant. Many resting ECG changes decrease or disappear during exercise; this finding is unique to athlete's heart, distinguishing it from pathologic conditions. However, pseudonormalization of T-wave inversions could reflect myocardial ischemia and thus warrants further investigation in older athletes.
Prognosis

Although gross structural changes resemble those in some cardiac disorders, no adverse effects are apparent. In most cases, structural changes and bradycardia regress with detraining, although up to 20% of elite athletes have residual chamber enlargement, raising questions, in the absence of long-term data, about whether athlete's heart is truly benign.

Treatment

No treatment is required, although 3 mo of deconditioning may be needed to monitor LV regression as a way of distinguishing this syndrome from cardiomyopathy. Such deconditioning can greatly interfere with an athlete's life and may meet with resistance.
Chapter 221. Cardiac Tumors

Introduction

Cardiac tumors may be primary (benign or malignant) or metastatic (malignant). Myxoma, a benign primary tumor, is the most common type. Cardiac tumors may occur in any cardiac tissue. They can cause valvular or inflow-outflow tract obstruction, thromboembolism, arrhythmias, or pericardial disorders. Diagnosis is by echocardiography followed by biopsy. Treatment of benign tumors is usually surgical resection; tumors may recur. Treatment of metastatic cancer depends on tumor type and origin; prognosis is generally poor.

Primary cardiac tumors are found in < 1/2000 people at autopsy. Metastatic tumors are 30 to 40 times more common. Usually, primary cardiac tumors originate in the myocardium or endocardium; they may also originate in valve tissue, cardiac connective tissue, or the pericardium.

Classification

Some of the more common primary and secondary cardiac tumors are listed (see Table 221-1).

Benign primary tumors: Examples are myxomas, papillary fibroelastomas, rhabdomyomas, fibromas, hemangiomas, teratomas, lipomas, paragangliomas, and pericardial cysts.

Myxoma is most common, accounting for 50% of all primary cardiac tumors. Incidence in women is 2 to 4 times that in men. In uncommon familial forms (Carney complex), men are affected more often. About 75% of myxomas occur in the left atrium, and the rest occur in the other chambers as a solitary tumor or, less commonly, at several sites. About 75% are pedunculated and may prolapse through the mitral valve and obstruct ventricular filling during diastole; the remainder are broad-based and sessile. Myxomas may be myxoid and gelatinous; smooth, firm, and lobular; or friable and irregular. Friable irregular myxomas increase risk of systemic embolism.

Carney complex is a familial, autosomal dominant syndrome of recurrent cardiac myxomas with some combination of cutaneous myxomas, myxoid mammary fibroadenomas, pigmented skin lesions (lentigines, ephelides, blue nevi), multiple endocrine neoplasia (primary pigmented nodular adreno-cortical disease causing Cushing's syndrome, growth hormone and prolactin-producing pituitary adenoma, testicular tumors, thyroid adenoma or carcinoma, and ovarian cysts), psammomatous melanotic schwannoma, breast ductal adenoma, and osteochondromyxoma. Patients are often younger at presentation (median age, 20 yr), have multiple myxomas (particularly in the ventricles), and have a higher risk of myxoma recurrence.

[Table 221-1. Types of Cardiac Tumors]

Papillary fibroelastomas are the 2nd most common benign primary tumor. They are avascular papillomas that predominantly occur on the aortic and mitral valves. Men and women are affected equally. They have papillary fronds branching from a central core, resembling sea anemones. About 45% are pedunculated. They do not cause valvular dysfunction but increase risk of embolism.

Rhabdomyomas account for 20% of all primary cardiac tumors and 90% of those in children. Rhabdomyomas affect mainly infants and children, 50% of whom also have tuberous sclerosis. Rhabdomyomas are usually multiple and located intramurally in the septum or free wall of the left ventricle, where they affect the cardiac conduction system. They are firm white lobules that typically regress with age. A minority of patients develop tachyarrhythmias and heart failure due to left ventricular outflow tract obstruction.

Fibromas occur mainly in children and are associated with adenoma sebaceum of the skin and kidney tumors. They occur primarily on valve tissue and may develop in response to inflammation. They can compress or invade the cardiac conduction system, causing arrhythmias and sudden death. Some fibromas occur as part of a syndrome with generalized body overgrowth, jaw keratocytes, skeletal
abnormalities, and various benign and malignant tumors (Gorlin's or basal cell nevus syndrome).

**Hemangiomas** account for 5 to 10% of benign tumors. They cause symptoms in a minority of patients. Most often, they are incidentally detected during examinations done for other reasons.

**Teratomas** of the pericardium affect mainly infants and children. They are often attached to the base of the great vessels. About 90% are located in the anterior mediastinum; the rest, mainly in the posterior mediastinum.

**Lipomas** can develop at a wide range of ages. They originate in the endocardium or epicardium and have a large pedunculated base. Many are asymptomatic, but some obstruct flow or cause arrhythmias.

**Paragangliomas**, including pheochromocytomas, rarely occur in the heart; when they do, they are usually localized to the base of the heart near vagus nerve endings. They may manifest with symptoms due to catecholamine secretion.

**Pericardial cysts** may resemble a cardiac tumor or pericardial effusion on chest x-ray. They are usually asymptomatic, although some cause compressive symptoms (eg, chest pain, dyspnea, cough).

**Malignant primary tumors**: Malignant primary tumors include sarcomas, pericardial mesothelioma, and primary lymphomas.

**Sarcoma** is the most common malignant and 2nd most common primary cardiac tumor (after myxoma). Sarcomas affect mainly middle-aged adults (mean, 41 yr). Almost 40% are angiosarcomas, most of which originate in the right atrium and involve the pericardium, causing right ventricular inflow tract obstruction, pericardial tamponade, and lung metastasis. Other types include undifferentiated sarcoma (25%), malignant fibrous histiocytoma (11 to 24%), leiomyosarcoma (8 to 9%), fibrosarcoma, rhabdomyosarcoma, liposarcoma, and osteosarcoma; these types are more likely to originate in the left atrium, causing mitral valve obstruction and heart failure.

**Pericardial mesothelioma** is rare. It affects all ages, males more than females. It causes tamponade and can metastasize to the spine, adjacent soft tissues, and brain.

**Primary lymphoma** is extremely rare. It usually occurs in AIDS patients or other people with immunodeficiency. These tumors grow rapidly and cause heart failure, arrhythmias, tamponade, and superior vena cava (SVC) syndrome.

**Metastatic tumors**: Lung and breast carcinoma, soft-tissue sarcoma, and renal cancer are the most common sources of metastases to the heart. Malignant melanoma, leukemia, and lymphoma often metastasize to the heart, but the metastases may not be clinically significant. When Kaposi's sarcoma spreads systemically in immunodeficient (usually AIDS) patients, it may spread to the heart, but clinical cardiac complications are uncommon.

**Symptoms and Signs**

Cardiac tumors cause symptoms and signs typical of much more common disorders (eg, heart failure, stroke, coronary artery disease). Symptoms and signs of benign primary cardiac tumors depend on tumor type, location, size, and friability and can be classified as extracardiac, intramyocardial, or intracavitary.

Extracardiac symptoms and signs may be constitutional or mechanical. Constitutional symptoms of fever, chills, lethargy, arthralgias, and weight loss are caused exclusively by myxomas, perhaps as a result of cytokine (eg, IL-6) release. Petechiae may also occur. These and other findings may erroneously suggest bacterial endocarditis, connective tissue disorders, and occult cancer. Mechanical symptoms (eg, dyspnea, chest discomfort) result from compression of cardiac chambers or coronary arteries or from pericardial irritation or tamponade caused by growth or hemorrhage within the pericardium. Pericardial tumors may produce pericardial friction rubs.

Intramyocardial symptoms and signs are caused by arrhythmias, usually atrioventricular or intraventricular
block or paroxysmal supraventricular or ventricular tachycardias due to compression or encroachment on the conduction system (notably rhabdomyomas and fibromas).

Intracavitary symptoms and signs are due to tumors that obstruct valvular function, blood flow, or both (causing valvular stenosis, valvular insufficiency, or heart failure) or to tumors (especially gelatinous myxomas) that cause thrombus or tumor fragments to embolize into the systemic circulation (brain, coronary arteries, kidneys, spleen, extremities) or the lungs. Intracavitary symptoms and signs may vary with body position, which can alter hemodynamics and physical forces associated with the tumor.

Myxomas usually cause some combination of constitutional and intracavitary symptoms and signs. Myxomas may cause a diastolic murmur that mimics that of mitral stenosis but whose loudness and location vary from beat to beat with body position. About 15% of pedunculated left atrial myxomas produce an audible "tumor plop" as they drop into the mitral orifice during diastole. Myxomas may also cause arrhythmias. Raynaud's syndrome and finger clubbing are less typical but may occur.

Fibroelastomas, often discovered incidentally at autopsy, are usually asymptomatic; however, they may be a source of systemic emboli. Rhabdomyomas are usually asymptomatic. Fibromas cause arrhythmias and sudden death. Hemangiomas are usually asymptomatic but may cause any of the extracardiac, intramyocardial, or intracavitary symptoms. Teratomas cause respiratory distress and cyanosis due to compression of the aortic and pulmonary artery or SVC syndrome.

Symptoms and signs of malignant cardiac tumors are more acute in onset and progress more rapidly. Cardiac sarcomas most commonly cause symptoms of ventricular inflow tract obstruction and pericardial tamponade. Mesothelioma causes symptoms of pericardiitis or tamponade. Primary lymphoma causes refractory progressive heart failure, tamponade, arrhythmias, and SVC syndrome. Metastatic cardiac tumors may manifest as sudden cardiac enlargement, tamponade (due to rapid accumulation of hemorrhagic pericardial effusion), heart block, other arrhythmias, or sudden unexplained heart failure. Fever, malaise, weight loss, night sweats, and loss of appetite may also be present.

**Diagnosis**

- Echocardiography
- Biopsy (during catheterization or thoracotomy)

Diagnosis, which is often delayed because symptoms and signs mimic those of much more common disorders, is confirmed by echocardiography and is tissue-typed by biopsy. Transesophageal echocardiography is better for visualizing atrial tumors, and transthoracic echocardiography is better for ventricular tumors. If results are equivocal, MRI is useful as are gated radionuclide imaging and CT. Infrequently, contrast ventriculography during cardiac catheterization is required. Biopsy is done during catheterization or open thoracotomy.

Extensive testing often precedes echocardiography in patients with myxomas because their symptoms are nonspecific. Anemia; thrombocytopenia; and elevation of WBC count, ESR, C-reactive protein, and γ-globulins are common. ECG may show left atrial enlargement. Routine chest x-ray may show Ca deposits in right atrial myxomas or in teratomas seen as anterior mediastinal masses. Myxomas are sometimes diagnosed when tumor cells are found in a surgically removed embolus.

Arrhythmias and heart failure with features of tuberous sclerosis suggest rhabdomyomas or fibromas. New cardiac symptoms and signs in a patient with a known extracardiac cancer suggest cardiac metastases. Chest x-ray may show bizarre changes in the cardiac silhouette.

**Treatment**

- Benign primary: Excision
- Malignant primary: Palliation
Treatment of benign primary tumors is surgical excision followed by serial echocardiography over 5 to 6 yr to monitor for recurrence. Tumors are excised unless another disorder (eg, dementia) contraindicates surgery. Surgery is usually curative (95% survival at 3 yr). Exceptions are rhabdomyomas, most of which regress spontaneously and do not require treatment, and pericardial teratoma, which may require urgent pericardiocentesis. Patients with fibroelastoma may also require valvular repair or replacement. When rhabdomyomas or fibromas are multi-focal, surgical excision is usually ineffective, and prognosis is poor after the first year of life; survival at 5 yr may be as low as 15%.

Treatment of malignant primary tumors is usually palliative (eg, radiation therapy, chemotherapy, management of complications) because prognosis is poor.

Treatment of metastatic cardiac tumors depends on tumor origin. It may include systemic chemotherapy or palliation.
Introduction

Critical care medicine specializes in caring for the most seriously ill patients. These patients are best treated in an ICU staffed by experienced personnel. Some hospitals maintain separate units for special populations (eg, cardiac, surgical, neurologic, pediatric, or neonatal patients). ICUs have a high nurse:patient ratio to provide the necessary high intensity of service, including treatment and monitoring of physiologic parameters.

Supportive care for the ICU patient includes provision of adequate nutrition (see p. 21) and prevention of infection, stress ulcers and gastritis (see p. 131), and pulmonary embolism (see p. 1920). Because 15 to 25% of patients admitted to ICUs die there, physicians should know how to minimize suffering and help dying patients maintain dignity (see p. 3480).

Patient Monitoring and Testing

Some monitoring is manual (ie, by direct observation and physical examination) and intermittent, with the frequency depending on the patient's illness. This monitoring usually includes measurement of vital signs (temperature, BP, pulse, and respiration rate), quantification of all fluid intake and output, and often daily weight. BP may be recorded by an automated sphygmomanometer; a transcutaneous sensor for pulse oximetry is used as well.

Other monitoring is ongoing and continuous, provided by complex devices that require special training and experience to operate. Most such devices generate an alarm if certain physiologic parameters are exceeded. Every ICU should strictly follow protocols for investigating alarms.

Blood Tests

Although frequent blood draws can destroy veins, cause pain, and lead to anemia, ICU patients typically have routine daily blood tests to help detect problems early. Generally, patients need a daily set of electrolytes and a CBC. Patients with arrhythmias should also have Mg, phosphate, and Ca levels measured. Patients receiving TPN need weekly liver enzymes and coagulation profiles. Other tests (eg, blood culture for fever, CBC after a bleeding episode) are done as needed.

Point-of-care testing uses miniaturized, highly automated devices to do certain blood tests at the patient's bedside or unit (particularly ICU, emergency department, and operating room). Commonly available tests include blood chemistries, glucose, ABGs, CBC, cardiac markers, and coagulation tests. Many are done in < 2 min and require < 0.5 mL blood.

Cardiac Monitoring

Most critical care patients have cardiac activity monitored by a 3-lead system; signals are usually sent to a central monitoring station by a small radio transmitter worn by the patient. Automated systems generate alarms for abnormal rates and rhythms and store abnormal tracings for subsequent review.

Some specialized cardiac monitors track advanced parameters associated with coronary ischemia, although their clinical benefit is unclear. These parameters include continuous ST-segment monitoring and heart rate variability. Loss of normal beat-to-beat variability signals a reduction in autonomic activity and possibly coronary ischemia and increased risk of death.

Pulmonary Artery Catheter Monitoring

Use of a pulmonary artery catheter (PAC) is becoming less common in ICU patients. This balloon-tipped, flow-directed catheter is inserted via central veins through the right side of the heart into the pulmonary artery. The catheter typically contains several ports that can monitor pressure or inject fluids. Some PACs
also include a sensor to measure central (mixed) venous O\textsubscript{2} saturation. Data from PACs are used mainly to determine cardiac output and preload. Preload is most commonly estimated by the pulmonary artery occlusion pressure (see p. 2245). However, preload may be more accurately determined by right ventricular end-diastolic volume, which is measured using fast-response thermistors gated to heart rate.

Despite longstanding use, PACs have not been shown to reduce morbidity and mortality. Rather, PAC use has been associated with excess mortality. This finding may be explained by complications of PAC use and misinterpretation of the data obtained. Nevertheless, some physicians believe PACs, when combined with other objective and clinical data, aid in the management of certain critically ill patients. As with many physiologic measurements, a changing trend is typically more significant than a single abnormal value. Possible indications for PACs are listed in Table 222-1.

**Procedure:** The PAC is inserted through a special catheter in the subclavian or internal jugular vein with the balloon deflated. Once the catheter tip reaches the superior vena cava, partial inflation of the balloon permits blood flow to guide the catheter. The position of the catheter tip is usually determined by pressure monitoring (see Table 222-2 for intracardiac and great vessel pressures) or occasionally by fluoroscopy. Entry into the right ventricle is indicated by a sudden increase in systolic pressure to about 30 mm Hg; diastolic pressure remains unchanged from right atrial or vena caval pressure. When the catheter enters the pulmonary artery, systolic pressure does not change, but diastolic pressure rises above right ventricular end-diastolic pressure or central venous pressure (CVP); ie, the pulse pressure narrows. Further movement of the catheter wedges the balloon in a distal pulmonary artery. A chest x-ray confirms proper placement.

The systolic pressure (normal, 15 to 30 mm Hg) and diastolic pressure (normal, 5 to 13 mm Hg) are recorded with the catheter balloon deflated. The diastolic pressure corresponds well to the occlusion pressure, although diastolic pressure can exceed occlusion pressure when pulmonary vascular resistance is elevated secondary to primary pulmonary disease (eg, pulmonary fibrosis, pulmonary hypertension).

**Pulmonary artery occlusion pressure (PAOP):** With the balloon inflated, pressure at the tip of the catheter reflects the static back pressure of the pulmonary veins. The balloon must not remain inflated for > 30 sec to prevent pulmonary infarction. Normally, PAOP approximates left atrial pressure, which in turn approximates left ventricular end-diastolic pressure (LVEDP). LVEDP reflects left ventricular end-diastolic volume (LVEDV). The LVEDV represents preload, which is the actual target parameter. Many factors cause PAOP to reflect LVEDV inaccurately. These factors include mitral stenosis, high levels of positive end-expiratory pressure (> 10 cm H\textsubscript{2}O), and changes in left ventricular compliance (eg, due to MI, pericardial effusion, or increased afterload). Technical difficulties result from excessive balloon inflation, improper catheter position, alveolar pressure exceeding pulmonary venous pressure, or severe pulmonary hypertension (which may make the balloon difficult to wedge).

Elevated PAOP occurs in left-sided heart failure. Decreased PAOP occurs in hypovolemia or decreased preload.

**Mixed venous oxygenation:** Mixed venous blood comprises blood from the superior and inferior vena cava that has passed through the right heart to the pulmonary artery. The blood may be sampled from the distal port of the PAC, but some catheters have embedded fiberoptic sensors that directly measure O\textsubscript{2} saturation.

Causes of low mixed venous O\textsubscript{2} content (SmvO\textsubscript{2}) include anemia, pulmonary disease, carboxyhemoglobin, low cardiac output, and increased tissue metabolic needs. The ratio of SaO\textsubscript{2} to
(SaO₂ - SmvO₂) determines the adequacy of O₂ delivery. The ideal ratio is 4:1, whereas 2:1 is the minimum acceptable ratio to maintain aerobic metabolic needs.

**Cardiac output:** Cardiac output (CO) is measured by intermittent bolus injection of ice water or, in new catheters, continuous warm thermodilution. The cardiac index divides the CO by body surface area to correct for patient size (see Table 222-3).

Other variables can be calculated from CO. They include systemic and pulmonary vascular resistance and right ventricular stroke work (RVSW) and left ventricular stroke work (LVSW).

**Complications and precautions:** PACs may be difficult to insert. Cardiac arrhythmias are the most common complication. Pulmonary infarction secondary to overinflated or permanently wedged balloons, pulmonary artery perforation, intracardiac perforation, valvular injury, and endocarditis may occur. Rarely, the catheter may curl into a knot within the right ventricle (especially in patients with heart failure, cardiomyopathy, or increased pulmonary pressure).

**Table 222-3. Normal Values for Cardiac Index and Related Measurements**

Pulmonary artery rupture occurs in < 0.1% of PAC insertions. This catastrophic complication is often fatal and occurs immediately on wedging the catheter either initially or during a subsequent occlusion pressure check. Thus, many physicians prefer to monitor pulmonary artery diastolic pressures rather than occlusion pressures.

**Noninvasive Cardiac Output**

Other methods of determining CO, such as thoracic bioimpedance and the esophageal Doppler monitor, are being developed to avoid the complications of PACs. Although these methods are potentially useful, neither is yet as reliable as a PAC.

**Thoracic bioimpedance:** These systems use topical electrodes on the anterior chest and neck to measure electrical impedance of the thorax. This value varies with beat-to-beat changes in thoracic blood volume and hence can estimate CO. The system is harmless and provides values quickly (within 2 to 5 min); however, the technique is very sensitive to alteration of the electrode contact with the patient. Thoracic bioimpedance is more valuable in recognizing changes in a given patient than in precisely measuring CO.

**Esophageal Doppler monitor (EDM):** This device is a soft 6-mm catheter that is passed nasopharyngeally into the esophagus and positioned behind the heart. A Doppler flow probe at its tip allows continuous monitoring of CO and stroke volume. Unlike the invasive PAC, the EDM does not cause pneumothorax, arrhythmia, or infection. An EDM may actually be more accurate than a PAC in patients with cardiac valvular lesions, septal defects, arrhythmias, or pulmonary hypertension. However, the EDM may lose its waveform with only a slight positional change and produce dampened, inaccurate readings.

**Intracranial Pressure Monitoring**

Intracranial pressure (ICP) monitoring is standard for patients with severe closed head injury. These devices are used to optimize cerebral perfusion pressure (mean arterial pressure minus intracranial pressure). Typically, the cerebral perfusion pressure should be kept > 60 mm Hg.

Several types of ICP monitors are available. The most useful method places a catheter through the skull into a cerebral ventricle (ventriculostomy catheter). This device is preferred because the catheter can also drain CSF and hence decrease ICP. However, the ventriculostomy is also the most invasive method, has the highest infection rate, and is the most difficult to place. Occasionally, the ventriculostomy becomes occluded due to severe brain edema.

Other types of intracranial devices include an intraparenchymal monitor and an epidural bolt. Of these,
the intraparenchymal monitor is more commonly used. All ICP devices should usually be changed or removed after 5 to 7 days because infection is a risk.

Other Types of Monitoring

Sublingual capnometry uses a similar correlation between elevated sublingual PCO$_2$ and systemic hypoperfusion to monitor shock states using a noninvasive sensor placed under the tongue. This device is easier to use than gastric tonometry and responds quickly to perfusion changes with resuscitation.

Tissue spectroscopy uses a noninvasive near infrared (NIR) sensor usually placed on the skin above the target tissue to monitor mitochondrial cytochrome $a,a$ redox states, which reflect tissue perfusion. NIR may help diagnose acute compartment syndromes (eg, in trauma) or ischemia after free tissue transfer and may be helpful in postoperative monitoring of lower-extremity vascular bypass grafts. NIR monitoring of small-bowel pH may be used to gauge the adequacy of resuscitation.

Scoring Systems

Several scoring systems have been developed to grade the severity of illness in critically ill patients. These systems are moderately accurate in predicting individual survival. However, these systems are more valuable for monitoring quality of care and for conducting research studies because they allow comparison of outcomes among groups of critically ill patients with similar illness severity.

The most common system is the 2nd version of the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score introduced in 1985. It generates a point score ranging from 0 to 71 based on 12 physiologic variables, age, and underlying health (see Table 222-4). The APACHE III system was developed in 1991. This system is more complex, has 17 physiologic variables, and is somewhat less used. There are many other systems, including the 2nd Simplified Acute Physiology Score (SAPS II) and several mortality probability models.

Vascular Access

A number of procedures are used to gain vascular access.

Peripheral Vein Catheterization

Most patients’ needs for IV fluid and drugs can be met with a percutaneous peripheral venous catheter. Venous cutdown can be used when percutaneous catheter insertion is not feasible. Typical cutdown sites are the cephalic vein in the arm and the saphenous vein at the ankle.

Common complications (eg, local infection, venous thrombosis, thrombophlebitis, interstitial fluid extravasation) can be reduced by using a meticulous sterile technique during insertion and by replacing or removing the catheters within 72 h.

Central Venous Catheterization

Patients needing secure or long-term vascular access (eg, to receive antibiotics, chemotherapy, or TPN) are best treated with a central venous catheter (CVC). CVCs allow infusion of solutions that are too concentrated or irritating for peripheral veins and allow monitoring of central venous pressure (CVP—see p. 2299).

Procedure: CVCs are inserted using sterile technique and a local anesthetic (eg, 1% lidocaine). The superior vena cava is entered via percutaneous puncture of the subclavian or the internal or external jugular vein or by venous cutdown on the basilic vein. The inferior vena cava may be entered through the common femoral vein percutaneously or by cutdown on the saphenous vein. The choice of site depends on operator preference and patient habitus and ambulatory status. However, femoral venous catheters have a slightly higher rate of complications than those above the waist. Also, during cardiac arrest, fluid and drugs given through a femoral or saphenous vein CVC often fail to circulate above the diaphragm because of the increased intrathoracic pressure generated by CPR. In this case, a subclavian or internal
jugular approach may be preferred.

If possible, the patient's coagulation status and platelet count should be normalized before CVC insertion. Percutaneous femoral lines must be inserted below the inguinal ligament. Otherwise, laceration of the external iliac vein or artery above the inguinal ligament may result in retroperitoneal hemorrhage; external compression of these vessels is nearly impossible. The subclavian vein also is not compressible with external pressure, and thus hemorrhage can be serious. A cutdown decreases the risk of bleeding-associated complications, particularly if coagulopathy is present.

After a subclavian or internal jugular catheter is inserted, a chest x-ray is taken to locate the catheter tip and to exclude a pneumothorax. To prevent cardiac arrhythmias, clinicians should withdraw catheters in the right atrium or ventricle until the tip is within the superior vena cava.

To reduce the risk of venous thrombosis and catheter sepsis, clinicians should remove CVCs as soon as possible. The skin entry site must be cleansed and inspected daily for local infection; the catheter must be replaced if local or systemic infection occurs. Some clinicians feel it is beneficial to change CVC catheters at regular intervals (eg, every 5 to 7 days) in patients with sepsis who remain febrile; this approach may reduce the risk of bacterial colonization of the catheter.

Complications: CVCs can cause many complications (see Table 222-5). Pneumothorax occurs in 1% of patients after CVC insertion. Atrial or ventricular arrhythmias frequently occur during catheter insertion but are generally self-limited and subside when the guide wire or catheter is withdrawn from within the heart. The incidence of catheter bacterial colonization without systemic infection may be as high as 35%, whereas that of true sepsis is 2 to 8%. Rarely, accidental arterial catheterization requires surgical repair of the artery. Hydrothorax and hydromediastinum may occur when catheters are positioned extravascularly. Catheter damage to the tricuspid valve, bacterial endocarditis, and air and catheter embolism occur rarely.

Arterial Catheterization

The use of automated noninvasive BP devices has diminished the use of arterial catheters simply for pressure monitoring. However, these catheters are beneficial in unstable patients who require minute-to-minute pressure measurement and in those requiring frequent ABG sampling. Indications include refractory shock and respiratory failure. BP is frequently somewhat higher when measured by an arterial catheter than by sphygmomanometry. Initial upstroke, maximum systolic pressure, and pulse pressure increase the more distal the point of measurement, whereas the diastolic and mean arterial pressures decline. Vessel calcification, atherosclerosis, proximal occlusion, and extremity position can all affect the value of arterial catheter measurements.

Procedure: Arterial catheters are inserted using sterile technique and a local anesthetic (eg, 1% lidocaine). They are typically inserted percutaneously into the radial, femoral, axillary, brachial, dorsalis pedis, and (in children) temporal arteries. The radial artery is most frequently used; insertion into the femoral artery has fewer complications but should be avoided after vascular bypass surgery (due to potential injury to the bypass graft) and in patients with distal vascular insufficiency (to avoid precipitating ischemia). When percutaneous insertion is unsuccessful, a cutdown may be done.

Before radial artery catheterization, Allen's test (digital compression of both ulnar and radial arteries causes palmar blanching followed by hyperemia when either artery is released) can determine whether there is sufficient ulnar collateral flow to perfuse the hand in the event of radial artery occlusion. If reperfusion does not occur within 8 sec of releasing the compressed ulnar artery, arterial catheterization should not be done.

Complications: At all sites, bleeding, infection, thrombosis, and distal embolism may occur. Catheters

[Table 222-4. Acute Physiologic Assessment and Chronic Health Evaluation (Apache) II Scoring System*]

[Table 222-5. Complications Associated with Central Venous Catheters]
should be removed if signs of local or systemic infection are present.

Radial arterial complications include ischemia of the hand and forearm due to thrombosis or embolism, intimal dissection, or spasm at the site of catheterization. The risk of arterial thrombosis is higher in small arteries (explaining the greater incidence in women) and with increased duration of catheterization. Occluded arteries nearly always recanalize after catheter removal.

Femoral arterial complications include atheroembolism during guide wire insertion. The incidence of thrombosis and distal ischemia is much lower than that for radial arterial catheterization.

Axillary arterial complications include hematomas, which are infrequent but may require urgent care because brachial plexus compression can result in permanent peripheral neuropathy. Flushing the axillary arterial catheter may introduce air or a clot. To avoid neurologic sequelae of these emboli, clinicians should select the left axillary artery for catheterization (the left axillary artery branches further distal to the carotid vessels than does the right).

Intraosseous Infusion

Any fluid or substance routinely given IV (including blood products) may be given via a sturdy needle inserted in the medullary cavity of select long bones. Fluids reach the central circulation as quickly as with venous infusion. This technique is used almost exclusively in infants and young children, whose bony cortices are thin and easily penetrated and in whom peripheral and central venous access can be quite difficult, particularly in shock or cardiac arrest. However, this technique can be used in older patients with special devices.

Procedure: A special-purpose intraosseous needle with stylet is used. The preferred insertion sites in children are the proximal tibia and distal femur; both areas are given a sterile preparation and are included in the operative field. For tibial insertion, the needle is placed on the broad, flat anteromedial surface 1 to 2 cm distal to the tibial tubercle. For the femur, the site is 3 cm above the lateral condyle in the midline. For older children, the medial surface of the distal tibia 2 cm above the medial malleolus may be easier.

For all sites, the needle is inserted with a rotary, coring motion. Stabilizing the needle shaft at the skin surface with a gloved fingertip aids control, allowing advancement to be stopped once the cortex is penetrated. On entering the medullary cavity, the stylet is removed and infusion is begun.

Complications: Poor control during insertion may result in the needle exiting the opposite cortex; then, subsequent infusion largely enters the soft tissues, so a site on another bone should be tried. Osteomyelitis may occur but is uncommon (eg, < 2 to 3%). Growth plate damage has not been reported. Other complications include bleeding and compartment syndrome.

Oxygen Desaturation

(Hypoxia)

ICU (and other) patients without respiratory disorders may develop hypoxia (O₂ saturation < 90%) during a hospital stay. Hypoxia in patients with known respiratory conditions is discussed under those disorders.

Etiology

Numerous disorders cause hypoxia (eg, dyspnea, respiratory failure; see Table 222-6); however, acute hypoxia developing in a patient hospitalized with a nonrespiratory illness usually has a more limited set of causes. These causes can be divided into

• Disorders of ventilation

• Disorders of oxygenation
Evaluation

Total fluid volume given during the hospital stay and, in particular, the previous 24 h should be ascertained to identify volume overload. Drugs should be reviewed for sedative administration and dosage. In significant hypoxia (O₂ saturation < 85%), treatment begins simultaneously with evaluation.

History: Very sudden onset dyspnea and hypoxia suggest pulmonary embolus (PE) or pneumothorax (mainly in a patient on positive pressure ventilation). Fever, chills, and productive cough (or increased secretions) suggest pneumonia. A history of cardiopulmonary disease (eg, asthma, COPD, heart failure) may indicate an exacerbation of the disease. Unilateral extremity pain suggests deep venous thrombosis (DVT) and hence possible

[Table 222-6, Some Causes of Oxygen Desaturation]

PE. Preceding major trauma or sepsis requiring significant resuscitation suggests acute respiratory distress syndrome. Preceding chest trauma suggests pulmonary contusion.

Physical examination: Patency of the airway and strength and adequacy of respirations should be assessed immediately. For patients on mechanical ventilation, it is important to determine that the endotracheal tube is not obstructed or dislodged. Unilateral decreased breath sounds with clear lung fields suggest pneumothorax or right mainstem bronchus intubation; with crackles and fever, pneumonia is more likely. Distended neck veins with bilateral lung crackles suggest volume overload; distention with clear lungs and tracheal deviation suggests tension pneumothorax. Bilateral lower-extremity edema suggests heart failure, but unilateral edema suggests DVT and hence possible PE. Wheezing represents bronchospasm (typically asthma or allergic reaction, but it occurs rarely with PE or heart failure). Decreased mental status suggests hypoventilation.

Testing: Hypoxia is generally recognized initially by pulse oximetry. Patients should have a chest x-ray, ECG, and ABGs (to confirm hypoxia and evaluate adequacy of ventilation). If diagnosis remains unclear after these tests, testing for PE (see p. 1909) should be considered. Bronchoscopy may be done in intubated patients to rule out (and remove) a tracheobronchial plug. Pulmonary artery catheterization may be needed to rule out heart failure if volume status is unclear.

Treatment

Identified causes are treated as discussed elsewhere in THE MANUAL. If hypoventilation persists, mechanical ventilation via noninvasive positive pressure ventilation or endotracheal intubation is necessary (see p. 2279). Persistent hypoxia requires supplemental O₂.

O₂ therapy: The amount of O₂ given is guided by ABG or pulse oximetry to maintain PaO₂ between 60 and 80 mm Hg (ie, 92 to 100% saturation) without causing O₂ toxicity. This level provides satisfactory tissue O₂ delivery; because the oxyhemoglobin dissociation curve is sigmoidal, increasing PaO₂ to > 80 mm Hg increases O₂ delivery very little and is not necessary. The lowest fractional inspired O₂ (FIO₂) that provides an acceptable PaO₂ should be provided. O₂ toxicity is both concentration- and time-dependent. Sustained elevations in FIO₂ > 60% result in inflammatory changes, alveolar infiltration, and, eventually, pulmonary fibrosis. An FIO₂ > 60% should be avoided unless necessary for survival. An FIO₂ < 60% is well tolerated for long periods.

An FIO₂ < 40% can be given via nasal cannula or simple face mask. A nasal cannula uses an O₂ flow of 1 to 6 L/min. Because 6 L/min is sufficient to fill the nasopharynx, higher flow rates are of no benefit. Simple face masks and nasal cannulas do not deliver a precise FIO₂ because of inconsistent admixture of O₂ with room air from leakage and mouth breathing. However, Venturi-type masks can deliver very accurate O₂ concentrations.

An FIO₂ > 40% requires use of an O₂ mask with a reservoir that is inflated by O₂ from the supply. In the
typical nonrebreather mask, the patient inhales 100% O\textsubscript{2} from the reservoir, but during exhalation, a rubber flap valve diverts exhaled breath to the environment, preventing admixture of CO\textsubscript{2} and water vapor with the inspired O\textsubscript{2}. Nonetheless, because of leakage, such masks deliver an FIO\textsubscript{2} of at most 80 to 90%.

**Oliguria**

Oliguria is urine output < 500 mL in 24 h in an adult or < 0.5 mL/kg/h in an adult or child (< 1 mL/kg/h in neonates).

**Etiology**

Causes of oliguria are typically divided into 3 categories:

- Prerenal (blood-flow related)
- Renal (intrinsic kidney disorders)
- Postrenal (outlet obstruction)

There are numerous such entities (see p. 2436), but a limited number cause most cases of acute oliguria in hospitalized patients (see Table 222-7).

**Evaluation**

**History:** In communicative patients, a marked urge to void suggests outlet obstruction, whereas thirst and no urge to void suggest volume depletion. In obtunded (and presumably catheterized) patients, a sudden decrease in urine flow in a normotensive patient suggests catheter occlusion (eg, caused by a clot or kinking) or displacement, whereas a gradual decrease is more likely due to acute tubular necrosis (ATN) or a prerenal cause.

Recent medical events are helpful; they include review of recent BP readings, surgical procedures, and drug and x-ray contrast administration. Recent surgery or trauma may be consistent with hypovolemia. A severe crush injury, deep electrical burn, or heatstroke suggests rhabdomyolysis.

**Physical examination:** Vital signs are reviewed, particularly for hypotension, tachycardia, or both (suggesting hypovolemia or sepsis) and fever (suggesting sepsis). Signs of focal infection and cardiac failure should be sought. Palpable bladder distention indicates an outlet obstruction. Dark brown urine suggests myoglobinuria.

**Testing:** In all catheterized patients (and those with an ileal conduit), patency should be ascertained by irrigation before further testing; this approach may solve the problem. In many of the remaining patients, etiology (eg, shock, sepsis) is clinically apparent. In others, particularly those with multiple disorders, testing is needed to differentiate prerenal from renal (ATN) causes. In patients without a urinary catheter, placement of a catheter should be considered; this will diagnose and treat obstruction and provide continuous monitoring of output.

[Table 222-7, Some Causes of Oliguria]

If a central venous or pulmonary artery catheter is in place, volume status (and with a pulmonary artery catheter, cardiac output) can be determined by measuring central venous pressure (see p. 2298) or pulmonary artery occlusion pressure (see p. 2245). However, many physicians would not insert such a line for acute oliguria unless other indications were present. An alternative in the patient without signs of volume overload is to rapidly give a test bolus of IV fluid, 500 mL 0.9% saline (20 mL/kg in children); an increase in output suggests a prerenal cause.
Laboratory tests should be done. Serum electrolytes, BUN, and creatinine are standard; often urine Na and creatinine concentration are also done. Prerenal conditions typically result in a BUN/creatinine ratio > 20, vs ≤ 10 in both normal states and ATN. In prerenal conditions, urine Na is < 20 mEq/L as the kidney attempts to retain maximum Na to preserve intravascular volume. In ATN, urine Na is usually > 40 mEq/L. The fractional Na excretion (FE\textsubscript{Na}) is a more accurate representation of the kidney’s ability to retain Na and is defined as

\[
\text{FE}\textsubscript{Na} = \frac{\text{urine Na/plasma Na}}{\text{urine creatinine/plasma creatinine}} \times 100
\]

A ratio < 1 indicates the kidney is able to reabsorb Na, and hence the problem is prerenal. A ratio > 3 indicates a probable renal cause.

Treatment

Identified causes are treated; outflow obstruction is corrected, volume is replaced, cardiac output is normalized. Nephrotoxic drugs are stopped, and another drug is substituted. Hypotension should be avoided to prevent further renal insults. Patients with renal failure that cannot be reversed may require renal replacement therapy (eg, continuous venovenous hemofiltration or hemodialysis).

Agitation, Confusion, and Neuromuscular Blockade

ICU patients are often agitated, confused, and uncomfortable. They can become delirious (ICU delirium). These symptoms are unpleasant for patients and often interfere with care and safety. At worst, they may be life threatening (eg, patients dislodge the endotracheal tube or IV lines).

Etiology

In a critically ill patient, agitation, confusion, or both can result from the original medical condition, from medical complications, or from treatment or the ICU environment (see Table 222-8). It is important to remember that neuromuscular blockade merely masks pain and agitation, it does not prevent it; paralyzed patients may be suffering significantly.

Evaluation

The chart should be reviewed and the patient examined before sedatives are ordered for “agitation.”

History: The presenting injury or illness is a prime causative suspect. Nursing notes and discussion with personnel may identify downward trends in BP and urine output (suggesting CNS hypoperfusion) and dysfunctional sleep patterns. Drug administration records are reviewed to identify inadequate or excessive analgesia and sedation.

[Table 222-8, Some Causes of Agitation or Confusion in Critical Care Patients]

Past medical history is reviewed for potential causes. Underlying liver disease suggests possible hepatic encephalopathy. Known substance dependency or abuse suggests a withdrawal syndrome.

Awake, coherent patients are asked what is troubling them and are questioned specifically about pain, dyspnea, and previously unreported substance dependency.

Physical examination: \(O_2\) saturation < 90% suggests a hypoxic etiology. Low BP and urine output suggest CNS hypoperfusion. Fever and tachycardia suggest sepsis or delirium tremens. Neck stiffness suggests meningitis, although this finding may be difficult to demonstrate in an agitated patient. Focal findings on neurologic examination suggest stroke, hemorrhage, or increased intracranial pressure (ICP).

The degree of agitation can be quantified using a scale such as the Riker Sedation-Agitation Scale (see Table 222-9) or the Ramsay Sedation Scale. Use of such scales allows better consistency between observers and the identification of trends. Patients who are under neuromuscular blockade are difficult to
evaluate because they may be highly agitated and uncomfortable despite appearing motionless. It is typically necessary to allow paralysis to wear off periodically (eg, daily) so that the patient can be assessed.

**Testing:** Identified abnormalities (eg, hypoxia, hypotension, fever) should be clarified further with appropriate testing. Head CT need not routinely be done unless focal neurologic findings are present or no other etiology is found. A bispectral index (BIS) monitor may be helpful in determining the level of sedation/agitation of patients under neuromuscular blockade.

**Treatment**

Underlying conditions (eg, hypoxia, shock, drugs) should be addressed. The environment should be optimized (eg, darkness, quiet, and minimal sleep interruption at night) as much as is compatible with medical care. Clocks, calendars, outside windows, and TV or radio programs also help connect the patient with the world, lessening confusion. Family presence and consistent nursing personnel may be calming.

Drug treatment is dictated by the most vexing symptoms. Pain is treated with analgesics; anxiety and insomnia are treated with sedatives; and psychosis and delirium are treated with small doses of an antipsychotic drug. Intubation may be needed when sedative and analgesic requirements are high enough to jeopardize the airway or respiratory drive. Many drugs are available; generally, short-acting drugs are preferred for patients who need frequent neurologic examination or who are being weaned to extubation.

**Analgesia:** Pain should be treated with appropriate doses of IV opioids; conscious patients with painful conditions (eg, fractures, surgical incisions) who are unable to communicate should be assumed to have pain and receive analgesics accordingly. Mechanical ventilation is somewhat uncomfortable, and patients generally should receive a combination of opioid and amnestic sedative drugs. Fentanyl is the opioid of choice because of its potency, short duration of action, and minimal cardiovascular effects. A common regimen can be 30 to 100 μg/h of fentanyl; individual requirements are highly variable.

**Sedation:** Despite analgesia, many patients remain sufficiently agitated as to require sedation. A sedative can also provide

[Table 222-9, Riker Sedation-Agitation Scale]

patient comfort at a lower dose of analgesic. Benzodiazepines (eg, lorazepam, midazolam) are most common, but propofol, a sedative-hypnotic drug, may be used. A common regimen for sedation is lorazepam 1 to 2 mg IV q 1 to 2 h or a continuous infusion at 1 to 2 mg/h if the patient is intubated. These drugs pose risks of respiratory depression, hypotension, delirium, and prolonged physiologic effects in some patients. Long-acting benzodiazepines such as diazepam, flurazepam, and chlordiazepoxide should be avoided in the elderly. Antipsychotics with less anticholinergic effect, such as haloperidol 1 to 3 mg IV, may work best when combined with benzodiazepines.

**Neuromuscular blockade:** For intubated patients, neuromuscular blockade is not a substitute for sedation; it only removes visible manifestations of the problem (agitation) without correcting it. However, neuromuscular blockade may be required during tests (eg CT, MRI) or procedures (eg, central line placement) that require patients to be motionless or in patients who cannot be ventilated despite adequate analgesia and sedation. Prolonged neuromuscular blockade should be avoided unless patients have severe lung injury and cannot do the work of breathing safely. Use for > 1 to 2 days may lead to prolonged weakness, particularly when corticosteroids are concomitantly given. Common regimens include vecuronium (continuous infusion as directed by stimulation).
Chapter 223. Cardiac Arrest

Introduction

Cardiac arrest is the terminal event in any fatal disorder. It may also occur suddenly (defined as within 24 h of onset of symptoms in a previously functioning person) and, as such, occurs outside the hospital in about 400,000 people/yr in the US, with a 90% mortality.

Respiratory arrest and cardiac arrest are distinct, but without treatment, one inevitably leads to the other. (See also respiratory failure in Ch. 225, dyspnea on p. 1832, and hypoxia on p. 2250.)

Etiology

In adults, sudden cardiac arrest results primarily from cardiac disease (of all types, but especially coronary artery disease). In a significant percentage of patients, sudden cardiac arrest is the first manifestation of heart disease. Other causes include circulatory shock due to noncardiac disorders (especially pulmonary embolism, GI hemorrhage, or trauma), ventilatory failure, and metabolic disturbance (including drug overdose).

In children, cardiac causes of sudden cardiac arrest are much less common (< 15 to 20%). Instead, predominant causes include trauma, poisoning, and various respiratory disorders (eg, airway obstruction, smoke inhalation, drowning, infection, sudden infant death syndrome).

Pathophysiology

Cardiac arrest causes global ischemia with consequences at the cellular level that adversely affect organ function after resuscitation. The main consequences involve direct cellular damage and edema formation. Edema is particularly harmful in the brain, which has minimal room to expand, and often results in increased intracranial pressure and corresponding decreased cerebral perfusion postresuscitation. A significant proportion of successfully resuscitated patients have short-term or long-term cerebral dysfunction manifested by altered alertness (from mild confusion to coma), seizures, or both.

Decreased ATP production leads to loss of membrane integrity with efflux of K and influx of Na and Ca. Excess Na causes cellular edema. Excess Ca damages mitochondria (depressing ATP production), increases nitric oxide production (leading to formation of damaging free radicals), and, in certain circumstances, activates proteases that further damage cells.

Abnormal ion flux also results in depolarization of neurons, releasing neurotransmitters, some of which are damaging (eg, glutamate activates a specific Ca channel, worsening intracellular Ca overload).

Inflammatory mediators (eg, IL-1B, tumor necrosis factor-α) are elaborated; some of them may cause microvascular thrombosis and loss of vascular integrity with further edema formation. Some mediators trigger apoptosis, resulting in accelerated cell death.

Symptoms and Signs

In critically or terminally ill patients, cardiac arrest is often preceded by a period of clinical deterioration with rapid, shallow breathing, arterial hypotension, and a progressive decrease in mental alertness. In other cases of cardiac arrest, collapse occurs without warning, occasionally accompanied by a brief (< 5 sec) seizure.

Diagnosis

- Clinical evaluation
- Cardiac monitor

- Sometimes testing for cause (eg, echocardiography, chest x-ray, or chest ultrasonography)
Diagnosis is by clinical findings of apnea, pulselessness, and unconsciousness. Arterial pressure is not measurable. Pupils dilate and become unreactive to light after about 1 to 2 min.

A cardiac monitor should be applied; it may indicate ventricular fibrillation (VF), ventricular tachycardia (VT), or asystole. Sometimes a perfusing rhythm (eg, extreme bradycardia) is present; this rhythm may represent true pulseless electrical activity ( electromechanical dissociation) or extreme hypotension with failure to detect a pulse.

The patient is evaluated for potentially treatable causes, such as hypoxia, massive volume loss, cardiac tamponade, tension pneumothorax, or massive pulmonary embolus. Unfortunately, many causes are not identified during CPR. Clinical examination, chest ultrasonography, and chest x-ray can detect tension pneumothorax. Cardiac ultrasonography can detect cardiac contractions and recognize cardiac tamponade, extreme hypovolemia (empty heart), right ventricular overload suggesting pulmonary embolism, and focal wall motion abnormalities suggesting MI.

Prognosis

Survival to hospital discharge, particularly neurologically intact survival, is a more meaningful outcome than simply return of spontaneous circulation.

Survival rates vary significantly; favorable factors include

- Witnessed arrest
- In-hospital location (particularly a monitored unit)
- Early and effective bystander-initiated CPR
- Initial rhythm of VF or VT
- Early defibrillation (of VT or VF after initial chest compression)
- Hypothermia (eg, submersion in ice water) preceding onset of cardiac arrest

If many factors are favorable (eg, VF is witnessed in an ICU or emergency department), about 20% of patients survive to hospital discharge. When factors are uniformly unfavorable (eg, patient in asystole after unwitnessed, out-of-hospital arrest), survival is unlikely. Overall, reported survival after out-of-hospital arrest ranges between 1% and 70%; the wide range reflects reporting differences and inclusion criteria as well as differences in system effectiveness. About 8 to 30% of survivors have neurologic dysfunction, and one third return to prearrest status. In-hospital arrest survival is 26%.

Treatment

- CPR (see below)
- When possible, treatment of primary cause
- Postresuscitative care

*Rapid intervention is essential.*

CPR is an organized, sequential response to cardiac arrest; rapid initiation of chest compressions and early defibrillation of patients who are in VF or VT (more commonly adults) are the keys to success.

In children, who most often have asphyxial causes of cardiac arrest, the presenting rhythm is typically a bradyarrhythmia followed by asystole. However, about 15 to 20% of children (particularly when sudden cardiac arrest has not been preceded by respiratory symptoms) present with VT or VF and thus also...
require prompt defibrillation. The incidence of VF as the initial recorded rhythm increases in children > 12 yr.

Primary causes must be promptly treated. If no treatable conditions are present but cardiac motion is detected or pulses are detected by Doppler, severe circulatory shock is identified, and IV fluid (eg, 1 L 0.9% saline, 5% serum albumin, whole blood, or a combination for blood loss) is given. If response to IV fluid is inadequate, most clinicians give one or more vasopressor drugs (eg, norepinephrine, epinephrine, dopamine, vasopressin); however, there is no firm proof that they improve survival.

In addition to treatment of cause, postresuscitative care typically includes methods to optimize O₂ delivery, antiplatelet therapy, and therapeutic hypothermia.

Cardiopulmonary Resuscitation

(For neonatal resuscitation, see p. 2768.)

Cardiopulmonary resuscitation (CPR) is an organized, sequential response to cardiac arrest, including

• Recognition of absent breathing and circulation
• Basic life support with chest compressions and rescue breathing
• Advanced cardiac life support (ACLS) with definitive airway and rhythm control
• Postresuscitative care

Prompt initiation of chest compression and early defibrillation (when indicated) are the keys to success. Speed, efficiency, and proper application of CPR determine successful outcome; the rare exception is profound hypothermia caused by cold water immersion, when successful resuscitation may be accomplished even after prolonged arrest (up to 60 min).

Overview: Guidelines for health care professionals from the American Heart Association are followed (see Fig. 223-1). If a person has collapsed with possible cardiac arrest, a rescuer first establishes unresponsiveness and confirms absence of breathing or the presence of only gasping respirations. Then, the rescuer calls for help. Anyone answering is directed to activate the emergency response system (or appropriate in-hospital resuscitation personnel) and, if possible, obtain a defibrillator. If no one responds, the rescuer first activates the emergency response system and then begins basic life support by giving 30 chest compressions at a rate of 100/min and then opening the airway (lifting the chin and tilting back the forehead) and giving 2 rescue breaths. The cycle of compressions and breaths is continued (see Table 223-1) without interruption; preferably each rescuer is relieved every 2 min. When a defibrillator (manual or automated) becomes available, a person in ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) is given an unsynchronized shock. If the cardiac arrest is witnessed and a defibrillator is on the scene, a person in VF or VT is immediately defibrillated; early defibrillation may promptly convert VF or pulseless VT to a perfusing rhythm. Defibrillation is further discussed on p. 2260.

For children, unless collapse is sudden and witnessed, the first step if no one answers the call for help is to do 5 cycles of CPR before activating the emergency response system.

Airway and Breathing

In a change from previous recommendations, opening the airway is given 2nd priority (see p. 2271) after beginning chest compressions.

Mouth-to-mouth (adults and children) or combined mouth-to-mouth-and-nose (infants) rescue breathing or bag-valve-mask ventilation is begun for asphyxial cardiac arrest. If available, an oropharyngeal airway may be inserted. Cricoid pressure is no longer recommended.
If abdominal distention develops, the airway is rechecked for patency and the amount of air delivered during rescue breathing is reduced. Nasogastric intubation to relieve gastric distention is delayed until suction equipment is available because regurgitation with aspiration of gastric contents may occur during insertion. If marked gastric distention interferes with ventilation and cannot be corrected by the above methods, patients are positioned on their side, the epigastrium is compressed, and the airway is cleared.

When qualified providers are present, an advanced airway (endotracheal tube or supraglottic device) is placed without interruption of chest compression as described under Airway Establishment and Control (see p. 2270). A breath is given every 6 to 8 sec (8 to 10 breaths/min) without interrupting chest compression. However, chest compression and defibrillation take precedence over endotracheal intubation. Unless highly experienced providers are available, endotracheal intubation may be delayed in favor of ventilation with bag-valve-mask, laryngeal mask airway, or similar device.

Circulation

**Chest compression:** In witnessed cardiac arrest, defibrillation, if available immediately, precedes chest compression. In an unresponsive patient whose collapse was unwitnessed, the trained rescuer should immediately begin external (closed chest) cardiac compression, followed by rescue breathing. Chest compressions must be interrupted as little as possible (eg, for intubation, central IV catheter placement, or transport). A compression cycle should consist of 50% compression and 50% release. Mechanical chest compression devices are available; these devices are no more effective than properly executed manual compressions but can minimize effects of performance error and fatigue and can be helpful during patient transport.

Ideally, external cardiac compression produces a palpable pulse with each compression, although cardiac output is only 20 to 30% of normal. However, palpation of pulses during chest compression is difficult, even for experienced clinicians, and often unreliable. End-tidal CO\(_2\) monitoring provides a better estimate of cardiac output during chest compression; patients with inadequate perfusion have little venous return to the lungs and hence a low end-tidal CO\(_2\). Normal-sized, light-responsive pupils signal adequate brain circulation and oxygenation. Light-responsive but dilated pupils may indicate inadequate cerebral oxygenation, although brain injury may not have occurred. However, persistently dilated, nonreactive pupils do not prove brain injury or death because adrenergic drugs, especially epinephrine and atropine, or cataracts may modify pupil size and reaction. Restoration of spontaneous breathing or eye opening indicates restoration of spontaneous circulation (ROSC).

Open-chest cardiac compression may be effective, but its use is restricted to patients after penetrating chest injuries, shortly after cardiac surgery (ie, within 48 h), in cases of cardiac tamponade, and most especially after cardiac arrest in the operating room when the patient's chest is already open. However, thoracotomy requires training and experience and is best done only within these limited indications.

**Complications of chest compression:** Laceration of the liver is a rare but potentially serious (sometimes fatal) complication and is usually caused by compressing the abdomen below the sternum. Rupture of the stomach (particularly if the stomach is distended with air) is also a rare complication. Delayed rupture of the spleen is very rare. An occasional complication, however, is regurgitation followed by aspiration of gastric contents, causing life-threatening aspiration pneumonia in resuscitated patients.

Costochondral separation and fractured ribs often cannot be avoided because it is important to compress the chest deeply enough to produce sufficient blood flow. Fractures are quite rare in children because of the flexibility of the chest wall. Bone marrow emboli to the lungs have rarely been reported after external cardiac compression, but there is no clear evidence that they contribute to mortality. Lung injury is rare, but pneumothorax after a penetrating rib fracture may occur. Serious myocardial injury caused by compression is very unlikely, with the possible exception of injury to a preexisting ventricular aneurysm.
Concern for these injuries should not deter the rescuer from doing CPR.

**Monitor and IV:** ECG monitoring is established to identify the underlying cardiac rhythm. An IV line is started; 2 lines minimize the risk of losing IV access during CPR. Large-bore peripheral lines in the antecubital veins are preferred. In adults, if a peripheral line cannot be established, a subclavian or internal jugular central line can be placed provided it can be done without stopping chest compression (often difficult). Intraosseous and femoral lines (see p. 2250) are the preferred alternatives, especially in children. Femoral vein catheters (preferably long catheters advanced centrally) are practical because CPR does not need to be stopped and they have less potential for lethal complications; however, they may have a lower rate of successful placement because no discrete femoral arterial pulsations are available to guide insertion.

The type and volume of fluids or drugs given depend on the clinical circumstances. Usually, IV 0.9% saline is given slowly (sufficient only to keep an IV line open); vigorous volume replacement (crystalloid and colloid solutions, blood) is required only when arrest results from hypovolemia (see p. 2297).

**Defibrillation**

The most common rhythm in witnessed adult cardiac arrest is VF; rapid conversion to a perfusing rhythm is essential. Pulseless VT is treated the same as VF.

A precordial thump is advised only when a defibrillator is not available. A forceful precordial thump can rarely convert VF or VT to a functional cardiac rhythm, and there is no evidence of deleterious effect (eg, converting VT to VF) in the cardiac arrest setting. However, it is not recommended for children. One or 2 blows can be delivered to the junction of the middle and lower third of the sternum with a clenched fist held 20 to 25 cm above the chest.

Prompt direct current cardioversion is more effective than antiarrhythmic drugs; however, the success of defibrillation is time dependent, with about a 10% decline in success after each minute of VF (or pulseless VT). Automated external defibrillators (AEDs) allow minimally trained rescuers to treat VT or VF. Their use by first responders (police and fire services) and their prominent availability in public locations has increased the likelihood of resuscitation.

Defibrillating paddles or AED pads are placed between the clavicle and the 2nd intercostal space along the right sternal border and over the 5th or 6th intercostal space at the apex of the heart. Conventional defibrillator paddles are used with conducting paste; pads have conductive gel incorporated into them. Only 1 initial countershock is now advised (the previous recommendation was 3 stacked shocks), after which chest compression is resumed. Energy level for biphasic defibrillators is between 120 and 200 joules (2 joules/kg in children); monophasic defibrillators are set at 360 joules. Postshock rhythm is not checked until after 2 min of chest compression. Subsequent shocks are delivered at the same or higher energy level (maximum 360 joules, 2 to 4 joules/kg in children). Patients remaining in VF or VT receive continued chest compression and ventilation and optional drug therapy as discussed below.

**Special Circumstances**

In accidental electrical shock, rescuers must be certain that the patient is no longer in contact with the electrical source to avoid shocking themselves. Use of nonmetallic grapples or rods and grounding of the rescuer allows for safe removal of the patient before starting CPR.

In near drowning, rescue breathing may be started in shallow water, although chest compression is not likely to be effectively done until the patient is placed horizontally on a firm surface, such as a surfboard or float.

If cardiac arrest follows traumatic injury, airway opening maneuvers and a brief period of external ventilation after clearing the airway have the highest priority because airway obstruction is the most likely treatable cause of arrest. To minimize cervical spine injury, jaw thrust, but not head tilt and chin lift, is advised. Other survivable causes of traumatic cardiac arrest include cardiac tamponade and tension pneumothorax, for which immediate needle decompression is lifesaving. However, most patients with...
traumatic cardiac arrest have severe hypovolemia due to blood loss (for which chest compressions may be ineffective) or nonsurvivable brain injuries.

**Drugs for ACLS**

Despite widespread and long-standing use, no drug or drug combination has been definitively shown to increase survival to hospital discharge in patients with cardiac arrest. Some drugs do seem to improve the likelihood of ROSC and thus may reasonably be given (for dosing, including pediatric, see Table 223-2). Drug therapy for shock and cardiac arrest continues to be researched.

In a patient with a peripheral IV line, drug administration is followed by a fluid bolus ("wide open" IV in adults; 3 to 5 mL in young children) to flush the drug into the central circulation. In a patient without IV or intraosseous access, atropine and epinephrine, when indicated, may be given via the endotracheal tube at 2 to 2.5 times the IV dose. During administration of a drug via endotracheal tube, compressions should be briefly stopped.

**First-line drugs:** First-line drugs include

- Epinephrine or vasopressin

Epinephrine has been the main drug used in cardiac arrest, although, as noted previously, its benefit is increasingly challenged. It may be given q 3 to 5 min. Epinephrine has combined α-adrenergic and β-adrenergic effects. The α-adrenergic effects may augment coronary diastolic pressure, thereby increasing subendocardial perfusion during chest compressions. Epinephrine also increases the likelihood of successful defibrillation. However, β-adrenergic effects may be detrimental because they increase O\textsubscript{2} requirements (especially of the heart) and cause vasodilation. Intracardiac injection of epinephrine is not recommended because, in addition to interrupting precordial compression, pneumothorax, coronary artery laceration, and cardiac tamponade may occur.

A single dose of vasopressin 40 units, which has a duration of activity of 40 min, is an alternative to epinephrine (adults only); it has not been proved more effective than epinephrine.

Amiodarone 300 mg can be given once if defibrillation is unsuccessful after epinephrine or vasopressin, followed by 1 dose of 150 mg. It is also of potential value if VT or VF recurs after successful defibrillation; a lower dose is given over 10 min followed by a continuous infusion. There is no persuasive proof that it increases survival to hospital discharge.

**Other drugs:** A range of additional drugs may be useful in specific settings.

Atropine sulfate is a vagolytic drug that increases heart rate and conduction through the atrioventricular node. It is given for symptomatic bradyarrhythmias and high-degree atrioventricular nodal block. It is no longer recommended for asystole or pulseless electrical activity.

Ca chloride is recommended for patients with hyperkalemia, hypermagnesemia, hypocalcemia, or Ca channel blocker toxicity. In others, because intracellular Ca is already higher than normal, additional Ca is likely to be detrimental. Because cardiac arrest in patients on renal dialysis is often a result of or accompanied by hyperkalemia, these patients may benefit from a trial of Ca if bedside K determination is unavailable. Caution is necessary because Ca exacerbates digitalis toxicity and can cause cardiac arrest.

Mg sulfate has not been shown to improve outcome in randomized clinical studies. However, it may be helpful in patients with torsades de pointes or known or suspected Mg deficiency (ie, alcoholics, patients with protracted diarrhea).

Procainamide is a 2nd-line drug for treatment of refractory VF or VT. However, procainamide is not recommended for pulseless arrest in children.
Phenytoin may rarely be used to treat VF or VT, but only when VF or VT is due to digitalis toxicity and is refractory to other drugs. A dose of 50 mg/min is given until rhythm improves or the total dose reaches 18 mg/kg.

NaHCO₃ (sodium bicarbonate) is no longer recommended unless cardiac arrest is caused by hyperkalemia, hypermagnesemia, or tricyclic antidepressant overdose with complex ventricular arrhythmias. In children, NaHCO₃ may be considered when cardiac arrest is prolonged (> 10 min); it is given only if there is good ventilation. When NaHCO₃ is used, arterial pH should be monitored before infusion and after each 50-mEq dose (1 to 2 mEq/kg in children).

Lidocaine and bretylium are no longer recommended for management of cardiac arrest.

**Dysrhythmia Treatment**

**VF or pulseless VT** is treated with one direct current shock, preferably with biphasic waveform, immediately after witnessed arrest and after 2 min of chest compression in patients with unwitnessed arrest; chest compression is interrupted as little as possible. Recommended energy levels vary: 120 to 200 joules for biphasic waveform and 360 joules for monophasic. If this treatment is unsuccessful, epinephrine 1 mg IV is administered and repeated q 3 to 5 min. Alternatively, vasopressin 40 U IV may be given only once (not in children) although its value is questioned. Cardioversion at the same energy level is attempted 1 min after each drug administration. If VF persists, amiodarone 300 mg IV is given. Then, if VF/VT recurs, 150 mg is given followed by infusion of 1 mg/min q 6 h, then 0.5 mg/min. Current versions of AEDs provide a pediatric cable that effectively reduces the energy delivered to children. (For pediatric energy levels, see Table 223-3; for drug doses, see Table 223-2.)

Asystole can be mimicked by a loose or disconnected monitor lead; thus, monitor connections should be checked and rhythm viewed in an alternative lead. If asystole is confirmed and heart block is suspected, transcutaneous pacing is done and the patient is given epinephrine 1 mg IV repeated q 3 to 5 min and atropine 1 mg IV repeated q 3 to 5 min to a total dose of 0.04 mg/kg. Electrical pacing is not successful in other settings. Pacing and atropine, however, are contraindicated in children with asystole. Defibrillation of apparent asystole (because it "might be fine VF") is discouraged because electrical shocks injure the nonperfused heart.

Pulseless electrical activity is circulatory collapse that occurs despite satisfactory electrical complexes on the ECG. Patients with pulseless electrical activity receive 500- to 1000-mL (20 mL/kg) infusion of 0.9% saline. Epinephrine may be given in amounts of 0.5 to 1.0 mg IV repeated q 3 to 5 min. If the heart rate is < 60/min, atropine 0.5 to 1 mg IV is given. Cardiac tamponade can cause pulseless electrical activity, but this disorder usually occurs in patients after thoracotomy and in patients with known pericardial effusion or major chest trauma. In such settings, immediate pericardiocentesis or thoracotomy is done (see Fig. 216-2 on p. 2206). Tamponade is rarely an occult cause of cardiac arrest but, if suspected, can be confirmed by ultrasonography or, if ultrasonography is unavailable, pericardiocentesis.

**Termination of Resuscitation**

CPR must be continued until the cardiopulmonary system is stabilized, the patient is pronounced dead, or a lone rescuer is physically unable to continue. If cardiac arrest occurs in hypothermic patients, CPR should be continued until the body is rewarmed to 34° C.

The decision to pronounce death is somewhat subjective, taking into account duration of arrest before treatment, age, prior medical conditions, and other factors but typically is made after failure to establish spontaneous circulation after 30 to 45 min of CPR and ACLS measures.

**Postresuscitative Care**

Restoration of spontaneous circulation (ROSC) is only an intermediate goal in resuscitation. Only 3 to 8% of patients with ROSC survive to hospital discharge. To maximize the likelihood of a good outcome,
clinicians must manage underlying conditions. In adults, it is particularly important to recognize MI (see p. 2101) and institute reperfusion therapy (preferably percutaneous transluminal coronary angioplasty) promptly. (CAUTION: Thrombolysis after aggressive CPR sometimes causes cardiac tamponade, and therefore angioplasty is preferred.)

Postresuscitation laboratory studies include ABG, CBC, and blood chemistries, including electrolytes, glucose, BUN, creatinine, and cardiac markers. (Creatine phosphokinase is usually elevated because of skeletal muscle damage caused by CPR.) Arterial PaO₂ should be kept near normal values (80 to 100 mm Hg). Hct should be maintained at ≥ 30, and glucose at < 200 mg/dL; electrolytes, especially K, should be within the normal range.

**BP support:** Current recommendations are to maintain a mean arterial pressure (MAP) of > 80 mm Hg in older adults or > 60 mm Hg in younger and previously healthy patients. In patients known to be hypertensive, a reasonable target is systolic BP 30 mm Hg below prearrest level. MAP is best measured with an intra-arterial catheter. Use of a flow-directed pulmonary artery catheter for hemodynamic monitoring has been largely discarded.

BP support includes

- IV 0.9% saline
- Sometimes inotropic or vasopressor drugs
- Rarely intra-aortic balloon counterpulsation

Patients with low MAP and low central venous pressure should have IV fluid challenge with 0.9% saline infused in 250-mL increments.

Although use of inotropic and vasopressor drugs is not proved to enhance long-term survival, older adults with moderately low MAP (70 to 80 mm Hg) and normal or high central venous pressure may receive an infusion of an inotrope (eg, dobutamine started at 2 to 5 μg/kg/min). Alternatively, amrinone or milrinone is used (see Table 223-2). If this therapy is ineffective, the inotrope and vasoconstrictor dopamine may be considered. Alternatives are epinephrine and the peripheral vasoconstrictors norepinephrine and phenylephrine (see Table 223-2). However, vasoactive drugs should be used at the minimal dose necessary to achieve low-normal MAP because they may increase vascular resistance and decrease organ perfusion, especially in the mesenteric bed. They also increase the workload of the heart at a time when its capability is decreased because of postresuscitation myocardial dysfunction. If MAP remains < 70 mm Hg in patients who may have sustained an MI, intra-aortic balloon counterpulsation should be considered. Patients with normal MAP and high central venous pressure may improve with either inotropic therapy or afterload reduction with nitroprusside or nitroglycerin.

Intra-aortic balloon counterpulsation can assist low-output circulatory states due to left ventricular pump failure that is refractory to drugs. A balloon catheter is introduced via the femoral artery, percutaneously or by arteriotomy, retrograde into the thoracic aorta just distal to the left subclavian artery. The balloon inflates during each diastole, augmenting coronary artery perfusion, and deflates during systole, decreasing afterload. Its primary value is as a temporizing measure when the cause of shock is potentially correctable by surgery or percutaneous intervention (eg, acute MI with major coronary obstruction, acute mitral insufficiency, ventricular septal defect).

**Dysrhythmia treatment:** Although VF or VT may recur after resuscitation, prophylactic antiarrhythmic drugs do not improve survival and are no longer routinely used. However, patients manifesting such rhythms may be treated with procainamide or amiodarone (see p. 2260).

Postresuscitation rapid supraventricular tachycardias occur frequently because of high levels of β-adrenergic catecholamines (both endogenous and exogenous) during cardiac arrest and resuscitation.
These rhythms should be treated if extreme, prolonged, or associated with hypotension or signs of coronary ischemia. An esmolol IV infusion is given, beginning at 50 μg/kg/min.

Patients who had arrest caused by VF or VT not associated with acute MI are candidates for an implantable cardioverter-defibrillator (ICD). Current ICDs are implanted similarly to pacemakers and have intracardiac leads and sometimes subcutaneous electrodes. They can sense arrhythmias and deliver either cardioversion or cardiac pacing as indicated.

**Neurologic support:** Between 8% and 30% of adults have CNS dysfunction after resuscitation from cardiac arrest. Hypoxic brain injury is a result of ischemic damage and cerebral edema (see also Pathophysiology on p. 2255). Both damage and recovery may evolve over 48 to 72 h after resuscitation.

Maintenance of oxygenation and cerebral perfusion pressure (avoiding hypotension) may reduce cerebral complications. Both hypoglycemia and hyperglycemia may damage the postischemic brain and should be treated.

Additionally, there is now persuasive evidence of the benefits of inducing mild hypothermia. Surface cooling with ice packs can reduce core body temperature to between 30° and 34°C. Alternative methods of cooling include cardiopulmonary bypass or intravascular cooling devices.

Numerous pharmacologic treatments, including free radical scavengers, antioxidants, glutamate inhibitors, and Ca channel blockers, are of theoretic benefit; many have been successful in animal models, but none have proved effective in human trials.

**CPR in Infants and Children**

Despite the use of CPR, mortality rates for cardiac arrest are 80 to 97% for infants and children. The mortality rate is almost 25% for respiratory arrest alone. Neurologic outcome is often severely compromised.

About 50 to 65% of children requiring CPR are < 1 yr; of these, most are < 6 mo. About 6% of neonates require resuscitation at delivery (see p. 2768); the incidence increases significantly if birth weight is < 1500 g.

Standardized outcome guidelines should be followed in reporting outcomes of CPR in children; eg, the modified Pittsburgh Outcome Categories Scale reflects cerebral and overall performance (see Table 223-4).

**Major Differences Between Pediatric and Adult CPR**

**Prearrest:** Bradycardia in a distressed child is a sign of impending cardiac arrest. Neonates, infants, and young children are more likely to develop bradycardia caused by hypoxemia, whereas older children initially tend to have tachycardia. An infant or child with a heart rate < 60/min and signs of poor perfusion that do not rise with ventilatory support should have cardiac compressions (see Fig. 223-2). Bradycardia secondary to heart block is unusual.

[Table 223-4, Pediatric Cerebral Performance Category Scale*]

After adequate oxygenation and ventilation, epinephrine is the drug of choice.

BP should be measured with an appropriatelysized cuff, but direct invasive arterial BP monitoring is mandatory in severely compromised children.

Because BP varies with age, an easy guideline to remember the lower limits of normal for systolic BP (< 5th percentile) by age is as follows: < 1 mo, 60 mm Hg; 1 mo to 1 yr, 70 mm Hg; > 1 yr, 70 + (2 × age in yr). Thus, in a 5-yr-old child, hypotension would be defined by a BP of < 80 mm Hg (70 + [2 × 5]). Of significant importance is that children maintain BP longer because of stronger compensatory mechanisms (increased heart rate, increased systemic vascular resistance). Once hypotension occurs,
cardiorespiratory arrest may rapidly follow. All effort should be made to start treatment when compensatory signs of shock (eg, increased heart rate, cool extremities, capillary refill > 2 sec, poor peripheral pulses) are present but before hypotension develops.

**Equipment and environment:** Equipment size, drug dosage, and CPR parameters vary with patient age and weight (see Tables 223-1, 223-2, and 223-3). Size-variable equipment includes defibrillator paddles or electrode pads, masks, ventilation bags, airways, laryngoscope blades, endotracheal tubes, and suction catheters. Weight should be measured rather than guessed; alternatively, commercially available measuring tapes that are calibrated to read standard patient weight based on body length can be used. Some tapes are printed with the recommended drug dose and equipment size for each weight. Dosages should be rounded down; eg, a 2 1/2-yr-old child should receive the dose for a 2-yr-old child.

Susceptibility to heat loss is greater in infants and children because of a large surface area relative to body mass and less subcutaneous tissue. A neutral external thermal environment is crucial during CPR and postresuscitation and may range from 36.5° C in a neonate to 35° C in a child. Hypothermia with core temperature < 35° C makes resuscitation more difficult (distinct from the beneficial effects of postresuscitation hypothermia discussed on p. 2266).

**Airway:** Upper airway anatomy is different in children. The head is large with a small face, mandible, and external nares, and the neck is relatively short. The tongue is large relative to the mouth, and the larynx lies higher in the neck and is angled more anteriorly. The epiglottis is long, and the narrowest portion of the trachea is inferior to the vocal cords at the cricoid ring, allowing the use of uncuffed endotracheal tubes. In younger children, a straight laryngoscope blade generally allows better visualization of the vocal cords than a curved blade because the larynx is more anterior and the epiglottis is more floppy and redundant.

**Rhythm disturbances:** In asystole, atropine and pacing are not used.

VF and pulseless VT occur in only about 15 to 20% of cardiac arrests. Vasopressin is not indicated. When cardioversion is used, the absolute energy dose is less than that for adults; waveform can be biphasic (preferred) or monophasic (see Table 223-3). For either waveform, the recommended energy dose is 2 joules/kg for the first shock, increasing to 4 joules/kg for subsequent attempts (if necessary—see p. 2260).

AEDs with adult cables may be used for children as young as 1 yr, but an AED with pediatric cables (maximum biphasic shock of 50 joules) is preferred for children between 1 yr and 8 yr. There is insufficient evidence to recommend for or against the use of AEDs in children < 1 yr.
Chapter 224. Respiratory Arrest

Introduction

Respiratory and cardiac arrest are distinct, but inevitably if untreated, one leads to the other. (See also respiratory failure on p. 2279, dyspnea on p. 1832, and hypoxia on p. 2250).

Interruption of pulmonary gas exchange for > 5 min may irreversibly damage vital organs, especially the brain. Cardiac arrest almost always follows unless respiratory function is immediately restored. However, aggressive ventilation may also have negative hemodynamic consequences, particularly in the periarrest period and in other circumstances when cardiac output is low. In most cases, the ultimate goal is to restore adequate ventilation and oxygenation without further compromising a tentative cardiovascular situation.

Etiology

Respiratory arrest (and impaired respiration that can progress to respiratory arrest) can be caused by

- Airway obstruction
- Decreased respiratory effort
- Respiratory muscle weakness

Airway obstruction: Obstruction may involve the

- Upper airway
- Lower airway

Infants < 3 mo are usually nose breathers and thus may have upper airway obstruction secondary to nasal blockage. At all ages, loss of muscular tone with decreased consciousness may cause upper airway obstruction as the posterior portion of the tongue displaces into the oropharynx. Other causes of upper airway obstruction include blood, mucus, vomitus, or foreign body; spasm or edema of the vocal cords; and pharyngolaryngeal tracheal inflammation (eg, epiglottitis, croup), tumor, or trauma. Patients with congenital developmental disorders often have abnormal upper airways that are more easily obstructed.

Lower airway obstruction may result from aspiration, bronchospasm, airspace filling disorders (eg, pneumonia, pulmonary edema, pulmonary hemorrhage), or drowning.

Decreased respiratory effort: Decreased respiratory effort reflects CNS impairment due to one of the following:

- CNS disorder
- Adverse drug effect
- Metabolic disorder

CNS disorders that affect the brain stem (eg, stroke, infection, tumor) can cause hypoventilation. Disorders that increase intracranial pressure usually cause hyperventilation initially, but hypoventilation may develop if the brain stem is compressed.

Drugs that decrease respiratory effort include opioids and sedative-hypnotics (eg, barbiturates, alcohol; less commonly, benzodiazepines). Usually, an overdose (iatrogenic, intentional, or unintentional) is involved, although a lower dose may decrease effort in patients who are more sensitive to the effects of these drugs (eg, the elderly, those with chronic respiratory insufficiency).
CNS depression due to severe hypoglycemia or hypotension ultimately compromises respiratory effort.

**Respiratory muscle weakness:** Weakness may be caused by

- Neuromuscular disorders
- Fatigue

Neuromuscular causes include spinal cord injury, neuromuscular diseases (eg, myasthenia gravis, botulism, poliomyelitis, Guillain-Barre syndrome), and neuromuscular blocking drugs.

Respiratory muscle fatigue can occur if patients breathe for extended periods at a minute ventilation exceeding about 70% of their maximum voluntary ventilation (eg, because of severe metabolic acidosis or hypoxemia).

**Symptoms and Signs**

With respiratory arrest, patients are unconscious or about to become so.

Patients with hypoxemia may be cyanotic, but cyanosis can be masked by anemia or by carbon monoxide or cyanide intoxication. Patients being treated with high-flow O₂ may not be hypoxemic and therefore may not exhibit cyanosis or desaturation until after respiration ceases for several minutes. Conversely, patients with chronic lung disease and polycythemia may exhibit cyanosis without respiratory arrest. If respiratory arrest remains uncorrected, cardiac arrest follows within minutes of onset of hypoxemia, hypercarbia, or both.

**Impending respiratory arrest:** Before complete respiratory arrest, patients with intact neurologic function may be agitated, confused, and struggling to breathe. Tachycardia and diaphoresis are present; there may be intercostal or sternoclavicular retractions. Patients with CNS impairment or respiratory muscle weakness have feeble, gasping, or irregular respirations and paradoxical breathing movements. Patients with a foreign body in the airway may choke and point to their necks, exhibit inspiratory stridor, or neither. Monitoring end-tidal CO₂ can alert practitioners to impending respiratory arrest in decompensating patients.

Infants, especially if < 3 mo, may develop acute apnea without warning, secondary to overwhelming infection, metabolic disorders, or respiratory fatigue. Asthmatics or patients with other chronic lung diseases may become hypercarbic and fatigued after prolonged periods of respiratory distress and suddenly become obtunded and apneic with little warning, despite adequate oxygen saturation.

**Diagnosis**

- Clinical evaluation

Respiratory arrest is usually clinically obvious; treatment begins simultaneously with diagnosis. The first consideration is to exclude a foreign body obstructing the airway; if a foreign body is present, resistance to ventilation is marked during mouth-to-mask or bag-valve-mask ventilation. Foreign material may be discovered during laryngoscopy for endotracheal intubation (see p. 2271 for removal).

**Treatment**

Treatment is clearing the airway, establishing an alternate airway, and providing mechanical ventilation (see p. 2279).

**Airway Establishment and Control**

Airway management consists of clearing the upper airway, maintaining an open air passage with a mechanical device, and sometimes assisting respirations. There are many indications for airway control.
Clearing and Opening the Upper Airway

To relieve airway obstruction caused by soft tissues of the upper airway and provide optimal position for bag-valve-mask (BVM) ventilation and laryngoscopy, the operator flexes the patient's neck to elevate the head until the external auditory meatus is in the same plane as the sternum and positions the face roughly parallel to the ceiling (see Fig. 224-1). This position is slightly different from the previously taught head tilt position. The mandible should be displaced upwards by lifting the lower jaw and submandibular soft tissue or by pushing the rami of the mandible upward (see Fig. 224-2).

Obstruction by dentures and oropharyngeal foreign material (eg, blood, secretions) may be removed by finger sweep of the oropharynx and suction, taking care not to push the material deeper (more likely in infants and young children, in whom a blind finger sweep is contraindicated). Deeper material can be removed with Magill forceps or by suction.

Heimlich maneuver (subdiaphragmatic abdominal thrusts): The Heimlich maneuver consists of manual thrusts to the upper abdomen or, in the case of pregnant or extremely obese patients, chest thrusts until the airway is clear or the patient becomes unconscious; it is the preferred initial method in the awake, choking patient and in the unconscious patient if the above methods are unsuccessful.

An unconscious adult is rolled into the supine position. The rescuer sits astride the patient above the knees with the heel of a hand in the upper abdominal area below the xiphoid process. To avoid damaging chest structures and the liver, the rescuer should never place the hand on the xiphoid process or lower rib cage. The other hand is placed on top of the first and a firm upward thrust is delivered (see Fig. 224-3). For chest thrusts, the hand is placed over the sternum similarly to the position used for cardiac compression. With both techniques, 5 quick, firm thrusts are recommended, followed by reevaluation of the airway.

In conscious adults, the rescuer stands behind the patient with arms encircling the patient's midsection. One fist is clenched and placed midway between the umbilicus and xiphoid. The other hand grabs the fist, and a firm inward and upward thrust is delivered by pulling with both arms (see Fig. 224-4).

In older children, the Heimlich maneuver may be used. However, in children < 20 kg (typically < 5 yr), very moderate pressure should be applied, and the rescuer should kneel at the child's feet rather than astride.
In infants < 1 yr, the Heimlich maneuver should not be done; they should be held in a prone, head-down position, supporting the head with the fingers of one hand, while delivering 5 back blows (see Fig. 224-5). Five chest thrusts should then be delivered with the infant in a head-down position with the infant's back on the rescuer's thigh (supine). This sequence of back blows and chest thrusts is repeated until the airway is cleared.

Airway and Respiratory Devices

If no spontaneous respiration occurs after airway opening and no respiratory devices are available, rescue breathing (mouth-to-mask or mouth-to-barrier device) is started; mouth-to-mouth ventilation is rarely recommended. Exhaled air contains 16 to 18% O\textsubscript{2} and 4 to 5% CO\textsubscript{2}, which is adequate to maintain blood O\textsubscript{2} and CO\textsubscript{2} values close to normal. Larger-than-necessary volumes of air may cause gastric distention with associated risk of aspiration.

Bag-valve-mask (BVM) devices: These devices consist of a self-inflating bag (resuscitator bag) with a nonrebreathing valve mechanism and a soft mask that conforms to the tissues of the face; when connected to an O\textsubscript{2} supply, they deliver from 60 to 100% inspired O\textsubscript{2}. In the hands of experienced practitioners, a BVM provides adequate temporary ventilation in many situations, allowing time to systematically achieve definitive airway control. However, if BVM ventilation is used for > 5 min, air is typically introduced into the stomach, and an NGT should be inserted to evacuate the accumulated air.

These devices do not maintain airway patency, so patients with soft-tissue relaxation require careful positioning and manual maneuvers (see Figs. 224-1 and 224-2), as well as additional devices to keep the airway open. An oropharyngeal airway or a nasal trumpet is used during BVM ventilation to keep soft tissues of the oropharynx from blocking the airway. These devices cause gagging and the potential for vomiting and aspiration in conscious patients. Devices must be sized appropriately; an oropharyngeal airway should be as long as the distance between the corner of the patient's mouth and the angle of the jaw.

Resuscitator bags are also used with artificial airways, including endotracheal tubes and supraglottic and pharyngeal airways. Pediatric bags have an adjustable pressure relief valve that limits peak airway pressures (usually to 35 to 45 cm H\textsubscript{2}O); practitioners must monitor the valve setting to avoid inadvertent hypoventilation.

Laryngeal mask airways (LMAs): An LMA or other supraglottic airway can be inserted into the lower oropharynx to prevent airway obstruction by soft tissues and to create an effective channel for ventilation (see Fig. 224-6). As the name implies, these devices seal the laryngeal inlet (rather than the face-mask interface) and thus avoid the difficulty of maintaining an adequate face-mask seal and the risk of displacing the jaw and tongue. LMAs have become the standard rescue ventilation technique for situations in which endotracheal intubation cannot be accomplished, as well as for certain elective anesthesia cases and emergencies. Complications include vomiting and aspiration in patients who have an intact gag reflex, who are receiving excessive ventilation, or both.

There are numerous techniques for LMA insertion. The standard approach is to press the deflated mask against the hard palate (using the long finger of the dominant hand) and rotate it past the base of the tongue until the mask reaches the hypopharynx so that the tip then sits in the upper esophagus. Once in the correct position, the mask is inflated. Inflating the mask with half the recommended volume before insertion stiffens the tip, possibly making insertion easier.

Although an LMA does not isolate the airway from the esophagus as well as an endotracheal tube, it has some advantages over BVM ventilation: It minimizes gastric inflation and provides some protection against passive regurgitation. Newer versions of LMAs have an opening through which a small tube can be
inserted to decompress the stomach.

The efficacy of the airway seal with an LMA, unlike endotracheal tubes, is not directly correlated with the mask inflation pressure. With endotracheal tubes, higher balloon pressure causes a tighter seal; with an LMA, overinflation makes the mask more rigid and less able to adapt to the patient's anatomy. If the seal is inadequate, mask pressure should be lowered somewhat; if this approach does not work, a larger mask size should be tried.

In emergencies, LMAs should be viewed as bridging devices. Prolonged placement, overinflation of the mask, or both may compress the tongue and cause tongue edema. Also, if noncomatose patients are given muscle relaxants before LMA insertion (eg, for laryngoscopy), they may gag and possibly aspirate when such drugs wear off. Either the device should be removed (assuming ventilation and gag reflexes are adequate), or drugs should be given to eliminate the gag response and provide time for an alternative intubation technique.

**Endotracheal tubes:** An endotracheal tube is inserted directly into the trachea via the mouth or, less commonly, the nose. Endotracheal tubes have high-volume, low-pressure balloon cuffs to prevent air leakage and minimize the risk of aspiration. Cuffed tubes were traditionally used only in adults and children > 8 yr; however, cuffed tubes are increasingly being used in infants and younger children to limit air leakage (particularly during transport); sometimes cuffs are not inflated or inflated only to the extent needed to prevent obvious leakage.

An endotracheal tube is the definitive method to secure a compromised airway, limit aspiration, and initiate mechanical ventilation in comatose patients, in patients who cannot protect their own airways, and in those who need prolonged mechanical ventilation. It also permits suctioning of the lower respiratory tract. Although drugs can be delivered via an endotracheal tube during cardiac arrest, this practice is discouraged.

Placement typically requires laryngoscopy by a skilled practitioner, but a variety of novel insertion devices that provide other options are becoming available.

**Other devices:** Another class of rescue ventilation devices is laryngeal tube or twin-lumen airways (eg, Combitube®, King LT®). These devices use 2 balloons to create a seal above and below the larynx and have ventilation ports overlying the laryngeal inlet (which is between the balloons). As with LMAs, prolonged placement and balloon overinflation can cause tongue edema.

**Tracheal Intubation**

Most patients requiring an artificial airway can be managed with tracheal intubation.

[Fig. 224-6. Laryngeal mask airway (LMA).]

Orotracheal intubation, typically done via direct laryngoscopy, is preferred in apneic and critically ill patients because it can usually be done faster than nasotracheal intubation, which is reserved for awake, spontaneously breathing patients or for cases when the mouth must be avoided.

**Before intubation:** Maneuvers to create a patent airway and to ventilate and oxygenate the patient are always indicated before attempting tracheal intubation. Once a decision to intubate has been made, preparatory measures include

• Correct patient positioning (see Fig. 224-1)

• Ventilation with 100% O_2

• Readying of necessary equipment (including suction devices)

• Sometimes drugs
Ventilation with 100% O\textsubscript{2} denitrogenates healthy patients and significantly prolongs the safe apneic time (effect is less in patients with severe cardiopulmonary disorders).

Strategies to predict difficult laryngoscopy (eg, Mallampati scoring, thyromental distance testing) are of limited value in emergencies. Practitioners should always be prepared to use an alternate technique (eg, LMA, BVM ventilation) if laryngoscopy does not work.

During cardiac arrest, chest compressions should not be halted for intubation attempts. If practitioners cannot intubate while compressions are being done (or during the brief pause that occurs during compressor changes), an alternate airway technique should be used.

Suction should be immediately available with a rigid tonsil-tip suction device to clear secretions and other material from the airway.

Anterior cricoid pressure (Sellick’s maneuver) has previously been recommended before and during intubation to prevent passive regurgitation. However, current literature suggests that this maneuver may be less effective than once thought and may compromise laryngeal view during laryngoscopy.

Drugs (see p. 2278), including sedatives, muscle relaxants, and sometimes vagolytics, are typically given to conscious or semiconscious patients before laryngoscopy.

**Tube selection and preparation:** Most adults can accept a tube with an internal diameter of ≥ 8 mm; these tubes are preferable to smaller ones because they have lower airflow resistance (reducing the work of breathing), facilitate suctioning of secretions, allow passage of a bronchoscope, and may aid in liberation from mechanical ventilation.

For infants and children ≥ 1 yr, uncuffed tube size is calculated by (patient's age + 16)/4; thus, a 4-yr-old should have a (4 + 16)/4 = 5 mm endotracheal tube. The tube size suggested by this formula should be reduced by 0.5 (1 tube size) if a cuffed tube is to be used. Reference charts (see Table 223-3) or devices such as the Broselow Tape or Pedi-Wheel can rapidly identify appropriate-sized laryngoscope blades and endotracheal tubes for infants and children.

For adults (and sometimes in children), a rigid stylet should be placed in the tube, taking care to stop the stylet 1 to 2 cm before the distal end of the endotracheal tube, so that the tube tip remains soft. The stylet should then be used to make the tube straight to the beginning of the distal cuff; from that point, the tube is bent upward about 35° to form a hockey stick shape. This straight-to-cuff shape improves tube delivery and avoids blocking the operator's view of the cords during tube passage. Routinely filling the distal ET tube cuff with air to check the balloon is not required; if this technique is used, care must be taken to remove all the air before tube insertion.

**Insertion technique:** Successful intubation on the first attempt is important. Repeated laryngoscopy (≥ 3 attempts) is associated with much higher rates of significant hypoxemia, aspiration, and cardiac arrest. In addition to correct positioning, several other general principles are critical for success:

- Visualizing the epiglottis
- Visualizing the posterior laryngeal structures (ideally, the vocal cords)
- Not passing the tube unless tracheal insertion is ensured

The laryngoscope is held in the left hand, and the blade is inserted into the mouth and used as a retractor to displace the mandible and tongue up and away from the laryngoscopist, revealing the posterior pharynx. Avoiding contact with the incisors and not placing undue pressure on laryngeal structures are important.

*The importance of identifying the epiglottis cannot be overstated.* Identifying the epiglottis allows the operator to recognize critical airway landmarks and correctly position the laryngoscope blade. The epiglottis may rest against the posterior pharyngeal wall, where it blends in with the other pink mucus.
membranes or gets lost in the pool of secretions that invariably exists in the cardiac arrest patient's airway.

Once the epiglottis is found, the operator may pick it up with the tip of the blade (the typical straight blade approach) or advance the tip of the blade into the vallecula to indirectly lift the epiglottis up and out of the line of sight (the typical curved blade approach). Success with the curved blade depends on the proper positioning of the blade tip in the vallecula and the direction of the lifting force (see Fig. 224-7). Lifting the epiglottis by either technique reveals the posterior laryngeal structures (arytenoid cartilages, interarytenoid notch), glottis, and vocal cords. If the tip of the blade is too deep, laryngeal landmarks may be entirely bypassed, and the dark, round hole of the esophagus may be mistaken for the glottis opening.

If identifying structures is difficult, manipulating the larynx with the right hand placed on the anterior neck (allowing the right and left hands to work together) may optimize the laryngeal view (see Fig. 224-7). Another technique involves lifting the head higher (lifting at the occiput, not atlanto-occipital extension), which distracts the jaw and improves the line of sight. Head elevation is inadvisable in patients with potential cervical spine injury and is difficult in the morbidly obese (who must be placed in a ramped or head-elevated position beforehand).

[Fig. 224-7. Bimanual laryngoscopy.]

In an optimal view, the vocal cords are clearly seen. If the vocal cords are not seen, at a minimum, the posterior laryngeal landmarks must be viewed and the tip of the tube must be seen passing above the interarytenoid notch and posterior cartilages. Operators must clearly identify laryngeal landmarks to avoid potentially fatal esophageal intubation. If operators are not confident that the tube is going into the trachea, the tube should not be inserted.

Once an optimal view has been achieved, the right hand inserts the tube through the larynx into the trachea (if operators have been applying anterior laryngeal pressure with the right hand, an assistant should continue applying this pressure). If the tube does not pass easily, a 90° clockwise twist of the tube may help it pass more smoothly over the anterior tracheal rings. Before withdrawing the laryngoscope, operators should confirm that the tube is passing between the cords. Appropriate tube depth is usually 21 to 23 cm in adults and 3 times the endotracheal tube size in children (for a 4.0-mm endotracheal tube, 12 cm; for a 5.5-mm endotracheal tube, 16.5 cm). In adults, the tube, if inadvertently advanced, typically migrates into the right mainstem bronchus.

Alternative intubation devices: A number of devices and techniques are increasingly used for intubation after failed laryngoscopy or as a primary means of intubation. Devices include

- Video laryngoscopes
- Mirror laryngoscopes
- LMA with a passage that allows tracheal intubation
- Fiberoptic scopes and optical stylets
- Tube introducers

Each device has its own subtleties; practitioners who are skilled in standard laryngoscopic intubation techniques should not assume they can use one of these devices (especially after use of muscle relaxants) without becoming thoroughly familiarized with it.

Video and mirror laryngoscopes enable practitioners to look around the curvature of the tongue and usually provide excellent laryngeal views. However, the tube requires an exaggerated bend angle to go around the tongue and thus may be more difficult to manipulate and insert.

To pass an endotracheal tube through an LMA, practitioners must understand how to optimally position
the mask over the laryngeal inlet; there are sometimes mechanical difficulties passing the endotracheal tube.

Flexible fiberoptic scopes and optical stylets are very maneuverable and can be used in patients with abnormal anatomy. However, practice is required to recognize laryngeal landmarks from a fiberoptic perspective. Compared with video and mirror laryngoscopes, fiberoptic scopes are more difficult to master and are more susceptible to problems with blood and secretions; also, they do not separate and divide tissue but instead must be moved through open channels.

Tube introducers (commonly called gum elastic bougies) are semirigid stylets that can be used when laryngeal visualization is suboptimal (eg, the epiglottis is visible, but the laryngeal opening is not). In such cases, the introducer is passed along the undersurface of the epiglottis; from this point, it is likely to enter the trachea. Tracheal entry is suggested by the tactile feedback, noted as the tip bounces over the tracheal rings. An endotracheal tube is then advanced over the introducer.

Postinsertion: The stylet is removed and the balloon cuff is inflated with air using a 10-mL syringe; a manometer is used to verify that balloon pressure is < 30 cm H₂O. Properly sized endotracheal tubes may need considerably < 10 mL of air to create the correct pressure.

After balloon inflation, tube placement should be checked using a variety of methods, including

- Inspection and auscultation
- CO₂ detection
- Esophageal detector devices
- Sometimes chest x-ray

When a tube is correctly placed, manual ventilation should produce symmetric chest rise, good breath sounds over both lungs, and no gurgling over the upper abdomen.

Exhaled air should contain CO₂ and gastric air should not; detecting CO₂ with a colori-metric end-tidal CO₂ device or waveform capnography confirms tracheal placement. However, in prolonged cardiac arrest (ie, with little or no metabolic activity), CO₂ may not be detectable even with correct tube placement. In such cases, an esophageal detector device may be used. These devices use an inflatable bulb or a large syringe to apply negative pressure to the endotracheal tube. The flexible esophagus collapses, and little or no air flows into the device; in contrast, the rigid trachea does not collapse, and the resultant airflow confirms tracheal placement.

In the absence of cardiac arrest, tube placement is typically also confirmed with a chest x-ray.

After correct placement is confirmed, the tube should be secured using a commercially available device or adhesive tape. Adapters connect the endotracheal tube to a resuscitator bag, T-piece supplying humidity and O₂, or a mechanical ventilator.

Endotracheal tubes can be displaced, particularly in chaotic resuscitation situations, so tube position should be rechecked frequently. If breath sounds are absent on the left, right mainstem bronchus intubation is probably more likely than a left-sided tension pneumothorax, but both should be considered.

Nasotracheal intubation: If patients are spontaneously breathing, this technique can be used in certain emergency situations—eg, when patients have severe oral or cervical disorders (eg, injuries, edema, limitation of motion) that make laryngoscopy difficult. Historically, nasal intubation was also used when muscle relaxants were unavailable or forbidden (eg, prehospital settings, certain emergency departments) and when patients with tachypnea, hyperpnea, and upright positioning (eg, those with heart failure) might literally inhale a tube. However, availability of noninvasive means of ventilation (eg, bilevel positive airway pressure [BiPAP]), improved access to and training in pharmacologic adjuncts to intubation, and newer
Airway devices have markedly decreased the use of nasal intubation. Additional considerations are problems with nasal intubation, including sinusitis (universal after 3 days), and the fact that tubes large enough to permit bronchoscopy (eg, ≥ 8 mm) can rarely be inserted nasotracheally.

When nasotracheal intubation is done, a vasoconstrictor (eg, phenylephrine) and topical anesthetic (eg, benzocaine, lidocaine) must be applied to the nasal mucosa and the larynx to prevent bleeding and to blunt protective reflexes. Some patients may also require IV sedatives, opioids, or dissociative drugs. After the nasal mucosa is prepared, a soft nasal trumpet should be inserted to ensure adequate patency of the selected nasal passage and to serve as a conduit for topical drugs to the pharynx and larynx. The trumpet may be placed using a plain or anesthetic (eg, lidocaine) lubricant. The nasal trumpet is removed after the pharyngeal mucosa has been sprayed. The nasotracheal tube is then inserted to about 14 cm depth (just above the laryngeal inlet in most adults); at this point, air movement should be audible. As the patient breathes in, opening the vocal cords, the tube is promptly passed into the trachea. More flexible endotracheal tubes with a controllable tip improve likelihood of success. Some practitioners soften tubes by placing them in warm water to lessen the risk of bleeding and make insertion easier. A small commercially available whistle can also be attached to the proximal tube connector to accentuate the noise of air movement when the tube is in the correct position above the larynx and in the trachea.

**Surgical Airway**

If the upper airway is obstructed because of a foreign body or massive trauma or if ventilation cannot be accomplished by other means, surgical entry into the trachea is required. Historically, a surgical airway was also the response to failed intubation. However, surgical airways require on average about 100 sec from initial incision to ventilation; LMAAs and other devices provide a faster means of rescue ventilation, and very few patients require an emergency surgical airway.

**Cricothyrotomy:** Cricothyrotomy (see Fig. 224-8) is typically used for emergency surgical access because it is faster and simpler than tracheostomy.

Unlike positioning for laryngoscopy or ventilation, the correct position for cricothyrotomy involves extending the neck and arching the shoulders backward. After sterile preparation, the larynx is grasped with the nondominant hand while a blade held in the dominant hand is used to incise the skin, subcutaneous tissue, and cricothyroid membrane. A tracheal hook helps keep the space open and prevent retraction of the trachea while a small endotracheal tube (6.0 mm internal diameter [ID]) or small tracheotomy tube (cuffed 4.0 Shiley preferred) is advanced through the surgical site into the trachea.

Complications include hemorrhage, subcutaneous emphysema, pneumomediastinum, and pneumothorax. Various commercial products allow rapid surgical access to the cricothyroid space and provide a tube that allows adequate oxygenation and ventilation.

**Tracheostomy:** Tracheostomy is a more complex procedure because the trachea rings are very close together and part of at least one ring usually must be removed to allow tube placement. Tracheostomy is preferably done in an operating room by a surgeon. In emergencies, the procedure has a higher rate of complications than cricothyrotomy and offers no advantage. However, it is the preferred procedure for patients requiring long-term ventilation.

Percutaneous tracheostomy is an attractive alternative for critically ill patients who cannot be moved to the operating room. This bedside technique uses skin puncture and dilators to insert a tracheostomy tube. Fiberoptic assistance (within the trachea) is usually used to prevent puncture of the membranous (posterior) trachea and esophagus.

**Complications of Tracheal Intubation**

Complications include
• Direct trauma

• Esophageal intubation

• Tracheal erosion or stenosis

Laryngoscopy can damage lips, teeth, tongue, and supraglottic and subglottic areas.

Tube placement in the esophagus, if unrecognized, causes failure to ventilate and potentially death or hypoxic injury. Insufflating a tube in the stomach causes regurgitation, which can result in aspiration, compromise subsequent BVM ventilation, and obscure visualization in subsequent intubation attempts.

Any translaryngeal tube injures the vocal cords somewhat; sometimes ulceration, ischemia, and prolonged cord paralysis occur. Subglottic stenosis can occur later (usually 3 to 4 wk).

Rarely, tracheostomy insertion causes hemorrhage, thyroid damage, pneumothorax, recurrent laryngeal nerve paralysis, injury to major vessels, or late tracheal stenosis at the insertion site.

Erosion of the trachea is uncommon. It results more commonly from excessively high cuff pressure. Rarely, hemorrhage from major vessels (eg, innominate artery), fistulas (especially tracheoesophageal), and tracheal stenosis occur. Using high-volume, low-pressure cuffs with tubes of appropriate size and measuring cuff pressure frequently (every 8 h) to maintain it at < 30 cm H₂O decrease the risk of ischemic pressure necrosis, but patients in shock, with low cardiac output, or with sepsis remain especially vulnerable.

**Drugs to Aid Intubation**

Pulseless and apneic or severely obtunded patients can (and should) be intubated without pharmacologic assistance. Other patients are given sedating and paralytic drugs to minimize discomfort and facilitate intubation (termed rapid sequence intubation).

**Pretreatment:** Pretreatment typically includes

• 100% O₂

• Lidocaine

• Sometimes atropine, a neuromuscular blocker, or both

If time permits, patients should be placed on 100% O₂ for 3 to 5 min; this measure may maintain satisfactory oxygenation in previously healthy patients for up to 8 min. However, O₂ demand and safe apnea times are very dependent on pulse rate, pulmonary function, RBC count, and numerous other metabolic factors.

Laryngoscopy causes a sympathetic-mediated pressor response with an increase in heart rate, BP, and possibly intracranial pressure. To blunt this response, when time permits, some practitioners give lidocaine 1.5 mg/kg IV 1 to 2 min before sedation and paralysis.

Children and adolescents often have a vagal response (marked bradycardia) in response to intubation and are given atropine 0.02 mg/kg IV (minimum: 0.1 mg in infants, 0.5 mg in children and adolescents) at the same time.

Some physicians include a small dose of a neuromuscular blocker (NMB), such as vecuronium 0.01 mg/kg IV, in patients > 4 yr to prevent muscle fasciculations caused by full doses of succinylcholine. Fasciculations may result in muscle pain on awakening and cause transient hyperkalemia; however, the actual benefit of such pretreatment is unclear.
Sedation and analgesia: Laryngoscopy and intubation are uncomfortable; in conscious patients, a short-acting IV drug with sedative or combined sedative and analgesic properties is mandatory.

Etomidate 0.3 mg/kg, a nonbarbiturate hypnotic, may be the preferred drug. Fentanyl 5 μg/kg (2 to 5 μg/kg in children; NOTE: this dose is higher than the analgesic dose) also works well and causes no cardiovascular depression. Fentanyl is an opioid and thus has analgesic as well as sedative properties. However, at higher doses, chest wall rigidity may occur. Ketamine 1 to 2 mg/kg is a dissociative anesthetic with cardiotonic properties. It is generally safe but may cause hallucinations or bizarre behavior on awakening. Thiopental 3 to 4 mg/kg and methohexital 1 to 2 mg/kg are effective but tend to cause hypotension and are used less often.

Paralysis: Skeletal muscle relaxation with an IV NMB markedly facilitates intubation.

Succinylcholine (1.5 mg/kg IV, 2.0 mg/kg for infants), a depolarizing NMB, has the most rapid onset (30 sec to 1 min) and shortest duration (3 to 5 min). It should be avoided in patients with burns, muscle crush injuries > 1 to 2 days old, spinal cord injury, neuromuscular disease, renal failure, or possibly penetrating eye injury. About 1/15,000 children (and fewer adults) have a genetic susceptibility to malignant hyperthermia (see p. 3266) from succinylcholine. Succinylcholine should always be given with atropine in children because pronounced bradycardia may occur.

Alternative nondepolarizing NMBs have longer duration of action (> 30 min) but also have slower onset unless used in high doses that prolong paralysis significantly. Drugs include atracurium 0.5 mg/kg, mivacurium 0.15 mg/kg, rocuronium 1.0 mg/kg, and vecuronium 0.1 to 0.2 mg/kg injected over 60 sec.

Topical anesthesia: Intubation of an awake patient (typically not done in children) requires anesthesia of the nose and pharynx. A commercial aerosol preparation of benzocaine, tetracaine, butyl aminobenzoate (butamben), and benzalkonium is commonly used. Alternatively, 4% lidocaine can be nebulized and inhaled via face mask.
Chapter 225. Respiratory Failure and Mechanical Ventilation

Introduction

Respiratory failure is a life-threatening impairment of oxygenation or CO\textsubscript{2} elimination. Respiratory failure may occur because of impaired gas exchange, decreased ventilation, or both. Common manifestations include dyspnea, use of accessory muscles of respiration, tachypnea, tachycardia, diaphoresis, cyanosis, altered consciousness, and, without treatment, eventually obtundation, respiratory arrest, and death. Diagnosis is clinical, supplemented by ABGs and chest x-ray. Treatment is usually in an ICU and involves correction of the underlying cause, supplemental O\textsubscript{2}, control of secretions, and ventilatory assistance if needed.

The respiratory system oxygenates and eliminates CO\textsubscript{2} from venous blood. Thus, a useful classification of respiratory failure is whether the principal abnormality is inadequate oxygenation or inadequate CO\textsubscript{2} elimination (which means inadequate ventilation), although many disorders affect both. Although temporizing measures exist, respiratory failure frequently necessitates mechanical ventilation.

Overview of Mechanical Ventilation

Mechanical ventilation can be noninvasive, involving various types of face masks, or invasive, involving endotracheal intubation. Selection and use of appropriate techniques require an understanding of respiratory mechanics.

Indications: There are numerous indications for endotracheal intubation and mechanical ventilation (see Table 224-1 on p. 2270), but in general, mechanical ventilation should be considered when there are clinical or laboratory signs that the patient cannot maintain an airway or adequate oxygenation or ventilation. Concerning findings include respiratory rate > 30/min, inability to maintain arterial O\textsubscript{2} saturation > 90% with fractional inspired O\textsubscript{2} (FIO\textsubscript{2}) > 0.60, and PaCO\textsubscript{2} > 50 mm Hg with pH < 7.25. The decision to initiate mechanical ventilation should be based on clinical judgment that considers the entire clinical situation and should not be delayed until the patient is in extremis.

Respiratory Mechanics

Normal inspiration generates negative intrapleural pressure, which creates a pressure gradient between the atmosphere and the alveoli, resulting in air inflow. In mechanical ventilation, the pressure gradient results from increased (positive) pressure of the air source.

Peak airway pressure is measured at the airway opening (Pao) and is routinely displayed by mechanical ventilators. It represents the total pressure needed to push a volume of gas into the lung and is composed of pressures resulting from inspiratory flow resistance (resistive pressure), the elastic recoil of the lung and chest wall (elastic pressure), and the alveolar pressure present at the beginning of the breath (positive end-expiratory pressure [PEEP]—see also Fig. 225-1). Thus

\[ \text{Peak airway pressure} = \text{resistive pressure} + \text{elastic pressure} + \text{PEEP} \]

Resistive pressure is the product of circuit resistance and airflow. In the mechanically ventilated patient, resistance to airflow occurs in the ventilator circuit, the endotracheal tube, and, most importantly, the patient's airways. NOTE: Even when these factors are constant, an increase in airflow increases resistive pressure.

Elastic pressure is the product of the elastic recoil of the lungs and chest wall (elastance) and the volume of gas delivered. For a given volume, elastic pressure is increased by increased lung stiffness (as in pulmonary fibrosis) or restricted excursion of the chest wall or diaphragm (eg, in tense ascites or massive obesity). Because elastance is the inverse of compliance, high elastance is the same as low compliance.
**End-expiratory pressure** in the alveoli is normally the same as atmospheric pressure. However, when the alveoli fail to empty completely because of airway obstruction, airflow limitation, or shortened expiratory time, end-expiratory pressure may be positive relative to the atmosphere. This pressure is called intrinsic PEEP or autoPEEP to differentiate it from externally applied (therapeutic) PEEP, which is created by adjusting the mechanical ventilator or by placing a tight-fitting mask that applies positive pressure throughout the respiratory cycle.

Any elevation in peak airway pressure (eg, > 25 cm H₂O) should prompt measurement of the end-inspiratory pressure (plateau pressure) by an end-inspiratory hold maneuver to determine the relative contributions of resistive and elastic pressures. The maneuver keeps the exhalation valve closed for an additional 0.3 to 0.5 sec after inspiration, delaying exhalation. During this time, airflow ceases. The resulting end-inspiratory pressure represents the elastic pressure once PEEP is subtracted (assuming the patient is not making active inspiratory or expiratory muscle contractions at the time of measurement). The difference between peak and plateau pressure is the resistive pressure.

Elevated resistive pressure (eg, > 10 cm H₂O) suggests that the endotracheal tube has been kinked or plugged with secretions or that an intraluminal mass, increased intraluminal secretions, or bronchospasm is present. An increase in elastic pressure (eg, > 10 cm H₂O) suggests decreased lung compliance due to edema, fibrosis, or lobar atelectasis; large pleural effusions, pneumothorax or fibrothorax; extrapulmonary restriction as may result from circumferential burns or other chest wall deformity, ascites, pregnancy, or massive obesity; or a tidal volume too large for the amount of lung being ventilated (eg, a normal tidal volume being delivered to a single lung because the endotracheal tube is malpositioned).

Intrinsic PEEP can be measured in the passive patient through an end-expiratory hold maneuver. Immediately before a breath, the expiratory port is closed for 2 sec. Flow ceases, eliminating resistive pressure; the resulting pressure reflects alveolar pressure at the end of expiration (intrinsic PEEP). A nonquantitative method of identifying intrinsic PEEP is to inspect the expiratory flow tracing. If expiratory flow continues until the next breath or the patient's chest fails to come to rest before the next breath, intrinsic PEEP is present. The consequences of elevated intrinsic PEEP include increased inspiratory work of breathing and decreased venous return, which may result in decreased cardiac output and hypotension.

The demonstration of intrinsic PEEP should prompt a search for causes of airflow obstruction (eg, airway secretions, bronchospasm); however, a high minute ventilation (> 20 L/min) alone can result in intrinsic PEEP in a patient with no airflow obstruction. If the cause is airflow limitation, intrinsic PEEP can be reduced by shortening inspiratory time (ie, increasing inspiratory flow) or reducing the respiratory rate, thereby allowing a greater fraction of the respiratory cycle to be spent in exhalation.

**Means and Modes of Mechanical Ventilation**

Mechanical ventilators are typically volume or pressure cycled; some newer models combine features of both. Because pressures and volumes are directly linked by the pressure-volume curve, any given volume will correspond to a specific pressure, and vice versa, regardless of whether the ventilator is pressure or volume cycled.

Adjustable ventilator settings differ with mode but include respiratory rate, tidal volume, trigger sensitivity, flow rate, waveform, and inspiratory/expiratory (I/E) ratio.

**Volume-cycled ventilation:** In this mode, which includes assist-control (A/C) and synchronized intermittent mandatory ventilation (SIMV), the ventilator delivers a set tidal volume. The resultant airway pressure is not fixed but varies with the resistance and elastance of the respiratory system and with the flow rate selected.
**A/C** ventilation is the simplest and most effective means of providing full mechanical ventilation. In this mode, each inspiratory effort beyond the set sensitivity threshold triggers delivery of the fixed tidal volume. If the patient does not trigger the ventilator frequently enough, the ventilator initiates a breath, ensuring the desired minimum respiratory rate.

**SIMV** also delivers breaths at a set rate and volume that is synchronized to the patient's efforts. In contrast to A/C, however, patient efforts above the set respiratory rate are unassisted, although the intake valve opens to allow the breath. This mode remains popular, despite the fact that it neither provides full ventilator support as does A/C nor facilitates liberating the patient from mechanical ventilation.

**Pressure-cycled ventilation:** This form of mechanical ventilation includes pressure control ventilation (PCV), pressure support ventilation (PSV), and several noninvasive modalities applied via a tight-fitting face mask. In all of these modalities, the ventilator delivers a set inspiratory pressure. Hence, tidal volume varies depending on the resistance and elastance of the respiratory system. In this mode, changes in respiratory system mechanics can result in unrecognized changes in minute ventilation. Because it limits the distending pressure of the lungs, this mode can theoretically benefit patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS); however, no clear clinical advantage over A/C has been shown.

**Pressure control ventilation** is similar to A/C; each inspiratory effort beyond the set sensitivity threshold delivers full pressure support maintained for a fixed inspiratory time. A minimum respiratory rate is maintained.

In **pressure support ventilation**, a minimum rate is not set; all breaths are triggered by the patient. Pressure is typically cut off when back-pressure causes flow to drop below a certain point. Thus, a longer or deeper inspiratory effort by the patient results in a larger tidal volume. This mode is commonly used to liberate patients from mechanical ventilation by letting them assume more of the work of breathing. However, no studies indicate that this approach is more successful.

**Noninvasive positive pressure ventilation (NIPPV):** NIPPV is the delivery of positive pressure ventilation via a tight-fitting mask that covers the nose or both the nose and mouth. Because of its use in spontaneously breathing patients, it is primarily applied as a form of PSV, although volume control can be used.

NIPPV can be given as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). In CPAP, constant pressure is maintained throughout the respiratory cycle with no additional inspiratory support. With BiPAP, the physician sets both the expiratory positive airway pressure (EPAP) and the inspiratory positive airway pressure (IPAP), with respirations triggered by the patient. Because the airway is unprotected, aspiration is possible, so patients must have adequate mentation and airway protective reflexes and no imminent indication for surgery or transport off the floor for prolonged procedures. NIPPV should be avoided in patients who are hemodynamically unstable and in those with evidence of impaired gastric emptying, as occurs with ileus, bowel obstruction, or pregnancy. In such circumstances, swallowing large quantities of air may result in vomiting and life-threatening aspiration. Indications for conversion to endotracheal intubation and conventional mechanical ventilation include the development of shock or frequent arrhythmias, myocardial ischemia, and transport to a cardiac catheterization laboratory or surgical suite where control of the airway and full ventilatory support are desired. Obtunded patients and patients with copious secretions are not good candidates. Also, IPAP must be set below esophageal opening pressure (20 cm H\(_2\)O) to avoid gastric insufflation.

NIPPV can be used in the outpatient setting. For example, CPAP is often used for patients with obstructive sleep apnea (see p. 1903), whereas BiPAP can be used for those with concomitant central sleep apnea (see p. 1907) and obstructive sleep apnea or for chronic ventilation in patients with progressive neuromuscular diseases.

**Ventilator settings:** Ventilator settings are tailored to the underlying condition, but the basic principles are as follows.
Tidal volume and respiratory rate set the minute ventilation. Too high a volume risks overinflation; too low a volume risks atelectasis. Too high a rate risks hyperventilation and respiratory alkalosis along with inadequate expiratory time and autoPEEP; too low a rate risks inadequate minute ventilation and respiratory acidosis. A tidal volume of 8 to 10 mL/kg ideal body weight is usually appropriate, although some patients with normal lung mechanics (particularly those with neuromuscular disease) benefit from tidal volumes on the high end of this range to prevent atelectasis, whereas patients with ALI/ARDS or acute exacerbations of COPD or asthma may require lower volumes. Ideal body weight (IBW) rather than actual body weight is used to determine the appropriate tidal volume for patients with lung disease and receiving mechanical ventilation:

Males: IBW (kg) =
50 + 2.3 (height in inches - 60)
or 50 + 0.91 (height in cm - 152.4)

Females: IBW (kg) =
45.5 + 2.3 (height in inches - 60)
or 45.5 + 0.91 (height in cm - 152.4)

Sensitivity adjusts the level of negative pressure required to trigger the ventilator. A typical setting is -2 cm H2O. Too high a setting causes weak patients to be unable to trigger a breath. Too low a setting may lead to overventilation by causing the machine to auto-cycle. Patients with high levels of autoPEEP may have difficulty inhaling deeply enough to achieve a sufficiently negative intra-airway pressure.

The ratio of time spent in inhalation versus that spent in exhalation (I:E ratio) can be adjusted in some modes of ventilation. A normal setting for patients with normal mechanics is 1:3. Patients with asthma or COPD exacerbations should have ratios of 1:4 or even more to limit the degree of autoPEEP.

The inspiratory flow rate can be adjusted in some modes of ventilation (ie, either the flow rate or the I:E ratio can be adjusted, not both). The inspiratory flow should generally be set at about 60 L/min but can be increased up to 120 L/min for patients with airflow limitation to facilitate having more time in exhalation, thereby limiting autoPEEP.

FIO2 is initially set at 1.0 and is subsequently decreased to the lowest level necessary to maintain adequate oxygenation.

PEEP can be applied in any ventilator mode. PEEP increases end-expired lung volume and reduces airspace closure at the end of expiration. Most patients undergoing mechanical ventilation may benefit from the application of PEEP at 5 cm H2O to limit the atelectasis that frequently accompanies endotracheal intubation, sedation, paralysis, and/or supine positioning. Higher levels of PEEP improve oxygenation in disorders such as cardiogenic pulmonary edema and ARDS. PEEP permits use of lower levels of FIO2 while preserving adequate arterial oxygenation. This effect may be important in limiting the lung injury that may result from prolonged exposure to a high FIO2 (≥ 0.6). PEEP increases intrathoracic pressure and thus may impede venous return, provoking hypotension in a hypovolemic patient, and may overdistend portions of the lung, thereby causing ventilator-associated lung injury (VALI). By contrast, if PEEP is too low, it may result in cyclic airspace opening and closing, which in turn may also cause VALI from the resultant repetitive shear forces.

Patient positioning: Mechanical ventilation is typically done with the patient in the semiprivate position. However, in patients with ALI/ARDS, prone positioning may result in better oxygenation primarily by creating more uniform ventilation. Uniform ventilation reduces the amount of lung that has no ventilation (ie, the amount of shunt), which is generally greatest in the dorsal and caudal lung regions, while having minimal effects on perfusion distribution.

Although many investigators advocate a trial of prone positioning in patients with ALI/ARDS who require high levels of PEEP (eg, > 12 cm H2O) and FIO2 (eg, > 0.6), trials have not shown any improvement in mortality with this strategy. Prone positioning is contraindicated in patients with spinal instability or increased intracranial pressure. This position also requires concerted effort by the ICU staff to avoid
complications, such as dislodgement of the endotracheal tube or intravascular lines.

**Sedation and comfort:** Although some patients tolerate mechanical ventilation via endotracheal tube without sedatives, most require continuous IV administration of sedatives (eg, propofol, lorazepam, midazolam) and analgesics (eg, morphine, fentanyl) to minimize stress and anxiety. These drugs can also reduce energy expenditure to some extent, thereby reducing CO₂ production and O₂ consumption. Doses should be titrated to the desired effect, guided by standard sedation/analgesia scoring systems.

Patients undergoing mechanical ventilation for ALI/ARDS typically require higher levels of sedation and analgesia. The use of propofol for longer than 24 to 48 h requires periodic monitoring of serum triglyceride levels.

Neuromuscular blocking agents are now rarely used in patients undergoing mechanical ventilation because of the risk of prolonged neuromuscular weakness and the need for continuous heavy sedation. Exceptions include for failure to tolerate some of the more sophisticated and complicated modes of mechanical ventilation and for prevention of shivering when cooling is used after cardiac arrest.

**Complications and safeguards:** Complications can be divided into those resulting from endotracheal intubation, from mechanical ventilation itself, or from prolonged immobility and inability to eat normally.

The presence of an endotracheal tube causes risk of sinusitis (which is rarely of clinical importance), ventilator-associated pneumonia (see p. 1929), tracheal stenosis, vocal cord injury, and rarely tracheal-esophageal or trachealvascular fistula.

Purulent tracheal aspirate in a febrile patient who has an elevated WBC count > 48 h after ventilation has begun suggests ventilator-associated pneumonia.

Complications of ongoing mechanical ventilation itself include pneumothorax, O₂ toxicity, hypotension, and VALI.

If acute hypotension develops in a mechanically ventilated patient, particularly when it is accompanied by tachycardia and/or a sudden increase in peak inspiratory pressure, tension pneumothorax must always be considered; patients with such findings should immediately have a chest examination and a chest x-ray (or immediate treatment if examination is confirmatory). More commonly, however, hypotension is a result of sympathetic lysis caused by sedatives or opioids used to facilitate intubation and ventilation. Hypotension can also be caused by decreased venous return due to high intrathoracic pressure in patients receiving high levels of PEEP or in those with high levels of intrinsic PEEP due to asthma or COPD. If there are no physical findings suggesting tension pneumothorax and if ventilation-related causes of hypotension are a possible etiology, pending a portable chest x-ray, the patient may be disconnected from the ventilator and gently bagged manually at 2 to 3 breaths/min with 100% O₂ while fluids are infused (eg, 500 to 1000 mL of 0.9% saline in adults, 20 mL/kg in children). An immediate improvement suggests a ventilation-related cause, and ventilator settings should be adjusted accordingly.

Relative immobility increases the risk of venous thromboembolic disease, skin breakdown, and atelectasis.

Most hospitals have standardized protocols to reduce complications. Elevating the head of the bed to > 30° decreases risk of ventilator-associated pneumonia, and routine turning of the patient every 2 h decreases the risk of skin breakdown. All patients receiving mechanical ventilation should receive deep venous thrombosis prophylaxis, either heparin 5000 units sc bid to tid or low molecular weight heparin or, if heparin is contraindicated, sequential compression devices. To prevent GI bleeding, patients should receive an H₂ blocker (eg, famotidine 20 mg enterally or IV bid) or sucralfate (1 g enterally qid). Proton pump inhibitors should be reserved for patients with a preexisting indication or active bleeding. Routine nutritional evaluations are mandatory, and enteral tube feedings should be initiated if ongoing mechanical ventilation is anticipated.

The most effective way to reduce complications of mechanical ventilation is to limit its duration. Daily “sedation vacations” and spontaneous breathing trials help determine the earliest point at which the patient may be liberated from mechanical support.
Acute Hypoxemic Respiratory Failure

Acute hypoxemic respiratory failure (AHRF) is severe arterial hypoxemia that is refractory to supplemental O₂. It is caused by intrapulmonary shunting of blood secondary to airspace filling or collapse. Findings include dyspnea and tachypnea. Diagnosis is by ABGs and chest x-ray. Treatment usually requires mechanical ventilation.

Etiology

Airspace filling in AHRF may result from

• Elevated alveolar capillary hydrostatic pressure, as occurs in left ventricular failure or hypovolemia

• Increased alveolar capillary permeability, as occurs in any of the conditions predisposing to acute lung injury/acute respiratory distress syndrome (ALI/ARDS)

• Blood, as seen in diffuse alveolar hemorrhage

Pathophysiology

ALI/ARDS: ALI resulting in more severe hypoxemia is known as ARDS. However, differentiation between these 2 forms (see Table 225-1) is arbitrary given that Pao₂ correlates poorly with lung pathology and clinical course.

In ALI/ARDS, pulmonary or systemic inflammation leads to release of cytokines and other proinflammatory molecules. The cytokines activate alveolar macrophages and recruit neutrophils to the lungs, which in turn release leukotrienes, oxidants, platelet-activating factor, and proteases. These substances damage capillary endothelium and alveolar epithelium, disrupting the barriers between capillaries and airspaces. Edema fluid, protein, and cellular debris flood the airspaces and interstitium, causing disruption of surfactant, airspace collapse, ventilation-perfusion mismatch, shunting, and pulmonary hypertension. The injury is distributed heterogeneously but mainly affects dependent lung zones.

Causes of ALI/ARDS (see Table 225-2) may involve direct lung injury (eg, pneumonia, acid aspiration) or indirect lung injury (eg, sepsis, pancreatitis, massive blood transfusion, nonthoracic trauma). Sepsis and pneumonia account for about 60% of cases.

Refractory hypoxemia: In both types of AHRF, flooded airspaces allow no inspired gas to enter, so the blood perfusing those alveoli remains at the mixed venous O₂ content no matter how high the fractional inspired O₂ (FIO₂). This effect ensures constant admixture of deoxygenated blood into the pulmonary vein and hence arterial hypoxemia. In contrast, hypoxemia that results from ventilating alveoli that have less ventilation than perfusion (ie, low ventilation-to-perfusion ratios as occurs in asthma or COPD and, to some extent, in ARDS/ALI) is readily corrected by supplemental O₂.

Symptoms and Signs

Acute hypoxemia (see also p. 2250) may cause dyspnea, restlessness, and anxiety. Signs include confusion or alteration of consciousness, cyanosis, tachypnea, tachycardia, and diaphoresis. Cardiac arrhythmia and coma can result. Airway flooding or closure causes crackles, detected during chest auscultation; the crackles are typically diffuse but sometimes worse at the lung bases. Jugular venous distention occurs with high levels of PEEP or severe right ventricular failure.
Diagnosis

• Chest x-ray and ABGs

• Clinical definition (see Table 225-1)

Hypoxemia is usually first recognized using pulse oximetry. Patients with low O$_2$ saturation should have a chest x-ray and ABGs. Symptomatic patients should be treated with supplemental O$_2$ while awaiting test results.

If supplemental O$_2$ does not improve the O$_2$ saturation to > 90%, right-to-left shunting of blood should be suspected. An obvious alveolar infiltrate on chest x-ray implicates alveolar flooding as the cause, rather than an intracardiac shunt. However, at the onset of illness, hypoxemia is often present before changes are seen on x-ray.

Once AHRF is diagnosed, the cause must be determined, considering both pulmonary and extrapulmonary causes. Sometimes a known ongoing disorder (eg, acute MI, pancreatitis, sepsis) is an obvious cause. In other cases, history is suggestive; pneumonia should be suspected in an immunocompromised patient, and alveolar hemorrhage is suspected after bone marrow transplant or in a patient with a connective tissue disease. Frequently, however, critically ill patients have received a large volume of IV fluids for resuscitation, and high-pressure AHRF (eg, caused by ventricular failure or fluid overload) resulting from treatment must be distinguished from an underlying low-pressure AHRF (eg, caused by sepsis or pneumonia).

High-pressure pulmonary edema is suggested by a 3rd heart sound, jugular venous distention, and peripheral edema on examination and by the presence of diffuse central infiltrates, cardiomegaly, and an abnormally wide vascular pedicle on chest x-ray. The diffuse, bilateral infiltrates of ALI/ARDS are generally more peripheral. Focal infiltrates are typically caused by lobar pneumonia, atelectasis, or lung contusion. Although echocardiography may show left ventricular dysfunction, implying a cardiac origin, this finding is not specific because sepsis can also reduce myocardial contractility.

When ALI/ARDS is diagnosed but the cause is not obvious (eg, trauma, sepsis, severe pulmonary infection, pancreatitis), a review of drugs and recent diagnostic tests, procedures, and treatments may suggest an unrecognized cause, such as use of a radiographic contrast agent, air embolism, or transfusion. When no predisposing cause can be uncovered, some experts recommend doing bronchoscopy with bronchoalveolar lavage to exclude alveolar hemorrhage and eosinophilic pneumonia and, if this procedure is not revealing, a lung biopsy to exclude other disorders (eg, extrinsic allergic alveolitis, acute interstitial pneumonitis).

Prognosis

Prognosis is highly variable and depends on a variety of factors, including etiology of respiratory failure, severity of disease, age, and chronic health status. In particular, mortality in ALI/ARDS was very high (40 to 60%) but has declined in recent years to 25 to 40%, probably because of improvements in mechanical ventilation and in treatment of sepsis. Most often, death is not caused by respiratory dysfunction but by sepsis and multiorgan failure. Persistence of neutrophils and high cytokine levels in bronchoalveolar lavage fluid predict a poor prognosis. Mortality otherwise increases with age, presence of sepsis, and severity of preexisting organ insufficiency or coexisting organ dysfunction. Pulmonary function returns to close to normal in 6 to 12 mo in most ALI/ARDS patients who survive; however, patients with a protracted clinical course or severe disease may have residual pulmonary symptoms, and many have persistent neuromuscular weakness.

Treatment

• Mechanical ventilation if saturation is < 90% on high-flow O$_2$
Underlying conditions must be addressed as discussed elsewhere in THE MANUAL. AHRF is initially treated with high flows of 70 to 100% $O_2$ by a nonrebreather face mask. If $O_2$ saturation > 90% is not obtained, mechanical ventilation probably should be instituted. Specific management varies by condition.

**Mechanical ventilation in cardiogenic pulmonary edema:** Mechanical ventilation benefits the failing left ventricle in several ways. Positive inspiratory pressure reduces left and right ventricular preload and left ventricular afterload and unloads the respiratory muscles, reducing the work of breathing. Reducing the work of breathing may allow redistribution of a limited cardiac output away from overworked respiratory muscles. Expiratory pressure (expiratory positive airway pressure [EPAP] or positive end-expiratory pressure [PEEP]) redistributes pulmonary edema from alveoli to the interstitium, allowing more alveoli to participate in gas exchange.

Noninvasive positive pressure ventilation (NIPPV) is useful in averting endotracheal intubation in many patients because drug therapy often leads to rapid improvement. Typical settings are inspiratory positive airway pressure (IPAP) of 10 to 15 cm H$_2$O and EPAP of 5 to 8 cm H$_2$O.

Conventional mechanical ventilation can use several ventilator modes. Most often, assist-control (A/C) is used in the acute setting, when full ventilatory support is desired. Initial settings are tidal volume of 6 mL/kg ideal body weight (see Sidebar 225-1), respiratory rate of 25/min, FIO$_2$ of 1.0, and PEEP of 5 to 8 cm H$_2$O. PEEP may then be titrated upward in 2.5-cm H$_2$O increments while the FIO$_2$ is decreased to nontoxic levels. Pressure support ventilation can also be used (with similar levels of PEEP). The initial pressure delivered should be sufficient to fully rest the respiratory muscles as judged by subjective patient assessment, respiratory rate, and accessory muscle use. Typically, a pressure support level of 10 to 20 cm H$_2$O over PEEP is required.

**Mechanical ventilation in ALI/ARDS:** Nearly all patients require mechanical ventilation (see Sidebar 225-1), which, in addition to improving oxygenation, reduces $O_2$ demand by resting respiratory muscles. Targets include

- Plateau transpulmonary pressures < 30 cm H$_2$O (estimated from plateau alveolar pressures and a consideration of factors that potentially decrease chest wall and abdominal compliance)
- Tidal volume 6 mL/kg predicted body weight to minimize further lung injury
- FIO$_2$ as low as is allowed to maintain adequate SaO$_2$ to minimize possible $O_2$ toxicity

NIPPV is occasionally useful with ALI/ARDS. However, compared with treatment of cardiogenic pulmonary edema, higher levels of support for a longer duration are often required, and EPAP of 8 to 12 cm H$_2$O is often necessary to maintain adequate oxygenation. Achieving this expiratory pressure requires inspiratory pressures > 18 to 20 cm H$_2$O, which are poorly tolerated; maintaining an adequate seal becomes difficult, the mask becomes more uncomfortable, and skin necrosis and gastric insufflation may occur. Also, NIPPV-treated patients who subsequently need intubation have generally progressed to a more advanced condition than if they had been intubated earlier; thus, critical desaturation is possible at the time of intubation. Intensive monitoring and careful selection of patients (see p. 2282) are required.

Conventional mechanical ventilation in ALI/ARDS previously focused on normalizing ABG values. It is now clear that ventilating with lower tidal volumes reduces mortality. Accordingly, in most patients, tidal volume should be set at 6 mL/kg ideal body weight (see Sidebar 225-1). This necessitates an increase in respiratory rate, even up to 35/min, to produce sufficient alveolar ventilation to allow for adequate CO$_2$ removal. On occasion, however, respiratory acidosis develops, some degree of which is accepted for the greater good of limiting ventilator-associated lung injury and is generally well tolerated, particularly when pH is ≥ 7.15. If pH drops below 7.15, bicarbonate infusion may be helpful. Because hypercapnia may cause dyspnea and cause the patient to breathe in a fashion that is not coordinated with the ventilator, analgesics (fentanyl or morphine) and sedatives may be needed (eg, propofol initiated at 5 μg/kg/min and increasing to effect up to 50 μg/kg/min; because of the risk of hypertriglyceridemia, triglyceride levels should be checked every 48 h). Sedation is preferred to neuromuscular blockade because blockade still
Sidebar 225-1 Initial Ventilator Management in ALI/ARDS

Generally, the following approach is recommended for ventilator management in ALI/ARDS:

- Assist-control mode is used initially with a tidal volume 6 mL/kg ideal body weight, respiratory rate 25/min, flow rate 60 L/min, FIO\textsubscript{2} 1.0, and PEEP 15 cm H\textsubscript{2}O.

- Once O\textsubscript{2} saturation is > 90%, FIO\textsubscript{2} is decreased.

- Then, PEEP is decreased in 2.5-cm H\textsubscript{2}O increments as tolerated to find the least PEEP associated with an arterial O\textsubscript{2} saturation of 90% on an FIO\textsubscript{2} of ≤ 0.6.

- The respiratory rate is increased up to 35/min to achieve a pH of > 7.15 or until the expiratory flow tracing shows end-expiratory flow.

Ideal body weight (IBW) rather than actual body weight is used to determine the appropriate tidal volume for patients with lung disease receiving mechanical ventilation:

Males: IBW (kg) = 
50 + 2.3 (height in inches - 60)
or 50 + 0.91 (height in cm - 152.4)
Females: IBW (kg) = 
45.5 + 2.3 (height in inches - 60)
or 45.5 + 0.91 (height in cm - 152.4)

PEEP improves oxygenation in ALI/ARDS by increasing the volume of aerated lung through alveolar recruitment, permitting the use of a lower FIO\textsubscript{2}. The optimal level of PEEP and the way to identify it have been debated. Many clinicians simply use the least amount of PEEP that results in an adequate arterial O\textsubscript{2} saturation on a nontoxic FIO\textsubscript{2}. In most patients, this level is a PEEP of 8 to 15 cm H\textsubscript{2}O, although occasionally, patients with severe ARDS require levels > 20 cm H\textsubscript{2}O. In these cases, close attention must be paid to other means of optimizing O\textsubscript{2} delivery and minimizing O\textsubscript{2} consumption (see p. 2283).

The best indicator of alveolar overdistention is measurement of a plateau pressure through an end-inspiratory hold maneuver (see p. 2286); it should be checked every 4 h and after each change in PEEP or tidal volume. The target plateau pressure is < 30 cm H\textsubscript{2}O. If the plateau pressure exceeds this value and there is no problem with the chest wall that could be contributing (eg, ascites, pleural effusion, acute abdomen, chest trauma), the physician should reduce the tidal volume in 0.5- to 1.0-mL/kg increments as tolerated to a minimum of 4 mL/kg, raising the respiratory rate to compensate for the reduction in minute ventilation and inspecting the ventilator waveform display to ensure that full exhalation occurs. The respiratory rate may often be raised as high as 35/min before overt gas trapping due to incomplete exhalation results. If plateau pressure is < 25 cm H\textsubscript{2}O and tidal volume is < 6 mL/kg, tidal volume may be increased to 6 mL/kg or until plateau pressure is > 25 cm H\textsubscript{2}O. Some investigators believe pressure control ventilation protects the lungs better, although supportive data are lacking and it is the peak pressure rather than the plateau pressure that is being controlled.

Prone positioning (see p. 2283) improves oxygenation in some patients by allowing recruitment of nonventilating lung regions. However, there is no evidence of improved survival.

Optimal fluid management of patients with ALI/ARDS balances the requirement for an adequate circulating volume to preserve end-organ perfusion with the goal of lowering preload and thereby limiting transudation of fluid in the lungs. Recently, a large multicenter trial has shown that a conservative
approach to fluid management, in which less fluid is given, shortens the duration of mechanical ventilation and ICU length of stay when compared with a more liberal strategy. However, there was no difference in survival between the 2 approaches, and use of a pulmonary artery catheter also did not improve outcome. Patients not in shock are candidates for such an approach but should be monitored closely for evidence of decreased end-organ perfusion, such as hypotension, oliguria, thready pulses, or cool extremities (see p. 2292).

A definitive pharmacologic treatment for ALI/ARDS that reduces morbidity and mortality remains elusive. Inhaled nitric oxide, surfactant replacement, and many other agents directed at modulating the inflammatory response have been studied and found not to reduce morbidity or mortality. Some small studies suggest that systemic corticosteroids may be beneficial in late-stage ALI/ARDS, but a larger, prospective randomized trial found no reduction in mortality. Corticosteroids may be deleterious when given early in the course of the condition.

Ventilatory Failure

Ventilatory failure is a rise in PaCO$_2$ (hypercapnia) that occurs when the respiratory load can no longer be supported by the strength or activity of the system. The most common causes are acute exacerbations of asthma and COPD, overdoses of drugs that suppress ventilatory drive, and conditions that cause respiratory muscle weakness (eg, Guillain-Barre syndrome, myasthenia gravis, botulism). Findings include dyspnea, tachypnea, and confusion. Death can result. Diagnosis is by ABGs and patient observation; chest x-ray and clinical evaluation may help delineate cause. Treatment varies by condition but often includes mechanical ventilation.

Pathophysiology

Hypercapnia occurs when alveolar ventilation either falls or fails to rise adequately in response to increased CO$_2$ production. A fall in alveolar ventilation results from a decrease in minute ventilation or an increase in dead space ventilation.

Minute ventilation decreases when there is an imbalance between the load on the respiratory system (including resistive loads, lung and chest wall elastic loads, and minute ventilation loads) and neuromuscular competence for an effective inspiratory effort (see Fig. 225-2 for causes).

Physiologic dead space is the part of the respiratory tree that does not participate in gas exchange. It includes the anatomic dead space (oropharynx, trachea, and airways) and alveolar dead space (ie, alveoli that are ventilated but not perfused). The physiologic dead space is normally about 30 to 40% of tidal volume but increases to 50% in intubated patients and to > 70% in massive pulmonary embolism, severe emphysema, and status asthmaticus. Thus, for any given minute ventilation, the greater the dead space, the poorer the CO$_2$ elimination.

Increased CO$_2$ production, as occurs with fever, sepsis, trauma, burns, hyperthyroidism, and malignant hyperthermia, is not a primary cause of ventilatory failure because patients should increase their ventilation to compensate. Ventilatory failure caused by these problems results only when the ability to compensate is compromised.

Hypercapnia lowers arterial pH (respiratory acidosis). Severe acidemia (pH < 7.2) contributes to pulmonary arteriolar vasoconstriction, systemic vascular dilation, reduced myocardial contractility, hyperkalemia, hypotension, and cardiac irritability, with the potential for life-threatening arrhythmias. Acute hypercapnia also causes cerebral vasodilation and increased intracranial pressure, a major problem in patients with acute head injury. Over time, tissue buffering and renal compensation can largely correct the acidemia. However, sudden increases in PaCO$_2$ can occur faster than compensatory changes (PaCO$_2$ rises 3 to 6 mm Hg/min in a totally apneic patient).

Symptoms and Signs
The predominant symptom is dyspnea. Signs include vigorous use of accessory ventilatory muscles, tachypnea, tachycardia, diaphoresis, anxiety, declining tidal volume, irregular or gasping breathing patterns, and paradoxical abdominal motion.

CNS manifestations range from subtle personality changes to marked confusion, obtundation, or coma. Chronic hypercapnia is better tolerated than acute and has fewer symptoms.

**Diagnosis**

- ABGs
- Chest x-ray
- Tests to determine etiology

Ventilatory failure should be suspected in patients with respiratory distress, visible ventilatory fatigue or cyanosis, or changes in sensorium and in those with disorders causing neuromuscular weakness. Tachypnea is also a concern; respiratory rates > 28 to 30/min cannot be sustained for very long, particularly in elderly or weakened patients.

If ventilatory failure is suspected, ABG analysis, continuous pulse oximetry, and a chest x-ray should be done. Respiratory acidosis on the ABG (eg, pH < 7.35 and PCO$_2$ > 50) confirms the diagnosis. Patients with chronic ventilatory failure often have quite elevated PCO$_2$ (eg, 60 to 90 mm Hg) at baseline, typically with a pH that is only slightly acidemic. In such patients, the degree of acidemia rather than the PCO$_2$ must serve as the primary marker for acute hypoventilation.

Because ABGs can be normal in patients with incipient ventilatory failure, certain bedside pulmonary function tests can help predict ventilatory failure, particularly in patients with neuromuscular weakness who may succumb to ventilatory failure without exhibiting respiratory distress. Vital capacity < 10 to 15 mL/kg and a maximum negative inspiratory force of ≤ 15 cm H$_2$O suggest imminent ventilatory failure.

Once ventilatory failure is diagnosed, the cause must be identified. Sometimes a known ongoing disorder (eg, coma, acute asthma, COPD exacerbation, myxedema, myasthenia gravis, botulism) is an obvious cause. In other cases, history is suggestive; sudden onset of tachypnea and hypotension after surgery suggests pulmonary embolism, and focal neurologic findings suggest a CNS or neuromuscular cause. Neuromuscular competence may be assessed through measurement of inspiratory muscle strength (negative inspiratory force and positive expiratory force), neuromuscular transmission (nerve conduction tests and electromyography), and investigations into causes of diminished drive (toxicology screens, brain imaging, sleep studies, and thyroid function tests).

**Treatment**

- Treatment of cause
- Often positive pressure ventilation

Treatment aims to correct the imbalance between the strength of the respiratory system and its load and varies with etiology. Obvious precipitants (eg, bronchospasm, mucus plugging, foreign bodies) should be corrected if possible.

The 2 most common causes are acute exacerbation of asthma (ie, status asthmaticus) and COPD.
Respiratory failure due to COPD is termed acute-on-chronic respiratory failure (ACRF).

**Status asthmaticus (SA):** Patients should be treated in an ICU by personnel skilled in airway management.

Noninvasive positive pressure ventilation (NIPPV) can immediately reduce the work of breathing and may forestall endotracheal intubation until drug therapy can take effect. In contrast to patients with COPD, who often welcome NIPPV, the mask often increases the perception of dyspnea in asthmatic patients, so introduction must be done carefully, perhaps starting with titration of expiratory positive airway pressure (EPAP) alone (because one of the major functions of inspiratory positive airway pressure [IPAP] is to increase tidal volume, and in these patients, end-expiratory lung volume approaches total lung capacity). After an explanation of its benefit, patients hold the mask against their face while modest amounts of pressure are applied (continuous positive airway pressure [CPAP] 3 to 5 cm H$_2$O). Once tolerated, the mask is strapped in place while pressures are increased to patient comfort and reduced work of breathing as assessed by respiratory rate and accessory muscle use. Final settings are typically IPAP 10 to 15 cm H$_2$O and EPAP 5 to 8 cm H$_2$O. Patients should be selected carefully (see p. 2282).

Conventional mechanical ventilation via endotracheal intubation is indicated for impending respiratory failure as indicated clinically by obtundation, monosyllabic speech, slumped posture, and shallow breathing. ABGs showing worsening hypercapnia are also an indication, although blood-gas confirmation is not required and should not replace the physician's judgment. Oral intubation is preferred over nasal because a larger endotracheal tube, which decreases airway resistance and permits easier suctioning, can be used.

Hypotension and pneumothorax occasionally occur after intubation for SA (see also p. 2283). These complications and their corresponding mortality have declined significantly because of a ventilator strategy that emphasizes limiting dynamic hyperinflation over achieving eucapnia. In SA, ventilation sufficient to achieve a normal pH typically causes severe hyperinflation. To avoid hyperinflation, initial ventilator settings include a tidal volume of 5 to 7 mL/kg and a respiratory rate of 10 to 18/min. Inspiratory flows may need to be quite high (eg, 70 to 120 L/min) with a square wave pattern to facilitate maximum time in exhalation. Dangerous dynamic hyperinflation is unlikely so long as the measured plateau pressure is < 30 to 35 cm H$_2$O and intrinsic positive end-expiratory pressure (PEEP) is < 15 cm H$_2$O (although these pressures may be difficult to measure because of inspiratory and expiratory respiratory muscle activity). Plateau pressure > 35 cm H$_2$O is managed by reducing the tidal volume (assuming that clinical evaluation does not indicate that the high pressures are the result of decreased compliance of the chest wall or abdomen) or the respiratory rate.

Although it is possible to reduce peak airway pressure by reducing peak flow rate or by changing the waveform to a descending profile, it should not be done. Although high flow rates require a high pressure to overcome the high airway resistance of SA, this pressure is dissipated across robust, cartilage-containing airways. Lower flow rates (eg, < 60 L/min) reduce time available for exhalation, thereby increasing the end-expiratory volume (and the resultant intrinsic PEEP) and allowing a greater inspiratory volume during the next breath.

Using low tidal volumes often results in hypercapnia, which is permitted for the greater good of reducing dynamic hyperinflation. An arterial pH > 7.15 is generally well tolerated but often requires large doses of sedatives and opioids. Neuromuscular blockers should be avoided after the peri-intubation period because use of these agents in combination with corticosteroids can cause a severe and occasionally irreversible myopathy, particularly after 24 h of combined use. Patient agitation should be managed with sedation rather than paralysis, but ideally ventilation can be adjusted to patients' needs so as to reduce the need for sedation.

Most patients with SA improve to the point of liberation from mechanical ventilation within 2 to 5 days, although a minority experience protracted severe airflow obstruction. The general approach to liberation is discussed on p. 2291.

**ACRF:** In patients with ACRF caused by COPD, the O$_2$ cost of breathing is several times that of patients
without underlying lung disease. This increased respiratory load occurs in the setting of barely adequate neuromuscular competence, so patients easily become too tired to maintain ventilation. These patients are vulnerable to respiratory failure from seemingly trivial insults, and recovery requires systematic identification and correction of these precipitants (see also p. 1889). To restore the balance between neuromuscular competence and load, clinicians reduce airflow obstruction and dynamic hyperinflation with bronchodilators and corticosteroids and treat infection with antibiotics. Low serum levels of K, phosphorus, and Mg may exacerbate muscle weakness, frustrating recovery, and must be identified and treated.

NIPPV is the preferred initial treatment for many patients with ACRF, resulting in decreased rates of ventilator-associated pneumonia, length of stay, and mortality compared with endotracheal intubation. Perhaps 75% of patients managed with NIPPV do not require endotracheal intubation. Advantages include the ease of application and removal; once initial stabilization has occurred, NIPPV may be stopped temporarily to allow oral intake in selected patients. Trials of unassisted breathing are easily done, and NIPPV can be reapplied as indicated.

Typical settings are IPAP of 10 to 15 cm H$_2$O and EPAP of 5 to 8 cm H$_2$O, titrated to the work of breathing as assessed by patient report, respiratory rate and tidal volume, and accessory muscle use. The same concerns regarding the potential effect of excessive IPAP on total lung capacity as discussed above exist in these patients as well. Deterioration (and need for endotracheal intubation) is best assessed clinically; ABGs may be misleading. Although worsening hypercapnia typically indicates treatment failure, patients differ markedly in tolerance of hypercapnia. Some with PaCO$_2$ > 100 mm Hg are alert and conversant on NIPPV, whereas others require intubation at much lower levels.

Conventional mechanical ventilation in ACRF aims to minimize dynamic hyperinflation and counter the adverse effects of intrinsic PEEP while resting the fatigued respiratory muscles. Initial recommended settings are assist-control (A/C) with a tidal volume of 5 to 7 mL/kg and a respiratory rate of 20 to 24/min, although some patients need lower initial rates to limit intrinsic PEEP. This intrinsic PEEP represents an inspiratory threshold load that must be overcome by the patient to trigger the ventilator, further increasing the work of breathing and preventing full rest on the ventilator. To counterbalance the effect of intrinsic PEEP, external PEEP should be applied to a level ≤ 85% of intrinsic PEEP (typical setting 5 to 10 cm H$_2$O). This application decreases the inspiratory work of breathing to maximize the time for expiration without increasing dynamic hyperinflation. High inspiratory flow rates should be used to maximize the time for expiration. These settings minimize the risk of alkalemia that follows overly vigorous initial ventilation. Hypotension may also occur immediately after intubation (see p. 2283).

Most patients require full ventilatory support for 24 to 48 h before spontaneous breathing trials are considered. It has not been determined whether this duration of treatment is needed to rest the respiratory muscles or to allow hyperinflation to diminish, thereby increasing respiratory muscle strength. The patient often sleeps heavily during this time and, in contrast to patients with asthma, typically requires little sedation. Adequate rest is often not achieved unless sufficient attention is paid to ongoing patient effort. This effort may manifest as accessory muscle use, inappropriately low airway pressures at the onset or throughout inspiration, or frequent failures to trigger the ventilator, indicating high intrinsic PEEP, weakness, or both.

Other Types of Respiratory Failure

**Perioperative respiratory failure** is usually caused by atelectasis. Effective means of preventing or treating atelectasis include incentive spirometry, ensuring adequate analgesia for chest and abdominal incisions, upright positioning, and early mobilization. Atelectasis caused by abdominal distention should be alleviated according to the cause (eg, nasogastric suction for excessive intraluminal air, paracentesis to evacuate tense ascites).

**Hypoperfusion**, regardless of cause, may result in respiratory failure through inadequate delivery of O$_2$ to respiratory muscles coupled with excess respiratory muscle load (eg, acidosis, sepsis). Mechanical ventilation is useful for diverting blood flow from overworked respiratory muscles to critical organs such as the brain, kidney, and gut.

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Liberation From Mechanical Ventilation

The discontinuation of ventilatory support is best achieved not by gradually reducing the level of ventilatory support (weaning) but by systematically identifying and eliminating the precipitants of respiratory failure. Once this goal has been achieved, the ventilator is no longer necessary. However, if precipitants are still present or recovery is incomplete, reducing needed ventilatory support is more likely to delay recovery. It is now clear that daily spontaneous breathing trials on a T-piece reduce the duration of mechanical ventilation compared with gradual reduction of the respiratory rate using synchronized intermittent mandatory ventilation and, in some studies, compared with pressure support trials.

Once the patient is no longer in shock, has an adequate arterial saturation on a fractional inspired O2 (FiO2) ≤ 0.5 with a positive end-expiratory pressure (PEEP) ≤ 7.5 cm H2O and does not have an obviously unsustainable respiratory load (e.g., minute ventilation > 20 L/min), a daily spontaneous breathing trial is done using a T-piece or continuous positive airway pressure (CPAP) of 5 cm H2O. Patients capable of sustaining spontaneous breathing generally breathe slowly and deeply, instead of rapidly and shallowly. This observation has been formalized as the rapid shallow breathing (RSB) index, determined by dividing the patient's unassisted respiratory rate (in breaths/min) by the tidal volume (in L). A value < 105 suggests that spontaneous breathing is likely to be successful, although a single isolated measurement is not perfectly predictive of success. Recently, the decision of whether to extubate a patient after a spontaneous breathing trial has shifted away from the use of the RSB index and has relied more on clinical assessment during the course of the trial, supplemented by measuring ABGs. Patients who fare well during a brief 1- to 2-h spontaneous breathing trial and who have favorable ABGs are good candidates for extubation. The decision to extubate is a separate one from the decision to stop ventilatory support and requires evaluation of the patient's mentation and airway protective reflexes, as well as the patency of the airway.

Although sedatives and opioids are essential for ensuring comfort, rest, and synchrony with the ventilator, their use may prolong mechanical ventilation. Such drugs may accumulate and cause protracted sedation, frustrating attempts to do spontaneous breathing trials even when the cause of respiratory failure has been corrected. The level of sedation should be continually assessed, and progressive sedative withdrawal should be begun as soon as possible. Formal protocols can be used, or simple daily interruption can be carried out. The infusion is stopped until the patient is either awake and following commands or needs re-sedation for agitation, breathing asynchronously with the ventilator, or other physiologic derangements. If sedation is still needed, it is restarted at half the previous dose and titrated as necessary. Several studies have shown that the mean duration of mechanical ventilation is reduced in institutions that use either daily "sedation vacations" or other sedation protocols, as well as daily spontaneous breathing trials.
Chapter 226. Shock and Fluid Resuscitation

Introduction

(See also Ch. 227.)

The fundamental defect in shock is reduced perfusion of vital tissues. Definitive treatment restores adequate tissue perfusion, usually by giving IV fluids.

Shock

Shock is a state of organ hypoperfusion with resultant cellular dysfunction and death. Mechanisms may involve decreased circulating volume, decreased cardiac output, and vasodilation, sometimes with shunting of blood to bypass capillary exchange beds. Symptoms include altered mental status, tachycardia, hypotension, and oliguria. Diagnosis is clinical, including BP measurement. Treatment is with IV fluids, correction of the underlying disorder, and sometimes vasopressors.

Pathophysiology

The fundamental defect in shock is reduced perfusion of vital tissues. Once perfusion declines so that O$_2$ is inadequate for aerobic metabolism, cells shift to anaerobic metabolism with increased production of CO$_2$ and accumulation of lactic acid. Cellular function declines, and if shock persists, irreversible cell damage and death occur.

During shock, both the inflammatory and clotting cascades may be triggered in areas of hypoperfusion. Hypoxic vascular endothelial cells activate WBCs, which bind to the endothelium and release directly damaging substances (eg, reactive O$_2$ species, proteolytic enzymes) and inflammatory mediators (eg, cytokines, leukotrienes, tumor necrosis factor [TNF]). Some of these mediators bind to cell surface receptors and activate nuclear factor kappa B (NFkB), which leads to production of additional cytokines and nitric oxide (NO), a potent vasodilator. Septic shock (see p. 2299) may be more proinflammatory than other forms because of the actions of bacterial toxins, especially endotoxin.

Vasodilation of capacitance vessels leads to pooling of blood and hypotension because of "relative" hypovolemia (ie, too much volume to be filled by the existing amount of blood). Localized vasodilation may shunt blood past the capillary exchange beds, causing focal hypoperfusion despite normal cardiac output and BP. Additionally, excess NO is converted to peroxynitrite, a free radical that damages mitochondria and decreases ATP production.

Blood flow to microvessels including capillaries is reduced even though large-vessel blood flow is preserved in settings of septic shock. Mechanical microvascular obstruction may, at least in part, account for such limiting of substrate delivery. Leukocytes and platelets adhere to the endothelium, and the clotting system is activated with fibrin deposition.

Multiple mediators, along with endothelial cell dysfunction, markedly increase microvascular permeability, allowing fluid and sometimes plasma proteins to escape into the interstitial space. In the GI tract, increased permeability possibly allows translocation of the enteric bacteria from the lumen to the bloodstream, potentially leading to sepsis or metastatic infection.

Neutrophil apoptosis may be inhibited, enhancing the release of inflammatory mediators. In other cells, apoptosis may be augmented, increasing cell death and thus worsening organ function.

BP is not always low in the early stages of shock (although hypotension eventually occurs if shock is not reversed). Similarly, not all patients with "low" BP have shock. The degree and consequences of hypotension vary with the adequacy of physiologic compensation and the patient's underlying diseases. Thus, a modest degree of hypotension that is well tolerated by a young, relatively healthy person might result in severe cerebral, cardiac, or renal dysfunction in a patient with significant arteriosclerosis.
Compensation: Initially, when $O_2$ delivery ($DO_2$) is decreased, tissues compensate by extracting a greater percentage of delivered $O_2$. Current guidelines provide for interventions that will maintain mixed-venous $O_2$ saturation above 30%. Additionally, low arterial pressure triggers an adrenergic response with sympathetic-mediated vasoconstriction and often increased heart rate. Initially, vasoconstriction is selective, shunting blood to the heart and brain. Circulating β-adrenergic amines (epinephrine, norepinephrine) also increase cardiac contractility and trigger release of corticosteroids from the adrenal gland, renin from the kidney, and glucose from the liver. Increased glucose may overwhelm ailing mitochondria, causing further lactate production.

Reperfusion: Reperfusion of ischemic cells can cause further injury. As substrate is reintroduced, neutrophil activity may increase, increasing production of damaging superoxide and hydroxyl radicals. After blood flow is restored, inflammatory mediators may be circulated to other organs.

Multiple organ dysfunction syndrome (MODS): The combination of direct and reperfusion injury may cause MODS—the progressive dysfunction of ≥ 2 organs consequent to life-threatening illness or injury. MODS can follow any type of shock but is most common when infection is involved; organ failure is one of the defining features of septic shock (see p. 2299). MODS also occurs in > 10% of patients with severe traumatic injury and is the primary cause of death in those surviving > 24 h.

Any organ system can be affected, but the most frequent target organ is the lung, in which increased membrane permeability leads to flooding of alveoli due to capillary leaks. Progressive hypoxia may be increasingly resistant to supplemental $O_2$ therapy. This condition is termed acute lung injury or, if severe, acute respiratory distress syndrome (ARDS—see p. 2284).

The kidneys are injured when renal perfusion is critically reduced, leading to acute tubular necrosis and renal insufficiency manifested by oliguria and progressive rise in serum creatinine.

In the heart, reduced coronary perfusion and mediators (including TNF and IL-1) may depress contractility, worsen myocardial compliance, and down-regulate β-receptors. These factors decrease cardiac output, further worsening both myocardial and systemic perfusion and causing a vicious circle often culminating in death.

In the GI tract, ileus and submucosal hemorrhage can develop. Liver hypoperfusion can cause focal or extensive hepatocellular necrosis, transaminase elevation, and decreased production of clotting factors.

Etiology and Classification

There are several mechanisms of organ hypoperfusion and shock. Shock may be due to a low circulating volume (hypovolemic shock), vasodilation (distributive shock), a primary decrease in cardiac output (both cardiogenic and obstructive shock), or a combination.

Hypovolemic shock: Hypovolemic shock is caused by a critical decrease in intravascular volume. Diminished venous return (preload) results in decreased ventricular filling and reduced stroke volume. Unless compensated for by increased heart rate, cardiac output decreases.

A common cause is bleeding (hemorrhagic shock), typically due to trauma, surgical interventions, peptic ulcer, esophageal varices, or aortic aneurysm. Bleeding may be overt (eg, hematemesis, melena) or concealed (eg, ruptured ectopic pregnancy).

Hypovolemic shock may also follow increased losses of body fluids other than blood (see Table 226-1).

Hypovolemic shock may be due to inadequate fluid intake (with or without increased fluid loss). Water may be unavailable, neurologic disability may impair the thirst mechanism, or physical disability may impair access.
Table 226-1. Hypovolemic Shock Caused by Body Fluid Loss

In hospitalized patients, hypovolemia can be compounded if early signs of circulatory insufficiency are incorrectly ascribed to heart failure and fluids are withheld or diuretics are given.

**Distributive shock:** Distributive shock results from a relative inadequacy of intravascular volume caused by arterial or venous vasodilation; circulating blood volume is normal. In some cases, cardiac output (and \( \text{DO}_2 \)) is high, but increased blood flow through arteriovenous shunts bypasses capillary beds, causing cellular hypoperfusion (demonstrated by decreased \( \text{O}_2 \) consumption). In other situations, blood pools in venous capacitance beds and cardiac output falls.

Distributive shock may be caused by anaphylaxis (anaphylactic shock—see p. 1120); bacterial infection with endotoxin release (septic shock—see p. 2299); severe injury to the brain or spinal cord (neurogenic shock); and ingestion of certain drugs or poisons, such as nitrates, opioids, and adrenergic blockers. Anaphylactic shock and septic shock often have a component of hypovolemia as well.

**Cardiogenic and obstructive shock:** Cardiogenic shock is a relative or absolute reduction in cardiac output due to a primary cardiac disorder. Mechanical factors that interfere with filling or emptying of the heart or great vessels explain obstructive shock. Causes are listed in Table 226-2.

**Symptoms and Signs**

Lethargy, confusion, and somnolence are common. The hands and feet are pale, cool, clammy, and often cyanotic, as are the earlobes, nose, and nail beds. Capillary filling time is prolonged, and except in distributive shock, the skin appears grayish or dusky and moist. Overt diaphoresis may occur. Peripheral pulses are weak and typically rapid; often, only femoral or carotid pulses are palpable. Tachypnea and hyperventilation may be present. BP tends to be low (< 90 mm Hg systolic) or unobtainable; direct measurement by intra-arterial catheter, if done, often gives higher and more accurate values. Urine output is low.

Distributive shock produces similar symptoms, except the skin may appear warm or flushed, especially during sepsis. The pulse may be bounding rather than weak. In septic shock, fever, usually preceded by chills, is generally present. Some patients with anaphylactic shock have urticaria or wheezing.

Numerous other symptoms (eg, chest pain, dyspnea, abdominal pain) may be due to the underlying disease or secondary organ failure.

Table 226-2. Mechanisms of Cardiogenic and Obstructive Shock

**Diagnosis**

Diagnosis is mostly clinical, based on evidence of insufficient tissue perfusion (obtundation, oliguria, peripheral cyanosis) and signs of compensatory mechanisms (tachycardia, tachypnea, diaphoresis). Specific criteria include obtundation, heart rate > 100, respiratory rate > 22, hypotension (systolic BP < 90 mm Hg) or a 30-mm Hg fall in baseline BP, and urine output < 0.5 mL/kg/h. Laboratory findings that support the diagnosis include lactate > 3 mmol/L, base deficit < -5 mEq/L, and PaCO\(_2\) < 32 mm Hg. However, none of these findings alone is diagnostic, and each is evaluated in the overall clinical context, including physical signs. Recently, measurement of sublingual PCO\(_2\) has been introduced as a noninvasive and rapid measurement of the severity of shock.

**Diagnosis of cause:** Recognizing the cause of shock is more important than categorizing the type. Often, the cause is obvious or can be recognized quickly by history and physical examination, aided by simple testing.

Chest pain (with or without dyspnea) suggests MI, aortic dissection, or pulmonary embolism. A systolic murmur may indicate ventricular septal rupture or mitral insufficiency due to acute MI. A diastolic murmur
may indicate aortic regurgitation due to aortic dissection involving the aortic root. Cardiac tamponade is suggested by jugular venous distention, muffled heart sounds, and a paradoxical pulse. Pulmonary embolism severe enough to produce shock typically produces decreased $O_2$ saturation and occurs more often in special settings, including prolonged bed rest and after a surgical procedure. Tests include ECG, troponin I, chest x-ray, ABG measurements, lung scan, helical CT, and echocardiography.

Abdominal or back pain or a tender abdomen suggests pancreatitis, ruptured abdominal aortic aneurysm, peritonitis, and, in women of childbearing age, ruptured ectopic pregnancy. A pulsatile midline mass suggests ruptured abdominal aortic aneurysm. A tender adnexal mass suggests ectopic pregnancy. Testing typically includes abdominal CT (if the patient is unstable, bedside ultrasound can be helpful), CBC, amylase, lipase, and, for women of childbearing age, urine pregnancy test.

Fever, chills, and focal signs of infection suggest septic shock, particularly in immunocompromised patients. Isolated fever, contingent on history and clinical settings, may point to heatstroke. Tests include chest x-ray; urinalysis; CBC; and cultures of wounds, blood, urine, and other relevant body fluids.

In a few patients, the cause is occult. Patients with no focal symptoms or signs indicative of cause should have ECG, cardiac enzymes, chest x-ray, and ABGs. If results of these tests are normal, the most likely causes include drug overdose, occult infection (including toxic shock), and obstructive shock.

**Ancillary testing:** If not already obtained, ECG, chest x-ray, CBC, serum electrolytes, BUN, creatinine, PT, PTT, liver function tests, and fibrinogen and fibrin split products are done to monitor patient status and serve as a baseline. If the patient's volume status is difficult to determine, monitoring of central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) may be useful. CVP < 5 mm Hg (< 7 cm H$_2$O) or PAOP < 8 mm Hg may indicate hypovolemia, although CVP may be greater in hypovolemic patients with preexisting pulmonary hypertension.

**Prognosis and Treatment**

Untreated shock is usually fatal. Even with treatment, mortality from cardiogenic shock after MI and from septic shock is high (60 to 65%). Prognosis depends on the cause, preexisting or complicating illness, time between onset and diagnosis, and promptness and adequacy of therapy.

**General management:** First aid involves keeping the patient warm. Hemorrhage is controlled, airway and ventilation are checked, and respiratory assistance is given if necessary. Nothing is given by mouth, and the patient's head is turned to one side to avoid aspiration if emesis occurs.

Treatment begins simultaneously with evaluation. Supplemental $O_2$ by face mask is provided. If shock is severe or if ventilation is inadequate, airway intubation with mechanical ventilation is necessary. Two large (16- to 18-gauge) IV catheters are inserted into separate peripheral veins. A central venous line or an intraosseous needle, especially in children, provides an alternative when peripheral veins cannot promptly be accessed (see also p. 2250).

Typically, 1 L (or 20 mL/kg in children) of 0.9% saline is infused over 15 min. In major hemorrhage, Ringer's lactate is commonly used. Unless clinical parameters return to normal, the infusion is repeated. Smaller volumes (eg, 250 to 500 mL) are used for patients with signs of high right-sided pressure (eg, distention of neck veins) or acute MI. A fluid challenge should probably not be done in a patient with signs of pulmonary edema. Further fluid therapy is based on the underlying condition and may require monitoring of CVP or PAOP.

Patients in shock are critically ill and should be admitted to an ICU. Monitoring includes ECG; systolic, diastolic, and mean BP, preferably by intra-arterial catheter; respiratory rate and depth; pulse oximetry; urine flow by indwelling bladder catheter; body temperature; and clinical status, including sensorium (eg, Glasgow Coma Scale—see Table 174-4 on p. 1661), pulse volume, skin temperature, and color. Measurement of CVP, PAOP, and thermodilution cardiac output using a balloon-tipped pulmonary arterial catheter may be helpful for diagnosis and initial management of patients with shock of uncertain or mixed etiology or with severe
shock, especially when accompanied by oliguria or pulmonary edema. Echocardiography (bedside or transesophageal) is a less invasive alternative. Serial measurements of ABGs, Hct, electrolytes, serum creatinine, and blood lactate are obtained. Sublingual CO₂ measurement (see p. 2247), if available, is a noninvasive monitor of visceral perfusion. A well-designed flow sheet is helpful.

Because tissue hypoperfusion makes intramuscular absorption unreliable, all parenteral drugs are given IV. Opioids generally are avoided because they may cause vasodilation, but severe pain may be treated with morphine 1 to 4 mg IV given over 2 min and repeated q 10 to 15 min if necessary. Although cerebral hypoperfusion may cause anxiety, sedatives or tranquilizers are not routinely given.

After initial resuscitation, specific treatment is directed at the underlying condition. Additional supportive care is guided by the type of shock.

**Hemorrhagic shock:** In hemorrhagic shock, surgical control of bleeding is primary. Vigorous volume replacement (see also p. 2297) accompanies rather than precedes surgical control. Blood transfusion is used for hemorrhagic shock unresponsive to 2 L (or 40 mL/kg in children) of crystalloid. Failure to respond usually indicates insufficient volume administration or unrecognized ongoing hemorrhage. Vasopressor agents are not indicated for treatment of hemorrhagic shock unless cardiogenic, obstructive, or distributive causes are also present.

**Distributive shock:** Distributive shock with profound hypotension after initial fluid replacement with 0.9% saline may be treated with inotropic or vasopressor agents (eg, dopamine, norepinephrine—see Table 226-3). Patients with septic shock also receive at least two broad-spectrum antibiotics (see p. 2302). Patients with anaphylactic shock unresponsive to fluid challenge (especially if accompanied by bronchoconstriction) receive epinephrine 0.05 to 0.1 mg IV, followed by epinephrine infusion of 5 mg in 500 mL 5% D/W at 10 mL/h or 0.02 μg/kg/min (see also p. 1121).

**Cardiogenic shock:** In cardiogenic shock, structural disorders (eg, valvular dysfunction, septal rupture) are repaired surgically. Coronary thrombosis is treated either by percutaneous interventions (angioplasty, stenting), coronary artery bypass surgery, or thrombolysis (see also Ch. 210). Tachydysrhythmia (eg, rapid atrial fibrillation, ventricular tachycardia) is slowed by cardioversion or with drugs. Bradycardia is treated with a transcutaneous or transvenous pacemaker; atropine 0.5 mg IV up to 4 doses q 5 min may be given pending pacemaker placement. Isoproterenol (2 mg/500 mL 5% D/W at 1 to 4 μg/min [0.25 to 1 mL/min]) is occasionally useful if atropine is ineffective, but it is not advised in patients with myocardial ischemia due to coronary artery disease.

Shock after acute MI is treated with volume expansion if PAOP is low or normal; 15 to 18 mm Hg is considered optimal. If a pulmonary artery catheter is not in place, cautious volume infusion (250- to 500-mL bolus of 0.9% saline) may be tried while auscultating the chest frequently for signs of fluid overload. Shock after right ventricular MI usually responds partially to volume expansion; however, vasopressor agents may be needed.

If hypotension is moderate (eg, mean arterial pressure [MAP] 70 to 90 mm Hg), dobutamine infusion may be used to improve cardiac output and reduce left ventricular filling pressure. Tachycardia and arrhythmias occasionally occur during dobutamine administration, particularly at higher doses, necessitating dose reduction. Vasodilators (eg, nitroprusside, nitroglycerin), which increase venous capacitance or lower systemic vascular resistance, reduce the workload on the damaged myocardium and may increase cardiac output in patients without severe hypotension. Combination therapy (eg, dopamine or dobutamine with nitroprusside or nitroglycerin) may be particularly useful but requires close ECG and pulmonary and systemic hemodynamic monitoring.

For more serious hypotension (MAP < 70 mm Hg), norepinephrine or dopamine may be given, with a target systolic pressure of 80 to 90 mm Hg (and not > 110 mm Hg). Intra-aortic balloon counterpulsation is valuable for temporarily reversing shock in patients with acute MI. This procedure should be considered as a bridge to permit cardiac catheterization and coronary angiography before possible surgical intervention in patients with acute MI complicated by ventricular septal rupture or severe acute mitral regurgitation who require vasopressor support for > 30 min.
In obstructive shock, cardiac tamponade requires immediate pericardiocentesis, which can be done at the bedside. Tension pneumothorax should be immediately decompressed with a catheter inserted into the 2nd intercostal space, midclavicular line. Massive pulmonary embolism resulting in shock is treated with thrombolysis or surgical embolectomy.

**Intravenous Fluid Resuscitation**

Almost all circulatory shock states require large-volume IV fluid replacement, as does severe intravascular volume depletion (eg, due to diarrhea or heatstroke). Intravascular volume deficiency is acutely compensated for by vasoconstriction, followed over hours by migration of fluid from the extravascular compartment to the intravascular compartment, maintaining circulating volume at the expense of total body water. However, this compensation is overwhelmed after major losses. See Ch. 97 for maintenance fluid requirement discussion, and see Ch. 278 for mild dehydration discussion.

**Fluids**

Choice of resuscitation fluid depends on the cause of the deficit.

**Hemorrhage:** Loss of RBCs diminishes $O_2$-carrying capacity. However, the body increases cardiac output to maintain $O_2$ delivery ($DO_2$) and increases $O_2$ extraction. These factors provide a safety margin of about 9 times the resting $O_2$ requirement. Thus, non-$O_2$-carrying fluids (eg, crystalloid or colloid solutions) may be used to restore intravascular volume in mild to moderate blood loss.

[Table 226-3. Inotropic and Vasoactive Catecholamines](#)

However, once Hb declines to < 7 g/dL, in the absence of cardiac or cerebral vascular disease, $O_2$-carrying capacity must be restored by infusion of blood (or in the future by blood substitutes). Patients with coronary or cerebral vascular disease require blood for Hb < 10 g/dL.

**Crystalloid solutions** for intravascular volume replenishment are typically isotonic (eg, 0.9% saline or Ringer's lactate [RL]). $H_2O$ freely travels outside the vasculature, so as little as 10% of isotonic fluid remains in the intravascular space. With hypotonic fluid (eg, 0.45% saline), even less remains in the vasculature, and thus, this fluid is not used for resuscitation. Both 0.9% saline and RL are equally effective; RL may be preferred in hemorrhagic shock because it somewhat minimizes acidosis. However, the Ca in RL may interfere with concurrently infused drugs and may trigger clotting in transfused blood unless the ratio of blood:RL is > 2:1. For patients with acute brain injury and hemorrhagic shock, 0.9% saline is preferred. Hypertonic saline (7.5%) is also an effective crystalloid; it shifts more volume from the extravascular space and therefore requires lower absolute volume, which has practical advantages in a prehospital setting.

**Colloid solutions** (eg, hydroxyethyl starch, albumin, dextrans) are also effective for volume replacement during major hemorrhage. Despite theoretical benefits over crystalloid, no differences in survival have been proved. Albumin is the colloid of choice, although it may have a negative inotropic effect. Both dextrans and hydroxyethyl starch may adversely affect coagulation when > 1.5 L is given.

**Blood** typically is given as packed RBCs, which should be cross-matched, but in an urgent situation, 1 to 2 units of type O Rh-negative blood are an acceptable alternative. When > 1 to 2 units are transfused (eg, in major trauma), blood is warmed to 37°C. Patients receiving > 8 to 10 units may require replacement of clotting factors with infusion of fresh frozen plasma or cryoprecipitate and platelet transfusion (see also p. 1039).

**Blood substitutes** are $O_2$-carrying fluids that can be Hb-based or perfluorocarbons. Hb-based fluids may contain free Hb that is liposome-encapsulated or modified (eg, by surface modification or cross-linking with other molecules) to limit renal excretion and toxicity. Because the antigen-bearing RBC membrane is not present, these substances do not require cross-matching. They can also be stored > 1 yr, providing a more stable source than banked blood. Perfluorocarbons are IV carbon-fluorine emulsions that carry large amounts of $O_2$. However, they have not been proved to increase survival and cannot be
given in amounts sufficient to compensate for critical RBC losses.

**Nonhemorrhagic hypovolemia:** Isotonic crystalloid solutions are typically given for intravascular repletion during shock and hypovolemia. Colloid solutions are generally not used. Patients with dehydration and adequate circulatory volume typically have a free water deficit, and hypotonic solutions (eg, D5 0.45% saline) are used.

**Route and Rate of Fluid Administration**

Standard, large (eg, 14- to 16-gauge) peripheral IV catheters are adequate for most fluid resuscitation. With an infusion pump, they typically allow infusion of 1 L of crystalloid in 10 to 15 min and 1 unit of packed RBCs in 20 min. For patients at risk of exsanguination, a large (eg, 8.5 French) central venous catheter provides more rapid infusion rates; a pressure infusion device can infuse 1 unit of packed RBCs in < 5 min.

Patients in shock typically require and tolerate infusion at the maximum rate. Adults are given 1 L of crystalloid (20 mL/kg in children) or, in hemorrhagic shock, 5 to 10 mL/kg of colloid or packed RBCs, and the patient is reassessed. An exception is a patient with cardiogenic shock who typically does not require large volume infusion.

Patients with intravascular volume depletion without shock can receive infusion at a controlled rate, typically 500 mL/h. Children should have fluid deficit calculated (see p. 2807) and replacement given over 24 h (one half in the first 8 h).

**End Point and Monitoring**

The actual end point of fluid therapy in shock is normalization of DO₂. However, this parameter is not often measured directly. Surrogate end points include clinical indicators of end-organ perfusion and measurements of preload.

Adequate end-organ perfusion is best indicated by urine output of > 0.5 to 1 mL/kg/h. Heart rate, mental status, and capillary refill may be affected by the underlying disease process and are less reliable markers. Because of compensatory vasoconstriction, mean arterial pressure (MAP) is only a rough guideline; organ hypoperfusion may be present despite apparently normal values. An elevated arterial blood lactate level reflects hypoperfusion; however, levels do not decline for several hours after successful resuscitation. Sublingual tissue CO₂ level responds more rapidly (eg, within minutes) and may be a more useful indicator.

**Central venous pressure:** Because urine output does not provide a minute-to-minute indication, measures of preload may be helpful in guiding fluid resuscitation for critically ill patients. Central venous pressure (CVP) is the mean pressure in the superior vena cava, reflecting right ventricular end-diastolic pressure or preload. Normal CVP ranges from 2 to 7 mm Hg (3 to 9 cm H₂O). A sick or injured patient with a CVP < 3 mm Hg is presumed to be volume depleted and may be given fluids with relative safety. When the CVP is within the normal range, volume depletion cannot be excluded, and the response to 100- to 200-mL fluid boluses should be assessed; a modest increase in CVP in response to fluid generally indicates hypovolemia. An increase of > 3 to 5 mm Hg in response to a 100-mL fluid bolus suggests limited cardiac reserve. A CVP > 12 to 15 mm Hg casts doubt on hypovolemia as the sole etiology of hypoperfusion, and fluid administration risks fluid overload.

Because CVP may be unreliable in assessing volume status or left ventricular function, pulmonary artery catheterization (see p. 2244) may be considered for diagnosis or for more precise titration of fluid therapy if there is no cardiovascular improvement after initial therapy. Care must be taken when interpreting filling pressures in patients during mechanical ventilation, particularly when positive end-expiratory pressure (PEEP) levels exceeding 10 cm H₂O are being used or during respiratory distress when pleural pressures fluctuate widely. Measurements are made at the end of expiration, and the transducer is referenced to atrial zero levels (mid chest) and carefully calibrated.
**Traumatic hemorrhagic shock:** These patients may require a slightly different approach. Experimental and clinical evidence indicates that internal hemorrhage (eg, due to visceral or vascular laceration or crush) may be worsened by resuscitation to normal or supranormal MAP. Some physicians advocate an MAP of 60 to 80 mm Hg as the resuscitation end point in such patients pending surgical control of bleeding.

After blood loss is controlled, Hct is used to guide the need for further transfusion. A target Hct of 23 to 28% is suggested to minimize the use of blood products. Patients who may have difficulty tolerating moderate anemia (eg, those with coronary or cerebral artery disease) are kept above 30%. A higher Hct does not improve outcome and, by causing increased blood viscosity, may impair perfusion of capillary beds.

**Complications**

Overly rapid infusion of any type of fluid may precipitate pulmonary edema.

Hemodilution from crystalloid infusion is not of itself injurious, although Hct must be monitored to note whether threshold values for transfusion are met.

RBC transfusion has a low risk of directly transmitting infection, but in critically ill patients, it seems to cause a slightly higher rate of hospital-acquired infection. This risk may be minimized by using blood < 12 days old; such RBCs are more plastic and less likely to cause sludging in the microvasculature. For other complications of massive transfusion, see p. 1040.
Chapter 227. Sepsis and Septic Shock

Introduction

(See also Ch. 226.)

Sepsis, severe sepsis, and septic shock are inflammatory states resulting from the systemic response to bacterial infection. In severe sepsis and septic shock, there is critical reduction in tissue perfusion. Common causes include gram-negative organisms, staphylococci, and meningococci. Symptoms often begin with shaking chills and include fever, hypotension, oliguria, and confusion. Acute failure of multiple organs, including the lungs, kidneys, and liver, can occur. Treatment is aggressive fluid resuscitation, antibiotics, surgical excision of infected or necrotic tissues and drainage of pus, supportive care, and sometimes intensive control of blood glucose and administration of corticosteroids and activated protein C.

A spectrum of severity exists (see Table 227-1).

Sepsis is infection accompanied by an acute inflammatory reaction with systemic manifestations associated with release into the bloodstream of numerous endogenous mediators of inflammation. Acute pancreatitis and major trauma, including burns, may manifest with signs of sepsis. The inflammatory reaction typically manifests with ≥ 2 of the following:

• Temperature > 38°C or < 36°C
• Heart rate > 90 beats/min
• Respiratory rate > 20 breaths/min or PaCO₂ < 32 mm Hg
• WBC count > 12,000 cells/µL or < 4,000 cells/µL or > 10% immature forms

However, these criteria are now viewed as suggestive but not sufficiently precise to be diagnostic.

Severe sepsis is sepsis accompanied by signs of failure of at least one organ. Cardiovascular failure is typically manifested by hypotension, respiratory failure by hypoxemia, renal failure by oliguria, and hematologic failure by coagulopathy.

Septic shock is severe sepsis with organ hypoperfusion and hypotension that are poorly responsive to initial fluid resuscitation.

Etiology

Most cases of septic shock are caused by hospital-acquired gram-negative bacilli or gram-positive cocci and often occur in immunocompromised patients and patients with chronic and debilitating diseases. Rarely, it is caused by Candida or other fungi. A unique form of shock caused by staphylococcal and streptococcal toxins is called toxic shock (see p. 1235).

Septic shock occurs more often in neonates (see p. 2832), patients > 35 yr, and pregnant women. Predisposing factors include diabetes mellitus; cirrhosis; leukopenia, especially that associated with cancer or treatment with cytotoxic drugs; invasive devices, including endotracheal tubes, vascular or urinary catheters, drainage tubes, and other foreign materials; and prior treatment with antibiotics or corticosteroids. Common causative sites of infection include the lungs and the urinary, biliary, and GI tracts.

Pathophysiology

The pathogenesis of septic shock is not completely understood. An inflammatory stimulus (eg, a bacterial
toxin) triggers production of proinflammatory mediators, including tumor necrosis factor and IL-1. These cytokines cause neutrophil-endothelial cell adhesion, activate the clotting mechanism, and generate microthrombi. They also release numerous other mediators, including leukotrienes, lipoxygenase, histamine, bradykinin, serotonin, and IL-2. They are opposed by anti-inflammatory mediators, such as IL-4 and IL-10, resulting in a negative feedback mechanism.

Initially, arteries and arterioles dilate, decreasing peripheral arterial resistance; cardiac output typically increases. This stage has been referred to as warm shock. Later, cardiac output may decrease, BP falls (with or without an increase in peripheral resistance), and typical features of shock appear.

Even in the stage of increased cardiac output, vasoactive mediators cause blood flow to bypass capillary exchange vessels (a distributive defect). Poor capillary flow from this shunting along with capillary obstruction by microthrombi decreases delivery of O₂ and impairs removal of CO₂ and waste products. Decreased perfusion causes dysfunction and sometimes failure of one or more organs, including the kidneys, lungs, liver, brain, and heart.

Coagulopathy may develop because of intravascular coagulation with consumption of major clotting factors, excessive fibrinolysis in reaction thereto, and more often a combination of both.

Symptoms and Signs

With sepsis, the patient typically has fever, tachycardia, and tachypnea; BP remains normal. Other signs of the causative infection are generally present. As severe sepsis or septic shock develops, the first sign may be confusion or decreased alertness. BP generally falls, yet the skin is paradoxically warm. Oliguria (< 0.5 mL/kg/h) is likely to be present. Later, extremities become cool and pale, with peripheral cyanosis and mottling. Organ failure causes additional symptoms and signs specific to the organ involved.

Diagnosis

Sepsis is suspected when a patient with a known infection develops systemic signs of inflammation or organ dysfunction. Similarly, a patient with otherwise unexplained signs of systemic inflammation should be evaluated for infection by history, physical examination, and tests, including urinalysis and urine culture (particularly in patients who have indwelling catheters), serial blood cultures, and cultures of other suspect body fluids. Blood levels of procalcitonin and C-reactive protein are elevated in severe sepsis and may facilitate diagnosis, but they are not specific. Ultimately, diagnosis is clinical.

Other causes of shock (eg, hypovolemia, MI) should be sought via history, physical examination, ECG, and serum cardiac markers. Even without MI, hypoperfusion may result in ECG findings of ischemia including non-specific ST-T wave abnormalities, T-wave inversions, and supraventricular and ventricular arrhythmias.

CBC, ABGs, chest x-ray, serum electrolytes, lactate levels or sublingual PCO₂, and liver function are monitored. At the onset of septic shock, the WBC count may initially decrease to < 4000/μL, and PMNs may be as low as 20%. However, this situation reverses within 1 to 4 h, and a significant increase in both the total WBC count to > 15,000/μL and PMNs to > 80% (with predominantly juvenile forms) usually occurs. A sharp decrease in platelet count to ≤ 50,000/μL is often present early.

Hyperventilation with respiratory alkalosis (low PaCO₂ and increased arterial pH) occurs early, in part as compensation for lactic acidemia. Serum HCO₃⁻ is usually low, and serum and blood lactate levels increase. As shock progresses, metabolic acidosis worsens, and blood pH decreases. Early respiratory failure leads to hypoxemia with PaO₂ < 70 mm Hg. Diffuse infiltrates may appear on the chest x-ray [see Respiratory Arrest on p. 2269]. BUN and creatinine usually increase progressively as a result of renal insufficiency. Bilirubin and transaminases may rise, although overt hepatic failure is uncommon.
Up to 50% of patients with severe sepsis develop relative adrenal insufficiency (ie, normal or slightly elevated baseline cortisol levels that do not increase significantly in response to further stress or exogenous ACTH). Adrenal function may be tested by measuring serum cortisol at 8 AM; a level < 5 mg/dL is inadequate. Alternatively, cortisol can be measured before and after injection of 250 μg of synthetic ACTH; a rise of < 9 μg/dL is considered insufficient. However, most physicians simply give replacement doses of corticosteroids without testing.

Hemodynamic measurements with a central venous or pulmonary artery catheter can be used when the specific type of shock is unclear or when large fluid volumes (eg, > 4 to 5 L 0.9% saline over 6 to 8 h) are needed. Unlike in hypovolemic shock, cardiac output in septic shock is more likely to be normal or increased, and peripheral resistance is decreased. Neither central venous pressure (CVP) nor pulmonary artery occlusive pressure (PAOP) is likely to be abnormal, unlike in hypovolemic, obstructive, or cardiogenic shock (see p. 2294). Echocardiography (including transesophageal echocardiography) is a useful alternative for evaluating cardiac performance.

Prognosis

Overall mortality in patients with septic shock is decreasing and now averages 40% (range 10 to 90%, depending on patient characteristics). Poor outcomes often follow failure to institute early aggressive therapy (eg, within 6 h of suspected diagnosis). Once severe lactic acidosis with decompensated metabolic acidosis becomes established, especially in conjunction with multiorgan failure, septic shock is likely to be irreversible and fatal.

Treatment

- Fluid resuscitation with 0.9% normal saline
- O₂
- Broad-spectrum antibiotics (modified by culture results)
- Drainage of abscesses and excision of necrotic tissue
- Normalization of blood glucose levels
- Replacement-dose corticosteroids

Patients with septic shock should be treated in an ICU. The following should be monitored frequently (see also p. 2244): systemic pressure; CVP, PAOP, or both; pulse oximetry; ABGs; blood glucose, lactate, and electrolyte levels; renal function, and possibly sublingual PCO₂. Urine output, a good indicator of renal perfusion, should be measured, usually with an indwelling catheter.

Fluid resuscitation with 0.9% saline should be given until CVP reaches 8 mm Hg (10 cm H₂O) or PAOP reaches 12 to 15 mm Hg. Oliguria with hypotension is not a contraindication to vigorous fluid resuscitation. The quantity of fluid required often far exceeds the normal blood volume and may reach 10 L over 4 to 12 h. PAOP or echocardiography can identify limitations in left ventricular function and incipient pulmonary edema due to fluid overload.

If a patient with septic shock remains hypotensive after CVP or PAOP has been raised to target levels, dopamine may be given to increase mean BP to at least 60 mm Hg. If dopamine dose exceeds 20 μg/kg/min, another vasopressor, typically norepinephrine, may be added. However, vasoconstriction caused by higher doses of dopamine and norepinephrine poses risks of organ hypoperfusion and acidosis, and these drugs have not been shown to improve survival.

O₂ is given by mask or nasal prongs. Tracheal intubation and mechanical ventilation may be needed subsequently for respiratory failure (see p. 2279).
Parenteral antibiotics should be given after specimens of blood, body fluids, and wound sites have been taken for Gram stain and culture. Very prompt empiric therapy, started immediately after suspecting sepsis, is essential and may be lifesaving. Antibiotic selection requires an educated guess based on the suspected source, clinical setting, knowledge or suspicion of causative organisms and of sensitivity patterns common to that specific inpatient unit, and previous culture results.

One regimen for septic shock of unknown cause is gentamicin or tobramycin 5.1 mg/kg IV once/day plus a 3rd-generation cephalosporin (ceftaxime 2 g q 6 to 8 h or ceftriaxone 2 g once/day or, if Pseudomonas is suspected, ceftazidime 2 g IV q 8 h). Alternatively, ceftazidime plus a fluoroquinolone (eg, ciprofloxacin) may be used. Monotherapy with maximal therapeutic doses of ceftazidime (2 g IV q 8 h) or imipenem (1 g IV q 6 h) may be effective but is not recommended.

Vancomycin must be added if resistant staphylococci or enterococci are suspected. If there is an abdominal source, a drug effective against anaerobes (eg, metronidazole) should be included. When culture and sensitivity results are available, the antibiotic regimen is changed accordingly. Antibiotics are continued for at least 5 days after shock resolves and evidence of infection subsides.

Abscesses must be drained, and necrotic tissues (eg, infarcted bowel, gangrenous gall-bladder, abscessed uterus) must be surgically excised. The patient's condition will continue to deteriorate despite antibiotic therapy unless septic foci are eliminated.

Normalization of blood glucose improves outcome in critically ill patients, even those not known to be diabetic. A continuous IV insulin infusion (crystalline zinc 1 to 4 U/h) is titrated to maintain glucose between 80 to 110 mg/dL (4.4 to 6.1 mmol/L). This approach necessitates frequent (eg, q 1 to 4 h) glucose measurement.

Corticosteroid therapy seems beneficial. Treatment is with replacement doses rather than pharmacologic doses. One regimen consists of hydrocortisone 50 mg IV q 6 h (or 100 mg q 8 h) plus fludrocortisone 50 μg po once/day during hemodynamic instability and for 3 days thereafter.

Activated protein C (drotrecogin alfa), a recombinant drug with fibrinolytic and anti-inflammatory activity, seems beneficial for severe sepsis and septic shock if it is begun early; benefit has been shown only in patients with significant risk of death as defined by an APACHE II score of > 25 (see Table 222-4 on p. 2248). Dosage is 24 μg/kg/h by continuous IV infusion for 96 h. Bleeding is the most common complication; thus, contraindications include hemorrhagic stroke within 3 mo, spinal or intracranial surgery within 2 mo, acute trauma with a risk of bleeding, and intracranial neoplasm. Risk-benefit assessment is required in other patients with increased risk of serious bleeding (eg, with thrombocytopenia or recent GI bleeding, receiving concurrent heparin, or with recent aspirin or other anticoagulant use).

Other emerging therapies for severe sepsis include cooling for hyperthermia and early treatment of renal failure (eg, with continuous venovenous hemofiltration).

Trials of monoclonal antibodies to the lipid A fraction of endotoxin, antileukotrienes, and antibodies to tumor necrosis factor have been unsuccessful.
Chapter 228. Approach to the Genitourinary Patient

Introduction

Although some disorders can affect both the kidneys and the lower urinary tract (eg, pyelonephritis, calculi), renal and urologic disorders usually require different approaches. Common GU symptoms include dysuria, hematospermia, hematuria, proteinuria, scrotal mass, testicular pain, and priapism. (See also Urinary Incontinence on p. 2352 and Urinary Tract Infections on p. 2373.)

Approach to the Renal Patient

In patients with renal disorders, symptoms and signs may be nonspecific, absent until the disorder is severe, or both. Findings most often are local (eg, reflecting kidney inflammation or mass), result from the systemic effects of kidney dysfunction, or affect urination (eg, changes in urine itself or in urine production).

History

History plays a limited role because symptoms are nonspecific.

Hematuria is relatively specific for a GU disorder, but patients who report red urine may instead have one of the following:

- Myoglobinuria
- Hemoglobinuria
- Porphyrinuria
- Porphobilinuria
- Food-induced urine coloring (some foods, eg, beets, rhubarb, sometimes food coloring, may make urine appear red)
- Drug-induced urine coloring (some drugs, most commonly phenazopyridine, but sometimes cascara, diphenylhydantoin, methyldopa, phenacetin, phenindione, phenolphthalein, phenothiazines, and senna may make urine appear red)

High concentrations of urinary protein cause frothy or sudsy urine. Urinary frequency (see p. 2337) should be distinguished from polyuria (see p. 2324) in patients who report excessive urination. Nocturia may be a feature of either but is often the result of excess fluid intake too close to bedtime or of chronic kidney disease. Family history is useful for identifying inheritance patterns and risk of polycystic kidney disease or other hereditary nephropathies (eg, hereditary nephritis, thin basement membrane disease, nail-patella syndrome, cystinuria, hyperoxaluria).

Physical Examination

Patients with moderate or severe chronic kidney disease sometimes appear pale, wasted, or ill. Deep (Kussmaul's) respirations suggest hyperventilation in response to metabolic acidosis with acidemia.

Chest examination: Pericardial and pleuritic friction rubs may be signs of uremia.

Abdominal examination: Visual fullness of the upper abdomen is an unusual, nonspecific finding of polycystic kidney disease. It may also indicate a kidney or abdominal mass or hydronephrosis. A soft, lateralizing bruit is occasionally audible in the epigastrium or the flank in renal artery stenosis; presence of a diastolic component increases the probability of renovascular hypertension.
Pain elicited by mild striking of the back, flanks, and angle formed by the 12th rib and lumbar spine with a fist (costovertebral tenderness) may indicate pyelonephritis or urinary tract obstruction (eg, due to calculi). Normal kidneys are not usually palpable. However, in some women, the lower pole of the right kidney can occasionally be felt with palpation during deep inspiration, and large kidneys or masses can sometimes be felt without special maneuvers. In neonates, the kidneys can be felt with the thumbs when the thumbs are placed anterior and the fingers posterior to the costovertebral angle.

Transillumination can distinguish solid from cystic renal masses in some children < 1 yr if the kidney and mass are manipulated against the abdominal wall.

**Skin examination:** Chronic kidney disease can cause any of the following:

- Xerosis due to sebaceous and eccrine sweat gland atrophy
- Pallor due to anemia
- Hyperpigmentation due to melanin deposition
- Sallow or yellow-brown skin due to urochrome deposition
- Petechiae or ecchymoses due to platelet dysfunction

Uremic frost, the deposition of white-to-tan urea crystals on the skin after sweat evaporation, is rare.

**Neurologic examination:** Patients with acute renal failure may be drowsy, confused, or inattentive; speech may be slurred. Asterixis can be detected in handwriting or by observation of outstretched hands maximally extended at the wrists; after several seconds in this position, a hand flap in the flexor direction is asterixis. Asterixis suggests one of the following:

- Chronic kidney disease
- Chronic liver failure
- CO₂ narcosis

**Testing**

Urinalysis and measurement of serum creatinine are the initial steps in evaluation of renal disorders. Other urine, blood, and imaging tests (eg, ultrasonography, CT, MRI) are done in specific circumstances. Ideally, after the urethral meatus is cleaned, the urine specimen is collected midstream (clean-catch specimen) during the first void of the morning; the urine should be examined immediately because delays can lead to changes in test results. Bladder catheterization or suprapubic aspiration can be used for collection when urine cannot be obtained by spontaneous voiding or when vaginal material contaminates the urine specimen. However, the trauma of catheterization may falsely increase the number of RBCs in the specimen, so catheterization is usually avoided if the outcome of interest is microscopic hematuria. A specimen from a catheter collection bag is not acceptable for microscopic or bacteriologic tests.

**Urinalysis:** A complete urinalysis includes the following:

- Inspection for color, appearance, and odor
- Measurement of pH, specific gravity, protein, glucose, RBCs, nitrites, and WBC esterase by dipstick reagents
- Microscopic analysis for casts, crystals, and cells (urine sediment)

Bilirubin and urobilinogen, although standard parts of many dipstick tests, no longer play significant roles.
in evaluation of renal or hepatic disorders.

**Color** is the most obvious of urine attributes, and observation of color is an integral part of urinalysis (see Table 228-1). Urine color may suggest possible causes and help direct additional testing.

**Odor**, often unintentionally noted during visual inspection, conveys useful information only in rare cases of inherited disorders of amino acid metabolism when urine has a distinctive smell (eg, maple syrup in maple syrup urine disease, sweaty feet in isovaleric acidemia, tomcat urine in multiple carboxylase deficiency).

![Table 228-1: Causes of Urine Color Changes](image)

**pH** is normally 5.0 to 6.0 (range 4.5 to 8.0). Measuring with a glass pH electrode is recommended when precise values are necessary for decision making, as when diagnosing renal tubular acidosis; in these cases, a layer of mineral oil should be added to the urine specimen to prevent escape of CO₂. Delay in processing a specimen may elevate pH because ammonia is released as bacteria break down urea. Infection with urease-producing pathogens can spuriously increase pH.

**Specific gravity** provides a rough measure of urine concentration (osmolality). Normal range is 1.001 to 1.035; values may be low in the elderly or in patients with impaired renal function, who are less able to concentrate urine. It is measured by hydrometer or refractometer or estimated with a dipstick. Accuracy of the dipstick test is controversial, but the test may be sufficient for patients who have calculi and are advised to self-monitor urine concentration to maintain dilute urine. Specific gravity by dipstick may be spuriously elevated when urine pH is < 6 or low when pH is > 7. Hydrometer and refractometer measurements may be elevated by high levels of large molecules (eg, radiopaque contrast agent, albumin, glucose, carbenicillin) in the urine.

**Protein**, detected by standard dipstick tests, reflects mainly urinary albumin concentration, classified as negative (< 10 mg/dL), trace (15 to 30 mg/dL), or 1+ (30 to 100 mg/dL) through 4+ (> 500 mg/dL). Microalbuminuria, an important marker for renal complications in patients with diabetes, is not detected by standard dipsticks, but special microalbumin dipsticks are available. Light-chain proteins (eg, due to multiple myeloma) also are not detected. Significance of proteinuria depends on total protein excretion rather than protein concentration estimated by dipstick; thus, when proteinuria is detected with dipstick testing, quantitative measures of urinary protein (see p. 2330) should be done. False-negative results can be caused by dilute urine. False-positive results can be caused by any of the following:

- High pH (> 9)
- Presence of cells
- Radiopaque contrast agents
- Concentrated urine

**Glucose** usually appears in the urine when serum glucose increases to > 180 mg/dL (> 10.1 mmol/L) and renal function is normal. Threshold for detection by urine dipstick is 50 mg/dL (2.8 mmol/L). Any amount is abnormal. Falsely low or negative results can result from any of the following:

- Ascorbic acid
- Ketones
- Aspirin
- Levodopa
- Tetracycline
• Very high urine pH

• Dilute urine

**Hematuria** is detected when RBCs lyse on a dipstick test strip, releasing Hb and causing a color change. Range is from negative (0) to 4+. Trace blood (corresponding to 3 to 5 RBCs/high-power field [HPF]) is normal under some circumstances (eg, exercise) in some people. Because the test strip reagent reacts with Hb, free Hb (eg, due to intravascular hemolysis) or myoglobin (eg, due to rhabdomyolysis) causes a positive result. Hemoglobinuria and myoglobinuria can be distinguished from hematuria by the absence of RBCs on microscopic examination and by the pattern of color change on the test strip. RBCs create a dotted or speckled pattern; free Hb and myoglobin create a uniform color change. Povidone iodine causes false-positive results (uniform coloring); ascorbic acid causes false-negative results.

**Nitrites** are produced when bacteria reduce urinary nitrates derived from amino acid metabolism. Nitrites are not normally present and signify bacteriuria. The test is either positive or negative. False-negative results may occur with any of the following:

- Infection with certain pathogens that cannot convert nitrate to nitrite (eg, *Enterococcus faecalis*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis*, *Pseudomonas* sp)
- Urine that has not stayed long enough (< 4 h) in the bladder
- Low urinary excretion of nitrate
- Enzymes (of certain bacteria) that reduce nitrates to nitrogen
- High urine urobilinogen level
- Presence of ascorbic acid
- Urine pH < 6.0

Nitrites are used mainly with WBC esterase testing to monitor patients with recurrent urine infections, particularly children with vesicoureteral reflux, and sometimes to confirm the diagnosis of uncomplicated UTI in women of childbearing age.

**WBC esterase** is released by lysed neutrophils. Its presence in urine reflects acute inflammation, most commonly due to bacterial infection but sometimes due to interstitial nephritis, nephrolithiasis, or renal TB. Threshold for detection is about 5 WBCs/HPF, and test results range from negative to 4+. The test is not very sensitive for detection of infection. Contamination of a urine specimen with vaginal flora is the most common cause of false-positive results. False-negative results may result from any of the following:

- Very dilute urine
- Glycosuria
- Urobilinogen
- Use of phenazopyridine, nitrofurantoin, rifampin, or large amounts of vitamin C

WBC esterase is used mainly with nitrite testing to monitor patients with recurrent urine infections and sometimes to diagnose uncomplicated UTI in women of childbearing age. If both tests are negative, the likelihood of a positive urine culture is small.

**Microscopic analysis:** Detection of solid elements (cells, casts, crystals) requires microscopic analysis, ideally done immediately after voiding, and dipstick testing. The specimen is prepared by centrifuging 10 to 15 mL of urine at 1500 to 2500 rpm for 5 min. The supernatant is fully decanted; a small amount of urine remains with the residue at the bottom of the centrifuge tube. The residue can be mixed back into
solution by gently agitating the tube or tapping the bottom. A single drop is pipetted onto a slide and covered with a coverslip. For routine microscopic analysis, staining is optional. The specimen is examined under reduced light with the low-power objective and under full-intensity light with the high-power objective; the latter is typically used for semiquantitative estimates (eg, 10 to 15 WBCs/HPF). Polarized light is used to identify some crystals and lipids in the urine. Phase-contrast microscopy enhances identification of cells and casts.

**Epithelial cells** (renal tubular, transitional, squamous cells) frequently are found in urine; most common are squamous cells lining the end of the urethra and contaminants from the vagina. Only renal tubular cells are diagnostically important; however, except when found in casts, they are difficult to distinguish from transitional cells. A few renal tubular cell casts appear in normal urine, but a large number suggests tubular injury (eg, acute tubular necrosis, tubulointerstitial nephropathy, nephrotoxins, nephrotic syndrome).

**RBCs** < 3/HPF may be normal (< 5/HPF is sometimes normal, eg, after exercise), and any hematuria should be interpreted in clinical context (see p. 2321). On microscopic analysis, glomerular RBCs are dysmorphic, with spicules, folding, and blebs; nonglomerular RBCs retain their normal shape.

**WBCs** < 5/HPF may be normal; special staining can distinguish eosinophils from neutrophils (see above). Pyuria is defined as > 5 WBCs/HPF in a sample of centrifuged urine.

**Lipiduria** is most characteristic of the nephrotic syndrome; renal tubular cells absorb filtered lipids, which appear microscopically as oval fat bodies, and cholesterol, which produces a Maltese cross pattern under polarized light. Lipids and cholesterol can also be free floating or incorporated into casts.

**Crystals** in urine are common and usually clinically insignificant (see Table 228-2). Crystal formation depends on all of the following:

- Urine concentration of crystal constituents
- pH
- Absence of crystallization inhibitors

Drugs are an underrecognized cause of crystals (see Table 228-3).

**Casts** are made up of glycoprotein of unknown function (Tamm-Horsfall protein) secreted from the thick ascending loop of Henle. They are cylindrical and have regular margins. Their presence indicates renal origin, which may be helpful diagnostically. Types of casts differ in constituents and appearance (see Table 228-4).

**Other urine tests:** Other tests are useful in specific instances.

**Total protein excretion** can be measured in a 24-h collection or can be estimated by the protein/creatinine ratio, which, in a random urine sample, correlates well with values in g/1.73 m^2 BSA from a 24-h collection (eg, 400 mg/dL protein and 100 mg/dL creatinine in a random sample equal 4 g/1.73 m^2 in a 24-h collection). The protein/creatinine ratio is less accurate when creatinine excretion is significantly increased (eg, in muscular athletes) or decreased (eg, in cachexia).

**Microalbuminuria** is albumin excretion persistently between 30 and 300 mg/day (20 to 200 μg/min); lesser amounts are considered within the range of normal, and amounts > 300 mg/day (> 200 μg/min) are
considered overt proteinuria. Use of the urine albumin/urine creatinine ratio is a reliable and more convenient screening test because it avoids timed urine specimens and correlates well with 24-h values. A value > 30 mg/g (> 0.03 mg/mg) suggests microalbuminuria. The reliability of the test is best when a midmorning specimen is used, vigorous exercise is avoided before the test, and unusual creatinine production (in cachectic or very muscular patients) is not present. Microalbuminuria can occur in all of the following:

- Diabetes mellitus
- Hypertension
- Renal allograft dysfunction
- Preeclampsia
- UTI

Microalbuminuria is highly predictive of subsequent nephropathy in type 1 but not type 2 diabetes. Microalbuminuria is a risk factor for cardiovascular disorders and early cardiovascular mortality independent of diabetes or hypertension.

**Sulfosalicylic acid** (SSA) test strips can be used to detect protein other than albumin (eg, lg's in multiple myeloma) when dipstick urine tests are negative; urine supernatant mixed with SSA becomes turbid if protein is present. The test is semiquantitative with a scale of 0 (no turbidity) to 4+ (flocculent precipitates). Readings are falsely elevated by radiopaque contrast agents.

**Ketones** spill into urine with ketonemia, but use of test strips to measure urinary ketones is no longer widely recommended because they measure only acetoacetic acid and acetone, not β-hydroxybutyric acid. Thus, a false-negative result is possible even without an exogenous cause (eg, vitamin C, phenazopyridine, N-acetylcysteine); direct measurement of serum ketones is more accurate. Ketonuria is caused by endocrine and metabolic disorders and does not reflect renal dysfunction.

**Osmolality**, the total number of solute particles per unit mass (mOsm/kg [mmol/kg]), can be measured directly by osmometer.Normally, osmolality is 50 to 1200 mOsm/kg. Measurement is most useful for evaluating hyponatremia, hypernatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and diabetes insipidus.

**Electrolyte measurements** help diagnose specific disorders. Na level can help distinguish whether volume depletion (urine Na < 10 mEq/L) or acute tubular necrosis (urine Na > 40 mEq/L) is the cause of acute renal insufficiency or failure. The fractional excretion of Na (FE\textsubscript{Na}) is the percentage of filtered Na that is excreted. It is calculated as the ratio of excreted to filtered Na, which can be simplified to the following:

\[
\text{FE}_{\text{Na}} = \frac{(U_{\text{Na}})(P_{\text{Cr}})}{(P_{\text{Na}})(U_{\text{Cr}}) \times 100%}
\]

where \(U_{\text{Na}}\) is urine Na, \(P_{\text{Na}}\) is plasma Na, \(P_{\text{Cr}}\) is plasma creatinine, and \(U_{\text{Cr}}\) is urine creatinine.

This ratio is a more reliable measure than \(U_{\text{Na}}\) alone because \(U_{\text{Na}}\) levels between 10 and 40 mEq/L are nonspecific. FE\textsubscript{Na} < 1% suggests prerenal causes, such as volume depletion; however, acute glomerulonephritis or certain types of acute tubular necrosis (eg, rhabdomyolysis, radiocontrast-induced renal failure) can result in FE\textsubscript{Na} < 1%. A value > 1% suggests acute tubular necrosis or acute interstitial nephritis.

Other useful measurements include the following:

- Fractional excretion of HCO\textsubscript{3} in evaluation of renal tubular acidosis (see p. 2426)
• Cl levels and urine anion gap for diagnosis of metabolic alkalosis (see p. 862) and nonanion gap metabolic acidosis (see p. 860)

• K levels in determining the cause of hypokalemia or hyperkalemia

(Table 228-4. Urinary Casts)

• Levels of Ca, Mg, uric acid, oxalate, citrate, and cystine in evaluation of calculi

Eosinophils, cells that stain bright red or pink-white with Wright's or Hansel staining, most commonly indicate one of the following:

• Acute interstitial nephritis

• Rapidly progressive glomerulonephritis

• Acute prostatitis

• Renal atheroembolism

Cytology is used for the following:

• To screen for cancer in high-risk populations (eg, petrochemical workers)

• To evaluate painless hematuria in the absence of glomerular disease (suggested by the absence of dysmorphic RBCs, proteinuria, and renal failure)

• To check for recurrence after bladder tumor resection

Sensitivity is about 90% for carcinoma in situ; however, sensitivity is considerably lower for low-grade transitional cell carcinomas. Inflammatory or reactive hyperplastic lesions or cytotoxic drugs for carcinoma may produce false-positive results. Accuracy for detecting bladder tumors may be increased by vigorous bladder lavage with a small volume of 0.9% saline solution (50 mL pushed in and then aspirated by syringe through a catheter). Cells collected in the saline are concentrated and examined.

Gram stain and cultures with susceptibility testing are indicated when GU tract infections are suspected; a positive result must be interpreted in the clinical context (see p. 2373).

Amino acids are normally filtered and reabsorbed by the proximal tubules. They may appear in urine when a hereditary or acquired tubular transport defect (eg, Fanconi syndrome, cystinuria) is present. Measuring type and amount of amino acids may help in the diagnosis of certain types of calculi, renal tubular acidosis, and inherited disorders of metabolism.

Blood tests: Blood tests are useful in evaluation of renal disorders.

Serum creatinine values > 1.3 mg/dL (> 114 μmol/L) in men and > 1 mg/dL (> 90 μmol/L) in women are usually abnormal. Serum creatinine depends on creatinine generation as well as renal creatinine excretion. Because creatinine turnover increases with higher muscle mass, muscular people have higher serum creatinine levels and elderly and undernourished people have lower levels.

Serum creatinine may also be increased in the following conditions:

• Use of ACE inhibitors and angiotensin II receptor blockers

• Consumption of large amounts of meat
• Use of some drugs (cimetidine, trimethoprim, cefoxitin, flucytosine)

ACE inhibitors and angiotensin II receptor blockers reversibly decrease GFR and increase serum creatinine because they vasodilate efferent more than afferent glomerular arterioles, mainly in people who are dehydrated or are receiving diuretics. In general, serum creatinine alone is not a good indicator of kidney function. The Cockcroft and Gault formula and the Modification of Diet in Renal Disease formula estimate GFR based on serum creatinine and other parameters and more reliably evaluate kidney function.

**BUN/creatinine ratio** is used to distinguish prerenal from renal or postrenal (obstructive) azotemia; a value > 15 is considered abnormal and may occur in prerenal and postrenal azotemia. However, BUN is affected by protein intake and by several nonrenal processes (eg, trauma, infection, GI bleeding, corticosteroids) and, although suggestive, is generally inconclusive as evidence of renal dysfunction.

**Cystatin C**, a serine proteinase inhibitor that is produced by all nucleated cells and filtered by the kidneys, can also be used to evaluate kidney function. Its plasma concentration is independent of sex, age, and body weight. Testing is not always available, and values are not standardized across laboratories.

**Serum electrolytes** (eg, Na, K, HCO$_3^-$) may become abnormal and the anion gap (Na - [Cl + HCO$_3^-$]) may increase in acute kidney injury and chronic kidney disease. Serum electrolytes should be monitored periodically.

**CBC** may detect anemia in chronic kidney disease or, rarely, polycythemia in renal cell carcinoma or polycystic kidney disease. Anemia is often multifactorial (mainly due to erythropoietin deficiency and sometimes worsened or caused by blood loss in dialysis circuits or the GI tract); it may be microcytic or normocytic, and may be hypochromic or normochromic.

**Renin**, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidneys. Renin secretion is stimulated by reduced blood volume and renal blood flow and is inhibited by Na and water retention. Plasma renin is assayed by measuring renin activity as the amount of angiotensin I generated per hour. Specimens should be drawn from well-hydrated, Na- and K-replete patients. Plasma renin, aldosterone, cortisol, and ACTH should be measured in evaluation of all of the following:

- Adrenal insufficiency
- Hyperaldosteronism
- Refractory hypertension (see Renovascular Hypertension on p. 2077)

The plasma aldosterone/renin ratio calculated from measurements obtained with the patient in an upright posture is the best screening test for hyperaldosteronism, provided that plasma renin activity is > 0.5 ng/mL/h and aldosterone is > 12 to 15 ng/dL.

**Evaluating Kidney Function**

Kidney function is evaluated using values calculated from formulas based on results of blood and urine tests.

**GFR**: Glomerular filtration rate (GFR), the volume of blood filtered through the kidney per minute, is the best overall measure of kidney function; it is expressed in mL/min. Because normal GFR increases with increasing body size, a correction factor using body surface area (BSA) typically is applied. This correction is necessary to compare a patient's GFR to normal and to define different stages of chronic kidney disease. Given the mean normal BSA of 1.73 m$^2$, the correction factor is 1.73/patient BSA; adjusted GFR results are then expressed as mL/min/1.73 m$^2$.

Normal GFR in young, healthy adults is about 120 to 130 mL/min/1.73 m$^2$ and declines with age to about
75 mL/min/1.73 m\(^2\) at age 70. Chronic kidney disease is defined by a GFR < 60 mL/min/1.73 m\(^2\) for > 3 mo. The gold standard for GFR measurement is inulin clearance. Inulin is neither absorbed nor secreted by the renal tubule and therefore it is the ideal marker for evaluation of kidney function. However, its measurement is cumbersome and therefore it is mostly used in research settings.

**Creatinine clearance:** Creatinine is produced at a constant rate by muscle metabolism and is freely filtered by the glomeruli and also is secreted by the renal tubules. Because creatinine is secreted, creatinine clearance (CrCl) overestimates GFR by about 10 to 20% in people with normal kidney function and by up to 50% in patients with advanced renal failure; thus, use of CrCl to estimate GFR in chronic kidney disease is discouraged.

Using a timed (usually 24-h) urine collection, CrCl can be calculated as

\[
\text{CrCl} = \frac{\text{UCr} \times \text{UVol}}{\text{PCr}}
\]

where UCr is urine creatinine in mg/mL, UVol is urine volume in mL/min of collection (1440 min for a full 24-h collection), and PCr is plasma creatinine in mg/mL.

**Estimating creatinine clearance:** Because serum creatinine by itself is inadequate for evaluation of kidney function, several formulas have been devised to estimate CrCl using serum creatinine and other factors.

The **Cockcroft and Gault** formula can be used to estimate CrCl. It uses age, lean body weight, and serum creatinine level. It is based on the premise that daily creatinine production is 28 mg/kg/day with a decrease of 0.2 mg/yr of age.

\[
\text{CrCl}_{\text{Cockcroft}} = \frac{(140 - \text{age [yr]} \times \text{lean body wt [kg]})}{(72 \times \text{serum creatinine [mg/dL]})} \\
\times 0.85 \text{ if female}
\]

The **modification of diet in renal disease (MDRD)** study formula (current 4-factor formula) can also be used, although it requires a calculator or computer:

\[
\text{CrCl}_{\text{MDRD}} = 186 \times (\text{serum creatinine})^{-1.154} \\
\times (\text{age})^{0.203} \times 0.742 \text{ (if female)} \\
\times 1.210 \text{ (if African-American)}
\]

**Approach to the Urologic Patient**

Urologic patients may have symptoms referable to the kidneys as well as to other parts of the GU tract.

**History**

Pain originating in the kidneys or ureters is usually vaguely localized to the flanks or lower back and may radiate into the ipsilateral iliac fossa, upper thigh, testis, or labium. Typically, pain caused by calculi is colicky and may be prostrating; it is more constant if caused by infection. Acute urinary retention distal to the bladder causes agonizing suprapubic pain; chronic urinary retention causes less pain and may be asymptomatic. Dysuria is a symptom of bladder or urethral irritation (see p. 2318). Prostatic pain manifests as vague discomfort or fullness in the perineal, rectal, or suprapubic regions.

Symptoms of bladder obstruction in men include urinary hesitancy, straining, decrease in force and caliber of the urinary stream, and terminal dribbling. Incontinence has various forms (see p. 2352). Enuresis after age 3 to 4 yr may be a symptom of urethral stenosis in girls, posterior urethral valves in boys, psychologic distress, or, if onset is new, infection.
Pneumaturia (air passed with urine) suggests a vesicovaginal, vesicoenteric, or ureteroenteric fistula; the last 2 may be caused by diverticulitis, Crohn’s disease, abscess, or colon cancer. Pneumaturia could also be due to emphysematous pyelonephritis.

**Physical Examination**

Physical examination focuses on the costovertebral angle, abdomen, rectum, groin, and genitals. Pelvic examination is usually done in women with urinary symptoms.

**Costovertebral angle:** Pain elicited by blunt striking of the back, flanks, and angle formed by the 12th rib and lumbar spine with a fist (costovertebral tenderness) may indicate pyelonephritis, calculi, or urinary tract obstruction.

**Abdomen:** Visual fullness of the upper abdomen is an extremely rare and nonspecific finding of hydronephrosis or a kidney or abdominal mass. Dullness to percussion in the lower abdomen suggests bladder distention; normally, even a full bladder cannot be percussed above the symphysis pubis. Bladder palpation can be used to confirm distention and urinary retention.

**Rectum:** During digital rectal examination, prostatitis may be detected as a boggy, tender prostate. Focal nodules and less discrete hard areas must be distinguished from prostate cancer. The prostate may be symmetrically enlarged, rubbery, and not tender with benign prostatic hyperplasia.

**Groin and genitals:** Inguinal and genital examination should be done with patients standing. Inguinal hernia or adenopathy may explain scrotal or groin pain. Gross asymmetry, swelling, erythema, or discoloration of the testes may indicate infection, torsion, tumor, or other mass. Horizontal testicular lie (bell-clapper deformity) indicates increased risk of testicular torsion. Elevation of one testis (normally the left is lower) may be a sign of testicular torsion. The penis is examined with and without retracting the foreskin. Inspection of the penis can detect

- Hypospadias or epispadias in young boys
- Peyronie’s disease in men
- Priapism, ulcers, and discharge in either group

Palpation may reveal an inguinal hernia. Cremasteric reflex may be absent with testicular torsion. Location of masses in relation to the testis and the degree and location of tenderness may help differentiate among testicular masses (eg, spermatoceles, epididymitis, hydroceles, tumors). If swelling is present, the area should be transilluminated to help determine whether the swelling is cystic or solid. Fibrous plaques on the penile shaft are signs of Peyronie’s disease.

**Testing**

Urinalysis (see p. 2307) is critical for evaluating urologic disorders. Imaging tests (eg, ultrasonography, CT, MRI) are frequently required. For semen testing, see p. 2592.

Bladder tumor antigen testing for transitional cell cancer of the urinary tract is more sensitive than urinary cytology for detecting low-grade cancer; it is not sensitive enough to replace endoscopic examination. Urine cytology is the best test to detect high-grade cancer.

Prostate-specific antigen (PSA) is a glycoprotein with unknown function produced by prostatic epithelial cells. Levels can be elevated in prostate cancer and in some common noncancerous disorders (eg, benign prostatic hyperplasia, infection, trauma). PSA is measured to detect recurrence of cancer after treatment; its widespread use for cancer screening is controversial (see p. 2470).

**Imaging Tests**

Imaging tests are often used to evaluate patients with renal and urologic disorders.
Plain X-Rays Without Contrast

Abdominal x-rays without radiopaque contrast agents are virtually useless in evaluation of renal and urologic disorders. These x-rays are not sensitive, showing only about 50 to 60% of renal calculi (Ca oxalate calculi and rarely staghorn calculi); calcifications consistent with calculi are also nonspecific.

X-Rays With Use of Contrast

Images taken after administration of water-soluble contrast agents highlight the kidneys and urinary collecting system. Nonionic isoosmolal agents (eg, iohexol, iopamidol) are now widely used; they have fewer adverse effects than older hyperosmolal agents but still pose a risk of acute renal injury (contrast nephropathy—see p. 3404).

In urography, an x-ray is taken after IV, percutaneous antegrade or retrograde, or cystoscopic retrograde administration of a radiopaque contrast agent. Primary contraindications for all patients are iodine allergy and risk factors for contrast nephropathy.

IVU (IV urography or pyelography): IVU has been largely superseded by rapid multidimensional CT and MRI with or without a contrast agent. When IVU is done, abdominal compression may improve visualization of the renal pelvis and proximal ureters (with application) and distal ureters (after release). Additional x-rays at 12 and 24 h after contrast administration may be indicated for detection of postrenal obstruction or hydronephrosis.

Percutaneous anterograde urography: For percutaneous anterograde urography, a radiopaque contrast agent is introduced through an existing nephrostomy tube or, less commonly, through percutaneous puncture of the renal pelvis guided by fluoroscopy. Occasionally, a ureterostomy or an ileal conduit can be used. Anterograde urography is used in the following circumstances:

• When retrograde urography is unsuccessful (eg, because of tumor obstruction at bladder level)

• When large kidney calculi requiring percutaneous surgery must be evaluated

• When transitional cell carcinoma of the upper collecting system is suspected

• When patients cannot tolerate general anesthesia or the degree of sedation required for retrograde urography

Complications relate to puncture and placement of the catheter in the GU tract and include bleeding, sepsis, injury to adjacent organs, microscopic hematuria, pain, and urinary extravasation.

Retrograde urography: Retrograde urography uses cystoscopy and ureteral catheterization to introduce a radiopaque contrast agent directly into the ureters and renal collecting system. Sedation or general anesthesia is required. This technique is used when CT or MRI is required (eg, to identify the exact location or cause of obstruction) but is unsuccessful.

It is also useful for detailed examination of the pelviccaliceal collecting system, ureters (eg, to check for ureterovaginal fistulas), and bladder. However, overdistention and back-flow may distort calyces and obscure details. Risk of infection is higher than that with other types of urography. Acute ureteral edema and secondary stricture formation are rare complications.

Cystourethrography: For cystourethrography, the radiopaque contrast agent is introduced directly into the urethra and bladder. This technique provides more details than other imaging studies for evaluation of the following:

• Vesicoureteral reflux

• Urinary incontinence
• Recurrent UTIs

• Urethral strictures

• Suspected urethral or bladder trauma

Voiding cystourethrograms are taken during urination and are used to identify posterior urethral valves. No patient preparation is necessary. Adverse effects include UTIs and urosepsis. Severe urethral stricture is a relative contraindication.

**Angiography:** Conventional catheter angiography has been largely replaced by noninvasive vascular imaging (eg, magnetic resonance angiography, CT angiography, ultrasonography, radionuclide scanning). Remaining indications include renal vein renin imaging, and, among patients with renal artery stenosis, angioplasty and stenting. Arteriography is also rarely used for evaluation and treatment of renal hemorrhage and before kidney-sparing surgery. Digital subtraction angiography is no longer used when rapid-sequence multidimensional CT or helical (spiral) CT is available.

**Ultrasoundography**

Doppler ultrasonography is widely used to image the renal arteries, kidneys, bladder, prostate, testes, and penis. The test is safe but provides no information about renal function, and renal images may be difficult to obtain in overweight or obese patients. Also, there is no means to improve distinction between types of tissues, and image quality is operator-dependent. No patient preparation is necessary, but a full bladder facilitates its imaging. Ultrasonography can show urine volume after micturition (postvoiding residual). Doppler ultrasonography in patients with testicular pain helps distinguish torsion from other causes by assessing testicular blood flow.

**Computed Tomography**

CT provides a broad view of the urinary tract and surrounding structures. Conventional or helical scanners are used for most purposes with or without IV contrast agents. Use of contrast agents with either technique resembles IVU but provides additional detail. Helical CT without contrast agents is the study of choice for imaging of calculi. Radiopaque contrast agents are also best avoided for CT evaluation of trauma and other disorders that may involve acute hemorrhage (which appears bright white and can be confused with contrast agents) or urine extravasation. CT angiography is a less invasive alternative to conventional angiography (see p. 3405).

**Magnetic Resonance Imaging**

MRI is safer than CT for patients at risk of contrast nephropathy and exposes patients to no ionizing radiation. Uses include all of the following:

• Differentiation between hemorrhage and infection within renal cysts

• Determination of extent of tumor invasion within the bladder wall

• Precise imaging of the pelvis and genitals using a pelvic or endorectal coil

Magnetic resonance angiography, used to enhance images of blood vessels, has virtually replaced conventional angiography for evaluating renal artery stenosis and renal vein thrombosis in patients with normal renal function. However, nephrogenic systemic fibrosis is a risk from gadolinium-containing contrast agents, particularly when GFR is < 30 mL/min/1.73 m² BSA. MRI defines intrarenal calcifications poorly because they have few mobile protons. MRI with IV lymphotropic superparamagnetic nanoparticles (eg, monocrystalline iron oxide) can identify lymph node metastases in prostate cancer but is not widely available.

**Radionuclide Scanning**
Cortical tracers that bind to proximal tubular cells (eg, technetium-99m dimercaptosuccinic acid [\(^{99m}\text{Tc}\) DMSA]) are used to image the renal parenchyma. Excretory tracers that are rapidly filtered and excreted into urine (eg, iodine-125 iothalmate, \(^{99m}\text{Tc}\) diethylenetriamine pentaacetic acid [DTPA], \(^{99m}\text{Tc}\) mercaptoacetyltriglycine-3 [MAG3]) are used to assess GFR and overall renal perfusion. Radionuclide scanning can be used to evaluate renal function when use of IV contrast is undesirable. Radionuclide scanning also provides more information than does IVU or cross-sectional imaging about the following:

- Segmental renal emboli
- Renal parenchymal scarring due to vesicoureteral reflux
- Functional significance of renal artery stenosis
- Kidney function in living donors before transplantation

\(^{99m}\text{Tc}\) pertechnetate can be used to image blood flow to the testes and to distinguish torsion from epididymitis in patients with acute testicular pain, although Doppler ultrasonography is used more commonly because it is quicker. No patient preparation is necessary for radionuclide scanning, but patients should be asked about known allergies to the tracer.

**Procedures**

Some procedures are used for diagnosis alone, and others can be used for either diagnosis or therapy.

**Bladder Catheterization**

Bladder catheterization is used to do the following:

- Obtain urine for examination
- Measure residual urine volume
- Relieve urinary retention or incontinence
- Deliver radiopaque contrast agents or drugs directly to the bladder
- Irrigate the bladder

Catheterization may be urethral or suprapubic.

**Catheters:** Catheters vary by caliber, tip configuration, number of ports, balloon size, type of material, and length:

**Caliber** is standardized in French (F) units—also known as Charriere (Ch) units. Each unit is 0.33 mm, so a 14-F catheter is 4.6 mm in diameter. Sizes range from 14 to 24 F for adults and 8 to 12 F for children. Smaller catheters are usually sufficient for uncomplicated urinary drainage and useful for urethral strictures and bladder neck obstruction; bigger catheters are indicated for bladder irrigation and some cases of hemorrhage (eg, postoperatively or in hemorrhagic cystitis) and pyuria, because clots could obstruct smaller caliber catheters.

**Tips** are straight in most catheters (eg, Robinson, whistle-tip) and are used for intermittent urethral catheterization (ie, catheter is removed immediately after bladder drainage). Foley catheters have a straight tip and an inflatable balloon for self-retention. Other self-retaining catheters may have an expanded tip shaped like a mushroom (de Pezzer catheter) or a 4-winged perforated mushroom (Malecot catheter); they are used in suprapubic catheterization or nephrostomy. Elbowed (coude) catheters, which may have balloons for self-retention, have a bent tip to ease catheterization through strictures or
obstructions (eg, prostatic obstruction).

Ports are present in all catheters used for continuous urinary drainage. Many catheters have ports for balloon inflation, irrigation, or both (eg, 3-way Foley).

Balloons on self-retaining catheters have different volumes, from 2.5 to 5 mL in balloons intended for use in children and 10 to 30 mL in balloons used in adults. Larger balloons and catheters are generally used to manage bleeding; traction on the catheter pulls the balloon against the base of the bladder and puts pressure on vessels.

Stylets are flexible metal guides inserted through the catheter to give stiffness and to facilitate insertion through strictures or obstructions.

Catheter material chosen depends on the intended use. Plastic, latex, or polyvinyl chloride catheters are for intermittent use. Latex with silicone, hydrogel, or polymer (to diminish bacterial colonization) catheters are for continuous use. Silicone catheters are used in patients with latex allergy.

Urethral catheterization: A urethral catheter can be inserted by any health care practitioner and sometimes by patients themselves. No prior patient preparation is necessary; thus, the bladder is catheterized through the urethra unless the urethral route is contraindicated. Relative contraindications are the following:

• Urethral strictures
• Current UTI
• Urethral reconstruction or bladder surgery
• Urethral trauma

After the urethral meatus is carefully cleaned with an antibacterial solution, using strict sterile technique, the catheter is lubricated with sterile gel and gently advanced through the urethra into the bladder. Lidocaine jelly may be injected through the male urethra before the catheter is passed to help relieve discomfort.

Complications of bladder catheterization include all of the following:

• Urethral or bladder trauma with bleeding or microscopic hematuria (common)
• UTI (common)
• Creation of false passages
• Scarring and strictures
• Bladder perforation (rare)

Suprapubic catheterization: Suprapubic catheterization via percutaneous cystostomy is done by a urologist or another experienced physician. No prior patient preparation is necessary. General indications include need for long-term bladder drainage and inability to pass a catheter through the urethra or contraindication to catheter use when bladder catheterization is necessary.

Contraindications include the following:

• Inability to define bladder location clinically or ultrasonographically
• An empty bladder
• Suspected pelvic or lower abdominal adhesions

After the abdomen above the pubic area is numbed with a local anesthetic, a spinal needle is inserted into the bladder; ultrasound guidance is used if available. A catheter is then placed through a special trocar or over a guide wire threaded through the spinal needle. Prior lower abdominal surgery contraindicates blind insertion. Complications include UTI, intestinal injury, and bleeding.

Cystoscopy

Cystoscopy is insertion of a rigid or flexible fiberoptic instrument into the bladder.

Indications include the following:

• Helping diagnose urologic disorders (eg, bladder tumors or calculi)

• Treating urethral strictures

• Accessing the bladder for ureteral x-rays or placement of JJ stents (stents with coiled ends placed in the renal pelvis and bladder)

The main contraindication is active UTI.

Cystoscopy is usually done in an outpatient setting with use of local anesthesia or, when necessary, conscious sedation or general anesthesia. Complications include UTI, bleeding, and bladder and urethral trauma.

Biopsy

Biopsy requires a trained specialist (nephrologist, urologist, or interventional radiologist).

Renal biopsy: Indications for diagnostic biopsy include unexplained nephritic or nephrotic syndrome or acute kidney injury. Biopsy is occasionally done to assess response to treatment. Relative contraindications include bleeding diathesis and uncontrolled hypertension. Mild preoperative sedation with a benzodiazepine may be needed. Complications are rare but may include renal bleeding requiring transfusion or radiologic or surgical intervention.

Bladder biopsy: Bladder biopsy is indicated to diagnose certain disorders (eg, bladder cancer, sometimes interstitial cystitis or schistosomiasis) and occasionally to assess response to treatment. Contraindications include bleeding diathesis and acute tuberculous cystitis. Preoperative antibiotics are necessary only if active UTI is present. The biopsy instrument is inserted into the bladder through a cystoscope; rigid or flexible instruments can be used. The biopsy site is cauterized to prevent bleeding. A drainage catheter is left in place to facilitate healing and drainage of clots. Complications include excessive bleeding, UTI, and bladder perforation.

Prostate biopsy: Prostate biopsy is usually done to diagnose prostate cancer. Contra-indications include bleeding diathesis, acute prostatitis, and UTIs. Patient preparation includes stopping maintenance aspirin a week before biopsy, preoperative antibiotics (usually a fluoroquinolone), and an enema to clear the rectum. With the patient in a lateral position, the prostate is located by palpation or, preferably, ultrasonography. Overlying structures (perineum or rectum) are anesthetized, a spring-loaded biopsy needle is inserted into the prostate, and usually 12 tissue cores are obtained. Complications include the following:

• Urosepsis

• Hemorrhage

• Urinary retention
Hematuria

Hematospermia (often for 3 to 6 mo after biopsy)

Urethral Dilation

Urethral dilation is used to treat the following:

- Urethral strictures
- Urethral (urgency-frequency) syndrome
- Meatal stenosis

Contraindications include untreated infection, bleeding diathesis, a long segment stenosis, and severe scarring of the urethra. In cases of stricture, a fine filiform probe is passed through, then followers (dilators) of progressively larger diameter are attached to the distal end of the filiform probe and passed behind the probe to dilate the stricture until urine stream becomes adequate; the procedure is usually done over several sessions.

Dysuria

Dysuria is painful or uncomfortable urination, typically a sharp, burning sensation. Some disorders cause a painful ache over the bladder or perineum. Dysuria is an extremely common symptom in women, but it can affect men and can occur at any age.

Pathophysiology

Dysuria results from irritation of the bladder trigone or urethra. Inflammation or stricture of the urethra causes difficulty in starting urination and burning on urination. Irritation of the trigone causes bladder contraction, leading to frequent and painful urination. Dysuria most frequently results from an infection in the lower urinary tract, but it could also be associated with an upper UTI. Impaired renal concentrating ability is the main reason for frequent urination in upper UTIs.

Etiology

Dysuria is typically caused by urethral or bladder inflammation, although perineal lesions in women (eg, from vulvovaginitis or herpes simplex virus infection) can be painful when exposed to urine. Most cases are caused by infection, but sometimes noninfectious inflammatory disorders are responsible (see Table 228-5).

Overall, the most common causes of dysuria are

- Cystitis
- Urethritis from a sexually transmitted disease (STD)

Evaluation

History: History of present illness should cover duration of symptoms and whether they have occurred in the past. Important accompanying symptoms include fever, flank pain, urethral or vaginal discharge, and symptoms of bladder irritation (frequency, urgency) or obstruction (hesitancy, dribbling). Patients should be asked whether the urine is bloody, cloudy, or malodorous and the nature of any discharge (eg, thin and watery or thick and purulent). Clinicians should also ask whether patients have recently engaged in unprotected intercourse, have applied potential irritants to the perineum, have had recent urinary instrumentation (eg, cystoscopy, catheterization, surgery), or might be pregnant.

Review of systems should seek symptoms of a possible cause, including back or joint pain and eye
irritation (connective tissue disorder) and GI symptoms, such as diarrhea (reactive arthritis).

**Past medical history** should note prior urinary infections (including those during childhood) and any known abnormality of the urinary tract. As with any potentially infectious illness, a history of immune compromise or recent hospitalization is important.

**Physical examination:** Examination begins with review of vital signs, particularly to note the presence of fever.

Skin, mucosa, and joints are examined for lesions suggesting reactive arthritis (eg, conjunctivitis, oral ulcers, vesicular or crusting lesions of palms, soles, and around nails, joint tenderness). The flank is percussed for tenderness over the kidneys. The abdomen is palpatated for tenderness over the bladder.

Women should have a pelvic examination to detect perineal inflammation or lesions and vaginal or cervical discharge. Swabs for STD testing and wet mount should be obtained at this time rather than doing a 2nd examination.

Men should undergo external inspection to detect penile lesions and discharge; the area under the foreskin should be examined. Testes and epididymis are palpatated to detect tenderness or swelling. Rectal examination is done to palpate the prostate for size, consistency, and tenderness.

**Red flags:** The following findings are of particular concern:

- Fever
- Flank pain or tenderness
- Recent instrumentation
- Immunocompromised patient
- Recurrent episodes (including frequent childhood infections)
- Known urinary tract abnormality

**Interpretation of findings:** Some findings are highly suggestive (see Table 228-5). In young, healthy women with dysuria and significant symptoms of bladder irritation, cystitis is the most likely cause. Visible urethral or cervical discharge suggests an STD. Thick purulent material is usually gonococcal; thin or watery discharge is nongonococcal. Vaginitis and the ulcerative lesions of herpes simplex virus infection are typically apparent on inspection. In men, a very tender prostate suggests prostatitis, and a tender, swollen epididymis suggests epididymitis. Other findings also are helpful but may not be diagnostic; eg, women with findings of vulvovaginitis may also have a UTI or another cause of dysuria.

Findings suggestive of infection are more concerning in patients with red flag findings. Fever, flank pain, or both suggest an accompanying pyelonephritis. History of frequent UTIs should raise concern for an underlying anatomic abnormality or compromised immune status. Infections following hospitalization or instrumentation may indicate an atypical or resistant pathogen.

**Testing:** No single approach is uniformly accepted. Many clinicians presumptively give antibiotics for cystitis without any testing (sometimes not even urinalysis) in young, otherwise healthy women presenting with classic dysuria, frequency, and urgency and without red flag findings. Others evaluate everyone with a clean-catch midstream urine sample for urinalysis and culture. Some clinicians defer culture unless dipstick testing detects WBCs. In women of childbearing age, a pregnancy test is done (UTI during pregnancy is of concern because it may increase the risk of preterm labor or premature rupture of the membranes).
membranes). Vaginal discharge warrants a wet mount. Many clinicians routinely obtain samples of cervical (women) or urethral (men) exudate for STD testing (gonococcus and chlamydia culture or PCR) because many infected patients do not have a typical presentation.

A finding of > $10^5$ bacteria colony-forming (CFU) units/mL suggests infection. In symptomatic patients, sometimes counts as low as $10^2$ or $10^3$ CFUs indicate UTI. WBCs detected with urinalysis in patients with sterile cultures are nonspecific and may occur with an STD, vulvovaginitis, prostatitis, TB, tumor, or other causes. RBCs detected with urinalysis in patients with no WBCs and sterile cultures may be due to cancer, calculus, foreign body, glomerular abnormalities, or recent instrumentation of the urinary tract.

Cystoscopy and imaging of the urinary tract may be indicated to check for obstruction, anatomic abnormalities, cancer, or other problems in patients who have no response to antibiotics, recurrent symptoms, or hematuria without infection. Pregnant patients, older patients, and patients with prolonged or recurrent dysuria need closer attention and a more thorough investigation.

**Treatment**

Treatment is directed at the cause. Many clinicians do not treat dysuria in women without red flag findings if no cause is apparent from examination and the results of a urinalysis. If treatment is decided upon, a 3-day course of trimethoprim/sulfamethoxazole, trimethoprim alone, or a fluoroquinolone is recommended. Some clinicians give presumptive treatment for an STD in men with similarly unremarkable findings; other clinicians await STD test results, particularly in reliable patients.

Acute, intolerable dysuria due to cystitis can be relieved somewhat by phenazopyridine 100 to 200 mg po tid for the first 24 to 48 h. This drug turns urine red-orange; patients should be cautioned not to confuse this effect with progression of infection or hematuria. Upper UTI requires 10 to 14 days of treatment with an antibiotic that is effective against gram-negative organisms, particularly *Escherichia coli*.

**Key Points**

- Dysuria is not always caused by a bladder infection.
- STDs should be considered.

**Hematospermia**

Hematospermia is blood in semen. It is often frightening to patients but is usually benign.

**Pathophysiology**

Semen is composed of sperm from the distal epididymis and fluids from the seminal vesicles, prostate, and Cowper's and bulbourethral glands. Thus, a lesion anywhere along this pathway could introduce blood into the semen.

**Etiology**

Most cases of hematospermia are

- Idiopathic

Such cases resolve spontaneously within a few days to a few months.

The most common known cause is

- Prostate biopsy

Less common causes include benign prostatic hyperplasia, infections (eg, prostatitis, urethritis,
epididymitis), and prostate cancer (in men > 35 to 40 yr). Occasionally, tumors of the seminal vesicles and testes are associated with hematospermia. Hemangiomas of the prostatic urethra or spermatic duct may cause massive hematospermia.

*Schistosoma haematobium*, a parasitic fluke that causes significant disease in Africa (and to a lesser extent India and parts of the Middle East), can invade the urinary tract, causing hematuria and not infrequently hematospermia. Schistosomiasis is a consideration only in men who have spent time in areas where the disorder is endemic.

**Evaluation**

**History:** History of present illness should note the duration of symptoms. Patients who do not volunteer information should be asked specifically about a recent prostate biopsy. Important associated symptoms include hematuria, difficulty starting or stopping urine flow, nocturia, burning with urination, and penile discharge.

**Review of systems** should note symptoms of excessive bleeding, including easy bruising, frequent nosebleeds, and excessive gum bleeding with tooth brushing or dental procedures.

**Past medical history** should specifically ask about known disorders of the prostate, history of or exposure to TB or HIV, risk factors for sexually transmitted diseases (STDs—eg, unprotected intercourse, multiple sex partners), known bleeding disorders, and known disorders that predispose to bleeding (eg, cirrhosis). Drug history should note use of anticoagulants or antiplatelet drugs. Patients should be asked about any family history of prostate cancer and travel to regions where schistosomiasis is endemic.

**Physical examination:** The external genitals should be inspected and palpated for signs of inflammation (erythema, mass, tenderness), particularly along the course of the epididymis. A digital rectal examination is done to examine the prostate for enlargement, tenderness, or a lump.

**Red flags:** The following findings are of particular concern:

- Symptoms lasting > 1 mo
- Palpable lesion along the epididymis or in the prostate
- Travel to a region where schistosomiasis is prevalent

**Interpretation of findings:** Patients whose symptoms followed prostate biopsy can be reassured that the hematospermia is harmless and will go away.

Healthy patients with a brief duration of hematospermia, an otherwise normal history and examination, and no travel history likely have an idiopathic disorder.

Patients with abnormal findings on prostate examination may have prostate cancer, benign prostatic hyperplasia, or prostatitis. Urethral discharge suggests an STD.

Epididymal tenderness suggests an STD or rarely TB (more likely in patients with risk factors of exposure or who are immunocompromised).

Characteristic findings of a bleeding disorder or use of drugs that increase risk of bleeding suggests a precipitating cause but does not rule out an underlying disorder.

**Testing:** In most cases, especially in men < 35 to 40 yr, hematospermia is almost always benign. If no significant abnormality is found on physical examination (including digital rectal examination), urinalysis and urine culture are done, but no further work-up is necessary.

Patients who may have a more serious underlying disorder and should have testing include those who have
• A longer duration of symptoms (> 1 mo)
• Hematuria
• Obstructive urinary symptoms
• Abnormal examination findings

These findings are of particular concern in men > 40 yr. Testing includes urinalysis, urine culture, prostate-specific antigen (PSA) testing, and transrectal ultrasonography (TRUS). Occasionally, MRI and cystoscopy are needed. Semen inspection and analysis are rarely done but can be useful when travel history suggests possible exposure to *S. haematobium*.

**Treatment**

Treatment is directed at the cause if known. For almost all men, reassurance that hematospermia is not a sign of cancer and does not affect sexual function is the only intervention necessary. If prostatitis is suspected, it can be treated with trimethoprim/sulfamethoxazole or a fluoroquinolone for 4 to 6 wk.

**Key Points**

• Most cases are idiopathic or follow prostate biopsy.
• Testing is required mainly for patients with prolonged symptoms or abnormal examination findings.
• Schistosomiasis should be considered in patients who have traveled to endemic areas.

**Isolated Hematuria**

Hematuria is RBCs in urine, specifically > 3 RBCs per high-power field on urine sediment examination. Urine may be red or bloody (gross hematuria) or not visibly discolored (microscopic hematuria). Isolated hematuria is urinary RBCs without other urine abnormalities (eg, proteinuria, casts).

Red urine is not always due to RBCs. Red or reddish brown discoloration may result from the following:

• Hb or myoglobin in urine
• Porphyria (most types)
• Foods (eg, beets, rhubarb, sometimes food coloring)
• Drugs (most commonly phenazopyridine, but sometimes cascara, diphenylhydantoin, methylidopa, phenacetin, phenindione, phenolphthalein, phenothiazine, and senna)

**Pathophysiology**

RBCs may enter urine from anywhere along the urinary tract—from the kidneys, collecting system and ureters, prostate, bladder, and urethra.

**Etiology**

Most cases involve transient microscopic hematuria that is self-limited and idiopathic. Transient microscopic hematuria is particularly common in children, present in up to 5% of their urine samples. There are numerous specific causes (see Table 228-6).

The most common specific causes differ somewhat by age, but overall the most common are
• UTI
• Prostatitis
• Urinary calculi (in adults)

Cancer and prostate disease are a concern mainly in patients > 50, although younger patients with risk factors may develop cancer.

Glomerular disorders can be a cause at all ages. Glomerular disorders may represent a primary renal disorder (acquired or hereditary) or be secondary to many causes, including infections (eg, group A β-hemolytic streptococcal infection), connective tissue disorders (eg, SLE at all ages, Henoch-Schönlein purpura [HSP] in children), and blood disorders (eg, mixed cryoglobulinemia, serum sickness). Worldwide, IgA nephropathy is the most common form of glomerulonephritis.

*Schistosoma haematobium*, a parasitic fluke that causes significant disease in Africa (and, to a lesser extent, in India and parts of the Middle East), can invade the urinary tract, causing hematuria. Schistosomiasis is considered only if people have spent time in endemic areas.

**Evaluation**

**History:** *History of present illness* includes duration of hematuria and any previous episodes. Urinary obstructive symptoms (eg, incomplete emptying, nocturia, difficulty starting or stopping) and irritative symptoms (eg, irritation, urgency, frequency, dysuria) should be noted. Patients should be asked about the presence of pain and its location and severity.

**Review of systems** should seek symptoms of possible causes, including joint pain and rashes (connective tissue disorder).

**Past medical history** should include questions about any recent infections, particularly a sore throat that may indicate a group A β-hemolytic streptococcal infection. Conditions known to cause urinary tract bleeding (particularly kidney calculi, sickle cell disease or trait, and glomerular disorders) should be sought. Also, conditions that predispose to a glomerular disorder, such as a connective tissue disorder (particularly SLE and RA), endocarditis, shunt infections, and abdominal abscesses, should be identified. Risk factors for GU cancer should be identified, including smoking (the most significant), drugs (eg, cyclophosphamide, phenacetin), and exposure to industrial chemicals (eg, nitrates, nitritolriacetate, nitrates, trichloroethylene).

Family history should identify relatives with known polycystic kidney disease, a glomerular disorder, or GU cancer. Patients should be asked about travel to areas where schistosomiasis is endemic. Drug history should note use of anticoagulants or antiplatelet drugs (although anticoagulation itself does not cause hematuria).

**Physical examination:** Vital signs should be reviewed for fever and hypertension.

The heart should be auscultated for murmurs (suggesting endocarditis).

The abdomen should be palpated for masses; flanks should be percussed for tenderness over the kidneys. In men, a digital rectal examination should be done to check for prostate enlargement, nodules, and tenderness.

The face and extremities should be inspected for edema (suggesting a glomerular disorder), and the skin should be inspected for rashes (suggesting vasculitis, SLE, or HSP).

**Red flags:** The following findings are of particular concern:

• Gross hematuria
• Persistent microscopic hematuria, especially in older patients

• Age > 50

• Hypertension and edema

**Interpretation of findings:** Clinical manifestations of the various causes overlap significantly, so urine and often blood tests are required. Depending on results, imaging tests may then be needed. However, some clinical findings provide helpful clues (see Table 228-6).

• Blood clots in urine essentially rule out a glomerular disorder. Glomerular disorders are often accompanied by edema, hypertension, or both; symptoms may be preceded by an infection (particularly a group Aβ-hemolytic streptococcal infection in children).

• Calculi usually manifest with excruciating, colicky pain. Less severe, more continuous pain is more likely to result from infection, cancer, polycystic kidney disease,

(Table 228-6. Some Common Specific Causes of Hematuria)

| glomerulonephritis, and loin pain-hematuria syndrome. |

• Urinary irritative symptoms suggest bladder or prostate infection but may accompany certain cancers (mainly bladder and prostate).

• Urinary obstructive symptoms usually suggest prostate disease.

• An abdominal mass suggests polycystic kidney disease or renal cell carcinoma.

• A family history of nephritis, sickle cell disease or trait, or polycystic kidney disease suggests that as a cause.

• Travel to Africa, the Middle East, or India suggests the possibility of schistosomiasis.

On the other hand, some common findings (eg, prostate enlargement, anticoagulant use), although potential causes of hematuria, should not be assumed to be the cause without further evaluation.

**Testing:** Before testing proceeds, true hematuria should be distinguished from red urine by urinalysis. In women with vaginal bleeding, the specimen should be obtained by straight catheterization to avoid contamination by a nonurinary source of blood. Red urine without RBCs suggests myoglobinuria or hemoglobinuria, porphyria, or ingestion of certain drugs or foods.

Presence of casts, protein, or dysmorphic RBCs (unusually shaped, with spicules, folding, and blebs) indicates a glomerular disorder. WBCs or bacteria suggest an infectious etiology. However, because urinalysis shows predominantly RBCs in some patients with cystitis, urine culture is usually done. A positive culture result warrants treatment with antibiotics. If hematuria resolves after treatment and no other symptoms are present, no further evaluation is required for patients < 50, especially women.

If patients < 50 (including children) have only microscopic hematuria and no urine findings suggesting a glomerular disorder, no clinical manifestations suggesting a cause, and no risk factors for cancer, they can be observed, with urinalysis repeated every 6 to 12 mo. If hematuria is persistent, ultrasonography or CT with contrast is suggested.

Patients < 50 with gross hematuria require ultrasonography or CT of the abdomen and pelvis.

If urine or clinical findings suggest a glomerular disorder, renal function is evaluated by measuring BUN, serum creatinine, and electrolytes; doing a urinalysis; and periodically determining the urine protein/creatinine ratio. Further evaluation of a glomerular disorder may require serologic tests, kidney
biopsy, or both.

All patients ≥ 50 yr require cystoscopy, as do patients who are < 50 but have risk factors, such as a family history of cancer. Men ≥ 50 require testing for prostate-specific antigen; those with elevated levels require further evaluation for prostate cancer.

Treatment

Treatment is directed at the cause.

Key Points

• Red urine should be differentiated from hematuria (RBCs in urine).

• Urinalysis and urine sediment examination help differentiate glomerular from nonglomerular causes.

• Risk of serious disease increases with aging and with duration and degree of hematuria.

• Cystoscopy and imaging tests are usually needed only for patients > 50 or for younger patients with risk factors for cancer.

Polyuria

Polyuria is urine output of > 3 L/day; it must be distinguished from urinary frequency, which is the need to urinate many times during the day or night but in normal or less-than-normal volumes. Either problem can include nocturia.

Pathophysiology

Water homeostasis is controlled by a complex balance of water intake (itself a matter of complex regulation), renal perfusion, glomerular filtration and tubular reabsorption of solutes, and reabsorption of water from the renal collecting ducts.

When water intake increases, blood volume increases and thus renal perfusion and GFR increase, resulting in increased urine volume. However, the increased water intake lowers blood osmolality, decreasing release of ADH (also referred to as arginine vasopressin) from the hypothalamic-pituitary system. Because ADH promotes water reabsorption in the renal collecting ducts, decreased levels of ADH increase urine volume, allowing body water to return to normal.

Additionally, high amounts of solutes within the renal tubule cause a passive osmotic diuresis (solute diuresis) and thus an increase in urine volume. The classic example of this process is the glucose-induced osmotic diuresis in uncontrolled diabetes mellitus, when high urinary glucose levels (> 250 mg/dL) exceed tubular reabsorption capacity, leading to high glucose levels in the renal tubules; water follows passively, resulting in glucosuria and increased urine volume.

Therefore, polyuria results from any process that involves

• Sustained increase in water intake (polydipsia)

• Decreased ADH secretion (central diabetes insipidus)

• Decreased peripheral ADH sensitivity (nephrogenic diabetes insipidus)

• Solute diuresis

Etiology

The most common cause of polyuria (see
Table 228-7) in both adults and children is

• Uncontrolled diabetes mellitus

[Table 228-7, Some Causes of Polyuria]

In the absence of diabetes mellitus, the most common causes are

• Primary polydipsia
• Central diabetes insipidus
• Nephrogenic diabetes insipidus

Evaluation

History: History of present illness should include the amounts of fluid consumed and voided to distinguish between polyuria and urinary frequency. If polyuria is present, patients should be asked about the age at onset, rate of onset (eg, abrupt vs gradual), and any recent clinical factors that may cause polyuria (eg, IV fluids, tube feedings, resolution of urinary obstruction, stroke, head trauma, surgery).

Review of systems should seek symptoms suggesting possible causes, including dry eyes and dry mouth (Sjogren's syndrome) and weight loss and night sweats (cancer).

Past medical history should be reviewed for conditions associated with polyuria, including diabetes mellitus, psychiatric disorders, sickle cell disease, sarcoidosis, amyloidosis, and hyperparathyroidism. A family history of polyuria should be noted. Drug history should note use of any drugs associated with nephrogenic diabetes insipidus (see Table 228-7) and agents that increase urine output (eg, diuretics, alcohol, caffeinated beverages).

Physical examination: The general examination should note signs of obesity (as a risk factor for type 2 diabetes mellitus) or undernutrition or cachexia that might reflect an underlying cancer or an eating disorder with surreptitious diuretic use.

The head and neck examination should note dry eyes or dry mouth (Sjogren's syndrome). Skin examination should note the presence of any hyperpigmented or hypopigmented lesions, ulcers, or subcutaneous nodules that may suggest sarcoidosis. Comprehensive neurologic examination should note any focal deficits that suggest an underlying neurologic insult and assess mental status for indications of a thought disorder.

Red flags: The following findings are of particular concern:

• Abrupt onset or onset during the first few years of life
• Night sweats, cough, and weight loss, especially when there is an extensive smoking history
• Psychiatric disorder

Interpretation of findings: History can often distinguish polyuria from frequency, but rarely a 24-h urine collection may be needed.

Clinical evaluation may suggest a cause (see Table 228-7), but testing is usually necessary. Diabetes insipidus is suggested by a history of cancer or chronic granulomatous disease (due to hypercalcemia), use of certain drugs (lithium, cidofovir, foscarnet, ifosfamide), and less common conditions (eg, sickle cell disease, renal amyloidosis, sarcoidosis, Sjogren's syndrome) that have manifestations that are often more prominent than and precede the polyuria.

Abrupt onset of polyuria at a precise time suggests central diabetes insipidus, as does preference for
extremely cold or iced water. Onset during the first few years of life is typically related to inherited central or nephrogenic diabetes insipidus or uncontrolled type 1 diabetes mellitus. Polyuria caused by diuresis is suggested by a history of diuretic use or diabetes mellitus. Psychogenic polydipsia is more common in patients with a history of a psychiatric disorder (primarily bipolar disorder or schizophrenia) rather than as an initial manifestation.

**Testing:** Once excess urine output has been verified by history or measurements, serum or fingerstick glucose determination should be done to rule out uncontrolled diabetes.

If hyperglycemia is not present, then testing is required:

- Serum and urine chemistries (electrolytes, Ca)
- Serum and urine osmolality and sometimes plasma ADH level

These tests look for hypercalcemia, hypokalemia (due to surreptitious diuretic use), and hypernatremia or hyponatremia:

- Hypernatremia (Na > 142 mEq/L) suggests excess free water loss due to central or nephrogenic diabetes insipidus.
- Hyponatremia (Na < 137 mEq/L) suggests excess free water intake secondary to polydipsia.
- Urine osmolality is typically < 300 mOsm/kg with water diuresis and > 300 mOsm/kg with solute diuresis.

If the diagnosis remains unclear, then measurement of serum and urine Na and osmolality in response to a **water deprivation test** and exogenous ADH administration should be done. Because serious dehydration may result from this testing, the test should be done only while patients are under constant supervision; hospitalization is usually required. Additionally, patients in whom psychogenic polydipsia is suspected must be observed to prevent surreptitious drinking.

The test is started in the morning by weighing the patient, obtaining venous blood to determine serum electrolyte concentrations and osmolality, and measuring urine osmolality. Voided urine is collected hourly, and its osmolality is measured. Dehydration is continued until orthostatic hypotension and postural tachycardia appear, ≥ 5% of the initial body weight has been lost, or the urinary concentration does not increase > 30 mOsm/kg in sequentially voided specimens. Serum electrolytes and osmolality are again determined, and 5 units of aqueous vasopressin are injected sc. Urine for osmolality measurement is collected one final time 60 min postinjection, and the test is terminated.

A normal response produces maximum urine osmolality after dehydration (> 700 mOsm/kg), and osmolality does not increase more than an additional 5% after injection of vasopressin.

In **central diabetes insipidus**, patients are typically unable to concentrate urine to greater than the plasma osmolality but are able to increase their urine osmolality after vasopressin administration. The increase in urine osmolality is 50 to 100% in central diabetes insipidus vs 15 to 45% with partial central diabetes insipidus.

In **nephrogenic diabetes insipidus**, patients are unable to concentrate urine to greater than the plasma osmolality and show no additional response to vasopressin administration. Occasionally in partial nephrogenic diabetes insipidus, the increase in urine osmolality can be up to 45%, but overall these numbers are much lower than those that occur in partial central diabetes insipidus (usually < 300 mOsm/kg).

In **psychogenic polydipsia**, urine osmolality is < 100 mOsm/kg. Decreasing water intake will lead to decreasing urine output, increasing plasma osmolality and serum Na concentration.

Measurement of circulating ADH is the most direct method of diagnosing central diabetes insipidus. Levels at the end of the water deprivation test (before the vasopressin injection) are low in central...
diabetes insipidus and appropriately elevated in nephrogenic diabetes insipidus. However, ADH levels are not routinely available. In addition, water deprivation is so accurate that direct measurement of ADH is rarely necessary. Plasma ADH levels are diagnostic after either dehydration or infusion of hypertonic saline.

**Treatment**

Treatment varies by cause.

**Key Points**

- Uncontrolled diabetes mellitus is the most common cause of polyuria in both adults and children.
- In the absence of diabetes mellitus, the most common causes of chronic polyuria are primary polydipsia, central diabetes insipidus, and nephrogenic diabetes insipidus.
- Hypernatremia usually indicates central or nephrogenic diabetes insipidus.
- Hyponatremia is more characteristic of polydipsia.
- Abrupt onset of polyuria suggests central diabetes insipidus.
- A water deprivation test can help with diagnosis but should only be done with the patient under close supervision.

**Priapism**

Priapism is painful, persistent, abnormal erection unaccompanied by sexual desire or excitation. It is most common in boys 5 to 10 yr and in men age 20 to 50 yr.

**Pathophysiology**

The penis is composed of 3 corporeal bodies: 2 corpora cavernosa and 1 corpus spongiosum. Erection is the result of smooth muscle relaxation and increased arterial flow into the corpora cavernosa, causing engorgement and rigidity.

**Ischemic priapism:** Most cases of priapism involve failure of detumescence and are most commonly due to failure of venous outflow (ie, low flow), also known as ischemic priapism. Severe pain from ischemia occurs after 4 h. If prolonged > 4 h, priapism can lead to corporeal fibrosis and subsequent erectile dysfunction or even penile necrosis and gangrene.

**Stuttering priapism** is a recurrent form of ischemic priapism with repeated episodes and intervening periods of detumescence.

**Nonischemic priapism:** Less commonly, priapism is due to unregulated arterial inflow (ie, high flow), usually as a result of formation of an arterial fistula after trauma. Nonischemic priapism is not painful and does not lead to necrosis. Subsequent erectile dysfunction is common.

**Etiology**

In adults, the most common cause (see Table 228-8) is

- Drug therapy for erectile dysfunction

  In children, the most common causes are

- Hematologic disorders (eg, sickle cell disease, less commonly leukemia)
In many cases, priapism may be idiopathic and recurrent.

**Evaluation**

Priapism requires urgent treatment to prevent chronic complications (primarily erectile dysfunction). Evaluation and treatment should be done simultaneously.

**History:** *History of present illness* should cover the duration of erection, presence of partial or complete rigidity, presence or absence of pain, and any recent or past genital trauma. The drug history should be reviewed for offending drugs, and patients should be directly asked about the use of recreational drugs and drugs used to treat erectile dysfunction.

**Review of systems** should seek symptoms suggesting a cause, including dysuria (UTIs), urinary hesitancy or frequency (prostate cancer), fever and night sweats (leukemia), and lower-extremity weakness (spinal cord pathology).

**Past medical history** should identify known conditions associated with priapism (see Table 228-8), particularly hematologic disorders. Patients should be asked about a family history of hemoglobinopathies (sickle cell disease or thalassemia).

**Physical examination:** A focused genital examination should be done to evaluate extent of rigidity and tenderness and determine whether the glans and corpus spongiosum are also affected. Penile or perineal trauma and signs of infection, inflammation, or gangrenous change should be noted.

The general examination should note any psychomotor agitation, and the head and neck examination should look for pupillary dilation associated with stimulant use. The abdomen and suprapubic area should be palpated to detect any masses or splenomegaly, and a digital rectal examination should be done to detect prostatic enlargement or other pathology. Neurologic examination is useful to detect any signs of lower-extremity weakness or saddle paresthesias that might indicate spinal pathology.

**Red flags:** The following findings are of particular concern:

- Pain
- Priapism in a child
- Recent trauma
- Fever and night sweats

**Interpretation of findings:** In most cases, the clinical history reveals a history of drug treatment for erectile dysfunction, illicit drug use, or a history of sickle cell disease or trait; in these cases, no testing is indicated.

In patients with ischemic priapism, physical examination typically reveals complete rigidity with pain and tenderness of the corpus cavernosa and sparing of the glans and corpus spongiosum. By contrast, nonischemic priapism is painless and nontender, and the penis may be partially or completely rigid.

**Testing:** If the cause is not obvious, screening is done for hemoglobinopathies, leukemia, lymphoma, UTI, and other causes:

- CBC
- Urinalysis and culture
Hb electrophoresis in blacks and men of Mediterranean descent

Many clinicians also do drug screening, intracavemosal ABG testing, and duplex ultrasonography. Penile duplex ultrasonography will show little or absent cavernosal blood flow in men with ischemic priapism and normal to high cavernosal blood flow in men with nonischemic priapism. Ultrasonography may also reveal anatomic abnormalities, such as cavernous arterial fistula or pseudoaneurysm, which usually indicate nonischemic priapism. Occasionally, MRI with contrast is useful to demonstrate arteriovenous fistulas or aneurysms.

Treatment

Treatment is often difficult and sometimes unsuccessful, even when the etiology is known. Whenever possible, patients should be referred to an emergency department; patients should preferably be seen and treated by a urologist. Other disorders should be treated. For example, priapism often resolves when sickle cell crisis is treated. Measures used to treat priapism itself depend on the type.

Ischemic priapism: Treatment should begin immediately, typically with aspiration of blood from the base of one of the corpora cavernosa using a nonheparinized syringe, often with saline irrigation and intracavemosal injection of the α-receptor agonist phenylephrine. For phenylephrine injections, 1 mL of 1% phenylephrine (10 mg/mL) is added to 19 mL of 0.9% saline to make 500 μg/mL; 100 to 500 μg (0.2 to 1 mL) is injected every 5 to 10 min until relief occurs or a total dose of 1000 μg is given. Before aspiration or injection, anesthesia is provided with a dorsal nerve block or local infiltration.

If these measures are unsuccessful or if priapism has lasted > 48 h (and is thus unlikely to resolve with these measures), a surgical shunt can be created between the corpus cavernosum and glans penis or corpus spongiosum and another vein.

Stuttering priapism: Stuttering priapism, when acute, is treated in the same way as other forms of ischemic priapism. There is a report of several cases caused by sickle cell disease that responded to a single oral dose of sildenafil. Treatments that may help prevent recurrences of stuttering priapism include antiandrogen therapy with gonadotropin-releasing hormone analogs, estrogen, bicalutamide, flutamide, phosphodiesterase type-5 inhibitors, and ketoconazole. The goal of antiandrogen therapy is to decrease the plasma testosterone level to < 10% of normal. Digoxin, terbutaline, gabapentin, and hydroxyurea have also been tried with some success.

Nonischemic priapism: Conservative therapy (eg, ice packs and analgesics) is usually successful; if not, selective embolization or surgery is indicated.

Refractory priapism: If other treatments are ineffective, a penile prosthesis can be placed.

Key Points

• Priapism requires urgent evaluation and treatment.
• Drugs (prescription and recreational) and sickle cell disease are the most common causes.
• Acute treatment is with α-agonists, needle decompression, or both.

Proteinuria

Proteinuria is protein, usually albumin, in urine. High concentrations of protein cause frothy or sudsy urine. In many renal disorders, proteinuria occurs with other urinary abnormalities (eg, hematuria). Isolated proteinuria is urinary protein without other symptoms or urinary abnormalities.

Pathophysiology

Although the glomerular basement membrane is a very effective barrier against larger molecules (eg, most plasma proteins, including albumin), a small amount of protein passes through the capillary
basement membranes into the glomerular filtrate. Some of this filtered protein is degraded and reabsorbed by the proximal tubules, but some is excreted in the urine. The upper limit of normal urinary protein excretion is considered to be 150 mg/day, which can be measured in a 24-h urine collection or estimated by random urine protein/creatinine ratio (values < 0.3 are abnormal); for albumin it is about 30 mg/day. Albumin excretion between 30 and 300 mg/day (20 to 200 μg/min) is considered microalbuminuria, and higher levels are considered macroalbuminuria. Mechanisms of proteinuria may be categorized as

- Glomerular
- Tubular
- Overflow
- Functional

**Glomerular proteinuria** results from glomerular disorders, which typically involve increased glomerular permeability; this permeability allows increased amounts of plasma proteins (sometimes very large amounts) to pass into the filtrate.

**Tubular proteinuria** results from renal tubulointerstitial disorders that impair reabsorption of protein by the proximal tubule, causing proteinuria (mostly from smaller proteins such as immunoglobulin light chains rather than albumin). Causative disorders are often accompanied by other defects of tubular function (eg, \( \text{HCO}_3 \) wasting, glycosuria, aminoaciduria) and sometimes by glomerular pathology (which also contributes to the proteinuria).

**Overflow proteinuria** occurs when excessive amounts of small plasma proteins (eg, immunoglobulin light chains produced in multiple myeloma) exceed the reabsorptive capacity of the proximal tubules.

**Functional proteinuria** occurs when increased renal blood flow (eg, due to exercise, fever, high-output heart failure) delivers increased amounts of protein to the nephron, resulting in increased protein in the urine (usually < 1 g/day). Functional proteinuria reverses when renal blood flow returns to normal.

**Orthostatic proteinuria** is a benign condition (most common among children and adolescents) in which proteinuria occurs mainly when the patient is upright. Thus, urine typically contains more protein during waking hours (when people are more often upright) than during sleep. It has a very good prognosis and requires no special intervention.

**Consequences:** Proteinuria caused by renal disorders usually is persistent (ie, present on serial testing) and, when in the nephrotic range, can cause significant protein wasting. Presence of protein in the urine is toxic to the kidneys and causes renal damage.

**Etiology**

Causes can be categorized by mechanism. The most common causes of proteinuria are glomerular disorders, typically manifesting as nephrotic syndrome (see Table 228-9).

The most common causes in adults are

- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Diabetic nephropathy

The most common causes in children are
• Minimal change disease (in young children)
• Focal segmental glomerulosclerosis (in older children)

Evaluation

Proteinuria itself is usually recognized only on urinalysis or urine dipstick testing. History and physical examination occasionally give clues to cause.

**History and physical examination:** The review of systems seeks symptoms suggesting cause, including red or brown urine (glomerulonephritis) or bone pain (myeloma).

Patients are asked about existing conditions that can cause proteinuria, including recent serious illness (particularly with fever), intense physical activity, known renal disorders, diabetes, pregnancy, sickle cell disease, SLE, and cancer (particularly myeloma and related disorders).

**Physical examination** is of limited use, but vital signs should be reviewed for increased BP, suggesting glomerulonephritis. The examination should seek signs of peripheral edema and ascites reflective of fluid overload and possibly a glomerular disorder.

**Testing:** Urine dipstick primarily detects albumin. Precipitation techniques, such as heating and sulfosalicylic acid test strips, detect all proteins. Thus, isolated proteinuria detected incidentally is usually albuminuria. Dipstick testing is relatively insensitive for detection of microalbuminuria, so a positive urine dipstick test usually suggests overt proteinuria. Dipstick testing is also unlikely to detect excretion of smaller proteins characteristic of tubular and overflow proteinuria.

Patients with a positive dipstick test (for protein or any other component) should have routine microscopic urinalysis. Abnormalities on urinalysis (eg, casts and dysmorphic RBCs suggesting glomerulonephritis; glucose, ketones, or both suggesting diabetes) or disorders suggested by history and physical examination (eg, peripheral edema suggesting a glomerular disorder) require further work up.

If urinalysis is otherwise normal, further testing can be deferred pending repeat urine protein assessment. If proteinuria is no longer present, particularly in patients who have had recent intense exercise, fever, or heart failure exacerbation, functional proteinuria is likely. Persistent proteinuria is a sign of a glomerular disorder and requires further testing and referral to a nephrologist. Further testing includes CBC; measurement of serum electrolytes, BUN, creatinine, and glucose; determination of GFR (see p. 2312); quantification of urinary protein (by 24-h measurement or random urine protein/creatinine ratio); and evaluation of kidney size (by ultrasonography or CT). In most patients with glomerulopathy, proteinuria is in the nephrotic range (> 3.5 g/day or urine protein/creatinine ratio > 2.7).

[Table 228-9. Causes of Proteinuria]

Other testing is usually done to determine the cause of a glomerular disorder, including lipid profile, complement levels, cryoglobulins, hepatitis B and C serology, antinuclear antibody testing, and urine and serum protein electrophoresis. If these noninvasive tests are not diagnostic (as is often the case), renal biopsy is necessary. Unexplained proteinuria and renal failure, especially in older patients, could be due to myelodysplastic disorders (eg, multiple myeloma) or amyloidosis.

Among patients < 30 yr, orthostatic proteinuria should be considered. Diagnosis requires 2 urine collections, one done from 7 AM to 11 PM (day sample) and the other from 11 PM to 7 AM (night sample). The diagnosis is confirmed if the urinary protein exceeds normal values in the day sample (or if urine protein/creatinine ratio is > 0.3) and does not in the night sample.

**Treatment**

Treatment is directed at the cause.

**Painless Scrotal Mass**
A painless scrotal mass is often noticed by the patient but may be an incidental finding on routine physical examination.

Scrotal pain and painful scrotal masses or swelling (see p. 2334) can be caused by testicular torsion, appendiceal torsion, epididymitis, epididymo-orchitis, scrotal abscess, trauma, strangulated inguinal hernias, orchitis, and Fournier's gangrene.

Etiology

There are several causes (see Table 228-10) of a painless scrotal mass but the most common include the following:

- Hydrocele
- Nonincarcerated inguinal hernia
- Varicocele (present in up to 20% of adult men)

Less common causes include spermatocele, hematocele, fluid overload, and occasionally testicular cancer. Testicular cancer is the most concerning cause of a painless scrotal mass. Although it is rare compared with the other listed causes, it is the most common solid cancer in men < 40 yr; because it responds well to treatment, prompt recognition is important.

Evaluation

History: History of present illness should address duration of symptoms, the effect of upright position and increase in intra-abdominal pressure, and presence and characteristics of associated symptoms such as pain.

Review of systems should seek symptoms suggesting possible causes, including abdominal pain, anorexia, or vomiting (inguinal hernia with intermittent strangulation); dyspnea and leg swelling (right heart failure); abdominal distention (ascites); and decreased libido, feminization, and infertility (testicular atrophy with bilateral varicoceles).

Past medical history should identify existing disorders that can cause masses (eg, right heart failure, ascites causing bilateral lymphedema); known scrotal disorders (eg, testicular tumor or epididymitis causing hydrocele); and inguinal hernia.

Physical examination: Physical examination includes evaluation for systemic disorders that can cause edema (eg, heart failure, ascites) and detailed inguinal and genital examination.

Inguinal and genital examination should be done with patients standing and recumbent. The inguinal area is inspected and palpated, particularly for reducible masses. The testes, epididymides, and spermatic cords should be palpated for swelling, masses, and tenderness. Careful palpation can usually localize a discrete mass to one of these structures. Nonreducible masses should be transilluminated to help determine whether they are cystic or solid.

Red flags: The following findings are of particular concern:

- Nonreducible mass that obscures normal spermatic cord structures
- Mass that is part of or attached to the testis and does not transilluminate

Interpretation of findings: A nonreducible mass that obscures normal spermatic cord structures suggests an incarcerated inguinal hernia. If a mass is part of or attached to the testis and does not transilluminate, testicular cancer is possible.
Other clinical characteristics can provide important clues (see Table 228-10). For example, a mass that transilluminates is probably cystic (eg, hydrocele, spermatocele). A mass that disappears or becomes smaller when recumbent suggests varicocele, inguinal hernia, or communicating hydrocele. The presence of a hydrocele makes assessment for other scrotal masses by examination difficult. Rarely, a varicocele persists when the patient is recumbent or is present on the right side; either finding suggests inferior vena cava obstruction.

**Testing:** Clinical evaluation may be diagnostic (eg, in varicocele, lymphedema, inguinal hernia); otherwise, testing is typically done. Ultrasonography is done when

- The diagnosis is uncertain
- Usually when hydrocele is present (to diagnose causative scrotal lesions)
- The mass does not transilluminate

If ultrasonography confirms a solid testicular mass, further testing is done for testicular cancer (see p. 2476), including the following:

- β-Human chorionic gonadotropin level (hCG)
- α-Fetoprotein level
- LDH level
- CT of the abdomen

**Treatment**

Treatment is directed at the cause. No treatment is indicated for all masses. If inguinal hernia is suspected, reduction can be attempted (see p. 114).

**Table 228-10. Some Causes of a Painless Scrotal Mass**

**Key Points**

- A nonreducible mass that obscures normal spermatic cord structures suggests an incarcerated inguinal hernia.
- A solid mass, one that does not transilluminate, or both mandates evaluation for testicular cancer.
- The cause of a hydrocele must be determined.

**Scrotal Pain**

Scrotal pain can occur in males of any age, from neonates to the elderly.

**Etiology**

The most common causes of scrotal pain include

- Testicular torsion
- Torsion of the testicular appendage
- Epididymitis

There are a number of less common causes (see
Evaluation

Expeditious evaluation, diagnosis, and treatment are required because untreated testicular torsion may cause loss of a testis.

History: History of present illness should determine location (unilateral or bilateral), onset (acute or subacute), and duration of pain. Important associated symptoms include fever, dysuria, penile discharge, and presence of scrotal mass. Patients should be asked about preceding events, including injury, straining or lifting, and sexual contact.

Review of systems should seek symptoms of causative disorders, including purpuric rash, abdominal pain, and arthralgias (Henoch-Schönlein purpura); intermittent scrotal masses, groin swelling, or both (inguinal hernia); fever and parotid gland swelling (mumps orchitis); and flank pain or hematuria (renal calculus).

Past medical history should identify known disorders that may cause referred pain, including hemias, abdominal aortic aneurysm, renal calculi, and risk factors for serious disorders, including diabetes and peripheral vascular disease (Fournier's gangrene).

Physical examination: Physical examination begins with a review of vital signs and assessment of the severity of pain. Examination focuses on the abdomen, inguinal region, and genitals.

The abdomen is examined for tenderness and masses (including bladder distention). Flanks are percussed for costovertebral angle tenderness.

Inguinal and genital examination should be done with the patient standing. Inguinal area is inspected and palpated for adenopathy, swelling, or erythema. Examination of the penis should note ulcerations, urethral discharge, and piercings and tattoos (sources of bacterial infections). Scrotal examination should note asymmetry, swelling, erythema or discoloration, and positioning of the testes (horizontal vs vertical, high vs low). Cremasteric reflex should be tested bilaterally. The testes, epididymides, and spermatic cords should be palpated for swelling and tenderness. If swelling is present, the area should be transilluminated to help determine whether the swelling is cystic or solid.

Red flags: The following findings are of particular concern:

- Sudden onset of pain; exquisite tenderness; and a high-riding, horizontally displaced testis (testicular torsion)
- Inguinal or scrotal nonreducible mass with severe pain, vomiting, and constipation (incarcerated hernia)
- Scrotal or perineal erythema, necrotic or blistered skin lesions, and toxic appearance (Fournier's gangrene)
- Sudden onset of pain, hypotension, weak pulse, pallor, dizziness, and confusion (ruptured abdominal aortic aneurysm)

Interpretation of findings: The focus is to distinguish causes that require immediate treatment from others. Clinical findings provide important clues (see Table 228-11).

Aortic catastrophes and Fournier's gangrene occur primarily in patients > 50 yr; the other conditions that require immediate treatment can occur at any age. However, testicular torsion is most common in neonates and postpubertal boys, torsion of the testicular appendage occurs most commonly in prepubertal boys (7 to 14 yr), and epididymitis is most common in adolescents and adults.

Severe, sudden onset of pain suggests testicular torsion or renal calculus. Pain from epididymitis, incarcerated hernia, or appendicitis is of more gradual onset. Patients with torsion of the testicular
appendage present with moderate pain that develops over a few days; pain is localized to the upper pole. Bilateral pain suggests infection (eg, orchitis, particularly if accompanied by fever and viral symptoms) or a referred cause. Flank pain that radiates to the scrotum suggests renal calculus or, in men > 55 yr, abdominal aortic aneurysm.

Normal findings on scrotal and perineal examination suggest referred pain. Attention must then be directed to extrascrotal disorders, particularly appendicitis, renal calculi, and, in men > 55, abdominal aortic aneurysm.

Abnormal scrotal and perineal examination findings often suggest a cause. Sometimes, early in epididymitis, tenderness and induration may be localized to the epididymis; early in torsion, the testis may be clearly high-riding, with a horizontal lie and the epididymis not particularly tender. However, frequently the testis and epididymis are both swollen and tender, there is scrotal edema, and it is not possible to differentiate epididymitis from torsion by palpation. However, the cremasteric reflex is absent in torsion, as are findings of a sexually transmitted disease (STD—eg, purulent urethral discharge); the presence of both of these findings makes epididymitis quite likely.

Sometimes, a scrotal mass caused by a hernia may be palpable in the inguinal canal; in other cases, hernia can be difficult to distinguish from testicular swelling.

Painful erythema of the scrotum with no tenderness of the testes or epididymides should raise suspicion of infection, either cellulitis or early Fournier's gangrene.

A vasculitic rash, abdominal pain, and arthralgias are consistent with a systemic vasculitis syndrome such as Henoch-Schonlein purpura or polyarteritis nodosa.

Testing: Testing is typically done.

• Urinalysis and culture (all patients)

• STD testing (all patients with positive urinalysis, discharge, or dysuria)

• Color Doppler ultrasonography to rule out torsion (no clear-cut alternate cause)

• Other testing as suggested by findings (see Table 228-11)

Urinalysis and culture are always required. Findings of UTI (eg, pyuria, bacteriuria) suggest epididymitis. Patients with findings that suggest UTI and patients with urethral discharge or dysuria should be tested for STDs as well as other bacterial causes of UTI.

Timely diagnosis of testicular torsion is critical. If findings are highly suggestive of torsion, immediate surgical exploration is done in preference to testing. If findings are equivocal and there is no clear alternate cause of acute scrotal pain, color Doppler ultrasonography is done. If Doppler ultrasonography is not available, radionuclide scanning may be used but is less sensitive and specific.

Treatment

Treatment is directed at the cause and can range from emergency surgery (testicular torsion) to bedrest (torsion of the testicular appendage). If testicular torsion is present, prompt surgery (< 12 h after presentation) is generally required. Delayed surgery may lead to testicular infarction, long-term testicular damage, or the loss of a testis. Surgical detorsion of the testis relieves the pain immediately, and simultaneous bilateral orchiopexy prevents recurrence of torsion.

Analgesics, such as morphine or other opioids, are indicated for the relief of acute pain. Antibiotics are indicated for cases of bacterial epididymitis or orchitis.
Geriatrics Essentials

Testicular torsion is uncommon in elderly men, and when present, the manifestations are usually atypical and therefore diagnosis is delayed. Epididymitis, orchitis, and trauma are more common in elderly men. Occasionally, inguinal hernia, colon perforation, or renal colic may cause scrotal pain in elderly men.

Key Points

• Always consider testicular torsion in patients with acute scrotal pain, particularly in children and adolescents; quick, accurate diagnosis is essential.

• Other common causes of scrotal pain are torsion of the testicular appendage and epididymitis.

• Color Doppler ultrasonography is usually done when the diagnosis is unclear.

• Normal findings on scrotal and perineal examination suggest referred pain.

Urinary Frequency

Urinary frequency is the need to urinate many times during the day, at night (nocturia), or both but in normal or less-than-normal volumes. Frequency may be accompanied by a sensation of an urgent need to void (urinary urgency). Urinary frequency is distinguished from polyuria, which is urine output of > 3 L/day.

Pathophysiology

Urinary frequency usually results from disorders of the lower GU tract. Inflammation of the bladder, urethra, or both causes a sensation of the need to urinate. However, this sensation is not relieved by emptying the bladder, so once the bladder is emptied, patients continue trying to void but pass only small volumes of urine.

Etiology

There are many causes of urinary frequency (see Table 228-12), but the most common include

• UTIs

• Urinary incontinence

• Benign prostatic hyperplasia (BPH)

• Urinary tract calculi

Evaluation

History: History of present illness should first ask about the amounts of fluid consumed and voided to distinguish between urinary frequency and polyuria. If urinary frequency is present, patients are asked about acuity of onset, presence or absence of irritative symptoms (eg, irritation, urgency, dysuria), obstructive symptoms (eg, hesitancy, poor flow, sensation of incomplete voiding, nocturia), and recent sexual contacts.

Review of systems should cover symptoms suggestive of a cause, including fever, flank or groin pain, and hematuria (infection); missed menses, breast swelling, and morning sickness (pregnancy); and arthritis and conjunctivitis (reactive arthritis).

Past medical history should ask about known causes, including prostate disease and previous pelvic
radiation or surgeries. Drugs and diet are reviewed for the use of agents that increase urine output (eg, diuretics, alcohol, caffeinated beverages).

**Physical examination:** Examination focuses on the GU system.

Any urethral discharge or any lesions consistent with sexually transmitted diseases are noted. Rectal examination in men should note the size and consistency of the prostate; pelvic examination in women should note the presence of any cystocele. Patients should be instructed to cough while the urethra is observed for signs of urinary leakage.

The costovertebral angle should be palpated for tenderness, and the abdominal examination should note the presence of any masses or suprapubic tenderness.

Neurologic examination should test for lower-extremity weakness.

**Red flags:** The following findings are of particular concern:

- Lower-extremity weakness
- Fever and back pain

**Interpretation of findings:** Dysuria suggests frequency is due to UTI or calculi. Prior pelvic surgery suggests incontinence. Weak urine stream, nocturia, or both suggests BPH. Urinary frequency in an otherwise healthy young patient may be due to excessive intake of alcohol or caffeinated beverages. Gross hematuria suggests UTI and calculi in younger patients and cancer in older patients.

**Testing:** All patients require urinalysis and culture, which are easily done and can detect infection and hematuria.

[Table 228-12. Some Causes of Urinary Frequency]

Cytoscopy, cystometry, and urethrography can be done to diagnose cystitis, bladder outlet obstruction, and cystocele. Prostate-specific antigen level determination, ultrasonography, and prostate biopsy may be required, especially in older men, to differentiate BPH from prostate cancer.

**Treatment**

Treatment varies by cause.

**Geriatrics Essentials**

Urinary frequency in elderly men is often caused by bladder neck obstruction secondary to prostate enlargement or cancer. These patients usually require postvoid residual urine volume determination. UTI or use of diuretics may be a cause in both sexes.

**Key Points**

- UTI is the most common cause in children and women.
- Prostate disease is a common cause in men > 50 yr.
- Excessive intake of caffeine can cause urinary frequency in healthy people.
Chapter 229. Male Reproductive Endocrinology

Introduction
Male sexual development and function depend on a complex feedback circuit involving the hypothalamus, pituitary, and testes. Male sexual dysfunction can be secondary to hypogonadism or numerous other disorders.

Physiology
The hypothalamus produces gonadotropin-releasing hormone (GnRH), which is released in a pulsatile fashion every 60 to 120 min. The anterior pituitary responds to each pulse of GnRH by producing a corresponding pulse of luteinizing hormone (LH) and, to a lesser degree, follicle-stimulating hormone (FSH). Continuous stimulation by GnRH (as might occur therapeutically) suppresses pituitary release of LH and FSH.

The Leydig cells of the testes respond to LH by producing between 5 and 10 mg of testosterone daily. Testosterone levels are highest in early morning, except in older men, who may lose circadian variation.

Testosterone is synthesized from cholesterol through several intermediate compounds, including dehydroepiandrosterone (DHEA) and androstenedione. Circulating testosterone is mostly protein-bound, about 40% to sex hormone-binding globulin (SHBG) and 58% to albumin. Because testosterone is avidly bound to SHBG, only albumin-bound testosterone (which is less avidly bound) and the 1 to 2% that constitute free testosterone are bioavailable.

In target tissues, about 4 to 8% of testosterone is converted to a more potent metabolite, dihydrotestosterone (DHT), by the enzyme 5α-reductase. DHT has important trophic effects in the prostate and mediates androgenic alopecia. In adults, spermatogenesis requires adequate intratesticular testosterone, but the role of DHT in spermatogenesis is unclear.

Testosterone and DHT have metabolic effects, including increasing protein anabolism and nitrogen retention, increasing bone density and muscle mass, and modulating the immune system. Testosterone undergoes conversion to estradiol; estrogen mediates much of the effect of testosterone on organs such as bones and the brain.

Testosterone, DHT, and estradiol provide negative feedback on the hypothalamic-pituitary axis. In males, estradiol is the main inhibitor of LH production, whereas both estradiol and inhibin B, a peptide produced by Sertoli cells of the testes, inhibit production of FSH. In the presence of testosterone, FSH stimulates the Sertoli cells and induces spermatogenesis. In spermatogenesis, each germinal cell (spermatogonium), located adjacent to the Sertoli cells, undergoes differentiation into 16 primary spermatocytes, each of which generates 4 spermatids. Each spermatid matures into a spermatozoon. Spermatogenesis takes 72 to 74 days and yields about 100 million new spermatozoa each day. Upon maturation, spermatozoa are released into the rete testis, where they migrate to the epididymis and eventually to the vas deferens. Migration requires an additional 14 days. Before ejaculation, spermatozoa are mixed with secretions from the seminal vesicles, prostate, and bulbourethral glands.

Sexual Differentiation, Adrenarche, and Puberty
In the embryo, the presence of a Y chromosome triggers development and growth of the testes, which begin secreting testosterone and a Mullerian duct inhibitor by about 7 wk of gestation. Testosterone virilizes the wolffian duct (which develops into the epididymis, vas deferens, and seminal vesicles). DHT promotes development of the remainder of the male genitals. Testosterone levels peak in the 2nd trimester and fall to almost zero by birth. Testosterone production rises briefly during the first 6 mo of life, the function of
which is unclear. Thereafter, testosterone levels remain low until puberty.

LH and FSH are elevated at birth but fall to low levels within a few months, remaining low or undetectable throughout the prepubertal years. Through an unknown mechanism, blood levels of the adrenal androgens DHEA and DHEA sulfate begin to increase several years before puberty. Their conversion to testosterone in small amounts initiates pubic and axillary hair growth (adrenarche).

The mechanisms that initiate puberty are unclear, although early in puberty the hypothalamus becomes less sensitive to the inhibitory effects of sex hormones. This desensitization increases secretion of LH and FSH, stimulating testosterone production. Secretion of LH and FSH increases initially only during sleep; later, secretion increases throughout the 24-h period. The increased testosterone levels in boys cause pubertal changes, the first of which are growth of the testes (> 2.5 cm on the long axis, > 3 to 4 mL in volume) and thinning of scrotal skin. Later, penile length, muscle mass, and bone density increase; the voice deepens; and pubic and axillary hair becomes denser and thicker (see Fig. 229-1).

Effects of Aging

Both hypothalamic secretion of GnRH and the response of Leydig cells to FSH and LH diminish with aging. Beginning at about age 30, a man's serum total testosterone level declines by 1%/yr. Men aged 70 to 80 tend to have serum testosterone levels that are about one half to two thirds of those of men in their 20s. In addition, SHBG levels increase with aging, causing an even greater decline in serum free and bioavailable testosterone. FSH and LH levels tend to be normal or high-normal. These age-related changes are sometimes referred to as the andropause, although there are no abrupt changes in hormone levels as occur in the menopause. The decline in testosterone may contribute to age-related muscle loss, osteopenia, loss of libido, and cognitive decline. Testosterone supplementation for men with low-normal levels of testosterone is controversial. Some experts recommend a trial of testosterone supplementation in older men with symptoms or signs of hypogonadism and whose serum testosterone levels are below the lower limit of normal for men aged 20 to 40 yr. No data favor any of the testosterone preparations specifically for use in older men.

Male Hypogonadism

(See also p. 2891.)

Hypogonadism is defined as testosterone deficiency with associated symptoms or signs, deficiency of spermatozoa production, or both. It may result from a disorder of the testes (primary hypogonadism) or of the hypothalamic-pituitary axis (secondary hypogonadism). Both may be congenital or acquired as the result of aging, disease, drugs, or other factors. Additionally, a number of congenital enzyme deficiencies cause varying degrees of target organ androgen resistance. Diagnosis is confirmed by hormone levels. Treatment varies with etiology but typically includes testosterone replacement.

Etiology

Primary hypogonadism involves failure of the testes to respond to follicle-stimulating hormone (FSH) and luteinizing hormone (LH). When primary hypogonadism affects testosterone production, testosterone is insufficient to inhibit production of FSH and LH; hence, FSH and LH levels are elevated. The most common cause of primary hypogonadism is Klinefelter's syndrome. It involves seminiferous tubule dysgenesis and a 47,XXY karyotype (see p. 3005).

Secondary hypogonadism is failure of the hypothalamus (or pituitary) to produce enough FSH and LH. With secondary hypogonadism, testosterone levels are low, but levels of FSH and LH are low or inappropriately normal. Any acute systemic illness can cause temporary secondary hypogonadism. Some syndromes of hypogonadism have both primary and secondary causes (mixed hypogonadism). Table 229-1 lists some common causes of hypogonadism by category.

Some syndromes of hypogonadism (eg, cryptorchidism, some systemic disorders) affect spermatozoon production more than testosterone levels.
Symptoms and Signs

Age at onset of testosterone deficiency dictates the clinical presentation: congenital, childhood-onset, or adult-onset hypogonadism. Congenital hypogonadism may be of 1st-, 2nd-, or 3rd-trimester onset. First-trimester onset results in inadequate male sexual differentiation. Complete absence of testosterone's effects results in normal-appearing female external genitals. Partial testosterone deficiency results in abnormalities ranging from ambiguous external genitals to hypospadias. Second- or 3rd-trimester onset of testosterone deficiency results in microphallus and undescended testes.

Childhood-onset testosterone deficiency (see p. 2891) has few consequences and usually is unrecognized until puberty is delayed. Untreated hypogonadism impairs development of secondary sexual characteristics. As adults, affected patients have poor muscle development, a high-pitched voice, a small scrotum, decreased phallic and testicular growth, sparse pubic and axillary hair, and an absence of body hair. They may develop gynecomastia and eunuchoidal body proportions (span > height by 5 cm and pubic to floor

Table 229-1. Causes of Hypogonadism*

length > crown to pubic length by > 5 cm) because of delayed fusion of the epiphyses and continued long bone growth.

Adult-onset testosterone deficiency has varied manifestations depending on the degree and duration of the deficiency. Decreased libido; erectile dysfunction; decline in cognitive skills, such as visual-spatial interpretation; sleep disturbances; vasomotor instability (in acute, severe male hypogonadism); and mood changes, such as depression and anger, are common. Decreased lean body mass, increased visceral fat, testicular atrophy, osteopenia, gynecomastia, and sparse body hair typically take months to years to develop. Testosterone deficiency may increase the risk of coronary artery disease.

Diagnosis

• Testing, beginning with FSH, LH, and testosterone levels

Congenital and childhood-onset hypogonadism are often suspected because of developmental abnormalities or delayed puberty. Adult-onset hypogonadism should be suspected on the basis of symptoms or signs but is easily missed because these markers are insensitive and nonspecific. Klinefelter's syndrome should be considered in adolescent males in whom puberty is delayed, young men with hypogonadism, and all adult men with very small testes. Hypogonadism requires confirmatory testing (see Fig. 229-2).

Diagnosis of primary and secondary hypogonadism: Increases in FSH and LH are more sensitive for primary hypogonadism than are decreases in testosterone levels. Levels of FSH and LH also help determine whether hypogonadism is primary or secondary; high gonadotropin levels, even with low-normal testosterone levels, indicate primary hypogonadism, whereas gonadotropin levels that are low or lower than expected for the level of testosterone indicate secondary hypogonadism. Alternatively, in boys of short stature with delayed puberty, low testosterone plus low gonadotropin levels might result from constitutional delay of puberty. Elevation of serum FSH with normal levels of serum testosterone and LH often occurs when spermatogenesis is impaired but testosterone production is normal. The cause of hypogonadism is often evident clinically. Primary hypogonadism requires no further testing, although some clinicians do a karyotype to definitively diagnose Klinefelter's syndrome.

Total (or calculated free and weakly bound) serum testosterone, serum FSH, and serum LH levels are measured simultaneously. The normal range for total testosterone is 300 to 1000 ng/dL (10.5 to 35 nmol/L). The initial screening testosterone level may be done at any time of day, but a second testosterone level should be drawn in the morning to confirm hypogonadism. Because of the increase in sex hormone-binding globulin (SHBG) with aging, total testosterone level is less sensitive for
hypogonadism after age 50. Although serum free testosterone more accurately reflects functional
testosterone levels, its measurement requires equilibrium dialysis, which is technically difficult and not
widely available. Some commercially available kits, including the analog free testosterone assay, attempt
to measure serum free testosterone levels, but the results are often inaccurate, particularly in conditions
such as type 2 diabetes, obesity, and hypothyroidism that alter SHBG levels. Free testosterone levels can
be calculated based on SHBG, albumin, and testosterone values: there are calculators available online.
Because of the pulsatile secretion of FSH and LH, they are sometimes measured as a pooled sample of
3 venipunctures taken at 20-min intervals, but these pooled samples seldom add clinically important
information compared with a single blood sample. Serum FSH and LH levels are usually ≤ 5 mIU/mL
before puberty and between 5 and 15 mIU/mL in adulthood.

Sperm count can be useful and should be assessed in men who are seeking fertility treatment. In
adolescents or adults, a semen sample collected by masturbation after 2 days of abstinence from
ejaculation provides an excellent index of seminiferous tubular function. A normal semen sample has a
volume of > 2.5 mL with > 20 million sperm/mL, of which 60% are of normal morphology and are motile
(see also p. 2592).

**Evaluation of secondary hypogonadism:** Because any systemic illness can temporarily decrease
levels of testosterone, FSH, and LH, secondary hypogonadism should be confirmed by measuring these
levels again after at least a 4-wk interval after resolution of the systemic illness. To confirm secondary
hypogonadism in adolescents, the gonadotropin-releasing hormone (GnRH) test is sometimes done. If, in
response to IV GnRH, levels of FSH and LH increase, puberty is simply delayed. If levels do not increase,
true hypogonadism is likely.

To help determine the cause of confirmed secondary hypogonadism, testing should

[Fig. 229-2. Laboratory evaluation of male hypogonadism.]

include serum prolactin level and transferrin saturation (to screen for hemochromatosis—see p. 1032).
Sella imaging with MRI or CT is done to exclude a pituitary macroadenoma or other mass in men < 60 yr
with no other identified cause for hypogonadism and in all men with very low total testosterone levels (<
200 ng/dL), elevated prolactin levels, or symptoms consistent with a pituitary tumor (eg, headache, visual
symptoms). Also, if there are symptoms or signs of Cushing's syndrome, 24-h urine collection for free
cortisol or a dexamethasone suppression test is done (see p. 797). If no abnormalities are identified, the
diagnosis is acquired idiopathic secondary hypogonadism.

**Treatment**

- Testosterone therapy
- Gonadotropin replacement therapy for restoration of fertility due to secondary hypogonadism

Treatment is directed toward providing adequate androgen replacement conveniently and safely. Although
patients with primary hypogonadism will not become fertile with any endocrine therapy, patients with
secondary hypogonadism often become fertile with gonadotropin therapy. Testosterone formulations
discussed here are those available in the US. Other formulations may be available in other countries.

**Testosterone therapy:** Males who have no signs of puberty and are near age 15 may be given long-
acting testosterone enanthate 50 mg IM once/mo for 4 to 8 mo. These low doses cause some virilization
without restricting adult height. Older adolescents with testosterone deficiency receive long-acting
testosterone enanthate or cypionate at a dose that is increased gradually over 18 to 24 mo from 50 to 100
to 200 mg IM q 1 to 2 wk. Transcutaneous gel may also be used, although it is more expensive, could
possibly be transferred to others during intimate contact, and is more difficult to accurately dose. It is
reasonable to convert older adolescents to testosterone gel 1% at adult dosages when their IM dosage
has reached the equivalent of 100 to 200 mg q 2 wk.

Adults with established testosterone deficiency may benefit from replacement therapy. Treatment prevents
or attenuates osteopenia, muscle loss, vasomotor instability, loss of libido, and occasionally erectile
dysfunction. Although the effects of testosterone on coronary artery disease are not completely understood, testosterone replacement therapy may improve coronary artery blood flow and may decrease the risk of coronary artery disease. Options for replacement therapy include testosterone gel 1% (5 to 10 g daily to deliver 5 to 10 mg daily), IM testosterone enanthate or cypionate (100 mg q 7 days or 200 mg q 10 to 14 days), a buccal mucosal patch (30 mg bid), or a transdermal testosterone patch (5 to 10 mg daily). Testosterone gel maintains physiologic blood levels more consistently than other treatments, but IM or patch systems are sometimes used because of their lower cost.

Potential adverse effects of testosterone and its analogs include erythrocytosis (particularly in men > 50 yr receiving IM testosterone), acne, gynecomastia, and very rarely prostatic enlargement or edema; prostatic obstructive symptoms are rare. Treatment may enhance growth of an existing prostate carcinoma and theoretically may awaken a dormant prostate cancer. Injectable or transdermal forms of testosterone are preferable to most oral formulations, which, except for testosterone undecanoate, carry a significant risk of hepatocellular dysfunction and hepatic adenoma.

Hct should be checked every 6 to 12 mo. Digital rectal examination and serum prostate-specific antigen (PSA) testing should be offered every 6 mo. If Hct is ≥ 54%, the testosterone dose should be reduced by one fourth or one third. Because the effect of testosterone replacement on PSA levels is not clear, significant increases in PSA level should prompt consideration of prostate biopsy in men who would otherwise be candidates for prostate cancer diagnosis and treatment.

Treatment of infertility due to hypogonadism: Infertility, which has many possible causes other than hypogonadism, is discussed in full elsewhere (see p. 2592). Infertility due to primary hypogonadism does not respond to hormonal therapy. Men with primary hypogonadism occasionally have a few intratesticular sperm that can be harvested with various microsurgical techniques and used to fertilize an egg by an assisted reproductive technique (eg, intracytoplasmic injection).

Infertility due to secondary hypogonadism usually responds to gonadotropin replacement therapy. Other symptoms of secondary hypogonadism respond well to testosterone replacement therapy alone. If secondary hypogonadism results from pituitary disease, gonadotropin replacement therapy usually is successful. Therapy begins with LH replacement. After all exogenous androgens are stopped, LH replacement is generally initiated using human chorionic gonadotropin (hCG). Doses begin at 375 to 750 IU sc 2 to 3 times/wk and are increased if necessary to 1000 to 2000 IU sc 2 to 3 times/wk. The dose is adjusted after 3 mo to achieve normal serum testosterone levels. Sperm counts are done monthly, but counts are not expected to increase for at least 4 mo. FSH replacement, which is expensive, begins if 6 to 12 mo of LH replacement does not stimulate spermatogenesis. FSH replacement uses human menotropic gonadotropin or human recombinant FSH, beginning with 75 to 150 IU 3 times/wk. The dose may be doubled if conception has not occurred within 6 mo of combination therapy with hCG. Many men become fertile with treatment despite sperm counts that do not usually result in fertility (eg, < 5 million/mL).

Secondary hypogonadism due to a hypothalamic defect (eg, Kallmann syndrome) is treated initially with LH and FSH because of their ready availability; if these treatments are ineffective, GnRH replacement therapy (q 2 h sc by a programmable minipump) might be more effective. Most (80 to 90%) of men respond successfully to these regimens.

Male Sexual Dysfunction

Male sexual dysfunction is a problem with 1 of the 4 main components of male sexual function (libido, erection, ejaculation, orgasm) that interferes with interest in or ability to engage in sexual intercourse. Many drugs and numerous physical and psychologic disorders affect sexual function.

Libido: Libido is the conscious component of sexual function. Decreased libido manifests as a lack of sexual interest or a decrease in the frequency and intensity of sexual thoughts, either spontaneous or in response to erotic stimuli. Libido is sensitive to testosterone levels as well as to general nutrition, health, and drugs. Conditions particularly likely to decrease libido include hypogonadism (see p. 2340), uremia, and depression. Drugs that sometimes decrease libido include weak androgen receptor antagonists, such as spironolactone or cimetidine, and virtually all drugs that are active in the CNS, such as SSRIs, tricyclic antidepressants, and antipsychotics. Loss of libido due to SSRIs or tricyclic anti-depressants sometimes
is reversible with the addition of bupropion or trazodone.

**Erection:** Erection occurs as the result of a complex neuropsychologic process. Higher cortical input and a sacral mediated parasympathetic reflex arc combine to stimulate erection. Nerve output travels through the pudendal nerves, which traverse the posterolateral aspect of the prostate. Terminating in the penis, these nonadrenergic, noncholinergic nerves activate nitric oxide synthase, producing nitric oxide, which relaxes smooth muscle lining the sinusoidal spaces that connect the arterioles and venules within the corpus cavernosa. The blood flow within the sinusoids increases markedly, distending them and compressing the venules, causing veno-occlusion. The increased inflow and veno-occlusion together produce penile rigidity. Many factors affect the ability to have an erection (see below).

**Ejaculation and orgasm:** Ejaculation is controlled by the sympathetic nervous system. α-Adrenergic stimulation causes contractions of the epididymis, vas deferens, prostate, and muscles of the pelvic floor. In addition, the neck of the bladder closes, preventing retrograde ejaculation of semen into the bladder. SSRIs may delay or inhibit ejaculation.

Orgasm is the highly pleasurable sensation that occurs in the brain generally simultaneously with ejaculation. Anorgasmia may be a physical phenomenon due to decreased penile sensation (eg, from neuropathy) or a neuropsychologic phenomenon due to psychiatric disorders or psychoactive drugs.

Ejaculatory insufficiency is reduced or absent semen volume that may result from retrograde ejaculation or interruption of sympathetic stimulation. Retrograde ejaculation is common in men with diabetes and can also be caused by surgery on the neck of the bladder or transurethral resection of the prostate. Sympathetic interruption, either from surgery or with drugs (eg, guanethidine, phentolamine, phenoxybenzamine, thioridazine), diminishes ejaculatory volume.

Premature ejaculation is ejaculation occurring sooner than desired by the man or his partner. It is usually caused by sexual inexperience, anxiety, and other psychologic factors instead of disease. It can be treated successfully with sex therapy and SSRIs.

**Erectile Dysfunction**

(Impotence)

**Erectile dysfunction (ED)** is the inability to attain or sustain an erection satisfactory for sexual intercourse. Most erectile dysfunction is related to vascular, neurologic, psychologic, and hormonal disorders; drug use can also be a cause. Evaluation typically includes screening for underlying disorders and measuring testosterone levels. Treatment options include oral phosphodiesterase inhibitors or apomorphine, intraurethral or intracavernosal prostaglandins, mechanical pump devices, and surgical implants.

The term impotence has been replaced by the term erectile dysfunction. In the US, at least 10 to 20 million men > 18 are affected. The prevalence of partial or complete ED is about 50% in men 40 to 70 and increases with aging. However, many men can be successfully treated.

**Etiology**

Primary ED (ie, the man has never been able to attain or sustain erections) is rare and is almost always due to psychologic factors (guilt, fear of intimacy, depression, severe anxiety) or clinically obvious anatomic abnormalities. Most often, ED is secondary (ie, a man who previously could attain and sustain erections no longer can). Over 80% of secondary ED cases have an organic etiology. However, in many men with organic disease, ED leads to secondary psychologic difficulties that compound the problem. Psychologic factors must be considered in every case.

Psychologic causes may relate to performance anxiety, stress, or a mood disorder (particularly depression). ED may be situational, involving a particular place, time, or partner.

The major organic causes of ED are vascular and neurologic disorders, often stemming from
atherosclerosis and diabetes. Complications of surgery, usually prostate surgery, are another common cause. Other causes include hormonal disorders, drugs, and structural disorders of the penis (eg, Peyronie's disease).

The most common vascular cause is atherosclerosis of penile arteries, often secondary to diabetes. Atherosclerosis and aging decrease the capacity for dilation of arterial blood vessels and smooth muscle relaxation, limiting the amount of blood that can enter the penis. Inadequate impedance of venous outflow (venous leaks) may cause ED or, more commonly, failure to maintain tumescence as long as desired. Venous leaks make it difficult for blood to remain in the penis during erection, so erections occur but cannot be sustained. Priapism, particularly as in sickle cell disease, may damage penile vasculature and lead to ED.

Stroke, partial complex seizures, multiple sclerosis, peripheral and autonomic neuropathies, and spinal cord injuries are among the neurologic causes. Diabetic neuropathy and surgical injury are particularly common causes.

Any endocrinopathy associated with testosterone deficiency (hypogonadism) may decrease libido and cause ED. However, erectile function only rarely improves with normalization of serum testosterone levels.

Numerous drug causes are possible (see Table 229-2). Alcohol can cause temporary ED.

Of men who have undergone transurethral resection of the prostate, up to 40% can experience problems with erections for reasons that are not clear. ED is more common after more extensive prostatic resection (eg, radical prostatectomy). Prolonged perineal pressure (as occurs during bicycle riding) can cause temporary ED.

**Diagnosis**

- Clinical evaluation
- Screening for depression
- Testosterone level

Evaluation should include history of drug and alcohol use, smoking, diabetes, hypertension, and atherosclerosis and symptoms of vascular, hormonal, neurologic, and psychologic disorders. It is vital to screen for depression, which may not always be apparent. The Beck Depression Scale or, in older men, the Yesavage Geriatric Depression Scale (see Table 307-7 on p. 3089) is easy to administer and may be useful. Satisfaction with sexual relationships should also be explored. Partner sexual dysfunction (eg, atrophic vaginitis, depression) must be considered and evaluated.

Examination is focused on the genitals and extragenital signs of hormonal, neurologic, and vascular disorders. Genitals are examined for anomalies, signs of hypogonadism, and fibrous bands or plaques (Peyronie's disease). Poor rectal tone, perineal sensation, or abnormal anal wink or bulbocavernosus reflexes may indicate neurologic dysfunction. Diminished peripheral pulses suggest vascular dysfunction.

A psychologic cause should be suspected in young healthy men with abrupt onset of ED, particularly if onset is associated with a specific emotional event or if the dysfunction occurs only in certain settings. A history of ED with spontaneous improvement also suggests psychologic origin (psychogenic ED). Men with psychogenic ED usually have normal nocturnal erections and erections upon awakening, whereas men with organic ED often do not.

Laboratory assessment should include measurement of testosterone level; if the level is low or low-normal, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) should be measured (see p. 2342). Evaluation for occult diabetes, dyslipidemias, hyperprolactinemia, thyroid disease, and Cushing's
syndrome should be done based on clinical suspicion.

[Table 229-2: Commonly Used Drugs that Can Cause Erectile Dysfunction]

A penile pressure-brachial pressure index (systolic BP in the penis divided by systolic BP in the arm) < 0.6 indicates impaired blood flow to the penis, but this test is seldom done in general clinical practice. Additional invasive or provocative penile tests include duplex ultrasonography before and after injection of a vasoactive drug and cavernosography or cavernosometry; these tests can be considered in some patients, such as those with posttraumatic erectile dysfunction or before penile reconstructive surgery (eg, for Peyronie's disease).

**Treatment**

• Treatment of cause

• Usually an oral phosphodiesterase inhibitor

• Sometimes a mechanical device or an intracavernosal or intraurethral prostaglandin

Underlying organic disorders require appropriate treatment. Drugs that are temporally related to onset of ED should be stopped or switched. Depression may require treatment. For all patients, reassurance and education (including of the patient's partner whenever possible) are important.

For further therapy, noninvasive methods (mechanical devices and drugs) are tried first. All drugs and devices should be tried ≥ 5 times before being considered ineffective.

**Mechanical devices:** Men who can develop but not sustain an erection may use a constriction ring. As soon as erection occurs, a metal or elastic ring or a leather band with snaps (sold by prescription in pharmacies or OTC in sex paraphernalia stores as a "cock ring") is placed around the base of the penis, preventing venous outflow. If the man cannot develop an erection, a vacuum device can draw blood into the penis, after which the band or ring is placed at the base of the penis to retain the erection. Bruising of the penis, coldness of the tip of the penis, and lack of spontaneity are some drawbacks to this modality. A constriction ring and vacuum devices might also be useful adjuncts for patients who do not respond satisfactorily to drug therapy.

**Drugs:** The primary drugs for ED are oral phosphodiesterase inhibitors, oral apomorphine (not available in the US), and intracavernosal or intraurethral prostaglandins. Almost all patients prefer oral drug therapy to other methods for treating ED.

**Oral phosphodiesterase inhibitors** selectively inhibit cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), the predominant phosphodiesterase isoform in the penis. These drugs include sildenafil, vardenafil, and tadalafil. By increasing cGMP, these drugs enhance the nitric oxide release essential for normal erection. Although vardenafil and tadalafil are more selective for the penile vasculature than sildenafil, adverse effects of these drugs are similar. Although no clinical trials directly compare the drugs, all 3 appear to be equally effective (60 to 75%). Sildenafil dose is 50 mg, although most men respond best to 100 mg. Tadalafil has a significantly longer half-life (24 to 48 h) than sildenafil and vardenafil (about 4 to 6 h), which might lead to more convenient dosing. The usual dosage for tadalafil and vardenafil is 5 to 20 mg. All PDE5 inhibitors are generally taken at least 1 h before sexual intercourse. Dosing frequency should not be ≤ 24 h for sildenafil and vardenafil and not ≤ 48 h for tadalafil. All PDE5 inhibitors cause direct coronary vasodilation and potentiate the hypotensive effects of other nitrates, including those used to treat cardiovascular disease as well as recreational amyl nitrate ("poppers"). Thus, all nitrates are contraindicated for 24 h after the administration of any PDE5 inhibitor. Other adverse effects of PDE5 inhibitors include flushing, visual abnormalities, and headache. Sildenafil and vardenafil may cause abnormal color perception. Tadalafil use has been linked with myalgias. Some users of PDE5 inhibitors have rarely developed anterior ischemic optic neuropathy, but whether there is a causal relationship is unclear. Vardenafil should be administered cautiously and at lower initial dosages to patients receiving α-blockers, such as prazosin, doxazosin, and tamsulosin, because of the risk of prolonged hypotension. One study showed that sildenafil may be safely administered with doxazosin.
Apomorphine increases erectile neurogenic signals by CNS mechanisms. It appears to be only moderately effective and can cause nausea, somnolence, and hypotension.

Alprostadil (the prostaglandin PGE$_1$), given via intraurethral insertion or intracavernosal injection, can produce erections with a mean duration of about 60 min. It causes priapism (see p. 2327) in ≤ 1% and penile pain in about 10%. The intracavernosal dose is adjusted by the physician to minimize priapism; the patient can then self-inject at home. Priapism is less common with intraurethral therapy, but intraurethral therapy is much less effective (50 to 60%) than intracavernosal injection, the most effective pharmacotherapy for erectile dysfunction (80 to 90%). Combination therapy with a PDE5 inhibitor and alprostadil may be useful for some patients who fail to respond to oral PDE5 inhibitors alone.

Surgery: For patients who do not respond to drug therapy, invasive treatment options include implantation of a penile prosthesis. Prostheses can be rigid plastic rods or hydraulically operated devices. Both involve the risks of general anesthesia, infection, and prosthetic malfunction.

Gynecomastia

Gynecomastia is hypertrophy of breast glandular tissue in males. It must be differentiated from pseudogynecomastia, which is increased breast fat, but no enlargement of breast glandular tissue.

Pathophysiology

During infancy and puberty, enlargement of the male breast is normal (physiologic gynecomastia). Enlargement is usually transient, bilateral, smooth, firm, and symmetrically distributed under the areola; breasts may be tender. Physiologic gynecomastia that develops during puberty usually resolves within about 6 mo to 2 yr. Similar changes may occur during old age and may be unilateral or bilateral. Most of the enlargement is due to proliferation of stroma, not of breast ducts. The mechanism is usually a decrease in androgen effect or an increase in estrogen effect (eg, decrease in androgen production, increase in estrogen production, androgen blockade, displacement of estrogen from sex-hormone binding globulin, androgen receptor defects).

If evaluation reveals no cause for gynecomastia, it is considered idiopathic. The cause may not be found because gynecomastia is physiologic or because there is no longer any evidence of the inciting event.

Etiology

In infants and boys, the most common cause is

- Physiologic gynecomastia

In men, the most common causes are (see Table 229-3)

- Persistent pubertal gynecomastia

- Idiopathic gynecomastia

- Drugs (particularly spironolactone, anabolic steroids, and antiandrogens—see Table 229-4)

Breast cancer, which is uncommon in males, may cause unilateral breast abnormalities but is rarely confused with gynecomastia.

Evaluation

History: History of present illness should help clarify the duration of breast enlargement, whether secondary sexual characteristics are fully developed, the relationship between onset of gynecomastia
and puberty, and the presence of any genital symptoms (eg, decreased libido, erectile dysfunction) and breast symptoms (eg, pain, nipple discharge).

**Review of systems** should seek symptoms that suggest possible causes, such as weight loss and fatigue (cirrhosis, undernutrition, chronic kidney disease, hyperthyroidism); skin discoloration (chronic kidney disease, cirrhosis); hair loss and frequent infections (undernutrition); fragility fractures (undernutrition, hypogonadism); mood and cognitive changes (hypogonadism); and tremor, heat intolerance, and diarrhea (hyperthyroidism).

**Past medical history** should address disorders that can cause gynecomastia and include a history of all prescribed and OTC drugs.

**Physical examination:** Complete examination is done, including assessment of vital signs, skin, and general appearance. The neck is examined for goiter. The abdomen is examined for ascites, venous distention, and suspected adrenal masses. Development of secondary sexual characteristics (eg, the penis, pubic hair, and axillary hair) is assessed. The testes are examined for masses and atrophy.

The breasts are examined while patients are recumbent with their hands behind their head. Examiners bring their thumb and forefinger together from opposite sides of the nipple until they meet. Lumps are assessed and characterized in terms of location, consistency, fixation to underlying tissues, and skin changes.

The following findings are of particular concern:

- **Red flags:**
  - Localized or eccentric breast swelling, particularly with nipple discharge, fixation to the skin, or hard consistency
  - Symptoms or signs of hypogonadism
  - Symptoms or signs of hyperthyroidism
  - Testicular mass
  - Recent onset of painful, tender gynecomastia in an adult

**Interpretation of findings:** With pseudogynecomastia, the examiner feels no resistance between the thumb and forefinger until they meet. In contrast, with gynecomastia, a rim of tissue > 0.5 cm in diameter surrounds the nipple symmetrically and is similar in consistency to the nipple itself. Breast cancer is suggested by swelling with any of the following characteristics:

- Eccentric unilateral location
- Firm or hard consistency
- Fixation to skin or fascia
- Nipple discharge
- Skin dimpling
Gynecomastia in an adult that is of recent onset and causes pain is more often caused by a hormonal abnormality (eg, tumor, hypogonadism) or drugs. Other examination findings may also be helpful (see Table 229-5).

**Testing:** If breast cancer is considered, mammography should be done. If another disorder is suspected, appropriate testing should be done (see Table 229-3). Extensive testing is often unnecessary, especially for patients in whom the gynecomastia is chronic and detected only on physical examination. Because hypogonadism is somewhat common with aging, some authorities recommend measuring the serum testosterone level in older men, particularly if other findings suggest hypogonadism. However, in adults with recent onset of painful gynecomastia without a drug or evident pathologic cause, measurement of serum levels of LH, FSH, testosterone, estradiol and human chorionic gonadotropin (hCG) are recommended. Patients with physiologic or idiopathic gynecomastia are evaluated again in 6 mo.

**Treatment**

In most cases, no specific treatment is needed because gynecomastia usually remits spontaneously or disappears after any causative drug (except perhaps anabolic steroids) is stopped or underlying disorder is treated. Some clinicians try tamoxifen 10 mg po bid if pain and tenderness are very troublesome in men or adolescents, but this treatment is not always effective. Tamoxifen may also help prevent gynecomastia in men being treated with high-dose antiandrogen (eg, bicalutamide) therapy for prostate cancer; breast radiation therapy is an alternative. Resolution of gynecomastia is unlikely after 12 mo. Thus, after 12 mo, if cosmetic appearance is unacceptable, surgical removal of excess breast tissue (eg, suction lipectomy alone or with cosmetic surgery) may be used.

**Key Points**

- Gynecomastia must be differentiated from increased fat tissue in the breast.
- Gynecomastia is often physiologic or idiopathic.
- A wide variety of drugs can cause gynecomastia.
- Patients should be evaluated for clinically suspected genital or systemic disorders.

[Table 229-5. Interpretation of Some Findings in Gynecomastia]
Chapter 230. Voiding Disorders

Introduction

Voiding disorders affect urine storage or release because both are controlled by the same neural and urinary tract mechanisms. The result is incontinence or retention.

For normal urinary function, the autonomic and voluntary nervous systems must be intact, and muscles of the urinary tract must be functional. Normally, bladder filling stimulates stretch receptors in the bladder wall to send impulses via spinal nerves S2 to S4 to the spinal cord, then to the sensory cortex, where the need to void is perceived. A threshold volume, which differs from person to person, triggers awareness of the need to void. However, the external urinary sphincter at the bladder outlet is under voluntary control and usually remains contracted until a person decides to urinate. The micturition inhibitory center in the frontal lobe also helps control urination. When the decision is made, voluntary signals in the motor cortex initiate urination. These impulses are transmitted to the pontine micturition center, which coordinates simultaneous signals to contract detrusor smooth muscle throughout the bladder (via parasympathetic cholinergic nerve fibers) and to relax the internal sphincter (via alpha sympathetic nerve fibers) and striated muscle of the external sphincter and pelvic floor (see Fig. 230-1). In addition to normal urinary function, continence and normal voiding require normal cognitive function (including motivation), mobility, access to a toilet, and manual dexterity.

Damage to or dysfunction of any of the components involved in voiding can cause urinary incontinence or retention.

Urinary Incontinence

(See also Incontinence in Children on p. 2923)

Urinary incontinence is involuntary loss of urine; some experts consider it present only when a patient thinks it is a problem. The disorder is greatly underrecognized and under-reported. Many patients do not report the problem to their physician, and many physicians do not ask about incontinence specifically. Incontinence can occur at any age but is more common among the elderly and among women, affecting about 30% of elderly women and 15% of elderly men.

Incontinence greatly reduces quality of life by causing embarrassment, stigmatization, isolation, and depression. Many elderly patients are institutionalized because incontinence is a burden to caregivers. In bedbound patients, urine irritates and macerates skin, contributing to sacral pressure ulcer formation. Elderly people with urgency are at increased risk of falls and fractures.

Types: Incontinence may manifest as near-constant dribbling or as intermittent voiding with or without awareness of the need to void. Some patients have extreme urgency (irrepressible need to void) with little or no warning and may be unable to inhibit voiding until reaching a bathroom. Incontinence may occur or worsen with maneuvers that increase intra-abdominal pressure. Postvoid dribbling is extremely common and probably a normal variant in men. Identifying the clinical pattern is sometimes useful, but causes often overlap and much of treatment is the same.

Urge incontinence is uncontrolled urine leakage (of moderate to large volume) that occurs immediately after an urgent, irrepressible need to void. Nocturia and nocturnal incontinence are common. Urge incontinence is the most common type of incontinence in the elderly but may affect younger people. It is often precipitated by use of a diuretic and is exacerbated by inability to quickly reach a bathroom. In women, atrophic vaginitis, common with aging, contributes to thinning and irritation of the urethra and urgency.

Stress incontinence is urine leakage due to abrupt increases in intra-abdominal pressure (eg, with coughing, sneezing, laughing, bending, or lifting). Leakage volume is usually low to moderate. It is the 2nd most common type of incontinence in women, largely because of complications of childbirth and development of atrophic urethritis. Stress incontinence is typically more severe in obese people because of pressure from abdominal contents on the top of the bladder.
Overflow incontinence is dribbling of urine from an overly full bladder. Volume is usually small, but leaks may be constant, resulting in large total losses. Overflow incontinence is the 2nd most common type of incontinence in men.

Functional incontinence is urine loss due to cognitive or physical impairments (eg, due to dementia or stroke) or environmental barriers that interfere with control of voiding. For example, the patient may not recognize the need to void, may not know where the toilet is, or may not be able to walk to a remotely located toilet. Neural pathways and urinary tract mechanisms that maintain continence may be normal.

Mixed incontinence is any combination of the above types. The most common combinations are urge with stress incontinence and urge or stress with functional incontinence.

Etiology

The disorder tends to differ among age groups. With aging, bladder capacity decreases, ability to inhibit urination declines, involuntary bladder contractions (detrusor overactivity) occur more often, and bladder contractility is impaired. Thus, voiding becomes more difficult to postpone and tends to be incomplete. Postvoid residual volume increases, probably to ≤ 100 mL (normal < 50 mL). Endopelvic fascia weakens. In postmenopausal women, decreased estrogen levels lead to atrophic urethritis and atrophic vaginitis and to decreasing urethral resistance, length, and maximum closure pressure. In men, prostate size increases, partially obstructing the urethra and leading to incomplete bladder emptying and strain on the detrusor muscle. These changes occur in many normal, continent elderly people and may facilitate incontinence but do not cause it.

In younger patients, incontinence often begins suddenly, may cause little leakage, and usually resolves quickly with little or no treatment. Often, incontinence has one cause in younger patients but has several in the elderly.

Conceptually, categorization into reversible (transient) or established causes may be useful. However, causes and mechanisms often overlap and occur in combination.

Transient incontinence: There are several causes of transient incontinence (see Table 230-1). A useful mnemonic for many transient causes is DIAPPERS (with an extra P): Delirium, Infection (commonly, symptomatic UTIs), Atrophic urethritis and vaginitis, Pharmaceuticals (eg, those with α-adrenergic, cholinergic, or anticholinergic properties; diuretics; sedatives), Psychiatric disorders (especially depression), Excess urine output (polyuria), Restricted mobility, and Stool impaction.

Established incontinence: Established incontinence is caused by a persistent problem affecting nerves or muscles. Mechanisms usually used to describe these problems are bladder outlet incompetence or obstruction, detrusor overactivity or underactivity, detrusor-sphincter dyssynergia, or a combination (see Table 230-2). However, these mechanisms are also involved in some transient causes.

Outlet incompetence is a common cause of stress incontinence. In women, it is usually due to weakness of the pelvic floor or of the endopelvic fascia. Such weakness commonly results from multiple vaginal deliveries, pelvic surgery (including hysterectomy), age-related changes (including atrophic urethritis), or a combination. As a result, the vesicourethral junction descends, the bladder neck and urethra become hypermobile, and pressure in the urethra falls below that of the bladder. In men, a common cause is damage to the sphincter or to the bladder neck and posterior urethra after radical prostatectomy.

Outlet obstruction is a common cause of incontinence in men, although most men with obstruction are not incontinent. Obstruction in men commonly results from benign prostatic hyperplasia, prostate cancer,
or urethral stricture. In women, outlet obstruction is rare but can result from previous surgery for incontinence or from a prolapsed cystocele that causes the urethra to kink during straining to void. In both sexes, fecal impaction can cause obstruction. Obstruction leads to a chronically overdistended bladder, which loses its ability to contract; then the bladder does not empty completely, resulting in overflow. Obstruction also may lead to detrusor overactivity and urge incontinence. If the detrusor muscle loses its ability to contract, overflow incontinence may follow. Some causes of outlet obstruction (eg, large bladder diverticula, cystoceles, bladder infections, calculi, and tumors) are reversible.

**Detrusor overactivity** is a common cause of urge incontinence in elderly and younger patients. The detrusor muscle contracts intermittently for no apparent reason, usually when the bladder is partially or nearly full. Detrusor overactivity may be idiopathic or may result from dysfunction of the frontal micturition inhibitory center (commonly due to age-related changes, dementia, or stroke) or outlet obstruction. Detrusor overactivity (hyperactivity) with impaired contractility (DHIC) is a variant of urge incontinence characterized by urgency, frequency, a weak flow rate, urinary retention, bladder trabeculation, and a postvoid residual volume of > 50 mL. This variant may mimic prostatism in men or stress incontinence in women.

**Detrusor underactivity** causes urinary retention and overflow incontinence in about 5% of patients with incontinence. It may be caused by injury to the spinal cord (see p. 3227) or to nerve roots supplying the bladder (eg, by disk compression, tumor, or surgery), by peripheral or autonomic neuropathies, or by other neurologic disorders (see Table 230-2). Anticholinergics and opioids greatly decrease detrusor contractility; these drugs are common transient causes. The detrusor may become underactive in men with chronic outlet obstruction as the detrusor is replaced by fibrosis and connective tissue, preventing the bladder from emptying even when the obstruction is removed. In women, detrusor underactivity is usually idiopathic. Less severe detrusor weakness is common among elderly women. Such weakness does not cause incontinence but can complicate treatment if other causes of incontinence coexist.

**Detrusor-sphincter dyssynergia** (loss of coordination between bladder contraction and external urinary sphincter relaxation) may cause outlet obstruction, with resultant overflow incontinence. Dyssynergia is often due to a spinal cord lesion that interrupts pathways to the pontine micturition center, which coordinates sphincter relaxation and bladder contraction. Rather than relaxing when the bladder contracts, the sphincter contracts, obstructing the bladder outlet. Dyssynergia causes severe trabeculation, diverticula, a "Christmas tree" deformation of the bladder, hydronephrosis, and renal failure.

**Functional impairment** (eg, cognitive impairment, reduced mobility, reduced manual dexterity, coexisting disorders, lack of motivation), particularly in the elderly, may contribute to established incontinence but rarely causes it.

### [Table 230-1. Causes of Transient Incontinence]

#### Evaluation

- **History**
- **Examination:** neurologic, pelvic, rectal
- **Testing:** urinalysis, urine culture, BUN, and creatinine; postvoid residual volume; sometimes urodynamic testing

Most patients, embarrassed to mention incontinence, do not volunteer information about it, although they may mention related symptoms (eg, frequency, nocturia, hesitancy). All adults should therefore be screened with a question such as "Do you ever leak urine?"

Clinicians should not assume that incontinence is irreversible just because it is longstanding. Also, urinary retention (see p. 2362) must be excluded before treatment for detrusor overactivity is started.

**History:** History focuses on duration and patterns of voiding, bowel function, drug use, and obstetric and pelvic surgical history. A voiding diary can provide clues to causes. Over 48 to 72 h, the patient or
caregiver records volume and time of each void and each incontinent episode in relation to associated activities (especially eating, drinking, and drug use) and during sleep. The amount of urine leakage can be estimated as drops, small, medium, or soaking; or by pad tests (measuring the weight of urine absorbed by feminine pads or incontinence pads during a 24-h period). If the volume of most nightly voids is much smaller than functional bladder capacity (defined as the largest single voided volume recorded in the diary), the cause is a sleep-related problem (patients void because they are awake anyway) or a bladder abnormality (patients without bladder dysfunction or a sleep-related problem awaken to void only when the bladder is full).

Of men with obstructive symptoms (hesitancy, weak urinary stream, intermittency, feeling of incomplete bladder emptying), about one third have detrusor overactivity without obstruction.

Urgency or an abrupt gush of urine without warning or without preceding increase in intra-abdominal pressure (often called reflex or unconscious incontinence) typically indicates detrusor overactivity.

**Physical examination:** Neurologic, pelvic, and rectal examinations are the focus.

Neurologic examination involves assessing mental status, gait, and lower extremity function and checking for signs of peripheral or autonomic neuropathy, including orthostatic hypotension. Neck and upper extremities should be checked for signs of cervical spondylosis or stenosis. The spinal column should be checked for evidence of prior surgeries and for deformities, dimples, or hair tufts suggesting neural tube defects.

Innervation of the external urethral sphincter, which shares the same sacral roots as the anal sphincter, can be tested by assessing:

- Perineal sensation
- Volitional anal sphincter contraction (S2 to S4)
- The anal wink reflex (S4 to S5), which is anal sphincter contraction triggered by lightly stroking perianal skin
- The bulbocavernosus reflex (S2 to S4), which is anal sphincter contraction triggered by pressure on the glans penis or clitoris

However, the absence of these reflexes is not necessarily pathologic.

Pelvic examination in women can identify atrophic vaginitis and urethritis, urethral hypermobility, and pelvic floor weakness. Pale, thin vaginal mucosae with loss of rugae indicate atrophic vaginitis. Urethral hypermobility can be seen during coughing when the posterior vaginal wall is stabilized with a speculum. A cystocele, an enterocele, a rectocele, or uterine prolapse suggests pelvic floor weakness (see p. 2529). When the opposite wall is stabilized with a speculum, bulging of the anterior wall indicates a cystocele, and bulging of the posterior wall indicates a rectocele or enterocele. Pelvic floor weakness does not suggest a cause, unless a large, prolapsed cystocele is present.

Rectal examination can identify fecal impaction, rectal masses, and, in men, prostate nodules or masses. Prostate size should be noted but correlates poorly with outlet obstruction. Suprapubic palpation and percussion to detect bladder distention are usually of little value except in extreme acute cases of urinary retention.

If stress incontinence is suspected, urinary stress testing can be done on the examination table; it has a sensitivity and specificity of > 90%. The bladder must be full; a patient sits upright or close to upright with the legs spread, relaxes the perineal area, and coughs vigorously once. Immediate leakage that starts
and stops with the cough confirms stress incontinence. Delayed or persistent leakage suggests detrusor overactivity triggered by the cough. If cough triggers incontinence, the maneuver can be repeated while the examiner places 1 or 2 fingers inside the vagina to elevate the urethra (Marshall-Bonney test); incontinence that is corrected by this maneuver may respond to surgery. Results can be false-positive if patients have an abrupt urge to void during the test or false-negative if patients do not relax, the bladder is not full, the cough is not strong, or a large cystocele is present (in women). In the last case, the test should be repeated with the patient supine and the cystocele reduced, if possible.

**Testing:** Urinalysis, urine culture, and measurement of BUN and serum creatinine are required. Other tests may include serum glucose and Ca (with albumin for estimation of protein-free Ca levels) if the voiding diary suggests polyuria, electrolytes if patients are confused, and vitamin B12 levels if clinical findings suggest a neuropathy.

Postvoid residual volume should be determined by catheterization or ultrasonography. Postvoid residual volume plus voided volume estimates total bladder capacity and helps assess bladder proprioception. A volume < 50 mL is normal; < 100 mL is usually acceptable in patients > 65 but abnormal in younger patients; and > 100 mL may suggest detrusor underactivity or outlet obstruction.

Urodynamic testing is indicated when clinical evaluation combined with the appropriate tests is not diagnostic or when abnormalities must be precisely characterized before surgery.

Cystometry may help diagnose urge incontinence, but sensitivity and specificity are unknown. Sterile water is introduced into the bladder in 50-mL increments using a 50-mL syringe and a 12- to 14-F urethral catheter until the patient experiences urgency or bladder contractions, detected by changes in fluid level in the syringe. If < 300 mL causes urgency or contractions, detrusor overactivity and urge incontinence are likely.

Peak urinary flow rate testing with a flow meter is used to confirm or exclude outlet obstruction in men. Results depend on initial bladder volume, but a peak flow rate of < 12 mL/sec with a urinary volume of ≥ 200 mL and prolonged voiding suggest outlet obstruction or detrusor underactivity. A rate of ≥ 12 mL/sec excludes obstruction and may suggest detrusor overactivity. During testing, patients are instructed to place their hand on their abdomen to check for straining during urination, especially if stress incontinence is suspected and surgery is contemplated. Straining suggests detrusor weakness that may predispose patients to postoperative retention.

In cystometrography, pressure-volume curves and bladder sensation are recorded while the bladder is filled with sterile water; provocative testing (with bethanechol or ice water) is used to stimulate bladder contractions. Electromyography of perineal muscle is used to assess sphincter innervation and function. Urethral, abdominal, and rectal pressures may be measured. Pressure-flow video studies, usually done with voiding cystourethrography (see p. 2315), can correlate bladder contraction, bladder neck competency, and detrusor-sphincter synergy, but equipment is not widely available.

**Treatment**

- Bladder training
- Kegel exercises
- Drugs

Specific causes are treated, and drugs that can cause or worsen incontinence are stopped or the dosing schedule is altered (eg, a diuretic dose is timed so that a bathroom is near when the drug takes effect). Other treatment is based on type of incontinence. Regardless of type and cause, some general measures are usually helpful.

**General measures:** Patients may benefit from bladder training (to change voiding habits) and changes in fluid intake. Bladder training usually involves timed voiding (every 2 to 3 h) while awake. Prompted voiding is used for cognitively impaired patients; they are asked about every 2 h whether they need to
void or whether they are wet or dry. A voiding diary helps establish how often and when voiding is indicated and whether patients can sense a full bladder. Patients are instructed to limit fluid intake at certain times (eg, before going out, 3 to 4 h before bedtime), to avoid fluids that irritate the bladder (eg, caffeine-containing fluids), and to drink 48 to 64 oz (1500 to 2000 mL) of fluid a day (because concentrated urine irritates the bladder).

Pelvic muscle exercises (eg, Kegel exercises) are often effective, especially for stress incontinence. Patients must contract the pelvic muscles (pubococcygeus and paravaginal) rather than the thigh, abdominal, or buttock muscles. The muscles are contracted for 10 sec, then relaxed for 10 sec 10 to 15 times tid. Re-instruction is often necessary, and biofeedback is often useful. In women < 75 yr, cure rate is 10 to 25%, and improvement occurs in an additional 40 to 50%, especially if patients are motivated; do the exercises as instructed; and receive written instructions, follow-up visits for encouragement, or both. Pelvic floor electrical stimulation is an automated version of Kegel exercises; it uses electrical current to inhibit detrusor overactivity and contract pelvic muscles. Advantages are improved compliance and contraction of the correct pelvic muscles, but benefits over behavioral changes alone are unclear.

Some patients, especially those with restricted mobility or cognitive impairment, benefit from a portable commode. Others use absorbent pads or specialized padded undergarments. These products can greatly improve the quality of life of patients and their caregivers. However, they should not be substituted for measures that can control or eliminate incontinence, and they must be changed often to avoid skin irritation and development of UTIs.

**Drugs:** Drugs are often useful (see Table 230-3). Such drugs include anticholinergics and antimuscarinics, which relax the detrusor, and α-agonists, which increase sphincter tone. Drugs with strong anticholinergic effects should be used judiciously in the elderly. α-Antagonists and 5α-reductase inhibitors may be used to treat outlet obstruction in men with urge or overflow incontinence.

**Urge incontinence:** Treatment aims to reduce detrusor overactivity; it begins with bladder training, Kegel exercises, and relaxation techniques. Biofeedback can be used with these treatments. Drugs may also be needed, as may intermittent self-catheterization (eg, when postvoid residual volume is large). Infrequently, sacral nerve stimulation, intravesical therapies, and surgery are used.

Bladder training helps patients tolerate and ultimately inhibit detrusor contractions. Regular voiding intervals are gradually lengthened (eg, 30 min every 3 days that urinary control is maintained) to improve tolerance of detrusor contractions. Relaxation techniques can improve emotional and physical responses to the urge to void. Relaxing, standing in place or sitting down (rather than rushing to the toilet), and tightening pelvic floor muscles can help patients suppress the urge to void.

Drugs (see Table 230-3) should supplement, not replace, behavioral changes. The most commonly used are oxybutynin and tolterodine; both are anticholinergic and antimuscarinic and are available in extended-release forms that can be taken po once/day. Oxybutynin is available as a skin patch that is changed twice/wk. Newer drugs with anticholinergic and antimuscarinic properties include solifenacin and darifenacin, which are taken po once/day, and trospium, which is taken once/day or bid. Drugs may be required to suppress urgency symptoms due to DHIC. Drugs with a rapid onset of action (eg, immediate-release oxybutynin) can be used prophylactically if incontinence occurs at predictable times. Combinations of drugs may increase both efficacy and adverse effects, possibly limiting this approach in the elderly.

Sacral nerve stimulation is indicated for patients with severe urge incontinence refractory to other treatments. It is thought to work by centrally inhibiting bladder sensory afferents. The procedure begins with percutaneous nerve stimulation for at least 3 days; if patients respond, a neurostimulator is permanently implanted.

Rarely, intravesical instillation of capsaicin or resiniferatoxin (a capsaicin analog) is used when urge incontinence results from spinal cord injuries and other CNS disorders. This experimental treatment desensitizes C-fiber bladder afferents responsible for reflex bladder emptying. Injecting botulinum toxin type A into the detrusor muscle is under study as an alternative.
Surgery is a last resort, usually used only for younger patients with severe urge incontinence refractory to other treatments. Augmentation cystoplasty, in which a section of intestine is sewn into the bladder to increase bladder capacity, is most common. Intermittent self-catheterization may be required if augmentation cystoplasty results in weak bladder contractions or poor coordination of abdominal pressure (Valsalva maneuver) with sphincter relaxation. Detrusor myomectomy may be done to decrease undesired bladder contractions. As a last resort, a urinary diversion can be created to divert the urine away from the bladder. Choice of procedure is based on presence of other disorders, physical limitations, and patient preference. Neuromodulation, in which electrodes are implanted around the spinal nerve roots, is under study.

**Stress incontinence:** Treatment includes bladder training and Kegel exercises. Drugs, surgery, other procedures, or, in women, occlusive devices are also usually needed. Treatment is generally directed at outlet incompetence but includes treatments for urge incontinence if detrusor overactivity is present. Avoiding physical stresses that provoke incontinence can help. Losing weight may help lessen incontinence in obese patients.

Drugs (see Table 230-3) include pseudo-ephedrine, which may be useful in women with outlet incompetence; imipramine, which may be used for mixed stress and urge incontinence or for either separately; and duloxetine. If stress incontinence is due to atrophic urethritis, topical estrogen (0.3 mg conjugated or 0.5 mg estradiol once/day for 3 wk, then twice/wk after) is often effective.

Surgery and other procedures provide the best chance of cure when noninvasive treatments are ineffective. Bladder neck suspension

[Table 230-3, Drugs Used to Treat Incontinence]

is used to correct urethral hypermobility. Suburethral slings, injection of periurethral bulking agents, or surgical insertion of an artificial sphincter is used to treat sphincter deficiency. Choice depends on the patient's ability to tolerate surgery and need for other surgeries (eg, hysterectomy, cystocele repair) and on local experience.

Occlusive devices may be used in elderly women with or without bladder or uterine prolapse if surgical risks are high or if prior surgery for stress incontinence was ineffective. Pessaries may be effective; they elevate the bladder neck, elevate the vesicourethral junction, and increase urethral resistance by pressing the urethra against the pubic symphysis. Newer, possibly more acceptable alternatives include silicone suction caps over the urethral meatus, intraurethral occlusive devices inserted with an applicator, and intravaginal bladder neck support prostheses. Removable intraurethral plugs are under study.

Exercise regimens using vaginal cones—in which progressively heavier cones are inserted into the vagina and retained for 15 min bid by contracting pelvic floor muscles—are also under study.

**Overflow incontinence:** Treatment depends on whether the cause is outlet obstruction, detrusor underactivity, or both.

Outlet obstruction due to benign prostatic hyperplasia (see p. 2461) or cancer (see p. 2472) is treated with drugs or surgery; that due to urethral stricture is treated with dilation or stenting. Cystoceles in women are treated with surgery or can be reduced using a pessary (see p. 2531); unilateral suture removal or urethral adhesiolysis may be effective if cystoceles resulted from surgery. If urethral hypermobility coexists, bladder neck suspension should be done.

Detrusor underactivity requires bladder decompression (reduction of residual volume) by intermittent self-catheterization or, rarely, temporary use of an indwelling catheter. Several weeks of decompression may be required to restore bladder function. If bladder function is not fully restored, maneuvers to augment voiding (eg, double voiding, Valsalva maneuver, application of suprapubic pressure [Crede's method] during voiding) are used. A completely acontractile detrusor requires intermittent self-catheterization or use of an indwelling catheter. Using antibiotics or methenamine mandelate to prevent UTIs in patients who require intermittent self-catheterization is controversial but probably indicated if patients have
frequent symptomatic UTIs or a valvular or orthopedic prosthesis. Such prophylaxis is not helpful with indwelling catheters.

Additional treatments that may induce bladder contraction and promote emptying include electrical stimulation and the cholinergic agonist bethanechol. However, bethanechol is usually ineffective and has adverse effects (see Table 230-3).

**Refractory incontinence:** Absorbent pads, special undergarments, and intermittent self-catheterization may be needed. Indwelling urethral catheters are an option for patients who cannot walk to the toilet or who have urinary retention and cannot self-catheterize; these catheters are not recommended for urge incontinence because they may exacerbate detrusor contractions. If a catheter is necessary (eg, to allow healing of a pressure ulcer in patients with refractory detrusor overactivity), a narrow catheter with a small balloon should be used because it will minimize irritability; irritability can force urine out, even around a catheter. For men who can comply with treatment, condom catheters may be preferable because they reduce risk of UTIs; however, these catheters may cause skin breakdown and reduce motivation to become dry. New external collection devices may be effective in women. If involuntary bladder contractions persist, oxybutynin or tolterodine can be used. If mobility is restricted, measures to prevent skin irritation and breakdown due to urine are essential (see p. 742).

**Urinary Retention**

Urinary retention is incomplete emptying of the bladder or cessation of urination; it may be acute or chronic. Causes include impaired bladder contractility, bladder outlet obstruction, detrusor-sphincter dyssynergia (lack of coordination between bladder contraction and sphincter relaxation), or a combination. Retention is most common among men, in whom prostate abnormalities or urethral strictures cause outlet obstruction. In either sex, retention may be due to drugs (particularly those with anticholinergic effects, including many OTC drugs), severe fecal impaction (which increases pressure on the bladder trigone), or neurogenic bladder in patients with diabetes, multiple sclerosis, Parkinson's disease, or prior pelvic surgery resulting in bladder denervation.

Urinary retention can cause urinary frequency and urge or overflow incontinence. It may cause abdominal distention and pain. When retention develops slowly, pain may be absent. Long-standing retention predisposes to UTI and can increase bladder pressure, causing obstructive uropathy (see p. 2365).

**Diagnosis**

Diagnosis is obvious in patients who cannot void. In those who can void, diagnosis is by postvoid catheterization showing a residual urine volume > 100 mL. Other tests (eg, urinalysis, blood tests, ultrasonography, uro-dynamic testing, cystoscopy, cystography) are done based on clinical findings.

**Treatment**

• Urethral catheterization and treatment of cause

Relief of acute urinary retention requires urethral catheterization. Subsequent treatment depends on cause. In men with benign prostatic hypertrophy, drugs (usually α-adrenergic blockers or 5α-reductase inhibitors) or surgery may help decrease bladder outlet resistance. No treatment is effective for impaired bladder contractility or a neurogenic bladder; intermittent self-catheterization or indwelling catheterization is usually required. Urinary diversion is a last resort.

**Neurogenic Bladder**

Neurogenic bladder is bladder dysfunction (flaccid or spastic) caused by neurologic damage. The primary symptom is overflow incontinence. Risk of serious complications (eg, recurrent infection, vesicoureteral reflux, autonomic dysreflexia) is high. Diagnosis involves imaging and cystoscopy or urodynamic testing. Treatment involves catheterization or measures to trigger urination.
Any condition that impairs bladder and bladder outlet afferent and efferent signaling can cause neurogenic bladder. Causes may involve the CNS (eg, stroke, spinal injury, meningomyelocele, amyotrophic lateral sclerosis), peripheral nerves (eg, diabetic, alcoholic, or vitamin B12 deficiency neuropathies; herniated disks; damage due to pelvic surgery), or both (eg, Parkinson's disease, multiple sclerosis, syphilis). Bladder outlet obstruction often coexists and may exacerbate symptoms.

In **flaccid (hypotonic) neurogenic bladder**, volume is large, pressure is low, and contractions are absent. It may result from peripheral nerve damage or spinal cord damage at the S2 to S4 level. After acute cord damage, initial flaccidity may be followed by long-term flaccidity or spasticity, or bladder function may improve after days, weeks, or months.

In **spastic bladder**, volume is normal or small, and involuntary contractions occur. It usually results from brain damage or spinal cord damage above T12. Precise symptoms vary by site and severity of the lesion. Bladder contraction and external urinary sphincter relaxation are typically uncoordinated (detrusor-sphincter dyssynergia).

**Mixed patterns** (flaccid and spastic bladder) may be caused by many disorders, including syphilis, diabetes mellitus, brain or spinal cord tumors, stroke, ruptured intervertebral disk, and demyelinating or degenerative disorders (eg, multiple sclerosis, amyotrophic lateral sclerosis).

**Symptoms and Signs**

Overflow incontinence is the primary symptom in patients with a flaccid or spastic bladder. Patients retain urine and have constant overflow dribbling. Men typically also have erectile dysfunction. Patients with spastic bladder may have frequency, nocturia, and urgency or spastic paralysis with sensory deficits.

Common complications include recurrent UTIs and urinary calculi. Hydronephrosis with vesicoureteral reflux may occur because the large urine volume puts pressure on the vesicoureteral junction, causing dysfunction with reflux and, in severe cases, nephropathy. Patients with high thoracic or cervical spinal cord lesions are at risk of autonomic dysreflexia (a life-threatening syndrome of malignant hypertension, bradycardia or tachycardia, headache, piloerection, and sweating due to unregulated sympathetic hyperactivity). This disorder may be triggered by acute bladder distention (due to urinary retention) or bowel distention (due to constipation or fecal impaction).

**Diagnosis**

- Postvoid residual volume
- Renal ultrasonography
- Serum creatinine
- Usually cystography, cystoscopy, and cystometrography with urodynamic testing

Diagnosis is suspected clinically. Usually, postvoid residual volume is measured, renal ultrasonography is done to detect hydronephrosis, and serum creatinine is measured to assess renal function. Further studies are often not obtained in patients who are not able to self-catheterize or ask to go to the bathroom (eg, severely debilitated elderly or post-stroke patients). In patients with hydronephrosis or nephropathy who are not severely debilitated, cystography, cystoscopy, and cystometrography with urodynamic testing are usually recommended and may guide further therapy. Cystography is used to evaluate bladder capacity and detect reflux. Cystoscopy is used to evaluate duration and severity of retention (by detecting bladder trabeculations) and to check for bladder outlet obstruction. Cystometrography can determine whether bladder volume and pressure are high or low; if done during the recovery phase of flaccid bladder after spinal cord injury, it can help evaluate detrusor functional capacity and predict rehabilitation prospects (see p. 2358). Urodynamic testing of voiding flow rates with sphincter electromyography can show whether bladder contraction and sphincter relaxation are coordinated (see p. 2358).

**Treatment**
• Catheterization
• Increased fluid intake
• Surgery as last resort

Prognosis is good if the disorder is diagnosed and treated before kidneys are damaged.

Specific treatment involves catheterization or measures to trigger urination. General treatment includes renal function monitoring, control of UTIs, high fluid intake to decrease risk of UTIs and urinary calculi (although this measure may exacerbate incontinence), early ambulation, frequent changes of position, and dietary Ca restriction to inhibit calculus formation.

For flaccid bladder, especially if the cause is an acute spinal cord injury, immediate continuous or intermittent catheterization is needed. Intermittent self-catheterization is preferable to indwelling urethral catheterization, which has a high risk of recurrent UTIs and, in men, a high risk of urethritis, periurethritis, prostatic abscesses, and urethral fistulas. Suprapubic catheterization may be used if patients cannot self-catheterize.

For spastic bladder, treatment depends on the patient's ability to retain urine. Patients who can retain normal volumes can use techniques to trigger voiding (eg, applying suprapubic pressure, scratching the thighs); anticholinergics may be effective. For patients who cannot retain normal volumes, treatment is the same as that of urge incontinence (see p. 2358), including drugs (see Table 230-3) and sacral nerve stimulation.

Surgery is a last resort. It is usually indicated if patients have had or are at risk of severe acute or chronic sequelae or if social circumstances, spasticity, or quadriplegia prevents use of continuous or intermittent bladder drainage. Sphincterotomy (for men) converts the bladder into an open draining conduit. Sacral (S3 and S4) rhizotomy converts a spastic into a flaccid bladder. Urinary diversion may involve an ileal conduit or ureterostomy.

An artificial, mechanically controlled urinary sphincter, surgically inserted, is an option for patients who have adequate bladder capacity, good bladder emptying, and upper extremity motor skills and who can comply with instructions for use of the device; if patients do not comply, life-threatening situations (eg, renal failure, urosepsis) can result.

**Interstitial Cystitis**

*Interstitial cystitis* is noninfectious bladder inflammation that causes pain (suprapubic, pelvic, and abdominal), urinary frequency, and urgency with incontinence. Diagnosis is by history and exclusion of other disorders clinically and by cystoscopy and biopsy. With treatment, most patients improve, but cure is rare. Treatment varies but includes dietary changes, bladder training, pentosan, analgesics, and intravesical therapies.

Incidence of interstitial cystitis is unknown, but the disorder appears to be more common than once thought and may underlie other clinical syndromes (eg, chronic pelvic pain). Whites are more susceptible, and 90% of cases occur in women.

Cause is unknown, but pathophysiology may involve loss of protective urothelial mucin, with penetration of urinary K and other substances into the bladder wall, activation of sensory nerves, and smooth muscle damage. Mast cells may mediate the process, but their role is unclear.

**Symptoms and Signs**

Interstitial cystitis is initially asymptomatic, but symptoms appear and worsen over years as the bladder wall is damaged. Suprapubic and pelvic pressure or pain occurs, usually with urinary frequency (up to 60 times/day) or urgency. These symptoms worsen as the bladder fills and diminish when patients void; in
some people, symptoms worsen during ovulation, menstruation, seasonal allergies, physical or emotional stress, or sexual intercourse. Foods with high K content (eg, citrus fruits, chocolate, caffeinated drinks, tomatoes) may cause exacerbations. Tobacco, alcohol, and spicy foods may worsen symptoms. If the bladder wall becomes scarred, bladder compliance and capacity decrease, causing urinary urgency and frequency.

**Diagnosis**

- Clinical
- Cystoscopy

Diagnosis is suggested by symptoms after testing has excluded more common disorders that cause similar symptoms (eg, UTIs, pelvic inflammatory disease, chronic prostatitis or prostatodynia, diverticulitis). Cystoscopy is necessary and sometimes reveals benign bladder (Hunner's) ulcers; biopsy is required to exclude bladder cancer. Assessment of symptoms with a standardized symptom scale or during intravesical KCl infusion (K sensitivity testing) may improve diagnostic accuracy but is not yet routine practice.

**Treatment**

- Diet modification
- Bladder training
- Drugs (eg, pentosan, tricyclic antidepressants, NSAIDs, dimethyl sulfoxide instillation)
- Surgery as last resort

Up to 90% of patients improve with treatment, but cure is rare. Treatment should involve avoidance of tobacco, alcohol, foods with high K content, and spicy foods as well as bladder training, drugs, intravesical therapies, and surgery as needed. Stress reduction and biofeedback (to strengthen pelvic floor muscles, eg, with Kegel exercises) may help. No treatment has been proved effective, but a combination of ≥ 2 nonsurgical treatments is recommended before surgery is considered.

The most commonly used drug is pentosan, a heparin similar to urothelial glycosaminoglycan; doses of 100 mg po tid may help restore the bladder's protective surface lining. Improvement may not be noticed for 2 to 4 mo. Intravesical instillation of 15 mL of a solution containing 100 mg of pentosan or 40,000 units of heparin plus 80 mg of lidocaine and 3 mL of Na bicarbonate may benefit patients unresponsive to oral drugs. Tricyclic antidepressants (eg, imipramine 25 to 50 mg po once/day) and NSAIDs in standard doses may relieve pain. Antihistamines (eg, hydroxyzine 10 to 50 mg once before bedtime) may help by directly inhibiting mast cells or by blocking allergic triggers.

Dimethyl sulfoxide instilled into the bladder through a catheter and retained for 15 min may deplete substance P and trigger mast cell granulation; 50 mL q 1 to 2 wk for 6 to 8 wk, repeated as needed, relieves symptoms in up to one half of patients. Intravesical instillation of BCG and hyaluronic acid are under study.

Bladder hydrodistention, cystoscopic resection of a Hunner's ulcer, and sacral nerve root (S3) stimulation help some patients.

Surgery (eg, partial cystectomy, bladder augmentation, neobladder, and urinary diversion) is a last resort for patients with intolerable pain refractory to all other treatments. Outcome is unpredictable; in some patients, symptoms persist.
Chapter 231. Obstructive Uropathy

Introduction

(Urinary Tract Obstruction)

Obstructive uropathy is structural or functional hindrance of normal urine flow, sometimes leading to renal dysfunction (obstructive nephropathy). Symptoms, less likely in chronic obstruction, are pain radiating to the T11 to T12 dermatomes, anuria, nocturia, or polyuria. Diagnosis is based on results of bladder catheterization, ultrasonography, CT, cystourethroscopy, cystourethrography, or pyelography, depending on the level of obstruction. Treatment, depending on cause, may require prompt drainage, instrumentation, surgery (e.g., endoscopy, lithotripsy), hormonal therapy, or a combination of these modalities.

Each year about 2/1000 people in the US are hospitalized for obstructive uropathy. The condition has a bimodal distribution. In childhood, it is due mainly to congenital anomalies of the urinary tract. Incidence then declines until after age 60, when incidence rises, particularly in men because of the increased incidence of benign prostatic hyperplasia (BPH) and prostate cancer. Overall, obstructive uropathy is responsible for about 4% of end-stage renal disease. Hydronephrosis is found at postmortem examination in 2 to 4% of patients.

Etiology

Many conditions can cause obstructive uropathy, which may be acute or chronic, partial or complete, and unilateral or bilateral (see Table 231-1). In children, the most common causes are anatomic abnormalities (including urethral valves or strictures and stenosis at the ureterovesical or ureteropelvic junction). In young adults, the most common cause is a calculus. In older adults, the most common causes are BPH or prostate cancer, retroperitoneal or pelvic tumors, and calculi. Obstruction may occur at any level, from the renal tubules (casts, crystals) to the external urethral meatus. Proximal to the obstruction, effects may include increased intraluminal pressure, urinary stasis, UTI, or calculus formation (which may also cause obstruction). Obstruction is much more common in males, but acquired and congenital urethral strictures and meatal stenosis occur in both males

Table 231-1. Causes of Obstructive Uropathy

and females. In females, urethral obstruction may occur secondary to a tumor or as a result of stricture formation after radiation therapy, surgery, or urologic instrumentation (usually repeated dilation).

Pathophysiology

Pathologic findings consist of dilation of the collecting ducts and distal tubules and chronic tubular atrophy with little glomerular damage. Dilation takes 3 days from the onset of obstructive uropathy to develop; before then, the collecting system is relatively noncompliant and less likely to dilate. Obstructive uropathy without dilation can also occur when fibrosis or a retroperitoneal tumor encases the collecting systems, when obstructive uropathy is mild and renal function is not impaired, and in the presence of an intrarenal pelvis.

Obstructive nephropathy: Obstructive nephropathy is renal dysfunction (renal insufficiency, renal failure, or tubulointerstitial damage) resulting from urinary tract obstruction. The mechanism involves, among many factors, increased intratubular pressure, local ischemia, and, often, UTI. Obstruction may result in type 1 renal tubular acidosis due to reduced distal hydrogen secretion probably because of a defect in the hydrogen ion transporter. In this case, Na wasting can occur and predispose to ECF volume depletion. If obstruction is bilateral, nephropathy may result in renal insufficiency. Renal insufficiency may rarely occur when obstruction is unilateral because autonomic-mediated vascular or ureteral spasm may affect the functioning kidney.

Symptoms and Signs
Symptoms and signs vary with the site, degree, and rapidity of onset of obstructive uropathy.

Pain is common when obstruction acutely distends the bladder, collecting system (ie, the ureter plus the renal calyces), or renal capsule. Upper ureteral or renal pelvic lesions cause flank pain or tenderness, whereas lower ureteral obstruction causes pain that may radiate to the ipsilateral testis or labia. The distribution of kidney and ureteral pain is usually along T11 to T12. Acute complete ureteral obstruction (eg, an obstructing ureteral calculus) may cause severe pain accompanied by nausea and vomiting. A large fluid load (eg, from beer drinking or osmotic diuresis due to an IV contrast agent) causes dilation and pain if urine production increases to a level greater than the flow rate through the area of obstruction. Pain is typically minimal or absent with partial or slowly developing obstructive uropathy (eg, congenital ureteropelvic junction obstruction, pelvic tumor). Hydronephrosis may occasionally produce a palpable flank mass, particularly in massive hydronephrosis of infancy and childhood.

Urine volume does not diminish in unilateral obstruction unless it occurs in the only functioning kidney. Absolute anuria occurs with complete obstruction at the level of the bladder or urethra. Partial obstruction at that level may cause difficulty voiding or abnormalities of the urine stream. In partial obstruction, urine output is often normal and is rarely increased. Increased urine output with polyuria and nocturia occur if the ensuing nephropathy causes impaired renal concentrating capacity and Na reabsorption. Long-standing nephropathy may also result in hypertension.

Infection complicating obstruction may cause dysuria, pyuria, urinary urgency and frequency, referred kidney and ureteral pain, costovertebral angle tenderness, fever, and, occasionally, septicemia.

**Diagnosis**

- Urinalysis and serum electrolytes, BUN, and creatinine
- Bladder catheterization, sometimes followed by cystourethroscopy and voiding cystourethrography for suspected urethral obstruction
- Imaging for suspected ureteral or more proximal obstruction or for hydronephrosis without apparent obstruction

Obstructive uropathy should be considered in patients with any of the following:

- Diminished or absent urine output
- Unexplained renal insufficiency
- Pain that suggests distention in the urinary tract
- A pattern of oliguria or anuria alternating with polyuria

The history may suggest symptoms of BPH, prior cancer, or urolithiasis. Because early relief of obstruction usually achieves the best outcome, diagnosis should be as rapid as possible.

Urinalysis and serum chemistries (serum electrolytes, BUN, creatinine) should be obtained. Other tests are done depending on symptoms and suspected level of obstruction. Infection with urinary obstruction requires immediate evaluation and treatment.

In an asymptomatic patient with longstanding obstructive uropathy, urinalysis may be normal or reveal only a few casts, WBCs, or RBCs. In a patient with acute renal failure who has a normal urinalysis, bilateral obstructive nephropathy should be considered.

If serum chemistries indicate renal insufficiency, obstruction is probably bilateral and severe or complete. Other findings in bilateral obstruction with nephropathy may include hyperkalemia. Hyperkalemia may result from type 1 renal tubular acidosis due to decreased hydrogen ion and K secretion by distal
segments of the nephron.

**Evaluation of suspected urethral obstruction:** If urine output is diminished or if there is a distended bladder or suprapubic pain, bladder catheterization should be done. If catheterization results in a normal flow of urine or if the catheter is difficult to pass, a urethral obstruction (eg, prostatic enlargement, stricture, or valve) is suspected. Patients with such findings should have cystourethroscopy along with voiding cystourethrography.

**Voiding cystourethrography** shows nearly all bladder neck and urethral obstructions as well as vesicoureteral reflux, adequately displaying the anatomy and the volume of urine left in the bladder after voiding (postvoiding residual volume).

If symptoms of urethral obstruction are absent or if cystourethroscopy and voiding cystourethrography show no obstruction, the site of obstruction is presumed to be at the ureters or proximal to them.

**Evaluation of ureteral or more proximal obstruction:** Patients undergo imaging tests to detect the presence and site of obstruction. The choice and sequencing of tests depend on the clinical scenario.

**Abdominal ultrasonography** is the initial imaging test of choice in most patients without urethral abnormalities because it avoids potential allergic and toxic complications of contrast agents and allows assessment of associated renal parenchymal atrophy. Ultrasonography is aimed at detection of hydronephrosis. However, the false-positive rate is 25% if only minimal criteria (visualization of the collecting systems) are considered in the diagnosis. Also, absence of hydronephrosis (and false-negative results) can occur if obstruction is early (in the first few days) or mild or if retroperitoneal fibrosis or tumor encases the collecting system, preventing dilation of the ureter.

**CT** is sensitive for diagnosing obstructive nephropathy and is used when obstruction cannot be shown by ultrasonography or by intravenous urography. Unenhanced helical CT is the modality of choice. It is particularly accurate for obstruction due to ureteral calculi. The combination of ultrasonography, plain abdominal x-ray, and, if necessary, CT reveals obstructive uropathy in > 90% of patients, but ultrasonography and CT may not be able to differentiate hydronephrosis from multiple renal or parapelvic cysts.

**Duplex Doppler ultrasonography** can usually show unilateral obstructive uropathy in the first few days of acute obstruction before the collecting system dilates by detecting an increased resistive index (a reflection of increased renal vascular resistance) in the affected kidney. This modality is less useful in obesity and in bilateral obstruction, which cannot be distinguished from intrinsic renal disease.

**IVU** (contrast urography, intravenous pyelography [IVP], excretory urography) has been largely superseded by CT and MRI (with or without contrast). However, when CT cannot identify the level of obstructive uropathy and when acute obstructive uropathy is thought to be caused by calculi, sloughed papilla, or a blood clot, IVU or retrograde pyelography may be indicated.

**Antegrade or retrograde pyelography** is preferred to studies that involve vascular administration of contrast agents in the azotemic patient. Retrograde studies are done through a cystoscope, whereas antegrade studies require placement of a catheter percutaneously into the renal pelvis. Patients with intermittent obstruction should be studied when they are having symptoms; otherwise, the obstruction may be missed.

**Radionuclide scans** also require some renal function but can detect obstruction without the use of contrast agents. When a kidney is assessed as nonfunctioning, a radionuclide scan can determine perfusion and identify functional renal parenchyma. Because this test cannot detect specific areas of obstruction, it is mainly used in conjunction with diuresis renography to evaluate hydronephrosis without apparent obstruction.

**MRI** can be used when avoiding ionizing radiation is important (eg, in young children or pregnant women). However, it is not superior in accuracy to ultrasonography or CT.
Evaluation of hydronephrosis without apparent obstruction: Testing may be necessary to determine whether back or flank pain is caused by obstruction in patients who have hydronephrosis but no obvious obstruction revealed by other imaging tests. Testing may also be done to detect otherwise unrecognized obstruction in patients with incidentally recognized hydronephrosis.

In diuresis renography, a loop diuretic (eg, furosemide 0.5 mg/kg IV) is given before a radionuclide renal scan (or an IVU). The patient must have sufficient renal function to respond to the diuretic. If obstruction is present, the rate of washout of the radionuclide (or contrast agent) from the time the tracer appears in the renal pelvis is reduced to a half-life of > 20 min (normal is < 15 min). If the renogram is negative or equivocal but the patient is symptomatic, a perfusion pressure flow study is done via percutaneous insertion of a catheter into the dilated renal pelvis, followed by fluid perfusion into the pelvis at 10 mL/min. The patient is in a prone position. If obstructive uropathy is present, in spite of the marked increase in urine flow, the rate of washout of the radionuclide during renal scanning is delayed, and there will be further dilation of the collecting system on IVU and elevation of the renal pelvic pressure to > 22 mm Hg during perfusion. A renogram or perfusion study that causes pain similar to the patient's initial complaint is interpreted as positive. If the perfusion study is negative, the pain probably has a nonrenal cause. False-positive and false-negative results are common for both tests.

Prognosis

Most obstruction can be corrected, but a delay in therapy can lead to irreversible renal damage. How long it takes for nephropathy to develop and how reversible nephropathy is vary depending on the underlying pathology, the presence or absence of UTI, and the degree and duration of the obstruction. In general, acute renal failure due to a ureteral calculus is reversible, with adequate return of renal function. With chronic progressive obstructive uropathy, renal dysfunction may be partially or completely irreversible. Prognosis is worse if UTI remains untreated.

Treatment

• Relief of obstruction

Treatment consists of eliminating the obstruction by surgery, instrumentation (eg, endoscopy, lithotripsy), or drug therapy (eg, hormonal therapy for prostate cancer). Prompt drainage in hydronephrosis is indicated if renal function is compromised, UTI persists, or pain is uncontrollable or persistent. Lower obstructive uropathy may require catheter or more proximal drainage. Indwelling pigtail ureteral catheters can be placed for acute or long-term drainage in selected patients. Temporary drainage using a percutaneous technique may be needed in severe obstructive uropathy, UTI, or calculi. Intensive treatment for UTI and renal failure is imperative.

In the case of hydronephrosis without evident obstruction, surgery should be considered if the patient has pain and a positive diuretic renogram. However, no therapy is necessary in an asymptomatic patient with a negative diuretic renogram or with a positive diuretic renogram but normal renal function.
Chapter 232. Urinary Calculi

Introduction

(Nephrolithiasis; Stones; Urolithiasis)

Urinary calculi are solid particles in the urinary system. They may cause pain, nausea, vomiting, hematuria, and, possibly, chills and fever from secondary infection. Diagnosis is based on urinalysis and radiologic imaging, usually noncontrast helical CT. Treatment is with analgesics, antibiotics for infection, and, sometimes, extracorporeal shock wave lithotripsy or endoscopic procedures.

About 1/1000 adults in the US is hospitalized annually because of urinary calculi, which are also found in about 1% of all autopsies. Up to 12% of men and 5% of women will develop a urinary calculus by age 70. Calculi vary from microscopic crystalline foci to calculi several centimeters in diameter. A large calculus, called a staghorn calculus, can fill an entire renal calyceal system.

Etiology

About 85% of calculi in the US are composed of Ca, mainly Ca oxalate (see Table 232-1); 10% are uric acid; 2% are cystine; and the remainder are Mg ammonium phosphate (struvite).

General risk factors include disorders that increase urinary salt concentration, either by increased excretion of Ca or uric acid salts, or by decreased excretion of urine or citrate.

For Ca calculi, risk factors vary by population. The main risk factor in the US is hypercalciuria, a hereditary condition present in 50% of men and 75% of women with Ca calculi; thus, patients with a family history of calculi are at increased risk of recurrent calculi. These patients have normal serum Ca but elevated urinary Ca: > 250 mg/day (> 6.2 mmol/day) in men and > 200 mg/day (> 5.0 mmol/day) in women. Hypocitruria (urinary citrate < 350 mg/day [1820 μmol/day]), present in about 40 to 50% of Ca calculi-formers, promotes Ca calculi formation because citrate normally binds urinary Ca and inhibits the crystallization of Ca salts. About 5 to 8% of calculi are caused by renal tubular acidosis. About 1 to 2% of patients with Ca calculi have primary hyperparathyroidism. Rare causes are sarcoidosis, vitamin D intoxication, hyperthyroidism, multiple myeloma, metastatic cancer, and hyperoxaluria. Hyperoxaluria (urinary oxalate > 40 mg/day [> 440 μmol/day]) can be primary or caused by excess ingestion of oxalate-containing foods (eg, rhubarb, spinach, cocoa, nuts, pepper, tea) or by excess oxalate absorption due to various enteric diseases (eg, bacterial overgrowth syndromes, chronic pancreatic or biliary disease) or ileojejunal surgery. Other risk factors include taking high doses of vitamin C, a Ca-restricted diet (possibly because dietary Ca binds dietary oxalate), and mild hyperuricosuria. Mild hyperuricosuria, defined as urinary uric acid > 800 mg/day (> 5 mmol/day) in men or > 750 mg/day (> 4 mmol/day) in women, is almost always caused by excess intake of purine (in proteins, usually from meat, fish, and poultry); it may cause Ca oxalate calculus formation. Uric acid calculi develop with increased urine acidity (urine pH < 5.5), or rarely with severe hyperuricosuria (urinary uric acid > 1500 mg/day (> 9 mmol/day)), which crystallizes undissociated uric acid. Uric acid crystals may comprise the entire calculus or, more commonly, provide a nidus on which Ca or mixed Ca and uric acid calculi can form.

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Cystine calculi occur only in the presence of cystinuria (see p. 2990).

Mg ammonium phosphate calculi (struvite, infection calculi) indicate the presence of a UTI caused by urea-splitting bacteria (eg, Proteus sp, Klebsiella sp). The calculus must be treated as infected foreign bodies and removed in their entirety. Unlike other types of calculi, Mg ammonium phosphate calculi occur 3 times
Pathophysiology

Urinary calculi may remain within the renal parenchyma or renal pelvis or be passed into the ureter and bladder. During passage, calculi irritate the ureter and may become lodged, obstructing urine flow and causing hydronephrosis. Common areas of lodgment include the ureteropelvic junction, the distal ureter (at the level of the iliac vessels), and the ureterovesical junction. Typically, a calculus must have a diameter > 5 mm to become lodged. Calculi ≤ 5 mm are likely to pass spontaneously.

Even partial obstruction causes decreased glomerular filtration, which may persist briefly after the calculus has passed. With hydronephrosis and elevated glomerular pressure, renal blood flow declines, further worsening renal function. Generally, however, permanent renal dysfunction occurs only after about 28 days of complete obstruction.

Secondary infection can occur with longstanding obstruction, but most patients with Ca-containing calculi do not have infected urine.

Symptoms and Signs

Even large calculi remaining in the renal parenchyma or renal pelvis are usually asymptomatic unless they cause obstruction. Symptoms, such as severe pain, often accompanied by nausea and vomiting, and sometimes gross hematuria, usually occur when calculi pass into the ureter, cause obstruction, or both. Pain (renal colic) is of variable intensity but is typically excruciating and intermittent, often occurs cyclically, and lasts 20 to 60 min. Nausea and vomiting are common. Pain in the flank or kidney area that radiates across the abdomen suggests upper ureteral or renal pelvic obstruction. Pain that radiates along the course of the ureter into the genital region suggests lower ureteral obstruction. Suprapubic pain along with urinary urgency and frequency suggests a distal ureteral, ureterovesical, or bladder calculus.

On examination, patients may be in obvious extreme discomfort, often ashen and diaphoretic. Patients with renal colic may be unable to lie still and may pace, writhe, or constantly shift position. The abdomen may be somewhat tender on the affected side as palpation increases pressure in the already-distended ureter, but peritoneal signs (guarding, rebound, rigidity) are lacking. For some patients, the first symptom is hematuria or either gravel or a calculus in the urine. Other patients may have symptoms of a UTI, such as fever, dysuria, or cloudy or foul-smelling urine.

Diagnosis

• Clinical differential diagnosis

• Urinalysis

• Imaging

• Determination of calculus composition

The symptoms and signs suggest the diagnosis. With peritonitis (eg, due to appendicitis, ectopic pregnancy, or pelvic inflammatory disease), pain is usually constant, and patients lie still because movement worsens pain. Patients often have rebound tenderness or rigidity. Cholecystitis may cause colicky pain, usually in the epigastrium or right upper quadrant, often with Murphy's sign. Bowel obstruction may cause colicky abdominal pain and vomiting, but the pain is usually bilateral and not located primarily in the flank or along the ureter. Pancreatitis may cause upper abdominal pain and vomiting, but the pain is usually constant, may be bilateral, and is usually not along the flank or ureter. With most of these disorders, urinary symptoms are uncommon and other symptoms may suggest which organ system is actually involved (eg, vaginal discharge or bleeding in pelvic disorders among females). Dissecting aortic aneurysm must be considered, particularly in the elderly, because, if a renal artery is affected, it can cause hematuria, pain that radiates along a ureteral distribution, or both. Other
considerations in the general evaluation of acute abdominal pain are discussed elsewhere (see p. 106).

Patients suspected of having a calculus causing colic require urinalysis and usually an imaging study. If calculus is confirmed, evaluation of the underlying disorder, including calculus composition testing, is required.

**Urinalysis:** Macroscopic or microscopic hematuria is common, but urine may be normal despite multiple calculi. Pyuria with or without bacteria may be present. Pyuria suggests infection, particularly if combined with suggestive clinical findings, such as foul-smelling urine or a fever. A calculus and various crystalline substances may be present in the sediment. If so, further testing is usually necessary because the composition of the calculus and crystals cannot be determined conclusively by microscopy. The only exception is when typical hexagonal crystals of cystine are found in a concentrated, acidified specimen, confirming cystinuria.

**Imaging tests:** Noncontrast helical CT should be done. This study can detect the location of a calculus as well as the degree of obstruction. Moreover, helical CT may also reveal another cause of the pain (eg, aortic aneurysm). For patients who have recurrent calculi, cumulative radiation exposure from multiple CT scans is a concern. For patients with typical symptoms, ultrasonography or plain abdominal x-rays can usually confirm presence of a calculus with minimal or no radiation exposure.

Although most urinary calculi are demonstrable on plain x-ray, neither their presence nor their absence obviates the need for more definitive imaging, so this study can be avoided. Both renal ultrasonography and intravenous urography (IVU) can identify calculi and hydronephrosis, but ultrasonography is less sensitive for small calculi in patients without hydronephrosis, and IVU is time consuming and exposes the patient to the risk of IV contrast agents; these studies are generally used if helical CT is unavailable.

**Identifying the cause:** The calculus is obtained by straining the urine (or, if necessary, during operative removal) and sent to the laboratory for crystallography. Some calculi are brought in by patients. Urine specimens that show microscopic crystals can also be sent for crystallography. Patients with a single Ca calculus without additional risk factors for calculi require only urinalysis and plasma Ca concentration on 2 occasions to exclude hyperparathyroidism. Predisposing factors, such as a high-protein diet or vitamin C or D supplements, should be sought. Patients with a strong family history of calculi, conditions that might predispose to calculus formation (eg, sarcoidosis, bone metastases, multiple myeloma), or conditions that would make it difficult to treat calculi (eg, solitary kidney, urinary tract anomalies) require evaluation for all possible causative disorders and risk factors. This evaluation should include serum electrolytes, uric acid, and Ca on 2 separate occasions. Follow-up determination of parathyroid hormone levels is done if necessary. Urine tests should include routine urinalysis and 2 separate 24-h urine collections for urine volume, pH, and excretion of Ca, uric acid, citrate, oxalate, Na, and creatinine.

**Treatment**

- Analgesia

- Facilitate calculus passage (eg, with α-receptor blockers or Ca channel blockers)

- For persistent or infection-causing calculi, removal using extracorporeal shock wave lithotripsy or endoscopic techniques

**Analgesia:** Renal colic may be relieved with opioids, such as morphine and, for a rapid onset, fentanyl. Ketorolac 30 mg IV is rapidly effective and nonsedating. Vomiting usually resolves as pain decreases, but persistent vomiting can be treated with an antiemetic (eg, ondansetron 10 mg IV).

**Facilitating calculus passage:** Although increasing fluids (either oral or IV) has traditionally been recommended, it has not been proved to speed the passage of calculi. Patients with calculi with a diameter of < 1 cm who have no infection or obstruction, whose pain is controlled with analgesics, and who can tolerate liquids can be treated at home with analgesics and with α-receptor blockers (eg, tamsulosin 0.4 mg po once/day) or Ca channel blockers to facilitate calculus passage. Calculi that have not passed within 6 wk typically require removal. In patients with infection and obstruction, calculi should
be removed as soon as possible.

**Calculus removal:** The technique used for removal depends on the location and size of the calculi. Techniques include extracorporeal shock wave lithotripsy and endoscopic techniques. Endoscopic techniques may involve rigid or flexible scopes and may involve direct-vision removal (basketing), fragmentation with some sort of lithotripsy (eg, pneumatic, electrohydraulic, laser), or both. For symptomatic calculi < 1 cm in diameter in the renal pelvis or proximal ureter, extracorporeal shock wave lithotripsy is a reasonable first option for therapy. For larger calculi or if lithotripsy is unsuccessful, ureteroscopy (done in a retrograde fashion) with holmium laser lithotripsy is usually used. Sometimes removal is possible using an endoscope inserted anterograde through the kidney. For midureteral calculi, ureteroscopy with holmium laser lithotripsy is usually the treatment of choice. Shock wave lithotripsy is an alternative. For distal ureteral calculi, endoscopic techniques, such as direct removal and use of lithotripsy (eg, pneumatic, electro-hydraulic, laser), are considered by many as the procedures of choice. Shock wave lithotripsy can also be used.

**Calculus dissolution:** Uric acid calculi in the upper or lower urinary tract occasionally may be dissolved by prolonged alkalinization of the urine with K citrate 20 mEq po bid to tid, but chemical dissolution of other calculi is not possible.

**Prevention**

In a patient who has passed a first Ca calculus, the likelihood of forming a 2nd calculus is about 15% at 1 yr, 40% at 5 yr, and 80% at 10 yr. Recovery and analysis of the calculus, measurement of calculus-forming substances in the urine, and the clinical history are needed to plan prophylaxis. In < 3% of patients, no metabolic abnormality is found. These patients seemingly cannot tolerate normal amounts of calculus-forming salts in their urine without crystallization. Thiazide diuretics, K citrate, and increased fluid intake may reduce their calculus production rate.

For hypercalciuria, patients may receive thiazide diuretics (eg, chlorthalidone 25 mg po once/day or indapamide 1.25 mg po once/day) to lower urine Ca excretion and thus prevent urinary supersaturation with Ca oxalate. Patients are encouraged to increase their fluid intake to ≥ 3 L/day. A diet that is low in Na and high in K is recommended. Restriction of dietary animal protein is also recommended.

For patients with hypocitruria, K citrate (20 mEq bid) enhances citrate excretion. A normal Ca intake is recommended, and Ca restriction is avoided. Oral orthophosphate has not been thoroughly studied.

**Hyperoxaluria** prevention varies. Patients with small-bowel disease can be treated with a combination of high fluid intake, Ca loading (usually in the form of Ca citrate 400 mg po bid), cholestyramine, and a low-oxalate, low-fat diet. Hyperoxaluria may respond to pyridoxine 5 to 500 mg po once/day, possibly by increasing transaminase activity, because this activity is responsible for the conversion of glyoxylate, the immediate oxalate precursor, to glycine.

In hyperuricosuria, intake of meat, fish, and poultry should be reduced. If the diet cannot be changed, allopurinol 300 mg each morning lowers uric acid production. For uric acid calculi, the urine pH must be increased to between 6 and 6.5 by giving an oral alkalinizing drug that contains K (eg, K citrate 20 mEq bid) along with increased fluid intake.

Infection with urea-splitting bacteria requires culture-specific antibiotics and complete removal of all calculi. If eradication of infection is impossible, long-term suppressive therapy (eg, with nitrofurantoin) may be necessary. In addition, acetohydroxamic acid can be used to reduce the recurrence of struvite calculi.

To prevent recurrent cystine calculi, urinary cystine levels must be reduced to < 250 mg cystine/L of urine. Any combination of increasing urine volume along with reducing cystine excretion (eg, with α-mercaptopropionylglycine or penicillamine) should reduce the urinary cystine concentration.
Chapter 233. Urinary Tract Infections

Introduction

Urinary tract infections (UTIs) can be divided into upper tract infections, which involve the kidneys, and lower tract infections, which involve the bladder, urethra, or prostate. However, in practice, and particularly in children, differentiating between the sites may be difficult or impossible. Moreover, infection often moves from one area to the other.

Most UTIs are caused by enteric bacteria. The remainder are due to sexually transmitted pathogens (see p. 1466), mycobacteria (see p. 1302), fungi (see pp. 1318 and 2380), viruses, and parasites. The predominant parasitic causes of UTIs are filariasis, trichomoniasis, leishmaniasis, malaria, and schistosomiasis. These parasitic diseases are discussed in other chapters of THE MANUAL. Of the parasitic diseases, only trichomoniasis is common in the US. Adenoviruses are implicated in hemorrhagic cystitis.

Bacterial Urinary Tract Infections

(See also Ch. 135 and Prostatitis on p. 2462.)

Bacterial UTIs can involve the urethra, prostate, bladder, or kidneys. Symptoms may be absent or include urinary frequency and urgency, dysuria, lower abdominal pain, and flank pain. Systemic symptoms and even sepsis may occur with kidney infection. Diagnosis is based on analysis and culture of urine. Treatment is with antibiotics.

Among adults aged 20 to 50 yr, UTIs are about 50-fold more common in women. The incidence increases in patients > 50 yr, but the female:male ratio decreases because of the increasing frequency of prostate disease.

Pathophysiology

The urinary tract, from the kidneys to the urethral meatus, is normally sterile and resistant to bacterial colonization despite frequent contamination of the distal urethra with colonic bacteria. Mechanisms that maintain the tract's sterility include urine acidity, emptying of the bladder at micturition, ureterovesical and urethral sphincters, and various immunologic and mucosal barriers.

About 95% of UTIs occur when bacteria ascend the urethra to the bladder and, in the case of acute uncomplicated pyelonephritis, ascend the ureter to the kidney. The remainder of UTIs are hematogenous. Systemic infection can result from UTI, particularly in the elderly. About 6.5% of cases of hospital-acquired bacteremia are attributable to UTI.

Complicated UTI is considered to be present when there are underlying factors that predispose to ascending bacterial infection. Predisposing factors include urinary instrumentation (eg, catheterization, cystoscopy), anatomic abnormalities, and obstruction of urine flow or poor bladder emptying. A common consequence of anatomic abnormality is vesicoureteral reflux (VUR), which is present in 30 to 45% of young children with symptomatic UTI (see p. 2844). VUR is usually caused by a congenital defect that results in incompetence of the ureterovesical valve. It is most often due to a short intramural segment (the ureter normally transits the bladder wall at an angle; the resultant lengthy segment is more readily closed by muscular contraction than the shorter segment that occurs when the ureter passes straight through the wall). VUR can also be acquired in patients with a flaccid bladder due to spinal cord injury. Other anatomic abnormalities predisposing to UTI include urethral valves (a congenital obstructive abnormality), delayed bladder neck maturation, bladder diverticulum, and urethral duplications. Urine flow can be compromised by calculi and tumors. Bladder emptying can be impaired by neurogenic dysfunction (see p. 2363), pregnancy, uterine prolapse, cystocele, and prostatic enlargement. UTI caused by congenital factors presents most commonly in childhood. Most other factors are more common in the elderly.

Uncomplicated UTI occurs without underlying abnormality or impairment of urine flow. It is most common in young women but also somewhat common in younger men who have unprotected anal intercourse, an
uncircumcised penis, unprotected intercourse with a woman whose vagina is colonized with urinary pathogens, or AIDS. Risk factors in women include sexual intercourse, diaphragm and spermicide use, antibiotic use, and a history of recurrent UTIs. Even use of spermicide-coated condoms increases risk of UTI in women. The increased risk of UTI in women using antibiotics or spermicides probably occurs because of alterations in vaginal flora that allow overgrowth of \textit{Escherichia coli}. In elderly women, soiling of the perineum due to fecal incontinence increases risk. Patients of both sexes with diabetes have an increased incidence and severity of infections.

**Etiology**

Commensal colonic gram-negative aerobic bacteria cause most bacterial UTIs. In relatively normal tracts, strains of \textit{E. coli} with specific attachment factors for transitional epithelium of the bladder and ureters are the most frequent causes. The remaining gram-negative urinary pathogens are other enterobacteria, especially \textit{Klebsiella, Proteus mirabilis}, and \textit{Pseudomonas aeruginosa}. Enterococci (group D streptococci) and coagulase-negative staphylococci (eg, \textit{Staphylococcus saprophyticus}) are the most frequently implicated gram-positive organisms.

\textit{E. coli} causes > 75% of community-acquired UTIs in all age groups; \textit{S. saprophyticus} accounts for about 10%. In hospitalized patients, \textit{E. coli} accounts for about 50% of cases. The gram-negative species \textit{Klebsiella, Proteus, Enterobacter}, and \textit{Serratia} account for about 40%, and the gram-positive bacterial cocci \textit{Enterococcus faecalis} and \textit{S. saprophyticus} and \textit{S. aureus} account for the remainder.

**Classification**

**Urethritis:** Infection of the urethra with bacteria (or with protozoa, viruses, or fungi) occurs when organisms that gain access to it acutely or chronically colonize the numerous periurethral glands in the bulbous and pendulous portions of the male urethra and in the entire female urethra. The sexually transmitted pathogens \textit{Chlamydia trachomatis} (see p. 1468), \textit{Neisseria gonorrhoeae} (see p. 1471), \textit{Trichomonas vaginalis} (see p. 1481), and herpes simplex virus (see p. 1417) are common causes in both sexes.

**Cystitis:** In women, sexual intercourse usually precedes uncomplicated cystitis (honeymoon cystitis). In men, bacterial infection of the bladder is usually complicated and generally results from ascending infection from the urethra or prostate or is secondary to urethral instrumentation. The most common cause of recurrent cystitis in men is chronic bacterial prostatitis.

**Acute urethral syndrome:** Acute urethral syndrome, which occurs in women, causes dysuria and pyuria (dysuria-pyuria syndrome) due to bacterial urinary pathogens. Occasionally, it is caused by \textit{N. gonorrhoeae}, TB, or fungal disease or by trauma or inflammation of the urethra. Patients with acute urethral syndrome have dysuria, frequency, and pyuria, but urine cultures are either negative or show colony counts that are < 10^5/mL, which is less than the traditional criterion for bacterial UTI.

**Asymptomatic bacteriuria:** Certain patients, primarily elderly women and patients with diabetes or those who require long-term use of indwelling catheters, have persistent bacteriuria with changing flora that is both asymptomatic and refractory to treatment. WBC count in urine may be modestly elevated. Most of these patients are best left untreated because the usual result of treatment is the establishment of highly resistant organisms. Asymptomatic bacteriuria can also occur in pregnant women and may cause infection of the urinary tract, sepsis, low birth weight, spontaneous abortion, premature delivery (see p. 2650), and stillbirth, so treatment is indicated.

**Acute pyelonephritis:** Pyelonephritis is bacterial infection of the kidney parenchyma. The term should not be used to describe tubulointerstitial nephropathy unless infection is documented. In women, about 20% of community-acquired bacteremias are due to pyelonephritis. Pyelonephritis is uncommon in men with a normal urinary tract.

Although obstruction (eg, strictures, calculi, tumors, neurogenic bladder, VUR) predisposes to pyelonephritis, most women with pyelonephritis have no demonstrable functional or anatomic defects.
Cystitis alone or anatomic defects may cause reflux. This tendency is greatly enhanced when ureteral peristalsis is inhibited (e.g., during pregnancy, by obstruction, by endotoxins of gram-negative bacteria). Pyelonephritis or focal abscess may be due to hematogenous spread, which is infrequent and usually results from bacteremia with virulent bacilli (e.g., *Salmonella* sp, *S. aureus*). Pyelonephritis is common in young girls and in pregnant women after instrumentation or bladder catheterization.

The kidney usually is enlarged because of inflammatory PMNs and edema. Infection is focal and patchy, beginning in the pelvis and medulla and extending into the cortex as an enlarging wedge. Chronic inflammatory cells appear within a few days, and medullary and subcortical abscesses may develop. Normal parenchymal tissue between foci of infection is common. Papillary necrosis may be evident in acute pyelonephritis associated with diabetes, obstruction, sickle cell disease, pyelonephritis in renal transplants, pyelonephritis due to candidiasis, or analgesic nephropathy. Although acute pyelonephritis is frequently associated with renal scarring in children, similar scarring in adults is not detectable in the absence of reflux or obstruction.

**Symptoms and Signs**

In the elderly, UTIs are often asymptomatic. Elderly patients, and those with a neurogenic bladder or an indwelling catheter, may present with sepsis and delirium but without symptoms referable to the urinary tract.

When symptoms are present, they may not correlate with the location of the infection within the urinary tract because there is considerable overlap; however, some generalizations are useful.

In **urethritis**, the main symptoms are dysuria and, primarily in males, urethral discharge. Discharge tends to be purulent when due to *N. gonorrhoeae* and whitish and mucoid when not.

**Cystitis** onset is usually sudden, typically with frequency, urgency, and burning or painful voiding of small volumes of urine. Nocturia, with suprapubic and often low back pain, is common. The urine is often turbid, and gross hematuria occurs in about 30% of patients. A low-grade fever may develop. Pneumaturia (passage of air in the urine) can occur when infection results from a vesicoenteric or vesicovaginal fistula or from emphysematous cystitis.

In **acute pyelonephritis**, symptoms may be the same as those of cystitis; one third of patients have frequency and dysuria. However, with pyelonephritis, symptoms typically include chills, fever, flank pain, colicky abdominal pain, nausea, and vomiting. If abdominal rigidity is absent or slight, a tender, enlarged kidney is sometimes palpable. Costovertebral angle percussion tenderness is generally present on the infected side. In children, symptoms often are meager and less characteristic (see p. 2845).

**Diagnosis**

- Urinalysis
- Sometimes urine culture

Diagnosis by culture is not always necessary. If done, diagnosis by culture requires demonstration of significant bacteriuria in properly collected urine.

**Urine collection**: If a sexually transmitted disease (STD) is suspected, a urethral swab for STD testing is obtained prior to voiding. Urine collection is then by clean-catch or catheterization.

To obtain a **clean-catch, midstream-voided specimen**, the urethral opening is washed with a mild, nonfoaming disinfectant and air dried. Contact of the urinary stream with the mucosa should be minimized by spreading the labia in women and by pulling back the foreskin in uncircumcised men. The first 5 mL of urine is not captured; the next 5 to 10 mL is collected in a sterile container.

A **specimen obtained by catheterization** is preferable in older women (who typically have difficulty...
obtaining a clean-catch specimen) and in women with vaginal bleeding or discharge. Many clinicians also use catheterization to obtain a specimen if evaluation includes a pelvic examination. Diagnosis in patients with indwelling catheters is discussed elsewhere (see p. 2378).

**Urine testing: Microscopic examination** of urine is useful but not definitive. Pyuria is defined as ≥ 8 WBCs/µL of uncentrifuged urine, which corresponds to 2 to 5 WBCs/high-power field in spun sediment. Most truly infected patients have > 10 WBCs/µL. The presence of bacteria in the absence of pyuria, especially when several strains are found, is usually due to contamination during sampling. Microscopic hematuria occurs in up to 50% of patients, but gross hematuria is uncommon. WBC casts, which require special stains to differentiate from renal tubular casts, indicate only an inflammatory reaction; they can be present in pyelonephritis, glomerulonephritis, and noninfective tubulointerstitial nephritis.

**Dipstick tests** also are commonly used. A positive nitrite test on a freshly voided specimen (bacterial replication in the container renders results unreliable if the specimen is not tested rapidly) is highly specific for UTI, but the test is not very sensitive. The leukocyte esterase test is very specific for the presence of > 10 WBCs/µL and is fairly sensitive. In adult women with uncomplicated UTI with typical symptoms, most clinicians consider positive microscopic and dipstick tests sufficient; in these cases, given the likely pathogens, cultures are unlikely to change treatment but add significant expense.

**Cultures** are recommended when symptoms are suggestive but urinalysis is nondiagnostic; for complicated UTI, including UTI in patients with diabetes, immunosuppression, recent hospitalization or urethral instrumentation, or recurrent UTI; for patients > 65 yr; and perhaps for patients with symptoms of pyelonephritis. All prepubertal children should have a urine culture when a UTI is suspected. Urine should be cultured as soon as possible or stored at 4°C if a delay of > 10 min is expected. Samples contaminated with large numbers of epithelial cells are unlikely to be helpful. An uncontaminated specimen should be obtained for culture. Criteria, based on the guidelines of the Infectious Diseases Society of America, for bacteriuria are:

- Among women with suspected asymptomatic bacteriuria, 2 consecutive clean-catch voided specimens from which the same bacterial strain is isolated in colony counts of > 10⁵/mL.
- Among women with suspected acute urethral syndrome, a clean-catch voided specimen from which a single bacterial species is isolated in colony counts from 10² to 10⁴/mL.
- Among men, a clean-catch voided specimen from which a single bacterial species is isolated in colony counts > 10⁵/mL.
- Among women or men, a catheter-obtained specimen from which a single bacterial species is isolated in colony counts of > 10²/mL.

Occasionally, UTI is present despite lower colony counts, possibly because of prior antibiotic therapy, very dilute urine (sp gr < 1.003), or obstruction to the flow of grossly infected urine. Repeating the culture improves the diagnostic accuracy of a positive result, ie, may differentiate between a contaminant and a true positive result.

**Infection localization:** Clinical differentiation between upper and lower UTI is impossible in many patients, and testing is not usually advisable. When the patient has high fever, costovertebral angle tenderness, and gross pyuria with casts, pyelonephritis is highly likely. The best noninvasive technique for differentiating bladder from kidney infection appears to be the response to a short course of antibiotic therapy. If the urine has not cleared after 3 days of treatment, pyelonephritis should be sought.

Symptoms similar to those of cystitis and urethritis can occur with vaginitis, which may cause dysuria from the passage of urine across inflamed labia. Vaginitis can often be distinguished by the presence of vaginal discharge, vaginal odor, and dyspareunia.

**Other testing:** Seriously ill patients require evaluation for sepsis, typically with CBC, electrolytes, BUN, creatinine, and blood cultures. Patients with abdominal pain or tenderness are evaluated for other causes.
of an acute abdomen (see p. 106). Pyuria without bacteriuria can be present with appendicitis, inflammatory bowel disease, and other extrarenal disorders.

Most adults do not require assessment for structural abnormalities unless infections recur or are complicated, nephrolithiasis is suspected, there is painless hematuria or new renal insufficiency, or fever persists for ≥ 72 h. Imaging choices include ultrasonography, CT, and IVU. Occasionally, voiding cystourethrography, retrograde urethrography, or cystoscopy is warranted. Urologic investigation is not routinely needed in women with symptomatic or asymptomatic recurrent cystitis, because findings do not influence therapy. Children with UTI often require imaging (see p. 2846).

**Treatment**

- Antibiotics
- Occasionally surgery (eg, to drain abscesses, correct underlying structural abnormalities, or relieve obstruction)

All forms of bacterial UTI require antibiotics. Obstructive uropathy, anatomic abnormalities, and neuropathic urinary tract lesions such as compression of the spinal cord usually require surgical correction. Catheter drainage of an obstructed urinary tract aids in prompt control of UTI. Occasionally, a renal cortical abscess or perinephric abscess requires surgical drainage. Instrumentation of the lower urinary tract in the presence of infected urine should be deferred if possible. Sterilization of the urine before instrumentation and antibiotic therapy for 3 to 7 days after instrumentation can prevent life-threatening urosepsis. For patients with troublesome dysuria, phenazopyridine may help control symptoms until the antibiotics do (usually within 48 h).

**Urethritis:** Sexually active patients with symptoms are usually treated presumptively for STDs pending test results. A typical regimen is ceftriaxone 125 mg IM plus either azithromycin 1 g po once or doxycycline 100 mg po bid for 7 days. For non-STD urethritis in men, trimethoprim/sulfamethoxazole (TMP/SMX) or a fluoroquinolone is given for 10 to 14 days; women are treated with a regimen for cystitis.

**Cystitis:** A 3-day oral course of TMP/SMX or a fluoroquinolone effectively treats acute cystitis and eradicates potential bacterial pathogens in vaginal and GI reservoirs. Single-dose therapy results in higher recurrence rates and is not recommended. Longer courses of therapy (7 to 14 days) are prescribed for patients with a history of recent UTI, diabetes mellitus, or symptoms lasting > 1 wk.

If pyuria but not bacteriuria is present in a sexually active woman, then *C. trachomatis* urethritis is diagnosed presumptively, and appropriate treatment is given to the patient and her sex partner. If symptoms recur and culture reveals an organism sensitive to the drugs used for 3-day antibiotic therapy or if pyelonephritis is suspected, a 14-day course of TMP/SMX or a fluoroquinolone is given as for pyelonephritis.

**Acute urethral syndrome:** Acute urethral syndrome with pyuria is treated with doxycycline 100 mg po bid for 7 to 10 days or TMP/SMX 160/800 mg po bid for 3 days. If neither pyuria nor bacteriuria is present, antibiotics are not indicated. A course of urinary analgesics may be appropriate.

**Asymptomatic bacteriuria:** Ordinarily, asymptomatic bacteriuria in patients with diabetes, elderly patients, or patients with chronically indwelling bladder catheters should not be treated. However, asymptomatic bacteriuria in pregnant women is actively sought and treated as a symptomatic UTI, although many antibiotics cannot be safely used. Oral β-lactams, sulfonamides, and nitrofurantoin are considered safe in early pregnancy, but sulfonamides should be avoided near parturition because of a possible role in the development of kernicterus.

Treatment may also be indicated in asymptomatic UTI in patients with neutropenia, patients with recent renal transplantation, patients scheduled for instrumentation of the urinary tract (after removal of a bladder catheter that has been in place for > 1 wk), young children with gross VUR, and patients with frequent UTI symptoms from a struvite calculus that cannot be removed. Therapy typically consists of an appropriate antibiotic (based on culture results) for 3 to 14 days or long-term suppressive therapy for
untreatable obstructive problems (eg, calculi, reflux).

**Acute pyelonephritis:** Outpatient treatment with oral antibiotics is possible if the patient is reliable in following medical advice and is immunocompetent and has no nausea or vomiting, signs of volume depletion, or evidence of septicemia. Typical regimens are 14 days of TMP/SMX 160/800 mg po bid or ciprofloxacin 500 mg po bid. Otherwise, patients should be hospitalized and given parenteral therapy selected on the basis of local sensitivity patterns of the most common strains. Common regimens include ampicillin plus gentamicin, TMP/SMX and a fluoroquinolone, and broad-spectrum cephalosporins (eg, ceftriaxone). Aztreonam, β-lactam/β-lactam inhibitor combinations (ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam), and imipenem/cilastatin are generally reserved for patients with more complicated pyelonephritis (eg, obstruction, calculi, resistant bacteria, hospital-acquired infection) or recent urinary tract instrumentation. If parenteral therapy is required, it is continued until defervescence and other signs of clinical improvement occur. In > 80% of patients, improvement occurs within 72 h. Oral therapy can then begin, and the patient can be discharged for the remainder of the 14-day treatment course. For complicated cases, prolonged antibiotic suppression may be needed as well as urologic correction of anatomic defects.

When pyelonephritis is diagnosed during pregnancy, hospitalization and parenteral therapy with a β-lactam with or without an aminoglycoside is appropriate.

**Prevention**

In women who experience ≥ 3 UTIs/yr, voiding immediately after sexual intercourse and avoiding use of a diaphragm may be helpful. Drinking cranberry juice (50 mL of concentrate or about 300 mL of juice daily) reduces pyuria and bacteriuria. Increasing total fluid intake may also help.

If these techniques are unsuccessful, low-dose oral antibiotic prophylaxis greatly reduces the incidence of recurrent UTIs—eg, TMP/SMX 40/200 mg once/day or 3 times/wk, nitrofurantoin (macrocrystals) 50 or 100 mg once/day, or a fluoroquinolone (eg, ciprofloxacin, ofloxacin, lomefloxacin, enoxacin). Long-term use of nitrofurantoin increases the risk of adverse effects and is contraindicated in patients with renal failure. Postcoital TMP/SMX or a fluoroquinolone may be effective. If UTI recurs after 6 mo of this therapy, prophylaxis may be reinstituted for 2 or 3 yr.

Because of potential injury to a fetus, users of fluoroquinolones should also use effective contraception. Some antibiotics (macrolides, tetracyclines, rifampin, metronidazole, penicillins, and TMP/SMX) interfere with the effectiveness of oral contraceptives by interrupting the enterohepatic recycling of estrogen or by inducing hepatic estrogen metabolism. Women who use oral contraceptives should use barrier contraceptives while they are taking these antibiotics.

In pregnant women, effective prophylaxis of UTI is similar to that in nonpregnant women. Appropriate patients include those with acute pyelonephritis during a pregnancy, patients with > 1 episode (despite treatment) of UTI or bacteriuria during pregnancy, and patients who required prophylaxis for recurrent UTI before pregnancy.

In postmenopausal women, antibiotic prophylaxis is similar to that described previously. Additionally, topical estrogen therapy markedly reduces the incidence of recurrent UTI in women with atrophic vaginitis or atrophic urethritis.

**Bacterial Urinary Tract Infections in Patients With Indwelling Bladder Catheters**

Patients with indwelling bladder catheters are predisposed to bacteriuria and UTIs. Symptoms may be vague or may suggest sepsis. Diagnosis depends on the presence of symptoms. Testing includes urinalysis and culture after the catheter has been removed and a new one inserted. The most effective preventive measures are avoiding unnecessary catheterization and removing catheters as soon as possible.

Bacteria can enter the bladder with the insertion of the catheter, through the catheter lumen, or from around the outside of the catheter. A biofilm develops around the outside of the catheter and on the
uroepithelium. Bacteria enter this biofilm, which protects them from the mechanical flow of urine, host defenses, and antibiotics, making bacterial elimination difficult. Even with thoroughly aseptic catheter care, the chance of developing significant bacteriuria every day the catheter is indwelling is 3 to 10%. Of patients who develop bacteriuria, 10 to 25% develop symptoms of UTI. Fewer develop symptoms of sepsis. Risk factors for UTI include duration of catheterization, female sex, diabetes mellitus, opening a closed system, and suboptimal aseptic techniques. Indwelling bladder catheters can also predispose to fungal UTI (see p. 2380).

UTI can also develop in women during the days after a catheter has been removed.

**Symptoms and Signs**

Patients with UTI who have indwelling catheters may not have symptoms typical of UTIs. Symptoms of lower tract UTI in patients with indwelling catheters may be caused by obstruction of the catheter, development of bladder stones, and periurinary tract infections. Symptoms of acute or chronic pyelonephritis may also develop without the typical urinary tract symptoms. Patients may have nonspecific symptoms such as malaise, fever, flank pain, anorexia, and sepsis with fever, altered mental status, decreased BP, and tachypnea.

**Diagnosis**

- Urinalysis and urine culture for patients with symptoms or at high risk of sepsis

Testing is done only in patients who have symptoms, because treatment of asymptomatic bacteriuria is not recommended except for patients at high risk of developing sepsis, such as patients with granulocytopenia, organ transplant patients taking immunosuppressants, pregnant women, and patients undergoing urologic surgery. Diagnostic testing includes urinalysis and urine culture. If bacteremia is suspected, blood cultures are done. Urine cultures should be taken by a direct needle stick of the catheter with aseptic technique, so that contamination of the specimen is minimized. Pyuria tends to predict bacteriuria but not necessarily symptoms of UTI or bacteremia, so whether to treat is a clinical decision.

Women who have had a catheter removed should receive urine culture within 48 h regardless of whether symptoms occur.

**Treatment**

- Antibiotics

Treatment includes antibiotics and supportive measures. A 14-day course of a fluoroquinolone is a reasonable empiric choice, depending on local resistance patterns. Antibiotic choice should be modified by the results of urine or blood culture and sensitivity testing. Asymptomatic women and men with recent catheter removal who have UTI diagnosed by urine culture should be treated based on the culture results.

**Prevention**

The most effective preventive measures are avoiding catheterization and removing catheters as soon as possible. Optimizing aseptic technique and maintaining a closed drainage system also reduce risk. Routine, periodic catheter replacement is not recommended. Routine use of prophylactic antibiotics is controversial: Fluoroquinolones may slightly decrease bacteriuria and symptomatic UTIs, although this finding is not firmly established. A recent study has shown a decrease in UTI using catheters impregnated with nitrofurazone in trauma patients. However, most patients with bacteriuria do not develop symptoms, and bacteriuria develops almost inevitably when antibiotics are stopped.

**Chronic Pyelonephritis**

*(Chronic Infective Tubulointerstitial Nephritis)*
Chronic pyelonephritis is chronic pyogenic infection of the kidney that occurs almost exclusively in patients with major anatomic abnormalities. Symptoms include fever, malaise, and flank pain. Diagnosis is with urinalysis, culture, and imaging tests. Treatment is with antibiotics and correction of any structural disorders.

Reflux of infected urine into the renal pelvis is the usual mechanism. Causes include obstructive uropathy, struvite calculi, and, most commonly, VUR.

Pathologically there is atrophy and calyceal deformity with overlying parenchymal scarring. The disease may progress to renal failure. Chronic pyelonephritis causes about 2 to 3% of end-stage renal disease. Patients with chronic pyelonephritis may have residual foci of infection that may predispose to bacteremia or, among kidney transplant patients, seed the urinary tract and transplanted kidney.

Xanthogranulomatous pyelonephritis (XPN) is an unusual variant that typically occurs in middle-aged women with a history of recurrent UTIs. It is a complication of obstruction due to renal calculi and is typically associated with Proteus infections. The kidney is enlarged, and perirenal fibrosis and adhesions to adjacent retroperitoneal structures are common. The disease is almost always unilateral and appears to represent an abnormal inflammatory response to infection. Giant cells, lipid-laden macrophages, and cholesterol clefts account for the yellow color of the infected tissue. The disease may also occur in children.

Symptoms and Signs

Symptoms and signs are often vague and inconsistent. Some patients have fever, flank or abdominal pain, malaise, or anorexia. In XPN, a unilateral renal mass can usually be palpated.

Diagnosis

• Urinalysis and urine culture

• Imaging

Chronic pyelonephritis is suspected in patients with a history of recurrent UTIs and acute pyelonephritis. However, most patients, except for children with VUR, do not have such a history. Sometimes the diagnosis is suspected because typical findings are incidentally noted on an imaging study. Symptoms, because they are vague and nonspecific, may not suggest the diagnosis.

Urinalysis and urine culture and usually imaging tests are done. On urinalysis, proteinuria is absent, minimal, or intermittent even when renal scarring is far advanced. Urinary sediment is usually scant, but renal epithelial cells, granular casts, and occasionally WBC casts are present. When both kidneys are involved, defects in concentrating ability and hyperchloremic acidosis may appear before significant azotemia occurs. Urine culture may be sterile or positive for gram-negative organisms.

Initial imaging is usually with ultrasonography or helical CT. The hallmark of chronic pyelonephritis (usually with reflux or obstruction) on imaging is classically a large, deep, segmental, coarse cortical scar usually extending to one or more of the renal calyces. The upper pole is the most common site. Initially, renal cortex is lost and the renal parenchyma thins. Uninvolved renal tissue may hypertrophy locally with segmental enlargement in patients with chronic pyelonephritis. Ureteral dilatation may be present, reflecting the changes induced by chronic severe reflux. Similar changes can occur with urinary tract TB (see p. 1312). Other studies are not done routinely.

In XPN, urinalysis and urine culture indicate the presence of infection, but diagnosis is confirmed by radiologic examination. CT can exclude renal carcinoma and other lesions and is preferred over IVU. Blood tests reveal nonspecific findings including anemia and mild liver dysfunction.

Prognosis
The course of chronic pyelonephritis is extremely variable, but the disease typically progresses very slowly. Most patients have adequate renal function for ≥ 20 yr after onset. Frequent exacerbations of acute pyelonephritis, although controlled, usually further deteriorate renal structure and function. Continued obstruction predisposes to or perpetuates pyelonephritis and increases intrapelvic pressure, which damages the kidney directly.

**Treatment**

If obstruction cannot be eliminated and recurrent UTIs are common, long-term therapy with antibiotics (eg, TMP/SMX, trimethoprim, a fluoroquinolone, nitrofurantoin) is useful and may be required indefinitely. Complications of uremia or hypertension must be treated appropriately.

For XPN, an initial course of antibiotics should be given to control local infection, followed by en bloc nephrectomy with removal of all involved tissue and closure of any fistulas.

Patients undergoing renal transplantation who have chronic pyelonephritis may require nephrectomy before the transplant.

**Fungal Urinary Tract Infections**

**Fungal infections of the urinary tract primarily affect the bladder and kidneys.**

Species of *Candida*, the most common cause, are normal commensals in humans. *Candida* colonization differs from infection in that infection produces tissue reaction. All invasive fungi (eg, *Cryptococcus neoformans*, *Aspergillus* sp, *Mucoraceae* sp, *Histoplasma capsulatum*, *Blastomyces* sp, *Coccidioides immitis*) may infect the kidneys as part of systemic or disseminated mycotic infection (see p. 1318). Their presence alone indicates infection.

**Lower UTI** with *Candida* usually occurs with urinary catheters, typically after bacteriuria and antibiotic therapy, although candidal and bacterial infections frequently occur simultaneously. *C. albicans* prostatitis occurs infrequently in patients with diabetes, usually after instrumentation.

**Renal candidiasis** is usually spread hematogenously and commonly originates from the GI tract. Ascending infection is possible and occurs mainly in patients with nephrostomy tubes, other permanent indwelling devices, and stents. At high risk are patients who are immunocompromised because of tumor, AIDS, chemotherapy, or immunosuppressants. A major source of candidemia in such high-risk hospitalized patients is an in-dwelling intravascular catheter. Renal transplantation increases the risk because of the combination of indwelling catheters, stents, antibiotics, anastomotic leaks, obstruction, and immunosuppressive therapy.

**Complications** of candidal infection can include emphysematous cystitis or pyelonephritis and fungus balls in the renal pelvis, ureter, or bladder. Bezoars may form in the bladder. Lower or upper tract obstruction may occur. Papillary necrosis and intrarenal and perinephric abscesses may form. Although renal function often declines, severe renal failure is rare without postrenal obstruction.

**Symptoms and Signs**

Most patients with candiduria are asymptomatic. Whether *Candida* can cause urethral symptoms (mild urethral itching, dysuria, watery discharge) in men is uncertain. Rarely, dysuria in women is caused by candidal urethritis, but it may result from the urine coming into contact with periurethral tissue that is inflamed due to candidal vaginitis.

Among **lower UTIs**, cystitis due to *Candida* may result in frequency, urgency, dysuria, and suprapubic pain. Hematuria is common, and, in patients with poorly controlled diabetes, pneumaturia due to emphysematous cystitis has occurred. Fungus balls or bezoars may cause symptoms of urethral obstruction.

With **renal candidiasis** that is hematogenously spread, most patients lack symptoms referable to the
kidney but may have antibiotic-resistant fever, candiduria, and unexplained deteriorating renal function. Fungus ball elements in the ureter and renal pelvis frequently cause hematuria and urinary obstruction. Occasionally, papillary necrosis or intrarenal or perinephric abscesses cause pain, fever, hypertension, and hematuria. Patients may have manifestations of candidiasis in other sites (eg, CNS, skin, eyes, liver, spleen).

**Diagnosis**

- Urine culture
- Evidence of tissue reaction (in cystitis) or pyelonephritis

*Candida* UTI is considered in patients with predisposing factors and symptoms suggesting UTI and in all patients with candidemia. *Candida* should be suspected in men with symptoms of urethritis only when all other causes of urethritis have been excluded.

Diagnosis of *Candida* UTI is by culture, usually from urine. The level at which candiduria reflects true *Candida* UTI and not merely colonization or contamination is unknown. Differentiating *Candida* colonization from infection requires evidence of tissue reaction.

**Cystitis** is usually diagnosed in high-risk patients with candiduria by the presence of bladder inflammation or irritation, as evidenced by pyuria. Cystoscopy and ultrasonography of the kidney and bladder may help detect bezoars and obstruction.

**Renal candidiasis** is considered in patients with fever, candiduria, or passage of fungus balls. Severe renal failure suggests postrenal obstruction. Imaging of the urinary tract may help reveal the degree of involvement. Blood cultures for *Candida* are often negative.

Unexplained candiduria should prompt evaluation of the urinary tract for structural abnormalities.

**Treatment**

- Only for symptomatic or high-risk patients
- Antifungal drugs

Fungal colonization of catheters does not require treatment. Asymptomatic candiduria rarely requires therapy. Candiduria should be treated in the following:

- Symptomatic patients
- Neutropenic patients
- Patients with renal allografts
- Patients who are undergoing urologic manipulation

Urinary stents and Foley catheters should be removed (if possible). Treatment with fluconazole (200 mg po once/day for 7 to 14 days) and with IV amphotericin B (see p. 1319) has been successful. In the absence of renal insufficiency, flucytosine (25 mg/kg po qid) may help eradicate candiduria due to non-albicans species of *Candida*; however, resistance may emerge rapidly when this compound is used alone. Bladder irrigation with amphotericin B may transiently clear candiduria but is rarely indicated. Even with apparently successful local or systemic antifungal therapy for candiduria, relapse is frequent, and this likelihood is increased by continued use of a urinary catheter.

In patients with **renal candidiasis**, IV amphotericin B and high-dose oral fluconazole (≥ 400 mg/day) are equally effective in the primary treatment of invasive infection with *C. albicans* and *C. tropicalis*. Even when amphotericin B is used initially, oral fluconazole should be substituted early in the course of
treatment. However, some less common *Candida* species are not susceptible to fluconazole.
Chapter 234. Cystic Kidney Disease

Introduction

Cystic kidney disease may be congenital or acquired. Congenital disorders may be inherited as autosomal dominant disorders or autosomal recessive disorders or have other causes (eg, sporadic mutations, chromosomal abnormalities, teratogens). Some are part of a malformation syndrome—see Table 234-1.

Acquired Renal Cysts

Acquired renal cysts are simple cysts that must be distinguished from more serious causes of cystic disease.

Acquired cysts are usually simple, ie, they are round and sharply demarcated with smooth walls. They may be solitary or multiple.

**Solitary cysts:** Isolated cysts are most often detected incidentally on imaging studies; they are distinguished from other cystic renal disorders and renal masses, such as renal cell carcinoma, which is typically irregular or multiloculated with irregular walls, septae, and areas of unclear demarcation. Their cause is unknown. They are generally clinically insignificant but rarely can cause hematuria or become infected.

**Multiple cysts:** Multiple cysts are most common in patients with chronic kidney disease, especially patients undergoing dialysis. Cause is unknown, but the cysts may be due to compensatory hyperplasia of residually functioning nephrons. Usual criterion for diagnosis is ≥ 4 cysts in each kidney detected with ultrasonography or CT. Multiple acquired cysts (acquired cystic disease) can usually be differentiated from autosomal dominant polycystic kidney disease by the absence of family history and by small or normal-sized kidneys.

Acquired cysts are usually asymptomatic, but occasional patients develop hematuria, renal or perirenal hemorrhage, infection, or flank pain. Acquired cysts are significant mainly because patients have a higher incidence of renal cell carcinoma; whether the cysts become malignant is unknown. For this reason, some physicians periodically screen patients with acquired cysts for renal carcinoma using ultrasonography or CT. Cysts that cause persistent bleeding or infection may require percutaneous drainage or, rarely, partial or complete nephrectomy.

Congenital Renal Cystic Dysplasia

Congenital renal cystic dysplasia is a broad category of congenital malformations involving metanephric malformation or congenital obstructive uropathies.

Congenital renal cystic dysplasia affects one or both kidneys. Renal cystic dysplasia may be an isolated congenital anomaly, or it may be part of a malformation syndrome (ie, associated with other clinical features—see Table 234-1). Associated urologic abnormalities may include ureteropelvic and urerovesiculureteral junction obstruction, neurogenic bladder, ureterocele, posterior urethral valves, and prune-belly syndrome (a triad of abdominal wall muscle defects, urinary tract abnormalities [eg, dilated ureters, enlarged bladder and urethra], and bilateral cryptorchidism—see p. 2988).

Symptoms and signs vary by how much renal parenchyma is preserved and whether involvement is unilateral or bilateral. Some degree of renal insufficiency or renal failure may develop. Congenital renal cystic dysplasia is commonly discovered by ultrasonography prenatally or during early childhood.

Prognosis is highly unpredictable due to an inability to quantify residual functional parenchyma. Treatment is surgical correction of any associated GU abnormalities and, if renal insufficiency or renal
failure is present, renal replacement therapy.

**Medullary Sponge Kidney**

Medullary sponge kidney is formation of diffuse, bilateral medullary cysts caused by abnormalities in pericalyceal terminal collecting ducts.

The cause of medullary sponge kidney is unknown, but genetic transmission occurs in < 5% of cases.

Most patients are asymptomatic, and the disorder usually remains undiagnosed. It predisposes to calculus formation and UTI, so the most common presenting symptoms are the following:

- Renal colic
- Hematuria
- Dysuria

Medullary sponge kidney is benign, and long-term prognosis is excellent. Obstruction by renal calculi may transiently reduce GFR and increase serum creatinine.

**Diagnosis**

- CT or IVU

The diagnosis is suspected in patients with recurrent calculi or UTIs or on the basis of incidental radiographic findings. Urinalysis typically shows evidence of incomplete distal renal tubular acidosis (overt metabolic acidosis is rare) and decreased urine-concentrating ability in patients without symptomatic polyuria.

Diagnosis is generally confirmed by CT, but IVU can be used. Ultrasonography is not helpful because cysts are small and located deep in the medulla.

**Treatment**

Treatment is indicated only for UTIs and for recurrent calculus formation. Thiazide diuretics (eg, hydrochlorothiazide 25 mg po bid) and high fluid intake inhibit calculus formation and may reduce incidence of obstructive complications in patients with recurrent calculi.

**Nephronophthisis and Medullary Cystic Kidney Disease Complex**

Nephronophthisis and medullary cystic kidney disease are inherited disorders that cause cysts restricted to the renal medulla or corticomedullary border and, eventually, end-stage renal disease.

Nephronophthisis and medullary cystic kidney disease are grouped together because they share many features. Pathologically, they cause cysts restricted to the renal medulla or corticomedullary border, as well as a triad of tubular atrophy, tubular basement membrane disintegration, and interstitial fibrosis. They probably share similar mechanisms, although these are not well characterized. Features of both disorders include the following:

- An ADH (vasopressin)-resistant urine-concentrating defect that leads to polyuria and polydipsia
- Na wasting severe enough to require supplementation
- Anemia
- A tendency toward mild proteinuria and a benign urinary sediment
• Eventually, end-stage renal disease

Key differences between nephronophthisis and medullary cystic kidney disease include inheritance patterns and age at onset of chronic kidney disease.

**Nephronophthisis**

Inheritance is autosomal recessive. Nephronophthisis accounts for up to 15% of chronic kidney disease with renal failure in children and young adults (< 20 yr). There are 3 types: infantile (median age at onset 1 yr), juvenile (median age at onset 13 yr), and adolescent (median age at onset 19 yr).

Nine gene mutations have been identified in patients with nephronophthisis. Mutations of the NPHP1 gene are the most common, identified in about 30 to 60% of patients. About 10% of patients with nephronophthisis also have other manifestations, including retinitis pigmentosa, hepatic fibrosis, intellectual disability, and other neurologic abnormalities.

End-stage renal disease often develops during childhood and causes growth retardation and bone disease. However, in many patients, these problems develop slowly over years and are so well compensated for that they are not recognized as abnormal until significant uremic symptoms appear. Hypertension sometimes develops.

**Diagnosis**

- Imaging, genetic testing, or both

The diagnosis should be suspected in children with the following, particularly if the urinary sediment is benign:

- Polydipsia and polyuria
- Progressively decreasing renal function, particularly without hypertension
- Associated extrarenal findings

Proteinuria is usually absent. Diagnosis is confirmed by imaging, but cysts often occur only late in disease. Ultrasonography, CT, or MRI may show smooth renal outlines with normal-sized or small kidneys, loss of corticomedullary differentiation, and multiple cysts at the corticomedullary junction. Hydronephrosis is typically absent. Genetic testing is available.

**Treatment**

- Supportive care

In early disease, treatment involves management of hypertension, electrolyte and acid-base disorders, and anemia. Children with growth retardation may respond to nutritional supplements and growth hormone therapy. Ultimately, all patients develop renal failure and require dialysis or transplantation.

**Medullary Cystic Kidney Disease**

Inheritance is autosomal dominant. The disease affects people in their 30s through 70s. There are 2 types, which differ by median age at onset (type 1, 62 yr; type 2, also known as familial juvenile hyperuricemic nephropathy, 32 yr) and by genetic mutation (type 1 is localized to chromosome 1; type 2, to chromosome 16). About 15% of patients have no family history, suggesting a sporadic new mutation. Hypertension is common. Hyperuricemia and gout are the only extrarenal manifestations; they tend to develop early in type 2 and late in type 1. End-stage renal disease typically develops at age 30 to 50.

Medullary cystic kidney disease should be suspected in patients with the following, particularly if the
urinary sediment is benign:

- Polydipsia and polyuria
- Gout at a young age
- Family history of gout and chronic kidney disease

Mild proteinuria is possible. Results of imaging studies have many similarities to that of nephronophthisis; however, renal medullary cysts are only sometimes visible. Genetic testing can confirm the diagnosis of type 2. Kidney biopsy may be necessary for diagnosis of type 1.

Treatment is generally similar to that of nephronophthisis. Allopurinol can help control gout.

**Autosomal Dominant Polycystic Kidney Disease**

Polycystic kidney disease (PKD) is a hereditary disorder of renal cyst formation causing gradual enlargement of both kidneys, sometimes with progression to renal failure. Almost all forms are caused by a familial genetic mutation. Symptoms and signs include flank and abdominal pain, hematuria, and hypertension. Diagnosis is by CT or ultrasonography. Treatment is symptomatic before renal failure and with dialysis or transplantation afterward.

**Etiology**

Inheritance of PKD is autosomal dominant or recessive; sporadic cases occur rarely. Autosomal dominant polycystic kidney disease (ADPKD) has an incidence of 1/1000 and accounts for about 5% of patients with end-stage renal disease requiring replacement therapy. Clinical manifestations are rare before adulthood, but penetrance is essentially complete; all patients ≥ 80 yr have some signs. In contrast, autosomal recessive PKD is rare; incidence is 1/10,000. It frequently causes renal failure during childhood (see p. 2982).

In 86 to 96% of cases, ADPKD is caused by mutations in the \textit{PKD1} gene on chromosome 16, which codes for the protein polycystin 1; most other cases are caused by mutations in the \textit{PKD2} gene on chromosome 4, which codes for polycystin 2. A few familial cases are unrelated to either locus.

**Pathophysiology**

Polycystin 1 may regulate tubular epithelial cell adhesion and differentiation; polycystin 2 may function as an ion channel, with mutations causing fluid secretion into cysts. Mutations in these proteins may alter the function of renal cilia, which enable tubular cells to sense flow rates. A leading hypothesis proposes that tubular cell proliferation and differentiation are linked to flow rate and that ciliary dysfunction may thus lead to cystic transformation.

Early in the disorder, tubules dilate and slowly fill with glomerular filtrate. Eventually, the tubules separate from the functioning nephron and fill with secreted rather than filtered fluid, forming cysts. Hemorrhage into cysts may occur, causing hematuria; patients are also at higher risk of acute pyelonephritis and urinary calculi (in 20%). Vascular sclerosis and interstitial fibrosis eventually develop via unknown mechanisms and typically affect < 10% of tubules; nonetheless, renal failure develops in about 35 to 45% of patients by age 60.

**Extrarenal manifestations** are common:

- Most patients have hepatic cysts, which typically do not affect liver function.
- Patients also have a higher incidence of pancreatic and intestinal cysts, colonic diverticula, and inguinal and abdominal wall hernias.
- Valvular heart disorders (most often mitral valve prolapse and aortic regurgitation) can be detected by
cardiac ultrasonography in 25 to 30% of patients; other valvular disorders may be due to collagen abnormalities.

• Aortic regurgitation results from aortic root dilation due to arterial wall changes (including aortic aneurysm).

• Coronary artery aneurysms occur.

• About 4% of young adults and up to 10% of elderly patients have cerebral aneurysms. Aneurysms rupture in 65 to 75% of patients, usually before age 50; risk factors include family history of aneurysm or rupture, larger aneurysms, and poorly controlled hypertension.

Symptoms and Signs

ADPKD usually causes no symptoms initially; one half of patients remain asymptomatic, never develop renal insufficiency or failure, and are never diagnosed. Most patients who develop symptoms do so by the end of their 20s. Symptoms include low-grade flank, abdominal, and lower back pain due to cystic enlargement and symptoms of infection. Acute pain, when it occurs, is usually due to hemorrhage into cysts or passage of a calculus; fever is common with acute pyelonephritis. Hepatic cysts may cause right upper quadrant pain if they enlarge or become infected. Valvular disorders rarely cause symptoms but occasionally cause heart failure and require valvular replacement. Symptoms and signs of unruptured cerebral aneurysm can be absent or may include headache, nausea and vomiting, and cranial nerve deficits; these manifestations warrant immediate intervention (see Sidebar 173-1 on p. 1653).

Signs are nonspecific and include hematuria and hypertension (each in about 40 to 50%) and proteinuria (in 20%). Anemia is less common than in other types of chronic renal failure, presumably because erythropoietin production is preserved. In advanced disease, the kidneys may become grossly enlarged and palpable, causing fullness in the upper abdomen and flank.

Diagnosis

• Ultrasonography

• Sometimes CT or MRI or genetic testing

The diagnosis is suspected in patients with the following:

• A positive family history

• Typical symptoms or signs

• Cysts detected incidentally on imaging studies

Patients should be counseled before undergoing diagnostic testing, particularly if they are asymptomatic. For example, many authorities recommend against testing asymptomatic young patients because no disease-modifying treatment is effective at this age and diagnosis has potential negative effects on ability to obtain health insurance and on mood. Diagnosis is usually by imaging, showing extensive cystic changes throughout the kidneys and a moth-eaten appearance due to cysts that displace functional tissue. These changes develop with age and are less often present or obvious in younger patients. Ultrasonography is usually done first. If ultrasonography results are inconclusive, CT or MRI, which are both more sensitive (particularly when done using contrast), is done. Urinalysis, renal function tests, and CBC are done, but results are not specific.

Urinalysis detects mild proteinuria and microscopic or macroscopic hematuria. Gross hematuria may be due to a dislodged calculus or to hemorrhage from a ruptured cyst. Pyuria is common even without bacterial infection. Initially, BUN and creatinine are normal or only mildly elevated, but they slowly increase, especially when hypertension is present. Rarely, CBC detects polycythemia.
Patients with symptoms of cerebral aneurysm require high-resolution CT or magnetic resonance angiography. However, there is no consensus on whether asymptomatic patients should be screened for cerebral aneurysm, at what age, and how often. A reasonable approach is to screen patients with ADPKD and a family history of hemorrhagic stroke or cerebral aneurysm.

**Genetic testing** for PKD mutations is currently reserved for any of the following:

- Patients with suspected PKD and no known family history
- Patients with inconclusive results on imaging
- Younger patients (eg, age < 30, in whom imaging results are often inconclusive) in whom the diagnosis must be made (eg, a potential kidney donor)

Genetic counseling is recommended for 1st-degree relatives of patients with ADPKD.

**Prognosis**

By age 75, 50 to 75% of patients with ADPKD require renal replacement therapy (dialysis or transplantation). Predictors of more rapid progression to renal failure include the following:

- Earlier age at diagnosis
- Male sex
- Sickle cell trait
- *PKD1* genotype
- Larger or rapidly increasing kidney size
- Gross hematuria
- Hypertension

ADPKD does not increase risk of renal cancer, but if patients with ADPKD develop renal cancer, it is more likely to be bilateral. Renal cancer rarely causes death. Patients usually die of heart disease (sometimes valvular), disseminated infection, or ruptured cerebral aneurysm.

**Treatment**

- Control of risk factors
- Supportive measures

Strict BP control is essential. UTIs should be treated promptly. Percutaneous aspiration of cysts may help manage severe pain due to hemorrhage or compression but has no effect on long-term outcome. Nephrectomy is an option to relieve severe symptoms due to massive kidney enlargement (eg, pain, hematuria) or recurrent UTIs. Hemodialysis, peritoneal dialysis, or kidney transplantation is required in patients who develop chronic renal failure. ADPKD does not recur in grafts. With dialysis, patients with ADPKD maintain higher Hb levels than any other group of patients with renal failure.
Chapter 235. Glomerular Disorders

Introduction

Glomerular disorders are classified as those that manifest predominantly with hematuria (nephritic syndrome), high-level proteinuria (nephrotic syndrome), or both. Disorders tend to manifest at different ages (see Table 235-1) although there is much overlap. The disorders may be primary or have secondary causes (see Tables 235-2 and 235-4).

The pathophysiology of nephritic and nephrotic disorders differs substantially, but their clinical overlap is considerable—eg, several disorders may manifest with the same clinical picture—and the presence of hematuria or proteinuria does not itself predict response to treatment or prognosis.

A glomerular disorder is usually suspected when screening or diagnostic testing reveals an elevated serum creatinine level and abnormal urinalysis (hematuria with or without casts, proteinuria, or both). Approach to the patient involves distinguishing predominant-nephritic from predominant-nephrotic features and identifying likely causes by patient age, accompanying illness (see Tables 235-1 and 235-4), and other elements of the history (eg, time course, systemic manifestations, family history).

Renal biopsy is indicated when diagnosis is unclear from history or when histology influences choice of treatment and outcomes (eg, lupus nephritis).

Nephritic Syndrome

Nephritic syndrome is defined by hematuria and the presence of dysmorphic RBCs and RBC casts on microscopic examination of urinary sediment. Often ≥ 1 of the following elements are present: mild to moderate proteinuria, edema, hypertension, elevated serum creatinine, and oliguria. It has both primary and secondary causes. Diagnosis is based on history, physical examination, and sometimes renal biopsy. Treatment and prognosis vary by cause.

Nephritic syndrome is a manifestation of glomerular inflammation (glomerulonephritis [GN]) and occurs at any age. Causes differ by age (see Table 235-1), and mechanisms differ by cause. The syndrome can be acute or chronic and primary (idiopathic) or secondary.

Postinfectious GN is the prototype of acute GN, but the condition may be caused by other glomerulopathies and by systemic disorders such as connective tissue disorders and hematologic dyscrasias (see Table 235-2). Chronic GN has features similar to those of acute GN but develops slowly and may cause mild to moderate proteinuria. Examples include IgA nephropathy and hereditary nephritis.

Hereditary Nephritis

(Alport's Syndrome)

Hereditary nephritis is a genetically heterogenous disorder characterized by hematuria,

impaired renal function, sensorineural deafness, and ocular abnormalities. Cause is a gene mutation affecting type IV collagen. Symptoms and signs are those of nephritic syndrome (ie, hematuria, eventual renal insufficiency) often with sensorineural deafness and, less commonly, ophthalmologic symptoms. Diagnosis is by history, including family history, urinalysis, and biopsy (renal or skin). Treatment is the same as that of chronic kidney disease.

Hereditary nephritis is caused by a mutation in the COL4A5 gene that encodes the α-5 chain of type IV collagen and results in altered type IV collagen strands. The mechanism by which collagen alteration...
causes a glomerular disorder is unknown, but impaired structure and function are presumed; in most families, thickening and thinning of the glomerular and tubular basement membranes occur, with multilamination of the lamina densa in a focal or local distribution. Glomerular scarring and interstitial fibrosis eventually result.

The disorder is most commonly inherited in X-linked fashion, although autosomal recessive varieties exist. There are 2 forms: a juvenile form with onset of renal insufficiency between ages 20 and 30 yr and an adult form with onset of renal insufficiency after age 30.

**Symptoms and Signs**

Because of X-linked transmission, women usually are asymptomatic and have little functional impairment. Most men eventually develop renal symptoms and signs similar to those of acute nephritic syndrome (eg, microscopic hematuria, eventually gross hematuria) and progress to renal insufficiency between ages 20 and 30 (juvenile form).

Sensorineural deafness frequently is present, affecting higher frequencies; it may not be noticed during early childhood. Some men develop renal insufficiency after age 30 (adult form) with deafness that occurs late or is mild. Some patients have sensorineural deafness alone without renal disease but can transmit renal disease to their children.

Ophthalmologic abnormalities—cataracts (most common), anterior lenticonus (a regular conical protrusion on the anterior aspect of the lens due to thinning of the lens capsule), spherophakia (spherical lens deformation that can predispose to lens subluxation), nystagmus, retinitis pigmentosa, blindness—also occur but less frequently than deafness.

Other nonrenal manifestations include polyneuropathy and thrombocytopenia.

**Diagnosis**

- Clinical findings and urinalysis
- Renal biopsy

Diagnosis is suggested in patients who have microscopic hematuria on urinalysis or recurrent episodes of gross hematuria, particularly if an abnormality of hearing or vision or a family history of chronic kidney disease is present.

Urinalysis and usually renal biopsy are done. The urine may contain small amounts of protein, WBCs, and casts of various types. Nephrotic syndrome occurs rarely. No distinguishing histologic changes are seen on light microscopy. The diagnosis can be confirmed by any of the following:

- Renal biopsy with immunostaining for the subtypes of type IV collagen
- Characteristic disorganization of the lamina densa of the glomerular capillary seen using electron microscopy
- Skin biopsy with immunostaining for the type IV collagen subtypes in a patient with a positive family history

A combination of immunostaining and electron microscopy is often needed to distinguish hereditary nephritis from some forms of thin basement membrane disease. Although not yet widely available, molecular techniques for evaluating DNA gene mutations or mRNA may become the diagnostic techniques of choice.
Treatment

• Same as that for other causes of chronic kidney disease

Treatment is indicated only when uremia occurs; its management is the same as that for other causes of chronic kidney disease (see p. 2444). Anecdotal reports suggest that ACE inhibitors or angiotensin II receptor blockers may slow progression of renal disease. Transplantation has been successful. Genetic counseling is indicated.

Immunoglobulin A Nephropathy

IgA nephropathy is deposition of IgA immune complexes in glomeruli, manifesting as slowly progressive hematuria, proteinuria, and, often, renal insufficiency. Diagnosis is based on urinalysis and renal biopsy. Prognosis is generally good. Treatment options include ACE inhibitors, angiotensin II receptor blockers, corticosteroids, immunosuppressants, and ω-3 polyunsaturated fatty acids.

IgA nephropathy is a form of chronic GN characterized by the deposition of IgA immune complexes in glomeruli. It is the most common form of GN worldwide. It occurs at all ages, with a peak onset in the teens and 20s; affects men 2 to 6 times more frequently than women; and is more common in whites and Asians than in blacks. Prevalence estimates for IgA kidney deposits are 5% in the US, 10 to 20% in southern Europe and Australia, and 30 to 40% in Asia. However, some people with IgA deposits do not develop clinical disease.

Cause is unknown, but evidence suggests that there may be several mechanisms, including increased IgA1 production, defective IgA1 glycosylation causing increased binding to mesangial cells, decreased IgA1 clearance, a defective mucosal immune system, and overproduction of cytokines stimulating mesangial cell proliferation. Familial clustering has also been observed, suggesting genetic factors at least in some cases.

Renal function is initially normal, but symptomatic renal disease may develop. A few patients present with acute renal failure or chronic kidney disease, severe hypertension, or nephrotic syndrome.

Symptoms and Signs

The most common manifestation is persistent or recurrent macroscopic hematuria (90% of involved children) or asymptomatic microscopic hematuria with mild proteinuria. Other symptoms are usually not prominent.

Gross hematuria usually begins 1 or 2 days after a febrile mucosal (upper respiratory, sinus, enteral) illness, thus mimicking acute postinfectious glomerulonephritis, except the onset of hematuria is earlier (coinciding with or immediately after the febrile illness). Rapidly progressive GN is the initial manifestation in < 10% of patients.

Diagnosis

• Clinical findings and urinalysis

• Sometimes renal biopsy

Diagnosis is suggested by any of the following:

• Gross hematuria, particularly within 2 days of a febrile mucosal illness or with flank pain

• Incidentally noted findings on urinalysis

• Occasionally, rapidly progressive GN
When manifestations are moderate or severe, diagnosis is confirmed by biopsy.

**Urinalysis** demonstrates microscopic hematuria, usually with dysmorphic RBCs and RBC casts. Mild proteinuria (< 1 g/day) is typical and may occur without hematuria; nephrotic syndrome develops in ≤ 20%. Serum creatinine level is usually normal.

**Renal biopsy** shows granular deposition of IgA and complement (C3) on immunofluorescent staining in an expanded mesangium with foci of segmental proliferative or necrotizing lesions. Importantly, mesangial IgA deposits are nonspecific and also occur in many other disorders, including Henoch-Schönlein purpura, cirrhosis, inflammatory bowel disease, psoriasis, HIV infection, lung cancer, and several connective tissue disorders. Glomerular IgA deposition is a primary feature of Henoch-Schönlein purpura, and the 2 disorders may be indistinguishable based on biopsy specimens, leading to speculation that Henoch-Schönlein purpura may be a systemic form of IgA nephropathy. However, Henoch-Schönlein purpura is clinically distinct from IgA nephropathy, usually manifesting as purpuric rash, arthralgias, and abdominal pain (see p. 321).

Other serum immunologic tests are usually unnecessary. Complement concentrations are usually normal. Plasma IgA concentration may be elevated and circulating IgA-fibronectin complexes are present; however, these findings are not helpful diagnostically.

**Prognosis**

IgA nephropathy usually progresses slowly; renal insufficiency and hypertension develop within 10 yr in 15 to 20% of patients. Progression to end-stage renal disease occurs in 25% of patients after 20 yr. When IgA nephropathy is diagnosed in childhood, prognosis is usually good. However, persistent hematuria invariably leads to hypertension, proteinuria, and renal insufficiency. Risk factors for progressive deterioration in renal function include the following:

- Proteinuria > 500 mg/24 h for > 6 mo
- Elevated creatinine
- Uncontrolled hypertension
- Microscopic hematuria for > 6 mo
- Extensive fibrotic changes in the glomerulus or interstitium
- Crescents on biopsy

**Treatment**

- Often ACE inhibitors or angiotensin II receptor blockers for hypertension, creatinine > 1.2 mg/dL, or urinary protein > 1 g/day
- Corticosteroids and possibly immunosuppressants for progressive disease, urinary protein > 2 g/day, or creatinine clearance < 60 mL/min
- Transplantation rather than dialysis if possible

Normotensive patients with intact renal function (creatinine < 1.2 mg/dL) and only mild proteinuria (< 0.5 g/day) usually are not treated. Patients with renal insufficiency or more severe proteinuria and hematuria are usually offered treatment, which ideally should be started before significant renal insufficiency develops.

**Angiotensin inhibition:** ACE inhibitors or angiotensin II receptor blockers are used on the premise that they reduce BP, proteinuria, and glomerular fibrosis. Patients with the DD genotype for the ACE gene may be at greater risk of disease progression but may also be more likely to respond to ACE inhibitors or
angiotensin II receptor blockers. For patients with hypertension, ACE inhibitors or angiotensin II receptor blockers are the antihypertensives of choice even for relatively mild chronic kidney disease.

**Corticosteroids and immunosuppressants:** Corticosteroids have been used for many years, but benefit is not well documented. One protocol uses methylprednisolone 1 g IV once/day for 3 days at the beginning of months 1, 3, and 5 plus prednisone 0.5 mg/kg po every other day for 6 mo. Because of the risk of adverse effects, corticosteroids should probably be reserved for patients with any of the following:

- Progression, as shown by worsening proteinuria or renal function
- Heavy proteinuria (> 2 g/day)
- Significant renal insufficiency (creatinine clearance < 60 mL/min)

Combinations of corticosteroids, cyclophosphamide, and azathioprine are also used, but efficacy and safety compared with corticosteroids alone are uncertain. Mycophenolate mofetil is under investigation. None of these drugs, however, prevents recurrence in transplant patients.

**Other treatments:** ω-3 Polyunsaturated fatty acids (eg, 4 to 12 g/day), available in fish oil supplements, have been used to treat IgA nephropathy, but data on efficacy are contradictory. Mechanism of effect may include alterations in inflammatory cytokines.

Other interventions have been tried to lower IgA overproduction and to inhibit mesangial proliferation. Elimination of gluten, dairy products, eggs, and meat from the diet; tonsillectomy; and immune globulin (1 g/kg IV 2 days/mo for 3 mo followed by immune globulin 0.35 mL/kg of 16.5% solution IM q 2 wk for 6 mo) all theoretically reduce IgA production. Heparin, dipyridamole, and statins are just a few examples of in vitro mesangial cell inhibitors. Data supporting any of these interventions are limited or absent, and none can be recommended for routine treatment.

Renal transplantation is better than dialysis because of excellent long-term disease-free survival. The condition recurs in ≤ 15% of graft recipients.

**Postinfectious Glomerulonephritis**

Postinfectious glomerulonephritis (PIGN) occurs after infection, usually with a nephritogenic strain of group A β-hemolytic streptococcus. Diagnosis is suggested by history and urinalysis and confirmed by finding a low complement level and sometimes by antibody testing. Prognosis is excellent. Treatment is supportive.

**Etiology**

PIGN is the most common cause of a glomerular disorder in children between 5 and 15 yr; it is rare in children < 2 yr and uncommon in adults > 40 yr.

Most cases are caused by nephritogenic strains of group A β-hemolytic streptococci, most notably type 12 (which causes pharyngitis) and type 49 (which causes impetigo); an estimated 5 to 10% of patients with streptococcal pharyngitis and about 25% of those with impetigo develop PIGN. A latency period of 6 to 21 days between infection and GN onset is typical, but latency may extend up to 6 wk.

Less common pathogens are nonstreptococcal bacteria, viruses, parasites, rickettsiae, and fungi (see **Table 235-2**). Bacterial endocarditis and ventriculatrial shunt infections are additional important conditions in which PIGN develops; ventriculoperitoneal shunts are more resistant to infection.

The mechanism is unknown, but microbial antigens are thought to bind to the glomerular basement membrane and activate complement both directly and via interaction with circulating antibodies, causing glomerular damage, which may be focal or diffuse.

**Symptoms and Signs**
Symptoms and signs range from asymptomatic hematuria (in about 50%) and mild proteinuria to full-blown nephritis with microscopic or gross hematuria (cola-colored, brown, smoky, or frankly bloody urine), proteinuria, oliguria, edema, hypertension, and renal insufficiency. Severe, late disease is a relatively uncommon cause of nephrotic syndrome. Renal failure that causes fluid overload with heart failure and urgent or malignant hypertension and requires dialysis affects 1 to 2% of patients and may manifest as a pulmonary-renal syndrome with hematuria and hemoptysis (see p. 1990). Fever is unusual and suggests persistent infection.

Clinical manifestations of nonstreptococcal PIGN may mimic other disorders (eg, polyarteritis nodosa, renal emboli, antimicrobial drug-induced acute interstitial nephritis).

**Diagnosis**

- Clinical evidence of recent infection
- Urinalysis showing GN
- Often hypocomplementemia

Streptococcal PIGN is suggested by history of pharyngitis or impetigo plus either typical symptoms of PIGN or incidental findings on urinalysis. Tests done to confirm the diagnosis depend on clinical findings. Antistreptolysin O, antihyaluronidase, and antideoxyribonuclease (anti-DNAase) antibodies are commonly measured. Serum creatinine and complement levels (C3 and total hemolytic complement activity) are also usually measured; however, in patients with classic findings, some tests can be omitted. Sometimes other tests are done. Biopsy confirms the diagnosis but is rarely necessary; demonstration of hypocomplementemia is essentially confirmatory.

**Antistreptolysin O** level, the most common laboratory evidence of recent streptococcal infection, increases and remains elevated for several months in about 75% of patients with pharyngitis and in about 50% of patients with impetigo, but it is not specific. An increase in antihyaluronidase and antideoxyribonuclease titers is more specific for detecting recent streptococcal skin infection but is not widely available.

**Urinalysis** shows proteinuria (0.5 to 2 g/m²/day); dysmorphic RBCs; WBCs; renal tubular cells; and RBC, WBC, and granular casts. Random (spot) urinary protein/creatinine ratio may be between 0.2 and 2 (normal, < 0.2).

**Serum creatinine** may rise rapidly but usually peaks below a level requiring dialysis.

C3 and total hemolytic complement activity (CH50) levels fall during active disease and return to normal within 6 to 8 wk in 80% of PIGN cases; C1q, C2, and C4 levels are only minimally decreased or remain normal. Cryoglobulinemia may appear and persist for several months, whereas circulating immune complexes are detectable for only a few weeks.

**Biopsy specimens** show enlarged and hypercellular glomeruli, initially with neutrophilic or eosinophilic infiltration and later with mononuclear infiltration. Epithelial cell hyperplasia is a common early, transient feature. Microthrombosis may occur; if damage is severe, hemodynamic changes produce oliguria, frequently accompanied by epithelial crescents (formed within Bowman's space from epithelial cell hyperplasia). Endothelial and mesangial cells multiply, and the mesangial regions often are greatly expanded by edema and contain neutrophils, dead cells, cellular debris, and subepithelial deposits of electron-dense material. Immunofluorescence microscopy usually shows immune complex deposition with IgG and complement in a granular pattern. On electron microscopy, these deposits are semilunar or hump-shaped and are located in the subepithelial area. The presence of these deposits initiates a complement-mediated inflammatory reaction that leads to glomerular damage. Although the immune complex is presumed to contain an antigen related to streptococcal organisms, no such antigen has been found.
Prognosis

Normal renal function is retained or regained by 85 to 95% of patients. GFR usually returns to normal over 1 to 3 mo, but proteinuria may persist for 6 to 12 mo and microscopic hematuria for several years. Transient changes in urinary sediment may recur with minor URIs. Renal cellular proliferation disappears within weeks, but residual sclerosis is common. In 10% of adults and 1% of children, PIGN evolves into rapidly progressive GN.

Treatment

• Supportive care

Treatment is supportive and may include restriction of dietary protein, Na, and fluid and, in more severe cases, treatment of edema and hypertension. Dialysis is occasionally necessary. Antimicrobial therapy is preventive only when given within 36 h of infection and before GN becomes established.

Rapidly Progressive Glomerulonephritis

(Crescentic Glomerulonephritis)

Rapidly progressive glomerulonephritis (RPGN) causes microscopic glomerular crescent formation with progression to renal failure within weeks to months. Diagnosis is based on history, urinalysis, serologic tests, and renal biopsy. Treatment is with corticosteroids, with or without cyclophosphamide, and sometimes plasmapheresis.

RPGN is extensive glomerular crescent formation (which can be seen in a biopsy specimen) that, if untreated, progresses to end-stage renal disease over weeks to months. It is relatively uncommon, affecting 10 to 15% of patients with GN, and occurs predominantly in patients 20 to 50 yr. Types and causes are classified by findings using immunofluorescence microscopy (see Table 235-3).

Anti-glomerular basement membrane (GBM) antibody disease (type 1 RPGN) is autoimmune GN and accounts for up to 10% of RPGN cases. It may arise when respiratory exposures (eg, cigarette smoke, viral URI) or some other stimulus exposes alveolar capillary collagen, triggering formation of anticollagen antibodies. The anticollagen antibodies cross-react with GBM, fixing complement and triggering a cell-mediated inflammatory response in the kidneys and usually the lungs. The term Goodpasture's syndrome usually refers to a combination of GN and alveolar hemorrhage in the presence of anti-GBM antibodies (see p. 1991) but sometimes refers to GN without alveolar hemorrhage in the presence of anti-GBM antibodies. Immunofluorescent staining of renal biopsy tissue demonstrates linear IgG deposits.

Immune complex RPGN (type 2 RPGN) complicates numerous infectious and connective tissue disorders and also occurs with other primary glomerulopathies. Immunofluorescent staining demonstrates nonspecific granular immune deposits. The condition accounts for up to 40% of RPGN cases. Pathogenesis is usually unknown.

Pauci-immune RPGN (type 3 RPGN) is distinguished by the absence of immune complex or complement deposition on immunofluorescent staining. It constitutes up to 50% of all RPGN cases. Almost all patients have elevated antineutrophil cytoplasmic antibodies (ANCAs, usually myeloperoxidase-ANCA) and systemic vasculitis.

Double-antibody disease (type 4 RPGN) has features of types 1 and 3, with the presence of anti-GBM and ANCA antibodies. It is rare.
Idiopathic cases are rare. They include patients with either of the following:

- Immune complexes (similar to type 2) but no obvious cause such as infection, connective tissue disorder, or glomerular disorder
- Pauci-immune features (similar to type 3) but absence of ANCA antibodies

Symptoms and Signs

Manifestations are usually insidious, with weakness, fatigue, fever, nausea and vomiting, anorexia, arthralgia, and abdominal pain. Some patients present similarly to those with PIGN, with abrupt-onset hematuria. About 50% of patients have edema and a history of an acute influenza-like illness within 4 wk of onset of renal failure, usually followed by severe oliguria. Nephrotic syndrome is present in 10 to 30%. Hypertension is uncommon and rarely severe. Patients with anti-GBM antibody disease may have pulmonary hemorrhage, which can manifest with hemoptysis or be detectable only by finding diffuse alveolar infiltrates on chest x-ray (pulmonary-renal or diffuse alveolar hemorrhage syndrome—see p. 1989).

Diagnosis

- Progressive renal failure over weeks to months
- Nephritic urinary sediment
- Serologic testing
- Renal biopsy

Diagnosis is suggested by acute renal failure in patients with hematuria and RBC casts. Testing includes serum creatinine, urinalysis, CBC, serologic tests, and renal biopsy. Diagnosis is usually by serologic tests and renal biopsy.

Serum creatinine is almost always elevated. Hematuria and RBC casts are always present, and telescopic sediment (ie, sediment with multiple elements, including WBCs and RBCs, and WBC, RBC, granular, waxy, and broad casts) is common.

On CBC, anemia is always present, and leukocytosis is common.

Serologic testing should include anti-GBM antibodies (anti-GBM antibody disease); antistreptolysin O antibodies, anti-DNA antibodies, or cryoglobulins (immune complex RPGN); and ANCA titers (pauci-immune RPGN). Complement measurement may be useful in suspected immune complex RPGN, because hypocomplementemia is common.

Early renal biopsy is essential. The feature common to all types of RPGN is focal proliferation of glomerular epithelial cells, sometimes interspersed with numerous neutrophils, that forms a crescentic cellular mass (crescents) and that fills Bowman’s space in > 50% of glomeruli. The glomerular tuft usually appears hypocellular and collapses. Necrosis within the tuft or involving the crescent may occur and may be the most prominent abnormality. In such patients, histologic evidence of vasculitis should be sought.

Immunofluorescence microscopy findings differ for each type.

- In anti-GBM antibody disease (type 1), linear or ribbon-like deposition of IgG along the GBM is most prominent and is often accompanied by linear and sometimes granular deposition of C3.
- In immune complex RPGN (type 2), immunofluorescence reveals diffuse, irregular mesangial IgG and C3 deposits.
- In pauci-immune RPGN (type 3), immune staining and deposits are not detected. However, fibrin occurs
within the crescents, regardless of the fluorescence pattern.

- In double antibody RPGN (type 4), linear staining of the GBM is present (similar to type 1).

- In idiopathic RPGN some patients have immune complexes (similar to those of type 2) and others have absence of immune staining and deposits (similar to type 3).

**Prognosis**

Spontaneous remission is rare, and 80 to 90% of untreated patients progress to end-stage renal disease within 6 mo. Prognosis improves with early treatment.

**Favorable prognostic factors** include RPGN caused by the following:

- Anti-GBM disease if treated early, especially when treated before oliguria occurs and when creatinine level is < 7 mg/dL

- PIGN

- SLE

- Wegener's granulomatosis

- Polyarteritis nodosa

**Unfavorable prognostic factors** include the following:

- Age > 60 yr

- Oliguric renal failure

- Higher serum creatinine level

- Circumferential crescents in > 75% of glomeruli

- Among patients with pauci-immune RPGN, no response to treatment

About 30% of patients with pauci-immune RPGN do not respond to treatment; among nonresponders, about 40% require dialysis, and 33% die within 4 yr. In contrast, among patients who respond to treatment, < 20% of patients require dialysis, and about 3% die.

Patients with double-antibody disease appear to have a renal prognosis no better than patients with anti-GBM antibody disease and worse than patients with pauci-immune RPGN.

Patients who recover normal renal function after RPGN demonstrate residual histologic changes principally in glomeruli, consisting chiefly of hypercellularity, with little or no sclerosis within the glomerular tuft or the epithelial cells and minimal fibrosis of the interstitium.

Death is usually due to infectious or cardiac causes, providing that a uremic death is prevented by dialysis.

**Treatment**

- Corticosteroids

- Cyclophosphamide

- Plasmapheresis for anti-GBM RPGN
Treatment varies by disease type, although no regimens have been rigorously studied. Therapy should be instituted early, ideally when serum creatinine is < 5 mg/dL and before the biopsy shows crescentic involvement of all glomeruli or organizing crescents as well as fibrotic interstitium and atrophic tubules. Treatment becomes less effective as these features become more prominent and may be harmful in some patients (eg, the elderly, patients with infection).

For **anti-GBM antibody disease**, plasma-apheresis (daily 3- to 4-L exchanges for 14 days) is recommended; the role of plasmapheresis is less well defined for immune complex and pauci-immune RPGN. Plasmapheresis is believed to be effective because it rapidly removes free antibody, intact immune complexes, and mediators of inflammation (eg, fibrinogen, complement). Prednisone and cyclophosphamide are typically started and continued to minimize new antibody formation.

For **immune complex** and **pauci-immune RPGN**, corticosteroids (methylprednisolone 1 g IV once/day over 30 min for 3 to 5 days followed by prednisone 1 mg/kg po once/day) may reduce serum creatinine levels or delay dialysis for > 3 yr in 50% of patients. Cyclophosphamide 1.5 to 2 mg/kg po once/day is usually given and may particularly benefit ANCA-positive patients; monthly pulse regimens may lessen adverse effects, but their role is not defined.

Lymphocytapheresis, a technique to remove peripheral lymphocytes from circulation, may benefit pauci-immune RPGN but requires further investigation. Patients with idiopathic disease are usually treated with corticosteroids and cyclophosphamide, but data regarding efficacy are scarce.

Renal transplantation is effective for all types, but disease may recur in the graft; risk diminishes with time. In anti-GBM antibody disease, the anti-GBM titers should be undetectable for at least 12 mo before transplantation.

**Thin Basement Membrane Disease**

(Benign Familial Hematuria)

**Thin basement membrane disease** is diffuse thinning of the glomerular basement membrane from a width of 300 to 400 nm in normal subjects to 150 to 225 nm.

Thin basement membrane disease is hereditary and usually transmitted in autosomal dominant fashion. Not all genetic mutations have been characterized, but in some families with thin basement membrane disease there is a mutation in the type IV collagen α4 gene. Prevalence is estimated to be 5 to 9%.

Most patients are asymptomatic and are incidentally noted to have microscopic hematuria on routine urinalysis, although mild proteinuria and gross hematuria are occasionally present. Renal function is typically normal, but a few patients develop progressive renal failure for unknown reasons. Recurrent flank pain, similar to that in IgA nephropathy, is a rare manifestation.

Diagnosis is based on family history and findings of hematuria without other symptoms or pathology, particularly if asymptomatic family members also have hematuria. Renal biopsy is unnecessary but is often done as part of a hematuria evaluation. Early on, thin basement membrane disease may be difficult to differentiate from hereditary nephritis because of histologic similarities.

Long-term prognosis is excellent, and no treatment is necessary in most cases. Patients with frequent gross hematuria, flank pain, or proteinuria (eg, urine protein/creatinine ratio of > 0.2) may benefit from ACE inhibitors or angiotensin receptor II blockers, which may lower intraglomerular pressure.

**Nephrotic Syndrome**

Nephrotic syndrome is urinary excretion of > 3 g of protein/day due to a glomerular disorder. It is more common among children and has both primary and secondary causes. Diagnosis is by determination of urine protein/creatinine ratio in a random urine sample or measurement of urinary protein in a 24-h urine collection; cause is diagnosed based on history, physical
examination, serologic testing, and renal biopsy. Prognosis and treatment vary by cause.

Etiology

Nephrotic syndrome occurs at any age but is more prevalent in children, mostly between ages 1 1/2 and 4 yr. At younger ages, boys are affected more often than girls, but both are affected equally at older ages. Causes differ by age (see Table 235-1) and may be primary or secondary (see Table 235-4).

The most common primary causes are the following:

• Minimal change disease
• Focal segmental glomerulosclerosis
• Membranous nephropathy

Secondary causes account for < 10% of childhood cases but > 50% of adult cases, most commonly the following:

• Diabetic nephropathy
• Preeclampsia

Amyloidosis, an underrecognized cause, is responsible for 4% of cases.

Pathophysiology

Proteinuria occurs because of changes to capillary endothelial cells, the glomerular basement membrane (GBM), or podocytes,

[Table 235-4, Causes of Nephrotic Syndrome]

which normally filter serum protein selectively by size and charge.

The mechanism of damage to these structures is unknown in primary and secondary glomerular diseases, but evidence suggests that T cells may up-regulate a circulating permeability factor or down-regulate an inhibitor of permeability factor in response to unidentified immunogens and cytokines. Other possible factors include hereditary defects in proteins that are integral to the slit diaphragms of the glomeruli, activation of complement leading to damage of the glomerular epithelial cells and loss of the negatively charged groups attached to proteins of the GBM and glomerular epithelial cells.

Complications: The disorder results in urinary loss of macromolecular proteins, primarily albumin but also opsonins, immunoglobulins, erythropoietin, transferrin, hormone-binding proteins (including thyroid-binding globulin and vitamin D-binding protein), and antithrombin III. Deficiency of these and other proteins contribute to a number of complications (see Table 235-5); other physiologic factors also play a role.

Symptoms and Signs

Primary symptoms include anorexia, malaise, and frothy urine (caused by high concentrations of protein). Fluid retention may cause dyspnea (pleural effusion or laryngeal edema), arthralgia (hydrarthrosis), or abdominal pain (ascites or, in children, mesenteric edema).

Corresponding signs may develop, including peripheral edema and ascites. Edema may obscure signs of muscle wasting and cause parallel white lines in fingernail beds (Muehrcke's lines).

Other symptoms and signs are attributable to the many complications of nephrotic syndrome (see Table 235-5).
Diagnosis

- Urine protein/creatinine ratio ≥ 3 or proteinuria ≥ 3 g/24 h
- Serologic testing and renal biopsy unless the cause is clinically obvious

Diagnosis is suspected in patients with edema and proteinuria on urinalysis and confirmed by random (spot) urine protein and creatinine levels or 24-h measurement of urinary protein. The cause may be suggested by clinical findings (eg, SLE, preeclampsia, cancer); when the cause is unclear, additional (eg, serologic) testing and renal biopsy are indicated.

Urine testing: A finding of significant proteinuria (3 g protein in a 24-h urine collection) is diagnostic (normal excretion is < 150 mg/day). Alternatively, the protein/creatinine ratio in a random urine specimen usually reliably estimates grams of protein/1.73 m^2 BSA in a 24-h collection (eg, values of 40 mg/dL protein and 10 mg/dL creatinine in a random urine sample are equivalent to the finding of 4 g/1.73 m^2 in a 24-h specimen). Calculations based on random specimens may be less reliable when creatinine excretion is high (eg, during athletic training) or low (eg, in cachexia). However, calculations based on random specimens are usually preferred to 24-h collection because random collection is more convenient and less prone to error (eg, due to lack of adherence); more convenient

[Table 235-5. Complications of Nephrotic Syndrome]

testing facilitates monitoring changes that occur during treatment.

Besides proteinuria, urinalysis may demonstrate RBCs and casts (hyaline, granular, fatty, waxy, RBC, or epithelial cell). Lipiduria, the presence of free lipid or lipid within tubular cells (oval fat bodies), within casts (fatty casts), or as free globules, suggests a glomerular disorder causing nephrotic syndrome. Urinary cholesterol can be detected with plain microscopy and demonstrates a Maltese cross pattern under crossed polarized light; Sudan staining must be used to show triglycerides.

Adjunctive testing: Adjunctive testing helps characterize severity and complications.

- BUN and creatinine concentrations vary by degree of renal impairment.
- Serum albumin often is < 2.5 g/dL.
- Total cholesterol and triglyceride levels are typically increased.

It is not routinely necessary to measure levels of α- and γ-globulins, immunoglobulins, hormone-binding proteins, ceruloplasmin, transferrin, and complement components, but these levels may also be low.

Secondary causes: The role of testing for secondary causes (see Table 235-4) is controversial because yield may be low. Tests are best done as indicated by clinical context. Tests may include the following:

- Serum glucose or glycosylated Hb (HbA_1C)
- Antinuclear antibodies
- Hepatitis B and C serologic tests
- Serum or urine protein electrophoresis
- Cryoglobulins

Test results may alter management and preclude the need for biopsy. For example, demonstration of cryoglobulins suggests mixed cryoglobulinemia (eg, from chronic inflammatory disorders such as SLE,
Sjogren's syndrome, or hepatitis C virus infection), and demonstration of a monoclonal protein on serum or urine protein electrophoresis suggests a monoclonal gammopathy (eg, multiple myeloma), especially in patients > 50 yr.

**Renal biopsy** is indicated in adults to diagnose the disorder causing idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome in children is most likely minimal change disease and is usually presumed without biopsy unless the patient fails to improve during a trial of corticosteroids. Specific biopsy findings are discussed under the individual disorders.

**Prognosis**

Prognosis varies by cause. Complete remissions may occur spontaneously or with treatment. The prognosis generally is favorable in corticosteroid-responsive disorders.

In all cases, prognosis may be worsened by the following:

- Infection
- Hypertension
- Significant azotemia
- Hematuria
- Thromboses in cerebral, pulmonary, peripheral, or renal veins

The recurrence rate is high in kidney transplantation patients with focal segmental glomerulosclerosis, SLE, IgA nephropathy, and membranoproliferative glomerulonephritis (especially type II).

**Treatment**

- Treatment of causative disorder
- Angiotensin inhibition
- Na restriction
- Statins
- Rarely, nephrectomy

**Causative disorder:** Treatment of underlying disorders may include prompt treatment of infections (eg, staphylococcal endocarditis, malaria, syphilis, schistosomiasis), allergic desensitization (eg, for poison oak or ivy and insect antigen exposures), and stopping drugs (eg, gold, penicillamine, NSAIDs); these measures may cure nephrotic syndrome in specific instances.

**Proteinuria:** Angiotensin inhibition (ACE inhibitors or angiotensin II receptor blockers) is indicated to reduce systemic and intraglomerular BP and proteinuria. These drugs may cause or exacerbate hyperkalemia in patients with moderate to severe renal insufficiency.

Protein restriction is no longer recommended because of lack of demonstrated effect on progression.

**Edema:** Na restriction (< 2 g Na, or about 100 mmol/day) is recommended for patients with symptomatic edema.

Loop diuretics are usually required to control edema but may worsen preexisting renal insufficiency and hypovolemia, hyperviscosity, and hypercoagulability and thus should be used only if Na restriction is ineffective.
Hyperlipidemia: Statins are indicated for hyperlipidemia. Limitation of saturated fat and cholesterol intake is recommended to help control hyperlipidemia.

Hypercoagulability: Anticoagulants are indicated for treatment of thromboembolism, but few data exist to support their use as primary prevention.

Infection risk: All patients should receive pneumococcal vaccination if not otherwise contraindicated.

Nephrectomy: Rarely, bilateral nephrectomy is necessary in severe nephrotic syndrome because of persistent hypoalbuminemia. The same result can sometimes be achieved by embolizing the renal arteries with coils, thus avoiding surgery in high-risk patients. Renal replacement therapy is used as necessary.

Congenital Nephrotic Syndromes

Congenital and infantile nephrotic syndromes are those that manifest during the first year of life. They include diffuse mesangial sclerosis and Finnish-type nephrotic syndrome.

Diffuse mesangial sclerosis: This nephrotic syndrome is rare. Inheritance is variable. Progression to end-stage renal failure occurs by age 2 or 3 yr.

Patients with severe proteinuria may require bilateral nephrectomy because of severe hypoalbuminemia; dialysis should be initiated early to ameliorate nutritional deficits and mitigate failure to thrive. The disorder usually recurs in a renal graft.

Finnish-type nephrotic syndrome: This syndrome is an autosomal recessive disorder that affects 1/8200 Finnish neonates and is caused by a mutation in the NPHS1 gene, which codes for a podocytic slit-diaphragm protein (nephrin).

Finnish-type nephrotic syndrome is rapidly progressive and usually necessitates dialysis within 1 yr. Most patients die within 1 yr, but a few have been supported nutritionally until renal failure occurs and then managed with dialysis or transplantation. However, the disorder may recur in a renal graft.

Other syndromes: Several other rare congenital nephrotic syndromes are now genetically characterized. These include corticosteroid-resistant nephrotic syndrome (defective NPS2 gene coding for podocin), familial focal segmental glomerulosclerosis (defective ACTN4 gene coding for α-actin 4), and Denys-Drash syndrome, which is characterized by diffuse mesangial sclerosis, male pseudohermaphroditism, and Wilms' tumor (defective WT1 gene).

Diabetic Nephropathy

(See also p. 869.)

Diabetic nephropathy (DN) is glomerular sclerosis and fibrosis caused by the metabolic and hemodynamic changes of diabetes mellitus. It manifests as slowly progressive albuminuria with worsening hypertension and renal insufficiency. Diagnosis is based on history, physical examination, urinalysis, and urine albumin/creatinine ratio. Treatment is strict glucose control, angiotensin inhibition (ACE inhibitors or angiotensin II receptor blockers), and control of BP and lipids.

DN is the most common cause of nephrotic syndrome in adults and of end-stage renal disease in the US, accounting for up to 80% of cases of the latter. The prevalence of renal failure is probably about 40% among patients with type 1 diabetes mellitus. The prevalence of renal failure among patients with type 2 diabetes mellitus is usually stated as 20 to 30%, but this figure is probably low. Renal failure is particularly common in certain ethnic groups, such as blacks, Mexican-Americans, Polynesians, and Pima Indians. Other risk factors include the following:
• Duration and degree of hyperglycemia

• Hypertension

• Dyslipidemia

• Cigarette smoking

• Certain polymorphisms affecting the renin-angiotensin-aldosterone axis

• Family history of diabetic nephropathy

• Genetic variables (decreased number of glomeruli)

Renal failure usually takes ≥ 10 yr after the onset of nephropathy to develop; however, because type 2 diabetes is often present for several years before being recognized, nephropathy often develops < 10 yr after diabetes is diagnosed.

Pathophysiology

Pathogenesis begins with small vessel disease. Pathophysiology is complex, involving glycosylation of proteins, hormonally influenced cytokine release (eg, transforming growth factor-β), deposition of mesangial matrix, and alteration of glomerular hemodynamics. Hyperfiltration, an early functional abnormality, is only a relative predictor for the development of renal failure.

Hyperglycemia causes glycosylation of glomerular proteins, which may be responsible for mesangial cell proliferation and matrix expansion and vascular endothelial damage. The GBM classically becomes thickened.

Lesions of diffuse or nodular intercapillary glomerulosclerosis are distinctive. There is marked hyalinosis of afferent and efferent arterioles as well as arteriosclerosis; interstitial fibrosis and tubular atrophy may be present. Only mesangial matrix expansion appears to correlate with progression to end-stage renal disease.

DN begins as glomerular hyperfiltration (increased GFR); GFR normalizes with early renal injury and mild hypertension, which worsens over time. Microalbuminuria, urinary excretion of albumin in a range of 30 to 300 mg albumin/day, then occurs. Urinary albumin in these concentrations is called microalbuminuria because detection of proteinuria by dipstick on routine urinalysis usually requires > 300 mg albumin/day. Microalbuminuria progresses to proteinuria > 0.5 g/day at a variable course, usually over years. Nephrotic syndrome (proteinuria ≥ 3 g/day) precedes end-stage renal disease, on average, by about 3 to 5 yr, but this timing is also highly variable. Other urinary tract abnormalities commonly occurring with DN that may accelerate the decline of renal function include papillary necrosis, type IV renal tubular acidosis, and UTIs. In DN, the kidneys are usually of normal size or larger.

Symptoms and Signs

DN is asymptomatic in early stages. Sustained microalbuminuria is the earliest warning sign. Hypertension and some measure of dependent edema eventually develop in most untreated patients. In later stages, patients develop symptoms and signs of uremia (eg, nausea, vomiting, anorexia) earlier (ie, with higher GFR) than do patients without DN, possibly because the combination of end-organ damage due to diabetes (eg, neuropathy) and renal failure worsens symptoms.

Diagnosis

• Screening of all patients with diabetes with random urine albumin/creatinine ratio

• Urinalysis for signs of other renal disorders (eg, hematuria, RBC casts)
The diagnosis is suspected in patients with diabetes who have proteinuria, particularly if they have diabetic retinopathy (indicating small vessel disease) or risk factors for DN. Other renal disorders should be considered if there are any of the following:

- Heavy proteinuria with only a brief history of diabetes
- Absence of diabetic retinopathy
- Rapid onset of heavy proteinuria
- Gross hematuria
- RBC casts
- Rapid decline in GFR
- Small kidney size

**Urinary protein:** Patients are tested for proteinuria by routine urinalysis; if proteinuria is present, testing for microalbuminuria is unnecessary because the patient already has macroalbuminuria suggestive of diabetic renal disease. In patients without proteinuria on urinalysis, an albumin/creatinine ratio should be calculated from a mid-morning urine specimen. A ratio ≥ 0.03 mg/mg (≥ 30 mg/g) indicates microalbuminuria if it is present on at least 2 of 3 specimens within 3 to 6 mo and if it cannot be explained by infection or exercise. Some experts recommend that microalbuminuria be measured from a 24-h urine collection, but this approach is less convenient, and many patients have difficulty accurately collecting a specimen. The random urine albumin/creatinine ratio overestimates 24-h collection of microalbuminuria in up to 30% of patients > 65 due to reduced creatinine production from reduced muscle mass. Inaccurate results can also occur in very muscular patients or if vigorous exercise precedes urine collection.

For most patients with diabetes who have proteinuria, the diagnosis is clinical. Renal biopsy can confirm the diagnosis but is rarely necessary.

**Screening:** Patients with type 1 diabetes without known renal disease should be screened for proteinuria and, if proteinuria is absent on routine urinalysis, for microalbuminuria, beginning 5 yr after diagnosis and at least annually thereafter.

Patients with type 2 diabetes should be screened at the time of diagnosis and annually thereafter.

**Prognosis**

Prognosis is good for patients who are meticulously treated and monitored. Such care is often difficult in practice, however, and most patients slowly lose renal function; even prehypertension (BP 120 to 139/80 to 89 mm Hg) or stage 1 hypertension (BP 140 to 159/90 to 99 mm Hg) may accelerate injury. Systemic atherosclerotic disease (stroke, MI, peripheral arterial disease) predicts an increase in mortality.

**Treatment**

- Maintenance of glycosylated Hb (HbA₁C) ≤ 7.0
- Aggressive BP control, beginning with angiotensin inhibition

Primary treatment is strict glucose control to maintain HbA₁C ≤ 7.0; maintenance of euglycemia reduces microalbuminuria but may not retard disease progression once DN is well established. Glucose control must also be accompanied by strict control of BP to < 130/80 mm Hg. Some experts suggest BP should be 110 to 120/65 to 80 mm Hg, particularly in patients with protein excretion of > 1 g/day; however, others claim that BP values < 120/85 mm Hg are associated with increased cardiovascular mortality and heart failure. Dyslipidemia should also be treated.
**Angiotensin inhibition** is first-line therapy. Thus, ACE inhibitors or angiotensin II receptor blockers are the antihypertensives of choice; they reduce BP and proteinuria and slow the progression of DN. ACE inhibitors are usually less expensive, but angiotensin II receptor blockers can be used instead if ACE inhibitors cause persistent cough. Treatment should be started when microalbuminuria is detected regardless of whether hypertension is present; some experts recommend drugs be used even before signs of renal disease appear.

**Diuretics** are required by most patients in addition to angiotensin inhibition to reach target BP levels. Dose should be decreased if symptoms of orthostatic hypotension develop or serum creatinine increases by more than 30%.

**Nondihydropyridine Ca channel blockers** (diltiazem and verapamil) are also antiproteinuric and renoprotective and can be used if proteinuria does not meaningfully decrease when target BP is reached or as alternatives for patients with hyperkalemia or other contraindications to ACE inhibitors or angiotensin II receptor blockers. In contrast, dihydropyridine Ca channel blockers (eg, nifedipine, felodipine, amlodipine) are relatively contraindicated because they may worsen proteinuria and renal function. ACE inhibitors and nondihydropyridine Ca channel blockers have greater antiproteinuric and renoprotective effects when used together, and their antiproteinuric effect is enhanced by Na restriction. Nondihydropyridine Ca channel blockers should be used with caution in patients taking β-blockers.

**Dietary protein restriction** yields mixed results. The American Diabetic Association recommends that people with diabetes and overt nephropathy be restricted to 0.8 g protein/kg/day. Significant protein restriction should be done only with close dietary monitoring to ensure a balanced supply of amino acids, because undernutrition may be a significant risk.

**Kidney transplantation** with or without simultaneous or subsequent pancreas transplantation (see p. 1133) is an option for patients with end-stage renal disease. The 5-yr survival rate for patients with type 2 diabetes receiving a kidney transplant is almost 60%, compared with 2% for dialysis-dependent patients who do not undergo transplantation (though this statistic probably represents significant selection bias). Renal allograft survival rate is > 85% at 2 yr.

**Focal Segmental Glomerulosclerosis**

Focal segmental glomerulosclerosis (FSGS) is scattered (segmental) mesangial sclerosis in some but not all (focal) glomeruli. It is most often idiopathic but may be secondary to use of heroin or other drugs, HIV infection, obesity, sickle cell disease, atheroembolic disease, or nephron loss (eg, in reflux nephropathy or subtotal nephrectomy). It manifests mainly in adolescents but also in young and middle-aged adults. Patients have insidious onset of proteinuria, mild hematuria, hypertension, and azotemia. Diagnosis is confirmed by renal biopsy. Treatment is with angiotensin inhibition and, for idiopathic disease, corticosteroids and sometimes cytotoxic drugs.

FSGS is now the most common cause of idiopathic (or primary) nephrotic syndrome among adults in the US. It is especially common in black men. Though usually idiopathic, FSGS can occur in association with other factors (secondary FSGS), including drugs (eg, heroin, interferon alfa, pamidronate, cyclosporine, or acetaminophen or NSAIDs [causing analgesic nephropathy]), atheroembolic disease affecting the kidneys, obesity, HIV infection (see p. 2404), and disorders causing nephron loss (eg, reflux nephropathy, subtotal nephrectomy, renal dysgenesis). Familial cases exist.

In FSGS, because charge as well as size ultrafiltration barriers are defective, proteinuria is typically nonselective, affecting high molecular-weight proteins (eg, lgs) as well as albumin. Kidneys tend to be small.

**Symptoms and Signs**

FSGS patients commonly present with heavy proteinuria, hypertension, renal dysfunction, edema, or a combination; however, asymptomatic, non-nephrotic-range proteinuria is sometimes the only sign.
Microscopic hematuria is occasionally present.

**Diagnosis**

- Renal biopsy, when possible, with immunostaining and electron microscopy

FSGS is suspected in patients with nephrotic syndrome, proteinuria, or renal dysfunction with no obvious cause, particularly patients who have disorders or use drugs associated with FSGS.

Urinalysis is done and BUN, serum creatinine, and 24-h urinary protein excretion are measured. Diagnosis is confirmed by renal biopsy, which shows focal and segmental hyalinization of the glomeruli, often with immunostaining showing IgM and complement (C3) deposits in a nodular and coarse granular pattern. Electron microscopy reveals diffuse effacement of podocyte foot processes. Global sclerosis may be visible, along with secondary atrophic glomeruli. Biopsy may be falsely negative if areas of focal abnormalities are not sampled.

**Prognosis**

Prognosis is poor. Spontaneous remissions occur in < 10% of patients. Renal failure occurs in > 50% of patients within 10 yr; in 20%, end-stage renal disease occurs within 2 yr despite treatment. The disorder is more rapidly progressive in adults than in children. The presence of segmental sclerosis consistently at the glomerular pole where the tubule originates (tip lesion) may portend a more favorable response to corticosteroid therapy. Another variant, in which the capillary walls are wrinkled or collapsed (collapsing glomerulopathy, which is typical in association with IV drug abuse or HIV infection), suggests more severe disease and rapid progression to renal failure. Pregnancy may exacerbate FSGS.

FSGS may recur after renal transplantation; proteinuria sometimes returns within hours of transplantation. Of patients whose transplant was for end-stage renal disease caused by FSGS, about 8 to 20% lose their graft due to recurrent FSGS; risk is highest in young children, patients who develop renal failure < 3 yr after disease onset, and patients with mesangial proliferation.

Heroin addicts with nephrotic syndrome due to FSGS can experience complete remission if they cease taking heroin early in the disease.

**Treatment**

- Angiotensin inhibition

- Corticosteroids and sometimes cytotoxic drugs for idiopathic FSGS

Treatment often is not effective. Patients with FSGS should be treated with angiotensin inhibition (an ACE inhibitor or an angiotensin II receptor blocker) unless contraindicated by angioedema or hyperkalemia. Patients with nephrotic syndrome should be treated with a statin. In patients with secondary FSGS, the primary disorder should be treated. A trial of immunosuppressive therapy is indicated in idiopathic FSGS if proteinuria reaches the nephrotic range or if any degree of renal dysfunction is present.

**Immunosuppressive therapy:** Corticosteroids (eg, prednisone 1 mg/kg po once/day or 2 mg/kg every other day) are recommended for at least 2 mo, although some experts recommend use for up to 9 mo. Response rates of 30 to 50% have been reported with prolonged therapy. After a 2-wk remission of proteinuria, the corticosteroid is slowly tapered over ≥ 2 mo. Secondary and familial cases are more likely to be corticosteroid-resistant.

If only slight improvement or relapse occurs with corticosteroid therapy, cyclosporine (1.5 to 2 mg/kg po bid for 6 mo) or, alternatively, mycophenolate mofetil (750 to 1000 mg po bid for 6 mo in patients > 1.25 m² BSA or 600 mg/m² BSA bid up to 1000 mg bid) may induce remission. In patients with contraindications to high-dose corticosteroids (eg, diabetes, osteoporosis), cyclosporine can be given along with a lower dose of corticosteroids (eg, prednisone 0.15 mg/kg po once/day). An alternative is plasmapheresis with tacrolimus immunosuppression.
HIV-Associated Nephropathy

HIV-associated nephropathy (HIVAN) is characterized by clinical findings similar to those of focal segmental glomerulosclerosis and often biopsy features of collapsing glomerulopathy (a variant of focal segmental glomerulosclerosis).

HIVAN seems to be more common among black patients with HIV who are injection drug users. Infection of renal cells with HIV may contribute.

Most clinical findings are similar to those of FSGS, but hypertension is less common and the kidneys remain enlarged. Most patients experience rapid progression to end-stage renal disease within 1 to 4 mo.

Diagnosis

- Renal biopsy

HIVAN is suspected in patients with nephrotic syndrome or nephropathy who have AIDS or symptoms of AIDS. HIVAN should be distinguished from the many other disorders that occur with higher frequency in HIV-infected patients and cause renal disease, such as thrombotic microangiopathy (hemolyticuremic syndrome and thrombotic thrombocytopenic purpura), immune complex-mediated glomerulonephritis, and drug-induced interstitial nephritis (due to indinavir and ritonavir) and rhabdomyolysis (due to statins).

In HIVAN, ultrasonography, if done, shows that the kidneys are enlarged and highly echogenic. Renal biopsy typically is done. Light microscopy shows capillary collapse of varying severity (collapsing glomerulopathy) and differing degrees of increased mesangial matrix. Tubular cells show marked degenerative changes and tubular atrophy or microcystic dilation. Interstitial immune cell infiltrate, fibrosis, and edema are common. Tubular reticular inclusions, similar to those in SLE, are found within endothelial cells but are now rare with more effective HIV therapy. Normotension and persistently enlarged kidneys help to differentiate HIVAN from FSGS.

Treatment

- Antiretroviral therapy and ACE inhibitors

Control of the HIV infection may help minimize renal damage. ACE inhibitors are probably of some benefit. The role of corticosteroids is not well defined. Dialysis is usually required. At some centers, outcomes after transplantation have been excellent.

Membranous Nephropathy

Membranous nephropathy (MN) is deposition of immune complexes on the GBM with GBM thickening. Cause is usually unknown, alctions, autoimmune disorders, and cancer. Manifestations include insidious onset of edema and heavy proteinuria with benign urinary sediment, normal renal function, and normal or elevated BP. Diagnosis is by renal biopsy. Spontaneous remission is common. Treatment of patients at high risk of progression is usually with corticosteroids and cyclophosphamide or chlorambucil.

MN mostly affects adults, in whom it is a common cause of nephrotic syndrome.

Etiology

MN is usually idiopathic but may be secondary to any of the following:

- Drugs (eg, gold, penicillamine, NSAIDs)
- Infections (eg, hepatitis B virus infection, syphilis)
• Autoimmune disorders (eg, SLE)
• Thyroiditis
• Cancer
• Parasitic diseases (eg, malaria, schistosomiasis, leishmaniasis)

Depending on the patient's age, 4 to 20% have an underlying cancer, including solid cancers of the lung, colon, stomach, breast, or kidney; Hodgkin or non-Hodgkin lymphoma; chronic lymphocytic leukemia; and melanoma.

MN is rare in children and, when it occurs, is usually due to hepatitis B virus infection or SLE.

Renal vein thrombosis is especially frequent in MN but is usually clinically silent unless it progresses to pulmonary embolism.

Symptoms and Signs

Patients typically present with edema and nephrotic-range proteinuria and occasionally with microscopic hematuria and hypertension. Symptoms and signs of a disorder causing MN (eg, a cancer) may be present initially.

Diagnosis

• Renal biopsy
• Evaluation for secondary causes

Diagnosis is suggested by development of nephrotic syndrome, particularly in patients who have potential causes of MN. The diagnosis is confirmed by biopsy.

Proteinuria is in the nephrotic range in 80%. Laboratory testing is done as indicated for nephrotic syndrome. The GFR, if measured, is normal or decreased. Immune complexes are seen as dense deposits on electron microscopy (see Fig. 235-1). Subepithelial dense deposits occur with early disease, with spikes of lamina densa between the deposits. Later, deposits appear within the GBM, and marked thickening occurs. A diffuse, granular pattern of IgG deposition occurs along the GBM without cellular proliferation, exudation, or necrosis.

Evaluation of patients diagnosed with MN usually includes the following:

• A search for occult cancer, particularly in a patient who has lost weight, has unexplained anemia or heme-positive stools, or is elderly
• Consideration of drug-induced MN
• Hepatitis B and C serologic testing
• Antinuclear antibody testing

The search for occult cancer is usually limited to age-appropriate screening (eg, colonoscopy for patients age > 50 or with other symptoms or risk factors, mammogram for women age > 40, prostate-specific antigen measurement for men age > 50 [age > 40 for blacks], chest x-ray and possibly chest CT for patients at risk of lung cancer).

Prognosis

About 25% of patients undergo spontaneous remission, 25% develop persistent, nonnephrotic-range
proteinuria, 25% develop persistent nephrotic syndrome, and 25% progress to end-stage renal disease. Women, children, and young adults with non-nephrotic-range proteinuria and patients with persistently normal renal function 3 yr after diagnosis tend to have little disease progression. More than 50% of patients with nephrotic-range proteinuria who are asymptomatic or who have edema that can be controlled with diuretics will have a partial or complete remission within 3 to 4 yr.

Risk of progression to renal failure is highest among patients with

- Proteinuria ≥ 10 g/day, particularly men age > 50 yr
- An elevated serum creatinine level at presentation or diagnosis
- Biopsy evidence of substantial interstitial inflammation

**Treatment**

- Treatment of secondary causes and of nephrotic syndrome as indicated
- Immunosuppressive therapy for patients at high risk of progression

Primary treatment is that of the causes. Among patients with idiopathic MN, asymptomatic patients with non-nephrotic-range proteinuria do not require treatment; renal function should be monitored periodically (eg, twice yearly when apparently stable). Patients with nephrotic-range proteinuria who are asymptomatic or who have edema that can be controlled with diuretics should be treated for nephrotic syndrome. Patients with hypertension should be given an ACE inhibitor or angiotensin II receptor blocker; these drugs may also benefit patients without hypertension by reducing proteinuria.

**Immunosuppressive therapy:** Immuno suppressants should be considered only for patients with symptomatic idiopathic nephrotic syndrome and for those most at risk of progressive disease. Older and chronically ill patients are at greater risk of infectious complications from immunosuppressants. No consensus protocol exists, but one approach

![Fig. 235-1. Electron microscopic features in immunologic glomerular disorders.](https://example.com)

uses methylprednisolone 1 g IV for 3 days, after which prednisone 0.5 mg/kg po once/day is given for the next 27 days. The following month, chlorambucil 0.1 to 0.2 mg/kg po once/day is given for 1 mo. These 2 monthly regimens are alternated for a total of 6 mo. This protocol remains controversial and should be used with caution, especially in the elderly because of the increased risk of infection. Some experts favor use of combinations of cyclophosphamide and corticosteroids because of their better safety profile.

For patients who are intolerant of cytotoxic drugs or who do not respond to them, cyclosporine 4 to 6 mg/kg po once/day for 4 mo may be beneficial. Therapies of unproven long-term value include IV immune globulin and NSAIDs.

**Minimal Change Disease**

(Lipoid Nephrosis; Nil Disease)

**Minimal change disease (MCD)** causes abrupt onset of edema and heavy proteinuria, mostly in children. Renal function is typically normal. Diagnosis is based on clinical findings or renal biopsy. Prognosis is excellent. Treatment is with corticosteroids or, in patients who do not respond, cyclophosphamide or cyclosporine.

MCD is the most common cause of nephrotic syndrome in children 4 to 8 yr (80 to 90% of childhood nephrotic syndrome), but it also occurs in adults (10 to 20% of adult nephrotic syndrome). The cause is almost always unknown, although rare cases may occur secondary to drug use (especially NSAIDs) and hematologic cancers (especially Hodgkin lymphoma).
MCD causes nephrotic syndrome, usually without hypertension or azotemia; microscopic hematuria occurs in about 20% of patients, mainly adults. Azotemia can occur in secondary cases and in patients > 60 yr. Albumin is lost in the urine of patients with MCD more so than larger serum proteins probably because MCD causes changes in the charge barrier that affect albumin selectively.

**Diagnosis**

- Renal biopsy in adults with idiopathic nephrotic syndrome

In children, the following:

- Sudden onset of unexplained nephrotic-range proteinuria that is mainly albumin
- Normal renal function
- Non-nephritic urine sediment
- Renal biopsy in atypical cases

Renal biopsy is required in atypical cases and in adults. Electron microscopy demonstrates edema with diffuse swelling (effacement) of foot processes of the epithelial podocytes (see Fig. 235-1). Complement and Ig deposits are absent on immunofluorescence. Although effacement is not observed in the absence of proteinuria, heavy proteinuria may occur with normal foot processes.

**Treatment**

- Corticosteroids
- Sometimes cyclophosphamide or cyclosporine

Spontaneous remissions occur in 40% of cases, but most patients are given corticosteroids. About 80 to 90% of patients respond to initial corticosteroid therapy (eg, prednisone 60 mg/m² po once/day for 4 to 6 wk in children and 1 to 1.5 mg/kg po once/day for 6 to 8 wk in adults), but 40 to 60% of responders relapse. Patients who respond (ie, have cessation of proteinuria or a diuresis if edema is present) should continue prednisone for another 2 wk and change to a maintenance regimen to minimize toxicity (2 to 3 mg/kg on alternate days for 4 to 6 wk in children and for 8 to 12 wk in adults, tapering during the next 4 mo). More prolonged initial therapy and slower tapering of prednisone lower relapse rates. Nonresponsiveness may be due to underlying focal sclerosis that was missed on biopsy due to sampling error.

In corticosteroid nonresponders (< 5% of children and > 10% of adults), frequent relapers, and corticosteroid-dependent patients, prolonged remission may be achieved with an oral cytotoxic drug (usually cyclophosphamide 2 to 3 mg/kg once/day for 12 wk or chlorambucil 0.15 mg/kg once/day for 8 wk). However, these drugs may suppress gonadal function (most serious in prepubertal adolescents), cause hemorrhagic cystitis, have mutagenic potential, and suppress bone marrow and lymphocyte function. Dosage should be monitored with frequent CBCs, and hemorrhagic cystitis should be sought by urinalysis. Adults, particularly if older or hypertensive, are more prone to adverse effects from these cytotoxic drugs. Another alternative is cyclosporine 3 mg/kg po bid, adjusted to obtain a whole-blood trough concentration of 50 to 150 μg/L (40 to 125 nmol/L).

Complete remission occurs in > 80% of patients treated with corticosteroids, and treatment is usually continued for 1 to 2 yr. However, half or more relapse, requiring treatment with the same or a different regimen. Patients responsive to cyclosporine frequently relapse when the drug is stopped.

Most patients who are unresponsive to these interventions respond to alternative therapies, including ACE inhibitors, thioguanine, levamisole, azathioprine, and mycophenolate mofetil; < 5% progress to renal failure.
Nephritic and Nephrotic Syndromes

Several glomerular disorders typically manifest with features of both nephritic and nephrotic syndromes. These disorders include fibrillary and immunotactoid glomerulopathies, membranoproliferative glomerulonephritis (GN), and lupus nephritis.

Fibrillary and Immunotactoid Glomerulopathies

Fibrillary and immunotactoid glomerulopathies are rare conditions defined pathologically by organized deposition of nonamyloid microfibrillar or microtubular structures within the renal mesangium and basement membrane.

Fibrillary and immunotactoid glomerulopathies are thought by some experts to be related disorders. They are found in about 0.6% of renal biopsy specimens, occur equally in men and women, and have been described in patients ≥ 10 yr. Average age at diagnosis is about 45. Mechanism is unknown, although deposition of immunoglobulin, particularly IgG κ and λ light chains and complement (C3), suggests immune system dysfunction. Patients may have accompanying paraproteinemia, cryoglobulinemia, plasma cell dyscrasia, hepatitis C infection, or SLE, or they may have a primary renal disease without evidence of systemic disease.

All patients have proteinuria, > 60% in the nephrotic range. Microscopic hematuria is present in about 60%; hypertension, in about 70%. Slightly > 50% have renal insufficiency at presentation.

Diagnosis

• Renal biopsy

Diagnosis is suggested by laboratory data and confirmed by renal biopsy. If nephrotic syndrome is present, testing is done as for other cases of nephrotic syndrome. Urinalysis usually shows features of nephritic and nephrotic syndromes. Serum C3 and C4 are usually measured and are occasionally decreased. Light microscopy of a biopsy specimen shows mesangial expansion by amorphous eosinophilic deposits and mild mesangial hypercellularity. Various other changes may be present on light microscopy (eg, crescent formation, membranoproliferative patterns). Congo red staining is negative for amyloid. Immunostaining reveals IgG and C3 and sometimes κ and λ light chains in the area of the deposits. Electron microscopy shows glomerular deposits consisting of extracellular, elongated, non-branching microfibrils or microtubules. The diameter of the microfibrils and microtubules varies from 9 nm to > 50 nm. Some experts distinguish immunotactoid from fibrillary glomerulopathy by the presence of microtubular (as opposed to smaller microfibrillar) structures in the deposits; others distinguish them by the presence of a related systemic illness such as a paraproteinemia, cryoglobulinemia, or SLE in immunotactoid GN.

Prognosis

The condition is usually slowly progressive with renal insufficiency, progressing to end-stage renal disease in 50% of patients within 2 to 4 yr. A more rapid decline is predicted within the presence of hypertension, nephrotic-range proteinuria, and renal insufficiency at presentation.

Treatment

Evidence to support specific treatments is lacking. Immunosuppressants have been used based on anecdotal evidence; success may be greater with corticosteroids when serum complement is decreased.

Membranoproliferative Glomerulonephritis

(Mesangiocapillary Glomerulonephritis; Lobular Glomerulonephritis)

Membranoproliferative GN is a heterogeneous group of disorders that share mixed nephritic and nephrotic features and microscopic findings. They mostly affect children. Cause is immune
complex deposition that is idiopathic or secondary to a systemic disorder. Diagnosis is by renal biopsy. Prognosis is generally poor. Treatment, when indicated, is with corticosteroids and antiplatelet drugs.

Membranoproliferative GN is a group of immune-mediated disorders characterized histologically by glomerular basement membrane (GBM) thickening and proliferative changes on light microscopy. There are 3 types, each of which may have primary (idiopathic) or secondary causes. Primary forms affect children and young adults between ages 8 and 30 and account for 10% of cases of nephrotic syndrome in children; secondary causes tend to affect adults > 30. Men and women are affected equally. Reported familial cases of some types suggest genetic factors play a role in at least some cases. Many factors contribute to hypocomplementemia.

**Type I** (mesangial proliferation with immune deposits) accounts for 80 to 85% of cases. The idiopathic form is rare. Type I most commonly occurs secondary to one of the following:

- Systemic immune complex disorder (eg, SLE, mixed cryoglobulinemia, Sjogren's syndrome)
- Chronic infection (eg, bacterial endocarditis, HIV infection, hepatitis B or C infection, visceral abscess, ventriculoatrial shunt infection)
- Cancer (eg, chronic lymphocytic leukemia, lymphomas, melanoma)
- Other disorders (eg, partial lipodystrophy, C2 or C3 deficiencies, sarcoidosis, thrombotic microangiopathies)

**Type II** (similar to type I with less mesangial proliferation and with GBM dense deposits) accounts for 15 to 20%. It is probably an autoimmune disorder in which an IgG autoantibody (C3 nephritic factor) binds C3 convertase, rendering C3 resistant to inactivation; immunofluorescent staining identifies C3 around dense deposits and in mesangium.

**Type III** is thought to be a disorder similar to type I and accounts for few cases. Cause is unknown but may be related to immune complex (IgG, C3) deposition. An IgG autoantibody against the terminal component of complement is found in 70% of patients. Subepithelial deposits can occur focally and appear to disrupt the GBM.

**Symptoms and Signs**

Symptoms and signs are those of nephrotic syndrome in 60 to 80% of cases. Symptoms and signs of nephritic syndrome (acute GN) are presenting features in 15 to 20% of cases of type I and III disease and in a higher percentage of type II disease. At diagnosis, 30% of patients have hypertension and 20% have renal insufficiency; hypertension often develops even before GFR declines. Patients with type II disease have a greater incidence of ocular abnormalities (basal laminar drusen, diffuse retinal pigment alterations, diskiform macular detachment, choroidal neovascularization), which ultimately impair vision.

**Diagnosis**

- Renal biopsy
- Serum complement profile
- Serologic tests

Diagnosis is confirmed by renal biopsy, but other tests are done.

**Serum complement profiles** are more frequently abnormal in membranoproliferative GN than in other glomerular disorders and provide supportive evidence of the diagnosis. C3 levels are often low. In type I disease, C3 is depressed more often than C4 at diagnosis and decreases further during follow-up, but eventually normalizes. In type II disease, C3 is more frequently and severely reduced. In type III disease,
C3 is reduced but C4 is normal. C3 nephritic factor is detectable in 80% of patients with type II and in some patients with type I disease. Terminal complement nephritic factor is detectable in 20% of patients with type I, rare patients with type II, and 70% of patients with type III disease.

Serologic tests (eg, for SLE, hepatitis B and C virus, and cryoglobulinemia) are warranted to check for secondary causes of type I disease.

CBC, often obtained in the course of diagnostic evaluation, demonstrates normochromic-normocytic anemia, often out of proportion to the stage of renal insufficiency (possibly because of hemolysis), and thrombocytopenia from platelet consumption.

Prognosis

Prognosis is good if a condition causing secondary membranoproliferative GN is successfully treated. Idiopathic type I membranoproliferative GN often progresses slowly; type II progresses more rapidly. In general, the long-term prognosis is poor. End-stage renal disease occurs in 50% of patients at 10 yr and in 90% at 20 yr. Spontaneous remission occurs in < 5% with type II. Type I membranoproliferative GN recurs in 30% of kidney transplantation patients; type II recurs in 90%. Outcome tends to be worse if proteinuria is in the nephrotic range.

Treatment

- Corticosteroids for children with nephrotic-range proteinuria
- Dipyridamole and aspirin for adults

Underlying disorders are treated when possible. Specific therapy is probably not indicated in patients with non-nephrotic-range proteinuria because the disorder usually progresses slowly.

Among children with nephrotic-range proteinuria, treatment with corticosteroids, eg, prednisone 2.5 mg/kg po once/day on alternate days (maximum 80 mg/day) for 1 yr, followed by tapering to a maintenance dose of 20 mg on alternate days for 3 to 10 yr, may stabilize renal function. However, corticosteroid treatment may retard growth and cause hypertension.

Among adults, dipyridamole (225 mg po once/day) with aspirin (975 mg po once/day) for 1 yr may stabilize renal function at 3 to 5 yr, but at 10 yr there is no difference from placebo. Studies of antiplatelet therapy yield inconsistent results.

Alternate therapies are sometimes substituted for the usual treatments (eg, corticosteroids could exacerbate underlying hepatitis C). Alternative therapies include pegylated interferon alfa 2A or 2B (with addition of ribavirin if creatinine clearance is > 50 mL/min) for hepatitis C virus-associated disease and plasmapheresis with corticosteroids for concomitant severe cryoglobulinemia or rapidly progressive GN. ACE inhibitors may decrease proteinuria and help control hypertension.

Lupus Nephritis

Lupus nephritis is GN caused by SLE. Clinical findings include hematuria, nephrotic-range proteinuria, and, in advanced stages, azotemia. Diagnosis is based on renal biopsy. Treatment is of the underlying disorder and usually involves corticosteroids and cytotoxic or other immunosuppressant drugs.

Lupus nephritis is diagnosed in about 50% of SLE patients (see p. 305) and typically develops within 1 yr of diagnosis. However, the total incidence is probably > 90%, because renal biopsy in patients with suspected SLE without clinical evidence of renal disease shows changes of GN.

Pathophysiology

Pathophysiology involves immune complex deposition with development of GN. The immune complexes
consist of nuclear antigens (especially DNA), high-affinity complement-fixing IgG antinuclear antibodies, and antibodies to DNA. Subendothelial, intramembranous, subepithelial, or mesangial deposits are characteristic. Wherever immune complexes are deposited, immunofluorescence staining is positive for complement and for IgG, IgA, and IgM in varying proportions. Epithelial cells may proliferate, forming crescents. Classification of lupus nephritis is based on histologic findings (see Table 235-6).

**Antiphospholipid syndrome nephropathy:** This syndrome may occur with or without lupus nephritis in up to one third of patients with SLE. In the antiphospholipid antibody syndrome, circulating lupus anticoagulant (see p. 975) causes microthrombi, endothelial damage, and cortical ischemic atrophy. Antiphospholipid syndrome nephropathy increases a patient’s risk of hypertension and renal insufficiency or failure compared with lupus nephritis alone.

**Symptom and Signs**

The most prominent symptoms and signs are those of SLE; patients who present with renal disease may have edema, foaming urine, hypertension, or a combination.

**Diagnosis**

- Urinalysis and serum creatinine (all patients with SLE)
- Renal biopsy

Diagnosis is suspected in all patients with SLE, particularly in patients who have proteinuria, microscopic hematuria, RBC casts, or hypertension. Diagnosis is also suspected in patients with unexplained hypertension, elevated serum creatinine levels, or abnormalities on urinalysis who have clinical features suggesting SLE.

Urinalysis is done and serum creatinine is measured. If either is abnormal, renal biopsy is usually done to confirm the diagnosis and classify the disorder histologically. Histologic classification helps determine prognosis and direct treatment.

Some of the histologic subtypes are similar to other glomerulopathies; eg, membranous and diffuse proliferative lupus nephritis are histologically similar to idiopathic membranous GN and type I membranoproliferative GN, respectively. Overlap between these categories is substantial, and patients may progress from one class to another over time.

Renal function and SLE activity should be monitored regularly. A rising serum creatinine level reflects deteriorating renal function, while a falling serum complement level or a rising anti-DNA antibody titer suggests increased disease activity.

**Prognosis**

Class of nephritis influences renal prognosis (see Table 235-6), as do other renal histologic features. Renal biopsies are scored with a semiquantitative activity score and with a chronicity index.

The **activity score** describes the degree of inflammation. The score is based on cellular proliferation, fibrinoid necrosis, cellular crescents, hyaline thrombi, wire loop lesions, glomerular leukocyte infiltration, and interstitial mononuclear cell infiltration.

The **chronicity index** describes the degree of scarring. It is based on presence of glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. The chronicity index predicts progression of lupus nephritis to renal failure. A mild to moderate chronicity score suggests at least partially reversible disease, whereas more severe chronicity scores may indicate irreversible disease. The activity score is
less well correlated with disease progression, perhaps because it is based on the degree of inflammation, which is more reversible with treatment.

Patients with lupus nephritis are at high risk of cancers, primarily B-cell lymphomas. Risk of atherosclerotic complications (eg, coronary artery disease, ischemic stroke) is also high, because of frequent vasculitis, hypertension, hyperlipidemia, and use of corticosteroids.

**Treatment**

- Angiotensin inhibition for hypertension or proteinuria
- Cyclophosphamide and prednisone for active, potentially reversible nephritis

**Immunosuppression:** Treatment is toxic and thus is reserved for nephritis that has the following characteristics:

- Is active
- Has the potential for a poor prognosis
- Is potentially reversible

Activity is estimated by the activity score as well as clinical criteria (eg, urine sediment, increasing urine protein, increasing serum creatinine). Many experts believe that a mild to moderate chronicity score, because it suggests reversibility, should provoke more aggressive therapy than a more severe chronicity score. Nephritis with the potential for deterioration and for reversibility is usually class III or IV; it is unclear whether class V nephritis warrants aggressive treatment.

Treatment usually combines cytotoxic drugs, corticosteroids, and sometimes other immunosuppressants. Induction is with cyclophosphamide, which is usually given in IV boluses (monthly for up to 6 mo) beginning with 0.75 g/m² in a saline solution over 30 to 60 min and, assuming a WBC count > 3000/µL, increasing to a maximum of 1 g/m². Oral or IV fluid administration to create rapid urine flow minimizes the bladder toxicity of cyclophosphamide, as does mesna (see p. 308). Prednisone is begun at 60 to 80 mg po once/day and tapered according to response to 20 to 25 mg every other day over 6 to 12 mo. The amount of prednisone is determined by the extrarenal manifestations and number of relapses. Relapses are usually treated with increasing doses of prednisone.

Many experts are replacing the more toxic cyclophosphamide maintenance regimens (after induction with 6 or 7 monthly IV cyclophosphamide doses) with protocols using mycophenolate mofetil (500 mg to 1 g po bid) or azathioprine (2 mg/kg po once/day, maximum 150 to 200 mg/day). Chlorambucil, cyclosporine, and tacrolimus have also been used, but relative efficacies are not clear. Low-dose prednisone (0.05 to 0.2 mg/kg po once/day) is continued and titrated based on disease activity. Duration of maintenance therapy is at least 1 yr.

**Other treatments:** Angiotensin inhibition with an ACE inhibitor or angiotensin II receptor blocker is indicated for patients with even mild hypertension (eg, BP > 130/80 mm Hg) or proteinuria. Also, hyperlipidemia and risk factors for atherosclerosis should be treated aggressively.

Anticoagulation is of theoretical benefit for patients with antiphospholipid syndrome nephropathy, but the value of such treatment has not been established.
Chapter 236. Tubulointerstitial Diseases

Introduction

Tubulointerstitial diseases are clinically heterogeneous disorders that share similar features of tubular and interstitial injury. In severe and prolonged cases, the entire kidney may become involved, with glomerular dysfunction and even renal failure. The primary categories of tubulointerstitial disease are acute tubular necrosis and acute or chronic tubulointerstitial nephritis.

Pathophysiology

The kidneys are exposed to unusually high concentrations of toxins. The kidneys have the highest blood supply of all tissues (about 3.5 mL/g/min), and unbound solutes leave the circulation via glomerular filtration at ≥ 100 mL/min; as a result, toxic agents are delivered at a rate 50 times that of other tissues and in much higher concentrations. When urine is concentrated, the luminal surfaces of tubular cells may be exposed to molecule concentrations 300 to 1000 times greater than those of plasma. The fine brush border of proximal tubular cells exposes an enormous surface area. A countercurrent flow mechanism increases ionic concentration of the interstitial fluid of the medulla (and thereby increases urine concentration) up to 4 times the plasma concentration.

In addition, factors can affect cellular vulnerability after exposure to toxins. Tubular transport mechanisms separate drugs from their binding proteins, which normally protect cells from toxicity. Transcellular transport exposes the interior of the cell and its organelles to newly encountered chemicals. Binding sites of some agents (eg, sulfhydryl groups) may facilitate entry but retard exit (eg, heavy metals). Chemical reactions (eg, alkalization, acidification) may alter transport in either direction. Blockade of transport receptors may alter tissue exposure (eg, diuresis from blockade of adenosine A1 receptors may decrease exposure). Finally, the kidneys have the highest O2 and glucose consumption per gram of tissue and are therefore vulnerable to toxins affecting cell energy metabolism.

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is kidney injury characterized by acute tubular cell injury and dysfunction. Common causes are hypotension causing renal hypoperfusion and nephrotoxic drugs. The condition is asymptomatic unless it causes renal failure. The diagnosis is suspected when azotemia develops after a hypotensive event, severe sepsis, or drug exposure and is distinguished from prerenal azotemia by laboratory testing and response to volume expansion. Treatment is supportive.

Causes of ATN include the following:

- Hypotension (ischemic ATN; common)
- Nephrotoxins (common)
- Sepsis (common)
- Major surgery
- Third-degree burns covering > 15% of BSA
- The heme pigments myoglobin and hemoglobin (uncommon)
- Disorders resulting in other endogenous toxins, such as tumor lysis or multiple myeloma (uncommon)
- Poisons, such as ethylene glycol (uncommon)
- Herbal and folk remedies, such as ingestion of fish gallbladder in Southeast Asia (uncommon)
Common nephrotoxins include the following:

- Aminoglycosides
- Amphotericin B
- Cisplatin
- Radioccontrast (particularly agents with osmolality > 100 mL)
- NSAIDs

Massive volume loss, particularly in patients with septic or hemorrhagic shock or pancreatitis or in patients who have had serious surgery, increases the risk of ischemic ATN; patients with serious comorbidities are at highest risk. Serious surgery and advanced hepatobiliary disease, poor perfusion states, and advanced age increase the risk of aminoglycoside toxicity. Certain drug combinations (eg, aminoglycosides with amphotericin B) may be especially nephrotoxic. NSAIDs may cause several types of intrinsic kidney disease, including ATN. Toxic exposures cause patchy, segmental, tubular luminal occlusion with casts and cellular debris or segmental tubular necrosis.

ATN is more likely to develop in patients with the following:

- Baseline creatinine clearance < 47 mL/min
- Diabetes mellitus
- Preexisting hypovolemia or poor renal perfusion

**Symptoms and Signs**

ATN is usually asymptomatic but may cause symptoms or signs of acute renal failure, typically oliguria (see p. 2252) initially.

**Diagnosis**

- Differentiation from prerenal azotemia, based mainly on laboratory findings and, in the case of blood or fluid loss, response to volume expansion

ATN is suspected when serum creatinine rises ≥ 0.5 mg/dL/day above baseline after an apparent trigger (eg, hypotensive event, exposure to a nephrotoxin); the rise in creatinine may occur days after exposure to some nephrotoxins. ATN must be differentiated from prerenal azotemia because treatment differs. In prerenal azotemia, renal perfusion is decreased enough to elevate serum BUN out of proportion to creatinine, but not enough to cause ischemic damage to tubular cells. Prerenal azotemia can be caused by direct intravascular fluid loss (eg, from hemorrhage, GI tract or urinary losses) or by a relative decrease in effective circulating volume *without* loss of total body fluid (eg, in heart failure, portal hypertension with ascites). If fluid loss is the cause, volume expansion using IV normal saline solution normalizes serum creatinine level. If ATN is the cause, IV saline typically causes no rapid change in serum creatinine.

Laboratory findings also help distinguish ATN from prerenal azotemia (see Table 236-1).

**Prognosis**

In otherwise healthy patients, prognosis is good when the underlying insult is corrected; serum creatinine typically returns to normal or near-normal within 1 to 3 wk. In sick patients, even when acute renal failure is mild, morbidity and mortality are increased. Prognosis is better in patients who do not require ICU care.
(32% mortality) than in those who do (72% mortality). Predictors of mortality include mainly decreased urine volume (eg, anuria, oliguria) and severity of the underlying illness and comorbid disorders.

Cause of death is usually infection or the underlying disorder.

**Treatment**

- Supportive care

Treatment is supportive and includes stopping nephrotoxins whenever possible, maintenance of euvolemia, nutritional support, and treatment of infections (preferably with drugs that are not nephrotoxic). Diuretics are commonly used to maintain urine output in oliguric ATN but are of unproven benefit; there is no evidence to support use of mannitol or dopamine. General management of acute renal failure is discussed on p. 2440.

**Prevention**

Prevention includes the following:

- Maintaining euvolemia and renal perfusion in critically ill patients
- Avoiding nephrotoxic drugs when possible
- Closely monitoring renal function when nephrotoxic drugs must be used
- Taking measures to prevent contrast nephropathy
- Among patients with diabetes, controlling blood sugar levels

There is no evidence that loop diuretics, mannitol, or dopamine helps prevent ATN.

[Table 236-1. Laboratory Findings Distinguishing Acute Tubular Necrosis From Prerenal Azotemia]

**Contrast Nephropathy**

**Contrast nephropathy** is worsening of renal function after IV administration of radiocontrast and is usually temporary. Diagnosis is based on a progressive rise in serum creatinine 24 to 48 h after contrast is given. Treatment is supportive. Volume loading with isotonic saline before and after contrast administration may help in prevention.

All iodinated radiocontrast agents are nephrotoxic. However, risk is lower with newer contrast agents, which have a lower osmolality than older agents, whose osmolality is about 1400 to 1800 mOsm/kg. For example, 2nd-generation, low-osmolal agents (eg, iohexol, iopamidol, ioxaglate) have an osmolality of about 500 to 850 mOsm/kg, which is still higher than blood osmolality. Iodixanol, the first of the even newer iso-osmolal agents, has an osmolality of 290 mOsm/kg, about equal to that of blood.

The precise mechanism of radiocontrast toxicity is unknown but is suspected to be some combination of renal vasoconstriction and direct cytotoxic effects, perhaps through formation of reactive O2 species, causing ATN.

**Risk factors:** Risk factors for nephrotoxicity are the following:

- Older age
- Preexisting renal insufficiency (eg, serum creatinine > 1.5 mg/dL)
- Diabetes mellitus
• Heart failure

• Multiple myeloma

• High doses (eg, > 100 mL) of a hyperosmolar contrast agent (eg, during percutaneous coronary interventions)

• Factors that reduce renal perfusion, such as volume depletion or the concurrent use of NSAIDs or ACE inhibitors

Diagnosis

Diagnosis is based on a progressive rise in serum creatinine 24 to 48 h after a contrast study. Most patients have no symptoms. Renal function typically later returns to normal.

After femoral artery catheterization, contrast nephropathy may be difficult to distinguish from renal atheroembolism. Factors that can suggest renal atheroemboli include the following:

• Delay in onset of increased creatinine > 48 h after the procedure

• Presence of other atheroembolic findings (eg, in skin, toes)

• Persistently poor renal function

• Transient eosinophilia or eosinophiluria and low complement levels (measured if atheroemboli are seriously considered)

Treatment

Treatment is supportive.

Prevention

Prevention involves avoiding contrast when possible (eg, not using CT to diagnose appendicitis) and, when contrast is necessary, using the agent with the lowest osmolality for patients with risk factors. When contrast is given, mild volume expansion with isotonic NaCl (ie, 154 mEq/L) is recommended; 1 mL/kg/h is given beginning 6 to 12 h before contrast is given and continued for 6 to 12 h after the procedure. Infusion of NaHCO₃ has no proven advantage over normal saline and may even be harmful. Nephrotoxic drugs are avoided before and after the procedure. Acetylcysteine is an antioxidant that may be helpful; protocols vary, but acetylcysteine, 600 mg po bid the day before and the day of the procedure, may be given, combined with NaCl infusion. Acetylcysteine and volume expansion may be most helpful in patients with mild preexisting renal disease and exposure to a low dose of contrast.

Periprocedural continuous venovenous hemofiltration has no proven benefit compared with other less invasive strategies in preventing acute kidney injury in patients who have chronic kidney disease and who require high doses of contrast and also is not practical. Therefore, this procedure is not recommended. Patients undergoing regular hemodialysis for end-stage renal disease who require contrast do not need supplementary, prophylactic hemodialysis after the procedure.

Tubulointerstitial Nephritis

Tubulointerstitial nephritis is primary injury to renal tubules and interstitium resulting in decreased renal function. The acute form is most often due to allergic drug reactions or to infections. The chronic form occurs with a diverse array of causes, including genetic or metabolic disorders, obstructive uropathy, and chronic exposure to environmental toxins or to certain drugs and herbs. Diagnosis is suggested by history and urinalysis and often confirmed by biopsy. Treatment and prognosis vary by the etiology and potential reversibility of the
disorder at the time of diagnosis.

Etiology

Tubulointerstitial nephritis can be primary, but a similar process can result from glomerular damage (see p. 2387) or renovascular disorders (see p. 2429).

Primary tubulointerstitial nephritis may be

- Acute (see Table 236-2)
- Chronic (see Table 236-3)

**Acute tubulointerstitial nephritis (ATIN):** ATIN involves an inflammatory infiltrate and edema affecting the renal interstitium that often develops over days to months. Over 95% of cases result from infection or an allergic drug reaction. A syndrome of ATIN associated with uveitis (renal-ocular syndrome) also occurs and is idiopathic. ATIN causes acute renal insufficiency or failure; severe cases, delayed therapy, or continuance of an offending drug can lead to permanent injury with chronic renal failure.

[Table 236-2. Causes of Acute Tubulointerstitial Nephritis]

[Table 236-3. Causes of Chronic Tubulointerstitial Nephritis]

**Chronic tubulointerstitial nephritis (CTIN):** CTIN arises when chronic tubular insults cause gradual interstitial infiltration and fibrosis, tubular atrophy and dysfunction, and a gradual deterioration of renal function, usually over years. Glomerular involvement (glomerulosclerosis) is much more common in CTIN than in ATIN. Causes of CTIN are myriad; they include immunologically mediated disorders, infections, reflux or obstructive nephropathy, drugs, and other disorders. CTIN due to toxins, metabolic derangements, hypertension, and inherited disorders results in symmetric and bilateral disease; with other causes, renal scarring may be unequal and involve only one kidney. Some well-characterized forms of CTIN include analgesic, metabolic, heavy metal, and reflux nephropathy and myeloma kidney (hereditary cystic kidney diseases are discussed in Ch. 234).

Symptoms and Signs

**ATIN:** Symptoms and signs of ATIN may be nonspecific and are often absent unless symptoms and signs of renal failure develop. Many patients develop polyuria and nocturia (due to a defect in urinary concentration and Na reabsorption). Symptom onset may be as long as several weeks after initial toxic exposure or as soon as 3 to 5 days after a 2nd exposure; extremes in latency range from 1 day with rifampin to 18 mo with an NSAID. Fever and urticarial rash are characteristic early manifestations of drug-induced ATIN, but the classically described triad of fever, rash, and eosinophilia is insensitive. Abdominal pain, weight loss, and bilateral renal masses (caused by interstitial edema) may also occur in ATIN and with fever may mistakenly suggest renal cancer or polycystic kidney disease. Peripheral edema and hypertension are uncommon unless renal insufficiency or renal failure occurs.

**CTIN:** Symptoms and signs are generally absent in CTIN unless renal failure develops. Edema usually is not present, and BP is normal or only mildly elevated in the early stages. Polyuria and nocturia may develop.

Diagnosis

- Risk factors
- Active urinary sediment, particularly with sterile pyuria (including eosinophils)
- Sometimes biopsy
Few clinical and routine laboratory findings are specific. Thus, suspicion should be high when the following are present:

- Typical symptoms or signs
- Risk factors, particularly a temporal relationship between onset and use of a potentially causative drug
- Characteristic urinalysis findings, particularly sterile pyuria (including eosinophils)
- Modest proteinuria, usually < 1 g/day (except with use of NSAIDs, which may cause nephrotic-range proteinuria)
- Evidence of tubular dysfunction (eg, renal tubular acidosis, Fanconi syndrome)

Other tests (eg, imaging) may be necessary to differentiate ATIN or CTIN from other disorders. Renal biopsy is sometimes done.

**ATIN:** Signs of active kidney inflammation (active urinary sediment), including RBCs, WBCs, and WBC casts, and absence of bacteria on culture (sterile pyuria) are typical; marked hematuria and dysmorphic RBCs are uncommon. Eosinophiluria has a positive predictive value of 50% (specificity of about 85 to 93%) and a negative predictive value of up to 90% for ATIN (sensitivity of about 63 to 91%). Thus, the presence of urinary eosinophils is not diagnostic, but their absence significantly decreases the likelihood of the diagnosis. Proteinuria is usually minimal but may reach nephrotic range with combined ATIN-glomerular disease induced by NSAIDs, ampicillin, rifampin, interferon alfa, or ranitidine. Blood test findings of tubular dysfunction include hypokalemia (caused by a defect in K reabsorption) and a nonanion gap metabolic acidosis (caused by a defect in HCO₃⁻ reabsorption or acid excretion).

Ultrasoundography, radionuclide scanning, or both may be needed to differentiate ATIN from other causes of acute renal failure, such as acute tubular necrosis. In ATIN, ultrasonography may show kidneys that are greatly enlarged and echogenic because of interstitial inflammatory cells and edema. Radionuclide scans may show kidneys avidly taking up radioactive gallium-67 or radionuclide-labeled WBCs. Positive scans strongly suggest ATIN (and indicate that acute tubular necrosis is less likely), but a negative scan does not exclude ATIN.

**Renal biopsy** is usually reserved for patients with the following:

- An uncertain diagnosis
- Progressive renal injury
- No improvement after potential causative drugs are stopped

In ATIN, glomeruli are usually normal. The earliest finding is interstitial edema, typically followed by interstitial infiltration with lymphocytes, plasma cells, eosinophils, and a few PMNs. In severe cases, inflammatory cells can be seen invading the space between the cells lining the tubular basement membrane (tubulitis); in other specimens, granulomatous reactions resulting from exposure to methicillin, sulfonamides, mycobacteria, or fungi may be seen. The presence of noncaseating granulomas suggests sarcoidosis. Immunofluorescence or electron microscopy seldom reveals any pathognomonic changes.

**CTIN:** Findings of CTIN are generally similar to those of ATIN, although urinary RBCs and WBCs are uncommon. Because CTIN is insidious in onset and interstitial fibrosis is common, imaging tests may show small kidneys with evidence of scarring and asymmetry.

In CTIN, renal biopsy is not often done for diagnostic purposes but has helped characterize the nature and progression of tubulointerstitial disease. Glomeruli vary from normal to completely destroyed. Tubules may be absent or atrophied. Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts. The interstitium contains varying degrees of inflammatory cells and fibrosis.
Nonscarred areas appear almost normal. Grossly, the kidneys are small and atrophic.

**Prognosis**

In drug-induced ATIN, renal function usually recovers within 6 to 8 wk when the offending drug is stopped, although some residual scarring is common. Recovery may be incomplete, with persistent azotemia above baseline. When other factors cause ATIN, histologic changes usually are reversible if the cause is recognized and removed; however, some severe cases progress to fibrosis and renal failure. Regardless of cause, irreversible injury is suggested by the following:

- Diffuse rather than patchy interstitial infiltrate
- Significant interstitial fibrosis
- Delayed response to prednisone
- Acute kidney injury lasting > 3 wk

In CTIN, prognosis depends on the cause and on the ability to recognize and stop the process before irreversible fibrosis occurs. Many genetic (eg, cystic kidney disease), metabolic (eg, cystinosis), and toxic (eg, heavy metal) causes may not be modifiable, in which case CTIN usually evolves to end-stage renal disease.

**Treatment**

- Treatment of cause

  - Corticosteroids for immune-mediated and sometimes drug-induced tubulointerstitial nephritis

Treatment of both ATIN and CTIN is management of the cause. For immunologically induced disease in ATIN and perhaps CTIN and sometimes drug-induced ATIN, corticosteroids (eg, prednisone 1 mg/kg po once/day with gradual tapering of the dose over 4 to 6 wk) may accelerate recovery. Treatment of CTIN often requires supportive measures such as controlling BP and treating anemia associated with kidney disease. In patients with CTIN and progressive renal injury, ACE inhibitors or angiotensin II receptor blockers may slow disease progression.

**Analgesic Nephropathy**

Analgesic nephropathy (AN) is CTIN caused by cumulative lifetime use of large amounts (eg, ≥ 2 kg) of certain analgesics.

AN was originally described in conjunction with overuse of combination analgesics containing phenacetin (typically with aspirin, acetaminophen, codeine, or caffeine). However, despite removal of phenacetin from the market, AN continued to occur. Studies to identify the causal agent are equivocal, but acetaminophen, aspirin, and other NSAIDs have been implicated. Mechanism is unclear. Whether COX-2 inhibitors cause AN is not known, but these drugs probably can cause ATIN and nephrotic syndrome due to minimal change disease or membranous nephropathy.

AN predominates in women (peak incidence, 50 to 55 yr) and, in the US, is responsible for 3 to 5% of cases of end-stage renal disease (13 to 20% in Australia and South Africa).

Patients present with renal insufficiency and usually non-nephrotic proteinuria with a bland urinary sediment or sterile pyuria. Hypertension, anemia, and impaired urinary concentration are common once renal insufficiency develops. Flank pain and hematuria are signs of papillary necrosis that occur late in the course of disease. Chronic complaints of musculoskeletal pain, headache, malaise, and dyspepsia may be related to long-term analgesic use rather than AN.

Diagnosis is based on history of chronic analgesic use and noncontrast CT. CT signs of AN are the
following:

- Decreased renal size
- Bumpy contours, defined as at least 3 indentations in the normally convex outline of the kidney
- Papillary calcifications

The combination of these findings has a sensitivity of 85% and a specificity of 93% for early diagnosis, but these specificity and sensitivity numbers are based on studies done when use of phenacetin-containing analgesics was widespread.

Renal function stabilizes when analgesics are stopped unless renal insufficiency is advanced, in which case it may progress to renal failure. Patients with AN are at greater risk of transitional cell carcinomas of the urinary tract.

**Metabolic Nephropathies**

Tubulointerstitial disorders can result from several metabolic disturbances.

**Acute urate nephropathy:** This disorder is not a true form of ATIN but rather an intraluminal obstructive uropathy caused by uric acid crystal deposition within the lumen of renal tubules; acute oliguric or anuric kidney injury results. Causes include the following:

- Tumor lysis syndrome (see p. 1075) after treatment of lymphoma, leukemia, or other myeloproliferative disorders (the most common cause)
- Seizures
- Treatment of solid tumors
- Rare primary disorders of urate overproduction (hypoxanthine-guanine phosphoribosyltransferase deficiency) or overexcretion due to decreased proximal tubule reabsorption (Fanconi-like syndromes).

Typically, no symptoms are present. Diagnosis is suspected when acute kidney injury occurs in patients with marked hyperuricemia (> 15 mg/dL). Urinalysis results may be normal or may show urate crystals.

Prognosis for complete recovery of renal function is excellent if treatment is initiated rapidly. Treatment is usually with allopurinol plus aggressive IV hydration in patients with normal cardiac and renal function. Supportive measures are indicated. Hemodialysis may be recommended to remove excess circulating urate in severe cases where diuresis cannot be induced with a loop diuretic and IV saline.

Prevention is indicated for patients at high risk (eg, those at risk of tumor lysis syndrome). Prevention is by use of allopurinol 300 mg po bid to tid plus saline loading to maintain a urine output > 2.5 L/day before chemotherapy or radiation therapy. Urate oxidase (rasburicase), which catalyzes urate to a much more soluble compound, is also preventive and is being more commonly used in patients with severe hyperuricemia. However, patients given rasburicase must be carefully monitored because the drug must be given IV and can cause anaphylaxis, hemolysis, and other adverse effects.

**Chronic urate nephropathy:** This condition is CTIN caused by deposition of Na urate crystals in the medullary interstitium in patients with chronic hyperuricemia. Sequelae are chronic inflammation and fibrosis, with ensuing chronic renal insufficiency and renal failure. Chronic urate nephropathy was once common in patients with tophaceous gout but is now rare because gout is more often effectively treated. A bland urine sediment and hyperuricemia disproportionate to the degree of renal insufficiency (eg, urate > 9 mg/dL with serum creatinine < 1.5 mg/dL, or > 10 mg/dL with serum creatinine 1.5 to 2 mg/dL, and > 12 mg/dL with more advanced renal failure) are suggestive but nonspecific; many causes of tubulointerstitial diseases may have these findings, lead nephropathy being the most common. Treatment is that of hyperuricosuria (see p. 353).
Hyperoxaluria: Hyperoxaluria is a common cause of nephrolithiasis but an uncommon cause of acute and chronic tubulointerstitial nephritis. Causes and prevention of hyperoxaluria are discussed elsewhere (see p. 2369).

Hypercalcemia: Hypercalcemia (see p. 843) causes nephropathy by 2 mechanisms. Severe (> 12 mg/dL) temporary hypercalcemia may cause reversible renal insufficiency by renal vasoconstriction and natriuresis-induced volume depletion. Long-standing hypercalcemia and hypercalciuria lead to CTIN with calcification and necrosis of tubular cells, interstitial fibrosis, and calcification (nephrocalcinosis). Common associated findings include

- Nephrolithiasis
- Renal tubular acidosis
- Nephrogenic diabetes insipidus

Diagnosis is based on presence of hypercalcemia and unexplained renal insufficiency; nephrocalcinosis can be detected by ultrasonography or noncontrast CT. Treatment is management of hypercalcemia.

Chronic hypokalemia: Chronic hypokalemia of a moderate to severe degree may cause nephropathy with impaired urinary concentration and vacuolation of proximal tubular cells and occasionally of distal tubular cells. Chronic interstitial inflammatory changes, fibrosis, and renal cysts have been found in renal biopsies of patients with hypokalemia of ≥ 1 mo. Treatment consists of correction of the underlying disorder and oral K supplements. Although the hypokalemia as well as the number and size of the cysts are reversible, the CTIN and renal insufficiency may be irreversible.

Heavy Metal Nephropathy

Exposure to heavy metals and other toxins can result in tubulointerstitial disorders.

Lead: CTIN results as lead accumulates in proximal tubular cells. Short-term lead exposure causes proximal tubular dysfunction, including decreased urate secretion and hyperuricemia (urate is the substrate for saturnine gout), aminoaciduria, and renal glucosuria. Chronic lead exposure (ie, for 5 to ≥ 30 yr) causes progressive tubular atrophy and interstitial fibrosis, with renal insufficiency, hypertension, and gout. However, chronic low-level exposure may cause renal insufficiency and hypertension independent of tubulointerstitial disease. The following groups are at highest risk:

- Children exposed to lead paint dust or chips
- Welders
- Battery workers
- Drinkers of moonshine alcohol

Exposed children may develop nephropathy during adulthood.

Hyperuricemia disproportionate to the degree of renal insufficiency (eg, urate > 9 mg/dL with serum creatinine < 1.5 mg/dL, or > 10 mg/dL with serum creatinine 1.5 to 2 mg/dL, and > 12 mg/dL with more advanced renal failure) and a bland urinary sediment are common. Diagnosis is usually made by measuring whole blood lead levels. Alternatively, x-ray fluorescence may be used to detect increased bone lead concentrations, which reflect high cumulative lead exposure. Treatment with chelation therapy (see p. 3344) can stabilize renal function, but recovery may be incomplete.

Cadmium: Cadmium from contaminated water, food, and tobacco and, mainly, from workplace exposures can cause nephropathy. It can also cause a glomerulopathy that is usually asymptomatic. Early manifestations of cadmium nephropathy are those of tubular dysfunction, including low molecular weight
tubular proteinuria (eg, β2-microglobulin), aminoaciduria, and renal glucosuria. Symptoms and signs, when they occur, are attributable to chronic renal insufficiency and failure. Renal disease follows a dose-response curve. Diagnosis is likely with the following:

- History of occupational exposure
- Increased levels of urinary β2-microglobulin (missed by urinary dipstick protein testing but detected using radioimmunoassay)
- Increased urinary cadmium levels (> 7 μg/g creatinine)

Treatment is elimination of cadmium exposure; chelation with Na calcium edetate (EDTA) may increase cadmium nephrotoxicity. Tubular proteinuria usually is irreversible.

**Other heavy metals:** Other heavy metals that are nephrotoxic include

- Copper
- Gold
- Uranium
- Arsenic
- Iron
- Mercury
- Bismuth
- Chromium

All cause tubular damage and dysfunction (eg, tubular proteinuria, aminoaciduria) as well as tubular necrosis, but glomerulopathies may predominate with some compounds (mercury, gold). Treatment involves removal of the patient from further exposure and either or both of the following:

- Chelating agents (copper, arsenic, bismuth)
- Dialysis (chromium, arsenic, bismuth), often used when chelation fails or simultaneously with chelation for severe arsenic poisoning

**Reflux Nephropathy**

Reflux nephropathy is renal scarring presumably induced by vesicoureteral reflux of infected urine into the renal parenchyma. The diagnosis is suspected in children with UTI or a family history. Diagnosis is by voiding cystourethrography or radionuclide cystography. Children with moderate or severe reflux are treated with prophylactic antibiotics or surgical correction.

Traditionally, the mechanism of renal scarring has been thought to be chronic pyelonephritis. However, reflux is probably the single most important factor, and factors unrelated to reflux or pyelonephritis (eg, congenital factors) can contribute. Vesicoureteral reflux (VUR) affects about 1% of newborns and 30 to 45% of young children with a febrile UTI (see p. 2844); it is common among children with renal scars and, for unknown reasons, is less common among black children than white children. Familial predisposition is common. Children with gross reflux (up to the renal pelvis plus ureteral dilatation) are at highest risk of scarring and subsequent renal failure.

Reflux requires incompetent ureterovesical valves or mechanical obstruction in the lower urinary tract. Young children with shorter intravesical portions of the ureter are most susceptible; normal growth usually
results in spontaneous cessation of intrarenal and vesicoureteral reflux by age 5. New scars in children > 5 yr are unusual but may occur after acute pyelonephritis.

**Symptoms and Signs**

Few symptoms and signs other than occasional UTI are present in young children, and the diagnosis is often overlooked until adolescence, when patients present with polyuria, nocturia, hypertension, symptoms and signs of renal insufficiency, laboratory abnormalities, or a combination.

**Diagnosis**

- Voiding cystourethrography or radionuclide cystography

The diagnosis may be suspected prenatally or postnatally. Diagnosis and staging of reflux nephropathy (prenatal or postnatal presentation) are made by a voiding cystourethrogram (VCUG), which can demonstrate the degree of ureteral dilatation. Radionuclide cystography (RNC) can also be used; it provides less anatomic detail than VCUG but involves less radiation exposure. Because these tests involve catheterization (and risk of UTI) as well as radiation exposure, thresholds for obtaining them can be controversial. Renal scarring is diagnosed with technetium-99m-labeled dimercaptosuccinic acid (DMSA) radionuclide scanning.

**Prenatal presentation:** The diagnosis is suspected prenatally if ultrasonography, done because of a family history or for unrelated reasons, shows hydronephrosis; 10 to 40% of such patients are diagnosed postnatally with VUR. Some experts recommend VCUG or RNC only if family history is strong or if postnatal renal ultrasonography is markedly or persistently abnormal; however, it is not clear whether renal ultrasonography is sufficiently sensitive to detect VUR. DMSA scanning is typically done in neonates (as well as infants < 6 mo) who have worrisome UTIs (eg, febrile or recurrent UTIs).

**Postnatal presentation:** VUR is suspected postnatally in patients with any of the following:

- UTI at age ≤ 3 yr
- Febrile UTI at age ≤ 5 yr
- Recurrent UTIs in children
- UTI in males
- Strong family history, such as a sibling with VUR (controversial)
- Adults (or children > 5 yr) with recurrent UTI in whom renal ultrasonography reveals scarring or a urinary tract anatomic abnormality

Laboratory abnormalities may include proteinuria, Na wasting, hyperkalemia, metabolic acidosis, renal insufficiency, or a combination. Testing for these patients is with RNC or VCUG. DMSA scanning may be done for infants or children with UTIs as listed above.

In older children in whom reflux is no longer active, a VCUG may not show reflux, although the DMSA scan shows scarring; cystoscopy can demonstrate evidence of previous reflux at ureteral orifices. Thus, DMSA scanning and cystoscopy may be done if prior reflux is suspected but not confirmed. Renal biopsy at this late stage shows CTIN and focal glomerulosclerosis, the cause of mild (1 to 1.5 g/day) to nephrotic-range proteinuria.

**Treatment**

- Usually prophylactic antibiotics
- Surgical treatment if VUR is moderate or severe
Treatment is based on the unproven assumption that decreasing reflux and UTIs prevents renal scarring. Children with very mild VUR require no treatment, but they should be closely observed for symptoms of UTI. Children with moderate reflux are usually given antibiotics. However, drug therapy predisposes to new episodes of acute pyelonephritis, and it is not clear whether prophylactic antibiotics are more effective than close observation. Patients with severe reflux are at higher risk of renal insufficiency and are usually given antibiotic prophylaxis or undergo surgical interventions, including ureteral reimplantation or endoscopic injection of materials behind the ureter to prevent reflux (bladder contraction during voiding compresses the ureter between the bladder and the material). Incidence of new renal scars is similar in patients treated with surgery and with drugs.

Reflux spontaneously resolves in about 80% of young children within 5 yr.

**Myeloma-Related Kidney Disease**

Patients with multiple myeloma overproduce monoclonal Ig light chains (Bence Jones proteins); these light chains are filtered by glomeruli, are nephrotoxic, and can damage virtually all areas of the kidney parenchyma. Diagnosis is by urine tests (sulfosalicylic acid test or protein electrophoresis) or renal biopsy. Treatment focuses on the multiple myeloma and ensuring adequate urine flow.

Tubulointerstitial and glomerular damage are the most common types of renal damage. The mechanisms by which light chains damage nephrons directly are unknown. Hypercalcemia contributes to renal insufficiency by decreasing renal blood flow.

**Tubulointerstitial disease:** Light chains saturate the reabsorptive capacity of the proximal tubule, reach the distal nephron, and combine with filtered proteins and Tamm-Horsfall mucoprotein (secreted by cells of the thick ascending limb of Henle) to form obstructive casts. The term myeloma kidney or myeloma cast nephropathy generally refers to renal insufficiency caused by the tubulointerstitial damage that results. Factors that predispose to cast formation include the following:

- Low urine flow
- Radiocontrast agents
- Hyperuricemia
- NSAIDs
- Elevation of luminal NaCl concentration (eg, due to a loop diuretic)
- Increased intratubular Ca from the hypercalcemia that often occurs secondary to bone lysis in multiple myeloma

Other types of tubulointerstitial lesions that occur with Bence Jones proteinuria include proximal tubular transport dysfunction causing Fanconi syndrome and light chain interstitial deposition with inflammatory infiltrates and active tubular damage.

**Glomerulopathies:** Myeloma glomerulopathy has 2 common mechanisms: primary (AL) amyloidosis (see also p. 905) and glomerular light chain or rarely heavy chain deposition. AL amyloidosis results in glomerular deposition of AL amyloid in the mesangial, subepithelial, or subendothelial areas or a combination. Amyloid deposition is with randomly oriented, nonbranching fibrils composed of the variable regions of \(\lambda\) light chains. Light chain deposition disease (LCDD), which also can occur with lymphoma and Waldenstrom's macroglobulinemia, is glomerular deposition of nonpolymerized light chains (ie, without fibrils), generally the constant regions of \(\kappa\) chains.

Rarely, a nonproliferative, noninflammatory glomerulopathy that causes nephrotic-range proteinuria can develop in advanced myeloma-related renal disease. A proliferative glomerulonephritis occasionally
develops as an early form of LCDD with progression to membranoproliferative glomerulonephritis and nodular glomerulopathy reminiscent of diabetic nephropathy; nephrotic-range proteinuria is common.

Symptoms and Signs

Symptoms and signs are predominantly those of the myeloma (eg, skeletal pain, pathologic fractures, diffuse osteoporosis) and a normochromic-normocytic anemia.

Diagnosis

- Urine sulfosalicylic acid test or urine protein electrophoresis (myeloma kidney)
- Biopsy (glomerulopathy)

Diagnosis of myeloma-related kidney disease is suggested by the following combination of findings:

- Renal insufficiency
- Bland urine sediment
- Negative or trace-positive dipstick for protein (unless urine albumin is elevated in a patient with an accompanying nephrotic syndrome)

The diagnosis should be suspected even in patients without a history of or findings suggesting multiple myeloma. Diagnosis of light chain tubulointerstitial disease (myeloma kidney) is confirmed by a markedly positive urine sulfosalicylic acid test suggesting significant nonalbumin proteins, by urine protein electrophoresis (UPEP), or both. Diagnosis of glomerulopathy is confirmed by renal biopsy. Renal biopsy may demonstrate light chain deposition in 30 to 50% of patients with myeloma despite the absence of detectable serum or urine paraproteins by immuno-electrophoresis.

Prognosis

Kidney disease is a major predictor of overall prognosis in multiple myeloma. Prognosis is good for patients with tubulointerstitial and glomerular LCDD who receive treatment. Prognosis is worse for patients with AL amyloidosis, in whom amyloid deposition continues and progresses to renal failure in most cases. In either form without treatment, virtually all renal lesions progress to renal failure.

Treatment

- Management of multiple myeloma
- Prevention of volume depletion and maintenance of a high urine flow rate

Management of multiple myeloma (see p. 1031), prevention of volume depletion, and maintenance of a high urine flow rate are the primary treatments. In addition, factors that worsen renal function (eg, hypercalcemia, hyperuricemia, use of nephrotoxic drugs) should be avoided or treated. Several measures are often recommended but are of unproven efficacy. Plasmapheresis may be tried to remove light chains. Alkalization of the urine to help change the net charge of the light chain and reduce charge interaction with Tamm-Horsfall mucoprotein may make the light chains more soluble. Colchicine may be given to decrease secretion of Tamm-Horsfall mucoprotein into the lumen and to decrease the interaction with light chains, thus decreasing toxicity. Loop diuretics may be avoided to prevent volume depletion and high distal Na concentrations that can worsen myeloma-related kidney disease (loop diuretics are indicated if hypercalcemia is present).
Chapter 237. Renal Transport Abnormalities

Introduction

Many substances are secreted or reabsorbed in the renal tubule system, including electrolytes, protons, HCO\(_3\) molecules, and free water. Dysfunction of these processes can result in clinical syndromes. Syndromes are inherited, acquired, or both. Syndromes that almost always manifest in childhood (eg, Bartter syndrome, Gitelman's syndrome, cystinuria, Hartnup disease, and hypophosphatemic rickets) are discussed in Chapter 297.

Fanconi Syndrome

Fanconi syndrome consists of multiple defects in renal proximal tubular reabsorption, causing glucosuria, phosphaturia, generalized aminoaciduria, and HCO\(_3\) wasting. Symptoms in children are failure to thrive, growth retardation, and rickets. Symptoms in adults are osteomalacia and muscle weakness. Diagnosis is by showing glucosuria, phosphaturia, and aminoaciduria. Treatment is HCO\(_3\) replacement and measures directed at renal failure.

Etiology

Fanconi syndrome can be

- Hereditary
- Acquired

**Hereditary Fanconi syndrome:** This disorder usually accompanies another genetic disorder, particularly cystinosis. Cystinosis is an inherited (autosomal recessive) metabolic disorder in which cystine accumulates within cells and tissues (and is not excreted to excess in the urine as occurs in cystinuria—see p. 2990). Besides renal tubular dysfunction, other complications of cystinosis include eye disorders, hepatomegaly, hypothyroidism, and other manifestations.

Fanconi syndrome may also accompany Wilson's disease, hereditary fructose intolerance, galactosemia, glycogen storage disease, oculocerebrorenal syndrome (Lowe syndrome), mitochondrial cytopathies, and tyrosinemia. Inheritance patterns vary with the associated disorder.

**Acquired Fanconi syndrome:** This disorder may be caused by various drugs, including certain cancer chemotherapy drugs (eg, ifosfamide, streptozocin), antiretrovirals (eg, didanosine, cidofovir), and outdated tetracycline. All of these drugs are nephrotoxic. Acquired Fanconi syndrome also may occur after renal transplantation and in patients with multiple myeloma, amyloidosis, intoxication with heavy metals or other chemicals, or vitamin D deficiency.

Pathophysiology

Various defects of proximal tubular transport function occur, including impaired resorption of glucose, phosphate, amino acids, HCO\(_3\), uric acid, water, K, and Na. The aminoaciduria is generalized, and, unlike that in cystinuria, increased cystine excretion is a minor component. The basic pathophysiologic abnormality is unknown but may involve a mitochondrial disturbance. Low levels of serum phosphate cause rickets, which is worsened by decreased proximal tubular conversion of vitamin D to its active form.

Symptoms and Signs

In hereditary Fanconi syndrome, the chief clinical features—proximal tubular acidosis, hypophosphatemic rickets, hypokalemia, polyuria, and polydipsia—usually appear in infancy.

When Fanconi syndrome occurs because of cystinosis, failure to thrive and growth retardation are common. The retinas show patchy depigmentation. Interstitial nephritis develops, leading to progressive
renal failure that may be fatal before adolescence.

In acquired Fanconi syndrome, adults present with the laboratory abnormalities of renal tubular acidosis (proximal type 2), hypophosphatemia, and hypokalemia. They may present with symptoms of bone disease (osteomalacia) and muscle weakness.

**Diagnosis**

- Urine testing for glucose, phosphates, and amino acids

Diagnosis is made by showing the abnormalities of renal function, particularly glucosuria (in the presence of normal serum glucose), phosphaturia, and aminoaciduria. In cystinosis, slit-lamp examination may show cystine crystals in the cornea.

**Treatment**

- Sometimes NaHCO$_3$ or KHCO$_3$ or Na citrate or K citrate
- Sometimes K supplementation

Other than removing the offending nephrotoxin, there is no specific treatment. Acidosis may be lessened by giving tablets or solutions of Na or K HCO$_3$ or citrate, eg, Shohl's solution (Na citrate and citric acid; 1 mL is equivalent to 1 mmol of HCO$_3$) given 1 mEq/kg bid to tid or 5 to 15 mL after meals and at bedtime. K depletion may require replacement therapy with a K-containing salt. Hypophosphatemic rickets can be treated (see p. 2991). Renal transplantation has been successful in treating renal failure. However, when cystinosis is the underlying disease, progressive damage may continue in other organs and eventually result in death.

**Liddle Syndrome**

Liddle syndrome is a rare hereditary disorder in which the kidneys excrete K but retain too much Na and water, leading to hypertension. Symptoms are of hypertension, fluid retention, and metabolic alkalosis. Diagnosis is through measurement of urinary electrolytes. K-sparing diuretics provide the best treatment.

Liddle syndrome is a rare autosomal dominant disorder of renal epithelial transport that clinically resembles primary aldosteronism (see p. 799), with hypertension and hypokalemic metabolic alkalosis but without elevated plasma renin or aldosterone levels. The syndrome results from an inherently increased activity of the luminal membrane Na channels, which accelerates Na resorption and K secretion in the collecting tubule.

Patients with Liddle syndrome present at age < 35 yr. Hypertension and symptoms and signs of hypokalemia (see p. 832) and metabolic alkalosis occur.

**Diagnosis**

- Urine Na level
- Plasma renin and aldosterone levels

Diagnosis is suggested by the presence of hypertension in a young patient, particularly one with a positive family history. Low urine Na (< 20 mEq), normal plasma renin and aldosterone levels, and response to empiric treatment usually are considered sufficient to confirm the diagnosis. Definitive diagnosis can be achieved through genetic testing.

**Treatment**
Triamterene 100 to 200 mg po bid and amiloride 5 to 20 mg po once/day are both effective because they close Na channels. Spironolactone is ineffective.

**Nephrogenic Diabetes Insipidus**

(See also Central Diabetes Insipidus on p. 772.)

Nephrogenic diabetes insipidus (NDI) is an inability to concentrate urine due to impaired renal tubule response to ADH (vasopressin), which leads to excretion of large amounts of dilute urine. It can be inherited or occur secondary to conditions that impair renal concentrating ability. Symptoms and signs include polyuria and those related to dehydration and hypernatremia. Diagnosis is based on measurement of urine osmolality changes after water deprivation and administration of exogenous ADH. Treatment consists of adequate free water intake, thiazide diuretics, NSAIDs, and a low-salt, low-protein diet.

NDI is characterized by inability to concentrate urine in response to ADH. Central diabetes insipidus is characterized by lack of ADH. Either type of diabetes insipidus may be complete or partial.

**Etiology**

NDI can be

• Inherited
• Acquired

**Inherited NDI:** The most common inherited disorder is an X-linked trait that affects the arginine vasopressin (AVP) receptor 2 gene. In rare cases, NDI is caused by an autosomal recessive or autosomal dominant mutation that affects the aquaporin-2 gene. Except with the autosomal dominant form, patients who are homozygous are completely unresponsive to ADH. Patients who are heterozygous have normal or slightly impaired responsiveness to ADH.

**Acquired NDI:** Acquired NDI can occur when disorders (some of them heritable) or drugs disrupt the medulla or distal nephrons and impair urine concentrating ability, making the kidneys appear insensitive to ADH. These disorders include the following:

• Autosomal dominant polycystic kidney disease
• Nephronophthisis and medullary cystic kidney disease
• Sickle cell nephropathy
• Release of obstructing periureteral fibrosis
• Medullary sponge kidney
• Pyelonephritis
• Hypokalemic and hypercalcemic nephropathies
• Amyloidosis
• Sjogren's syndrome
• Bardet-Biedl syndrome
• Certain cancers (eg, myeloma, sarcoma)
• Many drugs, especially lithium, but also others (eg, demeclocycline, amphotericin B, aminoglycosides, cidofovir, cisplatin, foscarnet, ifosfamide, methoxyflurane, ofloxacin, orlistat, rifampin)

Acquired NDI can also be idiopathic. A mild form of acquired NDI can occur in any patient who is elderly or sick or who has acute or chronic renal insufficiency.

In addition, certain clinical syndromes can resemble NDI:

• The placenta can secrete vasopressinase during the 2nd half of pregnancy (a syndrome called gestational diabetes insipidus).

• After pituitary surgery, some patients secrete an ineffective ADH precursor rather than ADH.

Symptoms and Signs

Generation of large amounts of dilute urine (3 to 20 L/day) is the hallmark. Patients typically have a good thirst response, and serum Na remains near normal. However, patients who do not have good access to water or who cannot communicate thirst (eg, infants, elderly patients with dementia) typically develop hypernatremia from extreme dehydration. Hypernatremia may cause neurologic symptoms, such as neuromuscular excitability, confusion, seizures, or coma.

Infants with inherited NDI may develop brain damage with permanent intellectual disability if treatment is not started early. Even with treatment, physical growth is often retarded in affected children presumably because of frequent dehydration.

Diagnosis

• 24-h urine volume and osmolality

• Serum electrolytes

• Water deprivation test

NDI is suspected in any patient with polyuria (see also p. 2324). Initial testing includes 24-h urine collection (without fluid restriction) for volume and osmolality, and serum electrolytes.

Patients with NDI excrete > 50 mL/kg of urine/day (polyuria). If urine osmolality is < 300 mOsm/kg (water diuresis), central or nephrogenic diabetes insipidus is likely. With NDI, urine osmolality is typically < 200 mOsm/kg despite clinical signs of hypovolemia (normally, urine osmolality is high in patients with hypovolemia). If osmolality is > 300 mOsm/kg, solute diuresis is likely. Glucosuria and other causes of solute diuresis must be excluded.

Serum Na is mildly elevated (142 to 145 mEq/L) in patients with adequate free water intake but can be dramatically elevated in patients who do not have adequate access to free water.

The diagnosis is confirmed by a water deprivation test (see p. 773), which assesses the maximum urine concentrating ability and response to exogenous ADH. After 3 to 6 h of water deprivation, the maximal osmolality of urine in patients with NDI is abnormally low (< 400 mOsm/kg, usually < 300 mOsm/kg). NDI can be distinguished from central diabetes insipidus (lack of ADH) by administering exogenous ADH (aqueous vasopressin 5 units sc or desmopressin 10 μg intranasally) and measuring urine osmolality. In patients with central diabetes insipidus (see p. 772), urine osmolality increases 50 to 100% over the 2 h after administration of exogenous ADH (15 to 45% in partial central diabetes insipidus). Patients with NDI usually have only a minimal rise in urine osmolality (< 50 mOsm/kg; up to 45% in partial NDI).

Treatment

• Adequate free water intake
• Restriction of dietary salt and protein

• Correction of the cause

• Sometimes a thiazide diuretic, an NSAID, or amiloride

Treatment consists of ensuring adequate free water intake; providing a low-salt, low-protein diet; and correcting the cause or stopping any likely nephrotoxin. Serious sequelae are rare if patients can drink at will.

If symptoms persist despite these measures, drugs can be given to lower urine output. Thiazide diuretics (hydrochlorothiazide, 25 mg po once/day or bid) can paradoxically reduce urine output by diminishing water delivery to ADH-sensitive sites in the collecting tubules. NSAIDs (eg, indomethacin) or amiloride can also help.

Renal Glucosuria

(Renal Glycosuria)

Renal glucosuria is glucose in the urine without hyperglycemia; it results from either an acquired or an inherited, isolated defect in glucose transport or occurs with other renal tubule disorders.

Renal glucosuria is the excretion of glucose in the urine in the presence of normal blood glucose levels. The inherited form usually involves a reduction in the glucose transport maximum (the maximum rate at which glucose can be resorbed) and subsequent escape of glucose in the urine. The acquired form of renal glucosuria occurs primarily in advanced chronic kidney disease.

The inherited disorder is usually transmitted as an autosomal dominant trait but is occasionally recessive. Renal glucosuria may occur without any other abnormalities of renal function or as part of a generalized defect in proximal tubule function (see p. 2427). It also may occur with various systemic disorders, including Fanconi syndrome, cystinosis, Wilson's disease, hereditary tyrosinemia, and oculocerebrorenal syndrome (Lowe syndrome).

Renal glucosuria is asymptomatic and without serious sequelae. However, if there is an associated generalized defect in proximal tubular function, symptoms and signs may include hypophosphatemic rickets, volume depletion, short stature, muscle hypotonia, and ocular changes of cataracts or glaucoma (oculocerebrorenal syndrome) or Kayser-Fleischer rings (Wilson's disease). With such findings, transport defects other than glucosuria should be sought.

The disorder is typically initially noted on routine urinalysis. Diagnosis is based on finding glucose in a 24-h urine collection (when the diet contains 50% carbohydrate) in the absence of hyperglycemia (serum glucose < 140 mg/dL). To confirm that the excreted sugar is glucose and to exclude pentosuria, fructosuria, sucrosuria, maltosuria, galactosuria, and lactosuria, the glucose oxidase method should be used for all laboratory measurements. A normal result on an oral glucose tolerance test is also required for the diagnosis according to some experts.

Isolated renal glucosuria is benign; no treatment is necessary.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is acidosis and electrolyte disturbances due to impaired renal hydrogen ion excretion (type 1), impaired HCO₃⁻ resorption (type 2), or abnormal aldosterone production or response (type 4). (Type 3 is extremely rare and is not discussed.) Patients may be asymptomatic, display symptoms and signs of electrolyte derangements, or progress to chronic kidney disease. Diagnosis is based on characteristic changes in urine pH and electrolytes in response to provocative testing. Treatment corrects pH and electrolyte imbalances using alkaline agents, electrolytes, and, rarely, drugs.
RTA defines a class of disorders in which excretion of hydrogen ions or reabsorption of filtered HCO$_3^-$ is impaired, leading to a chronic metabolic acidosis (see p. 859) with a normal anion gap. Hyperchloremia is usually present, and secondary derangements may involve other electrolytes, such as K (frequently) and Ca (rarely—see Table 237-1).

Chronic RTA is often associated with structural damage to renal tubules and may progress to chronic kidney disease (see p. 2442).

**Type 1 (distal) RTA:** Type 1 is impairment in hydrogen ion secretion in the distal tubule, resulting in a persistently high urine pH (> 5.5) and systemic acidosis. Plasma HCO$_3^-$ is usually < 15 mEq/L, and hypokalemia, hypercalciuria, and decreased citrate excretion are often present. Hypercalciuria is the primary abnormality in some familial cases, with Ca-induced tubulointerstitial damage causing distal RTA. Nephrocalcinosis and nephrolithiasis are possible complications of hypercalciuria and hypocitraturia if urine is relatively alkaline.

This syndrome is rare. Sporadic cases occur most often in adults and may be primary (nearly always in women) or secondary. Familial cases usually first manifest in childhood and are most often autosomal dominant. Secondary type 1 RTA may result from various disorders, drugs, or kidney transplantation:

- Autoimmune disease with hypergamma-globulinemia, particularly Sjogren's syndrome or RA
- Kidney transplantation
- Nephrocalcinosis
- Medullary sponge kidney
- Chronic obstructive uropathy

[Table 237-1, Some Features of Different Types of Renal Tubular Acidosis*]

- Drugs (mainly amphotericin B, ifosfamide, and lithium)
- Cirrhosis
- Sickle cell anemia

K level may be high with chronic obstructive uropathy or sickle cell anemia.

**Type 2 (proximal) RTA:** Type 2 is impairment in HCO$_3^-$ resorption in the proximal tubules, producing a urine pH > 7 if plasma HCO$_3^-$ concentration is normal, and a urine pH < 5.5 if plasma HCO$_3^-$ concentration is already depleted from ongoing losses. This syndrome may occur as part of a generalized dysfunction of proximal tubules and can be associated with increased urinary excretion of glucose, uric acid, phosphate, amino acids, citrate, Ca, K, and protein. Osteomalacia or osteopenia (including rickets in children) may develop. Mechanisms may include hypercalciuria, hyperphosphaturia, alterations in vitamin D metabolism, and secondary hyperparathyroidism. Type 2 RTA is very rare and most often occurs in patients who have one of the following:

- Fanconi syndrome
- Light chain nephropathy due to multiple myeloma
- Various drug exposures (usually acetazolamide, sulfonamides, ifosfamide, outdated tetracycline, or streptozocin)
It sometimes has other etiologies, including vitamin D deficiency, chronic hypocalcemia with secondary hyperparathyroidism, kidney transplantation, heavy metal exposure, and other inherited diseases (eg, fructose intolerance, Wilson's disease, oculocerebrorenal syndrome [Lowe syndrome], cystinosis).

**Type 4 (generalized) RTA:** Type 4 results from aldosterone deficiency or unresponsiveness of the distal tubule to aldosterone. Because aldosterone triggers Na resorption in exchange for K and hydrogen, there is reduced K excretion, causing hyperkalemia, and reduced acid excretion. Hyperkalemia may decrease ammonia excretion, contributing to metabolic acidosis. Urine pH is usually appropriate for serum pH (usually < 5.5 when there is serum acidosis). Plasma HCO$_3^-$ is usually > 17 mEq/L. This disorder is the most common type of RTA. It typically occurs sporadically secondary to impairment in the reninaldosterone-renal tubule axis (hyporeninemic hypoaldosteronism), which occurs in patients with the following:

- Diabetic nephropathy
- Chronic interstitial nephritis

Other factors that can contribute to type 4 RTA include the following:

- ACE inhibitor use
- Aldosterone synthase type I or II deficiency
- Angiotensin II receptor blocker use
- Chronic kidney disease, usually due to diabetic nephropathy or chronic interstitial nephritis
- Congenital adrenal hyperplasia, particularly 21-hydroxylase deficiency
- Critical illness
- Cyclosporine use
- Heparin use (including low molecular weight heparins)
- HIV nephropathy (due, possibly in part, to infection with *Mycobacterium avium* complex or cytomegalovirus)
- Interstitial renal damage (eg, due to SLE, obstructive uropathy, or sickle cell disease)
- K-sparing diuretics (eg, amiloride, eplerenone, spironolactone, triamterene)
- NSAID use
- Obstructive uropathy
- Other drugs (eg, pentamidine, trimethoprim)
- Primary adrenal insufficiency
- Pseudohypoaldosteronism (type I or II)
- Volume expansion (eg, in acute glomerulonephritis or chronic kidney disease)

**Symptoms and Signs**

RTA is usually asymptomatic. However, bony involvement (eg, bone pain and osteomalacia in adults and rickets in children) may occur in type 2 and sometimes in type 1 RTA. Nephrolithiasis and
nephrocalcinosis are possible, particularly with type 1 RTA. Severe electrolyte disturbances are rare but can be life threatening. People with type 1 or type 2 RTA may show symptoms and signs of hypokalemia, including muscle weakness, hyporeflexia, and paralysis. Type 4 RTA is usually asymptomatic with only mild acidosis, but cardiac arrhythmias or paralysis may develop if hyperkalemia is severe. Signs of ECF volume depletion may develop from urinary water loss accompanying electrolyte excretion in type 2 RTA.

Diagnosis

- Suspected in patients with metabolic acidosis with normal anion gap or with unexplained hyperkalemia
- Serum and urine pH, electrolyte levels, and osmolalities
- Often, testing after stimulation (eg, with ammonium Cl, HCO$_3$ or a loop diuretic)

RTA is suspected in any patient with unexplained metabolic acidosis (low plasma HCO$_3$ and low blood pH) with normal anion gap. Type 4 RTA should be suspected in patients who have persistent hyperkalemia with no obvious cause, such as K supplements, K-sparing diuretics, or chronic kidney disease. ABG sampling is done to help confirm RTA and to exclude respiratory alkalosis as a cause of compensatory metabolic acidosis. Serum electrolytes, BUN, creatinine, and urine pH are measured in all patients. Further tests and sometimes provocative tests are done, depending on which type of RTA is suspected:

- **Type 1 RTA** is confirmed by a urine pH that remains > 5.5 during systemic acidosis. The acidosis may occur spontaneously or be induced by an acid load test (administration of ammonium Cl, 100 mg/kg po). Normal kidneys reduce urine pH to < 5.2 within 6 h of acidosis.

- **Type 2 RTA** is diagnosed by measurement of the urine pH and fractional HCO$_3$ excretion during an HCO$_3$ infusion (NaHCO$_3$, 0.5 to 1.0 mEq/kg/h IV). In type 2, urine pH rises above 7.5, and the fractional excretion of HCO$_3$ is > 15%. Because IV HCO$_3$ can contribute to hypokalemia, K supplements should be given in adequate amounts before infusion.

- **Type 4 RTA** is confirmed by a transtubular K concentration gradient of < 5 (normal value > 10), which indicates inappropriately low urinary K excretion, suggesting hypoaldosteronism or tubular unresponsiveness to aldosterone. The gradient is calculated by

\[
\text{Transtubular K gradient} = \frac{\text{Urine K/Plasma K}}{\text{Urine osmolality/Plasma osmolality}}
\]

Definitive diagnosis can be obtained by measuring plasma renin and aldosterone levels after provocation (eg, administering a loop diuretic and having the patient remain upright for 3 h) but is usually not necessary.

Treatment

- Varies by type
- Often alkali therapy
- Treatment of concomitant abnormalities related to K, Ca, and phosphate metabolism

Treatment consists of correction of pH and electrolyte balance with alkali therapy. Failure to treat RTA in children slows growth.

Alkaline agents such as NaHCO$_3$ or Na citrate help achieve a relatively normal plasma HCO$_3$
concentration (22 to 24 mEq/L). K citrate can be substituted when persistent hypokalemia is present or, because Na increases Ca excretion, when Ca calculi are present. Vitamin D (eg, ergocalciferol, 800 IU po once/day) and oral Ca supplements (Ca carbonate, 1250 mg or 500 mg elemental Ca$^{2+}$ tid) may also be needed to help reduce skeletal deformities resulting from osteomalacia or rickets.

**Type 1 RTA:** Adults are given NaHCO$_3$ or Na citrate (0.25 to 0.5 mEq/kg po q 6 h). In children, the total daily dose may need to be as much as 2 mEq/kg q 8 h; this dose can be adjusted as the child grows.

**Type 2 RTA:** Plasma HCO$_3$ cannot be restored to the normal range, but HCO$_3$ replacement should exceed the acid load of the diet (eg, NaHCO$_3$, 1 mEq/kg po q 6 h in adults or 2 to 4 mEq/kg q 6 h in children) to maintain serum HCO$_3$ at about 22 to 24 mEq/L because lower levels risk growth disturbance. However, excess HCO$_3$ replacement increases KHCO$_3$ losses in the urine. Thus, citrate salts can be substituted for NaHCO$_3$ and may be better tolerated.

K supplements or K citrate may be required in patients who become hypokalemic when given NaHCO$_3$ but is not recommended in patients with normal or high serum K levels. In difficult cases, treatment with low-dose hydrochlorothiazide (25 mg po bid) may stimulate proximal tubule transport functions. In cases of generalized proximal tubule disorder, hypophosphatemia and bone disorders are treated with phosphate and vitamin D supplementation to normalize the plasma phosphate concentration.

**Type 4 RTA:** Hyperkalemia is treated with volume expansion, dietary K restriction, and K-wasting diuretics (eg, furosemide 20 to 40 mg po once/day or bid titrated to effect). Alkalization is often unnecessary. A few patients need mineralocorticoid replacement therapy (fludrocortisone, 0.1 to 0.2 mg po once/day, often higher in hyporeninemic hypoaldosteronism); mineralocorticoid replacement should be used with caution, because it may exacerbate underlying hypertension, heart failure, or edema.
Chapter 238. Renovascular Disorders

Introduction

(See also Renovascular Hypertension on p. 2077.)

Vascular disorders of the kidneys may involve partial or complete occlusion of large, medium, or small renal vessels and most commonly affect the glomeruli (see p. 2387). Systemic vasculitis (see p. 312) also may affect glomeruli.

Benign Hypertensive Arteriolar Nephrosclerosis

Benign hypertensive arteriolar nephrosclerosis is progressive renal impairment caused by chronic, poorly controlled hypertension. Symptoms and signs of chronic kidney disease may develop (eg, anorexia, nausea, vomiting, pruritus, somnolence or confusion), as may signs of end-organ damage secondary to hypertension. Diagnosis is primarily clinical, supported by routine laboratory test findings. Treatment is strict BP control and support of renal function.

Benign hypertensive arteriolar nephrosclerosis results when chronic hypertension damages small blood vessels, glomeruli, renal tubules, and interstitial tissues. As a result, progressive chronic kidney disease develops.

Benign nephrosclerosis progresses to end-stage renal disease in only a small percentage of patients. However, because chronic hypertension and benign nephrosclerosis are common, benign nephrosclerosis is one of the most common diagnoses in patients with end-stage renal disease. It is termed benign to distinguish it from malignant arteriolar nephrosclerosis, which is a synonym for hypertensive emergency (see p. 2078).

Risk factors include older age, poorly controlled moderate to severe hypertension, and other renal disorders (eg, diabetic nephropathy). Blacks are at increased risk; it is unclear if the risk is increased because poorly treated hypertension is more common among blacks or because blacks are more genetically susceptible to hypertension-induced renal damage.

Symptoms and Signs

Symptoms and signs of chronic kidney disease, such as anorexia, nausea, vomiting, pruritus, somnolence or confusion, weight loss, and an unpleasant taste in the mouth, may develop (see p. 2443). Signs of hypertension-related end-organ damage may occur in the vasculature of the eyes and in the skin, CNS, and periphery.

Diagnosis

• History of hypertension
• Blood tests indicating renal failure
• Signs of hypertensive end-organ damage
• No other cause of chronic kidney disease

The diagnosis may be suspected when routine blood tests indicate deteriorating renal function (eg, elevated creatinine and BUN, hyperphosphatemia) in a hypertensive patient. Diagnosis is usually inferred because of the history and evidence of hypertension-related end-organ damage (eg, retinal changes, left ventricular hypertrophy) on physical examination. Hypertension should be present before onset of proteinuria and renal failure, and there should be no other clinically suspected cause of renal failure.

Urine testing should not suggest other causes of renal failure (eg, glomerulonephritis or hypertensive emergency). On urinalysis, there should be few cells or casts in the sediment, and protein excretion is...
usually < 1 g/day (it is occasionally higher and in the nephrotic range).

Ultrascanography is done only if other causes of renal failure must be excluded. It may show that kidney size is reduced. Renal biopsy is done only if the diagnosis remains unclear.

**Prognosis**

Prognosis usually depends on adequacy of BP control and degree of renal failure. Usually, renal impairment progresses slowly; after 5 to 10 yr, only 1 to 2% of patients develop clinically significant renal dysfunction.

**Treatment**

- **BP control**

Treatment involves strict BP control (see p. 2069). The BP goal is < 140/90 mm Hg, although < 130/80 mm Hg is more appropriate for patients with diabetes or chronic kidney disease. Most experts suggest low-dose thiazide diuretic therapy. Among patients with proteinuria, an ACE inhibitor or angiotensin II receptor blocker is added. Ca channel blockers and β-blockers can be added as needed; most patients require combination therapy for BP control. Weight loss, exercise, and salt and water restriction also help control BP. Chronic renal failure should be managed (see p. 2444).

**Renal Artery Stenosis and Occlusion**

Renal artery stenosis is a decrease in blood flow through one or both of the main renal arteries or their branches. Renal artery occlusion is a complete blockage of blood flow through one or both of the main renal arteries or its branches. Stenosis and occlusion are usually due to thromboemboli, atherosclerosis, or fibromuscular dysplasia. Symptoms of acute occlusion include steady, aching flank pain, abdominal pain, fever, nausea, vomiting, and hematuria. Acute renal failure may develop. Chronic, progressive stenosis causes refractory hypertension and may lead to chronic kidney disease. Diagnosis is by imaging tests (eg, CT angiography, magnetic resonance angiography). Treatment of acute occlusion is with anticoagulation and sometimes fibrinolytics and surgical or catheter-based embolectomy, or a combination. Treatment of chronic, progressive stenosis includes angioplasty with stenting, surgical bypass, and removal of an infarcted kidney.

Renal hypoperfusion results in hypertension (see Renovascular Hypertension on p. 2077), renal failure, and, if complete occlusion occurs, renal infarction and necrosis.

**Etiology**

Occlusion may be acute or chronic. Acute occlusion is usually unilateral. Chronic occlusion may be unilateral or bilateral.

**Acute occlusion:** The most common cause is thromboembolism. Emboli may originate in the heart (due to atrial fibrillation, after MI, or from vegetations due to bacterial endocarditis) or the aorta (as atheroemboli); less often, fat or tumor emboli are the cause. Thrombosis may occur in a renal artery spontaneously or after trauma, surgery, angiography, or angioplasty. Other causes of acute occlusion include dissection or rupture of a renal artery aneurysm.

Rapid, total occlusion of large renal arteries for 30 to 60 min results in infarction. The infarct is typically wedge-shaped, radiating outward from the affected vessel.

**Chronic progressive stenosis:** About 90% of cases are due to atherosclerosis, which is usually bilateral. Almost 10% of cases are due to fibromuscular dysplasia (FMD), which is commonly unilateral. Less than 1% of cases result from Takayasu's arteritis, Kawasaki disease, neurofibromatosis type 1, aortic wall hematoma, or aortic dissection.
Atherosclerosis develops primarily in patients > 50 (more often men) and usually affects the aortic orifice or proximal segment of the renal artery. Chronic progressive stenosis tends to become clinically evident after about 10 yr of atherosclerosis, causing renal atrophy and chronic kidney disease.

FMD is pathologic thickening of the arterial wall, most often of the distal main renal artery or the intrarenal branches. This disorder develops primarily in younger adults, particularly in women aged 20 to 50. It is more common among 1st-degree relatives of patients with FMD and among people with the ACE1 gene.

**Symptoms and Signs**

Manifestations depend on rapidity of onset, extent, whether unilateral or bilateral, and duration of renal hypoperfusion. Stenosis of one renal artery is often asymptomatic for a considerable time.

Acute complete occlusion of one or both renal arteries causes steady and aching flank pain, abdominal pain, fever, nausea, and vomiting. Gross hematuria, oliguria, or anuria may occur; hypertension is rare. After 24 h, symptoms and signs of acute renal failure may develop (see p. 2438). If the cause was thromboembolic, features of thromboembolism at other sites (eg, blue toes, livedo reticularis, retinal lesions on funduscopic examination) also may be present.

Chronic progressive stenosis causes hypertension, which may begin at an atypical age (eg, < 30 yr or after age 50 yr) and which may be refractory to control despite use of multiple antihypertensives. Physical examination may detect an abdominal bruit or signs of atherosclerosis. Symptoms and signs of chronic kidney disease (see p. 2443) develop slowly.

**Diagnosis**

- Clinical suspicion
- Imaging

Diagnosis is suspected in patients with renal failure and who have

- Symptoms of acute renal artery occlusion
- Symptoms or signs of thromboembolism
- Hypertension that begins before age 30 or is refractory to treatment with > 3 antihypertensive drugs

Blood and urine tests are done to confirm renal failure. Diagnosis is confirmed by imaging tests (see Table 238-1). Which tests are done depends on the patient's renal function and other characteristics and on test availability.

Some tests (CT angiography, arteriography, digital subtraction angiography) require an IV ionic radiopaque contrast agent, which may be nephrotoxic; this risk is lower with the nonionic hypo-osmolar or iso-osmolar contrast agents that are now in widespread use (see p. 3403). Magnetic resonance angiography (MRA) requires the use of gadolinium contrast; in patients with severe chronic kidney disease, gadolinium contrast carries the risk of nephrogenic systemic fibrosis, a condition that closely resembles systemic sclerosis and that has no satisfactory method of treatment.

When results of other tests are inconclusive or negative but clinical suspicion is strong, arteriography is necessary for definitive diagnosis. Arteriography may also be needed before invasive interventions.

When a thromboembolic disorder is suspected, ECG (to detect atrial fibrillation) and hypercoagulability studies may be needed to identify treatable embolic sources. Transthoracic echocardiography is done to detect atheromatous lesions in the ascending and thoracic aorta and cardiac sources of thrombi or valvular vegetations.
Blood and urine tests are nondiagnostic but are done to confirm renal failure, indicated by elevated creatinine and BUN and by hyperkalemia. Leukocytosis, gross or microscopic hematuria, and proteinuria may also be present.

**Treatment**

- Restoration of vascular patency in acute occlusions and, if patients have refractory hypertension or potential for renal failure, in chronic stenosis

Treatment depends on the cause.

**Acute renal artery occlusion:** A renal thromboembolic disorder may be treated with a combination of anticoagulation, fibrinolytics, and surgical or catheter-based embolectomy. Treatment within 3 h of symptom onset is likely to improve renal function. However, complete recovery is unusual, and early and late mortality rates are high because of extrarenal embolization or underlying atherosclerotic heart disease.

Patients presenting within 3 h may benefit from fibrinolytic (thrombolytic) therapy (eg, streptokinase, alteplase) given IV or by local intra-arterial infusion (see p. 2110). However, such rapid diagnosis and treatment is rare.

All patients with a thromboembolic disorder require anticoagulation with IV heparin, unless contraindicated. Long-term anticoagulation with oral warfarin can be initiated simultaneously with heparin if no invasive intervention is planned. Anticoagulation should be continued for at least 6 to 12 mo—indefinitely for patients with a recurrent thromboembolic disorder or a hypercoagulability disorder.

Surgery to restore vascular patency has a higher mortality rate than fibrinolytic therapy and has no advantage in recovery of renal function. However, surgery, particularly if done within the first few hours, is preferred for patients with traumatic renal artery thrombosis. If patients with nontraumatic, severe renal failure do not recover function after 4 to 6 wk of drug therapy, surgical revascularization (embolectomy) can be considered, but it helps only a few.

If the cause is thromboemboli, the source should be identified and treated appropriately (see Deep Venous Thrombosis on p. 2224).

**Chronic progressive renal artery stenosis:** Treatment is indicated when > 75% of the arterial diameter is blocked (stenosis) and patients have any of the following:

- Unilateral stenosis with renal insufficiency
- Bilateral stenoses
- Stenosis in a solitary functioning kidney
- Unilateral or bilateral stenosis associated with hypertension that is refractory to treatment with ≥ 3 drugs

Treatment is with percutaneous transluminal angioplasty (PTA) plus stenting or with surgical bypass of the stenotic segment. Usually, an extensively infarcted kidney must be removed if revascularization is not expected to result in functional recovery. Surgery is usually more effective than PTA for atherosclerotic occlusion; it cures or attenuates hypertension in 60 to 70% of patients. PTA is preferred for FMD; risk is minimal, success rate is high, and restenosis rate is low. If PTA is ineffective, surgical revascularization is needed.

**Renovascular hypertension:** Treatments are typically ineffective unless vascular patency (see p. 2077) is restored. ACE inhibitors, angiotensin II receptor blockers, or renin inhibitors can be used in unilateral
but not in bilateral renal artery stenosis. These drugs can reduce GFR and increase serum BUN and creatinine levels. If GFR decreases enough to increase serum creatinine, Ca channel blockers (eg, amlodipine, felodipine) or vasodilators (eg, hydralazine, minoxidil) should be added or substituted (see p. 2071).

Renal Atheroembolism

Renal atheroembolism is occlusion of renal arterioles by atherosclerotic emboli, causing progressive chronic kidney disease. It results from rupture of atheromatous plaques. Symptoms are those of renal failure; symptoms and signs of widespread arterial embolic disease may be present. Diagnosis is by renal biopsy. Long-term prognosis is usually poor. Treatment aims to prevent further embolization.

Atheromatous plaque rupture usually results from manipulation of the aorta during vascular surgery, angioplasty, or arteriography. Spontaneous plaque rupture, which occurs most often in patients who have diffuse erosive atherosclerosis or who are being treated with anticoagulants or fibrinolytics, is rare.

Atheroemboli tend to cause incomplete occlusion with secondary ischemic atrophy rather than renal infarction. A foreign body immune reaction often follows embolization, leading to continued deterioration in renal function for 3 to 8 wk. Acute renal impairment may also result from massive or recurrent episodes of embolization.

Symptoms and Signs

Symptoms are usually those of acute or chronic renal dysfunction with uremia (see p. 2438). Renal atheroembolism rarely causes hypertension. Abdominal pain, nausea, and vomiting can result from concomitant compromised arterial microcirculation of abdominal organs (eg, pancreas, GI tract). Sudden blindness and formation of bright yellow retinal plaques (Hollenhorst plaques) can result from emboli in retinal arterioles. Signs of widespread peripheral embolism (eg, livedo reticularis, painful muscle nodules, overt gangrene, which is often referred to as the trash syndrome, are sometimes present.

Diagnosis

• Clinical suspicion

• Imaging (usually renal ultrasonography)

• Sometimes, renal biopsy

• Location of source of emboli

Diagnosis is suggested by worsening renal function in a patient with recent manipulation of the aorta, particularly if there are signs of atheroemboli. Differential diagnosis includes contrast-induced and drug-induced nephropathy. An imaging study (usually ultrasonography) should be done. If suspicion of atheroembolism remains high, percutaneous renal biopsy is done; it has a sensitivity of about 75%. Diagnosis is important because there may be treatable causes of emboli in the absence of vascular obstruction. Cholesterol crystals in the emboli dissolve during tissue fixation, leaving pathognomonic biconcave, needle-shaped clefts in the occluded vessel. Sometimes skin, muscle, or GI biopsy can provide the same information and indirectly help establish the diagnosis.

Blood and urine tests can confirm the diagnosis of acute renal failure or chronic kidney disease but do not establish cause. Urinalysis typically shows microscopic hematuria and minimal proteinuria; however, proteinuria is occasionally in the nephrotic range (> 3 g/day). Eosinophilia, eosinophiluria, and transient hypocomplementemia may be present.

If renal or systemic emboli recur and their source is unclear, transesophageal echocardiography is done to detect atheromatous lesions in the ascending and thoracic aorta and cardiac sources of emboli; dual helical CT may help characterize the ascending aorta and aortic arch.
Prognosis

With aggressive supportive therapy, survival has improved in recent years (eg, survival can be > 50% at 4 yr). Some patients require renal replacement therapy initially, but they improve later and dialysis may be stopped.

Treatment

- Treatment of embolic source when possible
- Supportive measures
- Modification of risk factors

Sometimes the source of emboli can be treated (eg, anticoagulation for patients with emboli from a cardiac source and atrial fibrillation and for patients in whom a clot becomes a source of new emboli). However, no direct treatment of existing renal emboli is effective. Corticosteroids, antiplatelet drugs, vasodilators, and plasma exchange are not helpful. There is no demonstrated benefit of anticoagulation, and, according to most experts, its use may actually enhance atheroembolism.

Treatment of renal dysfunction includes control of hypertension and management of electrolytes and fluid status; sometimes dialysis is required. Modifying risk factors for atherosclerosis may slow its progression and induce regression. Strategies include management of hypertension, hyperlipidemia, and diabetes; smoking cessation; and encouragement of regular aerobic exercise and good nutrition (see p. 2084).

Renal Cortical Necrosis

Renal cortical necrosis is destruction of cortical tissue resulting from renal arteriolar injury and leading to chronic kidney disease. This rare disorder typically occurs in neonates and in pregnant or postpartum women when sepsis or pregnancy complications occur. Symptoms and signs include gross hematuria, flank pain, decreased urine output, fever, and symptoms of uremia. Symptoms of the underlying disorder may predominate. Diagnosis is by MRI, CT, isotopic renal scanning, or renal biopsy. Mortality rate at 1 yr is > 20%. Treatment is directed at the underlying disorder and at preserving renal function.

In renal cortical necrosis, which may be patchy or diffuse, bilateral renal arteriolar injury results in destruction of cortical tissues and acute renal failure. Renal cortical tissues eventually calcify. The juxtamedullary cortex, medulla, and the area just under the capsule are spared.

Etiology

Injury usually results from reduced renal artery perfusion secondary to vascular spasm, microvascular injury, or intravascular coagulation.

About 10% of cases occur in infants and children. Pregnancy complications increase risk of this disorder in neonates and in women, as does sepsis. Other causes (eg, disseminated intravascular coagulation [DIC]) are less common (see Table 238-2).

Symptoms and Signs

Gross hematuria, flank pain, and sometimes decreased urine output or abrupt anuria occur. Fever is common, and chronic kidney disease with hypertension develops. However, these symptoms are often overshadowed by symptoms of the underlying disorder.

Diagnosis
Imaging, usually with CT angiography

[Table 238-2. Causes of Renal Cortical Necrosis]

Diagnosis is suspected when typical symptoms occur in patients with a potential cause.

Imaging tests can sometimes confirm the diagnosis. CT angiography is usually preferred despite the risks of using an iodinated contrast agent. Because of the risk of nephrogenic systemic fibrosis, use of magnetic resonance angiography with gadolinium contrast is not recommended in these patients, who usually have severe renal dysfunction.

An alternative is isotopic renal scanning using diethylenetriamine penta-acetic acid. It shows enlarged, nonobstructed kidneys, with little or no renal blood flow. Renal biopsy is done only if the diagnosis is unclear and no contraindications exist. It provides definitive diagnosis and prognostic information.

Urinalysis, CBC, liver function tests, and serum electrolytes and renal function tests are done routinely. These tests often confirm renal dysfunction (eg, indicated by elevated creatinine and BUN and by hyperkalemia) and may suggest a cause. Severe electrolyte abnormalities may be present depending on the cause (eg, hyperkalemia, hyperphosphatemia, hypocalcemia). CBC often detects leukocytosis (even when sepsis is not the cause) and may detect anemia and thrombocytopenia if hemolysis, DIC, or sepsis is the cause. Transaminases may be increased in relative hypovolemic states (eg, septic shock, postpartum hemorrhage). If DIC is suspected, coagulation studies are done. They may detect low fibrinogen levels, increased fibrin-degradation products, and increasing PT/INR and PTT. Urinalysis typically detects proteinuria and hematuria.

Prognosis

Prognosis of renal cortical necrosis was poor in the past, with mortality > 50% in the first year. More recently, with aggressive supportive therapy, 1-yr mortality can be about 20%, and up to 20% of survivors may recover some renal function.

Treatment

Treatment is directed at the underlying disorder and at preserving renal function (eg, with early dialysis).

Renal Vein Thrombosis

Renal vein thrombosis is thrombotic occlusion of one or both main renal veins, resulting in acute renal failure or chronic kidney disease. Common causes include nephrotic syndrome, primary hypercoagulability disorders, malignant renal tumors, extrinsic compression, trauma, and rarely inflammatory bowel disease. Symptoms of renal failure and sometimes nausea, vomiting, flank pain, gross hematuria, decreased urine output, or systemic manifestations of venous thromboembolism may occur. Diagnosis is by CT, magnetic resonance angiography, or renal venography. With treatment, prognosis is generally good. Treatment is anticoagulation, support of renal function, and treatment of the underlying disorder. Some patients benefit from thrombectomy or nephrectomy.

Etiology

Renal vein thrombosis usually results from local and systemic hypercoagulability due to nephrotic syndrome associated with membranous nephropathy or membranoproliferative glomerulonephritis. Overly aggressive diuresis or prolonged high-dose corticosteroid treatment may contribute to thrombosis of the renal vein in patients with these conditions (see p. 2408). Other causes include

• Allograft rejection
• Amyloidosis
Diabetic nephropathy

Estrogen therapy

Pregnancy

Primary hypercoagulability disorders (eg, antithrombin III deficiency, protein C or S deficiency, factor V Leiden, prothrombin G20210A mutations)

Renal vasculitis

Sickle cell nephropathy

SLE

Less common causes are related to reduced renal vein blood flow and include malignant renal tumors that extend into the renal veins (typically renal cell carcinoma), extrinsic compression of the renal vein or inferior vena cava (eg, by vascular abnormalities, tumor, retroperitoneal disease, ligation of the inferior vena cava, aortic aneurysm), oral contraceptive use, trauma, dehydration, and, rarely, thrombophlebitis migrans and cocaine abuse.

Symptoms and Signs

Usually, onset of renal dysfunction (see p. 2436) is insidious. However, onset may be acute, causing renal infarction with nausea, vomiting, flank pain, gross hematuria, and decreased urine output.

When the cause is a hypercoagulability disorder, signs of venous thromboembolic disorders (eg, deep venous thrombosis, pulmonary embolism) may occur. When the cause is a renal cancer, its signs (eg, hematuria, weight loss) predominate.

Diagnosis

Vascular imaging

Renal vein thrombosis should be considered in patients with renal infarction or any unexplained deterioration in renal function, particularly in patients with the nephrotic syndrome or other risk factors. The traditional diagnostic test of choice and the gold standard is venography of the inferior vena cava; this test is diagnostic, but it may mobilize clots. Because of the risks of conventional venography, magnetic resonance venography and Doppler ultrasonography are being used increasingly. Magnetic resonance venography can be done if GFR > 30 mL/min. Doppler ultrasonography sometimes detects renal vein thrombosis but has high false-negative and false-positive rates. Notching of the ureter due to dilated collateral veins is a characteristic finding in some chronic cases. CT angiography provides good detail with high sensitivity and specificity and is fast but requires administration of a radiocontrast agent, which may be nephrotoxic. Serum electrolytes and urinalysis are done and confirm deterioration of renal function. Microscopic hematuria is often present. Proteinuria may be in the nephrotic range.

If no cause is apparent, testing for hypercoagulability disorders should be initiated (see p. 973). Renal biopsy is nonspecific but may detect a coexisting renal disorder.

Treatment

Treatment of underlying disorder

Anticoagulation

Sometimes percutaneous catheter-directed thrombectomy or thrombolysis

Death is rare and usually related to complications such as pulmonary embolism and those due to
nephrotic syndrome or a malignant tumor.

The underlying disorder should be treated. Treatment options for renal vein thrombosis include anticoagulation with heparin, thrombolysis, and catheter-directed or surgical thrombectomy. Long-term anticoagulation with low molecular weight heparin or oral warfarin should be started immediately if no invasive intervention is planned. Anticoagulation minimizes risk of new thrombi, promotes recanalization of vessels with existing clots, and improves renal function. Anticoagulation should be continued for at least 6 to 12 mo and, if a hypercoagulability disorder (eg, persistent nephrotic syndrome) is present, indefinitely.

Use of a percutaneous catheter for thrombectomy or thrombolysis is a promising new technique that has a high success rate. Surgical thrombectomy is rarely used but may help if anticoagulation is ineffective or contraindicated. Inferior vena cava filters may also be used in these cases to help prevent pulmonary emboli.

Nephrectomy is done only if infarction is total (in certain cases) or if the underlying disorder warrants it.
Chapter 239. Renal Failure

Introduction

Renal failure is traditionally categorized as acute or chronic. The former develops rapidly, often over days, whereas the latter progresses slowly over months to years. Some causes overlap.

Acute Renal Failure

(Acute Kidney Injury)

Acute renal failure (ARF) is a rapid decrease in renal function over days to weeks, causing an accumulation of nitrogenous products in the blood (azotemia). It often results from severe trauma, illness, or surgery but is sometimes caused by a rapidly progressive, intrinsic renal disease. Symptoms include anorexia, nausea, and vomiting. Seizures and coma may occur if the condition is untreated. Fluid, electrolyte, and acid-base disorders develop quickly. Diagnosis is based on laboratory tests of renal function, including serum creatinine. Urinary indices, urinary sediment examination, and often imaging and other tests are needed to determine the cause. Treatment is directed at the cause but also includes fluid and electrolyte management and sometimes dialysis.

In all cases of ARF, creatinine and urea build up in the blood over several days, and fluid and electrolyte disorders develop. The most serious of these disorders are hyperkalemia and fluid overload (possibly causing pulmonary edema). Phosphate retention leads to hyperphosphatemia. Hypocalcemia is thought to occur because the impaired kidney no longer produces calcitriol and because hyperphosphatemia causes Ca phosphate precipitation in the tissues. Acidosis develops because hydrogen ions cannot be excreted. With significant uremia, coagulation may be impaired, and pericarditis may develop. Urine output varies with the type and cause of ARF.

Etiology

Causes of ARF can be classified as prerenal, renal, or postrenal (see Table 239-1).

Prerenal azotemia is due to inadequate renal perfusion. The main causes are ECF volume depletion and cardiovascular disease. Prerenal conditions cause about 50 to 80% of ARF but do not cause permanent renal damage (and hence are potentially reversible) unless hypoperfusion is severe enough to cause tubular ischemia. Hypoperfusion of an otherwise functioning kidney leads to enhanced reabsorption of Na and water, resulting in oliguria with high urine osmolality and low urine Na.

Renal causes of ARF involve intrinsic renal disease or damage. Renal causes are responsible for about 10 to 40% of cases. Overall, the most common causes are prolonged renal ischemia and nephrotoxins (including IV use of iodinated radiopaque contrast agents—see Contrast Nephropathy on p. 2414). Disorders may involve the glomeruli, tubules, or interstitium. Glomerular disease reduces GFR and increases glomerular capillary permeability to proteins; it may be inflammatory (glomerulonephritis) or the result of vascular damage from ischemia or vasculitis. Tubules also may be damaged by ischemia and may become obstructed by cellular debris, protein or crystal deposition, and cellular or interstitial edema. Tubular damage impairs reabsorption of Na, so urinary Na tends to be elevated, which is helpful diagnostically. Interstitial inflammation (nephritis) usually involves an immunologic or allergic phenomenon. These mechanisms of tubular damage are complex and interdependent, rendering the previously popular term acute tubular necrosis an inadequate description.

Postrenal azotemia (obstructive nephropathy—see also p. 2365) is due to various types of obstruction in the voiding and collecting parts of the urinary system and is responsible for about 5 to 10% of cases. Obstruction can also occur within the tubules when crystalline or proteinaceous material precipitates. This form of renal failure is often grouped with postrenal failure because the mechanism is obstructive. Obstructed ultrafiltrate flow in tubules or more distally increases pressure in the urinary space of the glomerulus, reducing GFR. Obstruction also affects renal blood flow, initially increasing the flow and
pressure in the glomerular capillary by reducing afferent arteriolar resistance. However, within 3 to 4 h, the renal blood flow is reduced, and by 24 h, it has fallen to < 50% of normal because of increased resistance of renal vasculature. Renovascular resistance may take up to a week to return to normal after relief of a 24-h obstruction. To produce significant azotemia, obstruction at the level of the ureter requires involvement of both ureters unless the patient has only a single functioning kidney. Bladder outlet obstruction is probably the most common cause of sudden, and often total, cessation of urinary output in men.

**Urine output:** Prerenal causes typically manifest with oliguria, not anuria. Anuria usually occurs only in obstructive uropathy or, less commonly, in bilateral renal artery occlusion, acute cortical necrosis, or rapidly progressive glomerulonephritis.

A relatively preserved urine output of 1 to 2.4 L/day is initially present in most renal causes. In acute tubular injury, output may have 3 phases.

- The **prodromal phase**, with usually normal urine output, varies in duration depending on causative factors (eg, the amount of toxin ingested, the duration and severity of hypotension).

- The **oliguric phase**, with output typically between 50 and 400 mL/day, lasts an average of 10 to 14 days but varies from 1 day to 8 wk. However, many patients are never oliguric. Nonoliguric patients have lower mortality and morbidity and less need for dialysis.

- In the **postoliguric phase**, urine output gradually returns to normal, but serum creatinine and urea levels may not fall for several more days. Tubular dysfunction may persist and is manifested by Na wasting, polyuria (possibly massive) unresponsive to vasopressin, or hyperchloremic metabolic acidosis.

**Symptoms and Signs**

Initially, weight gain and peripheral edema may be the only findings. Often, predominant symptoms are those of the underlying illness or those caused by the surgical complication that precipitated renal deterioration. Later, as nitrogenous products accumulate, symptoms of uremia may develop, including anorexia, nausea and vomiting, weakness, myoclonic jerks, seizures, confusion, and coma; asterixis and hyperreflexia may be present on examination. Chest pain (typically worse with inspiration or when recumbent), a pericardial friction rub, and findings of pericardial tamponade may occur if uremic pericarditis is present. Fluid accumulation in the lungs may cause dyspnea and crackles on auscultation.

Other findings depend on the cause. Urine may be cola-colored in glomerulonephritis or myoglobinuria. A palpable bladder may be present with outlet obstruction.

**Diagnosis**

- Serum creatinine
- Urinary sediment
- Urinary diagnostic indices
- Postvoid residual bladder volume if postrenal cause suspected

ARF is suspected when urine output falls or serum BUN and creatinine rise. Evaluation should determine the presence and type of ARF and seek a cause. Blood tests generally include CBC, BUN, creatinine, and electrolytes (including Ca and phosphate). Urine tests include Na and creatinine concentration and microscopic analysis of sediment. Early detection and treatment increase the chances of reversing renal failure.
A progressive daily rise in serum creatinine is diagnostic of ARF. Serum creatinine can increase by as much as 2 mg/dL/day (180 μmol/L/day), depending on the amount of creatinine produced (which varies with lean body mass) and total body water. A rise of > 2 mg/dL/day suggests overproduction due to rhabdomyolysis.

Urea nitrogen may increase by 10 to 20 mg/dL/day (3.6 to 7.1 mmol urea/L/day), but BUN may be misleading because it is frequently elevated in response to increased protein catabolism resulting from surgery, trauma, corticosteroids, burns, transfusion reactions, parenteral nutrition or GI or internal bleeding.

When creatinine is rising, 24-h urine collection for creatinine clearance and the various formulas used to calculate creatinine clearance from serum creatinine are inaccurate and should not be used in estimating GFR, because the rise in serum creatinine concentration is a delayed function of GFR decline.

Other laboratory findings are progressive acidosis, hyperkalemia, hyponatremia, and anemia. Acidosis is ordinarily moderate, with a plasma HCO₃⁻ content of 15 to 20 mmol/L. Serum K concentration increases slowly, but when catabolism is markedly accelerated, it may rise by 1 to 2 mmol/L/day. Hyponatremia usually is moderate (serum Na, 125 to 135 mmol/L) and correlates with a surplus of water. Normochromic-normocytic anemia with an Hct of 25 to 30% is typical.

Hypocalcemia is common and may be profound in patients with myoglobinuric ARF, apparently because of the combined effects of Ca deposition in necrotic muscle, reduced calcitriol production, and resistance of bone to parathyroid hormone (PTH). During recovery from ARF, hypercalcemia may supervene as renal calcitriol production increases, the bone becomes responsive to PTH, and Ca deposits are mobilized from damaged tissue.

**Determination of cause:** Immediately reversible prerenal or postrenal causes must be excluded first. ECF volume depletion and obstruction are considered in all patients. The drug history must be accurately reviewed and all potentially renal toxic drugs stopped. Urinary diagnostic indices (see Table 239-2) are helpful in distinguishing prerenal azotemia from acute tubular injury, which are the most common causes of ARF in hospitalized patients.

**Prerenal causes** are often apparent clinically. If so, correction of an underlying hemodynamic abnormality (eg, with volume infusion) should be attempted. Abatement of ARF confirms a prerenal cause.

**Postrenal causes** should be sought in most cases of acute renal failure. Immediately after the patient voids, a urethral catheter is placed or bedside ultrasonography is used to determine the residual urine in the bladder. A postvoid residual urine volume > 200 mL suggests bladder outlet obstruction, although detrusor muscle weakness and neurogenic bladder may also cause residual volume of this amount. The catheter may be kept in for the first day to monitor hourly output but is removed once oliguria is confirmed (if bladder outlet obstruction is not present) to decrease risk of infection. Renal ultrasonography is then done to diagnose more proximal obstruction. However, sensitivity for obstruction is only 80 to 85% when ultrasonography is used because the collecting system is not always dilated, especially when the condition is acute, an intrarenal pelvis is present, the ureter is encased (eg, in retroperitoneal fibrosis or neoplasm), or the patient has concomitant hypovolemia. If obstruction is strongly suspected, CT can establish the site of obstruction and guide therapy.

The **urinary sediment** may provide etiologic clues. A normal urine sediment occurs in prerenal azotemia and sometimes in obstructive uropathy. With renal tubular injury, the sediment characteristically contains tubular cells, tubular cell casts, and many brown-pigmented granular casts. Urinary eosinophils suggest allergic tubulointerstitial nephritis. RBC casts indicate glomerulonephritis or vasculitis.

**Renal causes** are sometimes suggested by clinical findings. Patients with glomerulonephritis (see Ch. 235) often have edema, marked proteinuria (nephrotic syndrome), or signs of arteritis in the skin and retina, often without a history of intrinsic renal disease. Hemoptysis suggests Wegener's granulomatosis or Goodpasture's syndrome. Certain rashes (eg, erythema nodosum, cutaneous vasculitis, discoid lupus) suggest polyarteritis, cryoglobulinemia, SLE, or Henoch-Schönlein purpura. Tubulointerstitial nephritis
and drug allergy are suggested by a history of drug ingestion and a maculopapular or purpuric rash.

To further differentiate renal causes, antistreptolysin-O and complement titers, antinuclear antibodies, and antineutrophil cytoplasmic antibodies are determined. Renal biopsy may be done if the diagnosis remains elusive (see Table 239-3).

**Imaging:** In addition to renal ultrasonography, other imaging tests are occasionally of use. In evaluating for ureteral obstruction, noncontrast CT is preferred over antegrade and retrograde urography. In addition to its ability to delineate soft-tissue structures and Ca-containing calculi, CT can detect nonradiopaque calculi.

Contrast agents should be avoided if possible. However, renal arteriography or venography may sometimes be indicated if vascular causes are suggested clinically. Magnetic resonance angiography was increasingly being used for diagnosing renal artery stenosis as well as thrombosis of both arteries and veins because MRI used gadolinium, which was thought to be safer than the iodinated contrast agents used in angiography and contrast-enhanced CT. However, recent evidence suggests that gadolinium may be involved in the pathogenesis of nephrogenic systemic fibrosis, a serious complication that occurs only in patients with renal failure. Thus, many experts recommend avoiding gadolinium in patients with renal failure.

Kidney size, as determined with imaging tests, is helpful to know, because a normal or enlarged kidney favors reversibility, whereas a small kidney suggests chronic renal insufficiency.

**Prognosis**

Although many causes are reversible if diagnosed and treated early, the overall survival rate remains about 50% because many patients with ARF have significant underlying disorders (eg, sepsis, respiratory failure). Death is usually the result of these disorders rather than the renal failure itself. Most survivors have adequate kidney function. About 10% require dialysis or transplantation—half right away and the others as renal function slowly deteriorates.

**Treatment**

- Immediate treatment of pulmonary edema and hyperkalemia
- Dialysis as needed to control hyperkalemia, pulmonary edema, metabolic acidosis, and uremic symptoms
- Adjustment of drug regimen
- Usually restriction of water, Na, and K intake, but provision of adequate protein
- Possibly phosphate binders and Na polystyrene sulfonate

**Emergency treatment:** Life-threatening complications are addressed, preferably in a critical care unit. Pulmonary edema (see p. 2131) is treated with O₂, IV vasodilators (eg, nitroglycerin), and diuretics (often ineffective in ARF). Hyperkalemia (see p. 835) is treated as needed with IV infusion of 10 mL of 10% Ca gluconate, 50 g of dextrose, and 5 to 10 units of insulin. These drugs do not reduce total body K, so further (but slower acting) treatment with 30 g of oral or rectal Na polystyrene sulfonate is begun. Although correction of an anion gap metabolic acidosis with NaHCO₃ is controversial, correction of the nonanion gap portion of severe metabolic acidosis (pH < 7.20) is less controversial. The nonanion gap
portion may be treated with IV NaHCO\textsubscript{3} in the form of a slow infusion (≤ 150 mEq NaHCO\textsubscript{3} in 1 L of 5% D/W at a rate of 50 to 100 mL/h). The nonanion gap portion of metabolic acidosis is determined by calculating the increase in anion gap above normal and then subtracting this number from the decrease in HCO\textsubscript{3} from 24 mmol/L. HCO\textsubscript{3} is given to raise the serum HCO\textsubscript{3} by this difference. Because variations in body buffer systems and the rate of acid production are hard to predict, calculating the amount of HCO\textsubscript{3} needed to achieve a full correction is usually not recommended. Instead, HCO\textsubscript{3} is given via continuous infusion and the anion gap is monitored serially.

**Hemodialysis** (see p. 2447) or **hemofiltration** (see p. 2449) is initiated when

- Severe electrolyte abnormalities cannot otherwise be controlled (eg, K > 6 mmol/L)
- Pulmonary edema persists despite drug treatment
- Metabolic acidosis is unresponsive to drug treatment
- Uremic symptoms occur (eg, vomiting thought to be due to uremia, asterixis, encephalopathy, pericarditis, seizures)

BUN and creatinine levels are probably not the best guides for initiating dialysis in ARF. In asymptomatic patients who are not seriously ill, particularly those in whom return of renal function is considered likely, dialysis can be deferred until symptoms occur, thus avoiding placement of a central venous catheter with its attendant complications.

**General measures:** Nephrotoxic drugs are stopped, and all drugs excreted by the kidneys (eg, digoxin, some antibiotics) are adjusted; serum levels are useful.

Daily water intake is restricted to a volume equal to the previous day’s urine output plus measured extrarenal losses (eg, vomitus) plus 500 to 1000 mL/day for insensible loss. Water intake can be further restricted for hyponatremia or increased for hypernatremia. Although weight gain indicates excess fluid, water intake is not decreased if serum Na remains normal; instead, dietary Na is restricted.

Na and K intake is minimized except in patients with prior deficiencies or GI losses. An adequate diet should be provided, including daily protein intake of about 0.8 to 1 g/kg. If oral or enteral nutrition is impossible, parenteral nutrition is used, but in ARF, risks of fluid overload, hyperosmolality, and infection are increased by IV nutrition. Ca salts (carbonate, acetate) or synthetic non-Ca-containing phosphate binders before meals help maintain serum phosphate at < 5 mg/dL (< 1.78 mmol/L). To help maintain serum K at < 6 mmol/L in the absence of dialysis, a cation-exchange resin, Na polystyrene sulfonate, is given 15 to 60 g po or rectally 1 to 4 times/day as a suspension in water or in a syrup (eg, 70% sorbitol). An indwelling bladder catheter is rarely needed and should be used only when necessary because of an increased risk of UTI and urosepsis.

In many patients, a brisk and even dramatic diuresis after relief of obstruction is a physiologic response to the expansion of ECF during obstruction and does not compromise volume status. However, polyuria accompanied by the excretion of large amounts of Na, K, Mg, and other solutes may cause hypokalemia, hyponatremia, hypernatremia, hypomagnesemia, or marked contraction of ECF volume with peripheral vascular collapse. In this postoliguric phase, close attention to fluid and electrolyte balance is mandatory. Overzealous administration of salt and water after relief of obstruction can prolong diuresis. When postoliguric diuresis occurs, replacement of urine output with 0.45% saline at about 75% of urine output prevents volume depletion and the tendency for excessive free water loss while allowing the body to eliminate excessive volume if this is the cause of the polyuria.

**Prevention**

ARF can often be prevented by maintaining normal fluid balance, blood volume, and BP in patients with trauma, burns, or major hemorrhage and in those undergoing major surgery. Infusion of isotonic saline and blood may be helpful. Use of contrast agents should be minimized, particularly in at-risk groups (eg,
the elderly and those with preexisting renal insufficiency, volume depletion, diabetes, or heart failure). If contrast agents are necessary, risk can be lowered by minimizing volume of the IV contrast agent, using nonionic and low osmolal or iso-osmolal contrast agents, avoiding NSAIDs, and pretreating with normal saline at 1 mL/kg/h IV for 12 h before the test. Isotonic NaHCO₃ has been used successfully instead of normal saline in some patients. However, further study is needed to confirm this finding. N-acetylcysteine 600 mg po bid the day before and the day of IV contrast administration has been used to prevent contrast nephropathy, but reports of its efficacy are conflicting.

Before cytolytic therapy is initiated in patients with certain neoplastic diseases (eg, lymphoma, leukemia), treatment with allopurinol should be considered along with increasing urine flow by increasing oral or IV fluids to reduce urate crystalluria. Making the urine more alkaline (by giving oral or IV NaHCO₃ or acetazolamide) has been recommended by some but is controversial because it may also induce urinary Ca phosphate precipitation and crystalluria, which may cause ARF.

The renal vasculature is very sensitive to endothelin, a potent vasoconstrictor that reduces renal blood flow and GFR. Endothelin is implicated in progressive renal damage, and endothelin receptor antagonists have successfully slowed or even halted experimental renal disease. Antiendothelin antibodies and endothelin-receptor antagonists are being studied to protect the kidney against ischemic ARF.

**Chronic Kidney Disease**

*(Chronic Renal Failure)*

Chronic kidney disease (CKD) is long-standing, progressive deterioration of renal function. Symptoms develop slowly and include anorexia, nausea, vomiting, stomatitis, dysgeusia, nocturia, lassitude, fatigue, pruritus, decreased mental acuity, muscle twitches and cramps, water retention, undernutrition, GI ulceration and bleeding, peripheral neuropathies, and seizures. Diagnosis is based on laboratory testing of renal function, sometimes followed by renal biopsy. Treatment is primarily directed at the underlying condition but includes fluid and electrolyte management, erythropoietin for anemia, and often dialysis or transplantation.

**Etiology**

CKD may result from any cause of renal dysfunction of sufficient magnitude (see Table 239-4). The most common cause in the US is diabetic nephropathy (see p. 869), followed by hypertensive nephroangiosclerosis and various primary and secondary glomerulopathies. Metabolic syndrome (see p. 64), in which hypertension and type 2 diabetes are present, is a large and growing cause of renal damage.

**Pathophysiology**

CKD can be roughly categorized as diminished renal reserve, renal insufficiency, or renal failure (end-stage renal disease). Initially, as renal tissue loses function, there are few abnormalities because the remaining tissue increases its performance (renal functional adaptation); a loss of 75% of renal tissue causes a fall in GFR to only 50% of normal.

Decreased renal function interferes with the kidneys' ability to maintain fluid and electrolyte homeostasis. Changes proceed predictably, but considerable overlap and individual variation exist. The ability to concentrate urine declines early and is followed by decreases in ability to excrete phosphate, acid, and K. When renal failure is advanced (GFR ≤ 10 mL/min/1.73 m²), the ability to dilute urine is lost; thus urine osmolality is usually fixed close to that of plasma (300 to 320 mOsm/kg), and urinary volume does not respond readily to variations in water intake.

Plasma concentrations of creatinine and urea (which are highly dependent on glomerular filtration) begin a nonlinear rise as GFR diminishes. These changes are minimal early on. When the GFR falls below 10 mL/min/1.73 m² (normal = 100 mL/min/1.73 m²), their levels increase rapidly and are usually
associated with systemic manifestations (uremia). Urea and creatinine are not major contributors to the uremic symptoms; they are markers for many other substances (some not yet well defined) that cause the symptoms.

Despite a diminishing GFR, Na and water balance is well maintained by increased fractional excretion of Na and a normal response to thirst. Thus, the plasma Na concentration is typically normal, and hypervolemia is infrequent unless dietary intake of Na or water is very restricted or excessive. Heart failure can occur from Na and water overload, particularly in patients with decreased cardiac reserve.

For substances whose secretion is controlled mainly through distal nephron secretion (eg, K), adaptation usually maintains plasma levels at normal until renal failure is advanced. K-sparing diuretics, ACE inhibitors, β-blockers, NSAIDs, cyclosporine, tacrolimus, or angiotensin II receptor blockers may raise plasma K levels in patients with less advanced renal failure.

Abnormalities of Ca, phosphate, parathyroid hormone (PTH), vitamin D metabolism, and renal osteodystrophy can occur. Decreased renal production of calcitriol contributes to hypocalcemia. Decreased renal excretion of phosphate results in hyperphosphatemia. Secondary hyperparathyroidism is common and can develop in renal failure before abnormalities in Ca or phosphate concentrations occur. For this reason, monitoring PTH in patients with moderate CKD, even before hyperphosphatemia occurs, has been recommended.

Renal osteodystrophy (abnormal bone mineralization resulting from hyperparathyroidism, calcitriol deficiency, elevated serum phosphate, or low or normal serum Ca) usually takes the form of increased bone turnover due to hyperparathyroid bone disease (osteitis fibrosa) but can also involve decreased bone turnover due to adynamic bone disease (with increased parathyroid suppression) or osteomalacia. Calcitriol deficiency may cause osteopenia or osteomalacia.

Moderate acidosis (plasma HCO₃ content 15 to 20 mmol/L) and anemia are characteristic. The anemia of CKD is normochromic-normocytic, with an Hct of 20 to 30% (35 to 50% in patients with polycystic kidney disease). It is usually caused by deficient erythropoietin production due to a reduction of functional renal mass (see Ch. 105). Other causes include deficiencies of iron, folate, and vitamin B₁₂.

**Symptoms and Signs**

Patients with mildly diminished renal reserve are asymptomatic. Even patients with mild to moderate renal insufficiency may have no symptoms despite elevated BUN and creatinine. Nocturia is often noted, principally due to a failure to concentrate the urine. Lassitude, fatigue, anorexia, and decreased mental acuity often are the earliest manifestations of uremia.

With more severe renal insufficiency (eg, creatinine clearance < 10 mL/min for patients without diabetes and < 15 mL/min for those with diabetes), neuromuscular symptoms may be present, including coarse muscular twitches, peripheral sensory and motor neuropathies, muscle cramps, hyperreflexia, and seizures (usually the result of hypertensive or metabolic encephalopathy). Anorexia, nausea, vomiting, weight loss, stomatitis, and an unpleasant taste in the mouth are almost uniformly present. The skin may be yellow-brown. Occasionally, urea from sweat crystallizes on the skin (uremic frost). Pruritus may be especially uncomfortable. Undernutrition leading to generalized tissue wasting is a prominent feature of chronic uremia.

In advanced CKD, pericarditis and GI ulceration and bleeding are common. Hypertension is present in > 80% of patients with advanced CKD, is usually related to hypervolemia, and is occasionally the result of activation of the renin-angiotensin-aldosterone system. Heart failure caused by hypertension or coronary artery disease and renal retention of Na and water may lead to dependent edema.

**Diagnosis**

- Electrolytes, BUN, creatinine, phosphate, Ca, CBC, urinalysis (including urinary sediment examination)
• Ultrasonography

• Sometimes renal biopsy

CKD is usually first suspected when serum creatinine rises. The initial step is to determine whether the renal failure is acute, chronic, or acute superimposed on chronic (i.e., an acute disease that further compromises renal function in a patient with CKD—see Table 239-5). The cause of renal failure is also determined. Sometimes determining the duration of renal failure helps determine the cause; sometimes it is easier to determine the cause than the duration, and determining the cause helps determine the duration.

Testing includes urinalysis with examination of the urinary sediment, electrolytes, urea nitrogen, and creatinine, phosphate, Ca, and CBC. Sometimes specific serologic tests are needed to determine the cause. Distinguishing acute from chronic renal failure is most helped by a history of an elevated creatinine

[Table 239-5. Distinguishing Acute Kidney Failure from Chronic Kidney Disease]

level or abnormal urinalysis. Urinalysis findings depend on the nature of the underlying disorder, but broad (> 3 WBC diameters wide) or especially waxy (highly refractile) casts often are prominent in advanced renal failure of any cause.

An ultrasound examination of the kidneys is usually helpful in evaluating for obstructive uropathy and in distinguishing acute from chronic renal failure based on kidney size. Except in certain conditions (see Table 239-4), patients with chronic renal failure have small shrunken kidneys (usually < 10 cm in length) with thinned, hyperechoic cortex. Obtaining a precise diagnosis becomes increasingly difficult as renal function reaches values close to those of end-stage renal disease. The definitive diagnostic tool is renal biopsy, but it is not recommended when ultrasonography indicates small, fibrotic kidneys.

Classification: Staging CKD is a way of quantifying its severity. CKD has been classified into 5 stages.

• Stage 1: Normal GFR (≥ 90 mL/min/1.73 m²) plus either persistent albuminuria or known structural or hereditary renal disease

• Stage 2: GFR 60 to 89 mL/min/1.73 m²

• Stage 3: GFR 30 to 59 mL/min/1.73 m²

• Stage 4: GFR 15 to 29 mL/min/1.73 m²

• Stage 5: GFR < 15 mL/min/1.73 m²

GFR (in mL/min/1.73 m²) in CKD can be estimated by: 186.3 × (serum creatinine)^-1.154 × (age)^-0.203. The result is multiplied by 0.742 if the patient is female and by 1.21 if African American. For female African Americans, the result is multiplied by 0.742 × 1.21 (0.898).

Prognosis

Progression of CKD is predicted in most cases by the degree of proteinuria. Patients with nephrotic-range proteinuria (> 3 g/24 h or urine protein/creatinine > 3) usually have a poorer prognosis and progress to renal failure more rapidly. Progression may occur even if the underlying disorder is not active. In patients with urine protein < 1.5 g/24 h, progression usually occurs more slowly if at all. Hypertension is associated with more rapid progression as well.

Treatment
Underlying disorders and contributory factors must be controlled. In particular, controlling hyperglycemia in patients with diabetic nephropathy and controlling hypertension in all patients substantially slows deterioration of GFR. Target BP should be about 110 to 130/< 80 mm Hg. ACE inhibitors and angiotensin II receptor blockers decrease the rate of decline in GFR in patients with most causes of CKD, particularly those with proteinuria.

Activity need not be restricted, although fatigue and lassitude usually limit a patient's capacity for exercise. Pruritus may respond to phosphate binders if serum phosphate is elevated. If patients do not respond, ultraviolet phototherapy may help.

**Nutrition:** Severe protein restriction in renal disease is controversial. However, moderate restriction (0.8 g/kg/day) is safe and easy for most patients to tolerate. Some experts recommend 0.6 g/kg/day for patients with diabetes and, for patients without diabetes, > 0.8 g/kg/day if GFR is 25 to 55 mL/min/1.73 m² or 0.6 g/kg/day if GFR is 13 to 24 mL/min/1.73 m². Many uremic symptoms markedly lessen when protein catabolism and urea generation are reduced. Sufficient carbohydrate and fat are given to meet energy requirements and prevent ketosis. Patients for whom < 0.8 g/kg/day has been prescribed should be closely followed by a dietician.

Because dietary restrictions may reduce necessary vitamin intake, patients should take a multivitamin containing water-soluble vitamins. Administration of vitamin A and E is unnecessary. Vitamin D in the form of 1,25-dihydroxyvitamin D (calcitriol) or its analogs should be given as indicated by PTH concentrations. Dose is determined by stage of CKD, PTH concentration, and phosphate concentrations (see Table 239-6). Target levels for Ca are 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L); for the Ca-phosphate product, < 55 mg²/dL².

A typical starting dose is calcitriol (or a calcitriol analog) 0.25 μg po once/day or 1 to 4 μg 2 times/wk. PTH levels are not corrected to normal because doing so risks precipitating adynamic bone disease.

Dietary modification may be helpful for hypertriglyceridemia. In patients with hypercholesterolemia, a statin is effective. Fibric acid derivatives (clofibrate, gemfibrozil) may increase risk of rhabdomyolysis in patients with CKD, especially if taken with statin drugs, whereas ezetimibe (which reduces cholesterol absorption) appears relatively safe. Correction of hypercholesterolemia may slow progression of the underlying renal disease and reduce coronary risk.

**Fluid and electrolytes:** Water intake is restricted only when serum Na concentration is < 135 mmol/L.

Na restriction of 2 g/day benefits patients, especially those with edema, heart failure, or hypertension.

K intake is closely related to meat, vegetable, and fruit ingestion and usually does not require adjustment. However, foods (especially salt substitutes) rich in K should generally be avoided. Hyperkalemia is infrequent (unless there is hyporeninemic hypoaldosteronism or K-sparing diuretic therapy) until end-stage renal failure, when intake may need to be restricted to ≤ 50 mmol/day. Mild hyperkalemia (< 6 mmol/L) can be treated by reducing K intake and correcting metabolic acidosis. More severe hyperkalemia (> 6 mmol/L) warrants urgent treatment (see pp.)
Phosphate restriction to < 1 g/day is often sufficient to maintain phosphate level in the target range during the early phase of stages 3 and 4 CKD. However, in the later phases, phosphate binders, such as Ca salts (acetate or carbonate but avoid citrate) or non-Ca-containing phosphate binders (sevelamer) are often necessary. No more than 1500 mg/day of elemental Ca should be given as binders (2000 mg/day of total Ca; binders plus dietary Ca).

Mild acidosis (pH 7.30 to 7.35) requires no therapy. However, most patients with chronic metabolic acidosis who have a pH < 7.3 have a plasma HCO$_3^-$ content < 15 mmol/L and symptoms of anorexia, lassitude, dyspnea, and exaggerated protein catabolism and renal osteodystrophy. NaHCO$_3$ 1 to 2 g po bid is given and amount is increased gradually until HCO$_3^-$ concentration is about 20 mEq/L or until evidence of Na overloading prevents further therapy.

Anemia and coagulation disorders: Anemia is treated to keep the Hb between 11 and 12 g/dL. Anemia slowly responds to recombinant human erythropoietin (eg, epoetin alfa 50 to 150 units/kg sc 1 to 3 times/wk). Because of increased iron utilization with stimulated erythropoiesis, iron stores must be replaced, usually with parenteral iron. Iron concentrations, iron-binding capacity, and ferritin concentrations should be followed closely. Transfusion should not be undertaken unless anemia is severe (Hb < 8 g/dL) or causes symptoms.

The bleeding tendency in CKD rarely needs treatment. Cryoprecipitate, RBC transfusions, desmopressin 0.3 to 0.4 μg/kg (20 μg maximum) in 20 mL of isotonic saline IV over 20 to 30 min, or conjugated estrogens 2.5 to 5 mg po once/day help when needed. The effects of these treatments last 12 to 48 h, except for conjugated estrogens, which may last for several days.

Heart failure: Symptomatic heart failure is treated with Na restriction and diuretics

[Table 239-6. Target Levels for PTH and Phosphate in Chronic Kidney Disease]

(see p. 2128). If left ventricular function is depressed, ACE inhibitors and β-blockers (carvedilol or metoprolol) should be used. Digoxin may be added, but the dosage must be reduced. Diuretics such as furosemide usually are effective even when renal function is markedly reduced, although large doses may be needed. Moderate or severe hypertension should be treated to avoid its deleterious effects on cardiac and renal function. Patients who do not respond to moderate reduction in Na intake (4 g/day) need further dietary Na restriction (2 g/day) and diuretic therapy (furosemide 80 to 240 mg po bid). Hydrochlorothiazide 50 mg po bid or metolazone 5 to 10 mg po once/day may be added to high-dose furosemide therapy if hypertension or edema is not controlled. Even in renal failure, the combination of a thiazide with a loop diuretic is quite potent and must be used with caution to avoid overdiuresis. Occasionally, dialysis may be required to control heart failure. If reduction of the ECF volume does not control BP, conventional antihypertensives are added. Azotemia may increase with such treatment but is acceptable short-term, even if temporary dialysis is required.

Drugs: Renal excretion of drugs is often impaired in patients with renal failure. Common drugs that require revised dosing include penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, and digoxin. Hemodialysis reduces the serum concentrations of some drugs, which should be supplemented after hemodialysis. It is strongly recommended that physicians consult a reference on drug dosing in renal failure before prescribing drugs to these very vulnerable patients.

Certain drugs should be avoided entirely in patients undergoing dialysis. They include nitrofurantoin, metformin, and phenazopyridine.

Dialysis: Dialysis is initiated when GFR reaches ≤ 10 mL/min in a patient without diabetes or ≤ 15 mL/min in a patient with diabetes. Patients with uremic symptoms (eg, anorexia, vomiting, weight loss, pericarditis, pleuritis) or fluid overload who have no other conditions that would explain these symptoms should be started on dialysis even if GFR has not reached these levels. Other indications for dialysis in chronic kidney disease include hyperkalemia that causes ECG changes or that is persistent (K > 6
mmol/L) despite dietary restriction, heart failure poorly controlled with drugs, and metabolic acidosis that is difficult to control. (For dialysis preparation, see p. 2447.)

**Transplantation:** If a living kidney donor is available, better long-term outcomes occur when a patient receives the transplanted kidney early, even before beginning dialysis. Patients who are transplant candidates but have no living donor should receive a cadaveric renal transplant as early after initiating dialysis as possible (see p. 1133).
Chapter 240. Renal Replacement Therapy

Introduction

Renal replacement therapy (RRT) replaces nonendocrine kidney function in patients with renal failure and is occasionally used for some forms of poisoning. Techniques include intermittent hemodialysis, continuous hemofiltration and hemodialysis, and peritoneal dialysis. All modalities exchange solute and remove fluid from the blood, using dialysis and filtration across permeable membranes.

RRT does not correct the endocrine abnormalities (decreased erythropoietin and 1,25-dihydroxyvitamin D$_3$ production) of renal failure. In dialysis, serum solute (eg, Na, Cl, K, HCO$_3$, Ca, Mg, phosphate, urea, creatinine, uric acid) diffuses passively between fluid compartments down a concentration gradient (diffusive transport). In filtration, serum water passes between compartments down a hydrostatic pressure gradient, dragging solute with it (convective transport). The two processes are often used in combination (hemodiafiltration). Hemoperfusion is a rarely used technique that removes toxins by flowing blood over a bed of adsorbent material (usually a resin compound or charcoal).

Dialysis and filtration can be done intermittently or continuously. Continuous therapy is used exclusively for acute renal failure; benefits over intermittent therapy are improved tolerability as a result of slower removal of solute and water. All forms of RRT except peritoneal dialysis require vascular access; continuous techniques require a direct arteriovenous or venovenous circuit.

The choice of technique depends on multiple factors, including the primary need (eg, solute or water removal or both), underlying indication (eg, acute or chronic kidney failure, poisoning), vascular access, hemodynamic stability, availability, local expertise, and patient preference. Table 240-1 lists indications and contraindications for the common forms of RRT.

Care of patients requiring long-term RRT ideally involves a nephrologist, a psychiatrist, a social worker, a renal dietitian, dialysis nurses, and the transplant surgical team. Patient assessment should begin when end-stage renal failure is anticipated but before RRT is needed, so that care can be coordinated and patients can be educated about their options, evaluated for resources and needs, and have vascular access created. Psychosocial evaluation is important because RRT makes patients socially and emotionally vulnerable. It interrupts routine work, school, and leisure activities; creates anger, frustration, tension, and guilt surrounding dependency; and alters body image because of reduced physical energy, loss or change in sexual function, changed appearance due to access surgery, dialysis catheter placement, needle marks, bone disease, or other physical deterioration. Some patients express these feelings by nonadherence or by being uncooperative with the treatment team. Personality traits that improve prognosis for successful long-term adjustment include adaptability, independence, self-control, tolerance for frustration, and optimism. Emotional stability, family encouragement, consistent treatment team support, and patient and family participation in decision making are also important. Programs that encourage patient independence and maximal resumption of former life interests are more successful in decreasing psychosocial problems.

Hemodialysis

(Intermittent Hemodialysis)

In hemodialysis, a patient's blood is pumped into a dialyzer containing 2 fluid compartments configured as bundles of hollow fiber capillary tubes or as parallel, sandwiched sheets of semipermeable membranes. In either configuration, blood in the first compartment is pumped along one side of a semi-permeable membrane while a crystalloid solution (dialysate) is pumped along the other side, in a separate compartment, in the opposite direction. Concentration gradients of solute between blood and dialysate lead to desired changes in the patient's serum solutes, such as a reduction in urea nitrogen and creatinine; an increase in HCO$_3$; and equilibration of Na, Cl, K, and Mg. The dialysate compartment is under negative pressure relative to the blood compartment to prevent filtration of dialysate into the bloodstream and to remove the excess fluid from the patient. The dialyzed blood is then returned to the patient.
The patient is usually systemically anticoagulated during hemodialysis to prevent blood from clotting in the dialysis machine. However hemodialysis treatment may also be done with regional anticoagulation of the dialysis circuit (using heparin or trisodium citrate) or with saline flush, in which 50 to 100 mL of saline every 15 to 30 min clears the dialysis circuit of any blood clots.

The immediate objectives of hemodialysis are to correct electrolyte and fluid imbalances and remove toxins. Longer-term objectives in patients with renal failure are to

- Optimize the patient's functional status, comfort, and BP
- Prevent uremia and its complications
- Improve survival

The optimal "dose" of hemodialysis is uncertain, but most patients do well with 3 to 5 h of hemodialysis 3 times/wk. One way to assess the adequacy of each session is by measuring BUN before and after each session. A ≥ 65% decrease of BUN from predialysis level ([predialysis BUN - postdialysis BUN]/predialysis BUN × 100% is ≥ 65%) indicates an adequate session. Specialists may use other, more calculation-intensive formulas, such as KT/V ≥ 1.2 (where K is the urea clearance of the dialyzer in mL/min, T is dialysis time in minutes, and V is volume of distribution of urea [total body water] in mL).

Hemodialysis dose can be increased by increasing time on dialysis, blood flow, membrane surface area, and membrane porosity, but benefits are unproven. Nightly hemodialysis sessions (6 to 8 h, 5 to 6 days/wk) and short (1.5- to 2.5-h) daily sessions are being studied as ways to increase effectiveness and decrease complications.

**Vascular access:** Hemodialysis is usually done through a surgically created arteriovenous fistula. However, dialysis can be done through a central vein catheter if an arteriovenous fistula has not yet been created or is not ready for use or if creation of an arteriovenous fistula is impossible. The primary disadvantages of central vein catheters are a relatively narrow caliber that does not allow for blood flow high enough to achieve optimal clearance and a high risk of catheter site infection and thrombosis. Central venous catheterization for hemodialysis is best done by using the right internal jugular vein. Most internal jugular vein catheters remain useful for 2 to 6 wk if strict aseptic skin care is practiced and if the catheter is used only for hemodialysis. Also, catheters with a subcutaneous tunnel and fabric cuff have a longer life span (50% functional at 1 yr) and may be useful for patients in whom creation of an arteriovenous fistula is impossible.

Surgically created arteriovenous fistulas are better than central venous catheters because they are more durable and less likely to become infected. But they are also prone to complications (thrombosis, infection, aneurysm or pseudoaneurysm). A newly created fistula may take 3 to 6 mo to mature and be useable, so in patients with chronic renal failure, the fistula should be created early, when GFR is between 25 and 30 mL/min. The surgical procedure anastomoses the radial, brachial, or femoral artery to an adjacent vein in an end-of-the-vein to the side-of-the-artery fashion. When the adjacent vein is not suitable for access creation, a piece of prosthetic graft is used. For patients who have poor veins, an autogenous saphenous vein graft is also an option.

**Vascular access complications:** Complications such as infection, thrombosis, and pseudoaneurysm or aneurysm, significantly limit the quality of hemodialysis that can be delivered, increase long-term morbidity and mortality, and are common enough that patients and practitioners should be vigilant for suggestive changes. These changes include pain, erythema, breaks in the skin overlying the access, absence of bruit and pulse in the access, hematoma around the access, and prolonged bleeding from the dialysis cannula puncture site. Infection is treated with antibiotics, surgery, or both.

The fistula may be monitored for signs of impending failure by serial Doppler dilution blood flow.
measurements, thermal or urea dilution techniques, or by measurement of the static venous chamber pressures. One of these tests is usually recommended at least monthly. Treatment of thrombosis, pseudoaneurysm, or aneurysm may involve angioplasty, stenting, and surgery.

**Dialysis complications:** Complications are listed in Table 240-2.

Hypotension is most common and has multiple causes, including too-rapid water removal, osmotic fluid shifts across cell membranes, acetate in dialysate, heat-related vasodilation, and underlying conditions (eg, autonomic neuropathy, myocardial ischemia, arrhythmias).

Many patients also experience cramps, pruritus, nausea and vomiting, headache, and chest and back pain. In most cases, these complications occur for unknown reasons, but some may be part of a first-use syndrome (when the patient's blood is exposed to cuprophane or cellulose membranes in the dialyzer) or dialysis disequilibrium syndrome, a syndrome thought to be caused by cerebral edema. More severe cases of dialysis dys-equilibrium manifest as disorientation, restlessness, blurred vision, confusion, seizures, and even death.

Dialysis amyloidosis affects patients who have been on hemodialysis for years and manifests as carpal tunnel syndrome, bone cysts, arthritis, and cervical spondyloarthropathy.

**Prognosis:** Overall adjusted annual mortality in hemodialysis-dependent patients tends to be about 20%. The 5-yr survival rate is lower for patients with diabetes than for patients with glomerulonephritis. Death is generally mostly attributable to cardiovascular disease, followed by infection and withdrawal from hemodialysis. Blacks have usually had a higher survival rate in all age groups. Nonhemodialysis contributors to mortality include comorbidities (eg, hyperparathyroidism, diabetes), age, undernutrition, and late referral for dialysis.

**Continuous Hemofiltration and Hemodialysis**

Continuous hemofiltration and hemodialysis procedures filter and dialyze blood without interruption. The principal advantage is the ability to remove large volumes of fluid while avoiding the hypotensive episodes caused by intermittent hemodialysis and its intermittent removal of large volumes of fluid. These procedures are therefore indicated for managing patients with acute renal failure who are hemodynamically unstable, who must receive large volumes of fluid (eg, patients with multiple organ system failure or shock who require hyperalimentation or vasopressor drips), or both.

In continuous hemofiltration, water and solutes up to 20,000 daltons in molecular weight filter from the blood by convection through a permeable membrane; the filtrate is discarded, and the patient must receive infusions of physiologically balanced water and electrolytes. A dialysis circuit can be added to the filter to improve solute clearance. Procedures may be arteriovenous or venovenous. In arteriovenous procedures, the femoral artery is cannulated, and arterial pressure pushes blood through the filter into the femoral vein. Filtration rates are typically low, especially in hypotensive patients. In continuous venovenous procedures, a pump is required to push blood from one large vein (femoral, subclavian, or internal jugular) through the dialysis circuit and back into the venous circulation. Using a double-lumen catheter, blood is drawn from and returned to the same vein.

The arteriovenous route has the advantage of a simple system without the requirement of a pump but may give unreliable blood flows in hypotensive patients. Advantages of the venovenous route include better control of BP and filtration rate with smoother removal of fluid. Also, the venovenous route requires cannulation of only one vessel. Neither procedure is proven more effective than the other. All require systemic anticoagulation.

**Peritoneal Dialysis**
Peritoneal dialysis uses the peritoneum as a natural permeable membrane through which water and solutes can equilibrate. Peritoneal dialysis is less physiologically stressful than hemodialysis, does not require vascular access, can be done at home, and allows patients much greater flexibility. However, it requires much more patient involvement. Of the total estimated resting splanchnic blood flow of 1200 mL/min, only about 70 mL/min comes into contact with the peritoneum, so solute equilibration occurs much more slowly than in hemodialysis. But because solute and water clearance is a function of contact time and peritoneal dialysis is done nearly continuously, efficacy in terms of solute removal is equivalent to that obtained with hemodialysis.

In general, dialysate is instilled through a catheter into the peritoneal space, is left to dwell, and then drained. In the double-bag technique, the patient drains the fluid instilled in the abdomen in one bag and then infuses fluid from the other bag into the peritoneal cavity.

**Continuous ambulatory peritoneal dialysis (CAPD)** is most commonly used because of ease of performance and lack of need for a machine to do the exchanges. A typical adult infuses 2 to 3 L (children, 30 to 40 mL/kg) of dialysate 4 to 5 times/day; dialysate is allowed to remain for 4 h during the day and 8 to 12 h at night. The solution is manually drained. Flushing the infusion set before filling reduces peritonitis rates.

**Continuous cyclic peritoneal dialysis (CCPD)** uses a long (12 to 15 h) daytime dwell and 3 to 6 nighttime exchanges done with an automated cycler. Patients have more freedom during the day, but cumbersome equipment inhibits nighttime mobility. Some patients require a combination of CAPD and CCPD to achieve adequate clearances.

**Intermittent peritoneal dialysis (IPD)** may be done using manual or automated techniques or both. Manual IPD is simplest, achieves the highest solute clearance, and is useful chiefly in the treatment of acute renal failure. In adults, 2 to 3 L (in children, 30 to 40 mL/kg) of dialysate, warmed to 37° C, is infused over 10 to 15 min, allowed to dwell in the peritoneal cavity for 30 to 40 min, and drained in about 10 to 15 min. Multiple exchanges may be needed over 12 to 48 h. Automated cycler IPD uses an automated system that cycles the infusion and removal of dialysate. The cycler is generally set up at bedtime, and treatment occurs while the patient sleeps.

**Access:** Peritoneal dialysis requires intraperitoneal access, usually via a soft silicone rubber or porous polyurethane catheter. The catheter may be implanted in the operating room under direct visualization or at the bedside by blind insertion of a trocar or under visualization through a peritoneoscope. Most catheters incorporate a polyester fabric cuff that allows tissue ingrowth from the skin or preperitoneal fascia, ideally resulting in a watertight, bacteria-impervious seal and preventing introduction of organisms along the catheter tract. Allowing 10 to 14 days between catheter implantation and use improves healing and reduces the frequency of early pericatheter leakage of dialysate. Double-cuff catheters are better than single-cuff catheters. Also, a caudally directed exit site (the opening of the tunnel through which the catheter enters the peritoneal cavity) lowers the incidence of exit site infections (eg, by collecting less water while showering).

Once access is established, the patient undergoes a peritoneal equilibration test, in which dialysate drained after a 4-h dwell time is analyzed and compared with serum to determine solute clearance rates. This procedure helps determine the patient's peritoneal transport characteristics, the dose of dialysis required, and the most appropriate technique. In general, adequacy is defined as a weekly KTV ≥ 1.7 (where K is the urea clearance in mL/min, T is dialysis time in minutes, and V is volume of distribution of urea [total body water] in mL).

**Complications:** (See also Table 240-2). The most important and common are peritonitis and catheter exit site infection. Symptoms and signs of peritonitis include abdominal pain, cloudy peritoneal fluid, fever, nausea, and tenderness to palpation. Diagnosis is made by clinical criteria and testing. A sample of peritoneal fluid is obtained for Gram stain, culture, and WBC count with differential. Gram stain is often unrevealing, but cultures are positive in > 90%. About 90% also have > 100 WBCs/μL, usually neutrophils (lymphocytes with fungal peritonitis). Negative cultures and WBC counts < 100/μL do not exclude peritonitis, so treatment is indicated if peritonitis is suspected based on clinical or laboratory criteria and should begin immediately, before culture results are available. Peritoneal fluid studies may be falsely
negative due to prior antibiotic use, infection limited to the catheter exit site or tunnel, or sampling of too little fluid.

Empiric treatment should be adapted to microbial resistance patterns of a given facility, but typical recommendations are for initial treatment with drugs active against gram-positive organisms, eg, either vancomycin or a 1st-generation cephalosporin, plus drugs active against gram-negative organisms, such as a 3rd-generation cephalosporin (eg, ceftazidime) or an aminoglycoside (eg, gentamicin). Drugs are adjusted based on the result of peritoneal dialysis fluid culture. Antibiotic therapy is usually given IV or intraperitoneally (IP) for peritonitis and orally for exit site infections. Patients with peritonitis are admitted to the hospital if IV treatment is necessary or if hemodynamic instability or other significant complications arise.

Catheter tunnel exit site infection manifests as tenderness over the tunnel or at the exit site along with crusting, erythema, or drainage. Diagnosis is clinical. Treatment of infection without drainage is topical antiseptics (eg, povidone iodine, chlorhexidine); if ineffective, a 1st-generation cephalosporin or a penicillinase-resistant penicillin is used empirically, with culture results guiding subsequent therapy.

**Prognosis:** Most cases of peritonitis respond to prompt antibiotic therapy, but those caused by staphylococci or fungi also require dialysis catheter removal. Overall, 5-yr survival rate in peritoneal dialysis patients is similar to that in hemodialysis patients (about 36%).

**Medical Aspects of Long-Term Renal Replacement Therapy**

All patients undergoing long-term renal replacement therapy (RRT) develop accompanying metabolic and other disorders. These disorders require appropriate attention and adjunctive treatment. Approach varies by patient but typically includes nutritional modifications and management of multiple metabolic abnormalities (see also p. 2445).

**Diet:** Diet should be tightly controlled. Generally, hemodialysis patients tend to be anorexic and should be encouraged to eat a daily diet of 35 kcal/kg ideal body weight (in children, 40 to 70 kcal/kg/day depending on age and activity). Daily Na intake should be limited to 2 g (88 mEq), K to 60 mEq, and P to 800 to 1000 mg. Fluid intake is limited to 1000 to 1500 mL/day and monitored by weight gain between dialysis treatments. Patients undergoing peritoneal dialysis need a protein intake of 1.25 to 1.5 g/kg/day (compared with 1.0 to 1.2 g/kg/day in hemodialysis patients) to replace peritoneal losses (10 to 20 g/day). Survival is best among patients (both hemodialysis and peritoneal dialysis) who maintain a serum albumin > 3.5 g/dL; serum albumin is the best predictor of survival in these patients.

**Anemia of renal failure:** The anemia that occurs in renal failure should be treated with recombinant human erythropoietin and iron supplementation (see p. 2445). Because the absorption of oral iron is limited, many patients require IV iron during hemodialysis (Na ferric gluconate and iron sucrose are preferred to iron dextran, which has a higher incidence of anaphylaxis). Iron stores are assessed using serum iron, total iron-binding capacity, and serum ferritin, typically before the start of erythropoietin therapy and thereafter every other month. Iron deficiency is the most common reason for erythropoietin resistance. However, some dialysis patients who have received multiple blood transfusions have iron overload (see p. 1032) and should not be given iron supplements.

**Coronary artery disease:** Risk factors must be managed aggressively because many patients who require RRT are hypertensive, dyslipidemic, or diabetic; smoke cigarettes; and ultimately die of cardiovascular disease. Continuous peritoneal dialysis is more effective than hemodialysis in removing fluid; as a result, these patients require fewer antihypertensive drugs. Hypertension can also be controlled in about 80% of hemodialysis patients by filtration alone. Antihypertensives are required in the remaining 20%. Patients given ACE inhibitors or angiotensin II receptor blockers may need closer monitoring of serum K⁺ to prevent hyperkalemia. For approaches to dyslipidemia, see p. 896; for diabetes management, see p. 871; and for smoking cessation, see p. 3432.

**Hyperphosphatemia:** Hyperphosphatemia, a consequence of phosphate retention from low GFR, increases risk for soft-tissue calcification, especially in coronary arteries and heart valves, when Ca × P > 70. It also stimulates development of secondary hyperparathyroidism. Initial treatment is Ca-based
antacids (eg, Ca carbonate 1.25 g po tid, Ca acetate 667 to 2001 mg po tid with meals), which function as phosphate binders and reduce P levels. Constipation and abdominal bloating are complications of chronic use. Patients should be monitored for hypercalcemia. Sevelamer hydrochloride 800 to 3200 mg or lanthanum carbonate 250 to 1000 mg with each meal is an option for patients who develop hypercalcemia while taking Ca-containing phosphate binders. Some patients (eg, those hospitalized with acute renal failure and very high serum phosphate concentrations) require addition of aluminum-based phosphate binders, but these should be used short-term only (eg, 1 to 2 wk as needed) to prevent aluminum toxicity.

**Hypocalcemia and secondary hyperparathyroidism:** These complications often coexist as a result of impaired renal production of vitamin D. Treatment of hypocalcemia is with calcitriol either orally (0.25 to 1.0 μg po once/day) or IV (1 to 3 μg in adults and 0.01 to 0.05 μg/kg in children per dialysis treatment). Treatment can increase serum phosphate level and should be withheld until the level is normalized to avoid soft-tissue calcification. Doses are titrated to suppress parathyroid hormone (PTH) levels, usually to 150 to 300 pg/mL (PTH reflects bone turnover better than serum Ca). Oversuppression decreases bone turnover and leads to adynamic bone disease, which carries a high risk of fracture. The vitamin D analogs doxercalciferol and paricalcitol have less effect on Ca and P absorption from the gut but suppress PTH equally well. Early hints that these drugs may reduce mortality compared with calcitriol require confirmation. Cinacalcet, a calcimimetic drug, increases sensitivity of parathyroid Ca-sensing receptors to Ca and may also be indicated for hyperparathyroidism, but its role in routine practice has yet to be defined. Its ability to decrease PTH levels by as much as 75% may decrease the need for parathyroidectomy in these patients.

**Aluminum toxicity:** Toxicity is a risk in hemodialysis patients who are exposed to aluminum-based phosphate binders. Manifestations are osteomalacia, microcytic anemia (iron-resistant), and probably dialysis dementia (a constellation of memory loss, dyspraxia, hallucinations, facial grimaces, myoclonus, seizures, and a characteristic EEG). Diagnosis is by measurement of plasma aluminum before and 2 days after IV infusion of defer-oxamine 5 mg/kg. Deferoxamine chelates aluminum, releasing it from tissues and increasing the blood level among patients with aluminum toxicity. A rise in aluminum level of ≥ 50 μg/L suggests toxicity. Aluminum-related osteomalacia can also be diagnosed by needle biopsy of bone (requires special stains for aluminum). Treatment is avoidance of aluminum-based binders plus IV or intraperitoneal deferoxamine.

**Bone disease:** Renal osteodystrophy is abnormal bone mineralization. It has multiple causes, including vitamin D deficiency, elevated serum phosphate, secondary hyperparathyroidism, chronic metabolic acidosis, and aluminum toxicity; treatment is that of the cause.

**Vitamin deficiencies:** Vitamin deficiencies result from dialysis-related loss of water-soluble vitamins (eg, B, C, folate) and can be replenished with daily multivitamin supplements.

**Calciphylaxis:** Calciphylaxis is a rare disorder of systemic arterial calcification causing ischemia and necrosis in localized areas of the fat and skin of the trunk, buttocks, and lower extremities. Cause is unknown, though hyperparathyroidism, vitamin D supplementation, and elevated Ca and P levels are thought to contribute. It manifests as painful, violaceous, purpuric plaques and nodules that ulcerate, form eschars, and become infected. It is often fatal. Treatment is usually supportive. Several cases have been reported in which Na thiosulfate given IV at the end of dialysis 3 times/wk along with aggressive efforts to reduce the serum Ca × phosphate product has resulted in considerable improvement.

**Constipation:** Constipation is a minor but troubling aspect of long-term RRT and, because of resulting bowel distention, may interfere with catheter drainage in peritoneal dialysis. Many patients require osmotic (eg, sorbitol) or bulk (eg, psyllium) laxatives. Laxatives containing Mg or phosphate should be avoided.
Chapter 241. Penile and Scrotal Disorders

Introduction

Abnormalities of the external male genitals are psychologically disturbing and sometimes serious (see p. 2985; for testicular and scrotal anomalies, see p. 2986).

Balanitis, Posthitis, and Balanoposthitis

Balanitis is inflammation of the glans penis, posthitis is inflammation of the prepuce, and balanoposthitis is inflammation of both.

Inflammation of the head of the penis has both infectious and noninfectious causes (see Table 241-1). Often, no cause can be found. Balanoposthitis often occurs in patients with a tight prepuce (phimosis), which interferes with adequate hygiene. The subpreputial secretions may become infected with anaerobic bacteria, resulting in inflammation. Diabetes mellitus predisposes to balanoposthitis. Balanitis usually leads to posthitis except in circumcised patients. Chronic balanoposthitis increases the risk of balanitis xerotica obliterans, phimosis, paraphimosis, and cancer.

Symptoms and Signs

Soreness, irritation, and a subpreputial discharge often occur 2 or 3 days after sexual intercourse. Phimosis, superficial ulcerations, and inguinal adenopathy may follow.

Diagnosis

Patients should be tested for the causes listed, especially candidiasis. Blood should be tested for glucose. The skin should be examined for lesions that suggest a dermatosis capable of genital involvement. History should include investigation of latex condom use.

Treatment

Hygiene measures should be instituted and specific causes treated. Subpreputial irrigation to remove secretions and detritus may be necessary. If phimosis persists after inflammation has resolved, circumcision should be considered.

Cutaneous Penile Lesions

Common skin disorders and infections can cause cutaneous penile lesions (see Table 241-2).

Balanitis xerotica obliterans: This lesion, another name for lichen sclerosus et atrophicus in men, is an indurated, blanched area near the tip of the glans surrounding and often constricting the meatus. It results from chronic inflammation and may lead to phimosis, paraphimosis, or urethral stricture. Topical drugs, including corticosteroids, tacrolimus, antibiotics, and anti-inflammatory drugs, may be used, but their efficacy is limited. Surgery is required in severe cases.

Carcinoma in situ: This lesion can include erythroplasia of Queyrat and Bowen's disease of the penis; both are well-circumscribed areas of reddish, velvety pigmentation in the genital area, usually on the glans or at the corona, primarily in uncircumcised men. Paget's disease of the nipple (not to be confused with Paget's disease of bone) is a rare intraepithelial adeno-carcinoma that can occur in extramammary locations, including the penis. These conditions (and Bowenoid papulosis, which involves smaller, often multiple papules on the shaft of the penis) are considered intraepithelial neoplasia or carcinoma in situ and should be biopsied. Treatment consists of 5% fluorouracil.

[Table 241-1, Causes of Penile Inflammation]
[Table 241-2, Causes of Cutaneous Penile Lesions]
cream, local excision, or laser therapy. Close follow-up is indicated.

**Penile lichen planus:** This lesion occurs as small papules or macules, sometimes annular, on the glans or shaft and may be mistaken for pemphigoid or erythema multiforme. Pruritus is common. A more severe form of erosive lichen planus occurs on both oral and genital mucosa and is known as penogingival syndrome in men and vulvogingival gingival syndrome in women. Ulcers may develop and cause pain. Lichen planus usually resolves spontaneously. If asymptomatic, it may not require treatment. Topical corticosteroids may help relieve symptoms.

**Pearly penile papules:** These papules are small, harmless angiofibromas that appear on the corona of the penis as dome-shaped or hairlike projections and tend to be skin-colored. They may also appear on the distal shaft. They are common, occurring in up to 10% of men. They are not associated with human papillomavirus, although they may be mistaken for genital warts. Treatment is not required.

**Contact dermatitis of the penis:** Contact dermatitis (see p. 666) of the penis has become more common with the widespread use of latex condoms. Dermatitis appears as red, pruritic lesions, sometimes with weeping or fissures. Treatment is with topical corticosteroids and use of nonlatex condoms (but not natural condoms, which do not provide adequate protection against HIV). Mild OTC corticosteroids can be tried first, with use of middle or high potency prescription preparations as needed.

**Epididymitis**

**Epididymitis is inflammation of the epididymis, occasionally accompanied by inflammation of the testis (epididymo-orchitis).** Scrotal pain and swelling usually occur unilaterally. Diagnosis is based on physical examination. Treatment is with antibiotics, analgesics, and scrotal support.

**Etiology**

**Bacterial:** Most epididymitis (and epididymo-orchitis) is caused by bacteria. When inflammation involves the vas deferens, vasitis ensues. When all spermatic cord structures also are involved, the diagnosis is funiculitis. Rarely, epididymal abscess, scrotal extra-epididymal abscess, pyocele (accumulation of pus within a hydrocele), or testicular infarction occurs.

In men < 35 yr, most cases are due to a sexually transmitted pathogen, especially *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Infection may begin as urethritis. In men > 35 yr, most cases are due to gram-negative coliform bacilli and typically occur in patients with urologic abnormalities, indwelling catheters, or recent urologic procedures. Tuberculous epididymitis and syphilitic gummas are rare in the US except in immunocompromised (eg, HIV-infected) patients.

**Nonbacterial:** Viral causes (eg, cytomegalovirus infection) and mycotic causes (eg, actinomycosis, blastomycosis) are rare in the US except in immunocompromised (eg, HIV-infected) patients. Epididymitis and epididymo-orchitis of noninfectious etiology may be due to chemical irritation secondary to a retrograde flow of urine into the epididymis, which may occur with Valsalva maneuver (eg, with heavy lifting) or after local trauma.

**Symptoms and Signs**

Scrotal pain occurs in both bacterial and nonbacterial epididymitis. Pain can be severe and is sometimes referred to the abdomen. In bacterial epididymitis, patients may also have fever, nausea, or urinary symptoms. Urethral discharge may be present if the cause is urethritis.

Physical examination reveals swelling, induration, marked tenderness, and sometimes erythema of a portion of or all of the affected epididymis and, sometimes, the adjacent testis. Sepsis is suggested by fever, tachycardia, hypotension, and a toxic appearance.

**Diagnosis**
Clinical evaluation

Sometimes urethral swab and urine culture

Diagnosis is confirmed by finding swelling and tenderness of the epididymis. However, unless findings are clearly isolated to the epididymis, testicular torsion (see p. 2457) must also be considered, particularly in patients < 30 yr; immediate color Doppler ultrasonography is indicated. A GU consultation is indicated if the cause is unclear or the disorder is recurrent.

Urethritis suggests that the cause of epididymitis is a sexually transmitted pathogen, and a urethral swab is sent for gonococcus and chlamydia culture or PCR. Otherwise, the infecting organism usually can be identified by urine culture. Urinalysis and culture are normal in nonbacterial causes.

Treatment

• Antibiotics

• Supportive measures

Treatment consists of bed rest, scrotal elevation (eg, with a jockstrap when upright) to decrease repetitive, minor bumps, scrotal ice packs, anti-inflammatory analgesics, and a broad-spectrum antibiotic such as ciprofloxacin 500 mg po bid or levofloxacin 500 mg po once/day for 21 to 30 days. Alternatively, doxycycline 100 mg po bid or trimethoprim/sulfamethoxazole double-strength (160/800 mg) po bid may by used. If sepsis is suspected, an aminoglycoside such as tobramycin 1 mg/kg IV q 8 h or a 3rd-generation cephalosporin such as ceftriaxone 1 to 2 g once/day IV may be useful until the infecting organism and its sensitivities are known. Abscess and pyocele usually require surgical drainage.

Recurrent bacterial epididymitis secondary to incurable chronic urethritis or prostatitis occasionally can be prevented by vasectomy. An epididymectomy, occasionally done for chronic epididymitis, may not relieve symptoms. Patients who must continuously wear an indwelling urethral catheter are prone to develop recurrent epididymitis and epididymo-orchitis. In such cases, placement of a suprapubic cystostomy or institution of a self-catheterization regimen may be useful.

Treatment of nonbacterial epididymitis includes the above general measures, but antimicrobial therapy is not warranted. Nerve block of the spermatic cord with local anesthesia can relieve symptoms in severe, persistent cases.

Orchitis

Orchitis is infection of the testes, typically with mumps virus. Symptoms are testicular pain and swelling. Diagnosis is clinical. Treatment is symptomatic. Antibiotics are given if bacterial infection is identified.

Isolated orchitis (ie, infection localized to the testes) is nearly always viral in origin, and most cases are due to mumps. Rare causes include congenital syphilis, TB, leprosy, echovirus infection, lymphocytic choriomeningitis, coxsackievirus infection, infectious mononucleosis, varicella, and infection with group B arborviruses. Most bacterial causes also involve the epididymis (epididymo-orchitis—see p. 2455).

Orchitis develops in 20 to 25% of males with mumps; 80% of cases occur in patients < 10 yr. Two thirds of cases are unilateral and one third bilateral. Sixty percent of patients with mumps orchitis develop testicular atrophy in at least one testis. Atrophy is unrelated to fertility or to the severity of the orchitis. The incidence of tumor does not appear to be increased, but unilateral disease diminishes fertility in one fourth of men after unilateral mumps orchitis and in two thirds of men who have had bilateral disease.

Symptoms and Signs

Unilateral mumps orchitis develops acutely between 4 and 7 days after parotid swelling in mumps. In 30% of cases, the disease spreads to the other testis in 1 to 9 days. Pain may be of any degree of severity. In
addition to pain and swelling of the testes, systemic symptoms may develop, such as malaise, fever, nausea, headache, and myalgias. Testicular examination reveals tenderness, enlargement, and induration of the testis and edema and erythema of the scrotal skin.

Other infectious agents cause similar symptoms with speed of onset and intensity related to their pathogenicity.

**Diagnosis**

- Clinical evaluation and selective testing

History and physical examination usually indicate the diagnosis. Urgent differentiation of orchitis from testicular torsion and other causes of acute scrotal swelling and pain is accomplished with color Doppler ultrasonography. Mumps can be confirmed by serum immunofluorescence antibody testing. Other infectious agents may be identified by urine culture or serology.

**Treatment**

Supportive care with analgesics and hot or cold packs is sufficient if bacterial infection has been ruled out. Bacterial causes are treated with appropriate antibiotics. Urologic follow-up is recommended.

**Peyronie’s Disease**

**Peyronie’s disease is fibrosis of the cavernous sheaths leading to contracture of the investing fascia of the corpora, resulting in a deviated and sometimes painful erection.**

The disease occurs in adults. The cause is unknown but appears to be similar to that of Dupuytren's contracture. The contracture usually results in deviation of the erect penis to the involved side, occasionally causes painful erections, and may prevent penetration. Fibrosis may extend into the corpus cavernosum, compromising tumescence distally.

Resolution may occur spontaneously over many months. Mild Peyronie's disease that does not cause sexual dysfunction does not warrant treatment.

**Treatment**

Treatment results are unpredictable. Oral vitamin E and K para-aminobenzoate have had varied success. Surgical removal of the fibrosis and replacement with a patch graft may be successful or may result in further scarring and exaggeration of the defect. A series of local injections of verapamil or high-potency corticosteroids into the plaque may be effective, but oral corticosteroids are not. Ultrasound treatments can stimulate blood flow, which may prevent further scarring. Radiation therapy may decrease pain; however, radiation often worsens tissue damage. To assist penetration, a prosthesis may be implanted but may require a patch procedure to straighten the penis.

**Phimosis and Paraphimosis**

**Phimosis is inability to retract the foreskin; paraphimosis is entrapment of the foreskin in the retracted position.**

**Phimosis:** Phimosis is normal in children and typically resolves by age 5. Treatment is not required in the absence of complications such as balanitis, UTIs, urinary outlet obstruction, unresponsive dermatologic disease, or suspicion of carcinoma.

Three months of betamethasone cream 0.05% bid to tid applied to the tip of the fore-skin and the area touching the glans is often effective. Stretching the foreskin gently with 2 fingers or over an erect penis for 2 to 3 wk with care not to cause paraphimosis is also successful. Circumcision is the preferred surgical option.
In adults, phimosis may result from balanoposthitis or prolonged irritation. Risk of UTI is increased. The usual treatment is circumcision.

**Paraphimosis:** Paraphimosis can occur when the foreskin is left retracted (behind the glans penis). Retraction may occur during catheterization or physical examination. If the retracted foreskin is somewhat tight, it functions as a tourniquet, causing the glans to swell, both blocking the foreskin from returning to its normal position and worsening the constriction.

Paraphimosis should be regarded as an emergency, because constriction leads quickly to vascular compromise and necrosis. Firm circumferential compression of the glans with the hand may relieve edema sufficiently to allow the foreskin to be restored to its normal position. If this technique is ineffective, a dorsal slit done using a local anesthetic relieves the condition temporarily. Circumcision is then done when edema has resolved.

**Testicular Torsion**

Testicular torsion is an emergency condition due to rotation of the testis and consequent strangulation of its blood supply. Symptoms are acute scrotal pain and swelling, nausea, and vomiting. Diagnosis is based on physical examination and confirmed by color Doppler ultrasonography. Treatment is immediate manual detorsion followed by surgical intervention.

Anomalous development of the tunica vaginalis and spermatic cord can lead to incomplete fixation of the testis to the tunica vaginalis (bell-clapper deformity—see Fig. 241-1). This anomaly predisposes the testis to twisting on its cord spontaneously or after trauma. The predisposing anomaly is present in about 12% of males. Torsion is most common between the ages of 12 and 18, with a secondary peak in infancy. It is uncommon in men > age 30. It is more common in the left testis.

**Symptoms and Signs**

Immediate symptoms are rapid onset of severe local pain, nausea, and vomiting,

![Fig. 241-1. Abnormal testicular fixation leading to torsion.](image)

followed by scrotal edema and induration. Fever and urinary frequency may be present. The testis is tender and may be elevated and horizontal. The contralateral testis may also be horizontal because the anatomic defect is usually bilateral. The cremasteric reflex is usually absent on the affected side. Sometimes, torsion can spontaneously resolve and then recur, which may appear to suggest a less acute onset. Usually, however, the onset and resolution of pain is very rapid with each episode.

**Diagnosis**

- Clinical evaluation
- Often color Doppler ultrasonography

Torsion must be rapidly identified. Similar symptoms result mainly from epididymitis. With epididymitis, pain and swelling are usually less acute and initially localized to the epididymis. However, in both conditions, generalized swelling and tenderness often develop, making it difficult to distinguish torsion from epididymitis. A clinical diagnosis usually is sufficient to proceed to treatment. An equivocal diagnosis may be resolved by immediate imaging if available. Color Doppler ultrasonography of the scrotum is preferred. Radioisotope scrotal scan is also diagnostic but takes longer and is less preferred.

**Treatment**

- Manual detorsion
- Surgery: Urgently if detorsion is unsuccessful, otherwise electively
Immediate manual detorsion without imaging can be attempted on the initial examination; its success is variable. Because testes usually rotate inward, for detorsion the testis is rotated in an outward direction (eg, for the left testis, detorsion is clockwise when viewed from the front—underneath the testis). More than one rotation may be needed to resolve the torsion; pain relief guides the procedure. If detorsion fails, immediate surgery is indicated, because exploration within a few hours offers the only hope of testicular salvage. Testicular salvage drops rapidly from 80 to 100% at 6 to 8 h to near zero at 12 h. Fixation of the contralateral testis is also done to prevent torsion on that side. When manual detorsion is successful, bilateral testicular fixation is done electively.

Urethral Stricture

Urethral stricture is scarring that obstructs the anterior urethral lumen.

Urethral stricture can be congenital (see p. 2986) or acquired. Anything that damages the urethral epithelium or corpus spongiosum can cause acquired stricture. The most common cause is trauma, such as straddle injury and occasionally iatrogenic injury (eg, after traumatic endoscopy). Less common causes may include lichen sclerosis and urethritis (usually chronic or untreated). Often strictures are idiopathic.

Symptoms and Signs

Symptoms may not develop until the urethral lumen has been decreased considerably. Strictures may cause a double-stream, obstructive voiding symptoms, or recurrent UTIs (including prostatitis). A urethral diverticulum may develop, sometimes accompanied by abscess formation and, rarely, a fistula with extravasation of urine into the scrotum and perineum.

Diagnosis

• Retrograde urethrography or cystoscopy

The diagnosis is usually suspected when urethral catheterization is difficult. It should also be considered in males with gradual onset of obstructive symptoms or recurrent UTIs, particularly if they have risk factors or are young. Diagnosis is usually by retrograde urethrography or cystoscopy.

Treatment

Treatment is determined by the type of obstruction. Often, dilation or endoscopy (internal urethrotomy) is done. However, with certain types of strictures (eg, complicated or recurrent strictures), dilation and endoscopy should be avoided; daily self-catheterization may be indicated. Open urethroplasty may be indicated if the stricture is localized and causes recurrent problems.
Chapter 242. Benign Prostate Disease

Introduction

(Prostate Cancer is discussed on p. 2470.)

The prostate can be affected by hyperplasia, infection, and cancer. The normal prostate is a walnut-sized organ composed of glandular tissue that makes ejaculatory fluid, its only known function. Because prostatic tissue surrounds the urethra, enlargement or other abnormalities may affect urination. The prostate may be examined by digital rectal examination to determine its size, symmetry, texture, and nodularity.

Benign Prostatic Hyperplasia

(Benign Prostatic Hypertrophy)

Benign prostatic hyperplasia (BPH) is nonmalignant adenomatous overgrowth of the periurethral prostate gland. Symptoms are those of bladder outlet obstruction—weak stream, hesitancy, urinary frequency, urgency, nocturia, incomplete emptying, terminal dribbling, overflow or urge incontinence, and complete urinary retention. Diagnosis is based primarily on digital rectal examination and symptoms; cystoscopy, transrectal ultrasonography, urodynamics, or other imaging studies may also be needed. Treatment options include 5α-reductase inhibitors, α-blockers, and surgery.

Using the criteria of a prostate volume > 30 mL and a high American Urological Association Symptom Score (see Table 242-1), the prevalence of BPH in men aged 55 to 74 without prostate cancer is 19%. But if voiding criteria of a maximal urinary flow rate < 10 mL/sec and a postvoid residual urine volume > 50 mL are included, the prevalence is only 4%. Based on autopsy studies, the prevalence of BPH increases from 8% in men aged 31 to 40 to 40 to 50% in men aged 51 to 60 and to > 80% in men > 80.

The etiology is unknown but probably involves hormonal changes associated with aging.

Pathophysiology

Multiple fibroadenomatous nodules develop in the periurethral region of the prostate, probably originating within the periurethral glands rather than in the true fibromuscular prostate (surgical capsule), which is displaced peripherally by progressive growth of the nodules.

As the lumen of the prostatic urethra narrows and lengthens, urine outflow is progressively obstructed. Increased pressure associated with micturition and bladder distention can progress to hypertrophy of the bladder detrusor, trabeculation, cellule formation, and diverticula. Incomplete bladder emptying causes stasis and predisposes to calculus formation and infection. Prolonged obstruction, even if incomplete, can cause hydronephrosis and compromise renal function.

Symptoms and Signs

Symptoms include progressive urinary frequency, urgency, and nocturia due to incomplete emptying and rapid refilling of the bladder. Pain and dysuria are usually not present. Decreased size and force of the urinary stream cause hesitancy and intermittency. Sensations of incomplete emptying, terminal dribbling, overflow incontinence, or complete urinary retention may ensue. Straining to void can cause congestion of superficial veins of the prostatic urethra and trigone, which may rupture and cause hematuria. Straining also may acutely cause vasovagal syncope and, over the long term, may cause dilation of hemorrhoidal veins or inguinal hernias.
Some patients present with sudden, complete urinary retention, with marked abdominal discomfort and bladder distention. Retention may be precipitated by any of the following:

- Prolonged attempts to retain urine
- Immobilization
- Exposure to cold
- Use of anesthetics, anticholinergics, sympathomimetics, opioids, or alcohol

Symptoms can be quantitated by the 7-question American Urological Association Symptom Score (see Table 242-1). This score also allows physicians to follow symptom progression: Scores > 10 but < 20 suggest moderate symptoms, and scores > 20 suggest severe symptoms.

On digital rectal examination, the prostate usually is enlarged and nontender, has a rubbery consistency, and in many cases has lost the median furrow. However, prostate size as detected with digital rectal examination may be misleading; an apparently small prostate may cause obstruction. If distended, the urinary bladder may be palpable or percussible during abdominal examination.

**Diagnosis**

- Digital rectal examination
- Urinalysis and culture
- Prostate-specific antigen level
- Sometimes uroflowmetry and bladder ultrasonography

The lower urinary tract symptoms of BPH can also be caused by other disorders, including infection and prostate cancer. Furthermore, BPH and prostate cancer may coexist. Although palpable prostate tenderness suggests infection, digital rectal examination findings in BPH and cancer often overlap. Although cancer may cause a stony, hard, nodular, irregularly enlarged prostate, most patients with cancer, BPH, or both have a benign-feeling, enlarged prostate. Thus, patients with symptoms or palpable prostatic abnormalities should undergo testing.

Typically, urinalysis and culture are done, and serum prostate-specific antigen (PSA) levels are measured. Men with moderate or severe symptoms of obstruction may also have uroflowmetry (an objective test of urine volume and flow rate) with measurement of postvoid residual volume by bladder ultrasonography. Flow rate < 15 mL/sec suggests obstruction, and postvoid residual volume > 100 mL suggests retention.

Interpreting PSA levels can be complex. The PSA level is moderately elevated in 30 to 50% of patients with BPH, depending on prostate size and degree of obstruction, and is elevated in 25 to 92% of patients with prostate cancer, depending on the tumor volume. Typically, if the PSA level is 4 ng/mL or if the digital rectal examination indicates an abnormality (other than smooth, symmetric enlargement), then a transrectal biopsy is recommended. For men < 50 or those at high risk of prostate cancer, a lower cutoff (PSA > 2.5 ng/mL) may be used. Other measures, including rate of PSA increase, free-to-bound PSA ratio, and other markers, may be useful (for full discussion of prostate cancer screening and diagnosis, see p. 2470).

Transrectal biopsy is usually done with ultrasound guidance. Transrectal ultrasonography can also measure prostate volume.

Clinical judgment must be used to evaluate the need for further testing. Contrast imaging studies (eg, CT or IVU) are rarely necessary unless obstructive symptoms have been severe and prolonged. Upper urinary tract abnormalities that usually result from bladder outlet obstruction include upward displacement...
of the terminal portions of the ureters (fish hooking), ureteral dilation, and hydronephrosis. If an upper tract imaging study is warranted due to pain or elevated serum creatinine level, ultrasonography may be preferred because it avoids radiation and IV contrast exposure.

Treatment

• Avoidance of anticholinergics, sympathomimetics, and opioids

• Use of α-adrenergic blockers (eg, terazosin, doxazosin, tamsulosin, alfuzosin) or 5α-reductase inhibitors (finasteride, dutasteride)

• Transurethral resection of the prostate or a less invasive procedure

Urinary retention: Urinary retention requires immediate decompression. Passage of a standard urinary catheter is first attempted; if a standard catheter cannot be passed, a catheter with a coude tip may be effective. If this catheter cannot be passed, flexible cystoscopy or insertion of filiforms and followers (guides and dilators that progressively open the urinary passage) may be necessary (this procedure should usually be done by a urologist). Suprapubic percutaneous decompression of the bladder may be used if transurethral approaches are unsuccessful.

Drug therapy: For partial obstruction with troublesome symptoms, all anticholinergics, sympathomimetics, and opioids should be stopped, and any infection should be treated with antibiotics. For patients with mild to moderate obstructive symptoms, α-adrenergic blockers (eg, terazosin, doxazosin, tamsulosin, alfuzosin) may improve voiding. The 5α-reductase inhibitors (finasteride, dutasteride) may reduce prostate size, decreasing voiding problems over months, especially in patients with larger (> 30 mL) glands. A combination of both classes of drugs is superior to monotherapy.

Surgery: Surgery is done when patients do not respond to drug therapy or develop recurrent UTI or upper tract dilation. Transurethral resection of the prostate (TURP) is the standard. Erectile function and continence are usually retained, although about 5 to 10% of patients experience some postsurgical problems, most commonly retrograde ejaculation. The incidence of erectile dysfunction after TURP is between 1 and 35%, and the incidence of incontinence is about 1 to 3%. About 10% of men undergoing TURP need the procedure repeated within 10 yr because the prostate continues to grow. Larger prostates (usually > 75 g) require open surgery via a suprapubic or retropubic approach. All surgical methods require postoperative catheter drainage for 1 to 7 days.

Other procedures: Less invasive procedures include microwave thermotherapy, laser ablation, electrovaporization, high-intensity focused ultrasound, transurethral needle ablation, radiofrequency vaporization, and intravesical stents. The circumstances under which these procedures should be used have not been firmly established, but those done in the physician’s office (microwave thermotherapy and radiofrequency procedures) are being more commonly used and do not require use of general or regional anesthesia. Their long-term ability to alter the natural history of BPH is under study.

Prostatitis

(Prostatodynia)

Prostatitis refers to a disparate group of disorders that manifests with a combination of predominantly irritative or obstructive urinary symptoms and perineal pain. Some cases result from bacterial infection of the prostate gland and others, which are more common, from a poorly understood combination of noninfectious inflammatory factors, spasm of the muscles of the urogenital diaphragm, or both. Diagnosis is clinical, along with microscopic examination and culture of urine samples obtained before and after prostate massage. Treatment is with an antibiotic if the cause is bacterial. Nonbacterial causes are treated with warm sitz baths, muscle relaxants, and anti-inflammatory drugs or anxiolytics.

Etiology
Prostatitis can be bacterial or, more commonly, nonbacterial. However, differentiating bacterial and nonbacterial causes can be difficult, particularly in chronic prostatitis.

**Bacterial prostatitis** can be acute or chronic and is usually caused by typical urinary pathogens (eg, *Klebsiella, Proteus, Escherichia coli*) and possibly by *Chlamydia*. How these pathogens enter and infect the prostate is unknown. Chronic infections may be caused by sequestered bacteria that antibiotics have not eradicated.

**Nonbacterial prostatitis** can be inflammatory or noninflammatory. The mechanism is unknown but may involve incomplete relaxation of the urinary sphincter and dyssynergic voiding. The resultant elevated urinary pressure may cause urine reflux into the prostate (triggering an inflammatory response) or increased pelvic autonomic activity leading to chronic pain (see p. 1629) without inflammation.

**Classification**

Prostatitis is classified into 4 categories (see Table 242-2). These categories are differentiated by clinical findings and by the presence or absence of signs of infection and inflammation in 2 urine samples. The first sample is a midstream collection. Then digital prostate massage is done, and patients void immediately; the first 10 mL of urine constitutes the 2nd sample. Infection is defined by bacterial growth in urine culture; inflammation is defined by the presence of WBCs in urine.

**Symptoms and Signs**

Symptoms vary by category but typically involve some degree of urinary irritation or obstruction and pain. Irritation is manifested by frequency and urgency, obstruction, a sensation of incomplete bladder emptying, a need to void again shortly after urinating, or nocturia. Pain is typically in the perineum but may be perceived at the tip of the penis, lower back, or testes. Some patients report painful ejaculation.

**Acute bacterial prostatitis** often causes such systemic symptoms as fever, chills, malaise, and myalgias. The prostate is exquisitely tender and focally or diffusely swollen, boggy, indurated, or a combination. A generalized sepsis syndrome may result, characterized by tachycardia, tachypnea, and sometimes hypotension.

**Chronic bacterial prostatitis** manifests with recurrent episodes of infection with or without complete resolution between bouts. Symptoms and signs tend to be milder than in acute prostatitis.

**Chronic prostatitis/chronic pelvic pain syndrome** typically has pain as the predominant complaint, often including pain with ejaculation. The discomfort can be significant and often markedly interferes with quality of life. Symptoms of urinary irritation or obstruction also may be present. On examination, the prostate may be tender but usually is not boggy or swollen.

**Asymptomatic inflammatory prostatitis** causes no symptoms and is discovered incidentally during evaluation for other prostate diseases when WBCs are present in the urine.

**Diagnosis**

- Urinalysis
- Prostate massage except possibly in acute bacterial prostatitis

Diagnosis of type I, II, or III is suspected clinically. Similar symptoms can result from urethritis, perirectal abscess, or UTI. Examination is helpful diagnostically only in acute bacterial prostatitis.

Febrile patients with typical symptoms and signs of acute bacterial prostatitis usually have WBCs and bacteria in a midstream urine sample. Prostate massage to obtain a postmassage urine sample is thought to be unnecessary and possibly dangerous in these patients (although danger remains unproved) because bacteremia can be induced. For the same reason, rectal examination should be done gently.
Blood cultures should be obtained in patients who have fever and severe weakness, confusion, disorientation, hypotension, or cool extremities. For afebrile patients, urine samples before and after massage are adequate for diagnosis.

For patients with acute or chronic bacterial prostatitis who do not respond favorably to antibiotics, transrectal ultrasonography and sometimes cystoscopy may be necessary to rule out prostatic abscess or destruction and inflammation of the seminal vesicles.

For patients with types II, III, and IV (non-acute prostatitis) disease, additional tests that can be considered are cystoscopy and urine cytology (if hematuria is also present) and urodynamic measurements (if there is suspicion of neurologic abnormalities or detrusorsphincter dyssynergia).

Treatment

Treatment varies significantly with etiology.

**Acute bacterial prostatitis:** Nontoxic patients can be treated at home with antibiotics, bed rest, analgesics, stool softeners, and hydration. Therapy with a fluoroquinolone (eg, ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid) is usually effective and can be given until culture and sensitivity results are known. If the clinical response is satisfactory, [Table 242-2. NIH Consensus Classification System for Prostatitis](#)
treatment is continued for about 30 days to prevent chronic bacterial prostatitis.

If sepsis is suspected, the patient is hospitalized and given broad-spectrum antibiotics IV (eg, ampicillin plus gentamicin) started after the appropriate cultures are taken and continued until the bacterial sensitivity is known. If the clinical response is adequate, IV therapy is continued until the patient is afebrile for 24 to 48 h, followed by oral therapy usually for 4 wk.

Adjunctive therapies include NSAIDs and potentially α-blockers (if bladder emptying is poor) and supportive measures such as sitz baths. Rarely, prostate abscess develops, requiring surgical drainage.

**Chronic bacterial prostatitis:** Chronic bacterial prostatitis is treated with oral antibiotics such as fluoroquinolones for at least 6 wk. Therapy is guided by culture results; empiric antibiotic treatment for patients with equivocal or negative culture results has a low success rate. Other treatments include anti-inflammatory drugs, muscle relaxants (eg, cyclobenzaprine to possibly relieve spasm of the pelvic muscles), α-adrenergic blockers, and other symptomatic measures, such as sitz baths.

**Chronic prostatitis/chronic pelvic pain syndrome:** Treatment is difficult and often unrewarding. In addition to considering any and all of the above treatments, anxiolytics (eg, SSRIs, benzodiazepines), sacral nerve stimulation, biofeedback, prostatic massage, and minimally invasive prostatic procedures (such as microwave thermotherapy) have been attempted with varying results.

**Asymptomatic inflammatory prostatitis:** Asymptomatic prostatitis requires no treatment.

**Prostate Abscess**

Prostate abscesses are focal purulent collections that develop as complications of acute bacterial prostatitis.

The usual infecting organisms are aerobic gram-negative bacilli or, less frequently, *Staphylococcus aureus*. Urinary frequency, dysuria, and urinary retention are common. Perineal pain, evidence of acute epididymitis, hematuria, and a purulent urethral discharge are less common. Fever is sometimes present. Rectal examination may disclose prostate tenderness and fluctuance, but prostate enlargement is often the only abnormality, and sometimes the gland feels normal.

**Diagnosis**
• Prostate ultrasonography and possibly cystoscopy

Abscess is suspected in patients with continued or recurrent UTIs despite antimicrobial therapy and persistent perineal pain. Such patients should undergo prostate ultrasonography and possibly cystoscopy. Many abscesses, however, are discovered unexpectedly during prostate surgery or endoscopy; bulging of a lateral lobe into the prostatic urethra or rupture during instrumentation reveals the abscess. Although pyuria and bacteriuria are common, urine may be normal. Blood cultures are positive in some patients.

Treatment

Treatment involves appropriate antibiotics plus drainage by transurethral evacuation or transperineal aspiration and drainage.
Chapter 243. Genitourinary Cancer

Introduction

GU cancers (bladder, penile, prostate, kidney and renal pelvic, testicular, ureteral, and urethral) account for about 40% of cancers in men (primarily as prostate cancer) and 5.6% in women. For discussion of gynecologic cancers, see Ch. 256.

Bladder Cancer

Bladder cancer is usually transitional cell carcinoma. Symptoms include hematuria; later, urinary obstruction can cause pain. Diagnosis is by cystoscopy and biopsy. Treatment is with fulguration, intravesical instillations, surgery, chemotherapy, or a combination.

In the US, > 70,000 new cases of bladder cancer and about 14,700 deaths occur each year. Bladder cancer is the 4th most common cancer among men and is less common among women; male:female incidence is about 3:1. Bladder cancer is more common among whites than blacks, and incidence increases with age.

Risk factors include the following:

• Smoking (the most common risk factor, causing ≥ 50% of new cases)
• Excess phenacetin use (analgesic abuse)
• Long-term cyclophosphamide use
• Chronic irritation (eg, in schistosomiasis or by bladder calculi)
• Exposure to hydrocarbons, tryptophan metabolites, or industrial chemicals, notably aromatic amines (aniine dyes, such as naphthylamine used in the dye industry) and chemicals used in the rubber, electric, cable, paint, and textile industries

Types of bladder cancer include

• Transitional cell carcinomas, which account for > 90% of bladder cancers. Most are papillary carcinomas, which tend to be superficial and well-differentiated and to grow outward; sessile tumors are more insidious, tending to invade early and metastasize.

• Squamous cell carcinomas, which are less common and usually occur in patients with parasitic bladder infestation or chronic mucosal irritation.

• Adenocarcinomas, which may occur as primary tumors or may reflect metastasis from intestinal carcinoma. Metastasis should be ruled out.

In > 40% of patients, tumors recur at the same or another site in the bladder, particularly if tumors are large or poorly differentiated or if several tumors are present. Bladder cancer tends to metastasize to the lymph nodes, lungs, liver, and bone. Expression of tumor gene p53 may be associated with progression.

In the bladder, carcinoma in situ is high grade but noninvasive and usually multifocal; it tends to recur.

Symptoms and Signs

Most patients present with unexplained hematuria (gross or microscopic). Some patients present with anemia, and hematuria is detected during evaluation. Irritative voiding symptoms (dysuria, burning, frequency) and pyuria are also common at presentation. Pelvic pain occurs with advanced cancer, when a pelvic mass may be palpable.
Diagnosis

- Cystoscopy with biopsy

Bladder cancer is suspected clinically. Urine cytology, which may detect malignant cells, may be done. Cystoscopy (see p. 2317) and biopsy of abnormal areas are usually also done initially because these tests are needed even if urine cytology is negative. The role for urinary antigen tests is still evolving, particularly for low-grade tumors.

For low-stage (superficial, stage T1) tumors, which comprise 70 to 80% of bladder cancers, cystoscopy with biopsy is sufficient for staging. If a tumor is found to invade muscle (≥ stage T2), abdominal and pelvic CT and chest x-ray are done to determine tumor extent and evaluate for metastases. Patients with invasive tumors undergo bimanual examination (rectal examination in men, rectovaginal examination in women) while under anesthesia for cystoscopy and biopsy. The standard TNM (tumor, node, metastasis) staging system is used (see Table 243-1).

Prognosis

Superficial bladder cancer (carcinoma in situ, stage Ta or T1) rarely causes death. For patients with invasion of the bladder musculature, the 5-yr survival rate is about 50%, but adjuvant chemotherapy may improve these results. Generally, prognosis for patients with progressive or recurrent invasive bladder cancer is poor. Prognosis for patients with squamous cell carcinoma or adenocarcinoma of the bladder is also poor, because these cancers are usually highly infiltrative and detected only at an advanced stage.

Treatment

- Transurethral resection and intravesical chemotherapy (for superficial cancers)
- Cystectomy (for invasive cancers)

Superficial cancers: Superficial cancers can be completely removed by transurethral resection or fulguration. Repeated bladder instillations of chemotherapeutic drugs, such as mitomycin C, may reduce risk of recurrence. Doxorubicin and thiotepa are alternatives but rarely used. For carcinoma in situ and other high-grade, superficial, transitional cell carcinomas, immunotherapeutic treatments, such as BCG instillation, alone or in conjunction with interferon alfa-2b, after transurethral resection is generally more effective than chemotherapy instillations.

Invasive cancers: Tumors that penetrate the muscle (ie, ≥ stage T2) usually require radical cystectomy (removal of bladder and adjacent structures) with concomitant urinary diversion; partial cystectomy is possible for < 5% of patients. Cystectomy is being done with increasing frequency after initial chemotherapy in patients with locally advanced disease. Urinary diversion traditionally involves routing urine through an ileal conduit to an abdominal stoma and collecting it in an external drainage bag. Alternatives such as orthotopic neobladder or continent cutaneous diversion are very common and are appropriate for many, if not most, patients. For both procedures, an internal reservoir is constructed from the intestine. For the orthotopic neo-bladder, the reservoir is connected to the urethra. Patients empty the reservoir by relaxing the pelvic floor muscles and increasing abdominal pressure, so that urine passes through the urethra almost naturally. Most patients maintain urinary control during the day, but some incontinence may occur at night. For continent cutaneous urinary diversion, the reservoir is connected to a continent abdominal stoma. Patients empty the reservoir by self-catheterization at regular intervals throughout the day.

If surgery is contraindicated or refused, radiation therapy alone or with chemotherapy may provide 5-yr survival rates of 20 to 40%. Radiation therapy may cause radiation cystitis or proctitis or bladder contracture.
Patients should be monitored every 3 to 6 mo for progression or recurrence.

**Metastatic and recurrent cancers:** Metastases require chemotherapy, which is frequently effective but rarely curative unless metastases are confined to lymph nodes. Combination chemotherapy may prolong life in patients with metastatic disease.

Treatment of recurrent cancer depends on clinical stage and site of recurrence and previous treatment. Recurrence after transurethral resection of superficial tumors is usually treated with a 2nd resection or fulguration.

**Metastatic Renal Cancer**

Nonrenal cancers may metastasize to the kidneys. The most common cancers that metastasize to the kidney are melanomas and solid tumors, particularly lung, breast, stomach, gynecologic, intestinal, and pancreatic. Leukemia and lymphoma may invade the kidneys, which then appear enlarged, often asymmetrically.

Despite extensive interstitial involvement, symptoms are rare, and renal function may not change from baseline. Proteinuria is absent or insignificant, and blood urea and creatinine levels rarely increase unless a complication (eg, uric acid nephropathy, hypercalcemia, bacterial infection) occurs.

Renal metastases are usually discovered during evaluation of the primary tumor or incidentally during abdominal imaging. If there is no known primary tumor, diagnosis proceeds as for renal cell carcinoma (see p. 2474).

Treatment is systemic therapy for the primary tumor, rarely surgery.

**Penile Cancer**

Most penile cancers are squamous cell carcinomas; they usually occur in elderly uncircumcised men, particularly those with poor local hygiene. Diagnosis is by biopsy. Treatment includes excision.

Human papillomavirus, particularly types 16 and 18, plays a role in etiology. Premalignant lesions include erythroplasia of Queyrat, Bowen's disease, and bowenoid papulosis. Erythroplasia of Queyrat and Bowen's disease progress to invasive squamous cell carcinoma in 5 to 10% of patients; bowenoid papulosis does not appear to do so. The 3 lesions have different clinical manifestations and biologic effects but are virtually the same histologically; they may be more appropriately called intraepithelial neoplasia or carcinoma in situ.

**Symptoms and Signs**

Most squamous cell carcinomas originate on the glans, in the coronal sulcus, or under the foreskin. They usually begin as a small erythematous lesion and may be confined to the skin for a long time. These carcinomas may be fungating and exophytic or ulcerative and infiltrative. The latter type metastasizes more commonly, usually to the superficial and deep inguinofernal and pelvic nodes. Metastases to distant sites (eg, lungs, liver, bone, brain) are rare until late in the disease.

Most patients present with a sore that has not healed, subtle induration of the skin, or sometimes a pus-filled or warty growth. The sore may be shallow or deep with rolled edges. Many patients do not notice the cancer or do not report it promptly. Pain is uncommon.

**Diagnosis**

If cancer is suspected, biopsy is required; if possible, tissue under the lesion should be sampled. CT or MRI helps in staging localized cancer, checking for invasion of the corpora, and evaluating lymph nodes. The standard TNM (tumor, node, metastasis) staging system is used (see Table 243-1).
Treatment

- Excision

Untreated penile cancer progresses, typically causing death within 2 yr. Treated early, penile cancer can usually be cured.

Circumcision or laser ablation may be effective for small, superficial lesions. Partial penectomy is appropriate if the tumor can be completely excised with adequate margins, leaving a penile stump that permits urination and sexual function. Total penectomy is required for large infiltrative lesions. If tumors are high-grade or invade the corpora cavernosa, bilateral ilioinguinal lymphadenectomy is required. The role of radiation therapy has not been established. For advanced, invasive cancer, palliation may include surgery and radiation therapy, but cure is unlikely. Chemotherapy for advanced cancer has had limited success.

Prostate Cancer

Prostate cancer is usually adenocarcinoma. Symptoms are rare until urethral obstruction occurs. Diagnosis is suggested by digital rectal examination or prostate-specific antigen measurement and confirmed by biopsy. Prognosis for most patients with prostate cancer, especially when it is localized or regional, is very good; more men die with prostate cancer than of it. Treatment is with prostatectomy, radiation therapy, palliative measures (eg, hormonal therapy, radiation therapy, chemotherapy), or, for many elderly and even carefully selected younger patients, active surveillance.

Adenocarcinoma of the prostate is the most common nondermatologic cancer in men > 50 in the US. In the US, about 217,750 new cases and about 32,000 deaths (2010 estimates) occur each year. Incidence increases with each decade of life; autopsy studies show prostate cancer in 15 to 60% of men age 60 to 90 yr, with incidence increasing with age. The lifetime risk of being diagnosed with prostate cancer is 1 in 6. Median age at diagnosis is 72, and > 75% of prostate cancers are diagnosed in men > 65. Risk is highest for black men.

Sarcoma of the prostate is rare, occurring primarily in children. Undifferentiated prostate cancer, squamous cell carcinoma, and ductal transitional carcinoma also occur infrequently. Prostatic intraepithelial neoplasia is considered a possible premalignant histologic change.

Hormonal influences contribute to the course of adenocarcinoma but almost certainly not to other types of prostate cancer.

Symptoms and Signs

Prostate cancer usually progresses slowly and rarely causes symptoms until advanced. In advanced disease, hematuria and symptoms of bladder outlet obstruction (eg, straining, hesitancy, weak or intermittent urine stream, a sense of incomplete emptying, terminal dribbling) may appear. Bone pain may result from osteoblastic metastases to bone (commonly pelvis, ribs, vertebral bodies).

Diagnosis

- Screening by digital rectal examination and prostate-specific antigen
- Assessment of abnormalities by transrectal needle biopsy
- Grading by histology
- Staging by CT and bone scanning

Sometimes stony, hard induration or nodules are palpable during digital rectal examination (DRE), but the examination is often normal; induration and nodularity suggest cancer but must be differentiated from
granulomatous prostatitis, prostatic calculi, and other prostate disorders. Extension of induration to the seminal vesicles and lateral fixation of the gland suggest locally advanced prostate cancer. Prostate cancers detected by DRE tend to be large, and > 50% extend through the capsule.

**Screening:** Most cancers today are found by screening with serum prostate-specific antigen (PSA) levels (and sometimes DRE), commonly done annually in men > 50 yr. Sometimes, annual screening is begun earlier for men at high risk (eg, those with a family history of prostate cancer and blacks). Abnormal findings require histologic confirmation, most commonly by transrectal ultrasound (TRUS)-guided transrectal needle biopsy, which can be done in an office with use of local anesthesia. Hypoechoic areas are more likely to represent cancer. Occasionally, prostate cancer is diagnosed incidentally in tissue removed during surgery for benign prostatic hyperplasia (BPH).

It is still not certain whether screening decreases morbidity or mortality or whether any gains resulting from screening outweigh the decreases in quality of life from treatment of asymptomatic cancers. Most clinicians recommend annual screening. However, most patients with newly diagnosed prostate cancers have a normal DRE, and serum PSA is not ideal as a screening test. Although PSA is elevated in 25 to 92% of patients with prostate cancer (depending on tumor volume), it also is moderately elevated in 30 to 50% of patients with BPH (depending on prostate size and degree of obstruction), in some smokers, and for several weeks after prostatitis. A level of ≥ 4 ng/mL has traditionally been considered an indication for biopsy in men > 50 yr (in younger patients, levels > 2.5 ng/mL probably warrant biopsy because BPH, the most common cause of PSA elevation, is rare in younger men). Although very high levels are significant (suggesting extracapsular extension of the tumor or metastases) and likelihood of cancer increases with increasing PSA levels, there is no cut-off below which there is no risk.

In asymptomatic patients, positive predictive value for cancer is 67% for PSA > 10 ng/mL and 25% for PSA 4 to 10 ng/mL; recent evidence indicates a 15% prevalence of cancer in men ≥ 55 yr with PSA < 4 ng/mL and a 10% incidence with PSA between 0.6 and 1.0 ng/mL. Cancer present in men with lower levels tends to be smaller (often < 1 mL) and of lower grade, although high-grade cancer (Gleason score 7 to 10) can be present at any level of PSA; perhaps 15% of cancers manifesting with PSA < 4 ng/mL are high grade. Although it appears that a cut-off of 4 ng/mL will miss some potentially serious cancers, the cost and morbidity resulting from the increased number of biopsies necessary to find them is unclear.

The decision whether to biopsy may be helped by other PSA-related factors, even in the absence of a family history of prostate cancer. For example, the rate of change in PSA (PSA velocity) should be < 0.75 ng/mL/yr (lower in younger patients). Biopsy is indicated for PSA velocities higher than this.

Assays that determine the free-to-total PSA ratio and complex PSA are more tumor-specific than standard total PSA measurements and may reduce the frequency of biopsies in patients without cancer. Prostate cancer is associated with less free PSA; no standard cut-off has been established, but generally, levels < 10 to 20% warrant biopsy. Other isoforms of PSA and new markers for prostate cancer are being studied. None of these other uses of PSA answers all of the concerns about possibly triggering too many biopsies.

Clinicians should discuss the risks and benefits of PSA testing with patients. Some patients prefer to eradicate cancer at all costs no matter how low the potential for progression and possible metastases is and may prefer annual PSA testing. Others may value quality of life highly and can accept some uncertainty; they may prefer less frequent (or no) PSA testing.

**Grading and staging:** Grading, based on the resemblance of tumor architecture to normal glandular structure, helps define the aggressiveness of the tumor. Grading takes into account histologic heterogeneity in the tumor. The Gleason score is commonly used. The most prevalent pattern and the next most prevalent pattern are each assigned a grade of 1 to 5, and the two grades are added to produce a total score. Most experts consider a score ≤ 6 to be well differentiated, 7 moderately differentiated, and 8 to 10 poorly differentiated. The lower the score, the less aggressive and invasive is the tumor and the better is the prognosis. For localized tumors, the Gleason score helps predict the likelihood of capsular penetration, seminal vesicle invasion, and spread to lymph nodes. Gleason score, clinical stage, and PSA level together (using tables or nomograms) predict pathologic stage and prognosis better than any of them alone.
Prostate cancer is staged to define extent of the tumor (see Table 243-1). TRUS may provide information for staging, particularly about capsular penetration and seminal vesicle invasion. Patients with clinical stage T1c to T2a tumors, low Gleason score (≤ 7), and PSA < 10 ng/mL usually get no additional staging tests before proceeding to treatment. Radionuclide bone scans are rarely helpful for finding bone metastases (they are frequently abnormal because of trauma of arthritic changes) until the PSA is > 20 ng/mL. CT (or MRI) of the abdomen and pelvis is commonly done to assess pelvic and retroperitoneal lymph nodes if the Gleason score is 8 to 10 and the PSA is over 10 ng/mL, or if the PSA is > 20 ng/mL with any Gleason score. Suspect lymph nodes can be further evaluated by using needle biopsy. An MRI with endorectal coil may also help define the local extent of the tumor in patients with locally advanced prostate cancer (stage T3). The role of IN-111 capromab pendetide scanning for staging is evolving but is certainly not needed for early, localized disease. Elevated serum acid phosphatase—especially the enzymatic assay—correlates well with the presence of metastases, particularly in lymph nodes. However, this enzyme may also be elevated in BPH (and is slightly elevated after vigorous prostatic massage), multiple myeloma, Gaucher's disease, and hemolytic anemia. It is rarely used today to guide treatment or to follow patients after treatment, especially because its value when done as a radioimmune assay (the way it is usually done) has not been established. Reverse transcriptase-PCR assays for circulating prostate cancer cells are being studied as staging and prognostic tools.

Risk of cancer spread is considered low if

- Stage is ≤ T2a
- Gleason score is ≤ 6
- PSA level is ≤ 10 ng/mL

T2b tumor, Gleason score 7, or PSA > 10 ng/mL are considered intermediate risk by most experts. T2c tumor, Gleason score ≥ 8, or PSA > 20 ng/mL (or 2 intermediate risk factors) are generally high risk.

Both acid phosphatase and PSA levels decrease after treatment and increase with recurrence, but PSA is the most sensitive marker for monitoring cancer progression and response to treatment and has virtually replaced acid phosphatase for this purpose.

Prognosis

Prognosis for most patients with prostate cancer, especially when it is localized or regional, is very good. Life expectancy for elderly men with prostate cancer may differ little from age-matched men without prostate cancer, depending on their age and comorbidities. For many patients, long-term local control, or even cure, is possible. Potential for cure, even when cancer is clinically localized, depends on the tumor's grade and stage. Without early treatment, patients with high-grade, poorly differentiated cancer have a poor prognosis. Undifferentiated prostate cancer, squamous cell carcinoma, and ductal transitional carcinoma respond poorly to conventional therapies. Metastatic cancer has no cure. Median life expectancy with metastatic disease is 1 to 3 yr, although some patients live for many years.

Treatment

- For localized cancer within the prostate, surgery or radiation therapy
- For cancer outside of the prostate, palliation with hormonal therapy, radiation therapy, or chemotherapy
- For some men who have low-risk cancers, active surveillance without treatment

Treatment is guided by PSA level, grade and stage of tumor, patient age, coexisting disorders, and life expectancy. The goal of therapy can be

- Active surveillance (formerly known as watchful waiting when used for elderly patients)
• Definitive (aimed at cure)

• Palliative

Most patients, regardless of age, prefer definitive therapy if cancer is potentially curable. However, therapy is palliative rather than definitive if cancer has spread outside the prostate, because cure is unlikely.

**Active surveillance:** Active surveillance is appropriate for many asymptomatic patients > 70 with low-risk, or possibly even intermediate-risk, localized prostate cancer or if life-limiting disorders coexist; in these patients, risk of death due to other causes is greater than that due to prostate cancer. This approach requires periodic DRE, PSA measurement, and monitoring of symptoms. In healthy younger men with low-risk cancer, active surveillance also requires periodic repeat biopsies. If the cancer progresses, treatment is required. About 30% of patients undergoing active surveillance eventually require therapy. In elderly men, active surveillance results in the same overall survival rate as prostatectomy; however, patients who had surgery have a significantly lower risk of distant metastases and disease-specific mortality.

**Definitive therapies:** Definitive therapy is aimed at curing prostate cancer. Radical prostatectomy and the minimally invasive techniques of cryotherapy and brachytherapy are used.

**Radical prostatectomy** (removal of prostate with seminal vesicles and regional lymph nodes) is probably best for patients < 70 with a tumor confined to the prostate. Prostatectomy is appropriate for some elderly patients, based on life expectancy, coexisting disorders, and ability to tolerate surgery and anesthesia. Prostatectomy is done through an incision in the lower abdomen. More recently, a robot-assisted laparoscopic approach has been developed that minimizes blood loss and hospital stay but has not been shown to alter outcomes. Complications include urinary incontinence (in about 5 to 10%), bladder neck contracture or urethral stricture (in about 7 to 20%), erectile dysfunction (in about 30 to 100%—heavily dependent on age and current function), and rectal injury (in 1 to 2%). Nerve-sparing radical prostatectomy reduces the likelihood of erectile dysfunction but cannot always be done, depending on tumor stage and location.

**Cryotherapy** (destruction of prostate cancer cells by freezing with cryoprobes, followed by thawing) is less well established; long-term outcomes are unknown. Adverse effects include bladder outlet obstruction, urinary incontinence, erectile dysfunction, and rectal pain or injury.

Standard external beam **radiation therapy** usually delivers 70 Gy in 7 wk, but this technique has been supplanted by conformal 3-dimensional radiation therapy and by intensity modulated radiation therapy (IMRT), which safely deliver doses approaching 80 Gy to the prostate; data indicate that the rate of local control is higher, especially for high-risk patients. Some decrease in erectile function occurs in at least 40%. Other adverse effects include radiation proctitis, cystitis, diarrhea, fatigue, and possibly urethral strictures, particularly in patients with a prior history of transurethral resection of the prostate. Results with radiation therapy and prostatectomy may be comparable, especially for patients with low pretreatment PSA levels.

**Brachytherapy** involves the implantation of radioactive seeds into the prostate through the perineum. These seeds emit a burst of radiation over a finite period (usually 3 to 6 mo) and are then inert. Research protocols are examining whether high-quality implants used as monotherapy or implants plus external beam radiation therapy are superior for intermediate-risk patients. Brachytherapy also decreases erectile function, although onset may be delayed and patients may be more responsive to phosphodiesterase type 5 inhibitors than patients whose neurovascular bundles are resected or injured during surgery. Urinary frequency, urgency, and, less often, retention are common but usually subside over time. Other adverse effects include increased bowel movements; rectal urgency, bleeding, or ulceration; and prostatorectal fistulas.

**Palliative therapies:** For short-term palliation, ≥ 1 drugs may be used, including antiandrogens, chemotherapy drugs (eg, mitoxantrone, estramustine, taxanes), corticosteroids, and ketoconazole; docetaxel plus prednisone is a common combination. Local radiation therapy is usually palliative for
Patients with symptomatic bone metastases may benefit from androgen deprivation by castration, either surgically with bilateral orchietomy or medically with luteinizing hormone-releasing hormone (LHRH) agonists, such as leuprolide, goserelin, and buserelin, with or without radiation therapy. Reduction in serum testosterone with LHRH agonists equals that with bilateral orchietomy. All of these treatments cause loss of libido and erectile dysfunction and may cause hot flashes. LHRH agonists may cause PSA levels to increase temporarily. Some patients benefit from adding antiandrogens (eg, flutamide, bicalutamide, nilutamide, cyproterone acetate [not available in US]) for total androgen blockade. Maximal androgen blockade usually refers to LHRH agonists plus antiandrogens, but its benefits appear minimally better than those of an LHRH agonist (or orchietomy) alone. Another approach is intermittent androgen blockade, which purports to delay emergence of androgen-independent prostate cancer. Total androgen ablation is given until PSA levels are reduced (usually to undetectable levels), then stopped. Treatment is started again when PSA levels rise above a certain threshold, although the ideal threshold is not yet defined. The optimal schedules for treatment and time off treatment have not been determined and vary widely among practitioners. Androgen deprivation may impair quality of life significantly (eg, self-image, attitude toward the cancer and its treatment, energy levels) and cause osteoporosis, anemia, and loss of muscle mass with long-term treatment. Exogenous estrogens are rarely used because they have a risk of cardiovascular and thromboembolic complications. There is no standard therapy for hormone-refractory prostate cancer.

Angiogenesis inhibitors (eg, thalidomide, endostatin), matrix metalloproteinase inhibitors, and cytotoxic and biologic drugs (eg, genetically designed vaccines, antisense therapy, monoclonal antibodies) are being studied and may provide palliation and prolong survival, but their superiority over corticosteroids alone has not been proved. Sipuleucel-T, an autologous cellular immunotherapy drug, is now available for some men with advanced prostate cancer.

For high-grade tumors that extend beyond the prostatic capsule, several treatment protocols exist. Chemotherapy, with or without hormonal therapy, is used before surgery in some protocols and along with radiation therapy in others. Chemotherapy regimens vary by center and trial.

**Renal Cell Carcinoma**

(Hypernephroma; Adenocarcinoma of the Kidneys)

Renal cell carcinoma (RCC) is the most common renal cancer. Symptoms appear late and include hematuria, flank pain, a palpable mass, and FUO. Diagnosis is by CT or MRI and occasionally by biopsy. Treatment is with surgery for early disease and targeted therapy, an experimental protocol, or palliative therapy for advanced disease.

RCC, an adenocarcinoma, accounts for 90 to 95% of primary malignant renal tumors. Less common primary renal tumors include transitional cell carcinoma, Wilms' tumor (most often in children), and sarcoma.

In the US, about 58,000 cases of RCC and pelvic tumors and 13,000 deaths occur each year. RCC occurs slightly more often in men (male:female incidence is about 3:2). People affected are usually between 50 and 70 yr. Risk factors include the following:

- Smoking, which doubles the risk (in 20 to 30% of patients)

- Obesity

- Excess use of phenacetin

- Acquired cystic kidney disease in dialysis patients

- Exposure to certain radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products
• Some familial syndromes, particularly von Hippel-Lindau disease

RCC can trigger thrombus formation in the renal vein, which occasionally propagates into the vena cava. Tumor invasion of the vein wall is uncommon. RCC metastasizes most often to the lymph nodes, lungs, adrenal glands, liver, and bone.

**Symptoms and Signs**

Symptoms usually do not appear until late, when the tumor may already be large and metastatic. Gross or microscopic hematuria is the most common manifestation, followed by flank pain, FUO, and a palpable mass. Sometimes hypertension results from segmental ischemia or pedicle compression. Paraneoplastic syndromes occur in 20% of patients. Polycythemia can result from increased erythropoietin activity. However, anemia may also occur. Hypercalcemia is common and may require treatment (see p. 847). Thrombocytosis, cachexia, or secondary amyloidosis may develop.

**Diagnosis**

• CT with contrast or MRI

Most often, a renal mass is detected incidentally during abdominal imaging (eg, CT, ultrasonography) done for other reasons. Otherwise, diagnosis is suggested by clinical findings and confirmed by abdominal CT before and after injection of a radiocontrast agent or by MRI. A renal mass that is enhanced by radiocontrast strongly suggests RCC. CT and MRI also provide information about local extension and nodal and venous involvement. MRI provides further information about extension into the renal vein and vena cava and has replaced inferior vena cavography. Ultrasonography and IVU may show a mass but provide less information about the characteristics of the mass and extent of disease than do CT or MRI. Often, nonmalignant and malignant masses can be distinguished radiographically, but sometimes surgery is needed for confirmation. Needle biopsy does not have sufficient sensitivity when findings are equivocal; it is recommended only when there is an infiltrative pattern instead of a discrete mass, when the renal mass may be a metastasis from another known cancer, or sometimes to confirm a diagnosis before chemotherapy for metastases.

Three-dimensional CT, CT angiography, or magnetic resonance angiography is used before surgery, particularly before nephronsparing surgery, to define the nature of RCC, to more accurately determine the number of renal arteries present, and to delineate the vascular pattern. These imaging techniques have replaced aortography and selective renal artery angiography.

A chest x-ray and liver function tests are essential. If chest x-ray is abnormal, chest CT is done. If alkaline phosphatase is elevated, bone scanning is needed. Serum electrolytes, BUN, creatinine, and Ca are measured. BUN and creatinine are unaffected unless both kidneys are diseased.

**Staging:** Information from the evaluation makes preliminary staging possible. Robson’s system is still used in the US, but the TNM (tumor, node, metastasis) system is more precise and has almost completely replaced it (see Table 243-1). At diagnosis, RCC is localized in 45%, locally invasive in about 33%, and spread to distant organs in 25%.

**Prognosis**

Five-year survival rates range from 95% for the American Joint Committee on Cancer (AJCC) stage grouping I (T1 N0 M0) to 20% for stage grouping IV (T4 with any N or M; or N2 with any T or M; or M1). Prognosis is poor for patients with metastatic or recurrent RCC because treatments are usually ineffective for cure, although they may be useful for palliation.

**Treatment**

• For early RCC, surgical treatment

• For advanced RCC, palliative therapies or experimental protocols
Curative treatments: Radical nephrectomy (removal of kidney, adrenal gland, perirenal fat, and Gerota's fascia) is standard treatment for localized RCC and provides a reasonable chance for cure. Results with open or laparoscopic procedures are comparable. Nephron-sparing surgery (partial nephrectomy) is possible and appropriate for many patients, even in patients with a normal contralateral kidney if the tumor is < 4 cm. Nonsurgical destruction of renal tumors via freezing (cryosurgery) or thermal energy (radiofrequency ablation) is being done in highly selected patients, but long-term data about efficacy and indications are not yet available.

For tumors involving the renal vein and vena cava, surgery may be curative if no nodal or distant metastases exist.

If both kidneys are affected, partial nephrectomy of one or both kidneys is preferable to bilateral radical nephrectomy if technically feasible.

Radiation therapy is no longer combined with nephrectomy.

Palliative treatments: Palliation can include nephrectomy, tumor embolization, and possibly external beam radiation therapy. Resection of metastases offers palliation and, if limited in number, prolongs life in some patients, particularly those with a long interval between initial treatment (nephrectomy) and development of metastases. Although metastatic RCC is traditionally characterized as radioresistant, radiation therapy can be palliative when metastatic in bone.

For some patients, drug therapy reduces tumor size and prolongs life. About 10 to 20% of patients respond to interferon alfa-2b or IL-2, although the response is long-lasting in < 5%. Five new targeted therapies have shown efficacy for advanced tumors: sunitinib, sorafenib, and pazopanib (tyrosine kinase inhibitors) and temsirolimus and everolimus, which inhibit the mammalian target of rapamycin (mTOR). Other treatments are experimental. They include stem cell transplantation, other inter-leukins, antiangiogenesis therapy (eg, bevacizumab, thalidomide), and vaccine therapy. Traditional chemotherapeutic drugs, alone or combined, and progestins are ineffective. Cytoreductive nephrectomy before systemic therapy, or as a delayed surgical procedure to remove the primary tumor after response in the metastases, is commonly done in patients healthy enough to undergo it.

Renal Pelvic and Ureteral Cancers

Cancers of the renal pelvis and ureters are usually transitional cell carcinomas (TCCs) and occasionally squamous cell carcinomas. Symptoms include hematuria and sometimes pain. Diagnosis is by CT, cytology, and sometimes biopsy. Treatment is surgery.

TCC of the renal pelvis accounts for about 7 to 15% of all kidney tumors. TCC of the ureters accounts for about 4% of upper tract tumors. Risk factors are the same as those for bladder cancer. Also, inhabitants of the Balkans with endemic familial nephropathy are inexplicably predisposed to develop upper tract TCC.

Symptoms and Signs

Most patients present with hematuria; dysuria and frequency may occur if the bladder also is involved. Colicky pain may accompany obstruction (see p. 2366). Uncommonly, hydronephrosis results from a renal pelvic tumor.

Diagnosis

• Ultrasonography or CT with contrast

• Cytology or histology

In patients with unexplained urinary tract symptoms, typically ultrasonography or CT with contrast is done. If the diagnosis cannot be excluded, cytologic or histologic analysis is done for confirmation.
Ureteroscopy is done when biopsy of the upper tract is needed or when urine cytology is positive but no source of the malignant cells is obvious. Abdominal and pelvic CT and chest x-ray are done to determine tumor extent and to check for metastases. The standard TNM (tumor, node, metastasis) staging system is used (see Table 243-1).

**Prognosis**

Prognosis depends on depth of penetration into or through the uroepithelial wall, which is difficult to determine. Likelihood of cure is > 90% for patients with a superficial, localized tumor but is 10 to 15% for those with a deeply invasive tumor. If tumors penetrate the wall or distant metastases occur, cure is unlikely.

**Treatment**

- Excision or ablation
- Posttreatment surveillance with cystoscopy

Usual treatment is radical nephroureterectomy, including excision of a cuff of bladder. Partial ureterectomy is indicated in some carefully selected patients (eg, patients with a distal ureteral tumor, decreased renal function, or a solitary kidney). Laser fulguration for accurately staged and adequately visualized renal pelvic or low-grade ureteral tumors is sometimes possible. Occasionally, a drug, such as mitomycin C or BCG, is instilled. However, efficacy of laser therapy and chemotherapy has not been established.

Periodic cystoscopy is indicated because renal pelvic and ureteral cancers tend to recur in the bladder, and such recurrence, if detected at an early stage, may be treated by fulguration, transurethral resection, or intravesical instillations. Management of metastases is the same as that for metastatic bladder cancer.

**Testicular Cancer**

Testicular cancer begins as a scrotal mass, which is usually not painful. Diagnosis is by ultrasonography. Treatment is with orchiectomy and sometimes lymph node dissection, radiation therapy, chemotherapy, or a combination, depending on histology and stage.

Testicular cancer is the most common solid cancer in males aged 15 to 35, with about 8500 cases annually. Incidence is 2.5 to 20 times higher in patients with cryptorchidism. This excess risk is decreased or eliminated if orchiopexy is done before age 10 yr. Cancer can also develop in the contralateral normally descended testis. The cause of testicular cancer is unknown.

Most testicular cancers originate in primordial germ cells. Germ cell tumors are categorized as seminomas (40%) or nonseminomas (tumors containing any nonseminomous elements). Nonseminomas include teratomas, embryonal carcinomas, endodermal sinus tumors (yolk sac tumors), and choriocarcinomas. Histologic combinations are common; eg, teratocarcinoma contains teratoma plus embryonal carcinoma. Functional interstitial cell carcinomas of the testis are rare.

Even patients with apparently localized tumors may have occult nodal or visceral metastases. For example, almost 30% of patients with nonseminomas will relapse with nodal or visceral metastases if they undergo no treatment after orchiectomy (surveillance). Risk of metastases is highest for choriocarcinoma and lowest for teratoma.

Tumors originating in the epididymis, testicular appendages, and spermatic cord are usually benign fibromas, fibroadenomas, adenomatoid tumors, and lipomas. Sarcomas, most commonly rhabdomyosarcoma, occur occasionally, primarily in children.

**Symptoms and Signs**

Most patients present with a scrotal mass, which is painless or sometimes associated with dull, aching
pain. In a few patients, hemorrhage into the tumor may cause acute local pain and tenderness. Many patients discover the mass themselves after minor scrotal trauma.

**Diagnosis**

- Ultrasonography for scrotal masses
- Exploration if testicular mass present
- Staging by abdominal, pelvic, and chest CT as well as tissue examination

Many patients discover the mass themselves during self-examination. Monthly self-examination should be encouraged among young men.

The origin and nature of scrotal masses must be determined accurately because most testicular masses are malignant, but most extratesticular masses are not; distinguishing between the two during physical examination may be difficult. Scrotal ultrasonography can confirm testicular origin. If a testicular mass is confirmed, serum markers α-fetoprotein and β-human chorionic gonadotropin should be measured and a chest x-ray taken. Then, inguinal exploration is indicated; the spermatic cord is exposed and clamped before the abnormal testis is manipulated.

If cancer is confirmed, abdominal, pelvic, and chest CT is needed for clinical staging using the standard TNM (tumor, node, metastasis) system (see Table 243-1). Tissue obtained during treatment (usually radical inguinal orchiectomy) helps provide important histopathologic information, particularly about the proportion of histologic types and presence of intratumoral vascular or lymphatic invasion. Such information can predict the risk of occult lymph node and visceral metastases. Patients with nonseminomas have about a 30% risk of recurrence despite normal x-rays and serum markers and having what appears to be localized disease. Seminomas recur in about 15% of such patients.

**Prognosis**

Prognosis depends on histology and extent of the tumor. The 5-yr survival rate is > 95% for patients with a seminoma or nonseminoma localized to the testis or with a nonseminoma and low-volume metastases in the retroperitoneum. The 5-yr survival rate for patients with extensive retroperitoneal metastases or with pulmonary or other visceral metastases ranges from 48% (for some nonseminomas) to > 80%, depending on site, volume, and histology of the metastases, but even patients with advanced disease at presentation may be cured.

**Treatment**

- Radical inguinal orchiectomy
- Radiation therapy for seminomas
- Usually retroperitoneal lymph node dissection for nonseminomas

Radical inguinal orchiectomy is the cornerstone of treatment and helps provide important diagnostic information; it also helps formulate the subsequent treatment plan.

**Radiation therapy**: Standard treatment for seminoma after unilateral orchiectomy is radiation therapy, usually 20 to 40 Gy (higher dose is used for patients with a nodal mass) to the para-aortic regions up to the diaphragm. The ipsilateral iliinguinal region is no longer routinely treated. Occasionally, the mediastinum and left supraclavicular regions are also irradiated, depending on clinical stage.

**Lymph node dissection**: For nonseminomas, many experts consider standard treatment to be retroperitoneal lymph node dissection. For clinical stage 1 tumors in patients who have no prognostic factors that predict relapse, an alternative is active surveillance (frequent serum marker measurements, chest x-rays, CT). Intermediate-sized retroperitoneal nodal masses may require retroperitoneal lymph
node dissection and chemotherapy (eg, bleomycin, etoposide, cisplatin), but the optimal sequence is undecided.

Lymph node dissection is done laparoscopically at some centers. The most common adverse effect of lymph node dissection overall is failure to ejaculate. However, a nerve-sparing dissection is often possible, particularly for early-stage tumors, which usually preserves ejaculation.

Chemotherapy: Nodal masses > 5 cm, lymph node metastases above the diaphragm, or visceral metastases require initial platinum-based combination chemotherapy followed by surgery for residual masses. Such treatment commonly controls the tumor long term. Fertility is often impaired, but no risk to the fetus has been proved if pregnancy does occur.

Supportive measures: A cosmetic testicular prosthesis may be placed during orchiectomy. Silicone prostheses are not widely available because of the problems with silicone breast implants. However, saline implants have been developed.

For men who wish to retain reproductive capacity, sperm banking is potentially available in anticipation of radiation therapy or chemotherapy.

Surveillance: Surveillance is appropriate for some patients, although many clinicians do not offer this option because it requires rigorous follow-up protocols and excellent patient compliance to be safe. It is more commonly offered to patients at low risk of relapse. High-risk patients usually get retroperitoneal lymph node dissections or, in some centers, 2 courses of chemotherapy after orchiectomy instead of surgery.

Recurrences: Nonseminoma recurrences are usually treated with chemotherapy, although delayed retroperitoneal lymph node dissection may be appropriate for some patients with nodal relapse and no evidence of visceral metastases. Surveillance is not used as often for seminomas because the morbidity of 2 wk of radiation therapy is so low and the results in preventing late relapse so high that there is less reason to try to avoid treatment.

Urethral Cancer

Urethral cancer is rare and occurs in both sexes; it may be squamous or transitional cell carcinoma or, occasionally, adenocarcinoma.

Most patients are age ≥ 50. Certain strains of human papillomavirus have been implicated in certain cases. Urethral tumors invade adjacent structures early and thus tend to be advanced when diagnosed. External groin or pelvic (obturator) lymph nodes are usually the first sites of metastasis.

Symptoms and Signs

Most women present with hematuria and obstructive voiding symptoms or urinary retention. Most have a history of urinary frequency or urethral syndrome (hypersensitivity of the pelvic floor muscles). Most men present with symptoms of urethral stricture; only a few present with hematuria or a bloody discharge. Sometimes if the tumor is advanced, a mass is felt.

Diagnosis

Diagnosis is suggested clinically and confirmed by cystourethroscopy. Biopsy may be required to differentiate urethral carcinoma, prolapse, and caruncle. CT or MRI is used for staging.

Prognosis

Prognosis depends on the precise location in the urethra and extent of the cancer, particularly depth of invasion. The 5-yr survival rates are > 60% for patients with distal tumors and 10 to 20% for patients with proximal tumors. Recurrence rate is > 50%.
Treatment

• Usually excision or ablation

For superficial or minimally invasive distal tumors in the anterior urethra, treatment is with surgical excision, radiation therapy (interstitial or a combination of interstitial and external beam), fulguration, or laser ablation. Larger and more deeply invasive anterior tumors and proximal tumors in the posterior urethra require multimodal therapy with radical surgery and urinary diversion, usually in combination with radiation therapy. Surgery includes bilateral pelvic and sometimes inguinal lymph node dissection, often with removal of part of the symphysis pubis and inferior pubic rami. The value of chemotherapy, which is sometimes used, has not been established.
Chapter 244. Approach to the Gynecologic Patient

Introduction

Gynecologic evaluation may be necessary to assess a specific problem such as pelvic pain, vaginal bleeding, or vaginal discharge (see also Ch. 253). Women also need routine gynecologic evaluations, which may be provided by a gynecologist, an internist, or a family practitioner; evaluations are recommended every year for all women who are sexually active or > 18 yr. Many women expect their gynecologist to provide general as well as gynecologic health care. Obstetric evaluation focuses on issues related to pregnancy (see Ch. 261).

General Gynecologic Evaluation

Most women, particularly those seeking general preventive care, require a complete history and physical examination as well as a gynecologic evaluation.

History

Gynecologic history consists of a description of the problem prompting the visit (chief complaint, history of present illness); menstrual, obstetric, and sexual history; and history of gynecologic symptoms, disorders, and treatments.

Current symptoms are explored using open-ended questions followed by specific questions about the following:

- Pelvic pain (location, duration, character, quality, triggering and relieving factors)
- Abnormal vaginal bleeding (quantity, duration, relation to the menstrual cycle)
- Vaginal discharge (color, odor, consistency), irritation, or both

Patients of reproductive age are asked about symptoms of pregnancy (eg, morning sickness, breast tenderness, delayed menses).

Menstrual history includes the following:

- Age at menarche
- Number of days of menses
- Length and regularity of the interval between cycles
- Start date of the last menstrual period (LMP)
- Dates of the preceding period (previous menstrual period, or PMP)
- Color and volume of flow
- Any symptoms that occur with menses (eg, cramping, loose stools)

Usually, menstrual fluid is medium or dark red, and flow lasts for 5 (± 2) days, with 21 to 35 days between menses; average blood loss is 30 mL (range, 13 to 80 mL), with the most bleeding on the 2nd day. A saturated pad or tampon absorbs 5 to 15 mL. Cramping is common on the day before and on the first day of menses. Vaginal bleeding that is painless, scant, and dark, is abnormally brief or prolonged, or occurs at irregular intervals suggests absence of ovulation (anovulation).
Obstetric history (see p. 2606) includes dates and outcomes of all pregnancies and previous ectopic or molar pregnancies.

Sexual history should be obtained in a professional and nonjudgmental way and includes the following:

• Frequency of sexual activity
• Number and sex of partners
• Use of contraception
• Participation in unsafe sex
• Effects of sexual activity (eg, pleasure, orgasm, dyspareunia)

Past gynecologic history includes questions about previous gynecologic symptoms (eg, pain), signs (eg, vaginal bleeding, discharge), and known diagnoses, as well the results of any testing.

Screening for domestic violence should be routine. Methods include self-administered questionnaires and a directed interview by a staff member or physician. In patients who do not admit to experiencing abuse, findings that suggest past abuse include the following:

• Inconsistent explanations for injuries
• Delay in seeking treatment for injuries
• Unusual somatic complaints
• Psychiatric symptoms
• Frequent emergency department visits
• Head and neck injuries
• Prior delivery of a low-birth-weight infant

Physical Examination

The examiner should explain the examination, which includes breasts (see p. 2552), abdomen, and pelvis, to the patient.

For the pelvic examination, the patient lies supine on an examination table with her legs in stirrups and is usually draped. A chaperone may be required, particularly when the examiner is male, and may also provide assistance. The pubic area and hair are inspected for lesions, folliculitis, and lice. The perineum is inspected for redness, swelling, excoriations, abnormal pigmentation, and lesions (eg, ulcers, pustules, nodules, warts, tumors). Structural abnormalities due to congenital malformations or female genital mutilation are noted. A vaginal opening that is < 3 cm may indicate infibulation, a severe form of genital mutilation (see p. 3067).

Next, the introitus is palpated between the thumb and index finger for cysts or abscesses in Bartholin's glands. While spreading the labia and asking the patient to bear down, the examiner checks the vaginal opening for signs of pelvic relaxation: an anterior bulge (suggesting cystocele), a posterior bulge (suggesting rectocele), and displacement of the cervix toward the introitus (suggesting prolapsed uterus —see p. 2531).

Before speculum and bimanual examination, the patient is asked to relax her legs and hips and breathe deeply.
**Speculum examination:** The speculum is sometimes kept warm with a heating pad and may be moistened or lubricated before insertion, particularly when the vagina is dry. If a Papanicolaou (Pap) test or cervical culture is planned, the speculum is rinsed with warm water; lubricant should not be used. A gloved finger is inserted into the vagina to determine the position of the cervix. Then, the speculum is inserted with the blades nearly in the vertical plane (at about 1 and 7 o'clock) while widening the vagina by pressing 2 fingers on the posterior vaginal wall (perineal body). The speculum is fully inserted toward the cervix, then rotated so that the handle is down, and gently opened; it is pulled back as needed to visualize the cervix. When the cervix is seen, the blades are positioned so that the posterior blade is deeper than the cervix (in the posterior fornix) and the anterior blade is allowed to rise gently and rest anterior to the cervix (in the anterior fornix). The examiner should take care to open the anterior blade slowly and gently and not to pinch the labia or perineum as the speculum is opened. Normally, the cervix is pink and shiny, and there is no discharge.

A specimen for the Pap test is taken from the endocervix and external cervix with a brush and plastic spatula or with a cervical sampler that can simultaneously collect cells from the cervical canal and the transition zone; the specimen is rinsed in a liquid, producing a cell suspension to be analyzed for cancerous cells and human papillomavirus. Specimens for detection of sexually transmitted diseases (STDs) are taken from the endocervix. The speculum is withdrawn, taking care not to pinch the labia with the speculum blades.

**Bimanual examination:** The index and middle fingers of the dominant hand are inserted into the vagina to just below the cervix. The other hand is placed just above the pubic symphysis and gently presses down to determine the size, position, and consistency of the uterus and, if possible, the ovaries. Normally, the uterus is about 6 cm by 4 cm and tilts anteriorly (anteversion), but it may tilt posteriorly (retroversion) to various degrees. The uterus may also be bent at an angle anteriorly (anteflexion) or posteriorly (retroflexion). The uterus is movable and smooth; irregularity suggests uterine fibroids (leiomyomas). Normally, the ovaries are about 2 cm by 3 cm in young women and are not palpable in postmenopausal women. With ovarian palpation, mild nausea and tenderness are normal. Significant pain when the cervix is gently moved from side to side (cervical motion tenderness) suggests pelvic inflammation.

**Rectal examination:** After bimanual palpation, the examiner palpates the rectovaginal septum by inserting the index finger in the vagina and the middle finger in the rectum.

**Children:** The examination should be adjusted according to children's psychosexual development and is usually limited to inspection of the external genitals. Young children can be examined on their mother’s lap. Older children can be examined in the knee-chest position or on their side with one knee drawn up to their chest. Vaginal discharge can be collected, examined, and cultured.

Sometimes a small catheter attached to a syringe of saline is used to obtain washings from the vagina. If cervical examination is required, a fiberoptic vaginoscope, cystoscope, or flexible hysteroscope with saline lavage should be used.

In children, pelvic masses may be palpable in the abdomen.

**Testing**

Testing is guided by the symptoms present.

**Pregnancy testing:** Most women who are of reproductive age and have gynecologic symptoms are tested for pregnancy (see p. 2623). Urine assays of the β subunit of human chorionic gonadotropin (β- hCG) are specific and highly sensitive; they become positive within about 1 wk of conception. Serum assays are specific and even more sensitive.

**Pap testing:** Specimens of cervical cells taken for the Pap test are examined for signs of cervical cancer; the examination may also detect uterine cancer and human papillomavirus. Pap tests are done routinely for most of a woman's life (see p. 2580).

**Microscopic examination of vaginal secretions:** This examination helps identify vaginal infections
(eg, trichomoniasis, bacterial vaginosis, yeast infection—see Ch. 253).

**Microbiologic testing:** Culture or molecular methods (eg, PCR) are used to analyze specimens for specific STD organisms (eg, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*) if patients have symptoms or risk factors; in some practices, such analysis is always done.

**Cervical mucus inspection:** Bedside inspection of a cervical mucus specimen by a trained examiner can provide information about the menstrual cycle and hormone states; this information may help in assessment of infertility and time of ovulation. The specimen is placed on a slide, allowed to dry, and assessed for degree of microscopic crystallization (ferning—see p. 2501), which reflects levels of circulating estrogens. Just before ovulation, cervical mucus is clear and copious with abundant ferning because estrogen levels are high. Just after ovulation, cervical mucus is thick and ferns little.

**Imaging tests:** Imaging of suspected masses and other lesions usually involves ultrasonography, which may be done in the office; both transvaginal and transabdominal probes are used. MRI is highly specific but expensive. CT is usually less desirable because it is somewhat less accurate, involves significant radiation exposure, and often requires a radiopaque agent.

**Laparoscopy:** This surgical procedure can detect structural abnormalities too small to be detected by imaging, as well as abnormalities on the surfaces of internal organs (eg, endometriosis, inflammation, scarring). It is also used to sample tissue.

**Culdocentesis:** Culdocentesis, now rarely used, is needle puncture of the posterior vaginal fornix to obtain fluid from the cul-de-sac (which is posterior to the uterus) for culture and for tests to detect blood from a ruptured ectopic pregnancy or ovarian cyst.

**Endometrial aspiration:** This procedure is done if women > 35 have unexplained vaginal bleeding. A thin, flexible, plastic suction curette is inserted through the cervix to the level of the uterine fundus; dilation is often not required. Suction is applied to the device, which is turned 360° and moved up and down a few times to sample different parts of the endometrial cavity. Sometimes the uterus must be stabilized with a cervical tenaculum.

**Other tests:** Pituitary and hypothalamic hormones (see p. 757) and ovarian hormones (see p. 2499) may be measured when infertility is evaluated or when abnormalities are suspected.

**Pelvic Mass**

(See also Chs. 250 and 256.)

A pelvic mass may be detected during routine gynecologic examination.

**Etiology**

Pelvic masses may originate from gynecologic organs (cervix, uterus, uterine adnexa) or from other pelvic organs (intestine, bladder, ureters, skeletal muscle, bone).

Type of mass tends to vary by age group.

In **infants**, in utero maternal hormones may stimulate development of adnexal cysts during the first few months of life. This effect is rare.

At **puberty**, menstrual fluid may accumulate and form a vaginal mass (hematocolpos) because outflow is obstructed. The cause is usually an imperforate hymen; other causes include congenital malformations of the uterus, cervix, or vagina.

In **women of reproductive age**, the most common cause of symmetric uterine enlargement is pregnancy, which may be unsuspected. Another common cause is fibroids, which may extend outward. Common adnexal masses include graafian follicles (usually 5 to 8 cm) that develop normally but do not
release an egg (called functional ovarian cysts). These cysts often resolve spontaneously within a few months. Adnexal masses may also result from ectopic pregnancy, ovarian or fallopian tube cancers, benign tumors (eg, benign cystic teratomas), or hydrosalpinges. Endometriosis can cause single or multiple masses anywhere in the pelvis, usually on the ovaries.

In postmenopausal women, masses are more likely to be cancerous. Many benign ovarian masses (eg, endometriomas, myomas) depend on ovarian hormone secretion and thus become less common after menopause.

**Evaluation**

**History:** General medical and complete gynecologic histories are obtained. Vaginal bleeding and pelvic pain suggest ectopic pregnancy or, rarely, gestational trophoblastic disease. Dysmenorrhea suggests endometriosis or uterine fibroids. In young girls, precocious puberty may indicate a masculinizing or feminizing ovarian tumor. In women, virilization may indicate a masculinizing ovarian tumor; menometrorrhagia or postmenopausal bleeding may indicate a feminizing ovarian tumor.

**Examination:** During the general examination, the examiner should look for signs of nongynecologic (eg, GI, endocrine) disorders and for ascites. A complete gynecologic examination is done. Distinguishing uterine from adnexal masses may be difficult. Endometriomas are usually nonmobile cul-de-sac masses. Adnexal cancers, benign tumors (eg, benign cystic teratomas), and adnexal masses due to ectopic pregnancy are mobile. Hydrosalpinges are usually fluctuant, tender, nonmobile, and sometimes bilateral. In young girls, pelvic organ masses may be palpable in the abdomen because the pelvis is too small to contain a large mass.

**Testing:** If the presence or origin (gynecologic vs nongynecologic) of a mass cannot be determined clinically, an imaging test can usually do so. Usually, pelvic ultrasonography is done first. If it does not clearly delineate size, location, and consistency of the mass, another imaging test (eg, CT, MRI) may. Ovarian masses with radiographic characteristics of cancer (eg, a solid component, surface excrescences, irregular shape) require needle aspiration or biopsy. Tumor markers may help in the diagnosis of specific tumors (see p. 1058).

Women of reproductive age are tested for pregnancy; if the test is positive, imaging is not always necessary (see p. 2608) unless ectopic pregnancy is suspected. In women of reproductive age, simple, thin-walled cystic adnexal masses that are 5 to 8 cm (usually graafian follicular cysts) do not require further investigation unless they persist for > 3 menstrual cycles.

**Pelvic Pain**

Pelvic pain is discomfort in the lower abdomen; it is a common complaint in women. It is considered separately from perineal pain, which occurs in the external genitals and nearby perineal skin.

**Etiology**

Pelvic pain may originate in reproductive organs (cervix, uterus, uterine adnexa) or other organs. Sometimes the cause is unknown.

**Gynecologic disorders:** Some gynecologic disorders (see Table 244-1) cause cyclic pain (ie, pain recurring during the same phase of the menstrual cycle). In others, pain is a discrete event unrelated to menstrual cycles. Whether onset of pain is sudden or gradual helps discriminate between the two.

**Table 244-1. Some Gynecologic Causes of Pelvic Pain**

Overall, the most common gynecologic causes of pelvic pain include

- Dysmenorrhea
• Ovulation (mittelschmerz)

• Endometriosis

**Nongynecologic disorders:** These disorders (see p. 105) may be

• GI (eg, gastroenteritis, inflammatory bowel disease, appendicitis, diverticulitis, tumors, constipation, intestinal obstruction, perirectal abscess, irritable bowel syndrome)

• Urinary (eg, cystitis, interstitial cystitis, pyelonephritis, calculi)

• Musculoskeletal (eg, diastasis of the pubic symphysis due to previous vaginal deliveries, abdominal muscle strains)

• Psychogenic (eg, somatization; effects of previous physical, psychologic, or sexual abuse)

The most common is difficult to specify.

**Evaluation**

Evaluation must be expeditious because some causes of pelvic pain (eg, ectopic pregnancy, adnexal torsion) require immediate treatment. Pregnancy should be excluded in women of childbearing age regardless of stated history.

**History:** History of present illness should include gynecologic history (gravity, parity, menstrual history, history of sexually transmitted disease) and onset, duration, location, and character of pain. Severity of pain and its relationship to the menstrual cycle are noted. Important associated symptoms include vaginal bleeding or discharge and symptoms of hemodynamic instability (eg, dizziness, light-headedness, syncope or near-syncope).

**Review of systems** should seek symptoms suggesting possible causes, including morning sickness, breast swelling or tenderness, or missed menses (pregnancy); fever and chills (infection); abdominal pain, nausea, vomiting, or change in stool habits (GI disorders); and urinary frequency, urgency, or dysuria (urinary disorders).

**Past medical history** should note history of infertility, ectopic pregnancy, pelvic inflammatory disease, urolithiasis, diverticulitis, and any GI or GU cancers. Any previous abdominal or pelvic surgery should be noted.

**Physical examination:** The physical examination begins with review of vital signs for signs of instability (eg, fever, hypotension) and focuses on abdominal and pelvic examinations.

The abdomen is palpated for tenderness, masses, and peritoneal signs. Rectal examination is done to check for tenderness, masses, and occult blood. Location of pain and any associated findings may provide clues to the cause (see Table 244-2).

Pelvic examination includes inspection of external genitals, speculum examination, and bimanual examination. The cervix is inspected for discharge, uterine prolapse, and cervical stenosis or lesions. Bimanual examination should assess cervical motion tenderness, adnexal masses or tenderness, and uterine enlargement or tenderness.

**Red flags:** The following findings are of particular concern:

• Syncope or hemorrhagic shock (eg, tachycardia, hypotension)

• Peritoneal signs (rebound, rigidity, guarding)
Postmenopausal vaginal bleeding

Fever or chills

Sudden severe pain with nausea, vomiting, diaphoresis, or agitation

**Interpretation of findings:** Acuity and severity of pain and its relationship to menstrual cycles can suggest the most likely causes (see Table 244-1). Quality and location of pain and associated findings also provide clues (see Table 244-2):

**Testing:** All patients should have

- Urinalysis
- Urine pregnancy test

If a patient is pregnant, ectopic pregnancy is assumed until excluded by ultrasonography or, if ultrasonography is unclear, by other tests (see p. 2609). If a suspected pregnancy may be < 5 wk, a serum pregnancy test should be done; a urine pregnancy test may not be sensitive enough to rule out pregnancy that early in gestation.

Other testing depends on which disorders are clinically suspected. If a patient cannot be adequately examined (eg, because of pain or inability to cooperate) or if a mass is suspected, pelvic ultrasonography is done. If the cause of severe or persistent pain remains unidentified, laparoscopy is done.

Pelvic ultrasonography using a vaginal probe can be a useful adjunct to pelvic examination; it can better define a mass or help diagnose a pregnancy after 5 wk gestation. For example, free pelvic fluid and a positive pregnancy test plus no evidence of an intrauterine pregnancy help confirm ectopic pregnancy.

**Treatment**

The underlying disorder is treated when possible.

[Table 244-2, Some Clues to Diagnosis of Pelvic Pain]

Pain is initially treated with oral NSAIDs. Patients who do not respond well to one NSAID may respond to another. If NSAIDs are ineffective, other analgesics or hypnosis may be tried. Musculoskeletal pain may also require rest, heat, physical therapy, or, for fibromyalgia, injection of tender points.

For patients with intractable pain due to dysmenorrhea or another disorder, uterosacral nerve ablation or presacral neurectomy can be tried. If all measures are ineffective, hysterectomy can be done, but it may be ineffective or even worsen the pain.

**Geriatrics Essentials**

Pelvic pain symptoms in elderly women may be vague. Careful review of systems with attention to bowel and bladder function is essential.

A sexual history should be obtained; clinicians often do not realize that many women remain sexually active throughout their life. Whether a woman's partner is living should be determined before inquiring about sexual activity. In elderly women, vaginal irritation, itching, urinary symptoms, or bleeding may occur secondary to sexual intercourse. Such problems often resolve after a few days of pelvic rest.

Acute loss of appetite, weight loss, dyspepsia, or a sudden change in bowel habits may be signs of ovarian or uterine cancer and requires thorough clinical evaluation.

**Key Points**
Pelvic pain is common and may have a gynecologic or nongynecologic cause.

Pregnancy should be ruled out in women of childbearing age.

Quality, severity, and location of pain and its relationship to the menstrual cycle can suggest the most likely causes.

Dysmenorrhea is a common cause of pelvic pain but is a diagnosis of exclusion.

**Vaginal Bleeding**

Abnormal vaginal bleeding includes

- Menses that are prolonged (menorrhagia), excessive (menorrhagia or hypermenorrhea), or too frequent (polymenorrhea)
- Bleeding that is unrelated to menses, occurring irregularly between menses (metrorrhagia)
- Postmenopausal bleeding (ie, >6 mo after the last normal menses)

Vaginal bleeding may occur during early pregnancy (see p. 2612) or late pregnancy (see p. 2620).

**Pathophysiology**

Most abnormal vaginal bleeding involves

- Hormonal abnormalities in the hypothalamic-pituitary-ovarian axis (most common)
- Structural, inflammatory, or other gynecologic disorders (eg, tumors)
- Bleeding disorders (uncommon)

With hormonal causes, ovulation does not occur or occurs infrequently. During an anovulatory cycle, the corpus luteum does not form, and thus the normal cyclical secretion of progesterone does not occur. Without progesterone, estrogen causes the endometrium to continue to proliferate, eventually outgrowing its blood supply. The endometrium then sloughs and bleeds incompletely, irregularly, and sometimes profusely or for a long time.

**Etiology**

Causes in adults (see Table 244-3) and children (see Table 244-4) vary.

Overall, the most common specific causes in adult women who are not known to be pregnant are

- Complications of an early, undiagnosed pregnancy
- Anovulatory bleeding
- Submucous myoma
- Midcycle bleeding associated with ovulation
- Breakthrough bleeding while women are taking oral contraceptives

**Evaluation**
Unrecognized pregnancy must be suspected and diagnosed in women of childbearing age because some causes of bleeding during pregnancy (eg, ectopic pregnancy) are life threatening.

**History: History of present illness** should include quantity (eg, by number of pads used per day or hour) and duration of bleeding, as well as the relationship of bleeding to menses and intercourse. Menstrual history should be obtained; it should include date of last normal menstrual period, age at menarche and menopause (when appropriate), cycle length and regularity, and quantity and duration of typical menstrual bleeding. Previous episodes of abnormal bleeding, including frequency, duration, quantity, and pattern (cyclicity) of bleeding, should be identified.

**Review of systems** should seek symptoms of possible causes, including missed menses, breast swelling, and nausea (pregnancy-related bleeding); abdominal pain, light-headedness, and syncope (ectopic pregnancy or ruptured ovarian cyst); chronic pain and weight loss (cancer); and easy bruising, excessive bleeding due to toothbrushing, minor lacerations, or venipuncture (a bleeding disorder).

**Past medical history** should identify disorders known to cause bleeding, including a recent spontaneous or therapeutic abortion and structural disorders (eg, uterine fibroids, ovarian cysts). Clinicians should identify risk factors for endometrial cancer, including obesity, diabetes, hypertension, prolonged unopposed estrogen use (ie, without progesterone), and polycystic ovary syndrome. Drug history should include specific questions about hormone use.

**Physical examination:** Vital signs are reviewed for signs of hypovolemia (eg, tachycardia, tachypnea, hypotension).

During the general examination, clinicians should look for signs of anemia (eg, conjunctival pallor) and evidence of possible causes of bleeding, including the following:

- Warm and moist or dry skin, eye abnormalities, tremor, abnormal reflexes, or goiter (a thyroid disorder)

[Table 244-3. Some Causes of Abnormal Vaginal Bleeding in Adult Women]

- Hepatomegaly, jaundice, asterixis, or splenomegaly (a liver disorder)

- Nipple discharge (hyperprolactinemia)

- Low body mass index and loss of subcutaneous fat (possibly anovulation)

- High body mass index and excess subcutaneous fat (androgen or estrogen excess or polycystic ovary syndrome)

- Hirsutism, acne, obesity, and enlarged ovaries (polycystic ovary syndrome)

- Easy bruising, petechiae, purpura, or mucosal (eg, gingival) bleeding (a bleeding disorder)

- In children, breast development and presence of pubic and axillary hair (puberty)

The abdomen is examined for distention, tenderness, and masses (particularly an enlarged uterus). If the uterus is enlarged, auscultation for fetal heart sounds is done.

A complete gynecologic examination is done unless abdominal examination suggests a late-stage pregnancy; then, digital pelvic examination is contraindicated until placental position is determined. In all other cases, speculum examination helps identify lesions of the urethra, vagina, and cervix. Bimanual examination is done to evaluate uterine size and ovarian enlargement. If no blood is present in the vagina, rectal examination is done to determine whether bleeding is GI in origin.

[Table 244-4. Common Causes of Vaginal Bleeding in Children]
Red flags: The following findings are of particular concern:

• Hemorrhagic shock (tachycardia, hypotension)

• Premenarchal and postmenopausal vaginal bleeding

• Vaginal bleeding in pregnant patients

Interpretation of findings: Significant hypovolemia or hemorrhagic shock is unlikely except with ruptured ectopic pregnancy or, rarely, ovarian cyst (particularly when a tender pelvic mass is present).

In children, breast development and pubic or axillary hair suggest precocious puberty and premature menses. In those without such findings, the possibility of sexual abuse should be investigated unless an explanatory lesion or foreign body is obvious.

In women of reproductive age, examination may detect a causative gynecologic lesion or other findings suggesting a cause. If younger patients taking hormone therapy have no apparent abnormalities during examination and bleeding is spotty, bleeding is probably related to the hormone therapy. If the problem is excessive menstrual bleeding only, a uterine disorder or bleeding diathesis should be considered. Inherited bleeding disorders may initially manifest as heavy menstrual bleeding beginning at menarche or during adolescence.

In postmenopausal women, gynecologic cancer should be suspected.

Dysfunctional uterine bleeding, the most common cause during reproductive years, is a diagnosis of exclusion after other causes are ruled out; testing is usually required.

Testing: All women of reproductive age require

• A urine pregnancy test

During early pregnancy (before 5 wk), a urine pregnancy test may not be sensitive enough. Urine contaminated with blood may lead to false results. A qualitative serum β subunit of human chorionic gonadotropin (β-hCG) test should be done if the urine test is negative and pregnancy is suspected. Vaginal bleeding during pregnancy requires a specific approach (see pp. 2612 and 2620).

Blood tests include CBC if bleeding is unusually heavy (eg, > 1 pad or tampon/h) or has lasted at least several days or if findings suggest anemia or hypovolemia. If anemia is identified and is not obviously due to iron deficiency (eg, based on microcytic, hypochromic RBC indices), iron studies are done.

Thyroid-stimulating hormone and prolactin levels are usually measured, even when galactorrhea is absent.

If a bleeding disorder is suspected, von Willebrand's factor, platelet count, PT, and PTT are determined.

If polycystic ovary syndrome is suspected, testosterone and dehydroepiandrosterone sulfate (DHEAS) levels are measured.

Imaging includes transvaginal ultrasonography if women have any of the following:

• Age > 35

• Risk factors for endometrial cancer

• Bleeding that continues despite use of empiric hormonal therapy

Focal thickening of the endometrium that is detected during screening ultrasonography may require hysteroscopy or saline-infusion sonohysterography to identify small intrauterine masses (eg, endometrial
polyps, submucous myomas).

**Other testing** includes endometrial sampling if examination and ultrasonography are inconclusive in women who are > 35, who have risk factors for cancer, or who have endometrial thickening > 4 mm. Sampling can be done by aspiration or, if the cervical canal requires dilation, by D & C.

**Treatment**

Hemorrhagic shock is treated. Women with iron deficiency anemia may require supplemental oral iron.

Definitive treatment of vaginal bleeding is directed at the cause. Hormones, usually oral contraceptives, are used to treat dysfunctional uterine bleeding.

**Geriatrics Essentials**

Postmenopausal bleeding (bleeding > 6 mo after menopause) is abnormal in most women and requires further evaluation to exclude cancer unless it clearly results from withdrawal of exogenous hormones.

In women not taking exogenous hormones, the most common cause of postmenopausal bleeding is endometrial and vaginal atrophy. In some older women, physical examination of the vagina can be difficult because lack of estrogen leads to increased friability of the vaginal mucosa, vaginal stenosis, and sometimes adhesions in the vagina. For these patients, a pediatric speculum may be more comfortable.

**Key Points**

- Pregnancy must be excluded in women of reproductive age even when history does not suggest it.
- Dysfunctional uterine bleeding is the most common cause of abnormal vaginal bleeding during the reproductive years.
- Vaginitis, foreign bodies, trauma, and sexual abuse are common causes of vaginal bleeding before menarche.
- Postmenopausal vaginal bleeding needs further evaluation to exclude cancer as the cause.

**Vaginal Itching and Discharge**

Vaginal itching (pruritus), discharge, or both result from infectious or noninfectious inflammation of the vaginal mucosa (vaginitis), often with inflammation of the vulva (vulvovaginitis). Symptoms may also include irritation, burning, erythema, and sometimes dysuria and dyspareunia. Symptoms of vaginitis are one of the most common gynecologic complaints.

**Pathophysiology**

Some vaginal discharge is normal, particularly when estrogen levels are high a few days before ovulation. Estrogen levels are also high during the first 2 wk of life (because maternal estrogens are transferred before birth), during the few months before menarche and during pregnancy (when estrogen production increases), and with use of drugs that contain estrogen or that increase estrogen production (eg, some fertility drugs). However, irritation, burning, and pruritus are never normal.

Normally in women of reproductive age, *Lactobacillus* sp is the predominant constituent of normal vaginal flora. Colonization by these bacteria keeps vaginal pH in the normal range (3.8 to 4.2), thereby preventing overgrowth of pathogenic bacteria. Also, high estrogen levels maintain vaginal thickness, bolstering local defenses.

Factors that predispose to overgrowth of bacterial vaginal pathogens include

- Use of antibiotics (which may decrease lactobacilli)
Etiology

The most common causes vary by patient age (see Table 244-5 and Geriatrics Essentials on p. 2497).

**Children:** Vaginitis usually involves infection with GI tract flora (nonspecific vulvovaginitis). A common contributing factor in girls aged 2 to 6 yr is poor perineal hygiene (eg, wiping from back to front after bowel movements, not washing their hands after bowel movements). Chemicals in bubble baths or soaps may cause inflammation and pruritus of the vulva, which often recur. Foreign bodies may cause nonspecific vaginitis, often with a scant bloody discharge.

**Women of reproductive age:** Vaginitis is usually infectious. The most common types are

- Bacterial vaginosis
- Candidal vaginitis
- Trichomonal vaginitis (usually sexually transmitted)

Vaginitis may also result from foreign bodies (eg, a forgotten tampon). Inflammatory noninfectious vaginitis is uncommon.

**Women of all ages:** At any age, conditions that predispose to vaginal or vulvar infection include fistulas between the intestine and genital tract (which allow intestinal flora to seed the genital tract) and pelvic radiation or tumors (which break down tissue and thus compromise normal host defenses). Fistulas are usually obstetric in origin (due to vaginal birth trauma or a complication of episiotomy infection) but are sometimes due to inflammatory bowel disease

[Table 244-5, Some Causes of Vaginal Pruritus and Discharge]

or occur as a complication of pelvic surgery (eg, hysterectomy, anal surgery).

Noninfectious vulvitis accounts for up to 30% of vulvovaginitis cases. It may result from hypersensitivity or irritant reactions to various agents, including hygiene sprays or perfumes, menstrual pads, laundry soaps, bleaches, fabric softeners, and sometimes spermicides, vaginal creams or lubricants, latex condoms, vaginal contraceptive rings, and diaphragms.

**Evaluation**

**History:** History of present illness includes nature of symptoms (eg, pruritus, burning, pain, discharge), duration, and intensity. If vaginal discharge is present, patients should be asked about the color and odor of the discharge and any exacerbating and remitting factors (particularly those related to menses and intercourse). They should also be asked about use of hygiene sprays or perfumes, spermicides, vaginal creams or lubricants, latex condoms, vaginal contraceptive rings, and diaphragms.

**Review of systems** should seek symptoms suggesting possible causes, including fever or chills and abdominal or suprapubic pain (pelvic inflammatory disease [PID] or cystitis) and polyuria and polydipsia.
Past medical history should note risk factors for candidal infection (eg, recent antibiotic use, diabetes, HIV infection, other immunosuppressive disorders), fistulas (eg, Crohn's disease, GU or GI cancer, pelvic or rectal surgery, lacerations during delivery), and sexually transmitted diseases (eg, unprotected intercourse, multiple partners).

Physical examination: Physical examination focuses on the pelvic examination.

The external genitals are examined for erythema, excoriations, and swelling. A water-lubricated speculum is used to check the vaginal walls for erythema, discharge, and fistulas. The cervix is inspected for inflammation (eg, trichomoniases) and discharge. Vaginal pH is measured, and samples of secretions are obtained for testing. A bimanual examination is done to identify cervical motion tenderness and adnexal or uterine tenderness (indicating PID).

Red flags: The following findings are of particular concern:

- Trichomonal vaginitis in children (suggesting sexual abuse)
- Fecal discharge (suggesting a fistula, even if not seen)

Interpretation of findings: Often, the history and physical examination help suggest a diagnosis (see Table 244-5), although there can be much overlap.

In children, a vaginal discharge suggests a foreign body in the vagina. If no foreign body is present and children have trichomonal vaginitis, sexual abuse is likely. If they have unexplained vaginal discharge, cervicitis, which may be due to a sexually transmitted disease, should be considered. Nonspecific vulvovaginitis is a diagnosis of exclusion.

In women of reproductive age, discharge due to vaginitis must be distinguished from normal discharge. Normal vaginal discharge is commonly milky white or mucoid, odorless, and nonirritating; it can result in vaginal wetness that dampens underwear.

Bacterial vaginosis produces a thin, gray discharge with a fishy odor. A trichomonal infection produces a frothy, yellow-green vaginal discharge and causes vulvovaginal soreness. Candidal vaginitis produces a white discharge that resembles cottage cheese, often increasing the week before menses; symptoms worsen after sexual intercourse.

Contact irritant or allergic reactions cause significant irritation and inflammation with comparatively minimal discharge.

Discharge due to cervicitis (eg, due to PID) can resemble that of vaginitis. Abdominal pain, cervical motion tenderness, or cervical inflammation suggests PID.

In women of all ages, vaginal pruritus and discharge may result from skin disorders (eg, psoriasis, tinea versicolor), which can usually be differentiated by history and skin findings.

Discharge that is watery, bloody, or both may result from vulvar, vaginal, or cervical cancer; cancers can be differentiated from vaginitis by examination and Papanicolaou (Pap) tests.

In atrophic vaginitis, discharge is scant, dyspareunia is common, and vaginal tissue appears thin and dry.

Testing: All patients require the following in-office testing:

- pH
- Wet mount
K hydroxide (KOH) preparation

Testing for gonorrhea and chlamydial infections is typically done unless a noninfectious cause (eg, allergy, foreign body) is obvious.

Vaginal secretions are tested using pH paper with 0.2 intervals from pH 4.0 to 6.0. Then, a cotton swab is used to place secretions on 2 slides; secretions are diluted with 0.9% NaCl on one slide (saline wet mount) and with 10% KOH on the other (KOH preparation).

The KOH preparation is sniffed (whiff test) for a fishy odor, which results from amines produced in trichomonal vaginitis and bacterial vaginosis. The slide is examined using a microscope; KOH dissolves most cellular material except yeast hyphae, making identification easier.

The saline wet mount is examined using a microscope as soon as possible to detect motile trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation.

If clinical criteria and in-office test results are inconclusive, the discharge may be cultured for fungi and trichomonads.

Treatment

Any specific cause is treated.

The vulva should be kept as clean as possible. Soaps and unnecessary topical preparations (eg, feminine hygiene sprays) should be avoided. Intermittent use of ice packs or warm sitz baths (with or without baking soda) may reduce soreness and pruritus. If chronic vulvar inflammation is due to being bedbound or incontinent, better vulvar hygiene may help.

If symptoms are moderate or severe or do not respond to other measures, drugs may be needed. For pruritus, topical corticosteroids (eg, 1% hydrocortisone bid prn) can be applied to the vulva but not into the vagina. Oral antihistamines lessen pruritus and cause drowsiness, helping patients sleep.

Prepubertal girls should be taught good perineal hygiene (eg, wiping front to back after bowel movements and voiding, washing their hands, avoiding fingering the perineum).

Geriatrics Essentials

In postmenopausal women, a marked decrease in estrogen causes vaginal thinning, increasing vulnerability to infection and inflammation (atrophic vaginitis). Other common causes of decreased estrogen in older women include oophorectomy, pelvic radiation, and certain chemotherapy drugs.

In atrophic vaginitis, discharge is scant, dyspareunia is common, and vaginal tissue appears thin and dry.

Poor hygiene (eg, in patients who are incontinent or bedbound) can lead to chronic vulvar inflammation due to chemical irritation by urine or feces.

Bacterial vaginosis, candidal vaginitis, and trichomonal vaginitis are uncommon among postmenopausal women but may occur in those with risk factors.

Key Points

• Vaginal complaints are often nonspecific.

• Causes vary depending on the patient's age.

• Most patients require measurement of vaginal pH, microscopic examination of secretions, and, if needed, culture for sexually transmitted organisms.
Chapter 245. Female Reproductive Endocrinology

Introduction

Hormonal communication between the hypothalamus, anterior pituitary gland, and ovaries regulates the female reproductive system. The hypothalamus secretes a small peptide, gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone. GnRH regulates release of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from specialized cells (gonadotropes) in the anterior pituitary gland (see Fig. 245-1 and p. 758). These hormones are released in short bursts (pulses) every 1 to 4 h. LH and FSH promote ovulation and stimulate secretion of the sex hormones estradiol (an estrogen) and progesterone from the ovaries.

Estrogen and progesterone circulate in the bloodstream almost entirely bound to plasma proteins. Only unbound estrogen and progesterone appear to be biologically active. They stimulate the target organs of the reproductive system (eg, breasts, uterus, vagina). They usually inhibit but, in certain situations (eg, around the time of ovulation), may stimulate gonadotropin secretion.

Puberty

Puberty is the sequence of events in which a child acquires adult physical characteristics and capacity for reproduction. Circulating LH and FSH levels are elevated at birth but fall to low levels within a few months and remain low until puberty. Until puberty, few qualitative changes occur in reproductive target organs.

Over the last 150 yr, the age at which puberty begins has been decreasing, primarily because of improved health and nutrition, but this trend has stabilized. Puberty often occurs earlier than average in moderately obese girls and later than average in severely under-weight and undernourished girls. Such observations suggest that a critical body weight is necessary for puberty. Puberty occurs earlier in girls whose mothers matured earlier and, for unknown reasons, in girls who live in urban areas or who are blind.

Physical changes of puberty occur sequentially during adolescence (Fig. 245-2). Breast budding (see Fig. 245-3) and onset of the growth spurt are usually the first changes recognized. Then, pubic and axillary hair appears (see Fig. 245-4), and the growth spurt peaks. Menarche (the first menstrual period) occurs about 2 yr after breast budding. The growth spurt peaks early in puberty; it is limited after menarche. Body habitus changes; the pelvis and hips widen. Body fat increases and accumulates in the hips and thighs.

Mechanisms initiating puberty are unclear. Central influences may inhibit release of GnRH during childhood, then initiate its release to induce puberty in early adolescence. Early in puberty, hypothalamic GnRH release becomes less sensitive to inhibition by estrogen and progesterone. The resulting increased release of GnRH promotes LH and FSH secretion, which stimulates production of sex hormones, primarily estrogen. Estrogen stimulates development of secondary sexual characteristics. Pubic and axillary hair growth may be stimulated by the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate; production of these androgens increases several years before puberty in a process called adrenarche.

Ovarian Follicular Development

A female is born with a finite number of egg precursors (germ cells). Germ cells begin

[Fig. 245-2. Puberty—when female sexual characteristics develop.]
as primordial oogonia that proliferate markedly by mitosis through the 4th mo of gestation. During the 3rd mo, some oogonia begin to undergo meiosis, which reduces the number of chromosomes by one half. By the 7th mo, all viable germ cells develop a surrounding layer of granulosa cells, forming a primordial follicle, and are arrested in meiotic prophase; these cells are primary oocytes. Beginning after the 4th mo of gestation, oogonia (and later oocytes) are lost spontaneously in a process called atresia; eventually, 99.9% are lost. In older mothers, the long time that surviving oocytes spend arrested in meiotic prophase may account for the increased incidence of genetically abnormal pregnancies.

During each menstrual cycle, 3 to 30 follicles are recruited for accelerated growth. Usually in each cycle, only one follicle is selected for ovulation. This dominant follicle releases its oocyte at ovulation and promotes atresia of the other recruited follicles.

**Menstrual Cycle**

Menstruation is the periodic discharge of blood and sloughed endometrium (collectively called menses or menstrual flow) through the vagina; menstruation occurs throughout a woman's reproductive life in the absence of pregnancy. Menopause is the permanent cessation of menses (see p. 2518).

Average duration of menses is 5 (± 2) days. Blood loss per cycle averages 30 mL (normal range, 13 to 80 mL) and is usually greatest on the 2nd day. A saturated pad or tampon absorbs 5 to 15 mL. Menstrual blood does not usually clot (unless bleeding is very heavy), probably because fibrinolysin and other factors inhibit clotting.

The median menstrual cycle length is 28 days (usual range, about 25 to 36 days). Generally, variation is maximal and intermenstrual intervals are longest in the years immediately after menarche and immediately before menopause, when ovulation occurs less regularly. The menstrual cycle begins and ends with the first day of menses (day 1).

The menstrual cycle can be divided into follicular (preovulatory), ovulatory, and luteal (postovulatory) phases (see Fig. 245-5).

**Follicular phase:** This phase varies in length more than other phases do. In the first half of the follicular phase (early follicular phase), the primary event is growth of recruited follicles. At this time, the gonadotropes in the anterior pituitary contain little LH and FSH, and estrogen and progesterone production is low. As a result, overall FSH secretion increases slightly, stimulating growth of recruited follicles. Also, circulating LH levels increase slowly, beginning 1 to 2 days after the increase in FSH. The recruited ovarian follicles soon increase production of

estradiol; estradiol stimulates LH and FSH synthesis but inhibits their secretion.

During the 2nd half of the follicular phase (late follicular phase), the follicle selected for ovulation matures and accumulates hormone-secreting granulosa cells; its antrum enlarges with follicular fluid, reaching 18 to 20 mm before ovulation. FSH levels decrease; LH levels are affected less. FSH and LH levels diverge partly because estradiol inhibits FSH secretion more than LH secretion. Also, developing follicles produce the hormone inhibin, which inhibits FSH secretion but not LH secretion. Other contributing factors may include disparate half-lives (20 to 30 min for LH; 2 to 3 h for FSH) and unknown factors. Levels of estrogen, particularly estradiol, increase exponentially.

**Ovulatory phase:** Ovulation (ovum release) occurs. Estradiol levels usually peak as the ovulatory phase begins. Progesterone levels also begin to increase. Stored LH is released in massive amounts (LH
The LH surge occurs because at this time, high levels of estradiol trigger LH secretion by gonadotropes (positive feedback). The LH surge is also stimulated by GnRH and progesterone. During the LH surge, estradiol levels decrease, but progesterone levels continue to increase. The LH surge stimulates enzymes that initiate breakdown of the follicle wall and release of the now mature ovum within about 16 to 32 h. The LH surge also triggers completion of the first meiotic division of the oocyte within about 36 h.

**Luteal phase:** The follicle is transformed into a corpus luteum. The length of this phase is the most constant, averaging 14 days, after which the corpus luteum degenerates. The corpus luteum secretes primarily progesterone in increasing quantities, peaking at about 25 mg/day 6 to 8 days after ovulation. Progesterone stimulates development of the secretory endometrium, which is necessary for embryonic implantation. Because progesterone is thermogenic, basal body temperature increases by 0.5°C for the duration of this phase. Because levels of circulating estradiol, progesterone, and inhibin are high during most of the luteal phase, LH and FSH levels decrease. Estradiol and progesterone levels decrease late in this phase.

If implantation occurs, the corpus luteum does not degenerate but remains, supported by human chorionic gonadotropin that is produced by the developing embryo.

**Cyclic Changes in Other Reproductive Organs**

**Endometrium:** The endometrium, which consists of glands and stroma, has a basal layer, an intermediate spongiosa layer, and a layer of compact epithelial cells that line the uterine cavity. Together, the spongiosa and epithelial layers form the functionalis, a transient layer that is sloughed during menses. After menstruation, the endometrium is typically < 2 mm thick with dense stroma and narrow, straight, tubular glands lined with low columnar epithelium. As estradiol levels increase, the intact basal layer regenerates the endometrium to a maximum thickness of 11 mm late in the follicular phase. The mucosa thickens and the glands lengthen and coil, becoming tortuous. During the luteal phase, progesterone stimulates the glands to dilate, fill with glycogen, and become secretory, while stromal vascularity increases. As estradiol and progesterone levels decrease late in the luteal phase, the stroma becomes edematous, and the endometrium and its blood vessels necrose, leading to bleeding and menstrual flow.

Because histologic changes are specific to the phase of the menstrual cycle, the cycle phase or tissue response to sex hormones can be determined accurately by endometrial biopsy. The endometrium can also be seen using transvaginal ultrasonography; late in the follicular phase, it characteristically has a trilaminar pattern, with hyperechoic basal and luminal layers and an intervening hypoechoic layer. After ovulation, the endometrium appears homogeneously echogenic.

**Cervix:** During the follicular phase, increasing estradiol levels increase cervical vascularity and edema and cervical mucus quantity, elasticity, and NaCl concentration. The external os opens slightly and fills with mucus at ovulation. During the luteal phase, increasing progesterone levels make the cervical mucus thicker and less elastic. Menstrual cycle phase can sometimes be identified by microscopic examination of cervical mucus dried on a glass slide; ferning (palm leaf arborization of mucus) indicates increased NaCl in cervical mucus. Ferning becomes prominent just before ovulation, when estrogen levels are high; it is minimal or absent during the luteal phase.

**Vagina:** Early in the follicular phase, when estradiol levels are low, the vaginal epithelium is thin and pale. Later in the follicular phase, as estradiol levels increase, squamous cells mature and become cornified, causing epithelial thickening. During the luteal phase, the number of precornified intermediate cells increases, and the number of leukocytes and amount of cellular debris increase as mature squamous cells are shed.
**Chapter 246. Menstrual Abnormalities**

**Introduction**

(For a description of the menstrual cycle, see p. 2499.)

Menstrual abnormalities include amenorrhea, dysfunctional uterine bleeding, dysmenorrhea, and premenstrual syndrome. Irregular or absent menses and nonmenstrual vaginal bleeding have many causes, but in women of reproductive age, pregnancy should always be suspected. Abnormal vaginal bleeding in nonpregnant women (see p. 2490) is evaluated differently from vaginal bleeding in pregnant women (see pp. 2612 and 2620).

**Amenorrhea**

Amenorrhea (the absence of menstruation) can be primary or secondary.

**Primary amenorrhea** is failure of menses to occur by any of the following:

- Age 16 or 2 yr after the onset of puberty
- About age 14 in girls who have not gone through puberty (eg, growth spurt, development of secondary sexual characteristics)

**Secondary amenorrhea** is cessation of menses after they have begun; evaluation for amenorrhea is usually done if menses are absent for > 6 mo.

**Pathophysiology**

Normally, the hypothalamus generates pulses of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to produce gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH])—see p. 2499). Gonadotropins stimulate the ovaries to produce estrogen (mainly estradiol), androgens (mainly testosterone), and progesterone. Estrogen stimulates the endometrium, causing it to proliferate. After ovulation, the corpus luteum produces progesterone, which causes the endometrium to become secretory and prepares it for egg implantation. If pregnancy does not occur, estrogen and progesterone production decreases, and the endometrium breaks down and is sloughed during menses.

When part of this system malfunctions, ovulatory dysfunction occurs; the cycle of gonadotropin-stimulated estrogen production and cyclic endometrial changes is disrupted, and menstrual flow does not occur, resulting in anovulatory amenorrhea. Most amenorrhea, particularly secondary amenorrhea, is anovulatory.

However, amenorrhea can occur when ovulation is normal, as occurs when genital anatomic abnormalities (eg, congenital anomalies causing outflow obstruction, intrauterine adhesions [Asherman's syndrome]) prevent normal menstrual flow despite normal hormonal stimulation.

**Etiology**

Amenorrhea is usually classified as anovulatory (see Table 246-1) or ovulatory (see Table 246-2). Each type has many causes, but overall, the most common causes of amenorrhea include

- Pregnancy (the most common cause in women of reproductive age)
- Constitutional delay of puberty
- Functional hypothalamic anovulation (eg, due to excessive exercise, eating disorders, or stress)
• Use or abuse of drugs (eg, oral contraceptives, depoprogesterone, antidepressants, antipsychotics)

• Breastfeeding

• Polycystic ovary syndrome

Contraceptives can cause the endometrium to thin, sometimes resulting in amenorrhea. Antidepressants and antipsychotics can elevate prolactin.

Some disorders can cause ovulatory or anovulatory amenorrhea. Congenital anatomic abnormalities cause only primary amenorrhea.

**Anovulatory amenorrhea:** The most common causes (see Table 246-1) involve a disruption of the hypothalamic-pituitary-ovarian axis. Thus, causes include

• Hypothalamic dysfunction (particularly functional hypothalamic anovulation)

• Pituitary dysfunction

• Premature ovarian failure

• Endocrine disorders that cause androgen excess (particularly polycystic ovary syndrome)

[Table 246-1, Some Causes of Anovulatory Amenorrhea]

Anovulatory amenorrhea is usually secondary but may be primary if ovulation never begins—eg, because of a genetic disorder. If ovulation never begins, puberty and development of secondary sexual characteristics are abnormal.

**Ovulatory amenorrhea:** The most common causes (see Table 246-2) include

• Chromosomal abnormalities

• Other congenital anatomic genital abnormalities that obstruct menstrual flow

Obstructive abnormalities are usually accompanied by normal hormonal function. Such obstruction may result in hematocolpos (accumulation of menstrual blood in the vagina), which can cause the vagina to bulge, or in hematometra (accumulation of blood in the uterus), which can cause uterine distention or a mass. Because ovarian function is normal, external genital organs and other secondary sexual characteristics develop normally. Some congenital disorders (eg, those accompanied by vaginal aplasia or a vaginal septum) also cause urinary tract and skeletal abnormalities.

Some acquired anatomic abnormalities, such as endometrial scarring after instrumentation or postpartum hemorrhage (Asherman's syndrome), cause secondary ovulatory amenorrhea.

**Evaluation**

Girls are evaluated if

• They have no signs of puberty (eg, breast development, growth spurt) by age 13 1/2.

• Pubic hair is absent at age 14.

• Menarche has not occurred by age 16 or by 2 yr after the onset of puberty (development of secondary...
Women of reproductive age should have a pregnancy test after missing one menses. They are evaluated for amenorrhea if

- They are not pregnant and have missed menstrual cycles for ≥ 3 mo.
- They have < 9 menses a year.
- They have a sudden change in menstrual pattern.

**History:** History of present illness includes whether menses have ever occurred (to distinguish primary from secondary amenorrhea) and, if so, how old patients were at menarche, whether periods have ever been regular, and when the last normal menstrual period occurred. History should also include duration and flow of menses; presence or absence of cyclic breast tenderness and mood changes; and growth, development, and age at thelarche (development of breasts at puberty).

**Review of systems** should cover symptoms suggesting possible causes, including galactorrhea, headaches, and visual field defects (pituitary disorders); fatigue, weight gain, and cold intolerance (hypothyroidism); palpitations, nervousness, tremor, and heat intolerance (hyperthyroidism); acne, hirsutism, and deepening of the voice (androgen excess); and, for patients with secondary amenorrhea, hot flushes, vaginal dryness, sleep disturbance, fragility fractures, and decreased libido (estrogen deficiency). Patients with primary amenorrhea are asked about symptoms of puberty (eg, breast development, growth spurt, presence of axillary and pubic hair) to help determine whether ovulation has occurred.

**Past medical history** should note risk factors for functional hypothalamic anovulation, such as stress; chronic illness; a recent change in weight, diet, or exercise intensity; and, in patients with secondary amenorrhea, risk factors for Asherman's syndrome (eg, D & C, endometritis, obstetric injury, uterine surgery).

**Drug history** should include specific questions about use of drugs that affect dopamine (eg, antihypertensives, antipsychotics, opioids, tricyclic antidepressants) and sex hormones that can cause virilization (eg, androgens, estrogens, high-dose progestins).

**Family history** should include height of family members and any cases of delayed puberty or genetic disorders in family members.

**Physical examination:** Clinicians should note vital signs and body composition and build, including height and weight, and should calculate body mass index (BMI). Secondary sexual characteristics are evaluated; breast and pubic hair development are staged using Tanner's method. If axillary and pubic hair is present, adrenarche has occurred.

With the patient seated, clinicians should check for breast secretion by applying pressure to all sections of the breast, beginning at the base and moving toward the nipple. Galactorrhea (breast milk secretion not temporally associated with childbirth) may be observed; it can be distinguished from other types of nipple discharge by finding fat globules in the fluid using a low-power microscope.

Pelvic examination is done to detect anatomic genital abnormalities; a bulging hymen may be caused by hematocolpos, which suggests genital outflow obstruction. Pelvic examination findings also help determine whether estrogen is adequate. In postpubertal females, thin, pale vaginal mucosa without rugae and pH > 6.0 indicate estrogen deficiency. The presence of cervical mucus with spinnbarkeit (a stringy, stretchy quality) usually indicates adequate estrogen.

General examination focuses on evidence of virilization, including hirsutism, temporal balding, acne, voice deepening, increased muscle mass, clitoromegaly (clitoral enlargement), and defeminization (a decrease in previously normal secondary sexual characteristics, such as decreased breast size and vaginal atrophy). Hypertrichosis (excessive growth of hair on the extremities, head, and back), which is common
in some families, is differentiated from true hirsutism, which is characterized by excess hair on the upper lip and chin and between the breasts. Skin discoloration (eg, yellow of jaundice or carotenemia, black patches of acanthosis nigricans) should be noted.

**Red flags:** The following findings are of particular concern:

- Delayed puberty
- Virilization
- Visual field defects

**Interpretation of findings:** Pregnancy should not be excluded by history; a pregnancy test is required.

In primary amenorrhea, the presence of normal secondary sexual characteristics usually reflects normal hormonal function; amenorrhea is usually ovulatory and typically due to a congenital anatomic genital tract obstruction. Primary amenorrhea accompanied by abnormal secondary sexual characteristics is usually anovulatory (eg, due to a genetic disorder).

In secondary amenorrhea, clinical findings sometimes suggest a mechanism (see [Table 246-3](#)).

- Galactorrhea suggests hyperprolactinemia (eg, pituitary dysfunction, use of certain drugs); if visual field defects and headaches are also present, pituitary tumors should be considered.

- Symptoms and signs of estrogen deficiency (eg, hot flushes, night sweats, vaginal dryness or atrophy) suggest premature ovarian failure.

- Virilization suggests androgen excess (eg, polycystic ovary syndrome, androgen-secreting tumor, Cushing's syndrome, use of certain drugs). If patients have a high BMI, acanthosis nigricans, or both, polycystic ovary syndrome is likely.

**Testing:** History and physical examination help direct testing.

If girls have secondary sexual characteristics, a pregnancy test should be done to exclude pregnancy and gestational trophoblastic disease as a cause of amenorrhea. Women of reproductive age should have a pregnancy test after missing one menses.

[Table 246-3, Findings Suggesting Possible Causes of Amenorrhea]

The approach to primary amenorrhea (see [Fig. 246-1](#)) differs from that to secondary amenorrhea (see [Fig. 246-2](#)), although no specific general approaches or algorithms are universally accepted.

If symptoms or signs suggest a specific disorder, specific tests may be indicated regardless of what an algorithm recommends. For example, patients with abdominal striae, moon facies, a buffalo hump, truncal obesity, and thin extremities should be tested for Cushing's syndrome (see p. 797). Patients with headaches and visual field defects or evidence of pituitary dysfunction require brain MRI.

If clinical evaluation suggests a chronic disease, liver and kidney function tests are done, and ESR is determined.
Often, testing includes measurement of hormone levels; total serum testosterone or dehydroepiandrosterone sulfate (DHEAS) levels are measured only if signs of virilization are present. Certain hormone levels should be remeasured to confirm the results. For example, if serum prolactin is high, it should be remeasured; if serum FSH is high, it should be remeasured monthly at least twice. Amenorrhea with high FSH levels (hypergonadotrophic hypogonadism) suggests ovarian dysfunction; amenorrhea with low FSH levels (hypogonadotrophic hypogonadism) suggests hypothalamic or pituitary dysfunction.

If patients have secondary amenorrhea without virilization and have normal prolactin and FSH levels and normal thyroid function, a trial of estrogen and a progestin to try to stimulate withdrawal bleeding can be done (progesterone challenge test). The trial begins by giving medroxyprogesterone 5 to 10 mg po once/day or another progestin for 7 to 10 days.

If bleeding occurs, amenorrhea is probably not caused by an endometrial lesion (eg, Asherman's syndrome) or outflow tract obstruction, and the cause is probably hypothalamic-pituitary dysfunction, ovarian failure, or estrogen excess.

If bleeding does not occur, an estrogen (eg, conjugated equine estrogen 1.25 mg, estradiol 2 mg) once/day is given for 21 days, followed by medroxyprogesterone 10 mg po once/day or another progestin for 7 to 10 days. Absence of bleeding suggests an endometrial lesion or outflow tract obstruction. However, because this trial takes weeks and results can be inaccurate, diagnosis of some serious disorders may be delayed significantly; thus, brain MRI should be considered before or during the trial.

Mildly elevated levels of testosterone or DHEAS suggest polycystic ovary syndrome, but levels can be elevated in women with hypothalamic or pituitary dysfunction and are sometimes normal in hirsute women with polycystic ovary syndrome. The cause of elevated levels can sometimes be determined by measuring serum LH. In polycystic ovary syndrome, circulating LH levels are often increased, increasing the ratio of LH to FSH.

**Treatment**

Treatment is directed at the underlying disorder; with such treatment, menses sometimes resume. For example, most abnormalities obstructing the genital outflow tract are surgically repaired.

If a Y chromosome is present, bilateral oophorectomy is recommended because risk of ovarian germ cell cancer is increased.

Problems associated with amenorrhea may also require treatment, including

- Inducing ovulation if pregnancy is desired

- Treating symptoms and long-term effects of estrogen deficiency (eg, osteoporosis)

- Treating symptoms of estrogen excess (eg, prolonged bleeding, persistent or marked breast tenderness)

- Minimizing hirsutism and long-term effects of androgen excess (eg, cardiovascular disorders, hypertension)

**Key Points**

- Pregnancy must always be excluded by testing.

- Primary amenorrhea is evaluated differently from secondary amenorrhea.

- Primary amenorrhea with normal secondary sexual characteristics suggests congenital anatomic genital...
tract obstruction; pelvic ultrasonography is indicated.

- Primary amenorrhea without normal secondary sexual characteristics is usually anovulatory (eg, due to a genetic disorder).
- Virilization suggests androgen excess (eg, due to polycystic ovary syndrome, an androgen-secreting tumor, Cushing's syndrome, or use of certain drugs).
- Symptoms and signs of estrogen deficiency (eg, hot flushes, night sweats, vaginal dryness or atrophy) suggest premature ovarian failure.
- Galactorrhea suggests hyperprolactinemia (eg, due to pituitary dysfunction or use of certain drugs).

**Dysfunctional Uterine Bleeding**

*(Functional Uterine Bleeding)*

Dysfunctional uterine bleeding is abnormal uterine bleeding that, after examination and ultrasonography, cannot be attributed to the usual causes (structural gynecologic abnormalities, cancer, inflammation, systemic disorders, pregnancy, complications of pregnancy, use of oral contraceptives or certain drugs). Treatment is usually with hormonal therapy, such as oral contraceptives.

Dysfunctional uterine bleeding (DUB), the most common cause of abnormal uterine bleeding, occurs most often in women > 45 (> 50% of cases) and in adolescents (20% of cases).

About 90% of cases are anovulatory; 10% are ovulatory.

**Pathophysiology**

During an anovulatory cycle, the corpus luteum does not form. Thus, the normal cyclical secretion of progesterone does not occur, and estrogen stimulates the endometrium unopposed. Without progesterone, the endometrium continues to proliferate, eventually outgrowing its blood supply; it then sloughs and bleeds incompletely, irregularly, and sometimes profusely or for a long time. When this abnormal process occurs repeatedly, the endometrium can become hyperplastic, sometimes with atypical or cancerous cells.

In ovulatory DUB, progesterone secretion is prolonged; irregular shedding of the endometrium results, probably because estrogen levels remain low, near the threshold for bleeding (as occurs during menses). In obese women, ovulatory DUB can occur if estrogen levels are high, resulting in amenorrhea alternating with irregular or prolonged bleeding.

**Complications:** Chronic bleeding may cause iron deficiency anemia. If DUB is due to chronic anovulation, infertility may also be present.

**Etiology**

Anovulatory DUB can result from any disorder or condition that causes anovulation (see Table 246-1). Anovulation is most often secondary to polycystic ovary syndrome or is idiopathic (sometimes occurring when gonadotropin levels are normal); sometimes anovulation results from hypothyroidism. During perimenopause, DUB may be an early sign of ovarian failure; follicles are still developing but, despite increasing levels of follicle-stimulating hormone (FSH), do not produce enough estrogen to trigger ovulation. About 20% of women with endometriosis (see p. 2538) have anovulatory DUB due to unknown mechanisms.

Ovulatory DUB may occur in polycystic ovary syndrome (because progesterone secretion is prolonged) or in endometriosis, which does not affect ovulation. Other causes are a short follicular phase and luteal phase dysfunction (due to inadequate progesterone stimulation of the endometrium); a rapid decrease in
estrogen before ovulation can cause spotting.

**Symptoms and Signs**

Compared with typical menses, bleeding may occur more frequently (< 21 days apart—polymenorrhea), last longer or involve more blood loss (> 7 days or > 80 mL—menorrhagia, or hypermenorrhea), or occur frequently and irregularly between menses (metrorrhagia).

Ovulatory DUB tends to cause excessive bleeding during regular menstrual cycles. Women may have other symptoms of ovulation, such as premenstrual symptoms, breast tenderness, midcycle cramping pain (mittelschmerz), a change in basal body temperature with ovulation (see p. 2595), and sometimes dysmenorrhea. Anovulatory DUB occurs at unpredictable times and in unpredictable patterns and is not accompanied by cyclic changes in basal body temperature.

**Diagnosis**

- Exclusion of other potential causes
- CBC, pregnancy test, and hormone measurement (thyroid-stimulating hormone, prolactin)
- Usually transvaginal ultrasonography and endometrial sampling

Women should be evaluated for DUB when the amount or timing of vaginal bleeding is inconsistent with normal menses. DUB is a diagnosis of exclusion; other conditions that can cause similar bleeding must be excluded (see p. 2490). Pregnancy should be excluded, even in young adolescents and perimenopausal women. Coagulation disorders should be considered, particularly in adolescents who have anemia or require hospitalization for bleeding. Regular cycles with prolonged or excessive bleeding (possible ovulatory DUB) suggest structural abnormalities.

**Laboratory testing:** Several tests are typically done:

- A urine pregnancy test
- CBC
- TSH, prolactin, and progesterone levels

All women of reproductive age should have a pregnancy test. CBC is routinely done. However, Hct may be normal in women who report heavy bleeding, or anemia may be severe in women who regularly have heavy periods.

Thyroid-stimulating hormone levels are usually measured, and prolactin levels are measured, even when galactorrhea is absent, because thyroid disorders and hyperprolactinemia are common causes of abnormal bleeding. To determine whether bleeding is anovulatory or ovulatory, some clinicians measure serum progesterone levels during the luteal phase (after day 14 of a normal menstrual cycle or after basal body temperature increases, as occurs during this phase). A level of ≥ 3 ng/mL (≥ 9.75 nmol/L) suggests that ovulation has occurred.

Other tests are done depending on results of the history and physical examination and include the following:

- Coagulation tests if women have risk factors or bruising or hemorrhage
- Liver function tests if a liver disorder is suspected
- Testosterone and dehydroepiandrosterone sulfate (DHEAS) levels if polycystic ovary syndrome is suspected
Follicle-stimulating hormone (FSH) and estradiol levels if premature ovarian failure is possible

A cervical cytology test (eg, Papanicolaou [Pap] test) if results are out-of-date

Testing for \textit{Neisseria gonorrhoea} and \textit{Chlamydia} sp if pelvic inflammatory disease or cervicitis is suspected

If all clinically indicated tests are normal, the diagnosis is DUB.

**Additional testing:** Transvaginal ultrasonography is done if women have any of the following:

- Age ≥ 35 or, if unopposed estrogen exposure is prolonged, younger
- Risk factors for endometrial cancer (eg, obesity, diabetes, hypertension, polycystic ovary syndrome, other conditions associated with prolonged unopposed estrogen)
- Bleeding that continues despite use of empiric hormonal therapy

These criteria include almost all women with DUB.

Transvaginal ultrasonography can detect structural abnormalities, including most masses and focal thickening of the endometrium. If focal thickening is detected, hysteroscopy or saline-infusion sonohysterography may be needed to identify smaller intrauterine masses (eg, endometrial polyps, submucous myomas).

Endometrial sampling is usually recommended to rule out hyperplasia or cancer in women with any of the following:

- Criteria indicating need for transvaginal ultrasonography
- Bleeding that is persistent, irregular, or heavy
- Irregular cycles that suggest chronic anovulatory bleeding
- Endometrial thickness > 4 mm or focal or irregular areas
- Inconclusive ultrasonography findings

Directed biopsy (with hysteroscopy) may be done to visualize the endometrial cavity directly and target the abnormal tissue.

**Treatment**

- Control of bleeding, usually with hormone therapy
- In women with endometrial hyperplasia, prevention of endometrial cancer

**Bleeding:** Patients with very heavy bleeding (which is uncommon) are stabilized hemo-dynamically with IV crystalloid fluid, blood products, and other measures as needed. If bleeding persists, a bladder catheter is inserted into the uterus and inflated with 30 mL of water to tamponade the bleeding. Once patients are stable, hormonal therapy is used to control bleeding.

For anovulatory DUB with very heavy bleeding, conjugated estrogens 25 mg IV q 4 to 6 h for a total of 4 doses may be used. Immediately afterward, women are given a combination (estrogen/progestin) oral contraceptive, which may be continued until bleeding abates. Otherwise, anovulatory DUB is usually treated with combination oral contraceptives (see p. 2584). Depending on the severity of bleeding, an oral contraceptive can be given bid or tid for 5 to 6 days, then once/day. After acute bleeding is controlled, a combination oral contraceptive is given continually for about 3 mo to prevent recurrence.
Other options include a levonorgestrel-releasing intrauterine device (IUD), depot medroxyprogesterone acetate injections, and cyclic use of a progestin (eg, medroxyprogesterone acetate 5 to 10 mg po once/day, norethindrone 5 mg po once/day for 10 to 14 days/mo). These treatments may be indicated when estrogen is contraindicated or when spontaneous cyclic menses do not resume after 3 mo of oral contraceptive therapy.

If pregnancy is desired and bleeding is not heavy, ovulation induction with clomiphene (50 mg po on days 5 through 9 of the menstrual cycle) can be tried.

Endometrial ablation (eg, using freezing or burning) may help control bleeding (in 60 to 80%). If this treatment does not control bleeding, bleeding is usually caused by adenomyosis and is thus not DUB.

Hysteroscopy with D & C may be therapeutic as well as diagnostic; it may be the treatment of choice when anovulatory bleeding is severe or when hormone therapy is ineffective. Structural causes such as polyps or fibroids may be identified or removed during hysteroscopy. This procedure may decrease bleeding but, in some women, causes amenorrhea due to endometrial scarring (Asherman’s syndrome).

For ovulatory DUB, oral contraceptives are usually effective. Other options include NSAIDs given during menses, ovarian suppression with depot leuprolide, depot medroxyprogesterone acetate, and a levonorgestrel-releasing IUD.

Endometrial hyperplasia: In postmenopausal women, atypical adenomatous endometrial hyperplasia is usually treated with hysterectomy. In premenopausal women, it is treated with medroxyprogesterone acetate 20 to 40 mg po once/day for 3 to 6 mo.

If repeat endometrial sampling indicates resolution of hyperplasia, women may be given cyclic medroxyprogesterone acetate (5 to 10 mg po once/day for 10 to 14 days each month) or, if pregnancy is desired, clomiphene. If sampling shows persistent or progressive atypical hyperplasia, hysterectomy is necessary.

More benign cystic or adenomatous hyperplasia can usually be treated with high-dose cyclic progesterone therapy (eg, cyclic medroxyprogesterone acetate); sampling is repeated after about 3 mo.

Dysmenorrhea

Dysmenorrhea is uterine pain around the time of menses. Pain may occur with menses or precede menses by 1 to 3 days. Pain tends to peak 24 h after onset of menses and subside after 2 to 3 days. It is usually sharp but may be cramping, throbbing, or a dull, constant ache; it may radiate to the legs. Headache, nausea, constipation or diarrhea, lower back pain, and urinary frequency are common; vomiting occurs occasionally. Symptoms of premenstrual syndrome may occur during part or all of menses. Sometimes endometrial clots or casts are expelled.

Etiology

Dysmenorrhea can be

- Primary (more common)
- Secondary (due to pelvic abnormalities)

Primary dysmenorrhea: Symptoms cannot be explained by structural gynecologic disorders. Pain is thought to result from uterine contractions and ischemia, probably mediated by prostaglandins and other inflammatory mediators produced in secretory endometrium and possibly associated with prolonged uterine contractions and decreased blood flow to the myometrium. Contributing factors may include passage of menstrual tissue through the cervix, a narrow cervical os, a malpositioned uterus, lack of exercise, and anxiety about menses. It occurs almost invariably in ovulatory cycles. Risk factors for severe symptoms include earlier age at menarche, long or heavy menstrual periods, smoking, and a
family history of dysmenorrhea.

Primary dysmenorrhea usually starts during adolescence and tends to lessen with age and after pregnancy.

Secondary dysmenorrhea: Symptoms are due to pelvic abnormalities. Common causes include

- Endometriosis (the most common cause)
- Uterine adenomyosis
- Fibroids

Less common causes include congenital malformations, ovarian cysts and tumors, pelvic inflammatory disease, pelvic congestion, and copper intrauterine devices (IUDs).

In a few women, pain occurs when the uterus attempts to expel tissue through an extremely tight cervical os (secondary to conization, loop electrosurgical excision procedure [LEEP], cryocautery, or thermocautery). Pain occasionally results from a pedunculated submucosal fibroid or an endometrial polyp extruding through the cervix.

Secondary dysmenorrhea usually begins during adulthood unless caused by congenital malformations.

Evaluation

History: History of present illness should cover complete menstrual history, including age at onset of menses, duration and amount of flow, time between menses, variability of timing, and relation of menses to symptoms. Clinicians should also ask about the age at which symptoms began, their nature and severity, factors that relieve or worsen symptoms, degree of disruption of daily life, and presence of pelvic pain unrelated to menses.

Review of systems should include accompanying symptoms such as cyclic nausea, vomiting, bloating, diarrhea, and fatigue. Sexual history should include effect of contraceptives on pain and prior or current history of sexual abuse.

Past medical history should identify known causes, including endometriosis, uterine adenomyosis, or fibroids. Method of contraception should be ascertained, specifically asking about IUD use.

Physical examination: Pelvic examination focuses on detecting causes of secondary dysmenorrhea. The vagina, vulva, and cervix are inspected for lesions and for masses protruding through the cervical os. Structures are palpated to check for a tight cervical os, prolapsed polyp or fibroid, uterine masses, adnexal masses, thickening of the rectovaginal septum, induration of the cul-de-sac, and nodularity of the uterosacral ligament.

Red flags: The following findings are of particular concern:

- New or sudden-onset pain
- Unremitting pain
- Fever
- Vaginal discharge

Interpretation of findings: Red flag findings suggest a cause of pelvic pain other than dysmenorrhea. Primary dysmenorrhea is suspected if symptoms begin soon after menarche or during adolescence.
Secondary dysmenorrhea is suspected if symptoms begin after adolescence or in patients with known causes, including uterine adenomyosis, fibroids, a tight cervical os, a mass protruding from the cervical os, or, particularly, endometriosis.

Endometriosis is considered in patients with adnexal masses, thickening of the rectovaginal septum, induration of the cul-de-sac, nodularity of the uterosacral ligament, or, occasionally, nonspecific vaginal, vulvar, or cervical lesions.

**Testing:** Testing aims to exclude structural gynecologic disorders. Most patients should have

- Pregnancy testing
- Pelvic ultrasonography

Intrauterine and ectopic pregnancy are ruled out by pregnancy testing. If pelvic inflammatory disease is suspected, cervical cultures are done.

Pelvic ultrasonography is highly sensitive for pelvic masses such as fibroids, endometriosis, and uterine adenomyosis.

If these tests are inconclusive and symptoms persist, other tests are done. Hysterosalpingography or sonohysterography can be used to identify endometrial polyps, submucous fibroids, or congenital abnormalities. MRI may be used to identify other abnormalities, including congenital abnormalities, or to further define previously identified abnormalities if surgery is planned. If results of all other tests are inconclusive, hysteroscopy or laparoscopy can be done.

**Treatment**

Underlying disorders are treated. Symptomatic treatment begins with adequate rest and sleep and regular exercise. A low-fat diet and nutritional supplements such as ω-3 fatty acids, flaxseed, magnesium, vitamin E, zinc, and vitamin B₁ are suggested as potentially effective. Women with primary dysmenorrhea are reassured about the absence of structural gynecologic disorders.

If pain persists, drugs, typically prostaglandin inhibitors such as NSAIDs, are tried. NSAIDs are usually started 24 to 48 h before and continued until 1 or 2 days after menses begins. If the NSAID is ineffective, suppression of ovulation with a low-dose estrogen/progestin oral contraceptive is advisable. Other hormonal treatments, such as danazol, progestins (eg, levonorgestrel, etonogestrel, depot medroxyprogesterone acetate), gonadotropin-releasing hormone agonists, or a progesterone IUD, may decrease dysmenorrheal symptoms.

Periodic adjunctive use of analgesics may be needed. Hypnosis is being evaluated as treatment. Other proposed nondrug therapies, including acupuncture, acupressure, chiropractic therapy, and transcutaneous electrical nerve stimulation, have not been well studied.

For intractable pain of unknown origin, presacral neurectomy and division of the sacrouterine ligaments to interrupt uterine nerves may help.

**Key Points**

- Most dysmenorrhea is primary.
- Underlying structural pelvic lesions need to be excluded.
- Usually, testing begins with ultrasonography.

**Polycystic Ovary Syndrome**

(Hyperandrogenic Chronic Anovulation; Stein-Leventhal Syndrome)
Polycystic ovary syndrome is a clinical syndrome characterized by mild obesity, irregular menses or amenorrhea, and signs of androgen excess (eg, hirsutism, acne). In most patients, the ovaries contain multiple cysts. Diagnosis is by pregnancy testing, hormone measurement, and imaging to exclude a virilizing tumor. Treatment is symptomatic.

Polycystic ovary syndrome occurs in 5 to 10% of women and involves anovulation or ovulatory dysfunction and androgen excess of unclear etiology. It is usually defined as a clinical syndrome, not by the presence of ovarian cysts. Ovaries may be enlarged with smooth, thickened capsules or may be normal in size. Typically, ovaries contain many 2- to 6-mm follicular cysts and sometimes larger cysts containing atretic cells. Estrogen levels are elevated, increasing risk of endometrial hyperplasia and, eventually, endometrial cancer. Androgen levels are often elevated, increasing risk of metabolic syndrome (see p. 64) and causing hirsutism. Over the long term, androgen excess increases risk of cardiovascular disorders, including hypertension.

Symptoms and Signs

Symptoms typically begin during puberty and worsen with time. The typical symptoms are mild obesity, hirsutism, and irregular menses or amenorrhea. Some women have other signs of virilization, such as acne and temporal balding. Areas of thickened, darkened skin (acanthosis nigricans) may appear in the axillae, on the nape of the neck, and in skinfolds; the cause is high insulin levels due to insulin resistance.

Diagnosis

• Clinical criteria

• Serum testosterone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone levels

• Pelvic ultrasonography

Ovulatory dysfunction is usually present at puberty, resulting in primary amenorrhea; thus, this syndrome is unlikely if regular menses occurred for a time after menarche. Examination usually detects abundant cervical mucus, reflecting high estrogen levels. The diagnosis is suspected if women have at least 2 typical symptoms.

Testing includes pregnancy testing, pelvic ultrasonography, and measurement of serum total testosterone, follicle-stimulating hormone (FSH), prolactin, and thyroid-stimulating hormone (TSH). Serum free testosterone level is more sensitive than total testosterone but is technically more difficult to measure (see p. 2342).

The diagnosis requires at least 2 of the following 3 criteria:

• Ovulatory dysfunction causing menstrual irregularity

• Clinical or biochemical evidence of hyperandrogenism

• More than 10 follicles per ovary (detected by pelvic ultrasonography), usually occurring in the periphery and resembling a string of pearls

In women meeting criteria, serum cortisol is measured to exclude Cushing's syndrome, and early-morning serum 17-hydroxyprogesterone is measured to exclude adrenal virilism. Serum dehydroepiandrosterone sulfate (DHEAS) is measured. If DHEAS is abnormal, women are evaluated as for amenorrhea (see p. 2504). Adult women with polycystic ovary syndrome are evaluated for metabolic syndrome by measuring BP and usually serum glucose.

Treatment

• Intermittent progestins or oral contraceptives
• Management of hirsutism and, in adult women, long-term effects of androgen excess

• Infertility treatments in women who desire pregnancy

To reduce the risk of endometrial hyperplasia and cancer in women who do not desire pregnancy, clinicians can use an intermittent progestin (eg, medroxyprogesterone 5 to 10 mg po once/day for 10 to 14 days q 1 to 2 mo) or oral contraceptives. These treatments also reduce circulating androgens.

For hirsutism (see p. 728), physical measures (eg, bleaching, electrolysis, plucking, waxing, depilation) can be used. Eflornithine cream 13.9% bid may help remove unwanted facial hair. In adult women who do not desire pregnancy, hormonal therapy that decreases androgen levels or spironolactone can be tried.

Weight loss is encouraged. It may help induce ovulation, increase insulin sensitivity, and reduce acanthosis nigricans and hirsutism.

Metformin 500 to 1000 mg bid is used to help increase insulin sensitivity if weight loss is unsuccessful or menses do not resume. Metformin can also reduce free testosterone levels. When metformin is used, serum glucose should be measured, and kidney and liver function tests should be done periodically. Because metformin may induce ovulation, contraception is needed if pregnancy is not desired.

For women who desire pregnancy, infertility treatments (eg, clomiphene, metformin) are used (see p. 2595). Weight loss may also be helpful. Hormonal therapy that may have contraceptive effects is avoided.

Premature Ovarian Failure

(Premature Menopause; Hypergonadotropic Hypogonadism)

In premature ovarian failure, ovaries do not produce enough estrogen despite high levels of circulating gonadotropins (especially follicle-stimulating hormone) in women < 40.

Etiology

Premature ovarian failure has various causes (see Table 246-4). Genetic disorders that confer a Y chromosome, which are usually evident by age 35, increase risk of ovarian cancer.

Symptoms and Signs

Typically, amenorrhea or irregular bleeding and symptoms or signs of estrogen deficiency (eg, osteoporosis, atrophic vaginitis, decreased libido) are present.

Diagnosis

• FSH and estradiol levels

• Sometimes karyotype analysis

Diagnosis is suspected in women < 40 with typical symptoms. A pregnancy test is done, and serum follicle-stimulating hormone (FSH) and estradiol levels are measured weekly for 2 to 4 wk; if FSH levels are high (> 20 mIU/mL, but usually > 30 mIU/mL) and estradiol levels are low (usually < 20 pg/mL), ovarian failure is confirmed. Then, further tests are done based on which cause is suspected. Karyotype is determined if women with confirmed ovarian failure are < 35.

Treatment

• Estrogen/progesterone therapy
Women who do not desire pregnancy are given estrogen/progesterone therapy (see p. 2519) until about age 51.

For women who desire pregnancy, in vitro fertilization of donated oocytes plus exogenous estrogen and a progestin, which enable the endometrium to support the transferred embryo (see p. 2597), can be tried. This technique is fairly successful, but even without this technique, 5 to 15% of women with diagnosed premature ovarian failure become pregnant.

Women with a Y chromosome require laparotomy or laparoscopy and excision of all gonadal tissue.

**Premenstrual Syndrome**

(Premenstrual Tension)

Premenstrual syndrome (PMS) is characterized by irritability, anxiety, emotional lability, depression, edema, breast pain, and headaches, occurring during the 7 to 10 days before and usually ending a few hours after onset of menses. Diagnosis is clinical, often based on the patient's daily recording of symptoms. Treatment is symptomatic and includes diet, drugs, and counseling.

**Etiology**

PMS appears to be caused by multiple endocrine factors (eg, hypoglycemia, other changes in carbohydrate metabolism, hyperprolactinemia, fluctuations in levels of circulating estrogen and progesterone, abnormal responses to estrogen and progesterone, excessive aldosterone or ADH). Estrogen and progesterone can cause transitory fluid retention, as can excess aldosterone or ADH.

**Symptoms and Signs**

Type and intensity of symptoms vary from woman to woman and from cycle to cycle. Symptoms last a few hours to ≥ 10 days, usually ending when menses begins. In perimenopausal women, symptoms may persist until after menses.

The most common symptoms are irritability, anxiety, agitation, anger, insomnia, difficulty concentrating, lethargy, depression, and severe fatigue. Fluid retention causes edema, transient weight gain, and breast fullness and pain. Pelvic heaviness or pressure and backache may occur. Some women, particularly younger ones, have dysmenorrhea when menses begins. Other nonspecific symptoms may include headache, vertigo, paresthesias of the extremities, syncope, palpitations, constipation, nausea, vomiting, and changes in appetite. Acne and neurodermatitis may also occur. Existing skin disorders may worsen, as may respiratory problems (eg, allergies, infection) and eye problems (eg, visual disturbances, conjunctivitis).

Premenstrual dysphoric disorder (PMDD): Some women have severe PMS symptoms that occur regularly and only during the 2nd half of the menstrual cycle; symptoms end with menses or shortly after. Mood is markedly depressed, and anxiety, irritability, and emotional lability are pronounced. Suicidal thoughts may be present. Interest in daily activities is greatly decreased. Symptoms are severe enough to interfere with routine daily activities or overall functioning.

**Diagnosis**

- For PMS, patient's reporting of symptoms
- For PMDD, clinical criteria

PMS is diagnosed based on physical symptoms (eg, bloating, weight gain, breast tenderness, swelling of...
hands and feet). Women may be asked to record their symptoms daily.

If PMDD is suspected, women are asked to rate their symptoms daily for ≥ 2 cycles to determine whether severe symptoms occur regularly. For PMDD to be diagnosed, women must have ≥ 5 of the following symptoms for most of the week before menses and at least one symptom must be from the first 4:

• Feelings of sadness, hopelessness, or self-depreciation
• A tense (on edge) feeling or anxiety
• Emotional lability with frequent tearfulness
• Irritability or anger that persists, leading to increased interpersonal conflicts
• Loss of interest in daily activities, possibly causing withdrawal
• Decreased concentration
• Fatigue, lethargy, or lack of energy
• Changes in eating habits, including bingeing
• Insomnia or hyperinsomnia
• Feelings of being overwhelmed or out of control
• Physical symptoms associated with PMS

Also, the symptom pattern must have occurred for most of the previous 12 mo, and symptoms must be severe enough to interfere with daily activities and function.

**Treatment**

• General measures

• Sometimes SSRIs or hormonal manipulation

Treatment is symptomatic, beginning with adequate rest and sleep and regular exercise. Regular exercise may help alleviate bloating as well as irritability, anxiety, and insomnia. Dietary changes—increasing protein, decreasing sugar, and taking vitamin B complex (especially pyridoxine, a form of vitamin B6) or Mg supplements—may help, as may counseling and avoiding stressful activities. Consuming foods high in Ca and vitamin D and, if needed, Ca and vitamin D supplements may help prevent PMS. Fluid retention may be relieved by reducing Na intake and taking a diuretic (eg, hydrochlorothiazide 25 to 50 mg po once/day in the morning) just before symptoms are expected. However, minimizing fluid retention does not relieve all symptoms and may have no effect.

SSRIs (eg, fluoxetine 20 mg po once/day) may be used to reduce anxiety, irritability, and other emotional symptoms, particularly if stress cannot be avoided. SSRIs are effective in relieving symptoms of PMDD.

For some women, hormonal manipulation is effective. Options include

• Oral contraceptives (eg, norethindrone 5 mg once/day)
• Progesterone by vaginal suppository (200 to 400 mg once/day)
• An oral progestin (eg, micronized progesterone 100 mg at bedtime) for 10 to 12 days before menses
• A long-acting progestin (eg, medroxyprogesterone 200 mg IM q 2 to 3 mo)
Rarely, for very severe or refractory symptoms, a gonadotropin-releasing hormone agonist (eg, leuprolide 3.75 mg IM, goserelin 3.6 mg sc q mo) with low-dose estrogen/progestin (eg, estradiol 0.5 mg once/day plus micronized progesterone 100 mg at bedtime) is given to minimize cyclic fluctuations.

Spironolactone, bromocriptine, and monoamine oxidase inhibitors are not useful.
Chapter 247. Menopause

Introduction

Menopause is physiologic or iatrogenic cessation of menses (amenorrhea) due to decreasing ovarian function. Manifestations may include hot flushes, atrophic vaginitis, and osteoporosis. Diagnosis is clinical: absence of menses for 1 yr. Manifestations may be treated (eg, with hormone therapy or SSRIs).

Physiologic menopause is established when menses have been absent for 1 yr. In the US, average age of physiologic menopause is 51. Perimenopause refers to the years before (duration varies greatly) and the 1 yr after the last menses. Perimenopause is usually characterized initially by an increase in frequency of menses, followed by a decrease (oligomenorrhea), but any pattern is possible; conception is possible during perimenopause. Climacteric refers to a longer phase in which women lose reproductive capacity; it begins before perimenopause.

As ovaries age, their response to the pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) decreases, initially causing a shorter follicular phase (with shorter and more irregular menstrual cycles), fewer ovulations, and thus decreased progesterone production (see Fig. 245-5 on p. 2500). Eventually, follicles do not respond, producing little estradiol. Some estrogens (mainly estrone) still circulate; they are produced by peripheral tissues (eg, fat, skin) from androgens (eg, androstenedione, testosterone). However, the total estrogen level is much lower. Around menopause, androstenedione levels decrease by half, but the decrease in testosterone levels, which begins gradually in young adulthood, does not accelerate during menopause because the stroma of the postmenopausal ovary and adrenal gland continue to secrete substantial amounts. Decreased levels of ovarian inhibin and estrogen, which inhibit pituitary release of LH and FSH, result in a substantial increase in circulating LH and FSH levels.

Premature menopause (premature ovarian failure—see p. 2516) is cessation of menses due to noniatrogenic ovarian failure before age 40. Contributory factors may include smoking, living at high altitude, and undernutrition. Iatrogenic (artificial) menopause results from medical interventions (eg, oophorectomy, chemotherapy, pelvic irradiation, any intervention that impairs ovarian blood supply).

Symptoms and Signs

Perimenopausal changes in menstruation usually begin during a woman's 40s. Menstrual flow and cycle length can vary. Menses become irregular, then are skipped.

Large daily fluctuations in estrogen levels usually begin at least 1 yr before menopause and are thought to cause perimenopausal symptoms. Symptoms can last from 6 mo to over 10 yr and range from nonexistent to severe.

Vasomotor: Hot flushes (flashes) and sweating due to vasomotor instability affect 75 to 85% of women and usually begin before menses stop. Hot flushes continue for > 1 yr in most women and for > 5 yr in 50%. Women feel warm or hot and may perspire, sometimes profusely; core temperature increases. The skin, especially of the head and neck, may become red and warm. The episodic flush, which may last from 30 sec to 5 min, may be followed by chills. Flushes may manifest during the night as night sweats. The mechanism of hot flushes is unknown, but they may be triggered by cigarette smoking, hot beverages, foods containing nitrates or sulfites, spicy food, alcohol, and possibly caffeine.

Neuropsychiatric: Neuropsychiatric changes (eg, poor concentration, memory loss, depression, anxiety) may accompany menopause but are not directly related to decreased estrogen. Recurrent night sweats, which can disrupt sleep, can contribute to insomnia, fatigue, irritability, and poor concentration.

Genital: Decreased estrogen leads to vaginal and vulvar dryness and thinning, which may result in inflammation of the vaginal mucosa (atrophic vaginitis). Atrophy may cause irritation, dyspareunia, and dysuria and may increase vaginal pH. The labia minora, clitoris, uterus, and ovaries decrease in size.
Other: Although menopause is normal, health problems can occur, and for some, quality of life may decrease. Risk of osteoporosis increases because estrogen is decreased, increasing bone resorption by osteoclasts (see p. 356). The most rapid loss occurs during the first 2 yr after estrogen begins to decrease.

**Diagnosis**

- Clinical evaluation
- FSH levels rarely needed

Diagnosis is clinical. Menopause is likely if menses have gradually decreased in frequency and have been absent for 6 mo. Women with amenorrhea are examined to exclude pregnancy if they are < 50 and are always examined to exclude ovarian tumors (for evaluation of amenorrhea, see p. 2504). Abnormal pelvic masses are evaluated (see p. 2485). If women in their 50s have a history of irregular menses followed by cessation of menses, with or without symptoms of estrogen deficiency, and no other abnormal findings, no diagnostic testing is necessary.

FSH levels may be measured, but this test is rarely necessary. Consistently elevated levels predict menopause, sometimes many months to a year in advance.

Postmenopausal women who have risk factors for osteoporosis and all women > 65 should be screened for osteoporosis (see p. 357).

**Treatment**

- Avoidance of triggers and stress
- Exercise and relaxation techniques
- Possibly SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Possibly hormone therapy

Discussing the physiologic causes of menopause and possible symptoms and signs with patients helps them manage the changes that occur. Treatment is symptomatic.

For hot flushes, avoiding triggers and wearing clothing in layers that can be removed as needed may help. Soy protein has been used, but its efficacy has not been confirmed. Black cohosh, other medicinal herbs, vitamin E, and acupuncture do not appear helpful. Regular exercise, stress avoidance, and relaxation techniques may improve sleep and reduce irritability; relaxation techniques can also reduce vasomotor symptoms. Paced respiration, a type of slow, deep breathing, may also help relieve hot flushes.

Nonhormonal drug treatments for hot flushes include SSRIs (eg, fluoxetine, sustained-release paroxetine, sertraline), SNRIs (eg, venlafaxine), and clonidine 0.1 mg transdermally once/day. Dose requirements for SSRIs and SNRIs vary; starting doses can be lower than those used to treat depression and increased as needed. It is not clear whether gabapentin is helpful.

OTC vaginal lubricants and moisturizers help relieve vaginal dryness. Measures to prevent and treat osteoporosis are considered (see p. 358).

**Hormone therapy:** For many women, risks of oral hormone therapy outweigh the benefits.

Hormone therapy may be used to relieve moderate to severe menopausal symptoms. For women who have had a hysterectomy, estrogen should be used alone. Forms may be oral, transdermal (a patch, lotions, or gels), or a tablet inserted vaginally. Women who have a uterus, if given estrogen in any form or
type, are also given a progestin (as combination therapy) because unopposed estrogen increases risk of endometrial cancer (and possibly ovarian cancer if unopposed estrogen is taken > 10 yr). Oral hormone therapy also has other risks (see Table 247-1). For most women, these risks outweigh benefits. For other forms of hormone therapy, risks and other effects are not as well known. The risk of venous thromboembolism may be lower with transdermal estrogen.

Benefits of oral combination therapy include reduction in yearly incidence of osteoporosis and colorectal cancer, as well as relief of menopausal symptoms. For asymptomatic women, overall effects of therapy on quality of life are not very meaningful.

Risks of oral combination therapy are reflected in an increased yearly incidence of breast cancer, ischemic stroke, deep venous thromboembolism, pulmonary embolism, dementia, and coronary artery disease. Risk of coronary

[Table 247-1. Effects of Oral Hormone Therapy on Yearly Incidence* of Selected Disorders in Postmenopausal Women]

artery disease almost doubles during the first year of therapy and is particularly high for women with high pretreatment low-density lipoprotein levels; aspirin and statins do not prevent the increase in risk. Also, the breast cancers that develop are larger and more likely to be metastatic, and false-positive mammograms are more common. Urinary incontinence, particularly stress incontinence, develops more often, and existing incontinence tends to worsen.

Oral estrogen-only therapy does not affect incidence of coronary artery disease but increases incidence of ischemic stroke and deep venous thromboembolism. It decreases incidence of hip fractures. Effects on breast cancer, colorectal cancer, and pulmonary embolism are less clear. Estrogen-only therapy, like combination therapy, contributes to urinary incontinence. Dementia risk is probably increased with estrogen-only therapy.

Despite its beneficial effects on bone, hormone therapy (with or without a progestin) is not recommended for prevention and treatment of osteoporosis because other effective measures (eg, raloxifene, bisphosphonates), which usually have fewer risks, are available.

Oral estrogen therapy can be used to relieve hot flushes, night sweats (with consequent sleep disturbance), and vaginal dryness. For vaginal dryness or atrophy, topical forms of estrogen (eg, creams, vaginal tablets or rings) are as effective as oral forms. Vaginal tablets and rings that contain low doses (eg, 25 μg) deliver less estrogen to the systemic circulation; vaginal estrogen creams usually deliver as much as oral therapy.

Progestins (eg, megestrol acetate 10 to 20 mg po once/day, medroxyprogesterone acetate 10 mg po once/day or depot 150 mg IM once/mo) can be used alone to relieve hot flushes, but they do not relieve vaginal dryness. Progestins may have adverse effects (eg, abdominal bloating, breast tenderness, increased breast density, headache, increased low-density lipoprotein, decreased high-density lipoprotein); micronized progesterone appears to have fewer adverse effects but may increase the risk of venous thromboembolism. There are no long-term safety data about use of progestins.

When prescribing solely for the prevention of postmenopausal osteoporosis, clinicians should consider hormone therapy only for women at significant risk of osteoporosis and for whom nonestrogen drugs are considered inappropriate.
Chapter 248. Sexual Dysfunction in Women

Introduction

Most people—men and women—engage in sexual activity because of attraction or a desire for pleasure, affection, love, romance or intimacy. However, women are more likely to report emotional motivations. Many women initiate or agree to sexual activity because they want one or more of the following:

- To experience emotional intimacy
- To increase their sense of well-being
- To confirm their desirability
- To please or placate a partner

Especially in established relationships, women often have little or no initial sense of sexual desire but access sexual desire (responsive desire) once sexual stimulation triggers excitement and pleasure (subjective arousal) and genital congestion (physical genital arousal). Desire for sexual satisfaction, which may or may not include one or multiple orgasms, builds as sexual activity and intimacy continue, and a physically and emotionally rewarding experience fulfills and reinforces the woman's original motivations.

A woman's sexual response cycle is strongly influenced by her mental health and by the quality of her relationship with her partner. Initial desire typically lessens with age but increases with a new partner at any age.

Physiology

Sexual response consists of the following:

- Arousal
- Genital congestion
- Orgasm

Physiology of the female sexual response is incompletely understood but involves hormonal and CNS factors.

Estrogens and androgens both appear to influence arousal. Androgens probably act via androgen receptors and estrogen receptors (after intracellular conversion of testosterone to estradiol).

After menopause, ovarian estrogen production ceases, while ovarian androgen production varies. However, adrenal production of prohormones (eg, DHEAS) that are converted to both androgens and estrogens in peripheral cells decreases starting in a woman's 30s. Ovarian production of prohormones also declines after menopause. Whether this decrease plays any role in diminishing sexual desire, interest, or arousal is unclear.

The brain produces sex hormones (neurosteroids) from cholesterol, and production may increase after menopause. Whether this documented increase is universal, whether it facilitates arousal as peripheral production decreases, and whether it is affected by exogenous hormone administration are all unknown.

Arousal: Brain areas involved in cognition, emotion, motivation, and organization of genital congestion are activated. Neurotransmitters acting on specific receptors are involved. Based on known actions of drugs and on animal studies, some neurotransmitters appear to be prosexual; they include dopamine, norepinephrine, and melanocortin. Serotonin is usually sexually inhibitory, as are prolactin and γ-aminobutyric acid (GABA).
**Genital congestion:** This reflexive autonomic response occurs within seconds of an erotic stimulus and causes genital engorgement and lubrication. Smooth muscle cells around blood spaces in the vulva, clitoris, and vaginal arterioles dilate, increasing blood flow (engorgement) and transudation of interstitial fluid across the vaginal epithelium (lubrication). Women are not always aware of congestion, and it may occur without subjective arousal. As women age, basal genital blood flow decreases, but genital congestion in response to erotic stimuli (eg, erotic videos) may not.

**Orgasm:** Peak excitement occurs, characterized by contractions of pelvic muscles every 0.8 sec, and is followed by slow release of genital congestion. Thoracolumbar sympathetic outflow tracts appear to be involved, but orgasm is possible even after complete spinal cord transection (eg, when a vibrator is used to stimulate the cervix). Prolactin, ADH, and oxytocin are released at orgasm and may contribute to the sense of well-being, relaxation, or fatigue that follows. However, many women experience a sense of well-being and relaxation without experiencing orgasm.

**Classification**

Female sexual dysfunction may involve decreased or increased sexual responsiveness. Classification is determined by symptoms. There are 5 major categories of decreased responsiveness and one of increased responsiveness (persistent genital arousal disorder).

**Sexual desire/interest disorder** is absence of or a decrease in sexual interest, desire, sexual thoughts, and fantasies and an absence of responsive desire.

**Sexual arousal disorder** is lack of subjective or genital arousal or both.

**Orgasmic disorder** involves orgasm that is absent, markedly diminished in intensity, or markedly delayed in response to stimulation despite high levels of subjective arousal.

**Vaginismus** is reflexive tightening around the vagina when vaginal entry is attempted or completed despite women's expressed desire for penetration and when no structural or other physical abnormalities are present.

**Dyspareunia** is pain during attempted or completed vaginal penetration or intercourse. Provoked vestibulodynia (PVD, formerly called vulvar vestibulitis), the most common type of superficial (introital) dyspareunia, is a chronic pain syndrome associated with altered immune function and sensitization of the nervous system.

**Persistent genital arousal disorder** involves excessive genital arousal.

A disorder is diagnosed when symptoms cause distress. Some women may not be distressed or bothered by decreased or absent sexual desire, interest, arousal, or orgasm.

Almost all women with sexual dysfunction have features of more than one disorder. For example, the chronic dyspareunia of PVD often leads to sexual desire/interest and arousal disorders; impaired arousal may make sex less enjoyable or even painful, decreasing the likelihood of orgasm and subsequent sexual desire. However, dyspareunia due to impaired lubrication may occur as an isolated symptom in women with a high level of sexual desire, interest, and subjective arousal.

Female sexual disorders may be secondarily categorized as lifelong or acquired; situation-specific or generalized; and mild, moderate, or severe based on the degree of distress it causes the woman.

Although research is limited, these disorders probably apply equally to women in heterosexual and homosexual relationships.

**Etiology**

The traditional separation of psychologic and physical etiologies is artificial; psychologic distress causes
changes in hormonal and neurologic physiology, and physical changes may generate psychologic reactions that compound the dysfunction. There are often several causes of symptoms within and between categories of dysfunction, and the cause is often unclear.

**Primarily psychologic factors:** Mood disorders are closely correlated with low desire and arousal. In up to 80% of women with major depression and sexual dysfunction, sexual dysfunction becomes less severe when anti-depressants effectively treat the depression. However, sexual dysfunction persists or worsens when antidepressants are ineffective. Women with an anxiety disorder are also more likely to have sexual dysfunction involving desire, arousal, and orgasm. Various fears—of letting go, of being vulnerable, of being rejected, or of losing control—and low self-esteem can contribute.

Previous experiences can affect a woman’s psychosexual development, as in the following:

- Past negative sexual or other experiences may lead to low self-esteem, shame, or guilt.
- Emotional, physical, or sexual abuse during childhood or adolescence can teach children to control and hide emotions—a useful defense mechanism—but such inhibition can make expressing sexual feelings difficult later.
- Early traumatic loss of a parent or another loved one may inhibit intimacy with a sex partner for fear of similar loss.

Concerns about a negative outcome (eg, unwanted pregnancy, sexually transmitted diseases [STDs], inability to have an orgasm, sexual dysfunction in a partner) can also impair sexual response.

Contextual causes (those specific to a woman’s current circumstances) include the following:

- **Relationship context:** Lack of trust, negative feelings, or reduced attraction toward a sex partner (eg, due to the partner’s behavior or to a growing awareness of a change in the partner’s sexual orientation)
- **Sexual context:** For example, surroundings that are not sufficiently erotic, private, or safe
- **Cultural context:** For example, cultural restrictions on sexual activity

Distractions (eg, from family, work, or finances) can interfere with arousal.

**Primarily physical factors:** Various genital lesions, systemic and hormonal factors, and drugs may lead or contribute to dysfunction (see Table 248-1).

SSRIs are a particularly common drug cause. Systemic estrogen therapy (postmenopausal or in hormonal contraceptives) has mixed effects. It can improve mood and help maintain skin and genital sexual sensitivity and vaginal lubrication. However, it also increases sex hormone-binding globulin (SHBG), decreasing the amount of free androgens available for tissue receptor binding. Decreasing free androgens can counteract the other sexual benefits of systemic estrogens, contributing to sexual dysfunction. Alcohol dependence can cause sexual dysfunction.

**Diagnosis**

- Interview with both partners, separately and together
- Gentle pelvic examination, primarily to identify causes of dyspareunia

Diagnosis of sexual dysfunction and its causes is based on history and physical examination. Ideally, history is taken from both partners, interviewed separately and together; it begins by asking the woman to
describe the problem in her own words and should include specific elements (see Table 248-2). Problematic areas (eg, past negative sexual experiences, negative sexual self-image) identified at the first visit can be investigated more fully at a follow-up visit.

Physical examination is most important for determining causes of dyspareunia; the technique may differ slightly from that used in a routine gynecologic examination. Explaining what will occur during the examination helps the woman relax and should be continued throughout the examination. The woman should be asked whether she wants to sit up and view her genitals in a mirror during the examination; doing so may impart a sense of control.

Wet-preparation examination of vaginal discharge and Gram stain with culture or DNA probe to detect Neisseria gonorrhoeae and chlamydiae are indicated when history or examination suggests vulvitis, vaginitis, or pelvic inflammatory disease.

Although low estrogen and testosterone activity may contribute to sexual dysfunction, measuring levels is rarely indicated. Low estrogen and testosterone are detected clinically. If hyperprolactinemia is clinically suspected, the prolactin level is measured. If hypothyroidism is clinically suspected, the TSH level is measured and sometimes other thyroid function tests are done.

**Treatment**

- Explanation of the female sexual response to the couple
- Treatment of the cause
- Substitution of other antidepressants for SSRIs or addition of bupropion

Treatment varies by disorder and cause; often, more than one treatment is required because disorders overlap. Sympathetic understanding of the patient and careful evaluation may themselves be therapeutic. Mood disorders are treated. Explaining what is involved in the female sexual response may also help.

Because SSRIs may contribute to several categories of sexual dysfunction, switching to an antidepressant that has fewer sexual adverse effects (eg, bupropion, moclobemide, mirtazapine, venlafaxine) may be considered. Alternatively, some evidence suggests that adding bupropion to an SSRI may help.

**Sexual Desire/Interest Disorder**

Sexual desire/interest disorder is absence of or a decrease in sexual interest, desire, sexual thoughts, and fantasies and absence of responsive desire.

[Table 248-2, Components of the Sexual History for Assessment of Female Sexual Dysfunction]

In sexual desire/interest disorder, motivations to become sexually aroused are scarce or absent. The decrease is greater than what might be expected based on a woman's age and the relationship duration.

Causes often involve primarily psychologic factors (eg, depression, anxiety, stress, relationship problems). Use of certain drugs (particularly SSRIs), anticonvulsants, chemotherapy drugs, β-blockers, and oral contraceptives, can reduce sexual desire, as can drinking excessive amounts of alcohol. Fluctuations in hormone levels (eg, at menopause, during pregnancy, with the menstrual cycle) can affect sexual desire.

Women with sexual desire/interest disorder tend to be anxious, to have a low self-image, and to have mood lability even if they do not have a clinical mood disorder.

Diagnosis is clinical (see p. 2523).

**Treatment**
If factors that limit trust, respect, attraction, and emotional intimacy between partners are the cause, the couple should be counseled that emotional intimacy is a normal requirement for female sexual response and needs to be enhanced with or without professional help. Education about sufficient and appropriate stimuli may help; women may need to remind their partner of their need for nonphysical, physical nongenital, and nonpenetrative genital stimulation. Recommendations for more intensely erotic stimuli and fantasies may help eliminate distractions; practical suggestions to improve privacy and a sense of security can help when fear of unwanted outcomes (eg, discovery, pregnancy, sexually transmitted diseases) inhibits arousability.

For patient-specific psychologic factors, psychologic therapies (eg, cognitive-behavioral therapy) may be required, although simple awareness of the importance of these factors may be sufficient for women to change patterns of thinking and behavior.

Hormonal causes require targeted treatment—eg, topical estrogen for atrophic vaginitis and bromocriptine for hyperprolactinemia.

**Systemic estrogen therapy:** Systemic estrogen therapy (see p. 2519) initiated at menopause or within the next few years may improve mood and help maintain skin and genital sexual sensitivity and vaginal lubrication. These benefits may enhance sexual desire and arousal despite decreasing free androgen levels. Transdermal preparations of estrogen are usually preferred after menopause, but no studies identify which preparations available in the US are the most beneficial sexually. Progestins or progesterone are also given to women who have not had a hysterectomy. If oral contraceptives or estrogen therapy appears to contribute to sexual desire/interest disorder, substituting another drug (eg, transdermal estrogen or barrier methods for oral contraceptives) may be indicated to increase free androgens.

**Testosterone therapy:** Benefits and risks of testosterone supplementation are under study. When no interpersonal, contextual, and intrapersonal factors are evident, some experienced clinicians consider supplementation (eg, with methyltestosterone 1.5 mg po once/day or transdermal testosterone 300 μg daily); preparations formulated for men are used.

Benefit has been shown mostly in women who are taking estrogen and who have had bilateral oophorectomy, but benefit is expected in some women who are taking estrogen and who have premature ovarian failure due to other conditions (eg, adrenal or pituitary dysfunction, chemotherapy, idiopathic). Benefit has been modest, but studies included only relatively sexually healthy women (with 2 to 3 sexually satisfying experiences/mo at baseline). Among postmenopausal women who are taking estrogen therapy and who can no longer be aroused by previously effective stimuli and contexts, benefit is conceivable; however, this group has not been studied.

However, testosterone therapy is not approved for women in the US. Also, the American Endocrine Society currently recommends against its use. Too little is known about long-term safety; in most studies, safety as well as efficacy data are limited to 6 mo. If testosterone is prescribed, full explanation of lack of long-term safety data and careful follow-up are essential. Periodically, the free testosterone level should be calculated or the bioavailable testosterone level should be measured (see p. 2342), and women should be checked for signs of hirsutism and for hyperlipidemia and impaired glucose tolerance.

**Sexual Arousal Disorders**

**Sexual arousal disorders involve a lack of response to one or more types of sexual stimulation—subjective, physical genital, or both.**

Sexual arousal disorders can be categorized as subjective, genital, or combined. All definitions are
clinically based, distinguished in part by the woman's response to genital and nongenital stimulation, as follows:

- **Subjective**: Women do not feel aroused by any type of sexual genital or nongenital stimulation (eg, kissing, dancing, watching an erotic video, physical stimulation), despite the occurrence of physical genital response (eg, genital congestion).

- **Genital**: Subjective arousal occurs in response to nongenital stimulation (eg, an erotic video) but not in response to genital stimulation. This disorder typically affects postmenopausal women and is often described as genital deadness. Testing confirms reduced genital congestion in response to sexual stimulation in some women; in others, genital congestion is normal, but genital sexual sensitivity seems reduced.

- **Combined**: Subjective arousal in response to any type of sexual stimulation is absent or low, and women report absence of physical genital arousal (ie, they report need of external lubricants and may state they know that swelling of the clitoris no longer occurs).

**Etiology**

Causes may involve psychologic (eg, depression, low self-esteem, anxiety, stress) or physical factors or both (see p. 2522). Inadequate sexual stimulation or the wrong setting for sexual activity can also contribute.

Genital arousal disorder may result from a low level of estrogen or possibly testosterone, as occurs during or after menopause, or from vulval dystrophy (eg, lichen sclerosus). Certain chronic disorders (eg, diabetes, multiple sclerosis) can damage autonomic or somatic nerves, leading to decreased congestion or sensation in the genital area.

**Diagnosis**

Diagnosis is clinical (see p. 2523).

**Treatment**

**Subjective arousal disorder**: See Sexual Desire/Interest Disorder on p. 2523.

**Genital arousal disorder**: When estrogen is deficient, initial treatment is local estrogen (or systemic estrogen if indicated for other postmenopausal symptoms). A phosphodiesterase inhibitor may be tried empirically if symptoms are refractory to estrogen therapy; it benefits only women with reduced genital congestion (eg, due to autonomic nerve damage). Other investigational therapy includes a trial of 0.2 mL topical 2% testosterone prepared by a pharmacist and applied twice weekly to the clitoris.

**Orgasmic Disorder**

Orgasmic disorder involves orgasm that is absent, markedly diminished in intensity, or markedly delayed in response to stimulation despite high levels of subjective arousal.

Women with orgasmic disorder often have difficulty relinquishing control in nonsexual circumstances.

Contextual factors (eg, consistently insufficient foreplay, poor communication about sexual preferences), psychologic factors (eg, anxiety, stress, lack of trust in a partner, fears), physical disorders, and drugs can contribute to orgasmic disorder (see p. 2522). Lack of knowledge about sexual function may also contribute.

Damage to genital sensory or autonomic nerves (eg, due to diabetes or multiple sclerosis) or, much more commonly, use of SSRIs may lead to acquired orgasmic disorder.

**Treatment**
• Self-stimulation

• Psychologic therapies

Data support encouraging self-stimulation. A vibrator placed on the mons pubis close to the clitoris may help, as may increasing the number and intensity of stimuli (mental, visual, tactile, auditory, written), simultaneously if necessary. Education about sexual function (eg, need to stimulate the clitoris) may help.

Psychologic therapies including cognitive-behavioral therapy and psychotherapy may help women identify and manage fear of relinquishing control, fear of vulnerability, or issues of trust with a partner.

In women taking an SSRI, symptoms may decrease when bupropion is added. One study supports the use of sildenafil.

**Vaginismus**

Vaginismus is reflexive tightening around the vagina when vaginal entry is attempted or completed (eg, using a penis, finger, or dildo) despite women's expressed desire for penetration and despite the absence of any structural or other physical abnormalities.

Vaginismus usually results from fear that intercourse will be painful; it usually begins with the first attempt at sexual intercourse. It may develop later after periods of stress. Women may develop a phobia-like avoidance of penetration. Most women with vaginismus thus cannot tolerate full or often even partial penetration. Some cannot tolerate insertion of a tampon or have never wanted to try. However, most women with vaginismus enjoy nonpenetrative sexual activity.

Reflex muscle tightening can also accompany dyspareunia of any cause, thereby adding to the pain and difficulty with entry. Women anticipate a recurrence of pain when intercourse is initiated, and muscles tighten, making attempts at sexual intercourse even more painful.

**Diagnosis**

• Clinical evaluation

Diagnosis is suspected based on symptoms. Physical abnormalities that cause pain, such as those that cause dyspareunia should be excluded by physical examination. However, the condition itself makes examination difficult. One strategy is to initiate treatment as described below and defer the confirmatory examination. When the examination is done, the physician can give the patient a sense of control by having her sit up and view her genitals using a mirror. The woman then spreads her labia and inserts her or the examiner's gloved finger past the hymen as she bears down. This simple digital examination can simultaneously confirm a normal vagina and the presumed diagnosis of vaginismus.

**Treatment**

• Progressive desensitization

Women progressively accustom themselves to self-touch near, on, and then through the introitus.

• The woman first touches herself daily as close to the introitus as possible, separating the labia with her fingers.

• Once her fear and anxiety due to introital self-touch has diminished, the woman will be more able to tolerate the physical examination.

• The next stage is to insert her finger past her hymen; pushing or bearing down during insertion enlarges the opening and eases entry.
• Once finger insertion causes no discomfort, vaginal cones in gradually increasing sizes are inserted progressively; leaving a cone inside for 10 to 15 min helps perivaginal muscles become accustomed to gently increasing pressure without reflex contraction. The woman first inserts a cone herself; when comfortable with the cone, she then allows her partner to help her insert one during a sexual encounter to confirm that it can go in comfortably when she is sexually excited.

• Once insertion in this context is comfortable, the couple should include penile vulvar stimulation during sexual play so that the woman becomes accustomed to feeling the penis on her vulva.

• Ultimately, the woman inserts her partner's penis partially or fully, holding it like an insert. She may feel more confident in the woman superior position.

Some men experience situational erectile dysfunction in this process and may benefit from a phosphodiesterase inhibitor.

Dyspareunia

Dyspareunia is pain during attempted or completed vaginal penetration.

Dyspareunia may occur at the moment of penetration (superficial or introital), with deeper entry, with penile movement, or post-coitally. Some pelvic muscle hypertonicity, manifested as both voluntary guarding and involuntary high muscle tension, is common in all types of chronic dyspareunia.

Etiology

Causes may involve psychologic and physical factors (see p. 2522).

Superficial dyspareunia may result from provoked vestibulodynia (PVD), atrophic vaginitis, vulvar disorders (eg, lichen sclerosus, vulvar dystrophies), congenital malformations, genital herpes simplex, radiation fibrosis, postsurgical introital narrowing, or recurrent tearing of the posterior fourchette.

Deep dyspareunia may result from pelvic muscle hypertonicity or uterine or ovarian disorders (eg, fibroids, chronic pelvic inflammatory disease, endometriosis).

Penile size and depth of penetration influence presence and severity of symptoms.

A subgroup of women with dyspareunia due to PVD (see p. 2528) have high self-expectations and fear of negative evaluation by other people, increased somatization, catastrophizing (gross exaggeration of possible consequences), and hypervigilance to pain.

Diagnosis

• Clinical evaluation

Diagnosis is based on symptoms and a pelvic examination.

For superficial dyspareunia, evaluation focuses on inspecting all the vulvar skin, including the creases between the labia minora and majora (eg, for fissures typical of chronic candidiasis), and the clitoral hood, urethral meatus, hymen, and openings of major vestibular gland ducts (for atrophy, signs of inflammation, and skin lesions typical of lichen sclerosus). PVD can be diagnosed using a cotton swab to elicit allodynia; nonpainful external areas are touched before moving to more typically painful areas (ie, outer edge of the hymenal ring, clefts adjacent to the urethral meatus). Pelvic muscle hypertonicity may be suspected if pain similar to the pain that occurs during intercourse can be elicited by palpating the deep levator ani muscles, particularly around the ischial spines. Palpating the urethra and bladder may identify abnormal tenderness.

For deep dyspareunia, evaluation requires a careful bimanual examination to determine whether cervical motion or uterine or adnexal palpation causes pain and to check for nodules in the cul-de-sac or vaginal
fornices. A rectovaginal examination is usually indicated to check the rectovaginal septum and posterior surface of the uterus and adnexa. Suspected uterine and ovarian disorders are evaluated with imaging studies as clinically indicated.

**Treatment**

- Treatment of cause (eg, topical estrogen for atrophic vaginitis)
- Education and counseling
- Pelvic muscle physiotherapy

Management should include the following:

- Encouraging and teaching the couple to develop satisfying forms of nonpenetrative sex
- Discussing psychologic issues contributing to and caused by the chronic pain
- When possible, treating the primarily physical abnormality that contributes to pain (eg, endometriosis, lichen sclerosus, vulvar dystrophies, vaginal infections, congenital malformations, radiation fibrosis —see elsewhere in THE MANUAL). PVD is also treated (see below).
- Treating coexisting pelvic muscle hypertonicity
- Treating comorbid sexual desire/interest or arousal disorders

Topical estrogen is helpful for atrophic vaginitis (see p. 2545) and recurrent posterior fourchette tearing.

Women with pelvic muscle hypertonicity, including some with PVD, may benefit from pelvic physical therapy using pelvic floor muscle training, possibly with biofeedback, to teach pelvic muscle relaxation. Sometimes a change in sexual position helps.

**Provoked Vestibulodynia**

Provoked vestibulodynia (vulvar vestibulitis, localized vulvar dysesthesia) is the most common type of superficial (introital) dyspareunia. Pain starts and stops precisely with introital pressure. Treatment may include measures used in chronic pain syndromes as well as topical lidocaine or cromoglycate, but efficacy of the latter is unproved.

Provoked vestibulodynia develops when the nervous system—from peripheral receptors to the cerebral cortex—is sensitized and remodeled. With sensitization, discomfort due to a stimulus that might otherwise be perceived as mild or trivial (eg, touch) is instead perceived as significant pain (allodynia). This disorder is probably a form of chronic pain syndrome (see p. 1629) of the vulva. The peripheral sensitization leads to a neurogenic inflammatory response. Some women also have GU disorders (eg, vulvovaginal candidiasis, hyperoxaluria), but the etiologic role of these disorders is unproved. Some women also have other pain disorders (eg, irritable bowel syndrome—see p. 162; interstitial cystitis—see p. 2364).

**Symptoms and Signs**

In vestibulodynia, introital pressure, penile movement, or a man's ejaculation typically causes immediate pain. Pain typically stops when penile movement stops and resumes when it starts again. Vestibulodynia may also cause postcoital vulvar burning and dysuria.

**Diagnosis**

- Clinical evaluation

Diagnosis is based on symptoms and confirmed by the Q-tip test for alldynia. Vaginismus causes similar
pain with introital pressure and penile containment and movement. However, unlike vestibulodynia, there is no allodynia. Also, pain due to vaginismus continues after penile movement stops but may progressively fade during intercourse despite continued penile movement.

**Treatment**

• Psychologic therapies used in chronic pain management

• Sometimes sex therapy

• Pelvic muscle physiotherapy

• Drugs to treat chronic pain

• Possibly topical lidocaine or cromoglycate

Optimal treatment of provoked vestibulodynia is unclear; many approaches are currently used, and there are probably still undefined subtypes that require different treatment. Because this disorder involves chronic pain, treatments are becoming more comprehensive, including management of stress and emotional reactions to pain.

Commonly used but unproven approaches involve avoiding topical irritants and using systemic drugs (eg, tricyclic antidepressants, anticonvulsants) or topical drugs (eg, 2% cromoglycate or 2 or 5% lidocaine in glaxal base) to interrupt chronic pain circuits. Cromoglycate stabilizes WBC membranes, including those of mast cells, interrupting the neurogenic inflammation thought to underlie vestibulodynia. Cromoglycate or lidocaine must be placed precisely on the area of allodynia using a 1-mL syringe without a needle. Physician supervision and use of a mirror (at least initially) are helpful. Psychologic therapies, including cognitive-behavioral therapy and sex therapy, may also help some women with vestibulodynia. Women with pelvic muscle hypertonicity may benefit from pelvic physical therapy using pelvic floor muscle training, possibly with biofeedback. Surgery (eg, excision of the hymen, proximal edge of the lower vagina, and innermost portion of the labia minora) is sometimes indicated to remove proliferated nerve endings. However, pain may recur as nerves regenerate. Investigational treatment includes botulinum toxin type A injection.

**Persistent Genital Arousal Disorder**

**Persistent genital arousal disorder is excessive unwanted unprovoked genital arousal.**

Cause is unknown. Anxiety and hypervigilance for recurrence of pain episodes may perpetuate the syndrome. Symptoms have been thought to sometimes be manifestations of seizure disorders, but in published series, brain imaging and EEG have not found abnormalities.

Unwanted, intrusive, spontaneous genital arousal (eg, tingling, throbbing) occurs, but sexual interest or desire is absent; arousal is unrelieved by orgasms. The feelings persist for hours or days. Older women may be very embarrassed by the symptoms.

**Treatment**

Treatment is unclear. Self-stimulation may provide relief but usually only temporarily. High-dose SSRI therapy has been reported effective, but data are few. Simple recognition of the existence of this disorder, with reassurance that it can spontaneously remit, may help some patients.
Chapter 249. Pelvic Relaxation Syndromes

Introduction

Pelvic relaxation syndromes result from laxities (similar to hernias) in the ligaments, fascia, and muscles supporting the pelvic organs (pelvic floor—see Fig. 249-1). About 9% of women require surgical repair for a pelvic relaxation syndrome. Common contributing factors include childbirth (particularly vaginal delivery), obesity, aging, injury (eg, due to pelvic surgery), and chronic straining. Less common factors include congenital malformations, increased abdominal pressure (eg, due to ascites, abdominal tumors, or chronic respiratory disorders), sacral nerve disorders, and connective tissue disorders. Pelvic relaxation syndromes involve various sites of prolapse and include cystocele, urethrocele, enterocele, rectocele, and uterine and vaginal prolapse. Usually, prolapse occurs in multiple sites.

Cystoceles, Urethroceles, Enteroceles, and Rectoceles

These disorders involve protrusion of an organ into the vaginal canal: cystoceles (bladder), urethroceles (urethra), enteroceles (small intestine and peritoneum), and rectoceles (rectum). Symptoms include pelvic or vaginal fullness or pressure. Diagnosis is clinical. Treatment includes pessaries, pelvic muscle exercises, and surgery.

Cystocele, urethrocele, enterocele, and rectocele are particularly likely to occur together. Urethrocele is virtually always accompanied by cystocele (cystourethrocele). Cystocele and cystourethrocele commonly develop when the pubocervical vesical fascia is weakened. Enterocele usually occurs after a hysterectomy. Weakness in the pubocervical fascia and rectovaginal fascia allows the apex of the vagina, which contains the peritoneum and small bowel, to descend. Rectocele results from disruption of the levator ani muscles.

Severity of these disorders can be graded based on level of protrusion:

- 1st degree: To the upper vagina
- 2nd degree: To the introitus
- 3rd degree: External to the introitus

Symptoms and Signs

Pelvic or vaginal fullness, pressure, and a sensation of organs falling out are common. Organs may bulge into the vaginal canal or introitus, particularly during straining or coughing. Dyspareunia can occur. Stress incontinence often accompanies cystocele or cystourethrocele. Overflow incontinence or, particularly when sacral nerves are damaged, urge incontinence may also develop. Enteroceles may cause lower back pain. Rectoceles may cause constipation and incomplete defecation; patients may have to manually press the posterior vaginal wall to defecate.

Diagnosis

- Examination of the anterior or posterior vaginal wall while patients strain

Diagnosis is confirmed by examination.

Cystoceles and cystourethroceles are detected by applying a single-bladed speculum against the posterior vaginal wall while patients are in the lithotomy position. Asking patients to strain makes cystoceles or cystourethroceles visible or palpable as soft reducible masses bulging into the anterior vaginal wall. Inflamed paraurethral (Skene's) glands are differentiated by their more anterior and lateral
urethral location, tenderness, and occasionally expression of pus during palpation. Enlarged Bartholin’s glands can be differentiated because they develop in the medial labia majora and may be tender if infected.

Enterocoeles and rectoceles are detected by retracting the anterior vaginal wall while patients are in the lithotomy position. Asking patients to strain can make enterocoeles and rectoceles visible and palpable during rectovaginal examination. Patients are also examined while standing with one knee elevated (e.g., on a stool) and straining; sometimes abnormalities are detected only by rectovaginal examination during this maneuver.

Urinary incontinence, if present, is also evaluated.

**Treatment**

- Pessary and Kegel exercises
- Surgical repair of supporting structures if necessary

Treatment may initially consist of a pessary and Kegel exercises.

**Pessaries** are prostheses inserted in the vagina to maintain reduction of the prolapsed structures. Pessaries are of varying shapes and sizes, and some are inflatable. They may cause vaginal ulceration if they are not correctly sized and routinely cleansed (at least monthly if not more frequently).

**Kegel exercises** involve isometric contractions of the pubococcygeus muscle. Isolation of the correct muscle is difficult (about 50% of patients cannot do it) but important because a Valsalva maneuver is detrimental and buttock or thigh contraction is unhelpful. Contraction of the correct muscle is best initiated by asking patients to simulate attempting to hold in urine. Three sets of 8 to 10 contractions are done daily; contractions are initially held for 1 to 2 sec and increased up to 10 sec each when possible. Exercises can be facilitated by use of weighted vaginal cones, which help patients focus on contracting the correct muscle, by biofeedback devices, or by electrical stimulation, which causes the muscle to contract.

**Surgical repair** of supporting structures (anterior and posterior colporrhaphy) can help relieve symptoms that are severe or do not resolve with nonsurgical treatment. Perineorrhaphy (surgical shortening and tightening of the perineum) may also be needed. Colporrhaphy (surgical repair of the vagina) is usually deferred, if possible, until future childbearing is no longer desired because subsequent vaginal birth may disrupt the repair. Urinary incontinence can be surgically treated at the same time as colporrhaphy. After surgery, patients should avoid heavy lifting for 3 mo. After surgery to repair a cystocele or cystourethrocele, a urethral catheter is used for < 24 h.

**Uterine and Vaginal Prolapse**

Uterine prolapse is descent of the uterus toward or past the introitus. Vaginal prolapse is descent of the vagina or vaginal cuff after hysterectomy. Symptoms include vaginal pressure and fullness. Diagnosis is clinical. Treatment includes reduction, pessaries, and surgery.

Uterine prolapse is graded based on level of descent:

- 1st degree: To the upper vagina
- 2nd degree: To the introitus
- 3rd degree: Cervix is outside the introitus
- 4th degree (sometimes referred to as procidentia): Uterus and cervix entirely outside the introitus

Vaginal prolapse may be 2nd or 3rd degree.
Symptoms and Signs

Symptoms tend to be minimal with 1st-degree uterine prolapse. In 2nd- or 3rd-degree uterine prolapse, fullness, pressure, dyspareunia, and a sensation of organs falling out are common. Lower back or coccygeal pain may develop. Constipation is possible.

Third-degree uterine prolapse manifests as a bulge or protrusion of the cervix or cuff, although spontaneous reduction may occur before patients present. Vaginal mucosa may become dried, thickened, chronically inflamed, secondarily infected, and ulcerated. Ulcers may be painful or bleed and may resemble vaginal cancer. The cervix, if protruding, may also become ulcerated.

Symptoms of vaginal prolapse are similar. Cystocele or rectocele is usually present.

Urinary incontinence is common. The descending pelvic mass may intermittently obstruct urine flow, causing urinary retention and masking stress or overflow incontinence. Urinary frequency and urge incontinence may accompany vaginal prolapse.

Diagnosis

• Pelvic examination

Diagnosis is confirmed by speculum or bi-manual pelvic examination. Vaginal ulcers are biopsied to exclude cancer. Simultaneous urinary incontinence requires evaluation.

Treatment

• Treatment of symptomatic or 3rd-degree prolapse, beginning with pessaries and Kegel exercises

• Surgical repair of supporting structures if necessary, usually with hysterectomy

Asymptomatic 1st- or 2nd-degree uterine prolapse does not require treatment. Symptomatic or 3rd-degree prolapse can be treated nonsurgically if the perineum can structurally support a pessary. Severe or persistent symptoms require surgery, usually hysterectomy with surgical repair of the pelvic support structures (colporrhaphy) and suspension of the vagina (suturing of the upper vagina to a stable structure nearby). The abdominal approach results in greater structural support than the vaginal approach, but risk of short-term morbidity and mesh-related complications is greater. Surgery is delayed until all ulcers, if present, have healed.

Vaginal prolapse is treated similarly to uterine prolapse. Urinary incontinence requires concurrent treatment.
Chapter 250. Benign Gynecologic Lesions

Introduction

Benign gynecologic lesions include vulvar and vaginal cysts, cervical stenosis and polyps, uterine myomas, and benign ovarian masses, which can predispose to adnexal torsion.

Adnexal Torsion

Adnexal torsion is twisting of the ovary and sometimes the fallopian tube, interrupting the arterial supply and causing ischemia.

Adnexal torsion is uncommon, occurring most often during reproductive years. It usually indicates an ovarian abnormality. Risk factors include the following:

- Pregnancy
- Induction of ovulation
- Ovarian enlargement to > 4 cm (particularly by benign tumors)

Benign tumors are more likely to cause torsion than malignant ones. Torsion of normal adnexa, which is rare, is more common among children than adults.

Typically, one ovary is involved, but sometimes the fallopian tube is also involved. Adnexal torsion can cause peritonitis.

Symptoms

Torsion causes sudden, severe pelvic pain and sometimes nausea and vomiting. For days or occasionally weeks before the sudden pain, women may have intermittent, colicky pain, presumably resulting from intermittent torsion that spontaneously resolves. Cervical motion tenderness, a unilateral tender adnexal mass, and peritoneal signs are usually present.

Diagnosis

- Color Doppler transvaginal ultrasonography

Adnexal torsion is suspected based on typical symptoms and unexplained peritoneal signs plus severe cervical motion tenderness or an adnexal mass, particularly when criteria for pelvic inflammatory disease are not met or when symptoms are unilateral. Diagnosis is usually confirmed by color Doppler transvaginal ultrasonography.

Treatment

- Surgery to untwist the ovary

If torsion is suspected or confirmed by ultrasonography, laparoscopy or laparotomy is done immediately to attempt to salvage the ovary and fallopian tube by untwisting them. Salpingo-oophorectomy is required for nonviable or necrotic tissue. If an ovarian cyst or mass is present, cystectomy or oophorectomy is done.

Bartholin's Gland Cysts

Bartholin's gland cysts are mucus-filled and occur on either side of the vaginal opening (see Plate 69). They are the most common large vulvar cysts. Symptoms of large cysts include vulvar irritation, dyspareunia, pain during walking, and vulvar asymmetry. Bartholin's cysts may form abscesses, which are painful and usually red. Diagnosis is by physical examination. Large cysts and abscesses require drainage and sometimes excision; abscesses sometimes require
Bartholin's glands are round, very small, nonpalpable, and located deep in the postero-lateral vaginal orifice. Obstruction of the Bartholin duct causes the gland to enlarge with mucus, resulting in a cyst. Cause of obstruction is usually unknown. Rarely, the cysts result from a sexually transmitted disease (eg, gonorrhea).

These cysts develop in about 2% of women, usually those in their 20s. With aging, cysts are less likely to develop.

A cyst may become infected, forming an abscess. Vulvar cancers rarely originate in Bartholin's glands (see p. 2581).

### Symptoms and Signs

Most cysts are asymptomatic, but large cysts can be irritating, interfering with sexual intercourse and walking. Most cysts are non-tender, unilateral, and palpable near the vaginal orifice. Cysts distend the affected labia majora, causing vulvar asymmetry.

Abscesses cause severe vulvar pain and sometimes fever; they are tender and typically erythematous. A vaginal discharge may be present. Sexually transmitted diseases may coexist.

### Diagnosis

- **Clinical evaluation**

Diagnosis is usually by physical examination. A sample of discharge, if present, may be tested for sexually transmitted diseases. In women > 40, excisional biopsy must be done to exclude vulvar cancer.

### Treatment

- **Surgery for symptomatic cysts and for all cysts in women > 40**

In women < 40, asymptomatic cysts do not require treatment. Symptomatic cysts may require surgery. Because cysts often recur after simple drainage, surgery aims to produce a permanent opening from the duct to the exterior. Usually, one of the following is done:

  - **Catheter insertion:** A small balloon-tipped catheter may be inserted, inflated, and left in the cyst for 4 to 6 wk; this procedure stimulates fibrosis and produces a permanent opening.
  
  - **Marsupialization:** The everted edges of the cyst are sutured to the exterior.

Recurrent cysts may require excision.

In women > 40, all cysts must be surgically explored and removed by excisional biopsy.

Abscesses are treated with oral broad-spectrum antibiotics (eg, cephalexin 500 mg q 6 h for 7 to 10 days) and insertion of a balloon-tipped catheter.

### Benign Ovarian Masses

Benign ovarian masses include functional cysts and tumors; most are asymptomatic.

### Functional cysts:

There are 2 types of functional cysts:

- **Follicular cysts:** These cysts develop from graafian follicles.
- **Corpus luteum cysts:** These cysts develop from the corpus luteum. They may hemorrhage into the
Benign ovarian tumors usually grow slowly and rarely become malignant. They include the following:

- **Benign cystic teratomas**: These tumors are also called dermoid cysts because although derived from all 3 germ cell layers, they consist mainly of ectodermal tissue.

- **Fibromas**: These slow-growing tumors are usually < 7 cm in diameter.

- **Cystadenomas**: These tumors are most commonly serous or mucinous.

**Symptoms and Signs**

Most functional cysts and benign tumors are asymptomatic. Sometimes they cause menstrual abnormalities. Hemorrhagic corpus luteum cysts may cause pain or signs of peritonitis, particularly when they rupture. Occasionally, severe abdominal pain results from adnexal torsion of a cyst or mass, usually > 4 cm. Ascites and rarely pleural effusion may accompany fibromas.

**Diagnosis**

- Transvaginal ultrasonography

Masses are usually detected incidentally but may be suggested by symptoms and signs. A pregnancy test is done to exclude ectopic pregnancy. Transvaginal ultrasonography can usually confirm the diagnosis. If results are indeterminate, MRI or CT may help.

Masses with radiographic characteristics of cancer (eg, cystic and solid components, surface excrescences, multilocular appearance, irregular shape) require excision. Tumor markers may help in the diagnosis of specific tumors (see p. 2568). In women of reproductive age, simple, thin-walled cystic adnexal masses 5 to 8 cm (usually follicular) without characteristics of cancer do not require further evaluation unless they persist for > 3 menstrual cycles.

**Treatment**

- Removal of selected cysts

Most ovarian cysts < 8 cm resolve without treatment; serial ultrasonography is done to document resolution. If technically feasible, cyst removal from the ovary (ovarian cystectomy) via laparoscopy or laparotomy may be necessary for the following:

- Most cysts that are ≥ 10 cm and that persist for > 3 menstrual cycles

- **Cystic teratomas < 10 cm**

- **Hemorrhagic corpus luteum cysts with peritonitis**

- **Fibromas and other solid tumors**

Oophorectomy is done for the following:

- **Fibromas that cannot be removed by cystectomy**

- **Cystadenomas**
Cystic teratomas > 10 cm

Cysts that cannot be surgically removed separately from the ovary

Most cysts that are detected in postmenopausal women and that are > 5 cm

Cervical Myomas

Cervical myomas are smooth, benign tumors of the cervix.

Cervical myomas are uncommon. Uterine myomas (fibroids) usually coexist. Large cervical myomas may partially obstruct the urinary tract or may prolapse into the vagina. Prolapsed myomas sometimes ulcerate, become infected, bleed, or a combination.

Symptoms and Signs

Most cervical myomas eventually cause symptoms. The most common symptom is bleeding, which may be irregular or heavy, sometimes causing anemia. Dyspareunia may occur. Infection may cause pain, bleeding, or discharge. Rarely, prolapse causes a feeling of pressure or a mass in the pelvis. Urinary outflow obstruction causes hesitancy, dribbling, or urine retention; UTIs may develop.

Diagnosis

• Physical examination

Diagnosis is by physical examination. Cervical myomas, particularly if prolapsed, may be visible with use of a speculum. Some are palpable during bimanual examination.

Transvaginal ultrasonography is done only for the following:

• To confirm an uncertain diagnosis

• To exclude urinary outflow obstruction

• To identify additional myomas

Hb, Hct, or CBC is measured to exclude anemia. Cervical cytology is done to exclude cervical cancer.

Treatment

• Removal of symptomatic myomas

Treatment is similar to that of fibroids (see p. 2537). Small, asymptomatic myomas are not treated. Most symptomatic cervical myomas are removed by myomectomy (particularly if childbearing capacity is important) or, if myomectomy is technically difficult, by hysterectomy. Prolapsed myomas should be removed transvaginally if possible.

Cervical Polyps

Cervical polyps are common benign growths of the cervix and endocervix.

Cervical polyps occur in about 2 to 5% of women. They usually originate in the endocervical canal. Endocervical polyps are probably caused by chronic inflammation. They rarely become malignant.

Most cervical polyps are asymptomatic. Endocervical polyps may bleed between menses or after intercourse or become infected, causing purulent vaginal discharge (leukorrhea). Endocervical polyps are usually reddish pink, glistening, and < 1 cm in all dimensions; they may be friable.
Diagnosis

Diagnosis is by speculum examination.

Treatment

Polyps that cause bleeding or discharge should be removed. Excision can be done in the office and does not require anesthetics. Bleeding after excision is rare and can be controlled with chemical cautery.

If bleeding or discharge persists after treatment, cervical cytology and endometrial biopsy are done to exclude cancer.

Cervical Stenosis

Cervical stenosis is stricture of the internal cervical os.

Cervical stenosis may be congenital or acquired. The most common acquired causes are

- Menopause
- Cervical surgery (eg, conization, cautery)
- Endometrial ablation procedures to treat uterine abnormalities that cause menorrhagia
- Cervical or uterine cancer
- Radiation therapy

Cervical stenosis may be complete or partial. It may result in a hematometra (accumulation of blood in the uterus) or, in premenopausal women, retrograde flow of menstrual blood into the pelvis, possibly causing endometriosis. A pyometra (accumulation of pus in the uterus) may also develop, particularly in women with cervical or uterine cancer.

Symptoms and Signs

Common symptoms in premenopausal women include amenorrhea, dysmenorrhea, abnormal bleeding, and infertility. Postmenopausal women may be asymptomatic for long periods. Hematometra or pyometra may cause uterine distention or sometimes a palpable mass.

Diagnosis

- Clinical evaluation

Diagnosis may be suspected based on symptoms and signs (particularly development of amenorrhea or dysmenorrhea after cervical surgery) or on inability to obtain endocervical cells or an endometrial sample for diagnostic tests (eg, for a Papanicolaou [Pap] test). Diagnosis of complete stenosis is established if a 1- to 2-mm diameter probe cannot be passed into the uterine cavity.

If cervical stenosis causes symptoms or uterine abnormalities (eg, hematometra, pyometra), cervical cytology and endometrial biopsy should be done to exclude cancer. For postmenopausal women with no history of abnormal Pap tests and for women without symptoms or uterine abnormalities, no further evaluation is needed.

Treatment

- Dilation and stenting if symptomatic

Treatment is indicated only if symptoms or uterine abnormalities are present and typically involves...
cervical dilation and placement of cervical stent.

**Skene’s Duct Cyst**

Skene’s duct cysts develop adjacent to the distal urethra, sometimes causing perineal discharge, dyspareunia, urinary obstruction, or abscess formation.

Skene’s glands (periurethral or paraurethral glands) are located adjacent to the distal urethra. Cysts form if the duct is obstructed, usually because the gland is infected. They occur mainly in adults. Cysts may form abscesses or cause urethral obstruction and recurrent UTIs.

Most cysts are < 1 cm and asymptomatic. Some are larger and cause dyspareunia. The first symptoms may be those of urinary out-flow obstruction (eg, hesitancy, dribbling, retention) or of UTIs. Abscesses are painful, swollen, tender, and erythematous but usually do not cause fever.

**Diagnosis**

- Clinical evaluation

Diagnosis is usually clinical. Most symptomatic cysts and abscesses are palpable adjacent to the distal urethra; however, a diverticulum of the distal urethra may be clinically indistinguishable, requiring ultrasonography or cystoscopy for differentiation.

**Treatment**

- Surgical excision if the cyst causes symptoms

Symptomatic cysts are excised. Abscesses are treated initially with oral broad-spectrum antibiotics (eg, cephalaxin 500 mg q 6 h for 7 to 10 days) and are excised or marsupialized.

**Vulvar Endometriomas**

Vulvar endometriomas are rare, painful cysts that result from extrauterine implantation of functioning endometrial tissue (endometriosis—see p. 2538).

Rarely, endometriosis occurs in the vulva (or the vagina), sometimes producing cysts (endometriomas), often at the site of previous surgery (eg, episiotomy).

Endometriomas usually develop in the mid-line. They may be painful, particularly during intercourse. During menstruation, pain increases and endometriomas may enlarge. Endometriomas are tender and may appear blue. They can rupture, causing severe pain.

Diagnosis is by physical examination and biopsy. Treatment involves excisional biopsy.

**Vulvar Inclusion and Epidermal Cysts**

Vulvar inclusion cysts contain epithelial tissue; vulvar epidermal cysts develop from sebaceous glands. Both cysts eventually enlarge with cellular debris and sometimes become infected.

Inclusion cysts are the most common vulvar cysts; they may also occur in the vagina. They may result from trauma (eg, laceration, episiotomy repair) that entraps viable epithelial tissue below the surface, or they may develop spontaneously. Epidermal cysts result from obstruction of sebaceous gland ducts.

Uninfected cysts are usually asymptomatic but occasionally cause irritation; they are white or yellow and usually < 1 cm. Infected cysts may be red and tender and cause dyspareunia.

Diagnosis is clinical. Treatment, indicated only for symptomatic cysts, is excision; a local anesthetic can be used.
Chapter 251. Uterine Fibroids

(Leiomyomas; Myomas; Fibromyomas)

Uterine fibroids are benign uterine tumors of smooth muscle origin. Fibroids frequently cause abnormal vaginal bleeding (eg, menorrhagia, menometrorrhagia), pelvic pain and pressure, urinary and intestinal symptoms, and pregnancy complications. Diagnosis is by pelvic examination and ultrasonography. Treatment of symptomatic patients depends on the patient's desire for fertility and desire to keep her uterus and may include oral contraceptives, brief presurgical gonadotropin-releasing hormone therapy to shrink fibroids, and more definitive surgical procedures (eg, hysterectomy, myomectomy, endometrial ablation).

Uterine fibroids are the most common pelvic tumor, occurring in about 70% of women by age 45. However, many fibroids are small and asymptomatic. About 25% of white and 50% of black women have symptomatic fibroids. Fibroids are more common among women who have a high body mass index. Potentially protective factors include parturition and cigarette smoking.

Most fibroids in the uterus are subserous, followed by intramural, then submucosal. Occasionally, fibroids occur in the broad ligaments (intraligamentous), fallopian tubes, or cervix. Some fibroids are pedunculated. Most fibroids are multiple and develop from a single monoclonal smooth muscle cell. Because they have estrogen receptors, fibroids tend to enlarge during the reproductive years and regress after menopause.

Large fibroids may outgrow their blood supply and degenerate. Degeneration is described as hyaline, myxomatous, calcific, cystic, fatty, red (usually only during pregnancy), or necrotic. Although patients are often concerned about cancer in fibroids, sarcomatous change is extremely rare.

Symptoms and Signs

Fibroids can cause menorrhagia or menometrorrhagia. If fibroids grow, degenerate, or hemorrhage or if pedunculated fibroids twist, severe acute or chronic pressure or pain can result. Urinary symptoms (eg, urinary frequency or urgency) can result from bladder compression, and intestinal symptoms (eg, constipation) can result from intestinal compression.

Fibroids may prevent pregnancy; during pregnancy, they may cause recurrent spontaneous abortion, premature contractions, or abnormal presentation or make cesarean delivery necessary.

Diagnosis

• Ultrasonography or sonohysterography

The diagnosis is likely if bimanual pelvic examination detects an enlarged, mobile, irregular uterus that is palpable above the pelvic symphysis. Confirmation requires imaging, usually with ultrasonography or sonohysterography. In sonohysterography, saline is instilled into the uterus, enabling the sonographer to more specifically locate the fibroid in the uterus. If ultrasonography is inconclusive, MRI, the most accurate imaging test, is done.

Treatment

• Sometimes gonadotropin-releasing hormone (GnRH) analogs or other drugs for temporary relief of minor symptoms

• Myomectomy (to preserve fertility) or hysterectomy for symptomatic fibroids

Asymptomatic fibroids do not require treatment. Patients are reevaluated periodically (eg, every 6 to 12 mo).

For symptomatic fibroids, medical options, including suppression of ovarian hormones to stop the
bleeding, are suboptimal and limited. However, menorrhagia or menometrorrhagia should be treated before surgery is considered. GnRH analogs are commonly given before surgery to shrink fibroid tissues, often stopping menses and allowing blood counts to increase. In postmenopausal women, expectant management can be tried because symptoms may resolve as fibroids regress.

**Drugs:** Several drugs are used to relieve symptoms, reduce fibroid growth, or both.

**GnRH analogs** given IM or sc (eg, leuprolide 3.75 mg IM q mo, goserelin 3.6 mg sc q 28 days), as a subdermal pellet, or as nasal spray can decrease estrogen production. These drugs are most commonly used. GnRH analogs are most helpful when given preoperatively to reduce fibroid and uterine volume, making surgery technically more feasible and reducing blood loss. In general, these drugs should not be used in the long term because rebound growth to pretreatment size within 6 mo is common and bone demineralization may occur.

**Exogenous progestins** can partially suppress estrogen stimulation of uterine fibroid growth. Medroxyprogesterone acetate 5 to 10 mg po once/day or megestrol acetate 10 to 20 mg po once/day given 10 to 14 days each menstrual cycle can limit heavy bleeding, beginning after 1 or 2 treatment cycles. Alternatively, oral therapy every day of the month (continuous therapy) may be given; it often reduces bleeding and provides contraception. Depot medroxyprogesterone acetate 150 mg IM q 3 mo has effects similar to those of continuous oral therapy. Before IM therapy, oral progestins should be tried to determine whether patients can tolerate the adverse effects (eg, weight gain, depression, irregular bleeding). Progestin therapy causes fibroids to grow in some women.

**Antiprogestins** (eg, mifepristone) can also help reduce fibroid growth. The dose is 5 to 50 mg (once/day for 3 to 6 mo), which is lower than the 200-mg dose used for termination of pregnancy; thus, it must be mixed specially by the pharmacy and may not always be available.

**Selective estrogen receptor modulators** (SERMs; eg, raloxifene) may help reduce fibroid growth. However, whether efficacy in reducing symptoms is comparable to that of other drugs is unclear.

**Danazol,** an androgenic agonist, can suppress fibroid growth but has a high rate of adverse effects (eg, weight gain, acne, hirsutism, edema, hair loss, deepening of the voice, flushing, sweating, vaginal dryness) and is thus often less acceptable to patients.

**NSAIDs** can be used to treat pain but probably do not decrease bleeding.

**Surgery:** Surgery is usually reserved for women with any of the following:

- Rapidly enlarging pelvic mass
- Recurrent uterine bleeding refractory to drug therapy
- Persistent or intolerable pain or pressure
- Urinary or intestinal symptoms
- Infertility (if pregnancy is desired)
- Recurrent spontaneous abortions (if pregnancy is desired)

**Hysterectomy** or **myomectomy** is traditionally done; both are major surgery and have similar indications. Hysterectomy is the definitive treatment. After myomectomy, new fibroids may begin another growth phase, and about 25% of women who have a myomectomy have a hysterectomy about 4 to 8 yr later. However, if women desire pregnancy or want to keep their uterus, myomectomy is used. In about 55% of women with infertility due to fibroids alone, myomectomy can restore fertility, resulting in pregnancy after about 15 mo. Multiple myomectomy can be much more difficult to do than hysterectomy. Patient choice is important but must be based on full information about anticipated difficulties and sequelae of myomectomy vs hysterectomy.
**Newer procedures** may relieve symptoms, but duration of symptom relief and efficacy of the procedures in restoring fertility have not been evaluated. Such procedures include laparoscopic and hysteroscopic myomectomy (using an instrument with a wide-angle telescope and electrical wire loop for excision), high-intensity focused sonography, cryotherapy, and radiofrequency ablation. Complication rates after laparoscopic myomectomy may be higher, but rates appear to be operator-dependent. Uterine artery embolization has been used with the aim of causing infarction of fibroids throughout the uterus while preserving normal uterine tissue. After this procedure, women recover more quickly than after hysterectomy or myomectomy, but rates of complications and return visits tend to be higher.

**Choice of treatment:** Treatment should be individualized, but some factors can help with the decision:

- Asymptomatic fibroids: No treatment
- Postmenopausal women: Trial of expectant management (because symptoms tend to remit as fibroids regress)
- Surgically accessible symptomatic fibroids, particularly if conception may be desired: Myomectomy
- Symptomatic fibroids that are not clearly surgically accessible: Uterine artery embolization or another new technique (eg, high-intensity focused sonography)
- Intolerable symptoms when other treatments were ineffective, particularly if conception is not desired: Hysterectomy, possibly preceded by drug therapy (eg, with GnRH analogs)
Introduction

Endometriosis is a noncancerous disorder in which functioning endometrial tissue is implanted outside the uterine cavity. Symptoms depend on location of the implants and may include dysmenorrhea, dyspareunia, infertility, dysuria, and pain during defecation. Diagnosis is by biopsy, usually via laparoscopy. Treatments include anti-inflammatory drugs, drugs to suppress ovarian function and endometrial tissue growth, surgical ablation and excision of endometriotic implants, and, if disease is severe and no childbearing is planned, hysterectomy plus oophorectomy.

Endometriosis is usually confined to the peritoneal or serosal surfaces of pelvic organs, commonly the ovaries, broad ligaments, posterior cul-de-sac, and uterosacral ligaments. Less common sites include the serosal surfaces of the small and large intestines, ureters, bladder, vagina, cervix, surgical scars, pleura, and pericardium. Bleeding from peritoneal implants is thought to initiate inflammation, followed by fibrin deposition, adhesion formation, and, eventually, scarring, which distorts peritoneal surfaces of organs and pelvic anatomy.

Etiology and Pathophysiology

The most widely accepted hypothesis is that endometrial cells are transported from the uterine cavity and subsequently become implanted at ectopic sites. Retrograde flow of menstrual tissue through the fallopian tubes could transport endometrial cells intraabdominally; the lymphatic or circulatory system could transport endometrial cells to distant sites (eg, the pleural cavity). Another hypothesis is coelomic metaplasia: Coelomic epithelium is transformed into endometrium-like glands.

Microscopically, endometriotic implants consist of glands and stroma identical to intrauterine endometrium. These tissues contain estrogen and progesterone receptors and thus usually grow, differentiate, and bleed in response to changes in hormone levels during the menstrual cycle.

Incidence of endometriosis is increased in 1st-degree relatives of women with endometriosis, suggesting that heredity is a factor. Incidence is also increased in women who delay childbearing, who have shortened menstrual cycles (< 27 days) with menses that are abnormally long (> 8 days), or who have mullerian duct defects.

Reported incidence varies but is probably about 10 to 15% in actively menstruating women aged 25 to 44. Average age at diagnosis is 27, but endometriosis also occurs among adolescents. About 25 to 50% of infertile women have endometriosis. In patients with severe endometriosis and distorted pelvic anatomy, incidence of infertility is high because mechanisms of ovum pickup and tubal transport are impaired. Some patients with minimal endometriosis and normal pelvic anatomy are also infertile; reasons for impaired fertility include the following:

- Increased incidence of luteinized unruptured ovarian follicle syndrome (trapped oocyte)
- Increased peritoneal prostaglandin production or peritoneal macrophage activity (resulting in oocyte phagocytosis)
- Nonreceptive endometrium (because of luteal phase dysfunction or other abnormalities)

Potential protective factors seem to be multiple pregnancies, use of low-dose oral contraceptives (continuous or cyclic), and regular exercise (especially if begun before age 15, if done for > 7 h/wk, or both).

Symptoms and Signs

Pelvic pain, pelvic mass, alteration of menses, and infertility are typical. Some women with extensive endometriosis are asymptomatic; some with minimal disease have incapacitating pain. Dyspareunia and
midline pelvic pain before or during menses may develop. Such dysmenorrhea is an important diagnostic clue, particularly if it begins after several years of pain-free menses.

Symptoms can vary depending on location of implants.

- **Large intestine**: Pain during defecation, abdominal bloating, or rectal bleeding during menses
- **Bladder**: Dysuria, hematuria, suprapubic pain (particularly during urination), or a combination
- **Ovaries**: Formation of an endometrioma (a 2- to 10-cm cystic mass localized to an ovary), which occasionally ruptures or leaks, causing acute abdominal pain and peritoneal signs
- **Adnexal structures**: Formation of adnexal adhesions, resulting in a pelvic mass
- **Extrapelvic structures**: Vague abdominal pain (sometimes)

Pelvic examination may be normal, or findings may include a retroverted and fixed uterus, enlarged ovaries, fixed ovarian masses, thickened rectovaginal septum, induration of the cul-de-sac, and nodules on the uterosacral ligament. Rarely, lesions can be seen on the vulva or cervix or in the vagina, umbilicus, or surgical scars.

**Diagnosis**

- Biopsy, usually laparoscopic
- Sometimes imaging tests (to follow progression) but not for diagnosis

Diagnosis is suspected based on typical symptoms but must be confirmed by biopsy, usually via pelvic laparoscopy but sometimes via laparotomy, vaginal examination, sigmoidoscopy, or cystoscopy. Macroscopic appearance (e.g., clear, red, brown, black) and size of implants vary during the menstrual cycle. However, typically, areas of endometriosis on the pelvic peritoneum are punctate red, blue, or purplish brown spots that are > 5 mm, often called powder burn lesions. Microscopically, both endometrial glands and stroma must be present to diagnose endometriosis.

Imaging tests (e.g., ultrasonography, barium enema, IV urography, CT, MRI) are not specific or adequate for diagnosis. However, if they are done to rule out other disorders, they sometimes show the extent of endometriosis. They can also be used to monitor the disorder once it is diagnosed. Investigational serum markers for endometriosis (e.g., serum cancer antigen 125 level > 35 units/mL, antiendometrial antibody) may help monitor the disorder but require further refinement before they are used routinely. Testing for other infertility disorders may be indicated (see p. 2592).

Staging the disorder helps physicians formulate a treatment plan and evaluate response to therapy. According to the American Society for Reproductive Medicine, endometriosis may be classified as stage I (minimal), II (mild), III (moderate), or IV (severe), based on number, location, and depth of implants and presence of filmy or dense adhesions (see Table 252-1).

Another staging system is based primarily on the presence and severity of pelvic pain.

**Table 252-1. Stages of Endometriosis**

However, because intraobserver and interobserver variability is high in the staging systems, a more reliable method of staging is being sought.

**Treatment**

- NSAIDs for discomfort
• Drugs to suppress ovarian function

• Conservative surgical resection or ablation of endometriotic tissue

• Conservative surgery plus drugs

• Total abdominal hysterectomy with bilateral salpingo-oophorectomy if disease is severe and patient has completed childbearing

Symptomatic treatment begins with NSAIDs. More definitive treatment must be individualized based on the patient's age, symptoms, and desire to preserve fertility and on the extent of the disorder.

Drugs and conservative surgery are symptomatic treatments; in most patients, endometriosis recurs after treatment is stopped unless ovarian function is permanently and completely ablated.

Drugs that suppress ovarian function inhibit the growth and activity of endometriotic implants. These drugs include continuous oral contraceptives (commonly used), gonadotropin-releasing hormone (GnRH) agonists, and danazol (see Table 252-2).

GnRH agonists temporarily suppress estrogen production; however, treatment is limited to ≤ 6 mo because long-term use may result in bone loss. If treatment lasts > 4 to 6 mo, add-back therapy, usually a low-dose oral contraceptive taken daily, can be given. Danazol, a synthetic androgen and an antigonadotropin, inhibits ovulation. However, its androgenic adverse effects limit its use. Cyclic or continuous oral contraceptives given after danazol or GnRH agonists may slow disease progression and are warranted for women who wish to delay childbearing. After drug treatment, fertility rates range from 40 to 60%. Whether treating minimal or mild endometriosis improves fertility rates is unclear because the fertility rate among untreated women is unknown.

Most women with moderate to severe endometriosis are treated most effectively by ablating or excising as many implants as possible while preserving fertility. Specific indications for surgery include presence of endometriomas, significant pelvic adhesions, fallopian tube obstruction, incapacitating pelvic pain, and a desire to preserve fertility. Microsurgical techniques are used to prevent adhesions if women desire to preserve fertility. Laparoscopy can sometimes be used to remove lesions; peritoneal or ovarian lesions can sometimes be electrocauterized, excised, or vaporized with a laser. After this treatment, fertility rates are 40 to 70% and are inversely proportional to severity of the endometriosis. If resection is incomplete, use of oral contraceptives or GnRH agonists may increase fertility rates. Laparoscopic resection of the uterosacral ligaments with electrocautery or a laser may reduce midline pelvic pain. Some patients require presacral neurectomy.

Hysterectomy should usually be reserved for patients who have intractable pelvic pain and who have completed childbearing. If women < 50 require hysterectomy with oophorectomy, supplemental estrogen should be considered. Continuous progestin (eg, medroxyprogesterone acetate 2.5 mg po once/day) should be given with estrogen because if estrogen is given alone, residual tissue may grow. Hormone replacement can be started postoperatively or, if a substantial amount of endometriotic tissue remains, may be delayed for 4 to 6 mo; during this interval, progestins to suppress the remaining endometriotic tissue may be necessary.
Chapter 253. Vaginitis and Pelvic Inflammatory Disease

Introduction

The lower and upper female genital tracts are separated by the cervix. Inflammation of the lower tract may involve the vagina (vaginitis), vulva (vulvitis), or both (vulvovaginitis). Pelvic inflammatory disease is infection of the upper tract: uterus, fallopian tubes, and, if infection is severe, ovaries (one or both).

Vaginitis

Vaginitis is infectious or noninfectious inflammation of the vaginal mucosa, sometimes with inflammation of the vulva. Symptoms include vaginal discharge, irritation, pruritus, and erythema. Diagnosis is by in-office testing of vaginal secretions. Treatment is directed at the cause and at any severe symptoms.

Vaginitis is one of the most common gynecologic disorders. Some of its causes affect the vulva alone (vulvitis) or in addition (vulvovaginitis).

Etiology

The most common causes vary by patient age.

Children: In children, vaginitis usually involves infection with GI tract flora (nonspecific vulvovaginitis). A common contributing factor in girls aged 2 to 6 yr is poor perineal hygiene (eg, wiping from back to front after bowel movements; not washing hands after bowel movements; fingering, particularly in response to pruritus). Chemicals in bubble baths or soaps may cause inflammation. Foreign bodies (eg, tissue paper) may cause nonspecific vaginitis with a bloody discharge. Sometimes childhood vulvovaginitis is due to infection with a specific pathogen (eg, streptococci, staphylococci, Candida sp; occasionally, pinworm).

Women of reproductive age: In these women, vaginitis is usually infectious. The most common types are bacterial vaginosis (see p. 2543), candidal vaginitis (see p. 2544), and trichomonal vaginitis (see p. 1481), which is sexually transmitted. Normally in women of reproductive age, Lactobacillus sp is the predominant constituent of normal vaginal flora. Colonization by these bacteria keeps vaginal pH in the normal range (3.8 to 4.2), thereby preventing overgrowth of pathogenic bacteria. Also, high estrogen levels maintain vaginal thickness, bolstering local defenses. Factors that predispose to overgrowth of bacterial vaginal pathogens may include the following:

• An alkaline vaginal pH due to menstrual blood, semen, or a decrease in lactobacilli

• Poor hygiene

• Frequent douching

Vaginitis may result from foreign bodies (eg, forgotten tampons). Inflammatory vaginitis, which is noninfectious, is uncommon.

Postmenopausal women: Usually, a marked decrease in estrogen causes vaginal thinning, increasing vulnerability to infection and inflammation. Some treatments (eg, oophorectomy, pelvic radiation, certain chemotherapy drugs) also result in loss of estrogen. Decreased estrogen predisposes to atrophic vaginitis. Poor hygiene (eg, in patients who are incontinent or bedbound) can lead to chronic vulvar inflammation due to chemical irritation from urine or feces or due to nonspecific infection. Bacterial vaginosis, candidal vaginitis, and trichomonal vaginitis are uncommon among postmenopausal women but may occur in those with risk factors.

Women of all ages: At any age, conditions that predispose to vaginal or vulvar infection include fistulas between the intestine and genital tract, which allow intestinal flora to seed the genital tract, and pelvic radiation or tumors, which break down tissue and thus compromise normal host defenses. Noninfectious
Vulvitis accounts for up to 30% of vulvovaginitis cases. It may result from hypersensitivity or irritant reactions to hygiene sprays or perfumes, menstrual pads, laundry soaps, bleaches, fabric softeners, fabric dyes, synthetic fibers, bathwater additives, toilet tissue, or, occasionally, spermicides, vaginal lubricants or creams, latex condoms, vaginal contraceptive rings, or diaphragms.

**Symptoms and Signs**

Vaginitis causes vaginal discharge, which must be distinguished from normal discharge. Normal discharge is common when estrogen levels are high—eg, during the first 2 wk of life because maternal estrogen is transferred before birth (slight bleeding often occurs when estrogen levels abruptly decrease) and during the few months before menarche, when estrogen production increases. Normal vaginal discharge is commonly milky white or mucoid, odorless, and nonirritating; it can result in vaginal wetness that dampens underwear. Discharge due to vaginitis is accompanied by pruritus, erythema, and sometimes burning, pain, or mild bleeding. Pruritus may interfere with sleep. Dysuria or dyspareunia may occur. In atrophic vaginitis, discharge is scant, dyspareunia is common, and vaginal tissue appears thin and dry. Although symptoms vary among particular types of vaginitis, there is much overlap (see Table 253-1).

**Table 253-1. Common Types of Vaginitis**

Vulvitis can cause erythema, pruritus, and sometimes tenderness and discharge from the vulva.

**Diagnosis**

- Clinical evaluation
- Vaginal pH and saline and KOH wet mounts

Vaginitis is diagnosed using clinical criteria and in-office testing. First, vaginal secretions are obtained with a water-lubricated speculum, and pH paper is used to measure pH in 0.2 intervals from 4.0 to 6.0. Then, secretions are placed on 2 slides with a cotton swab and diluted with 0.9% NaCl on one slide (saline wet mount) and with 10% K hydroxide on the other (KOH wet mount). The KOH wet mount is checked for a fishy odor (whiff test), which results from amines produced in trichomonal vaginitis or bacterial vaginosis. The saline wet mount is examined microscopically as soon as possible to detect trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation. The KOH dissolves most cellular material except for yeast hyphae, making identification easier. If clinical criteria and in-office test results are inconclusive, the discharge may be cultured for fungi or trichomonads.

Other causes of discharge are ruled out. If children have vaginal discharge, a vaginal foreign body is suspected. Cervical discharge due to cervicitis (eg, due to pelvic inflammatory disease [PID]) can resemble that of vaginitis; abdominal pain, cervical motion tenderness, or cervical inflammation suggests PID. Discharge that is watery, bloody, or both may result from vulvar, vaginal, or cervical cancer; cancers can be differentiated from vaginitis by examination and Papanicolaou (Pap) tests. Vaginal pruritus and discharge may result from skin disorders (eg, psoriasis, tinea versicolor), which can usually be differentiated by history and skin findings.

If children have trichomonal vaginitis, evaluation for sexual abuse is required. If they have unexplained vaginal discharge, cervicitis, which may be due to a sexually transmitted disease, should be considered. If women have bacterial vaginosis or trichomonal vaginitis (and thus are at increased risk of sexually transmitted diseases), cervical tests for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, common causes of sexually transmitted PID, are done.

**Treatment**

- Hygienic measures
- Symptomatic treatment
• Treatment of cause

The vulva should be kept as clean as possible. Soaps and unnecessary topical preparations (eg, feminine hygiene sprays) should be avoided. Intermittent use of ice packs or warm sitz baths with or without baking soda may reduce soreness and pruritus.

If symptoms are moderate or severe or do not respond to other measures, drugs may be needed. For pruritus, topical corticosteroids (eg, topical 1% hydrocortisone bid prn) can be applied to the vulva but not in the vagina. Oral antihistamines decrease pruritus and cause drowsiness, helping patients sleep.

Any infection or other cause is treated. Foreign bodies are removed. Prepubertal girls are taught good perineal hygiene (eg, wiping front to back after bowel movements and voiding, washing hands, avoiding finger ing the perineum). If chronic vulvar inflammation is due to being bedbound or incontinent, better vulvar hygiene may help.

Bacterial Vaginosis

Bacterial vaginosis is vaginitis due to a complex alteration of vaginal flora in which lactobacilli decrease and anaerobic pathogens overgrow. Symptoms include a gray, thin, fishy-smelling vaginal discharge and itching. Diagnosis is confirmed by testing vaginal secretions. Treatment is usually with oral or topical metronidazole or topical clindamycin.

Bacterial vaginosis is the most common infectious vaginitis. The cause is unknown. Anaerobic pathogens that overgrow include Prevotella sp, Peptostreptococcus sp, Gardnerella vaginalis, Mobiluncus sp, and Mycoplasma hominis, which increase in concentration 10-fold to 100-fold and replace the normally protective lactobacilli. Risk factors include those for sexually transmitted diseases (see p. 1466). However, bacterial vaginosis can occur in virgins, and treating the male sex partner does not appear to affect subsequent incidence in sexually active women. Use of an intrauterine device is also a risk factor.

Bacterial vaginosis, once considered inconsequential, appears to increase risk of pelvic inflammatory disease, postabortion and postpartum endometritis, posthysterectomy vaginal cuff infection, chorioamnionitis, premature rupture of membranes, preterm labor, and preterm birth.

Symptoms and Signs

Vaginal discharge is malodorous, gray, and thin. Usually, a fishy odor is present, often becoming stronger when the discharge is more alkaline—after coitus and menses. Pruritus and irritation are common. Erythema and edema are uncommon.

Diagnosis

For the diagnosis, 3 of 4 criteria must be present:

• Gray discharge
• Vaginal secretion pH > 4.5
• Fishy odor on the whiff test
• Clue cells

Clue cells (bacteria adherent to epithelial cells obscuring their cell margins—see Plate 70) are identified by microscopic examination of a saline wet mount. Presence of WBCs on a saline wet mount suggests a concomitant infection (possibly trichomonal, gonorrheal, or chlamydial cervicitis) and the need for additional testing.

Treatment
Topical metronidazole or clindamycin

Metronidazole 0.75% vaginal gel bid for 5 days or 2% clindamycin vaginal cream once/day for 7 days is the treatment of choice. Oral metronidazole 500 mg bid for 7 days or 2 g po once is effective but can have systemic adverse effects. Women who use clindamycin cream cannot use latex products (ie, condoms or diaphragms) for contraception because the drug weakens latex. Treatment of asymptomatic sex partners is unnecessary.

For vaginitis during the 1st trimester of pregnancy, metronidazole vaginal gel should be used, although treatment during pregnancy has not been shown to lower the risk of pregnancy complications. To prevent endometritis, clinicians may give metronidazole prophylactically before elective abortion to all patients or only to those who test positive for bacterial vaginosis.

Candidal Vaginitis

Candidal vaginitis is vaginal infection with *Candida* sp, usually *C. albicans*.

Most fungal vaginitis is caused by *C. albicans* (see also p. 703), which colonizes 15 to 20% of nonpregnant and 20 to 40% of pregnant women. Risk factors for candidal vaginitis include the following:

- Diabetes
- Use of a broad-spectrum antibiotic or corticosteroids
- Pregnancy
- Constrictive nonporous undergarments
- Immunocompromise
- Use of an intrauterine device

Candidal vaginitis is uncommon among postmenopausal women except among those taking systemic hormone therapy.

**Symptoms and Signs**

Vaginal vulvar pruritus, burning, or irritation (which may be worse with intercourse) and dyspareunia are common, as is a thick, white, cottage cheese-like vaginal discharge that adheres to the vaginal walls. Symptoms and signs increase the week before menses. Erythema, edema, and excoriation are common. Infected male sex partners may or may not have symptoms. Recurrences after treatment are uncommon.

**Diagnosis**

- Vaginal pH and wet mount

Vaginal pH is < 4.5; budding yeast, pseudohyphae, or mycelia are visible on a wet mount, especially with KOH (see Plate 71). If symptoms suggest candidal vaginitis but signs (including vulvar irritation) are absent and microscopy does not detect fungal elements, fungal culture is done. Women with frequent recurrences require culture to confirm the diagnosis and to rule out non-albicans *Candida*.

**Treatment**

- Antifungal drugs
- Avoidance of excess moisture accumulation
Keeping the vulva clean and wearing loose, absorbent cotton clothing that allows air to circulate can reduce vulvar moisture and fungal growth. Topical or oral drugs are highly effective (see Table 253-2). Adherence to treatment is better when a one-dose oral regimen of fluconazole 150 mg is used. Topical butoconazole, clotrimazole, miconazole, and tioconazole are available OTC. However, patients should be warned that topical creams and ointments containing mineral oil or vegetable oil weaken latex-based condoms. If symptoms persist or worsen during topical therapy, hypersensitivity to topical antifungals should be considered.

Frequent recurrences require long-term suppression with oral drugs (fluconazole 150 mg weekly to monthly or ketoconazole 100 mg once/day for 6 mo). Suppression is effective only while the drugs are being taken. These drugs may be contraindicated in patients with liver disorders. Patients taking ketoconazole should be monitored periodically with liver function tests.

[Table 253-2. Drugs for Candidal Vaginitis]

Inflammatory Vaginitis

Inflammatory vaginitis is vaginal inflammation without evidence of the usual infectious causes of vaginitis.

Etiology may be autoimmune. Vaginal epithelial cells slough superficially, and streptococci overgrow. The major risk factor is estrogen loss, which can result from menopause or premature ovarian failure (eg, due to oophorectomy, pelvic radiation, or chemotherapy). Genital atrophy predisposes to inflammatory vaginitis and increases risk of recurrence.

Symptoms and Signs

Purulent vaginal discharge, dyspareunia, dysuria, and vaginal irritation are common. Vaginal pruritus and erythema may occur. Burning, pain, or mild bleeding occurs less often. Vaginal tissue may appear thin and dry. Vaginitis may recur.

Diagnosis

• Vaginal pH and wet mount

Because symptoms overlap with other forms of vaginitis, testing (eg, vaginal fluid pH measurement, microscopy, whiff test) is necessary. The diagnosis is made if vaginal fluid pH is > 6, whiff test is negative, and microscopy shows predominantly WBCs and parabasal cells.

Treatment

• Clindamycin vaginal cream

Treatment is with clindamycin vaginal cream 5 g every evening for 1 wk. After treatment with clindamycin, women are evaluated for genital atrophy. Genital atrophy, if present, can be treated with topical estrogens (eg, 0.01% estradiol vaginal cream 2 to 4 g once/day for 1 to 2 wk, followed by 1 to 2 g once/day for 1 to 2 wk, then 1 g 1 to 3 times weekly; estradiol hemihydrate vaginal tablets 25 μg twice/wk; estradiol rings q 3 mo). Topical therapy is usually preferred because of concerns about the safety of oral hormonal therapy; topical therapy may have fewer systemic effects.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is infection of the upper female genital tract: the cervix, uterus, fallopian tubes, and ovaries; abscesses may occur. Common symptoms and signs include lower abdominal pain, cervical discharge, and irregular vaginal bleeding. Long-term complications include infertility, chronic pelvic pain, and ectopic pregnancy. Diagnosis includes PCR of cervical specimens for Neisseria gonorrhoeae and chlamydiae, microscopic examination of cervical discharge (usually), and ultrasonography or laparoscopy (occasionally). Treatment is
with antibiotics.

PID results from microorganisms ascending from the vagina and cervix into the endometrium and fallopian tubes. Infection of the cervix (cervicitis) causes mucopurulent discharge. Infection of the fallopian tubes (salpingitis) and uterus (endometritis) tend to occur together. If severe, infection can spread to the ovaries (oophoritis) and then the peritoneum (peritonitis). Salpingitis with endometritis and oophoritis, with or without peritonitis, is often called salpingitis even though other structures are involved.

*Neisseria gonorrhoeae* and *Chlamydia trachomatis* are common causes of PID; they are transmitted sexually. PID usually also involves other aerobic and anaerobic bacteria, including pathogens that cause bacterial vaginosis (see p. 2543).

PID commonly occurs in women < 35. It is rare before menarche, after menopause, and during pregnancy. Risk factors include previous PID and presence of bacterial vaginosis or any sexually transmitted disease. Other risk factors, particularly for gonorrheal or chlamydial PID, include younger age, non-white race, low socioeconomic status, and multiple or new sex partners.

**Symptoms and Signs**

Lower abdominal pain, fever, cervical discharge, and abnormal uterine bleeding are common, particularly during or after menses.

**Cervicitis:** The cervix appears red and bleeds easily. Mucopurulent discharge is common; usually, it is yellow-green and can be seen exuding from the endocervical canal.

**Acute salpingitis:** Lower abdominal pain is usually present and bilateral but may be unilateral, even when both tubes are involved. Pain can also occur in the upper abdomen. Nausea and vomiting are common when pain is severe. Irregular bleeding and fever each occur in up to one third of patients. In the early stages, signs may be mild or absent. Later, cervical motion tenderness, guarding, and rebound tenderness are common. Occasionally, dyspareunia or dysuria occurs. Many women with inflammation that is severe enough to cause scarring have minimal or no symptoms.

PID due to *N. gonorrhoeae* is usually more acute and causes more severe symptoms than that due to *C. trachomatis*, which can be indolent.

**Complications:** Acute gonococcal or chlamydial salpingitis may lead to the Fitz-Hugh-Curtis syndrome (pericholangitis that causes upper right quadrant pain). Infection may become chronic, characterized by intermittent exacerbations and remissions.

A tubo-ovarian abscess (collection of pus in the adnexa) develops in about 15% of women with salpingitis. It can accompany acute or chronic infection and is more likely if treatment is late or incomplete. Pain, fever, and peritoneal signs are usually present and may be severe. The abscess may rupture, causing progressively severe symptoms and possibly septic shock. Hydrosalpinx (fimbrial obstruction and tubal distention with nonpurulent fluid) is usually asymptomatic but can cause pelvic pressure, chronic pelvic pain, or dyspareunia. Tubo-ovarian abscess, hydrosalpinx, or pyosalpinx (pus confined to one or both fallopian tubes) may produce a palpable adnexal mass and may lead to infertility.

Salpingitis may cause tubal scarring and adhesions, which commonly result in chronic pelvic pain, infertility, and increased risk of ectopic pregnancy. Salpingitis may also result in menstrual irregularities.

**Diagnosis**

- High index of suspicion
- PCR or culture
- Pregnancy test
PID is suspected when women of reproductive age, particularly those with risk factors, have lower abdominal pain or cervical or unexplained vaginal discharge. PID is considered when irregular vaginal bleeding, dyspareunia, or dysuria is unexplained. PID is more likely if lower abdominal, unilateral or bilateral adnexal, and cervical motion tenderness are present. A palpable adnexal mass suggests tubo-ovarian abscess. Because even minimally symptomatic infection may have severe sequelae, index of suspicion should be high.

If PID is suspected, PCR of cervical specimens for *N. gonorrhoeae* and *C. trachomatis* (which is nearly 100% sensitive and specific) and a pregnancy test are done. If PCR is unavailable, cultures are done. At the point of care, cervical discharge is usually examined to confirm purulence; a Gram stain or saline wet mount is used, but these tests are neither sensitive nor specific. If a patient cannot be adequately examined because of tenderness, ultrasonography is done as soon as possible. WBC count may be elevated but is not helpful diagnostically.

If the pregnancy test is positive, ectopic pregnancy, which can produce similar findings, should be considered. Other common causes of pelvic pain include endometriosis, adnexal torsion, ovarian cyst rupture, and appendicitis. Differentiating features of these disorders are discussed elsewhere (see p. 2486). Fitz-Hugh-Curtis syndrome may mimic acute cholecystitis but can usually be differentiated by evidence of salpingitis during pelvic examination or, if necessary, with ultrasonography.

### Table 253-3. Regimens for Treatment of Pelvic Inflammatory Disease*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Antibiotics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cefoxitin</td>
<td>Empirically given for suspected <em>N. gonorrhoeae</em> and <em>C. trachomatis</em>, modified based on laboratory test results.</td>
</tr>
<tr>
<td>2</td>
<td>Ceftriaxone</td>
<td>Always as first-line therapy.</td>
</tr>
<tr>
<td>3</td>
<td>Ceftriaxone plus doxycycline</td>
<td>Recommended for severe cases.</td>
</tr>
</tbody>
</table>

If an adnexal or pelvic mass is suspected clinically or if patients do not respond to antibiotics within 48 to 72 h, ultrasonography is done as soon as possible to exclude tubo-ovarian abscess, pyosalpinx, and disorders unrelated to PID (eg, ectopic pregnancy, adnexal torsion). If the diagnosis is uncertain after ultrasonography, laparoscopy should be done; purulent peritoneal material obtained by laparoscopy is the diagnostic gold standard.

### Treatment

- **Antibiotics to cover** *N. gonorrhoeae*, *C. trachomatis*, and sometimes other organisms

Antibiotics are given empirically to cover *N. gonorrhoeae* and *C. trachomatis* and are modified based on laboratory test results. Patients with cervicitis or clinically mild to moderate PID do not require hospitalization. Outpatient treatment regimens (see Table 253-3) usually also aim to eradicate bacterial vaginosis (see p. 2543), which often coexists. Sex partners of patients with *N. gonorrhoeae* or *C. trachomatis* infection should be treated.

General indications for inpatient treatment include the following:

- Severe illness (eg, peritonitis, dehydration)
- Moderate or severe vomiting
- Pregnancy
- Suspicion of a pelvic mass
- Inability to exclude a surgical emergency (eg, appendicitis)

In these cases, IV antibiotics (see Table 253-3) are started as soon as cultures are obtained and are continued until patients have been afebrile for 24 h.

Tubo-ovarian abscess may require more prolonged IV antibiotics and hospitalization. Treatment with ultrasound- or CT-guided percutaneous or transvaginal drainage can be considered if response to antibiotics alone is incomplete. Laparoscopy or laparotomy is sometimes required for drainage. Suspicion of a ruptured tubo-ovarian abscess requires immediate laparotomy. In women of reproductive age,
surgery should aim to preserve the pelvic organs (with the hope of preserving fertility).
Chapter 254. Medical Examination of the Rape Victim

Introduction

Although legal and medical definitions vary, rape is typically defined as oral, anal, or vaginal penetration that involves threats or force against an unwilling person. Such penetration, whether wanted or not, is considered statutory rape if victims are younger than the age of consent. Sexual assault is rape or any other sexual contact that results from coercion, including seduction of a child through offers of affection or bribes; it also includes being touched, grabbed, kissed, or shown genitals. Rape and sexual assault, including childhood sexual assault, are common; the lifetime prevalence estimates for both ranges from 2 to 30% but tends to be about 15 to 20%. However, actual prevalence may be higher because rape and sexual assault tend to be underreported.

Typically, rape is an expression of aggression, anger, or need for power; psychologically, it is more violent than sexual. Nongenital or genital injury occurs in about 50% of rapes of females.

Females are raped and sexually assaulted more often than males. Male rape is often committed by another man, often in prison. Males who are raped are more likely than females to be physically injured, to be unwilling to report the crime, and to have multiple assailants.

Symptoms and Signs

Rape may result in the following:

- Extragenital injury
- Genital injury
- Psychologic symptoms
- Sexually transmitted diseases (STDs—eg, hepatitis, syphilis, gonorrhea, chlamydial infection, trichomoniasis, HIV infection [rarely])
- Pregnancy (uncommonly)

Most physical injuries are relatively minor, but some lacerations of the upper vagina are severe. Additional injuries may result from being struck, pushed, stabbed, or shot.

Psychologic symptoms of rape are potentially the most prominent. In the short term, most patients experience fear, nightmares, sleep problems, anger, embarrassment, shame, guilt, or a combination. Immediately after an assault, patient behavior can range from talkativeness, tenseness, crying, and trembling to shock and disbelief with dispassion, quiescence, and smiling. The latter responses rarely indicate lack of concern; rather, they reflect avoidance reactions, physical exhaustion, or coping mechanisms that require control of emotion. Anger may be displaced onto hospital staff members.

Friends, family members, and officials often react judgmentally, derisively, or in another negative way. Such reactions can impede recovery after an assault.

Eventually, most patients recover; however, long-range effects of rape may include post-traumatic stress disorder (PTSD—see p. 1500), particularly among women. PTSD is an anxiety disorder; symptoms include re-experiencing (eg, flashbacks, intrusive upsetting thoughts or images), avoidance (eg, of trauma-related situations, thoughts, and feelings), and hyperarousal (eg, sleep difficulties, irritability, concentration problems). Symptoms last for > 1 mo and significantly impair social and occupational functioning.

Evaluation

Goals of rape evaluation are
• Medical assessment and treatment of injuries and assessment, treatment, and prevention of pregnancy and STDs

• Collection of forensic evidence

• Psychologic evaluation

• Psychologic support

If patients seek advice before medical evaluation, they are told not to throw out or change clothing, wash, shower, douche, brush their teeth, or use mouthwash; doing so may destroy evidence.

Whenever possible, all people who are raped are referred to a local rape center, often a hospital emergency department; such centers are staffed by specially trained practitioners (eg, sexual assault nurse examiners). Benefits of a rape evaluation are explained, but patients are free to consent to or decline the evaluation. The police are notified if patients consent. Most patients are greatly traumatized, and their care requires sensitivity, empathy, and compassion. Females may feel more comfortable with a female physician; a female staff member should accompany all males evaluating a female. Patients are provided privacy and quiet whenever possible.

A form (sometimes part of a rape kit) is used to record legal evidence and medical findings (for typical elements in the form, see Table 254-1); it should be adapted to local requirements. Because the medical record may be used in court, results should be written legibly and in nontechnical language that can be understood by a jury.

**History and examination:** Before beginning, the examiner asks the patient's permission. Because recounting the events often frightens or embarrasses the patient, the examiner must be reassuring, empathetic, and nonjudgmental and should not rush the patient. Privacy should be ensured. The examiner elicits specific details, including

• Type of injuries sustained (particularly to the mouth, breasts, vagina, and rectum)

• Any bleeding from or abrasions on the patient or assailant (to help assess the risk of transmission of HIV and hepatitis)

• Description of the attack (eg, which orifices were penetrated, whether ejaculation occurred or a condom was used)

• Assailant's use of aggression, threats, weapons, and violent behavior

• Description of the assailant

Many rape forms include most or all of these questions (see Table 254-1). The patient should be told why questions are being asked (eg, information about contraceptive use helps determine risk of pregnancy after rape; information about previous coitus helps determine validity of sperm testing).

The examination should be explained step by step as it proceeds. Results should be reviewed with the patient. When feasible, photographs of possible injuries are taken. The mouth, breasts, genitals, and rectum are examined closely. Common sites of injury include the labia minora and posterior vagina. Examination using a Wood's lamp may detect semen or foreign debris on the skin. Colposcopy is particularly sensitive for subtle genital injuries. Some colposcopes have cameras attached, making it possible to detect and photograph injuries simultaneously. Whether use of toluidine blue to highlight areas of injury is accepted as evidence varies by jurisdiction.

**Testing and evidence collection:** Routine testing includes a pregnancy test and serologic tests for syphilis, hepatitis B, and HIV; if done within a few hours of rape, these tests provide information about pregnancy or infections present before the rape but not those that develop after the rape. Vaginal
discharge is examined to check for trichomonal vaginitis and bacterial vaginosis; samples from every penetrated orifice (vaginal, oral, or rectal) are obtained for gonorrheal and chlamydial testing. If the patient has amnesia for events around the time of rape, drug screening for flunitrazepam (the date rape drug) and gamma hydroxybutyrate should be considered. Testing for drugs of abuse and alcohol is controversial because evidence of intoxication may be used to discredit the patient.

Follow-up tests for the following are done:

• At 6 wk: Gonorrhea, chlamydial infection, human papillomavirus infection (initially using a cervical sample from a Papanicolaou test), syphilis, and hepatitis

• At 90 days: HIV infection

• At 6 mo: Syphilis, hepatitis, and HIV infection

However, testing for STDs is controversial because evidence of preexisting STDs may be used to discredit the patient in court.

If the vagina was penetrated and the pregnancy test was negative at the first visit, the test is repeated within the next 2 wk. Patients with lacerations of the upper vagina, especially children, may require laparoscopy to determine depth of the injury.

Evidence that can provide proof of rape is collected; it typically includes clothing; smears of the buccal, vaginal, and rectal mucosa; combed samples of scalp and pubic hair as well as control samples (pulled from the patient); fingernail clippings and scrapings; blood and saliva samples; and, if available, semen (see Table 254-1). Many types of evidence collection kits are available commercially, and some states recommend specific kits. Evidence is often absent or inconclusive after showering, changing clothes, or activities that involve sites of penetration, such as douching. Evidence becomes weaker or disappears as time passes, particularly after > 36 h; however, depending on the jurisdiction, evidence may be collected up to 7 days after rape.

A chain of custody, in which evidence is in the possession of an identified person at all times, must be maintained. Thus, specimens are placed in individual packages, labeled, dated, sealed, and held until delivery to another person (typically, law enforcement or laboratory personnel), who signs a receipt. In some jurisdictions, samples for DNA testing to identify the assailant are collected.

Treatment

• Psychologic support or intervention

• Prophylaxis for STDs and possibly hepatitis B or HIV infection

• Possibly emergency contraception

After the evaluation, the patient is provided with facilities to wash, change clothing, use mouthwash, and urinate or defecate if needed. A local rape crisis team can provide referrals for medical, psychologic, and legal support services.

Most injuries are minor and are treated conservatively. Vaginal lacerations may require surgical repair.

Psychologic support: Sometimes examiners can use commonsense measures (eg, reassurance, general support, nonjudgmental attitude) to relieve strong emotions of guilt or [Table 254-1, Typical Examination for Alleged Rape]

anxiety. Possible psychologic and social effects are explained, and the patient is introduced to a specialist trained in rape crisis intervention. Because the full psychologic effects cannot always be ascertained at the first examination, follow-up visits are scheduled at 2-wk intervals. Severe psychologic effects (eg,
persistent flashbacks, significant sleep disruption, fear leading to significant avoidance) or psychologic effects still present at follow-up visits warrant psychiatric or psychologic referral.

Family members and friends can provide vital support, but they may need help from rape crisis specialists in handling their own negative reactions.

PTSD can be effectively treated psychosocially and pharmacologically (see p. 1501).

**Prevention of infections:** Routine empiric prophylaxis for STDs consists of ceftriaxone 125 mg IM in a single dose (for gonorrhea), metronidazole 2 g po in a single dose (for trichomoniasis and bacterial vaginosis), and either doxycycline 100 mg po bid for 7 days or azithromycin 1 g po once (for chlamydial infection). Alternatively, azithromycin 2 g po (which covers gonorrhea and chlamydial infection) can be given with metronidazole 2 g po, both as a single dose.

Empiric prophylactic treatment of hepatitis B and HIV after rape is controversial. For hepatitis B, the CDC recommends hepatitis B vaccination unless the patient has been previously vaccinated and has documented immunity. The vaccine is repeated 1 and 6 mo after the first dose. Hepatitis B immune globulin (HBIG) is not given. For HIV, most authorities recommend offering prophylaxis; however, the patient should be told that on average, the risk after rape from an unknown assailant is only about 0.2%. Risk may be higher with any of the following:

- Anal penetration
- Bleeding (assailant or victim)
- Male-male rape
- Rape by multiple assailants (eg, male victims in prisons)
- Rape in areas with a high prevalence of HIV infection

Treatment is best begun < 4 h after penetration and should not be given after > 72 h. Usually, a fixed-dose combination of zidovudine (ZDV) 300 mg and lamivudine (3TC) 150 mg is given bid for 4 wk if exposure appears low risk. If risk is higher, a protease inhibitor is added (see p. 1455).

**Prevention of pregnancy:** Although pregnancy caused by rape is rare (except in the few days before ovulation), emergency contraception (see p. 2590) should be offered to all women with a negative pregnancy test. Usually, oral contraceptives are used; if used > 72 h after rape, they are much less likely to be effective. An antiemetic may help if nausea develops. An intrauterine device may be effective if used up to 10 days after rape. If pregnancy results from rape, the patient's attitude toward the pregnancy and abortion should be determined, and if appropriate, the option of elective termination should be discussed.
Chapter 255. Breast Disorders

Introduction

Breast symptoms (eg, lumps, nipple discharge, pain) are common, accounting for > 15 million physician visits/yr. Although > 90% of symptoms have benign causes, breast cancer is always a concern. Because breast cancer is common and may mimic benign disorders, the approach to all breast symptoms and findings is to conclusively exclude or confirm cancer.

Evaluation

History: History includes the following:

• Duration of symptoms

• Relation of symptoms to menses and pregnancy

• Presence and type of pain, discharge, and skin changes

• Use of drugs, including hormone therapy

• Personal and family history of breast cancer

• Date and results of last mammogram

Breast examination: Principles of examination are similar for physician and patient. Breasts are inspected for asymmetry in shape, nipple inversion, bulging, and dimpling (see Fig. 255-1A and B for usual positions). Although size differential is common, each breast should have a regular contour. An underlying cancer is sometimes detected by having the patient press both hands against the hips or the palms together in front of the forehead (see Fig. 255-1C and D). In these positions, the pectoral muscles are contracted, and a subtle dimpling of the skin may appear if a growing tumor has entrapped a Cooper's ligament. The nipples are squeezed to check for discharge.

The axillary and supraclavicular lymph nodes are most easily examined with the patient seated or standing (see Fig. 255-1E). Supporting the patient's arm during the axillary examination allows the arm to be fully relaxed so that nodes deep within the axilla can be palpated.

The breast is palpated with the patient seated and again with the patient supine, the ipsilateral arm above the head, and a pillow under the ipsilateral shoulder (see Fig. 255-1F). The latter position is also used for breast self-examination; the patient examines the breast with her contralateral hand. Having the patient roll to one side, so that the breast on the examined side falls medially, may help differentiate breast and chest wall tenderness because the chest wall can be palpated separately from breast tissue.

(Fig. 255-1, Breast examination.)

The breast should be palpated with the palmar surfaces of the 2nd, 3rd, and 4th fingers, moving systematically in a small circular pattern from the nipple to the outer edges (see Fig. 255-1G). Precise location and size (measured with a caliper) of any abnormality should be noted on a drawing of the breast, which becomes part of the patient's record. A written description of the consistency of the abnormality and degree to which it can be distinguished from surrounding breast tissue should also be included. Detection of abnormalities during physical examination largely determines whether a biopsy is needed, even if a subsequent mammogram shows no abnormalities.

Testing: Imaging tests are used for screening and for evaluation of breast abnormalities. Annual screening mammography is recommended for women ≥ 50 yr and sometimes for women 40 to 50 yr (see p. 2561). Mammography is more effective in older women because with aging, fibroglandular tissue in breasts tends to be replaced with fatty tissue, which can be more easily distinguished from abnormal tissue. Low-dose x-rays of both breasts are taken in 1 (oblique) or 2 views (oblique and craniocaudal).
Only about 10% of abnormalities detected result from cancer. Accuracy of mammography depends partly on the techniques used and experience of the mammographer; false-negative results may exceed 15%. Some centers use computer analysis of digitized mammography images to help in diagnosis. Such systems are not recommended for stand-alone diagnosis, but they appear to improve sensitivity for detecting small cancers by radiologists.

Mammography is also used diagnostically to evaluate lumps, pain, and nipple discharge. It can determine size and location of a lesion and provide images of surrounding tissues and lymph nodes. Diagnostic mammography requires more views than screening mammography. For biopsy of a lesion seen on a mammogram but not detectable during physical examination, 2 needles or wires can be inserted via radiologic guidance to localize the lesion. The excised specimen should be x-rayed, and the x-ray compared with the prebiopsy mammogram to determine whether the lesion has been removed. Mammography is repeated when the breast is no longer tender, usually 6 to 12 wk after biopsy, to confirm removal of the lesion.

MRI is thought to be more accurate than clinical breast examination or mammography for screening women with a high (eg, > 15%) risk of breast cancer, such as those with a BRCA gene mutation. It is not considered appropriate for screening women with average or slightly increased risk. Because MRI can accurately determine tumor size, chest wall involvement, and presence of multiple tumors, it is often used in evaluation after breast cancer is diagnosed. Use of MRI to identify axillary node involvement is under study.

**Breast Lumps**

A breast lump may be discovered by patients incidentally or during breast self-examination or by the clinician during routine physical examination. Lumps may be painless or painful and are sometimes accompanied by nipple discharge or skin changes.

**Etiology**

Although cancer is the most feared cause, most breast lumps are nonmalignant. The most common causes include

- Fibrocystic changes
- Fibroadenomas

**Fibrocystic changes** (previously, fibrocystic disease) is a catchall term that refers to mastalgia, breast cysts, and nondescript lumpiness, which may occur in isolation or together; breasts have a nodular and dense texture and are frequently tender when palpated. Fibrocystic changes cause the most commonly reported breast symptoms and have many causes. Most causes are not associated with increased risk of cancer; they include adenosis, ductal ectasia, simple fibroadenoma, fibrosis, mastitis, mild hyperplasia, cysts, and apocrine or squamous metaplasia. Other causes, particularly if fibrocystic changes require biopsy, may slightly increase risk of breast cancer. Fibrocystic changes are more common among women who had early menarche, who had their first live birth at age > 30, or who are nulliparous.

**Fibroadenomas** are typically painless lumps that feel like small, slippery marbles. They usually develop in young women, often in adolescents, and may be mistaken for cancer, although they are benign and tend to be more circumscribed and mobile. Simple fibroadenoma does not appear to increase risk of breast cancer; complex fibroadenoma may increase risk slightly.

**Breast infections** (mastitis) causes pain, erythema, and swelling; an abscess can produce a discrete mass. Infections are extremely rare except during the puerperium (postpartum) or after penetrating trauma. They may occur after breast surgery. Puerperal mastitis, usually due to Staphylococcus aureus, can cause massive inflammation and severe breast pain, sometimes with an abscess. If infection occurs under other circumstances, an underlying cancer should be sought promptly.

**Galactocele** is a round, easily movable milk-filled cyst that usually occurs up to 6 to 10 mo after lactation.
Cancers of various types can manifest as a lump. About 5% of patients have pain.

Evaluation

History: History of present illness should include how long the lump has been present and whether it comes and goes or is painful. Previous occurrence of lumps and the outcome of their evaluation should be queried.

Review of systems should determine whether nipple discharge is present and, if present, whether it is clear, milky, or bloody. Symptoms of advanced cancer (eg, weight loss, malaise, bone pain) should be sought.

Past medical history should include risk factors for breast cancer, including previous diagnosis of breast cancer, history of radiation therapy to the chest area before age 30 (eg, for Hodgkin lymphoma). Family history should note breast cancer in a 1st-degree relative (mother, sister, daughter) and, if family history is positive, whether the relative carried one of the 2 known breast cancer genes, BRCA1 or BRCA2.

Physical examination: Examination focuses on the breast and adjacent tissue. The breast is inspected for skin changes over the area of the lump and the presence of any nipple discharge. Skin changes include erythema, exaggeration of normal skin markings, and trace edema sometimes termed peau d'orange (orange peel). The lump is palpated for size, tenderness, consistency (ie, hard or soft, smooth or irregular), and mobility (whether it feels freely mobile or fixed to the skin or chest wall). The axillary, supraclavicular, and infraclavicular areas are palpated for masses and adenopathy.

Red flags: Certain findings are of particular concern:

- Lump fixed to the skin or chest wall
- Stony hard, irregular lump
- Skin dimpling
- Matted or fixed axillary lymph nodes
- Bloody nipple discharge

Interpretation of findings: Painful, tender, rubbery lumps in younger women with a history of similar findings suggest fibrocystic changes.

Red flag findings suggest cancer. However, the characteristics of benign and malignant lesions, including presence or absence of risk factors, overlap considerably. For this reason and because failure to recognize cancer has serious consequences, most patients require testing to more conclusively exclude breast cancer.

Testing: Initially, physicians try to differentiate solid from cystic lumps because cysts are rarely cancerous. Typically, ultrasonography is done. Lesions that appear cystic are sometimes aspirated, and solid lumps are evaluated with mammography followed by imaging-guided biopsy (see p. 2560). Some physicians evaluate all lumps with needle aspiration; if no fluid is obtained or if aspiration does not eliminate the lump, mammography followed by imaging-guided biopsy is done.

Fluid aspirated from a cyst is sent for cytology only if it is bloody, if minimal fluid is obtained, or if a mass remains after aspiration. Patients are reexamined in 4 to 8 wk. If the cyst is no longer palpable, it is considered benign. If the cyst has recurred, it is reaspirated, and any fluid is sent for cytology regardless of appearance. A 3rd recurrence or persistence of the mass after initial aspiration (even if cytology was negative) requires biopsy.
Treatment

Treatment is directed at the cause. Fibroadenomas can usually be excised using a local anesthetic, but they frequently recur. After patients have had several fibroadenomas established as benign, they may decide against having subsequent ones excised.

Acetaminophen, NSAIDs, and athletic bras (to reduce trauma) can be used to relieve symptoms of fibrocystic changes. Vitamin E is sometimes used but has not been proved to be effective.

Key Points

• Most breast lumps are not cancer.

• Clinical features of benign and malignant disease overlap so much that testing should usually be done.

Nipple Discharge

Nipple discharge is a common complaint in women who are not pregnant or breastfeeding, especially during the reproductive years. Nipple discharge is not necessarily abnormal, even among postmenopausal women, although it is always abnormal in men.

Nipple discharge can be serous (yellow), mucinous (clear and watery), milky, sanguineous (bloody), purulent, multicolored and sticky, or serosanguineous (pink). It may occur spontaneously or only in response to breast manipulation.

Pathophysiology

Nipple discharge may be breast milk or an exudate produced by a number of conditions.

Breast milk production in nonpregnant and nonlactating women (galactorrhea) typically involves an elevated prolactin level, which stimulates glandular tissue of the breast. However, only some patients with elevated prolactin levels develop galactorrhea.

Etiology

Most frequently, nipple discharge has a benign cause (see Table 255-1). Cancer (usually intraductal carcinoma or invasive ductal carcinoma) causes < 10% of cases. The rest result from benign ductal disorders (eg, intraductal papilloma, mammary duct ectasia, fibrocystic changes), endocrine disorders, or breast abscesses or infections. Of these causes, intraductal papilloma is probably the most common; it is also the most common cause of a bloody nipple discharge without a breast mass.

Endocrine causes involve elevation of prolactin levels, which has numerous causes.

Evaluation

History: History of present illness should include whether the current discharge is unilateral or bilateral, what its color is, how long it has lasted, whether it is spontaneous or occurs only with nipple stimulation, and whether a lump or pain is present.

Review of symptoms should seek symptoms suggesting possible causes, including fever (mastitis or breast abscess); cold intolerance, constipation, or weight gain (hypothyroidism); amenorrhea, infertility, headache, or visual disturbances (pituitary tumor); and ascites or jaundice (liver disorders).

Past medical history should include possible causes of hyperprolactinemia, including chronic renal failure, pregnancy, liver disorders,
Table 255-1. Some Causes of Nipple Discharge

and thyroid disorders, as well as history of infertility, hypertension, depression, breastfeeding, menstrual patterns, and cancer. Clinicians should ask specifically about drugs that can cause prolactin release such as oral contraceptives, antihypertensive drugs (eg, methyldopa, reserpine, verapamil), H2-antagonists (eg, cimetidine, ranitidine), opioids, and dopamine D2 antagonists (eg, many psychoactive drugs, including phenothiazines and tricyclic anti-depressants).

**Physical examination:** Physical examination focuses on the breasts. The breasts are inspected for symmetry, dimpling of the skin, erythema, swelling, color changes in the nipple and skin, and crusting, ulceration, or retraction of the nipple. The breasts are palpated for masses and evidence of lymphadenopathy in the axillary or supraclavicular region. If there is no spontaneous discharge, the area around the nipples is systematically palpated to try to stimulate a discharge. A bright light and magnifying lens can help assess whether the nipple discharge is uniductal or multiductal.

**Red flags:** Certain findings are of particular concern:

- Spontaneous discharge
- Age ≥ 40
- Unilateral discharge
- Bloody or guaiac-positive discharge
- Palpable mass
- Male sex

**Interpretation of findings:** Important differentiating points are whether a mass is present, whether the discharge involves one or multiple ducts (either one or more ducts in both breasts or more than one duct in one breast), and whether the discharge is bloody (including guaiac-positive).

If a mass is present, cancer must be considered. Because cancer rarely involves both breasts or multiple ducts at presentation, a bilateral, guaiac-negative discharge suggests an endocrine cause, as does unilateral, multiductal discharge. However, if the discharge is guaiac-positive or involves only one duct, cancer must be considered.

For other suggestive findings, see Table 255-1.

**Testing:** If endocrine causes are suspected, the following are done:

- Prolactin level
- Thyroid-stimulating hormone (TSH) level

If discharge is guaiac-positive, the following is done:

- Cytology

If there is a palpable mass, evaluation as for breast lump, usually beginning with

- Ultrasonography

Lesions that appear cystic are sometimes aspirated, and solid lumps or any that remain after aspiration are evaluated with mammography followed by imaging-guided biopsy.

If there is no mass but cancer is otherwise suspected or if other tests are indeterminate
• Mammography

Abnormal results are evaluated by imaging-guided biopsy. If no lump is palpable and mammogram is normal, cancer is highly unlikely.

**Treatment**

Treatment is based on the cause.

If the cause is benign and the discharge is persistent and annoying, a nipple-flap duct resection, usually done as an outpatient procedure using a local anesthetic, can eliminate the discharge and relieve the patient's anxiety.

**Key Points**

• Nipple discharge is most often benign.
• Bilateral, multiductal, guaiac-negative discharge is usually benign and has an endocrine etiology.
• Unilateral, uniductal, bloody (or guaiac-positive) discharge could be cancer, especially in patients ≥ 40.
• Presence of a breast mass, a bloody (or guaiac-positive) discharge, or history of an abnormal mammogram or abnormal ultrasound requires follow-up with a surgical clinician who is experienced with breast disorders.

**Mastalgia**

Mastalgia (breast pain) is common and can be localized or diffuse and unilateral or bilateral.

**Etiology**

Localized breast pain is usually caused by a focal disorder that causes a lump (see p. 2554), such as a breast cyst, or an infection (eg, mastitis, abscess). Most breast cancers do not cause pain.

Diffuse, bilateral pain may be caused by fibrocystic changes or, uncommonly, diffuse, bilateral mastitis. However, diffuse bilateral pain is very common in women without breast abnormalities. The most common causes are

• Hormonal changes that cause breast tissue proliferation (eg, during the luteal phase or early pregnancy, in women taking estrogens or progestins)
• Large, pendulous breasts that stretch Cooper's ligaments

**Evaluation**

**History: History of present illness** should address the temporal pattern of pain and its nature (focal or diffuse, unilateral or bilateral). The relation between chronic or recurrent pain and menstrual cycle phase should be ascertained.

**Review of systems** should address other symptoms suggesting pregnancy (eg, abdominal enlargement, amenorrhea, morning nausea) or fibrocystic changes (eg, lumpiness).

**Past medical history** should cover disorders that could cause diffuse pain (eg, fibrocystic changes) and use of estrogens and progestins.

**Physical examination:** Examination focuses on the breast and adjacent tissue, looking for abnormalities such as skin changes (as for breast lumps—see p. 2554) and signs of infection, such as redness,
warmth, and tenderness.

Red flags: The following are of particular concern:

• Signs of infection

Interpretation of findings: Absence of abnormal findings suggests that pain is due to hormonal changes or large, pendulous breasts. Abnormal findings may suggest other specific problems.

Testing: Pregnancy testing should be done if pain is unexplained and has lasted less than several months, particularly if other symptoms or signs are consistent with pregnancy. Other testing is indicated infrequently—only if physical findings suggest another problem that requires testing.

Treatment

For menstrual-related mastalgia, acetaminophen or an NSAID is usually effective. If pain is severe, a brief course of danazol or tamoxifen may be given. These drugs inhibit estrogen and progesterone. If estrogen or a progestin is being taken, stopping may be necessary. For pregnancy-related breast pain, wearing a firm, supportive brassiere, taking acetaminophen, or both, can help.

Key Points

• Diffuse, bilateral breast pain is usually caused by hormonal changes or large, pendulous breasts and causes no abnormal physical findings.

Breast Cancer

Breast cancer most often involves glandular breast cells in the ducts or lobules. Most patients present with an asymptomatic lump discovered during examination or screening mammography. Diagnosis is confirmed by biopsy. Treatment usually includes surgical excision, often with radiation therapy, with or without adjuvant chemotherapy, hormonal therapy, or both.

About 213,000 new cases were identified in 2006. It is the 2nd leading cause of cancer death in women (after lung cancer), with about 41,000 deaths in 2006. Male breast cancer accounts for < 1% of total cases; manifestations, diagnosis, and management are the same, although men tend to present later.

Risk Factors

In the US, cumulative risk of developing breast cancer is 12% (1 in 8) by age 95, and risk of dying of it is about 4%. Much of the risk is incurred after age 60 (see Table 255-2). These statistics can be misleading because most people die before age 95, and cumulative risk of developing the cancer in any 20-yr period is considerably lower.

Factors that may affect breast cancer risk include the following:

• Family history: Having a 1st-degree relative (mother, sister, daughter) with breast cancer doubles or triples risk of developing the cancer, but breast cancer in more distant relatives increases risk only slightly. When ≥ 2 1st-degree relatives have breast cancer, risk may be 5 to 6 times higher.

• Breast cancer gene: About 5% of women with breast cancer carry a mutation in one of the 2 known breast cancer genes, BRCA1 or BRCA2. If relatives of such a woman also carry the gene, they have a 50 to 85% lifetime risk of developing breast cancer. Women with BRCA1 mutations also have a 20 to 40% lifetime risk of developing ovarian cancer; risk among women with BRCA2 mutations is increased less. Women without a family history of breast cancer in at least 2 1st-degree relatives are unlikely to carry this gene and thus do not require screening for BRCA1 and BRCA2 mutations. Men who carry a BRCA2 mutation also have an increased risk of developing breast cancer. The genes are more
common among Ashkenazi Jews. Women with BRCA1 or BRCA2 mutations may require closer surveillance or preventive measures, such as taking tamoxifen or raloxifene or undergoing double mastectomy.

**Personal history:** Having had in situ or invasive breast cancer increases risk. Risk of developing cancer in the contralateral breast after mastectomy is about 0.5 to 1%/yr of follow-up.

**Gynecologic history:** Early menarche, late menopause, or late first pregnancy increases risk. Women who have a first pregnancy after age 30 are at higher risk than those who are nulliparous.

**Breast changes:** History of fibrocystic changes that require biopsy for diagnosis increases risk slightly. Women with multiple breast lumps but no histologic confirmation of a high-risk pattern should not be considered at high risk. Benign lesions that may slightly increase risk of developing invasive breast cancer include complex fibroadenoma, moderate or florid hyperplasia (with or without atypia), sclerosing adenosis, and papilloma. Risk is about 4 or 5 times higher than average in patients with atypical ductal or lobular hyperplasia and about 10 times higher if they also have a family history of invasive breast cancer in a 1st-degree relative. Increased breast density seen on screening mammography is associated with an increased risk of breast cancer.

**Use of oral contraceptives:** Oral contraceptive use increases risk very slightly (by about 5 more cases per 100,000 women). Risk increases primarily during the years of contraceptive use and tapers off during the 10 yr after stopping. Risk is highest in women who began to use contraceptives before age 20 (although absolute risk is still very low).

**Hormonal therapy:** Postmenopausal hormone (estrogen plus a progestin) therapy appears to increase risk modestly after only 3 yr of use (see also p. 2519). After 5 yr of use, the increased risk is about 7 or 8 more cases per 10,000 women for each year of use (about a 24% increase in relative risk). Use of estrogen alone does not appear to increase risk of breast cancer. Selective estrogen-receptor modulators (eg, raloxifene) reduce the risk of developing breast cancer.

**Radiation therapy:** Exposure to radiation therapy before age 30 increases risk. Mantle-field radiation therapy for Hodgkin lymphoma about quadruples risk of breast cancer over the next 20 to 30 yr.

**Diet:** Diet may contribute to development or growth of breast cancers, but conclusive evidence about the effect of a particular diet (eg, one high in fats) is lacking. Obese postmenopausal women are at increased risk, but there is no evidence that dietary modification reduces risk. For obese women who are menstruating later than normal, risk may be decreased.

### Pathology

Most breast cancers are epithelial tumors that develop from cells lining ducts or lobules; less common are nonepithelial cancers of the supporting stroma (eg, angiosarcoma, primary stromal sarcomas, phyllodes tumor). Cancers are divided into carcinoma in situ and invasive cancer.

Carcinoma in situ is proliferation of cancer cells within ducts or lobules and without invasion of stromal tissue. Usually, ductal carcinoma in situ (DCIS) is detected only by mammography and is localized to one area; it may become invasive. Lobular carcinoma in situ (LCIS) is a nonpalpable lesion usually discovered via biopsy; it is rarely visualized with mammography. LCIS is often multifocal and bilateral. It is not malignant, but its presence indicates increased risk of subsequent invasive carcinoma in either breast; about 1 to 2% of patients with LCIS develop cancer annually.

Invasive carcinoma is primarily adenocarcinoma. About 80% is the infiltrating ductal type; most of the remaining cases are infiltrating lobular. Rare types include medullary, mucinous, and tubular carcinomas.

Paget's disease of the nipple (not to be confused with the metabolic bone disease also called Paget's disease) is a form of ductal carcinoma in situ that extends into the overlying skin of the nipple and areola, manifesting with an inflammatory skin lesion (see p. 754). Characteristic malignant cells called Paget cells are present in the epidermis. The cancer may become invasive.
Pathophysiology

Breast cancer invades locally and spreads initially through the regional lymph nodes, bloodstream, or both. Metastatic breast cancer may affect almost any organ in the body—most commonly, lungs, liver, bone, brain, and skin.

Most skin metastases occur near the site of breast surgery; scalp metastases are also common. Metastatic breast cancer frequently appears years or decades after initial diagnosis and treatment.

Estrogen and progesterone receptors, present in some breast cancers, are nuclear hormone receptors that promote DNA replication and cell division when the appropriate hormones bind to them. Thus, drugs that block these receptors may be useful in treating tumors with the receptors. About two thirds of postmenopausal patients have an estrogen-receptor positive (ER+) tumor. Incidence of ER+ tumors is lower among premenopausal patients.

Another cellular receptor is human epidermal growth factor receptor 2 (HER2; also, HER2/neu or ErbB2); its presence correlates with a poorer prognosis at any given stage of cancer.

Symptoms and Signs

Most breast cancers are discovered as a lump by the patient or during routine physical examination or mammography. Less commonly, the presenting symptom is breast pain or enlargement or a nondescript thickening in the breast. Paget's disease of the nipple manifests as skin changes, including erythema, crusting, scaling, and discharge; these changes usually appear so benign that the patient ignores them, delaying diagnosis for a year or more. About 50% of patients with Paget's disease of the nipple have a palpable mass at presentation. A few patients with breast cancer present with signs of metastatic disease (eg, pathologic fracture, pulmonary dysfunction).

A common finding during physical examination is a dominant mass—a lump distinctly different from the surrounding breast tissue. Diffuse fibrotic changes in a quadrant of the breast, usually the upper outer quadrant, are more characteristic of benign disorders; a slightly firmer thickening in one breast but not the other may be a sign of cancer. More advanced breast cancers are characterized by fixation of the lump to the chest wall or to overlying skin, by satellite nodules or ulcers in the skin, or by exaggeration of the usual skin markings resulting from lymphedema (so-called peau d'orange). Matted or fixed axillary lymph nodes suggest tumor spread, as does supraclavicular or infraclavicular lymphadenopathy. Inflammatory breast cancer is characterized by diffuse inflammation and enlargement of the breast, often without a lump, and has a particularly aggressive course.

Diagnosis

- Screening by mammography, breast examination, or sometimes MRI
- Biopsy, including analysis for estrogen and progesterone receptors and for HER2 protein

Testing is required to differentiate benign lesions from cancer. Because early detection and treatment of breast cancer improves prognosis, this differentiation must be conclusive before evaluation is terminated.

If advanced cancer is suspected based on physical examination, biopsy should be done first; otherwise, the approach is as for breast lumps (see p. 2554). A prebiopsy bilateral mammogram may help delineate other areas that should be biopsied and provides a baseline for future reference. However, mammogram results should not alter the decision to do a biopsy if that decision is based on physical findings. Biopsy can be needle or incisional biopsy or, if the tumor is small, excisional biopsy. Any skin taken with the biopsy specimen should be examined because it may show cancer cells in dermal lymphatic vessels. Routinely, stereotactic biopsy (needle biopsy during mammography) or ultrasound-guided biopsy is being used to improve accuracy.

Evaluation after cancer diagnosis: Part of a positive biopsy specimen should be analyzed for estrogen
and progesterone receptors and for HER2 protein.

WBCs should be tested for **BRCA1** and **BRCA2** genes when

- Family history includes multiple cases of early-onset breast cancer.
- Ovarian cancer develops in patients with a family history of breast or ovarian cancer.
- Breast and ovarian cancers occur in the same patient.
- Patients have an Ashkenazi Jewish heritage.
- Family history includes a single case of male breast cancer.

Chest x-ray, CBC, and liver function tests and serum Ca should be done to check for metastatic disease. Generally, measuring serum carcinoembryonic antigen (CEA), cancer antigen (CA) 15-3, or CA 27-29 is not recommended because results have no effect on treatment or outcome.

Bone scanning should be done if patients have any of the following:

- Tumors > 2 cm
- Bone pain
- Lymph node involvement
- Elevated serum alkaline phosphatase or Ca levels

Abdominal CT is done if patients have any of the following:

- Abnormal liver function results
- Hepatomegaly
- Locally advanced cancer with or without axillary lymph node involvement

MRI is often used to evaluate breast cancer after it is diagnosed because MRI can accurately determine tumor size, chest wall involvement, and presence of multiple tumors. Use of MRI to identify axillary node involvement is under study.

**Grading** is based on histologic examination of the tissue taken during biopsy.

**Staging** follows the TNM (tumor, node, metastasis) classification. Staging is refined during surgery, when regional lymph nodes can be evaluated.

**Screening:** Screening includes mammography, clinical breast examination (CBE) by health care practitioners, MRI (for high-risk patients), and monthly breast self-examination (BSE).

**Mammography**, done annually, is recommended for women ≥ 50; it reduces mortality rate by 25 to 35% in this age group. Mammography is more accurate in older women, partly because with aging, fibroglandular tissue in breasts tends to be replaced with fatty tissue, which can be more easily distinguished from abnormal tissue. However, there is considerable disagreement about screening for women 40 to 50 yr; recommendations include annual mammography (American Cancer Society), mammography every 1 to 2 yr (National Cancer Institute), and no periodic mammography (American College of Physicians). Concerns about screening too soon or too often include increased radiation exposure and overdiagnosis of tumors (eg, DCIS) that may not develop into invasive cancer during the patient's lifetime. Young age at the time of radiation exposure increases the risk of cancer.
Only about 10% of abnormalities detected on screening mammography result from cancer, and false-negative results may exceed 15%. Accuracy depends partly on the techniques used and experience of the mammographer. Some centers use computer analysis of digitized mammography images (full-field digital mammography) to help in diagnosis. Such systems may be slightly more sensitive for invasive cancers in women < 50 when results are interpreted by radiologists, but probably not when interpreted primarily via computer detection.

CBE is usually part of routine annual care for women > 35; it can detect 7 to 10% of cancers that cannot be seen on a mammogram. In the US, CBE augments rather than replaces screening mammography. However, in some countries where mammography is considered too expensive, CBE is the sole screen; reports on its effectiveness in this role vary.

MRI is thought to be better than CBE or mammography for screening women with a high (eg, > 15%) risk of breast cancer, such as those with a BRCA gene mutation. MRI has higher sensitivity but may be less specific. Because specificity is lower, MRI is not considered appropriate for screening women with average or slightly increased risk.

BSE alone has not been shown to reduce mortality rate, but evidence of its usefulness is mixed, and it is widely practiced. Because a negative BSE may tempt some women to forego mammography or CBE, the need for these procedures should be reinforced when BSE is taught. Patients should be instructed to do BSE on the same day each month. For menstruating women, 2 or 3 days after menses ends is recommended because breasts are less likely to be tender and swollen.

Prognosis

Long-term prognosis depends on tumor stage (see Table 255-3). Nodal status (including number and location of nodes) correlates with disease-free and overall survival better than any other prognostic factor.

Poor prognosis is associated with the following other factors:

• **Young age**: Prognosis appears worse for patients diagnosed with breast cancer during their 20s and 30s than for patients diagnosed during middle age.

• **Larger primary tumor**: Larger tumors are more likely to be node-positive, but they also confer a worse prognosis independent of nodal status.

• **High-grade tumor**: Patients with poorly differentiated tumors have a worse prognosis.

• **Absence of estrogen and progesterone receptors**: Patients with ER+ tumors have a somewhat better prognosis and are more likely to benefit from hormone therapy. Patients with progesterone receptors on a tumor may also have a better prognosis. Patients with both estrogen and progesterone receptors on a tumor may have a better prognosis than those who have only one of these receptors, but this benefit is not clear.

• **Presence of HER2 protein**: When the HER2 gene (HER2/neu [erb-b2]) is amplified, HER2 is overexpressed, increasing cell growth and reproduction and often resulting in more aggressive tumor cells. Overexpression of HER2 is an independent risk factor for a poor prognosis; it may also be associated with high histologic grade, ER-tumors, greater proliferation, and larger tumor size, which are all poor prognostic factors.

• **Presence of BRCA genes**: For any given stage, patients with the BRCA1 gene appear to have a worse prognosis than those with sporadic tumors, perhaps because they have a higher proportion of high-grade, hormone receptor-negative cancers. Patients with the BRCA2 gene probably have the same prognosis as those without the genes if the tumors have
similar characteristics. With either gene, risk of a 2nd cancer in remaining breast tissue is increased (to perhaps as high as 40%).

**Treatment**

- **Surgery**

- **Usually radiation therapy**

- **Sometimes hormone therapy, chemotherapy, or both**

For most patients, primary treatment is surgery, often with radiation therapy. Chemotherapy, hormone therapy, or both may also be used, depending on tumor and patient characteristics (see Table 255-4).

**Surgery:** For patients with invasive cancer, survival rates do not differ significantly whether modified radical mastectomy (simple mastectomy plus lymph node dissection) or breast-conserving surgery plus radiation therapy is used. Breast-conserving surgery includes lumpectomy, wide excision, and quadrantectomy (see Fig. 255-2). Thus, patient preference can guide choice of treatment within limits. The main advantage of breast-conserving surgery plus radiation therapy is cosmetic. In 15% of patients thus treated, cosmetic results are excellent. However, the need for total removal of the tumor with a tumor-free margin overrides cosmetic considerations. With both types of surgery, lymph node dissection or node sampling should be done. Routine use of extensive procedures is not justified because the main value of lymph node removal is diagnostic, not therapeutic. However, results of frozen section analysis may change the extent of surgery needed. Some surgeons get prior agreement for more invasive surgery in case nodes are positive; others wake the patient and do a 2nd procedure if needed.

Some physicians use preoperative chemotherapy to shrink the tumor before removing it and applying radiation therapy; thus, some patients who might otherwise have required mastectomy can have breast-conserving surgery. Early data suggest that this approach does not affect survival.

Radiation therapy after mastectomy significantly reduces incidence of local recurrence on the chest wall and in regional lymph nodes and may improve overall survival in patients with primary tumors > 5 cm or with involvement of ≥ 4 axillary nodes. Adverse effects of radiation therapy (eg, fatigue, skin changes) are usually transient and mild. Late adverse effects (eg, lymphedema, brachial plexopathy, radiation pneumonitis, rib damage, secondary cancers, cardiac toxicity) are less common.

After axillary dissection (or radiation therapy), lymphatic drainage of the ipsilateral arm can be impaired, sometimes resulting in substantial swelling due to lymphedema; magnitude of the effect is roughly proportional to the number of nodes removed.

If lymphedema develops, venipuncture, BP measurement, and IV infusions are usually avoided on the affected side. A specially trained therapist must treat lymphedema. Special massage techniques once or twice daily may help drain fluid from congested areas toward functioning lymph basins; low-stretch bandaging is applied immediately after manual drainage, and patients should exercise daily as prescribed. After the lymphedema resolves, typically in 1 to 4 wk, patients continue daily exercise and overnight bandaging of the affected limb indefinitely.

Alternative node sampling methods include selective fine-needle aspiration of abnormalities identified at the time of breast biopsy (eg, by ultrasonography) and the commonly done sentinel node biopsy. Both result in less lymphedema than lymph node dissection. With sentinel node biopsy, sensitivity for axillary node involvement is ≥ 95%. However, the effect on mortality rate has not been established. For this
biopsy, blue dye or radioactive colloid is injected around the breast, and a scanner is used to locate the first nodes the substance drains into (ie, sentinel nodes). If the sentinel node is cancerous, lymph node dissection is necessary.

**Reconstructive procedures include**

- Submuscular or subcutaneous (less common) placement of a silicone or saline implant
- Use of a tissue expander with delayed placement of the implant
- Muscle flap transfer using the latissimus dorsi or the lower rectus abdominis
- Creation of a free flap by anastomosing the gluteus maximus to the internal mammary vessels

Free flap transfer is being increasingly used for DCIS.

**Adjuvant systemic therapy:** Patients with LCIS are often treated with daily oral tamoxifen. For postmenopausal women, raloxifene is an alternative.

For patients with invasive cancer, chemotherapy or hormone therapy is usually begun soon after surgery and continued for months or years; these therapies delay or prevent recurrence in almost all patients and prolong survival in some. However, some experts believe that these therapies are not necessary for tumors < 1 cm with no lymph node involvement (particularly in postmenopausal patients) because the prognosis is already excellent. If tumors are > 5 cm, adjuvant systemic therapy may be started before surgery.

Relative reduction in risk of recurrence and death with chemotherapy or hormone therapy is the same regardless of the clinical-pathologic stage of the cancer. Thus, absolute benefit is greater for patients with a greater risk of recurrence or death (ie, a 20% relative risk reduction reduces a 10% recurrence rate to 8% but a 50% rate to 40%). Adjuvant chemotherapy reduces annual odds of death (relative risk) on average by 25 to 35% for premenopausal patients; for postmenopausal patients, the reduction is about half of that (9 to 19%), and the absolute benefit in 10-yr survival is much smaller.

Postmenopausal patients with ER-tumors benefit the most from adjuvant chemotherapy (see Table 255-5). However, predictive genomic testing of the primary breast cancer is being used increasingly to determine whether combination chemotherapy or hormone therapy alone is indicated.

Combination chemotherapy regimens (eg, cyclophosphamide, methotrexate, plus 5-fluorouracil; doxorubicin plus cyclophosphamide; docetaxel plus cyclophosphamide) are more effective than a single drug. Regimens given for 4 to 6 mo are preferred; they are as effective as regimens given for 6 to 24 mo. Acute adverse effects depend on the regimen but usually include nausea, vomiting, mucositis, fatigue, alopecia, myelosuppression, and thrombocytopenia. Growth factors that stimulate bone marrow (eg, filgrastim, pegfilgrastim) are commonly used to reduce risk of fever and infection due to chemotherapy. Long-term adverse effects are infrequent with most regimens; death due to infection or bleeding is rare (< 0.2%).

High-dose chemotherapy plus bone marrow or stem cell transplantation offers no therapeutic advantage over standard therapy and should not be used.

If tumors overexpress HER2 (HER2+), adding the humanized monoclonal antibody trastuzumab to chemotherapy provides substantial benefit. Trastuzumab is usually continued for a year, although the optimal duration of therapy is unknown. A serious potential side effect is decreased cardiac ejection fraction.

With hormone therapy (eg, tamoxifen, raloxifene, aromatase inhibitors), benefit is greatest when tumors have estrogen and progesterone receptors, nearly as great when they have only estrogen receptors, minimal when they have only progesterone receptors, and absent when they have neither receptor. In patients with ER+ tumors, particularly low-risk tumors, hormone therapy may be used instead of
chemotherapy.

- **Tamoxifen**: This drug competitively binds with estrogen receptors. Adjuvant tamoxifen for 5 yr reduces annual odds of death by about 25% in premenopausal and postmenopausal women regardless of axillary lymph node involvement; treatment for 2 yr is not as effective, but treatment for > 5 yr has no advantage and may increase the likelihood that any recurrent cancer is tamoxifen-resistant. Tamoxifen can induce or exacerbate menopausal symptoms but reduces incidence of contralateral breast cancer and lowers serum cholesterol. Tamoxifen increases bone density in postmenopausal women and may reduce risk of fractures and ischemic heart disease. However, it significantly increases risk of developing endometrial cancer; reported incidence is 1% in postmenopausal women after 5 yr of use. Thus, if such women have spotting or bleeding, they must be evaluated for endometrial cancer (see p. 2571). Nonetheless, the improved survival for women with breast cancer far outweighs increased risk of death due to endometrial cancer. Risk of thromboembolism is also increased. Raloxifene, although indicated for prevention, is not indicated for treatment.

- **Aromatase inhibitors**: These drugs (anastrozole, exemestane, letrozole) block peripheral production of estrogen in postmenopausal women. More effective than tamoxifen, these drugs are becoming the preferred treatment for early-stage hormone receptor-positive cancer in postmenopausal patients. Letrozole may be used in postmenopausal women who have completed 5 yr of daily tamoxifen. Optimal duration of aromatase inhibitor therapy is uncertain.

**Metastatic disease**: Any indication of metastases should prompt immediate evaluation. Treatment of metastases increases median survival by 6 mo or longer. These treatments (eg, chemotherapy), although relatively toxic, may palliate symptoms and improve quality of life. Thus, the decision to be treated may be highly personal.

Choice of therapy depends on the following:

- Hormone-receptor status of the tumor
- Length of the disease-free interval (from remission to manifestation of metastases)
- Number of metastatic sites and organs affected
- Patient's menopausal status

Systemic hormone therapy or chemotherapy is usually used to treat symptomatic metastatic disease. Initially, patients with multiple metastatic sites outside the CNS should be given systemic therapy. If metastases are asymptomatic, there is no proof that treatment substantially increases survival, and it may reduce quality of life.

Hormone therapy is preferred over chemotherapy for patients with ER+ tumors, a disease-free interval of > 2 yr, or disease that is not immediately life threatening. In premenopausal women, tamoxifen is often used first. Reasonable alternatives include ovarian ablation by surgery, radiation therapy, and use of a luteinizing-releasing hormone agonist (eg, buserelin, goserelin, leuprolide). Some experts combine ovarian ablation with tamoxifen or an aromatase inhibitor. In postmenopausal women, aromatase inhibitors are being increasingly used as primary hormone therapy. If the cancer initially responds to hormone therapy but progresses months or years later, additional forms of hormone therapy (eg, progestins, the antiestrogen fulvestrant) may be used sequentially until no further response occurs.

The most effective chemotherapy drugs are capecitabine, doxorubicin (including its liposomal formulation), gemcitabine, the taxanes paclitaxel and docetaxel, and vinorelbine. Response rate to a combination of drugs is higher than that to a single drug, but survival is not improved and toxicity is increased. Thus, some oncologists use single drugs sequentially.
For tumors that overexpress HER2, trastuzumab is effective in treating and controlling visceral metastatic sites. It is used alone or with hormone therapy or chemotherapy. Lapatinib is being used increasingly. Its role is evolving.

Radiation therapy alone may be used to treat isolated, symptomatic bone lesions or local skin recurrences not amenable to surgical resection. Radiation therapy is the most effective treatment for brain metastases, occasionally providing long-term control.

IV bisphosphonates (eg, pamidronate, zoledronate) decrease bone pain and bone loss and prevent or delay skeletal complications due to bone metastases. About 10% of patients with bone metastases eventually develop hypercalcemia, which can also be treated with IV bisphosphonates.

Prevention

Chemoprevention with tamoxifen or raloxifene is indicated for women with the following:

• Age > 60
• Age > 35 and previous LCIS
• Presence of \textit{BRCA1} or \textit{BRCA2} mutations
• 5-yr risk of developing breast cancer > 1.66% based on the multivariable Gail model, which includes the women's current age, age at menarche, age at first live childbirth, number of 1st-degree relatives with breast cancer, and results of prior breast biopsies


Patients should be informed of risks before beginning chemoprevention. Risks of tamoxifen include uterine cancer, thromboembolic complications, cataracts, and possibly stroke. Risks are higher for older women. Raloxifene appears to be about as effective as tamoxifen in postmenopausal women and to have a lower risk of thromboembolic complications and cataracts. Raloxifene, like tamoxifen, may also increase bone density. Raloxifene should be considered as an alternative to tamoxifen for chemoprevention in postmenopausal women.

Phyllodes Tumor

Phyllodes tumor (cystosarcoma phyllodes) is a nonepithelial breast tumor that may be benign or malignant.

Tumors are frequently large (4 to 5 cm) at diagnosis. About half are malignant, accounting for < 1% of breast cancers. Between 20% and 35% of these tumors recur locally, and distant metastases occur in 10 to 20% of patients.

Usual treatment is wide excision, but a mastectomy may be more appropriate if the mass is large or histology suggests cancer. Prognosis is good unless metastases are present.
Chapter 256. Gynecologic Tumors

Introduction

Gynecologic cancers often involve the uterus, ovaries, cervix, vulva, vagina, fallopian tubes, or, usually secondarily, the peritoneum. The most common gynecologic cancer in the US is endometrial cancer, followed by ovarian cancer. Cervical cancer is not very common in developed countries because Papanicolaou (Pap) test screening is widely available and effective. Gestational trophoblastic disease is a gynecologic tumor that may behave aggressively whether malignant or not.

Many gynecologic cancers manifest as pelvic masses (for diagnostic approach to pelvic masses, see p. 2485).

Ovarian Cancer

Ovarian cancer is often fatal because it is usually advanced when diagnosed. Symptoms are usually absent in early stages and nonspecific in advanced stages. Evaluation usually includes ultrasonography, CT or MRI, and measurement of tumor markers (eg, cancer antigen 125). Diagnosis is by histologic analysis. Staging is surgical. Treatment requires hysterectomy, bilateral salpingo-oophorectomy, excision of as much involved tissue as possible, and, unless cancer is localized, chemotherapy.

In the US, ovarian cancer is the 2nd most common gynecologic cancer (affecting about 1/70) and the deadliest (1% of all women die of it); it is the 5th leading cause of cancer-related deaths in women, causing an estimated 15,000 deaths in 2008. Incidence is higher in developed countries.

Etiology


A personal or family history of endometrial, breast, or colon cancer increases risk. Probably 5 to 10% of ovarian cancer cases are related to mutations in the autosomal dominant BRCA gene, which is associated with a 50 to 85% lifetime risk of developing breast cancer. Women with BRCA1 mutations have a 20 to 40% lifetime risk of developing ovarian cancer; risk among women with BRCA2 mutations is increased less.

XY gonadal dysgenesis predisposes to ovarian germ cell cancer.

Pathology

Ovarian cancers are histologically diverse (see Table 256-1). At least 80% originate in the epithelium; 75% of these cancers are serous cystadenocarcinoma. The remaining 20% of ovarian cancers originate in primary ovarian germ cells or in sex cord and stromal cells or are metastases to the ovary (most commonly, from the breast or GI tract). Germ cell cancers usually occur in women < 30.

Ovarian cancer spreads by direct extension, exfoliation of cells into the peritoneal cavity (peritoneal seeding), lymphatic dissemination to the pelvis and around the aorta, or, less often, hematogenously to the liver or lungs.

Symptoms and Signs

Early cancer is usually asymptomatic; an adnexal mass, often solid, irregular, and fixed, may be
discovered incidentally. Pelvic and rectovaginal examinations typically detect diffuse nodularity. A few women present with severe abdominal pain secondary to torsion of the ovarian mass (see p. 2532). Most women with advanced cancer present with nonspecific symptoms (eg, dyspepsia, bloating, early satiety, gas pains, backache). Later, pelvic pain, anemia, cachexia, and abdominal swelling due to ovarian enlargement or ascites usually occur.

Germ cell or stromal tumors may have functional effects (eg, hyperthyroidism, feminization, virilization).

**Diagnosis**

- Ultrasonography (for suspected early cancers) or CT or MRI (for suspected advanced cancers)
- Tumor markers
- Surgical staging

Ovarian cancer is suspected in women with the following:

- Unexplained adnexal masses
- Unexplained abdominal bloating
- Changes in bowel habits
- Unintended weight loss
- Unexplained abdominal pain

An ovarian mass is more likely to be cancer in older women. Benign functional cysts (see p. 2533) can simulate functional germ cell or stromal tumors in young women.

A pelvic mass plus ascites usually indicates ovarian cancer but sometimes indicates Meigs’ syndrome (a benign fibroma with ascites and right hydrothorax).

**Imaging:** If early cancer is suspected, ultrasonography is done first; the following findings suggest cancer:

- A solid component
- Surface excrescences
- Size > 6 cm
- Irregular shape
- Low vascular resistance detected by transvaginal Doppler flow studies

If advanced cancer is suspected (eg, based on ascites, abdominal distention, or nodularity or fixation detected during physical examination), CT or MRI is usually done before surgery to determine extent of the cancer.

**Tumor markers:** Tumor markers, including the β subunit of human chorionic gonadotropin (β-hCG), LDH, α-fetoprotein, inhibin, and cancer antigen (CA) 125, are typically measured in young patients, who are at higher risk of nonepithelial tumors (eg, germ cell tumors, stromal tumors). In perimenopausal and postmenopausal patients, only CA 125 is measured because most ovarian cancers in this age group are epithelial tumors. CA 125 is elevated in 80% of advanced epithelial ovarian cancers but may be mildly elevated in endometriosis, pelvic inflammatory disease, pregnancy, fibroids, peritoneal inflammation, or nonovarian peritoneal cancer. A mixed solid and cystic pelvic mass in postmenopausal women, especially
if CA 125 is elevated, suggests ovarian cancer.

**Biopsy:** A biopsy is not routinely recommended unless a patient is not a surgical candidate. In those rare cases, samples are obtained by needle biopsy for masses or by needle aspiration for ascitic fluid.

For masses that appear benign on ultrasonography, histologic analysis is not required, and ultrasonography is repeated after 6 wk. Such benign-appearing masses include benign cystic teratomas (dermoid cysts), follicular cysts, and endometriomas.

**Staging:** Suspected or confirmed ovarian cancer is staged surgically (see Table 256-2). If early-stage cancer is suspected, staging may be done by laparoscopy. Otherwise, an abdominal midline incision that allows adequate access to the upper abdomen is required. All peritoneal surfaces, hemidiaphragms, and abdominal and pelvic viscera are inspected and palpated. Washings from the pelvis, abdominal gutters, and diaphragmatic recesses are obtained, and multiple biopsies of the peritoneum in the central and lateral pelvis and in the abdomen are done. For early-stage cancer, the infracolic omentum is removed, and pelvic and para-aortic lymph nodes are sampled.

Cancers are also graded histologically from 1 (least aggressive) to 3 (most aggressive).

**Screening:** Screening asymptomatic women using ultrasonography and serum CA 125 measurements can detect some cases of ovarian cancer but has not been shown to improve outcome, even for high-risk subgroups (including women with *BRCA* mutations). However, women should be screened for abnormalities of the *BRCA* gene if their family history includes any of the following:

- Diagnosis of ovarian cancer in a 1st-degree relative before age 40
- Diagnosis of breast and ovarian cancer in only one 1st-degree relative if one of the cancers was diagnosed before age 50
- Two cases of ovarian cancer among 1st- and 2nd-degree relatives of the same lineage

[Table 256-2. Surgical Staging of Ovarian Carcinoma*]

- Two cases of breast cancer and one case of ovarian cancer among 1st- or 2nd-degree relatives of the same lineage
- One case of breast and one case of ovarian cancer among 1st- or 2nd-degree relatives of the same lineage if breast cancer was diagnosed before age 40 or if ovarian cancer was diagnosed before age 50
- Two cases of breast cancer among 1st- or 2nd-degree relatives of the same lineage if both cases were diagnosed before age 50
- Two cases of breast cancer among 1st- or 2nd-degree relatives of the same lineage if one was diagnosed before age 40

Also, if Ashkenazi Jewish women have one family member with breast cancer diagnosed before age 50 or with ovarian cancer, screening should be considered.

**Prognosis**

The 5-yr survival rates with treatment are

- Stage I: 70 to 100%
- Stage II: 50 to 70%
- Stage III: 20 to 50%
• Stage IV: 10 to 20%

Prognosis is worse when tumor grade is higher or when surgery cannot remove all visibly involved tissue; then, prognosis is best when the involved tissue can be reduced to < 1 cm in diameter. With stages III and IV, recurrence rate is about 70%.

Treatment

• Usually hysterectomy and bilateral salpingooophorectomy

• Usually postoperative chemotherapy, often with carboplatin and paclitaxel

Hysterectomy and bilateral salpingooophorectomy are usually indicated except for stage I nonepithelial or low-grade unilateral epithelial cancers in young patients; fertility can be preserved by not removing the unaffected ovary and uterus. All visibly involved tissue is surgically removed if possible. If it cannot be removed completely, removing as much as possible (cytoreductive surgery) improves the efficacy of other therapies. Cytoreductive surgery usually includes supracolic omentectomy, sometimes with rectosigmoid resection (usually with primary reanastomosis), radical peritoneal stripping, resection of diaphragmatic peritoneum, or splenectomy.

Postoperative treatment depends on the stage and grade (see [Table 256-3](#)).

[Table 256-3. Postoperative Treatment of Ovarian Cancer by Stage and Type]

Even if chemotherapy results in a complete clinical response (ie, normal physical examination, normal serum CA 125, and negative CT scan of the abdomen and pelvis), about 50% of patients with stage III or IV cancer have residual tumor. Of patients with persistent elevation of CA 125, 90 to 95% have residual tumor. Recurrence rate in patients with a clinical complete response after initial chemotherapy (6 courses of carboplatin and paclitaxel) is 60 to 70%.

If cancer recurs or progresses after effective chemotherapy, chemotherapy is restarted. Other useful drugs may include topotecan, liposomal doxorubicin, docetaxel, vinorelbine, gemcitabine, hexamethylmelamine, and oral etoposide. Targeted therapy with biologic agents is under study.

Prevention

For patients with BRCA1 or BRCA2 gene mutations, risk of ovarian and, to a lesser degree, breast cancer is reduced if prophylactic bilateral salpingooophorectomy is done after childbearing is completed. These patients should be referred to a gynecologic oncologist for evaluation. Other resources include the National Cancer Institute Cancer Information Service (1-800-4-CANCER) and the Women's Cancer Network (www.wcn.org).

Fallopian Tube Cancer

Fallopian tube cancer is usually adenocarcinoma, manifesting as an adnexal mass or as vague symptoms. Diagnosis, staging, and treatment are surgical.

Primary fallopian tube cancer is rare. Average age at diagnosis is 50 to 60. Risk factors include chronic salpingitis, other inflammatory disorders (eg, TB), and infertility.

Most (> 95%) fallopian tube cancers are papillary serous adenocarcinomas; a few are sarcomas. Spread, like that of ovarian cancer, is by direct extension, by peritoneal seeding, or through the lymphatics.

Symptoms and Signs

Most patients present with an adnexal mass or vague abdominal or pelvic symptoms (eg, abdominal
discomfort, bloating, pain). A few patients present with hydrops tubae profluens (a triad of pelvic pain, copious watery discharge, and adnexal mass), which is more specific.

**Diagnosis**

- CT
- Surgery to confirm diagnosis and to stage

Typically, CT is done. A distended solid adnexal mass and normal ovary suggest fallopian tube cancer. A pregnancy test is done to rule out ectopic pregnancy unless patients are postmenopausal.

If cancer is suspected, surgery is necessary for diagnosis, staging, and treatment. Staging (similar to that of ovarian cancer) requires the following:

- Washings from the pelvis, abdominal gutters, and diaphragmatic recesses
- Multiple pelvic and abdominal peritoneal biopsies
- Pelvic and para-aortic lymph node dissection

**Treatment**

- Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and supracolic omentectomy

Treatment includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and supracolic omentectomy. If cancer appears advanced, cytoreductive surgery is indicated.

Postoperative treatment is identical to that for ovarian cancer. External beam radiation is rarely indicated.

**Endometrial Cancer**

Endometrial cancer is usually adenocarcinoma. Typically, postmenopausal vaginal bleeding occurs. Diagnosis is by biopsy. Staging is surgical. Treatment requires hysterectomy, bilateral salpingo-oophorectomy, usually pelvic and para-aortic lymph node dissection, and excision of all tissue likely to be involved. For advanced cancer, radiation, hormone, or cytotoxic therapy is usually indicated.

Endometrial cancer is more common in developed countries where the diet is high in fat. In the US, this cancer is the 4th most common cancer among women, affecting 1 in 50.

**Etiology**

Endometrial cancer affects mainly postmenopausal women, particularly those aged 50 to 65. Major risk factors are

- Obesity
- Diabetes
- Hypertension

Other risk factors include

- Unopposed estrogen
- Tamoxifen use for > 5 yr
• Previous pelvic radiation therapy

• A personal or family history of breast or ovarian cancer

• Family history of hereditary nonpolyposis colorectal cancer or possibly, among 1st-degree relatives, endometrial cancer

Unopposed estrogen (high circulating levels of estrogen with no or low levels of progesterone) may be associated with obesity, polycystic ovary syndrome, nulliparity, late menopause, estrogen-producing tumors, anovulation (ovulatory dysfunction), and estrogen therapy without progesterone. Heredity contributes to endometrial cancer in about 6% of cases, usually in families with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome.

Pathology

Endometrial cancer is usually preceded by endometrial hyperplasia. Adenocarcinoma accounts for > 80% of endometrial cancers. Other types include papillary serous, clear cell, squamous, mucinous carcinoma, and sarcomas.

The cancer may spread from the surface of the uterine cavity to the cervical canal; through the myometrium to the serosa and into the peritoneal cavity; via the lumen of the fallopian tube to the ovary, broad ligament, and peritoneal surfaces; via the bloodstream, leading to distant metastases; or via the lymphatics. The higher (more undifferentiated) the grade of the tumor, the greater the likelihood of deep myometrial invasion, pelvic or para-aortic lymph node metastases, or extra-uterine spread.

Symptoms and Signs

Most (> 90%) women have abnormal uterine bleeding (eg, postmenopausal bleeding, premenopausal recurrent metrorrhagia); one third of women with postmenopausal bleeding have endometrial cancer. A vaginal discharge may occur weeks or months before postmenopausal bleeding.

Diagnosis

• Endometrial biopsy

• Surgical staging

The following suggest endometrial cancer:

• Postmenopausal bleeding

• Abnormal bleeding in premenopausal women

• A routine Papanicolaou (Pap) test showing endometrial cells in postmenopausal women

• A routine Pap test showing atypical endometrial cells in any woman

If cancer is suspected, outpatient endometrial biopsy is done; it is > 90% accurate. If results are inconclusive or suggest cancer, outpatient fractional D & C with hysteroscopy is done. An alternative is transvaginal ultrasonography; however, a histologic diagnosis is required.

Once cancer is diagnosed, pretreatment evaluation includes serum electrolytes, kidney and liver function tests, CBC, chest x-ray, and ECG. If an abdominal mass or hepatomegaly is detected during physical examination or if liver function tests are abnormal, pelvic and abdominal CT are also done to check for extraperitoneal or metastatic cancer.

Staging: Staging is based on histologic differentiation (grade 1 [least aggressive] to 3 [most aggressive]) and extent of spread, including invasion depth, cervical involvement (glandular involvement vs stromal...
invasion), and extrauterine metastases (see Table 256-4). Staging is surgical and includes peritoneal fluid cytology, exploration of the abdomen and pelvis, and biopsy or excision of suspect extrauterine lesions. Pelvic and para-aortic lymph nodes are removed. During staging, a total abdominal hysterectomy and bilateral salpingo-oophorectomy are done. Surgical staging is traditionally done via laparotomy but may be done via laparoscopy or use of a robotics surgical system.

**Prognosis**

Prognosis is worse with higher-grade tumors, more extensive spread, and older patient age. Average 5-yr survival rates are 70 to 95% with stage I or II and 10 to 60% with stage III or IV. Overall, 63% of patients are cancer-free ≥ 5 yr after treatment.

**Treatment**

- Usually total hysterectomy and bilateral salpingo-oophorectomy

- Pelvic and para-aortic lymphadenectomy for deep (> 50% myometrial invasion) grade 1 and 2 and for grade 3

- Pelvic radiation therapy with or without chemotherapy for stage II or III

- Multimodal, individualized therapy for stage IV

If cancer appears to be stage I/grade 1 without deep myometrial invasion, the probability of unrecognized lymph node metastasis is < 2%. Treatment is usually total hysterectomy and bilateral salpingo-oophorectomy via laparotomy, laparoscopy, or robotics.

For grade 1 or 2 with ≥ 50% myometrial invasion or grade 3, complete pelvic and paraaortic lymphadenectomy is also done. Whether the extent of para-aortic node dissection should reach the inferior mesenteric artery vs the renal vessels remains a topic of debate.

Stage II or III cancer requires pelvic radiation therapy with or without chemotherapy. Treatment of stage III cancer must be individualized, but surgery is an option; generally, patients who undergo combined surgery and radiation therapy have a better prognosis. Except in patients with bulky parametrial disease, a total abdominal hysterectomy and bilateral salpingo-oophorectomy should be done.

Treatment of stage IV is variable and patient dependent but typically involves a combination of surgery, radiation therapy, and chemotherapy. Occasionally, hormonal therapy should also be considered.

Hormone therapy with a progestin causes regression for up to 3 yr in 20 to 25% of patients. Pulmonary, vaginal, and mediastinal metastases may regress. Treatment continues as long as the response is favorable.

Several cytotoxic drugs (particularly carboplatin plus paclitaxel) are effective. They are given mainly to women with metastatic or recurrent cancer. With monthly regimens of doxorubicin 60 mg/m² plus cisplatin 60 mg/m² IV, overall response rate may be ≥ 50%.

Treatment of endometrial hyperplasia consists of progestins or surgery (eg, D & C), depending on the complexity of the lesion and the patient's desire to avoid hysterectomy. If young patients with grade 1 tumors and no myometrial invasion (documented by MRI) wish to preserve fertility, progestin alone is an option. About 46 to 80% of patients have a complete response within 3 mo on average. After 3 mo, patients should be evaluated via D & C rather than endometrial biopsy.
Uterine Sarcomas

Uterine sarcomas are a group of disparate, highly malignant cancers developing from the uterine corpus.

Sarcomas account for < 5% of uterine cancers. Risk factors are similar to those for endometrial carcinoma (see p. 2571). The most common types are mixed mesodermal tumors (malignant mixed mullerian tumor, in which the sarcoma is mixed with adenocarcinoma; recently renamed carcinosarcoma), leiomyosarcomas, and endometrial stromal tumors.

Symptoms and Signs

Most sarcomas manifest as abnormal vaginal bleeding and, less commonly, as pelvic pain or a palpable pelvic mass.

Diagnosis

- Transvaginal ultrasonography and endometrial biopsy or fractional D & C

Symptoms usually prompt transvaginal ultrasonography and endometrial biopsy or fractional D & C. If cancer is identified, CT or MRI is typically done preoperatively.

Staging is done surgically, as follows:

- Stage I: Confined to the corpus
- Stage II: Confined to the corpus and cervix
- Stage III: Spread outside the uterus but confined to the pelvis
- Stage IV: Spread outside the true pelvis or into the mucosa of the bladder or rectum

Prognosis

Prognosis is generally poorer than that with endometrial cancer of similar stage; survival is generally poor when the cancer has spread beyond the uterus. Histology is not an independent prognostic factor. In one study, 5-yr survival rates were 51% for stage I, 13% for stage II, 10% for stage III, and 3% for stage IV. Most commonly, the cancer recurs locally, in the abdomen, and the lungs.

Treatment

- Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and complete exploration of the abdomen

Treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy with complete exploration of the abdomen. Pelvic and para-aortic nodes are dissected in patients with carcinosarcoma. The usefulness of lymphadenectomy in patients with leiomyosarcoma or endometrial stromal sarcoma is controversial; no therapeutic value has been shown.

Adjuvant radiation therapy is typically used and appears to delay local recurrence but does not improve overall survival rate. Chemotherapy drugs vary with tumor type. Overall, response to chemotherapy is poor, although progestins are frequently effective for endometrial stromal tumors.

Gestational Trophoblastic Disease

Gestational trophoblastic disease is proliferation of trophoblastic tissue in pregnant or recently pregnant women. Manifestations may include excessive uterine enlargement, vomiting, vaginal bleeding, and preeclampsia, particularly during early pregnancy. Diagnosis includes
measurement of the β subunit of human chorionic gonadotropin, pelvic ultrasonography, and confirmation by biopsy. Tumors are removed by suction curettage. If disease persists after removal, chemotherapy is indicated.

Gestational trophoblastic disease is a tumor originating from the trophoblast, which surrounds the blastocyst and develops into the chorion and amnion (see p. 2605). This disease can occur during or after an intrauterine or ectopic pregnancy. If the disease occurs during a pregnancy, spontaneous abortion, eclampsia, or fetal death typically occurs; the fetus rarely survives. Some forms are malignant; others are benign but behave aggressively.

Pathology

Classification is morphologic:

- **Hydatidiform mole**: In this abnormal pregnancy, villi become edematous (hydropic), and trophoblastic tissue proliferates.

- **Chorioadenoma destruens (invasive mole)**: The myometrium is invaded locally by a hydatidiform mole.

- **Choriocarcinoma**: This invasive, usually widely metastatic tumor is composed of malignant trophoblastic cells and lacks hydropic villi; most of these tumors develop after a hydatidiform mole.

- **Placental site trophoblastic tumor**: This rare tumor consists of intermediate trophoblastic cells that persist after a term pregnancy; it may invade adjacent tissues or metastasize.

Hydatidiform moles are most common among women < 17 or > 35 and those who have had previous gestational trophoblastic disease. They occur in about 1/2000 gestations in the US. For unknown reasons, incidence in Asian countries approaches 1/200. Most (> 80%) hydatidiform moles are benign. The rest may persist, tending to become invasive; 2 to 3% of hydatidiform moles are followed by choriocarcinoma.

Symptoms and Signs

Initial manifestations of a hydatidiform mole suggest early pregnancy, but the uterus often becomes larger than expected within 10 to 16 wk gestation. Commonly, women test positive for pregnancy, have vaginal bleeding and severe vomiting, and fetal movement and fetal heart sounds are absent. Passage of grape-like tissue strongly suggests the diagnosis. Complications may include uterine infection, sepsis, hemorrhagic shock, and preeclampsia, which may occur during early pregnancy.

Placental site trophoblastic tumors tend to cause bleeding.

Choriocarcinoma usually manifests with symptoms due to metastases.

Gestational trophoblastic disease does not impair fertility or predispose to prenatal or perinatal complications (eg, congenital malformations, spontaneous abortions).

Diagnosis

- Serum β-hCG

- Pelvic ultrasonography

Gestational trophoblastic disease is suspected in women with a positive pregnancy test and any of the following:

- Uterine size much larger than expected for dates
• Symptoms or signs of preeclampsia
• Passage of grapelike tissue
• Suggestive findings (eg, mass containing multiple cysts instead of a fetus) seen during ultrasonography done to evaluate pregnancy
• Unexplained metastases in women of child-bearing age
• Unexpectedly high levels of human chorionic gonadotropin (β-hCG) detected during pregnancy testing
• Unexplained complications of pregnancy

If gestational trophoblastic disease is suspected, testing includes measurement of serum β-hCG and pelvic ultrasonography. Findings (eg, very high β-hCG levels, classic ultrasonographic findings) may suggest the diagnosis, but biopsy is required. Invasive mole and choriocarcinoma are suspected if biopsy findings suggest invasive disease or if β-hCG levels remain higher than expected after treatment for hydatidiform mole (see below).

**Treatment**

• Tumor removal by suction curettage
• Further evaluation for persistent disease and spread of tumor
• Chemotherapy for persistent disease
• Posttreatment contraception for persistent disease

Hydatidiform mole, invasive mole, and placental site trophoblastic tumor are evacuated by suction curettage. Alternatively, if childbearing is not planned, hysterectomy may be done.

After tumor removal, gestational trophoblastic disease is classified clinically to determine whether additional treatment is needed. The clinical classification system does not correspond to the morphologic classification system. Invasive mole and choriocarcinoma are classified clinically as persistent disease. The clinical classification is used because both are treated similarly and because exact histologic diagnosis may require hysterectomy.

A chest x-ray is taken, and serum β-hCG is measured. If the β-hCG level does not normalize within 10 wk, the disease is classified as persistent. Persistent disease requires CT of the brain, chest, abdomen, and pelvis. Results dictate whether disease is classified as nonmetastatic or metastatic. In metastatic disease, prognosis (including risk of death) may be poor or good (see Table 256-5). Poor prognosis is suggested by the following (National Institutes of Health [NIH] criteria):

• Urinary hCG excretion > 100,000 IU in 24 h
• Duration of disease > 4 mo (interval since prior pregnancy)
• Brain or liver metastases
• Disease after full-term pregnancy
• Serum hCG > 40,000 mIU/mL
• Unsuccessful prior chemotherapy
• WHO score > 8
Persistent disease is usually treated with chemotherapy. Treatment is considered successful if at least 3 consecutive serum $\beta$-hCG measurements at 1-wk intervals are normal. Typically, oral contraceptives (any is acceptable) are given for 6 to 12 mo; alternatively, any effective contraceptive method can be used.

Nonmetastatic disease can be treated with a single chemotherapy drug (methotrexate or dactinomycin). Alternatively, hysterectomy is considered for patients $>$ 40 or those desiring sterilization and may be required for those with severe infection or uncontrolled bleeding. If single-drug chemotherapy is ineffective, hysterectomy or multidrug chemotherapy is indicated. Virtually 100% of patients with nonmetastatic disease can be cured.

Low-risk metastatic disease is treated with single-drug or multidrug chemotherapy. High-risk metastatic disease requires aggressive multidrug chemotherapy. Cure rates are 90 to 95% for low-risk and 60 to 80% for high-risk disease.

Hydatidiform mole recurs in about 1% of subsequent pregnancies. Patients who have had a mole require ultrasonography early in subsequent pregnancies, and the placenta should be sent for pathologic evaluation.

Cervical Cancer

Cervical cancer is usually a squamous cell carcinoma caused by human papillomavirus infection; less often, it is an adenocarcinoma. Cervical neoplasia is asymptomatic; the first symptom of early cervical cancer is usually irregular, often postcoital vaginal bleeding. Diagnosis is by a screening cervical Papanicolaou test and biopsy. Staging is clinical. Treatment usually involves surgical resection, or radiation therapy plus chemotherapy. If the cancer has widely metastasized, chemotherapy is often used alone.

Cervical cancer is the 3rd most common gynecologic cancer and the 8th most common cancer among women in the US. Mean age at diagnosis is about 50, but the cancer can occur as early as age 20.

Cervical cancer results from cervical intraepithelial neoplasia (CIN), which appears to be caused by infection with human papillomavirus (HPV) type 16, 18, 31, 33, 35, or 39. Risk factors for cervical cancer include

- Younger age at first intercourse
- A high lifetime number of sex partners
- Intercourse with men whose previous partners had cervical cancer

Other factors such as cigarette smoking and immunodeficiency also appear to contribute.

Pathology

CIN is graded as 1 (mild cervical dysplasia), 2 (moderate dysplasia), or 3 (severe dysplasia and carcinoma in situ). CIN 3 is unlikely to regress spontaneously; if untreated, it may, over months or years, penetrate the basement membrane, becoming invasive carcinoma.

About 80 to 85% of all cervical cancers are squamous cell carcinoma; most of the rest are adenocarcinomas. Sarcomas and small cell neuroendocrine tumors are rare.

Invasive cervical cancer usually spreads by direct extension into surrounding tissues or via the lymphatics to the pelvic and paraaortic lymph nodes. Hematogenous spread is possible but rare.

Symptoms and Signs
CIN is usually asymptomatic. Early cervical cancer can be asymptomatic. The first symptom is usually irregular vaginal bleeding, which is most often postcoital but may occur spontaneously between menses. Larger cancers are more likely to bleed spontaneously and may cause a foul-smelling vaginal discharge or pelvic pain. More widespread cancer may cause obstructive uropathy, back pain, and leg swelling due to venous or lymphatic obstruction; pelvic examination may detect an exophytic necrotic tumor in the cervix.

**Diagnosis**

- Papanicolaou (Pap) test
- Biopsy
- Clinical staging, usually by biopsy, pelvic examination, and chest x-ray

Cervical cancer may be diagnosed during a routine gynecologic examination. It is considered in women with

- Visible cervical lesions
- Abnormal routine Pap test results
- Abnormal vaginal bleeding

CIN is usually evident on Pap tests, but about 50% of patients with cervical cancer have not had a Pap test for ≥ 10 yr. Patients at highest risk are the least likely to obtain regular preventive health care and to be tested regularly.

Reporting of cervical cytology results is standardized (see Table 256-6). Further evaluation is indicated if atypical or cancerous cells are found, particularly in women at risk. If cytology does not show any obvious cancer, colposcopy (examination of the vagina and cervix with a magnifying lens) can be used to identify areas that require biopsy. Colposcopy-directed biopsy with endocervical curettage is usually diagnostic. If not, cone biopsy (conization) is required; a cone of tissue is removed using a loop electrical excision procedure (LEEP), laser, or cold knife.

**Staging:** Cancers are clinically staged based on biopsy, physical examination, and chest x-ray results (see Table 256-7). If the stage is > IB1, CT or MRI of the abdomen and pelvis is typically done to identify metastases, although results are not used for staging. If MRI and CT are not available, cystoscopy, sigmoidoscopy, and IV urography, when clinically indicated, may be used for staging.

[Table 256-6. Bethesda Classification of Cervical Cytology*]

The purpose of this staging system is to establish a large database for study; thus, the system uses worldwide uniform diagnostic criteria. The system excludes results of tests that are less likely to be available worldwide (eg, MRI) because most cases of cervical cancer occur in developing countries. Because such tests are not used, findings such as parametrial invasion and lymph node metastases are often missed, and thus understaging is possible.

[Table 256-7. Clinical Staging of Cervical Carcinoma*]

When imaging tests suggest that pelvic or para-aortic lymph nodes are grossly enlarged (> 2 cm), surgical exploration, typically with a retroperitoneal approach, is occasionally indicated. Its sole purpose is to remove enlarged lymph nodes so that radiation therapy can be more precisely targeted and more effective.

**Prognosis**
In squamous cell carcinoma, distant metastases usually occur only when the cancer is advanced or recurrent. The 5-yr survival rates are as follows:

- Stage I: 80 to 90%
- Stage II: 60 to 75%
- Stage III: 30 to 40%
- Stage IV: 0 to 15%

Nearly 80% of recurrences manifest within 2 yr. Adverse prognostic factors include lymph node involvement, large tumor size and volume, deep cervical stromal invasion, parametrial invasion, vascular space invasion, and nonsquamous histology.

**Treatment**

- Excision or curative radiation therapy if there is no spread to parametria or beyond
- Radiation therapy and chemotherapy if there is spread to the parametria or beyond
- Chemotherapy for metastatic and recurrent cancer

Treatment may include surgery, radiation therapy, and chemotherapy. If hysterectomy is indicated but patients cannot tolerate it, radiation therapy plus chemotherapy is used.

**CIN and squamous cell carcinoma stage IA1:** Cone biopsy with LEEP, laser, or cold knife is usually sufficient treatment. Hysterectomy is done for stage IA1 cancer if there are adverse prognostic factors (nonsquamous histology or lymphatic or vascular invasion). Radical hysterectomy is recommended by some experts; it includes bilateral pelvic lymphadenectomy and removal of all adjacent ligaments (eg, cardinal, uterosacral) and parametria and the upper 2 cm of the vagina. Hysterectomy can also be done if women no longer desire fertility. If there are no adverse prognostic factors, simple (extrafascial) hysterectomy is usually sufficient because risk of recurrence and lymph node metastasis is < 1%. Pelvic lymph node dissection is not indicated.

**Stages IA2 to IIA:** Treatment options include a radical hysterectomy and pelvic lymphadenectomy alone (stages IA2 to IB1) or a radical hysterectomy and pelvic lymphadenectomy with possible combined chemotherapy and pelvic radiation (stages IB2 to IIA). Chemotherapy is usually given concurrently. With either treatment, the 5-yr cure rates in stage IB or IIA are 85 to 90%. Surgery provides additional staging data and preserves the ovaries. If extracervical spread is noted during surgery, postoperative radiation therapy may prevent local recurrence.

In some patients who have early-stage cervical cancer and who wish to preserve fertility, a radical trachelectomy may be done. In this procedure, the cervix, parametria immediately adjacent to the cervix, upper 2 cm of the vagina, and pelvic lymph nodes are removed. The remaining uterus is reattached to the upper vagina, preserving the potential for fertility. Ideal candidates for this procedure are patients with the following:

- Histologic subtypes such as squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma
- Stage IA1/grade 2 or 3 with vascular space invasion
- Stage IA2
- Stage IB1 with lesions < 2 cm in size

Invasion of the upper cervix and lower uterine segment should be excluded by MRI. Rates of recurrence and death are similar to those after radical hysterectomy. If patients who have this procedure plan to have...
children, delivery must be cesarean.

Stages IIB to IVA: Radiation therapy plus chemotherapy (eg, cisplatin) is more suitable as primary therapy. Surgical staging should be considered to determine whether paraaortic lymph nodes are involved and thus whether extended-field radiation therapy is indicated; a retroperitoneal approach is used. Staging may be done via laparoscopy. External beam radiation therapy shrinks the central tumor and treats regional lymph nodes. This therapy is followed by brachytherapy (local radioactive implants, usually using cesium) to the cervix, which destroys the central tumor. Radiation therapy may cause acute complications (eg, radiation proctitis and cystitis) and, occasionally, late complications (eg, vaginal stenosis, intestinal obstruction, rectovaginal and vesicovaginal fistula formation).

Chemotherapy is usually given with radiation therapy, often to sensitize the tumor to radiation. Treatment is often ineffective for bulky and advanced-stage tumors.

Although stage IVA cancers are usually treated with radiation therapy initially, pelvic exenteration (excision of all pelvic organs) may be considered. If after radiation therapy, cancer remains but is confined to the central pelvis, exenteration is indicated and cures up to 50% of patients. The procedure may include a continent urostomy, low anterior rectal anastomosis without colostomy, omental carpet to close the pelvic floor (J-flap), and vaginal reconstruction with gracilis or rectus abdominis myocutaneous flaps.

Stage IVB and recurrent cancer: Chemotherapy is the primary treatment, but only 15 to 25% of patients respond to it and only briefly. Cisplatin is the most active drug and the current standard, but adding topotecan appears to improve overall response and survival. Combinations of paclitaxel, topotecan, gemcitabine, cisplatin, and vinorelbine are under study for treatment of recurrent squamous cell carcinoma. Paclitaxel is also used to treat recurrent or metastatic nonsquamous cancer. Metastases outside the radiation field appear to respond better to chemotherapy than does previously irradiated cancer or metastases in the pelvis.

Prevention

Pap tests: Routine cervical Pap tests are recommended yearly, starting when patients first begin having sexual intercourse or reach age 18. Pap test and HPV test can be done simultaneously. If both are normal or if 3 consecutive Pap tests are normal, some physicians test at 2- to 3-yr intervals. Testing continues until patients are age 65 to 70, have normal results for 10 yr, or have a hysterectomy. Sexually active women are advised that condoms should be used during intercourse to prevent spread of HPV. HPV testing is the preferred method of follow-up evaluation for women ages 20 to 30 with inconclusive Pap results such as ASCUS (atypical squamous cells of undetermined significance). If testing shows that the patient does not have HPV, a repeat Pap is recommended in 12 mo. If HPV is present, colposcopy should be done. Routine HPV testing plus a Pap test is recommended for women ≥ 30.

HPV vaccine: A newly developed vaccine (see p. 1176) targets the 4 viral subtypes (HPV 6, 11, 16, and 18) most commonly associated with cervical intraepithelial lesions, genital warts, and cervical cancer. The vaccine aims to prevent cervical cancer but does not treat it. Three doses are given: the first dose is followed by one 2 mo and one 6 mo later. The vaccine is best given before sexual activity begins, but women who are sexually active should be vaccinated.

Vaginal Cancer

Vaginal cancer is usually a squamous cell carcinoma, most often occurring in women > 60. The most common symptom is abnormal vaginal bleeding. Diagnosis is by biopsy. Treatment for many small localized cancers is hysterectomy plus vaginectomy and lymph node dissection; for most others, radiation therapy is used.

Vaginal cancer accounts for 1% of gynecologic cancers in the US. Average age at diagnosis is 60 to 65. Risk factors include human papillomavirus infection and cervical or vulvar cancer. Exposure to diethylstilbestrol in utero predisposes to clear cell adenocarcinoma of the vagina, which is rare; mean age at diagnosis is 19.
Most (95%) primary vaginal cancers are squamous cell carcinomas; others include primary and secondary adenocarcinomas, secondary squamous cell carcinomas (in older women), clear cell adenocarcinomas (in young women), and melanomas. The most common vaginal sarcoma is sarcoma botryoides (embryonal rhabdomyosarcoma); peak incidence is at age 3.

Most vaginal cancers occur in the upper third of the posterior vaginal wall. They may spread by direct extension (into the local paravaginal tissues, bladder, or rectum), through inguinal lymph nodes from lesions in the lower vagina, through pelvic lymph nodes from lesions in the upper vagina, or hematogenously.

**Symptoms and Signs**

Most patients present with abnormal vaginal bleeding: postmenopausal, postcoital, or intermenstrual. Some also present with a watery vaginal discharge or dyspareunia. A few patients are asymptomatic, and the lesion is discovered during routine pelvic examination or evaluation of an abnormal Papanicolaou (Pap) test. Vesicovaginal or rectovaginal fistulas are manifestations of advanced disease.

**Diagnosis**

- Biopsy
- Clinical staging

Punch biopsy is usually diagnostic, but wide local excision is occasionally necessary. Cancers are staged clinically (see Table 256-8), based primarily on physical examination, endoscopy (ie, cystoscopy, proctoscopy), chest x-ray (for pulmonary metastases), and usually CT (for abdominal or pelvic metastases). Survival rates depend on the stage.

[Table 256-8. Vaginal Cancer by Stage]

**Treatment**

- Hysterectomy plus vaginectomy and lymph node dissection for tumors confined to the wall of the upper third of the vagina
- Radiation therapy for most others

Stage I tumors within the upper third of the vagina can be treated with radical hysterectomy, upper vaginectomy, and pelvic lymph node dissection. Most other primary tumors are treated with radiation therapy, usually a combination of external beam radiation therapy and brachytherapy. If radiation therapy is contraindicated because of vesicovaginal or rectovaginal fistulas, pelvic exenteration is done.

**Vulvar Cancer**

Vulvar cancer is usually a squamous cell skin cancer, most often occurring in elderly women. It usually manifests as a palpable lesion. Diagnosis is by biopsy. Treatment includes excision and inguinal and femoral lymph node dissection.

Vulvar cancer accounts for about 3 to 4% of gynecologic cancers in the US. Average age at diagnosis is about 70, and incidence increases with age. Risk factors include vulvar intraepithelial neoplasia (VIN), human papillomavirus infection, heavy cigarette smoking, lichen sclerosus, squamous hyperplasia, squamous carcinoma of the vagina or cervix, and chronic granulomatous diseases.

**Pathology**

VIN is a precursor to vulvar cancer. VIN may be multifocal. Sometimes adenocarcinoma of the vulva, breast, or Bartholin's glands also develops.
About 90% of vulvar cancers are squamous cell carcinomas; about 5% are melanomas. Others include adenocarcinomas and transitional cell, adenoid cystic, and adenosquamous carcinomas; all may originate in Bartholin’s glands. Sarcomas and basal cell carcinomas with underlying adenocarcinoma also occur.

Vulvar cancer may spread by direct extension (e.g., into the urethra, bladder, vagina, perineum, anus, or rectum), hematogenously, to the inguinal lymph nodes, or from the inguinal lymph nodes to the pelvic and paraaortic lymph nodes.

**Symptoms and Signs**

The most common presentation is a palpable vulvar lesion, frequently noticed by the woman or by a clinician during pelvic examination. Women often have a long history of pruritus. They may not present until cancer is advanced. The lesion may become necrotic or ulcerated, sometimes resulting in bleeding or a watery vaginal discharge. Melanomas may appear bluish black, pigmented, or papillary.

**Diagnosis**

- Biopsy
- Surgical staging

Vulvar cancer may mimic sexually transmitted genital ulcers (see p. 1468), basal cell carcinoma, vulvar Paget’s disease (a pale eczematoso lesion), Bartholin’s gland cyst, or condyloma acuminatum. A dermal punch biopsy using a local anesthetic is usually diagnostic. Occasionally, wide local excision is necessary to differentiate VIN from cancer. Subtle lesions may be delineated by staining the vulva with toluidine blue or by using colposcopy.

**Staging:** Staging is based on tumor size and location and on regional lymph node spread as determined by lymph node dissection done as part of initial surgical treatment (see Table 256-9).

**Prognosis**

Overall 5-yr survival rates depend on stage. Risk of lymph node spread is proportional to

<table>
<thead>
<tr>
<th>Table 256-9, Vulvar Cancer by Stage</th>
</tr>
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<tbody>
<tr>
<td>the tumor size and invasion depth. Melanomas metastasize frequently, depending mostly on invasion depth but also on tumor size.</td>
</tr>
</tbody>
</table>

**Treatment**

- Wide excision and lymph node dissection for all cancers
- Radiation therapy, chemotherapy, or both for stage III or IV cancer

Wide (≥ 2-cm margin) radical excision of the local tumor and a unilateral or bilateral inguinal and femoral lymph node dissection are necessary for cancers of all stages and are sufficient for stages I and II. For lateralized lesions ≤ 2 cm, unilateral wide local excision and unilateral lymph node dissection can be used. Lesions near the midline and most lesions > 2 cm require bilateral lymph node dissection.

For stage III, lymph node dissection followed by postoperative external beam radiation therapy, often with chemotherapy (e.g., 5-fluourouracil, cisplatin), is usually done before wide radical excision. The alternative is more radical or exenterative surgery.

For stage IV, treatment is some combination of pelvic exenteration, radiation therapy, and systemic chemotherapy.
Chapter 257. Family Planning

Introduction

A couple’s decision to begin, prevent, or interrupt a pregnancy may be influenced by many medical factors, including maternal medical disorders, risks involved in pregnancy, and genetic evaluation. Often, religious, social, and other factors also affect family planning decisions; health care practitioners must be sensitive to these factors.

One or both members of a couple can use contraception to prevent pregnancy temporarily or sterilization to prevent pregnancy permanently. If contraception fails, abortion (termination of pregnancy) can be induced.

Contraception

The contraceptive methods most commonly used in the US (in order of popularity) are oral contraceptives, female sterilization, condoms, male sterilization, progestin injections, withdrawal (coitus interruptus), intrauterine devices (IUDs), periodic abstinence, spermicides, and diaphragms (see Table 257-1). Over several years, pregnancy rates are < 1%/yr with methods unrelated to coitus (IUDs, progestin injections, subdermal progestin implants, and oral contraceptives when taken consistently) and about 5%/yr with coitus-related methods (eg, condoms, diaphragms, spermicides, withdrawal); pregnancy rates tend to be higher during the first year, then decrease in later years as users become more facile and women’s fertility decreases. In contrast, the pregnancy rate is 90%/yr with frequent, unprotected intercourse. Condoms are often preferred despite their relatively high failure rate because they protect against sexually transmitted diseases, especially HIV. Emergency contraception, done post-coitus, should not be used as a regular method of contraception.

Table 257-1. Comparison of Common Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Contraceptives</td>
<td>Provide negative feedback to the hypothalamus, inhibiting ovulation</td>
</tr>
<tr>
<td>Progestin alone</td>
<td>Commonly used in combination with estrogen to prevent pregnancy</td>
</tr>
<tr>
<td>Combination OCs</td>
<td>Most effective and widely used</td>
</tr>
<tr>
<td>Progestin injections</td>
<td>Used as an alternative to estrogen</td>
</tr>
<tr>
<td>Intradermic progestins</td>
<td>Used for long-term contraception</td>
</tr>
<tr>
<td>Condoms</td>
<td>Provide a barrier to protect against sexually transmitted diseases</td>
</tr>
<tr>
<td>Diaphragms</td>
<td>Protect against sexually transmitted diseases</td>
</tr>
</tbody>
</table>

Adverse effects: OCs may cause breakthrough bleeding (which may resolve with time or when the
estrogen dose is increased) or amenorrhea (which may resolve when the progestin dose is decreased). In a few women, ovulation remains inhibited for a few months after they stop taking OCs. OCs do not adversely affect the outcome of pregnancy when conception occurs during or after their use.

Estrogens increase aldosterone production and cause Na retention, which can produce dose-related, reversible increases in BP and weight, up to about 2 kg; weight gain may be accompanied by bloating, edema, and breast tenderness. Most progestins used in OCs are related to 19-nortestosterone and are androgenic; norgestimate and desogestrel are less androgenic than levonorgestrel, norethindrone, norethindrone acetate, and ethynodiol diacetate. Androgenic effects may include acne, nervousness, and an anabolic effect resulting in weight gain. If a woman gains > 4.5 kg/yr, a less androgenic OC should be used. Drospirenone, a new progestin, is related to spironolactone, not 19-nortestosterone; it is antiandrogenic and diuretic.

OCs increase the risk of certain disorders and decrease the risk of others (see Table 257-3).

Table 257-2. Contraindications to Combination Oral Contraceptive Use

Incidence of deep venous thrombosis and thromboembolism increases in relation to estrogen dose; formulations with 20 to 35 μg increase risk to about 3 to 4 times normal (but risk is still only about half of that during pregnancy). Formulations containing the less androgenic progestin desogestrel may have a slightly higher risk than formulations containing levonorgestrel, but this difference has not been established. Varicose veins do not appear to further increase risk. Hypercoagulability is probably caused by increases in clotting factors, particularly VII and X, and possibly increased platelet adhesion. If deep vein thrombophlebitis or pulmonary embolism is suspected, OCs should be stopped, pending results of diagnostic tests. OCs should be stopped as soon as possible before any major surgery and 1 mo before elective major surgery; they should not be restarted until 1 mo after the surgery.

Current use of OCs does not increase overall risk of breast cancer, nor does former use in women aged 35 to 65. Also, use does not increase risk in high-risk groups (eg, women with certain benign breast disorders or a family history of breast cancer). Risk of cervical cancer is increased in women who have used OCs for > 5 yr; the reason is unknown. OC users should have annual cervical cytology screening (eg, Papanicolaou [Pap] test).

Although increased stroke risk has been attributed to OCs, low-dose combination OCs do not appear to increase risk in healthy, normotensive, nonsmoking women. Nonetheless,

Table 257-3. Some Risks and Benefits of Combination Oral Contraceptives

if focal neurologic symptoms, aphasia, or other symptoms that may herald stroke develop, OCs should be stopped. CNS effects of OCs include nausea, vomiting, headache, depression, and sleep disturbances.

Although progestins may cause reversible, dose-related insulin resistance, use of current OCs, which have a low progestin dose, rarely results in hyperglycemia. Serum high-density lipoprotein (HDL) cholesterol levels may decrease when OCs with a high progestin dose are used but usually increase when OCs with low progestin and estrogen doses are used. Most alterations in serum levels of other metabolites are not clinically significant. Thyroxine-binding globulin capacity may increase; free thyroxine levels, thyroid-stimulating hormone levels, and thyroid function are not affected. Levels of pyridoxine, folate, most other B vitamins, ascorbic acid, Ca, manganese, and zinc decrease; vitamin A levels increase.

OCs accelerate growth of existing gallstones but do not cause new stones to form. Thus, incidence of cholelithiasis increases during the first few years of OC use, then decreases. Women who develop idiopathic recurrent jaundice of pregnancy (cholestasis of pregnancy) may become jaundiced if they take OCs; these women should not take OCs.

Rarely, benign hepatic adenomas that can spontaneously rupture develop. Incidence increases as duration of use and OC dose increase; adenomas usually regress spontaneously after the OC is stopped.
Melasma occurs in some women; it is accentuated by sunlight and disappears slowly after OCs are stopped. Because treatment is difficult (see p. 721), OCs are stopped when melasma first appears. OCs do not increase risk of malignant melanoma.

**Benefits:** OCs decrease risk of endometrial and ovarian cancers by about 50% for at least 20 yr after OCs are stopped. They also decrease risk of benign ovarian tumors, abnormal uterine bleeding, dysmenorrhea, premenstrual syndrome, iron deficiency anemia, benign breast disorders, and functional ovarian cysts. Ectopic pregnancy and salpingitis, which can impair fertility, are also less likely.

**Drug interactions:** Although OCs can slow the metabolism of certain drugs (eg, meperidine), the effects are not clinically important.

Some drugs (eg, cyclophosphamide, rifampin) can induce liver enzymes that accelerate transformation of OCs to less biologically active metabolites; women who take these drugs should not be given OCs concurrently. Whether certain antibiotics (eg, penicillin, ampicillin, sulfonamides) and anticonvulsants (eg, carbamazepine, phenytoin, phenobarbital, primidone, topiramate) reduce the effectiveness of OCs is less clear. If therapeutic doses of antibiotics are prescribed, using a barrier method in addition to OCs may be prudent. Women who take anticonvulsants should use a 50-μg estrogen formulation because a lower dose often causes breakthrough bleeding.

**Administration:** Before OCs are started and annually thereafter, breast and pelvic examinations, liver palpation, and measurement of BP and weight are necessary. BP is also measured 3 mo after starting OCs. OC users should have annual cervical cytology screening (eg, Pap test), particularly if they have taken OCs > 5 yr or if they are young, sexually active women. For women with a history of a liver disorder, normal liver function must be documented before OCs are prescribed. Women at risk of diabetes (eg, those who have a family history or who have had high-birth-weight infants or unexplained fetal deaths in previous pregnancies) require annual plasma glucose screening and a complete serum lipid profile (repeated annually if results are abnormal). Use of low-dose OCs is not contraindicated by abnormal glucose or lipid test results, except for triglycerides > 250 mg/dL.

When to start OCs after pregnancy is guided by when ovulation is expected. After an abortion, ovulation usually occurs after 2 to 4 wk and before the first menses; older gestational age predicts later ovulation. In women who have a term delivery and are not breastfeeding, ovulation occasionally occurs as early as 4 wk after delivery but usually not until after menses. In women who are breastfeeding, ovulation usually occurs ≥ 10 wk after delivery and after menses.

After spontaneous or induced abortion of a fetus < 12 wk gestation, OCs are started immediately. If the fetus is 12 to 28 wk gestation, OCs are delayed 1 wk.

After a term delivery, risk of thromboembolism, which normally increases postpartum, also influences when OCs are started. If women deliver after 28 wk and are not breast-feeding, combination OCs are delayed 2 wk because combination OCs may enhance risk of thromboembolism. For women who are breast-feeding, progestin-only OCs are started a few days after delivery because progestin-only OCs are not thrombogenic. Progestin-only OCs are used because OCs that contain estrogen reduce the amount of milk produced as well as the protein and fat concentration in milk.

**Barrier Contraceptives**

Barrier contraceptives include condoms, diaphragms, cervical caps, vaginal spermicides (foams, creams, suppositories), and the contraceptive sponge.

**Condoms:** Condom use is the only reversible male method other than withdrawal, which is probably much less effective. Condoms decrease risk of sexually transmitted diseases (only latex condoms can fully protect against HIV) and may prevent precancerous changes in the cervix.

The condom is applied before penetration; the tip should extend about 1 cm beyond the penis to collect the ejaculate. During removal, care is taken to avoid spilling condom contents. A new condom is used for
each act of coitus. Pregnancy rates in the 1st yr are 2% with perfect use but 15% with typical (ie, inconsistent) use. Adding a spermicide, which may be included in the condom's lubricant or inserted into the vagina, may lower these rates.

**Diaphragm:** The diaphragm, a dome-shaped rubber cup with a flexible rim that fits over the cervix, is a barrier to sperm. Diaphragms are made in various sizes. A health care practitioner fits a diaphragm to a woman so that it is comfortable for her and her partner. After childbirth or a significant weight change, the woman is refitted. The diaphragm should remain in place for > 8 h after the last coitus. Spermicides should be used before each coitus in case the diaphragm is displaced. Pregnancy rates in the 1st yr are about 6% with perfect use but about 16% with typical use.

**Cervical cap:** The cervical cap resembles the diaphragm but is smaller and more rigid. It comes in several sizes and is fitted by a health care practitioner. It can be left in place for 48 h. For nulliparous women, pregnancy rates in the 1st yr are 9% with perfect use and about 18% with typical use. Pregnancy rates for parous women are about twice as high because obtaining a secure fit is difficult.

**Vaginal spermicides:** Vaginal foams, creams, and suppositories provide a physical barrier to sperm and contain a spermicide, usually nonoxynol-9. They are combined with other barrier methods and are placed in the vagina before each coitus. These products appear to have similar efficacy.

**Contraceptive sponge:** The contraceptive sponge, previously off the market, is available again. It contains nonoxynol-9, does not need to be fitted by a health care practitioner, and can be inserted before coitus. Its efficacy is less than that of the diaphragm.

**Periodic Abstinence**

*(Natural Family Planning)*

Although the ovum can be fertilized for only about 12 h after ovulation, sperm can fertilize an ovum for up to 5 days after coitus. Thus, periodic abstinence requires abstinence from coitus during the 5 days before ovulation. Several methods can be used to identify the time of ovulation; they include the calendar method, basal body temperature, and the characteristics of cervical mucus.

The calendar rhythm method aims to predict ovulation solely by menstrual dates. Ovulation occurs about 14 days before onset of menses; but even when menstrual cycles are regular, this method is often inaccurate. The interval of abstinence during the menstrual cycle is determined by subtracting 18 days from the shortest of the previous 12 cycles and 11 days from the longest (see Fig. 257-1). For example, if cycles vary between 26 and 29 days, abstinence is required from days 8 through 18 of each cycle. The greater the variance in cycle length, the longer abstinence lasts.

Methods that incorporate better predictors of ovulation are more effective but require training and effort:

- **Basal body temperature:** Women measure their temperature with a basal temperature thermometer daily for several minutes before they arise in the morning. Temperature increases by about 0.5° C, usually to > 37° C, after ovulation. Abstinence is required from the onset of menses until > 72 h after the temperature increase.

- **Cervical mucus:** Cervical mucus may be absent for a few days after menses. After cervical mucus appears, it tends to be cloudy, thick, and inelastic. A change in cervical mucus indicates ovulation more accurately than body temperature. The amount of mucus increases, and the mucus becomes thinner, clearer, and more elastic (stretching between the fingers) than usual. It resembles raw egg whites. Coitus is avoided completely during menses (because mucus cannot be checked). Coitus is permitted during the days when mucus is completely absent, but during these days, coitus is restricted to every other day (so that semen is not confused with mucus). Coitus is avoided from the time mucus first appears after menses until 4 days after the amount peaks. Coitus is permitted without restriction from 4 days after the amount of mucus peaks until menses begin.

- **Symptothermal method:** This method relies on the combination of increase in temperature,
appearance of cervical mucus, and calendar rhythm method. Intercourse is avoided from the 1st day requiring abstinence according to the calendar method until 3 days after the amount of cervical mucus decreases and the temperature increases.

[Fig. 257-1. Natural family planning methods.]

The 1-yr pregnancy rates with of any of these methods is 25% with typical use. With perfect use, rates are 9% for the calendar method, 2% for the temperature method, 3% with the mucus method, and 2% with the symptothermal method. The symptothermal method is considered the most effective method of periodic abstinence because achieving perfect use is easier.

**Progestin Injections**

Depot medroxyprogesterone acetate (DMPA) is a long-acting injectable formulation of medroxyprogesterone acetate. Pregnancy rates in the 1st yr are 0.3% with perfect use and are slightly higher with typical use (ie, delays between injections).

The injection must be given during the first 5 days of the menstrual cycle to prevent ovulation. The dose is 150 mg q 3 mo by deep gluteal or deltoid IM injection. The injection site is not massaged, ensuring slow absorption. Alternatively, a formulation can be injected sc; the dose is 104 mg sc q 3 mo. Levels are usually effective starting 24 h after IM or sc injection and are maintained up to 4 mo or more. If the interval between injections is > 13 wk, a negative pregnancy test is required before giving the next injection.

The most common adverse effect is disruption of the menstrual cycle. In the 3 mo after the first DMPA injection, about 30% of women have amenorrhea. Another 30% have spotting or irregular bleeding (usually light) > 11 days/mo; anemia does not usually result. As use continues, bleeding and menses tend to decrease; after 2 yr, about 70% of women receiving DMPA have amenorrhea. Because DMPA has a long duration of action, ovulation may be delayed for up to 1 yr after the last injection; after ovulation occurs, fertility is usually rapidly restored.

Women typically gain 1.5 to 4 kg during the 1st yr of DMPA use and continue to gain weight thereafter. Usually, women who want to take DMPA are advised to decrease caloric intake and increase energy expenditure. Headache is a common reason for stopping DMPA, but severity tends to decrease over time. Most women using DMPA do not have headaches, and preexisting tension headaches and migraines usually do not worsen. Mild, reversible, clinically insignificant deterioration of glucose tolerance and lipid profile may occur. There is no evidence of increased fracture risk. Adolescents and young women using DMPA should consume 1500 mg of Ca and 400 units of vitamin D daily; supplements should be taken if necessary. Unlike OCs, DMPA does not contribute to hypertension or thromboembolism.

DMPA does not appear to increase risk of breast, ovarian, or invasive cervical cancer. DMPA reduces risk of endometrial cancer and pelvic inflammatory disease. By stimulating erythropoiesis, DMPA reduces risk of iron deficiency anemia and, for women with sickle cell disease, risks of anemia and crises.

**Transdermal and Intravaginal Steroid Contraceptives**

A 20-cm² transdermal patch can deliver 150 μg of the progestin norelgestromin (the active metabolite of norgestimate) and 20 μg of ethinyl estradiol daily into the systemic circulation for 7 days; then, the patch is removed, and a new patch is applied to a different area of the skin. Steroid blood levels are much more constant than with OCs. After 3 patches, no patch is used for the 4th wk to allow withdrawal bleeding. Overall contraceptive efficacy, incidence of bleeding, and adverse effects are similar to those of OCs, but adherence may be better. The patch may be less effective in overweight women.

Use of a flexible vaginal ring containing ethinyl estradiol and the progestin etonogestrel, which are absorbed through the vaginal epithelium, provides relatively constant blood levels. The ring is 58 mm in diameter and 4 mm thick. It is inserted and removed by the woman; it is left in place for 3 wk, then removed for 1 wk to allow for withdrawal bleeding. Bleeding with the ring in place is uncommon. Contraceptive efficacy and adverse effects are similar to those of OCs, and adherence may be better.
**Subdermal Implants**

Progestin subdermal implants are available as a new, single-rod implant that can be inserted through a trocar without a skin incision. The implant releases etonogestrel at a rate of 50 μg/day. The implant provides effective contraception for 3 yr.

The most common adverse effects are similar to those of other progestins (uterine bleeding, amenorrhea, headache). Whether weight gain results is unclear. Removing the implant requires a skin incision. After implant removal, ovarian activity normalizes immediately.

**Intrauterine Devices**

Only about 1 million women in the US use intrauterine devices (IUDs), despite their advantages over OCs:

- IUDs are highly effective.
- IUDs have no systemic effects.
- Only one contraceptive decision every 5 or 10 yr is required.

IUDs induce endometrial inflammation; this inflammation attracts neutrophils, which are toxic to sperm and prevent fertilization of the ovum.

In the US, 2 types are used: levonorgestrel-releasing IUD (effective for 5 yr; cumulative pregnancy rate of 0.5%) and copper-bearing T380A (effective for ≥ 10 yr; cumulative pregnancy rate of < 2%). IUDs are inserted high in the fundus at any time during the cycle. Contraindications include pregnancy and untreated cervicitis or vaginitis. After IUD removal, fertility rate returns to normal after about 1 yr.

**Adverse effects:** During the 1st yr, 10 to 15% of women stop use; fewer stop thereafter. Of those who stop, > 50% do so because of bleeding and pain, which occur in about 15% of users during the 1st yr and 7% during the 2nd yr. Bleeding stops completely within 1 yr in 20% of women using the levonorgestrel-releasing IUD.

Spontaneous expulsion occurs in about 5% during the 1st yr (usually within the first few weeks) and in fewer women thereafter. Expulsion is more common among younger women and among nulligravids. If another IUD is inserted, it is usually retained. Because about 20% of expulsions are unnoticed, a plastic string is attached to the IUD so that the user can check for its presence periodically.

Uterine perforation occurs in about 1/1000. Perforation occurs only during IUD insertion. Sometimes only the distal portion of the IUD penetrates; then over the next few months, uterine contractions force the IUD into the peritoneal cavity. Perforation is considered if a woman cannot feel the string but did not notice expulsion. If the string is not visible during pelvic examination, the uterine cavity is probed with a sound or biopsy instrument unless pregnancy is suspected. If the IUD cannot be felt, ultrasonography is done. If the IUD is not seen, an abdominal x-ray is taken to exclude an intraperitoneal location. Intraperitoneal IUDs may cause intestinal adhesions. IUDs that have perforated the uterus are removed, often via laparoscopy.

Occasionally, salpingitis develops during the 1st mo because of contamination during insertion; risk is not high enough to warrant routine antibiotic prophylaxis. IUD strings do not provide access for bacteria. Pelvic infections that occur after 1 mo are sexually transmitted; unless severe, they can be treated with the IUD in place.

Pregnancies that occur with an IUD in place are usually intrauterine (95%). About 5% are an ectopic pregnancy (see p. 2663), which must be ruled out in any woman who becomes pregnant with an IUD in place. With intrauterine pregnancies, there is a high risk of spontaneous abortion (about 55%) and preterm delivery but not of congenital defects, fetal death, or pelvic infection during pregnancy. Risk of abortion decreases to 20% if the IUD is removed.
IUDs do not increase and may decrease risk of endometrial adenocarcinoma and cervical cancer.

**Emergency Contraception**

- Levonorgestrel 0.75 mg po in 2 doses 12 h apart
- Levonorgestrel 1.5 mg po once

Emergency contraception is use of contraceptive hormones within 72 h of unprotected coitus. Emergency contraception can decrease the pregnancy rate for a single act of unprotected coitus at midcycle, which is typically about 8%. The most commonly used regimen is 2 doses of levonorgestrel 0.75 mg; one is taken within 72 h of unprotected intercourse, followed by one 12 h later. If taken within 72 h of one act of unprotected intercourse, levonorgestrel reduces risk of pregnancy by 89%, but if taken within 24 h, it reduces risk by 95%. Taking levonorgestrel 1.5 mg once seems to be equally effective. Another regimen—2 tablets, each containing ethinyl estradiol 50 μg and levonorgestrel 0.25 mg, followed by 2 more tablets 12 h later—has been used, but it is slightly less effective. The high estrogen dose often causes nausea and may cause vomiting.

Inserting a copper IUD within 10 days of coitus is more expensive but more effective than hormone tablets; pregnancy rate is 0.1%.

**Sterilization**

In the US, one third of couples attempting to prevent pregnancy, particularly if the woman is > 30, choose sterilization with vasectomy or tubal ligation. Sterilization should be assumed to be permanent. However, if pregnancy is desired, reanastomosis may restore fertility in 45 to 60% of men after vasectomy and in 50 to 80% of women after tubal ligation. Also, in vitro fertilization may be used successfully.

**Vasectomy**: The vasa deferentia are cut, and the cut ends are ligated or fulgurated. Vasectomy can be done in about 20 min; a local anesthetic is used. Sterility requires about 15 to 20 ejaculations after the operation and should be documented by 2 sperm-free ejaculates. Complications of vasectomy include hematoma (≤ 5%), sperm granulomas (inflammatory responses to sperm leakage), and spontaneous reanastomosis, which usually occurs shortly after the procedure.

**Tubal ligation**: The fallopian tubes are cut and a segment is excised, or the tubes are closed by ligation, fulguration, or various mechanical devices (plastic bands, spring-loaded clips). Sterilization using mechanical devices causes less tissue damage and thus may be more reversible. Via laparoscopy, tubal ligation can be done using a small periumbilical incision and a general or local anesthetic. Tubal ligation is often done immediately after or the day after delivery.

Another method is to occlude the lumen of the tubes by inserting microinserts with inner coils via hysteroscopy. This procedure does not require incisions or cutting, clipping, or burning of the tubes. After microinserts are placed, tubal occlusion (and thus sterility) is confirmed by hysterosalpingography done about 3 mo after the procedure.

Pregnancy rates after tubal ligation are < 0.5% during the 1st yr and 1.5 to 2% after 10 yr. Rates are lower if the tube has been partly excised.

Adverse effects are uncommon: death in a few patients per 100,000, hemorrhage or intestinal injuries in about 0.5%, and other complications (eg, infarction, failure of occlusion) in up to about 5%. About 30% of pregnancies that occur after tubal ligation are ectopic.

**Induced Abortion**

Induced abortion is legally available to about two thirds of women worldwide. In the US, abortion is legal during the 1st trimester (≤ 12 wk); after that, legality varies by state. In the US, about half of pregnancies are unintended; about 40% of these are terminated by elective abortion, with 90% during the 1st
Common methods of inducing abortion are instrumental evacuation through the vagina and medical induction (stimulation of uterine contractions). Uterine surgery (hysterotomy or hysterectomy) is a last resort, which is usually avoided because mortality rates are higher. Hysterotomy also results in a uterine scar, which may rupture in subsequent pregnancies.

Typically, gestational age, which usually dictates abortion method, is established by ultrasonography. Rh0(D) immune globulin, when indicated, is given to women with Rh-negative blood to prevent sensitization. First-trimester abortions often require only local anesthesia; later abortions sometimes require general anesthesia.

**Instrumental evacuation:** Instrumental evacuation is used in 97% of all abortions.

At 4 to 6 wk, the uterus can be curetted gently via a cannula attached to a vacuum source. Because failure to terminate the pregnancy is more common in early than in later weeks, instrumental evacuation should usually not be done until a gestational sac is seen. Before this time, abortion is usually induced medically.

At 7 to 12 wk, dilation and curettage (D & C) is usually used; large-diameter suction cannulas are usually required, so the cervix must be dilated. Typically, progressively increasing sizes of tapered dilators are used. Cervical damage due to dilation can be prevented or minimized by using laminaria (dried seaweed stems) or other osmotic dilators, which can be inserted into the cervix and left for ≥ 4 h (usually overnight). They dilate the cervix by expanding or stimulating prostaglandin release.

At 12 to 18 wk, dilation and evacuation (D & E) is usually used. The cervix is dilated, usually with laminaria or other osmotic dilators and dilating instruments. Forceps are used to dismember and remove the fetus, and a suction cannula is used to aspirate the amniotic fluid, placenta, and fetal debris. D & E requires more skill than do other methods of instrumental evacuation.

**Medical induction:** Medical induction can be done for pregnancies of < 7 to 9 wk or > 15 wk.

For pregnancies of up to 9 wk, mifepristone (RU 486) 200 to 600 mg po, a progesterone-receptor blocker, followed by misoprostol 400 μg po or 800 μg intravaginally, is about 95% effective in terminating pregnancies.

After 15 wk, prostaglandins are used. They include vaginal prostaglandin E2(dinoprostone) suppositories, intravaginal prostaglandin E1 analog (misoprostol) tablets, and IM injections of prostaglandin F2α (dinoprost tromethamine). Using two 200-μg intravaginal tablets of misoprostol q 6 h is nearly 100% successful within 48 h of treatment.

Adverse effects of prostaglandins include nausea, vomiting, diarrhea, hyperthermia, facial flushing, vasovagal symptoms, bronchospasm, and decreased seizure threshold. In women with a severe kidney or liver disorder, activation of the prostaglandin may be decreased, so dose should be increased.

**Complications**

Complication rates with abortion (serious complications in < 1%; mortality in < 1 in 100,000) are higher than those with contraception, although the rates have decreased in the last few decades. Complication rates increase as gestational age increases.

Serious early complications include perforation of the uterus (0.1%) or, less often, of the intestine or another organ by an instrument. Major hemorrhage (0.06%) may result from trauma or an atonic uterus. Laceration of the cervix (0.1 to 1%) ranges from superficial tenaculum tears to cervicovaginal tears, rarely with fistulas. General or local anesthesia rarely causes serious complications.

The most common delayed complications include bleeding and significant infection (0.1 to 2%), which
usually occur simultaneously because placental fragments are retained, and thrombophlebitis. If bleeding occurs or infection is suspected, pelvic ultrasonography is done; retained placental fragments may be visible on ultrasound scans. Mild inflammation is expected, but if infection is moderate or severe, peritonitis or sepsis may occur. Sterility may result from synechiae in the endometrial cavity or tubal fibrosis due to infection. Forceful dilation of the cervix in more advanced pregnancies may contribute to incompetent cervix. Elective abortion probably does not increase risks for the fetus or woman during subsequent pregnancies.

Psychologic complications do not typically occur but may occur in women who had psychologic symptoms before pregnancy, who terminated a desired pregnancy for medical reasons (maternal or fetal), who have considerable ambivalence about the abortion, who are adolescents, who had a late abortion, or who obtained an abortion illegally.
Chapter 258. Infertility

Introduction

Infertility is inability of a couple to conceive after 1 yr of unprotected intercourse.

Frequent, unprotected intercourse results in conception for 50% of couples within 3 mo, for 75% within 6 mo, and for 90% within 1 yr. Infertility can be caused by the following:

- Sperm disorders (35% of couples)
- Decreased ovarian reserve or ovulatory dysfunction (20%)
- Tubal dysfunction and pelvic lesions (30%)
- Abnormal cervical mucus (≤ 5%)
- Unidentified factors (10%)

Inability to conceive often leads to feelings of frustration, anger, guilt, resentment, and inadequacy.

Couples wishing to conceive are encouraged to have frequent intercourse for the few days when ovulation is most likely, probably midway between menstrual cycles. Measuring morning basal body temperature (BBT) daily can help determine when ovulation is occurring in women with regular menstrual cycles. A decrease suggests impending ovulation; an increase of ≥ 0.5°C suggests ovulation has just occurred. Commercially available luteinizing hormone (LH) prediction test kits, which identify the midcycle LH surge, can also help determine when ovulation occurs and are less disruptive than measuring BBT. Use of caffeine and tobacco, which can impair fertility, is discouraged.

If these measures do not result in pregnancy, a diagnostic evaluation is done. It begins with history, examination, and counseling of both partners. Men are evaluated for sperm disorders, and women for ovulatory and tubal dysfunction and pelvic lesions.

Support groups for couples (eg, American Fertility Association, RESOLVE) may help. If the likelihood of conceiving is low (usually after 2 yr of treatment), the clinician should mention adoption.

Sperm Disorders

Sperm disorders include defects in quality or quantity of sperm produced and defects in sperm emission. Diagnosis is by semen and genetic testing. The most effective treatment is usually in vitro fertilization via intracytoplasmic sperm injection.

Pathophysiology

Spermatogenesis occurs continuously. Each germ cell requires about 72 to 74 days to mature fully. Spermatogenesis is most efficient at 34°C. Within the seminiferous tubules, Sertoli cells regulate maturation, and Leydig cells produce the necessary testosterone. Fructose is normally produced in the seminal vesicles and secreted through the ejaculatory ducts. Sperm disorders may result in an inadequate quantity of sperm—too few (oligospermia) or none (azoospermia)—or defects in sperm quality, such as abnormal motility or structure.

Etiology

Impaired spermatogenesis: Spermatogenesis can be impaired by heat, disorders (GU, endocrine, or genetic), drugs, or toxins (see Table 258-1), resulting in an inadequate quantity or defective quality of sperm.

Impaired sperm emission: Sperm emission may be impaired because of retrograde ejaculation into the...
bladder, which is often due to

- Diabetes
- Neurologic dysfunction
- Retroperitoneal dissection (eg, for Hodgkin lymphoma)
- Prostatectomy

Sperm emission can also be impaired by

- Obstruction of the vas deferens
- Congenital absence of both vasa deferentia or epididymides, often in men with mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Absence of both seminal vesicles

Almost all men with symptomatic cystic fibrosis have congenital bilateral absence of the vas deferens.

**Other causes:** Men with microdeletions affecting the Y chromosome can develop oligospermia via various mechanisms, depending on the specific deletion. Another rare mechanism of infertility is destruction or inactivation of sperm by sperm antibodies, which are usually produced by the man.

**Diagnosis**

- Semen analysis
- Sometimes genetic testing

When couples are infertile, the man should always be evaluated for sperm disorders. History and physical examination focus on

*Table 258-1. Causes of Impaired Spermatogenesis*

potential causes (eg, GU disorders). Normal volume of each testis is 20 to 25 mL. Semen analysis should be done. If oligospermia or azoospermia is detected, genetic testing, including standard karyotyping, PCR of tagged chromosomal sites (to detect microdeletions affecting the Y chromosome), and evaluation for mutations of the CFTR gene, should be done. Before a man with a CFTR gene mutation and his partner attempt to conceive, the partner should also be tested to exclude cystic fibrosis carrier status.

Before semen analysis, the man is typically asked to refrain from ejaculation for 2 to 3 days. However, recent data indicate that daily ejaculation does not reduce the sperm count in men unless there is a problem. Because sperm count varies, testing requires ≥ 2 specimens obtained ≥ 1 wk apart; each specimen is obtained by masturbation into a glass jar, preferably at the laboratory site. If this method is difficult, the man can use a condom at home; the condom must be free of lubricants and chemicals. After being at room temperature for 20 to 30 min, the ejaculate is evaluated (see *Table 258-2*). Additional computer-assisted measures of sperm motility (eg, linear sperm velocity) are available; however, their correlation with fertility is unclear.

If a man without hypogonadism or congenital bilateral absence of the vas deferens has an ejaculate volume < 1 mL, urine is analyzed for sperm after ejaculation. A disproportionately large number of sperm in urine vs semen suggests retrograde ejaculation.

Endocrine evaluation is warranted if the semen analysis is abnormal and especially if the sperm concentration is < 10 million/mL.
Minimum initial testing should include serum follicle-stimulating hormone (FSH) and testosterone levels. If testosterone is low, serum luteinizing hormone (LH) and prolactin should also be measured. Men with abnormal spermatogenesis often have normal FSH levels, but any increase in FSH is a clear indication of abnormal spermatogenesis. Elevations in prolactin require evaluation for a tumor involving or impinging on the anterior pituitary or may indicate ingestion of various prescription or recreational drugs.

Specialized sperm tests, available at some infertility centers, may be considered if routine tests of both partners do not explain infertility and in vitro fertilization or gamete intrafallopian tube transfer is being contemplated. The immunobead test detects sperm antibodies, and the hypo-osmotic swelling test measures the structural integrity of sperm plasma membranes. The hemizona assay and sperm penetration assay determine the ability of sperm to fertilize the egg in vitro. The usefulness of these specialized tests is controversial.

If necessary, testicular biopsy can distinguish between obstructive and nonobstructive azoospermia.

**Treatment**

- Clomiphene
- Assisted reproductive techniques if clomiphene is ineffective

Underlying GU disorders are treated. For men with sperm counts of 10 to 20 million/mL and no endocrine disorder, clomiphene citrate (25 to 50 mg po once/day taken 25 days/mo for 3 to 4 mo) can be tried. Clomiphene, an anti-estrogen, may stimulate sperm production and increase sperm counts. However, whether it improves sperm motility or morphology is unclear, and it has not been proved to increase fertility.

If sperm count is < 10 million/mL or clomiphene is unsuccessful in men with normal sperm motility, the most effective treatment is usually in vitro fertilization with injection of a single sperm into a single egg (intracytoplasmic sperm injection). Alternatively, intrauterine insemination using washed semen samples and timed to coincide with ovulation is sometimes tried. If pregnancy is going to occur, it usually occurs by the 6th treatment cycle.

Decreased number and viability of sperm may not preclude pregnancy. In such cases, fertility may be enhanced by controlled ovarian hyperstimulation of the woman plus artificial insemination or assisted reproductive techniques (eg, in vitro fertilization, intracytoplasmic sperm injection).

If the male partner cannot produce enough fertile sperm, a couple may consider insemination using donor sperm. Risk of AIDS and other sexually transmitted diseases is minimized by freezing donor sperm for ≥ 6 mo, after which donors are retested for infection before insemination proceeds.

**Abnormal Cervical Mucus**

Abnormal cervical mucus may impair fertility by inhibiting penetration or increasing destruction of sperm.

Normally, cervical mucus is stimulated to change from thick and impenetrable to thin and stretchable by an increase in estradiol levels during the follicular phase of the menstrual cycle. Abnormal cervical mucus may

- Remain impenetrable to sperm around the time of ovulation
- Promote sperm destruction by facilitating influx of vaginal bacteria (eg, due to cervicitis)
- Contain antibodies to sperm (occasionally)
Abnormal mucus rarely impairs fertility significantly, except in women with chronic cervicitis or cervical stenosis due to prior treatment for cervical intraepithelial neoplasia.

**Diagnosis**

Women are examined to check for cervicitis and cervical stenosis. Unless they have one of these disorders, postcoital testing of cervical mucus to determine whether viable sperm are present (which used to be routine during infertility evaluation) is usually unnecessary. Usefulness of postcoital testing has not been documented.

**Treatment**

Treatment may include intrauterine insemination or drugs to thin the mucus (eg, guaifenesin). Neither treatment has been proved effective.

**Decreased Ovarian Reserve**

**Decreased ovarian reserve is a decrease in the quantity or quality of oocytes, leading to impaired fertility.**

Ovarian reserve may begin to decrease at age 30 or even earlier and decreases rapidly after age 40. Ovarian lesions also decrease reserve. Although older age is a risk factor for decreased ovarian reserve, age and decreased ovarian reserve are each independent predictors of infertility and thus of a poorer response to fertility treatment.

**Diagnosis**

- FSH and estradiol levels, sometimes after stimulation with clomiphene

Testing for decreased ovarian reserve is considered for women who are ≥ 35, who have had ovarian surgery, or who have responded poorly to treatments such as ovarian stimulation with exogenous gonadotropins. Follicle-stimulating hormone (FSH) levels > 10 mIU/mL or estradiol levels of < 80 pg/mL on day 3 of the menstrual cycle suggest the diagnosis. Diagnosis can also be made by giving the woman clomiphene 100 mg po once/day on days 5 to 9 of the menstrual cycle (clomiphene citrate challenge test). A dramatic increase in FSH and estradiol levels from day 3 to day 10 of the cycle indicates decreased reserve.

**Treatment**

If women are > 42 or ovarian reserve is decreased, assisted reproduction using donor oocytes may be necessary.

**Ovulatory Dysfunction**

**Ovulatory dysfunction is abnormal, irregular, or absent ovulation. Menses are often irregular or absent. Diagnosis is often possible by history or can be confirmed by measurement of hormone levels or serial pelvic ultrasonography. Treatment is usually induction of ovulation with clomiphene or other drugs.**

**Etiology**

Chronic ovulatory dysfunction in premenopausal women is most commonly caused by polycystic ovary syndrome (PCOS—see p. 2514) but has many other causes, including hyperprolactinemia, hypothalamic dysfunction (eg, hypothalamic amenorrhea), and other disorders that cause anovulatory amenorrhea (see Table 246-1 on p. 2502).

**Symptoms and Signs**
Ovulatory dysfunction is suspected if menses are absent, irregular, or not preceded by symptoms, such as breast tenderness, lower abdominal bloating, or moodiness.

**Diagnosis**

- Basal body temperature monitoring
- Measurement of urinary or serum hormones or ultrasonography

Measuring morning body temperature daily can help determine whether and when ovulation is occurring (see p. 2587). However, this method is often inaccurate and has an error margin of 2 days. More accurate methods include home testing kits, which detect an increase in urinary luteinizing hormone (LH) excretion 24 to 36 h before ovulation (requiring daily testing for several days around midcycle, usually beginning about or after cycle day 9), and pelvic ultrasonography, which is used to monitor ovarian follicle diameter and rupture (and should begin in the late follicular phase as well). Also, serum progesterone levels of ≥ 3 ng/mL (≥ 9.75 nmol/L) or elevated levels of one of its urinary metabolites, pregnanediol glucuronide (measured, if possible, 1 wk before onset of the next menstrual period), indicate that ovulation has occurred.

Intermittent or absent ovulation should prompt evaluation for disorders of the pituitary, hypothalamus, or ovaries (eg, PCOS).

**Treatment**

- Clomiphene
- Possibly metformin if body mass index is ≥ 35
- Gonadotropins if clomiphene is ineffective

Ovulation can usually be induced with drugs. Commonly, chronic anovulation that is not due to hyperprolactinemia is initially treated with the antiestrogen clomiphene citrate. Clomiphene is most effective when the cause is PCOS. First, uterine bleeding, unless it has occurred spontaneously, is induced with medroxyprogesterone acetate 5 to 10 mg po once/day for 5 to 10 days. Clomiphene 50 mg po once/day is started between the 3rd and 5th day after bleeding begins; it is continued for 5 days. Ovulation usually occurs 5 to 10 days (mean 7 days) after the last day of clomiphene; if ovulation occurs, menses follows within 35 days of the induced bleeding episode. The daily dose can be increased by up to 50 mg every 2 cycles to a maximum of 200 mg/dose as needed to induce ovulation. Treatment is continued as needed for up to 4 ovulatory cycles. Ovulation occurs in 75 to 80% of women treated with clomiphene, but the pregnancy rate is only about 40 to 50%.

Adverse effects of clomiphene include vasomotor flushes (10%), abdominal distention (6%), breast tenderness (2%), nausea (3%), visual symptoms (1 to 2%), and headaches (1 to 2%). Multifetal pregnancy (primarily twins) occurs in about 5%, and ovarian hyperstimulation syndrome occurs in ≤ 1%. Ovarian cysts are common. A previously suggested association between clomiphene taken for > 12 cycles and ovarian cancer has not been confirmed.

For women with PCOS, metformin (750 to 1000 mg po bid) may be a useful adjunct in inducing ovulation, particularly if the patient is insulin resistant, as many patients with PCOS are. However, clomiphene alone is more effective than metformin and is just as effective as metformin and clomiphene together. Metformin may be useful for women with a body mass index > 35 and should be considered for women with PCOS and glucose intolerance.

For all women with ovulatory dysfunction that does not respond to clomiphene, human gonadotropins (ie, preparations that contain purified or recombinant follicle-stimulating hormone [FSH] and variable amounts of LH) can be used. Several IM and sc preparations with similar efficacy are available; they typically contain 75 IU of FSH activity with or without LH activity. They are usually given once/day, beginning on the 3rd to 5th day after induced or spontaneous bleeding; ideally, they stimulate maturation of 1 to 3
follicles, determined ultrasonographically, within 7 to 14 days. Ovulation is induced with human chorionic gonadotropin (hCG) 5,000 to 10,000 IU IM after follicle maturation; criteria for induction may vary, but typically, at least one follicle should be > 16 mm in diameter. However, ovulation is not induced if women are at high risk of multifetal pregnancy or ovarian hyperstimulation syndrome. Risk factors for these problems include presence of > 3 follicles > 16 mm in diameter and preovulatory serum estradiol levels > 1500 pg/mL (or possibly > 1000 pg/mL) in women with several small ovarian follicles. When exogenous gonadotropins are used appropriately, > 95% of women treated with them ovulate, but the pregnancy rate is only 50 to 75%.

After gonadotropin therapy, 10 to 30% of successful pregnancies are multiple. Ovarian hyperstimulation syndrome occurs in 10 to 20% of patients; ovaries can become massively enlarged, and intravascular fluid volume shifts into the peritoneal space, causing potentially life-threatening ascites and hypovolemia.

Underlying disorders (eg, hyperprolactinemia—see p. 772) are treated. If the cause is hypothalamic amenorrhea, gonadorelin acetate, a synthetic gonadotropin-releasing hormone (GnRH) given as a pulsatile IV infusion, can induce ovulation. Doses of 2.5 to 5.0 μg boluses (pulse doses) regularly q 60 to 90 min are most effective. Gonadorelin acetate is unlikely to cause multifetal pregnancy. Because gonadorelin is no longer available in the US, clomiphene citrate is the first drug used to treat hypothalamic amenorrhea, followed by exogenous gonadotropins, if ovulation induction is unsuccessful.

**Tubal Dysfunction and Pelvic Lesions**

Tubal dysfunction is fallopian tube obstruction or epithelial dysfunction that impairs zygote motility; pelvic lesions are structural abnormalities that can impede fertilization or implantation.

**Etiology**

Tubal dysfunction can result from

• Pelvic inflammatory disease

• Use of an intrauterine device (a rare cause of pelvic infection)

• Ruptured appendix

• Lower abdominal surgery leading to pelvic adhesions

• Inflammatory disorders (eg, TB)

• Ectopic pregnancy

Pelvic lesions that can impede fertility include

• Intrauterine adhesions (Asherman's syndrome)

• Fibroids obstructing the fallopian tubes or distorting the uterine cavity

• Certain malformations

• Pelvic adhesions

Endometriosis can cause tubal, uterine, or other lesions that impair fertility.

**Diagnosis**

• Hysterosalpingography

• Sometimes laparoscopy or sonohysterography
All infertility evaluations include assessment of the fallopian tubes. Most often, hysterosalpingography (fluoroscopic imaging of the uterus and fallopian tubes after injection of a radiopaque agent into the uterus) is done 2 to 5 days after cessation of menstrual flow. Hysterosalpingography rarely indicates tubal patency falsely but indicates tubal obstruction falsely in about 15% of cases. This test can also detect some pelvic and intrauterine lesions. For unexplained reasons, fertility appears to be enhanced after hysterosalpingography if the test result is normal. Thus, if hysterosalpingography results are normal, additional diagnostic tests of tubal function can be delayed for several cycles.

Tubal lesions can be further evaluated with laparoscopy. Intrauterine and tubal lesions can be detected or further evaluated by sonohysterography (injection of isotonic fluid through the cervix into the uterus during ultrasonography) or hysteroscopy. Diagnosis and treatment are often done simultaneously during laparoscopy or hysteroscopy.

**Treatment**

- Laparoscopy or hysteroscopy to restore patency

During laparoscopy, pelvic adhesions can be lysed, or pelvic endometriosis can be fulgurated or ablated by laser. During hysteroscopy, adhesions can be lysed, and submucous fibroids and intrauterine polyps can be removed. Success rates are low, so assisted reproductive techniques are often necessary.

**Unexplained Infertility**

Infertility is considered unexplained when semen in the man and ovulation and fallopian tubes in the woman are normal.

When infertility remains unexplained after initial evaluation, empiric treatments are instituted.

Controlled ovarian hyperstimulation (COH) can be used to make pregnancy more likely and to achieve it sooner. This procedure stimulates development of multiple follicles; the goal is to induce ovulation of > 1 oocyte (superovulation). However, COH may result in multifetal pregnancy, which has increased risks and morbidity. COH involves the following:

- Giving clomiphene, with human chorionic gonadotropin (hCG) to trigger ovulation, for up to 3 menstrual cycles

- Intrauterine insemination within 2 days of hCG administration

- If pregnancy does not result, other assisted reproductive techniques

Alternatively, before trying assisted reproduction, some clinicians use gonadotropins (preparations that contain purified or recombinant follicle-stimulating hormone and variable amounts of luteinizing hormone), followed by hCG as for ovulatory dysfunction, then intrauterine insemination within 2 days of hCG administration. A progestin may be needed during the luteal phase to maximize the chance of implantation. Gonadotropin dosage depends on the patient's age and ovarian reserve.

The pregnancy rate is the same (about 65%) whether in vitro fertilization is used immediately after unsuccessful treatment with clomiphene plus hCG or whether gonadotropins with intrauterine insemination are used next before trying in vitro fertilization. However, when in vitro fertilization is done immediately after treatment with clomiphene plus hCG, women become pregnant more quickly.

**Assisted Reproductive Techniques**

Assisted reproductive techniques (ARTs) involve manipulation of sperm and ova in vitro with the goal of producing an embryo.

ARTs may result in multifetal pregnancy, but risk is less than that with controlled ovarian hyperstimulation.
If risk of genetic defects is high, the embryo can often be tested for defects before transfer and implantation (preimplantation genetic diagnosis).

In women < 35, > 43% of ART cycles result in pregnancy, and almost 87% of the pregnancies end in live births in the US (2005 data). The pregnancy rate decreases with increasing age; for women aged 41 to 42, the pregnancy rate is 17.5%, and only about 60% of these pregnancies end in live births. Use of donor oocytes is usually recommended for women > 42.

In vitro fertilization (IVF): IVF can be used to treat infertility due to oligospermia, sperm antibodies, tubal dysfunction, or endometriosis as well as unexplained infertility. The procedure involves the following:

- **Controlled ovarian hyperstimulation:** Clomiphene plus gonadotropins or gonadotropins alone can be used. A gonadotropin-releasing hormone (GnRH) agonist or antagonist is often given to prevent premature ovulation. After sufficient follicular growth, human chorionic gonadotropin (hCG) is given to induce final follicular maturation and ovulation.

- **Oocyte retrieval:** About 34 h after hCG is given, oocytes are retrieved by direct needle puncture of the follicle, usually transvaginally with ultrasound guidance or less commonly laparoscopically.

- **Fertilization:** The oocytes are inseminated in vitro. The semen sample is typically washed several times with tissue culture medium and concentrated for motile sperm, which are then added.

- **Embryo culture:** After sperm are added, the oocytes are cultured for about 2 to 5 days.

- **Embryo transfer:** Only 1 or a few of the resulting embryos are transferred to the uterine cavity, minimizing the chance of a multi-fetal pregnancy, the greatest risk of IVF. The number of embryos transferred is determined by the woman's age and likelihood of response to IVF. Other embryos may be frozen in liquid nitrogen for transfer in a subsequent cycle.

Gamete intrafallopian tube transfer (GIFT): GIFT is an alternative to IVF but is used infrequently, typically for women with unexplained infertility or with normal tubal function plus endometriosis. Multiple oocytes and sperm are obtained as for IVF but are transferred—transvaginally with ultrasound guidance or laparoscopically—to the distal fallopian tubes, where fertilization occurs. Live birth rates per cycle are about 25 to 35% at most infertility centers.

Intracytoplasmic sperm injection: This technique is useful when other techniques are not successful or are unlikely to be so or when a severe sperm disorder is present. Oocytes are obtained as for IVF. A single sperm is injected into each oocyte to avoid fertilization by abnormal sperm. The embryo is then cultured and transferred as for IVF. In 2005, about 60% of all ART cycles in the US involved intracytoplasmic sperm injection.

Other techniques: A combination of IVF and GIFT, zygote intrafallopian tube transfer, use of donor oocytes, and transfer of frozen embryos to a surrogate mother are sometimes used. Some of these techniques raise moral and ethical issues (eg, rightful parentage in surrogate motherhood, selective reduction of the number of implanted embryos if multi-fetal pregnancy results).
Chapter 259. Prenatal Genetic Counseling and Evaluation

Introduction

(See also Ch. 341)

Prenatal genetic counseling is provided for all prospective parents, ideally before conception, to assess risk factors for congenital disorders. (Certain precautions to help prevent birth defects (eg, avoiding teratogens, taking supplemental folate—see p. 2608) are recommended for all women who are planning to become pregnant.) Parents with risk factors are advised about possible outcomes and options for evaluation. If testing identifies a disorder, reproductive options are discussed.

Preconception options include

- Contraception
- Artificial insemination if the man is a carrier
- Oocyte donation if the woman is a carrier

Postconception options include

- Pregnancy termination
- Sometimes treatment (eg, dexamethasone to prevent virilization in a female fetus with 21-hydroxylase deficiency)

Information presented at genetic counseling should be as simple, nondirective, and jargon-free as possible to help anxious couples understand it. Frequent repetition may be necessary. Couples should be given time alone to formulate questions. Couples can be told about information that is available on the Internet (www.modimes.org) for many common problems (eg, advanced maternal age, recurrent spontaneous abortions, previous offspring with neural tube defects, previous offspring with trisomy). Many couples (eg, those with known or suspected risk factors) benefit from referral to genetic specialists for presentation of information and testing options.

Risk factors: Some risk of genetic abnormality exists in all pregnancies. Among live births, incidence is

- 0.5% for numeric or structural chromosomal disorders
- 1% for single-gene (mendelian) disorders
- 1% for multiple-gene (polygenic) disorders

Among stillbirths, rates of abnormalities are higher. Most malformations involving a single organ system (eg, neural tube defects, most congenital heart defects) result from polygenic or multifactorial (ie, also influenced by environmental factors) inheritance.

Risk of having a fetus with a chromosomal disorder is increased for most couples who have had a previous fetus or infant with a chromosomal disorder (recognized or missed), except for a few specific types (eg, 45,X; triploidy; de novo chromosomal rearrangements). Chromosomal disorders are more likely to be present in the following:

- Fetuses that spontaneously abort during the 1st trimester (50 to 60%)
- Fetuses with a major malformation (30%)
- Stillborns (5%)
Rarely, a parent has a chromosomal disorder that increases risk of a chromosomal disorder in the fetus. Asymptomatic parental chromosomal disorders (eg, balanced abnormalities such as certain translocations and inversions) may not be suspected. A balanced parental chromosomal rearrangement should be suspected if couples have had recurrent spontaneous abortions, infertility, or a child with a malformation.

For unclear reasons, risk of a fetal chromosomal disorder increases as maternal age increases. Among live births, the rate is about

- 0.2% at age 20
- 0.5% at age 35
- 1.5% at age 40
- 14% at age 49

Most chromosomal disorders due to older maternal age involve an extra chromosome (trisomy), particularly trisomy 21 (Down syndrome). Paternal age > 50 increases risk of some spontaneous dominant mutations, such as achondroplasia, in offspring.

An autosomal dominant disorder is suspected if there is a family history in more than one generation; autosomal disorders affect males and females equally. If one parent has an autosomal dominant disorder, risk is 50% that the disorder will be transmitted to an offspring.

For an autosomal recessive disorder to be expressed, an offspring must receive a mutant gene for that disorder from both parents. Parents may be heterozygous (carriers) and, if so, are usually clinically normal. If both parents are carriers, offspring (male or female) are at a 25% risk of being homozygous for the mutant gene and thus affected, 50% are likely to be heterozygous, and 25% are likely to be genetically normal. If only siblings and no other relatives are affected, an autosomal recessive disorder should be suspected. Likelihood that both parents carry the same autosomal recessive trait is increased if they are consanguineous.

Because females have 2 X chromosomes and males have only one, X-linked recessive disorders are expressed in all males who carry the mutation. Such disorders are usually transmitted through clinically normal, heterozygous (carrier) females. Thus, for each son of a carrier female, risk of having the disorder is 50%, and for each daughter, risk of being a carrier is 50%. Affected males do not transmit the gene to their sons, but they transmit it to all their daughters, who thus are carriers. Unaffected males do not transmit the gene.

**Genetic Evaluation**

Genetic evaluation is part of routine prenatal care and is ideally done before conception. The extent of genetic evaluation a woman chooses is related to how the woman weighs factors such as

- The probability of a fetal abnormality based on risk factors and the results of any previous testing
- The probability of a complication from invasive fetal testing
- The importance of knowing the results (eg, would the pregnancy be terminated if an abnormality was diagnosed, would not knowing the results cause anxiety)

For these reasons, the decision is individual, and recommendations often cannot be generalized to all women, even those with similar risk.

A screening history is part of the evaluation. The history is summarized as a pedigree (see Fig. 341-1 on p. 3375). Information should include the health status and presence of genetic disorders or carrier status of both parents, of 1st-degree relatives (parents, siblings, offspring), and of 2nd-degree relatives (aunts, uncles, grandparents), as well as ethnic and racial background and consanguineous
Genetic screening tests are best done before conception. Tests are offered to parents at risk of being asymptomatic carriers for certain common mendelian disorders (see Table 259-1). Diagnostic tests for specific abnormalities are offered to parents when appropriate (see Table 259-2).

Pregnant women should be offered screening using multiple maternal serum markers (α-fetoprotein, β-human chorionic gonadotropin [β-hCG], estriol, inhibin A—see p. 2604) to detect neural tube defects, Down syndrome (and other chromosomal abnormalities), and some other birth defects. This screening is done at 15 to 20 wk of pregnancy.

**Fetal genetic diagnostic tests:** These tests are usually done via chorionic villus sampling, amniocentesis, or, rarely, percutaneous umbilical blood sampling. They can detect all trisomies, many other chromosomal abnormalities, and several hundred mendelian abnormalities. They are usually recommended if risk of a fetal chromosomal abnormality is increased (see Table 259-2). Fetal genetic diagnostic tests, unlike screening tests, are usually invasive and involve fetal risk. Thus, in the past, these tests were not routinely recommended for women without risk factors. However, because fetal genetic diagnostic tests are now more widely available and safety has improved, offering fetal genetic testing to all pregnant women, regardless of risk, is recommended.

[Table 259-1, Genetic Screening for Some Ethnic Groups]

Preimplantation diagnosis is not commonly used because the procedure requires technical expertise and is expensive.

**Procedures**

All procedures used to diagnose genetic disorders, except ultrasonography, are invasive and involve slight fetal risk. If testing detects a serious abnormality, the pregnancy can be terminated, or in some cases, a disorder can be treated (eg, dexamethasone to prevent virilization in a female fetus with 21-hydroxylase deficiency). Even if neither of these possibilities is anticipated, some women prefer to know of fetal abnormalities before birth.

**Ultrasonography**

Some experts recommend ultrasonography routinely for all pregnant women. Others use ultrasonography only for specific indications, such as checking for suspected genetic or obstetric abnormalities or helping interpret abnormal maternal serum marker levels. If ultrasonography is done by skilled operators, sensitivity for major congenital malformations is high. However, some conditions (eg, oligohydramnios, maternal obesity, fetal position) interfere with obtaining optimal images. Ultrasonography is noninvasive and has no known risks to the woman or fetus.

**Basic ultrasonography** is done to

- Confirm gestational age
- Determine fetal viability
- Detect a multifetal pregnancy
- During the 2nd or 3rd trimester, possibly identify major malformations in the fetal intracranial structures, spine, heart, bladder, kidneys, stomach, thorax, abdominal wall, long bones, and umbilical cord
Although ultrasonography provides only structural information, some structural abnormalities strongly suggest genetic abnormalities. Multiple malformations may suggest a chromosomal disorder.

**Targeted ultrasonography**, with high-resolution ultrasonography equipment, is available at certain referral centers and provides more detailed images than basic ultrasonography. This test may be indicated for couples with a family history of a congenital malformation (eg, congenital heart defects, cleft lip and palate, pyloric stenosis), particularly one that may be treated effectively before birth (eg, posterior urethral valves with megacystis) or at delivery (eg, diaphragmatic hernia). High-resolution ultrasonography may also be used if maternal serum marker levels are abnormal. High-resolution ultrasonography may allow detection of the following:

- Renal malformations (eg, renal agenesis [Potter's syndrome], polycystic kidney disease)
- Lethal forms of short-limbed skeletal dysplasias (eg, thanatophoric skeletal dysplasia, achondrogenesis)
- Gut malformations (eg, obstruction)
- Diaphragmatic hernia
- Microcephalus
- Hydrocephalus

During the 2nd trimester, identifying structures that are statistically associated with increased risk of fetal chromosomal abnormalities helps refine risk estimate.

**Amniocentesis**

In amniocentesis, a needle is inserted transabdominally, using ultrasonographic guidance, into the amniotic sac to withdraw amniotic fluid and fetal cells for testing, including measurement of chemical markers (eg, α-fetoprotein, acetylcholinesterase). The safest time for amniocentesis is after 14 wk gestation. Immediately before amniocentesis, ultrasonography is done to assess fetal cardiac motion and determine gestational age, placental position, amniotic fluid location, and fetal number. If the mother has Rh-negative blood and is unsensitized, Rh(D) immune globulin 300 μg is given after the procedure to reduce the likelihood of sensitization (see p. 2666). Amniocentesis has traditionally been offered to pregnant women > 35 because their risk of having an infant with Down syndrome or another chromosomal abnormality is increased. However, with the widespread availability and improved safety of amniocentesis, the American College of Obstetricians and Gynecologists recommends all pregnant women be offered amniocentesis to assess the presence of fetal chromosomal disorders.

Occasionally, the amniotic fluid obtained is bloody. Usually, the blood does not affect amniotic cell growth and is maternal; however, if the blood is fetal, it may falsely elevate amniotic fluid α-fetoprotein level. Dark red or brown fluid indicates previous intra-amniotic bleeding and an increased risk of fetal loss. Green fluid, which usually results from meconium staining, does not appear to indicate increased risk of fetal loss.

Amniocentesis rarely results in significant maternal morbidity (eg, symptomatic amnionitis). With experienced operators, risk of fetal loss is about 0.1 to 0.2%. Vaginal spotting or amniotic fluid leakage, usually self-limited, occurs in 1 to 2% of women tested. Amniocentesis done before 14 wk gestation, particularly before 13 wk, results in a higher rate of fetal loss and an increased risk of talipes equinovarus (clubbed feet).

**Chorionic Villus Sampling**

In chorionic villus sampling (CVS), chorionic villi are aspirated into a syringe and cultured. CVS provides the same information about fetal genetic and chromosomal status as amniocentesis and has similar
accuracy. However, CVS is done between 10 wk gestation and the end of the 1st trimester and thus provides earlier results. Therefore, if needed, pregnancy may be terminated earlier (and more safely and simply), or if results are normal, parental anxiety may be relieved earlier. Unlike amniocentesis, amniotic fluid is not obtained at the time of CVS, and α-fetoprotein cannot be measured. Thus, women who have CVS should be offered maternal screening for serum α-fetoprotein at 16 to 18 wk to assess risk of fetal neural tube defects (see p. 2603).

Depending on placental location (identified by ultrasonography), CVS can be done by passing a catheter through the cervix or by inserting a needle through the woman's abdominal wall. After CVS, Rh₀(D) immune globulin 300 μg is given to Rh-negative unsensitized women.

Errors in diagnosis due to maternal cell contamination are rare. Detection of certain chromosomal abnormalities (eg, tetraploidy) may not reflect true fetal status but rather mosaicism confined to the placenta. Confined placental mosaicism is detected in about 1% of CVS specimens. Consultation with experts familiar with these abnormalities is advised. Rarely, subsequent amniocentesis is required to obtain additional information.

Rate of fetal loss due to CVS is similar to that of amniocentesis (ie, about 0.2%). Transverse limb defects and oromandibular-limb hypogenesis have been attributed to CVS but are exceedingly rare if CVS is done after 10 wk gestation by an experienced operator.

Percutaneous Umbilical Blood Sampling

Fetal blood samples can be obtained by percutaneous puncture of the umbilical cord vein (funipuncture) using ultrasound guidance. Chromosome analysis can be completed in 48 to 72 h. For this reason, percutaneous umbilical blood sampling (PUBS) was formerly often done when results were needed rapidly. This test was especially useful late in the 3rd trimester, particularly if fetal abnormalities were first suspected at that time. Now, genetic analysis of amniotic fluid cells or chorionic villi via interphase fluorescent in situ hybridization (FISH) allows preliminary diagnosis (or exclusion) of more common chromosomal abnormalities within 24 to 48 h, and PUBS is rarely done for genetic indications.

Procedure-related fetal loss rate with PUBS is about 1%.

Preimplantation Diagnosis

Genetic diagnosis is sometimes possible before implantation when in vitro fertilization is done; polar bodies from oocytes, blastomeres from 6- to 8-cell embryos, or a trophectoderm sample from the blastocyst is used. These tests are available only in specialized centers and are used primarily for couples with a high risk of certain mendelian disorders (eg, cystic fibrosis) or chromosomal abnormalities. Newer techniques may reduce costs and make such tests more widely available. Preimplantation genetic diagnosis to screen embryos from older women does not appear to increase the chance of successful pregnancy.

Noninvasive Maternal Screening Strategies

Noninvasive maternal screening, unlike invasive testing, has no risk of test-related complications. By more precisely assessing the risk of fetal abnormalities, particularly for women at otherwise low risk, noninvasive maternal screening can help women decide whether to have invasive testing. Noninvasive maternal screening for fetal chromosomal abnormalities should be offered to all pregnant women who have not already decided to have amniocentesis or CVS. However, if CVS is to be done, maternal serum screening should still be offered for detection of fetal neural tube defects.

Normal values vary with gestational age. Corrections for maternal weight, diabetes mellitus, race, and other factors may be necessary. Screening can be done during the 1st trimester, 2nd trimester, or both (called sequential or integrated screening). Any of the 3 approaches are acceptable. Regardless of which is done, maternal levels of α-fetoprotein should be measured during the 2nd trimester.

1st-Trimester Screening
First-trimester combined screening includes measurement of

- Maternal serum β-hCG (total or free)
- Pregnancy-associated plasma protein A (PAPP-A)
- Fetal nuchal translucency (by ultrasonography)

Fetal Down syndrome is typically associated with high levels of β-hCG, low levels of PAPP-A, and presence of enlarged fetal nuchal translucency (NT). Although an enlarged NT is associated with increase in risk for fetal Down syndrome, no threshold NT value is considered diagnostic. In large prospective US trials involving women of various ages, overall sensitivity for detection of Down syndrome was about 85%, with a false-positive rate of 5%. Specialized ultrasound training and adherence to rigorous quality-assurance monitoring of NT measurements are necessary to achieve this level of screening accuracy. First-trimester screening is being used increasingly in the US, particularly in large centers. It provides information early so that a definitive diagnosis can be made with CVS. An important advantage of 1st-trimester screening is that termination of pregnancy is safer during the 1st rather than the 2nd trimester.

2nd-Trimester Screening

Second-trimester screening may include the multiple marker screening approach, which includes

- Maternal levels of serum α-fetoprotein (MSAFP): MSAFP may be used independently as a screen for neural tube defects only, not for risk of Down syndrome. An elevated level suggests open spina bifida, anencephaly, abdominal wall defects, increased risk of pregnancy complications (eg, spontaneous abortion, abruptio placentae), or, occasionally, twins or multifetal pregnancy. Unexplained elevated MSAFP may be associated with increased risk of later pregnancy complications, such as stillbirth or intrauterine growth retardation.

- Maternal levels of β-hCG, unconjugated estriol, α-fetoprotein, and sometimes inhibin A: This screening may be used as an alternative or adjunct to 1st-trimester screening.

Second-trimester multiple marker screening is used to help assess the risk of Down syndrome, trisomy 18, and a few rarer single-gene syndromes (eg, Smith-Lemli-Opitz syndrome). Maternal serum tests are widely available, but detection rates for Down syndrome are not as high as those obtained with 1st-trimester screening. Also, termination of pregnancy is riskier in the 2nd trimester than in the 1st trimester.

Second-trimester screening may also include

- Targed ultrasonography

Maternal serum screening for neural tube defects: An elevated level of MSAFP may indicate a fetal malformation such as open spina bifida. Results are most accurate when the initial sample is obtained between 16 and 18 wk gestation, although screening can be done from about 15 to 20 wk. Designating a cutoff value to determine whether further testing is warranted involves weighing the risk of missed abnormalities against the risk of complications from unnecessary testing. Usually, a cutoff value in the 95th to 98th percentile or 2.0 to 2.5 times the normal pregnancy median (multiples of the median, or MOM) is used. This value is about 80% sensitive for open spina bifida and 90% sensitive for anencephaly. Closed spina bifida is usually not detected. Amniocentesis is eventually required in 1 to 2% of women originally screened. Lower cutoff values of MSAFP increase sensitivity but decrease specificity, resulting in more amniocenteses.

Ultrasonography is the next step if further testing is warranted. Targeted ultrasonography (see below) with or without amniocentesis is done if no explanation can be determined with basic ultrasonography. Ultrasonography can confirm gestational age (which may be underestimated) or detect multifetal pregnancy, fetal death, or congenital malformations. In some women, ultrasonography cannot identify a
cause for elevated α-fetoprotein levels. Some experts believe that if high-resolution ultrasonography done by an experienced operator is normal, further testing is unnecessary. However, because this test occasionally misses neural tube defects, many experts recommend further testing by amniocentesis regardless of ultrasonography results.

**Amniocentesis** with measurement of α-fetoprotein and acetylcholinesterase levels in amniotic fluid is done if further testing is needed. Elevated α-fetoprotein in amniotic fluid suggests

- A neural tube defect
- Another malformation (eg, omphalocele, congenital nephrosis, cystic hygroma, gastroschisis, upper Gl atresia)
- Contamination of the sample with fetal blood

Presence of acetylcholinesterase in amniotic fluid suggests a neural tube defect or another malformation. Elevated α-fetoprotein plus presence of acetylcholinesterase in amniotic fluid is virtually 100% sensitive for anencephaly and 90 to 95% sensitive for open spina bifida. Abnormal amniotic fluid markers indicate that a malformation is likely even if high-resolution ultrasonography (which can detect most of these malformations) does not detect a malformation, and parents should be informed.

**Maternal serum screening for chromosomal abnormalities:** During the 2nd trimester, the most common approach to screening is with multiple serum markers. These markers, adjusted for gestational age, are used mainly to refine estimates of Down syndrome risk beyond that associated with maternal age. With triple screening (ie, α-fetoprotein, hCG, and unconjugated estriol), sensitivity for Down syndrome is about 65 to 70%, with a false-positive rate of about 5%.

Quad screening is triple screening plus measurement of inhibin A. Quad screening increases sensitivity to about 80%, with a 5% false-positive rate.

If maternal serum screening suggests Down syndrome, ultrasonography is done to confirm gestational age, and risk is recalculated if the presumed gestational age is incorrect. If the original sample was drawn too early, another one must be drawn at the appropriate time. Amniocentesis is offered particularly if risk exceeds a specific prespecified threshold (usually 1 in 270, which is about the same as risk when maternal age is > 35).

Triple screening can also assess risk of trisomy 18, indicated by low levels of all 3 serum markers. Sensitivity for trisomy 18 is 60 to 70%; the false-positive rate is about 0.5%. Combining ultrasonography and serum screening increases sensitivity to about 80%.

**Targeted ultrasonography:** Targeted ultrasonography is offered at some perinatal centers and is used to assess risk for chromosomal abnormalities by searching for structural features associated with fetal aneuploidy (so-called soft markers). However, no structural finding is diagnostic for a given chromosomal abnormality, and all soft markers may also be seen in fetuses that are chromosomally normal. Nonetheless, the discovery of such a marker may lead to offering the woman amniocentesis to confirm or exclude a chromosomal abnormality. If a major structural malformation is present, a fetal chromosomal abnormality is more likely. Disadvantages include unnecessary anxiety if a soft marker is detected and unnecessary amniocentesis. Several experienced centers report high sensitivity, but whether a normal ultrasound indicates a substantially reduced risk of fetal chromosomal abnormalities is unclear.

**Sequential 1st- and 2nd-Trimester Screening**

Noninvasive 1st-trimester and 2nd-trimester quad screening can be combined sequentially, with invasive fetal genetic testing withheld until results of 2nd-trimester screening are available—whether 1st-trimester test results are abnormal or not. Sequential screening followed by amniocentesis for high-risk patterns increases sensitivity for Down syndrome to 95%, with a false-positive rate of only 5%.

A variation of sequential screening, called contingent sequential screening, is based on the level of risk
indicated by 1st-trimester screening:

• High risk: Invasive testing is offered without doing 2nd-trimester screening.

• Intermediate risk: 2nd-trimester screening is offered.

• Low risk (eg, < 1 in 1500): 2nd-trimester screening for Down syndrome is not offered because the 1st-trimester risk is so low.
Chapter 260. Conception and Prenatal Development

Introduction

For conception (fertilization), a live sperm must unite with an ovum in a fallopian tube with normally functioning epithelium. Conception occurs just after ovulation, about 14 days after a menstrual period. At ovulation, cervical mucus becomes less viscid, facilitating rapid movement of sperm to the ovum, usually near the fimbriated end of the tube. Sperm may remain alive in the vagina for about 3 days after intercourse.

The fertilized egg (zygote) divides repeatedly as it travels to the implantation site in the endometrium (usually near the fundus) over a period of 5 to 8 days. By the time of implantation, the zygote has become a layer of cells around a cavity, called a blastocyst. The blastocyst wall is 1 cell thick except for the embryonic pole, which is 3 or 4 cells thick. The embryonic pole, which becomes the embryo, implants first.

Amniotic sac and placenta: Within 1 or 2 days of implantation, a layer of cells (trophoblast cells) develops around the blastocyst. The progenitor villous trophoblast cell, the stem cell of the placenta, develops along 2 cell lines:

- Nonproliferative extravillous trophoblast: These cells penetrate the endometrium, facilitating implantation and anchoring of the placenta.

- Syncytiotrophoblast: These cells produce chorionic gonadotropin by day 10 and other trophic hormones shortly thereafter.

An inner layer (amnion) and outer layer (chorion) of membranes develop from the trophoblast; these membranes form the amniotic sac (see Fig. 260-1), which contains the conceptus (term used for derivatives of the zygote at any stage). When the sac is formed and the blastocyst cavity closes (by about 10 days), the conceptus is considered an embryo. The amniotic sac fills with fluid and expands with the growing embryo, filling the endometrial cavity by about 12 wk after conception; then, the amniotic sac is the only cavity remaining in the uterus.

Trophoblast cells develop into those that form the placenta. The extravillous trophoblast forms villi, which penetrate the uterus. The syncytiotrophoblast covers the villi. The syncytiotrophoblast synthesizes trophic hormones and provides arterial and venous exchange between the circulation of the conceptus and that of the mother.

The placenta is fully formed by wk 18 to 20 but continues to grow, weighing about 500 g by term.

Embryo: Around day 10, 3 germ layers (ectoderm, mesoderm, endoderm) are usually distinct in the embryo. Then the primitive streak, which becomes the neural tube, begins to develop. Around day 16, the cephalad portion of the mesoderm thickens, forming a central channel that develops into the heart and great vessels. The heart begins to pump plasma around day 20, and on the next day, fetal RBCs, which are immature and nucleated, appear. Fetal RBCs are soon replaced by mature RBCs, and blood vessels develop throughout the embryo. Eventually, the umbilical artery and vein develop, connecting the embryonic vessels with the placenta.

Most organs form between 21 and 57 days after fertilization (between 5 and 10 wk gestation); however, the CNS continues to develop throughout pregnancy. Susceptibility to malformations induced by teratogens is highest when organs are forming.
Chapter 261. Approach to the Pregnant Woman and Prenatal Care

Introduction

Pregnant women require routine prenatal care to help ensure their health and the health of the fetus. Also, evaluation is often required for symptoms and signs of illness. Common symptoms that are often pregnancy-related include vaginal bleeding, pelvic pain, vomiting, and lower-extremity edema (for specific obstetric disorders, see Ch. 265; for nonobstetric disorders in pregnant women, see Ch. 263).

Ideally, women who are planning to become pregnant should see a physician before conception, so that they can be counseled about pregnancy risks and ways to reduce them. The initial routine prenatal visit should occur between 6 and 8 wk gestation. Follow-up visits should occur at about 4-wk intervals until 28 wk, at 2-wk intervals from 28 to 36 wk, and weekly thereafter until delivery. Prenatal care includes screening for disorders, taking measures to reduce fetal and maternal risks, and counseling.

History

During the initial visit, clinicians should obtain a full medical history, including

- Previous and current disorders
- Drug use (therapeutic, social, and illicit)
- Risk factors for complications of pregnancy (see Table 264-1)

- Obstetric history, with the outcome of all previous pregnancies, including maternal and fetal complications (eg, gestational diabetes, preeclampsia, congenital malformations, stillbirth)

Family history should include all chronic disorders in family members to identify possible hereditary disorders (see p. 2599).

During subsequent visits, queries focus on interim developments, particularly vaginal bleeding or fluid discharge, headache, changes in vision, edema of face or fingers, and changes in frequency or intensity of fetal movement.

Gravidity and parity: Gravidity is the number of confirmed pregnancies; a pregnant woman is a gravida. Parity is the number of deliveries after 20 wk. Multifetal pregnancy is counted as one in terms of gravidity and parity. Abortus is the number of pregnancy losses (abortions) before 20 wk regardless of cause (eg, spontaneous, therapeutic, or elective abortion; ectopic pregnancy). Sum of parity and abortus equals gravidity.

Parity is often recorded as 4 numbers:

- Number of term deliveries (after 37 wk)
- Number of premature deliveries (> 20 and < 37 wk)
- Number of abortions
- Number of living children

Thus, a woman who is pregnant and has had one term delivery, one set of twins born at 32 wk, and 2 abortions is gravida 5, para 1-1-2-3.

Physical Examination

A full general examination, including height and weight, is done first.
In the initial obstetric examination, speculum and bimanual pelvic examination is done

- To check for lesions or discharge
- To note the color and consistency of the cervix
- To obtain cervical samples for testing

Also, fetal heart rate and, in patients presenting later in pregnancy, lie of the fetus are assessed (see Fig. 262-1 on p. 2629).

Pelvic capacity can be estimated clinically by evaluating various measurements with the middle finger during bimanual examination. If the distance from the underside of the pubic symphysis to the sacral promontory is > 11.5 cm, the pelvic inlet is almost certainly adequate. Normally, distance between the ischial spines is ≥ 9 cm, length of the sacrospinous ligaments is 4 to ≥ 5 cm, and the subpubic arch is ≥ 90°.

During subsequent visits, BP and weight assessment is important. Obstetric examination focuses on uterine size, fundal height (in cm above the symphysis pubis), fetal heart rate and activity, and maternal diet, weight gain, and overall well-being. Speculum and bimanual examination is usually not needed unless vaginal discharge or bleeding, leakage of fluid, or pain is present.

Testing

**Laboratory testing:** For diagnosis of pregnancy, see p. 2623. Initial laboratory evaluation is thorough; some components are repeated during follow-up visits (see Table 261-1).

If a woman has Rh-negative blood, she may be at risk of developing Rh(D) antibodies (see Pretransfusion Testing on p. 1037), and the fetus may be at risk of developing erythroblastosis fetalis. Rh(D) antibody levels should be measured in pregnant women at

[Table 261-1. Components of Routine Prenatal Evaluation]

18 to 20 wk and again at about 26 to 28 wk. Additional measures may be necessary to prevent development of maternal Rh antibodies (see Erythroblastosis Fetalis on p. 2665).

Generally, women are routinely screened for gestational diabetes between 24 and 28 wk using a 50-g, 1-h glucose tolerance test (see p. 2654). If women have risk factors for gestational diabetes, they are screened during the 1st trimester. Risk factors include gestational diabetes or a macrosomic neonate (weight > 4500 g at birth) in a previous pregnancy, unexplained fetal losses, a family history of diabetes in close relatives, a history of persistent glucosuria, and a body mass index (BMI) > 30 kg/m².

**Ultrasoundography:** Most obstetricians recommend at least one ultrasound examination during each pregnancy, ideally between 16 and 20 wk, when estimated delivery date (EDD) can still be confirmed fairly accurately and when placental location and fetal anatomy can be evaluated. Estimates of gestational age are based on measurements of fetal head circumference, biparietal diameter, abdominal circumference, and femur length. Measurement of fetal crown-rump length during the 1st trimester is particularly accurate in predicting EDD: to within about 5 days when measurements are made at < 12 wk gestation and to within about 7 days at 12 to 15 wk. Ultrasonography during the 3rd trimester is accurate for predicting EDD to within about 2 to 3 wk.

**Specific indications** for ultrasonography include

- Investigation of abnormalities during the 1st trimester
• Need for detailed assessment of fetal anatomy

• Detection of multifetal pregnancy, hydatidiform mole, polyhydramnios, placenta previa, or ectopic pregnancy

• Determination of placental location, fetal position and size, and size of the uterus in relation to given gestational dates (too small or too large)

Ultrasonography is also used for needle guidance during chorionic villus sampling, amniocentesis, and fetal transfusion. High-resolution ultrasonography includes techniques that maximize sensitivity for detecting fetal malformations.

If ultrasonography is needed during the 1st trimester (eg, to evaluate pain, bleeding, or viability of pregnancy), use of an endovaginal transducer maximizes diagnostic accuracy; evidence of an intrauterine pregnancy (gestational sac or fetal pole) can be seen as early as 4 to 5 wk and is seen at 7 to 8 wk in >95% of cases. With real-time ultrasonography, fetal movements and heart motion can be directly observed as early as 5 to 6 wk.

Other imaging: Conventional x-rays can induce spontaneous abortion or congenital malformations, particularly during early pregnancy. Risk is low (up to about 1/million) with each x-ray of an extremity or of the neck, head, or chest if the uterus is shielded. Risk is higher with abdominal, pelvic, and lower back x-rays. Thus, for all women of childbearing age, an imaging test with less ionizing radiation (eg, ultrasonography) should be substituted when possible, or if x-rays are needed, the uterus should be shielded (because pregnancy is possible). Medically necessary x-rays or other imaging should not be postponed because of pregnancy. However, elective x-rays are postponed until after pregnancy.

Treatment

Problems identified during evaluation are managed. Women are counseled about exercise and diet, and nutritional supplements are prescribed. What to avoid, what to expect, and when to obtain further evaluation are explained. Couples are encouraged to attend childbirth classes.

Diet and supplements: To provide nutrition for the fetus, most women require about 250 kcal extra daily; most should come from protein. If maternal weight gain is excessive (> 1.4 kg/mo during the early months) or inadequate (< 0.9 kg/mo), diet must be modified further. Weight-loss dieting during pregnancy is not recommended, even for morbidly obese women.

Most pregnant women need a daily oral iron supplement of ferrous sulfate 300 mg or ferrous gluconate 450 mg, which may be better tolerated. Woman with anemia should take the supplements bid. All women should be given oral prenatal vitamins that contain folate 400 μg (0.4 mg), taken once/day; folate reduces risk of neural tube defects. For women who have had a fetus or an infant with a neural tube defect, the recommended daily dose is 4000 μg (4 mg).

Physical activity: Pregnant women can continue to do moderate physical activities and exercise but should take care not to injure the abdomen. Sexual intercourse can be continued throughout pregnancy unless vaginal bleeding, pain, leakage of amniotic fluid, or uterine contractions occur.

Travel: The safest time to travel during pregnancy is between 14 and 28 wk, but there is no absolute contraindication to travel at any time during pregnancy. Pregnant women should wear seat belts regardless of gestational age and type of vehicle. Travel on airplanes is safe until 36 wk gestation. On long flights, pregnant patients should walk or stretch every 2 to 3 h to prevent venous stasis.

Immunizations: Vaccines for measles, mumps, rubella, and varicella should not be used during pregnancy (see p. 2626). The hepatitis B vaccine can be safely used if indicated, and the influenza vaccine is strongly recommended for women who are pregnant or postpartum during influenza season.

Pregnant women with Rh-negative blood and thus at risk of developing Rh(D) antibodies are given Rh(D) immune globulin 300 μg IM after any significant vaginal bleeding or other sign of placental
hemorrhage or separation (abruptio placentae), after a spontaneous or therapeutic abortion, after amniocentesis or chorionic villus sampling, prophylactically at 28 wk, and, if the neonate has Rh(D)-positive blood, after delivery.

**Modifiable risk factors:** Women should not use alcohol and tobacco and should avoid exposure to secondhand smoke. They should also avoid exposure to chemicals or paint fumes, direct handling of cat litter (due to risk of toxoplasmosis), prolonged temperature elevation (eg, in a hot tub or sauna), and exposure to people with active viral infections (eg, rubella, parvovirus infection [fifth disease], varicella).

Women with substance abuse problems should be monitored by a specialist in high-risk pregnancy.

Drugs and vitamins that are not medically indicated should be discouraged (see Drugs in Pregnancy on p. 2625).

**Symptoms requiring evaluation:** Women should be advised to seek evaluation for unusual headaches, visual disturbances, pelvic pain or cramping, vaginal bleeding, rupture of membranes, extreme swelling of the hands or face, diminished urine volume, any prolonged illness or infection, or persistent symptoms of labor. Multiparous women with a history of rapid labor should notify the physician at the first symptom of labor.

**Pelvic Pain During Early Pregnancy**

Pelvic pain is common during early pregnancy and may accompany serious or minor disorders. Some conditions causing pelvic pain also cause vaginal bleeding. In some of these disorders (eg, ruptured ectopic pregnancy, ruptured hemorrhagic corpus luteum cyst), bleeding may be severe, sometimes leading to hemorrhagic shock.

Causes of upper and generalized abdominal pain are similar to those in nonpregnant patients.

**Etiology**

Causes of pelvic pain during early pregnancy (see Table 261-2) may be

- Obstetric
- Gynecologic, nonobstetric
- Nongynecologic

Sometimes no particular disorder is identified.

The most common obstetric cause is

- Spontaneous abortion (threatened, inevitable, incomplete, complete, septic, or missed)

The most common serious obstetric cause is

- Ruptured ectopic pregnancy

Nonobstetric gynecologic causes include adnexal torsion, which is more common during pregnancy because during pregnancy, the corpus luteum causes the ovaries to enlarge, increasing the risk of the ovary twisting around the pedicle.

Common nongynecologic causes include various common GI and GU disorders:

- Viral gastroenteritis
Pelvic pain during late pregnancy may result from labor or one of the many nonobstetric causes of pelvic pain.

**Evaluation**

Evaluation should exclude potentially serious treatable causes (eg, ruptured or un-ruptured ectopic pregnancy, septic abortion, appendicitis).

**History:** History of present illness should include the patient's gravidity and parity as well as the pain's onset (sudden or gradual), location (localized or diffuse), and character (crampy or colicky). A history of illicitly attempted termination of pregnancy suggests septic abortion, but absence of this history does not exclude this diagnosis.

**Review of systems** should seek GU and GI symptoms that suggest a cause. Important GU symptoms include vaginal bleeding (ectopic pregnancy or abortion); syncope or near syncope (ectopic pregnancy); urinary frequency, urgency, or dysuria (UTI); and vaginal discharge and history of unprotected intercourse (pelvic inflammatory disease).

**Table 261-2. Some Causes of Pelvic Pain During Early Pregnancy**

Important GI symptoms include diarrhea (gastroenteritis, inflammatory bowel disease, or irritable bowel syndrome), vomiting (due to many disorders, including gastroenteritis and bowel obstruction), and obstipation (bowel obstruction, irritable bowel, or a functional disorder).

**Past medical history** should seek disorders known to cause pelvic pain (eg, inflammatory bowel disease, irritable bowel syndrome, nephrolithiasis, ectopic pregnancy, spontaneous abortion). Risk factors for these disorders should be identified.

Risk factors for ectopic pregnancy include

- History of sexually transmitted disease or pelvic inflammatory disease
- Cigarette smoking
- Use of intrauterine device
- Age > 35
- Previous abdominal surgery (especially tubal surgery)
- Use of fertility drugs or assisted reproductive techniques
- Previous ectopic pregnancy (the most important)
- Multiple sex partners
- Douching
Risk factors for spontaneous abortion include

- Age > 35
- History of spontaneous abortion
- Cigarette smoking
- Drugs (e.g., cocaine, alcohol, high doses of caffeine)
- Uterine abnormalities (e.g., leiomyoma, adhesions)

Risk factors for bowel obstruction include

- Previous abdominal surgery
- Hernia

**Physical examination:** Physical examination begins with a review of vital signs, particularly for fever and signs of hypovolemia (hypotension, tachycardia).

Evaluation focuses on abdominal and pelvic examinations. The abdomen is palpated for tenderness, peritoneal signs (rebound, rigidity, guarding), and uterine size and is percussed for tympany. Fetal heart sounds are checked using a Doppler probe.

Pelvic examination includes inspection of the cervix for discharge, dilation, and bleeding. Discharge, if present, should be sampled and sent for culture. Any blood or clots in the vaginal vault are gently removed. Bimanual examination should check for cervical motion tenderness, adnexal masses or tenderness, and uterine size.

**Red flags:** The following findings are of particular concern:

- Hemodynamic instability (hypotension, tachycardia, or both)
- Syncope or near syncope
- Peritoneal signs (rebound, rigidity, guarding)
- Fever, chills, and purulent vaginal discharge
- Vaginal bleeding

**Interpretation of findings:** Certain findings suggest causes of pelvic pain but are not always diagnostic (see Table 261-2).

For all women who present with pelvic pain during early pregnancy, the most serious cause—ectopic pregnancy—must be excluded, regardless of any other findings. Nonobstetric causes of pelvic pain (e.g., acute appendicitis) must always be considered and investigated as in nonpregnant women.

As in any patient, findings of peritoneal irritation (e.g., focal tenderness, guarding, rebound, rigidity) are a concern. Common causes include appendicitis, ruptured ectopic pregnancy, and, less often, ruptured ovarian cyst. However, absence of peritoneal irritation does not rule out such disorders, and index of suspicion must be high.

Vaginal bleeding accompanying the pain suggests spontaneous abortion or ectopic pregnancy. An open cervical os or tissue passed through the cervix strongly suggests an inevitable, incomplete, or complete abortion. The presence of fever, chills, and a purulent vaginal discharge suggests a septic abortion (particularly in patients with a history of instrumentation of the uterus or illicitly attempted termination of pregnancy).
pregnancy). Pelvic inflammatory disease is rare during pregnancy but may occur.

Testing: If an obstetric cause of pelvic pain is suspected, quantitative measurement of β-hCG, CBC, blood type, and Rh typing should be done. If the patient is hemodynamically unstable (with hypotension, persistent tachycardia, or both), blood should be cross-matched, and fibrinogen level, fibrin split products, and PT/PTT are determined.

Pelvic ultrasonography is done to confirm an intrauterine pregnancy. However, ultrasonography can and should be deferred in the hemodynamically unstable patient with a positive pregnancy test, given the very high likelihood of either ectopic pregnancy or spontaneous abortion with hemorrhage. Both transabdominal and transvaginal ultrasonography should be used as necessary. If the uterus is empty and tissue has not been passed, ectopic pregnancy is suspected. If Doppler ultrasonography shows that blood flow to the adnexa is absent or decreased, adnexal (ovarian) torsion is suspected. However, this finding is not always present because spontaneous detorsion can occur.

Treatment

Treatment is directed at the cause. If ectopic pregnancy is confirmed and is not ruptured, methotrexate can often be considered, or surgical salpingotomy or salpingectomy may be done. If the ectopic pregnancy is ruptured or leaking, treatment is immediate laparoscopy or laparotomy.

Treatment of spontaneous abortions depends on the type of abortion and the patient's hemodynamic stability. Threatened abortions are treated conservatively with oral analgesics. Inevitable, incomplete, or missed abortions are treated medically with misoprostol or surgically with uterine evacuation via D & C. Septic abortions are treated with uterine evacuation plus IV antibiotics.

Women who have Rh-negative blood should be given Rh\(_0\)(D) immune globulin if they have vaginal bleeding or an ectopic pregnancy.

Ruptured corpus luteum cysts and degeneration of a uterine fibroid are treated conservatively with oral analgesics.

Treatment of adnexal torsion is surgical: manual detorsion if the ovary is viable; oophorectomy or salpingectomy if the ovary is infarcted and nonviable.

Key Points

• Clinicians should always be alert for ectopic pregnancy.

• Nonobstetric causes should be considered; acute abdomen may develop during pregnancy.

• If no clear nonobstetric cause is identified, ultrasonography is usually necessary.

• A septic abortion is suspected when there is a history of recent uterine instrumentation or induced abortion.

• If vaginal bleeding occurred, Rh status is determined, and all women with Rh-negative blood are given Rh\(_0\)(D) immune globulin.

Vaginal Bleeding During Early Pregnancy

Vaginal bleeding occurs in 20 to 30% of confirmed pregnancies during the first 20 wk of gestation; about half of these cases end in spontaneous abortion. Vaginal bleeding is also associated with other adverse pregnancy outcomes such as low birth weight, preterm birth, stillbirth, and perinatal death.

Etiology

Obstetric or nonobstetric disorders may cause vaginal bleeding during early pregnancy (see...
Table 261-3.

The most dangerous cause is

• Ruptured ectopic pregnancy

The most common cause is

• Spontaneous abortion (threatened, inevitable, incomplete, complete, septic, missed)

[Table 261-3: Some Causes of Vaginal Bleeding During Early Pregnancy]

Evaluation

A pregnant woman with vaginal bleeding must be evaluated promptly.

Ectopic pregnancy or other causes of copious vaginal bleeding (eg, inevitable abortion, ruptured hemorrhagic corpus luteum cyst) can lead to hemorrhagic shock. IV access should be established early during evaluation in case such complications occur.

History: History of present illness should include the patient's gravidity (number of confirmed pregnancies), parity (number of deliveries after 20 wk), and number of abortions (spontaneous or induced); description and amount of bleeding, including how many pads were soaked and whether clots or tissue were passed; and presence or absence of pain. If pain is present, onset, location, duration, and character should be determined.

Review of symptoms should note fever, chills, abdominal or pelvic pain, vaginal discharge, and neurologic symptoms such as dizziness, light-headedness, syncope, or near syncope.

Past medical history should include risk factors for ectopic pregnancy and spontaneous abortion (see p. 2611).

Physical examination: Physical examination includes review of vital signs for fever and signs of hypovolemia (tachycardia, hypotension).

Evaluation focuses on abdominal and pelvic examinations. The abdomen is palpated for tenderness, peritoneal signs (rebound, rigidity, guarding), and uterine size. Fetal heart sounds should be checked with a Doppler ultrasound probe.

Pelvic examination includes inspection of external genitals, speculum examination, and bimanual examination. Blood or products of conception in the vaginal vault, if present, are removed; products of conception are sent to a laboratory for confirmation. The cervix should be inspected for discharge, dilation, lesions, polyps, and tissue in the os. If the pregnancy is < 14 wk, the cervical os may be gently probed (but no more than fingertip depth) using ringed forceps to determine the integrity of the internal cervical os. If the pregnancy is ≥ 14 wk, the cervix should not be probed because the vascular placenta may tear, especially if it covers the internal os (placenta previa). Bimanual examination should check for cervical motion tenderness, adnexal masses or tenderness, and uterine size.

Red flags: The following findings are of particular concern:

• Hemodynamic instability (hypotension, tachycardia, or both)

• Orthostatic changes in pulse or BP

• Syncope or near syncope

• Peritoneal signs (rebound, rigidity, guarding)
• Fever, chills, and mucopurulent vaginal discharge

Interpretation of findings: Clinical findings help suggest a cause but are rarely diagnostic (see Table 261-3). However, a dilated cervix plus passage of fetal tissue and crampy abdominal pain strongly suggests spontaneous abortion, and septic abortion is usually apparent from the circumstances and signs of severe infection (fever, toxic appearance, purulent or bloody discharge). Even if these classic manifestations are not present, threatened or missed abortion is possible, and the most serious cause—ruptured ectopic pregnancy—must be excluded. Although the classic description of ectopic pregnancy includes severe pain, peritoneal signs, and a tender adnexal mass, ectopic pregnancy can manifest in many ways and should always be considered, even when bleeding appears scant and pain appears minimal.

Testing: A self-diagnosed pregnancy is verified with a urine test. For women with a documented pregnancy, several tests are done:

• Quantitative β-hCG level

• Blood typing and Rh testing

• Usually ultrasonography

Rh testing is done to determine whether Rh(D) immune globulin is needed to prevent maternal sensitization. If bleeding is substantial, testing should also include CBC and either type and screen (for abnormal antibodies) or cross-matching. For major hemorrhage or shock, PT/PTT is also determined.

Transvaginal pelvic ultrasonography is done to confirm an intrauterine pregnancy unless products of conception have been obtained intact (indicating completed abortion). If patients are in shock or bleeding is substantial, ultrasonography should be done at the bedside. The quantitative β-hCG level helps interpret ultrasound results. If the level is ≥ 1500 mIU/mL and ultrasonography does not confirm an intrauterine pregnancy (a live or dead fetus), ectopic pregnancy is likely. If the level is < 1500 mIU/mL and no intrauterine pregnancy is seen, intrauterine pregnancy is still possible.

If the patient is stable and clinical suspicion for ectopic pregnancy is low, serial β-hCG levels may be done on an outpatient basis. Normally, the level doubles every 1.4 to 2.1 days up to 41 days gestation; in ectopic pregnancy (and in abortions), levels may be lower than expected by dates and usually do not double as rapidly. If clinical suspicion for ectopic pregnancy is moderate or high (eg, because of substantial blood loss, adnexal tenderness, or both), diagnostic uterine evacuation or D & C and possibly diagnostic laparoscopy should be done.

Ultrasonography can also help identify a ruptured corpus luteum cyst and gestational trophoblastic disease. It can show products of conception in the uterus, which are present in patients with incomplete, septic, or missed abortion.

Treatment

Treatment is directed at the underlying disorder:

• Ruptured ectopic pregnancy: Immediate laparoscopy or laparotomy

• Unruptured ectopic pregnancy: Methotrexate or salpingotomy or salpingectomy via laparoscopy or laparotomy

• Threatened abortion: Expectant management for hemodynamically stable patients

• Inevitable, incomplete, or missed abortions: D & C or uterine evacuation

• Septic abortion: IV antibiotics and urgent uterine evacuation if retained products of conception are identified during ultrasonography
• Complete abortion: Obstetric follow-up

**Key Points**

• Clinicians should always be alert for ectopic pregnancy; symptoms can be mild or severe.

• Spontaneous abortion is the most common cause of bleeding during early pregnancy.

• Rh testing is required for all women who present with vaginal bleeding during early pregnancy to determine whether Rh(D) immune globulin is needed.

**Nausea and Vomiting During Early Pregnancy**

Nausea and vomiting affect up to 80% of pregnant women. Symptoms are most common and most severe during the 1st trimester. Although common usage refers to morning sickness, nausea, vomiting, or both typically may occur at any point during the day. Symptoms vary from mild to severe (hyperemesis gravidarum).

**Hyperemesis gravidarum** is persistent, severe pregnancy-induced vomiting that causes significant dehydration, often with electrolyte abnormalities, ketosis, and weight loss (see p. 2667).

**Pathophysiology**

The pathophysiology of nausea and vomiting during early pregnancy is unknown, although metabolic, endocrine, GI, and psychologic factors probably all play a role. Estrogen may contribute because estrogen levels are elevated in patients with hyperemesis gravidarum.

**Etiology**

The most common causes of uncomplicated nausea and vomiting during early pregnancy (see Table 261-4) are

• Morning sickness (most common)

• Hyperemesis gravidarum

• Gastroenteritis

Occasionally, prenatal vitamin preparations with iron cause nausea. Rarely, severe, persistent vomiting results from a hydatidiform mole.

**[Table 261-4, Some Causes of Nausea and Vomiting During Early Pregnancy]**

Vomiting can also result from many nonobstetric disorders. Common causes of acute abdomen (eg, appendicitis, cholecystitis) may occur during pregnancy and may be accompanied by vomiting, but the chief complaint is typically pain rather than vomiting. Similarly, some CNS disorders (eg, migraine, CNS hemorrhage, increased intracranial pressure) may be accompanied by vomiting, but headache or other neurologic symptoms are typically the chief complaint.

**Evaluation**

Evaluation aims to exclude serious or life-threatening causes of nausea and vomiting. Morning sickness (uncomplicated nausea and vomiting) and hyperemesis gravidarum are diagnoses of exclusion.

**History:** **History of present illness** should particularly note the following:

• Onset and duration of vomiting
• Exacerbating and relieving factors

• Type (eg, bloody, watery, bilious) and amount of emesis

• Frequency (intermittent or persistent)

Important associated symptoms include diarrhea, constipation, and abdominal pain. If pain is present, the location, radiation, and severity should be queried. The examiner should also ask what social effects the symptoms have had on the patient and her family (eg, whether she is able to work or to care for her children).

Review of systems should seek symptoms of nonobstetric causes of nausea and vomiting, including fever or chills, particularly if accompanied by flank pain or voiding symptoms (UTI or pyelonephritis), and neurologic symptoms such as headache, weakness, focal deficits, and confusion (migraine or CNS hemorrhage).

Past medical history includes questions about morning sickness or hyperemesis in past pregnancies. Past surgical history should include questions about any prior abdominal surgery, which would predispose a patient to mechanical bowel obstruction.

Drugs taken by the patient are reviewed for drugs that could contribute (eg, iron-containing compounds, hormonal therapy) and for safety during pregnancy.

Physical examination: Examination begins with review of vital signs for fever, tachycardia, and abnormal BP (too low or too high).

A general assessment is done to look for signs of toxicity (eg, lethargy, confusion, agitation). A complete physical examination, including pelvic examination, is done to check for findings suggesting serious or potentially life-threatening causes of nausea and vomiting (see Table 261-5).

Red flags: The following findings are of particular concern:

• Abdominal pain

• Signs of dehydration (eg, orthostatic hypotension, tachycardia)

[Table 261-5. Relevant Physical Examination Findings in a Pregnant Patient with Vomiting]

• Fever

• Bloody or bilious emesis

• No fetal motion or heart sounds

• Abnormal neurologic examination

• Persistent or worsening symptoms

Interpretation of findings: Distinguishing pregnancy-related vomiting from vomiting due to other causes is important. Clinical manifestations help (see Table 261-4).

Vomiting is less likely to be due to pregnancy if it begins after the 1st trimester or is accompanied by abdominal pain, diarrhea, or both. Abdominal tenderness may suggest acute abdomen. Meningismus, neurologic abnormalities, or both suggest a neurologic cause.

Vomiting is more likely to be due to pregnancy if it begins during the 1st trimester, it lasts or recurs over
several days to weeks, abdominal pain is absent, and there are no symptoms or signs involving other
organ systems.

If vomiting appears to be pregnancy-related and is severe (ie, frequent, prolonged, accompanied by
dehydration), hyperemesis gravidarum and hydatidiform mole should be considered.

**Testing:** Patients with significant vomiting, signs of dehydration, or both usually require testing. If
hyperemesis gravidarum is suspected, urine ketones are measured; if symptoms are particularly severe
or persistent, serum electrolytes are measured. If fetal heart sounds are not clearly audible or detected by
fetal Doppler, pelvic ultrasonography should be done to rule out hydatidiform mole. Other tests are done
based on clinically suspected nonobstetric disorders (see Table 261-4).

**Treatment**

Pregnancy-induced vomiting may be relieved by drinking or eating frequently (5 or 6 small meals/day), but
only bland foods (eg, crackers, soft drinks, BRAT diet [bananas, rice, apple-sauce, dry toast]) should be
eaten. Eating before rising may help. If dehydration (eg, due to hyperemesis gravidarum) is suspected, 1
to 2 L of normal saline or Ringer's lactate is given IV, and any identified electrolyte abnormalities are
corrected.

Certain drugs (see Table 261-6) can be used to relieve nausea and vomiting during the 1st trimester without evidence of
adverse effects on the fetus.

Vitamin B<sub>6</sub> is used as monotherapy; other drugs are added if symptoms are not relieved.

Ginger (eg, ginger capsules 250 mg po tid or qid, ginger lollipops), acupuncture, motion sickness bands,
and hypnosis may help, as may switching from prenatal vitamins to a children's chewable vitamin with
folate.

**Key Points**

- Vomiting during pregnancy is usually self-limited and responds to dietary modification.
- Hyperemesis gravidarum is less common but is severe, leading to dehydration, ketosis, and weight loss.
- Nonobstetric causes should be considered.

**Lower-Extremity Edema During Late Pregnancy**

Edema is common during late pregnancy. It typically involves the lower extremities but occasionally
appears as swelling or puffiness in the face or hands.

**Etiology**

The most common cause of edema in pregnancy is

- Physiologic edema

Physiologic edema results from hormone-induced Na retention. Edema may also occur when the enlarged
uterus intermittently compresses the inferior vena cava during recumbency, obstructing outflow from both
femoral veins.

Pathologic causes of edema are less common but often dangerous. They include deep venous
thrombosis (DVT) and preeclampsia (see Table 261-7). DVT is more common during pregnancy because pregnancy is a hypercoagulable state,
and women may be less mobile. Preeclampsia results from pregnancy-induced hypertension; however, not all women with

[Table 261-7, Some Causes of Edema During Late Pregnancy]

preeclampsia develop edema. When extensive, cellulitis, which usually causes focal erythema, may resemble general edema.

**Evaluation**

Evaluation aims to exclude DVT and preeclampsia. Physiologic edema is a diagnosis of exclusion.

**History:** History of present illness should include symptom onset and duration, exacerbating and relieving factors (physiologic edema is reduced by lying in the left lateral decubitus position), and risk factors for DVT and preeclampsia. Risk factors for DVT include

- Venous insufficiency
- Trauma
- Hypercoagulability disorder
- Thrombotic disorders
- Cigarette smoking
- Immobility
- Cancer

Risk factors for preeclampsia include

- Chronic hypertension
- Personal or family history of preeclampsia
- Age < 17 or > 35
- First pregnancy
- Multifetal pregnancy
- Diabetes
- Vascular disorders
- Hydatidiform mole
- Abnormal maternal serum screening results

**Review of symptoms** should seek symptoms of possible causes, including nausea and vomiting, abdominal pain, and jaundice (preeclampsia); pain, redness, or warmth in an extremity (DVT or cellulitis); dyspnea (pulmonary edema or preeclampsia); sudden increase in weight or edema of the hands and face (preeclampsia); and headache, confusion, mental status changes, blurry vision, or seizures (preeclampsia).

**Past medical history** should include history of DVT, pulmonary embolism, preeclampsia, and hypertension.
**Physical examination:** Examination begins with review of vital signs, particularly BP.

Areas of edema are evaluated for distribution (ie, whether bilateral and symmetric or unilateral) and presence of redness, warmth, and tenderness.

General examination focuses on systems that may show findings of preeclampsia. Eye examination includes testing visual fields for deficits, and funduscopic examination should check for papilledema.

Cardiovascular examination includes auscultation of the heart and lungs for evidence of fluid overload (eg, audible S3 or S4 heart sounds, tachypnea, rales, crackles) and inspection of neck veins for jugular venous distention. The abdomen should be palpated for tenderness, especially in the epigastric or right upper quadrant region. Neurologic examination should assess mental status for confusion and seek focal neurologic deficits.

**Red flags:** The following findings are of particular concern:

- BP ≥ 140/90 mm Hg
- Unilateral leg or calf warmth, redness, or tenderness, with or without fever
- Hypertension and any systemic symptoms or signs, particularly mental status changes

**Interpretation of findings:** Although edema is common during pregnancy, considering and ruling out the most dangerous causes (preeclampsia and DVT) are important:

- If BP is > 140/90 mm Hg, preeclampsia should be considered.
- If edema involves only one leg, particularly when redness, warmth, and tenderness are present, DVT and cellulitis should be considered.
- Bilateral leg edema suggests a physiologic process or preeclampsia as the cause.

Clinical findings help suggest a cause (see Table 261-7). Additional findings may suggest preeclampsia (see Table 261-8).

**Testing:** If preeclampsia is suspected, urine protein is measured; hypertension plus proteinuria indicates preeclampsia. Urine dipstick testing is used routinely, but if diagnosis is unclear, urine protein may be measured in a 24-h collection. Many laboratories can more rapidly assess urine protein by measuring and calculating the urine protein:urine creatinine ratio.

If DVT is suspected, lower-extremity duplex ultrasonography is done.

**Treatment**

Specific causes are treated.

Physiologic edema can be reduced by intermittently lying on the left side (which moves the uterus off the inferior vena cava), by intermittently elevating the lower extremities, and by wearing elastic compression stockings.

**Key Points**

- Edema is common and usually benign (physiologic) during late pregnancy.
- Physiologic edema is reduced by lying in the left lateral decubitus position, elevating the lower extremities, and using compression stockings.
Table 261-8: Some Findings that Suggest Preeclampsia

• Hypertension and proteinuria indicate preeclampsia.

• Unilateral leg edema, redness, warmth, and tenderness require evaluation for DVT.

Vaginal Bleeding During Late Pregnancy

Bleeding during late pregnancy (≥ 20 wk gestation, but before birth) occurs in 3 to 4% of pregnancies.

Pathophysiology

Some disorders can cause substantial blood loss, occasionally enough to cause hemorrhagic shock or disseminated intravascular coagulation.

Etiology

The most common cause of bleeding during late pregnancy is

• Bloody show of labor

Bloody show heralds onset of labor, is scant and mixed with mucus, and results from tearing of small veins as the cervix dilates and effaces at the start of labor.

More serious but less common causes (see Table 261-9) include

• Abruptio placentae (placental abruption)

• Placenta previa

• Vasa previa

• Uterine rupture (rare)

Abruptio placentae is premature separation of a normally implanted placenta from the uterine wall. The mechanism is unclear, but it is probably a late consequence of chronic uteroplacental vascular insufficiency. Some cases follow trauma (eg, assault, motor vehicle crash). Because some or most of the bleeding may be concealed between the placenta and uterine wall, the amount of external (ie, vaginal) bleeding does not necessarily reflect the extent of blood loss or placental separation. Abruptio placentae is the most common life-threatening cause of bleeding during late pregnancy, accounting for about 30% of cases. It may occur at any time but is most common during the 3rd trimester.

Placenta previa is abnormal implantation of the placenta over or near the internal cervical os. It results from various risk factors. Bleeding may be spontaneous or triggered by digital examination or by onset of labor. Placenta previa accounts for about 20% of bleeding during late pregnancy and is most common during the 3rd trimester.

In vasa previa, the fetal blood vessels connecting the cord and placenta overlie the internal cervical os and are in front of the fetal presenting part. Usually, this abnormal connection occurs when vessels from the cord run through part of the chorionic membrane rather than directly into the placenta (velamentous insertion). The mechanical forces of labor can disrupt these small blood vessels, causing them to rupture. Because of the relatively small fetal blood volume, even a small blood loss due to vasa previa can represent catastrophic hemorrhage for the fetus and cause fetal death.

Uterine rupture may occur during labor—almost always in women who have had scarring of the uterus (eg, due to cesarean delivery, uterine surgery, or uterine infection)—or after severe abdominal trauma.
**Table 261-9. Some Causes of Bleeding During Late Pregnancy**

**Evaluation**

The evaluation aims to exclude potentially serious causes of bleeding (abruptio placentae, placenta previa, vasa previa, uterine rupture). Bloody show of labor and abruptio placentae are diagnoses of exclusion.

**History: History of present illness** should include the patient's gravidity (number of confirmed pregnancies), parity (number of deliveries after 20 wk), and number of abortions (spontaneous or induced); duration of bleeding; and amount and color (bright red vs dark) of blood. Important associated symptoms include abdominal pain and rupture of membranes. Clinicians should note whether these symptoms are present or not and describe them (eg, whether pain is intermittent and crampy, as in labor, or constant and severe, suggesting abruptio placentae or uterine rupture).

**Review of systems** should elicit any history of syncope or near syncope (suggesting major hemorrhage).

**Past medical history** should note risk factors for major causes of bleeding (see Table 261-10), particularly previous cesarean delivery. Clinicians should determine whether patients have a history of hypertension, cigarette smoking, in vitro fertilization, or any illicit drug use (particularly cocaine).

**Physical examination:** Examination starts with review of vital signs, particularly BP, for signs of hypovolemia. Fetal heart rate is assessed, and continuous fetal monitoring is started if possible.

The abdomen is palpated for uterine size, tenderness, and tonicity (normal, increased, or decreased).

A digital cervical examination is contraindicated when bleeding occurs during late pregnancy until ultrasonography confirms normal placental and vessel location (and excludes placenta previa and vasa previa). Careful speculum examination can be done. If ultrasonography is normal, clinicians may proceed with a digital examination to determine cervical dilation and effacement.

**Red flags:** The following findings are of particular concern:

- Hypotension
- Tense, tender uterus
- Fetal distress (loss of heart sounds, bradycardia, variable or late decelerations detected during monitoring)
- Cessation of labor and atonic uterus

**Interpretation of findings:** If more than a few drops of blood are observed or there are signs of fetal distress, the more serious causes must be ruled out: abruptio placentae, placenta previa, vasa previa, and uterine rupture. However, some patients with abruptio placentae or uterine rupture have minimal visible bleeding despite major intra-abdominal or intrauterine hemorrhage.

Clinical findings help suggest a cause (see also Table 261-9). Light bleeding with mucus suggests bloody show of labor. Sudden, painless bleeding with bright red blood suggests placenta previa or vasa previa. Dark red clotted blood suggests abruptio placentae or uterine rupture. A tense, contracted, tender uterus suggests abruptio placentae; an atonic or abnormally shaped uterus with abdominal tenderness suggests uterine rupture.
Testing: The tests should include the following:

- Ultrasonography
- CBC and type and screen
- Possibly Kleihauer-Betke testing

All women with bleeding during late pregnancy require transvaginal ultrasonography, done at the bedside if the patient is unstable. A normal placenta and normal cord and vessel insertion exclude placenta previa and vasa previa. Although ultrasonography sometimes shows abruptio placentae, this test is not sufficiently reliable to distinguish abruptio placentae from uterine rupture. These diagnoses are made clinically, based on risk factors and examination findings (a tense uterus is more common in abruptio placentae; loss of tone is more common in rupture). Rupture is confirmed during laparotomy.

In addition, CBC and type and screen (blood typing and screening for abnormal antibodies) should be done. If bleeding is severe, if moderate to severe abruptio placentae is suspected, or if maternal hypotension is present, several units of blood are cross-matched and tests for disseminated intravascular coagulation (PT/PTT, fibrinogen level, D-dimer level) are done.

The Kleihauer-Betke test can be done to measure the amount of fetal blood in the maternal circulation and determine the need for additional doses of Rh0(D) immune globulin to prevent maternal sensitization.

Treatment

Treatment is aimed at the specific cause. Patients with signs of hypovolemia require IV fluid resuscitation, starting with 20 mL/kg of normal saline solution. Blood transfusion should be considered for patients not responding to 2 L of saline.

Key Points

- All patients require IV access for fluid or blood resuscitation, as well as continuous maternal and fetal monitoring.
- A digital cervical examination is contraindicated in evaluation of bleeding during late pregnancy until placenta previa and vasa previa are excluded.
- In abruptio placentae, vaginal bleeding may be absent if blood is concealed between the placenta and uterine wall.
- Uterine rupture is suspected in women with a history of cesarean delivery or other uterine surgery.
- Vaginal bleeding may be mild despite maternal hypotension.
Introduction

The earliest sign of pregnancy and the reason most pregnant women initially see a physician is missing a menstrual period. For sexually active women who are of reproductive age and have regular periods, missing a period for ≥ 1 wk is presumptive evidence of pregnancy.

Pregnancy is considered to last 266 days from the time of conception or 280 days from the first day of the last menstrual period if periods occur regularly every 28 days. Delivery date is estimated based on the last menstrual period. Delivery up to 2 wk earlier or later than the estimated date is normal.

Symptoms and Signs

Pregnancy may cause breasts to be engorged because of increased levels of estrogen (primarily) and progesterone—an extension of premenstrual breast engorgement. Nausea, occasionally with vomiting, may occur because of increased secretion of estrogen and the β subunit of human chorionic gonadotropin (β-hCG) by syncytial cells of the placenta, beginning 10 days after fertilization (see p. 2605). The corpus luteum in the ovary, stimulated by β-hCG, continues secreting large amounts of estrogen and progesterone to maintain the pregnancy. Many women become fatigued at this time, and a few women notice abdominal bloating very early. Women usually begin to feel fetal movement between 16 and 20 wk.

Pelvic examination findings include a softer cervix and an irregularly softened, enlarged uterus. The cervix usually becomes bluish to purple, probably because blood supply to the uterus is increased. Around 12 wk gestation, the uterus extends above the true pelvis into the abdomen; at 20 wk, it reaches the umbilicus; and by 36 wk, the upper pole almost reaches the xiphoid process.

Diagnosis

Usually urine and occasionally blood tests are used to confirm or exclude pregnancy; results are usually accurate several days before a missed menstrual period and often as early as several days after conception. Levels of β-hCG, which correlate with gestational age in normal pregnancies, can be used to determine whether a fetus is growing normally. The best approach is to compare 2 serum β-hCG values, obtained 48 to 72 h apart and measured by the same laboratory. In a normal single pregnancy, β-hCG levels double about every 1.4 to 2.1 days during the first 60 days (7.5 wk), then begin to decrease between 10 and 18 wk. Regular doubling of the β-hCG level during the 1st trimester strongly suggests normal growth.

Other accepted signs of pregnancy include the following:

- Presence of a gestational sac in the uterus, seen with ultrasonography typically at about 4 to 5 wk and typically corresponding to a serum β-hCG level of about 1500 mIU/mL (a yolk sac can usually be seen in the gestational sac by 5 wk)
- Fetal heart motion, seen with real-time ultrasonography as early as 5 to 6 wk
- Fetal heart sounds, heard with Doppler ultrasonography as early as 8 to 10 wk if the uterus is accessible abdominally
- Fetal movements felt by the examining physician after 20 wk

Physiology of Pregnancy

Pregnancy causes physiologic changes in all maternal organ systems; most return to normal after delivery. In general, the changes are more dramatic in multifetal than in single pregnancies.

Cardiovascular: Cardiac output (CO) increases 30 to 50%, beginning by 6 wk gestation and peaking
between 16 and 28 wk (usually at about 24 wk). It remains near peak levels until after 30 wk. Then, CO becomes sensitive to body position. Positions that cause the enlarging uterus to obstruct the vena cava the most (eg, the recumbent position) cause CO to decrease the most. On average, CO usually decreases slightly from 30 wk until labor begins. During labor, CO increases another 30%. After delivery, the uterus contracts, and CO drops rapidly to about 15 to 25% above normal, then gradually decreases (mostly over the next 3 to 4 wk) until it reaches the prepregnancy level at about 6 wk postpartum.

The increase in CO during pregnancy is due mainly to demands of the uteroplacental circulation; volume of the uteroplacental circulation increases markedly, and circulation within the intervillous space acts partly as an arteriovenous shunt. As the placenta and fetus develop, blood flow to the uterus must increase to about 1 L/min (20% of normal CO) at term. Increased needs of the skin (to regulate temperature) and kidneys (to excrete fetal wastes) account for some of the increased CO.

To increase CO, heart rate increases from the normal 70 to as high as 90 beats/min, and stroke volume increases. During the 2nd trimester, BP usually drops (and pulse pressure widens), even though CO and renin and angiotensin levels increase, because uteroplacental circulation expands (the placental intervillous space develops) and systemic vascular resistance decreases. Resistance decreases because blood viscosity and sensitivity to angiotensin decrease. During the 3rd trimester, BP may return to normal. With twins, CO increases more and diastolic BP is lower at 20 wk than with a single fetus.

Exercise increases CO, heart rate, O₂ consumption, and respiratory volume/min more during pregnancy than at other times. The hyperdynamic circulation of pregnancy increases frequency of functional murmurs and accentuates heart sounds. X-ray or ECG may show the heart displaced into a horizontal position, rotating to the left, with increased transverse diameter. Premature atrial and ventricular beats are common during pregnancy. All these changes are normal and should not be erroneously diagnosed as a heart disorder; they can usually be managed with reassurance alone. However, paroxysms of atrial tachycardia occur more frequently in pregnant women and may require prophylactic digitalization or other antiarrhythmic drugs. Pregnancy does not affect the indications for or safety of cardioversion.

**Hematologic:** Total blood volume increases proportionally with CO, but the increase in plasma volume is greater (close to 50%, usually by about 1600 mL for a total of 5200 mL) than that in RBC mass (about 25%); thus, Hb is lowered by dilution, from about 13.3 to 12.1 g/dL. This dilutional anemia decreases blood viscosity. With twins, total maternal blood volume increases more (closer to 60%).

WBC count increases slightly to 9,000 to 12,000/μL. Marked leukocytosis (≥ 20,000/μL) occurs during labor and the first few days postpartum.

Iron requirements increase by a total of about 1 g during the entire pregnancy and are higher during the 2nd half of pregnancy—6 to 7 mg/day. The fetus and placenta use about 300 mg of iron, and the increased maternal RBC mass requires an additional 500 mg. Excretion accounts for 200 mg. Iron supplements are needed to prevent a further decrease in Hb levels because the amount absorbed from the diet and recruited from iron stores (average total of 300 to 500 mg) is usually insufficient to meet the demands of pregnancy.

**Urinary:** Changes in renal function roughly parallel those in cardiac function. GFR increases 30 to 50%, peaks between 16 and 24 wk gestation, and remains at that level until nearly term, when it may decrease slightly because uterine pressure on the vena cava often causes venous stasis in the lower extremities. Renal plasma flow increases in proportion to GFR. As a result, BUN decreases, usually to < 10 mg/dL (< 3.6 mmol urea/L), and creatinine levels decrease proportionally to 0.5 to 0.7 mg/dL (44 to 62 μmol/L). Marked dilation of the ureters (hydroureter) is caused by hormonal influences (predominantly progesterone) and by backup due to pressure from the enlarged uterus on the ureters, which can also cause hydronephrosis. Postpartum, the urinary collecting system may take as long as 12 wk to return to normal.

Postural changes affect renal function more during pregnancy than at other times; ie, the supine position increases renal function more, and upright positions decrease renal function more. Renal function also markedly increases in the lateral position; this position relieves the pressure that the enlarged uterus puts on the great vessels when pregnant women are supine. This positional increase in renal function is one
reason pregnant women need to urinate frequently when trying to sleep.

**Respiratory:** Lung function changes partly because progesterone increases and partly because the enlarging uterus interferes with lung expansion. Progesterone signals the brain to lower CO₂ levels. To lower CO₂ levels, tidal and minute volume and respiratory rate increase, thus increasing plasma pH. O₂ consumption increases by about 20% to meet the increased metabolic needs of the fetus, placenta, and several maternal organs. Inspiratory and expiratory reserve, residual volume and capacity, and plasma PCO₂ decrease. Vital capacity and plasma PO₂ do not change. Thoracic circumference increases by about 10 cm. Considerable hyperemia and edema of the respiratory tract occur. Occasionally, symptomatic nasopharyngeal obstruction and nasal stuffiness occur, eustachian tubes are transiently blocked, and tone and quality of voice change. Mild dyspnea during exertion is common, and deep respirations are more frequent.

**GI and hepatobiliary:** As pregnancy progresses, pressure from the enlarging uterus on the rectum and lower portion of the colon may cause constipation. GI motility decreases because elevated progesterone levels relax smooth muscle. Heartburn and belching are common, possibly resulting from delayed gastric emptying and gastroesophageal reflux due to relaxation of the lower esophageal sphincter and diaphragmatic hiatus. HCl production decreases; thus, peptic ulcer disease is uncommon during pregnancy, and preexisting ulcers often become less severe.

Incidence of gallbladder disorders increases somewhat. Pregnancy subtly affects hepatic function, especially bile transport. Routine liver function test values are normal, except for alkaline phosphatase levels, which increase progressively during the 3rd trimester and may be 2 to 3 times normal at term; the increase is due to placental production of this enzyme rather than hepatic dysfunction.

**Endocrine:** Pregnancy alters the function of most endocrine glands, partly because the placenta produces hormones and partly because most hormones circulate in protein-bound forms and protein binding increases during pregnancy.

The placenta produces a hormone (similar to thyroid-stimulating hormone) that stimulates the thyroid, causing hyperplasia, increased vascularity, and moderate enlargement. Estrogen stimulates hepatocytes, causing increased thyroid-binding globulin levels; thus, although total thyroxine levels may increase, levels of free thyroid hormones remain normal. Effects of thyroid hormone tend to increase and may resemble hyperthyroidism, with tachycardia, palpitations, excessive perspiration, and emotional instability. However, true hyperthyroidism occurs in only 0.08% of pregnancies.

The placenta produces corticotropin-releasing hormone (CRH), which stimulates maternal ACTH production. Increased ACTH levels increase levels of adrenal hormones, especially aldosterone and cortisol, and thus contribute to edema. Increased production of corticosteroids and increased placental production of progesterone lead to insulin resistance and an increased need for insulin, as does the stress of pregnancy and possibly the increased level of human placental lactogen. Insulinase, produced by the placenta, may also increase insulin requirements, so that many women with gestational diabetes develop more overt forms of diabetes (see pp. 866 and 2638).

The placenta produces melanocyte-stimulating hormone (MSH), which increases skin pigmentation late in pregnancy. The placenta also produces the β subunit of human chorionic gonadotropin (β-hCG), a trophic hormone that, like follicle-stimulating and luteinizing hormones, maintains the corpus luteum and thereby prevents ovulation.

The pituitary gland enlarges by about 135% during pregnancy. The maternal plasma prolactin level increases by 10-fold. Increased prolactin is related to an increase in thyrotropin-releasing hormone production, stimulated by estrogen. The primary function of increased prolactin is to ensure lactation. The level returns to normal postpartum, even in women who breastfeed.

**Dermatologic:** Increased levels of estrogens, progesterone, and MSH contribute to pigmenitary changes, although exact pathogenesis is unknown. These changes include melasma (mask of pregnancy), which is a blotchy, brownish pigment over the forehead and malar eminences; darkening of the mammary areolae,
axilla, and genitals; and linea nigra, a dark line that appears down the midabdomen. Melasma due to pregnancy usually regresses within a year.

Incidence of spider angiomas, usually only above the waist, and thin-walled, dilated capillaries, especially in the lower legs, increases.

**Drugs in Pregnancy**

The most commonly used drugs include anti-emetics, antacids, antihistamines, analgesics, antimicrobials, diuretics, hypnotics, tranquilizers, and social and illicit drugs.

The FDA classifies drugs into 5 categories of safety for use during pregnancy (see Table 262-1). However, few well-controlled studies of therapeutic drugs have been conducted in pregnant women. Most information about drug safety during pregnancy is derived from animal studies and uncontrolled studies in people (eg, postmarketing reports). During pregnancy, drugs are often required to treat certain disorders (see Table 264-2 on p. 2656). Despite widespread concern about drug safety, exposure to therapeutic drugs accounts for only 2 to 3% of all fetal congenital malformations; most malformations result from genetic, environmental, or unknown causes.

Not all maternal drugs cross the placenta to the fetus. Those that do can have a direct toxic or teratogenic effect (for known and suspected teratogens, see Table 262-2). Those that do not cross the placenta may still harm the fetus by constricting placental vessels and thus impairing gas and nutrient exchange, by producing severe uterine hypertonia resulting in anoxic injury, or by altering maternal physiology (eg, causing hypotension).

**Table 262-1. FDA Categories of Drug Safety During Pregnancy**

Drugs diffuse across the placenta similarly to the way they cross other epithelial barriers (see p. 3172). Whether and how quickly a drug crosses the placenta depend on the drug's molecular weight, extent of its binding to another substance (eg, carrier protein), area available for exchange across the villi, and amount of drug metabolized by the placenta. Most drugs with a molecular weight < 500 daltons readily cross the placenta and enter fetal circulation. Substances with a high molecular weight (eg, protein-bound drugs) usually do not cross the placenta. The exception is immune globulin G, which is occasionally used to treat disorders such as fetal alloimmune thrombocytopenia. Generally, equilibration between maternal blood and fetal tissues takes at least 40 min.

A drug's effect on the fetus is determined largely by fetal age at exposure, drug potency, and drug dosage. Fetal age affects the type of drug effect:

- **Before the 20th day after fertilization:** Drugs given at this time may have an all-or-nothing effect, killing the embryo or not affecting it at all. Teratogenesis is not likely during this stage.

- **During organogenesis (between 20 and 56 days after fertilization):** Teratogenesis is most likely at this stage. Drugs reaching the embryo at this stage may result in abortion, a sublethal gross anatomic defect (true teratogenic effect), or covert embryopathy (a permanent subtle metabolic or functional defect that may manifest later in life), or the drugs may have no measurable effect.

- **After organogenesis (in the 2nd and 3rd trimesters):** Teratogenesis is unlikely, but drugs may alter growth and function of normally formed fetal organs and tissues.

**Vaccines:** Immunization is as effective in women who are pregnant as in those who are not. Influenza vaccine is recommended for all pregnant women in the 2nd or 3rd trimester during influenza season. Other vaccines should be reserved for situations in which the woman or fetus is at significant risk of exposure to a hazardous infection and risk of adverse effects from the vaccine is low. Vaccinations for cholera, hepatitis A and B, measles, mumps, plague, poliomyelitis, rabies, tetanus-diphtheria, typhoid, and yellow fever may be given during pregnancy if risk of infection is substantial.
Live-virus vaccines should not be given to women who are or may be pregnant. Rubella vaccine, an attenuated live-virus vaccine, may cause subclinical placental and fetal infection. However, no defects in neonates have been attributed to rubella vaccine, and women vaccinated inadvertently during early pregnancy need not be advised to terminate pregnancy based solely on theoretical risk from the vaccine. Varicella is another attenuated live-virus vaccine that can potentially infect the fetus; risk is highest between 13 wk and 22 wk gestation. This vaccine is contraindicated during pregnancy.

**Table 262-2. Known or Suspected Teratogens**

Vitamin A: In the amount typically present in prenatal vitamins (5000 IU/day), vitamin A has not been associated with teratogenic risk. However, doses > 10,000 IU/day during early pregnancy may increase risk of congenital malformations.

Social and illicit drugs: Cigarette smoking and use of alcohol during pregnancy can cause significant problems in fetuses and neonates (see p. 2655).

Although marijuana’s main metabolite can cross the placenta, recreational use of this drug does not appear to consistently increase risk of congenital malformations, fetal growth restriction, or postnatal neurobehavioral abnormalities.

Many mothers of children with congenital heart defects used amphetamines during pregnancy, suggesting a possible teratogenic association.

Women who used cocaine during pregnancy have had perinatal complications, including abruptio placentae and stillbirth; however, no consistent teratogenic effects have been shown.

Whether consuming large amounts of caffeine can increase risk of perinatal complications is unclear. Consuming caffeine in small amounts (eg, 1 cup of coffee/day) appears to pose little or no risk to the fetus, but some data, which did not account for tobacco or alcohol use, suggest that consuming large amounts (> 7 cups of coffee/day) increases risk of stillbirths, preterm deliveries, low birth weight, and spontaneous abortions. Decaffeinated beverages theoretically pose little risk to the fetus.

Use of the dietary sugar substitute aspartame during pregnancy is often questioned. The most common metabolite of aspartame, phenylalanine, is concentrated in the fetus by active placental transport; toxic levels may cause intellectual disability (mental retardation). However, when ingestion is within the usual range, fetal phenylalanine levels are far below toxic levels. Thus, moderate ingestion of aspartame (eg, no more than 1 liter of diet soda per day) during pregnancy appears to pose little risk of fetal toxicity. However, in pregnant women with phenylketonuria (see p. 3011), intake of phenylalanine and thus aspartame is prohibited.

**Management of Normal Labor**

Labor consists of a series of rhythmic, involuntary, progressive contractions of the uterus that cause effacement (thinning and shortening) and dilation of the uterine cervix. The stimulus for labor is unknown, but digitally manipulating or mechanically stretching the cervix during examination enhances uterine contractile activity, most likely by stimulating release of oxytocin by the posterior pituitary gland. Normal labor usually begins within 2 wk (before or after) the estimated delivery date. In a first pregnancy, labor usually lasts 12 to 18 h on average; subsequent labors are often shorter, averaging 6 to 8 h. Management of complications during labor requires additional measures (see p. 2676).

**Beginning of labor:** Bloody show (a small amount of blood with mucous discharge from the cervix) may precede onset of labor by as much as 72 h. Bloody show can be differentiated from abnormal 3rd-trimester vaginal bleeding because the amount is small, bloody show is typically mixed with mucus, and the pain due to abruptio placentae (premature separation) is absent. In most pregnant women, previous ultrasonography has been done and ruled out placenta previa. However, if ultrasonography has not ruled out placenta previa and vaginal bleeding occurs, placenta previa is assumed to be present until it is ruled out.
out. Digital vaginal examination is contraindicated, and ultrasonography is done as soon as possible.

Labor begins with irregular uterine contractions of varying intensity; they apparently soften (ripen) the cervix, which begins to efface and dilate. As labor progresses, contractions increase in duration, intensity, and frequency.

**Stages of labor:** There are 3 stages of labor.

**The 1st stage**—from onset of labor to full dilation of the cervix (about 10 cm)—has 2 phases, latent and active.

During the latent phase, irregular contractions become progressively better coordinated, discomfort is minimal, and the cervix effaces and dilates to 4 cm. The latent phase is difficult to time precisely, and duration varies, averaging 8 h in nulliparas and 5 h in multiparas; duration is considered abnormal if it lasts > 20 h in nulliparas or > 12 h in multiparas.

During the active phase, the cervix becomes fully dilated, and the presenting part descends well into the midpelvis. On average, the active phase lasts 5 to 7 h in nulliparas and 2 to 4 h in multiparas. The cervix should dilate 1.2 cm/h in nulliparas and 1.5 cm/h in multiparas. Pelvic examinations are done every 2 to 3 h to evaluate labor progress. Lack of progress in dilation and descent of the presenting part may indicate dystocia (fetopelvic disproportion). If the membranes have not spontaneously ruptured, some clinicians routinely use amniotomy (artificial rupture of membranes) during the active phase. As a result, labor may progress more rapidly, and meconium-stained amniotic fluid may be detected earlier. Amniotomy during this stage may be necessary for specific indications, such as facilitating internal fetal monitoring to confirm fetal well-being. Amniotomy should be avoided in women with HIV infection or hepatitis B or C, so that the fetus is not exposed to these organisms.

Maternal heart rate and BP and fetal heart rate should be checked continuously by electronic monitoring or intermittently by auscultation during the 1st stage of labor (see p. 2630). Women may begin to feel the urge to bear down as the presenting part descends into the pelvis. However, they should be discouraged from bearing down until the cervix is fully dilated so that they do not tear the cervix or waste energy.

**The 2nd stage** is the time from full cervical dilation to delivery of the fetus. On average, it lasts 2 h in nulliparas (median 50 min) and 1 h in multiparas (median 20 min). It may last another hour or more if conduction (epidural) analgesia or intense opioid sedation is used. For spontaneous delivery, women must supplement uterine contractions by expulsively bearing down. In the 2nd stage, women should be attended constantly, and fetal heart sounds should be checked continuously or after every contraction. Contractions may be monitored by palpation or electronically.

**The 3rd stage** of labor begins after delivery of the infant and ends with delivery of the placenta.

**Rupture of membranes:** Occasionally, the membranes (amniotic and chorionic sac) rupture before labor begins, and amniotic fluid leaks through the cervix and vagina. Rupture of membranes at any stage before the onset of labor is called premature rupture of membranes (PROM—see p. 2682). Some women with PROM feel a gush of fluid from the vagina, followed by steady leaking. Further confirmation is not needed if during examination, fluid is seen leaking from the cervix.

Confirmation of more subtle cases may require testing. For example, the pH of vaginal fluid may be tested with Nitrazine paper, which turns deep blue at a pH > 6.5 (pH of amniotic fluid: 7.0 to 7.6); false-positive results can occur if vaginal fluid contains blood or semen or if certain infections are present. A sample of the secretions from the posterior vaginal fornix or cervix may be obtained, placed on a slide, air dried, and viewed microscopically for ferning. Ferning (crystallization of NaCl in a palm leaf pattern in amniotic fluid) usually confirms rupture of membranes. If rupture is still unconfirmed, ultrasonography showing oligohydramnios (deficient amniotic fluid) provides further evidence suggesting rupture. Rarely, amniocentesis with instillation of dye is done to confirm rupture; dye detected in the vagina or on a tampon confirms rupture.

When a woman's membranes rupture, she should contact her physician immediately. About 80 to 90% of
women with PROM at term and about 50% of women with PROM preterm go into labor spontaneously within 24 h; > 90% of women with PROM go into labor within 2 wk. The earlier the membranes rupture before 37 wk, the longer the delay between rupture and labor onset. If membranes rupture at term but labor does not start within several hours, labor is typically induced to lower risk of maternal and fetal infection.

**Birthing options:** Most women prefer hospital delivery, and most health care practitioners recommend it because unexpected maternal and fetal complications may occur during labor and delivery or postpartum, even in women without risk factors. About 30% of hospital deliveries involve an obstetric complication (eg, laceration, postpartum hemorrhage). Other complications include abruptio placentae, nonreassuring fetal heart rate pattern, shoulder dystocia, need for emergency cesarean delivery, and neonatal depression or abnormality. Nonetheless, many women want a more homelike environment for delivery; in response, some hospitals provide birthing facilities with fewer formalities and rigid regulations but with emergency equipment and personnel available. Birthing centers may be freestanding or located in hospitals; care at either site is similar or identical. In some hospitals, certified nurse-midwives provide much of the care for low-risk pregnancies. Midwives work with a physician, who is continuously available for consultation and operative deliveries (eg, by forceps, vacuum extractor, or cesarean). All birthing options should be discussed.

For many women, presence of the father or another support person during labor is helpful and should be encouraged. Moral support, encouragement, and expressions of affection decrease anxiety and make labor less frightening and unpleasant. Childbirth education classes can prepare parents for a normal or complicated labor and delivery. Sharing the stresses of labor and the sight and sound of their own child tends to create strong bonds between the parents and between parents and child. The parents should be fully informed of any complications.

**Admission:** Typically, pregnant women are advised to go to the hospital if they believe their membranes have ruptured or if they are experiencing contractions lasting at least 30 sec and occurring regularly at intervals of about ≤ 6 min. Within an hour after presentation at a hospital, whether a woman is in labor can usually be determined based on occurrence of regular and sustained painful uterine contractions, bloody show, membrane rupture, and complete cervical effacement. If these criteria are not met, false labor may be tentatively diagnosed, and the pregnant woman is typically observed for a time and, if labor does not begin within several hours, is sent home.

When pregnant women are admitted, their BP, heart and respiratory rates, temperature, and weight are recorded, and presence or absence of edema is noted. A urine specimen is collected for protein and glucose analysis, and blood is drawn for a CBC and blood typing. A physical examination is done. While examining the abdomen, the clinician estimates size, position, and presentation of the fetus, using Leopold’s maneuvers (see Fig. 262-1). The clinician notes the presence and rate of fetal heart sounds, as well as location for auscultation. Preliminary estimates of the strength, frequency, and duration of contractions are also recorded. A helpful mnemonic device for evaluation is the 3 Ps: powers (contraction strength, frequency, and duration), passage (pelvic measurements), and passenger (eg, fetal size, position, heart rate pattern).

If labor is active and the pregnancy is at term, a clinician examines the vagina with 2 fingers of a gloved hand to evaluate progress of labor. If bleeding (particularly if heavy) is present, the examination is delayed until placental location is confirmed by ultrasonography. If bleeding results from placenta previa, vaginal examination can initiate severe hemorrhage. If labor is not active but membranes are ruptured, a speculum examination is done initially

[Fig. 262-1, Leopold maneuver.]

to document cervical dilation and effacement and to estimate station (location of the presenting part); however, digital examinations are delayed until the active phase of labor or problems (eg, decreased fetal heart sounds) occur. If the membranes have ruptured, any fetal meconium (producing greenish-brown discoloration) should be noted because it may be a sign of fetal stress. If labor is preterm (< 37 wk) or has not begun, only a sterile speculum examination should be done, and a culture should be taken for

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gonococci, chlamydiae, and group B streptococci.

Cervical dilation is recorded in centimeters as the diameter of a circle; 10 cm is considered complete. Effacement is estimated in percentages, from 0 to 100%. Because effacement involves cervical shortening as well as thinning, it may be recorded in centimeters using the normal, uneffaced average cervical length of 3.5 to 4.0 cm as a guide.

Station is expressed in centimeters above or below the level of the maternal ischial spines. Level with the ischial spines corresponds to 0 station; levels above (+) or below (-) the spines are recorded in cm increments. Fetal lie, position, and presentation are noted. Lie describes the relationship of the long axis of the fetus to that of the mother (longitudinal, oblique, transverse); presentation describes the part of the fetus at the cervical opening (eg, breech, vertex, shoulder). Position describes the relationship of the presenting part to the maternal pelvis (eg, occiput left anterior [OLa] for cephalic, sacrum right posterior [SRP] for breech).

**Preparation for delivery:** Women are admitted to the labor suite for frequent observation until delivery. If labor is active, they should receive little or nothing by mouth to prevent possible vomiting and aspiration during delivery or in case emergency delivery with general anesthesia is necessary. Enemas and shaving or clipping of vulvar hair are no longer indicated. An IV infusion of Ringer's lactate may be started, preferably using a large-bore indwelling catheter inserted into a vein in the hand or forearm. During a normal labor of 6 to 10 h, women should be given 500 to 1000 mL of this solution. The infusion prevents dehydration during labor and subsequent hemoconcentration and maintains an adequate circulating blood volume. The catheter also provides immediate access for drugs or blood if needed. Fluid preloading is valuable if epidural or spinal anesthesia is planned.

**Analgesia:** Analgesics may be given during labor as needed, but as little as possible should be given because they cross the placenta and may depress the neonate's breathing. Neonatal toxicity can occur because after the umbilical cord is cut, the neonate, whose metabolic and excretory processes are immature, clears the transferred drug much more slowly, by liver metabolism or by urinary excretion. Preparation for and education about childbirth lessen anxiety, markedly decreasing the need for analgesics.

Physicians are increasingly offering epidural injection (providing regional anesthesia) as the first choice for analgesia during labor. Typically, a local anesthetic (eg, 0.2% ropivacaine, 0.125% bupivacaine) is continuously infused, often with an opioid (eg, fentanyl, sufentanil), into the lumbar epidural space. Initially, the anesthetic is given cautiously to avoid masking the awareness of pressure that helps stimulate pushing and to avoid motor block; both effects can slow labor.

If epidural injection is inadequate or if IV administration is preferred, fentanyl (100 μg), meperidine (up to 25 mg), or morphine sulfate (up to 10 mg) given IV q 60 to 90 min is commonly used. These opioids provide good analgesia with only a small total dose. If toxicity results, respiration is supported, and naloxone 0.01 mg/kg can be given IM, IV, sc, or endotracheally to the neonate as a specific antagonist. Naloxone may be repeated in 1 to 2 min as needed based on the neonate's response. Clinicians should check the neonate 1 to 2 h after the initial dosing with naloxone because the effects of the earlier dose abate. If fentanyl, meperidine, or morphine provides insufficient analgesia, an additional dose of the opioid or another analgesic should be used rather than the so-called synergistic drugs (eg, promethazine), which have no antidote. (These drugs are actually additive, not synergistic.) Synergistic drugs are still sometimes used because they lessen nausea due to the opioid; doses should be small.

**Fetal Monitoring**

Fetal status must be monitored during labor. The main parameters are fetal heart rate (HR) and fetal HR variability, particularly as it relates to uterine contractions and maternal movement. Several patterns are recognized. One is considered normal and reassuring; the others are considered abnormal and nonreassuring. A normal pattern is a baseline HR with the following characteristics:

- 120 to 160 beats/min
• Varies by 6 to 25 beats with movement or contractions (normal HR variability)

• Accelerates appropriately for gestational age

• Does not decelerate during contractions

Patterns that indicate possible nonreassuring fetal heart status include the following:

• Late decelerations: HR gradually decreases and returns to baseline with contractions, but the decrease begins late, and most of it occurs (and HR is slowest) after contractions peak.

• Variable decelerations: HR decreases abruptly by ≥ 15 beats/min; the decrease may or may not occur simultaneously with contractions and varies in onset, depth, and duration (≥ 15 sec but < 2 min).

• Tachycardia

• Severe bradycardia: HR is ≤ 110 beats/min.

• Loss of normal HR variability

Nonreassuring patterns require more intensive monitoring.

Monitoring can be manual and intermittent, using a fetoscope for auscultation of fetal HR. However, in the US, electronic fetal HR monitoring (external or internal) has become standard of care for high-risk pregnancies, and many clinicians use it for all pregnancies. Although this practice has been lifesaving, its value is debated, partly because many apparent abnormalities are false positives, leading to unnecessary cesarean deliveries. Rate of cesarean delivery is higher among women monitored electronically than among those monitored by auscultation. Fetal pulse oximetry is being studied as a way to confirm abnormal or equivocal results of electronic monitoring; fetal oxygenation may help determine whether a cesarean delivery is needed. For oximetry, an internal sensor must be placed inside the uterus and against the fetal skin to ensure an accurate reading of fetal oxygenation. However, fetal pulse oximetry does not appear to change the rate of cesarean delivery from that based on results of fetal HR monitoring alone.

If manual auscultation of fetal HR is used, it must be done throughout labor according to specific guidelines, and one-on-one nursing care is needed. For low-risk pregnancies with normal labor, fetal HR must be checked after each contraction or at least every 30 min during the 1st stage of labor and every 15 min during the 2nd stage. For high-risk pregnancies, fetal HR must be checked every 15 min during the 1st stage and every 3 to 5 min during the 2nd stage. Listening for at least 1 to 2 min beginning at a contraction's peak is recommended to check for late deceleration. Periodic auscultation has a lower false-positive rate for abnormalities and incidence of intervention than continuous electronic monitoring, and it provides opportunities for more personal contact with women during labor. However, following the standard guidelines for auscultation is often difficult and may not be cost-effective. Also, unless done accurately, auscultation may not detect abnormalities.

For external electronic fetal HR monitoring, devices are applied to the maternal abdomen to record fetal heart sounds and uterine contractions. For internal monitoring, amniotic membranes must be ruptured. Then, leads are inserted through the cervix; an electrode is attached to the fetal scalp to monitor HR, and a catheter is placed in the uterine cavity to measure intrauterine pressure. Usually, external and internal monitoring are similarly reliable. External devices are used for women in normal labor; internal methods are used when external monitoring does not supply enough information about fetal well-being or uterine contraction intensity (eg, if the external sensor is not functioning correctly).

External electronic fetal monitoring can be used during labor or electively to continuously record fetal HR and correlate it with fetal movements (called a nonstress test). A nonstress test is interpreted as nonreassuring if no accelerations occur during a 40-min period. External monitoring can be used similarly with a contraction stress test; fetal movements and HR are monitored during contractions induced by oxytocin (oxytocin challenge test) or breast stimulation or during spontaneous contractions. Nonstress
and contraction stress tests are frequently used to monitor complicated or high-risk pregnancies (eg, complicated by maternal diabetes or hypertension or by prior stillbirth or fetal growth restriction).

If a problem (eg, fetal HR decelerations, lack of normal HR variability) is detected during labor, intrauterine fetal resuscitation is tried; women may be given O\textsubscript{2} via a tight non-rebreather face mask or rapid IV fluid infusion or may be positioned laterally. If fetal heart pattern does not improve in a reasonable period and delivery is not imminent, urgent cesarean delivery is needed.

**Management of Normal Delivery**

Many obstetric units now use a combined labor, delivery, recovery, and postpartum (LDRP) room, so that the woman, father or other support person, and neonate remain in the same room throughout their stay. Some units use a traditional labor room and separate delivery suite, to which the woman is transferred when delivery is imminent. The support person should be offered the opportunity to accompany her. In the delivery room, the perineum is washed and draped, and the neonate is delivered. After delivery, the woman may remain there or be transferred to a postpartum unit. Management of complications during delivery requires additional measures (see p. 2676).

**Anesthesia**

Options include regional, local, and general anesthesia. Local anesthetics and opioids are commonly used. These drugs pass through the placenta; thus, during the hour before delivery, such drugs should be given in small doses to avoid toxicity (eg, CNS depression, bradycardia) in the neonate. Opioids used alone do not provide adequate analgesia and so are most often used with anesthetics.

**Regional anesthesia:** Several methods are available.

**Lumbar epidural injection** of a local anesthetic (see p. 2630) is the most commonly used method. Epidural injection is being increasingly used for delivery, including cesarean, and has essentially replaced pudendal and paracervical blocks. The local anesthetics often used for epidural injection (eg, bupivacaine) have a longer duration of action and slower onset than those used for pudendal block (eg, lidocaine).

Other methods include caudal injection (into the sacral canal), which is rarely used, and spinal injection (into the paraspinal subarachnoid space). Spinal injection may be used for cesarean delivery, but it is used less often for vaginal deliveries because it is short-lasting (preventing its use during labor) and has a small risk of spinal headache afterward. When spinal injection is used, patients must be constantly attended, and vital signs must be checked every 5 min to detect and treat possible hypotension.

**Local anesthesia:** Methods include pudendal block, perineal infiltration, and paracervical block.

**Pudendal block,** rarely used because epidural injections are used instead, involves injecting a local anesthetic through the vaginal wall so that the anesthetic bathes the pudendal nerve as it crosses the ischial spine. This block anesthetizes the lower vagina, perineum, and posterior vulva; the anterior vulva, innervated by lumbar dermatomes, is not anesthetized. Pudendal block is a safe, simple method for uncomplicated spontaneous vaginal deliveries if women wish to bear down and push or if labor is advanced and there is no time for epidural injection.

**Infiltration of the perineum** with an anesthetic is commonly used, although this method is not as effective as a well-administered pudendal block.

**Paracervical block** is rarely appropriate for delivery because incidence of fetal bradycardia is > 15%. It is used mainly for 1st- or early 2nd-trimester abortions. The technique involves injecting 5 to 10 mL of 1% lidocaine at the 3 and 9 o’clock positions; the analgesic response is short-lasting.

**General anesthesia:** Because potent and volatile inhalation drugs (eg, isoflurane) can cause marked depression in mother and fetus, general anesthesia is not recommended for routine delivery. Rarely, nitrous oxide 40% with O\textsubscript{2} may be used for analgesia during vaginal delivery as long as verbal contact
with the woman is maintained. Thiopental, a hypnotic, is commonly given IV with other drugs (eg, succinylcholine, nitrous oxide plus O₂) for induction of general anesthesia during cesarean delivery; used alone, thiopental provides inadequate analgesia. With thiopental, induction is rapid and recovery is prompt. It becomes concentrated in the fetal liver, preventing levels from becoming high in the CNS; high levels in the CNS may cause neonatal depression. Increased interest in preparation for childbirth has reduced the need for general anesthesia except for cesarean delivery.

Delivery Procedures

A vaginal examination is done to determine position and station of the fetal head; the head is usually the presenting part (see Fig. 262-2). When effacement is complete and the cervix is fully dilated, the woman is told to bear down and strain with each contraction to move the head through the pelvis and progressively dilate the vaginal introitus so that more and more of the head appears. When about 3 or 4 cm of the head is visible during a contraction in nulliparas (somewhat less in multiparas), the following maneuvers can facilitate delivery and reduce risk of perineal laceration.

- The clinician, if right-handed, places the left palm over the infant's head during a contraction to control and, if necessary, slightly slow progress.
- Simultaneously, the clinician places the curved fingers of the right hand against the dilating perineum, through which the infant's brow or chin is felt.
- To advance the head, the clinician can wrap a hand in a towel and, with curved fingers, apply pressure against the underside of the brow or chin (modified Ritgen maneuver).

[Fig. 262-2. Sequence of events in delivery for vertex presentations.]

Thus, the clinician controls the progress of the head to effect a slow, safe delivery.

Forceps or a vacuum extractor (see p. 2676) is often used for vaginal delivery when the 2nd stage of labor is likely to be prolonged (eg, because the mother is too exhausted to bear down adequately or because regional epidural anesthesia precludes vigorous bearing down). If anesthesia is local (pudendal block or infiltration of the perineum), forceps or a vacuum extractor is usually not needed unless complications develop; local anesthesia may not interfere with bearing down. Indications for forceps and vacuum extractor are essentially the same.

An episiotomy is not routine and is done only if the perineum does not stretch adequately and is obstructing delivery, usually only for first deliveries at term. A local anesthetic can be infiltrated if epidural analgesia is inadequate. Episiotomy prevents excessive stretching and possible tearing of the perineal tissues, including anterior tears. The incision is easier to repair than a tear.

The most common type is a midline incision made from the midpoint of the fourchette directly back toward the rectum. Extension into the rectal sphincter or rectum is a risk, but if recognized promptly, the extension can be repaired successfully and heals well. Tears or extensions into the rectum can usually be prevented by keeping the infant's head well flexed until the occipital prominence passes under the symphysis pubis.

Another type of episiotomy is a mediolateral incision made from the midpoint of the fourchette at a 45° angle laterally on either side. This type usually does not extend into the sphincter or rectum, but it causes greater postoperative pain and takes longer to heal than midline episiotomy. Thus, for episiotomy, a midline cut is preferred. However, use of episiotomy is decreasing because extension or tearing into the sphincter or rectum is a concern. Episioproctotomy (intentionally cutting into the rectum) is not recommended because rectovaginal fistula is a risk.

When the head is delivered, the clinician determines whether the umbilical cord is wrapped around the neck. If it is, the clinician should try to unwrap the cord; if the cord cannot be rapidly removed this way, the cord may be clamped and cut.
After delivery of the head, the infant's body rotates so that the shoulders are in an anteroposterior position; gentle downward pressure on the head delivers the anterior shoulder under the symphysis. The head is gently lifted, the posterior shoulder slides over the perineum, and the rest of the body follows without difficulty. The nose, mouth, and pharynx are aspirated with a bulb syringe to remove mucus and fluids and help start respirations. The cord should be double-clamped and cut between the clamps, and a plastic cord clip should be applied about 2 to 3 cm distal from the cord insertion on the infant. If fetal or neonatal compromise is suspected, a segment of umbilical cord is double-clamped so that arterial blood gas analysis can be done. An arterial pH > 7.15 to 7.20 is considered normal. The infant is thoroughly dried, then placed on the mother's abdomen or, if resuscitation is needed, in a warmed resuscitation bassinet.

Placenta: After delivery of the infant, the clinician places a hand gently on the abdomen over the uterine fundus to detect contractions; placental separation usually occurs during the 1st or 2nd contraction, often with a gush of blood from behind the separating placenta. The mother can usually help deliver the placenta by bearing down. If she cannot and if substantial bleeding occurs, the placenta can usually be evacuated (expressed) by placing a hand on the abdomen and exerting firm downward (caudal) pressure on the uterus; this procedure is done only if the uterus feels firm because pressure on a flaccid uterus can cause it to invert. If this procedure is not effective, the clinician holds the umbilical cord taut while placing the other hand on the abdomen and pushing upward (cephalad) on the firm uterus, away from the placenta; traction on the umbilical cord is avoided because it may invert the uterus. If the placenta has not been delivered within 45 to 60 min of delivery, manual removal may be necessary; the clinician inserts an entire hand into the uterine cavity, separating the placenta from its attachment, then extracts the placenta. In such cases, an abnormally adherent placenta (placenta accreta—see p. 2669) should be suspected.

The placenta should be examined for completeness because fragments left in the uterus can cause hemorrhage or infection later. If the placenta is incomplete, the uterine cavity should be explored manually. Some obstetricians routinely explore the uterus after each delivery. However, exploration is uncomfortable and is not routinely recommended. Immediately after delivery of the placenta, an oxytocic drug (oxytocin 10 units IM or as an infusion of 20 units/1000 mL saline at 125 mL/h) is given to help the uterus contract firmly. Oxytocin should not be given as an IV bolus because cardiac arrhythmia may occur.

Postdelivery: The cervix and vagina are inspected for lacerations, which, if present, are repaired, as is episiotomy if done. Then if the mother and infant are recovering normally, they can begin bonding. Many mothers wish to begin breastfeeding soon after delivery, and this activity should be encouraged. Mother, infant, and father should remain together in a warm, private area for an hour or more to enhance parent-infant bonding. Then, the infant may be taken to the nursery or left with the mother depending on her wishes.

For the first hour after delivery, the mother should be observed closely to make sure the uterus is contracting (detected by palpation during abdominal examination) and to check for bleeding, BP abnormalities, and general well-being. The time from delivery of the placenta to 4 h postpartum has been called the 4th stage of labor; most complications, especially hemorrhage (see p. 2680), occur at this time, and frequent observation is mandatory.
Chapter 263. Pregnancy Complicated by Disease

Introduction

Nonobstetric disorders often complicate pregnancy; management sometimes differs from that for nonpregnant patients. Coordination of care between the obstetrician and medical specialist often helps.

Anemia in Pregnancy

Normally during pregnancy, erythroid hyperplasia of the marrow occurs, and RBC mass increases. However, a disproportionate increase in plasma volume results in hemodilution (hydremia of pregnancy): Hct decreases from between 38 and 45% in healthy women who are not pregnant to about 34% during late single pregnancy and to 30% during late multifetal pregnancy. Thus during pregnancy, anemia is defined as Hb < 10 g/dL (Hct < 30%). If Hb is < 11.5 g/dL at the onset of pregnancy, women may be treated prophylactically because subsequent hemodilution usually reduces Hb to < 10 g/dL. Despite hemodilution, O₂-carrying capacity remains normal throughout pregnancy. Hct normally increases immediately after birth.

Anemia occurs in up to one third of women during the 3rd trimester. The most common causes are iron deficiency and folate deficiency.

Symptoms and Signs

Early symptoms are usually nonexistent or nonspecific (eg, fatigue, weakness, light-headedness, mild dyspnea during exertion). Other symptoms and signs may include pallor and, if anemia is severe, tachycardia or hypotension. Anemia increases risk of preterm delivery and postpartum maternal infections.

Diagnosis

Diagnosis begins with CBC; usually, if women have anemia, subsequent testing is based on whether the MCV is low (< 79 fL) or high (> 100 fL):

- For microcytic anemias: Evaluation includes testing for iron deficiency (measuring serum ferritin) and hemoglobinopathies (using hemoglobin electrophoresis). If these tests are nondiagnostic and there is no response to empiric treatment, consultation with a hematologist is usually warranted.

- For macrocytic anemias: Evaluation includes serum folate and B₁₂ levels.

Treatment

Treatment is directed at reversing the anemia. Transfusion is usually indicated for any anemia if severe constitutional symptoms (eg, light-headedness, weakness, fatigue) or cardiopulmonary symptoms or signs (eg, dyspnea, tachycardia, tachypnea) are present; the decision is not based on the Hct.

Iron Deficiency Anemia

About 95% of anemia cases during pregnancy are due to iron deficiency (see p. 924). The cause is usually inadequate dietary intake (especially in adolescent girls), a previous pregnancy, or the normal recurrent loss of iron in menstrual blood (which approximates the amount normally ingested each month and thus prevents iron stores from building up).

Diagnosis

Typically, Hct is ≤ 30%, and MCV is < 79 fL. Decreased serum iron and ferritin and increased serum transferrin levels confirm the diagnosis.
Treatment

• Ferrous sulfate 325 mg po once/day

One 325-mg ferrous sulfate tablet taken mid-morning is usually effective. Higher or more frequent doses increase GI adverse effects, especially constipation, and one dose blocks absorption of the next dose, thereby reducing percentage intake. About 20% of pregnant women do not absorb enough supplemental oral iron; a few of them require parenteral therapy, usually iron dextran 100 mg IM every other day for a total of ≥ 1000 mg over 3 wk. Hct or Hb is measured weekly to determine response. If iron supplements are ineffective, concomitant folate deficiency should be suspected.

Neonates of mothers with iron deficiency anemia usually have a normal Hct but decreased total iron stores and a need for early dietary iron supplements.

Prevention

Although the practice is controversial, iron supplements (usually ferrous sulfate 325 mg po once/day) are usually given routinely to pregnant women to prevent depletion of body iron stores and prevent the anemia that may result from abnormal bleeding or a subsequent pregnancy.

Folate Deficiency Anemia

Folate deficiency (see pp. 29 and 932) increases risk of neural tube defects and possibly fetal alcohol syndrome. Deficiency occurs in 0.5 to 1.5% of pregnant women; macrocytic, megaloblastic anemia is present if deficiency is moderate or severe. Rarely, severe anemia and glossitis occur.

Diagnosis

Folate deficiency is suspected if CBC shows anemia with macrocytic indices or high RBC distribution width (RDW). Low serum folate levels confirm the diagnosis.

Treatment

Treatment is folate 1 mg po bid. Severe megaloblastic anemia may warrant bone marrow examination and further treatment in a hospital.

Prevention

For prevention, all pregnant women are given folate 0.4 mg po once/day. Women who have had a fetus with spina bifida should take 4.0 mg once/day, starting before conception.

Hemoglobinopathies

(See also Sidebar 106-1 on p. 943)

During pregnancy, hemoglobinopathies, particularly sickle cell disease, Hb S-C disease, β-thalassemia disease, and α-thalassemia, can worsen maternal and perinatal outcomes (for genetic screening, see Table 259-1 on p. 2600).

Preexisting sickle cell disease, particularly if severe, increases risk of maternal infection (most often, pneumonia, UTIs, and endometritis), pregnancy-induced hypertension, heart failure, and pulmonary infarction. Fetal growth restriction, preterm delivery, and low birth weight are common. Anemia almost always becomes more severe as pregnancy progresses. Sickle cell trait increases the risk of UTIs but is not associated with severe pregnancy-related complications.

Treatment of sickle cell disease during pregnancy is complex. Painful crises should be treated aggressively. Prophylactic exchange transfusions to keep Hb A at ≥ 60% reduce risk of hemolytic crises and pulmonary complications, but they are not routinely recommended because they increase risk of...
transfusion reactions, hepatitis, HIV transmission, and blood group isoimmunization. Prophylactic transfusion does not appear to decrease perinatal risk. Therapeutic transfusion is indicated for the following:

• Symptomatic anemia

• Heart failure

• Severe bacterial infection

• Severe complications of labor and delivery (eg, bleeding, sepsis)

**Hb S-C disease** may first cause symptoms during pregnancy. The disease increases risk of pulmonary infarction by occasionally causing bony spicule embolization. Effects on the fetus are uncommon but, if they occur, often include fetal growth restriction.

**Sickle cell-β-thalassemia** is similar to Hb S-C disease but is less common and more benign.

**α-Thalassemia** does not cause maternal morbidity, but if the fetus is homozygous, hydrops and fetal death occur during the 2nd or early 3rd trimester.

**Asthma in Pregnancy**

The effect of pregnancy on asthma varies; deterioration is slightly more common than improvement, but most pregnant women do not have severe attacks. The effect of asthma on pregnancy also varies, but risk of preterm delivery and fetal growth restriction is increased.

**Treatment**

Pregnancy does not usually change treatment of asthma (see p. 1873). Inhaled bronchodilators and corticosteroid inhalers are first-line maintenance therapy. Theophylline is no longer recommended routinely during pregnancy. For an acute exacerbation, in addition to bronchodilators, methylprednisolone 60 mg IV q 6 h for 24 to 48 h may be used, followed by oral prednisone in a tapering dose.

**Autoimmune Disorders in Pregnancy**

Autoimmune disorders are 5 times more common among women, and incidence tends to peak during reproductive years. Thus, these disorders commonly occur in pregnant women.

**Systemic lupus erythematosus:** SLE (see p. 305) may first appear during pregnancy; women who have had an unexplained 2nd trimester stillbirth, a fetus with growth restriction, preterm delivery, or recurrent spontaneous abortions are often later diagnosed with SLE.

The course of preexisting SLE during pregnancy cannot be predicted, but SLE may worsen, particularly immediately postpartum. Complications may include fetal growth restriction, preterm delivery due to preeclampsia, and congenital heart block due to maternal antibodies that cross the placenta. Significant preexisting renal or cardiac complications increase risk of maternal morbidity and mortality. Diffuse nephritis, hypertension, or the presence of circulating antiphospholipid antibodies (usually anticardiolipin antibody or lupus anticoagulant) increases risk of perinatal mortality. Women with antiphospholipid antibodies also have an increased risk of maternal thromboembolic disorders. Neonates may have anemia, thrombocytopenia, or leukopenia; these disorders tend to resolve during the first weeks after birth when maternal antibodies disappear.

Treatment may require prednisone; the lowest possible dose is used. However, 10 to 60 mg po once/day is often needed. Women with antiphospholipid antibodies are also often treated with aspirin (81 mg po once/day) and prophylactic heparin (5,000 to 10,000 units bid sc). For women with severe, refractory SLE, the need to continue immunosuppressants (eg, hydroxychloroquine) during pregnancy is reviewed individually.
Rheumatoid arthritis: RA (see p. 332) may begin during pregnancy or, even more often, during the postpartum period. Preexisting RA generally abates temporarily during pregnancy. The fetus is not specifically affected, but delivery may be difficult if the woman's hip joints or lumbar spine is affected. If a woman develops an RA flare during pregnancy, first-line treatment usually begins with prednisone. For refractory cases, other immunosuppressants may be required.

Myasthenia gravis: Myasthenia gravis (see p. 1793) varies in its course during pregnancy. Frequent acute myasthenic episodes may require increasing doses of anticholinesterase drugs (eg, neostigmine), which may cause symptoms of cholinergic excess (eg, abdominal pain, diarrhea, vomiting, increasing weakness); atropine may then be required. Sometimes myasthenia becomes refractory to standard therapy and requires corticosteroids or immunosuppressants. During labor, women may need assisted ventilation and are extremely sensitive to drugs that depress respiration (eg, sedatives, opioids, Mg sulfate). Because the IgG responsible for myasthenia crosses the placenta, transient myasthenia occurs in 20% of neonates, even more if mothers have not had a thymectomy.

Immune thrombocytopenic purpura (ITP): ITP (see p. 958), mediated by maternal anti-platelet IgG, tends to worsen during pregnancy and increases risk of maternal morbidity. Corticosteroids reduce IgG levels and cause remission in most women, but improvement is sustained in only 50%. Immunosuppressive therapy and plasmapheresis further reduce IgG, increasing platelet counts. Rarely, splenectomy is required for refractory cases; it is best done during the 2nd trimester, when it causes sustained remission in about 80%. IV immune globulin increases platelet count significantly but briefly, so that labor can be induced in women with low platelet counts. Platelet transfusions are indicated only when cesarean delivery is required and maternal platelet counts are < 50,000/μL.

Although antiplatelet IgG can cross the placenta, it only very rarely causes fetal or neonatal thrombocytopenia. Maternal anti-platelet antibody levels (measured by direct or indirect assay) cannot predict fetal involvement. Percutaneous umbilical blood sampling can be diagnostic. If fetal platelet count is < 50,000/μL, intracranial bleeding can occur during labor or vaginal delivery; cesarean delivery is necessary.

Cancer in Pregnancy

(See also Ch. 256.)

Pregnancy should not delay treatment of cancer. Treatment is similar to that in nonpregnant women except for rectal and gynecologic cancers.

Because embryonic tissues grow rapidly and have a high DNA turnover rate, they resemble cancer tissues and are thus very vulnerable to antineoplastic drugs. Many antimetabolites and alkylating drugs (eg, busulfan, chlorambucil, cyclophosphamide, 6-mercaptopurine, methotrexate) can cause fetal abnormalities. Methotrexate is particularly problematic; use during the 1st trimester increases risk of spontaneous abortion and, if the pregnancy continues, multiple congenital malformations. Although pregnancy often concludes successfully despite cancer treatment, risk of fetal injury due to treatment leads some women to choose abortion.

Rectal cancer: Rectal cancers may require hysterectomy to ensure complete tumor removal. Cesarean delivery may be done as early as 28 wk, followed by hysterectomy so that the infant can be saved and aggressive cancer treatment started.

Cervical cancer: Pregnancy does not appear to worsen cervical cancer. Cervical cancer can develop during pregnancy, and an abnormal Papanicolaou (Pap) test should not be attributed to pregnancy. Abnormal Pap tests are followed by colposcopy and directed biopsies when indicated. Usually, conization can be avoided. If biopsy shows mild dysplasia, normal delivery is possible, and follow-up evaluation can start 6 wk postpartum. Severe dysplasia or carcinoma in situ warrants further evaluation during pregnancy; colposcopy is usually accurate, but sometimes biopsy is necessary.

For carcinoma in situ (Federation of Gynecology and Obstetrics [FIGO] stage 0—see
If invasive cancer (FIGO stage IA2 or higher) is diagnosed during early pregnancy, immediate therapy appropriate for the cancer is traditionally recommended. If invasive cancer is diagnosed after 20 wk and if the woman accepts the unquantified increase in risk, treatment can be deferred until into the 3rd trimester (eg, 32 wk) to maximize fetal maturity but not delay treatment too long. When hysterectomy is delayed until delivery, some experts recommend that it be done immediately after delivery. Others recommend delaying hysterectomy until 6 wk postpartum because risks due to hysterectomy are thought to be much greater at delivery because of the increased blood supply to the pelvic organs at that time.

In certain cancers, chemotherapy may induce tumor regression, allowing the fetus to mature to a viable stage before definitive treatment (surgery or radiation therapy). Delivery is usually cesarean, but vaginal delivery, although controversial, may be as safe.

**Other gynecologic cancers:** After 12 wk gestation, ovarian cancer is easily missed; then, the ovaries, with the uterus, rise out of the pelvis and are no longer easily palpable. If very advanced, ovarian cancer during pregnancy may be fatal before completion of the pregnancy. Affected women require bilateral oophorectomy as soon as possible. Endometrial and fallopian tube cancers rarely occur during pregnancy.

**Leukemia and Hodgkin lymphoma:** These disorders (see Chs. 117 and 118) are uncommon during pregnancy. Antineoplastic drugs typically used increase risk of fetal loss and congenital malformations. Because leukemias can become fatal rapidly, treatment is given as soon as possible, without any significant delay to allow the fetus to mature. If Hodgkin lymphoma is confined to above the diaphragm, radiation therapy may be used; the abdomen must be shielded. If lymphoma is below the diaphragm, abortion may be recommended.

**Breast cancer:** Breast engorgement during pregnancy may make recognizing breast cancer difficult. Any solid or cystic breast mass should be evaluated (see Ch. 255).

**Diabetes Mellitus in Pregnancy**

(See also Ch. 99)

Pregnancy aggravates preexisting type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes but does not appear to exacerbate diabetic retinopathy, nephropathy, or neuropathy.

**Gestational diabetes** (diabetes that begins during pregnancy) can develop in overweight, hyperinsulinemic, insulin-resistant women or in thin, relatively insulin-deficient women. Gestational diabetes occurs in 1 to 3% of all pregnancies, but the rate may be much higher in certain groups (eg, Mexican Americans, American Indians, Asians, Indians, Pacific Islanders).

Diabetes during pregnancy increases fetal and maternal morbidity and mortality. Neonates are at risk of respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, and hyperviscosity. Poor control of preexisting or gestational diabetes during organogenesis (up to about 10 wk gestation) increases risk of major congenital malformations and spontaneous abortion. Poor control of diabetes later in pregnancy increases risk of fetal macrosomia (usually defined as fetal weight > 4000 or > 4500 g at birth), preeclampsia, and spontaneous abortion. However, gestational diabetes can result in fetal macrosomia even if blood glucose is kept nearly normal.

**Treatment**

- Close monitoring
- Tight control of blood glucose
- Management of complications
Preconception counseling and optimal control of diabetes before, during, and after pregnancy minimize maternal and fetal risks, including congenital malformations. Because malformations may develop before pregnancy is diagnosed, the need for constant, strict control of glucose levels is stressed to women who have diabetes and who are considering pregnancy (or who are not using contraception).

Most experts recommend that all pregnant women be screened for gestational diabetes (see p. 2608). A glucose tolerance test is usually recommended, but the diagnosis can probably be made by a fasting plasma glucose of > 126 mg/dL or a random plasma glucose > 200 mg/dL.

To minimize risks, clinicians should do all of the following:

- Involve a diabetes team (eg, physicians, nurses, nutritionists, social workers) and a pediatrician
- Promptly diagnose and treat complications of pregnancy, no matter how trivial
- Plan for delivery and have an experienced pediatrician present
- Ensure that neonatal intensive care is available

In regional perinatal centers, specialists in management of diabetic complications are available.

**During pregnancy:** Treatment can vary, but some general management guidelines are useful (see Tables 263-1, 263-2, and 263-3).

[Table 263-1. Management of Type 1 Diabetes Mellitus* During Pregnancy]

Women with type 1 or 2 should monitor their blood glucose levels at home. During pregnancy, normal fasting blood glucose levels are about 76 mg/dL (4.2 mmol/L); treatment aims to keep fasting blood glucose levels at < 95 mg/dL (< 5.3 mmol/L) and 2-h postprandial levels at ≤ 120 mg/dL (≤ 6.6 mmol/L). The goals are no wide blood glucose fluctuations and glycosylated Hb (Hb A\textsubscript{1c}) levels kept at < 8%.

[Table 263-2. Management of Type 2 Diabetes Mellitus* During Pregnancy]

**Insulin** is the traditional drug of choice because it cannot cross the placenta and provides more predictable glucose control; it is used for types 1 and 2 diabetes and for some women with gestational diabetes. Human insulin is used if possible because it minimizes antibody formation. Insulin antibodies cross the placenta, but their effect on the fetus is unknown. In some women with long-standing type 1 diabetes, hypoglycemia does not trigger the normal release of counterregulatory hormones (catecholamines, glucagon, cortisol, and growth hormone); thus, too much insulin can trigger hypoglycemic coma without premonitory symptoms. All pregnant women with type 1 should have glucagon kits and be instructed (as should family members) in giving glucagon if severe hypoglycemia (indicated by unconsciousness, confusion, or blood glucose levels < 40 mg/dL [< 2.2 mmol/L]) occurs.

**Oral hypoglycemic drugs** (eg, glyburide) are being increasingly used to manage diabetes in pregnant women because of the ease of administration (pills compared to injections), low cost, and single daily dosing. Several studies have shown that glyburide is safe during pregnancy and that it provides control equivalent to that of insulin for women with gestational diabetes. For women with type II diabetes before pregnancy, data for use of oral drugs during pregnancy are scant; insulin is most often preferred. Oral hypoglycemics taken during pregnancy may be continued postpartum during breastfeeding, but the infant should be closely monitored for signs of hypoglycemia.

**Management of complications:** Although diabetic retinopathy, nephropathy, and mild neuropathy are not contraindications to pregnancy, they require preconception counseling and close management before and during pregnancy.
Retinopathy requires that an ophthalmologic examination be done every trimester. If proliferative retinopathy is noted at the first prenatal visit, photocoagulation should be used as soon as possible to prevent progressive deterioration.

Nephropathy, particularly in women with renal transplants, predisposes to pregnancy-induced hypertension. Risk of preterm delivery is higher if maternal renal function is impaired or if transplantation was recent. Prognosis is best if delivery occurs ≥ 2 yr after transplantation.

Congenital malformations of major organs are predicted by elevated Hb A₁C levels at conception and during the first 8 wk of pregnancy. If the level is ≥ 8.5% during the 1st trimester, risk of congenital malformations is significantly increased, and targeted ultrasonography and fetal echocardiography are done during the 2nd trimester to check for malformations. If women with type 2 diabetes take oral hypoglycemic drugs during the 1st trimester, fetal risk of congenital malformations is unknown (see Table 264-2).

Labor and delivery: Certain precautions are required to ensure an optimal outcome.

Timing of delivery depends on fetal well-being. Women are told to count fetal movements during a 60-min period daily (fetal kick count) and to report any sudden decreases to the obstetrician immediately. Nonstress testing (see p. 2630) is begun at 32 wk and, if results are nonreassuring, is followed by a biophysical profile (measurement of amniotic fluid and fetal muscle tone, movement, and breathing pattern). These tests and similar noninvasive prenatal fetal monitoring tests (called antenatal testing) are initiated earlier if women have severe hypertension or a renal disorder or if fetal growth restriction is suspected. Amniocentesis to assess fetal lung maturity is often necessary for women with the following:

- Obstetric complications in past pregnancies
- Elective delivery before 39 wk
- Inadequate prenatal care
- Uncertain delivery date
- Poor glucose control

Type of delivery is usually spontaneous vaginal delivery at term. If labor does not begin spontaneously by 38 to 40 wk, induction is necessary because of the increasing risk of stillbirth and shoulder dystocia. Dysfunctional labor, fetopelvic disproportion, or risk of shoulder dystocia may make cesarean delivery necessary.

Blood glucose levels are best controlled during labor and delivery by a continuous low-dose insulin infusion. If induction is planned, women eat their usual diet the day before and take their usual insulin dose. On the morning of labor induction, breakfast and insulin are withheld, baseline fasting plasma glucose is measured, and an IV infusion of 5% dextrose in 0.45% saline solution is started at 125 mL/h, using an infusion pump. Initial insulin infusion rate is determined by capillary glucose level. Insulin dose is determined as followed:

- Initially: 0 units for a capillary level of < 80 mg/dL (< 4.4 mmol/L) or 0.5 units/h for a level of 80 to 100 mg/dL (4.4 to 5.5 mmol/L)
- Thereafter: Increased by 0.5 units/h for each 40-mg/dL (2.2-mmol/L) increase in glucose level over 100 mg/dL up to 2.5 units/h for levels > 220 mg/dL (> 12.2 mmol/L)
- Every hour during labor: Measurement of glucose level at bedside and adjustment of dose to keep the level at 70 to 120 mg/dL (3.8 to 6.6 mmol/L)
• If the glucose level is significantly elevated: Possibly additional bolus doses

For spontaneous labor, the procedure is the same, except that if intermediate-acting insulin was taken in the previous 12 h, the insulin dose is decreased. For women who have fever, infection, or other complications and for obese women who have type 2 and have required > 100 units of insulin/day before pregnancy, the insulin dose is increased.

**Postpartum:** After delivery, loss of the placenta, which synthesizes large amounts of insulin antagonist hormones throughout pregnancy, decreases the insulin requirement immediately. Thus, women with gestational diabetes and many of those with type 2 require no insulin postpartum. For women with type 1, insulin requirements decrease dramatically but then gradually increase after about 72 h.

During the first 6 wk postpartum, the goal is tight glucose control. Glucose levels are checked before meals and at bedtime. Breast-feeding is not contraindicated but may result in hypoglycemia if oral hypoglycemics are taken. Women who have had gestational diabetes should have a 2-h oral glucose tolerance test with 75 g of glucose at 6 to 12 wk postpartum to determine whether diabetes has resolved.

**Fever in Pregnancy**

A temperature > 39.5° C (> 103° F) during the 1st trimester increases risk of spontaneous abortion and fetal brain or spinal cord defects. Fever late in pregnancy increases risk of preterm labor.

Treatment is directed at the cause, but anti-pyretics are indicated to decrease maternal temperature. In women with severe hyperthermia, cooling blankets may be used.

**Fibroids in Pregnancy**

Fibroids may increase risk of preterm labor, abnormal fetal presentation, placenta previa, and recurrent spontaneous abortions. Rarely, fibroids partially obstruct the birth canal.

Preconception evaluation is recommended for women who have very large fibroids or who have fibroids and have had a spontaneous abortion.

**Heart Disorders in Pregnancy**

Heart disorders account for about 10% of maternal obstetric deaths. In the US, because incidence of rheumatic heart disease has markedly declined, most heart problems during pregnancy result from congenital heart disease. Pregnancy is inadvisable for women with certain high-risk disorders (eg, pulmonary hypertension, severe valvular disorders, prior postpartum cardiomyopathy).

**Pathophysiology**

Pregnancy stresses the cardiovascular system, often worsening known heart disorders; mild heart disorders may first become evident during pregnancy. Stresses include decreased Hb and increased blood volume, stroke volume, and eventually heart rate. Cardiac output increases by 30 to 50%. These changes become maximal between 28 and 34 wk gestation. During labor, cardiac output increases about 20% with each uterine contraction; other stresses include straining during the 2nd stage of labor and the increase in venous blood returning to the heart from the contracting uterus. Cardiovascular stresses do not return to prepregnancy levels until several weeks after delivery.

**Symptoms and Signs**

Findings resembling heart failure (eg, mild dyspnea, systolic murmurs, jugular venous distention, tachycardia, dependent edema, mild cardiomegaly seen on chest x-ray—see p. 2118) typically occur during normal pregnancy or may result from a heart disorder. Diastolic or presystolic murmurs are more specific for heart disorders.
Heart failure can cause premature labor or arrhythmias. Risk of maternal or fetal death correlates with New York Heart Association functional classification, which is based on the amount of physical activity that causes symptoms of heart failure. Risk is not increased if symptoms

- Do not occur during exertion (class I)
- Occur only during significant exertion (class II)

Risk is increased if symptoms

- Occur during mild exertion (class III)
- Occur during minimal or no exertion (class IV)

**Diagnosis**

Diagnosis is usually based on clinical evaluation and echocardiography.

**Treatment**

- Avoidance of warfarin, ACE inhibitors, aldosterone antagonists, and certain anti-arrhythmics (eg, amiodarone)
- For NYHA class III or IV, activity restriction and possible bed rest after 20 wk
- Most other usual treatments for heart failure and arrhythmias

Frequent prenatal visits, ample rest, avoidance of excessive weight gain and stress, and treatment of anemia are required. An anesthesiologist familiar with heart disorders in pregnancy should attend the labor. During labor, pain and anxiety are treated aggressively to minimize tachycardia. Women are closely monitored immediately postpartum and are followed for several weeks postpartum by a cardiologist.

Before women with NYHA class III or IV status conceive, the disorder should be optimally treated medically and, if indicated (eg, if due to a valvular heart disorder), treated surgically.

Some women with a heart disorder and poor cardiac function require digoxin 0.25 mg po once/day plus bed rest, beginning at 20 wk. Cardiac glycosides (eg, digoxin, digitoxin) cross the placenta, but neonates (and children) are relatively resistant to their toxicity. Women with class IV heart failure may be advised to obtain early therapeutic abortion. ACE inhibitors are contraindicated because they may cause fetal renal damage. Aldosterone antagonists (spironolactone, eplerenone) should be avoided because they may cause feminization of a male fetus. Other treatments for heart failure (eg, diuretics, nitrates, inotropes) may be continued during pregnancy depending on disease severity and fetal risk, as determined by a cardiologist and a perinatologist.

**Arrhythmias:** Atrial fibrillation may accompany cardiomyopathy or valvular lesions. Rate control is usually similar to that in nonpregnant patients, with β-blockers, Ca channel blockers, or digoxin (see p. 2147). Certain antiarrhythmics (eg, amiodarone) should be avoided. In pregnant patients with new-onset atrial fibrillation or hemodynamic instability, cardioversion may be used to restore sinus rhythm. Anticoagulation may be required because the relative hypercoagulability during pregnancy makes atrial thrombi (and subsequent systemic or pulmonary embolization) more likely. Neither standard heparin nor low molecular weight heparins cross the placenta, but low molecular weight heparins may have less risk of thrombocytopenia. Warfarin crosses the placenta and may cause fetal abnormalities (see Table 264-2 on p. 2656), particularly during the 1st trimester. Warfarin use during the last month of pregnancy has risks. Rapid reversal of warfarin's anticoagulant effects may be difficult and may be required because of fetal or neonatal intracranial hemorrhage resulting from birth trauma or because of maternal bleeding (eg, resulting from trauma or emergency cesarean delivery).

Management of acute supraventricular or ventricular tachycardia is the same as for non-pregnant
Endocarditis prophylaxis: For pregnant patients with a structural heart disorder, indications and use of endocarditis prophylaxis for nonobstetric events are the same as those for nonpregnant patients (see p. 2199). Although rate of bacteremia with uncomplicated vaginal or caesarean delivery is low and routine prophylaxis is not recommended by the American College of Cardiology, many obstetricians give patients with valvular disease prophylactic antibiotics shortly before and after delivery.

Valvular Stenosis and Insufficiency

During pregnancy, stenosis and regurgitation (insufficiency) most often affect the mitral and aortic valves. Pregnancy amplifies the murmurs of mitral and aortic stenosis but diminishes those of mitral and aortic regurgitation. During pregnancy, mild mitral or aortic regurgitation is usually easy to tolerate; stenosis is more difficult to tolerate and predisposes to maternal and fetal complications. Mitral stenosis is especially dangerous; the tachycardia, increased blood volume, and increased cardiac output during pregnancy interact with this disorder to rapidly increase pulmonary capillary pressure, causing pulmonary edema. Atrial fibrillation is also common.

Treatment

Ideally, valvular disorders are diagnosed and treated medically before conception; surgical correction is often recommended for severe disorders. Prophylactic antibiotics are required in certain situations (see p. 2643).

Mitral stenosis: Patients must be closely observed throughout pregnancy because mitral stenosis may rapidly become more severe. If required, valvotomy is relatively safe during pregnancy; however, open heart surgery increases fetal risk. During labor, conduction anesthesia (eg, epidural or spinal nerve block by a local anesthetic) is usually preferred.

Aortic stenosis: During labor, local anesthesia is preferred, but if necessary, general anesthesia is used. Conduction anesthesia should be avoided because it decreases filling pressures (preload), which may already be decreased by aortic stenosis. Straining, which can suddenly reduce filling pressures and impair cardiac output, is discouraged during the 2nd stage of labor; operative vaginal delivery may be preferred, if feasible. Cesarean delivery is done if indicated (see p. 2678).

Other Heart Disorders

Mitral valve prolapse: This disorder occurs more frequently in younger women and tends to be familial. Mitral valve prolapse is usually an isolated abnormality but may cause some degree of mitral regurgitation or be accompanied by Marfan syndrome or an atrial septal defect.

Women with mitral valve prolapse generally tolerate pregnancy well. The relative increase in ventricular size during normal pregnancy reduces the discrepancy between the disproportionately large mitral valve and the ventricle.

Patients with mitral regurgitation may require prophylactic antibiotics during delivery. β-Blockers are indicated for recurrent arrhythmias. Rarely, thrombi and systemic emboli develop and require anticoagulation.

Congenital heart disease: For most asymptomatic patients, risk is not increased during pregnancy. However, patients with Eisenmenger's syndrome (now rare), primary pulmonary hypertension, or perhaps isolated pulmonary stenosis are predisposed, for unknown reasons, to sudden death during labor, during the postpartum period (the 6 wk after delivery), or after abortion at > 20 wk gestation. Thus, pregnancy is inadvisable. If these patients become pregnant, they should be closely monitored with a pulmonary artery catheter and an arterial line during delivery. For patients with intracardiac shunts, the goal is to prevent right-to-left shunting by maintaining peripheral vascular resistance and by minimizing pulmonary vascular resistance.
Patients with Marfan syndrome are at increased risk of aortic dissection and rupture of aortic aneurysms during pregnancy. Bed rest, avoidance of Valsalva maneuvers, and measurement of aortic diameter with echocardiography are required.

**Peripartum cardiomyopathy:** Heart failure with no identifiable cause (eg, MI, valvular disorder) can develop between the last month of pregnancy and 5 mo postpartum in patients without a previous heart disorder. Risk factors include multiparity, age ≥ 30, multifetal pregnancy, and preeclampsia. The 5-yr mortality rate is 50%. Recurrence is likely in subsequent pregnancies, particularly in patients with residual cardiac dysfunction; future pregnancies are therefore not recommended. Treatment is as for heart failure (see p. 2643).

**Hepatic Disorders in Pregnancy**

Jaundice (see p. 212) may result from nonobstetric or obstetric conditions. Nonobstetric causes include drugs, acute cholecystitis, and biliary obstruction by gallstones. Gallstones appear to be more common during pregnancy, probably because bile lithogenicity is increased and gallbladder contractility is impaired. Obstetric causes include hyperemesis gravidarum (usually causing mild jaundice) and septic abortion; both cause hepatocellular injury and hemolysis.

**Acute viral hepatitis:** The most common cause of jaundice during pregnancy is acute viral hepatitis. It may predispose to preterm delivery but does not appear to be teratogenic. Acute viral hepatitis is generally mild, but hepatitis E, common in underdeveloped countries, may be severe. Hepatitis B virus may be transmitted to the neonate immediately after delivery or, less often, to the fetus transplacentally. Transmission is particularly likely if women are e-antigen-positive and are chronic carriers of hepatitis B surface antigen (HBsAg) or if they contract hepatitis during the 3rd trimester. Affected neonates are more likely to develop subclinical hepatic dysfunction and become carriers than to develop clinical hepatitis. All pregnant women are tested for HBsAg to determine whether precautions against vertical transmission are needed (for prenatal prophylaxis with immune globulin and vaccination for neonates exposed to hepatitis B virus, see p. 2826).

**Chronic active hepatitis:** Chronic active hepatitis, especially with cirrhosis, impairs fertility. When pregnancy occurs, risk of spontaneous abortion and prematurity is increased, but risk of maternal mortality is not. Corticosteroids given for chronic active hepatitis can be continued during pregnancy because fetal risks due to corticosteroids have not been proved to exceed those due to maternal chronic active hepatitis. Azathioprine and other immunosuppressants, despite fetal risks, are sometimes indicated for severe disease.

**Cholestasis (pruritus) of pregnancy:** This relatively common disorder apparently results from idiosyncratic exaggeration of normal bile stasis due to hormonal changes. Intense pruritus, the earliest symptom, develops during the 2nd or 3rd trimester; dark urine and jaundice sometimes follow. Acute pain and systemic symptoms are absent. The disorder usually resolves after delivery but tends to recur with each pregnancy or with use of oral contraceptives.

For severe pruritus, oral cholestyramine 4 to 6 g bid or 3 to 4 g tid is usually effective. Bleeding due to hypoprothrombinemia occasionally develops but is readily reversed by vitamin K (phytonadione) 5 to 10 mg IM once/day for 2 to 3 days.

**Fatty liver of pregnancy:** This rare, poorly understood disorder occurs near term, sometimes with preeclampsia. Symptoms include acute nausea and vomiting, abdominal discomfort, and jaundice, followed in severe cases by rapidly progressive hepatocellular failure. Maternal and fetal mortality rates are high in severe cases.

Clinical and laboratory findings resemble those of fulminant viral hepatitis except that aminotransferase levels may be < 500 units/L and hyperuricemia may be present.

Diagnosis is based on clinical criteria, liver function tests, hepatitis serologic tests, and liver biopsy. Biopsy shows diffuse small droplets of fat in hepatocytes, usually with minimal apparent necrosis, but in some cases, findings are indistinguishable from viral hepatitis.
Depending on gestational age, prompt delivery or termination of pregnancy is usually advised, although whether either alters maternal outcome is unclear. Survivors recover completely and have no recurrences. A seemingly identical disorder may develop at any stage of pregnancy if high doses of tetracyclines are given IV.

**Preeclampsia:** Severe preeclampsia (see p. 2670) can cause liver problems with hepatic fibrin deposition, necrosis, and hemorrhage that can result in abdominal pain, nausea, vomiting, and mild jaundice. Subcapsular hematoma with intra-abdominal hemorrhage occasionally occurs, most often in women with preeclampsia that progresses to the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Rarely, the hematoma causes the liver to rupture spontaneously; rupture is life threatening, and pathogenesis is unknown.

**Chronic hepatic disorders:** Pregnancy may temporarily worsen cholestasis in primary biliary cirrhosis and other chronic cholestatic disorders, and the increased plasma volume during the 3rd trimester slightly increases risk of variceal hemorrhage in women with cirrhosis. However, pregnancy usually does not harm women with a chronic hepatic disorder. Cesarean delivery is reserved for the usual obstetric indications.

**Hypertension in Pregnancy**

(See also Ch. 208.)

Hypertension (BP ≥ 140/90 mm Hg) during pregnancy can be classified as one of the following:

- **Chronic:** BP is high before pregnancy or before 20 wk gestation. Chronic hypertension complicates about 1 to 5% of all pregnancies.

- **Gestational:** Hypertension develops after 20 wk gestation (typically after 37 wk) and remits by 6 wk postpartum; it occurs in about 5 to 10% of pregnancies, more commonly in multifetal pregnancy.

Both types of hypertension increase risk of preeclampsia, eclampsia (see p. 2670), and other causes of maternal mortality or morbidity, including hypertensive encephalopathy, stroke, renal failure, left ventricular failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Risk of fetal mortality or morbidity increases because of decreased uteroplacental blood flow, which can cause vasospasm, growth restriction, hypoxia, and abruptio placentae. Outcomes are worse if hypertension is severe (BP > 180/100 mm Hg) or accompanied by renal insufficiency (eg, creatinine clearance < 60 mL/min, serum creatinine > 2 mg/dL [> 180 μmol/L]).

**Diagnosis**

BP is measured routinely at prenatal visits. If severe hypertension occurs for the first time in pregnant women who do not have a multi-fetal pregnancy or gestational trophoblastic disease, tests to rule out renal artery stenosis, coarctation of the aorta, Cushing's syndrome, SLE, and pheochromocytoma should be considered (see p. 2068).

**Treatment**

- For mild hypertension, conservative measures followed by antihypertensives if needed

- Methyldopa, β-blockers, or Ca channel blockers tried first

- Avoidance of ACE inhibitors, aldosterone antagonists, and thiazides

- For moderate or severe hypertension, anti-hypertensive therapy, close monitoring, and, if condition worsens, possibly termination of pregnancy or delivery, depending on gestational age

Treatment of mild to moderate hypertension without renal insufficiency during pregnancy is controversial;
the issues are whether treatment improves outcome and whether the risks of drug treatment outweigh risks of untreated disease. Because the uteroplacental circulation is maximally dilated and cannot autoregulate, decreasing maternal BP with drugs may abruptly decrease uteroplacental blood flow. Diuretics reduce effective maternal circulating blood volume; consistent reduction increases risk of fetal growth restriction. However, hypertension with renal insufficiency is treated even if hypertension is mild or moderate.

Recommendations for chronic and gestational hypertension are similar and depend on severity. However, chronic hypertension may be more severe, and the BP ranges in gestational diabetes often do not require treatment.

If hypertension is mild (140/90 to 150/100 mm Hg) and if BP is labile, reduced physical activity may decrease BP and improve fetal growth, making perinatal risks similar to those for women without hypertension. However, if these conservative measures do not decrease BP, many experts recommend drug therapy.

If hypertension is moderate (150/100 to 180/110 mm Hg), drug therapy is indicated. Women who are taking methyldopa, a β-blocker, a Ca channel blocker, or a combination before pregnancy may continue these drugs. However, ACE inhibitors and diuretics should be stopped once pregnancy is confirmed. Women must be taught to self-monitor BP and should have renal function testing every trimester. Fetal growth is monitored with monthly ultrasound examinations; antenatal testing begins at 32 wk. Delivery should be accomplished at 38 to 39 wk but may be done earlier if severe preeclampsia or fetal growth restriction is detected or if fetal testing is non-reassuring.

If hypertension is severe (≥ 180/110 mm Hg), immediate evaluation, including BUN and serum creatinine, creatinine clearance, 24-h urinary protein level, and funduscopy, is indicated. Risk of complications—maternal (progression of end-organ dysfunction or preeclampsia) and fetal (prematurity, growth restriction, stillbirth)—is increased significantly. If continuation of pregnancy is strongly desired despite the risk, several antihypertensives are often required. Hospitalization is also often required for much of the latter part of pregnancy. If the woman's condition worsens, pregnancy termination may be recommended.

**Drugs:** First-line drugs for hypertension during pregnancy include methyldopa, β-blockers, and Ca channel blockers. Initial methyldopa dose is 250 mg po bid, increased as needed to 2 g/day or sometimes more unless excessive somnolence, depression, and symptomatic orthostatic hypotension occur. The most commonly used β-blocker is labetalol (a β-blocker with some α1-blocking effects), which can be used alone or with methyldopa when the maximum daily dose of methyldopa has been reached. Usual dose of labetalol is 100 mg bid to tid, increased as needed to a total daily dose of 2400 mg. Adverse effects of β-blockers include increased risk of fetal growth restriction, decreased maternal energy levels, and maternal depression. Extended-release nifedipine, a Ca-channel blocker, may be preferred because it is given once/day (initial dose of 30 to 60 mg); adverse effects include headaches and pretibial edema.

Several classes of antihypertensives are usually avoided during pregnancy:

- **ACE inhibitors** are contraindicated because risk of fetal urinary tract abnormalities is increased.
- **Thiazide diuretics** can adversely affect the fetus and should be avoided during pregnancy if possible.
- **Aldosterone antagonists** (spironolactone and eplerenone) should be avoided because they may cause feminization of a male fetus.

**Infectious Disease in Pregnancy**

Most common maternal infections (eg, UTIs, skin and respiratory tract infections) are usually not serious problems during pregnancy, although some genital infections (bacterial vaginosis and genital herpes) affect labor or choice of delivery method. Thus, the main issue is usually use and safety of antimicrobial drugs. However, certain maternal infections can damage the fetus (for congenital cytomegalovirus or herpes simplex virus infection, rubella, toxoplasmosis, hepatitis, or syphilis, see Ch. 279; for HIV infection,
Listeriosis is more common during pregnancy. Listeriosis increases risk of spontaneous abortion, premature labor, and stillbirth. Neonatal transmission is possible.

Bacterial vaginosis and possibly genital chlamydial infection predispose to premature rupture of the membranes and preterm labor. Tests for these infections are done during routine prenatal evaluations or if symptoms develop.

Genital herpes can be transmitted to the neonate during delivery. Risk is high enough that cesarean delivery is preferred in the following situations:

• When women have visible herpetic lesions

• When women who have a known history of infection develop prodromal symptoms before labor

• When herpes infection first occurs during the late 3rd trimester (when the virus is likely to be excreted from the cervix at delivery)

If visible lesions or prodrome is absent, even in women with recurrent infections, risk is low, and vaginal delivery is possible. If women are asymptomatic, serial antepartum cultures do not help identify those at risk of transmission. If women have recurrent herpes infections during pregnancy but no other risk factors for transmission, labor can sometimes be induced so that delivery occurs between recurrences. When delivery is vaginal, cervical and neonatal herpesvirus cultures are done. Acyclovir (oral and topical) appears to be safe during pregnancy.

Antibacterials: Not giving antibacterials to pregnant patients without strong evidence of a bacterial infection is particularly important. Generally, penicillins, cephalosporins, and macrolides are considered safe. Use of any antibacterial during pregnancy should be based on whether benefits outweigh risk, which varies by trimester (see Table 264-2 on p. 2656 for specific adverse effects). Severity of the infection and other options for treatment are also considered.

Aminoglycosides may be used during pregnancy to treat pyelonephritis and chorioamnionitis, but treatment should be carefully monitored to avoid maternal or fetal damage.

Chloramphenicol, even in large doses, does not harm the fetus; however, neonates cannot adequately metabolize chloramphenicol, and the resulting high blood levels may lead to circulatory collapse (gray baby syndrome). Chloramphenicol is rarely used in the US.

Metronidazole use during the 1st trimester is controversial, but the drug is routinely used to treat bacterial vaginosis and trichomoniasis during the 2nd and 3rd trimesters.

Fluoroquinolones are not used during pregnancy; they tend to have a high affinity for bone and cartilage and thus may have adverse musculoskeletal effects.

Sulfonamides are usually safe during pregnancy. However, long-acting sulfonamides cross the placenta and can displace bilirubin from binding sites. These drugs are often avoided after 34 wk gestation because neonatal kernicterus is a risk.

Tetracyclines cross the placenta and are concentrated and deposited in fetal bones and teeth, where they combine with Ca and impair development (see Table 264-2 on p. 2656); they are not used from the middle to the end of pregnancy.

Renal Insufficiency in Pregnancy

Pregnancy often does not worsen renal disorders; it seems to exacerbate noninfectious renal disorders only when uncontrolled hypertension coexists. However, significant renal insufficiency (serum creatinine > 3 mg/dL [> 270 μmol/L] or BUN > 30 mg/dL [> 10.5 mmol urea/L]) before pregnancy usually prevents
women from maintaining a pregnancy to term. Maternal renal insufficiency may cause fetal growth restriction and stillbirth.

After renal transplantation, full-term, un-complicated pregnancy is often possible if women have all of the following:

- A transplanted kidney that has been in place for > 2 yr
- Normal renal function
- No episodes of rejection
- Normal BP

Treatment requires close consultation with a nephrologist. BP and weight are measured every 2 wk; BUN and creatinine levels plus creatinine clearance are measured often, at intervals dictated by severity and progression of disease. Furosemide is given only to control BP or excessive edema; some women require other drugs to control BP. Women with severe renal insufficiency may require hospitalization after 28 wk gestation for bed rest, BP control, and close fetal monitoring. Which antenatal tests are done depends on the stage of pregnancy. Nonstress tests are usually done first, followed by an oxytocin challenge test or a biophysical profile if required. If results remain normal and reassuring, the pregnancy continues.

Delivery is usually required before term because preeclampsia, fetal growth restriction, or uteroplacental insufficiency develop. Sometimes amniocentesis to check fetal lung maturity can help determine when delivery should be done; a lecithin/sphingomyelin ratio of > 2:1 or presence of phosphatidylglycerol indicates maturity. Cesarean delivery is very common, although vaginal delivery may be possible if the cervix is ripe and no impediments to vaginal delivery are evident.

Seizure Disorders in Pregnancy

Seizure disorders may impair fertility. But certain anticonvulsants may make oral contraceptives less effective, resulting in unintentional pregnancy.

The dose of anticonvulsant drugs may have to be increased during pregnancy to maintain therapeutic levels. If women get enough sleep and anticonvulsant levels are kept in the therapeutic range, seizure frequency does not usually increase during pregnancy, and pregnancy outcome is good; however, risks of preeclampsia, fetal growth restriction, and stillbirth are slightly increased. Generally, uncontrolled seizures are more harmful during pregnancy than is use of anticonvulsants; thus, the top priority of treatment during pregnancy is to control seizures. Preconception consultation with a neurologist is recommended to stabilize maternal seizures before pregnancy; the lowest possible dose of anticonvulsant should be used.

Anticonvulsants slightly increase risk of congenital malformations and may tend to slightly decrease intelligence in offspring; risk of intellectual disability may be increased. Risk of hemorrhagic disease of the newborn (erythroblastosis neonatorum) may be increased by in utero exposure to certain anticonvulsants (eg, phenytoin, carbamazepine, pheno-barbital); however, if prenatal vitamins with vitamin D are taken and vitamin K is given to the neonate, hemorrhagic disease is rare.

Taken during pregnancy, phenobarbital may reduce the physiologic jaundice neonates commonly have, perhaps because the drug induces neonatal hepatic conjugating enzymes. Phenytoin is generally preferred.

All anticonvulsants increase the need for supplemental folate; 1 mg po is given once/day. Ideally, it is started before conception.

Vaginal delivery is usually preferred, but if women have repeated seizures during labor, cesarean delivery is indicated. Anticonvulsant levels can rapidly change postpartum and should be closely monitored then.

Disorders Requiring Surgery During Pregnancy
Certain disorders treated with surgery are difficult to diagnose during pregnancy. A high level of suspicion is required; assuming that all abdominal symptoms are pregnancy-related is an error.

Major surgery, particularly intra-abdominal, increases risk of preterm labor and fetal death. However, surgery is tolerated well by pregnant women and the fetus when appropriate supportive care and anesthesia (maintaining BP and oxygenation at normal levels) are provided, so physicians should not be reluctant to operate; delaying treatment of an abdominal emergency is far more dangerous.

**Appendicitis:** Appendicitis may occur during pregnancy but is more common immediately postpartum. Because the appendix rises in the abdomen as pregnancy progresses, pain and tenderness may not occur in the classic right lower quadrant location, and pain may be mild and cramping, mimicking pregnancy-related symptoms. Also, WBC count is normally somewhat elevated during pregnancy, making WBC count even less useful than usual. Serial clinical assessment and compression-graded ultrasonography are useful. Because diagnosis is often delayed, mortality rate from ruptured appendix is increased during pregnancy and particularly postpartum. Thus, if appendicitis is suspected, surgical evaluation (laparoscopy or laparotomy depending on the stage of pregnancy) should proceed without delay.

**Benign ovarian cysts:** These cysts are common during pregnancy. Cysts that occur during the first 14 to 16 wk are often corpus luteal cysts, which spontaneously resolve. Adnexal torsion may occur (see p. 2532). If adnexal torsion does not resolve, surgical therapy to unwind the adnexa or removal may be required. After 12 wk, cysts become difficult to palpate because the ovaries, with the uterus, rise out of the pelvis. Ovarian masses are evaluated first by ultrasonography (see p. 2533). Definitive evaluation (eg, excision) is delayed, if possible, until after 14 wk unless any of the following occur:

- The cyst enlarges continuously.
- The cyst is tender.
- The cyst has radiographic characteristics of cancer (eg, a solid component, surface excrescences, size > 6 cm, irregular shape).

**Gallbladder disease:** This disease occurs occasionally. If possible, treatment is expectant; if women do not improve, immediate surgery is needed.

**Intestinal obstruction:** During pregnancy, intestinal obstruction may cause intestinal gangrene with peritonitis and maternal or fetal morbidity or mortality. If pregnant women have symptoms and signs of intestinal obstruction and risk factors (eg, previous abdominal surgery, intra-abdominal infection), prompt exploratory laparotomy is indicated.

**Thromboembolic Disorders in Pregnancy**

In the US, thromboembolic disorders—deep venous thrombosis (DVT—see p. 2224) or pulmonary embolism (PE—see p. 1908)—are a leading cause of maternal mortality. During pregnancy, risk is increased because venous capacitance and venous pressure in the legs are increased, resulting in stasis, and because pregnancy causes a degree of hypercoagulability. However, most thromboemboli develop postpartum and result from vascular trauma during delivery. Cesarean delivery also increases risk.

Symptoms of thrombophlebitis or their absence does not accurately predict the diagnosis, disease severity, or risk of embolization. Thromboembolic disorders can occur without symptoms, with only minimal symptoms, or with significant symptoms. Also, calf edema, cramping, and tenderness, which may occur normally during pregnancy, may simulate Homans’ sign.

**Diagnosis**

- Doppler ultrasonography or sometimes CT with contrast for DVT
• Helical CT for PE

Diagnosis of DVT is usually by Doppler ultrasonography. In the postpartum period, if Doppler ultrasonography and plethysmography are normal but iliac, ovarian, or other pelvic venous thrombosis is suspected, CT with contrast is used.

Diagnosis of PE is increasingly being made by helical CT rather than ventilation-perfusion scanning because CT involves less radiation and is equally sensitive. If the diagnosis of PE is uncertain, pulmonary angiography is required.

Treatment

• Similar to that in nonpregnant patients, except for avoidance of warfarin

If DVT or PE is detected during pregnancy, the anticoagulant of choice is a low molecular weight heparin (LMWH). LMWH, because of its molecular size, does not cross the placenta. It does not cause maternal osteoporosis and may be less likely to cause thrombocytopenia, which can result from prolonged (≥ 6 mo) use of unfractionated heparin. Warfarin crosses the placenta and may cause fetal abnormalities or death (see Table 264-2 on p. 2656). Indications for thrombolysis during pregnancy are the same as for patients who are not pregnant.

If PE recurs despite effective anticoagulation, surgery, usually placement of an inferior vena cava filter just distal to the renal vessels, is indicated.

If women developed DVT or PE during a previous pregnancy or have an underlying thrombophilic disorder, they are treated with prophylactic LMWH 5000 units sc bid beginning at the first diagnosis of pregnancy and continuing until 6 wk postpartum.

Thyroid Disorders in Pregnancy

(See also Ch. 93.)

Thyroid disorders may predate or develop during pregnancy. Pregnancy does not change the symptoms of hypothyroidism and hyperthyroidism or the normal values and ranges of free serum thyroxine (T4) and thyroid-stimulating hormone (TSH).

Fetal effects vary with the disorder and the drugs used for treatment. But generally, hyperthyroidism causes fetal growth restriction and stillbirth, and hypothyroidism causes intellectual deficits in offspring and miscarriage. The most common causes of maternal hypothyroidism are Hashimoto's thyroiditis and treatment of Graves' disease.

If women have or have had a thyroid disorder, thyroid status should be closely monitored during and after pregnancy in the women and in the offspring.

Graves' disease: Maternal Graves' disease is monitored clinically and with free T4 and high-sensitivity TSH assays.

Treatment varies. Usually, pregnant women are given the lowest possible dose of oral propylthiouracil (50 to 100 mg q 8 h). Therapeutic response occurs over 3 to 4 wk; then the dose is changed if needed. Propylthiouracil crosses the placenta and may cause goiter and hypothyroidism in the fetus. Simultaneous use of L-thyroxine or L-triiodothyronine is contraindicated because these hormones may mask the effects of excessive propylthiouracil in pregnant women and result in hypothyroidism in the fetus. Methimazole is an alternative to propylthiouracil. Graves' disease commonly abates during the 3rd trimester, often allowing dose reduction or discontinuation of the drug.

In centers with experienced thyroid surgeons, a 2nd-trimester thyroidectomy, although very uncommon, may be considered after drug treatment restores euthyroidism. After thyroidectomy, women are given full
replacement of L-thyroxine (0.15 to 0.2 mg/day), beginning 24 h later.

Radioactive iodine (diagnostic or therapeutic) and iodide solutions are contraindicated during pregnancy because of adverse effects on the fetal thyroid gland. β-Blockers are used only for thyroid storm or severe maternal symptoms.

If pregnant women have or have had Graves' disease, fetal hyperthyroidism may develop. Whether these women are clinically euthyroid, hyperthyroid, or hypothyroid, thyroid-stimulating immunoglobulins (Igs) and thyroid-blocking Igs (if present) cross the placenta. Fetal thyroid function reflects the relative fetal levels of these stimulating and blocking Igs. Hyperthyroidism can cause fetal tachycardia (> 160 beats/min), growth restriction, and goiter, which can lead to decreased fetal swallowing, polyhydramnios, and preterm labor. Ultrasonography is used to evaluate fetal growth, thyroid gland, and heart.

**Congenital Graves' disease:** If pregnant women have taken propylthiouracil, congenital Graves' disease in the fetus may be masked until 7 to 10 days after birth, when the drug's effect subsides.

**Maternal hypothyroidism:** Women with mild to moderate hypothyroidism frequently have normal menstrual cycles and can become pregnant. During pregnancy, the usual dose of L-thyroxine is continued. As pregnancy progresses, minor dose adjustments may be necessary, ideally based on TSH measurement after several weeks. If hypothyroidism is first diagnosed during pregnancy, L-thyroxine is started at 0.1 mg po once/day.

**Hashimoto's thyroiditis:** Maternal immune suppression during pregnancy often ameliorates this disorder; however, hypothyroidism or hyperthyroidism that requires treatment sometimes develops.

**Acute (subacute) thyroiditis:** Common during pregnancy, this disorder usually produces a tender goiter during or after a respiratory infection. Transient, symptomatic hyperthyroidism with elevated T₄ can occur, often resulting in misdiagnosis as Graves' disease. Usually, treatment is unnecessary.

**Postpartum maternal thyroid dysfunction:** Hypothyroid or hyperthyroid dysfunction occurs in 4 to 7% of women during the first 6 mo after delivery. Incidence seems to be higher among pregnant women with any of the following:

- Goiter
- Hashimoto's thyroiditis
- A strong family history of autoimmune thyroid disorders
- Type 1 (insulin-dependent) diabetes mellitus

In women with any of these risk factors, TSH and free serum T₄ levels should be checked during the 1st trimester and postpartum. Dysfunction is usually transient but may require treatment. After delivery, Graves' disease may recur transiently or persistently.

Painless thyroiditis with transient hyperthyroidism is a recently recognized postpartum, probably autoimmune disorder. It occurs abruptly in the first few weeks postpartum, results in a low radioactive iodine uptake, and is characterized by lymphocytic infiltration. Diagnosis is based on symptoms, thyroid function tests, and exclusion of other conditions. This disorder may persist, recur transiently, or progress.

**Urinary Tract Infection in Pregnancy**

(See also Ch. 233.)

UTI is common during pregnancy, apparently because of urinary stasis, which results from hormonal ureteral dilation, hormonal ureteral hypoperistalsis, and pressure of the expanding uterus against the ureters. Asymptomatic bacteriuria occurs in about 15% of pregnancies and sometimes progresses to symptomatic cystitis or pyelonephritis. Frank UTI is not always preceded by asymptomatic bacteriuria.
Asymptomatic bacteriuria, UTI, and pyelonephritis increase risk of preterm labor and premature rupture of the membranes.

**Diagnosis**

Urinalysis and culture are routinely done at initial evaluation to check for asymptomatic bacteriuria. Diagnosis of symptomatic UTI is not changed by pregnancy.

**Treatment**

- Antibacterial drugs such as cephalexin, nitrofurantoin, or trimethoprim/sulfamethoxazole
- Proof-of-cure cultures and sometimes suppressive therapy

Treatment of symptomatic UTI is not changed by pregnancy, except drugs that may harm the fetus are avoided (see Table 264-2 on p. 2656). Because asymptomatic bacteriuria may lead to pyelonephritis, it should be treated with antibiotics similar to an acute UTI.

Antibacterial drug selection is based on individual and local susceptibility and resistance patterns, but good initial empiric choices include the following:

- Cephalexin
- Nitrofurantoin
- Trimethoprim/sulfamethoxazole

After treatment, proof-of-cure cultures are required. Women who have pyelonephritis or have had > 1 UTI may require suppressive therapy, usually with trimethoprim/sulfamethoxazole (before 34 wk) or nitrofurantoin, for the rest of the pregnancy. In women who have bacteriuria with or without UTI or pyelonephritis, urine should be cultured monthly.
Chapter 264. High-Risk Pregnancy

Introduction

In a high-risk (at-risk) pregnancy, the mother, fetus, or neonate is at increased risk of morbidity or mortality before or after delivery.

In the US, overall maternal mortality rate is 6/100,000 deliveries; incidence is 3 to 4 times higher in nonwhite women. The most common causes of death are hemorrhage, preeclampsia, pulmonary embolism, and infection.

Perinatal mortality rate in offspring is 11.5/1000 deliveries: 6.7/1000 are fetal, and 4.8/1000 are neonatal (age < 28 days). The most common causes of death are congenital malformations and preterm delivery.

Risk assessment is part of routine prenatal care. Risk is also assessed during or shortly after labor and at any time that events may modify risk status. Risk factors (see Table 264-1) are assessed systematically because each risk factor present increases overall risk. High-risk pregnancies require close monitoring and sometimes referral to a perinatal center. When referral is needed, transfer before rather than after delivery results in lower neonatal morbidity and mortality rates. The most common reasons for referral before delivery are

- Preterm labor (often due to premature rupture of the membranes)
- Preeclampsia
- Hemorrhage

Risk Factors

Risk factors include preexisting maternal disorders (see Ch. 263), physical and social characteristics, age, problems in previous pregnancies (eg, spontaneous abortions), and problems that develop during pregnancy (see Ch. 265) or during labor and delivery (see Ch. 266).

Hypertension: Pregnant women are considered to have chronic hypertension (CHTN) if hypertension was present before the pregnancy or if it develops before 20 wk of pregnancy. CHTN is differentiated from gestational hypertension, which develops after 20 wk of pregnancy. In either case, hypertension is defined as systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg on 2 occasions > 24 h apart. Hypertension increases risk of fetal growth restriction by decreasing uteroplacental blood flow and risk of adverse fetal and maternal outcomes (see p. 2645).

Before attempting to conceive, women with hypertension should be counseled about the risks of pregnancy. If they become pregnant, prenatal care begins as early as possible and includes measurements of baseline renal function (eg, serum creatinine, BUN), funduscopic examination, and directed cardiovascular evaluation (auscultation and sometimes ECG, echocardiography, or both). Each trimester, 24-h urine protein, serum uric acid, serum creatinine, and Hct are measured. Ultrasonography to monitor fetal growth is done at 28 wk and every 4 wk thereafter. Delayed growth is evaluated with multivessel Doppler testing by a maternal-fetal medicine specialist (for management of hypertension during pregnancy, see p. 2646).

Diabetes: Diabetes mellitus occurs in 3 to 5% of pregnancies, but incidence is increasing as the incidence of obesity increases.

If pregnant women have preexisting insulin-dependent diabetes, risk is increased for pyelonephritis, ketoacidosis, preeclampsia, fetal death, major fetal malformations, fetal macrosomia (fetal weight > 4.5 kg), and, if vasculopathy is present, fetal growth restriction. Insulin requirements usually increase during...
pregnancy.

If women have gestational diabetes, risk of hypertensive disorders and fetal macrosomia is increased. Gestational diabetes is routinely screened for at 24 to 28 wk or, if women have risk factors, also during the 1st trimester. Risk factors include previous gestational diabetes, a macrosomic infant in a previous pregnancy, family history of non-insulin-dependent diabetes, unexplained fetal losses, and body mass index (BMI) > 30 kg/m$^2$. Some clinicians think the diagnosis can be based on a fasting plasma glucose of $\geq 126$ mg/dL or a random plasma glucose of $\geq 200$ mg/dL. However, most accurate results are obtained with a glucose tolerance test. A 50-g, 1-h glucose tolerance test is used. If the result is 140 to 199 mg/dL, a full glucose tolerance test is done (see Table 99-2 on p. 867); if glucose is $\geq 200$ mg/dL, insulin is begun. If $\geq 2$ test results are abnormal, women are treated for the rest of the pregnancy with diet and, if necessary, insulin or oral hypoglycemic drugs.

Good control of plasma glucose during pregnancy almost eliminates the risk of adverse outcomes attributable to diabetes (for management of diabetes during pregnancy, see p. 2638).

Sexually transmitted diseases (STDs—see Ch. 156): (Fetal syphilis in utero can cause fetal death, congenital malformations, and severe disability. Risk of transmission of HIV from woman to offspring in utero or perinatally is 30 to 50% within 6 mo (see pp. 1439 and 2847). During pregnancy, bacterial vaginosis, gonorrhea, and genital chlamydial infection increase risk of preterm labor and premature rupture of the membranes. Routine prenatal care includes screening tests for these infections at the first prenatal visit. Syphilis testing is repeated during pregnancy if risk continues and at delivery for all women. Pregnant women who have any of these infections are treated with antimicrobials.

Treatment of bacterial vaginosis, gonorrhea, or chlamydial infection may prolong the interval from rupture of the membranes to delivery and may improve fetal outcome by decreasing fetal inflammation. Treating HIV with zidovudine or nevirapine reduces risk of transmission by two thirds; risk is probably lower (< 2%) with a combination of 2 or 3 antivirals (see p. 2858). These drugs are recommended despite potential toxic effects in the fetus and woman.

Pyelonephritis: Pyelonephritis increases risk of premature rupture of the membranes, preterm labor, and infant respiratory distress syndrome. Pregnant women with pyelonephritis are hospitalized for evaluation and treatment, primarily with urine culture plus sensitivities, IV antibiotics (eg, a 3rd-generation cephalosporin with or without an aminoglycoside), antipyretics, and hydration. Pyelonephritis is the most common nonobstetric cause of hospitalization during pregnancy. Oral antibiotics specific to the causative organism are begun 24 to 48 h after fever resolves and continued to complete the whole course of antibiotic therapy, usually 7 to 10 days. Prophylactic antibiotics (eg, nitrofurantoin, trimethoprim/sulfamethoxazole) with periodic urine cultures are continued for the rest of the pregnancy.

Acute surgical problems: Major surgery, particularly intra-abdominal, increases risk of preterm labor and fetal death. However, surgery is usually tolerated well by pregnant women and the fetus when appropriate supportive care and anesthesia (maintaining BP and oxygenation at normal levels) are provided, so physicians should not be reluctant to operate; delaying treatment of an abdominal emergency is far more dangerous.

After surgery, antibiotics and tocolytic drugs are given for 12 to 24 h. If nonemergency surgery is necessary during pregnancy, it is most safely done during the 2nd trimester.

Genital tract abnormalities: Structural abnormalities of the uterus and cervix (eg, uterine septum, bicornuate uterus) make fetal malpresentation, dysfunctional labor, and the need for cesarean delivery more likely. Although unlikely, uterine fibroids can cause placental abnormalities (eg, placenta previa), preterm labor, and recurrent spontaneous abortion. Fibroids may grow rapidly or degenerate during pregnancy; degeneration often causes severe pain and peritoneal signs. Cervical insufficiency (incompetence—see p. 2661) makes preterm delivery more likely. If women have had a myomectomy before pregnancy in which the uterine cavity was entered, cesarean delivery is required because uterine rupture is a risk during subsequent vaginal delivery. Uterine abnormalities that lead to poor obstetric outcomes often require surgical correction, which is done after delivery.
Maternal age: Adolescents, who account for 13% of all pregnancies, have an increased incidence of preeclampsia, preterm labor, and anemia, which often leads to fetal growth restriction. The cause, at least in part, is that adolescents tend to neglect prenatal care, frequently smoke, and have higher rates of STDs.

In women > 35, the incidence of preeclampsia is increased, as is that of gestational diabetes, dysfunctional labor, abruptio placenta, stillbirth, and placenta previa. These women are also more likely to have preexisting disorders (eg, CHTN, diabetes). Because risk of fetal chromosomal abnormalities increases as maternal age increases, genetic testing should be offered (see p. 2599).

Maternal weight: Pregnant women whose BMI was < 19.8 kg/m$^2$ before pregnancy are considered underweight, which predisposes to low birth weight (< 2.5 kg) in neonates. Such women are encouraged to gain at least 12.5 kg during pregnancy.

Pregnant women whose BMI was > 29.0 kg/m$^2$ before pregnancy are considered overweight, making maternal hypertension and diabetes, postterm pregnancy, fetal macrosomia, and the need for cesarean delivery more likely. Such women are encouraged to limit weight gain during pregnancy to < 11.5 kg.

Maternal height: Short (about < 152 cm) women are more likely to have a small pelvis, which can lead to dystocia with fetopelvic disproportion or shoulder dystocia. For short women, preterm labor and intrauterine growth restriction are also more likely.

Exposure to teratogens: Common teratogens (agents that cause fetal malformation) include infections, drugs, and physical agents. Malformations are most likely to result if exposure occurs between the 2nd and 8th wk after conception (the 4th to 10th wk after the last menstrual period), when organs are forming. Other adverse pregnancy outcomes are also more likely. Pregnant women exposed to teratogens are counseled about increased risks and referred for detailed ultrasound evaluation to detect malformations.

Common infections that may be teratogenic include herpes simplex, viral hepatitis, rubella, varicella, syphilis, toxoplasmosis, and cytomegalovirus and coxsackievirus infections.

Commonly used drugs that may be teratogenic include alcohol, tobacco, cocaine, and some prescription drugs (see Table 264-2).

Cigarette smoking is the most common addiction among pregnant women. Also, percentages of women who smoke and of those who smoke heavily appear to be increasing. Only 20% of smokers quit during pregnancy. Carbon monoxide and nicotine in cigarettes cause hypoxia and vasoconstriction, increasing risk of spontaneous abortion (fetal loss or delivery at < 20 wk), fetal growth restriction, abruptio placenta, placenta previa, premature rupture of the membranes, preterm birth, chorioamnionitis, and stillbirth. Neonates whose mothers smoke are also more likely to have anencephaly, congenital heart defects, orofacial clefts, sudden infant death syndrome, deficiencies in physical growth and intelligence, and behavioral problems. Smoking cessation or limitation reduces risks.

Alcohol is the most commonly used teratogen. Drinking alcohol during pregnancy increases risk of spontaneous abortion. Risk is probably related to amount of alcohol consumed, but no amount is known to be risk-free. Regular drinking decreases birth weight by about 1 to 1.3 kg. Binge drinking in particular, possibly as little as 45 mL of pure alcohol (equivalent to about 3 drinks) a day, can cause fetal alcohol syndrome. This syndrome occurs in 2.2/1000 live births; it includes fetal growth restriction, facial and cardiovascular defects, and neurologic dysfunction. It is a leading cause of intellectual disability (mental retardation) and can cause neonatal death due to failure to thrive.

Cocaine use has indirect fetal risks (eg, maternal stroke or death during pregnancy). It also directly causes fetal vasoconstriction and hypoxia. Repeated use increases risk of spontaneous abortion, fetal growth restriction, abruptio placenta, preterm birth, stillbirth, and congenital malformations (eg, CNS, GU, and skeletal malformations; isolated atresias).
Although marijuana's main metabolite can cross the placenta, recreational use of marijuana use does not consistently appear to increase risk of congenital malformations, fetal growth restriction, or postnatal neurobehavioral abnormalities.

**Prior stillbirth:** Causes of stillbirth (fetal death at > 20 wk) may be maternal, placental, or fetal (see p. 2675). Having had a stillbirth or late abortion (ie, at 16 to 20 wk) increases risk of fetal death in subsequent pregnancies. Fetal surveillance using antepartum testing (eg, nonstress testing, biophysical profile) is recommended. Treatment of maternal disorders (eg, CHTN, diabetes, infections) may lower risk of stillbirth in a current pregnancy.

**Prior preterm delivery:** Preterm delivery is delivery before 37 wk (see p. 2683). Previous preterm delivery due to preterm labor increases risk of future preterm deliveries; if the previous preterm neonate weighed < 1.5 kg, risk of preterm delivery in the next pregnancy is 50%. Women with prior preterm delivery due to

[Table 264-2. Drugs with Adverse Effects During Pregnancy]

- Ultrasound evaluation, including measurement of cervical length and shape, at 16 to 18 wk
- Uterine contraction monitoring
- Testing for bacterial vaginosis
- Measurement of fetal fibronectin

Women with prior preterm birth due to preterm labor or with shortening (< 25 mm) or funneling of the cervix should be given 17 α-OH-progesterone 250 mg IM once/wk.

**Prior neonate with a genetic or congenital disorder:** Risk of having a fetus with a chromosomal disorder is increased for most couples who have had a fetus or neonate with a chromosomal disorder (recognized or missed—see p. 2598). Recurrence risk for most genetic disorders is unknown. Most congenital malformations are multifactorial; risk of having a subsequent fetus with malformations is ≤ 1%. If couples have had a neonate with a genetic or chromosomal disorder, genetic screening is recommended. If couples have had a neonate with a congenital malformation, genetic screening, high-resolution ultrasonography, and evaluation by a maternal-fetal medicine specialist is recommended.

**Polyhydramnios (hydramnios) and oligohydramnios:** Polyhydramnios (excess amniotic fluid) can lead to severe maternal shortness of breath and preterm labor. Risk factors include uncontrolled maternal diabetes, multifetal pregnancy, isoimmunization, and fetal malformations (eg, esophageal atresia, anencephaly, spina bifida).

Oligohydramnios (deficient amniotic fluid) often accompanies congenital malformations of the fetal urinary tract and severe fetal growth restriction (< 3rd percentile). Also, Potter's syndrome with pulmonary hypoplasia or fetal surface compression abnormalities may result, usually in the 2nd trimester, and cause fetal death.

Polyhydramnios and oligohydramnios are suspected if uterine size does not correspond to gestational date or may be discovered incidentally via ultrasonography, which is diagnostic.

**Multifetal (multiple) pregnancy:** Multifetal pregnancy increases risk of fetal growth restriction, preterm labor, abruptio placentae, congenital malformations, perinatal morbidity and mortality, and, after delivery, uterine atony and hemorrhage (see p. 2680). Multifetal pregnancy is detected during routine ultrasonography at 18 to 20 wk.

**Prior birth injury:** Most cases of cerebral palsy and developmental delay are caused by factors unrelated to a birth injury.
Injuries such as brachial plexus damage can result from procedures such as forceps or vacuum extractor delivery but often result from intrauterine forces during labor or malposition during the last weeks of pregnancy. Previous shoulder dystocia is a risk factor for future dystocia, and the delivery records should be reviewed for potentially modifiable risk factors (eg, fetal macrosomia, operative vaginal delivery) that may have predisposed to the injury.
Chapter 265. Abnormalities of Pregnancy

Introduction

Abnormalities that develop during pregnancy may be directly related to the pregnancy or not (for nonobstetric disorders, see Ch. 263). Obstetric abnormalities increase the risk of morbidity or mortality for the woman, fetus, or neonate, as do such factors as maternal characteristics, problems in previous pregnancies, and drug use (see Ch. 264).

Abruptio Placentae

Abruptio placentae is premature separation of a normally implanted placenta from the uterus after 20 wk gestation. It is an obstetric emergency. Manifestations may include vaginal bleeding, uterine pain and tenderness, hemorrhagic shock, and disseminated intravascular coagulation. Diagnosis is clinical and sometimes by ultrasonography. Treatment is bed rest for mild symptoms and prompt delivery for severe or persistent symptoms.

Abruptio placentae occurs in 0.4 to 1.5% of all pregnancies; incidence peaks at 24 to 26 wk gestation.

Abruptio placentae may involve any degree of placental separation, from a few millimeters to complete detachment. Separation can be acute or chronic. Separation results in bleeding into the decidua basalis behind the placenta (retroplacentally). Cause is unknown.

Risk factors: Risk factors include the following:

• Older maternal age
• Hypertension (pregnancy-induced or chronic)
• Placental ischemia (ischemic placental disease) manifesting as intrauterine growth restriction
• Polyhydramnios
• Intra-amniotic infection (chorioamnionitis)
• Vasculitis
• Other vascular disorders
• Prior abruptio placentae
• Abdominal trauma
• Maternal thrombotic disorders
• Tobacco use
• Premature rupture of membranes
• Cocaine use (risk of up to 10%)

Complications: Complications include the following:

• Maternal blood loss (possibly with shock, disseminated intravascular coagulation [DIC], or both)
• Fetal ischemia (causing fetal distress or death if ischemia is acute or severe growth restriction if ischemia is chronic and mild)
Sometimes fetomaternal transfusion and Rh sensitization

**Symptoms and Signs**

Acute abruptio placentae may result in bright red blood exiting through the cervix (external hemorrhage). Blood may also remain behind the placenta (concealed hemorrhage). Severity of symptoms and signs depends on degree of separation and blood loss. As separation continues, the uterus may be painful, tender, and irritable to palpation. Hemorrhagic shock may occur, as may signs of DIC. Chronic abruptio placentae may cause continued or intermittent dark brown spotting.

Abruptio placentae may cause no or minimal symptoms and signs.

**Diagnosis**

• Combination of clinical, laboratory, and ultrasonographic findings

Diagnosis is suggested if any of the following occur during late pregnancy:

• Vaginal bleeding

• Uterine pain and tenderness

• Fetal distress or death

• Hemorrhagic shock

• DIC

• Tenderness or shock disproportionate to the degree of vaginal bleeding

The diagnosis should also be considered in women who have had abdominal trauma. If bleeding occurs during late pregnancy, placenta previa, which has similar symptoms, must be ruled out before pelvic examination is done; if placenta previa is present, examination may increase bleeding.

Evaluation includes the following:

• Fetal heart monitoring

• CBC

• Blood and Rh typing

• PT/PTT

• Serum fibrinogen and fibrin-split products (the most sensitive indicator)

• Transabdominal or pelvic ultrasonography

• Kleihauer-Betke test if the patient has Rh-negative blood—to calculate the dose of Rh\(_0^+(D)\) immune globulin needed

Fetal heart monitoring may detect a nonreassuring pattern or fetal death.

Transvaginal ultrasonography may be done if transabdominal ultrasonography rules out placenta previa. However, ultrasonography is insensitive; thus, diagnosis may ultimately be clinical.

**Treatment**
• Usually prompt delivery and aggressive supportive measures

• Trial of hospitalization and bed rest if the pregnancy is not near term and if mother and fetus are stable

Prompt cesarean delivery is usually indicated if any of the following is present:

• Maternal hemodynamic instability

• Nonreassuring fetal heart rate pattern

• Near-term pregnancy

However, oxytocin may be given to accelerate vaginal delivery, depending on the stage of labor and the rapidity of maternal and fetal deterioration (eg, oxytocin may be given if delivery appears imminent and the mother and fetus are stable). Amniotomy (deliberate rupture of membranes) is done early because it may accelerate delivery, preventing DIC.

Hospitalization and bed rest are advised if all of the following are present:

• Bleeding does not threaten the life of the mother or fetus.

• The fetal heart rate pattern is reassuring.

• The pregnancy is not near term.

This approach ensures that mother and fetus can be closely monitored and, if needed, rapidly treated. Corticosteroids should be considered (to accelerate fetal lung maturity) if gestational age is < 34 wk. If bleeding resolves and maternal and fetal status remains stable, ambulation and usually hospital discharge are allowed. If bleeding continues or if status deteriorates, prompt cesarean delivery is indicated.

Complications (eg, shock, DIC) are managed with aggressive replacement of blood and blood products.

**Cervical Insufficiency**

Cervical insufficiency (formerly called cervical incompetence) is painless cervical dilation resulting in delivery of a live fetus during the 2nd trimester. Transvaginal cervical ultrasonography during the 2nd trimester may help assess risk. Treatment is reinforcement of the cervical ring with suture material (cerclage).

Cervical insufficiency refers to presumed weakness of cervical tissue that contributes to or causes premature delivery not explained by another abnormality. Estimated incidence varies greatly (1/100 to 1/2000).

**Etiology**

The cause is not well understood but seems to involve some combination of structural abnormalities and biochemical factors (eg, inflammation, infection); these factors may be acquired or genetic.

**Risk factors**: Most women with cervical insufficiency do not have risk factors; however, the following risk factors have been identified:

• Congenital disorders of collagen synthesis (eg, Ehlers-Danlos syndrome)

• Prior cone biopsies (particularly when ≥ 1.7 to 2.0 cm of the cervix was removed)

• Prior deep cervical lacerations (usually secondary to vaginal or cesarean delivery)
• Prior excessive or rapid dilation with instruments (now uncommon)

• Mullerian duct defects (eg, bicornuate or septate uterus)

• ≥ 3 prior fetal losses during the 2nd trimester

**Recurrence:** Overall risk of recurrence of fetal loss due to cervical insufficiency is probably ≤ 30%, leading to the question of how large a role fixed structural abnormalities have. Risk is greatest for women with ≥ 3 prior 2nd-trimester fetal losses.

**Symptoms and Signs**

Cervical insufficiency is often asymptomatic until premature delivery occurs. Some women have earlier symptoms, such as vaginal pressure, vaginal bleeding or spotting, nonspecific abdominal or lower back pain, or vaginal discharge. The cervix may be soft, effaced, or dilated.

**Diagnosis**

• Transvaginal ultrasonography at > 16 wk for women with symptoms or risk factors

The diagnosis is suspected in women with risk factors or characteristic symptoms or signs. Then, transvaginal ultrasonography is done. Results are most accurate after 16 wk gestation. Suggestive ultrasonographic findings include cervical shortening to < 2.5 cm, cervical dilation, and protrusion of fetal membranes into the cervical canal.

Ultrasonography of women without symptoms or risk factors is not recommended because results do not accurately predict preterm delivery.

**Treatment**

• Cerclage

Cerclage (reinforcement of the cervical ring with suture material) appears to prevent preterm delivery in patients with ≥ 3 prior 2nd-trimester fetal losses. For other patients, the procedure should probably be done only if they have a history strongly suggesting cervical insufficiency and if cervical shortening is detected by ultrasonography before 22 to 24 wk gestation; restricting cerclage to such patients does not appear to increase risk of preterm delivery and reduces the number of cerclages currently being done by two thirds. Evidence does not support use of cerclage simply for ultrasound-detected cervical shortening.

Treatments such as corticosteroids, progesterone, and bed rest are often used when preterm labor is suspected.

**Intra-Amniotic Infection**

(Chorioamnionitis)

*Intra-amniotic infection (formerly called chorioamnionitis)* is infection of the chorion, amnion, amniotic fluid, placenta, or a combination. Infection increases risk of obstetric complications and problems in the fetus. Symptoms include fever, uterine tenderness, foul-smelling vaginal discharge, and maternal and fetal tachycardia. Diagnosis is by specific criteria or, for subclinical infection, analysis of amniotic fluid. Treatment includes broad-spectrum antibiotics and delivery.

Intra-amniotic infection typically results from an infection that ascends through the genital tract.

**Risk factors:** Risk factors include the following:

• Preterm labor
• Nulliparity

• Meconium-stained amniotic fluid

• Internal fetal or uterine monitoring

• Presence of genital tract pathogens (eg, those that cause sexually transmitted diseases or bacterial vaginosis, group B streptococci)

• Digital examinations during labor in women with ruptured membranes

• Long labor

• Preterm premature rupture of membranes

Complications: Intra-amniotic infection can cause as well as result from preterm premature rupture of membranes or preterm delivery. This infection accounts for 50% of deliveries before 30 wk gestation. It occurs in 33% of women who have preterm labor with intact membranes, 40% who have premature rupture of membranes (PROM) and are having contractions when admitted, and 75% who go into labor after admission for PROM.

Fetal complications include increased risk of the following:

• Preterm delivery

• Apgar score < 3

• Infection (eg, sepsis, pneumonia, meningitis)

• Seizures

• Cerebral palsy

• Death

Maternal complications include increased risk of the following:

• Bacteremia

• Need for cesarean delivery

• Uterine atony

• Postpartum hemorrhage

• Pelvic abscess

• Thromboembolism

• Wound complications

Septic shock, coagulopathy, and adult respiratory distress syndrome are also risks but are uncommon if infection is treated.

Symptoms and Signs

Intra-amniotic infection typically causes fever. Other findings can include maternal tachycardia, fetal tachycardia, uterine tenderness, and foul-smelling amniotic fluid. However, infection may not cause typical
symptoms (ie, subclinical infection).

**Diagnosis**

- Clinical criteria
- Amniocentesis for suspected subclinical infection

Diagnosis usually requires a maternal temperature of > 38° C (> 100.4° F) plus ≥ 2 of the following:

- Maternal WBC count > 15,000 cells/μL
- Maternal tachycardia (heart rate > 100 beats/min)
- Fetal tachycardia (heart rate > 160 beats/min)
- Uterine tenderness
- Foul-smelling amniotic fluid

Presence of a single symptom or sign, which may have other causes, is less reliable. For example, uterine pain and tenderness may result from abruptio placentae. Maternal tachycardia may be due to pain, epidural anesthesia, or drugs (eg, ephedrine); fetal tachycardia may be due to maternal use of drugs or fetal hypoxemia. Maternal and fetal heart rates also increase during fever. However, if intra-amniotic infection is absent, heart rates return to baseline as these conditions resolve. If fetal or maternal tachycardia is disproportionate to or occurs without such conditions or if it persists despite resolution of these conditions, intra-amniotic infection is suspected.

**Subclinical infection:** Refractory preterm labor (persisting despite tocolysis) may suggest subclinical infection. If membranes rupture prematurely before term, clinicians should also consider subclinical infection so that they can determine whether induction of labor is indicated.

Amniocentesis with culture of amniotic fluid is the best way to diagnose subclinical infection. The following fluid findings suggest infection:

- Presence of any bacteria or leukocytes using Gram staining
- Glucose level < 15 mg/dL
- WBC count > 30 cells/μL
- Leukocyte esterase level at trace or higher levels

Other diagnostic tests for subclinical infection are under study.

**Treatment**

- Broad-spectrum antibiotics

Treatment is broad-spectrum IV antibiotics plus delivery. A typical antibiotic regimen is ampicillin 2 g IV q 6 h plus gentamicin 1.5 mg/kg IV q 8 h. The antibiotics reduce risk of morbidity due to infection for mother and neonate.

Risk of intra-amniotic infection is decreased by avoiding or minimizing digital pelvic examinations in patients with preterm PROM (see p. 2682).

**Ectopic Pregnancy**
In ectopic pregnancy, implantation occurs in a site other than the endometrial lining of the uterine cavity—in the fallopian tube, uterine cornua, cervix, ovary, or abdominal or pelvic cavity. Ectopic pregnancies cannot be carried to term and eventually rupture or involute. Early symptoms and signs include pelvic pain, vaginal bleeding, and cervical motion tenderness. Syncope or hemorrhagic shock can occur with rupture. Diagnosis is by measurement of the β subunit of human chorionic gonadotropin and ultrasonography. Treatment is with laparoscopic or open surgical resection or with IM methotrexate.

Incidence of ectopic pregnancy is about 2/100 diagnosed pregnancies.

Etiology

Tubal lesions increase risk. Factors that particularly increase risk include

- Prior ectopic pregnancy (10 to 25% risk of recurrence)
- History of pelvic inflammatory disease (particularly due to *Chlamydia trachomatis*)
- Prior abdominal or particularly tubal surgery, including tubal ligation

Other specific risk factors include

- Intrauterine device (IUD) use
- Infertility
- Multiple sex partners
- Cigarette smoking
- Exposure to diethylstilbestrol
- Prior induced abortion

Pregnancy is less likely to occur when an IUD is in place; however, about 5% of such pregnancies are ectopic.

Pathophysiology

The most common site of ectopic implantation is a fallopian tube, followed by the uterine cornua. Pregnancies in the cervix, a cesarean delivery scar, an ovary, the abdomen, or fallopian tube interstitium are rare.

Heterotopic pregnancy (simultaneous ectopic and intrauterine pregnancies) occurs in only 1/10,000 to 30,000 pregnancies but may be more common among women who have had ovulation induction or used assisted reproductive techniques such as in vitro fertilization and gamete intrafallopian tube transfer (GIFT); in these women, the overall reported ectopic pregnancy rate is ≤ 1%.

The structure containing the fetus usually ruptures after about 6 to 16 wk. Rupture results in bleeding that can be gradual or rapid enough to cause hemorrhagic shock. Intraperitoneal blood irritates the peritoneum. The later the rupture, the more rapidly blood is lost and the higher the risk of death.

Symptoms and Signs

Symptoms vary and are often absent until rupture occurs. Most patients have pelvic pain (which is sometimes crampy), vaginal bleeding, or both. Menses may or may not be delayed or missed, and patients may not be aware that they are pregnant.
Rupture may be heralded by sudden, severe pain, followed by syncope or by symptoms and signs of hemorrhagic shock or peritonitis. Rapid hemorrhage is more likely in ruptured cornual pregnancies.

Cervical motion tenderness, unilateral or bilateral adnexal tenderness, or an adnexal mass may be present. The uterus may be slightly enlarged (but often less than anticipated based on date of the last menstrual period).

**Diagnosis**

- Serum $\beta$-human chorionic gonadotropin ($\beta$-hCG) levels
- Pelvic ultrasonography
- Sometimes laparoscopy

Ectopic pregnancy is suspected in any female of reproductive age with pelvic pain, vaginal bleeding, or unexplained syncope or hemorrhagic shock, regardless of sexual, contraceptive, and menstrual history. Findings of physical (including pelvic) examination are neither sensitive nor specific.

The first step is doing a urine pregnancy test, which is about 99% sensitive for pregnancy (ectopic and otherwise). If urine $\beta$-hCG is negative and if clinical findings do not strongly suggest ectopic pregnancy, further evaluation is unnecessary unless symptoms recur or worsen. If urine $\beta$-hCG is positive or if clinical findings strongly suggest ectopic pregnancy, quantitative serum $\beta$-hCG and pelvic ultrasonography are indicated.

If quantitative serum $\beta$-hCG is $< 5$ mIU/mL, ectopic pregnancy is excluded. If ultrasonography detects an intrauterine gestational sac, ectopic pregnancy is extremely unlikely except in women who have used assisted reproductive techniques (which increase risk of heterotopic pregnancy); however, cornual and intra-abdominal pregnancies may appear to be intrauterine pregnancies. Ultrasonographic findings suggesting ectopic pregnancy (noted in 16 to 32%) include complex (mixed solid and cystic) masses, particularly in the adnexa, and free fluid in the cul-de-sac.

If serum $\beta$-hCG is above a certain level (called the discriminatory zone), ultrasonography should detect a gestational sac in patients with an intrauterine pregnancy. This level is usually about 2000 mIU/mL. If the $\beta$-hCG level is higher than the discriminatory zone and an intrauterine gestational sac is not detected, an ectopic pregnancy is likely. Use of transvaginal and color Doppler ultrasonography may improve detection rates.

If the $\beta$-hCG level is below the discriminatory zone and ultrasonography is unremarkable, patients may have an early intrauterine pregnancy or an ectopic pregnancy. If clinical evaluation suggests ectopic pregnancy (eg, signs of significant hemorrhage or peritoneal irritation), diagnostic laparoscopy may be necessary for confirmation. If ectopic pregnancy appears unlikely and patients are stable, serum levels of $\beta$-hCG can be measured serially on an outpatient basis (typically every 2 days). Normally, the level doubles every 1.4 to 2.1 days up to 41 days; in ectopic pregnancy (and in abortions), levels may be lower than expected by dates and usually do not double as rapidly. If $\beta$-hCG levels do not increase as expected or if they decrease, the diagnoses of spontaneous abortion and ectopic pregnancy are reconsidered.

**Prognosis**

Ectopic pregnancy is fatal to the fetus, but if treatment occurs before rupture, maternal death is very rare. In the US, ectopic pregnancy probably accounts for 9% of pregnancy-related maternal deaths.

**Treatment**

- Surgical resection (usually)
- Methotrexate for some small, unruptured ectopic pregnancies
Surgical resection: Hemodynamically unstable patients require immediate laparotomy and treatment of hemorrhagic shock (see p. 2296). For stable patients, treatment is usually laparoscopic surgery; sometimes laparotomy is required. If possible, salpingotomy, usually using cautery, high-frequency (harmonic) ultrasound devices, or a laser, is done to conserve the tube, and the products of conception are evacuated.

Salpingectomy is indicated in any of the following cases:

- When ectopic pregnancies recur or are > 5 cm
- When the tubes are severely damaged
- When no future childbearing is planned

Only the irreversibly damaged portion of the tube is removed, maximizing the chance that tubal repair can restore fertility. The tube may or may not be repaired. After a cornual pregnancy, the tube and ovary involved can usually be salvaged, but occasionally repair is impossible, making hysterectomy necessary.

Methotrexate: If unruptured tubal pregnancies are < 3.0 cm in diameter, no fetal heart activity is detected, and the β-hCG level is < 5,000 mIU/mL ideally but up to 15,000 mIU/mL, women can be given a single dose of methotrexate 50 mg/m² IM. β-hCG measurement and ultrasonography are repeated on about days 4 and 7. If the β-hCG level does not decrease by 15%, a 2nd dose of methotrexate or surgery is needed. Alternatively, the β-hCG level is measured on days 1 and 7, and a 2nd dose of methotrexate is given if the level does not decrease by 25%. About 15 to 20% of women treated with methotrexate eventually require a 2nd dose.

The β-hCG level is measured weekly until it is undetectable. Success rates with methotrexate are about 87%; 7% of women have serious complications (eg, rupture). Surgery is indicated when methotrexate is ineffective.

Erythroblastosis Fetalis

Erythroblastosis fetalis is hemolytic anemia in the fetus or neonate caused by transplacental transmission of maternal antibodies to fetal RBCs. The disorder usually results from incompatibility between maternal and fetal blood groups, often Rh₀(D) antigens. Diagnosis begins with prenatal maternal antigenic and antibody screening and may require paternal screening, serial measurement of maternal antibody titers, and fetal testing. Treatment may involve intrauterine fetal transfusion or neonatal exchange transfusion. Prevention is Rh₀(D) immune globulin injection for women at risk.

Erythroblastosis fetalis classically results from Rh₀(D) incompatibility, which may develop when a woman with Rh-negative blood is impregnated by a man with Rh-positive blood and conceives a fetus with Rh-positive blood (see also p. 2784). Other fetomaternal incompatibilities that can cause erythroblastosis fetalis involve the Kell, Duffy, Kidd, MNSs, Lutheran, Diego, Xg, P, Ee, and Cc antigen systems, as well as other antigens. Incompatibilities of ABO blood types do not cause erythroblastosis fetalis.

Pathophysiology

Fetal RBCs normally move across the placenta to the maternal circulation throughout pregnancy. Movement is greatest at delivery or termination of pregnancy. Movement of large volumes (eg, 10 to 150 mL) is considered significant fetomaternal hemorrhage; it can occur after trauma and sometimes after delivery or termination of pregnancy. In women who have Rh-negative blood and who are carrying a fetus with Rh-positive blood, fetal RBCs stimulate maternal antibody production against the Rh antigens. The larger the fetomaternal hemorrhage, the more antibodies produced. The mechanism is the same when other antigen systems are involved; however, Kell antibody incompatibility also directly suppresses RBC production in bone marrow.
Other causes of maternal anti-Rh antibody production include injection with needles contaminated with Rh-positive blood and inadvertent transfusion of Rh-positive blood.

No complications develop during the initial sensitizing pregnancy; however, in subsequent pregnancies, maternal antibodies cross the placenta and lyse fetal RBCs, causing anemia, hypoalbuminemia, and possibly high-output heart failure or fetal death. Anemia stimulates fetal bone marrow to produce and release immature RBCs (erythroblasts) into fetal peripheral circulation (erythroblastosis fetalis). Hemolysis results in elevated indirect bilirubin levels in neonates, causing kernicterus (see p. 2793). Usually, isoimmunization does not cause symptoms in pregnant women.

**Diagnosis**

- Maternal blood and Rh typing and reflex antibody screening
- Serial antibody level measurements and sometimes middle cerebral artery blood flow measurements for pregnancies at risk

At the first prenatal visit, all women are screened for blood type, Rh type, and anti-Rh\(\text{0}(\text{D})\) and other antibodies that are formed in response to antigens and that can cause erythroblastosis fetalis (reflex antibody screening). If women have Rh-negative blood and test positive for anti-Rh\(\text{0}(\text{D})\) or they test positive for another antibody that can cause erythroblastosis fetalis, the father's blood type and zygosity (if paternity is certain) are determined. If he has Rh-negative blood and is negative for the antigen corresponding to the antibody identified in the mother, no further testing is necessary. If he has Rh-positive blood or has the antigen, maternal anti-Rh antibody titers are measured. If titers are positive but less than a laboratory-specific critical value (usually 1:8 to 1:32), they are measured monthly until 24 wk, then every 2 wk. If the critical value is exceeded, fetal middle cerebral artery blood flow is measured at intervals of 1 to 2 wk depending on titers and patient history; the purpose is to detect high-output heart failure, indicating high risk of anemia. Elevated blood flow for gestational age should prompt percutaneous umbilical blood sampling to obtain a sample of fetal blood. If paternity is reasonably certain and the father is likely to be heterozygous for Rh\(\text{0}(\text{D})\), the fetus's Rh type is determined. If fetal blood is Rh positive or status is unknown and if middle cerebral artery flow is elevated, fetal anemia is likely.

**Treatment**

- Fetal blood transfusions
- Delivery at 32 to 34 wk

If fetal blood is Rh negative or if middle cerebral artery blood flow remains normal, pregnancy can continue to term untreated. If fetal anemia is likely, the fetus can be given intravascular intrauterine blood transfusions by a specialist at an institution equipped to care for high-risk pregnancies. Transfusions occur every 1 to 2 wk until fetal lung maturity is confirmed (usually at 32 to 34 wk), when delivery should be done. Corticosteroids should be given before the first transfusion if the pregnancy is > 24 wk, possibly > 23 wk.

Neonates with erythroblastosis are immediately evaluated by a pediatrician to determine need for exchange transfusion (see p. 2786).

**Prevention**

Prevention involves giving the mother

- Rh\(\text{0}(\text{D})\) immune globulin at 28 wk gestation and within 72 h of pregnancy termination

Delivery should be as atraumatic as possible. Manual removal of the placenta should be avoided because it may force fetal cells into maternal circulation.
Maternal sensitization and antibody production due to Rh incompatibility can be prevented by giving the woman Rh
0 (D) immune globulin. This preparation contains high titers of anti-Rh antibodies, which neutralize Rh-positive fetal RBCs. Because fetomaternal transfer and likelihood of sensitization is greatest at termination of pregnancy, the preparation is given within 72 h after termination of each pregnancy, whether by delivery, abortion, or treatment of ectopic pregnancy. The standard dose is 300 μg IM. A rosette test can be used to rule out significant fetomaternal hemorrhage, and if results are positive, a Kleihauer-Betke (acid elution) test can measure the amount of fetal blood in the maternal circulation. If test results indicate fetomaternal hemorrhage is massive (> 30 mL whole blood), additional injections (300 μg for every 30 mL of fetal whole blood, up to 5 doses within 24 h) are necessary.

Treatment at termination of pregnancy is occasionally ineffective because sensitization occurred earlier during pregnancy. Therefore, at about 28 wk, all pregnant women with Rh-negative blood and no known prior sensitization are given a dose. Some experts recommend a 2nd dose if delivery has not occurred by 40 wk. Rh0(D) immune globulin should also be given after any episode of vaginal bleeding and after amniocentesis or chorionic villus sampling. Anti-Rh antibodies persist for > 3 mo after one dose.

Pemphigoid Gestationis

(Herpes Gestationis)

Pemphigoid gestationis is a pruritic papular and vesicobullous eruption that occurs during pregnancy or postpartum. Diagnosis is clinical or by skin biopsy. Treatment is with topical or systemic corticosteroids.

Pemphigoid gestationis appears to be an autoimmune phenomenon, probably caused by an IgG antibody to a 180-kD antigen in the basement membrane zone of the epidermis. Although previously called herpes gestationis, this disorder is not caused by herpesvirus.

Pemphigoid gestationis occurs in 1/2,000 to 50,000 pregnancies; it usually begins during the 2nd or 3rd trimester but may begin during the 1st trimester or immediately postpartum. It usually recurs with subsequent pregnancies and occurs after oral contraceptive use in about 25% of women. Flare-ups can occur during subsequent menses or ovulation.

Most fetuses are unaffected; however, transient lesions occur in < 5% of neonates born to mothers with pemphigoid gestationis. Risks are increased after premature delivery and in infants who are small for gestational age.

Symptoms and Signs

The rash is very pruritic. Lesions often start around the umbilicus, then become widespread. Vesicles and bullae are the most specific lesions; erythematous plaques may develop. The palms, soles, trunk, buttocks, and extremities may be affected but usually not the face or mucous membranes.

The rash worsens during labor or immediately postpartum in up to 75% of women, typically remitting within a few weeks or months.

Neonates may have erythematous plaques or vesicles that resolve spontaneously in a few weeks.

Diagnosis

• Clinical evaluation

• Sometimes biopsy with direct immunofluorescence

Pemphigoid gestationis may be confused clinically with several other pruritic eruptions of pregnancy, particularly pruritic urticarial papules and plaques of pregnancy. Pemphigoid gestationis can often be distinguished because it usually begins in the periumbilical area; pruritic urticarial papules and plaques of pregnancy usually begin in the striae.
Direct immunofluorescence examination of perilesional skin is diagnostic. It detects a linear band of C3 at the basement membrane zone.

**Treatment**

- Corticosteroids topically or, for severe symptoms, orally

For mild symptoms, topical corticosteroids (eg, 0.1% triamcinolone acetonide cream up to 6 times/day) may be effective. Prednisone (eg, 40 mg po once/day) relieves moderate or severe pruritus and prevents new lesions; dose is tapered until few new lesions erupt, but it may need to be increased if symptoms become more severe (eg, during labor). Systemic corticosteroids given late in pregnancy do not seem to harm the fetus.

Nonsedating oral antihistamines can also be used to relieve pruritus.

**Hyperemesis Gravidarum**

Hyperemesis gravidarum is uncontrollable vomiting during pregnancy that results in dehydration, weight loss, and ketosis. Diagnosis is clinical and by measurement of urine ketones and renal function. Treatment is with temporary suspension of oral intake and with IV fluids, antiemetics if needed, and vitamin and electrolyte repletion.

Pregnancy frequently causes nausea and vomiting; the cause appears to be rapidly increasing levels of estrogens or the β subunit of human chorionic gonadotropin (β-hCG). Vomiting usually develops at about 5 wk gestation, peaks at about 9 wk, and disappears by about 16 or 18 wk. It usually occurs in the morning (as so-called morning sickness), although it can occur any time of day. Women with morning sickness continue to gain weight and do not become dehydrated. Hyperemesis gravidarum is probably an extreme form of normal nausea and vomiting during pregnancy. It is distinguished because it causes the following:

- Weight loss (> 5% of weight)
- Dehydration
- Ketosis
- Electrolyte abnormalities (in many women)

Psychologic factors (eg, ambivalence, anxiety) may trigger hyperemesis gravidarum. Hyperemesis gravidarum may cause mild, transient hyperthyroidism. Hyperemesis gravidarum that persists past 16 to 18 wk is uncommon but may seriously damage the liver, causing severe centrilobular necrosis or widespread fatty degeneration, and may cause Wernicke's encephalopathy or esophageal rupture.

**Diagnosis**

- Clinical evaluation (including serial weights)
- Urine ketones
- Exclusion of other causes (eg, acute abdomen)

If hyperemesis gravidarum is suspected, urine ketones, thyroid-stimulating hormone, serum electrolytes, BUN, creatinine, AST, ALT, Mg, P, and sometimes body weight are measured. Obstetric ultrasonography should be done to rule out hydatidiform mole and multifetal pregnancy.

Other disorders that can cause vomiting must be excluded; they include gastroenteritis, hepatitis, appendicitis, cholecystitis, other biliary tract disorders, peptic ulcer disease, intestinal obstruction,
hyperthyroidism not caused by hyperemesis gravidarum (eg, caused by Graves' disease), gestational trophoblastic disease, nephrolithiasis, pyelonephritis, diabetic ketoacidosis or gastroparesis, benign intracranial hypertension, and migraine headaches. Prominent symptoms in addition to nausea and vomiting often suggest another cause. Tests for alternative diagnoses are done based on laboratory, clinical, or ultrasound findings.

**Treatment**

- Temporary suspension of oral intake, followed by gradual resumption
- Fluids, thiamin, multivitamins, and electrolytes as needed
- Antiemetics if needed

At first, patients are given nothing by mouth. Initial treatment is IV fluid resuscitation, beginning with 2 L of Ringer's lactate infused over 3 h to maintain a urine output of > 100 mL/h. If dextrose is given, thiamin 100 mg should be given IV first, to prevent Wernicke's encephalopathy. This dose of thiamin should be given daily for 3 days.

Subsequent fluid requirements vary with patient response but may be as much as 1 L q 4 h or so for up to 3 days. Electrolyte deficiencies are treated; K, Mg, and P are replaced as needed. Care must be taken not to correct low plasma Na levels too quickly because too rapid correction can cause osmotic demyelination syndrome.

Vomiting that persists after initial fluid and electrolyte replacement is treated with an antiemetic taken as needed; antiemetics include

- Vitamin B₆ 10 to 25 mg po q 8 h or q 6 h
- Doxylamine 12.5 mg po q 8 h or q 6 h (can be taken in addition to vitamin B₆)
- Promethazine 12.5 to 25 mg po, IM, or rectally q 4 to 8 h
- Metoclopramide 5 to 10 mg IV or po q 8 h
- Ondansetron 8 mg po or IM q 12 h
- Prochlorperazine 5 to 10 mg po or IM q 3 to 4 h

After dehydration and acute vomiting resolve, small amounts of oral liquids are given. Patients who cannot tolerate any oral fluids after IV rehydration and antiemetics may need to be hospitalized or given IV therapy at home and take nothing by mouth for a longer period (sometimes several days or more). Once patients tolerate fluids, they can eat small, bland meals, and diet is expanded as tolerated. IV vitamin therapy is required initially and until vitamins can be taken by mouth.

If treatment is ineffective, TPN may be necessary, and corticosteroids, although controversial, can be tried; eg, methylprednisolone 16 mg q 8 h po or IV may be given for 3 days, then tapered over 2 wk to the lowest effective dose. Corticosteroids should be used for < 6 wk and with extreme caution. They should not be used during fetal organogenesis (between 20 and 56 days after fertilization); use of these drugs during the 1st trimester is weakly associated with facial clefting. The mechanism for corticosteroids' effect on nausea is unclear.

If progressive weight loss, jaundice, or persistent tachycardia occurs despite treatment, termination of the pregnancy should be considered.

**Placenta Previa**

Placenta previa is implantation of the placenta over or near the internal os of the cervix.
Typically, painless vaginal bleeding with bright red blood occurs after 20 wk gestation. Diagnosis is by transvaginal or abdominal ultrasonography. Treatment is bed rest for minor vaginal bleeding before 36 wk gestation, with cesarean delivery at 36 wk if fetal lung maturity is documented. If bleeding is severe or refractory or if fetal status is nonreassuring, immediate delivery, usually cesarean, is indicated.

Placenta previa may be total (covering the internal os completely), partial (covering part of the os), or marginal (at the edge of the os), or the placenta may be low-lying (near the os without reaching it). Incidence of placenta previa is 1/200 deliveries. If placenta previa occurs during early pregnancy, it usually resolves by 20 wk as the uterus enlarges.

Risk factors: Risk factors include the following:

- Multiparity
- Prior cesarean delivery
- Uterine abnormalities that inhibit normal implantation (eg, fibroids, prior curettage)
- Smoking
- Multifetal pregnancy
- Older maternal age

Complications: For patients with placenta previa or a low-lying placenta, risks include fetal malpresentation, preterm premature rupture of the membranes, fetal growth restriction, vasa previa, and velamentous insertion of the umbilical cord.

Symptoms and Signs

Symptoms usually begin during late pregnancy. Then, sudden, painless vaginal bleeding often begins; the blood may be bright red, and bleeding may be heavy, sometimes resulting in hemorrhagic shock. In some patients, uterine contractions accompany bleeding.

Diagnosis

- Transvaginal ultrasonography

Placenta previa is considered in all women with vaginal bleeding after 20 wk. If placenta previa is present, digital pelvic examination may increase bleeding, sometimes causing sudden, massive bleeding; thus, if vaginal bleeding occurs after 20 wk, digital pelvic examination is contraindicated unless placenta previa is first ruled out by ultrasonography. Placenta previa frequently cannot be distinguished from abruptio placentae except by ultrasonography. Transvaginal ultrasonography is an accurate, safe way to diagnose placenta previa.

In all women with suspected symptomatic placenta previa, fetal heart rate monitoring is indicated. Unless the case is an emergency (requiring immediate delivery), amniotic fluid is tested at 36 wk to assess fetal lung maturity and thus document whether delivery at this time is safe.

Treatment

- Hospitalization and bed rest for a first episode of bleeding before 36 wk
- Delivery if mother or fetus is unstable or if fetal lungs are mature

For a first (sentinel) episode of vaginal bleeding before 36 wk, management consists of hospitalization, bed rest, and avoidance of sexual intercourse, which can cause bleeding by initiating contractions or
causing direct trauma. If bleeding stops, ambulation and usually hospital discharge are allowed.

Some experts recommend giving corticosteroids to accelerate fetal lung maturity when early delivery may become necessary and gestational age is < 34 wk. Typically for a 2nd bleeding episode, patients are readmitted and kept for observation until delivery.

Delivery is indicated for any of the following:

- Heavy or uncontrolled bleeding
- Nonreassuring results of fetal heart monitoring
- Maternal hemodynamic instability
- Fetal lung maturity (usually at 36 wk)

Delivery is almost always cesarean, but vaginal delivery may be possible for women with a low-lying placenta if the fetal head effectively compresses the placenta and labor is already advanced or if the pregnancy is < 23 wk and rapid delivery is expected.

Hemorrhagic shock is treated (see p. 2296). Prophylactic Rh0(D) immune globulin should be given if the mother has Rh-negative blood.

**Placenta Accreta**

Placenta accreta is an abnormally adherent placenta, resulting in delayed delivery of the placenta. Placental function is normal, but trophoblastic invasion extends beyond the normal boundary (called Nitabuch's layer). In such cases, manual removal of the placenta, unless scrupulously done, results in massive postpartum hemorrhage. Prenatal diagnosis is by ultrasonography. Treatment is usually with scheduled cesarean hysterectomy.

In placenta accreta, the placental villi are not contained by uterine decidual cells, as occurs normally, but extend to the myometrium. Related abnormalities include placenta increta (invasion of chorionic villi into the myometrium) and placenta percreta (penetration of chorionic villi into or through the uterine serosa). All 3 abnormalities cause similar problems.

**Etiology**

The main risk factor for placenta accreta is

- Prior uterine surgery

In the US, placenta accreta most commonly occurs in women who have had placenta previa after cesarean delivery in a previous pregnancy. Incidence of placenta accreta has increased from about 1/30,000 in the 1950s to about 1/500 to 2000 in the 1980s and 1990s. Risk in women who have had placenta previa increases from about 10 to 25% if they have had one cesarean delivery to about 50 to 67% if they have had > 4 cesarean deliveries.

Other risk factors include the following:

- Maternal age > 35
- Increasing parity
- Submucosal fibroids
- Smoking
Endometrial lesions such as Asherman's syndrome

Symptoms and Signs

Usually, women present with profuse vaginal bleeding during manual separation of the placenta after delivery of the fetus.

Diagnosis

- Ultrasonography for women at risk

Thorough evaluation of the uteroplacental interface by ultrasonography (transvaginal or transabdominal) is warranted in women at risk; it can be done periodically, beginning at 20 to 24 wk gestation. If ultrasonography is inconclusive, MRI or Doppler flow studies may help.

During delivery, the disorder is suspected if the placenta has not been delivered within 30 min of the infant's delivery, if no plane of separation can be created with attempts at manual removal, or if placental traction causes large-volume hemorrhage. When placenta accreta is suspected, laparotomy with preparation for large-volume hemorrhage is required.

Treatment

- Scheduled cesarean hysterectomy

Preparation for delivery is best. Unless the patient objects, scheduled cesarean hysterectomy is done as soon as fetal lung maturity is confirmed (usually at about 35 to 36 wk).

If cesarean hysterectomy is done (preferably by an experienced pelvic surgeon), a fundal incision followed by immediate clamping of the cord after delivery can help minimize blood loss. The placenta is left in situ while hysterectomy is done. Balloon occlusion of the aorta or internal iliac vessels may be done preoperatively but requires a skilled angiographer and may cause serious thromboembolic complications.

Preeclampsia and Eclampsia

Preeclampsia is new-onset hypertension and proteinuria after 20 wk gestation. Eclampsia is unexplained generalized seizures in patients with preeclampsia. Diagnosis is clinical and by urine protein measurement. Treatment is usually with IV Mg sulfate and delivery at term.

Preeclampsia affects 3 to 7% of pregnant women. Preeclampsia and eclampsia develop after 20 wk gestation; up to 25% of cases develop postpartum, most often within the first 4 days but sometimes up to 6 wk postpartum.

Untreated preeclampsia usually smolders for a variable time, then suddenly progresses to eclampsia, which occurs in 1/200 patients with preeclampsia. Untreated eclampsia is usually fatal.

Etiology

Etiology is unknown; however, risk factors include the following:

- Nulliparity
- Preexisting chronic hypertension
- Vascular disorders (eg, renal disorders, diabetic vasculopathy)
- Pregestational or gestational diabetes
- Older (> 35) or very young (eg, < 17) maternal age
• Family history of preeclampsia
• Preeclampsia or poor outcome in previous pregnancies
• Multifetal pregnancy
• Obesity
• Thrombotic disorders (eg, antiphospholipid antibody syndrome—see p. 975)

Pathophysiology

Pathophysiology of preeclampsia and eclampsia is poorly understood. Factors may include poorly developed uterine placental spiral arterioles (which decrease uteroplacental blood flow during late pregnancy), a genetic abnormality on chromosome 13, immunologic abnormalities, and placental ischemia or infarction. Lipid peroxidation of cell membranes induced by free radicals may contribute to preeclampsia.

Complications: Fetal growth restriction may result. Diffuse or multifocal vasospasm can result in ischemia, eventually damaging multiple organs, particularly the brain, kidneys, and liver. Factors that may contribute to vasospasm include decreased prostacyclin (an endothelium-derived vasodilator), increased endothelin (an endothelium-derived vasoconstrictor), and increased soluble Flt-1 (a circulating receptor for vascular endothelial growth factor).

The coagulation system is activated, possibly secondary to endothelial cell dysfunction, leading to platelet activation. The HELLP syndrome (hemolysis, elevated liver function tests, and low platelet count) develops in 10 to 20% of women with severe preeclampsia or eclampsia; this incidence is about 100 times that for all pregnancies (1 to 2/1000).

Symptoms and Signs

Preeclampsia may be asymptomatic or may cause edema or excessive weight gain. Non-dependent edema, such as facial or hand swelling (the patient's ring may no longer fit her finger), is more specific than dependent edema. Reflex reactivity may be increased, indicating neuromuscular irritability, which can progress to seizures (eclampsia). Petechiae may develop, as may other signs of bleeding.

Severe preeclampsia may cause organ damage; manifestations may include headache, visual disturbances, confusion, epigastric or right upper quadrant abdominal pain (reflecting hepatic ischemia or capsular distention), nausea, vomiting, dyspnea (reflecting pulmonary edema or acute respiratory distress syndrome [ARDS]), stroke (rarely), and oliguria (reflecting decreased plasma volume or ischemic acute tubular necrosis).

Diagnosis

• New-onset hypertension (BP > 140/90 mm Hg) plus new unexplained proteinuria > 300 mg/24 h after 20 wk

Diagnosis is suggested by symptoms or presence of hypertension, defined as systolic BP > 140 mm Hg, diastolic BP > 90 mm Hg, or both. Except in emergencies, hypertension should be documented in > 2 measurements taken > 6 h apart. Urine protein excretion is measured in a 24-h collection.

The following points help differentiate among hypertensive disorders in pregnant women:

• Chronic hypertension is identified if hypertension precedes pregnancy, is present at < 20 wk gestation, or persists for > 6 wk (usually > 12 wk) postpartum (even if hypertension is first documented at > 20 wk gestation). Chronic hypertension may be masked during early pregnancy by the physiologic decrease in BP.
• **Gestational hypertension** is hypertension without proteinuria or other findings of preeclampsia; it first occurs at > 20 wk gestation in women known not to have hypertension before pregnancy and resolves by 12 wk (usually by 6 wk) postpartum.

• **Preeclampsia superimposed on chronic hypertension** is diagnosed when a woman with hypertension develops new-onset proteinuria after 20 wk gestation.

• **Preeclampsia** is diagnosed in women who have known hypertension and proteinuria if BP increases to ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic in the last half of pregnancy even if they do not have proteinuria, particularly if the increase is accompanied by symptoms, increased liver enzymes (aminotransferases), or thrombocytopenia.

**Further evaluation:** If preeclampsia is diagnosed, tests include urinalysis, CBC, platelet count, uric acid, liver function tests, and measurement of serum electrolytes, BUN, creatinine, and creatine clearance. The fetus is assessed with a nonstress test or biophysical profile.

**HELLP syndrome** is suggested by micro-angiopathic findings (eg, schistocytes, helmet cells) on peripheral blood smears, elevated liver enzymes, and a low platelet count.

**Severe preeclampsia** is differentiated from mild by one or more of the following:

- CNS dysfunction (eg, blurred vision, scotomata, altered mental status, severe headache unrelieved by acetaminophen)
- Symptoms of liver capsule distention (eg, right upper quadrant or epigastric pain)
- Nausea and vomiting
- Serum AST or ALT > 2 times normal
- Systolic BP > 160 mm Hg or diastolic BP > 110 mm Hg on 2 occasions ≥ 6 h apart
- Platelet count < 100,000/μL
- Urine protein > 5 g/24 h
- Urine output < 500 mL/24 h
- Severe fetal growth restriction
- Pulmonary edema or cyanosis
- Stroke

**Treatment**

- Usually hospitalization and sometimes anti-hypertensive treatment
- Delivery, depending on factors such as fetal maturity and severity of preeclampsia
- Mg sulfate for prevention or treatment of seizures

**General approach:** Definitive treatment is delivery. However, risk of early delivery is balanced against severity of preeclampsia and response to other treatments. Usually, immediate delivery after maternal stabilization (eg, controlling seizures, beginning to control BP) is indicated for the following:

- Pregnancy of ≥ 37 wk
• Eclampsia

• Severe preeclampsia if pregnancy is > 34 wk or if fetal lung maturity is documented

• Deteriorating renal or hepatic function

• Nonreassuring results of fetal monitoring

Other treatments aim to optimize maternal health, which usually optimizes fetal health. If delivery can be delayed in pregnancies of about 32 to 34 wk, corticosteroids are given for 48 h to accelerate fetal lung maturity.

Most patients are hospitalized. Patients with eclampsia or severe preeclampsia are often admitted to an ICU.

Mild preeclampsia: If preeclampsia is mild, outpatient treatment is possible; it includes strict bed rest, lying on the left side whenever possible, BP evaluation and physician visits 2 to 3 times/wk, a normal salt intake, and increased fluid intake.

However, most patients with mild eclampsia require hospitalization; some also need drug treatment for a few hours to stabilize them and to lower systolic BP to 140 to 155 mm Hg and diastolic BP to 90 to 105 mm Hg. Delivery follows unless preeclampsia does not progress and the fetus is very premature.

Monitoring: Outpatients are usually evaluated once every 2 or 3 days for seizures, symptoms of severe preeclampsia, and vaginal bleeding. BP, reflexes, and fetal heart status (with nonstress testing or a biophysical profile) are also checked. Platelet count, serum creatinine, and serum liver enzymes are measured at least weekly. All hospitalized patients are followed by an obstetrician and evaluated as described above but more frequently, particularly patients that are in an ICU.

Mg sulfate: As soon as eclampsia or severe preeclampsia is diagnosed, Mg sulfate must be given to stop or prevent seizures and reduce reflex reactivity. Whether patients with mild preeclampsia always require Mg sulfate before delivery is controversial.

Mg sulfate 4 g IV over 20 min is given, followed by a constant IV infusion of about 1 to 3 g/h, with supplemental doses as necessary. Dose is adjusted based on the patient's reflexes, BP, and serum Mg levels (therapeutic range, 4 to 7 mEq/L). Patients with excess Mg levels (eg, with Mg levels > 10 mEq/L or a sudden decrease in reflex reactivity) or hypoventilation are treated with Ca gluconate 1 g IV.

IV Mg sulfate may cause lethargy, hypotonia, and transient respiratory depression in neonates. However, serious neonatal complications are uncommon.

Supportive treatments: Hospitalized patients are given IV Ringer's lactate or 0.9% normal saline solution, beginning at about 125 mL/h (to increase urine output). Persistent oliguria is treated with a fluid challenge, followed by furosemide 10 to 20 mg IV; diuretics are not used otherwise. If fluids plus furosemide are ineffective, determining intravascular volume and cardiac output with a pulmonary artery catheter may be considered. Anuric patients with normovolemia may require renal vasodilators or dialysis.

If seizures occur despite Mg therapy, diazepam or lorazepam can be given IV to stop seizures, and IV hydralazine or labetalol is given in a dose titrated to lower systolic BP to 140 to 155 mm Hg and diastolic BP to 90 to 105 mm Hg.

Delivery method: The most efficient method of delivery should be used. If the cervix is favorable and rapid vaginal delivery seems feasible, a dilute IV infusion of oxytocin is given to accelerate labor; if labor is active, the membranes are ruptured. If the cervix is unfavorable and prompt vaginal delivery is unlikely, cesarean delivery is indicated. Preeclampsia and eclampsia, if not resolved before delivery, usually resolve rapidly afterward, beginning within 6 to 12 h.
All patients are typically given Mg sulfate for 24 h postpartum.

Follow-up: Patients should be evaluated every 1 to 2 wk postpartum with periodic BP measurement. If BP remains high after 6 wk postpartum, patients may have chronic hypertension.

Pruritic Urticarial Papules and Plaques of Pregnancy

Pruritic urticarial papules and plaques of pregnancy are pruritic eruptions of unknown cause that develop during pregnancy.

Most cases occur during a first pregnancy. Overall incidence is 1/160 to 300 pregnancies; however, with multiple gestation, risk is 8 to 12 times higher.

Symptoms and Signs

Lesions are intensely itchy, erythematous, solid, superficial, and elevated; some are surrounded by blanching, and some have minute vesicles in the center. Itching keeps most patients awake, but excoriation is uncommon. Lesions begin on the abdomen, frequently on striae atrophicae (stretch marks), and spread to the thighs, buttocks, and occasionally the arms. The palms, soles, and face are usually spared. Most patients have hundreds of lesions.

Lesions develop during the 3rd trimester, most often in the last 2 to 3 wk and occasionally in the last few days or postpartum. They usually resolve within 15 days after delivery. They may recur in up to 5% of subsequent pregnancies.

Diagnosis

Diagnosis is clinical. Differentiation from other pruritic eruptions may be difficult.

Treatment

• Corticosteroids

Mild symptoms are treated with topical corticosteroids (eg, 0.1% triamcinolone acetonide cream up to 6 times/day). Rarely, more severe symptoms require systemic corticosteroids (eg, prednisone 40 mg po once/day, tapered as tolerated). Systemic corticosteroids given late in pregnancy do not seem to harm the fetus.

Spontaneous Abortion

(Miscarriage)

Spontaneous abortion is noninduced embryonic or fetal death or passage of products of conception before 20 wk gestation. Threatened abortion is vaginal bleeding occurring during this time frame, indicating that spontaneous abortion may occur. Diagnosis is by clinical criteria and ultrasonography. Treatment is usually observation for threatened abortion and, if spontaneous abortion has occurred or appears unavoidable, uterine evacuation.

Fetal death and early delivery are classified as follows:

• Abortion: Death of the fetus or passage of products of conception (fetus and placenta) before 20 wk gestation

• Late fetal death: Fetal death after 20 wk

• Stillbirth: Delivery after late fetal death

• Preterm delivery: Passage of a live fetus between 20 and 37 wk (see p. 2683)
Abortions may be classified as early or late, spontaneous or induced for therapeutic or elective reasons (see p. 2591), threatened or inevitable, incomplete or complete, recurrent (also called recurrent pregnancy loss), missed, or septic (see Table 265-1).

About 20 to 30% of women with confirmed pregnancies bleed during the first 20 wk of pregnancy; half of these women spontaneously abort. Thus, incidence of spontaneous abortion is about 10 to 15% in confirmed pregnancies. Incidence in all pregnancies is probably higher because some very early abortions are mistaken for a late menstrual period.

**Etiology**

Isolated spontaneous abortions may result from certain viruses—most notably cytomegalovirus, herpesvirus, parvovirus, and rubella virus—or from disorders that can cause sporadic abortions or recurrent pregnancy loss (eg, chromosomal or mendelian abnormalities, luteal phase defects). Acquired and hereditary thrombophilias appear to cause abortions after ≥ 10 wk. Immunologic abnormalities and major trauma may be causes. Cause is often unknown.

Risk factors include

- Age > 35
- History of spontaneous abortion
- Cigarette smoking
- Use of certain drugs (eg, cocaine, alcohol, high doses of caffeine)
- Uterine abnormalities (eg, leiomyoma, adhesions)

Subclinical thyroid disorders, well-controlled or subclinical diabetes mellitus, retroverted uterus, and minor trauma have not been shown to cause spontaneous abortions.

**Symptoms and Signs**

Symptoms include crampy pelvic pain, bleeding, and eventually expulsion of tissue. Late spontaneous abortion may begin with a gush of fluid when the membranes rupture. Hemorrhage is rarely massive. A dilated cervix indicates that abortion is inevitable.

If products of conception remain in the uterus after spontaneous abortion, vaginal bleeding may occur, usually after a delay of hours to days. Infection may also develop, causing fever, pain, and sometimes sepsis.

**Diagnosis**

- Clinical criteria
- Usually ultrasonography and quantitative β subunit of human chorionic gonadotropin (β-hCG)

Diagnosis of threatened, inevitable, incomplete, or complete abortion is often possible based on clinical criteria (Table 265-2) and a positive urine pregnancy test. However, ultrasonography and quantitative measurement of serum β-hCG are usually done to exclude ectopic pregnancy and to determine whether
products of conception remain in the uterus (suggesting that abortion is incomplete rather than complete). However, results may be inconclusive, particularly during early pregnancy.

**Missed abortion** is suspected if the uterus does not progressively enlarge or if quantitative $\beta$-hCG is low for gestational age or does not double within 48 to 72 h. Missed abortion is confirmed if ultrasonography shows any of the following:

- Disappearance of previously detected embryonic cardiac activity
- Absence of such activity when the fetal crown-rump length is $> 5$ mm (determined by transvaginal ultrasonography)

**Table 265-2. Characteristic Symptoms and Signs in Spontaneous Abortions**

- Absence of a fetal pole (determined by transvaginal ultrasonography) when the mean sac diameter (average of diameters measured in 3 orthogonal planes) is $> 18$ mm

For recurrent pregnancy loss, testing to determine the cause of abortion is necessary (see below).

**Treatment**

- Observation for threatened abortion
- Uterine evacuation for inevitable, incomplete, or missed abortions
- Emotional support

For threatened abortion, treatment is observation. No evidence suggests that bed rest decreases risk of subsequent completed abortion. If the cervix is dilated, avoidance of intercourse is often recommended to prevent infection; however, intercourse has not been shown to cause loss.

For inevitable, incomplete, or missed abortions, treatment is uterine evacuation or waiting for spontaneous passage of the products of conception. Evacuation usually involves suction curettage at $< 12$ wk, dilation and evacuation at 12 to 23 wk, or medical induction (for women without prior uterine surgery) at $> 16$ to 23 wk (for treatment of late fetal death, see Stillbirth on p. 2675). The later the uterus is evacuated, the greater the likelihood of placental bleeding, uterine perforation by long bones of the fetus, and difficulty dilating the cervix. These complications are reduced by preoperative use of osmotic cervical dilators (eg, laminaria), misoprostol, or mifepristone (RU 486).

If complete abortion is suspected, uterine evacuation is done when bleeding occurs or other signs indicate that products of conception may be retained. Uterine evacuation need not be done routinely.

After an induced or spontaneous abortion, parents commonly feel grief and guilt. They are given emotional support and, in the case of spontaneous abortions, reassured that their actions were not the cause. Formal counseling is rarely indicated but should be made available.

**Recurrent Pregnancy Loss**

(Recurrent or Habitual Abortion)

**Recurrent pregnancy loss is $\geq 3$ consecutive spontaneous abortions. Determining the cause may require extensive evaluation of both parents. Some causes can be treated.**

**Etiology**

Recurrent pregnancy loss usually results from disorders that cause intrauterine fetal damage, such as maternal or paternal chromosomal abnormalities (eg, balanced translocations). Chromosomal abnormalities may cause 50% of recurrent pregnancy losses, which are more common during early
pregnancy; aneuploidy is involved in up to 80% of all spontaneous abortions occurring at < 10 wk gestation but in < 15% of those occurring at 20 wk.

Other common causes may include maternal luteal phase defects (particularly at < 6 wk), overt endocrine disorders (eg, polycystic ovary syndrome, hypothyroidism, hyperthyroidism, poorly controlled diabetes mellitus), severe chronic renal disorders, immunologic abnormalities (eg, lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein I), and, particularly after 10 wk, inherited maternal thrombotic disorders (eg, activated protein C resistance; factor V Leiden mutation; prothrombin G20210A gene mutation; hyperhomocysteinemia; deficiencies of antithrombin or protein Z, C, or S). Cervical incompetence and structural abnormalities of the uterine cavity (eg, polyps, fibroids, congenital malformations) may predispose to delivery at < 20 wk but do not necessarily cause intrauterine fetal damage.

For women who have a history of recurrent pregnancy loss and who become pregnant, risk of fetal growth restriction and premature delivery may be higher.

**Diagnosis**

Evaluation should include the following to determine the cause:

- Genetic evaluation (karyotyping) as clinically indicated to exclude possible genetic causes (see p. 2599)
- Anticardiolipin antibodies, anti-β2 glycoprotein I, and lupus anticoagulant
- Thyroid-stimulating hormone
- Evaluation of ovarian reserve including measuring follicle-stimulating hormone level on day 3 of the menstrual cycle
- Hysterosalpingography or sonohysterography to check for structural uterine abnormalities
- Screening for activated protein C resistance, factor V Leiden mutation, prothrombin G20210A mutation, antithrombin activity, protein Z and C deficiencies, and protein S deficiency (if fetal losses occurred at > 9 wk gestation)

Cause cannot be determined in up to 50% of women.

**Treatment**

Some causes can be treated. If the cause cannot be identified, the chance of a live birth in the next pregnancy is 35 to 85%.

**Septic Abortion**

**Septic abortion is serious uterine infection during or shortly before or after an abortion.**

Septic abortions usually result from induced abortions done by untrained practitioners using nonsterile techniques; they are much more common when induced abortion is illegal. Typical causative organisms include *Escherichia coli, Enterobacter aerogenes, Proteus vulgaris*, hemolytic streptococci, staphylococci, and some anaerobic organisms (eg, *Clostridium perfringens*).

**Symptoms and Signs**

Symptoms and signs are similar to those of pelvic inflammatory disease (eg, chills, fever, vaginal discharge, often peritonitis) and often those of threatened or incomplete abortion (eg, vaginal bleeding, cervical dilation, passage of products of conception). Septic shock may result, causing hypothermia, hypotension, oliguria, and respiratory distress. Sepsis due to *C. perfringens* may result in
thrombocytopenia, ecchymoses, and findings of intravascular hemolysis (eg, anuria, anemia, jaundice, hemoglobinuria, hemosiderinuria).

**Diagnosis**

Septic abortion is usually obvious clinically but must be confirmed by pregnancy testing and usually ultrasonography.

**Treatment**

Treatment is intensive antibiotic therapy plus uterine evacuation as soon as possible. A typical antibiotic regimen includes clindamycin 900 mg IV q 8 h plus gentamicin 5 mg/kg IV once/day, with or without ampicillin 2 g IV q 4 h. Alternatively, a combination of ampicillin, gentamicin, and metronidazole 500 mg IV q 8 h can be used.

**Stillbirth**

Stillbirth is delivery of a dead fetus at > 20 wk gestation. Maternal and fetal testing is done to determine the cause. Management is as for routine care after live delivery.

**Etiology**

Fetal death during late pregnancy may have maternal, placental, or fetal anatomic or genetic causes (see Table 265-3). Overall, the most common cause is

- Abruptio placentae

**Complications:** If a fetus dies during late pregnancy or near term but remains in the uterus for weeks, disseminated intravascular coagulation (DIC) may occur.

**Diagnosis**

Tests to determine cause include the following:

- Fetal karyotype and autopsy
- Maternal CBC (for evidence of anemia or leukocytosis)
- Kleihauer-Betke test
- Thrombotic screening (including factor V Leiden mutation; prothrombin G20210A mutation; protein C, S, and Z levels; activated protein C resistance; antithrombin activity; fasting homocysteine level; anti-phospholipid antibody)
- TORCH test (toxoplasmosis [with IgG and IgM], other pathogens [eg, human parvovirus B19, varicella-zoster viruses], rubella, cytomegalovirus, herpes simplex)

[Table 265-3, Common Causes of Stillbirth]

- Rapid plasma reagin (RPR)
- Examination of the placenta

Often, cause cannot be determined.

**Treatment**

- Routine postdelivery care
• Emotional support

Postdelivery management is similar to that for live birth. If DIC occurs, labor is induced (eg, with IV oxytocin infusion, sometimes preceded by a prostaglandin to make the cervix favorable—ie, open and effaced). Any coagulopathy that develops should be promptly and aggressively managed by replacing blood or blood products as needed while preparations for delivery are being made.

After the products of conception are expelled, curettage may be needed to remove placental fragments.

Alternatively, dilation and extraction (D&E) may be done. In all cases, preabortion osmotic dilator cervical ripening should be used with or without misoprostol.

Parents typically feel significant grief and require emotional support and sometimes formal counseling. Risks with future pregnancy should be discussed with patients; risks are based on the stillbirth's cause.
Chapter 266. Abnormalities and Complications of Labor and Delivery

Introduction

Abnormalities and complications of labor and delivery should be diagnosed and managed as early as possible. Most (eg, multifetal pregnancy, postterm pregnancy, premature rupture of membranes, abnormal fetal presentation) are usually evident before onset of labor. Some (eg, amniotic fluid embolism, shoulder dystocia, fetopelvic disproportion, preterm labor, protracted labor, umbilical cord prolapse) develop or become evident during labor or the delivery period. Alternatives to spontaneous labor and vaginal delivery may be needed. Some complications (eg, postpartum hemorrhage, inverted uterus) occur immediately after delivery of the fetus and around the time the placenta is delivered. Placenta accreta (see p. 2669) may be discovered during pregnancy or only after delivery.

For neonatal resuscitation and disorders of the birth process, see Ch. 274; for meconium aspiration syndrome, see p. 2872.

Alternatives to Spontaneous Labor and Delivery

Abnormalities or difficulties in pregnancy or during labor and delivery can necessitate alternative delivery methods.

Operative vaginal delivery

Operative vaginal delivery involves application of forceps or a vacuum extractor to the fetal head to assist during the 2nd stage of labor and facilitate delivery.

Forceps delivery and vacuum extraction have essentially the same indications:

• Prolonged 2nd stage of labor (from full cervical dilation until delivery of the fetus)
• Suspicion of fetal compromise (eg, abnormal heart rate pattern)
• Need to shorten the 2nd stage for maternal benefit—eg, if maternal cardiac dysfunction (eg, left-to-right shunting) or neurologic disorders (eg, spinal cord trauma) contraindicate pushing or maternal exhaustion prevents it

A prolonged 2nd stage is defined in nulliparous women as lack of continuing progress for 3 h with a regional anesthetic or 2 h without a regional anesthetic or in multiparous women as lack of continuing progress for 2 h with a regional anesthetic or 1 h without a regional anesthetic.

Choice of device depends largely on user preference and operator experience and varies greatly. These procedures are used when the station of the fetal head is low (≥ +2 cm); then, minimal traction or rotation is required to deliver the head.

Before starting an operative vaginal delivery, the clinician should do the following:

• Confirm complete cervical dilation
• Confirm an engaged fetal vertex
• Confirm rupture of membranes
• Confirm that fetal position is compatible with operative vaginal delivery
• Drain the maternal bladder
• Clinically assess pelvic dimensions (clinical pelvimetry) to ensure that the pelvis is adequate
Also required are informed consent, adequate support and personnel, and adequate analgesia or anesthesia.

**Contraindications** include unengaged fetal head, unknown fetal position, and certain fetal disorders such as hemophilia. Vacuum extraction is typically considered contraindicated in preterm pregnancies of < 34 wk because risk of intraventricular hemorrhage is increased.

**Major complications** are maternal and fetal injuries and hemorrhage, particularly if the operator is inexperienced or if candidates are not appropriately chosen. Significant perineal trauma and neonatal bruising are more common with forceps delivery; shoulder dystocia, cephalohematoma, and retinal bleeding are more common with vacuum-assisted delivery.

**Induction of Labor**

Induction of labor is **stimulation of uterine contractions before spontaneous labor to achieve vaginal delivery.**

**Indications:** Induction of labor can be medically indicated (eg, for preeclampsia or fetal compromise) or elective (to control when delivery occurs). Before elective induction, gestational age and fetal lung maturity must be assessed; if gestational age is < 39 wk by best obstetric estimates, amniocentesis is done to determine lecithin/sphingomyelin ratio or other indexes of fetal lung maturity.

**Contraindications** to induction include the following:

- Fundal uterine surgery
- Prior classic or vertical cesarean incision in the thickened, muscular portion of the uterus
- Active genital herpes
- Placenta or vasa previa
- Abnormal fetal presentation (eg, transverse lie, umbilical cord presentation, certain types of fetopelvic disproportion)

Multiple prior uterine scars and breech presentation are relative contraindications.

**Technique:** If the cervix is closed, long, and firm (unfavorable), the goal is to cause the cervix to open and become effaced (favorable). Various pharmacologic or mechanical methods can be used. Misoprostol 25 μg vaginally q 3 to 6 h is effective. Alternatives include prostaglandin E₂ given intracervically (0.5 mg) or as an intravaginal pessary (10 mg). Prostaglandins are contraindicated in women with prior cesarean delivery or uterine surgery because these drugs increase the risk of uterine rupture. Oxytocin in low or high doses can also be given. Effective mechanical methods include use of laminaria and transcervical balloon catheters, which may be useful when other methods are ineffective or contraindications exist.

Once the cervix is favorable, labor is induced. Constant IV infusion of oxytocin is the most commonly used method; it is safe and cost-effective. Low-dose oxytocin is given at 0.5 to 2 milliunits/min, increased by 1 to 2 milliunits/min, usually q 15 to 60 min. High-dose oxytocin is given at 6 milliunits/min, increased by 1 to 6 milliunits/min q 15 to 40 min to a maximum of 40 milliunits/min. With doses > 40 milliunits/min, excessive water retention may lead to water intoxication. Use of oxytocin must be supervised to prevent hypertonic uterine contractions, which may compromise the fetus. External fetal monitoring (see p. 2630) is routine; after amniotomy (deliberate rupture of the membranes), internal monitoring may be indicated if fetal status cannot be assessed externally. Amniotomy can be done to augment labor when the fetal head is well applied to a favorable cervix.

**Cesarean Delivery**

Cesarean delivery is surgical delivery by incision into the uterus.
Up to 30% of deliveries in the US are cesarean. The rate of cesarean delivery fluctuates. It has recently increased, partly because of concern about increased risk of uterine rupture in women attempting vaginal birth after cesarean delivery (VBAC).

**Indications:** Although morbidity and mortality rates of cesarean delivery are low, they are still several times higher than those of vaginal delivery; thus, cesarean delivery should be done only when it is safer for the woman or fetus than vaginal delivery. The most common specific indications are

- Previous cesarean delivery
- Protracted labor
- Fetal dystocia (particularly breech presentation)
- A nonreassuring fetal heart rate, which requires rapid delivery

Many women are interested in elective cesarean delivery on demand. The rationale includes avoiding damage to the pelvic floor (and subsequent incontinence) and serious intrapartum fetal complications. However, such use is controversial, has limited supporting data, and requires discussion between the woman and her physician; the discussion should include immediate risks and long-term reproductive planning (eg, how many children the woman intends to have).

Many cesarean deliveries are done in women with previous cesarean deliveries because for them, vaginal delivery increases risk of uterine rupture; however, risk of rupture with vaginal delivery is only about 1% overall (risk is higher for women who have had multiple cesarean deliveries or a vertical incision, particularly if it extends through the thickened, muscular portion of the uterus). Vaginal birth is successful in about 75% of women who have had a single prior cesarean delivery and should be offered to those who have had a single prior cesarean delivery by lower uterine transverse incision. Success of VBAC depends on the indication for the initial cesarean delivery. VBAC should be done in a facility where an obstetrician, anesthesiologist, and surgical team are immediately available, which makes VBAC impractical in some situations.

**Technique:** During cesarean delivery, practitioners skilled in neonatal resuscitation should be readily available. The uterine incision can be classic or lower segment.

- **Classic:** The incision is made vertically in the anterior wall of the uterus, ascending to the upper uterine segment or fundus. This incision typically results in more blood loss than a lower-segment incision and is usually done only when placenta previa is present, fetal position is transverse with the back down, presentation is breech, the fetus is preterm, or the lower uterine segment is poorly developed.

- **Lower segment:** Lower-segment incisions are done most often. A low transverse incision is made in the thinned, elongated lower portion of the uterine body under the bladder reflection. A vertical lower-segment incision is used only for certain abnormal presentations and for excessively large fetuses. In such cases, a transverse incision is not used because it can extend laterally into the uterine arteries, sometimes causing excessive blood loss. Women who have had deliveries by a low transverse uterine incision are advised about the safety of a trial of labor in subsequent pregnancies.

**Amniotic Fluid Embolism**

**Amniotic fluid embolism is entrance of amniotic fluid and fetal cells into the maternal circulation initiating an abnormal response.**

Amniotic fluid embolism is a rare obstetric emergency. It usually occurs during late pregnancy; risk is increased with cesarean delivery, advanced maternal age, abruptio placentae, abdominal trauma, placenta previa, and forceps delivery. Amniotic fluid embolizes to the maternal circulation, causing tachycardia, hypotension, respiratory failure, disseminated intravascular coagulation, and often rapid maternal death. Autopsy may show fetal squamous cells and hair in the pulmonary circulation.
About 20% of affected women die, although mortality estimates often vary widely. Survival depends on early recognition and immediate institution of treatment.

Diagnosis is clinical.

Treatment is supportive. It includes transfusion of RBCs (as needed to replace lost blood), fresh frozen plasma and clotting factors (as needed to reverse the coagulopathy), and ventilatory and circulatory support, with inotropic drugs as needed.

**Fetal Dystocia**

Fetal dystocia is abnormal fetal size or position resulting in difficult delivery. Diagnosis is by examination, ultrasonography, or response to augmentation of labor. Treatment is with physical maneuvers to reposition the fetus, operative vaginal delivery, or cesarean delivery.

Fetal dystocia may occur when the fetus is too large for the pelvic opening (fetopelvic disproportion) or is abnormally positioned (eg, breech presentation). Normal fetal presentation is vertex, with the occiput anterior.

**Fetopelvic disproportion:** Diagnosis is suggested by prenatal clinical estimates of pelvic dimensions (see p. 2607), ultrasonography, and protracted labor. If augmentation of labor restores normal progress and fetal weight is < 5000 g in women without diabetes or < 4500 g in women with diabetes, labor can safely continue. If progress is slower than expected in the 2nd stage of labor, women are evaluated to determine whether operative vaginal delivery (by forceps or vacuum extractor) is safe and appropriate.

**Occiput posterior presentation:** The most common abnormal presentation is occiput posterior. The fetal neck is usually somewhat deflexed; thus, a larger diameter of the head must pass through the pelvis. Many occiput posterior presentations require operative vaginal delivery or cesarean delivery.

**Face or brow presentation:** In face presentation, the head is hyperextended, and position is designated by the position of the chin (mentum). When the chin is posterior, the head is less likely to rotate and less likely to deliver vaginally, necessitating cesarean delivery. Brow presentation usually converts spontaneously to occiput or face presentation.

**Breech presentation:** The 2nd most common abnormal presentation is breech (buttocks before the head). There are several types:

- Frank breech: The fetal hips are flexed, and the knees extended (pike position).
- Complete breech: The fetus seems to be sitting with hips and knees flexed.
- Single or double footling presentation: One or both legs are completely extended and present before the buttocks.

Breech presentation is a problem primarily because the presenting part is a poor dilating wedge, which can cause the head, which follows, to be trapped during delivery, often compressing the umbilical cord.

Umbilical cord compression may cause fetal hypoxemia. The fetal head is probably compressing the umbilical cord if the fetal umbilicus is visible at the introitus, particularly in primiparas whose pelvic tissues have not been dilated by previous deliveries.

Predisposing factors for breech presentation include premature labor, uterine abnormalities, and fetal anomalies. If delivery is vaginal, breech presentation may increase risk of birth trauma, dystocia, and perinatal death. Preventing complications is more effective and easier than treating them, so abnormal presentation must be identified before delivery. Cesarean delivery is usually done at 39 wk or when the patient presents in labor, although external cephalic version can sometimes move the fetus to vertex position.
presentation before labor, usually at 37 or 38 wk. This technique involves gently pressing on the maternal abdomen to reposition the fetus. A dose of a short-acting tocolytic (terbutaline 0.25 mg sc) may help. The success rate is about 50 to 75%.

**Transverse lie:** Fetal position is transverse, with the fetal long axis oblique or perpendicular rather than parallel to the maternal long axis. Shoulder-first presentation requires cesarean delivery unless the fetus is a 2nd twin.

**Shoulder dystocia:** In this infrequent condition, presentation is vertex, but the anterior fetal shoulder is lodged behind the symphysis pubis, preventing vaginal delivery. Shoulder dystocia is recognized when the fetal head is delivered onto the perineum but appears to be pulled back tightly against the perineum (turtle sign). Risk factors include a large fetus, maternal obesity, diabetes mellitus, prior shoulder dystocia, operative vaginal delivery, and prolonged labor. Risk of neonatal morbidity (eg, brachial plexus injury, bone fractures) and mortality is increased.

Once shoulder dystocia is recognized, extra personnel are summoned to the room, and various maneuvers are tried sequentially to disengage the anterior shoulder:

- The woman's thighs are hyperflexed to widen the pelvic outlet (McRobert's maneuver), and suprapubic pressure is applied to rotate and dislodge the anterior shoulder. Fundal pressure is avoided because it may worsen the condition or cause uterine rupture.

- The obstetrician inserts a hand into the posterior vagina and presses the posterior shoulder to rotate the fetus in whichever direction is easier (Wood's screw maneuver).

- The obstetrician inserts a hand, flexes the posterior elbow, and sweeps the arm and hand across the fetal chest to deliver the infant's entire posterior arm.

These maneuvers increase risk of fracture of the humerus or clavicle. Sometimes the clavicle is intentionally fractured in a direction away from fetal lung to disengage the shoulder. An episiotomy can be done at any time to facilitate the maneuvers.

If all maneuvers are ineffective, the obstetrician flexes the infant's head and reverses the cardinal movements of labor, replacing the fetal head back into the vagina or uterus; the infant is then delivered by cesarean (Zavanelli maneuver).

**Inverted Uterus**

**Inverted uterus is a rare medical emergency in which the corpus turns inside out and protrudes into the vagina or beyond the introitus.**

The uterus is most commonly inverted when too much traction is applied to the umbilical cord in an attempt to deliver the placenta. Excessive pressure on the fundus during delivery of the placenta, a flaccid uterus, or placenta accreta (abnormally adherent placenta) can contribute.

**Treatment**

- **Manual reduction**

Treatment is immediate manual reduction by pushing up on the fundus until the uterus is returned to its normal position. If the placenta is still attached, the uterus should be replaced before the placenta is removed. Because of discomfort, IV analgesics and sedatives or a general anesthetic are sometimes needed. Terbutaline 0.25 mg IV or nitroglycerin 50 μg IV may also be needed.

If attempts to return the uterus are unsuccessful, a laparotomy may be necessary; the fundus is manipulated vaginally and abdominally to return it to its normal position. Once the uterus is in place, an oxytocin infusion should be started.
**Multifetal Pregnancy**

Multifetal pregnancy is presence of > 1 fetus in the uterus.

Multifetal (multiple) pregnancy occurs in 1 of 70 to 80 deliveries. Risk factors include

- Ovarian stimulation (usually with clomiphene or gonadotropins)
- Assisted reproduction (eg, in vitro fertilization)
- Prior multifetal pregnancy
- Advanced maternal age

The overdistended uterus tends to stimulate early labor, causing preterm delivery (average gestation is 35 to 36 wk with twins, 32 wk with triplets, and 30 wk with quadruplets). Fetal presentation may be abnormal. The uterus may contract after delivery of the first child, shearing away the placenta and increasing risk for the remaining fetuses. Sometimes uterine distention impairs postpartum uterine contraction, leading to atony and maternal hemorrhage. Multifetal pregnancy increases the risk of preeclampsia, gestational diabetes, postpartum hemorrhage, cesarean delivery, preterm delivery, and growth restriction.

Multifetal pregnancy is suspected if the uterus is large for dates; it is evident on prenatal ultrasonography. Cesarean delivery is done when indicated. Cesarean delivery is recommended for twins unless the presenting twin is in vertex presentation. Higher-order multiples are typically delivered by cesarean regardless of presentation. (see p. 2678).

**Postpartum Hemorrhage**

Postpartum hemorrhage is blood loss of > 500 mL during or immediately after the 3rd stage of labor in a vaginal delivery or > 1000 mL in a cesarean delivery. Diagnosis is clinical. Treatment depends on etiology of the hemorrhage.

Causes of postpartum hemorrhage include

- Uterine atony (the most common)
- Lacerations of the genital tract
- Extension of an episiotomy
- Uterine rupture
- Bleeding disorders
- Retained placental tissues
- Hematoma
- Uterine inversion
- Subinvolution (incomplete involution) of the placental site (which usually occurs early but may occur as late as 1 mo after delivery)

Risk factors for uterine atony include uterine overdistention (caused by multifetal pregnancy, polyhydramnios, or an abnormally large fetus), prolonged or dysfunctional labor, grand multi-parity (delivery of ≥ 5 viable fetuses), relaxant anesthetics, rapid labor, and chorioamnionitis.
Uterine fibroids may contribute to postpartum hemorrhage. A history of prior postpartum hemorrhage may indicate increased risk.

**Treatment**

- Removal of retained placental tissues and repair of genital lacerations
- Uterotonics (eg, oxytocin, prostaglandins)
- Sometimes surgical procedures

Intravascular volume is replenished with 0.9% saline up to 2 L IV; blood transfusion is used if this volume of saline is inadequate. Hemostasis is attempted by bimanual uterine massage and IV oxytocin infusion, and the uterus is explored for lacerations and retained placental tissues. The cervix and vagina are also examined; lacerations are repaired. Bladder drainage via catheter can sometimes reduce uterine atony.

15-Methyl prostaglandin $F_{2\alpha}$ 250 μg IM q 15 to 90 min up to 8 doses or methylergonovine 0.2 mg IM q 2 to 4 h (which may be followed by 0.2 mg po tid to qid for 1 wk) should be tried if excessive bleeding continues during oxytocin infusion; during cesarean delivery, these drugs may be injected directly into the myometrium. Prostaglandins should be avoided in women with asthma; methylergonovine should be avoided in women with hypertension. Sometimes misoprostol 800 to 1000 μg rectally can be used to increase uterine tone.

Uterine packing or placement of a Bakri balloon can sometimes provide tamponade. This silicone balloon can hold up to 500 mL and withstand internal and external pressures of up to 300 mm Hg. If hemostasis cannot be achieved, surgical placement of a B-Lynch suture (a suture used to compress the lower uterine segment via multiple insertions), hypogastric artery ligation, or hysterectomy may be required. Uterine rupture requires surgical repair.

Blood products are transfused as necessary, depending on the degree of blood loss and clinical evidence of shock. Infusion of factor VIIa (50 to 100 μg/kg, as a slow IV bolus over 2 to 5 min) can produce hemostasis in women with severe life-threatening hemorrhage. The dose is given q 2 to 3 h until hemostasis occurs.

**Prevention**

Predisposing conditions (eg, uterine fibroids, polyhydramnios, multifetal pregnancy, a maternal bleeding disorder, history of puerperal hemorrhage) are identified antepartum and, when possible, corrected. If women have an unusual blood type, that blood type is made available. Careful, unhurried delivery with a minimum of intervention is always wise.

After placental separation, oxytocin 10 units IM or dilute oxytocin infusion (10 or 20 units in 1000 mL of an IV solution at 125 to 200 mL/h for 1 to 2 h) usually ensures uterine contraction and reduces blood loss. After the placenta is delivered, it is thoroughly examined for completeness; if it is incomplete, the uterus is manually explored and retained fragments are removed. Rarely, curettage is required. Uterine contraction and amount of vaginal bleeding must be observed for 1 h after completion of the 3rd stage of labor.

**Postterm Pregnancy**

Postterm pregnancy refers to gestation that lasts ≥ 42 wk. Nonstress testing, a full or modified biophysical profile, and often routine delivery are recommended at 41 wk.

Accurate gestational age estimation is essential in making a diagnosis of postterm pregnancy. In women with regular, normal menstrual cycles, gestational age can be estimated based on the first day of the last normal menstrual period. If dating is uncertain or inconsistent with menstrual dating, ultrasonography early in gestation (up to 20 wk) is the most accurate with accepted variation of +/- 7 days. Later in gestation, the variation increases to +/- 14 days at 20 to 30 wk gestation and +/- 21 days after 30 wk.
Postterm pregnancy increases risks for the woman and fetus. Risks include

- Abnormal fetal growth (macrosomia and dysmaturity syndrome)
- Oligohydramnios
- Meconium-stained amniotic fluid
- Nonreassuring fetal test results
- Fetal and neonatal death
- Dystocia (abnormal or difficult labor)
- Cesarean delivery

Most experts recommend that antenatal surveillance be initiated at 41 wk; it involves a modified biophysical profile (nonstress testing and assessment of amniotic fluid volume) or a full biophysical profile (assessment of amniotic fluid volume and fetal movement, tone, breathing, and heart rate). If there is evidence of fetal compromise or oligohydramnios, delivery is required. For many obstetricians, the trend is to induce labor (see p. 2677) in all pregnancies > 41 wk, particularly in patients with a favorable cervix.

**Premature Rupture of Membranes**

Rupture of membranes before onset of labor is considered premature. Diagnosis is clinical. Delivery is sometimes indicated when gestational age is ≥ 34 wk or fetal lungs are mature and is generally indicated for infection or fetal compromise.

Premature rupture of membranes (PROM) may occur at term (≥ 37 wk) or earlier (called preterm PROM if < 37 wk). Preterm PROM predisposes to preterm delivery. PROM at any time increases risk of infection in the woman (chorioamnionitis), neonate (sepsis), or both, as well as risk of abnormal fetal presentation and abruptio placentae. Group B streptococci and *Escherichia coli* are common causes of infection. Other organisms in the vagina may also cause infection. Prolonged preterm PROM before viability (at < 24 wk) increases risk of abnormal joint positioning and pulmonary hypoplasia.

The interval between PROM and onset of spontaneous labor (latent period) and delivery varies inversely with gestational age. At term, > 90% of women with PROM begin labor within 24 h; at 32 to 34 wk, mean latency period is about 4 days.

**Symptoms and Signs**

Typically, unless complications occur, the only symptom is leakage or a sudden gush of fluid from the vagina. Fever, heavy vaginal discharge, abdominal pain, and fetal tachycardia, particularly if out of proportion to maternal temperature, strongly suggest chorioamnionitis.

**Diagnosis**

- Visible amniotic fluid or meconium
- Evaluation of vaginal fluid showing ferning or alkalinity (blue color) on Nitrazine paper
- Sometimes ultrasonography showing oligohydramnios

Sterile speculum examination is done to verify PROM, estimate cervical dilation, collect amniotic fluid for fetal maturity tests, and obtain samples for cervical cultures. Digital pelvic examination, particularly multiple examinations, increases risk of infection and is best avoided unless imminent delivery is anticipated. Fetal position should be assessed. If subclinical intra-amniotic infection is a concern, amniocentesis (obtaining amniotic fluid using sterile technique) can confirm this infection.
Diagnosis is assumed if amniotic fluid appears to be escaping from the cervix or if the vernix or meconium is visible. Other less accurate indicators include vaginal fluid that ferns when dried on a glass slide or turns Nitrazine paper blue (indicating alkalinity and hence amniotic fluid; normal vaginal fluid is acidic). Ultrasonography showing oligohydramnios suggests the diagnosis.

If the diagnosis is questionable, indigo carmine dye can be instilled using ultrasound-guided amniocentesis. Appearance of the blue dye on a vaginal tampon or peripad confirms the diagnosis.

If the fetus is viable, women are typically admitted to the hospital for daily fetal assessment.

**Treatment**

- Delivery if there is fetal compromise, infection, or possibly gestational age > 34 wk or fetal lung maturity
- Otherwise, pelvic rest, close monitoring, antibiotics, and sometimes corticosteroids

Management requires balancing risk of infection when delivery is delayed with risks due to fetal immaturity when delivery is immediate. No one strategy is correct, but generally, signs of fetal compromise or infection (eg, persistently nonreassuring fetal testing results, uterine tenderness plus fever) should prompt delivery. Otherwise, delivery can be delayed for a variable period if fetal lungs are still immature or if labor could start spontaneously (ie, later in the pregnancy). Induction of labor is recommended when gestational age is > 34 wk. When appropriate management is unclear, amniotic fluid tests can be done to assess fetal lung maturity and thus guide management; the sample may be obtained from the vagina or by amniocentesis.

When expectant management is used, the woman's activity is limited to modified bed rest and complete pelvic rest. BP and temperature must be measured ≥ 3 times/day. Antibiotics (usually 48 h of IV ampicillin and erythromycin, followed by 5 days of oral amoxicillin and erythromycin) are given; they lengthen the latency period and reduce risk of neonatal morbidity. In pregnancies of < 32 wk, corticosteroids should be given to accelerate fetal lung maturity (see p. 2683). Their use between 32 and 34 wk is controversial. Use of tocolytics (drugs that stop uterine contractions) to manage preterm PROM is controversial; their use must be determined case by case.

**Preterm Labor**

Labor (contractions resulting in cervical change) that begins before 37 wk gestation is considered preterm. Risk factors include premature rupture of membranes, infection, cervical incompetence, prior preterm birth, multifetal pregnancy, and placental abnormalities. Diagnosis is clinical. Causes are identified and treated if possible. Management typically includes bed rest, tocolytics (if labor persists), and corticosteroids (if gestational age is < 34 wk). Antistreptococcal antibiotics are given pending negative anovaginal culture results.

Preterm labor may be triggered by premature rupture of membranes, chorioamnionitis (see p. 2662), or another ascending uterine infection; group B streptococci are a common cause of such infections. Preterm labor may also be due to multifetal pregnancy, fetal or placental abnormalities, uterine abnormalities, pyelonephritis, or some sexually transmitted diseases; a cause may not be evident. Prior preterm delivery and cervical incompetence increase the risk.

Cervical cultures are done for causes suggested by clinical findings. Anovaginal cultures for group B streptococci are done, and prophylaxis is appropriately initiated. Most women with a presumptive diagnosis of preterm labor do not progress to delivery.

**Treatment**

- Antibiotics for group B streptococci, pending anovaginal culture results
- Tocolytics
• Corticosteroids if < 34 wk

Bed rest and hydration are commonly used initially.

Antibiotics effective against group B streptococci are given pending negative anovaginal cultures. Choices include the following:

• For women without penicillin allergy: Penicillin G 5 million units IV followed by 2.5 million units q 4 h or ampicillin 2 g IV followed by 1 g q 4 h

• For women with penicillin allergy but a low risk of anaphylaxis (eg, maculopapular rash with prior use): Cefazolin 2 g IV followed by 1 g q 8 h

• For women with penicillin allergy and an increased risk of anaphylaxis (eg, bronchospasm, angioneurotic edema, or hypotension with prior use, particularly within 30 min of exposure): Clindamycin 900 mg IV q 8 h or erythromycin 500 mg IV q 6 h if anovaginal cultures show susceptibility; if cultures document resistance or results are unavailable, vancomycin 1 g IV q 12 h

If the cervix dilates, tocolytics (drugs that stop uterine contractions) can usually delay labor for at least 48 h so that corticosteroids can be given to reduce risks to the fetus. Tocolytics include Mg sulfate, β-adrenergic agonists (eg, terbutaline), Ca channel blockers, and prostaglandin inhibitors. No tocolytic is clearly the first-line choice; choice should be individualized to minimize adverse effects. Mg sulfate is commonly used and is typically well tolerated (see p. 2671). Prostaglandin inhibitors may cause transient oligohydramnios. They are contraindicated after 32 wk gestation because they may cause premature narrowing or closure of the ductus arteriosus.

If the fetus is < 34 wk, women are given corticosteroids: betamethasone 12 mg IM q 24 h for 2 doses or dexamethasone 6 mg IM q 12 h for 4 doses unless delivery is imminent. These corticosteroids accelerate maturation of fetal lungs and decrease risk of neonatal respiratory distress syndrome, intracranial bleeding, and mortality.

A progestin may be recommended in future pregnancies for women who have a preterm delivery to reduce the risk of recurrence.

Protracted Labor

Protracted labor is abnormally slow cervical dilation or fetal descent during active labor. Diagnosis is clinical. Treatment is with oxytocin, operative vaginal delivery, or cesarean delivery.

Active labor usually occurs after the cervix dilates to ≥ 4 cm. Normally, cervical dilation and descent of the head into the pelvis proceed at a rate of at least 1 cm/h and more quickly in multiparous women.

Etiology

Protracted labor may result from fetopelvic disproportion (the fetus cannot fit through the maternal pelvis), which can occur because the maternal pelvis is abnormally small or because the fetus is abnormally large or abnormally positioned (fetal dystocia).

Another cause is uterine contractions that are too weak or infrequent (hypotonic uterine dysfunction) or, occasionally, too strong or close together (hypertonic uterine dysfunction).

Diagnosis

• Assessment of pelvic dimensions, fetal size and position, and uterine contractions

• Response to treatment
Diagnosis is clinical. The cause must be identified because it determines treatment. Assessing fetal and pelvic dimensions and fetal position (see p. 2607) can sometimes determine whether the cause is fetopelvic disproportion. For example, fetal weight > 5000 g (> 4500 g in diabetic women) suggests fetopelvic disproportion. Uterine dysfunction is diagnosed by evaluating the strength and frequency of contractions via palpation of the uterus or an intrauterine pressure catheter.

Diagnosis is often based on response to treatment.

**Treatment**

- Oxytocin
- Cesarean delivery for fetopelvic disproportion or intractable hypotonic dysfunction
- Sometimes operative delivery during the 2nd stage of labor

If the 1st or 2nd stage of labor proceeds too slowly and fetal weight is < 5000 g (< 4500 g in diabetic women), labor can be augmented with oxytocin, which is the treatment for hypotonic dysfunction. If normal progress is restored, labor can then proceed. If not, fetopelvic disproportion or intractable hypotonic dysfunction may be present, and cesarean delivery may be required. In the 2nd stage of labor, forceps or vacuum extraction may be appropriate after evaluation of fetal size, presentation, and station (≥ +2 cm) and evaluation of the maternal pelvis. Hypertonic uterine dysfunction is difficult to treat, but repositioning, short-acting tocolytics (eg, terbutaline 0.25 mg IV once), discontinuation of oxytocin if it is being used, and analgesics may help.

**Umbilical Cord Prolapse**

Umbilical cord prolapse is abnormal position of the cord in front of the fetal presenting part, so that the fetus compresses the cord during labor, causing fetal hypoxemia.

The prolapsed umbilical cord may be contained within the uterus (occult) or may protrude into the vagina (overt). Both are uncommon.

In **occult prolapse**, the cord is often compressed by a shoulder or the head. A fetal heart rate pattern that suggests cord compression and progression to hypoxemia (eg, severe bradycardia, severe variable accelerations) may be the only clue. Changing the woman's position may relieve pressure on the cord; however, if the abnormal fetal heart rate pattern persists, immediate cesarean delivery is necessary.

**Overt prolapse** occurs with ruptured membranes and is more common with breech presentation or a transverse lie. Overt prolapse can also occur with vertex presentation, particularly if membranes rupture (spontaneously or iatrogenically) before the head is engaged. Treatment begins with gently lifting the presenting part and continuously holding it off the prolapsed cord to restore fetal blood flow while immediate cesarean delivery is done. Placing the woman in the knee-to-chest position and giving her terbutaline 0.25 mg IV once may help by reducing contractions.

**Uterine Rupture**

Uterine rupture is rare. It occurs most often along healed scar lines in women who have had prior cesarean deliveries. Other predisposing factors include congenital uterine abnormalities, trauma, and other uterine surgical procedures such as myomectomies. Uterine rupture can occur before or during labor.

Causes of uterine rupture include uterine overdistention (multiple gestation, polyhydramnios, fetal anomalies), external or internal fetal version, iatrogenic perforation, excessive use of uterotonics, and failure to recognize labor dystocia with excessive uterine contractions against a lower uterine restriction ring. Use of prostaglandins in women who attempt a trial of labor after cesarean delivery increases the risk of uterine rupture and is not recommended.
Symptoms and signs include fetal bradycardia, evidence of hypovolemia, loss of fetal station (detected during cervical examination), and severe or constant abdominal pain.

Diagnosis is confirmed by laparotomy. If the fetus has been expelled from the uterus and is located within the peritoneal cavity, morbidity and mortality increase significantly.

Treatment is immediate laparotomy with cesarean delivery and, if necessary, hysterectomy.
Chapter 267. Postpartum Care

Introduction

Clinical manifestations during the puerperium (6-wk period after delivery) generally reflect reversal of the physiologic changes that occurred during pregnancy (see **Table 267-1**). These changes are mild and temporary and should not be confused with pathologic conditions.

**Clinical parameters**: Within the first 24 h, the woman's pulse rate begins to drop, and her temperature may be slightly elevated. Vaginal discharge is grossly bloody (lochia rubra) for 3 to 4 days, then becomes pale brown (lochia serosa), and after the next 10 to 12 days, it changes to yellowish white (lochia alba). About 1 to 2 wk after delivery, eschar from the placental site sloughs off and bleeding occurs; bleeding is usually self-limited. Total blood loss is about 250 mL; comfortably fitting intravaginal tampons (changed frequently) or external pads may be used to absorb it. Tampons should not be used if they might inhibit healing of perineal or vaginal lacerations. Prolonged bleeding (see p. 2680) may be a sign of infection or retained placenta.

[**Table 267-1. Normal Postpartum Changes**]

and should be investigated. The uterus involutes progressively; after 5 to 7 days, it is firm and no longer tender, extending midway between the symphysis and umbilicus. By 2 wk, it is no longer palpable abdominally and typically by 4 to 6 wk returns to a prepregnancy size. Contractions of the involuting uterus, if painful (afterpains), may require analgesics.

**Laboratory parameters**: During the first week, urine temporarily increases in volume; care must be taken when interpreting urinalysis results as lochia can interfere. Because blood volume is redistributed, Hct may fluctuate, although it tends to remain in the prepregnancy range if women do not hemorrhage. Because WBC count increases during labor, marked leukocytosis (up to 20,000 to 30,000/μL) occurs in the first 24 h postpartum; WBC count returns to normal within 1 wk. Plasma fibrinogen and ESR remain elevated during the first week postpartum.

Initial Management

Risk of infection, hemorrhage, and pain must be minimized. Women are typically observed for at least 1 h after the 3rd stage of labor and for several hours longer if general anesthesia was used during delivery (eg, by forceps, vacuum extractor, or cesarean).

**Hemorrhage**: Minimizing bleeding is the first priority; measures include

- Uterine massage
- Sometimes parenteral oxytocin

During the first hour after the 3rd stage of labor, the uterus is massaged periodically to ensure that it contracts, preventing excessive bleeding. If the uterus does not remain contracted after massage alone, oxytocin 10 units IM or a dilute oxytocin IV infusion (10 or 20 (up to 80) units/1000 mL of IV fluid) at 125 to 200 mL/h is given immediately after delivery of the placenta. The drug is continued until the uterus is firm; then it is decreased or stopped. Oxytocin should not be given as an IV bolus because severe hypotension may occur.

For all women, O₂, type O-negative blood or blood tested for compatibility, and IV fluids must be available during the recovery period. If blood loss was excessive, a CBC to verify that women are not anemic is required before discharge. If blood loss was not excessive, CBC is not required.

**Diet and activity**: After the first 24 h, recovery is rapid. A regular diet should be offered as soon as women desire food. Full ambulation is encouraged as soon as possible.
Exercise recommendations are individualized depending on presence of other maternal disorders or complications. Usually, exercises to strengthen abdominal muscles can be started once the discomfort of delivery has subsided, typically within 1 day for women who deliver vaginally and later for those who deliver by cesarean. Curl-ups, done in bed with the hips and knees flexed, tighten only abdominal muscles, usually without causing backache. Whether pelvic floor (eg, Kegel) exercises are helpful is unclear, but these exercises can begin as soon as the patient is ready.

Perineal care: If delivery was uncomplicated, showering and bathing are allowed, but vaginal douching is prohibited in the early puerperium. The vulva should be cleaned from front to back. Immediately after delivery, ice packs may help reduce pain and edema at the site of an episiotomy or repaired laceration; later, warm sitz baths can be used several times a day.

Analgesics: NSAIDs, such as ibuprofen 400 mg po q 4 to 6 h, work effectively on both perineal discomfort and uterine cramping. Acetaminophen 500 to 1000 mg po q 4 to 6 h can also be used. Acetaminophen and ibuprofen appear to be relatively safe during breast-feeding. Many other analgesics are secreted in breast milk. After surgery or repair of significant laceration, women may require opioids to relieve discomfort.

Bladder and bowel function: Urine retention, bladder overdistention, and catheterization should be avoided if possible. Rapid diuresis may occur, especially when oxytocin is stopped. Voiding must be encouraged and monitored to prevent asymptomatic bladder overfilling. A midline mass palpable in the suprapubic region or elevation of the uterine fundus above the umbilicus suggests bladder overdistention. If overdistention occurs, catheterization is necessary to promptly relieve discomfort and to prevent long-term urinary dysfunction.

Women are encouraged to defecate before leaving the hospital, although with early discharge, this recommendation is often impractical. If defecation has not occurred within 3 days, a mild cathartic (eg, psyllium, docusate, bisacodyl) can be given. Avoiding constipation can prevent or help relieve existing hemorrhoids, which can also be treated with warm sitz baths. Women with an extensive perineal laceration repair involving the rectum or anal sphincter can be given stool softeners (eg, docusate). Regional (spinal or epidural) anesthesia may delay defecation and spontaneous urination, in part by delaying ambulation.

Vaccination and Rh desensitization: Women who are seronegative for rubella should be vaccinated against rubella on the day of discharge. If women have not yet received tetanus-diphtheria-acellular pertussis (Tdap) vaccination and have not had a tetanus and diphtheria toxoids (Td) booster in ≥ 2 yr, they should be given Tdap before discharge from the hospital or birthing center, regardless of their breast-feeding status.

If women with Rh-negative blood have an infant with Rh-positive blood but are not sensitized, they should be given Rh\(_0\)(D) immune globulin 300 μg IM within 72 h of delivery to prevent sensitization (see p. 2666).

Breast engorgement: Milk accumulation may cause painful breast engorgement during early lactation. Breastfeeding helps reduce engorgement. Expressing milk by hand in a warm shower or using a breast pump between feedings can relieve pressure temporarily. However, doing so tends to encourage lactation, so it should be done only when necessary.

For women who are not going to breastfeed, firm support of the breasts is recommended to suppress lactation; gravity stimulates the let-down reflex and encourages milk flow. For many women, tight binding of the breasts, cold packs, and analgesics as needed, followed by firm support, effectively control temporary symptoms while lactation is being suppressed. Suppression of lactation with drugs is not recommended.

Mental disorders: Transient depression (baby blues) is very common during the first week after delivery. Symptoms are typically mild and usually subside by 7 to 10 days. Physicians should ask women about symptoms of depression before and after delivery and be alert to recognizing symptoms of depression, which may resemble the normal effects of new motherhood (eg, fatigue, difficulty concentrating). They
should also advise women to contact them if depressive symptoms continue for > 2 wk or interfere with daily activities or if women have suicidal or homicidal thoughts. In such cases, postpartum depression (see p. 2689) or another mental disorder may be present. A preexisting mental disorder is likely to recur or worsen during the puerperium, so affected women should be monitored closely.

Management at Home

The woman and infant can be discharged within 24 to 48 h postpartum; many family-centered obstetric units discharge them as early as 6 h postpartum if major anesthesia was not used and no complications occurred. Serious problems are rare, but a home visit, office visit, or phone call within 24 to 48 h is necessary. A routine postpartum visit is usually scheduled at 6 wk for women with an un-complicated vaginal delivery. If delivery was cesarean or other complications occurred, follow-up may be scheduled sooner.

Normal activities may be resumed as soon as the woman feels ready.

Intercourse may be resumed as soon as desired and comfortable; however, a laceration or episiotomy repair must be allowed to heal first.

Family planning: Pregnancy must be delayed for 1 mo if women were vaccinated against rubella at hospital discharge; also, subsequent obstetric outcomes are improved by delaying conception for at least 6 mo but preferably 18 mo after delivery. To minimize the chance of pregnancy, women should start using contraception as soon as they are discharged. If women are not breastfeeding, ovulation usually occurs about 4 to 6 wk postpartum, 2 wk before the first menses. However, ovulation can occur earlier; women have conceived as early as 2 wk postpartum. Women who are breastfeeding tend to ovulate and menstruate later, usually closer to 6 mo postpartum, although a few ovulate and menstruate (and become pregnant) as quickly as those who are not breastfeeding.

Women should choose a method of contraception based on the specific risks and benefits of various options. Breastfeeding status affects choice of contraceptive. For breast-feeding women, nonhormonal methods are usually preferred; among hormonal methods, progestin-only oral contraceptives, depot medroxyprogesterone acetate injections, and progestin implants are preferred because they do not affect milk production. Estrogen-progesterone contraceptives can interfere with milk production and should not be initiated until milk production is well established. Combined estrogen-progesterin vaginal rings can be used after 4 wk postpartum if women are not breastfeeding.

A diaphragm should be fitted only after complete involution of the uterus, at 6 to 8 wk; meanwhile, foams, jellies, and condoms should be used. Intrauterine devices are typically best placed after 4 to 6 wk postpartum to minimize risk of expulsion.

Mastitis

Mastitis is painful inflammation of the breast, usually accompanied by infection.

Fever later in the puerperium is frequently due to mastitis. Staphylococcal species are the most common causes. Symptoms may include high fever, erythema, induration, tenderness, pain, swelling, and warmth to the touch. Mastitis is different from the pain and cracking of nipples that frequently accompanies the start of breastfeeding. Breast abscesses are very rare and occasionally caused by methicillin-resistant Staphylococcus aureus.

Diagnosis is clinical.

Treatment

• Antistaphylococcal antibiotics

Treatment includes encouragement of fluid intake and antibiotics aimed at Staphylococcus aureus, the most common causative pathogen. Examples are dicloxacillin 500 mg po q 6 h for 7 to 10 days and, for
women allergic to penicillin, erythromycin 250 mg po q 6 h. If women do not improve and do not have an abscess, vancomycin 1 g IV q 12 h or cefotetan 1 to 2 g IV q 12 h to cover resistant organisms should be considered. Breastfeeding should be continued during treatment because treatment includes emptying the affected breast.

Breast abscesses are treated mainly with incision and drainage. Antibiotics aimed at *S. aureus* are often used.

It is not clear whether antibiotics aimed at methicillin-resistant *S. aureus* are necessary for treatment of mastitis or breast abscess.

**Puerperal Endometritis**

Puerperal endometritis is uterine infection, typically caused by bacteria ascending from the lower genital or GI tract. Symptoms are uterine tenderness, abdominal or pelvic pain, fever, malaise, and sometimes discharge. Diagnosis is clinical, rarely aided by culture. Treatment is with broad-spectrum antibiotics (eg, clindamycin plus gentamicin).

Incidence of postpartum endometritis is affected mainly by the mode of delivery:

- Vaginal deliveries: 1 to 3%
- Scheduled caesarean deliveries (done before labor starts): 5 to 15%
- Unscheduled caesarean deliveries (done after labor starts): 15 to 20%

Patient characteristics also affect incidence.

**Etiology**

Endometritis may develop after chorioamnionitis during labor or postpartum. Predisposing conditions include

- Prolonged rupture of the membranes
- Internal fetal monitoring
- Prolonged labor
- Cesarean delivery
- Repeated digital examination
- Retention of placental fragments in the uterus
- Postpartum hemorrhage
- Colonization of the lower genital tract
- Anemia
- Bacterial vaginosis
- Young maternal age
- Low socioeconomic status

Infection tends to be polymicrobial; the most common pathogens include
Gram-positive cocci (predominantly group *B streptococci*, *Staphylococcus epidermidis*, and *Enterococcus* sp)

Anaerobes (predominantly peptostreptococci, *Bacteroides* sp, and *Prevotella* sp)

Gram-negative bacteria (predominantly *Gardnerella vaginalis*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*).

Uncommonly, peritonitis, pelvic abscess, pelvic thrombophlebitis (with risk of pulmonary embolism), or a combination develop. Rarely, septic shock and its sequelae, including death, occur.

**Symptoms and Signs**

Typically, the first symptoms are lower abdominal pain and uterine tenderness, followed by fever—most commonly within the first 24 to 72 h postpartum. Chills, headache, malaise, and anorexia are common. Sometimes the only symptom is a low-grade fever.

Pallor, tachycardia, and leukocytosis usually occur, and the uterus is soft, large, and tender. Discharge may be decreased or profuse and malodorous, with or without blood. When parametria are affected, pain and fever are severe; the large, tender uterus is indurated at the base of the broad ligaments, extending to the pelvic walls or posterior cul-de-sac. Pelvic abscess may manifest as a palpable mass separate from and adjacent to the uterus.

**Diagnosis**

- Clinical evaluation
- Usually tests to exclude other causes (eg, urinalysis and urine culture)

Diagnosis within 24 h of delivery is based on clinical findings of pain, tenderness, and temperature > 38° C after delivery. After the first 24 h, puerperal endometritis is presumed present if no other cause is apparent in patients with temperature ≥ 38° C on 2 successive days. Other causes of fever and lower abdominal symptoms include UTI, wound infection, septic pelvic thrombophlebitis, and perineal infection. Uterine tenderness is often difficult to distinguish from incisional tenderness in patients who have had a cesarean delivery.

Patients with low-grade fever and no abdominal pain are evaluated for other occult causes, such as atelectasis, breast engorgement or infection, UTI, and leg thrombophlebitis. Fever due to breast engorgement tends to remain ≤ 39° C. If temperature abruptly rises after 2 or 3 days of low-grade fever, the cause is probably an infection rather than breast engorgement.

Urinalysis and urine culture are usually done.

Endometrial cultures are rarely indicated because specimens collected through the cervix are almost always contaminated by vaginal and cervical flora. Endometrial cultures should be done only when endometritis is refractory to routine antibiotic regimens and no other cause of infection is obvious; sterile technique with a speculum is used to avoid vaginal contamination, and the sample is sent for aerobic and anaerobic cultures.

Blood cultures are rarely indicated and should be done only when endometritis is refractory to routine antibiotic regimens or clinical findings suggest septicemia. If fever persists for > 48 h (some clinicians use a 72-h cutoff) after endometritis is adequately treated, other causes such as pelvic abscess and pelvic thrombophlebitis should be considered. Abdominal and pelvic imaging, usually by CT, is sensitive for abscess but detects pelvic thrombophlebitis only if the clots are large. If imaging shows neither abnormality, a trial of heparin is typically begun to treat presumed pelvic thrombophlebitis, usually a diagnosis of exclusion. A therapeutic response confirms the diagnosis.
Treatment

• Clindamycin plus gentamicin, with or without ampicillin

Treatment is a broad-spectrum antibiotic regimen given IV until women are afebrile for 48 h. The first-line choice is clindamycin 900 mg q 8 h plus gentamicin 1.5 mg/kg q 8 h or 5 mg/kg once/day; ampicillin 1 g q 6 h is added if enterococcal infection is suspected or if no improvement occurs by 48 h. Continuing treatment with oral antibiotics is not necessary.

Prevention

Preventing or minimizing predisposing factors is essential. Appropriate hand washing should be encouraged. Vaginal delivery cannot be sterile, but aseptic techniques are used. Prophylactic antibiotics given when delivery is cesarean can reduce risk of endometritis by up to three fourths.

Postpartum Pyelonephritis

Pyelonephritis is a bacterial infection of the renal parenchyma.

Pyelonephritis may occur postpartum if bacteria ascend from the bladder. The infection may begin as asymptomatic bacteriuria during pregnancy and is sometimes associated with bladder catheterization to relieve urinary distention during or after labor. The causative organism is usually a type of coliform bacteria (e.g., *Escherichia coli*).

Symptoms include fever, flank pain, general malaise, and, occasionally, painful urination.

Diagnosis is by urinalysis and urine culture (see p. 2375).

Treatment

• Antibiotics

Initial treatment is ceftriaxone 1 to 2 g IV q 12 to 24 h alone or ampicillin 1 g IV q 6 h plus gentamicin 1.5 mg/kg IV q 8 h until women are afebrile for 48 h. Sensitivities with culture should be checked. Treatment is adjusted accordingly and continued for a total of 7 to 14 days; oral antibiotics are used after the initial IV antibiotics. Women should be encouraged to consume large amounts of liquids.

A urine culture should be repeated 6 to 8 wk after delivery to verify cure. If episodes of pyelonephritis recur, imaging should be considered to look for calculi or congenital malformations. Imaging during pregnancy is usually with ultrasonography; imaging after pregnancy is usually with contrast CT.

Postpartum Depression

Postpartum depression is depressive symptoms that last > 2 wk after delivery and that interfere with activities of daily living.

Postpartum depression occurs in 10 to 15% of women after delivery. Although every woman is at risk, women with the following are at higher risk:

• Baby blues

• Prior episode of postpartum depression

• Prior diagnosis of depression

• Family history of depression

• Significant life stressors
• Lack of support (eg, from partner or family members)

• Perimenstrual mood disorders

• Poor obstetric outcomes

The exact etiology is unknown; however, prior depression is the major risk, and hormonal changes during the puerperium, sleep deprivation, and genetic susceptibility may contribute.

Unlike the baby blues, which typically lasts 2 to 3 days (up to 2 wk) and is relatively mild, postpartum depression lasts > 2 wk and is disabling, interfering with activities of daily living.

**Symptoms and Signs**

Symptoms may include

• Extreme sadness

• Uncontrollable crying

• Insomnia or increased sleep

• Loss of appetite or overeating

• Irritability

• Headaches and body aches and pains

• Extreme fatigue

• Unrealistic worries about or disinterest in the baby

• Fear of harming the baby

• Suicidal ideation

• Anxiety

Typically, symptoms develop insidiously over 3 mo, but onset can be more sudden. Postpartum depression interferes with women's ability to care for themselves and the baby.

Psychosis rarely develops, but postpartum depression increases the risk of suicide and infanticide, which are the most severe complications.

Women may not bond with their infant, resulting in emotional, social, and cognitive problems in the child later.

Fathers are at increased risk of depression, and marital stress is increased.

Without treatment, postpartum depression can resolve spontaneously or become chronic depression. Risk of recurrence is about 1 in 3 to 4.

**Diagnosis**

• Clinical evaluation

• Sometimes formal depression scales
Early diagnosis and treatment substantially improve outcomes for women and their infant. Because of cultural and social factors, women may not volunteer symptoms of depression, so they should be asked about such symptoms before and after delivery. They also should be taught to recognize symptoms of depression, which they may mistake for the normal effects of new motherhood (eg, fatigue, difficulty concentrating). Women can be screened at the postpartum visit for postpartum depression using various depression scales (eg, Edinburgh Postnatal Depression Scale, Postpartum Depression Prediction Inventory, Postpartum Depression Screening Scale).

Postpartum depression (or other serious mental disorders) should be suspected if women have the following:

- Symptoms for > 2 wk
- Symptoms that interfere with daily activities
- Suicidal or homicidal thoughts (women should be asked specifically about such thoughts)
- Hallucinations, delusions, or psychotic behavior

Treatment

Treatment includes antidepressants and psychotherapy. Exercise therapy, light therapy, massage therapy, acupuncture, and ω-3 fatty acid supplementation have shown some benefit in small studies.
Chapter 268. Approach to the Care of Normal Infants and Children

Introduction

Routine care for infants and children aims to promote healthy development through education, routine vaccination, and early detection and treatment of disease.

Evaluation and Care of the Normal Neonate

Hand washing is critical for all personnel to prevent transmission of infection.

Active participation in the birth by the mother and her partner helps them adapt to parenting.

The First Few Hours

Immediately at delivery, the neonate's respiratory effort, heart rate, color, tone, and reflex irritability should be assessed; all are key components of the Apgar score assigned at 1 min and 5 min after birth (see Table 274-2 on p. 2770). Apgar scores between 8 and 10 indicate that the neonate is making a smooth transition to extrauterine life; scores ≤ 7 at 5 min (particularly if sustained beyond 10 min) are linked to higher neonatal morbidity and mortality rates. Many normal neonates have cyanosis 1 min after birth that clears by 5 min. Cyanosis that does not clear may indicate congenital cardiopulmonary anomalies or CNS depression.

In addition to Apgar scoring, neonates should be evaluated for gross deformities (eg, clubfoot, polydactyly) and other important abnormalities (eg, heart murmurs). The evaluation should ideally be done under a radiant warmer with the family close by.

Preventive interventions include administration into both eyes of an antimicrobial agent (eg, 0.5% erythromycin 1 cm ribbon, 1% tetracycline 1 cm ribbon, 1% silver nitrate solution 2 drops; in some countries, 2.5% povidone iodine drops) to prevent gonococcal and chlamydial ophthalmia and administration of vitamin K 1 mg IM to prevent hemorrhagic disease of the newborn.

Subsequently, the neonate is bathed, wrapped, and brought to the family. The head should be covered with a cap to prevent heat loss. Rooming-in and early breastfeeding should be encouraged so the family can get to know the baby and can receive guidance from staff members during the hospital stay. Breastfeeding is more likely to be successful when the family is given frequent and adequate support.

The First Few Days

Physical Examination

A thorough physical examination should be done within 24 h. Doing the examination with the mother and other family members present allows them to ask questions and the clinician to point out physical findings and provide anticipatory guidance.

Basic measurements include length, weight, and head circumference (see p. 2756). Length is measured from crown to heel; normal values are based on gestational age and should be plotted on a standard growth chart. When gestational age is uncertain or when the infant seems large or small for age, the gestational age can be precisely determined using physical and neuromuscular findings (see Fig. 268-1). These methods are typically accurate to ± 2 wk.

Many clinicians begin with examination of the heart and lungs, followed by a systematic head-to-toe examination, looking particularly for signs of birth trauma and congenital abnormalities.

Cardiorespiratory system: The heart and lungs are evaluated when the infant is quiet.
The clinician should identify where the heart sounds are loudest to exclude dextrocardia. Heart rate (normal: 100 to 160 beats/min) and rhythm are checked. Rhythm should be regular, although an irregular rhythm from premature atrial or ventricular contractions is not uncommon. A murmur heard in the first 24 h is most commonly caused by a patent ductus arteriosus. Daily heart examination confirms the disappearance of this murmur, usually within 3 days. Femoral pulses are checked and compared with brachial pulses. A weak or delayed femoral pulse suggests aortic coarctation or other left ventricular outflow tract obstruction. Central cyanosis suggests congenital heart disease, pulmonary disease, or sepsis.

The respiratory system is evaluated by counting respirations over a full minute because breathing in neonates is irregular; normal rate is 40 to 60 breaths/min. The chest wall should be examined for symmetry, and lung sounds should be equal throughout. Grunting, nasal flaring, and retractions are signs of respiratory distress.

Head and neck: In a vertex delivery, the head is commonly molded with overriding of the cranial bones at the sutures and some swelling and ecchymosis of the scalp (caput succedaneum). In a breech delivery, the head has less molding, with swelling and ecchymosis occurring in the presenting part (ie, buttocks, genitals, or feet). The fontanelles vary in diameter from a fingertip breadth to several centimeters. A large anterior fontanelle may be a sign of hypothyroidism.

A cephalohematoma is a common finding; blood accumulates between the periosteum and the bone, producing a swelling that does not cross suture lines. It may occur over one or both parietal bones and occasionally over the occiput. Cephalohematomas usually are not evident until soft-tissue edema subsides; they gradually disappear over several months.

Head size and shape are inspected to detect congenital hydrocephalus.

Numerous genetic syndromes cause craniofacial abnormalities (see p. 2970). The face is inspected for symmetry and normal development (particularly of the mandible, palate, pinnae, and external auditory canals).

The eyes may be easier to examine the day after birth because the birth process causes swelling around the eyelids. Eyes should be examined for the red reflex; its absence may indicate glaucoma, cataracts, or retinoblastoma. Subconjunctival hemorrhages are common and caused by forces exerted during delivery.

Low-set ears may indicate genetic anomalies, including trisomy 21. Malformed ears, external auditory canals, or both may be present in many genetic syndromes. Clinicians should look for external ear pits or tags, which are sometimes associated with hearing loss and kidney abnormalities.

The clinician should inspect and palpate the palate to check for soft or hard palate defects. Orofacial clefts are among the most common congenital defects. Some neonates are born with an epulis (a benign hamartoma of the gum), which, if large enough, can cause feeding difficulties and may obstruct the airway. These lesions can be removed; they do not recur. Some neonates are born with primary or natal teeth. Natal teeth do not have roots and may need to be removed to prevent them from falling out and being aspirated. Inclusion cysts called Epstein's pearls may occur on the roof of the mouth.

When examining the neck, the clinician must lift the chin to look for abnormalities such as cystic hygromas, goiters, and branchial arch remnants. Torticollis can be caused by a sternocleidomastoid hematoma due to birth trauma.

Abdomen and pelvis: The abdomen should be round and symmetric. A scaphoid abdomen may indicate a diaphragmatic hernia, allowing the intestine to migrate through it to the chest cavity in utero; pulmonary hypoplasia and postnatal respiratory distress may result. An asymmetric abdomen suggests an abdominal mass. Splenomegaly suggests congenital infection or hemolytic anemia. The kidneys may be palpable with deep palpation; the left is more easily palpated than the right. Large kidneys may indicate obstruction, tumor, or cystic disease. The liver is normally palpable 1 to 2 cm below the costal margin. An
umbilical hernia, due to a weakness of the umbilical ring musculature, is common but rarely significant. The presence of a normally placed, patent anus should be confirmed.

In boys, the penis should be examined for hypospadias or epispadias. In term boys, the testes should be in the scrotum. Scrotal swelling may signify hydrocele, inguinal hernia, or, more rarely, testicular torsion. With hydrocele, the scrotum transilluminates. Torsion, a surgical emergency, causes ecchymosis and firmness.

In term girls, the labia are prominent. Mucoid vaginal and serosanguineous secretions (pseudomenses) are normal; they result from exposure to maternal hormones in utero and withdrawal at birth. A small tag of hymenal tissue at the posterior fourchette, believed to be due to maternal hormonal stimulation, is sometimes present but disappears over a few weeks.

Ambiguous genitals (intersex) may indicate several uncommon disorders (eg, congenital adrenal hyperplasia; 5α-reductase deficiency; Klinefelter's, Turner's, or Swyer syndrome). Referral to an endocrinologist is indicated for evaluation and a discussion with the family about benefits and risks of immediate vs delayed sex assignment.

**Musculoskeletal system:** The extremities are examined for deformities, amputations (incomplete or missing limbs), contractures, and maldevelopment. Brachial nerve palsy due to birth trauma may manifest as limited or no spontaneous arm movement on the affected side, sometimes with adduction and internal rotation of the shoulder and pronation of the forearm.

The spine is inspected for signs of spina bifida, particularly exposure of the meninges, spinal cord, or both (meningomyelocele).

Orthopedic examination includes palpation of long bones for birth trauma (particularly clavicle fracture) but focuses on detection of hip dysplasia. Risk factors for dysplasia include female sex, breech position in utero, twin gestation, and family history. The Barlow and Ortolani maneuvers are used to check for dysplasia. These maneuvers must be done when neonates are quiet. The position is the same for both: Neonates are placed on their back with their hips and knees flexed to 90° (the feet will be off the bed), feet facing the clinician, who places an index finger on the greater trochanter and a thumb on the lesser trochanter.

For the Barlow maneuver, the clinician adducts the hip (ie, the knee is drawn across the body) while pushing the thigh posteriorly. A clunk indicates that the head of the femur has moved out of the acetabulum; the Ortolani maneuver then relocates it and confirms the diagnosis.

For the Ortolani maneuver, the hip is returned to the starting position; then the hip being tested is abducted (ie, the knee is moved away from the midline toward the examining table into a frog-leg position) and gently pulled anteriorly. A palpable clunk of the femoral head with abduction signifies movement of an already dislocated femoral head into the acetabulum and constitutes a positive test for hip dysplasia.

The maneuver may be falsely negative in infants > 3 mo because of tighter hip muscles and ligaments. If the examination is equivocal or the infant is at high risk (eg, girls who were in the breech position), hip ultrasonography should be done at 4 to 6 wk; some experts recommend screening ultrasonography at 4 to 6 wk for all infants with risk factors.

**Neurologic system:** The neonate's tone, level of alertness, movement of extremities, and reflexes are evaluated. Typically, neonatal reflexes, including the Moro, suck, and rooting reflexes, are elicited:

- **Moro reflex:** The neonate's response to startle is elicited by pulling the arms slightly off the bed and releasing suddenly. In response, the neonate extends the arms with fingers extended, flexes the hips, and cries.

- **Rooting reflex:** Stroking the neonate's cheek or lateral lip prompts the neonate to turn the head toward the touch and open the mouth.
**Suck reflex**: A pacifier or gloved finger is used to elicit this reflex.

These reflexes are present for several months after birth and are markers of a normal peripheral nervous system.

**Skin**: A neonate's skin is usually ruddy; cyanosis of fingers and toes is common in the first few hours. Vernix caseosa covers most neonates > 24 wk gestation. Dryness and peeling often develop within days, especially at wrist and ankle creases.

Petechiae may occur in areas traumatized during delivery, such as the face when the face is the presenting part; however, neonates with diffuse petechiae should be evaluated for thrombocytopenia.

Many neonates have erythema toxicum, a benign rash with an erythematous base and a white or yellow papule. This rash, which usually appears 24 h after birth, is scattered over the body and can last for up to 2 wk.

**Screening**

Screening recommendations vary by clinical context and state requirements.

Blood typing is indicated when the mother has type O or Rh-negative blood or when minor blood antigens are present because hemolytic disease of the newborn (see p. 2665) is a risk.

All neonates are evaluated for jaundice throughout the hospital stay and before discharge. The risk of hyperbilirubinemia is assessed using risk criteria, measurement of bilirubin, or both (see also p. 2788). Bilirubin can be measured transcutaneously or in serum. Many hospitals screen all neonates and use a predictive nomogram to determine the risk of extreme hyperbilirubinemia. Follow-up is based on age at discharge, predischarge bilirubin level, and risk of developing jaundice.

Most states test for specific inherited diseases (see p. 3009), including phenylketonuria, tyrosinemia, biotinidase deficiency, homocystinuria, maple syrup urine disease, galactosemia, congenital adrenal hyperplasia, sickle cell disease, and hypothyroidism. Some states also include testing for cystic fibrosis, disorders of fatty acid oxidation, and other organic acidemias.

HIV screening is required by some states and is indicated for children of mothers known to be HIV-positive or those engaging in HIV high-risk behaviors.

Toxicology screening is indicated when any of the following are present: maternal history of drug use, unexplained placental abruption, unexplained premature labor, poor prenatal care, or evidence of drug withdrawal in the neonate.

**Hearing screening** varies by state. Some screen only high-risk neonates (see Table 268-1); others screen all. Initial screening often involves using a handheld device to test for echoes produced by healthy ears in response to soft clicks (otoacoustic emissions); if this test is abnormal, auditory brain stem response (ABR) testing is done. Some institutions use ABR testing as an initial screening test. Further testing by an audiologist may be needed.

**Routine Care and Observation**

Neonates can be bathed (if the parents wish) once their temperature has stabilized at 37° C for 2 h. The umbilical cord clamp can be removed when the cord appears dry, usually at 24 h. The umbilical stump should be kept clean and dry to prevent infection. Some centers apply isopropyl alcohol several times a day or a single dose of triple dye, a bacteriostatic agent believed to decrease bacterial colonization of the cord. The cord should be observed daily for redness or drainage because it can be a portal for infection.

[Circumcision, if desired by the family, can be safely done, using a local anesthetic, within the first few days.]
days of life. Circumcision should be delayed if the mother has taken anticoagulants or aspirin, if there is a family history of bleeding disorders, or if the neonate has displacement of the urethral meatus, hypospadias, or any other abnormality of the glans or penis (because the prepuce may be used later in plastic surgical repair). Circumcision should not be done if the neonate has hemophilia or another bleeding disorder.

Most neonates lose 5 to 7% of their birth weight during the first few days of life, primarily because fluid is lost in urine and insensibly and secondarily because meconium is passed, vernix caseosa is lost, and the umbilical cord dries.

In the first 2 days, urine may stain the diaper orange or pink because of urate crystals, which are a normal result of urine concentration. Most neonates void within 24 h after birth; the average time of first void is 7 to 9 h after birth, and most void at least 2 times in the 2nd 24 h of life. A delay in voiding is more common among male neonates and may result from a tight foreskin; a male neonate’s inability to void may indicate posterior urethral valves. Circumcision is usually delayed until at least after the first void; not voiding within 12 h of the procedure may indicate a complication.

If meconium has not been passed within 24 h, the clinician should consider evaluating the neonate for anatomic abnormalities, such as imperforate anus, Hirschsprung’s disease, and cystic fibrosis, which can cause meconium ileus.

Hospital Discharge

Neonates discharged within 48 h should be evaluated within 2 to 3 days to assess feeding success (breast or formula), hydration, and jaundice (for those at increased risk). Follow-up for neonates discharged after 48 h should be based on risk factors, including those for jaundice and for breastfeeding difficulties.

Nutrition in Infants

If the delivery was uncomplicated and the neonate is alert and healthy, the neonate can be brought to the mother for feeding immediately. Successful breastfeeding is enhanced by putting the neonate to the breast as soon as possible after delivery. Spitting mucus after feeding is common (because gastroesophageal smooth muscle is lax) but should subside within 48 h. If spitting mucus or emesis persists past 48 h or if vomit is bilious, complete evaluation of the upper GI and respiratory tracts is needed to detect congenital GI anomalies (see p. 2975).

Daily fluid and calorie requirements vary with age and are proportionately greater in neonates and infants than in older children and adults (see Tables 268-2 and 268-3). Relative requirements for protein and energy (g or kcal/kg body weight) decline progressively from the end of infancy through adolescence (see Table 1-4 on p. 5), although absolute requirements increase. For example, protein requirements decrease from 1.2 g/kg/day at 1 yr to 0.9 g/kg/day at 18 yr, and mean relative energy requirements decrease from 100 kcal/kg at 1 yr to 40 kcal/kg in late adolescence. Nutritional recommendations are generally not evidence-based. Requirements for vitamins depend on the intake of calories, protein, fat, carbohydrate, and amino acids.

Feeding problems: Minor variations in day-to-day food intake are common and, although often of concern to parents, usually require only reassurance and guidance unless there are signs of disease or changes in growth parameters, particularly weight (changes in the child’s percentile rank on standard growth curves are more significant than absolute changes).

[Table 268-2, Range of Average Water Requirements of Children at Different Ages Under Ordinary Conditions]

Loss of > 5 to 7% of birth weight in the first week indicates undernutrition. Birth weight should be regained by 2 wk, and a subsequent gain of about 20 to 30 g/day (1 oz/day) is expected for the first few
months. Infants should double their birth weight by about 6 mo.

**Breastfeeding**

Breast milk is the nutrition of choice. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for a minimum of 6 mo and introduction of appropriate solid food from 6 mo to 1 yr. Beyond 1 yr, breastfeeding continues for as long as both infant and mother desire, although after 1 yr breastfeeding should complement a full diet of solid foods and fluids. To encourage breastfeeding, practitioners should begin discussions prenatally, mentioning the multiple advantages:

- **For the child:** Nutritional and cognitive advantages and protection against infection, allergies, obesity, Crohn's disease, and diabetes
- **For the mother:** Reduced fertility during lactation, more rapid return to normal prepartum condition (eg, uterine involution, weight loss), and protection against osteoporosis, obesity, and ovarian and premenopausal breast cancers

Milk production is fully established in primiparas by 72 to 96 h and in less time in multiparas. The first milk produced is colostrum, a high-calorie, high-protein, thin yellow fluid that is immunoprotective because it is rich in antibodies, lymphocytes, and macrophages; colostrum also stimulates passage of meconium. Subsequent breast milk has the following characteristics:

- Has a high lactose content, providing a readily available energy source compatible with neonatal enzymes
- Contains large amounts of vitamin E, an important antioxidant that may help prevent anemia by increasing erythrocyte life span
- Has a Ca:P ratio of 2:1, which prevents Ca-deficiency tetany
- Favorably changes the pH of stools and the intestinal flora, thus protecting against bacterial diarrhea
- Transfers protective antibodies from mother to infant
- Contains cholesterol and taurine, which are important to brain growth, regardless of the mother's diet
- Is a natural source of ω-3 and ω-6 fatty acids

These fatty acids and their very long-chain polyunsaturated derivatives (LC-PUFAS), arachidonic acid (ARA) and docosahexaenoic acid (DHA), are believed to contribute to the enhanced visual and cognitive outcomes of breastfed compared with formula-fed infants.

If the mother's diet is sufficiently diverse, no dietary or vitamin supplementation is needed [Table 268-3: Calorie Requirements at Different Ages*]

for the mother or her term breastfed infant, with the exception of vitamin D 200 units once/day beginning in the first 2 mo for all infants exclusively breastfed. Premature and dark-skinned infants and infants with limited sunlight exposure (residence in northern climates) are especially at risk. After 6 mo, breastfed infants in homes where the water does not have adequate fluoride (supplemental or natural) should be given fluoride drops. Clinicians can obtain information about fluoride content from a local dentist.

Infants < 6 mo should not be given additional water because hyponatremia is a risk.

**Technique**

The mother should use whatever comfortable, relaxed position works best and should support her breast with her hand to ensure that it is centered in the infant's mouth, minimizing any soreness. The center of
the infant's lower lip should be stimulated with the nipple so that rooting occurs and the mouth opens wide. The infant should be encouraged to take in as much of the breast and areola as possible, placing the lips 2.5 to 4 cm from the base of the nipple. The infant's tongue then compresses the nipple against the hard palate. Initially, it takes at least 2 min for the let-down reflex to occur. Volume of milk increases as the infant grows and stimulation from suckling increases. Feeding duration is usually determined by the infant. Some mothers require a breast pump to increase or maintain milk production; in most mothers, a total of 90 min/day of breast pumping divided into 6 to 8 sessions produces enough milk for an infant who is not directly breastfed.

The infant should nurse on one breast until the breast softens and suckling slows or stops. The mother can then break suction with a finger before removing the infant from one breast and offering the infant the second. In the first days after birth, infants may nurse on only one side; then the mother should alternate sides with each feeding. If the infant tends to fall asleep before adequately nursing, the mother can remove the infant when suckling slows, burp the infant, and move the infant to the other side. This switch keeps the infant awake for feedings and stimulates milk production in both breasts. Mothers should be encouraged to feed on demand or about every 1 1/2 to 3 h (8 to 12 feedings/day), a frequency that gradually decreases over time; some neonates < 2500 g may need to feed even more frequently to prevent hypoglycemia. In the first few days, neonates may need to be wakened and stimulated; small infants and late preterm infants should not be allowed to sleep long periods at night. Large full-term infants who are feeding well (as evidenced by stooling pattern) can sleep longer. Eventually, a schedule that allows infants to sleep as long as possible at night is usually best for the infant and family.

Mothers who work outside the home can pump breast milk to maintain milk production while they are separated from their infants. Frequency varies but should approximate the infant's feeding schedule. Pumped breast milk should be immediately refrigerated if it is to be used within 48 h and immediately frozen if it is to be used after 48 h. Refrigerated milk that is not used within 96 h should be discarded because risk of bacterial contamination is high. Frozen milk should be thawed by placing it in warm water; microwaving is not recommended.

**Infant Complications**

The primary complication is underfeeding, which may lead to dehydration and hyperbilirubinemia. Risk factors for underfeeding include small or premature infants and mothers who are primiparous, who become ill, or who have had difficult or operative deliveries. A rough assessment of feeding adequacy can be made by daily diaper counts. By age 5 days, a normal neonate wets at least 6 diapers/day and soils at least 4 diapers/day; lower numbers suggest underhydration and undernutrition. Also, stools should have changed from dark meconium at birth to light brown and then yellow. Weight is also a reasonable parameter to follow (see p. 2704); not attaining growth landmarks suggests undernutrition. Constant fussiness before age 6 wk (when colic may develop unrelated to hunger or thirst) may also indicate underfeeding. Dehydration should be suspected if vigor of the infant's cry decreases or skin becomes turgid; lethargy and sleepiness are extreme signs of dehydration and should prompt testing for hyponatremia.

**Maternal Complications**

Common maternal complications include breast engorgement, sore nipples, plugged ducts, mastitis, and anxiety.

**Breast engorgement**, which occurs during early lactation and may last 24 to 48 h, may be minimized by early frequent feeding. A comfortable nursing brassiere worn 24 h/day can help, as can applying cool compresses after breastfeeding and taking a mild analgesic (eg, ibuprofen). Just before breastfeeding, mothers may have to use massage and warm compresses and express breast milk manually to allow
infants to get the swollen areola into their mouth. Excessive expression of milk between feedings facilitates engorgement, so expression should be done only enough to relieve discomfort.

For **sore nipples**, the infant's position should be checked; sometimes the infant draws in a lip and sucks it, which irritates the nipple. The mother can ease the lip out with her thumb. After feedings, she can express a little milk, letting the milk dry on the nipples. After breastfeeding, cool compresses reduce engorgement and provide further relief.

**Plugged ducts** manifest as mildly tender lumps in the breasts of lactating women who have no other systemic signs of illness. The lumps appear in different places and are not tender. Continued breastfeeding ensures adequate emptying of the breast. Warm compresses and massage of the affected area before breastfeeding may further aid emptying. Women may also alternate positions because different areas of the breast empty better depending on the infant's position at the breast. A good nursing brassiere is helpful because regular brassieres with wire stays or constricting straps may contribute to milk stasis in a compressed area.

**Mastitis** is common and manifests as a tender, warm, swollen, wedge-shaped area of breast. It is caused by engorgement, blocking, or plugging of an area of the breast; infection may occur secondarily, most often with penicillin-resistant *Staphylococcus aureus* and less commonly with *Streptococcus* sp or *Escherichia coli*. With infection, fever ≥ 38.5°C, chills, and flu-like aching may develop. Diagnosis is by history and examination. Cell counts (WBCs > 10^6/mL) and cultures of breast milk (bacteria > 10^3/mL) may distinguish infectious from noninfectious mastitis. If symptoms are mild and present < 24 h, conservative management (milk removal via breastfeeding or pumping, compresses, analgesics, a supportive brassiere, and stress reduction) may be sufficient. If symptoms do not lessen in 12 to 24 h or if the woman is acutely ill, antibiotics that are safe for breastfeeding infants and effective against *S. aureus* (eg, dicloxacillin, cloxacillin, or cephalaxin 500 mg po qid) should be started; duration of treatment is 10 to 14 days. Community-acquired methicillin-resistant *S. aureus* should be considered if cases do not respond promptly to these measures or if an abscess is present. Complications of delayed treatment are recurrence and abscess formation. Breastfeeding may continue during treatment.

**Maternal anxiety**, frustration, and feelings of inadequacy may result from lack of experience with breastfeeding, mechanical difficulties holding the infant and getting the infant to latch on and suck, fatigue, difficulty assessing whether nourishment is adequate, and postpartum physiologic changes. These factors and emotions are the most common reasons mothers stop breastfeeding. Early follow-up with a pediatrician or consultation with a lactation specialist is helpful and effective for preventing early breastfeeding termination.

**Drugs**

Breastfeeding mothers should avoid taking drugs if possible. When drug therapy is necessary, the mother should avoid contraindicated drugs and drugs that suppress lactation (eg, bromocriptine, levodopa, trazodone). The US National Library of Medicine maintains an extensive database regarding drugs and breastfeeding, which should be consulted regarding use of or exposure to specific drugs or classes of drugs. For some common drugs contraindicated for breastfeeding mothers, see Table 268-4.

When drug treatment is necessary, the safest known alternative should be used; when possible, most drugs should be taken immediately after breastfeeding or before the infant's longest sleep period, although this strategy is less helpful with neonates who nurse frequently and exclusively. Knowledge of the adverse effects of most drugs comes from case reports and small studies. Safety of some (eg, acetaminophen, ibuprofen, cephalosporins, insulin) has been determined by extensive research, but others are considered safe only because there are no case reports of adverse effects. Drugs with a long history of use are generally safer than newer drugs for which few data exist.

**Weaning**

Weaning can occur whenever the mother and infant mutually desire, although preferably not until the infant is at least 12 mo old. Gradual weaning over weeks or months during the time solid food is
introduced is most common; some mothers and infants stop abruptly without problems, but others continue breastfeeding 1 or 2 times/day for 18 to 24 mo or longer. There is no correct schedule.

### Formula Feeding

The only acceptable alternative to breastfeeding during the first year is formula; water can cause hyponatremia, and whole cow's milk is not nutritionally complete. Advantages of formula feeding include the ability to quantify the amount of nourishment and the ability of family members to participate in feedings. But all other factors being equal, these advantages are outweighed by the undisputed health benefits of breastfeeding.

Commercial infant formulas are available as powders, concentrated liquids, and prediluted (ready-to-feed) liquids; each contains vitamins, and most are supplemented with iron. Formula should be prepared with fluoridated water; fluoride drops (0.25 mg/day po) should be given after age 6 mo in areas where fluoridated water is unavailable and when using prediluted liquid formula, which is prepared with nonfluoridated water.

Choice of formula is based on infant need. Cow's milk-based formula is the standard choice unless excessive fussiness, spitting up, or gas suggests sensitivity to cow's milk protein or lactose intolerance (extremely rare in neonates); then, a soy formula may be recommended. All soy formulas in the US are lactose free, but some infants allergic to cow's milk protein may also be allergic to soy protein; then, a hydrolyzed formula is indicated. This formula may be derived from cow's milk but has triglycerides, proteins, and monosaccharides predigested to smaller, nonallergenic components. True elemental formulas (proteins broken down to amino acids) are available for the few infants who have allergic reactions to hydrolyzed formula. Special carbohydrate-free formulas are also available.

Bottle-fed infants are fed on demand, but because formula is digested more slowly than breast milk, they typically can go longer between feedings, initially every 3 to 4 h. Initial volumes of 15 to 60 mL (0.5 to 2 oz) can be increased gradually during the first week of life up to 90 mL (3 oz) about 6 times/day, which supplies about 120 kcal/kg at 1 wk for a 3-kg infant.

### Solid Foods

The WHO recommends exclusive breastfeeding for about 6 mo, with introduction of solid foods thereafter. Other organizations suggest introducing solid food between age 4 mo and 6 mo while continuing breastfeeding or bottle-feeding. Before 4 mo, solid food is not needed nutritionally, and the extrusion reflex, in which the tongue pushes out anything placed in the mouth, makes feeding of solids difficult.

Initially, solid foods should be introduced after breastfeeding or bottle-feeding to ensure adequate nourishment. Iron-fortified rice cereal is traditionally the first food introduced because it is nonallergenic, easily digested, and a needed source of iron. It is generally recommended that one new, single-ingredient food be introduced per week so that food allergies can be identified. Foods need not be introduced in any specific order, although in general they can gradually be introduced by increasingly coarser textures—eg, from rice cereal to soft table food to chopped table food. Meat, pureed to prevent aspiration, is a good source of iron and zinc (both of which can be limited in the diet of an exclusively breastfed infant) and is therefore a good early complementary food. Vegetarian infants can get adequate iron from iron-fortified cereals and grains, peas, and dried beans and adequate zinc from yeast-fermented whole-grain breads and fortified infant cereals.

Home preparations are equivalent to commercial foods, but commercial preparations of carrots, beets, turnips, collard greens, and spinach are preferable before 1 yr if available because they are screened for nitrates. High nitrate levels, which can induce methemoglobinemia in young children, are present when vegetables are grown using water supplies contaminated by fertilizer.

Foods to avoid include

- Eggs, peanuts, and cow's milk, usually until children are 1 yr to prevent food sensitivities
• Honey until 1 yr because infant botulism is a risk

• Foods that, if aspirated, could obstruct the child's airway (eg, nuts, round candies, popcorn, hot dogs, meat unless it is pureed, grapes unless they are cut into small pieces)

Nuts should be avoided until age 2 or 3 because they do not fully dissolve with mastication and small pieces can be aspirated whether bronchial obstruction is present or not, causing pneumonia and other complications.

At or after 1 yr, children can begin drinking whole cow's milk; reduced-fat milk is avoided until 2 yr, when their diet essentially resembles that of the rest of the family. Parents should be advised to limit milk intake to 16 to 20 oz/day in young children; higher intake can reduce intake of other important sources of nutrition and contribute to iron deficiency.

Juice is a poor source of nutrition, contributes to dental caries, and should be limited to 4 to 6 oz/day or avoided altogether.

By about 1 yr, growth rate usually slows. Children require less food and may refuse it at some meals. Parents should be reassured and advised to assess a child's intake over a week rather than at a single meal or during a day. Underfeeding of solid food is only a concern when children do not achieve expected weights at an appropriate rate.

**Health Supervision of the Well Child**

Well-child visits aim to do the following:

• Promote health

• Prevent disease through routine vaccinations and education

• Detect and treat disease early

• Guide parents to optimize the child's emotional and intellectual development

The American Academy of Pediatrics (AAP) has recommended preventive health care schedules (see Tables 268-5, 268-6, and 268-7) for children who have no significant health problems and who are growing and developing satisfactorily. Those who do not meet these criteria should have more frequent and intensive visits. If children come under care for the first time late on the schedule or if any items are not done at the suggested age, children should be brought up to date as soon as possible. Children who have developmental, psychosocial, or chronic disease may require more frequent counseling and treatment visits that are separate from preventive care visits. If parents are high risk, are parents for the first time, or wish to have a conference, a prenatal visit with the pediatrician is appropriate.

In addition to physical examination, practitioners should evaluate the child's motor, cognitive, and social development and parent-child interactions. These assessments can be made by taking a thorough history from parents and child, making direct observations, and sometimes seeking information from outside sources such as teachers and child care providers. Tools are available for office use to facilitate evaluation of cognitive and social development (see p. 2757).

Both physical examination and screening are important parts of preventive health care in infants and children. Most parameters, such as weight, are included for all children; others are applicable to selected patients, such as lead screening in 1- and 2-yr-olds.

**Anticipatory guidance** is also important to preventive health care. It includes

• Obtaining information about the child and parents (eg, via questionnaire, interview, or evaluation)
• Working with parents to promote health (forming a therapeutic alliance)

• Teaching parents what to expect in their child's development, how they can help enhance development (e.g., by establishing a healthy lifestyle), and what the benefits of a healthy lifestyle are

[Table 268-5. Recommendations for Preventive Care During Infancy]\(^3\)

[Table 268-6. Recommendations for Preventive Care During Early and Middle Childhood]\(^3\)

[Table 268-7. Recommendations for Preventive Care During Adolescence]\(^3\)

Physical Examination

**Growth:** Length (crown-heel) or height (once children can stand) and weight should be measured at each visit. Head circumference should be measured at each visit through 24 mo. Growth rate should be monitored using a growth curve with percentiles; deviations in these parameters should be evaluated (see Ch. 271).

**Blood pressure:** Starting at age 3 yr, BP should be routinely checked by using an appropriately sized cuff. The width of the inflatable rubber bag portion of the BP cuff should be about 40% of the circumference of the upper arm, and its length should cover 80 to 100% of the circumference. If no available cuff fits the criteria, using the larger cuff is better.

Systolic and diastolic BPs are considered normal if they are < 90th percentile; actual values for each percentile vary by sex, age, and size (as height percentile), so reference to published tables is essential. Systolic and diastolic BP measurements between the 90th and 95th percentiles should prompt continued observation and assessment of hypertensive risk factors. If measurements are consistently ≥ 95th percentile, children should be considered hypertensive, and a cause should be determined.

**Head:** The most common abnormality is fluid in the middle ear (otitis media with effusion), manifesting as a change in the appearance of the tympanic membrane. Clinicians should screen for hearing deficits (see p. 2717).

Eyes should be assessed at each visit. Clinicians should check for esotropia or exotropia; for abnormalities in globe size (suggested congenital glaucoma); for a difference in pupil size, iris color, or both (suggesting Homer's syndrome, trauma, or neuroblastoma; asymmetric pupils may be normal or represent an ocular, autonomic, or intracranial disorder); and for absence or distortion of the red reflex (suggesting cataract or retinoblastoma).

Ptosis and eyelid hemangioma obscure vision and require attention. Infants born at < 32 wk gestation should be assessed by an ophthalmologist for evidence of retinopathy of prematurity (see p. 2781) and for refractive errors, which are more common. By age 3 or 4 yr, vision testing by Snellen charts or newer testing machines can be used. E charts are better than pictures; visual acuity of < 20/30 should be evaluated by an ophthalmologist.

Detection of dental caries is important, and referral to a dentist should be made if cavities are present, even in children who have only deciduous teeth. Thrush is common among infants and not usually a sign of immunosuppression.

**Heart:** Auscultation is done to identify new murmurs, heart rate abnormalities, or rhythm disturbances; benign flow murmurs are common and need to be distinguished from pathologic murmurs. The chest wall is palpated for the apical impulse to check for cardiomegaly; femoral pulses are palpated to check for asymmetry, which suggests aortic coarctation.

**Abdomen:** Palpation is repeated at every visit because many masses, particularly Wilms' tumor and neuroblastoma, may be apparent only as children grow. Stool is often palpable in the left lower quadrant.
**Spine and extremities:** Children old enough to stand should be screened for scoliosis by observing posture, shoulder tip and scapular symmetry, torso list, and especially paraspinal asymmetry when children bend forward (see p. 2912).

At each visit before children start to walk, they should be checked for developmental dysplasia of the hip. The Barlow and Ortolani maneuvers (see p. 2701) are used until about age 4 mo. After that, dysplasia may be suggested by unequal leg length, adductor tightness, or asymmetry of abduction or leg creases.

Toeing-in can result from adduction of the forefoot, tibial torsion, or femoral torsion. Only pronounced cases require therapy and referral to an orthopedist.

**Genital examination:** Girls should be offered a pelvic examination and Papanicolaou (Pap) testing at age 18 or when they become sexually active—whichever occurs first. All sexually active patients should be screened for sexually transmitted diseases.

Testicular and inguinal evaluation should be done at every visit, specifically looking for undescended testes in infants and young boys, testicular masses in older adolescents, and inguinal hemia in boys of all ages.

**Screening**

**Blood tests:** To detect iron deficiency, clinicians should determine Hct or Hb at age 9 to 12 mo in term infants, at age 5 to 6 mo in premature infants, and annually in menstruating adolescents. Testing for Hb S can be done at age 6 to 9 mo (see p. 944) if not done as part of neonatal screening.

Recommendations for blood testing for lead exposure vary by state. In general, testing should be done between ages 9 mo and 1 yr in children at risk of exposure (those living in housing built before 1980) and should be repeated at 24 mo. If the clinician is not sure of a child's risk, testing should be done. Levels > 10 μg/dL (> 0.48 μmol/L) pose a risk of neurologic damage (see p. 3343), although some experts question this threshold because they believe that any lead in the system can be toxic.

Cholesterol screening is indicated for children > 2 yr who are at high risk because of family history. If other risk factors are present or family history is uncertain, testing is at the discretion of the physician.

**Hearing tests:** (See also Ch. 47.) Parents may suspect a hearing deficit if their child ceases responding appropriately to noises or voices or does not understand or develop speech (see Table 268-8). Because hearing deficits impair language development, hearing problems must be remedied as early as possible. The clinician therefore should seek parental input about hearing at every visit during early childhood and be prepared to do formal testing or refer to an audiologist whenever there is any question of the child's ability to hear.

Audiometry can be done in the primary care setting; most other audiologic procedures (eg, otoacoustic emission testing, brain stem auditory evoked response) should be done by an audiologist. Conventional audiometry can be used for children beginning at about age 3 yr; young children can also be tested by observing their responses to sounds made through headphones, watching their attempts to localize the sound or complete a simple task. Tympanometry, another in-office procedure (see p. 435), can be used with children of any age and is useful for evaluating middle ear function. Abnormal tympanograms often denote eustachian tube dysfunction or the presence of middle ear fluid that cannot be detected during otoscopic examination. Pneumatic otoscopy is helpful in evaluating middle ear status, but combining it with tympanometry is more informative than either procedure alone.

[Table 268-8. Normal Hearing in Very Young Children*]

[Table 268-9. Case Rates of Some Diseases Preventable by Vaccines]

**Other screening tests:** Tuberculin testing should be done if children have been exposed to TB (eg, to
an infected family member or close contact), if they have had a family member with a positive tuberculin test, if they were born in developing countries, or if their parents are new immigrants from those countries or have been recently incarcerated.

For sexually active adolescents, dipstick analysis for leukocytes and urinary testing for chlamydial infection should be done annually. Screening for cervical dysplasia should be begun within 3 yr of onset of sexual activity.

**Prevention**

Preventive counseling is part of every well-child visit and covers a broad spectrum of topics, such as recommendations to have infants sleep on their backs, injury prevention, nutritional and exercise advice, and discussions of violence, firearms, and substance abuse.

[Table 268-10. Recommended Immunization Schedule for Ages 0-6 yr]

[Table 268-11. Recommended Immunization Schedule for Ages 7-18 yr]

**Safety:** Recommendations for injury prevention vary by age. Some examples follow.

For infants from birth to 6 mo:

• Using a rear-facing car seat

• Reducing home water temperature to < 49° C (< 120° F)

• Preventing falls

• Using sleeping precautions: Placing infants on their back, not sharing a bed, using a firm mattress, and not allowing stuffed animals, pillows, and blankets in the crib

• Avoiding foods and objects that children can aspirate

For infants from 6 to 12 mo:

• Continuing to use a rear-facing car seat

• Continuing to place infants on their back to sleep

• Not using baby walkers

• Using safety latches on cabinets

• Preventing falls from changing tables and around stairs

• Vigilantly supervising children when in bathtubs and while learning to walk

For children aged 1 to 4 yr:

• Using an age- and weight-appropriate car seat (infants can face forward when they reach 9 kg [20 lb] and age 12 mo, but rear-facing is still the safest position)

• Reviewing automobile safety both as passenger and pedestrian

• Tying window cords
• Using safety caps and latches

• Preventing falls

• Removing handguns from the home

[Table 268-12. Catch-Up Immunization Schedule for Ages 4 Mo-18 yr]

For children ≥ 5 yr:

• All of the above

• Using a bicycle helmet and protective sports gear

• Instructing children about safe street crossing

• Closely supervising swimming and sometimes requiring the use of life jackets during swimming

**Nutrition:** Poor nutrition underlies the epidemic of obesity in children (see p. 60). Recommendations vary by age; for children up to 2 yr, see p. 2703. As children grow older, parents can allow them some discretion in food choices, while keeping the diet within healthy parameters. Children should be guided away from frequent snacking and foods that are high in calories, salt, and sugar. Soda has been implicated as a major contributor to obesity.

**Exercise:** Physical inactivity also underlies the epidemic of obesity in children, and the benefits of exercise in maintaining good physical and emotional health should induce parents to make sure their children develop good habits early in life. During infancy and early childhood, children should be allowed to roam and explore in a safe environment under close supervision. Outdoor play should be encouraged from infancy.

As children grow older, play becomes more complex, often evolving to formal school-based athletics. Parents should set good examples and encourage both informal and formal play, always keeping safety issues in mind and promoting healthy attitudes about sportsmanship and competition. Participation in sports and activities as a family provides children with exercise and has important psychologic and developmental benefits. Screening of children before sports participation is recommended (see p. 3295).

Limits to television watching, which is linked directly to inactivity and obesity, should start at birth and be maintained throughout adolescence. Similar limits should be set for video games and noneducational computer time as children grow older.

**Vaccination**

**Effectiveness of vaccination:** Vaccination has been profoundly effective in preventing serious disease (see Table 268-9). Many health care practitioners currently in practice have seen few or no cases of diseases that were once extremely common and fatal.

**Vaccination schedule:** Vaccination follows a schedule recommended by the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the American Academy of Family Physicians (see Tables 268-10, 268-11, and 268-12). The latest recommendations can be obtained at www.cdc.gov/vaccines; vaccination status should be reassessed at every visit. For adverse effects and details of administration of specific vaccines, see Ch. 131.

**Colic**

**Colic is paroxysms of crying and irritability in an infant.**

Although the term colic suggests an intestinal origin, etiology is unknown. Colic often begins at about 6
wk and spontaneously abates between 3 and 4 mo. Paroxysms of crying and unhappiness develop at about the same time of day or night and continue for hours for no apparent reason. A few infants cry almost incessantly. Excessive crying may cause aerophagia, which results in flatulence and abdominal distention. Typically, colicky infants eat and gain weight well, although vigorous nonnutritive sucking may suggest excessive hunger. Colic probably has no relation to development of an insistent, impatient personality.

**Evaluation**

**History and physical examination:** History should establish whether the infant’s crying is outside the normal range (up to 3 h/day in a 6-wk-old infant). Then it must distinguish colic from other causes of excessive crying (see p. 2735), including fever, UTI, ear infection, and maltreatment. Thorough questioning may reveal that crying is not the chief concern but a symptom that the parents have used to justify their visiting the physician to present another problem—eg, concern over the death of a previous child or over their feelings of inability to cope with a new infant. A thorough physical examination typically detects no abnormalities but reassures parents. Physicians should also offer reassurance that they understand how stressful a colicky infant can be for parents.

**Testing:** No testing is necessary unless specific abnormalities are detected by history and examination.

**Treatment**

Parents should be reassured that the infant is healthy, that the irritability is not due to poor parenting, and that colic will resolve on its own with no long-term adverse effects. The following may help:

- For infants who cry for short periods: Being held, rocked, or patted gently
- For infants who have a strong sucking urge and who fuss soon after a feeding: Opportunity to suck more (eg, a pacifier)
- If bottle-feeding takes < 15 to 20 min: Nipples with smaller holes, a pacifier, or both
- For very active, restless infants: Paradoxically, being swaddled tightly

An infant swing, music, and white noise (eg, from a vacuum cleaner, car engine, or clothes or hair dryer) may also be calming.

A milk-substitute formula may be tried briefly to determine whether infants have milk intolerance, but frequent formula switching should be avoided. Sometimes in breastfed infants, removing milk or another food from the mother's diet brings relief.

**Constipation**

Constipation is responsible for up to 5% of pediatric office visits. It is defined as delay or difficulty in the passing of hard, sometimes large stools for ≥ 2 wk.

The frequency of normal bowel movements varies for infants. In the first year, the average number of bowel movements ranges from 2 to 4/day. This number also varies depending on whether infants are breastfed or formula-fed (breastfed infants have more frequent bowel movements). In general, signs of effort (eg, straining) do not signify constipation; infants only gradually develop the muscles to assist a bowel movement. After age 1 yr, children average 1 bowel movement/day.

**Etiology**

Constipation in children is divided into 2 main types:

- Organic (5%)
Functional (95%)

Organic: Organic causes involve specific structural, neurologic, toxic/metabolic, or intestinal disorders. They are rare but important to recognize (see Table 268-13).

The most common cause is

- Hirschsprung's disease

Other organic causes that may manifest in the neonatal period or later include

- Anorectal malformations
- Cystic fibrosis
- Metabolic disorders (eg, hypothyroidism, hypercalcemia, hyperkalemia)
- Spinal cord abnormalities

Functional: Functional constipation is difficulty passing stools for reasons other than organic causes.

In infants, the use of formula can lead to small, hard stools.

In older children, diets low in fiber and high in dairy lead to hard stools that are uncomfortable to pass and can cause anal fissures. Children sometimes put off having bowel movements because they have discomfort caused by fissures or because they do not want to interrupt play. To avoid having a bowel movement, children may tighten the external sphincter muscles, pushing the stool higher in the rectal vault. If this behavior is repeated, the rectum stretches to accommodate the retained stool. The urge to defecate is then decreased, and the stool becomes harder, leading to a vicious circle of painful defecation and worsened constipation. Occasionally, soft stool passes around the impacted stool and leads to stool incontinence.

Stress, toilet training, desire for control, and sexual abuse are also some of the functional causes of stool retention and subsequent constipation.

Evaluation

Evaluation should focus on differentiating functional constipation from constipation with an organic cause.

History: History of present illness in neonates should determine whether meconium has been passed at all and, if so, when. For older infants and children, history should note onset and duration of constipation, frequency and consistency of stools, and timing of symptoms—whether they began after a specific event, such as introduction of certain foods or a stressor that could lead to stool retention (eg, introduction of toilet training). Important associated symptoms include soiling (stool incontinence), discomfort during defecation, and blood on or in the stool. The composition of the diet, especially the amount of fluids and fiber, should be noted.

Review of systems should ask about symptoms that suggest an organic cause, including new onset of poor suck, hypotonia, and ingestion of honey before age 12 mo (infantile botulism); cold intolerance, dry skin, fatigue, hypotonia, prolonged neonatal hyperbilirubinemia, urinary frequency, and excessive thirst (endocrinopathies); change in gait, pain or weakness in lower extremities, and urinary incontinence (spinal cord defects); night sweats, fever, and weight loss (cancer); and vomiting, abdominal pain, poor growth, intermittent diarrhea, and constipation (intestinal disorders).

Past medical history should ask about known disorders that can cause constipation, including cystic fibrosis and celiac sprue. Exposure to constipating drugs or lead paint dust should be noted. Clinicians should ask about delayed passage of meconium within the first 24 to 48 h of life, as well as previous
episodes of constipation and family history of constipation.

**Physical examination:** The physical examination begins with general assessment of the child's level of comfort or distress and overall appearance (including skin and hair condition). Height and weight should be measured and plotted on growth charts.

Examination should focus on the abdomen and anus and on the neurologic examination.

The abdomen is inspected for distention, auscultated for bowel sounds, and palpated for masses and tenderness. The anus is inspected for a fissure (taking care not to spread the buttocks so forcefully as to cause one). A digital rectal examination is done gently to check stool consistency and to obtain a sample for occult blood testing. Rectal examination should note the tightness of the rectal opening and presence or absence of stool in the rectal vault. Examination includes placement of the anus and presence of any hair tuft or pit superior to the sacrum.

**Interpretation of findings:** A primary finding that suggests an organic cause in neonates is constipation from birth; those who have had a normal bowel movement are unlikely to have a significant structural disorder.

In older children, clues to an organic cause include constitutional symptoms (particularly weight loss, fever, or vomiting), poor growth (decreasing percentile on growth charts), an overall ill appearance, and any focal abnormalities detected during examination (see Table 268-13). A well-appearing child who has no other complaints besides constipation, who is not on any constipating drugs, and who has a normal examination likely has a functional disorder.

A distended rectum filled with stool or the presence of an anal fissure is consistent with functional constipation in an otherwise normal child. Constipation that began after starting a constipating drug or that coincides with a dietary change can be attributed to that drug or food. Foods that are known to be constipating include dairy (eg, milk, cheese, yogurt) and starches and processed foods that do not contain fiber. However, if constipation complaints begin after ingestion of wheat, celiac sprue should be considered. History of a new stress (eg, a new sibling) or other potential causes of stool retention behavior, with normal physical findings, support a functional etiology.

**Red flags:** The following findings are of particular concern:

- Delayed passage of meconium (> 24 to 48 h after birth)
- Hypotonia and poor suck (suggesting infant botulism)
- Abnormal gait and deep tendon reflexes (suggesting spinal cord involvement)

**Testing:** For patients whose histories are consistent with functional constipation, no tests are needed unless there is no response to conventional treatment. An abdominal x-ray should be done if patients have been unresponsive to treatment or an organic cause is suspected. Tests for organic causes should be done based on the history and physical examination (see Table 268-13):

- Barium enema, rectal manometry, and biopsy (Hirschsprung's disease)
- Plain x-rays of lumbosacral spine; MRI considered (tethered spinal cord or tumor)
• Thyroid-stimulating hormone and thyroxine (hypothyroidism)

• Blood lead level (lead poisoning)

• Stool for botulinum toxin (infant botulism)

• Sweat test and genetic testing (cystic fibrosis)

• Ca and electrolytes (metabolic derangement)

• IgA and IgG antigliadin antibodies, IgA antiendomysium antibodies, IgA antitissue glutaminase (celiac disease)

**Treatment**

Specific organic causes should be treated.

Functional constipation is ideally initially treated with

• Dietary changes

• Behavior modification

**Dietary changes** include adding prune juice to formula for infants, increasing fruits and vegetables for older infants and children, increasing water intake, and decreasing the amount of constipating foods (eg, milk, cheese).

**Behavior modification** for older children involves encouraging regular stool passage after meals if they are toilet trained and providing a reinforcement chart and encouragement to them. For children who are in the process of toilet training, it is sometimes worthwhile to give them a break from training until the constipation concern has passed.

Unresponsive constipation is treated by disimpacting the bowel and maintaining a regular diet and stool routine. Disimpaction can occur through oral or rectal agents. Oral agents require consumption of large volumes of liquid. Rectal agents can feel invasive and can be difficult to give. Both methods can be done by parents under medical supervision; however, disimpaction sometimes requires hospitalization if outpatient management is unsuccessful. Usually, infants do not require extreme measures, but if intervention is required, a glycerin suppository is typically adequate. For maintenance of healthy bowels, some children may require OTC dietary fiber supplements. These supplements require consuming 32 to 64 oz of water/day to be effective (see Table 268-14).

**Key Points**

• Functional constipation accounts for about 95% of cases.

• Organic causes are rare but need to be considered.

• Delayed passage of meconium for > 24 to 48 h after birth raises suspicion of structural disorders, especially Hirschsprung's disease.

• Early intervention with dietary and behavior changes can successfully treat functional constipation.

**Cough**

Cough is a reflex that helps clear the airways of secretions, protects the airway from foreign body aspiration, and can be the manifesting symptom of a disease. Cough is one of the most common complaints for which parents bring their children to a health care practitioner.
Etiology

Causes of cough differ depending on whether the symptoms are acute (< 4 wk) or chronic (see Table 268-15).

For **acute cough**, the most common cause is

- Viral URI

For **chronic cough**, the most common causes are

- Asthma (most common)
- Gastroesophageal reflux disorder (GERD)
- Postnasal drip

Foreign body aspiration and diseases such as cystic fibrosis and primary ciliary dyskinesia are less common, although they can all result in persistent cough.

Evaluation

**History:** History of present illness should cover duration and quality of cough (barky, staccato, paroxysmal) and onset (sudden or indolent). The physician should ask about associated symptoms, some of which are ubiquitous (eg, runny nose, sore throat, fever). Other associated symptoms suggest a cause; they include headache, itchy eyes, and sore throat (postnasal drip); wheezing and cough with exertion (asthma); night sweats (TB); post-tussive emesis, spitting up after feedings, or apparent discomfort or arching with lying down (GERD). For children 6 mo to 4 yr, the parents should be asked about potential for foreign body aspiration, including older siblings or visitors with small toys, access to small objects, and consumption of small, smooth foods (eg, peanuts, grapes).

**Review of systems** should note symptoms of possible causes, including abdominal pain (some bacterial pneumonias), weight loss or poor weight gain and foul-smelling stools (cystic fibrosis), and muscle soreness (possible association with viral illness or atypical pneumonia but usually not with bacterial pneumonia).

**Past medical history** should cover recent respiratory infections, repeated pneumonias, history of known allergies or asthma, risk factors for TB (eg, exposure to person who has known or suspected TB infection, exposure to prisons, HIV infection, travel to or immigration from countries that have endemic infection), and exposure to respiratory irritants.

**Physical examination:** Vital signs, including respiratory rate, temperature, and $O_2$ saturation, should be noted. Signs of respiratory distress (eg, nasal flaring, intercostal retractions, cyanosis, grunting, stridor, marked anxiety) should be noted.

Head and neck examination should focus on presence and amount of nasal discharge and the condition of the nasal turbinates (pale, boggy, or inflamed). The pharynx should be checked for postnasal drip.

The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy.

Lung examination focuses on presence of stridor, wheezing, rales, rhonchi, decreased breath sounds, and signs of consolidation (eg, egophony, E to A change, dullness to percussion).

Abdominal examination should focus on presence of abdominal pain, especially in the upper quadrants
Examination of extremities should note clubbing or cyanosis of nail beds (cystic fibrosis).

**Red flags:** The following findings are of particular concern:

- Cyanosis or hypoxia on pulse oximetry
- Stridor
- Respiratory distress
- Toxic appearance
- Abnormal lung examination

**Interpretation of findings:** Clinical findings frequently indicate a specific cause (see Table 268-15); the distinction between acute and chronic cough is particularly helpful.

Other characteristics of the cough are helpful but less specific. A barky cough suggests croup or tracheitis; it can also be characteristic of psychogenic cough or a postrespiratory tract infection cough. A staccato cough is consistent with a viral or atypical pneumonia. A paroxysmal cough is characteristic of pertussis or certain viral pneumonias (adenovirus). Failure to thrive or weight loss can occur with TB or cystic fibrosis. Nighttime cough can indicate postnasal drip or asthma. Coughing at the beginning of sleep and in the morning with waking usually indicates sinusitis; coughing in the middle of the night is more consistent with asthma. In young children with sudden cough and no fever or URI symptoms, the examiner should have a high index of suspicion for foreign body aspiration.

**Testing:** Children with red flag findings should have pulse oximetry and chest x-ray, as should those whose symptoms are prolonged (eg, > 4 wk) or worsening.

Children with stridor, drooling, fever, and marked anxiety need to be evaluated for epiglottitis, typically in the operating room by an ENT specialist prepared to immediately place an endotracheal or tracheostomy tube. If foreign body aspiration is suspected, chest x-ray with inspiratory and expiratory views should be done.

Children with TB risk factors or weight loss should have a chest x-ray and PPD testing for TB.

Children with repeated episodes of pneumonia, poor growth, or foul-smelling stools should have a chest x-ray and sweat testing for cystic fibrosis.

Acute cough in children with URI symptoms and no red flag findings is usually caused by a viral infection, and testing is rarely indicated. Many other children without red flag findings have a presumptive diagnosis after the history and physical examination. Testing is not necessary in such cases; however, if empiric treatment has been instituted and has not been successful, testing may be necessary. For example, if allergic sinusitis is suspected and treated with an antihistamine that does not alleviate symptoms, a head CT may be necessary for further evaluation. Suspected GERD unsuccessfully treated with an H2 blocker may require evaluation with a pH probe and a swallowing study.

**Treatment**

Treatment is management of the underlying disorder. For example, antibiotics should be given for bacterial pneumonia; bronchodilators and anti-inflammatory drugs should be given for asthma. Children with viral infections should receive supportive care, including O2 and bronchodilators as needed.

Little evidence exists to support the use of cough suppressants and mucolytic agents. Coughing is an important mechanism for clearing secretions from the airways and can assist in recovery from respiratory infections. Use of nonspecific drugs for cough suppression is discouraged in children.
Key Points

• Clinical diagnosis is usually adequate.
• A high index of suspicion for foreign body aspiration is needed if children are age 6 mo to 4 yr.
• Antitussives and expectorants lack proof of effect in most cases.
• Chest x-rays should be taken in patients with red flag findings or chronic cough.

Crying

All infants and young children cry as a form of communication; it is the only means they have to express a need. Thus, most crying is in response to hunger, discomfort (eg, a wet diaper), or separation, and it ceases when the needs are met (eg, by feeding, changing, cuddling). This crying is normal and tends to lessen in duration and frequency after 3 mo of age. However, crying that persists after attempts to address routine needs and efforts to console or that is prolonged in relation to the child’s baseline should be investigated to identify a specific cause.

Etiology

Cause of crying is

• Organic in < 5%
• Functional in 95%

Organic: Organic causes, although rare, must always be considered. Causes to consider are classified as cardiac, GI, infectious, and traumatic (see Table 268-16). Of these, potential life threats include heart failure, intussusception, volvulus, meningitis, and intracranial bleeding due to head trauma.

Colic (see p. 2725) is excessive crying that has no identifiable organic cause and that occurs at least 3 h/day > 3 days/wk for > 3 wk.

Evaluation

History: History of present illness focuses on onset of crying, duration, response to attempts to console, and frequency or uniqueness of episodes. Parents should be asked about associated events or conditions, including recent immunizations, trauma (eg, falls), interaction with a sibling, infections, drug use, and relationship of crying with feedings and bowel movements.

Review of systems focuses on symptoms of causative disorders, including constipation, diarrhea, vomiting, arching of back, explosive stools, and bloody stools (GI disorders); fever, cough, wheezing, nasal congestion, and difficulty breathing (respiratory infection); and apparent pain during bathing or changing (trauma).

Past medical history should note previous episodes of crying and conditions that can potentially predispose to crying (eg, history of heart disease, developmental delay).

Physical examination: Examination begins with a review of vital signs, particularly for fever and tachypnea. Initial observation assesses the infant or child for signs of lethargy or distress and notes how the parents are interacting with the child.

The infant or child is undressed and observed for signs of respiratory distress (eg, super-clavicular and subcostal retractions, cyanosis). The entire body surface is inspected for swelling, bruising, and abrasions.
Auscultatory examination focuses on signs of respiratory infection (eg, wheezing, rales, decreased breath sounds) and cardiac compromise (eg, tachycardia, gallop, holosystolic murmur, systolic click). The abdomen is palpated for signs of tenderness. The diaper is removed for examination of the genitals and anus to look for signs of testicular torsion (eg, red-ecchymotic scrotum, pain on palpation), hair tourniquet on the penis, inguinal hernia (eg, swelling in the inguinal region or scrotum), and anal fissures.

Extremities are examined for signs of fracture (eg, swelling, erythema, tenderness, pain with passive motion). Fingers and toes are checked for hair tourniquets.

The ears are examined for signs of trauma (eg, blood in the canal or behind the tympanic membrane) or infection (eg, red, bulging tympanic membrane). The corneas are stained with fluorescein and examined with a blue light to rule out corneal abrasion, and the fundi are examined with an ophthalmoscope for signs of hemorrhage. (If retinal hemorrhages are suspected, examination by an ophthalmologist is advised.) The oropharynx is examined for signs of thrush or oral abrasions. The skull is gently palpated for signs of fracture.

**Red flags:** The following findings are of particular concern:

- Respiratory distress
- Bruising and abrasions
- Extreme irritability
- Fever and inconsolability (meningitis)
- Fever in an infant ≤ 6 wk of age

*[Table 268-16. Some Causes of Crying]*

**Interpretation of findings:** A high index of suspicion is warranted when evaluating crying. Parental concern is an important variable. When concern is high, the clinician should be wary even when there are no conclusive findings because the parents may be reacting subconsciously to subtle but significant changes. Conversely, a very low level of concern, particularly if there is lack of parental interaction with the infant or child, can indicate a bonding problem or an inability to assess and manage the child's needs. Inconsistency of the history and the child's clinical presentation should raise concerns about possible abuse.

It is helpful to distinguish the general area of concern. For example, with fever, the most likely etiology is infectious; respiratory distress without fever indicates possible cardiac etiology or pain. Abnormalities in stool history or abdominal pain during examination is consistent with a GI etiology. Specific findings often suggest certain causes (see [Table 268-16]).

The time frame is also helpful. Crying that has been intermittent over a number of days is of less concern than sudden, constant crying. Whether the cry is exclusive to a time of day or night is helpful. For example, recent onset of crying at night in an otherwise happy, healthy infant or child may be consistent with night terrors or constipation.

The character of the cry is also revealing. Parents frequently can distinguish a cry that is painful in character from a frantic or scared cry. It is also important to determine the level of acuity. An inconsolable infant or child is of more concern than an infant or child who is well-appearing and consolable in the office.

**Testing:** Testing is targeted at the suspected cause (see [Table 268-16]) and pays particular attention to potential life threats, unless the history and physical examination are sufficient for diagnosis. When there are few or no specific clinical findings and no testing is immediately indicated, close follow-up and reevaluation are appropriate.
Treatment

The underlying organic disorder should be treated. Support and encouragement are important for parents when the infant or child has no apparent underlying disorder. Swaddling an infant in the first month of life can be helpful. Holding an infant or child and responding to crying as quickly as possible are helpful in decreasing the duration of crying. It is also valuable to encourage parents, if they are feeling frustrated, to take a break from a crying baby and put the infant or child down in a safe environment for a few minutes. Educating parents and "giving permission" to take a break are helpful in preventing abuse. Supplying resources for support services to parents who seem overwhelmed may prevent future concerns.

Key Points

• Crying is part of normal development and is most prevalent during the first 3 mo of life.
• Excessive crying with organic causes needs to be differentiated from colic.
• Less than 5% of crying has an organic cause.
• When no organic cause is identified, parents may need support.

Diarrhea

Diarrhea is frequent loose or watery bowel movements that deviate from a child's normal pattern. However, breastfed infants who are not yet receiving solid food often have frequent loose bowel movements that are considered normal.

Diarrhea may be accompanied by anorexia, vomiting, acute weight loss, fever, or passage of blood. If diarrhea is severe or prolonged, dehydration is likely. Even in the absence of dehydration, chronic diarrhea usually results in weight loss or failure to gain weight.

Diarrhea is a very common pediatric concern and causes 2 to 3 million deaths/yr worldwide. It accounts for about 9% of hospitalizations in the US among children aged < 5 yr.

For diarrhea in adults, see p. 88.

Pathophysiology

Mechanisms of diarrhea may include the following:

• Osmotic
• Secretory
• Inflammatory
• Malabsorptive

Osmotic diarrhea results from the presence of nonabsorbable solutes in the GI tract, as with lactose intolerance. Fasting for 2 to 3 days stops osmotic diarrhea.

Secretory diarrhea results from substances (eg, bacterial toxins) that increase secretion of Cl ions and water into the intestinal lumen. Secretory diarrhea does not stop with fasting.

Inflammatory diarrhea is associated with conditions that cause inflammation or ulceration of the intestinal mucosa (eg, Crohn's disease, ulcerative colitis). The resultant out-pouring of plasma, serum proteins, blood, and mucous increases fecal bulk and fluid content.
Malabsorption may result from osmotic or secretory mechanisms or conditions that lead to less surface area in the bowel. Conditions such as short bowel syndrome and conditions that speed up transit time cause diarrhea due to decreased absorption.

**Etiology**

The causes and significance of diarrhea (see Table 268-17) differ depending on whether it is acute (< 2 wk) or chronic (> 2 wk). Most cases of diarrhea are acute.

**Acute diarrhea** usually is caused by

- Gastroenteritis
- Antibiotic use
- Food allergies
- Food poisoning

Most gastroenteritis is caused by a virus; however, any enteric pathogen can cause acute diarrhea.

**Chronic diarrhea** usually is caused by

- Dietary factors
- Infection
- Celiac disease

Chronic diarrhea can also be caused by anatomic disorders and disorders that interfere with absorption or digestion.

[Table 268-17. Some Causes of Diarrhea]

**Evaluation**

**History:** History of present illness focuses on quality, frequency, and duration of stools, as well as on any accompanying fever, vomiting, abdominal pain, or blood in the stool. Parents are asked about current or recent (within 2 mo) antibiotic use. Elements of the diet should be established; they include amounts of juice, foods high in sugar, and processed foods. Any history of hard stools or constipation should be noted. Risk factors for infection should be assessed; they include recent travel; exposure to questionable food sources; and recent contact with animals at a petting zoo, reptiles, or someone with similar symptoms.

**Review of systems** should seek symptoms of complications and causes. Symptoms of complications include weight loss and decreased frequency of urination and fluid intake (dehydration). Symptoms of causes include urticarial rash associated with food intake (food allergy); nasal polyps, sinusitis, and poor growth (cystic fibrosis); arthritis and anal fissures (inflammatory bowel disease); and anorexia, anemia, and rash (celiac sprue).

**Past medical history** should assess known causative disorders (eg, immunocompromise, cystic fibrosis, celiac sprue, inflammatory bowel disease) in the patient and family members. Drug history should be reviewed for current or recent antibiotic use.

**Physical examination:** Vital signs should be reviewed for indications of dehydration (eg, tachycardia, hypotension) and fever.
General assessment includes checking for signs of lethargy or distress. Growth parameters should be noted.

Because the abdominal examination may elicit discomfort, it is advisable to begin the examination with the head. Examination should focus on the mucous membranes to assess whether they are moist or dry. Nasal polyps; psoriasiform dermatitis around the eyes, nose, and mouth; and oral ulcerations should be noted.

Examination of the extremities focuses on skin turgor, capillary refill time, and presence of petechiae or purpura. Other forms of rash and signs of erythematous, swollen joints should be noted.

Abdominal examination focuses on distention, tenderness, and quality of bowel sounds (e.g., high-pitched, normal, absent). Examination of the genitals focuses on presence of rashes and signs of anal fissures or ulcerative lesions.

Red flags: The following findings are of particular concern:

- Tachycardia, hypotension, and lethargy (significant dehydration)
- Bloody stools and extreme abdominal tenderness (volvulus, intussusception, partial obstruction)
- Bloody stool, fever, petechiae, and purpura (hemolytic-uremic syndrome)

Interpretation of findings: Antibiotic-related, postinfectious, and anatomic-related causes of diarrhea are typically clear from the history. Determination of the time frame helps establish whether diarrhea is acute or chronic. Establishing the level of acuity is also important. Most cases of acute diarrhea have a viral etiology, are low acuity, and cause fever and nonbloody diarrhea. However, bacterial diarrhea can lead to serious consequences; manifestations include fever, bloody diarrhea, and possibly a petechial or purpuric rash.

Symptoms associated with chronic diarrhea can vary and those of different conditions can overlap. For example, Crohn's disease and celiac sprue can cause oral ulcerations, a number of conditions can cause rashes, and any condition can lead to a poor growth pattern. If the cause is unclear, further tests are done based on clinical findings (see Table 268-17).

Testing: Testing is unnecessary in most cases of acute self-limited diarrhea. However, if the evaluation suggests an etiology other than viral gastroenteritis, testing should be directed by the suspected etiology (see Table 268-17).

If dehydration is suspected, screening laboratory tests should be done (for electrolytes).

Treatment

Specific causes are treated (e.g., gluten-free diet for children with celiac disease).

General treatment focuses on hydration, which can usually be done orally; IV hydration is rarely essential. (CAUTION: Antidiarrheal drugs [e.g., loperamide] are not recommended for infants and young children.

Rehydration: Oral rehydration solution (ORS) should contain complex carbohydrate or 75 mEq/L glucose and 75 mEq/L Na (total 245 mOsm/L solution). Sports drinks, sodas, juices, and similar drinks do not meet these criteria and should not be used. They generally have too little Na and too much carbohydrate to take advantage of Na/glucose cotransport, and the osmotic effect of the excess carbohydrate may result in additional fluid loss.

ORS is recommended by the WHO and is widely available in the US without a prescription. Premixed solutions are also available at most pharmacies and supermarkets.

Small, frequent amounts are used, starting with 5 mL q 5 min and increasing gradually as tolerated (see
also p. 2809). Generally, 50 mL/kg is given over 4 h for mild dehydration, and 100 mL/kg is given over 4 h for moderate dehydration. For each diarrheal stool, an additional 10 mL/kg (up to 240 mL) is given. After 4 h, the patient is reassessed. If signs of dehydration persist, the same volume is repeated.

Diet and nutrition: Children should eat an age-appropriate diet as soon as they have been rehydrated and are not vomiting. Infants may resume breast milk or formula.

For chronic diarrhea, adequate nutrition must be maintained, particularly of fat-soluble vitamins.

Key Points

• Diarrhea is a common pediatric concern.

• Gastroenteritis is the most common cause.

• Testing is rarely necessary in acute diarrhea.

• Dehydration is likely if diarrhea is severe or prolonged.

• Oral rehydration is effective in most cases.

• Antidiarrheal drugs (eg, loperamide) are not recommended for infants and young children.

Fever

Normal body temperature varies from person to person and throughout the day, but fever usually is defined as a core body (rectal) temperature ≥ 38.0° C.

Significance of fever depends on clinical context rather than peak temperature; some minor illnesses cause high fever, whereas some serious illnesses cause only a mild temperature elevation. Although parental assessment is frequently clouded by fear of fever, the history of a temperature taken at home should be considered equivalent to a temperature taken in the office.

Pathophysiology

Normal body temperature varies during the day by as much as 0.5° C and, in a child with a febrile illness, by as much as 1.0° C.

Fever occurs in response to the release of endogenous pyogenic mediators called cytokines. Cytokines stimulate the production of prostaglandins by the hypothalamus, which readjust and elevate the temperature set point (see p. 1152).

Fever plays an integral role in fighting infection and, although it is uncomfortable, does not necessitate treatment in an otherwise healthy child. Some studies even indicate that lowering the temperature can prolong some illnesses. However, fever increases the metabolic rate and the demands on the cardiopulmonary system. Therefore, fever can be detrimental to children with pulmonary or cardiac compromise or neurologic impairment. It can also be the catalyst for febrile seizures, a typically benign childhood condition (see p. 2898).

Etiology

Causes of fever (see Table 268-18) differ based on whether the fever is acute (≤ 7 days) or chronic (> 7 days). Response to antipyretics and height of the temperature have no direct relationship to the etiology or its seriousness.

Acute: Most acute fevers in infants and young children are caused by infection. The most common are
Viral respiratory or GI infections (most common causes overall)

Certain bacterial infections (otitis media, pneumonia, UTIs)

However, potential causes vary with the child’s age. Causes vary because neonates (infants < 28 days) and young infants have decreased immunologic function and are therefore at greater risk of infection and because neonates may have perinatally acquired infection. Common perinatal infections include those with group B streptococci, *Escherichia coli*, *Listeria monocytogenes*, and herpes simplex virus; these organisms can cause bacteremia, pneumonia, meningitis, or sepsis.

Febrile children < 36 mo are at special risk of occult bacteremia (pathogenic bacteria in the bloodstream but without focal symptoms or signs). The most common causative organisms of occult bacteremia used to be *Streptococcus pneumoniae* and *Haemophilus influenzae*; vaccination against both is now widespread in the US and Europe, making occult bacteremia less common and potentially changing the common causative organisms.

Rare, noninfectious causes of acute fevers include heatstroke and toxic ingestions (eg, of drugs with anticholinergic effects). Some vaccinations can cause fever for days (eg, with pertussis vaccination) and even 1 or 2 wk (eg, with measles vaccination) after administration. These fevers typically last from a few hours to a day. If the child is otherwise well, no evaluation is necessary. Teething does not cause fever.

Chronic: Chronic fever suggests various potential causes, including autoimmune disorders, collagen vascular diseases (eg, juvenile idiopathic arthritis, inflammatory bowel disease), cancer (eg, leukemia, lymphoma), and chronic infections (eg, osteomyelitis, TB). Miscellaneous causes include factitious fever and cases in which etiology is not identified.

The most common causes include

Benign infectious causes (prolonged viral illnesses, back-to-back illnesses—especially in young children)

Collagen vascular diseases, autoimmune disorders, and cancer are much less common.

Evaluation

History: **History of present illness** should note degree and duration of fever, method of measurement, and the dose and frequency of antipyretics (if any). Important associated symptoms that suggest serious illness include poor appetite, irritability, lethargy, and change in crying (eg, duration, character). Associated symptoms that may suggest the cause include vomiting, diarrhea (including presence of blood or mucus), cough, difficulty breathing, favoring of an extremity or joint, and strong or foul-smelling urine. Drug history should be reviewed for indications of drug-induced fever.

Factors that predispose to infection are identified. In neonates, these factors include prematurity, prolonged rupture of membranes, maternal fever, and positive prenatal tests (usually for group B streptococcal infections, cytomegalovirus infections, or sexually transmitted diseases). For all children, predisposing factors include recent exposures to infection (including family and caretaker infection), indwelling medical devices (eg, catheters, ventriculoperitoneal shunts), recent surgery, and travel and environmental exposures (eg, to ticks, mosquitoes, cats, farm animals, or reptiles).

Review of systems should note symptoms suggesting possible causes, including runny nose and congestion (viral URI), headache (sinusitis, Lyme disease, meningitis), ear pain or waking in the night with signs of discomfort (otitis media), cough or wheezing (pneumonia, bronchiolitis), abdominal pain (pneumonia, gastroenteritis, UTI, abdominal abscess), back pain (pyelonephritis), and any history of joint swelling or redness (Lyme disease, osteomyelitis). A history of repeated infections (immunodeficiency) or symptoms that suggest a chronic illness, such as poor weight gain or weight loss (TB, cancer), is
identified. Certain symptoms can help direct the evaluation toward noninfectious causes; they include heart palpitations, sweating, and heat intolerance (hyperthyroidism) and recurrent or cyclic symptoms (a rheumatoid, inflammatory, or hereditary disorder).

**Past medical history** should note previous fevers or infections and known conditions predisposing to infection (eg, congenital heart disease, sickle cell anemia, cancer, immunodeficiency). A family history of an autoimmune disorder or other hereditary conditions (eg, familial dysautonomia, familial Mediterranean fever) is sought. Vaccination history is reviewed to identify patients at risk of infections that can be prevented by a vaccine.

**Physical examination:** Vital signs are reviewed, noting abnormalities in temperature and respiratory rate. In ill-appearing children, BP should also be measured. Temperature should be measured rectally in infants for accuracy. Any child with cough, tachypnea, or labored breathing requires pulse oximetry. The child's overall appearance and response to the examination are important. A febrile child who is overly compliant or listless is of more concern than one who is unco-operative. However, an irritable infant or child who is inconsolable is also of concern. The febrile child who looks quite ill, especially when the temperature has come down, is of great concern and requires in-depth evaluation and continued observation. However, children who appear more comfortable after antipyretic therapy do not always have a benign disorder.

The examination seeks signs of causative disorders (see Table 268-19).

**Red flags:** The following findings are of particular concern:

- Age < 1 mo
- Lethargy, listlessness, or toxic appearance
- Respiratory distress
- Petechiae or purpura
- Inconsolability

**Interpretation of findings:** Although serious illness does not always cause high fever, and many high fevers result from self-limited viral infections, a temperature of ≥ 39°C in children < 3 yr indicates higher risk of occult bacteremia.

**Acute fever** is infectious in most cases, and of these, most are viral. History and examination are adequate to make a diagnosis in older children who are otherwise well and not toxic-appearing. Typically, they have a viral respiratory illness (recent ill contact, runny nose, wheeze, or cough) or GI illness (ill contact, diarrhea, and vomiting). Other findings also suggest specific causes (see Table 268-19).

However in infants < 36 mo, the possibility of occult bacteremia, plus the frequent absence of focal findings in neonates and young infants with serious bacterial infection, necessitates a different approach. Evaluation varies by age group. Accepted categories are neonates (≤ 28 days), young infants (1 to 3 mo), and older infants and children (3 to 36 mo). Regardless of clinical findings, a neonate with fever requires immediate hospitalization and testing to rule out a dangerous infection. Young infants may require hospitalization depending on screening laboratory results and the likelihood that they will be brought in for follow-up.

**Chronic fever** requires a high index of suspicion for the many potential causes. However, certain findings can suggest the disorder: erythema chronicum migrans rash, intermittent joint swelling, and neck pain (Lyme disease); intermittent headaches with runny nose or congestion (sinusitis); weight loss, high-risk exposure, and night sweats (TB); weight loss or difficulty gaining weight, heart palpitations, and sweating (hyperthyroidism); and weight loss, anorexia, and night sweats (cancer). Certain conditions (eg,
granulomatous diseases) may manifest with non-specific symptoms and a history that involves repeated infections (eg, pneumonia, skin infections, abscesses, septicemia).

**Testing:** Testing depends on whether fever is acute or chronic.

For **acute fever**, testing for infectious causes is directed by the age of the child (see [Fig. 280-1](#) on p. 2842 and [Fig. 280-2](#) on p. 2843).

**All febrile children** < 3 mo require a WBC count with a manual differential, blood cultures, and urinalysis and urine culture (urine obtained by catheterization, not an external bag). Lumbar puncture is mandatory for children < 28 days; expert opinion varies about the need for the test in children aged 29 days to Table 268-19, Examination of the Febrile Child

2 mo. Chest x-ray, stool swabs for WBCs, stool cultures, and acute-phase reactant tests (eg, ESR, C-reactive protein) are done depending on symptoms and degree of suspicion.

**Febrile children between 3 mo and 36 mo** who look well and can be watched carefully do not require laboratory testing. If the child has symptoms or signs of specific infections, clinicians should order appropriate tests (eg, chest x-ray when there is hypoxemia, dyspnea, or grunting; urinalysis and culture when there is foul-smelling urine; lumbar puncture when there is abnormal behavior or meningismus). If the child looks ill or has a temperature > 39° C but has no localizing signs, blood counts and cultures and urine tests should be considered as well as a lumbar puncture.

For **febrile children** > 36 mo, testing should be directed by history and examination; screening blood cultures and WBC counts are not indicated.

For **chronic fever**, testing for noninfectious causes should be directed by history, physical examination, and suspected disorder (eg, thyroid-stimulating hormone [TSH] and thyroxine [T₄] for suspected hyperthyroidism; antinuclear antibodies and Rh factor for suspected juvenile idiopathic arthritis).

Children without focal findings should have initial screening tests, including

- CBC with differential
- Urinalysis and culture
- ESR (C-reactive protein is also considered, although one is not necessarily better than the other)
- PPD for TB screening

An elevated ESR suggests inflammation (infection, TB, autoimmune disorder, cancer), and further testing can be done. If the WBC count is normal, indolent infection is less likely; however, if infection is suspected clinically, serologic testing for possible causes (eg, Lyme disease, cat-scratch disease, mononucleosis, cytomegalovirus) can be done, as well as blood cultures. Imaging tests can be helpful in detecting tumors, collections of purulent material, or osteomyelitis. The type of test is determined by the specific concern. For example, head CT is used for diagnosis of sinusitis; both CT and MRI are used for identification of a tumor and metastatic lesions, and bone scanning is used for detection of osteomyelitis. Bone marrow aspiration can be done to detect cancers such as leukemia.

**Treatment**

Treatment is directed at the underlying disorder.

Fever in an otherwise healthy child does not necessarily require treatment. Although antipyretics can provide comfort, they do not change the course of an infection. In fact, fever is an integral part of the
inflammatory response to infection and can help the child fight the infection. However, most clinicians use antipyretics to help alleviate discomfort and to reduce physiologic stresses in children who have cardiopulmonary disorders, neurologic disorders, or a history of febrile seizures.

**Antipyretic drugs** that are typically used include

- Acetaminophen
- Ibuprofen

Acetaminophen tends to be preferred because ibuprofen decreases the protective effect of prostaglandins in the stomach and, if used chronically, can lead to gastritis. The dosage of acetaminophen is 10 to 15 mg/kg po or rectally q 4 to 6 h. Ibuprofen dosage is 10 mg/kg po q 6 h. Use of one antipyretic at a time is preferred; however, some clinicians alternate the 2 drugs to treat high fever (eg, acetaminophen at 6 AM, 12 PM, and 6 PM and ibuprofen at 9 AM, 3 PM, and 9 PM). This approach is not encouraged because caregivers may become confused and inadvertently exceed the recommended daily dose. Aspirin should be avoided because it increases the risk of Reye's syndrome (see p. 2937) if certain viral illnesses such as influenza and varicella are present.

**Nondrug approaches** to fever include putting the child in a warm or tepid bath, using cool compresses, and undressing the child. Caregivers should be cautioned not to use a cold water bath, which is uncomfortable and, by inducing shivering, may paradoxically elevate body temperature. As long as the temperature of the water is slightly cooler than the temperature of the child, a bath provides temporary relief.

**Things to avoid:** Wiping the body down with isopropyl alcohol should be strongly discouraged because alcohol can be absorbed through the skin and cause toxicity. Numerous folk remedies exist, ranging from the harmless (eg, putting onions or potatoes in socks) to the uncomfortable (eg, coining, cupping).

**Key Points**

- Most acute fever is caused by viral infections.
- Causes and evaluation of acute fever differ depending on the age of a child.
- Children < 36 mo can have a bacterial bloodstream infection without localizing signs (occult bacteremia).
- Teething does not cause fever.
- Antipyretics do not alter the outcome but may make children feel better.

**Nausea and Vomiting**

Nausea is the sensation of impending emesis and is frequently accompanied by autonomic changes, such as increased heart rate and salivation. Nausea and vomiting typically occur in sequence; however, they can occur separately (eg, vomiting can occur without preceding nausea as a result of increased intracranial pressure).

Vomiting is uncomfortable and can cause dehydration because fluid is lost and because the ability to rehydrate by drinking is limited.

**Pathophysiology**

Vomiting is the final part of a sequence of events coordinated by the emetic center located in the medulla. The emetic center can be activated by afferent neural pathways from digestive (eg, pharynx, stomach, small bowel) and nondigestive (eg, heart, testes) organs, the chemoreceptor trigger zone located in the area postrema on the floor of the 4th ventricle (containing dopamine and serotonin receptors), and other CNS centers (eg, brain stem, vestibular system).
Etiology

The causes of vomiting vary with age and range from relatively benign to potentially life threatening (see Table 268-20). Vomiting is a protective mechanism that provides a means to expel potential toxins; however, it can also indicate serious disease (eg, intestinal obstruction). Bilious vomiting indicates a high intestinal obstruction and, especially in an infant, requires immediate evaluation.

Infants: Infants normally spit up small amounts (usually < 5 to 10 mL) during or soon after feedings, often when being burped. Rapid feeding, air swallowing, and overfeeding may be causes, although spitting up occurs even without these factors. Occasional vomiting may also be normal, but repeated vomiting is abnormal.

The most common causes of vomiting in infants and neonates include the following:

- Acute viral gastroenteritis
- Gastroesophageal reflux disease

Other important causes in infants and neonates include the following:

- Pyloric stenosis
- Intestinal obstruction (eg, meconium ileus, volvulus, intestinal atresia, stenosis)
- Intussusception (should be considered in an infant ≥ 3 mo)

Less common causes of recurrent vomiting include sepsis and food intolerance. Metabolic disorders (eg, urea cycle disorders, organic acidemias) are uncommon but can manifest with vomiting.

Older children: The most common cause is

- Acute viral gastroenteritis

Non-GI infections may cause a few episodes of vomiting. Other causes to consider include serious infection (eg, meningitis, pyelonephritis), acute abdomen (eg, appendicitis), increased intracranial pressure secondary to a space-occupying lesion (eg, caused by trauma or tumor), and cyclic vomiting.

In adolescents, causes of vomiting also include pregnancy, eating disorders, and toxic ingestions.

Evaluation

Evaluation includes assessment of severity (eg, presence of dehydration, surgical or other life-threatening disorder) and diagnosis of cause.

History: History of present illness should determine when vomiting episodes started, frequency, and character of episodes (particularly whether vomiting is projectile, bilious, or small in amount and more consistent with spitting up). Any pattern to the vomiting (eg, after feeding, only with certain foods, primarily in the morning or in recurrent cyclic episodes) should be established. Important associated symptoms include diarrhea (with or without blood), fever, anorexia, and abdominal pain, distention, or both. Stool frequency and consistency and urinary output should be noted.

Review of systems should seek symptoms of causative disorders, including weakness, poor suck, and failure to thrive (metabolic disorders); delay in passage of meconium, abdominal distention, and lethargy (intestinal obstruction); headache, nuchal rigidity, and vision change (intracranial disorders); food bingeing or signs of distorted body image (eating disorders); missed periods and breast swelling (pregnancy); rashes (eczematous suggests food intolerance, petechial suggests CNS infection, urticarial suggests food allergy); ear pain and sore throat (focal non-GI infection); and fever with headache, back
pain, or abdominal pain (meningitis, pyelonephritis, or appendicitis).

**Past medical history** should note history of travel (possible infectious gastroenteritis), any recent head trauma, and unprotected sex (pregnancy).

[Table 268-20. Some Causes of Vomiting in Infants, Children, and Adolescents]

**Physical examination:** Vital signs are reviewed for indicators of infection (eg, fever) and volume depletion (eg, tachycardia, hypotension).

During the general examination, signs of distress (eg, lethargy, irritability, inconsolable crying) and signs of weight loss ( cachexia) or gain are noted.

Because the abdominal examination may cause discomfort, the physical examination should begin with the head. The head and neck examination should focus on signs of infection (eg, red, bulging tympanic membrane; bulging anterior fontanelle;erythematous tonsils) and dehydration (eg, dry mucous membranes, lack of tears). The neck should be passively flexed to detect resistance or discomfort, suggesting meningeal irritation.

Cardiac examination should note presence of tachycardia (eg, dehydration, fever, distress). Abdominal examination should note distention; presence and quality of bowel sounds (eg, high-pitched, normal, absent); tenderness and any associated guarding, rigidity, or rebound ( peritoneal signs); and presence of organomegaly or mass.

The skin and extremities are examined for petechiae or purpura (severe infection) or other rashes (possible viral infection or signs of atopy), jaundice (possible metabolic disorder), and signs of dehydration (eg, poor skin turgor, delayed capillary refill).

Growth parameters and signs of developmental progress should be noted.

**Red flags:** The following findings are of particular concern:

- Lethargy and listlessness
- Inconsolability and bulging fontanelle in infant
- Nuchal rigidity, photophobia, and fever in older child
- Peritoneal signs or abdominal distention ("surgical" abdomen)
- Persistent vomiting with poor growth or development

**Interpretation of findings:** Initial findings help determine severity of diagnosis and need for immediate intervention.

- Any neonate or infant with recurrent or bilious (yellow or green) emesis or projectile vomiting most likely has a GI obstruction and probably requires surgical intervention.
- An infant or young child with colicky abdominal pain, signs of intermittent pain or listlessness, and absent or bloody stools needs to be evaluated for an intussusception.
- A child or adolescent with fever, nuchal rigidity, and photophobia should be evaluated for meningitis.
- A child or adolescent with fever and abdominal pain followed by vomiting, anorexia, and decreased bowel sounds should be evaluated for appendicitis.
- Recent history of head trauma or progressive headaches and visual changes indicate intracranial hypertension.
Other findings can be interpreted primarily depending on age (see Table 268-20).

In **infants**, irritability, choking, and respiratory signs (eg, stridor) may be manifestations of gastroesophageal reflux. A history of poor development or neurologic manifestations suggests a CNS or metabolic disorder. Delayed passage of meconium, later onset of vomiting, or both may indicate Hirschsprung's disease or an intestinal stenosis.

In **children and adolescents**, fever suggests infection; the combination of vomiting and diarrhea suggests acute gastroenteritis. Lesions on fingers and erosion of tooth enamel or an adolescent unconcerned about weight loss suggests an eating disorder. Morning nausea and vomiting, amenorrhea, and possibly weight gain suggest pregnancy. Vomiting that has occurred in the past and is episodic, short-lived, and has no other accompanying symptoms suggests cyclic vomiting.

**Testing:** Testing should be directed by suspected causative disorders (see Table 268-20). Imaging studies are typically done to evaluate abdominal pathology. Various specific blood tests are done to diagnose inherited metabolic disorders.

If dehydration is suspected, serum electrolytes should be measured.

**Treatment**

Treatment is targeted at the causative disorder. Drugs frequently used in adults to decrease nausea and vomiting are rarely used in children because the usefulness of treatment has not been proved and because they have potential risks of adverse effects and of masking an underlying condition.

Rehydration is important (see p. 2809).

**Key Points**

- In general, the most common cause of vomiting is acute viral gastroenteritis.

- Not all vomiting is caused by gastroenteritis.

- Diarrhea suggests an infectious GI cause.

- Bloody stools or lack of bowel movements suggests an obstructive cause.

- Persistent vomiting (especially in an infant) requires immediate evaluation.

**Separation and Stranger Anxiety**

**Separation anxiety:** Separation anxiety is crying when a parent leaves the room. It is normal when it starts at about 8 mo, peaks in intensity between 10 and 18 mo, and generally resolves by 24 mo. It should be distinguished from separation anxiety disorder (see p. 3052), which occurs at an older age, when such a reaction is developmentally inappropriate; refusal to go to school (or preschool) is a common manifestation.

Separation anxiety occurs at a time when infants start to become emotionally attached to their parents. Because they have no object permanence (incomplete memory and no sense of time), children fear that the departure of their parents is permanent. Separation anxiety resolves as children develop a sense of memory; they can keep an image of their parents in mind when the parents are gone and can recall that in the past, the parents returned.

Parents should be advised not to limit or forego separations in response to separation anxiety; this response could compromise the child's maturation and development. When parents leave the home (or leave the child at a child care center), they can try the following strategies:
Encouraging the person caring for the child to create distractions

Leaving without responding at length to a child's crying

Remaining calm and reassuring

Establishing routines at separations to ease the child's anxiety

Feeding the child and letting the child nap before parents leave (because separation anxiety may be worse when a child is hungry or tired)

If the parents must momentarily go to another room in the home, they should call to the child while in the other room to reassure the child. This strategy gradually teaches the child that parents are still present even though the child cannot see them.

Separation anxiety causes no long-term harm to children if it resolves by age 2 yr. If it persists beyond age 2, separation anxiety may or may not be a problem depending how much it interferes with the child's development. For children, feeling some fear when they leave for preschool or kindergarten is normal. This feeling should diminish with time. Rarely, excessive fear of separations inhibits children from attending child care or preschool or keeps them from playing normally with peers. This anxiety is probably abnormal (separation anxiety disorder—see p. 3052). In such cases, children require medical attention.

**Stranger anxiety:** Stranger anxiety is manifested by crying when an unfamiliar person approaches. It is normal when it starts at about 8 to 9 mo and usually abates by age 2 yr. Stranger anxiety is linked with the infant's developmental task of distinguishing the familiar from the unfamiliar. Both the duration and intensity of the anxiety vary greatly among children.

Some infants and young children show a strong preference for one parent over another at a given age, and grandparents may suddenly be viewed as strangers. Anticipating these occurrences during well-child visits helps prevent misinterpretation of the behavior. Comforting the child and avoiding overreaction to the behavior are usually the only therapy needed.

Common sense should dictate management. If a new sitter is coming, having that person spend some time with the family before the actual day makes sense. When the event arrives, having parents spend some time with the child and sitter before they leave is prudent. If grandparents are coming to watch the child for a few days while parents go away, they should arrive a day or two early. Similar techniques can be used in anticipation of hospitalization.

 Stranger anxiety of pronounced intensity or extended duration may be a sign of more generalized anxiety and should prompt evaluation of the family situation, parenting techniques, and the child's overall emotional state.

**Sleeping**

Sleep behaviors are culturally determined, and problems tend to be defined as behaviors that vary from accepted customs or norms. In cultures where children sleep separately from their parents in the same house, sleep problems are among the most common that parents and children face.

Infants usually adapt to a day-night sleep schedule between 4 and 6 mo. Sleep problems beyond these ages take many forms, including difficulty falling asleep at night, frequent nighttime awakening, atypical daytime napping, and dependence on feeding or on being held before being able to go to sleep. These problems are related to parental expectations, the child's temperament and biologic rhythms, and child-parent interactions.

Factors that influence sleep patterns vary by age. For infants, inborn biologic patterns are central. At 9 mo and again around 18 mo, sleep disturbances become common for these reasons:

Separation anxiety develops.
• Children can move independently and control their environment.
• They may take long late-afternoon naps.
• They may become overstimulated while playing before bedtime.
• Nightmares tend to become more common.

In toddlers and older children, emotional factors and established habits become more important. Stressful events (eg, moving, illness) may cause acute sleep problems in older children.

Evaluation

History: History focuses on the child's sleeping environment, consistency of bedtime, bedtime routines, and parental expectations. A detailed description of the child's average day can be useful. The history should probe for stressors in the child's life, such as difficulties in school, as well as exposure to unsettling television programs and caffeinated beverages (eg, sodas). Reports of inconsistent bedtimes, a noisy or chaotic environment, or frequent attempts by the child to manipulate parents by using sleep behaviors suggest the need for lifestyle changes. Extreme parental frustration suggests tension within the family or parents who are having difficulty being consistent and firm.

A sleep diary compiled over several nights may help identify unusual sleep patterns and sleep disorders (eg, sleepwalking, night terrors—see p. 1713). Careful questioning of older children and adolescents about school, friends, anxieties, depressive symptoms, and overall state of mind often reveals a source for a sleep problem.

Physical examination and testing: Examination and diagnostic testing generally yield little useful information.

Treatment

The clinician's role in treatment is to present explanations and options to parents, who must implement changes to get the child on an acceptable sleep schedule. Approaches vary with age and circumstances. Infants are often comforted by swaddling, ambient noise, and movement. However, always rocking infants to sleep does not allow them to learn how to fall asleep on their own, which is an important developmental task. As a substitute for rocking, the parent can sit quietly by the crib until the infant falls asleep; the infant eventually learns to be comforted and to fall asleep without being held. All children awaken during the night, but children who have been taught to fall asleep by themselves usually settle themselves back to sleep. When children cannot get back to sleep, parents can check on them to make sure they are safe and to reassure them, but children should then be allowed to settle themselves back to sleep.

In older children, a period of winding down with quiet activities such as reading at bedtime facilitates sleep. A consistent bedtime is important, and a fixed ritual is helpful for young children. Asking fully verbal children to recount the events of the day often eliminates nightmares and waking. Encouraging exercise in the daytime, avoiding scary television programs and movies, and refusing to allow bedtime to become an element of manipulation can also help prevent sleep problems.

If stressful events are the cause, reassurance and encouragement are always ultimately effective. Allowing children to sleep in their parents' bed in such instances almost always prolongs rather than resolves the problem.

Toilet Training

Toilet training involves recognition of readiness for and implementation of the separate steps of toileting: discussion, undressing, eliminating, dressing again, flushing, and hand washing. Most children can be trained for bowel control between age 2 yr and 3 yr and for urinary control between age 3 yr and 4 yr. By
age 5 yr, the average child can go to the toilet alone. For children ≥ 4 yr, see p. 2923 for incontinence of urine (enuresis) and p. 2928 for incontinence of stool (encopresis).

The key to successful toilet training is recognizing signs of readiness to train (usually at age 18 to 24 mo):

• Children can remain dry for several hours.

• They show interest in sitting on a potty chair and express visible signs of preparing to urinate or defecate.

• They want to be changed after either.

• They can place things where they belong and can understand and carry out simple verbal commands.

Approaches to toilet training must be consistent among all caregivers.

The timing method is the most common approach. Once children have demonstrated readiness, the parent discusses with them what will be happening, selecting words that they can readily understand and say. Children are gradually introduced to the potty chair and briefly sit on it fully clothed; they then practice taking their pants down, sitting on the potty chair for ≤ 5 or 10 min, and redressing. The purpose of the exercise is explained repeatedly and emphasized by placing wet or dirty diapers in the potty. Once this connection between the potty and elimination has been made, the parent should try to anticipate children's need to eliminate and provide positive reinforcement for successful elimination. Children are also encouraged to practice using the potty whenever the need to eliminate is sensed. They should be taught about flushing and hand washing after each elimination. For children with an unpredictable schedule, this type of plan is difficult, and training must be delayed until they can anticipate elimination themselves. Anger or punishment for accidents or lack of success is counterproductive.

Children who resist sitting on the potty should try again after a meal. If resistance continues for days, postponing toilet training for at least several weeks is the best strategy. Behavior modification with a reward given for successful toileting is one option; once the pattern is established, rewards are gradually withdrawn. Power struggles must be avoided because they often cause regression from any progress that has been made and may strain the parent-child relationship. Toilet-trained children may also regress when they are ill or emotionally upset or when they feel the need for more attention, as when a new sibling arrives. Refusal to use the potty may also represent manipulation. In these situations, parents are advised to avoid pressuring children, offer incentives, and, if possible, give children more care and attention at times other than when toileting is involved.
Chapter 269. Approach to the Care of Adolescents

Adolescence is a developmental period during which dependent children grow into independent adults. This period usually begins at about 10 yr and lasts until the late teens or early 20s. During adolescence, children undergo striking physical, intellectual, and emotional growth. Guiding adolescents through this period is a challenge for parents as well as clinicians. Preventive care is also important (see Table 268-7 on p. 2714).

Fortunately, most adolescents enjoy good physical health. Psychosocial adjustment is a hallmark of this phase of development because even normal individuals struggle with issues of identity, autonomy, sexuality, and relationships. "Who am I, where am I going, and how do I relate to all of these people in my life?" are constant preoccupations for most adolescents. Psychosocial disorders are more common during adolescence than during childhood, and many unhealthy behaviors that begin during adolescence (eg, smoking, drug use, violence) can lead to acute health problems, chronic disorders, or morbidity later in life.

Physical Growth

All organ systems and the body as a whole undergo major growth during adolescence; breasts in girls and genitals and body hair in both sexes undergo the most obvious changes. Even when this process goes normally, substantial emotional adjustments are required. If the timing is atypical, particularly in a boy whose physical development is delayed or in a girl whose development occurs early, additional emotional stress is likely. Most boys who grow slowly have a constitutional delay and catch up eventually. Evaluation to exclude pathologic causes and reassurance are needed.

Guidance concerning nutrition, fitness, and lifestyle should be given to all adolescents, with special attention paid to the role of activities such as sports, the arts, social activities, and community service in the adolescent's life. Relative requirements for protein and energy (g or kcal/kg body weight) decline progressively from the end of infancy through adolescence (see Table 1-4 on p. 5), although absolute requirements increase. Protein requirements are 0.9 g/kg/day in late adolescence; mean relative energy requirements are 40 kcal/kg.

Sexuality

In addition to adapting to bodily changes, the adolescent must become comfortable with the role of adult and must put sexual urges, which can be very strong and sometimes frightening, into perspective. Some adolescents struggle with the issue of sexual identity and may be afraid to reveal their sexual orientation to friends or family members. Acceptance from a clinician and, if indicated, a referral for supportive counseling, may help the adolescent adjust to life as a healthy adult.

Few elements of the human experience combine physical, intellectual, and emotional aspects as thoroughly as sexuality. Helping adolescents put sexuality into a healthy context through honest answers regarding reproduction and sexually transmitted diseases is extremely important. Adolescents and their parents should be encouraged to speak openly regarding their attitudes toward sex and sexuality; parents’ opinions remain an important determinant of adolescent behavior.

Intellectual Growth

As adolescents encounter schoolwork that is more complex, they begin to identify areas of interest as well as relative strengths and weaknesses. Adolescence is a period during which young people begin to consider career options, although most do not have a clearly defined goal. Parents and clinicians must be aware of the adolescent's capabilities, help the adolescent formulate realistic expectations, and be prepared to identify impediments to learning that need remediation, such as learning disabilities, attention problems, or inappropriate learning environments. Parents and clinicians should facilitate apprenticeships and experiences that expose older adolescents to potential career opportunities either during school or during school vacations. These opportunities may help adolescents focus their career choices and future studies.
Emotional Growth

The emotional aspect of growth is most trying, often taxing the patience of parents, teachers, and clinicians. Emotional lability is a direct result of neurologic development during this period, as the parts of the brain that control emotions mature. Frustration may also arise from growth in multiple domains. A major area of conflict arises from the adolescent's desire for more freedom, which clashes with the parents' strong instincts to protect their children from harm. Parents may need help in renegotiating their role and slowly allowing their adolescents more privileges as well as expecting them to accept greater responsibility for themselves and within the family. Communication within even stable families can be difficult and is worsened when families are divided or parents have emotional problems of their own. Clinicians can be of great help by offering adolescents and parents sensible, practical, concrete, supportive help while facilitating communication within the family.

Physical Problems

Although adolescents are susceptible to the same kinds of illness that afflict younger children, generally they are a healthy group. Adolescents should continue to receive vaccinations according to the recommended schedule (see Table 268-11 on p. 2720).

Acne is extremely common and needs to be addressed because of its impact on self-esteem.

Trauma is very common among adolescents, with sports and motor vehicle injuries most frequent. Violence, sometimes involving weapons, is an everyday threat among certain adolescent groups.

Obesity is one of the most common reasons for visits to adolescent clinics. Most cases of obesity are due to eating more than is needed, often in conjunction with a sedentary lifestyle. Genetic influences are common, and responsible genes are now being identified (see also Ch. 6). Determination of the body mass index (BMI) is recognized as an important aspect of physical assessment. Primary endocrine (eg, hyperadrenocorticism, hypothyroidism) or metabolic causes are uncommon. Hypothyroidism should be ruled out as a cause and should be suspected if height growth slows significantly. If the child is short and has hypertension, Cushing's syndrome should be considered. Type 2 diabetes mellitus is occurring with increasing frequency due to obesity in adolescents. Despite many therapeutic approaches, obesity is one of the most difficult and discouraging problems to treat, and long-term success rates remain low.

Infectious mononucleosis is particularly prevalent among adolescents. Sexually transmitted diseases become an important concern, and UTIs are common among girls. Some endocrine disorders, particularly thyroid disorders, are common among adolescents, as are menstrual abnormalities. Iron deficiency is relatively common among adolescent girls. Pregnancy also is not a rare occurrence and must be kept in mind when treating adolescent girls. Although not common, neoplastic diseases such as leukemia, lymphoma, bone cancers, and brain tumors also occur.

Psychosocial Disorders

Clinicians must be aware of the high frequency of psychosocial disorders that occur during this unsettled stage of life. Depression is common and should be looked for actively (see p. 3055). Although suicide is a rare occurrence (5/100,000), suicidal ideation is common (as many as 1 in 10 in some studies). Anxiety often manifests during adolescence (see p. 3049), as do bipolar disease and problems with anger management. Adolescence is also a time when some people who will develop a psychotic disorder experience their first psychotic break. Eating disorders, especially in girls, are common (see p. 1535). Some patients go to extraordinary lengths to hide an anorexic or bulimic state.

School problems, especially when related to learning or attention difficulties, can be dealt with by clinicians, who must work closely with school personnel and parents. Learning disorders may manifest for the first time as school becomes more demanding, particularly among bright children who previously had been able to accommodate for their areas of weakness. If a learning disorder is suspected, the clinician should recommend a complete learning evaluation followed by provision of appropriate services. Environmental changes and sometimes drug therapy can be of great help to struggling students.
A constant concern is substance use, which begins as a psychosocial problem but may develop into a physiologic disorder. Alcohol and cigarette use is extremely common, followed by marijuana and a long list of other substances available in all strata of society. Inhalant use is also a problem, particularly among young adolescents. Prescription and OTC drugs are now misused by adolescents more than any other substances other than alcohol and marijuana. All of these psychoactive substances are addictive, and delaying the onset of substance use from adolescence into adulthood both prevents the acute problems associated with substance use and decreases the lifetime risk of developing a substance use disorder. Clinicians should screen for use of alcohol and other drugs at every health maintenance visit and also should advise both adolescents and parents about safely using and monitoring OTC and prescription drugs.

The clinician who has developed an open, trusting relationship with an adolescent often can identify these problems, can supply support and practical advice, and can get the adolescent to accept a referral to specialized care if necessary.
Chapter 270. Caring for Sick Children and Their Families

Introduction

Illness and death cause emotional stresses in children and their families.

Sick Neonates

Difficulties arise when a sick or premature infant must be taken away from the family after birth because of illness. The parents may not be able to see a critically ill infant during stabilization and may be separated from the infant because of transport to a different hospital. Some infants require prolonged separation from their families because of lengthy hospitalizations and treatments.

Many hospitals have recognized the importance of encouraging contact between infants and their families. In most places, parents are encouraged to visit, taking precautions to minimize the risk of spreading infections. Many hospitals have unlimited visiting hours for parents. Some hospitals have areas in which parents can stay for prolonged periods to be near their infants.

In most hospitals, parents are encouraged to interact with their sick infant as much as possible. No infant, even one on a respirator, is too ill for the parents to see and touch.

Parents are also encouraged to provide direct care for the infant as a way to get to know the infant and to prepare for taking the infant home. Some hospitals increase contact between parents and premature or sick infants by encouraging skin-to-skin contact; this may help parents feel more confident about taking care of their infant at home. Infants who experience skin-to-skin contact gain weight faster when compared with those who do not receive such care. Mothers can also provide breast milk directly or pumped to be given through a feeding tube.

When an infant has a birth defect, the parents should see the infant as soon after birth as possible, regardless of the medical condition. Otherwise, they may imagine the appearance and condition to be much worse than the reality. Intensive parental support is essential, with as many counseling sessions as are needed for parents to understand their infant’s condition and recommended treatment and to accept the infant psychologically. To balance discussion of abnormalities, the physician should emphasize what is normal about the infant and the infant’s potential.

When neonates die without having been seen or touched by their parents, the parents may later feel as though they never really had a child. Such parents have reported exaggerated feelings of emptiness and may develop prolonged depression because they could not mourn the loss of a “real” child. Parents who have not been able to see or hold their infant while alive will usually be helped in the long term if allowed to do so after the infant has died. In all cases, follow-up visits with the physician and a social worker are helpful to review the circumstances of the infant’s illness and death, answer questions that often arise later, and assess and alleviate feelings of guilt. The physician can also evaluate the parents’ grieving process and provide appropriate guidance or a referral for more extensive support if necessary.

Children with Chronic Health Conditions

Chronic health conditions (both chronic illnesses and chronic physical disabilities) are generally defined as those conditions that last > 12 mo and are severe enough to create some limitations in usual activity. It has been estimated that chronic health conditions affect 10 to 30% of children, depending on the criteria. Examples of chronic illnesses include asthma, cystic fibrosis, congenital heart disease, diabetes mellitus, attention-deficit/hyperactivity disorder, and depression. Examples of chronic physical disabilities include meningomyelocele, hearing or visual impairments, cerebral palsy, and loss of limb function.

Effects on the children: Children with chronic health conditions may experience limitations in some activities; frequent pain or discomfort; abnormal growth and development; and more hospitalizations, outpatient visits, and medical treatments. Those with severe disabilities may be unable at times to participate in school and peer activities.
Children's response to a chronic health condition largely depends on their developmental stage when the condition occurs. Children with chronic conditions that appear in infancy will respond differently than children who develop conditions during adolescence. School-aged children may be most affected by the inability to attend school and form relationships with peers. Adolescents may struggle with their inability to achieve independence if they require assistance from parents and others for many of their daily needs; parents should encourage self-reliance within the adolescent's capability and avoid overprotection. Adolescents also find it particularly difficult to be viewed as different from their peers.

Health care practitioners can be advocates for appropriate hospital services for children with chronic health conditions. Age-appropriate playrooms can be set up and a school program can be initiated with the oversight of a trained child life specialist. Children can be encouraged to interact with peers whenever possible. All procedures and plans should be explained to families and children whenever possible so the families know what to expect during the hospitalization, thus relieving the anxiety that can be created by uncertainty.

**Effects on the family:** For families, having a child who has a chronic health condition can lead to loss of their hope for an "ideal" child, neglected siblings, major expense and time commitment, confusion caused by conflicting systems of health care management, lost opportunities (eg, family members providing primary care to the child are therefore unable to return to work), and social isolation. Siblings may resent the extra attention the ill child receives. Such stress may cause family breakup, especially when there are preexisting difficulties with family function.

Conditions that affect the physical appearance of an infant (eg, cleft lip and palate, hydrocephalus) can affect the bond between the infant and family members or caretakers. Once the diagnosis of abnormality is made, parents may react with shock, denial, anger, sadness or depression, guilt, and anxiety. These reactions may occur at any time in the child's development, and each parent may be at a different stage of acceptance, making communication between them difficult. Parents may express their anger at the health care practitioner, or their denial may cause them to seek many opinions about their child's condition.

**Care coordination:** Without coordination of services, care is crisis-oriented. Some services will be duplicated, whereas others will be neglected. Care coordination requires knowledge of the children's condition, their family and support systems, and the community in which they function.

All professionals who care for children with chronic health conditions must ensure that someone is coordinating care. Sometimes the coordinator can be the child's parent. However, the systems that must be negotiated are often so complex that even the most capable parents need assistance. Other possible coordinators include the primary care physician, the subspecialty program staff, the community health nurse, and staff of the 3rd-party payer. Regardless of who coordinates services, families and children must be partners in the process. In general, children from low-income families who have chronic conditions fare worse than others, in part because of lack of access to health care and care coordination services. Some children with terminal illness benefit from hospice care.

**Death and Dying**

Families often have difficulty dealing with an ill and dying child. Children who are trying to make sense of the death of a friend or family member may have particular difficulty (see also Ch. 353).

**Death of a child:** Most often the death of a child happens in the hospital or emergency department. Death can occur after a prolonged illness, such as cancer, or suddenly and unexpectedly, such as following injury or sudden infant death. The death of a child can be difficult for families to comprehend and accept. For parents, the death of a child means that they must give up their dreams and hopes for their child. The grieving process may also mean that they are unable to attend to the needs of other family members, including other children. Health care practitioners can help in the process by being available to the family for consultation and to provide comfort whenever possible. In some circumstances, referral to specialists skilled in working with families who have experienced the death of a child is appropriate.
Death of a family member or friend: Many children experience the death of a loved one. The way children perceive the event (and hence the best response by parents and health care practitioners) is affected by their developmental level. Preschool children may have limited understanding of death. Relating the event to previous experience with a beloved pet may be helpful. Older children may be able to understand the event more easily. Death should never be equated with going to sleep and never waking up because children may become fearful of sleeping.

Parents should discuss with health care practitioners whether to have children visit severely ill children or adults. Some children may express a specific desire to visit family members or friends who are dying. Children should be adequately prepared for such a visit so they will know what to expect. In the same way, adults often wonder whether to bring children to a funeral. This decision should be made individually, in consultation with the children whenever possible. When children attend a funeral, a close friend or relative should accompany them to provide support throughout, and children should be allowed to leave if necessary.
Chapter 271. Physical Growth and Development

Introduction

Physical growth is an increase in size. Development is growth in function and capability. Both processes are highly dependent on genetic, nutritional, and environmental factors.

Physical Growth

(See also Failure to Thrive on p. 2931.)

Physical growth includes attainment of full height and appropriate weight and an increase in size of all organs (except lymphatic tissue, which decreases in size). Growth from birth to adolescence occurs in 2 distinct phases. The 1st phase (from birth to about age 1 to 2 yr) is one of rapid growth, although the rate of growth decreases over that period. In the 2nd phase (from about 2 yr to the onset of puberty), growth occurs in relatively constant annual increments. Puberty is the process of physical maturation from child to adult. Adolescence defines an age group; puberty occurs during adolescence. At puberty, a 2nd growth spurt occurs, affecting boys and girls slightly differently. All growth parameters can be charted on standard growth curves available from the Centers for Disease Control and Prevention.

Length: Length is measured in children too young to stand; height is measured once the child can stand. In general, length in normal term infants increases about 30% by 5 mo and > 50% by 12 mo; infants grow 25 cm during the 1st yr; and height at 5 yr is about double birth length. In boys, half the adult height is attained by about age 2; in girls, height at 19 mo is about half the adult height.

Rate of change in height (height velocity) is a more sensitive measure of growth than time-specific height measures. In general, healthy term infants and children grow about 2.5 cm/mo between birth and 6 mo, 1.3 cm/mo from 7 to 12 mo, and about 7.6 cm/yr between 12 mo and 10 yr. Before 12 mo, height velocity varies and is due in part to perinatal factors (eg, prematurity). After 12 mo, height is mostly genetically determined, and height velocity stays constant until puberty; a child's height relative to peers tends to remain the same. Some small-for-gestational age infants tend to be shorter throughout life than infants whose size is appropriate for their gestational age. Boys and girls show little difference in height and growth rate during infancy and childhood.

Extremities grow faster than the trunk, leading to a gradual change in relative proportions; the crown-to-pubis/pubis-to-heel ratio is 1.7 at birth, 1.5 at 12 mo, 1.2 at 5 yr, and 1.0 after 7 yr.

A growth spurt in boys occurs sometime between ages 12 and 17, with the peak typically between ages 13 and 15; a gain of > 10 cm can be expected in the year of peak velocity. A growth spurt in girls occurs sometime between ages 9 1/2 and 14 1/2, with the peak typically between ages 11 and 13 1/2; gain may reach 9 cm in the year of peak velocity. If puberty is delayed (see p. 2894), growth in height may slow considerably. If the delay is not pathologic, the adolescent growth spurt occurs later and growth catches up, with height crossing percentile lines until the child reaches a genetically determined stature. At age 18, almost 2.5 cm of growth remains for boys and slightly less for girls, for whom growth is 99% complete. In girls with true precocious puberty (prior to age 6 1/2), an early growth spurt occurs along with menarche at a young age and, ultimately, short stature results because of early closure of growth plates.

Weight: Weight follows a similar pattern. Normal term neonates generally lose 5 to 8% of birth weight in the days after delivery but regain their birth weight within 2 wk. They then gain 14 to 28 g/day until 3 mo, then 4000 g between 3 and 12 mo, doubling their birth weight by 5 mo, tripling it by 12 mo, and almost quadrupling it by 2 yr. Between age 2 yr and puberty, weight increases 2 kg/yr. The recent epidemic of childhood obesity has involved markedly greater weight gain, even among very young children. In general, boys are heavier and taller than girls when growth is complete because boys have a longer prepubertal growth period, increased peak velocity during the pubertal growth spurt, and a longer adolescent growth spurt.

Head circumference: Head circumference reflects brain size and is routinely measured up to 2 yr. At birth, the brain is 25% of adult size, and head circumference averages 35 cm. Head circumference
increases an average 1 cm/mo during the 1st yr; growth is more rapid in the 1st 8 mo, and by 12 mo, the brain has completed half its postnatal growth and is 75% of adult size. Head circumference increases 3.5 cm over the next 2 yr; the brain is 80% of adult size by age 3 yr and 90% by age 7 yr.

**Body composition:** Body composition (proportions of body fat and water) changes and affects volume of distribution of drugs (see p. 2762). Proportion of fat increases rapidly from 13% at birth to 20 to 25% by 12 mo, accounting for the chubby appearance of most infants. Subsequently, a slow fall occurs until preadolescence, when body fat returns to about 13%. There is a slow rise again until the onset of puberty, when body fat may again fall, especially in boys. After puberty, the percentage generally stays stable in girls, whereas in boys there tends to be a slight decline.

Body water measured as a percentage of body weight is 70% at birth, dropping to 61% at 12 mo (about equal to the adult percentage). This change is fundamentally due to a decrease in ECF from 45% to 28% of body weight. ICF stays relatively constant. After age 12 mo, there is a slow and variable fall in ECF to adult levels of about 20% and a rise in ICF to adult levels of about 40%. The relatively larger amount of body water, its high turnover rate, and the comparatively high surface losses (due to a proportionately large surface area) make infants more susceptible to fluid deprivation than older children and adults.

**Tooth eruption:** Tooth eruption is variable (see Table 271-1), primarily because of genetic factors. On average, normal infants should have 6 teeth by 12 mo, 12 teeth by 18 mo, 16 teeth by 2 yr, and all teeth (20) by 2 1/2 yr; deciduous teeth are replaced by permanent teeth between the ages of 5 and 13 yr. Eruption of deciduous teeth is similar in both sexes; permanent teeth tend to appear earlier in girls. Tooth eruption may be delayed by familial patterns or by conditions such as rickets, hypopituitarism, hypothyroidism, or Down syndrome. Supernumerary teeth and congenital absence of teeth are probably normal variants.

[Table 271-1. Tooth Eruption Times]

**Development**

(See also Ch. 304.)

Development is often divided into specific domains, such as gross motor, fine motor, language, cognition, and social/emotional growth. These designations are useful, but substantial overlap exists. Studies have established average ages at which specific milestones are reached, as well as ranges of normality. In a normal child, progress within the different domains varies, as in the toddler who walks late but speaks in sentences early (see Table 271-2).

Environmental influences, ranging from nutrition to stimulation and from the impact of disease to the effects of psychologic factors, interact with genetic factors to determine the pace and pattern of development.

Assessment of development occurs constantly as parents, school personnel, and clinicians evaluate children. Many tools are available for monitoring development more specifically. The Denver Developmental Screening Test facilitates evaluation in several domains. The scoring sheet indicates the average ages for achieving certain milestones and nicely shows the critical concept of a range of normality. Other tools can also be used (see Table 271-2).

**Motor development:** Motor development includes fine motor (eg, picking up small objects, drawing) and gross motor (eg, walking, climbing stairs) skills. It is a continuous process that depends on familial patterns, environmental factors (eg, when activity is limited by prolonged illness), and specific disorders (eg, cerebral palsy, intellectual disability, muscular dystrophy). Children typically begin to walk at 12 mo,
can climb stairs at 21 mo, and run well at 2 yr, but the age at which these milestones are achieved by normal children varies widely. Motor development cannot be significantly accelerated by applying increased stimulation.

**Language development:** The ability to understand language precedes the ability to speak; children with few words usually can understand a great deal. Although delays in expressive speech are typically not accompanied by other developmental delays, all children with excessive language delays should be evaluated for the presence of other delays in development. Children who have delays in both receptive and expressive speech more often have additional developmental problems. Evaluation of any delay should start with an assessment of hearing. Most children who experience speech delay have normal intelligence. In contrast, children with accelerated speech development are often of above-average intelligence.

Speech progresses from the utterance of vowel sounds (cooing) to the introduction of syllables that start with consonants (ba-ba-ba). Most children can say "Dada" and "Mama" specifically by 12 mo, use several words by 18 mo, and combine words into some sentences by 2 yr. The average 3-yr-old can carry on a conversation. These milestones are highly variable.

**Cognitive and social/emotional development:** Cognitive and social/emotional development refers to the intellectual and psychologic maturation of children as their physical development allows them to interact more with other people and the external world. There are multiple theories of these forms of development in children and adolescents; the oldest and most famous are those proposed by Freud, Piaget, and Erikson. All are based on clinical observations, but none has been tested in large groups of children. In general, these models are considered useful for describing aspects of development in some children, but none is universally applicable. Increasingly, appropriate attachments and nurturing in infancy and early childhood are recognized as critical factors in cognitive growth and emotional health. For example, reading to children from an early age, providing intellectually stimulating experiences, and providing warm and nurturing relationships all have a major impact on growth in these domains. Intellect is appraised in young children by observations of language skills, curiosity, and problem-solving abilities. As children become more verbal, intellectual functioning becomes easier to assess using a number of specialized clinical tools. Once children start school, they undergo constant monitoring as part of the academic process.

Emotional growth and the acquisition of social skills are assessed by watching children interact with others in everyday situations. When children acquire speech, the understanding of their emotional state becomes much more accurate. As with intellect, emotional functioning can be delineated more precisely with specialized tools.

**Sexual Development**

Sexual maturation generally proceeds in an established sequence in both sexes. The age at onset and rapidity of sexual development vary and are influenced by genetic and environmental factors. Sexual maturity begins earlier today than a century ago, probably because of improvements in nutrition, general health, and living conditions—eg, the average age of menarche has decreased by about 3 yr over the past 100 yr. The physiologic changes that underlie sexual maturation are discussed in Chs. 229 and 245.

In boys, sexual changes begin with enlargement of the scrotum and testes, followed by lengthening of the penis and enlargement of the seminal vesicles and prostate. Next, pubic hair appears. Axillary and facial hair appears about 2 yr after pubic hair. The growth spurt usually begins a year after the testes start enlarging. The median age for first ejaculation (between 12 1/2 and 14 yr in the US) is affected by psychologic, cultural, and biologic factors. First ejaculation takes place about 1 yr after penis growth accelerates. Gynecomastia, usually in the form of breast buds, is common among young adolescent boys and usually resolves within several years.

In most girls, breast budding is the first visible sign of sexual maturation, followed closely by the initiation of the growth spurt. Shortly thereafter, pubic and axillary hair appears. Menarche generally occurs about 2 yr after onset of breast development and when growth in height slows after reaching its peak. Menarche occurs within a wide range, with most girls in the US starting their periods at 12 or 13 yr. The
stages of breast growth and pubic hair development can be detailed using Tanner's method (see Figs. 245-2 and 245-3 on p. 2498).

If the order of sexual changes is disturbed, growth may be abnormal, and the physician should consider pathologic reasons.
Chapter 272. Principles of Drug Treatment in Children

Introduction

Drug treatment in children differs from that in adults, most obviously because it is usually based on weight or surface area. Doses (and dosing intervals) differ because of age-related variations in drug absorption, distribution, metabolism, and elimination. A child cannot safely receive an adult drug dose, nor can it be assumed that a child's dose is proportional to an adult's dose (i.e., that a 7-kg child requires one tenth the dose of a 70-kg adult). Most drugs have not been adequately studied in children, although federal legislation (the Best Pharmaceuticals for Children Act of 2001 and the Pediatric Research Equity Act of 2003 [both renewed in 2007]) provides the statutory and regulatory authority to begin those studies.

Adverse effects and toxicity: Children are generally subject to the same adverse effects as adults (see p. 3184), but they have increased risk with certain drugs because of differences in pharmacokinetics or because of drug effects on growth and development. Common drugs with unique or higher risk of adverse effects in children are listed in Table 272-1.

Younger children are at especially high risk of accidental poisoning when they discover and take caregivers' vitamins or drugs. Infants are at risk of toxicity from drugs used by adults; toxicity can occur prenatally when they are exposed via placental transfer or postnatally when exposed through breast milk (numerous agents—see p. 2708 and Table 268-4 on p. 2706) or skin contact with caregivers who have recently applied certain topical drugs (e.g., scopolamine for motion sickness, malathion for lice, diphenhydramine for poison ivy).

Adverse effects, including death, have occurred in children receiving OTC cough and cold preparations containing some combination of an antihistamine, sympathomimetic decongestant, and the antitussive dextromethorphan. Current recommendations are that such products should not be given to children < 4 yr.

Pharmacokinetics in Children

Pharmacokinetics refers to the processes of drug absorption, distribution, metabolism, and elimination (see p. 3172).

[Table 272-1, Drugs Manifesting Unusual Toxicity in Children]

Absorption: Absorption from the GI tract is affected by

- Gastric acid secretion
- Bile salt formation
- Gastric emptying time
- Intestinal motility
- Bowel length and effective absorptive surface
- Microbial flora

All these factors are reduced in neonates and all may be reduced or increased in an ill child of any age. Reduced gastric acid secretion increases bioavailability of acid-labile drugs (e.g., penicillin) and decreases bioavailability of weakly acidic drugs (e.g., phenobarbital). Reduced bile salt formation decreases bioavailability of lipophilic drugs (e.g., diazepam). Reduced gastric emptying and intestinal motility increase the time it takes to reach therapeutic concentrations when enteral drugs are given to infants < 3 mo.

Drug-metabolizing enzymes present in the intestines of young infants are another cause of reduced drug absorption. Infants with congenital atretic bowel or surgically removed bowel or who have jejunal feeding
tubes may have specific absorptive defects depending on the length of bowel lost or bypassed and the location of the lost segment.

Injected drugs are often erratically absorbed because of

- Variability in their chemical characteristics
- Differences in absorption by site of injection (IM or sc)
- Variability in muscle mass among children
- Illness (eg, compromised circulatory status)

IM injections are generally avoided in children because of pain and the possibility of tissue damage, but, when needed, water-soluble drugs are best because they do not precipitate at the injection site.

Transdermal absorption may be enhanced in neonates and young infants because the stratum corneum is thin and because the ratio of surface area to weight is much greater than for older children and adults. Skin disruptions (eg, abrasions, eczema, burns) increase absorption in children of any age.

Transrectal drug therapy is generally appropriate only for emergencies when an IV route is not available (eg, use of rectal diazepam for status epilepticus). Site of placement of the drug within the rectal cavity may influence absorption because of the difference in venous drainage systems. Expulsion of the drug may also be enhanced in the young infant.

Absorption of drugs from the lungs (eg, β-agonists for asthma, pulmonary surfactant for respiratory distress syndrome) varies less by physiologic parameters and more by reliability of the delivery device and patient or caregiver technique.

Distribution: The volume of distribution of drugs changes in children with aging. These age-related changes are due to changes in body composition (especially the extracellular and total body water spaces) and plasma protein binding.

Higher doses (per kg of body weight) of water-soluble drugs are required in younger children because a higher percentage of their body weight is water (see Fig. 272-1). Conversely, lower doses are required to avoid toxicity as children grow older because of the decline in water as a percentage of body weight.

Many drugs bind to proteins (primarily albumin, α1-acid glycoprotein, and lipoproteins); protein binding limits distribution of free drug throughout the body. Albumin and total protein concentrations are lower in neonates but approach adult levels by 10 to 12 mo. Decreased protein binding in neonates is also due to qualitative differences in binding proteins and to competitive binding by molecules such as bilirubin and free fatty acids, which circulate in higher concentrations in neonates and infants. The net result may be increased free drug concentrations, greater drug availability at receptor sites, and both pharmacologic effects and higher frequency of adverse effects at lower drug concentrations.

Metabolism and elimination: Drug metabolism and elimination vary with age and depend on the substrate or drug, but most drugs, and most notably phenytoin, barbiturates, analgesics, and cardiac glycosides, have plasma half-lives 2 to 3 times longer in neonates than in adults.

The cytochrome P-450 (CYP450) enzyme system in the small bowel and liver is the most important known system for drug metabolism. CYP450 enzymes inactivate drugs via

- Oxidation, reduction, and hydrolysis (phase I metabolism)
• Hydroxylation and conjugation (phase II metabolism)

Phase I activity is reduced in neonates, increases progressively during the first 6 mo of life, exceeds adult rates by the first few years for some drugs, slows during adolescence, and usually attains adult rates by late puberty. However, adult rates of metabolism may be achieved for some drugs (eg, barbiturates, phenytoin) 2 to 4 wk postnatally. CYP450 activity can also be induced (reducing drug concentrations and effect) or inhibited (augmenting concentrations and effect) by coadministered drugs. These drug interactions may lead to drug toxicity when CYP450 activity is inhibited or an inadequate drug level when CYP450 activity is induced. Kidneys, lungs, and skin also play a role in the metabolism of some drugs, as do intestinal drug-metabolizing enzymes in neonates. Phase II metabolism varies considerably by substrate. Maturation of enzymes responsible for bilirubin and acetaminophen conjugation is delayed; enzymes responsible for morphine conjugation are fully mature even in preterm infants.

Drug metabolites are eliminated primarily through bile or the kidneys. Renal elimination depends on

• Plasma protein binding
• Renal blood flow
• GFR
• Tubular secretion

All of these factors are altered in the first 2 yr of life. Renal plasma flow is low at birth (12 mL/min) and reaches adult levels of 140 mL/min by age 1 yr. Similarly, GFR is 2 to 4 mL/min at birth, increases to 8 to 20 mL/min by 2 to 3 days, and reaches adult levels of 120 mL/min by 3 to 5 mo.

**Drug dosing:** Because of the above factors, drug dosing in children < 12 yr is always a function of age, body weight, or both. This approach is practical but not ideal. Even within a population of similar age and weight, drug requirements may differ because of maturational differences in absorption, metabolism, and elimination. Thus, when practical, dose adjustments should be based on plasma drug concentration. Unfortunately, these adjustments are not feasible for most drugs. Studies done as a result of federal legislation (the Best Pharmaceuticals for Children Act of 2001 and the Pediatric Research Equity Act of 2003 [both renewed in 2007]) have provided dosing for > 150 drugs that previously did not have pediatric dosing information.

**Nonadherence in Children**

Nonadherence with drug recommendations (see also p. 3166) may occur at any age because of cost; painful or inconvenient administration; or the need for frequent doses, complex regimens, or both. But many unique factors contribute to nonadherence in children. Children < 6 yr may have difficulty swallowing pills and may resist taking forms of drugs that taste bad. Older children often resist drugs or regimens (eg, insulin, metered-dose inhalers) that require them to leave their classes or activities or that make them appear different from their peers. Adolescents may express rebellion and assert independence from parents by not taking their drugs. Parents or caregivers of younger children may only partially remember or understand the rationale and instructions for taking a drug, and their work schedules may preclude their being available to give children their scheduled doses. Some may wish to try folk or herbal remedies initially. Some caregivers have limited incomes and are forced to spend their money on other priorities, such as food; others have beliefs and attitudes that prevent them from giving children drugs.

To minimize nonadherence, a prescribing provider can do the following:

• Ascertain whether the patient or caregiver agrees with the diagnosis, perceives it as serious, and believes the treatment will work.
• Correct misunderstandings and guide the patient or caregiver toward reliable sources of information.
• Give written as well as oral instructions in a language the patient or caregiver can review and understand.

• Make early follow-up telephone calls to families to answer residual questions.

• Assess progress and remind the patient or caregiver of follow-up visits.

• Review drug bottles at follow-up office visits for pill counts.

• Educate the patient or caregiver about how to keep a daily symptom or drug diary.

Adolescents in particular need to feel in control of their illness and treatment and should be encouraged to communicate freely and to take as much responsibility as is possible for their own treatment. Regimens should be simplified (eg, synchronizing multiple drugs and minimizing the number of daily doses while maintaining efficacy) and matched to the patient's and caregivers' schedules. Critical aspects of the treatment should be emphasized (eg, taking the full course of an antibiotic). If lifestyle changes (eg, in diet or exercise) are also needed, such changes should be introduced incrementally over several visits, and realistic goals should be set (eg, to lose 1 of 14 kg [2 of 30 lb] by a 2-wk follow-up visit). Success in achieving a goal should be reinforced with praise, and only then should the next goal be added. For patients who require expensive long-term regimens, a list of pharmaceutical patient-assistance programs is available at www.needymeds.org.
Chapter 273. Perinatal Physiology

The transition from life in utero to life outside the womb involves multiple changes in physiology and function.

Bilirubin Metabolism

Aged or damaged fetal RBCs are removed from the circulation by reticuloendothelial cells, which convert heme to bilirubin (1 g of Hb yields 35 mg of bilirubin). This bilirubin is transported to the liver, where it is transferred into hepatocytes. Glucuronyl transferase then conjugates the bilirubin with uridine diphosphoglucuronic acid (UDPGA) to form bilirubin diglucuronide (conjugated bilirubin), which is secreted actively into the bile ducts. Bilirubin diglucuronide makes its way into meconium in the GI tract but cannot be eliminated from the body, because the fetus does not normally pass stool. The enzyme \( \beta \)-glucuronidase, present in the fetus' small-bowel luminal brush border, is released into the intestinal lumen, where it deconjugates bilirubin glucuronide; free (unconjugated) bilirubin is then reabsorbed from the intestinal tract and reenters the fetal circulation. Fetal bilirubin is cleared from the circulation by placental transfer into the mother's plasma following a concentration gradient. The maternal liver then conjugates and excretes the fetal bilirubin.

At birth, the placenta is "lost," and although the neonatal liver continues to take up, conjugate, and excrete bilirubin into bile so it can be eliminated in the stool, neonates lack proper intestinal bacteria for oxidizing bilirubin to urobilinogen in the gut; consequently, unaltered bilirubin remains in the stool, imparting a typical bright-yellow color. Additionally, the neonatal GI tract (like that of the fetus) contains \( \beta \)-glucuronidase, which deconjugates some of the bilirubin. In many neonates, feedings cause the gastrocolic reflex, and bilirubin is excreted in stool before most of it can be deconjugated and reabsorbed. However in many other neonates, the unconjugated bilirubin is reabsorbed and returned to the circulation from the intestinal lumen (enterohepatic circulation of bilirubin), contributing to physiologic hyperbilirubinemia and jaundice (see p. 2788).

Cardiovascular Function

Fetal circulation is marked by right-to-left shunting of blood around the unventilated lungs through a patent ductus arteriosus (connecting the pulmonary artery to the aorta) and foramen ovale (connecting the right and left atria). Shunting is encouraged by high pulmonary arteriolar resistance and relatively low resistance to blood flow in the systemic (including placental) circulation. About 90 to 95% of the right heart output bypasses the lungs and goes directly to the systemic circulation. The fetal ductus arteriosus is kept open by low fetal systemic PaO\(_2\) (about 25 mm Hg) along with locally produced prostaglandins. The foramen ovale is kept open by differences in atrial pressures: left atrial pressure is relatively low because little blood is returned from the lungs, but right atrial pressure is relatively high because large volumes of blood return from the placenta.

As pulmonary blood flow is established, venous return from the lungs increases, raising left atrial pressure. Air breathing increases the PaO\(_2\), which constricts the umbilical arteries. Placental blood flow is reduced or stops, reducing blood return to the right atrium. Thus, right atrial pressure decreases while left atrial pressure increases; as a result, the foramen ovale closes.

Soon after birth, systemic resistance becomes higher than pulmonary resistance, a reversal from the fetal state. Therefore, the direction of blood flow through the patent ductus arteriosus reverses, creating left-to-right shunting of blood (called transitional circulation). This state lasts from moments after birth (when the pulmonary blood flow increases and functional closure of the foramen ovale occurs) until about 24 to
72 h of age, when the ductus arteriosus usually closes. Blood entering the ductus and its vasa vasorum from the aorta has a high PO2, which, along with alterations in prostaglandin metabolism, leads to constriction and closure of the ductus arteriosus. Once the ductus arteriosus closes, an adult-type circulation exists. The 2 ventricles now pump in series, and there are no major shunts between the pulmonary and systemic circulations.

During the days immediately after birth, a stressed neonate may revert to a fetal-type circulation. Asphyxia with hypoxia and hypercarbia causes the pulmonary arterioles to constrict and the ductus arteriosus to dilate, reversing the processes described previously and resulting in right-to-left shunting through the now-patent ductus arteriosus, the reopened foramen ovale, or both. Consequently, the neonate becomes severely hypoxemic, a condition called persistent pulmonary hypertension or persistent fetal circulation (although there is no umbilical circulation). The goal of treatment is to reverse the conditions that caused pulmonary vasoconstriction.

Endocrine Function

The fetus depends completely on the maternal supply of glucose via the placenta and does not contribute to glucose production. The fetus begins to build a hepatic glycogen supply early in gestation, accumulating most glycogen stores during the 2nd half of the 3rd trimester. The neonate's glucose supply terminates when the umbilical cord is cut; concurrently, levels of circulating epinephrine, norepinephrine, and glucagon surge, while insulin levels decline. These changes stimulate gluconeogenesis and mobilization of hepatic glycogen stores. In healthy, term neonates, glucose levels reach a nadir 30 to 90 min after birth, after which neonates are typically able to maintain normal glucose homeostasis. Infants at highest risk of neonatal hypoglycemia include those with reduced glycogen stores (small-for-gestational age and premature infants), critically ill infants with increased glucose catabolism, and infants of diabetic mothers (secondary to temporary fetal hyperinsulinemia).

Hematopoietic Function

In utero, RBC production is controlled exclusively by fetal erythropoietin produced in the liver; maternal erythropoietin does not cross the placenta. About 55 to 90% of fetal RBCs contain fetal Hb, which has high O2 affinity. As a result, a high O2 concentration gradient is maintained across the placenta, resulting in abundant O2 transfer from the maternal to the fetal circulation. This increased O2 affinity is less useful after birth, because fetal Hb gives up O2 to tissues less readily, and it may be deleterious if severe pulmonary or cardiac disease with hypoxemia exists. The transition from fetal to adult Hb begins before birth; at delivery, the site of erythropoietin production changes from the liver to the kidney by an unknown mechanism. The abrupt increase in PaO2 from about 25 to 30 mm Hg in the fetus to 90 to 95 mm Hg in the neonate just after delivery causes serum erythropoietin to fall, and RBC production shuts down between birth and about 6 to 8 wk, causing physiologic anemia and contributing to anemia of prematurity (see p. 2783).

Immunologic Function

At term, most immune mechanisms are not fully functional, more so with increasing prematurity. Thus, all neonates and young infants are immunodeficient relative to adults and are at increased risk of overwhelming infection. This risk is enhanced by prematurity, maternal illness, neonatal stress, and drugs (eg, immunosuppressants, anticonvulsants). Neonates' decreased immune response may explain the absence of localized clinical signs (eg, fever or meningismus) with infection.

In the fetus, phagocytic cells, present at the yolk sac stage of development, are critical for the inflammatory response that combats bacterial and fungal infection. Granulocytes can be identified in the 2nd mo of gestation and monocytes can be identified in the 4th mo of gestation. Their level of function increases with gestational age but is still low at term.

At birth, the ultrastructure of neutrophils is normal, but in most neonates, chemotaxis of neutrophils and monocytes is decreased because of an intrinsic abnormality of cellular locomotion and adherence to
surfaces. These functional deficits are more pronounced in premature infants.

By about the 14th wk of gestation, the thymus is functioning and producing lymphocytes. Also by 14 wk, T cells are present in the fetal liver and spleen, indicating that mature T cells are established in the peripheral lymphoid organs by this age. The thymus is most active during fetal development and in early postnatal life. It grows rapidly in utero and is readily noted on chest x-ray in a healthy neonate, reaching a peak size at age 10 yr then involuting gradually over many years.

The number of T cells in the fetal circulation gradually increases during the 2nd trimester and reaches nearly normal levels by 30 to 32 wk gestation. At birth, neonates have a relative T lymphocytosis compared to adults. However, neonatal T cells do not function as effectively as adult T cells. For example, neonatal T cells may not respond adequately to antigens and may not produce cytokines.

B cells are present in fetal bone marrow, blood, liver, and spleen by the 12th wk of gestation. Trace amounts of IgM and IgG can be detected by the 20th wk and trace amounts of IgA can be detected by the 30th wk; because the fetus is normally in an antigen-free environment, only small amounts of immunoglobulin (predominantly IgM) are produced in utero. Elevated levels of cord serum IgM indicate in utero antigen challenge, usually caused by congenital infection. Almost all IgG is acquired maternally from the placenta. After 22 wk gestation, placental transfer of IgG increases to reach maternal levels or greater at term. IgG levels at birth in premature infants are decreased relative to gestational age.

The passive transfer of maternal immunity from transplacental IgG and secretory IgA and antimicrobial factors in breast milk (eg, IgG, secretory IgA, WBCs, complement proteins, lysozyme, lactoferrin) compensate for the neonate's immature immune system and confer immunity to many bacteria and viruses. Protective immune factors in breast milk coat the GI and upper respiratory tracts via mucosa-associated lymphoid tissue and prevent invasion of mucous membranes by respiratory and enteric pathogens.

Over time, passive immunity begins to wane, reaching a nadir when the infant is 3 to 6 mo old. Premature infants, in particular, may become profoundly hypogammaglobulinemic during the first 6 mo of life. By 1 yr, the IgG level rises to about 60% of average adult levels. IgA, IgM, IgD, and IgE, which do not cross the placenta and therefore are detectable only in trace amounts at birth, increase slowly during childhood. IgG, IgM, and IgA reach adult levels by about age 10 yr.

Pulmonary Function

Fetal lungs develop throughout gestation, and fairly well-developed alveoli are present by the 25th wk. The lungs continually produce fluid—a transudate from pulmonary capillaries plus surfactant secreted by type II pneumocytes. For normal gas exchange to occur at birth, pulmonary alveolar fluid and interstitial fluid must be cleared promptly by compression of the fetal thorax during delivery and by absorption of fluid into cells in the lung. Transient tachypnea of the newborn (see p. 2877) is probably caused by delay in this clearance process.

On delivery, when elastic recoil of ribs and strong inspiratory efforts draw air into the pulmonary tree, air-fluid interfaces are formed in alveoli. At the first breath, large amounts of surfactant are released into the air-fluid interfaces of infants ≥ 34 to 35 wk. Surfactant, a mixture of phospholipids (phosphatidylcholine, phosphatidyl glycerol, phosphatidylinositol), neutral lipids, and 3 surface active proteins all stored in lamellar inclusions in type II pneumocytes, reduces high surface tension, which would otherwise cause atelectasis and increase the work of breathing. Surfactant works more effectively in small alveoli than in large alveoli, thus opposing the normal tendency of small alveoli to collapse into large alveoli (per Laplace's law, which states that in an elastic cavity, pressure decreases as volume increases).

Before 34 to 35 wk gestation, surfactant is often not produced in sufficient quantities to prevent diffuse atelectasis, and respiratory distress syndrome develops (see p. 2876).

Renal Function

At birth, renal function is generally reduced, particularly in premature infants. GFR increases
progressively during gestation, particularly during the 3rd trimester. GFR rapidly increases in the first months of life; however, GFR, urea clearance, and maximum tubular clearances do not reach adult levels until age 1 to 2 yr.
Chapter 274. Perinatal Problems

Introduction

Extensive physiologic changes accompany the birth process, sometimes revealing conditions that posed no problem during intrauterine life. For that reason, a person with resuscitation skills must attend each birth. Each neonate is classified as premature, full-term, or postmature to help determine the risk of various complications.

Gestational age, the primary determinant of organ maturity, can be determined in the days immediately after birth using the Ballard score (see Fig. 268-1 on p. 2700). Through plotting of weight vs gestational age (see Fig. 274-1), each infant is classified as small, appropriate, or large for gestational age. Head circumference and length are also plotted against gestational age (see Fig. 274-2). These parameters are influenced by genetic factors and intrauterine conditions. They also help to predict subsequent growth and development.

Neonatal Resuscitation

About 10% of neonates require some degree of resuscitation at delivery. Causes are numerous (see Table 274-1), but most involve asphyxia or respiratory depression. Incidence rises significantly if birth weight is < 1500 g.

Assessment: The Apgar score assigns 0 to 2 points for each of 5 measures of neonatal health (Appearance, Pulse, Grimace, Activity, Respiration—see Table 274-2). Scores depend on physiologic maturity, maternal perinatal therapy, and fetal cardiorespiratory and neurologic conditions. A score of 7 to 10 at 5 min is considered normal; 4 to 6, intermediate; and 0 to 3, low. A low Apgar score is not by itself diagnostic of perinatal asphyxia but is associated with a risk of long-term neurologic dysfunction. An unduly prolonged (> 10 min) low Apgar score predicts increased risk of mortality in the first year of life.

The earliest sign of asphyxia is acral (peripheral) cyanosis, followed by decreases in respiration, muscle tone, reflex response, and heart rate. Effective resuscitation leads initially to increased heart rate, followed by improved reflex response, color, respiration, and muscle tone. Evidence of intrapartum fetal distress, persistence of an Apgar score of 0 to 3 for > 5 min; an umbilical arterial blood pH < 7; and a sustained neonatal neurologic syndrome that includes hypotonia, coma, seizures, and evidence of multiorgan dysfunction are manifestations of perinatal asphyxia. The severity and prognosis of posthypoxic encephalopathy can be estimated with the Sarnat classification (see Table 274-3) in conjunction with EEG, neuroradiologic imaging, and brain stem auditory and cortical evoked responses.

Resuscitation: Initial measures for all neonates include suctioning and tactile stimulation. Suctioning requires appropriately sized catheters (see Table 223-3 on p. 2264) and pressure limits of 100 mm Hg (136 cm H₂O). Tactile stimulation (eg, flicking the soles of the feet, rubbing the back) may be necessary to encourage regular, spontaneous breathing. Infants not responding with appropriate respirations and heart rate require O₂ therapy, bag-mask ventilation, sometimes endo-tracheal intubation, and much less commonly, chest compressions (see Fig. 274-3 and Fig. 223-2 on p. 2268).
circumference \(B\) at birth.]

[Table 274-1. Problems that may Require Resuscitation]

The infant is quickly dried and placed supine under a preheated overhead warmer in the delivery room. The neck is supported in the neutral position with a rolled towel under the shoulders.

\(O_2\) should be given at 10 L/min through a face mask attached to a self-inflatable or anesthesia bag; if no mask is available, \(O_2\) tubing may be placed adjacent to the face and set to deliver 5 L/min. If spontaneous respirations are absent or heart rate is < 100 beats/min, respirations are assisted with the bag-mask. Bradycardia in a distressed child is a sign of impending cardiac arrest; neonates tend to develop bradycardia with hypoxemia. Advanced resuscitation techniques, including endotracheal intubation, and selection of equipment size, drugs and dosages, and CPR parameters are discussed elsewhere (see p. 2266).

**Birth Injuries**

The forces of labor and delivery occasionally cause physical injury to the infant. The incidence of neonatal injury from difficult or traumatic deliveries is decreasing due to increasing use of cesarean section in place of difficult versions, vacuum extractions, or mid- or high-forceps deliveries.

A traumatic delivery is anticipated when the mother has small pelvic measurements, when the infant seems large for gestational age (often the case with diabetic mothers), or when there is a breech or other abnormal presentation, especially in a primipara. In such situations, labor and the fetal condition should be monitored closely. If fetal distress is detected, the mother should be positioned on her side and given \(O_2\). If fetal distress persists, an immediate cesarean section should be done.

**Head Injuries**

Head molding is common in vaginal delivery due to the high pressure exerted by uterine contractions on the infant's malleable cranium as it passes through the birth canal. This molding rarely causes problems or requires treatment.

**Caput succedaneum** is edema of the presenting portion of the scalp. It occurs when the area is forced against the uterine cervix. Subgaleal hemorrhage results from greater trauma and is characterized by a boggy feeling over the entire scalp, including the temporal regions. Treatment is not required.

**Cephalhematoma**, or hemorrhage beneath the periosteum, can be differentiated from subgaleal hemorrhage because it is sharply limited to the area overlying a single bone, the periosteum being adherent at the sutures. Cephalhematomas are commonly unilateral and parietal. In a small percentage, there is a linear fracture of the underlying bone. Treatment is not required, but anemia or hyperbilirubinemia may result.

**Depressed skull fractures** are uncommon. Most result from forceps pressure or rarely from the head resting on a bony prominence in utero. Infants with depressed skull fractures or other head trauma may also have subdural bleeding, subarachnoid hemorrhage, or contusion or laceration of the brain itself (see p. 2773). Depressed skull fractures cause a palpable (and sometimes visible) step-off deformity,

[Table 274-2, Apgar Score]

which must be differentiated from the palpable elevated periosteal rim occurring with cephalhematomas. CT is done to confirm the diagnosis and rule out complications. Neuro-surgical elevation may be needed.

**Cranial Nerve Injury**

The facial nerve is injured most often. Although frequently attributed to forceps pressure, most injuries probably result from pressure on the nerve in utero, which may be due to fetal positioning (eg, from the
head lying against the shoulder, the sacral promontory, or a uterine fibroid).

Facial nerve injury usually occurs at or distal to its exit from the stylomastoid foramen and results in facial asymmetry, especially during crying. Identifying which side of the face is affected can be confusing, but the facial muscles on the side of the nerve injury cannot move. Injury can also occur to individual branches of the nerve, most often the mandibular. Another cause of facial asymmetry is mandibular asymmetry resulting from intrauterine pressure; in this case, muscle innervation is intact and both sides of the face can move. In mandibular asymmetry, the maxillary and the mandibular occlusal surfaces are not parallel, which differentiates it from a facial nerve injury.

Testing or treatment is not needed for peripheral facial nerve injuries or mandibular asymmetry. They usually resolve by age 2 to 3 mo.

**Brachial Plexus Injuries**

Brachial plexus injuries follow stretching caused by shoulder dystocia, breech extraction, or hyperabduction of the neck in cephalic presentations. Injuries can be due to simple stretching, hemorrhage within a nerve, tearing of the nerve or root, or avulsion of the roots with accompanying cervical cord injury. Associated injuries (eg, fractures of the clavicle or humerus or subluxations of the shoulder or cervical spine) may occur.

Injuries of the upper brachial plexus (C5 to C6) affect muscles around the shoulder and elbow, whereas lesions of the lower plexus (C7 to C8 and T1) primarily affect muscles of the forearm and hand. The site and type of nerve root injury determine the prognosis.

Erb's palsy is an upper brachial plexus injury causing adduction and internal rotation of the shoulder with pronation of the forearm. Ipsilateral paralysis of the diaphragm is common. Treatment includes protecting the shoulder from excessive motion by immobilizing the arm across the upper abdomen and preventing contractures by passive range-of-motion exercises to involved joints done gently every day starting at 1 wk of age.

Klumpke's palsy is a lower plexus injury resulting in paralysis of the hand and wrist, often with ipsilateral Horner's syndrome (miosis, ptosis, facial anhidrosis). Passive range-of-motion exercises are the only treatment needed.

Neither Erb's palsy nor Klumpke's palsy usually causes demonstrable sensory loss, which suggests a tear or avulsion. These conditions usually improve rapidly, but deficits can persist. If a significant deficit persists > 3 mo, MRI is done to determine the extent of injury to the plexus, roots, and cervical cord. Surgical exploration and repair have sometimes been helpful.

[Table 274-3. Clinical Staging of Posthypoxic Encephalopathy]

When the entire brachial plexus is injured, the involved upper extremity cannot move, and sensory loss is usually present. Ipsilateral pyramidal signs indicate spinal cord trauma; an MRI should be done. The involved extremity's subsequent growth may be impaired. The prognosis for recovery is poor. Management may include neurosurgical exploration. Passive range-of-motion exercises can prevent contractures.

**Other Peripheral Nerve Injuries**

Injuries to other peripheral nerves (eg, the radial, sciatic, obturator) are rare in neonates and are usually not related to labor and delivery. They are usually secondary to a local traumatic event (eg, an injection in or near the sciatic nerve). Treatment includes placing the muscles antagonistic to those paralyzed at rest until recovery. Neurosurgical exploration of the nerve is seldom indicated. In most peripheral nerve injuries, recovery is complete.

**Spinal Cord Injury**
Spinal cord injury (see also p. 3231) is rare and involves variable degrees of cord disruption, often with hemorrhage. Complete disruption of the cord is very rare. Trauma usually occurs in breech deliveries after excess longitudinal traction to the spine. It can also follow hyperextension of the fetal neck in utero (the “flying fetus”). Injury usually affects the lower cervical region (C5 to C7). When the injury is higher, lesions are usually fatal because respiration is completely compromised. Sometimes a click or snap is heard at delivery.

Spinal shock with flaccidity below the level of injury occurs initially. Usually, there is patchy retention of sensation or movement below the lesion. Spasticity develops within days or weeks. Breathing is diaphragmatic because the phrenic nerve remains intact as its origin is higher (at C3 to C5) than the typical cord lesion. When the spinal cord lesion is complete, the intercostal and abdominal muscles become paralyzed and rectal and bladder sphincters cannot develop voluntary control. Sensation and sweating are lost below the involved level, which can cause fluctuations of body temperature with environmental changes.

An MRI of the cervical cord may show the lesion and excludes surgically treatable lesions, such as congenital tumors or hematomas pressing on the cord. The CSF is usually bloody.

With appropriate care, most infants survive for many years. The usual causes of death are recurring pneumonia and progressive loss of renal function. Treatment includes nursing care to prevent skin ulcerations, prompt treatment of urinary and respiratory infections, and regular evaluations to identify obstructive uropathy early.

**Intracranial Hemorrhage**

Hemorrhage in or around the brain can occur in any neonate but is particularly common in those born prematurely; about 20% of premature infants < 1500 g have intracranial hemorrhage. Hypoxia-ischemia, variations in BP, and pressures exerted on the head during labor are major causes. The presence of the germinal matrix (a mass of embryonic cells lying over the caudate nucleus on the lateral wall of the lateral ventricles and present only in the fetus) makes hemorrhage more likely. Risk also is increased by hematologic disorders (eg, vitamin K deficiency, hemophilia, disseminated intravascular coagulation).

Hemorrhage can occur in several CNS spaces. Small hemorrhages in the subarachnoid space, falx, and tentorium are frequent incidental findings at autopsy of neonates that have died from non-CNS causes. Larger hemorrhages in the subarachnoid or subdural space, brain parenchyma, or ventricles are less common but more serious.

**Subarachnoid hemorrhage** probably is the most common type of intracranial hemorrhage. Neonates may present with apnea, seizures, lethargy, or an abnormal neurologic examination. With large hemorrhages, the associated meningeal inflammation may lead to a communicating hydrocephalus as the infant grows.

**Subdural hemorrhage**, which is now less common because of improved obstetric techniques, results from tears in the falx, tentorium, or bridging veins. Such tears tend to occur in neonates of primiparas, in large neonates, or after difficult deliveries—conditions that can produce unusual pressures on intracranial vessels. The presenting finding may be seizures; a rapidly enlarging head; or an abnormal neurologic examination with hypotonia, a poor Moro reflex, or extensive retinal hemorrhages.

**Intraventricular and/or intraparenchymal hemorrhage** usually occurs during the 1st 3 days of life and is the most serious type of intracranial bleeding. Hemorrhages occur most often in premature infants, are often bilateral, and usually arise in the germinal matrix. Most bleeding episodes are subependymal or intraventricular and involve a small amount of blood. In severe hemorrhage, there may be bleeding into the parenchyma or a cast of the ventricular system with large amounts of blood in the cisterna magna and basal cisterns. Hypoxia-ischemia often precedes intraventricular and subarachnoid bleeding. Hypoxia-ischemia damages the capillary endothelium, impairs cerebral vascular autoregulation, and can increase
cerebral blood flow and venous pressure, all of which make hemorrhage more likely. Most intraventricular hemorrhages are asymptomatic, but larger hemorrhages may cause apnea, cyanosis, or sudden collapse.

**Diagnosis**

- **CT**

Intracranial hemorrhage should be suspected in any neonate with apnea, seizures, lethargy, or an abnormal neurologic examination; such infants should have head CT. Although cranial ultrasonography is risk free, requires no sedation, and can readily identify blood within the ventricles or brain substance, CT is more sensitive for thin layers of blood in the subarachnoid or subdural spaces. However, for screening of very premature infants (eg, < 30 wk gestation), some clinicians prefer the logistical simplicity of ultrasonography. If the diagnosis is in doubt, the CSF can be examined for RBCs: it usually contains gross blood. However, some RBCs are often present in the CSF of term neonates. In subdural hemorrhage, transillumination of the skull may reveal the diagnosis after the blood has lysed.

Additionally, clotting studies, a CBC, and metabolic studies to identify other causes of neurologic dysfunction (eg, hypoglycemia, hypocalcemia, electrolyte imbalance) should be done. An EEG may help establish prognosis if the infant survives the acute bleeding episode.

**Prognosis**

The prognosis for subarachnoid hemorrhage is usually good. The prognosis for subdural hemorrhage is guarded, but some infants do well. Most infants with small intraventricular hemorrhages survive the acute bleeding episode and do well. Infants with large intraventricular hemorrhages have a poor prognosis, especially if the hemorrhage extends into the parenchyma. Preterm infants with a history of severe intraventricular hemorrhage are at risk of developing posthemorrhagic hydrocephalus and must be monitored carefully with serial cranial ultrasound examinations and frequent serial head circumference measurements. Infants with progressive hydrocephalus require neurosurgical evaluation for the placement of a subcutaneous ventricular reservoir (to aspirate CSF) or for the placement of a ventriculoperitoneal shunt. The CSF associated with posthemorrhagic hydrocephalus has a very low glucose concentration known as hypoglycorrhachia. Because many infants will be left with neurologic deficits, careful follow-up and referral for early intervention services are important.

**Treatment**

Treatment is mostly supportive unless a hematologic abnormality contributed to the bleeding. All infants should receive vitamin K if not previously given. If deficient, platelets or clotting factors should be given. Subdural hematomas should be managed by a neuro-surgeon; evacuation of the hemorrhage may be needed.

**Fractures**

Midclavicular fracture, the most common fracture during birth, occurs with shoulder dystocia and with normal, nontraumatic deliveries. Initially, the neonate is irritable and does not move the arm on the involved side either spontaneously or when the Moro reflex is elicited. Most clavicular fractures are greenstick and heal rapidly and uneventfully. A large callus forms at the fracture site within a week, and remodeling is completed within a month. Treatment consists of making a sling by pinning the shirt sleeve of the involved side to the opposite side of the infant's shirt.

The humerus and femur may be fractured in difficult deliveries. Most of these are green-stick, mid-shaft fractures, and excellent remodeling of the bone usually follows, even if moderate angulation occurs initially. A long bone may be fractured through its epiphysis, but prognosis is excellent.

**Soft-Tissue Injuries**

All soft tissues are susceptible to injury during birth if they have been the presenting part or the fulcrum for the forces of uterine contraction. Edema and ecchymosis often follow injury, particularly of the
periorbital and facial tissues in face presentations and of the scrotum or labia during breech deliveries. Breakdown of blood within the tissues and conversion of heme to bilirubin result whenever a hematoma develops. This added burden of bilirubin may cause sufficient neonatal hyperbilirubinemia to require phototherapy, and rarely, exchange transfusion (see p. 2793). No other treatment is needed.

**Hypothermia**

**Hypothermia is a core temperature < 35 to 35.5° C. The condition may be purely environmental or represent intercurrent illness. Treatment is rewarming.**

Thermal equilibrium is affected by relative humidity, air flow, proximity of cold surfaces, and ambient air temperature. Neonates are particularly prone to rapid heat loss and consequent hypothermia because of a high surface area to volume ratio, which is particularly high in low-birth-weight neonates. Radiant heat loss occurs when bare skin is exposed to an environment containing objects of cooler temperature. Evaporative heat loss occurs when neonates are wet with amniotic fluid. Conductive heat loss occurs when the neonate is placed in contact with a cool surface or object. Hypothermia also may be caused by pathologic conditions that impair thermoregulation (eg, sepsis, intracranial hemorrhage).

**Pathophysiology**

Prolonged, unrecognized cold stress may divert calories to produce heat, impairing growth. Neonates respond to cooling by sympathetic nerve discharge of norepinephrine in the brown fat. This specialized tissue of the neonate, located in the nape of the neck, between the scapulae, and around the kidneys and adrenals, responds by lipolysis followed by oxidation or re-esterification of the fatty acids that are released. These reactions produce heat locally, and a rich blood supply to the brown fat helps transfer this heat to the rest of the neonate's body. This reaction increases the metabolic rate and \( \text{O}_2 \) consumption 2- to 3-fold. Thus, in neonates with respiratory insufficiency (eg, the preterm infant with respiratory distress syndrome), cold stress may also result in tissue hypoxia and neurologic damage. Additionally, hypothermia can result in hypoglycemia, metabolic acidosis, and death.

**Treatment**

Hypothermia is treated by rewarming in an incubator or under a radiant warmer. The neonate should be monitored and treated as needed for hypoglycemia, hypoxemia, and apnea. Underlying conditions such as sepsis or intracranial hemorrhage require specific treatment.

**Prevention**

Hypothermia can be prevented by immediately drying and then swaddling the neonate (including the head) in a warm blanket. A neonate exposed for resuscitation or observation should be placed under a radiant warmer. Sick neonates should be maintained in a neutral thermal environment to minimize the metabolic rate. The proper incubator temperature varies depending on the neonate's birth weight and postnatal age. Alternatively, heating can be adjusted with a servomechanism set to maintain skin temperature at 36.5° C.

**Large-for-Gestational-Age Infant**

Infants whose weight is > the 90th percentile for gestational age are classified as large for gestational age (LGA). The predominant cause is maternal diabetes. Complications include birth trauma, hypoglycemia, and hyperbilirubinemia.

Other than genetically determined size, the major cause of an infant's being LGA is maternal diabetes mellitus. The macrosomia results from the anabolic effects of high fetal insulin levels produced in response to excessive blood glucose during gestation. The less well controlled the mother's diabetes during pregnancy, the more severe is the fetal macrosomia. A rare nongenetic cause of macrosomia is Beckwith-Wiedemann syndrome (characterized by macrosomia, omphalocele, macroglossia, and hypoglycemia).
Symptoms, Signs, and Treatment

LGA infants are large, obese, and plethoric. These infants are often listless and limp and may feed poorly. Delivery complications can occur in any LGA infant. Metabolic and respiratory complications are specific to LGA infants of diabetic mothers.

Delivery complications: Because of the infant's large size, vaginal delivery may be difficult and occasionally results in birth injury. Shoulder dystocia, fractures of the clavicles or limbs, and perinatal asphyxia may occur. Therefore, cesarean section should be considered when the fetus is thought to be LGA, especially if the mother's pelvic measurements are at the lower end of normal.

Infants of diabetic mothers: These infants are very likely to become hypoglycemic in the first 1 to 2 h after delivery because of the state of hyperinsulinism and the sudden termination of maternal glucose when the umbilical cord is cut. Neonatal hypoglycemia can be prevented by close prenatal control of the mother's diabetes and by the prophylactic IV infusion of 10% dextrose in water into the infant until early frequent feedings can be established. Blood glucose levels should be closely monitored by bedside testing during the transition period.

Hyperbilirubinemia (see also p. 2788) is common because of intolerance for oral feedings in the earliest days of life, which increases the enterohepatic circulation of bilirubin. Hyperbilirubinemia can also result from the infant's high Hct (another accompanying problem in infants of diabetic mothers).

Because surfactant production (and hence pulmonary maturation) may be delayed until late in gestation, respiratory distress syndrome may develop even if the infant is delivered only a few weeks prematurely. The lecithin/sphingomyelin ratio, and especially the presence of phosphatidyl glycerol, in amniotic fluid obtained by amniocentesis can evaluate fetal lung maturity and help determine the optimal time for safe delivery. Lung maturity can be assumed only if phosphatidyl glycerol is present. Treatment is discussed on p. 2877.

Postmature Infant

A postmature infant is an infant born after 42 wk gestation.

The cause of postmaturity is generally unknown. Very rarely, it may be caused by abnormalities that affect the fetal pituitary-adrenal axis (eg, anencephaly or adrenal agenesis).

Pathophysiology

Past term, the placenta involutes, and multiple infarcts and villous degeneration cause placental insufficiency syndrome. In this syndrome, the fetus receives inadequate nutrients from the mother, resulting in soft-tissue wasting. During labor, postmature infants are prone to develop asphyxia; meconium aspiration syndrome, which may be unusually severe because post-term amniotic fluid volume is decreased and the aspirated meconium is less diluted; and neonatal hypoglycemia caused by insufficient glycogen stores at birth. Because anaerobic metabolism rapidly uses the remaining glycogen stores, hypoglycemia is exaggerated if perinatal asphyxia has occurred.

Symptoms and Signs

Postmature infants are alert and appear mature but have a decreased amount of soft-tissue mass, particularly subcutaneous fat. The skin may hang loosely on the extremities and is often dry and peeling. The fingernails and toenails are long. The nails and umbilical cord may be stained with meconium passed in utero.

Diagnosis

Diagnosis is by clinical appearance (see Fig. 268-1 on p. 2700) and estimated date of delivery.

Treatment
Prognosis and treatment depend on complications. Neonates with meconium aspiration may have chronic respiratory insufficiency and secondary pulmonary hypertension if untreated; surfactant replacement therapy is frequently helpful.

**Premature Infant**

A premature infant is an infant born before 37 wk gestation.

Full-term gestation is 40 wk. Infants born before 37 wk have an increased incidence of complications and mortality roughly proportional to the degree of prematurity. Preterm delivery occurs in about 12.5% of pregnancies in the US and is one of the chief causes of neonatal morbidity and mortality. The rate of prematurity for black infants is 17.9%.

Previously, any infant weighing < 2.5 kg was termed premature. This definition is inappropriate because many infants weighing < 2.5 kg are mature or postmature but small for gestational age; they have a different appearance and different problems. Infants < 2.5 kg at birth are considered low-birth-weight infants, and those < 1500 g are considered very low-birth-weight infants.

**Etiology**

The cause of premature labor and delivery, whether preceded by premature rupture of the membranes or not, is usually unknown. However, maternal history commonly shows low socioeconomic status; inadequate prenatal care; poor nutrition; poor education; unwed state; previous preterm birth; and intercurrent, untreated illness or infection (eg, bacterial vaginosis). Other risk factors include placental abruption, preeclampsia, multiple pregnancies, cervical incompetence, and multiple abortions.

**Symptoms and Signs**

The premature infant is small, usually weighing < 2.5 kg, and tends to have thin, shiny, pink skin through which the underlying veins are easily seen. Little subcutaneous fat, hair, or external ear cartilage exists. Spontaneous activity and tone are reduced, and extremities are not held in the flexed position typical of term infants. In males, the scrotum may have few rugae, and the testes may be undescended. In females, the labia majora do not yet cover the labia minora. Reflexes develop at different times during gestation. The Moro reflex begins by 28 to 32 wk gestation and is well established by 37 wk. The palmar reflex starts at 28 wk and is well established by 32 wk. The tonic neck reflex starts at 35 wk and is most prominent at 1 mo postterm.

**Diagnosis**

Findings on physical examination correlate with gestational age (see Fig. 268-1 on p. 2700). Estimated date of delivery and prenatal ultra-sonography, if done, also determine gestational age.

**Initial testing:** Along with appropriate testing for any identified problems or disorders, routine evaluations include pulse oximetry, serum Ca and electrolytes, CBC, bilirubin level, blood culture, hearing evaluation, cranial ultra-sonography to screen for intraventricular hemorrhage and periventricular leukomalacia, and screening by an ophthalmologist for retinopathy of prematurity. Weight, length, and head circumference should be plotted on an appropriate growth chart at weekly intervals.

**Subsequent screening:** Preterm infants must be monitored for apnea and bradycardia until they are 34.5 to 35 wk adjusted age. Before discharge from the hospital, premature infants should undergo a car seat monitoring evaluation using pulse oximetry to make sure that they can maintain a patent airway and good O₂ saturation while positioned in the car seat. After discharge, premature infants should receive careful neurodevelopmental follow-up and appropriate early referral to intervention programs as needed for physical, occupational, and language therapy.

**Complications**
Most complications relate to dysfunction of immature organ systems. In some cases, complications resolve completely; in others, there is residual organ dysfunction.

**Lungs:** Surfactant production is often inadequate to prevent alveolar collapse and atelectasis, which result in respiratory distress syndrome (see p. 2876). Surfactant replacement therapy is used to both prevent and treat respiratory distress syndrome. In spite of this therapy, many premature infants develop a chronic form of lung disease known as bronchopulmonary dysplasia with a prolonged need for ventilator therapy and supplemental O\textsubscript{2} therapy. Palivizumab prophylaxis for respiratory syncytial virus is important for infants with chronic lung disease (see p. 2870).

**CNS:** Infants born before 34 wk gestation have inadequate coordination of sucking and swallowing reflexes and need to be fed intravenously or by gavage. Immaturity of the respiratory center in the brain stem results in apneic spells (central apnea—see p. 2869). Apnea may also result from hypopharyngeal obstruction alone (obstructive apnea). Both may be present (mixed apnea).

The periventricular germinal matrix (a mass of embryonic cells on the lateral wall of the lateral ventricles and present only in the fetus) is prone to hemorrhage, which may extend into the cerebral ventricles (intraventricular hemorrhage). Infarction of the periventricular white matter (periventricular leukomalacia) may also occur for reasons that are incompletely understood. Hypotension, inadequate or unstable brain perfusion, and BP peaks (as when fluid or colloid is given rapidly IV) may contribute to cerebral infarction or hemorrhage. Periventricular white matter injury is a major risk factor for cerebral palsy and neuro-developmental delays.

Premature infants, particularly those with a history of sepsis, hypoxia, and intraventricular or periventricular hemorrhages, are at risk of developmental and cognitive delays. These infants require careful follow-up during the first year of life to identify auditory, visual, and neurodevelopmental delays. Careful attention must be paid to developmental milestones, muscle tone, language skills, and growth (weight, length, and head circumference). Infants with identified delays in visual skills should be referred to a pediatric ophthalmologist. Infants with auditory and neurodevelopmental delays (including increased muscle tone and abnormal protective reflexes) should be referred to early intervention programs that provide physical, occupational, and speech therapy. Infants with severe neurodevelopmental problems may need to be referred to a pediatric neurologist.

**Infection:** Sepsis (see p. 2832) or meningitis (see p. 2830) is about 4 times more likely in the premature infant. The increased likelihood results from indwelling intravascular catheters and endotracheal tubes, areas of skin breakdown, and markedly reduced serum immunoglobulin levels (see p. 2766).

**Cardiac:** The ductus arteriosus is more likely to fail to close after birth in premature infant. The incidence of patent ductus arteriosus (PDA—see p. 2955) increases with increasing prematurity; PDA occurs in almost half of infants < 1750 g birth weight and in about 80% of those < 1200 g. About one third to one half of those with PDA have some degree of heart failure. Premature infants ≤ 29 wk gestation at birth who have respiratory distress syndrome have a 65 to 88% risk of a symptomatic PDA.

**Temperature regulation:** Premature infants have an exceptionally large body surface area to volume ratio. Therefore, when exposed to temperatures below the neutral thermal environment (see p. 2774), they rapidly lose heat and have difficulty maintaining body temperature.

**GI tract:** The small stomach and immature sucking and swallowing reflexes hinder oral or NGT feedings and create a risk of aspiration. Necrotizing enterocolitis (see p. 2803) usually manifests with bloody stool, feeding intolerance, and a distended, tender abdomen. Necrotizing enterocolitis is the most common surgical emergency in the premature infant. Complications of neonatal necrotizing enterocolitis include bowel perforation with pneumoperitoneum, intra-abdominal abscess formation, stricture formation, and short bowel syndrome.

**Kidneys:** Renal function is limited, so the concentrating and diluting limits of urine are decreased. Late metabolic acidosis and growth failure may result from the immature kidneys’ inability to excrete fixed acids, which accumulate with high-protein formula feedings and as a result of bone growth. Na and HCO\textsubscript{3} are lost in the urine.
Eyes: Retinal vascularization is not complete until near term. Preterm delivery may interfere with this process, resulting in abnormal vessel development and sometimes defects in vision (retinopathy of prematurity—(see p. 2781). Incidence of myopia and strabismus increases independently of retinopathy of prematurity.

Metabolic problems: Hypoglycemia (see p. 2796) and hyperglycemia (see p. 2795) are discussed elsewhere.

Hyperbilirubinemia (see also p. 2788) occurs more commonly in the premature as compared to the term infant, and kernicterus may occur at serum bilirubin levels as low as 10 mg/dL (170 μmol/L) in small, sick, premature infants. The higher bilirubin levels may be partially due to inadequately developed hepatic excretion mechanisms, including deficiencies in the uptake of bilirubin from the serum, its hepatic conjugation to bilirubin diglucuronide, and its excretion into the biliary tree. Decreased intestinal motility enables more bilirubin diglucuronide to be deconjugated within the intestinal lumen by the luminal enzyme β-glucuronidase, thus permitting increased reabsorption of unconjugated bilirubin (enterohepatic circulation of bilirubin). Conversely, early feedings increase intestinal motility and reduce bilirubin reabsorption and can thereby significantly decrease the incidence and severity of physiologic jaundice. Uncommonly, delayed clamping of the umbilical cord increases the risk of significant hyperbilirubinemia by allowing the transfusion of a large RBC mass, thus increasing RBC breakdown and bilirubin production.

Prognosis

Prognosis varies with presence and severity of complications, but usually mortality and likelihood of complications decrease greatly with increasing gestational age and birth weight (see Table 274-4).

Treatment

• Supportive care

Specific disorders are treated as discussed elsewhere in THE manual. General supportive care of the premature infant is best provided in a neonatal ICU or special care nursery and involves careful attention to the thermal environment, using servo-controlled incubators. Scrupulous adherence is paid to handwashing before and after all patient contact. Infants are continually monitored for apnea, bradycardia, and hypoxemia until 34.5 or 35 wk gestation.

Parents should be encouraged to visit and interact with the infant as much as possible within the constraints of the infant's medical condition.

Preterm infants should be transitioned to the supine sleeping position before hospital discharge. Parents should be instructed to keep cribs free of fluffy materials including blankets, quilts, pillows, and stuffed toys, which have been associated with an increased risk of SIDS.

Feeding: Feeding should be by NGT until coordination of sucking, swallowing, and breathing is established at about 34 wk gestation, at which time breastfeeding is strongly encouraged. Most premature infants tolerate breast milk, which provides immunologic and nutritional factors that are absent in cow's milk formulas. However, breast milk does not provide sufficient Ca, phosphorus, and protein for very low-birth-weight infants (ie, < 1500 g), for whom it should be mixed with a breast milk fortifier. Alternatively, specific premature infant formulas that contain 20 to 24 kcal/oz (2.8 to 3.3 joules/mL) can be used.

In the initial 1 or 2 days, if adequate fluids and calories cannot be given by mouth or NGT because of the infant's condition, a 10% glucose solution with maintenance electrolytes is given IV to prevent dehydration and undernutrition. Continuous breast milk or formula feeding via NGT or nasojejunal tube can satisfactorily maintain caloric intake in small, sick, premature infants, especially those with respiratory distress or recurrent apneic spells. Feedings are begun with small amounts (eg, 1 to 2 mL q 3 to 6 h) to
stimulate the GI tract. If tolerated, the volume and concentration of feedings are slowly increased over 7 to 10 days. In very small or critically sick infants, total parenteral hyperalimentation via a peripheral IV or a percutaneously or surgically placed central catheter may be required until full enteral feedings can be tolerated.

**Prevention**

The risk of preterm delivery can be reduced by ensuring that all women, especially those in high-risk groups, have access to early and appropriate prenatal care, including advice on the importance of avoiding alcohol, tobacco,

[Table 274-4. Survival Estimates for Premature Infants]

and illicit drugs. The use of tocolytics to arrest premature labor and provide time for prenatal administration of corticosteroids to hasten lung maturation is discussed elsewhere (see p. 2683).

**Retinopathy of Prematurity**

(Retrolental Fibroplasia)

Retinopathy of prematurity (ROP) is a bilateral disorder of abnormal retinal vascularization in premature infants, especially those of lowest birth weight. Outcomes range from normal vision to blindness. Diagnosis is by ophthalmoscopy. Treatment of severe disease may include cryotherapy or photocoagulation; other treatment is directed at complications (eg, retinal detachment).

The inner retinal blood vessels start growing about midpregnancy, but the retina is not fully vascularized until term. ROP results if these vessels continue their growth in an abnormal pattern, forming a ridge of tissue between the vascularized central retina and the nonvascularized peripheral retina. In severe ROP, these new vessels invade the vitreous. Sometimes the entire vasculature of the eye becomes engorged (plus disease).

Susceptibility to ROP correlates with the proportion of retina that remains avascular at birth. More than 80% of neonates weighing < 1 kg at birth develop ROP. The percentage is higher when many medical complications exist. Excessive (especially prolonged) O₂ therapy increases the risk. However, supplemental O₂ is often needed to adequately oxygenate the infant even though a safe level and duration of O₂ therapy have not been determined.

**Diagnosis**

- **Ophthalmoscopy**

Diagnosis is made by ophthalmoscopic examination, which shows a line of demarcation and a ridge in mild cases and proliferation of retinal vessels in more severe cases. Because significant ROP is rare in appropriately managed infants weighing > 1500 g at birth, alternative diagnoses should be considered in these infants (eg, familial exudative retinopathy, Norrie's disease).

**Prognosis**

Abnormal vessel growth often subsides spontaneously but, in about 4% of survivors weighing < 1 kg at birth, progresses to produce retinal detachments and vision loss within 2 to 12 mo postpartum. Children with healed ROP have a higher incidence of myopia, strabismus, and amblyopia. A few children with moderate, healed ROP are left with cicatricial scars (eg, dragged retina or retinal folds) and are at risk of retinal detachments later in life; rarely, glaucoma and cataracts can also occur.

**Treatment**
Cryotherapy or laser photocoagulation

In severe ROP, cryotherapy or laser photo-coagulation to ablate the peripheral avascular retina reduces the incidence of retinal fold and detachment. Therefore, all high-risk infants should be examined by an ophthalmologist before 6 wk of age. Retinal vascularization must be followed at 1- to 2-wk intervals until the vessels have matured sufficiently. If retinal detachments occur in infancy, scleral buckling surgery or vitrectomy with lens extraction may be considered, but these procedures are late rescue efforts with low benefit.

Patients with residual scarring should be followed at least annually for life. Treatment of amblyopia and refractive errors in the 1st year optimizes vision. Infants with total retinal detachments should be monitored for secondary glaucoma and poor eye growth and referred to intervention programs for the visually impaired.

Prevention

Prevention of premature birth is the best way to prevent ROP. After a preterm birth, O<sub>2</sub> should be supplemented only as needed to avoid hypoxia documented by ABG or pulse oximetry. Vitamin E and restricted light are not effective.

Small-for-Gestational-Age Infant

(Dysmaturity; Intrauterine Growth Restriction)

Infants whose weight is < the 10th percentile for gestational age are classified as small for gestational age (SGA). Complications include perinatal asphyxia, meconium aspiration, and hypoglycemia.

Etiology

An infant may be small at birth because of genetic factors. Nongenetic factors that can restrict intrauterine growth usually are not apparent before 32 to 34 wk gestation; these factors include placental insufficiency from maternal disease involving the small blood vessels (as in preeclampsia, primary hypertension, renal disease, or long-standing diabetes); placental involution accompanying postmaturity; and infectious agents such as cytomegalovirus, rubella virus, or *Toxoplasma gondii*. An infant may also be SGA if the mother is an opioid or cocaine addict or a heavy user of alcohol or, to a lesser degree, if she smoked cigarettes during pregnancy.

Symptoms and Signs

Despite their size, SGA infants have physical characteristics (eg, skin appearance, ear cartilage, sole creases) and behavior (eg, alertness, spontaneous activity, zest for feeding) similar to those of normal-sized infants of like gestational age.

If growth restriction is caused by placental insufficiency and, therefore, undernutrition, the infant's weight is most affected, with a relative sparing of growth of the brain, cranium, and long bones (asymmetric growth restriction). In contrast, many genetic disorders and congenital infections cause symmetric growth restriction, in which height, weight, and head circumference are about equally affected.

Complications: Full-term SGA infants do not have the complications related to organ system immaturity that premature infants of similar size have. They are, however, at risk of perinatal asphyxia, meconium aspiration, and hypoglycemia.

Perinatal asphyxia is the most serious potential complication. It is a risk during labor if intrauterine growth restriction is caused by placental insufficiency (with marginally adequate placental perfusion), because each uterine contraction slows or stops maternal placental perfusion by compressing the spiral arteries. Therefore, when placental insufficiency is suspected, the fetus should be assessed before labor and the fetal heart rate monitored during labor. If fetal compromise is detected, rapid delivery, often by
cesarean section, is indicated.

**Meconium aspiration** may occur during perinatal asphyxia. SGA infants, especially those who are postmature, may pass meconium into the amniotic sac and begin deep gasping movements. The consequent aspiration is likely to result in meconium aspiration syndrome (often most severe in growth-restricted or postmature infants, because the meconium is contained in a smaller volume of amniotic fluid—see p. 2872).

**Hypoglycemia** often occurs in the early hours and days of life due to a lack of adequate glycogen stores (see p. 2796).

**Polycythemia** may occur when SGA fetuses experience chronic mild hypoxia caused by placental insufficiency. Erythropoietin release is increased, leading to an increased rate of erythrocyte production. The neonate with polycythemia at birth appears ruddy and may be tachypneic or lethargic.

**Prognosis**

If asphyxia can be avoided, neurologic prognosis is quite good.

Infants who are SGA because of genetic factors, congenital infection, or maternal drug use often have a worse prognosis, depending on the specific diagnosis. If intrauterine growth restriction is caused by chronic placental insufficiency, adequate nutrition may allow SGA infants to demonstrate remarkable "catch-up" growth after delivery.

**Treatment**

Underlying conditions and complications are treated. There is no specific intervention for the SGA state, but prevention is aided by prenatal advice on the importance of avoiding alcohol, tobacco, and illicit drugs.
Chapter 275. Perinatal Hematologic Disorders

Introduction

Anemia and polycythemia are the most common hematologic disorders diagnosed at birth. Prenatal and perinatal changes in erythropoiesis are discussed in Ch. 273.

Perinatal Anemia

(See also Ch. 104.)

Anemia is Hb or Hct > 2 standard deviations below the mean for age. Both Hb and Hct change rapidly as a neonate matures, so lower limits of normal also change (see Table 275-1). Variables such as gestational age, sampling site (capillary vs vein), and position of the neonate relative to the placenta before cord clamping (lower position causes blood to transfer in to the neonate; higher position causes blood to transfer out of the neonate) also affect test results.

Etiology

Causes of anemia in neonates include

• Physiologic processes
• Blood loss
• Decreased RBC production
• Increased RBC destruction (hemolysis)

Physiologic anemia: Normal physiologic processes often cause normocytic-normochromic anemia in term and preterm infants. Physiologic anemias do not generally require extensive evaluation or treatment.

In term infants, the increase in oxygenation that occurs with normal breathing after birth causes an abrupt rise in tissue O_2 level, resulting in negative feedback on erythropoietin production and erythropoiesis. This reduction in erythropoiesis, as well as the shorter life span of neonatal RBCs (60 to 70 days vs 120 days in adults), causes Hb concentration to fall over the first 2 to 3 mo of life, usually to no lower than 9.4 g/dL. Hb remains stable over the next several weeks, and then slowly rises in the 4th to 6th mo secondary to renewed erythropoietin stimulation.

The same mechanism causes anemia in preterm infants during the first 4 to 12 wk, but lower erythropoietin production, shorter RBC life span (35 to 50 days), rapid growth, and more frequent phlebotomy contribute to a faster and lower Hb nadir (8 to 10 g/dL). Infants < 32 wk gestation are most affected.

Blood loss: Anemia may develop because of prenatal, perinatal (at delivery), or postpartum hemorrhage. In neonates, absolute blood volume is low (eg, preterm, 90 to 105 mL/kg; term, 78 to 86 mL/kg); therefore, acute loss of as little as 15 to 20 mL of blood may result in anemia. An infant with chronic blood loss can compensate physiologically and is typically more clinically stable than an infant with acute blood loss.

Prenatal hemorrhage may be caused by

• Fetal-to-maternal hemorrhage
• Twin-to-twin transfusion

• Cord malformations

• Placental abnormalities

• Diagnostic procedures

Fetal-to-maternal hemorrhage occurs spontaneously or as a result of maternal trauma, amniocentesis, external cephalic version, or placental tumor. It affects about 50% of pregnancies, although in most cases the volume of blood lost is extremely small (about 2 mL); "massive" blood loss, defined as > 30 mL, occurs in 3/1000 pregnancies.

Twin-to-twin transfusion is the unequal sharing of blood supply between twins that affects 13 to 33% of monozygotic, monochorionic twin pregnancies. When significant blood transfer occurs, the donor twin may become very anemic and develop heart failure, while the recipient may become polycythemic and develop hyperviscosity syndrome (see p. 2787).

Cord malformations include velamentous insertion of the umbilical cord, vasa previa, or abdominal or placental insertion; the mechanism of hemorrhage, which is often massive and rapid, is by cord vessel shearing or rupture.

The 2 important placental abnormalities causing hemorrhage are placenta previa and abruptio placentae.

Diagnostic procedures causing hemorrhage include amniocentesis, chorionic villus sampling, and umbilical cord blood sampling.

**Perinatal hemorrhage** may be caused by

• Precipitous delivery (ie, rapid, spontaneous delivery < 3 h after onset of labor, which causes hemorrhage due to umbilical cord tearing)

• Obstetric accidents (eg, incision of the placenta during cesarean delivery, birth trauma)

• Coagulopathies

Cephalhematomas resulting from procedures such as vacuum or forceps delivery are usually relatively harmless, but subgaleal bleeds can extend into soft tissue, sequestering sufficient blood volumes to result in anemia, hypotension, shock, and death. Far less often, rupture of the liver, spleen, or adrenal gland during delivery may lead to internal bleeding. Intraventricular hemorrhage, most common among preterm infants (see p. 2773), as well as subarachnoid and subdural bleeding also can result in a significantly lowered Hct.

Hemorrhagic disease of the newborn (see also **Vitamin K Deficiency** on p. 46) is hemorrhage within a few days of a normal delivery caused by transient physiologic deficiency in vitamin K-dependent coagulation factors. Other possible causes of hemorrhage in the first few days of life are other coagulopathies (eg, hemophilia), disseminated intravascular coagulation caused by sepsis, vascular malformations, or prenatal maternal use of vitamin K antagonists (eg, phenytoin, warfarin, isoniazid).

**Decreased RBC production:** Defects in RBC production may be

• Congenital

• Acquired

**Congenital defects** are extremely rare, but Diamond-Blackfan anemia and Fanconi’s anemia are the most common.
Diamond-Blackfan anemia is characterized by lack of RBC precursors in bone marrow, macrocytic RBCs, lack of reticulocytes in peripheral blood, and lack of involvement of other blood cell lineages. It is often part of a syndrome of congenital anomalies including microcephaly, cleft palate, eye anomalies, thumb deformities, and webbed neck. Up to 25% of affected infants are anemic at birth, and low birth weight occurs in about 10%. It is thought to be caused by defective stem cell differentiation.

Fanconi's anemia is an autosomal recessive disorder of bone marrow progenitor cells that causes macrocytosis and reticulocytopenia with progressive failure of all hematopoietic cell lines. It is usually diagnosed after the neonatal period. The cause is a genetic defect that prevents cells from repairing damaged DNA or removing toxic free radicals that damage cells.

Other congenital anemias include Pearson's syndrome, a rare, multisystem disease involving mitochondrial defects that cause refractory sideroblastic anemia, pancytopenia, and variable hepatic, renal, and pancreatic insufficiency or failure; and congenital dyserythropoietic anemia, in which chronic anemia (typically macrocytic) results from ineffective or abnormal RBC production, and hemolysis caused by RBC abnormalities.

**Acquired defects** are those that occur after birth. The most common causes are

- Infections
- Nutritional deficiencies

Infections (eg, malaria, rubella, syphilis, HIV, cytomegalovirus, adenovirus, bacterial sepsis) may impair RBC production in the bone marrow. Congenital parvovirus B19 infection may result in the absence of RBC production.

Nutritional deficiencies of iron, copper, folate (folic acid), and vitamins E and B₁₂ may cause anemia in the early months of life but not usually at birth. The incidence of iron deficiency, the most common nutritional deficiency, is higher in less developed countries where it results from dietary insufficiency and exclusive and prolonged breastfeeding. Iron deficiency is common among neonates whose mothers have an iron deficit and among premature infants who have not been transfused and whose formula is not supplemented with iron; premature infants deplete iron stores by 10 to 14 wk if not supplemented.

**Hemolysis:** Hemolysis (see also p. 934) may be caused by

- Immune-mediated disorders
- RBC membrane disorders
- Enzyme deficiencies
- Hemoglobinopathies
- Infections

All also cause hyperbilirubinemia, which may cause jaundice and kernicterus (see p. 2793).

**Immune-mediated hemolysis** may occur when fetal RBCs with surface antigens (most commonly Rh and ABO blood antigens but also Kell, Duffy, and other minor group antigens) that differ from maternal RBC antigens enter the maternal circulation and stimulate production of IgG antibody directed against fetal RBCs. The most common severe scenario is that an Rh (D antigen)-negative mother becomes sensitized to the D antigen during a previous pregnancy with an Rh-positive fetus; a 2nd Rh-positive pregnancy may then prompt an IgG response that may result in fetal and neonatal hemolysis (see also erythroblastosis fetalis on p. 2665). Intrauterine hemolysis may be severe enough to cause hydrops or death; postpartum, there may be significant anemia and hyperbilirubinemia with ongoing hemolysis secondary to persistent maternal IgG (half-life about 28 days). With widespread prophylactic use of anti-Rh D to prevent sensitization (see p. 2666), < 0.11% of pregnancies in Rh-negative women are affected.
ABO incompatibility may cause hemolysis by a similar mechanism. ABO incompatibility usually occurs in type O mothers. Mothers with type A, B, or AB blood make anti-A or anti-B antibodies that are predominantly IgM and are incapable of crossing the placenta. Hemolysis caused by ABO incompatibility can occur in a first pregnancy because mothers are often sensitized by antigens in foods or bacteria.

**RBC membrane disorders** alter RBC shape and deformability, resulting in premature removal of RBCs from the circulation. The most common disorders are hereditary spherocytosis and hereditary elliptocytosis (see p. 940).

**Enzyme deficiencies** of G6PD (see p. 941) and pyruvate kinase (see also Embden-Meyerhof Pathway Defects on p. 941) are the most common enzyme disorders causing hemolysis.

**Hemoglobinopathies** are caused by deficiencies and structural abnormalities of globin chains. At birth, 55 to 90% of the neonate’s Hb is composed of 2 α and 2 γ globin chains (fetal Hb or Hb F [α²γ²]). After birth, γ-chain production decreases (to < 2% by 2 to 4 yr of age) and β-chain production increases until adult Hb (Hb A [α²β²]) becomes predominant. α-Thalassemia (see p. 946) is a genetically inherited disorder of depressed α globin chain production and is the most common hemoglobinopathy causing anemia in the neonatal period. β-Thalassemia is an inherited decrease in β-chain production. Because β globin is naturally low at birth, β-thalassemia and structural abnormalities of the β globin chain (eg, Hb S [sickle cell disease], Hb C) are rarely apparent at birth and symptoms do not appear until fetal Hb levels have fallen to sufficiently low levels at 3 to 4 mo of age.

**Intrauterine infections** by certain bacteria, viruses, fungi, and protozoa (most notably toxoplasmosis and malaria) also may trigger hemolytic anemia. In malaria, the *Plasmodium* parasite invades and ultimately ruptures the RBC. Immune-mediated destruction of parasitized RBCs and excess removal of nonparasitized cells occur. Associated bone marrow dyserythropoiesis results in inadequate compensatory erythropoiesis. Intravascular hemolysis, extravascular phagocytosis, and dyserythropoiesis can lead to anemia.

**Symptoms and Signs**

Symptoms and signs are similar regardless of the cause but vary with severity and rate of onset of the anemia. Neonates are generally pale and, if anemia is severe, have tachypnea, tachycardia, and sometimes a flow murmur; hypotension is present with acute blood loss. Jaundice may be present with hemolysis.

**Evaluation**

**History**: History should focus on maternal factors (eg, bleeding diatheses, hereditary RBC disorders, nutritional deficiencies, drugs), family history of hereditary disorders that may cause neonatal anemia (eg, hemoglobinopathies, enzyme deficiencies, red cell membrane disorders, RBC aplasias), and obstetric factors (eg, infections, vaginal bleeding, obstetric interventions, mode of delivery, blood loss, treatment and appearance of the cord, placental pathology, fetal distress, number of fetuses).

Nonspecific maternal factors may provide additional clues. Splenectomy would indicate a possible history of hemolysis, red cell membrane disorder, or autoimmune anemia; cholecystectomy might indicate a history of hemolysis-induced gallstones. Important neonatal factors include gestational age at delivery, age at presentation, sex, race, and ethnicity.

**Physical examination**: Tachycardia and hypotension suggest acute, significant blood loss. Jaundice suggests hemolysis, either systemic (caused by ABO incompatibility or G6PD deficiency) or localized (caused by breakdown of sequestered blood in cephalhematomas). Hepatosplenomegaly suggests hemolysis, congenital infection, or heart failure. Hematomas, ecchymoses, or petechiae suggest bleeding diathesis. Congenital anomalies may suggest a bone marrow failure syndrome.

**Testing**: Anemia may be suspected prenatally if ultrasonography shows hydrops fetalis, which, by definition, is abnormal, excessive fluid in 2 or more body compartments (eg, pleura, peritoneum,
After birth, if anemia is suspected, initial testing consists of

- Reticulocyte count
- Peripheral smear examination

If the reticulocyte count is low, anemia is caused by acquired or congenital bone marrow dysfunction, and the infant should be evaluated for causes of bone marrow suppression with

- Titers or PCR studies for congenital infection (rubella, syphilis, HIV, cytomegalovirus, adenovirus, parvovirus)
- Folate and vitamin B₁₂ levels
- Iron and copper levels

If these studies do not identify a cause of anemia, a bone marrow biopsy, genetic testing for congenital disorders of RBC production, or both may be necessary.

If the reticulocyte count is elevated or normal (reflecting an appropriate bone marrow response), anemia is caused by blood loss or hemolysis. If there is no apparent blood loss or if signs of hemolysis are noted on the peripheral smear, a direct antiglobulin test (DAT [Coombs' test]) should be done.

If the DAT is positive, anemia is likely secondary to Rh, ABO, or other blood group incompatibility.

If the DAT is negative, the RBC mean corpuscular volume (MCV) may prove helpful. A significantly low MCV suggests α-thalassemia or chronic intrauterine blood loss. With a normal or high MCV, peripheral blood smear may show abnormal RBC morphology compatible with a membrane disorder, microangiopathy, disseminated intravascular coagulation, vitamin E deficiency, or hemoglobinopathy. If the smear is normal, blood loss, enzyme deficiency, or infection should be considered and an appropriate assessment, including testing for fetal-to-maternal hemorrhage, should ensue.

Fetal-to-maternal hemorrhage can be diagnosed by testing for fetal RBCs in maternal blood. The Kleihauer-Betke acid elution technique is the most frequently used test, but other tests include fluorescent antibody techniques and differential or mixed agglutination testing. In the Kleihauer-Betke technique, citric acid-phosphate buffer of pH 3.5 elutes Hb from adult but not fetal RBCs; thus, fetal RBCs stain with eosin and are visible on microscopy, whereas adult RBCs appear as red cell ghosts. The Kleihauer-Betke technique is not useful when the mother has a hemoglobinopathy.

Treatment

Need for treatment varies with degree of anemia and associated medical conditions. Mild anemia in otherwise healthy term and preterm infants generally does not require specific treatment; treatment is directed at the underlying diagnosis. Some patients require transfusion or exchange transfusion of packed RBCs.

**Transfusion:** Transfusion is indicated to treat severe anemia. Infants should be considered for transfusion if symptomatic due to anemia or if a decrease in tissue O₂ delivery is suspected. The decision to transfuse should be based on symptoms, patient age, and degree of illness. Hct alone should not be the deciding factor regarding transfusion because some infants may be asymptomatic with lower levels and others may be symptomatic with higher levels.

Guidelines for when to transfuse vary, but one accepted set is described in **Table 275-2**.

Before the first transfusion, if not already done, maternal and fetal blood should be screened for ABO and...
Rh types and the presence of atypical RBC antibodies, and a DAT should be done on the infant's RBCs.

Blood for transfusion should be the same as or compatible with the neonate's ABO and Rh group and with any ABO or RBC antibody present in maternal or neonatal serum. Neonates produce RBC antibodies only rarely, so in cases where the need for transfusion persists, repeat antibody screening is usually not necessary until 4 mo of age.

[Table 275-2. Transfusion Guidelines for Infants < 4 Mo]

Packed RBCs used for transfusion should be filtered (leukocyte depleted), irradiated, and given in aliquots of 10 to 20 mL/kg derived from a single donation; sequential transfusions from the same unit of blood minimize recipient exposure and transfusion complications. Blood from cytomegalovirus-negative donors should be considered for extremely premature infants.

Exchange transfusion: Exchange transfusion, in which blood from the neonate is removed in aliquots in sequence with packed RBC transfusion, is indicated for some cases of hemolytic anemia with elevation of serum bilirubin and some cases of severe anemia with heart failure. This procedure decreases plasma antibody titers and bilirubin levels and minimizes fluid overload. Serious adverse effects (eg, thrombocytopenia; necrotizing enterocolitis; hypoglycemia; hypocalcemia; shock, pulmonary edema, or both [caused by shifts in fluid balance]) are common, so the procedure should be done by experienced staff. Guidelines for when to begin exchange transfusion differ and are not evidence based.

Other treatments: Recombinant human erythropoietin is not routinely recommended, in part because it has not been shown to reduce transfusion requirements in the first 2 wk of life.

Iron therapy is restricted to cases of repetitive blood loss (eg, hemorrhagic diathesis, GI bleeding, frequent phlebotomy). Oral iron supplements are preferred; parenteral iron sometimes causes anaphylaxis, so therapy should be guided by a hematologist.

Treatment of more unusual causes of anemia is disorder specific (eg, corticosteroids in Diamond-Blackfan anemia, and vitamin B$_{12}$ for B$_{12}$ deficiency).

Perinatal Polycythemia and Hyperviscosity Syndrome

Polycythemia is an abnormal increase in RBC mass, defined in neonates as a venous Hct ≥ 65%; this increase can lead to hyperviscosity with sludging of blood within vessels and sometimes thrombosis. The main symptoms and signs of neonatal polycythemia are nonspecific and include ruddy complexion, feeding difficulties, lethargy, hypoglycemia, hyperbilirubinemia, cyanosis, respiratory distress, and seizures. Diagnosis is made clinically and with an Hct measurement. Treatment is with partial exchange transfusion.

The terms polycythemia and hyperviscosity are often used interchangeably but are not equivalent. Polycythemia is significant only because it increases risk of hyperviscosity syndrome. Hyperviscosity is a clinical syndrome caused by sludging of blood within vessels. Sludging occurs because increased RBC mass causes a relative decrease in plasma volume and a relative increase in proteins and platelets.

Incidence of polycythemia is about 3 to 4% (range 0.4 to 12%), and about half of infants with polycythemia have hyperviscosity.

Etiology

Dehydration causing relative hemoconcentration and an elevated Hct mimics polycythemia, but RBC mass is not increased. Causes of true polycythemia include intrauterine hypoxia, perinatal asphyxia, placental transfusion (including twin-to-twin transfusion), some congenital abnormalities (eg, cyanotic congenital heart disease, renovascular malformations, congenital adrenal hyperplasia), certain delivery procedures (eg, delayed cord clamping, holding neonate below the level of the mother before cord clamping, stripping the cord toward the neonate at delivery), maternal insulin-dependent diabetes, Down syndrome, Beckwith-Wiedemann syndrome, and intrauterine growth restriction. Polycythemia is also more
common when the mother resides at a high altitude. Premature infants rarely develop hyperviscosity syndrome.

**Symptoms and Signs**

Symptoms and signs of hyperviscosity syndrome are those of heart failure, thrombosis (cerebral and renal vessels), and CNS dysfunction, including tachypnea, respiratory distress, cyanosis, plethora, apnea, lethargy, irritability, hypotonia, tremulousness, seizures, and feeding problems. Renal vein thrombosis may also cause renal tubular damage, proteinuria, or both.

**Diagnosis**

- Hct
- Clinical evaluation

Diagnosis of polycythemia is by Hct. Diagnosis of hyperviscosity syndrome is clinical. Capillary samples often overestimate Hct, so a venous or arterial Hct should be obtained before the diagnosis is made; most published studies of polycythemia use spun Hcts, which are no longer routinely done and are generally higher than those done on automated counters. Laboratory measure of viscosity is not readily available.

Other laboratory abnormalities may include low blood glucose and Ca^{++} levels, maternal diabetes, or both; RBC lysis; thrombocytopenia (secondary to consumption with thrombosis); hyperbilirubinemia (caused by turnover of a higher number of RBCs); and reticulocytosis and increased peripheral nucleated RBCs (caused by increased erythropoiesis secondary to fetal hypoxia).

**Treatment**

- IV hydration
- Sometimes phlebotomy plus saline replacement

Asymptomatic infants should be treated with IV hydration (see p. 2807). Symptomatic infants with Hct > 65 to 70% should undergo an isovolemic hemodilution (sometimes called partial exchange transfusion, although no blood products are given) to reduce the Hct to ≤ 55% and thereby decrease blood viscosity. Partial exchange is done by removing blood in aliquots of 5 mL/kg (about 10 to 12 mL) and immediately replacing it with an equal volume of 0.9% saline. Asymptomatic infants whose Hct remains persistently > 70% despite hydration may also benefit from this procedure.

Although many studies show immediate measurable effects of partial exchange, the long-term benefits remain in question. Most studies have failed to document differences in long-term growth or neurodevelopment between children who have received a partial exchange transfusion in the neonatal period and those who have not.
Chapter 276. Metabolic, Electrolyte, and Toxic Disorders in Neonates

Introduction

Inherited disorders of metabolism are discussed in Ch. 301. Electrolyte disorders also are discussed elsewhere in THE MANUAL.

Neonatal Hyperbilirubinemia

Jaundice is a yellow discoloration of the skin and eyes caused by hyperbilirubinemia (elevated serum bilirubin concentration). The serum bilirubin level required to cause jaundice varies with skin tone and body region, but jaundice usually becomes visible on the sclera at a level of 2 to 3 mg/dL (34 to 51 μmol/L) and on the face at about 4 to 5 mg/dL (68 to 86 μmol/L). With increasing bilirubin levels, jaundice seems to advance in a head-to-foot direction, appearing at the umbilicus at about 15 mg/dL (258 μmol/L) and at the feet at about 20 mg/dL (340 μmol/L). Slightly more than half of all neonates become visibly jaundiced in the first week of life.

Consequences of hyperbilirubinemia: Hyperbilirubinemia may be harmless or harmful depending on its cause and the degree of elevation. Some causes of jaundice are intrinsically dangerous whatever the bilirubin level. But hyperbilirubinemia of any etiology is a concern once the level is high enough. The threshold for concern varies by age (see Fig. 276-1), degree of prematurity, and health status; however, among term infants, the threshold typically is considered to be a level > 18 mg/dL (> 308 μmol/L).

Kernicterus (see p. 2793) is the major consequence of neonatal hyperbilirubinemia. Although it is now rare, kernicterus still occurs and can nearly always be prevented. Kernicterus is brain damage caused by unconjugated bilirubin deposition in basal ganglia and brain stem nuclei, caused by either acute or chronic hyperbilirubinemia. Normally, bilirubin bound to serum albumin stays in the intravascular space. However, bilirubin can cross the blood-brain barrier and cause kernicterus in certain situations:

• When serum bilirubin concentration is markedly elevated
• When serum albumin concentration is markedly low (eg, in preterm infants)
• When bilirubin is displaced from albumin by competitive binders

Competitive binders include drugs (eg, sulfisoxazole, ceftriaxone, aspirin) and free fatty acids and hydrogen ions (eg, in fasting, septic, or acidotic infants).

Pathophysiology

The majority of bilirubin is produced from the breakdown of Hb into unconjugated bilirubin (and other substances). Unconjugated bilirubin binds to albumin in the blood for transport to the liver, where it is taken up by hepatocytes and conjugated with glucuronic acid by the enzyme uridine diphosphoglucuronurate glucuronosyltransferase (UGT) to make it water-soluble. The conjugated bilirubin is excreted in bile into the duodenum. In adults, conjugated bilirubin is reduced by gut bacteria to urobilin and excreted. Neonates, however, have sterile digestive tracts. They do have the enzyme β-glucuronidase, which deconjugates the conjugated bilirubin, which is then reabsorbed by the intestines and recycled into the circulation. This is called enterohepatic circulation of bilirubin (see p. 2764).

Mechanisms of hyperbilirubinemia: Hyperbilirubinemia can be caused by one or more of the following processes:

• Increased production
• Decreased hepatic uptake
• Decreased conjugation
• Impaired excretion
• Impaired bile flow (cholestasis)
• Increased enterohepatic circulation

**Etiology**

**Classification:** There are several ways to classify and discuss causes of hyperbilirubinemia. Because transient jaundice is common among healthy neonates (unlike adults, in whom jaundice always signifies a disorder), hyperbilirubinemia can be classified as physiologic or pathologic. It can be classified by whether the hyperbilirubinemia is unconjugated, conjugated, or both. It also can be classified by mechanism (see Table 276-1).

**Causes:** Most cases involve unconjugated hyperbilirubinemia. Some of the most common causes of neonatal jaundice include

• Physiologic hyperbilirubinemia
• Breastfeeding jaundice
• Breast milk jaundice
• Pathologic hyperbilirubinemia due to hemolytic disease

Liver dysfunction (eg, caused by parenteral alimentation causing cholestasis, neonatal sepsis, neonatal hepatitis) may cause a conjugated or mixed hyperbilirubinemia.

**Physiologic hyperbilirubinemia** occurs in almost all neonates. Shorter neonatal RBC life span increases bilirubin production; deficient conjugation due to the deficiency of UGT decreases clearance; and low bacterial levels in the intestine combined with increased hydrolysis of conjugated bilirubin increase enterohepatic circulation. Bilirubin levels can rise up to 18 mg/dL by 3 to 4 days of life (7 days in Asian infants) and fall thereafter.

**Breastfeeding jaundice** develops in one sixth of breastfed infants during the first week of life. Breastfeeding increases enterohepatic circulation of bilirubin in some infants who have decreased milk intake and who also have dehydration or low caloric intake. The increased enterohepatic circulation also may result from reduced intestinal bacteria that convert bilirubin to nonresorbed metabolites.

**Breast milk jaundice** is different from breastfeeding jaundice. It develops after the first 5 to 7 days of life and peaks at about 2 wk. It is thought to be caused by an increased concentration of β-glucuronidase in breast milk, causing an increase in the deconjugation and reabsorption of bilirubin.

**Pathologic hyperbilirubinemia** in term infants is diagnosed if

• Jaundice appears in the first 24 h, after the first week of life, or lasts > 2 wk
• Total serum bilirubin (TSB) rises by > 5 mg/dL/day
• TSB is > 18 mg/dL
• Infant shows symptoms or signs of a serious illness
Some of the most common pathologic causes are

[Table 276-1. Causes of Neonatal Hyperbilirubinemia]

- Immune and nonimmune hemolytic anemia
- G6PD deficiency
- Hematoma resorption
- Sepsis
- Hypothyroidism

**Evaluation**

**History:** History of present illness should note age of onset and duration of jaundice. Important associated symptoms include lethargy and poor feeding (suggesting possible kernicterus), which may progress to stupor, hypotonia, or seizures and eventually to hypertonia. Patterns of feeding can be suggestive of possible breastfeeding failure or underfeeding. Therefore, history should include what the infant is being fed, how much and how frequently, urine and stool production (possible breastfeeding failure or underfeeding), how well the infant is latching on to the breast or taking the nipple of the bottle, whether the mother feels that her milk has come in, and whether the infant is swallowing during feedings and seems satiated after feedings.

**Review of systems** should seek symptoms of causes, including respiratory distress, fever, and irritability or lethargy (sepsis); hypotonia and poor feeding (hypothyroidism, metabolic disorder); and repeated episodes of vomiting (intestinal obstruction).

**Past medical history** should focus on maternal infections (toxoplasmosis, other pathogens, rubella, cytomegalovirus, and herpes simplex [TORCH] infections), disorders that can cause early hyperbilirubinemia (maternal diabetes), maternal Rh factor and blood group (maternofetal blood group incompatibility), and a history of a prolonged or difficult birth (hematoma or forceps trauma).

Family history should note known inherited disorders that can cause jaundice, including G6PD deficiency, thalassemias, and spherocytosis, and also any history of siblings who have had jaundice.

Drug history should specifically note drugs that may promote jaundice (eg, ceftriaxone, sulfonamides, antimalarials).

**Physical examination:** Overall clinical appearance and vital signs are reviewed.

The skin is inspected for extent of jaundice. Gentle pressure on the skin can help reveal the presence of jaundice. Also, ecchymoses or petechiae (suggestive of hemolytic anemia) are noted.

The physical examination should focus on signs of causative disorders.

The general appearance is inspected for plethora (maternofetal transfusion); macrosomia (maternal diabetes); lethargy or extreme irritability (sepsis or infection); and any dysmorphic features such as macroglossia (hypothyroidism) and flat nasal bridge or bilateral epicanthal folds (Down syndrome).

For the head and neck examination, any bruising and swelling of the scalp consistent with a cephalohematoma are noted. Lungs are examined for crackles, rhonchi, and decreased breath sounds (pneumonia). The abdomen is examined for distention, mass (hepatosplenomegaly), or pain (intestinal obstruction). Neurologic examination should focus on signs of hypotonia or weakness (metabolic disorder, hypothyroidism, sepsis).
Red flags: The following findings are of particular concern:

• Jaundice in the first day of life
• TSB > 18 mg/dL
• Rate of rise of TSB > 0.2 mg/dL/h (> 3.4 μmol/L/h) or > 5 mg/dL/day
• Conjugated bilirubin concentration > 1 mg/dL (> 17 μmol/L) if TSB is < 5 mg/dL or > 20% of TSB (suggests neonatal cholestasis)
• Jaundice after 2 wk of age
• Lethargy, irritability, respiratory distress

Interpretation of findings: Evaluation should focus on distinguishing physiologic from pathologic jaundice. History, physical examination, and timing can help (see Table 276-2), but typically TSB and conjugated serum bilirubin levels are measured.

Timing: Jaundice that develops in the first 24 to 48 h, or that persists > 2 wk, is most likely pathologic. Jaundice that does not become evident until after 2 to 3 days is more consistent with physiologic, breastfeeding, or breast milk jaundice. An exception is undersecretion of bilirubin due to metabolic factors (eg, Crigler-Najjar syndrome, hypothyroidism, drugs), which may take 2 to 3 days to become evident. In such cases, bilirubin typically peaks in the first week, accumulates at a rate of < 5 mg/dL/day, and can remain evident for a prolonged period. Because most neonates are now discharged from the hospital or nursery within 48 h, many cases of hyperbilirubinemia are detected only after discharge.

Testing: Diagnosis is suspected by the infant's color and is confirmed by measurement of serum bilirubin. Noninvasive techniques for transcutaneous measurement of bilirubin levels in infants are being used increasingly, with good correlation with serum bilirubin measurements. Risk of hyperbilirubinemia is based on age-specific TSB levels.

A bilirubin concentration > 10 mg/dL (> 170 μmol/L) in preterm infants or > 18 mg/dL in term infants warrants additional testing.

[Table 276-2. Physical Findings in Neonatal Jaundice]

including Hct, blood smear, reticulocyte count, direct Coombs' test, TSB and direct serum bilirubin concentrations, and blood type and Rh group of the infant and mother.

Other tests, such as blood, urine, and CSF cultures to detect sepsis and measurement of RBC enzyme levels to detect unusual causes of hemolysis, may be indicated by the history and physical examination. Such tests also may be indicated for any neonates with an initial bilirubin level > 25 mg/dL (> 428 μmol/L).

Treatment

Treatment is directed at the underlying disorder. In addition, treatment for hyperbilirubinemia itself may be necessary.

Physiologic jaundice usually is not clinically significant and resolves within 1 wk. Frequent formula feedings can reduce the incidence and severity of hyperbilirubinemia by increasing GI motility and frequency of stools, thereby minimizing the enterohepatic circulation of bilirubin. The type of formula does not seem important in increasing bilirubin excretion.

Breastfeeding jaundice may be prevented or reduced by increasing the frequency of feedings. If the bilirubin level continues to increase > 18 mg/dL in a term infant with early breastfeeding jaundice, a temporary change from breast milk to formula may be appropriate; phototherapy also may be indicated at higher levels. Stopping breastfeeding is necessary for only 1 or 2 days, and the mother should be
encouraged to continue expressing breast milk regularly so she can resume nursing as soon as the
infant's bilirubin level starts to decline. She also should be assured that the hyperbilirubinemia has not
casted any harm and that she may safely resume breastfeeding. It is not advisable to supplement with
water or dextrose because that may disrupt the mother's production of milk.

Definitive treatment involves

• Phototherapy

• Exchange transfusion

Phototherapy: This treatment remains the standard of care, most commonly using fluorescent white
light. (Blue light is most effective for intensive phototherapy.) Phototherapy is the use of light to
photoisomerize unconjugated bilirubin into forms that are more water-soluble and can be excreted rapidly
by the liver and kidney without glucuronidation. It provides definitive treatment of neonatal
hyperbilirubinemia and prevention of kernicterus. Photo-therapy is an option when unconjugated bilirubin
is > 12 mg/dL (> 205.2 μmol/L) and may be indicated when unconjugated bilirubin is > 15 mg/dL at 25 to
48 h, 18 mg/dL at 49 to 72 h, and 20 mg/dL at > 72 h (see Fig. 276-1). Phototherapy is not indicated for
conjugated hyperbilirubinemia. Because visible jaundice may disappear during phototherapy though
serum bilirubin remains elevated, skin color cannot be used to evaluate jaundice severity. Blood taken for
bilirubin determinations should be shielded from bright light, because bilirubin in the collection tubes may
rapidly photo-oxidize.

Exchange transfusion: This treatment can rapidly remove bilirubin from circulation and is indicated for
severe hyperbilirubinemia, which most often occurs with immune-mediated hemolysis. Small amounts of
blood are withdrawn and replaced through an umbilical vein catheter to remove partially hemolyzed and
antibody-coated RBCs as well as circulating Igs. The blood is replaced with uncoated donor RBCs. Only
unconjugated hyperbilirubinemia can cause kernicterus, so if conjugated bilirubin is elevated, the level of
unconjugated rather than total bilirubin is used to determine the need for exchange transfusion.

Specific indications are serum bilirubin ≥ 20 mg/dL at 24 to 48 h or ≥ 25 mg/dL at > 48 h and failure of
phototherapy to result in a 1- to 2-mg/dL (17- to 34-μmol/L) decrease within 4 to 6 h of initiation or at the
first clinical signs of kernicterus regardless of bilirubin levels. If the serum bilirubin level is > 25 mg/dL
when the neonate is initially examined, preparation for an exchange transfusion should be made in case
intensive phototherapy fails to lower the bilirubin level. An alternative approach uses the weight of the
neonate in grams divided by 100 to determine the bilirubin level (in mg/dL) at which exchange transfusion
is indicated. Thus, a 1000-g neonate would receive an exchange transfusion at a bilirubin level of ≥ 10
mg/dL, and a 1500-g neonate would receive an exchange transfusion at a bilirubin level of ≥ 15 mg/dL.

Most often, 160 mL/kg (twice the infant's total blood volume) of packed RBCs is exchanged over 2 to 4 h;
an alternative is to give 2 successive exchanges of 80 mL/kg each over 1 to 2 h. To do an exchange, 20
mL of blood is withdrawn and then immediately replaced by 20 mL of transfused blood. This procedure is
repeated until the total desired volume is exchanged. For critically ill or premature infants, aliquots of 5 to
10 mL are used to avoid sudden major changes in blood volume. The goal is to reduce bilirubin by nearly
50%, with the knowledge that hyperbilirubinemia may rebound to about 60% of pretransfusion level within
1 to 2 h. It is also customary to lower the target level by 1 to 2 mg/dL in conditions that increase the risk of
kernicterus (eg, fasting, sepsis, acidosis). Exchange transfusions may need to be repeated if bilirubin
levels remain high. Finally, there are risks and complications with the procedure, and the success of
phototherapy has reduced the frequency of exchange transfusion.

Key Points

• Neonatal jaundice is caused by increased bilirubin production, decreased bilirubin clearance, or
increased enterohepatic circulation.

• Some jaundice is normal in neonates.

• Risk varies with postnatal age, TSB value, prematurity, and health of the neonate.
• Treatment depends on cause and degree of elevation.

• Definitive treatments include phototherapy and exchange transfusion.

**Kernicterus**

(Bilirubin Encephalopathy)

*Kernicterus is brain damage caused by unconjugated bilirubin deposition in basal ganglia and brain stem nuclei.*

Normally, bilirubin bound to serum albumin stays in the intravascular space. However, bilirubin can cross the blood-brain barrier and cause kernicterus when serum bilirubin concentration is markedly elevated; serum albumin concentration is markedly low (eg, in preterm infants); or bilirubin is displaced from albumin by competitive binders (eg, sulfisoxazole, ceftriaxone, and aspirin; free fatty acids and hydrogen ions in fasting, septic, or acidotic infants).

In preterm infants, kernicterus may not cause recognizable clinical symptoms or signs. Early symptoms in term infants are lethargy, poor feeding, and vomiting. Opisthotonos, oculogyric crisis, seizures, and death may follow. Kernicterus may result in intellectual disability, choreoathetoid cerebral palsy, sensorineural hearing loss, and paralysis of upward gaze later in childhood. It is unknown whether minor degrees of kernicterus can cause less severe neurologic impairment (eg, perceptual-motor problems, learning disorders).

There is no reliable test to determine the risk of kernicterus, and the diagnosis is made presumptively. A definite diagnosis can be made only by autopsy.

There is no treatment once kernicterus develops; it can be prevented by treating hyperbilirubinemia (see p. 2788).

**Neonatal Hypercalcemia**

Hypercalcemia is total serum Ca > 12 mg/dL (> 3 mmol/L) or ionized Ca > 6 mg/dL (> 1.5 mmol/L). The most common cause is iatrogenic. GI signs may occur (eg, anorexia, vomiting, constipation) and sometimes lethargy or seizures. Treatment is IV normal saline plus furosemide and sometimes corticosteroids, calcitonin, and bisphosphonates.

**Etiology**

The most common cause is

• iatrogenic

Iatrogenic causes usually involve excess Ca or vitamin D, or phosphate deprivation, which can result from prolonged feeding with incorrectly prepared formula or from dairy milk containing excess vitamin D.

Other causes include maternal hypoparathyroidism, subcutaneous fat necrosis, parathyroid hyperplasia, abnormal renal function, Williams syndrome, and idiopathic. Williams syndrome includes supravalvular aortic stenosis, an elfin facies, and hypercalcemia of unknown pathophysiology; infants may also be small for gestational age, and hypercalcemia can be noted early in infancy, usually resolving by age 12 mo. Idiopathic neonatal hypercalcemia is a diagnosis of exclusion and is difficult to differentiate from Williams syndrome. Neonatal hyperparathyroidism is very rare. Subcutaneous fat necrosis may occur after major trauma and causes hypercalcemia that usually resolves spontaneously. Maternal hypoparathyroidism or maternal hypocalcemia may cause secondary fetal hyperparathyroidism, with changes in fetal mineralization (eg, osteopenia).

**Symptoms and Signs**
Symptoms and signs may be noted when total serum Ca is > 12 mg/dL (> 3 mmol/L). These signs can include anorexia, GI reflux, nausea, vomiting, lethargy or seizures or generalized irritability, and hypertension. Other symptoms and signs include constipation, abdominal pain, dehydration, feeding intolerance, and failure to thrive. Some neonates have vague symptoms of muscle or joint aches and weakness. With subcutaneous fat necrosis, firm purple nodules may be observed on trunk, buttocks, or legs.

Diagnosis

Diagnosis is made by measuring total serum Ca concentration.

Treatment

- IV normal saline plus furosemide
- Sometimes corticosteroids, calcitonin, and bisphosphonates

Marked elevation of serum Ca may be treated with normal saline 20 mL/kg IV plus furosemide 2 mg/kg IV and, when persistent, with corticosteroids and calcitonin. Bisphosphonates are also increasingly used in this context (eg, etidronate by mouth or pamidronate IV). Treatment of subcutaneous fat necrosis is with a low-Ca formula; fluids, furosemide, calcitonin, and corticosteroids are used as indicated by the degree of hypercalcemia. Fetal hypercalcemia caused by maternal hypoparathyroidism can be treated expectantly, because it usually resolves spontaneously within a few weeks. Treatment of chronic conditions includes a low-Ca, low-vitamin D formula.

Neonatal Hypocalcemia

Hypocalcemia is a serum total Ca concentration < 8 mg/dL (< 2 mmol/L) in term infants or < 7 mg/dL (< 1.75 mmol/L) in preterm infants. It is also defined as an ionized Ca level < 3.0 to 4.4 mg/dL (< 0.75 to 1.10 mmol/L), depending on the method (type of electrode) used. Signs are primarily neurologic and include hypotonia, apnea, and tetany. Treatment is IV or oral Ca supplementation.

Etiology

Neonatal hypocalcemia occurs in 2 forms:

- Early onset (in the first 2 days of life)
- Late onset (> 3 days), which is rare

Some infants with congenital hypoparathyroidism (eg, caused by DiGeorge syndrome with agenesis or dysgenesis of the parathyroid glands [see p. 1103]) have both early and late (prolonged) hypocalcemia.

Early-onset hypocalcemia: Risk factors for early-onset hypocalcemia include prematurity, being small for gestational age, maternal diabetes, and perinatal asphyxia. Mechanisms vary. Normally, parathyroid hormone helps maintain normal Ca levels when the constant infusion of ionized Ca across the placenta is interrupted at birth. A transient, relative hypoparathyroidism may cause hypocalcemia in preterm and some small-for-gestational-age neonates, who have parathyroid glands that do not yet function adequately, and in infants of mothers with diabetes or hyperparathyroidism, because these women have higher-than-normal ionized Ca levels during pregnancy. Perinatal asphyxia may also increase serum calcitonin, which inhibits Ca release from bone and results in hypocalcemia. In other neonates, the normal phosphaturic renal response to parathyroid hormone is absent; the elevated phosphate (PO₄) level leads to hypocalcemia.

Late-onset hypocalcemia: The cause of late-onset hypocalcemia is usually ingestion of cow's milk or formula with a too-high PO₄ load; elevated serum PO₄ leads to hypocalcemia.
Symptoms and Signs

Symptoms and signs rarely occur unless total serum Ca is < 7 mg/dL (< 1.75 mmol/L) or the ionized Ca is < 3.0 mg/dL (< 0.75 mmol/L). Signs include hypotonia, tachycardia, tachypnea, apnea, poor feeding, jitteriness, tetany, and seizures. Similar symptoms may occur with hypoglycemia and opioid withdrawal.

Diagnosis

- Total or ionized serum Ca level

Diagnosis is by measurement of serum total or ionized Ca; ionized Ca is the more physiologic measurement, because it obviates concerns about protein concentration and pH. Prolongation of the corrected QT interval (QT<sub>c</sub>) on ECG also suggests hypocalcemia.

Treatment

- Early onset: IV 10% Ca gluconate
- Late onset: Oral calcitriol or Ca

Early-onset hypocalcemia ordinarily resolves in a few days, and asymptomatic neonates with serum Ca levels > 7 mg/dL or ionized Ca > 3.5 mg/dL rarely require treatment. Those term infants with levels < 7 mg/dL and preterm infants with Ca < 6 mg/dL (< 1.5 mmol/L) should be treated with 2 mL/kg of 10% Ca gluconate (200 mg/kg) by slow IV infusion over 30 min. Too-rapid infusion can cause bradycardia, so heart rate should be monitored during the infusion. The IV site should also be watched closely because tissue infiltration by a Ca solution is irritating and may cause local tissue damage or necrosis. Manifestations of Ca infiltration include skin redness, calcification, and necrosis or slough; there can be radial nerve damage at the wrist.

After acute correction of hypocalcemia, Ca gluconate may be mixed in the maintenance IV infusion and given continuously. Starting with 400 mg/kg/day of Ca gluconate, the dose may be increased gradually to 800 mg/kg/day, if needed, to prevent a recurrence. When oral feedings are begun, the formula may be supplemented with the same daily dose of Ca gluconate, if needed, by adding the 10% Ca gluconate solution into the day’s formula. Supplementation is usually required for only a few days.

Treatment of late-onset hypocalcemia is addition of calcitriol or additional Ca to infant formula to provide a 4:1 molar ratio of Ca:PO<sub>4</sub> until normal Ca levels are maintained. Oral Ca preparations have a high sucrose content, which may lead to diarrhea in preterm infants.

Neonatal Hyperglycemia

Hyperglycemia is a serum glucose concentration > 150 mg/dL (> 8.3 mmol/L).

The most common cause of neonatal hyperglycemia is

- Iatrogenic

Iatrogenic causes usually involve too-rapid IV infusions of dextrose during the first few days of life in very low-birth-weight infants (< 1.5 kg).

The other important cause is physiologic stress caused by surgery, hypoxia, respiratory distress syndrome, or sepsis; fungal sepsis poses a special risk. In premature infants, partially defective processing of proinsulin to insulin and relative insulin resistance may cause hyperglycemia. In addition, transient neonatal diabetes mellitus is a rare self-limited cause that usually occurs in small-for-gestational-age infants; corticosteroid therapy may also result in transient hyperglycemia. Hyperglycemia is less common than hypoglycemia, but it is important because it increases morbidity and mortality of the underlying causes.
Symptoms and signs are those of the underlying disorder; diagnosis is by serum glucose testing. Additional laboratory findings may include glycosuria and marked serum hyperosmolarity.

**Treatment**

- Reduction of IV dextrose concentration, rate, or both
- Sometimes IV insulin

Treatment of iatrogenic hyperglycemia is reduction of the IV dextrose concentration (eg, from 10% to 5%) or of the infusion rate; hyperglycemia persisting at low dextrose infusion rates (eg, 4 mg/kg/min) may indicate relative insulin deficiency or insulin resistance. Treatment of other causes is fast-acting insulin. One approach is to add fast-acting insulin to an IV infusion of 10% dextrose at a uniform rate of 0.01 to 0.1 unit/kg/h, then titrate the rate until the glucose level is normalized. Another approach is to add insulin to a separate IV of 10% D/W given simultaneously with the maintenance IV infusion so that the insulin can be adjusted without changing the total infusion rate. Responses to insulin are unpredictable, and it is extremely important to monitor serum glucose levels and to titrate the insulin infusion rate carefully.

In transient neonatal diabetes mellitus, glucose levels and hydration should be carefully maintained until hyperglycemia resolves spontaneously, usually within a few weeks.

Any fluid or electrolytes lost through osmotic diuresis should be replaced.

**Neonatal Hypoglycemia**

Hypoglycemia is a serum glucose concentration < 40 mg/dL (< 2.2 mmol/L) in term neonates or < 30 mg/dL (< 1.7 mmol/L) in preterm neonates. Risk factors include prematurity, being small for gestational age, and perinatal asphyxia. The most common causes are deficient glycogen stores, delayed feeding, and hyperinsulinemia. Signs include tachycardia, cyanosis, seizures, and apnea. Diagnosis is suspected empirically and is confirmed by glucose testing. Prognosis depends on the underlying condition. Treatment is enteral feeding or IV dextrose.

**Etiology**

Neonatal hypoglycemia may be transient or persistent.

Causes of **transient hypoglycemia** are

- Inadequate substrate
- Immature enzyme function leading to deficient glycogen stores

Causes of **persistent hypoglycemia** include

- Hyperinsulinism
- Defective counter-regulatory hormone release
- Inherited disorders of metabolism (eg, glycogen storage diseases, disorders of gluconeogenesis, fatty acid oxidation disorders—see Ch. 301)

Deficiency of glycogen stores at birth is common in very low-birth-weight preterm infants, infants who are small for gestational age (SGA) because of placental insufficiency, and infants who have perinatal asphyxia. Anaerobic glycolysis consumes glycogen stores in these infants, and hypoglycemia may develop at any time in the first few days, especially if there is a prolonged interval between feedings or if nutritional intake is poor. A sustained input of exogenous glucose is therefore important to prevent hypoglycemia.
Transient hyperinsulinism most often occurs in infants of diabetic mothers and is inversely related to the degree of maternal diabetic control. It also commonly occurs in physiologically stressed infants who are SGA. Less common causes include congenital hyperinsulinism (genetic conditions transmitted in both autosomal dominant and recessive fashion), severe erythroblastosis fetalis, and Beckwith-Wiedemann syndrome (in which islet cell hyperplasia accompanies features of macroglossia and umbilical hernia). Hyperinsulinemia characteristically results in a rapid fall in serum glucose in the first 1 to 2 h after birth when the continuous supply of glucose from the placenta is interrupted.

Hypoglycemia may also occur if an IV infusion of D/W is abruptly interrupted. Finally, hypoglycemia can be due to malposition of an umbilical catheter or sepsis.

**Symptoms and Signs**

Many infants remain asymptomatic. Prolonged or severe hypoglycemia causes both adrenergic and neuroglycopenic signs. Adrenergic signs include diaphoresis, tachycardia, lethargy or weakness, and shakiness. Neuroglycopenic signs include seizure, coma, cyanotic episodes, apnea, bradycardia or respiratory distress, and hypothermia. Listlessness, poor feeding, hypotonia, and tachypnea may occur.

**Diagnosis**

- Bedside glucose check

All signs are nonspecific and also occur in neonates who have asphyxia, sepsis or hypocalcemia, or opioid withdrawal (see p. 2800). Therefore, at-risk neonates with or without these signs require an immediate bedside serum glucose check from a capillary sample. Abnormally low levels are confirmed by a venous sample.

**Treatment**

- IV dextrose (for prevention and treatment)
- Enteral feeding
- Sometimes IM glucagon

Most high-risk neonates are treated preventively. For example, infants of diabetic women who have been using insulin are often started at birth on a 10% D/W infusion IV or given oral glucose, as are those who are sick, are extremely premature, or have respiratory distress. Other at-risk neonates who are not sick should be started on early, frequent formula feedings to provide carbohydrates.

Any neonate whose glucose falls to ≤ 50 mg/dL (≤ 2.75 mmol/L) should begin prompt treatment with enteral feeding or with an IV infusion of up to 12.5% D/W, 2 mL/kg over 10 min; higher concentrations of dextrose can be infused if necessary through a central catheter. The infusion should then continue at a rate that provides 4 to 8 mg/kg/min of glucose (ie, 10% D/W at about 2.5 to 5 mL/kg/h). Serum glucose levels must be monitored to guide adjustments in the infusion rate. Once the neonate's condition has improved, enteral feedings can gradually replace the IV infusion while the glucose concentration continues to be monitored. IV dextrose infusion should always be tapered, because sudden discontinuation can cause hypoglycemia.

If starting an IV infusion promptly in a hypoglycemic neonate is difficult, glucagon 100 to 300 μg/kg IM (maximum, 1 mg) usually raises the serum glucose rapidly, an effect that lasts 2 to 3 h, except in neonates with depleted glycogen stores. Hypoglycemia refractory to high rates of glucose infusion may be treated with hydrocortisone 2.5 mg/kg IM bid. If hypoglycemia is refractory to treatment, other causes (eg, sepsis) and possibly an endocrine evaluation for persistent hyperinsulinism and disorders of defective gluconeogenesis or glycogenolysis should be considered.

**Neonatal Hypernatremia**
Hypernatremia is a serum Na concentration > 150 mEq/L, usually caused by dehydration. Signs include lethargy and seizures. Treatment is cautious hydration with IV saline solution.

**Etiology**

Hypernatremia develops when

- Water is lost in excess of Na (hypernatremic dehydration)
- Na intake exceeds Na losses (salt poisoning)
- Both

Water loss in excess of Na intake is most commonly caused by diarrhea, vomiting, or high fever. It may also be caused by poor feeding in the early days of life (eg, when mother and infant are both learning to breastfeed) and may occur in very low-birth-weight (VLBW) infants born at 24 to 28 wk. In VLBW infants, insensible water losses through an immature, water-permeable stratum corneum combine with immature renal function and a reduced ability to produce concentrated urine to facilitate free water loss. Insensible water loss through the skin is also significantly increased by radiant warmers and phototherapy lights; exposed VLBW infants may require up to 250 mL/kg/day of water IV in the first few days, after which the stratum corneum develops and insensible water loss decreases. A rare cause is central or nephrogenic diabetes insipidus. Infants with hypernatremia and dehydration are often more dehydrated than is apparent by physical examination, because the increased osmolality helps maintain the extracellular fluid space (and hence circulating blood volume).

Solute overload most commonly results from adding too much salt when preparing homemade infant formula or from giving hyperosmolar solutions. Fresh frozen plasma and human albumin contain Na and can contribute to hypernatremia when given repeatedly to very premature infants.

**Symptoms and Signs**

Symptoms and signs include lethargy, restlessness, hyperreflexia, spasticity, and seizures. Skin texture may be doughy rather than diminished. Intracranial hemorrhage, venous sinus thrombosis, and acute renal tubular necrosis are major complications.

**Diagnosis**

- Serum Na concentration

Diagnosis is suspected by symptoms and signs and is confirmed by measuring serum Na concentration. Additional laboratory findings may include an increase in BUN, a modest increase in serum glucose, and, if serum K is low, a depression in the level of serum Ca.

**Treatment**

- IV 0.9% saline, then hypotonic saline (0.3% or 0.45% saline)

Severely dehydrated infants must have their circulating blood volume restored first, usually with 0.9% saline in aliquots of 20 mL/kg IV. Treatment is then with 5% D/W/0.3% to 0.45% saline solution IV in volumes equal to the calculated fluid deficit (see p. 2807), given over 2 to 3 days to avoid a rapid fall in serum osmolality, which would cause rapid movement of water into cells and potentially lead to cerebral edema. Maintenance fluids should be provided concurrently. The goal of treatment is to decrease serum Na by about 10 mEq/L/day. Body weight, serum electrolytes, and urine volume and specific gravity must be monitored regularly so that fluid therapy can be adjusted appropriately. Once adequate urine output is
shown, K is added to provide maintenance requirements or replace urinary losses.

Extreme hypernatremia (Na > 200 mEq/L) caused by salt poisoning should be treated with peritoneal dialysis, especially if poisoning causes a rapid rise in serum Na.

Prevention

Prevention requires attention to the volume and composition of unusual fluid losses and of solutions used to maintain homeostasis. In neonates and young infants, who are unable to signal thirst effectively and to replace losses voluntarily, the risk of dehydration is greatest. The composition of feedings whenever mixing is involved (eg, some infant formulas and concentrated preparations for tube feeding) requires particular attention, especially when the potential for developing dehydration is high, such as during episodes of diarrhea, poor fluid intake, vomiting, or high fever.

**Neonatal Hyponatremia**

(See also p. 823.)

Hyponatremia is a serum Na concentration < 135 mEq/L. Significant hyponatremia may cause seizures or coma. Treatment is cautious Na replacement with IV 0.9% saline solution; rarely, 3% saline solution is required, particularly if seizures are occurring.

**Etiology**

The most frequent cause of neonatal hyponatremia is hypovolemic dehydration caused by vomiting, diarrhea, or both, when large GI losses are replaced with fluids that have little or no Na (eg, some juices).

A less frequent cause is euvolemic hyponatremia caused by inappropriate ADH secretion and consequent water retention. Possible causes of inappropriate ADH secretion include CNS tumors and infection. Also, overdilution of infant formula can lead to water intoxication.

Finally, hypervolemic hyponatremia occurs in the setting of water retention and excess Na retention, such as in heart failure or renal failure.

**Symptoms and Signs**

Symptoms and signs include nausea and vomiting, apathy, headache, seizures, and coma; other symptoms include cramps and weakness. Infants with hyponatremic dehydration may appear quite ill, because hyponatremia causes disproportionate reductions in ECF volume. Symptoms and signs are related to duration and degree of hyponatremia.

**Diagnosis**

- Serum Na concentration

Diagnosis is suspected because of symptoms and signs and confirmed by measuring serum Na concentration. In dehydration, an increase in BUN may be observed.

**Treatment**

- IV 5% D/W/0.45% to 0.9% saline solution
- Rarely IV hypertonic (3%) saline solution

Treatment is with 5% D/W/0.45% to 0.9% saline solution IV in volumes equal to the calculated deficit, given over as many days as it takes to correct the Na concentration by no more than 10 to 12 mEq/L/day to avoid rapid fluid shifts in the brain. Neonates with hypovolemic hyponatremia need volume expansion, using a solution containing salt to correct the Na deficit (10 to 12 mEq/kg of body weight or even 15...
mEq/kg in young infants with severe hyponatremia) and include Na maintenance needs (3 mEq/kg/day in 5% D/W solution). Neonates with symptomatic hyponatremia (eg, lethargy, confusion) require emergency treatment with 3% saline solution IV to prevent seizure or coma. (For prevention, see Prevention in left column.)

**Prenatal Drug Exposure**

Alcohol and illicit drugs are toxic to the placenta and developing fetus and can cause congenital syndromes and withdrawal symptoms. Prescription drugs also may have adverse effects on the fetus (see Table 262-2 on p. 2626). For effects of cigarette smoking, see p. 2655.

Although some toxic substances used by the mother are not illegal, many are. In any case, the home situation should be evaluated to determine whether the infant will be safely cared for after discharge. With the supportive help of relatives, friends, and visiting nurses, the mother may be able to care for her infant. If not, foster home care or an alternative care plan may be best.

**Alcohol:** Alcohol exposure in utero increases the risk of spontaneous abortion, decreases birth weight, and can cause fetal alcohol syndrome (FAS), a constellation of variable physical and cognitive abnormalities. At birth, infants with FAS can be identified by small stature and a typical set of facial traits including microcephaly, microphthalmia, short palpebral fissures, epicanthal folds, a small or flat midface, a flat elongated philtrum, a thin upper lip, and a small chin. Abnormal palmar creases, cardiac defects, and joint contractures may also be evident. After birth, cognitive deficits become apparent. The most serious manifestation is severe intellectual disability, thought to be a teratogenic effect of alcohol given the high number of intellectually disabled infants of alcoholic women; FAS may be the most common cause of noninherited intellectual disability. No single physical or cognitive finding is pathognomonic; lesser degrees of alcohol use cause less severe manifestations, and the diagnosis of mild cases can be difficult because partial expression occurs. It is often difficult to distinguish the effects of alcohol on the developing fetus from those of other exposures (eg, tobacco, other drugs) and factors (eg, poor nutrition, lack of health care, violence) that affect women who drink excessively.

Diagnosis is given to infants with characteristic findings born to women who used alcohol excessively during pregnancy.

Because it is unknown when during pregnancy alcohol is most likely to harm the fetus and whether there is a lower limit of alcohol use that is completely safe, pregnant women should be advised to avoid all alcohol intake. Siblings of an infant diagnosed with FAS should be examined for subtle manifestations of the disorder.

**Amphetamines:** Prenatal exposure to amphetamines has lasting subtle effects on neonatal brain structure and function. Some studies have shown decreased volume of the caudate, putamen, and globus pallidus (anatomic components of brain) in methamphetamine-exposed children, whereas other studies have not uniformly confirmed these findings. Other studies indicate that prenatal methamphetamine exposure may be associated with abnormal neurobehavioral patterns or fetal growth restriction, but these findings are not yet fully established.

**Barbiturates:** Prolonged maternal abuse of barbiturates may cause neonatal drug withdrawal with jitteriness, irritability, and fussiness that often do not develop until 7 to 10 days postpartum, after the neonate has been discharged home. Sedation with phenobarbital 0.75 to 1.5 mg/kg po or IM q 6 h may be required and then tapered over a few days or weeks, depending on the duration of symptoms.

**Cocaine:** Cocaine inhibits reuptake of the neurotransmitters norepinephrine and epinephrine; it crosses the placenta and causes vasoconstriction and hypertension in the fetus. Cocaine abuse in pregnancy is associated with a higher rate of placental abruption and spontaneous abortion, perhaps caused by reduced maternal blood flow to the placental vascular bed; abruption may also lead to intrauterine fetal death or to neurologic damage if the infant survives. Neonates born to addicted mothers have low birth weight, reduced body length and head circumference, and lower Apgar scores. Cerebral infarcts may occur, and rare anomalies associated with prenatal cocaine use include limb amputations; GU malformations, including prune-belly syndrome; and intestinal atresia or necrosis. All are caused by
vascular disruption, presumably secondary to local ischemia caused by the intense vasoconstriction of fetal arteries caused by cocaine. In addition, a pattern of mild neurobehavioral effects has also been observed, including decreases in attention and alertness, lower IQ, and impaired gross and fine motor skills.

Some neonates may show withdrawal symptoms if the mother used cocaine shortly before delivery, but symptoms are less common and less severe than for opioid withdrawal, and signs and treatment are the same.

**Marijuana:** Marijuana does not consistently seem to increase risk of congenital malformations, fetal growth restriction, or postnatal neurobehavioral abnormalities. However, women who use marijuana during pregnancy often also use alcohol, cigarettes, or both, which can cause fetal problems.

**Opioids:** Opioid exposure in utero can cause withdrawal on delivery. The neonate of a woman addicted to opioids should be observed for withdrawal symptoms, which usually occur within 72 h after delivery. Characteristic signs of withdrawal include irritability, jitteriness, hypertonicity, vomiting, diarrhea, sweating, seizures, and hyperventilation that causes respiratory alkalosis. Prenatal benzodiazepine exposure may cause similar effects.

Mild withdrawal symptoms are treated by a few days of swaddling and soothing care to alleviate the physical overarousal and giving frequent feedings to reduce restlessness. With patience, most problems resolve in no more than a week. Severe symptoms can be controlled by diluting tincture of opium (which contains 10 mg morphine/mL) 25-fold with water and giving 2 drops (0.1 mL)/kg po q 4 h. The dose can be increased by 0.1 mL/kg q 4 h as needed. Phenobarbital 0.75 to 1.5 mg/kg po q 6 h may also control withdrawal symptoms. Treatment is tapered and stopped over several days or weeks as symptoms subside.

The incidence of sudden infant death syndrome is greater among infants born to women addicted to opioids but still is < 10/1000 infants, so routine use of home cardiorespiratory monitors is not recommended for these infants.
Chapter 277. Gastrointestinal Disorders in Neonates and Infants

Introduction

Infectious gastroenteritis is the most common pediatric GI disorder. About 1 billion episodes occur worldwide each year, most commonly in developing countries among children < 5 yr. Death due to dehydration occurs in 3 to 6 million cases/yr. In the US, 25 to 35 million cases occur annually, resulting in 300 to 400 deaths. In addition, infectious gastroenteritis in the US results in an estimated 200,000 hospitalizations and 1.5 million outpatient visits at a cost in excess of 1 billion dollars. For a full discussion of causative agents, evaluation, and treatment, see Ch. 16. For dehydration and fluid therapy in children, see Ch. 278.

Hypertrophic Pyloric Stenosis

Hypertrophic pyloric stenosis is obstruction of the pyloric lumen due to pyloric muscular hypertrophy.

Hypertrophic pyloric stenosis may cause almost complete gastric outlet obstruction. It affects 1 of 250 infants and is more common among males by a 4:1 ratio, particularly first-born males. It occurs most often between 3 to 5 wk of age and rarely after 12 wk. The exact etiology is uncertain, but a genetic component is likely because siblings and offspring of affected people are at increased risk. Proposed mechanisms include lack of neuronal nitric oxide synthase and abnormal innervation of the muscular layer. Infants exposed to certain macrolide antibiotics in the first few weeks of life are at significantly increased risk.

Symptoms and Signs

Symptoms can develop between 2 and 6 wk of life. Projectile vomiting (without bile) occurs shortly after eating. Until dehydration sets in, the child feeds avidly and otherwise appears well, unlike many of those with vomiting caused by systemic illness. Gastric peristaltic waves may be visible, crossing the epigastrium from left to right. A discrete, 2- to 3-cm, firm, movable, and olive-like pyloric mass is sometimes palpable deep in the right side of the epigastrium. With progression of illness, the child fails to gain weight, and signs of dehydration (see p. 2806) appear.

Diagnosis

Diagnosis is by abdominal ultrasonography showing increased thickness of the pylorus (typically to ≥ 4 mm; normal, < 2 mm) along with an elongated pylorus (> 16 mm). If the diagnosis remains uncertain, ultrasonography can be repeated serially or an upper GI series can be done, which typically shows delayed gastric emptying and a "string" sign or "railroad track" sign of a markedly narrowed, elongated pyloric lumen. In rare cases, upper endoscopy is required for confirmation. The classic electrolyte pattern of an infant with pyloric stenosis is that of hypochloremic metabolic alkalosis. About 5% of infants are jaundiced.

Treatment

Initial treatment is directed at hydration and correcting electrolyte abnormalities. Definitive treatment is a longitudinal pyloromyotomy, which leaves the mucosa intact and separates the incised muscle fibers. Postoperatively, the infant usually tolerates feeding within a day.

Intussusception

Intussusception is telescoping of one portion of the intestine (intussusceptum) into an adjacent segment (intussuscipiens), causing intestinal obstruction and sometimes intestinal ischemia.

Intussusception generally occurs between ages 3 mo and 3 yr, with 65% of cases occurring before age 1. It is the most common cause of intestinal obstruction in this age group. Most cases are idiopathic. However, there is a slight male predominance as well as a seasonal variation; peak incidence coincides with the viral enteritis season. In older children, there may be a lead point (ie, a mass or other intestinal...
abnormality that triggers the telescoping). Examples include polyps, lymphoma, Meckel's diverticulum, and Henoch-Schönlein purpura. Cystic fibrosis is also a risk factor.

The telescoping segment obstructs the intestine and ultimately impairs blood flow (see Fig. 277-1), causing ischemia, gangrene, and perforation.

**Symptoms and Signs**

The initial symptoms are recurrent colicky abdominal pain that occurs every 15 to 20 min, often with vomiting. The child appears relatively well between episodes. Later, as intestinal ischemia develops, pain becomes steady, the child becomes lethargic, and mucosal hemorrhage causes heme-positive stool on rectal examination and sometimes spontaneous passage of a currant-jelly stool. The latter, however, is a late occurrence, and physicians should not wait for this symptom to occur to suspect intussusception. A palpable abdominal mass, described as sausage-shaped, is sometimes present. Perforation results in signs of peritonitis, with significant tenderness, guarding, and rigidity. Pallor, tachycardia, and diaphoresis indicate shock.

[Fig. 277-1. Intussusception.]

**Diagnosis**

- Ultrasonography

Studies and intervention must be done urgently, because survival and likelihood of non-operative reduction decrease significantly with time. Approach depends on clinical findings. Ill children with signs of peritonitis require fluid resuscitation (see p. 2809), broad-spectrum antibiotics (eg, ampicillin, gentamicin, clindamycin), nasogastric suction, and surgery. Others require imaging studies to confirm diagnosis and treat the disorder.

Barium enema was once the preferred initial study because it revealed the classic "coiled spring" appearance around the intussusceptum. In addition to being diagnostic, barium enema was also usually therapeutic; the pressure of the barium often reduced the telescoped segments. However, barium occasionally enters the peritoneum through a clinically unsuspected perforation and causes significant peritonitis. Currently, ultrasonography is the preferred means of diagnosis; it is easily done, relatively inexpensive, and safe.

**Treatment**

If intussusception is confirmed, an air enema is used for reduction, which lessens the likelihood and consequences of perforation. The intussusceptum can be successfully reduced in 75 to 90% of children. Children are observed overnight after reduction to rule out occult perforation. If reduction is unsuccessful, immediate surgery is required. Without surgery, the recurrence rate is 5 to 10%.

**Meconium Ileus**

Meconium ileus is obstruction of the terminal ileum by abnormally tenacious meconium; it almost universally occurs in neonates with cystic fibrosis. Meconium ileus accounts for up to 33% of neonatal small-bowel obstructions. Symptoms include emesis that may be bilious, abdominal distention, and failure to pass meconium. Diagnosis is based on clinical presentation and x-rays. Treatment is enemas with dilute contrast under fluoroscopy and surgery if enemas fail.

Meconium ileus is almost always an early manifestation of cystic fibrosis, which causes GI secretions to be extremely viscid and adherent to the intestinal mucosa. These secretions are the presenting manifestation of cystic fibrosis in 10 to 25% of cases. Obstruction occurs at the level of the terminal ileum (unlike the colonic obstruction caused by meconium plug syndrome) and may be diagnosed by prenatal ultrasonography. Distal to the obstruction, the colon is narrow and empty or contains small amounts of desiccated meconium pellets. The relatively empty, small-caliber colon is called a microcolon.
About 50% of cases are complicated by malrotation, intestinal atresia, or perforation. The distended loops of small bowel may twist to form a volvulus in utero. If the intestine loses its vascular supply and infarcts, sterile meconium peritonitis can result. The infarcted intestinal loop may be resorbed, leaving an area or areas of intestinal atresia.

**Symptoms and Signs**

After birth, infants fail to pass meconium in the first 12 to 24 h, which is typical for normal neonates. They have signs of intestinal obstruction, including bilious emesis and abdominal distention. Loops of distended small bowel sometimes can be palpated through the abdominal wall and may feel characteristically doughy. Meconium peritonitis with respiratory distress and ascites can occur secondary to perforation.

**Diagnosis**

- Plain x-rays
- If positive, tests for cystic fibrosis

Prenatal ultrasonography can detect changes in utero suggestive of cystic fibrosis and meconium ileus, but these changes are not specific. Diagnosis is suspected in a neonate with signs of intestinal obstruction, particularly if a family history of cystic fibrosis exists. Patients should undergo abdominal x-rays, which show dilated intestinal loops; however, fluid levels are often absent. A "soap bubble" or "ground glass" appearance due to small air bubbles mixed with the meconium is diagnostic of meconium ileus. If meconium peritonitis is present, calcified meconium flecks may line the peritoneal surfaces and even the scrotum. A barium enema reveals a microcolon with an obstruction in the terminal ileum.

Patients diagnosed with meconium ileus should be tested for cystic fibrosis (see p. 2881).

**Treatment**

- Radiographic contrast enema
- Sometimes surgery

Obstruction may be relieved in uncomplicated cases (eg, without perforation, volvulus, or atresia) by giving ≥ 1 enema with a dilute radiographic contrast medium plus N-acetylcysteine under fluoroscopy; hypertonic contrast material may cause large GI water losses requiring IV rehydration. If the enema does not relieve the obstruction, laparotomy is required. A double-barreled ileostomy with repeated N-acetylcysteine lavage of the proximal and distal loops is usually required to liquefy and remove the abnormal meconium.

**Meconium Plug Syndrome**

(Small Left Colon Syndrome)

**Meconium plug syndrome is colonic obstruction caused by thick meconium.**

Meconium plug syndrome usually occurs in infants who are otherwise healthy, but it is more common among infants of diabetic mothers and toxemic mothers treated with Mg sulfate. It is generally regarded as a functional immaturity of the colon, resulting in failure to pass the first stool.

**Symptoms and Signs**

Infants present in the first few days of life with failure to pass stools, abdominal distention, and vomiting. Thick, inspissated, rubbery meconium forms a cast of the colon, resulting in complete obstruction.
Diagnosis

- Radiographic contrast enema
- Sometimes testing for Hirschsprung's disease

Diagnosis is of exclusion and should be differentiated primarily from Hirschsprung's disease (see p. 2980).

Plain abdominal x-rays are nonspecific and can show signs of low intestinal obstruction. Conversely, contrast enema shows the characteristic appearance of the outline of the inspissated meconium against the wall of the colon, providing a double-contrast impression. Unlike meconium ileus, microcolon is not typically seen on x-ray with meconium plug syndrome.

Treatment

- Radiographic contrast enema

The water-soluble contrast enema can be therapeutic by separating the plug from the intestinal wall and expelling it. Occasionally, repeated enemas are required. Rarely, surgical decompression is required. Although most infants are healthy thereafter, diagnostic studies may be needed to rule out Hirschsprung's disease (see p. 2980) or cystic fibrosis (see p. 2883).

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is an acquired disease, primarily of preterm or sick neonates, characterized by mucosal or even deeper intestinal necrosis. It is the most common GI emergency among neonates. Symptoms and signs include feeding intolerance, lethargy, temperature instability, ileus, bloating, bilious emesis, hematochezia, reducing substances in the stool, apnea, and sometimes signs of sepsis. Diagnosis is clinical and is confirmed by imaging studies. Treatment is primarily supportive and includes nasogastric suction, parenteral fluids, TPN, antibiotics, isolation in cases of infection, and, often, surgery.

Over 85% of cases of NEC occur in premature infants. It occurs in about 1 to 8% of neonatal ICU admissions. Risk factors include prolonged rupture of the membranes with amnionitis, birth asphyxia, small-for-gestational-age infants, congenital heart disease, and exchange transfusions. The incidence may also be higher in infants fed hypertonic formulas.

Etiology

In infants who develop NEC, 3 intestinal factors are usually present: a preceding ischemic insult, bacterial colonization, and intraluminal substrate (ie, enteral feedings).

The exact etiology is not clear. It is believed that an ischemic insult damages the intestinal lining, leading to increased intestinal permeability and leaving the intestine susceptible to bacterial invasion. NEC rarely occurs before enteral feedings and is less common among breastfed infants. However, once feedings are begun, ample substrate is present for proliferation of luminal bacteria, which can penetrate the damaged intestinal wall, producing hydrogen gas. The gas may collect within the intestinal wall (pneumatosis intestinalis) or enter the portal veins.

The initial ischemic insult may result from vasospasm of the mesenteric arteries, which can be caused by an anoxic insult triggering the primitive diving reflex that markedly diminishes intestinal blood flow. Intestinal ischemia may also result from low blood flow during an exchange transfusion, during sepsis, or from the use of hyperosmolar formulas. Similarly, congenital heart disease with reduced systemic blood flow or arterial O₂ desaturation may lead to intestinal hypoxia/ischemia and predispose to NEC.

Necrosis begins in the mucosa and may progress to involve the full thickness of the intestinal wall,
causing perforation with subsequent peritonitis and often free intra-abdominal air. Perforation occurs most commonly in the terminal ileum; the colon and the proximal small bowel are involved less frequently. Sepsis occurs in 33% of infants, and death may occur.

NEC may occur as clusters of cases or as outbreaks in neonatal ICUs. Some clusters appear to be associated with specific organisms (e.g., *Klebsiella*, *Escherichia coli*, coagulase-negative staphylococci), but often no specific pathogen is identified.

**Symptoms and Signs**

Infants may present with feeding difficulties, bilious gastric residuals (after feedings) that may progress to bilious emesis, ileus manifested by abdominal distention, or gross or microscopic blood in stool. Sepsis may be manifested by lethargy, temperature instability, increased apneic spells, and metabolic acidosis.

**Diagnosis**

- Detection of blood in stool
- Usually abdominal x-rays

Screening the stools of enterally fed premature infants for occult blood or reducing substances may help diagnose NEC early. Early x-rays may be nonspecific and reveal only ileus. However, a fixed, dilated intestinal loop that does not change on repeated x-rays indicates NEC. X-ray signs diagnostic of NEC are pneumatosis intestinalis and portal vein gas. Pneumoperitoneum indicates bowel perforation and an urgent need for surgery.

**Treatment**

- Stoppage of feedings
- NGT
- Fluid resuscitation
- Broad-spectrum antibiotics
- TPN
- Possibly surgery

The mortality rate is 20 to 30%. Aggressive support and judicious timing of surgical intervention maximize the chance of survival.

**Support:** Nonsurgical support is sufficient in over 75% of cases. Feedings must be stopped immediately if NEC is suspected, and the intestine should be decompressed with a double-lumen NGT attached to intermittent suction. Appropriate colloid and crystalloid parenteral fluids must be given to support circulation, because extensive intestinal inflammation and peritonitis may lead to considerable 3rd-space fluid loss. TPN is needed for 14 to 21 days while the intestine heals. Systemic antibiotics should be started at once with a β-lactam antibiotic (e.g., ampicillin, ticarcillin) and an aminoglycoside. Additional anaerobic coverage (e.g., clindamycin, metronidazole) may also be considered and should continue for 10 days (for dosage, see Table 279-1 on p. 2812). Because some outbreaks may be infectious, patient isolation should be considered, particularly if several cases occur within a short time.

The infant requires close monitoring; frequent complete reevaluation (e.g., at least every 12 h); and serial abdominal x-rays, CBCs, platelet counts, and blood gases. Intestinal strictures are the most common long-term complication of NEC, occurring in 10 to 36% of infants who survive the initial event. Strictures typically manifest within 2 to 3 mo of an NEC episode. Strictures are most commonly noted in the colon,
Surgery: Surgical intervention is needed in < 25% of infants. Absolute indications are intestinal perforation (pneumoperitoneum), signs of peritonitis (absent intestinal sounds and diffuse guarding and tenderness or erythema and edema of the abdominal wall), or aspiration of purulent material from the peritoneal cavity by paracentesis. Surgery should be considered for an infant with NEC whose clinical and laboratory condition worsens despite nonsurgical support. During surgery, gangrenous bowel is resected, and ostomies are created. (Primary reanastomosis may be done if the remaining intestine shows no signs of ischemia.) With resolution of sepsis and peritonitis, intestinal continuity can be reestablished several weeks or months later.

Prevention: Risk may be decreased by delaying feedings for several days to weeks in tiny or sick premature infants while providing TPN; feedings are slowly advanced over weeks. However, in some studies this approach was not beneficial. Breast milk seems to offer protection. For this and other reasons, breast milk should be encouraged for enteral feeding. Hypertonic formula, drugs, or contrast material should be avoided. Umbilical catheters, if required, should be placed below the renal arteries. Polycythemia should be treated promptly. Recent evidence suggests that probiotics (eg, *Bifidus infantis*, *Lactobacillus acidophilus*) may help prevent NEC, but further studies are required before they can be recommended routinely.

Neonatal Cholestasis

Cholestasis is failure of bilirubin secretion, resulting in conjugated hyperbilirubinemia and jaundice. There are numerous causes, which are identified by laboratory testing, hepatobiliary scan, and, sometimes, liver biopsy and surgery. Treatment depends on cause.

Etiology

Cholestasis (see also p. 212) may result from extrahepatic or intrahepatic disorders, although some conditions overlap. The most common extrahepatic disorder is biliary atresia. There are numerous intrahepatic disorders, collectively termed the neonatal hepatitis syndrome.

Biliary atresia is obstruction of the biliary tree due to progressive sclerosis of the extrahepatic bile duct. In most cases, biliary atresia develops several weeks after birth, probably after inflammation and scarring of the extrahepatic (and sometimes intrahepatic) bile ducts. It is rarely present in premature infants or in neonates at birth. The cause of the inflammatory response is unknown, but infectious organisms have been implicated.

Neonatal hepatitis syndrome (giant cell hepatitis) is an inflammatory condition of the neonatal liver. It has numerous metabolic, infectious, and genetic causes; some cases are idiopathic. Metabolic diseases include α1-antitrypsin deficiency, cystic fibrosis, neonatal iron storage disease, respiratory chain defects, and fatty acid oxidation defects. Infectious causes include congenital syphilis, echovirus, and some herpesviruses (simplex and cytomegalovirus); the classic hepatitis viruses (A, B, and C) are less common causes. There are also a number of less common genetic defects, such as Alagille syndrome and progressive familial intrahepatic cholestasis.

Pathophysiology

In cholestasis, the primary failure is of bilirubin excretion, resulting in excess conjugated bilirubin in the bloodstream and decreased bile salts in the GI tract. As a result of inadequate bile in the GI tract, there is malabsorption of fat and fat-soluble vitamins (A, D, E, and K), leading to vitamin deficiency, undernutrition, and growth failure.

Symptoms and Signs

Cholestasis typically is noted in the first 2 wk of life. Infants are jaundiced and often have dark urine (containing conjugated bilirubin), acholic stools, and hepatomegaly. If cholestasis persists, chronic pruritus is common, as are symptoms and signs of fat-soluble vitamin deficiency; progression on growth
charts may show a decline. If the underlying disorder causes hepatic fibrosis and cirrhosis, portal hypertension with subsequent abdominal distention from ascites, dilated abdominal veins, and upper GI bleeding from esophageal varices may develop.

**Diagnosis**

- Total and direct bilirubin
- Liver function tests
- Tests for metabolic, infectious, and genetic causes
- Hepatobiliary scan
- Occasionally liver biopsy

Any infant who is jaundiced after age 2 wk should be evaluated for cholestasis. The initial approach should be directed at diagnosing treatable conditions (eg, extrahepatic biliary atresia, in which early surgical intervention improves outcome).

Cholestasis is identified by an elevation in both total and direct bilirubin. Tests that are needed to further evaluate liver function include albumin, fractionated serum bilirubin, liver enzymes, PT, and PTT. Once cholestasis is confirmed, testing is required to determine etiology (see Table 277-1).

A hepatobiliary scan should also be done; excretion of contrast into the intestine rules out biliary atresia, but lack of excretion can occur with both biliary atresia and severe neonatal hepatitis. An abdominal ultrasound can aid in assessing liver size and in attempting to visualize the gallbladder and common bile duct but is nonspecific. When no diagnosis has been made, a liver biopsy is generally performed relatively early on. Patients with biliary atresia typically have enlarged portal triads, bile duct proliferation, and increased fibrosis. Neonatal hepatitis is characterized by lobular disarray with multinucleated giant cells. Sometimes diagnosis remains unclear, and surgical exploration with operative cholangiography is required.

**Prognosis**

Biliary atresia is progressive and, if untreated, results in liver failure, cirrhosis with portal hypertension by several months of age, and death by 1 yr of age.

[Table 277-1. Diagnostic Evaluation for Neonatal Cholestasis]

Prognosis of cholestasis due to specific disorders (eg, metabolic disease) is variable, ranging from a completely benign course to a progressive disease resulting in cirrhosis.

Idiopathic neonatal hepatitis syndrome usually resolves slowly, but permanent liver damage may result and lead to death.

**Treatment**

- Specific cause treated
- Vitamin A, D, E, and K supplements
- Medium-chain triglycerides
- Sometimes ursodeoxycholic acid

Specific treatment is directed at the cause. If there is no specific therapy, treatment is supportive and
consists primarily of nutritional therapy, including supplements of vitamins A, D, E, and K. For formula-fed infants, a formula that is high in medium-chain triglycerides should be used because it is absorbed better in the presence of bile salt deficiency. Adequate calories are required; infants may need > 130 calories/kg day. In infants with some bile flow, ursodeoxycholic acid 10 to 15 mg/kg once/day or bid may relieve itching.

Infants with presumed biliary atresia require surgical exploration with an intraoperative cholangiogram. If biliary atresia is confirmed, a portoenterostomy (Kasai procedure) should be done. Ideally, this procedure should be done in the first 1 to 2 mo of life. After this period, the prognosis significantly worsens. Postoperatively, many patients have significant chronic problems, including persistent cholestasis, recurrent ascending cholangitis, and failure to thrive. Even with optimal therapy, many infants develop cirrhosis and require liver transplantation.

**Miscellaneous Surgical Emergencies**

**Inguinal hernia:** Inguinal hernias (see p. 113) develop most often in male neonates, particularly if they are premature. About 10% of inguinal hernias are bilateral. Because inguinal hernias can become incarcerated, repair should be done shortly after diagnosis. For premature infants, repair typically is not done until they have reached a weight of 2 kg. In contrast, umbilical hernias rarely become incarcerated, close spontaneously after several years, and do not ordinarily need surgical repair.

**Gastric perforation:** In neonates, gastric perforations are often spontaneous and may be due to a congenital defect in the stomach wall, usually along the greater curvature. The abdomen suddenly becomes distended, and massive pneumoperitoneum is seen on abdominal x-ray. Treatment with corticosteroids increases risk of this disorder. Giving an H₂ blocker raises the gastric pH in premature infants and may reduce risk by inhibiting HCl production. Prognosis is usually good after surgical repair of the perforation.

**Ileal perforation:** In premature infants, ileal perforation has been reported after indomethacin has been given to close a patent ductus arteriosis. Ileal perforation is probably related to local ischemia resulting from vasoconstriction caused by indomethacin.

**Mesenteric arterial occlusion:** Mural thrombi or emboli may occlude a mesenteric artery after high placement of an umbilical artery catheter. Such an occurrence is extremely rare but can cause extensive intestinal infarction requiring surgery and intestinal resection.
Chapter 278. Dehydration and Fluid Therapy

Introduction

(See also Neonatal Hypernatremia on p. 2797; and Neonatal Hyponatremia on p. 2798.)

Unlike in adults, fluid management in children is based on weight and on specific guidelines, because children are more sensitive to fluid depletion (and excess). All guidelines are approximations; individualized adjustments based on close monitoring are essential.

Dehydration

Dehydration is significant depletion of body water and, to varying degrees, electrolytes. Symptoms and signs include thirst, lethargy, dry mucosae, decreased urine output, and, as the degree of dehydration progresses, tachycardia, hypotension, and shock. Diagnosis is based on history and physical examination. Treatment is with oral or IV replacement of fluid and electrolytes.

Dehydration, usually caused by diarrhea, remains a major cause of morbidity and mortality in infants and young children worldwide. Infants are particularly susceptible to the ill effects of dehydration because of their greater baseline fluid requirements (due to a higher metabolic rate), higher evaporative losses (due to a higher ratio of surface area to volume), and inability to communicate thirst or seek fluid.

Etiology

Dehydration results from increased fluid loss, decreased fluid intake, or both.

The most common source of increased fluid loss is the GI tract from vomiting, diarrhea, or both (eg, gastroenteritis). Other sources are renal (eg, diabetic ketoacidosis), cutaneous (eg, excessive sweating, burns), and 3rd-space losses (eg, into the intestinal lumen in bowel obstruction). All types of lost fluid contain electrolytes in varying concentrations, so fluid loss is always accompanied by electrolyte loss.

Decreased fluid intake is common during serious illness of any kind and is particularly problematic when the child is vomiting and during hot weather. It may also be a sign of neglect.

Symptoms and Signs

Symptoms and signs vary according to degree of deficit (see Table 278-1) and are affected by serum Na concentration: hemodynamic findings are exaggerated by hyponatremia and reduced by hypernatremia.

Diagnosis

• Clinical evaluation

In general, dehydration without hemodynamic changes is considered mild (about 5% body wt in infants and 3% in adolescents); tachycardia defines moderate dehydration (about 10% body wt in infants and 6% in adolescents); and hypotension with impaired perfusion defines severe dehydration (about 15% body wt in infants and 9% in adolescents). A more accurate method in children with acute dehydration is change in body weight; all short-term weight loss > 1%/day is presumed to represent fluid deficit. However, this method depends on knowing a precise, recent preillness weight. Parental estimates are usually inadequate; a 1-kg error in a 10-kg child causes a 10% error in the calculated percentage of dehydration—the difference between mild and severe dehydration.

Laboratory testing is usually reserved for moderately or severely ill children, in whom electrolyte disturbances (eg, hypernatremia, hypokalemia, metabolic acidosis) are more common. Other laboratory abnormalities include relative polycythemia from hemoconcentration, elevated BUN, and increased urine specific gravity.
Treatment

• Fluid replacement (oral if possible)

Treatment is best approached by considering separately the fluid resuscitation requirements, current deficit, ongoing losses, and maintenance requirements. The volume (eg, amount of fluid), composition, and rate of replacement differ for each. Formulas and estimates used to determine treatment parameters provide a starting place, but treatment requires ongoing monitoring of vital signs, clinical appearance, urine output and specific gravity, weight, and sometimes serum electrolyte levels. Children with severe dehydtration (eg, evidence of circulatory compromise) should receive fluids IV. Those unable or unwilling to drink or who have repetitive vomiting can receive fluid replacement IV, through an NGT, or sometimes orally through frequently repeated small amounts (see p. 2809).

Resuscitation: Patients with signs of hypoperfusion should receive fluid resuscitation with boluses of isotonic fluid (eg, 0.9% saline or Ringer's lactate). The goal is to restore adequate circulating volume to restore BP and perfusion. The resuscitation phase should reduce moderate or severe dehydration to a deficit of about 8% body wt. If dehydration is moderate, 20 mL/kg (2% body wt) is given IV over 20 to 30 min, reducing a 10% deficit to 8%. If dehydration is severe, 3 boluses of 20 mL/kg (2% body wt) will likely be required. The end point of the fluid resuscitation phase is restoring peripheral perfusion and BP and returning increased heart rate toward normal.

Deficit replacement: Total deficit volume is estimated clinically as described previously. Na deficits are usually about 80 mEq/L of fluid deficit, and K deficits are usually about 30 mEq/L of fluid deficit. The resuscitation phase should have reduced moderate or severe dehydration to a deficit of about 8% body wt;

[this remaining deficit can be replaced by providing 10 mL/kg (1% body wt)/h for 8 h. Because 0.45% saline has 77 mEq Na per liter, it is usually an appropriate fluid choice. K replacement (usually by adding 20 to 40 mEq K per liter of replacement fluid) should not begin until adequate urine output is established.

Dehydration with significant hypernatremia (eg, serum Na > 160 mEq/L) or hyponatremia (eg, serum Na < 120 mEq/L) requires special consideration to avoid complications (see p. 2798).

Ongoing losses: Volume of ongoing losses should be measured directly (eg, NGT, catheter, stool measurements) or estimated (eg, 10 mL/kg per diarrheal stool). Replacement should be milliliter for milliliter in time intervals appropriate for the rapidity and extent of the loss. Ongoing electrolyte losses can be estimated by source or cause (see Table 278-2). Urinary electrolyte losses vary with intake and disease process but can be measured if deficits fail to respond to replacement therapy.

Maintenance requirements: Fluid and electrolyte needs from basal metabolism must also be accounted for. Maintenance requirements are related to metabolic rate and affected by body temperature. Insensible losses (evaporative free water losses from the skin and respiratory tract in a ratio of 2:1) account for about one half of maintenance needs.

Volume rarely must be exactly determined but generally should aim to provide an amount of water that does not require the kidney to significantly concentrate or dilute the urine. The most common estimate uses patient weight to calculate metabolic expenditure in kcal/24 h, which approximates fluid needs in mL/24 h (see Table 278-3). A simpler calculation (the Holliday-Segar formula) uses 3 weight classes (see Table 278-4). Body surface area derived from a nomogram (see Fig. 278-2) also can be used, allowing 1500 to 2000 mL/m²/24 h. More complex calculations are rarely required. These fluid volumes can be given as a separate simultaneous infusion, so that the infusion rate for replacing deficits and ongoing losses can be set and adjusted independently of the maintenance infusion rate.
Baseline estimates are affected by fever (increasing by 12% for each degree > 37.8° C), hypothermia, and activity (eg, increased for hyperthyroidism or status epilepticus, decreased for coma).

Composition differs from solutions used to replace deficits and ongoing losses. Patients require Na 3 mEq/100 kcal/24 h (3 mEq/100 mL/24 h) and K 2 mEq/100 kcal/24 h (2 mEq/100 mL/24 h). This need is met by using 0.2% to 0.3% saline with 20 mEq/L of K in a 5% dextrose solution. Other electrolytes (eg, Mg, Ca) are not routinely added. It is inappropriate to replace deficits and ongoing losses solely by increasing the amount or rate of maintenance fluids.

**Practical Example**

A 7-mo-old infant has diarrhea for 3 days with weight loss from 10 kg to 9 kg. The infant is currently producing 1 diarrheal stool every 3 h and refusing to drink. Clinical findings of dry mucous membranes, poor skin turgor, markedly decreased urine output, and tachycardia with normal BP and capillary refill suggest 10% fluid deficit. Rectal temperature is 37° C; serum Na, 136 mEq/L; K, 4 mEq/L; Cl, 104 mEq/L; and HCO₃, 20 mEq/L.

**Fluid volume** is estimated by deficits, ongoing losses, and maintenance requirements.

The total fluid deficit given 1 kg wt loss = 1 L.

Ongoing diarrheal losses are measured as they occur by weighing the infant's diaper before application and after the diarrheal stool.

Baseline maintenance requirements by the weight-based Holliday-Segar method are 100 mL/kg × 10 kg = 1000 mL/day = 1000/24 or 40 mL/h.

**Electrolyte losses** from diarrhea (see Table 278-2) are an estimated 80 mEq of Na and 80 mEq of K.

**Procedure**

**Resuscitation:** The patient is given an initial bolus of Ringer's lactate 200 mL (20 mL/kg × 10 kg) over 30 min. This amount replaces 26 mEq of the estimated 80 mEq Na deficit.

**Deficits:** Residual fluid deficit is 800 mL (1000 initial - 200 mL resuscitation), and Na deficit is 54 mEq (80-26 mEq). This residual amount is given over 8 h as 5% dextrose/0.45% saline at 100 mL/h. This amount replaces the Na deficit (0.8 L × 77 mEq Na/L = 62 mEq Na). When urine output is established, K is added at a concentration of 20 mEq/L (for safety reasons, no attempt is made to replace complete K deficit acutely).

**Ongoing losses:** Five percent dextrose/0.45% saline also is used to replace ongoing losses; volume and rate are determined by the amount of diarrhea.

**Maintenance fluid:** Five percent dextrose/0.2% saline is given at 40 mL/h with 20 mEq/L of K added when urine output is established. Alternatively, the deficit could be replaced during the initial 8 h followed by the entire day's maintenance fluid in the next 16 h (ie, 60 mL/h); 24 h of maintenance fluid given in 16 h reduces mathematically to a rate of 1.5 times the usual maintenance rate and obviates the need for simultaneous infusions (which may require 2 rate-controlling pumps).
Oral Rehydration

Oral fluid therapy is effective, safe, convenient, and inexpensive compared with IV therapy. It should be used for children with mild to moderate dehydration who are accepting fluids orally unless prohibited by copious vomiting or underlying disorders (eg, surgical abdomen, intestinal obstruction).

Solutions: Oral rehydration solution should contain complex carbohydrate or 2% glucose and 50 to 90 mEq/L of Na. Sports drinks, sodas, juices, and similar drinks do not meet these criteria and should not be used. They generally have too little Na and too much carbohydrate to take advantage of Na/glucose cotransport, and the osmotic effect of the excess carbohydrate may result in additional fluid loss.

Oral rehydration solution (ORS) is recommended by the WHO and is widely available in the US without prescription. Most solutions come as powders that are mixed with tap water. Premixed solutions also are available in most pharmacies and supermarkets. An ORS packet is dissolved in 1 L of water to produce a solution containing (in mmol/L) Na 90, K 20, Cl 80, citrate 10, and glucose 111 (standard WHO ORS) or Na 75, K 20, Cl 65, citrate 10, and glucose 75 (WHO reduced-osmolarity ORS). It can also be made manually by adding 1 L of water to 3.5 g NaCl, 2.9 g trisodium citrate (or 2.5 g NaHCO₃), 1.5 g KCl, and 20 g glucose. ORS is effective in patients with dehydration regardless of age, cause, or type of electrolyte imbalance (hyponatremia, hypernatremia, or isonatremia) as long as their kidneys are functioning adequately. After rehydration, this solution must be replaced by a lower-Na fluid to avoid hypernatremia.

If specific rehydration solutions (powders or premixed) are unavailable, some clinicians advise caretakers to prepare a homemade solution using sugar and table salt. However, even with written instructions (and in some cases, dispensing 2 color-coded scoops), errors in preparation have at times caused fatal hypernatremia. Therefore, if specific rehydration solutions are unavailable, infants with mild to moderate dehydration should be continued on breast milk or formula, but the threshold for using IV hydration in those with moderate dehydration should be lower. Clinicians in practice situations where patients may be unable to obtain appropriate ORS on their own should explore alternative means of making the solution available.

Administration: Generally, 50 mL/kg is given over 4 h for mild dehydration and 100 mL/kg for moderate. For each diarrheal stool, an additional 10 mL/kg (up to 240 mL) is given. After 4 h, the patient is reassessed. If signs of dehydration persist, the same volume is repeated. Patients with cholera may require many liters of fluid/day.

Vomiting usually should not deter oral rehydration (unless there is bowel obstruction or other contraindication). Small, frequent amounts are used, starting with 5 mL q 5 min and increasing gradually as tolerated.

Once the deficit has been replaced, an oral maintenance solution containing less Na should be used. Children should eat an age-appropriate diet as soon as they have been rehydrated and are not vomiting. Infants may resume breastfeeding or formula. Infants with diarrhea who develop signs or symptoms of malabsorption (see p. 152) should be given lactose-free formula.
Chapter 279. Infections in Neonates

Introduction

Neonatal infection can be acquired in utero transplacentally, through the birth canal during delivery (intrapartum), and from external sources after birth (postpartum).

In utero infection, which can occur any time before birth, results from overt or subclinical maternal infection. Consequences depend on the agent and timing of infection in gestation and include spontaneous abortion, intrauterine growth restriction, premature birth, stillbirth, congenital malformation (eg, rubella), and symptomatic neonatal infection (eg, cytomegalovirus [CMV], toxoplasmosis, syphilis).

Common viral agents include herpes simplex, HIV, CMV, and hepatitis B. Intrapartum infection with HIV or hepatitis B occurs from passage through an infected birth canal or by ascending infection if delivery is delayed after rupture of membranes; these viruses can less commonly be transmitted transplacentally. CMV is commonly transmitted transplacentally. Bacterial agents include group B streptococci, enteric gram-negative organisms (primarily *Escherichia coli*), gonococci, and chlamydiae.

Postpartum infections are acquired from contact with an infected mother either directly (eg, TB, which also is sometimes transmitted in utero) or through breastfeeding (eg, HIV, CMV) or from contact with health care practitioners and the hospital environment (numerous organisms—see p. 2828).

Risk factors: Risk of contracting intrapartum and postpartum infection is inversely proportional to gestational age. Neonates are immunologically immature, with decreased polymorphonuclear leukocyte and monocyte function; premature infants are particularly so (see p. 2766). Maternal IgG antibodies are actively transported across the placenta, but effective levels for all organisms are not achieved until near term. IgM antibodies do not cross the placenta. Premature infants have decreased intrinsic antibody production and reduced complement activity. Premature infants are also more likely to require invasive procedures (eg, endotracheal intubation, prolonged IV access) that predispose to infection.

Symptoms and Signs

Symptoms and signs in neonates tend to be nonspecific (eg, vomiting, fever, petechiae, rashes, diarrhea, fever, hypothermia). Many congenital infections acquired before birth can cause or be accompanied by various symptoms or abnormalities (eg, growth restriction, deafness, microcephaly, anomalies, failure to thrive, hepatosplenomegaly, neurologic abnormalities).

Diagnosis

A wide variety of infections should be considered in neonates who are ill, febrile, or hypothermic. Infections such as congenital rubella, syphilis, toxoplasmosis, and CMV should be considered, particularly in neonates with abnormalities such as growth restriction, deafness, microcephaly, anomalies, failure to thrive, hepatosplenomegaly, or neurologic abnormalities.

Treatment

• Antimicrobial therapy

The primary treatment is usually antimicrobial therapy. Drug selection is similar to that in adults, because infecting organisms and their sensitivities are not specific to neonates. However, numerous factors, including age and weight, affect dose and frequency (see Tables 279-1 and 279-2).

In neonates, the ECF constitutes up to 45% of total body weight, requiring relatively larger doses of certain antibiotics (eg, aminoglycosides) compared with adults. Lower serum albumin concentrations in premature infants may reduce antibiotic protein binding. Drugs that displace bilirubin from albumin (eg, sulfonamides, ceftriaxone) increase the risk of kernicterus.
Absence or deficiency of certain enzymes in neonates may prolong the half-life of certain antibiotics (eg, chloramphenicol) and increase the risk of toxicity. Changes in GFR and renal tubular secretion during the first month of life necessitate dosing changes for other drugs (eg, penicillins, aminoglycosides, vancomycin).

**Congenital and Perinatal Cytomegalovirus Infection**

(See also [Cytomegalovirus Infection on p. 1416.])

Cytomegalovirus (CMV) infection may be acquired prenatally or perinatally and is the most common congenital viral infection. Signs at birth, if present, are intrauterine growth restriction, prematurity,

- [Table 279-1. Recommended Dosages of Selected Parenteral Antibiotics for Neonates]
- [Table 279-2. Recommended Dosages of Selected Oral Antibiotics for Neonates*]

microcephaly, jaundice, petechiae, hepatosplenomegaly, periventricular calcifications, chorioretinitis, and pneumonitis. If acquired later in infancy, signs may include pneumonia, hepatosplenomegaly, hepatitis, thrombocytopenia, and atypical lymphocytosis. Diagnosis of neonatal infection is best made by virus isolation. Treatment is supportive. Parenteral ganciclovir can prevent hearing deterioration, but its use remains controversial.

CMV is frequently isolated from neonates. Although most infants shedding this virus are asymptomatic, others have life-threatening illness and devastating long-term sequelae.

It is not known when a woman with primary CMV can safely conceive. Because risk to the fetus is difficult to assess, women who develop primary CMV during pregnancy should be counseled, but few experts recommend routine serologic testing for CMV before or during pregnancy in healthy women.

**Etiology**

**Congenital CMV infection**, which occurs in 0.2 to 2.2% of live births worldwide, may result from transplacental acquisition of either a primary or recurrent maternal infection. Clinically apparent disease in the neonate is much more likely to occur after a primary maternal exposure, particularly in the first half of pregnancy. In some higher socioeconomic groups in the US, 50% of young women lack antibody to CMV, making them susceptible to primary infection.

**Perinatal CMV infection** is acquired by exposure to infected cervical secretions, breast milk, or blood products. Maternal antibody is thought to be protective, and most exposed term infants are asymptomatic or not infected. In contrast, preterm infants (who lack antibody to CMV) can develop serious infection or can die, particularly when transfused with CMV-positive blood. Efforts should be made to transfuse these infants with only CMV-negative blood or components or to use blood that has been filtered to remove leukocytes (leukoreduced).

**Symptoms and Signs**

Many women who become infected with CMV during pregnancy are asymptomatic, but some develop a mononucleosis-like illness.

About 10% of infants with congenital CMV infection are symptomatic at birth. Manifestations include the following:

- Intrauterine growth restriction
- Prematurity
Infants who acquire CMV after birth, especially if they are premature, may develop a sepsis-like syndrome, pneumonia, hepatosplenomegaly, hepatitis, thrombocytopenia, and atypical lymphocytosis, as well as sensorineural hearing loss.

Diagnosis

- Viral culture using urine, saliva, or tissue
- PCR using urine, saliva, blood, or tissue

Symptomatic congenital CMV infection must be distinguished from other congenital infections, including toxoplasmosis, rubella, and syphilis.

In neonates, viral culture of a urine, saliva, or tissue sample is the primary diagnostic tool; maternal diagnosis can also be made by serologic testing (see p. 1416). Culture specimens should be refrigerated until inoculation of fibroblast cells. Congenital CMV is diagnosed if the virus is isolated from urine or other body fluids obtained within the first 3 wk of life. After 3 wk, positive cultures may indicate perinatal or congenital infection. Infants may shed CMV for several years after either type of infection. A positive PCR result using neonatal urine, saliva, blood, or tissue is helpful in making a diagnosis, but a negative PCR result does not rule out an infection. PCR can also establish maternal infection.

A CBC and differential and liver function tests may be helpful but are not specific. Cranial ultrasonography or CT and an ophthalmologic evaluation should also be done. Periventricular calcifications are commonly found on CT. Hearing tests should be routinely done at birth in all infected neonates, but close monitoring is required because hearing loss may be progressive.

Prognosis

Symptomatic neonates have a mortality rate of up to 30%, and 70 to 90% of survivors have some neurologic impairment, including

- Hearing loss
- Intellectual disability
- Visual disturbances

Among asymptomatic neonates, 10% eventually develop neurologic sequelae.

Treatment

No specific therapy is available. Ganciclovir decreases viral shedding in neonates with congenital CMV and may prevent hearing deterioration at 6 mo. When therapy stops, the virus is again shed; therefore, its role in treatment remains controversial.

Prevention
Nonimmune pregnant women should attempt to limit exposure to the virus. For instance, because CMV infection is common among children attending day care centers, pregnant women should always wash their hands thoroughly after exposure to urine and oral or respiratory secretions from children.

Transfusion-associated perinatal CMV disease can be avoided by giving preterm neonates blood products from CMV-seronegative donors or leukoreduced products.

A vaccine to prevent congenital CMV is being developed. Using CMV hyper immune globulin in pregnant women with primary CMV infection to prevent or treat congenital infection is also under investigation.

**Congenital Rubella**

(See also Rubella on p. 1462.)

Congenital rubella is a viral infection acquired from the mother during pregnancy. **Signs are multiple congenital anomalies that can result in fetal death. Diagnosis is by serology and viral culture. There is no specific treatment. Prevention is by routine vaccination.**

Congenital rubella typically results from a primary maternal infection. Congenital rubella is rare in the US.

Rubella is believed to invade the upper respiratory tract, with subsequent viremia and dissemination of virus to different sites, including the placenta. The fetus is at highest risk of developmental abnormalities when infected during the first 16 wk of gestation, particularly the first 8 to 10 wk. Early in gestation, the virus is thought to establish a chronic intrauterine infection. Its effects include endothelial damage to blood vessels, direct cytolysis of cells, and disruption of cellular mitosis.

**Symptoms and Signs**

Rubella in a pregnant woman may be asymptomatic or characterized by upper respiratory tract symptoms, fever, lymphadenopathy (especially in the suboccipital and posterior auricular areas), and a maculopapular rash. This illness may be followed by joint symptoms.

In the fetus there may be no effects, multiple anomalies, or death in utero. The most frequent abnormalities include intrauterine growth restriction, microcephaly, meningoencephalitis, cataracts, retinopathy, hearing loss, cardiac defects (patent ductus arteriosus and pulmonary artery stenosis), hepatosplenomegaly, and bone radiolucencies. Others are thrombocytopenia with purpura, dermal erythropoiesis resulting in bluish red skin lesions, adenopathy, hemolytic anemia, and interstitial pneumonia. Close observation is needed to detect subsequent hearing loss, intellectual disability, abnormal behavior, endocrinopathies (eg, diabetes mellitus), or a rare progressive encephalitis. Infants with congenital rubella infections may develop immune deficiencies such as hypogammaglobulinemia.

**Diagnosis**

- Maternal serum rubella titers
- Sometimes viral isolation from amniotic fluid
- Infant antibody titers (measured serially) and viral cultures

Pregnant women routinely have a serum rubella titer measured early in pregnancy. Titer is repeated in seronegative women who develop symptoms or signs of rubella; diagnosis is made by seroconversion or a ≥ 4-fold rise between acute and convalescent titers. Virus may be cultured from nasopharyngeal swabs but grows very slowly, making swabs an inefficient method of diagnosis.

Infants suspected of having congenital rubella should have antibody titers and viral cultures. Persistence of rubella-specific IgG in the infant after 6 to 12 mo suggests congenital infection. Increased rubella-specific IgM antibodies also indicate rubella. Specimens from the nasopharynx, urine, CSF, buffy coat,
and conjunctiva may grow virus; samples from the nasopharynx usually offer the best sensitivity, and the laboratory should be notified that rubella virus is suspected. In a few centers, diagnoses can be made prenatally by isolating the virus from amniotic fluid, detecting rubella-specific IgM in fetal blood, or applying reverse transcriptase-PCR (RTPCR) techniques to fetal blood or chorionic villus biopsy specimens.

Other tests include a CBC with differential, CSF analysis, and x-ray examination of the bones to detect characteristic radioluencies. Thorough ophthalmologic and cardiac evaluations are also useful.

**Treatment**

- Counseling
- Possibly immune globulin

No specific therapy is available for maternal or congenital rubella infection. Women exposed to rubella early in pregnancy should be informed of the potential risks to the fetus. Some experts recommend giving nonspecific immune globulin (0.55 mL/kg IM) for exposure early in pregnancy, but this treatment does not guarantee prevention, and the use of immune globulin should be considered only in women who decline termination.

**Prevention**

Rubella can easily be prevented by vaccination. In the US, infants should receive vaccination for rubella together with measles and mumps vaccinations at 12 to 15 mo of age and again at entry to grade school or junior high school (see Table 268-11 on p. 2720). Postpubertal females who are not known to be immune to rubella should be vaccinated. (CAUTION: Rubella vaccination is contraindicated in immunodeficient or pregnant women.) After vaccination, women should be advised not to become pregnant for 28 days. Efforts should also be made to screen and vaccinate high-risk groups, such as hospital and child care workers, military recruits, recent immigrants, and college students. Women who are found to be susceptible during prenatal screening should be vaccinated after delivery and before hospital discharge.

**Congenital Syphilis**

(See also Syphilis on p. 1475.)

Congenital syphilis is a multisystem infection caused by *Treponema pallidum* and transmitted to the fetus via the placenta. Early signs are characteristic skin lesions, lymphadenopathy, hepatosplenomegaly, failure to thrive, blood-stained nasal discharge, perioral fissures, meningitis, choroiditis, hydrocephalus, seizures, intellectual disability, osteochondritis, and pseudoparalysis (Parrot’s atrophy of newborn). Later signs are gummatous ulcers, periosteal lesions, paresis, tabes, optic atrophy, interstitial keratitis, sensorineural deafness, and dental deformities. Diagnosis is clinical, confirmed by microscopy or serology. Treatment is penicillin.

Overall risk of transplacental infection of the fetus is about 60 to 80%, and likelihood is increased during the 2nd half of the pregnancy. Untreated primary or secondary syphilis in the mother usually is transmitted, but latent or tertiary syphilis usually is not. In neonates, manifestations of syphilis are classified as early congenital (ie, birth through age 2 yr) and late congenital (ie, after age 2 yr).

**Symptoms and Signs**

Many patients are asymptomatic, and the infection may remain clinically silent throughout their life.

**Early congenital syphilis** commonly manifests during the first 3 mo of life. Manifestations include characteristic vesiculobullous eruptions or a macular, copper-colored rash on the palms and soles and papular lesions around the nose and mouth and in the diaper area, as well as petechial lesions. Generalized lymphadenopathy and hepatosplenomegaly often occur. The infant may fail to thrive and...
have a characteristic mucopurulent or bloodstained nasal discharge causing snuffles. A few infants develop meningitis, choroiditis, hydrocephalus, or seizures, and others may be intellectually disabled. Within the first 8 mo of life, osteochondritis (chondroepiphysitis), especially of the long bones and ribs, may cause pseudoparalysis of the limbs with characteristic radiologic changes in the bones.

**Late congenital syphilis** typically manifests after 2 yr of life and causes gummatous ulcers that tend to involve the nose, septum, and hard palate and periosteal lesions that result in saber shins and bossing of the frontal and parietal bones. Neurosyphilis is usually asymptomatic, but juvenile paresis and tabes may develop. Optic atrophy, sometimes leading to blindness, may occur. Interstitial keratitis, the most common eye lesion, frequently recurs, often resulting in corneal scarring. Sensorineural deafness, which is often progressive, may appear at any age. Hutchinson's incisors, mulberry molars, perilous fissures (rhagades), and maldevelopment of the maxilla resulting in "bulldog" facies are characteristic, if infrequent, sequelae.

**Diagnosis**

- **Early congenital syphilis:** Clinical evaluation, darkfield microscopy of lesions and placenta or umbilical cord, infant serum quantitative nontreponemal tests, possibly CSF analysis
- **Late congenital syphilis:** Clinical evaluation, serologic testing

**Early congenital syphilis:** Diagnosis is usually suspected based on maternal serologic testing, which is routinely done early in pregnancy, and often in the 3rd trimester and at delivery. Neonates of mothers with positive tests should have a thorough examination, darkfield microscopy of any skin or mucosal lesions, and a quantitative nontreponemal serum test (eg, rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]); cord blood is not used for serum testing because results are less sensitive and specific. The placenta or umbilical cord should be analyzed using darkfield microscopy or fluorescent antibody staining. Infants with clinical signs of illness or suggestive serologic test results also should have a lumbar puncture with CSF analysis for cell count, VDRL, and protein; CBC; liver function tests; and long-bone x-rays.

Diagnosis is confirmed by microscopic visualization of spirochetes in samples from the neonate or the placenta. Diagnosis based on neonatal serologic testing is complicated by the transplacental transfer of maternal IgG antibodies, which can cause a positive test in the absence of infection. However, a neonatal titer > 4 times the maternal titer would not generally result from passive transfer, and diagnosis is considered confirmed or highly probable. Maternal disease acquired late in pregnancy may be transmitted before development of antibodies. Thus, in neonates with lower titers but typical clinical manifestations, syphilis is also considered highly probable. In neonates with no signs of illness and low or (if maternal infection is diagnosed) negative serologic titers, syphilis is considered possible; subsequent approach depends on various maternal and neonatal factors (see also Follow up, below). The utility of fluorescent assays for antitreponemal IgM, which is not transferred across the placenta, is controversial, but such assays have been used to detect neonatal infection. Any positive nontreponemal test should be confirmed with a specific treponemal test to exclude false-positive results, but confirmative testing should not delay treatment in a symptomatic infant or an infant at high risk of infection.

**Late congenital syphilis:** Diagnosis is by clinical history, distinctive physical signs, and positive serologic tests (see also p. 1478). Hutchinson's triad of interstitial keratitis, Hutchinson's incisors, and 8th cranial nerve deafness is diagnostic. Sometimes the standard serologic tests for syphilis are negative, but the fluorescent treponemal antibody absorption test (FTA-ABS) is usually positive. The diagnosis should be considered in cases of unexplained deafness, progressive intellectual deterioration, or keratitis.

**Follow up:** All seropositive infants and those whose mothers were seropositive should have VDRL or RPR titers every 2 to 3 mo until the test is nonreactive or the titer has decreased 4-fold. In uninfected and successfully treated infants, nontreponemal antibody titers are usually non-reactive by 6 mo. Passively acquired treponemal antibodies may be present for longer, perhaps 15 mo. It is important to remember to use the same specific nontreponemal test to monitor titers.

If VDRL or RPR remain reactive past 6 to 12 mo or titers increase, the infant should be reevaluated (including lumbar puncture for CSF analysis, and CBC with platelet count, long-bone x-rays, and other
tests as clinically indicated).

**Treatment**

- Parenteral penicillin

**Pregnant women:** Pregnant women in the early stages of syphilis receive one dose of benzathine penicillin G (1.2 million units IM in each buttock for a total of 2.4 million units). For later stages of syphilis or neurosyphilis, the appropriate regimen for nonpregnant patients should be followed (see p. 1480). Occasionally, a severe Jarisch-Herxheimer reaction occurs after such therapy, leading to spontaneous abortion. Patients allergic to penicillin may be desensitized and then treated with penicillin. RPR and VDRL tests become negative by 3 mo after adequate treatment in most patients and by 6 mo in nearly all patients. Erythromycin therapy is inadequate for both the mother and fetus and is not recommended. Tetracycline is **contraindicated**.

**Early congenital syphilis:** In confirmed or highly probable cases, 2006 Centers for Disease Control and Prevention (CDC) guidelines recommend aqueous penicillin G 50,000 units/kg IV q 12 h for the first 7 days of life and q 8 h thereafter for a total of 10 days or procaine penicillin G 50,000 units/kg IM once/day for 10 days. This regimen also is used for infants with possible syphilis if the mother fits any of the following criteria:

- Untreated
- Treatment status is unknown
- Treated ≤ 4 wk before delivery
- Inadequately treated (a nonpenicillin regimen, or maternal titers did not decrease 4-fold)

In infants with possible syphilis and a negative evaluation, a single dose of benzathine penicillin 50,000 units/kg IM is an alternative treatment choice in selected circumstances, but only if follow-up is assured.

Infants with possible syphilis whose mothers were adequately treated and who are clinically well can also be given a single dose of benzathine penicillin 50,000 units/kg IM. Alternatively, if close follow-up is assured, some clinicians defer penicillin and do nontreponemal serologic testing monthly for 3 mo and then at 6 mo; antibiotics are given if titers rise or are positive at 6 mo.

**Older infants and children with newly diagnosed congenital syphilis:** CSF should be examined before treatment starts. The CDC recommends that any child with late congenital syphilis be treated with aqueous crystalline penicillin G 50,000 units/kg IV q 4 to 6 h for 10 days. Many patients do not revert to seronegativity but do have a 4-fold decrease in titer of reagin (eg, VDRL) antibody. Interstitial keratitis is usually treated with corticosteroid and atropine drops in consultation with an ophthalmologist. Patients with nerve deafness may benefit from penicillin plus a corticosteroid such as prednisone 0.5 mg/kg po once/day for 1 wk, followed by 0.3 mg/kg once/day for 4 wk, after which the dose is gradually reduced over 2 to 3 mo. (Corticosteroids have not been critically evaluated in these conditions.) Contacts should be traced, and patients should be kept under long-term surveillance.

**Prevention**

Pregnant women should be routinely tested for syphilis and retested if they acquire other sexually transmitted diseases during pregnancy. In 99% of cases, adequate treatment during pregnancy cures both mother and fetus. However, in some cases, treatment late in pregnancy eliminates the infection but not some signs of syphilis that appear at birth.

When congenital syphilis is diagnosed, other family members should be examined regularly for physical and serologic evidence of infection. Retreatment of the mother in subsequent pregnancies is necessary only if serologic titers remain positive. Women who remain seropositive after adequate treatment may have been reinfected and should be retreated. A mother without lesions who is seronegative but who has
had venereal exposure to a known person with syphilis should be treated, because there is a 25 to 50% chance that she acquired syphilis.

**Congenital Toxoplasmosis**

(See also [Toxoplasmosis](#) on p. 1390.)

**Congenital toxoplasmosis** is caused by transplacental acquisition of *Toxoplasma gondii*. Manifestations, if present, are prematurity, intrauterine growth restriction, jaundice, hepatosplenomegaly, myocarditis, pneumonitis, rash, chorioretinitis, hydrocephalus, intracranial calcifications, microcephaly, and seizures. Diagnosis is by serologic testing. Treatment is with pyrimethamine, sulfadiazine, and leucovorin.

*Toxoplasma gondii*, a parasite found worldwide, causes congenital infection in about 1/10,000 to 80/10,000 births.

**Etiology**

With rare exception, congenital toxoplasmosis is due to a primary maternal infection during pregnancy. Infection with *T. gondii* occurs primarily from ingestion of inadequately cooked meat containing cysts or from ingestion of oocysts derived from cat feces. The rate of transmission to the fetus is higher in women infected later during pregnancy. However, those infected earlier in gestation generally have more severe disease. Overall, 30 to 40% of women infected during pregnancy will have a congenitally infected child.

**Symptoms and Signs**

Pregnant women infected with *T. gondii* generally do not have clinical manifestations, although some may have a mild mononucleosis-like syndrome, regional lymphadenopathy, or occasionally chorioretinitis. Similarly, infected neonates are usually asymptomatic at birth, but manifestations may include

- Prematurity
- Intrauterine growth restriction
- Jaundice
- Hepatosplenomegaly
- Myocarditis
- Pneumonitis
- Various rashes

Neurologic involvement, often prominent, includes chorioretinitis, hydrocephalus, intracranial calcifications, microcephaly, and seizures. The classic triad of findings consists of chorioretinitis, hydrocephalus, and intracranial calcifications.

**Diagnosis**

- Serial IgG measurement (for maternal infection)
- Amniotic fluid PCR (for fetal infection)
- Serologic testing, brain imaging, CSF analysis, and ophthalmologic evaluation (for neonatal infection)

Serologic testing is important in diagnosing maternal and congenital infection. Maternal infection should be suspected if women have a mononucleosis-like syndrome and a negative heterophil antibody test,
isolated regional adenopathy not due to another cause (eg, HIV), or chorioretinitis. Acute maternal infection is suggested by seroconversion or a ≥ 4-fold rise between acute and convalescent IgG titers. However, maternal IgG antibodies may be detectable in the infant through the first year. PCR analysis of amniotic fluid is emerging as the method of choice for diagnosis of fetal infection. There are numerous other serologic tests, some of which are done only in reference laboratories. The most reliable are the Sabin-Feldman dye test, the indirect immunofluorescent antibody (IFA) test, and the direct agglutination assay. Tests to isolate the organism include inoculation into mice and tissue culture, but these tests are not usually done because they are expensive, not highly sensitive, and can take weeks before yielding results.

In suspected congenital toxoplasmosis, serologic tests, MRI or CT imaging of the brain, CSF analysis, and a thorough eye examination by an ophthalmologist should be done. CSF abnormalities include xanthochromia, pleocytosis, and increased protein concentration. The placenta is inspected for characteristic signs of *T. gondii* infection. Nonspecific laboratory findings include thrombocytopenia, lymphocytosis, monocytosis, eosinophilia, and elevated transaminases.

**Prognosis**

Some children have a fulminant course with early death, whereas others have long-term neurologic sequelae. Occasionally, neurologic manifestations (eg, chorioretinitis, intellectual disability, deafness, seizures) develop years later in children who appeared normal at birth. Consequently, children with congenital toxoplasmosis should be closely monitored beyond the neonatal period.

**Treatment**

- Sometimes spiramycin for pregnant women
- Pyrimethamine, sulfadiazine, and leucovorin for neonates

Limited data suggest that treatment of infected women during pregnancy may be beneficial to the fetus. Spiramycin (available in the US with special permission from the FDA) has been used to prevent maternofetal transmission. Pyrimethamine and sulfonamides have been used later in gestation to treat the infected fetus.

Treatment of symptomatic and asymptomatic neonates may improve outcome. Therefore, treatment is begun with pyrimethamine (initial loading dose of 1 mg/kg po bid for 2 days followed by 1 mg/kg po once/day, maximum 25 mg), sulfadiazine (50 mg/kg po bid, maximum 4 g), and leucovorin (5 to 10 mg po q 3 days). After the initial 6 mo of treatment, sulfadiazine and leucovorin are continued at the same dose, but the pyrimethamine is given less frequently (only on Monday, Wednesday, and Friday). This regimen is continued for at least 6 more mo. All treatment should be over-seen by an expert. The use of corticosteroids is controversial and should be determined case by case.

**Prevention**

Pregnant women should avoid contact with cat litter boxes and other areas contaminated with cat feces. Meat should be thoroughly cooked before consumption, and hands should be washed after handling raw meat or unwashed produce. Women at risk of primary infection (eg, those frequently exposed to cat feces) should be screened during pregnancy. Those infected during the 1st or 2nd trimester should be counseled regarding available treatments.

**Neonatal Conjunctivitis**

(Ophthalmia Neonatorum)

Neonatal conjunctivitis is purulent ocular drainage due to a chemical irritant or a pathogenic organism. Prevention with anticonococcal drops at birth is routine. Diagnosis is clinical and usually confirmed by laboratory testing. Treatment is with organism-specific antimicrobials.
Etiology

The major causes (in decreasing order) are

• Chemical inflammation

• Bacterial infection

• Viral infection (see also p. 580)

Chemical conjunctivitis is generally secondary to the instillation of silver nitrate drops for ocular prophylaxis. Bacterial infection is acquired from infected mothers during passage through the birth canal. Chlamydial ophthalmia (caused by *Chlamydia trachomatis*) is the most common bacterial cause, occurring in 2 to 4% of births; it accounts for about 30 to 50% of conjunctivitis in neonates < 4 wk of age. The prevalence of maternal chlamydial infection ranges from 2 to 20%. About 30 to 50% of neonates born to acutely infected women develop conjunctivitis (and 5 to 20% develop pneumonia). Other bacteria, including *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae*, account for another 15% of cases. The incidence of gonorrheal ophthalmia (conjunctivitis due to *Neisseria gonorrhoeae*) in the US is 2 to 3/10,000 births. Isolation of bacteria other than *H. influenzae*, *S. pneumoniae*, and *N. gonorrhoeae*, including *Staphylococcus aureus*, usually represents colonization rather than infection. The major viral cause is herpes simplex virus types 1 and 2 (herpetic keratoconjunctivitis).

Symptoms and Signs

Because they overlap in both manifestation and onset, causes of neonatal conjunctivitis are difficult to distinguish clinically. Conjunctivae are injected, and discharge (watery or purulent) is present.

Chemical conjunctivitis secondary to silver nitrate usually appears within 6 to 8 h after instillation and disappears spontaneously within 48 to 96 h.

Chlamydial ophthalmia usually occurs 5 to 14 days after birth. It may range from mild conjunctivitis with minimal mucopurulent discharge to severe eyelid edema with copious drainage and pseudomembrane formation. Follicles are not present in the conjunctiva, as they are in older children and adults.

Gonorrheal ophthalmia causes an acute purulent conjunctivitis that appears 2 to 5 days after birth or earlier with premature rupture of membranes. The neonate has severe eyelid edema followed by chemosis and a profuse purulent exudate that may be under pressure. If untreated, corneal ulcerations and blindness may occur.

Conjunctivitis caused by other bacteria has a variable onset, ranging from 4 days to several weeks.

Herpetic keratoconjunctivitis can occur as an isolated infection or with disseminated or CNS infection. It can be mistaken for bacterial or chemical conjunctivitis, but the presence of dendritic keratitis is pathognomonic.

Diagnosis

• Testing of conjunctival material for gonorrhea, chlamydia, and, sometimes, herpes

Conjunctival material is Gram stained, cultured for gonorrhea (eg, on modified Thayer-Martin medium), and tested for chlamydia (eg, by culture, direct immunofluorescence, or enzyme-linked immunosorbent assay [samples must contain cells]). Conjunctival scrapings can also be examined with Giemsa stain; if blue intracytoplasmic inclusions are identified, chlamydial ophthalmia is confirmed. Viral culture is done only if viral infection is suspected because of skin lesions or maternal infection.

Treatment

• Systemic, topical, or combined antimicrobial therapy
Neonates with conjunctivitis and known maternal gonococcal infection or with gram-negative intracellular diplococci identified in conjunctival exudates should be treated with ceftriaxone before results of confirmatory tests are available.

In chlamydial ophthalmia, systemic therapy is the treatment of choice, because at least half of affected neonates also have nasopharyngeal infection and some develop chlamydial pneumonia. Erythromycin ethylsuccinate 10 mg/kg po q 6 h for 2 wk is recommended. Efficacy of this therapy is only 80%, so a 2nd treatment course may be needed. Because use of erythromycin in neonates is associated with the development of hypertrophic pyloric stenosis (HPS—see p. 2800), all neonates treated with erythromycin should be monitored for symptoms and signs of HPS.

A neonate with gonorrheal ophthalmia is hospitalized to be evaluated for possible systemic gonococcal infection and given a single dose of ceftriaxone 25 to 50 mg/kg IM to a maximum dose of 125 mg (infants with hyperbilirubinemia or those receiving Ca-containing fluids may be given cefotaxime 100 mg/kg IV or IM). Frequent saline irrigation of the eye prevents secretions from adhering. Topical antimicrobial ointments alone are ineffective.

Conjunctivitis due to other bacteria usually responds to topical ointments containing polymyxin plus bacitracin, erythromycin, or tetracycline.

Herpetic keratoconjunctivitis should be treated (with an ophthalmologist's consultation) with systemic acyclovir 20 mg/kg q 8 h for 14 to 21 days and topical 1% trifluridine opthalmic drops or ointment, vidarabine 3% ointment, or 0.1% iododeoxyuridine q 2 to 3 h, with a maximum of 9 doses/24 h. Systemic therapy is important, because dissemination to the CNS and other organs can occur.

Corticosteroid-containing ointments may seriously exacerbate eye infections due to C. trachomatis, and herpes simplex virus and should be avoided.

Prevention

Routine use of 1% silver nitrate drops, 0.5% erythromycin, or 1% tetracycline opthalmic ointments or drops instilled into each eye after delivery effectively prevents gonorrheal ophthalmia. However, none of these agents prevents chlamydial ophthalmia; povidone iodine 2.5% drops may be effective against chlamydia and is effective against gonococci but is not available in the US. Silver nitrate and tetracycline opthalmic ointments are also no longer available in the US.

Neonates of mothers with untreated gonorrhea should receive a single injection of ceftriaxone 25 to 50 mg/kg IM or IV, up to 125 mg, and both mother and neonate should be screened for chlamydia infection, HIV, and syphilis.

**Neonatal Hepatitis B Virus Infection**

(See also Ch. 28.)

Neonatal hepatitis B virus (HBV) infection is usually acquired during delivery. It is usually asymptomatic but can cause chronic subclinical disease. Symptomatic infection causes jaundice, lethargy, failure to thrive, abdominal distention, and clay-colored stools. Diagnosis is by serology. Rarely, severe illness may cause acute liver failure requiring liver transplantation. Less severe illness is treated supportively. Active and passive immunization help prevent vertical transmission.

Of the recognized forms of primary viral hepatitis, only HBV is a major cause of neonatal hepatitis. Infection with other viruses (eg, cytomegalovirus, herpes simplex virus) may cause liver inflammation along with other manifestations.

**Etiology**
HBV infection occurs during delivery from an infected mother. Maternal acute hepatitis B occurring within 2 to 3 mo of delivery has about a 70% risk of transmission, but disease occurring during the 1st or 2nd trimester has only about a 5% risk. Risk of transmission is also high from asymptomatic hepatitis B surface antigen (HBsAg) carriers with the e antigen (HBe—see p. 251). Carriers without the e antigen or with anti-HBe are less likely to transmit the disease.

Mother-infant HBV transmission results primarily from maternofetal microtransfusions during labor or contact with infectious secretions in the birth canal. Transplacental transmission is unusual. Postpartum transmission occurs rarely through exposure to infectious maternal blood, saliva, stool, urine, or breast milk. Neonatal HBV infection may be an important viral reservoir in certain communities.

**Symptoms and Signs**

Most neonates with HBV infection are asymptomatic but develop chronic, subclinical hepatitis characterized by persistent HBsAg antigenemia and variably elevated transaminase activity. Many neonates born to women with acute hepatitis B during pregnancy are of low birth weight, regardless of whether they are infected.

Infrequently, infected neonates develop acute hepatitis B, which is usually mild and self-limited. They develop jaundice, lethargy, failure to thrive, abdominal distention, and clay-colored stools. Occasionally, severe infection with hepatomegaly, ascites, and hyperbilirubinemia (primarily conjugated bilirubin) occurs. Rarely, the disease is fulminant and even fatal. Fulminant disease occurs more often in neonates whose mothers are chronic carriers of hepatitis B.

**Diagnosis**

Diagnosis is by serologic testing (discussed on p. 251).

**Prognosis**

Long-term prognosis is unknown, although HBsAg carriage early in life seems to increase the risk of subsequent liver disease (eg, chronic hepatitis, cirrhosis, hepatocellular carcinoma).

**Treatment**

- Supportive care

Symptomatic care and adequate nutrition are needed. Neither corticosteroids nor hepatitis B immune globulin (HBIG) is valuable. No therapy prevents the development of chronic, subclinical hepatitis once infection is acquired. Because of the risk of developing significant disease, liver function should be monitored periodically.

**Prevention**

Pregnant women should be tested for HBsAg during an early prenatal visit. Failing that, they should be tested when admitted for delivery. Some women who are HBsAg-positive are treated with lamivudine during the 3rd trimester, which may prevent perinatal transmission of hepatitis B.

Neonates whose mothers are HBsAg-positive should be given 1 dose of HBIG 0.5mL IM within 12 h of birth. Recombinant hepatitis B virus vaccine should be given IM in a series of 3 doses. (NOTE: Doses vary among proprietary vaccines.) The first dose is given concurrently with HBIG but at a different site. The 2nd dose is given at 1 to 2 mo, and the 3rd dose is given 6 mo after the first. If the infant weighs < 2 kg, the first dose of vaccine may be less effective. Subsequent vaccine doses are given at age 30 days (or when discharged from the hospital), and then 2 other doses are given at 1 to 2 mo and 6 mo after the 30-day dose. Testing for HBsAg and anti-HBs at 9 to 15 mo is recommended.

Particularly where hepatitis B infection is highly endemic or HBsAg screening of mothers is impractical, all neonates should be vaccinated.
Separating a neonate from its HBsAg-positive mother is not recommended, and breastfeeding does not seem to increase the risk of postpartum HBV transmission, particularly if HBIG and hepatitis B virus vaccine have been given. However, if a mother has cracked nipples, abscesses, or other breast pathology, breast-feeding could potentially transmit HBV.

**Neonatal Herpes Simplex Virus Infection**

(See also Herpes Simplex Virus Infections on p. 1417.)

**Neonatal herpes simplex virus (HSV) infection is usually transmitted during delivery. Signs are typically a vesicular eruption and subsequent disseminated disease.** Diagnosis is by viral culture, PCR, immunofluorescence, or electron microscopy. Treatment is with high-dose parenteral acyclovir and supportive care.

Neonatal HSV infection has high mortality and significant morbidity. Incidence estimates range from 1/3,000 to 1/20,000 births. HSV type 2 causes more cases than HSV type 1.

HSV is usually transmitted during delivery through an infected maternal genital tract. Transplacental transmission of virus and hospital-acquired spread from one neonate to another by hospital personnel or family may account for some cases. Mothers of neonates with HSV infection tend to have newly acquired genital infection, but many have not yet developed symptoms at the time of delivery.

**Symptoms and Signs**

Manifestations generally occur between the 1st and 2nd wk of life but may not appear until as late as the 4th wk. Patients may present with local or disseminated disease. Skin vesicles are common with either type, occurring in about 55% overall. Those with no skin vesicles usually present with localized CNS disease. In patients with isolated skin or mucosal disease, progressive or more serious forms of disease frequently follow within 7 to 10 days if left untreated.

**Localized disease:** Neonates with localized disease can be divided into 2 groups. One group has encephalitis manifested by neurologic findings, CSF pleocytosis, and elevated protein concentration, with or without concomitant involvement of the skin, eyes, and mouth. The other group has only skin, eye, and mouth involvement and no evidence of CNS or organ disease.

**Disseminated disease:** Neonates with disseminated disease and visceral organ involvement have hepatitis, pneumonitis, disseminated intravascular coagulation, or a combination, with or without encephalitis or skin disease.

Other signs, which can occur singly or in combination, include temperature instability, lethargy, hypotonia, respiratory distress, apnea, and seizures.

**Diagnosis**

- HSV culture or PCR
- Sometimes immunofluorescent testing of lesions or electron microscopy

Rapid diagnosis by viral culture or HSV PCR is essential. The most common site of retrieval is skin vesicles. The mouth, eyes, and CSF are also high-yield sites. In some neonates with encephalitis, virus is present only in the brain. Diagnosis also can be made by immunofluorescence of lesion scrapings, particularly with use of monoclonal antibodies; and electron microscopy. If no diagnostic virology facilities are available, a Tzanck test of the lesion base may show characteristic multinucleated giant cells and intranuclear inclusions, but this test is less sensitive than culture, and false-positives also occur.

**Prognosis**
The mortality rate of untreated disseminated disease is 85%; among those with untreated encephalitis, it is about 50%. Without treatment, at least 65% of survivors have severe neurologic sequelae.

Death is uncommon in neonates with local disease limited to the skin, eyes, or mouth. However, without treatment, many of these neonates will progress to disseminated disease or CNS disease that may be unrecognized; about 30% develop neurologic impairment, which may not manifest until 2 to 3 yr of age.

**Treatment**

- Parenteral and topical acyclovir
- Supportive therapy

Acyclovir decreases the mortality rate in CNS and disseminated disease by 50% and increases the percentage of children who develop normally from about 35% to 50 to 80%; the dose is 20 mg/kg IV q 8 h for 21 days. Vigorous supportive therapy is required, including appropriate IV fluids, alimentation, respiratory support, correction of clotting abnormalities, and control of seizure disorders.

For localized disease (skin or mouth), treatment is acyclovir 20 mg/kg IV q 8 h for 14 days. Herpetic keratoconjunctivitis requires concomitant systemic acyclovir for 14 days and topical therapy with a drug such as trifluridine, iododeoxyuridine, or vidarabine (see p. 2825).

**Prevention**

Efforts to prevent neonatal transmission have not been very effective. Universal screening has not been recommended or shown to be effective, and most maternal infections with risk of transmission are asymptomatic. However, cesarean delivery for women known to have a high risk of transmission (eg, active genital lesions present at term) has been shown to decrease transmission and is recommended. Also, fetal scalp monitors should not be used during labor on infants whose mothers have suspected active genital herpes.

**Neonatal Hospital-Acquired Infection**

Some infections are acquired after admission to the nursery rather than from the mother in utero or intrapartum. For some infections (eg, group B streptococci, herpes simplex virus [HSV]) it may not be clear whether the source is maternal or the hospital environment.

Hospital-acquired infection is primarily a problem for premature infants and for term infants with medical disorders requiring prolonged hospitalization. Healthy, term neonates have infection rates < 1%. For those in special care nurseries, the incidence increases as birth weight decreases. The most common infections, sepsis and pneumonia, have a combined rate of 6.2 cases per 1000 catheter or ventilator days for infants weighing 1501 to 2500 g, 8.9 cases for those weighing 1001 to 1500 g, and 13.9 cases for those weighing ≤ 1000 g.

Overall mortality rates are about 33%; for neonates whose birth weight is < 1000 g, the mortality rate is 16 to 45%, and for those whose birth weight is > 2000 g, the mortality rate is 2 to 12%.

**Etiology**

In term neonates, skin infection due to *Staphylococcus aureus* (both methicillin sensitive and methicillin resistant) is the most frequent hospital-acquired infection. Although nursery personnel who are *S. aureus* nasal carriers are potential sources of infection, colonized neonates are usually the reservoir. The umbilical stump and groin are most frequently colonized during the first few days of life, whereas the nares are more frequently colonized later. Often, infections do not manifest until the neonate is at home.

In very-low-birth-weight (VLBW; < 1500 g) infants, gram-positive organisms cause about 70% of infections, the majority being with coagulase-negative staphylococci. Gram-negative organisms, including *Escherichia coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, and *Serratia*, cause about 18%. Fungi
(Candida albicans and C. parapsilosis) cause about 12%. Patterns of infection (and antibiotic resistance) vary among institutions and units and change with time. Intermittent "epidemics" sometimes occur as a particularly virulent organism colonizes a unit.

Infection is facilitated by the multiple invasive procedures VLBW infants undergo (eg, long-term arterial and venous catheterization, endotracheal intubation, continuous positive airway pressure, NGTs or nasojejunal feeding tubes). The longer the stay in special care nurseries and the more procedures done, the higher is the likelihood of infection.

**Prevention**

Bathing neonates with 3% hexachlorophene decreases frequency of S. aureus colonization, but this product can cause neurotoxicity, particularly in low-birth-weight infants, and is no longer used. The American Academy of Pediatrics recommends dry umbilical cord care, but this care may result in high rates of colonization with S. aureus, and epidemics have occurred in some hospitals. During disease outbreaks, application of triple dye to the cord area or bacitracin or mupirocin ointment to the cord, nares, and circumcision site reduces colonization. Routine cultures of personnel or of the environment are not recommended.

Prevention of colonization and infection in special care nurseries requires provision of sufficient space and personnel. In intensive care, 150 sq ft (about 14 sq m)/infant and 8 ft (about 2.4 m) between incubators or warmers, edge-to-edge in each direction, and a nurse:patient ratio of 1:1 to 1:2 are required. In intermediate care, 120 sq ft (about 11.2 sq m)/infant and 4 ft (about 1.2 m) between incubators or warmers, edge-to-edge in each direction, and a nurse:patient ratio of 1:3 to 1:4 are required. Proper techniques are required, including placement and care of invasive devices and meticulous cleaning and disinfection or sterilization of equipment. Active surveillance for infection (not colonization) and monitoring of techniques are essential.

Other preventive measures include frequent hand washing and wearing gowns and gloves. Washing with alcohol preparations is more effective than soap and water in decreasing bacterial colony counts on hands but does not eliminate Clostridium difficile spores. Incubators provide limited protective isolation; the exteriors and interiors of the units rapidly become heavily contaminated, and personnel are likely to contaminate their hands and forearms. Universal blood and body fluid precautions add further protection.

In an epidemic, establishing a cohort of diseased or colonized infants and assigning them a separate nursing staff are useful. Continuing surveillance for 1 mo after discharge is necessary to assess the adequacy of controls instituted to end an epidemic.

Prophylactic antimicrobial therapy is generally not effective, hastens development of resistant bacteria, and alters the balance of normal flora in the neonate. However, during a confirmed nursery epidemic, antibiotics against specific pathogens may be considered—eg, penicillin G for prophylaxis against group A streptococcal infection or oral colistin or neomycin for prophylaxis against enterotoxigenic or enteropathogenic E. coli.

Vaccination according to the routine schedule (see Table 268-10 on p. 2718) should be given to any infant who is in the hospital at that time.

**Neonatal Listeriosis**

(See also Listeriosis on p. 1242.)

Neonatal listeriosis is acquired transplacentally or during or after delivery. Symptoms are those of sepsis. Diagnosis is by culture of mother and infant. Treatment is antibiotics, initially ampicillin plus an aminoglycoside.

Transplacental infection with Listeria monocytogenes can result in fetal dissemination with granuloma formation (eg, in the skin, liver, adrenal glands, lymphatic tissue, lungs, and brain). If a rash is present, it is referred to as granulomatosis infantisepticum. Aspiration or swallowing of amniotic fluid or vaginal
secretions can lead to perinatal infection of the lungs, manifesting in the first several days of life with respiratory distress, shock, and a fulminant course.

**Symptoms and Signs**

Infections in pregnant women may be asymptomatic or characterized by a primary bacteremia manifesting first as a nonspecific flu-like illness.

In the fetus and neonate, clinical presentation depends on the timing and route of infection. Abortion, premature delivery with amnionitis (with a characteristic brown, murky amniotic fluid), stillbirth, or neonatal sepsis is common. Infection may be apparent within hours or days of birth (early onset) or it may be delayed up to several weeks. Neonates with early-onset disease frequently are of low birth weight, have associated obstetric complications, and show evidence of sepsis with circulatory or respiratory insufficiency or both. Those with the delayed-onset form are full-term, previously healthy neonates presenting with meningitis or sepsis.

**Diagnosis**

- Culture of blood and cervix of febrile pregnant woman
- Culture of blood, CSF, gastric aspirate, and meconium of sick neonate

Blood and cervix specimens should be obtained from any pregnant woman with an unexplained febrile disease and cultured for *L. monocytogenes*. A sick neonate whose mother has listeriosis should be evaluated for sepsis (see p. 2832), including cultures of umbilical cord or peripheral blood; the CSF, gastric aspirate, and meconium; the mother's lochia and exudates from cervix and vagina; and grossly diseased parts of the placenta. CSF examination may show a predominance of mononuclear cells. Gram-stained smears frequently are negative but may show pleomorphic, gram-variable coccobacillary forms, which should not be disregarded as diphtheroid contaminants. Laboratory confirmation of the organism involves biochemical testing and observation of motility using a slide test or showing motility in semisolid media. To do the slide test, colonies of the organism that have grown on solid media are mixed with saline and examined under a microscope. *L. monocytogenes* exhibits a distinctive end-over-end “tumbling” motility due to the presence of flagella at both ends. Serologic tests are not useful.

**Prognosis**

Mortality, ranging from 10 to 50%, is higher in neonates with early-onset disease.

**Treatment**

- Initially ampicillin plus an aminoglycoside

Initial treatment is with ampicillin plus an aminoglycoside (see also p. 1198). After clinical response is observed, the aminoglycoside is stopped. A 14-day course is usually satisfactory (21 days for meningitis), but the optimal duration is unknown. Other possible drugs include ampicillin or penicillin with rifampin, trimethoprim/sulfamethoxazole, and imipenem, but they have not been well evaluated.

Neonates with sepsis require other measures (see p. 2836). In heavy infection, drainage/secretion precautions may be considered.

**Prevention**

Food products that may be contaminated by *L. monocytogenes* (eg, unpasteurized dairy products or raw vegetables exposed to cattle or sheep manure) should be avoided by pregnant women. If infection during pregnancy is recognized, treatment may then be given before delivery or intrapartum to prevent vertical transmission, but the usefulness of such treatment is unproved.
Neonatal Bacterial Meningitis

(See also Ch. 180.)

Neonatal bacterial meningitis is inflammation of the meninges due to bacterial invasion. Signs are those of sepsis, CNS irritation (eg, lethargy, seizures, vomiting, irritability [particularly paradoxical irritability], nuchal rigidity, a bulging or full fontanelle), and cranial nerve abnormalities. Diagnosis is by lumbar puncture. Treatment is with antibiotics.

Neonatal bacterial meningitis occurs in 2/10,000 full-term and 2/1,000 low-birth-weight (LBW) neonates, with a male predominance. It occurs in about 15% of neonates with sepsis and occasionally occurs in isolation.

Etiology

The predominant pathogens are

- Group B streptococcus (GBS—predominantly type III)
- Escherichia coli (particularly those strains containing the K1 polysaccharide)
- Listeria monocytogenes

Enterococci, nonenterococcal group D streptococci, α-hemolytic streptococci, and other gram-negative enteric organisms (eg, Klebsiella sp, Enterobacter sp, Citrobacter diversus) also are common pathogens. Haemophilus influenzae type b, Neisseria meningitidis, and Streptococcus pneumoniae have been reported as causes.

Neonatal bacterial meningitis most frequently results from the bacteremia that occurs with neonatal sepsis; the higher the colony count in the blood culture, the higher the risk of meningitis. Neonatal bacterial meningitis may also result from scalp lesions, particularly when developmental defects lead to communication between the skin surface and the subarachnoid space, which predisposes to thrombophlebitis of the diploic veins. Rarely, there is direct extension to the CNS from a contiguous otic focus (eg, otitis media).

Symptoms and Signs

Frequently, only those findings typical of neonatal sepsis (eg, temperature instability, respiratory distress, jaundice, apnea) are manifest. CNS signs (eg, lethargy, seizures [particularly focal], vomiting, irritability) more specifically suggest neonatal bacterial meningitis. So-called paradoxical irritability, in which cuddling and consoling by a parent irritates rather than comforts the neonate, is more specific for the diagnosis. A bulging or full fontanelle occurs in about 25% and nuchal rigidity in only 15%. The younger the patient, the less common are these findings. Cranial nerve abnormalities (particularly those involving the 3rd, 6th, and 7th nerves) may also be present.

Meningitis due to GBS may occur in the first week of life, accompanying early-onset neonatal sepsis and frequently manifesting initially as a systemic illness with prominent respiratory signs. Usually, however, GBS meningitis occurs after this period (most commonly in the first 3 mo of life) as an isolated illness characterized by absence of antecedent obstetric or perinatal complications and the presence of more specific signs of meningitis (eg, fever, lethargy, seizures).

Ventriculitis frequently accompanies neonatal bacterial meningitis, particularly when caused by gram-negative enteric bacilli. Organisms that cause meningitis together with severe vasculitis, particularly C. diversus and Enterobacter sakazaki, are likely to cause cysts and abscesses. Pseudomonas aeruginosa, E. coli K1, and Serratia sp also may cause brain abscesses. An early clinical sign of brain abscess is increased intracranial pressure (ICP), commonly manifested by vomiting, a bulging fontanelle, and sometimes enlarging head size. Deterioration in an otherwise stable neonate with meningitis suggests progressive increased ICP caused by abscess or hydrocephalus, or rupture of an abscess into
the ventricular system.

**Diagnosis**

- CSF glucose and protein levels, Gram stain, and culture
- Sometimes brain CT or MRI

Definitive diagnosis is made by CSF examination via lumbar puncture (LP), which should be done in any neonate suspected of having sepsis or meningitis. However, LP can be difficult to do in a neonate, and there is some risk of hypoxia. Poor clinical condition (eg, respiratory distress, shock, thrombocytopenia) makes LP risky. If LP is delayed, the neonate should be treated as though meningitis is present. Even when the clinical condition improves, the presence of inflammatory cells and abnormal electrolytes in CSF days after illness onset can still suggest the diagnosis. A needle with a trocar should be used for LP to avoid introducing epithelial rests and subsequent development of epitheliomas. The CSF, even if bloody or acellular, should be cultured. About 15 to 30% of neonates with negative blood cultures have positive CSF cultures depending on the population studied. LP should be repeated at 24 to 48 h if clinical response is questionable and at 72 h when gram-negative organisms are involved (to ensure sterilization). Repeating the CSF analysis helps guide duration of therapy and predict prognosis. Some experts believe that a repeat LP at 24 h in neonates with GBS meningitis has prognostic value. LP should not be repeated at the end of therapy if the neonate is doing well.

Normal CSF values are controversial and in part age-related. In general, both term infants and preterm infants without meningitis have ≤ 20 WBCs/μL (one fifth of which may be PMNs) in their CSF. CSF protein levels in the absence of meningitis are more variable; term infants have levels of < 100 mg/dL, whereas preterm infants have levels up to 150 mg/dL. CSF glucose levels in the absence of meningitis are > 75% of the serum value measured at the same time. These levels may be as low as 20 to 30 mg/dL (1.1 to 1.7 mmol/L).

Ventriculitis is suspected in a neonate not responding appropriately to antimicrobial therapy. The diagnosis is made when a ventricular puncture yields a WBC count greater than that from the LP, by a positive Gram stain or culture, or by increased ventricular pressure. When ventriculitis or brain abscess is suspected, an MRI or CT with contrast may aid diagnosis; dilated ventricles also confirm ventriculitis.

**Prognosis**

Without treatment, the mortality rate for neonatal bacterial meningitis approaches 100%. With treatment, prognosis is determined by birth weight, organism, and clinical severity. Mortality rate for gram-negative neonatal bacterial meningitis is 15 to 20%, and for gram-positive (eg, GBS) meningitis it is 6 to 10%. For organisms that cause vasculitis or brain abscess (necrotizing meningitis), the mortality rate may approach 75%. Neurologic sequelae (eg, hydrocephalus, hearing loss, intellectual disability) develop in 20 to 50% of infants who survive, with a poorer prognosis when gram-negative enteric bacilli are the cause.

Prognosis also depends partly on the number of organisms present in CSF at diagnosis. The duration of positive CSF cultures correlates directly with the incidence of complications. In general, CSF cultures from neonates with GBS are usually sterilized within the first 24 h of antimicrobial therapy. Those from gram-negative bacillary meningitis remain positive longer, with a median of 2 days.

GBS meningitis has a mortality rate significantly lower than that of early-onset GBS sepsis.

**Treatment**

- Empiric ampicillin plus gentamicin, cefotaxime, or both, followed by culture-specific drugs

**Empiric antibiotic therapy:** Initial empiric treatment depends on patient age and is still debated. Most experts recommend ampicillin plus an aminoglycoside, a 3rd-generation cephalosporin (eg, cefotaxime), or both. Ampicillin is active against organisms such as GBS, enterococci, and *Listeria*. Gentamicin provides synergy and added efficacy against these organisms and adequate gram-negative coverage.
Cephalosporins provide adequate gram-negative coverage but do not provide synergy with ampicillin for gram-positive organisms and may allow for some resistant organisms. Hospitalized neonates who previously received antibiotics (eg, for early-onset sepsis) may have resistant organisms; fungal disease may also be considered in a septic-appearing neonate after prolonged hospitalization. Ill neonates with hospital-acquired infection should initially receive vancomycin plus an aminoglycoside with or without a 3rd-generation cephalosporin. Antibiotics are adjusted when results of CSF culture and sensitivities are known. The results of the Gram stain should not change antibiotic therapy.

**Organism-specific antibiotic therapy:** The recommended initial treatment for GBS meningitis in neonates < 1 wk of age is penicillin G 100,000 to 150,000 units/kg IV q 8 h or ampicillin 100 mg/kg IV q 8 h, plus gentamicin 4 mg/kg IV once/day if the infant is 32 to 35 wk gestational age or 5 mg/kg IV once/day if the infant is > 35 wk gestational age. If clinical improvement occurs or sterilization of CSF is documented, gentamicin can be stopped.

For enterococci or *L. monocytogenes*, treatment is generally ampicillin plus gentamicin.

In gram-negative bacillary meningitis, treatment is difficult. The traditional regimen of ampicillin plus an aminoglycoside results in a 15 to 20% mortality rate, with a high rate of sequelae in survivors. A 3rd-generation cephalosporin (eg, cefotaxime) should be strongly considered in neonates with *proven* gram-negative meningitis (or sepsis) or those *convincingly* septic. If antibiotic resistance is a concern, both an aminoglycoside and a 3rd-generation cephalosporin may be used until sensitivities are known. However, except for initial empiric therapy, 3rd-generation cephalosporins are generally not used routinely, because certain gram-negative organisms are induced to produce β-lactamase, resulting in rapid development of resistance.

Parenteral therapy for gram-positive meningitis is given for a minimum of 14 days, and for complicated gram-positive or gram-negative meningitis, a minimum of 21 days.

**Adjunctive measures:** Because meningitis may be considered part of the continuum of neonatal sepsis, the adjunctive measures used in treating neonatal sepsis (see p. 2836) should also be used to treat neonatal meningitis. Corticosteroids are not used in treatment of neonatal meningitis. Patients should be closely monitored for neurologic complications during the first 2 yr of life.

**Neonatal Pneumonia**

Neonatal pneumonia is lung infection in a neonate. Onset may be within hours of birth and part of a generalized sepsis syndrome or after 7 days and confined to the lungs. Signs may be limited to respiratory distress or progress to shock and death. Diagnosis is by clinical and laboratory evaluation for sepsis. Treatment is initial broad-spectrum antibiotics changed to organism-specific drugs as soon as possible.

Pneumonia is the most common invasive bacterial infection after primary sepsis. Early-onset pneumonia is part of generalized sepsis that first manifests at or within hours of birth. Late-onset pneumonia usually occurs after 7 days of age, most commonly in neonatal ICUs among infants who require prolonged endotracheal intubation because of lung disease.

**Etiology**

Organisms are acquired from the maternal genital tract or the nursery. These organisms include gram-positive coccis (eg, groups A and B streptococci, *Staphylococcus aureus*) and gram-negative bacilli (eg, *Escherichia coli*, *Klebsiella* sp, *Proteus* sp). Methicillin-resistant *S. aureus* is common in late-onset hospital-acquired pneumonia. In infants who have received broad-spectrum antibiotics, many other pathogens may be found, including *Pseudomonas*, *Citrobacter*, *Bacillus*, and *Serratia*. Viruses or fungi cause some cases.

**Symptoms and Signs**

Late-onset hospital-acquired pneumonia may begin gradually, with more secretions being suctioned from
the endotracheal tube and higher ventilator settings. Other infants may be acutely ill, with temperature instability and neutropenia. New infiltrates may be visible on chest x-ray but may be difficult to recognize if the infant has severe bronchopulmonary dysplasia.

**Diagnosis**

Evaluation includes cultures of blood and tracheal aspirate, chest x-ray, and pulse oximetry. Because bacterial pneumonia in neonates may disseminate, a full evaluation for sepsis, including a lumbar puncture, should also be done.

**Treatment**

- Usually vancomycin and cefotaxime

Antimicrobial therapy in early-onset disease is similar to that for neonatal sepsis. Vancomycin and cefotaxime are the initial treatment of choice for most late-onset hospital-acquired pneumonia. This regimen treats sepsis as well as pneumonia. More specific antibiotics are substituted after sensitivity results are available. General treatment is the same as that for neonatal sepsis (see p. 2836).

**Chlamydial Pneumonia**

Contamination with chlamydial organisms during delivery may result in development of chlamydial pneumonia at 2 to 12 wk. Infants are tachypneic but usually not critically ill and may also have a history of conjunctivitis caused by the same organism. Eosinophilia may be present, and x-rays show bilateral interstitial infiltrates. Treatment with erythromycin leads to rapid resolution. The diagnosis of pneumonia secondary to *Chlamydia trachomatis* should prompt an evaluation of the mother and her partner because untreated maternal chlamydial infection may have complications such as pelvic inflammatory disease and sterility.

**Neonatal Sepsis**

*(Sepsis Neonatorum)*

(See also Ch. 227.)

Neonatal sepsis is invasive infection, usually bacterial, occurring during the neonatal period. Signs are multiple and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice. Diagnosis is clinical and based on culture results. Treatment is initially with ampicillin plus either gentamicin or cefotaxime, narrowed to organism-specific drugs as soon as possible.

Neonatal sepsis occurs in 0.5 to 8.0/1000 births. The highest rates occur in low-birth-weight (LBW) infants, those with depressed respiratory function at birth, those with maternal perinatal risk factors, males, and those with congenital anomalies.

**Etiology**

Neonatal sepsis can be early onset (within 7 days of birth) or late onset (after 7 days).

**Early onset:** Early-onset sepsis usually results from organisms acquired intrapartum. Most infants have symptoms within 6 h of birth, and almost all cases occur within 72 h.

Group B streptococcus (GBS) and gram-negative enteric organisms (predominantly *Escherichia coli*) account for most cases of early-onset sepsis. Vaginal or rectal cultures of women at term may show GBS colonization rates of up to 30%. At least 35% of their infants also become colonized. The density of infant colonization determines the risk of early-onset invasive disease, which is 40 times higher with heavy colonization. Although only 1/100 of infants colonized develop invasive disease due to GBS, > 50% of
those present within the first 6 h of life. Nontypeable *Haemophilus influenzae* sepsis has been increasingly identified in neonates, especially premature neonates.

Other gram-negative enteric bacilli (eg, *Klebsiella* sp) and gram-positive organisms—*Listeria monocytogenes*, enterococci (eg, *Enterococcus faecalis, Enterococcus faecium*), group D streptococci (eg, *Streptococcus bovis*), α-hemolytic streptococci, and staphylococci—account for most other cases. *Streptococcus pneumoniae, H. influenzae* type b, and, less commonly, *Neisseria meningitidis* have been isolated. Asymptomatic gonorrhea occurs occasionally in pregnancy, so *Neisseria gonorrhoeae* may be a pathogen.

**Late onset:** Late-onset sepsis is usually acquired from the environment (see also Neonatal Hospital-Acquired Infection on p. 2828). Staphylococci account for 30 to 60% of late-onset cases and are most frequently due to intravascular devices (particularly umbilical artery or vein catheters). *E. coli* is also becoming increasingly recognized as a significant cause of late-onset sepsis, especially in very LBW infants. Isolation of *Enterobacter cloacae* or *E. sakazakii* from blood or CSF suggests contaminated feedings. Contaminated respiratory equipment is suspected in outbreaks of hospital-acquired *Pseudomonas aeruginosa* pneumonia or sepsis. Although universal screening and intrapartum antibiotic prophylaxis for GBS have significantly decreased the rate of early-onset disease due to this organism, the rate of late-onset GBS sepsis has remained unchanged, which is consistent with the hypothesis that late-onset disease is usually acquired from the environment.

The role of anaerobes (particularly *Bacteroides fragilis*) in late-onset sepsis remains unclear, although deaths have been attributed to *Bacteroides* bacteremia. Anaerobes may account for some culture-negative cases in which autopsy findings indicate sepsis.

*Candida* sp are increasingly important causes of late-onset sepsis, occurring in 12 to 13% of very LBW infants.

**Early and late onset:** Certain viral infections (eg, disseminated herpes simplex, enterovirus, adenovirus, respiratory syncytial virus) may manifest as early-onset or late-onset sepsis.

**Pathophysiology**

**Early onset:** Certain maternal perinatal and obstetric factors increase risk, particularly of early-onset sepsis, such as the following:

- Premature rupture of membranes (PROM—see p. 2682) occurring ≥ 18 h before birth
- Maternal bleeding (eg, placenta previa, abruptio placentae)
- Preeclampsia
- Precipitous delivery
- Maternal infection (particularly of the urinary tract or endometrium, most commonly manifests as maternal fever shortly before or during delivery)
- Heavy colonization with GBS
- Preterm delivery

Hematogenous and transplacental dissemination of maternal infection occurs in the transmission of certain viral (eg, rubella, cytomegalovirus), protozoal (eg, *Toxoplasma gondii*), and treponemal (eg, *Treponema pallidum*) pathogens. A few bacterial pathogens (eg, *L. monocytogenes, Mycobacterium tuberculosis*) may reach the fetus transplacentally, but most are acquired by the ascending route in utero or as the fetus passes through the colonized birth canal.
Though the intensity of maternal colonization is directly related to risk of invasive disease in the neonate, many mothers with low-density colonization give birth to infants with high-density colonization who are therefore at risk. Amniotic fluid contaminated with meconium or vernix caseosa promotes growth of GBS and *E. coli*. Hence, the few organisms in the vaginal vault are able to proliferate rapidly after PROM, possibly contributing to this paradox. Organisms usually reach the bloodstream by fetal aspiration or swallowing of contaminated amniotic fluid, leading to bacteremia. The ascending route of infection helps to explain such phenomena as the high incidence of PROM in neonatal infections, the significance of adnexal inflammation (amnionitis is more commonly associated with neonatal sepsis than is central placentitis), the increased risk of infection in the twin closer to the birth canal, and the bacteriologic characteristics of neonatal sepsis, which reflect the flora of the maternal vaginal vault.

**Late onset:** The most important risk factor in late-onset sepsis is preterm delivery. Others include
- Prolonged use of intravascular catheters
- Associated illnesses (which may, however, be only a marker for the use of invasive procedures)
- Exposure to antibiotics (which selects resistant bacterial strains)
- Prolonged hospitalization
- Contaminated equipment or IV or enteral solutions

Gram-positive organisms (eg, coagulase-negative staphylococci and *Staphylococcus aureus*) may be introduced from the environment or the patient's skin. Gram-negative enteric bacteria are usually derived from the patient's endogenous flora, which may have been altered by antecedent antibiotic therapy or populated by resistant organisms transferred from the hands of personnel (the major means of spread) or contaminated equipment. Therefore, situations that increase exposure to these bacteria (eg, crowding, inadequate nurse staffing or provider hand washing) result in higher rates of hospital-acquired infection. Risk factors for *Candida* sp sepsis include prolonged (> 10 days) use of central IV catheters, hyperalimentation, use of antecedent antibiotics, necrotizing enterocolitis or other abdominal pathology, and previous surgery.

Initial foci of infection can be in the urinary tract, paranasal sinuses, middle ear, lungs, or GI tract, and may later disseminate to meninges, kidneys, bones, joints, peritoneum, and skin.

**Symptoms and Signs**

Early signs are frequently nonspecific and subtle and do not distinguish among organisms (including viral). Particularly common early signs include
- Diminished spontaneous activity
- Less vigorous sucking
- Apnea
- Bradycardia
- Temperature instability (hypothermia or hyperthermia)

Fever is present in only 10 to 15% but, when sustained (eg, > 1 h), generally indicates infection. Other symptoms and signs include respiratory distress, neurologic findings (eg, seizures, jitteriness), jaundice (especially occurring within the first 24 h without Rh or ABO blood group incompatibility and with a higher than expected direct bilirubin concentration), vomiting, diarrhea, and abdominal distention. Anaerobic infection is often indicated by foul-smelling amniotic fluid at birth.

Specific signs of an infected organ may pinpoint the primary site or a metastatic site.
• Most neonates with early-onset GBS (and many with *L. monocytogenes*) infection present with respiratory distress that is difficult to distinguish from respiratory distress syndrome.

• Periumbilical erythema, discharge, or bleeding without a hemorrhagic diathesis suggests omphalitis (infection prevents obliteration of the umbilical vessels).

• Coma, seizures, opisthotonos, or a bulging fontanelle suggests meningitis, encephalitis, or brain abscess.

• Decreased spontaneous movement of an extremity and swelling, warmth, erythema, or tenderness over a joint indicates osteomyelitis or pyogenic arthritis.

• Unexplained abdominal distention may indicate peritonitis or necrotizing enterocolitis (particularly when accompanied by bloody diarrhea and fecal leukocytes).

• Cutaneous vesicles, mouth ulcers, and hepatosplenomegaly (particularly with disseminated intravascular coagulation [DIC]) can identify disseminated herpes simplex.

Early-onset GBS infection may manifest as a fulminating pneumonia. Often, obstetric complications (particularly prematurity, PROM, or chorioamnionitis) have occurred. In > 50% of neonates, GBS infection manifests within 6 h of birth; 45% have an Apgar score of < 5. Meningitis may also be present but is not common. In late-onset GBS infection (at 1 to 12 wk), meningitis is often present. Late-onset GBS infection is generally not associated with perinatal risk factors or demonstrable maternal cervical colonization and may be acquired postpartum.

**Diagnosis**

• High index of suspicion

• Blood, urine, and CSF culture

Early diagnosis is important and requires awareness of risk factors (particularly in LBW neonates) and a high index of suspicion when any neonate deviates from the norm in the first few weeks of life. Neonates with suspected sepsis, and those whose mother was thought to have chorioamnionitis, should have a CBC, differential with smear, platelet count, blood culture, urine culture, and lumbar puncture (LP), if clinically feasible, as soon as possible. Those with respiratory symptoms require chest x-ray. Diagnosis is confirmed by isolation of a pathogen in culture. Other tests may have abnormal results but are not necessarily diagnostic.

For preterm neonates who appear well but whose mother received inadequate intrapartum antibiotics for GBS, the American Academy of Pediatrics recommends a limited evaluation (CBC and blood culture with at least a 48-h observation).

**CBC, differential, and smear:** The normal WBC count in neonates varies, but values < 4,000/µL or > 25,000/µL are abnormal. The absolute band count is not sensitive enough to predict sepsis, but a ratio of immature:total polymorphonuclear leukocytes of < 0.2 has a high negative predictive value. A precipitous fall in a known absolute eosinophil count and morphologic changes in neutrophils (eg, toxic granulation, Dohle bodies, intracytoplasmic vacuolization in noncitrated blood or ethylenediaminetetraacetic acid [EDTA]) suggest sepsis.

The platelet count may fall hours to days before the onset of clinical sepsis but more often remains elevated until a day or so after the neonate becomes ill. This fall is sometimes accompanied by other findings of DIC (eg, increased fibrin degradation products, decreased fibrinogen, prolonged INR).

Because of the large numbers of circulating bacteria, organisms can sometimes be seen in or associated with PMNs by applying Gram stain, methylene blue, or acridine orange to the buffy coat.
Regardless of the results of the CBC or LP, in all neonates with suspected sepsis (eg, those who look sick or are febrile or hypothermic), antibiotics should be started after cultures (eg, blood, urine, and CSF [if possible]) are taken.

**Lumbar puncture:** There is a risk of increasing hypoxia during an LP in already hypoxemic neonates. However, LP should be done in neonates with suspected sepsis as soon as they are able to tolerate the procedure (see also p. 2830 under Neonatal Bacterial Meningitis). Supplemental O\textsubscript{2} is given before and during LP to prevent hypoxia. Because GBS pneumonia manifesting in the first day of life can be confused with respiratory distress syndrome, LP is often done routinely in neonates suspected of having these diseases.

**Blood cultures:** Umbilical vessels are frequently contaminated by organisms on the umbilical stump, especially after a number of hours, so blood cultures from umbilical lines may not be reliable. Therefore, blood for culture should be obtained by venipuncture, preferably at 2 peripheral sites, each meticulously prepared by applying an iodine-containing liquid, then applying 95% alcohol, and finally allowing the site to dry. Blood should be cultured for both aerobic and anaerobic organisms. If catheter-associated sepsis is suspected, a culture specimen should be obtained through the catheter as well as peripherally. In > 90% of positive bacterial blood cultures, growth occurs within 48 h of incubation. Because bacteremia in neonates is associated with a high density of organisms and delayed clearance, a small amount of blood (eg, ≥ 1 mL) is usually sufficient for detecting organisms. Data on capillary blood cultures are insufficient to recommend them.

*Candida* sp grow in blood cultures and on blood agar plates, but if other fungi are suspected, a fungal culture medium should be used. For species other than *Candida*, fungal blood cultures may require 4 to 5 days of incubation before becoming positive and may be negative even in obviously disseminated disease. Proof of colonization (in mouth or stool or on skin) may be helpful before culture results are available. If disseminated candidiasis is suspected, indirect ophthalmoscopy with dilation of the pupils is done to identify retinal candidal lesions. Renal ultrasonography is done to detect renal mycetoma.

**Urinalysis and culture:** Urine should be obtained by catheterization or suprapubic aspiration, not by urine collection bags. Although only culture is diagnostic, a finding of ≥ 5 WBCs/high-power field in the spun urine or any organisms in a fresh unspun gram-stained sample is presumptive evidence of a UTI. Absence of pyuria does not rule out UTI.

**Other tests for infection and inflammation:** Numerous tests are often abnormal in sepsis and have been evaluated as possible early markers. In general, however, sensitivities tend to be low until later in illness, and specificities are suboptimal.

Acute-phase reactants are proteins produced by the liver under the influence of IL-1 when inflammation is present. The most valuable of these is quantitative C-reactive protein. A concentration of 1 mg/dL (measured by nephelometry) has both a false-positive and a false-negative rate of about 10%. Elevated levels occur within a day, peak at 2 to 3 days, and fall to normal within 5 to 10 days in neonates who recover.

The ESR is often elevated in sepsis. The micro-ESR correlates well with the standard Wintrobe method but has the same high false-negative rate (especially early in the course and with DIC) and a slow return to normal, well beyond the time of clinical cure. IL-6 and other inflammatory cytokines are being investigated as markers for sepsis.

**Prognosis**

The fatality rate is 2 to 4 times higher in LBW infants than in full-term infants. The overall mortality rate of early-onset sepsis is 3 to 40% (that of early-onset GBS infection is 2 to 30%) and of late-onset sepsis is 2 to 20% (that of late-onset GBS is about 2%). More recent studies have shown lower mortality rates.

Neonates who are both septic and granulocytopenic are less likely to survive, particularly if their bone marrow neutrophil storage pool (NSP) is depleted to < 7% of total nucleated cells (mortality rate, 75%). Because NSP levels may not be readily available, the peripheral blood immature:total (I:T) neutrophil ratio
can approximate bone marrow NSP levels. I:T ratios of > 0.80 correlate with NSP depletion and death; such a ratio may identify neonates who might benefit from granulocyte transfusion.

**Treatment**

- **Antibiotic therapy**
- **Supportive therapy**

Because sepsis may manifest with non-specific clinical signs and its effects may be devastating, rapid empiric antibiotic therapy is recommended (see p. 1182); drugs are later adjusted according to sensitivities and the site of infection. If bacterial cultures show no growth by 48 h (although some pathogens may require 72 h) and the neonate appears well, antibiotics are stopped.

General supportive measures, including respiratory and hemodynamic management, are combined with antibiotic treatment.

**Antimicrobials:** In early-onset sepsis, initial therapy should include ampicillin or penicillin G plus an aminoglycoside. Cefotaxime may be added to or substituted for the aminoglycoside if meningitis is suspected. If foul-smelling amniotic fluid is present at birth, therapy for anaerobes (eg, clindamycin, metronidazole) should be added. Antibiotics may be changed as soon as an organism is identified.

Previously well infants admitted from the community with presumed late-onset sepsis should also receive therapy with ampicillin plus gentamicin or ampicillin plus cefotaxime. If gram-negative meningitis is suspected, ampicillin, cefotaxime, and an aminoglycoside may be used. In late-onset hospital-acquired sepsis, initial therapy should include vancomycin (active against methicillin-resistant *S. aureus*) plus an aminoglycoside. If *P. aeruginosa* is prevalent in the nursery, ceftazidime may be used instead of an aminoglycoside. For neonates previously treated with a full 7- to 14-day aminoglycoside course who need retreatment, a different aminoglycoside or a 3rd-generation cephalosporin should be considered.

If coagulase-negative staphylococci are suspected (eg, an indwelling catheter has been in place for > 72 h) or are isolated from blood or other normally sterile fluid and considered a pathogen, initial therapy for late-onset sepsis should include vancomycin. However, if the organism is sensitive to nafcillin, cefazolin or nafillin should replace vancomycin. Removal of the presumptive source of the organism (usually an indwelling intravascular catheter) may be necessary to cure the infection because coagulase-negative staphylococci may be protected by a biofilm (a covering that encourages adherence of organisms to the catheter).

Because *Candida* may take 2 to 3 days to grow in blood culture, initiation of amphotericin B therapy and removal of the infected catheter without positive blood or CSF cultures may be life saving.

**Other treatment:** Exchange transfusions have been used for severely ill (particularly hypotensive and metabolically acidic) neonates. Their purported value is to increase levels of circulating immunoglobulins, decrease circulating endotoxin, increase Hb levels (with higher 2,3-diphosphoglycerate levels), and improve perfusion. However, no controlled prospective studies of their use have been conducted.

Fresh frozen plasma may help reverse the heat-stable and heat-labile opsonin deficiencies that occur in LBW neonates, but controlled studies of its use are unavailable, and transfusion-associated risks must be considered.

Granulocyte transfusions (see p. 1039) have been used in septic and granulocytopenic neonates but have not convincingly improved outcome.

Recombinant colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF])

[Fig. 279-1. Indications for intrapartum antibiotic prophylaxis to prevent perinatal group B streptococcal]
disease.

and granulocyte-macrophage colony-stimulating factor (GM-CSF)) have increased neutrophil number and function in neonates with presumed sepsis but do not seem to be of routine benefit in neonates with severe neutropenia; further study is required.

Prevention

IV immune globulin given at birth may prevent sepsis in certain high-risk LBW infants but does not help in established infection.

Because invasive disease due to GBS often manifests within the first 6 h of life, women who have previously given birth to an infant with GBS disease should receive intrapartum antibiotics, and women who have symptomatic or asymptomatic GBS bacteriuria during pregnancy should receive antibiotics at the time of diagnosis and intrapartum (see Fig. 279-1).

Perinatal Tuberculosis

(See also Tuberculosis on p. 1302.)

Tuberculosis (TB) can be acquired during the perinatal period. Symptoms and signs are nonspecific. Diagnosis is by culture and sometimes x-ray and biopsy. Treatment is with isoniazid and other antituberculous drugs.

Infants may acquire TB by the following means:

- Transplacental spread through the umbilical vein to the fetal liver
- Aspiration or ingestion of infected amniotic fluid
- Airborne inoculation from close contacts (family members or nursery personnel)

About 50% of children born to mothers with active pulmonary TB develop the disease during the first year of life if chemoprophylaxis or BCG vaccine is not given.

Symptoms and Signs

The clinical presentation of neonatal TB is nonspecific but is usually marked by multiple organ involvement. The neonate may look acutely or chronically ill and may have fever, lethargy, respiratory distress, hepatosplenomegaly, or failure to thrive.

Diagnosis

- Culture of tracheal aspirate, gastric washings, urine, and CSF
- Chest x-ray
- Sometimes skin testing

All neonates with suspected congenital TB and infants born to mothers who have active TB should have a chest x-ray and culture of tracheal aspirates, gastric washings, urine, and CSF for acid-fast bacilli; the placenta should be examined and cultured as well. Skin testing is not extremely sensitive, particularly initially, but should be done. Biopsy of the liver, lymph nodes, lungs, or pleurae may be needed to confirm the diagnosis.

Well-appearing neonates whose mothers have a positive skin test but a negative chest x-ray and no evidence of active disease should have close follow-up and evaluation of all household members. If there is no exposure to a case of active TB, the neonate does not need treatment or testing. If significant
exposure to a case of active TB is found in the neonate's environment after birth, the neonate should be evaluated for suspected congenital TB as described previously. If the neonate is well and active and disease is reasonably excluded by the chest x-ray and physical examination, the neonate should begin treatment with isoniazid (INH) 10 mg/kg po once/day. Further follow-up and management is then identical to that for an asymptomatic neonate born to a woman with active TB (see p. 2839), including a skin test at age 3 or 4 mo.

**Treatment**

- INH for positive skin test or high-risk exposure
- Addition of other drugs (eg, rifampin, ethambutol, pyridoxine, pyrazinamide, an aminoglycoside) if TB is present

Management depends on the whether there is active TB or only a positive skin test (in mother, infant, or both).

**Pregnant women with a positive tuberculin test:** Women are evaluated for active TB. Because the hepatotoxicity of INH is increased in pregnancy, and because the risk of contracting TB from a mother with a positive tuberculin test is greater for the neonate than for the fetus, INH use may be deferred until after the postpartum period unless the woman has active TB or recent contact with a person with contagious TB (in which case the benefit outweighs the risk). Treatment is given for 9 mo, along with supplemental pyridoxine. Treatment for a pregnant woman exposed to contagious TB should be deferred until the 1st trimester is complete.

**Neonates with a positive tuberculin test:** If there is no clinical or x-ray evidence of disease, the infant should receive INH 10 mg/kg po once/day for 9 mo and should be closely monitored.

**Pregnant women with active TB:** INH, ethambutol, and rifampin use in recommended doses during pregnancy has not been shown to be teratogenic to the human fetus. The recommended initial treatment regimen in the US includes INH 300 mg po, ethambutol 15 to 25 mg/kg po, and rifampin 600 mg po. All pregnant and breastfeeding women receiving INH should also receive pyridoxine 25 mg po. All these drugs can be given once/day. The recommended duration of therapy is at least 9 mo; if the organism is drug-resistant, an infectious disease consultation is recommended, and therapy may need to be extended to 18 mo. Streptomycin is potentially ototoxic to the developing fetus and should not be used early in pregnancy unless rifampin is contraindicated. If possible, other antituberculous drugs should be avoided because of teratogenicity (eg, ethionamide) or lack of clinical experience during pregnancy. Breastfeeding is not contraindicated for mothers receiving therapy who are not infective.

Patients with active TB should be reported to the local health department. Mothers with active TB should be tested for HIV.

**Asymptomatic neonates of women with active TB:** The neonate usually is separated from the mother only until effective treatment of both mother and neonate is under way. Once the neonate is receiving INH, separation is not necessary unless the mother (or household contact) has possible multidrug-resistant organisms or poorly adheres to treatment (including not wearing a mask if TB is active) and directly observed therapy is not possible. Family contacts should be investigated for undiagnosed TB before the infant goes home.

If adherence can be reasonably assured and the family is nontuberculous (ie, the mother is being treated and no other transmission risks are present), the neonate is started on a regimen of INH 10 mg/kg po once/day and sent home at the usual time. Skin testing should be done at age 3 or 4 mo. If the neonate is tuberculin-negative, INH is stopped. If the skin test is positive, chest x-ray and cultures for acid-fast bacilli are done as described previously and, if active disease is excluded, treatment with INH is continued for a total of 9 mo. If cultures become positive for TB at any time, the neonate should be treated for TB.

If adherence in a nontuberculous environment cannot be ensured, BCG vaccine may be considered for the neonate, and INH therapy should be started as soon as possible. (Although INH inhibits the
multiplication of BCG organisms, the combination of BCG vaccine and INH is supported by clinical trials and anecdotal reports.) BCG vaccination does not ensure against exposure to and development of TB, but offers significant protection against serious and widespread invasion (eg, tuberculous meningitis). BCG should only be given if skin testing of the neonate is negative. Neonates should be monitored for development of TB, particularly during the first year. (CAUTION: BCG vaccine is contraindicated in immunosuppressed patients and those suspected of being infected with HIV. However, in high-risk populations, the WHO recommends that asymptomatic HIV-infected neonates receive BCG vaccine at birth or shortly thereafter.)

Neonates with active TB: For congenital TB, the American Academy of Pediatrics recommends treatment once/day with INH 10 to 15 mg/kg po, rifampin 10 to 20 mg/kg po, pyrazinamide 30 to 40 mg/kg po, and an aminoglycoside (eg, amikacin or streptomycin). This regimen should be modified as indicated based on results of testing for resistance.

For TB acquired after birth, the suggested regimen is treatment once/day with INH 10 to 15 mg/kg po, rifampin 10 to 20 mg/kg po, and pyrazinamide 30 to 40 mg/kg. A fourth drug such as ethambutol 20 to 25 mg/kg once/day or an aminoglycoside should be added if drug resistance or tuberculous meningitis is suspected. After the first 2 mo of treatment, INH and rifampin are continued to complete a 6- to 12-mo course (depending on disease category) and other drugs are stopped. Breastfed infants should also receive pyridoxine supplementation.

When the CNS is involved, initial therapy also includes corticosteroids (prednisone 2 mg/kg po once/day for 4 to 6 wk, then gradually tapered). Other therapy continues until all signs of meningitis have disappeared and cultures are negative on 2 successive lumbar punctures at least 1 wk apart. Therapy can then be continued with INH and rifampin once/day or twice/wk for another 10 mo. Corticosteroids may also be considered for infants and children with severe miliary disease, pleural or pericardial effusions, endobronchial disease, or those with abdominal TB.

TB in infants and children that is not congenitally acquired or disseminated; does not involve the CNS, bones, or joints; and results from drug-susceptible organisms can be treated effectively with a 6- to 9-mo (total) course of therapy. Organisms recovered from the child or mother should be tested for drug sensitivity. Hematologic, hepatic, and otologic symptoms should be monitored frequently to determine response to therapy and drug toxicity. Frequent laboratory analysis is not usually necessary.

Directly observed therapy is used whenever possible to improve adherence and the success of therapy. Many anti-TB drugs are not available in pediatric dosages. When possible, experienced personnel should give these drugs to children.

Prevention

Routine neonatal BCG vaccination is not routinely indicated in developed countries but may curb the incidence of childhood TB or decrease its severity in populations at increased risk of infection.
Chapter 280. Miscellaneous Infections in Infants and Children

Introduction

Infants and young children develop infections more frequently than do adults and older children. Infections may be present at birth (see p. 2811) but are more typically contracted afterward. A child's immune system is neither as mature nor as responsive as an adult's, perhaps because of hyporesponsiveness to T-cell-independent antigens, lower immunoglobulin concentrations, a greater proportion of naive T and B cells compared to memory lymphocytes, or other factors. Children also are exposed to more pathogens from peers in day care centers or school.

Many infectious illnesses that affect infants and children also occur in adults and are discussed elsewhere in THE MANUAL.

Erythema Infectiosum

(Eighth Disease; Parovirus B19 Infection)

Erythema infectiosum, acute infection with parvovirus B19, causes mild constitutional symptoms and a blotchy or maculopapular rash beginning on the cheeks and spreading primarily to exposed extremities. Diagnosis is clinical, and treatment is generally not needed.

The disease is caused by human parvovirus B19. It occurs mostly during the spring, commonly causing localized outbreaks every few years among children (particularly children 5 to 7 yr). Spread seems to be by respiratory droplets, with high rates of secondary infection among household contacts; infection can occur without symptoms or signs.

Pathophysiology

Parvovirus B19 causes transient suppression of erythropoiesis that is mild and asymptomatic except in children with underlying hemoglobinopathies (eg, sickle cell disease) or other RBC disorders (eg, hereditary spherocytosis), who may develop transient aplastic crisis. Also, immunocompromised children can develop protracted viremia (lasting weeks to months), leading to severe anemia (pure RBC aplasia).

Erythema infectiosum can be transmitted transplacentally, sometimes resulting in stillbirth or severe fetal anemia with widespread edema (hydrops fetalis). However, about half of pregnant women are immune because of previous infection. The risk of fetal death is 5 to 9% after maternal infection, with risk greatest during the 2nd trimester.

Symptoms and Signs

The incubation period is 4 to 14 days. Typical initial manifestations are nonspecific flu-like symptoms (eg, low-grade fever, slight malaise). Several days later, an indurated, confluent erythema appears over the cheeks ("slapped-cheek" appearance) and a symmetric rash appears that is most prominent on the arms, legs, and trunk, usually sparing the palms and soles. The rash is maculopapular, tending toward confluence; it forms reticular or lacy patterns of slightly raised, blotchy areas with central clearing, usually most prominent on exposed areas. The rash, and the entire illness, generally lasts 5 to 10 days. However, the rash may recur for several weeks, exacerbated by sunlight, exercise, heat, fever, or emotional stress. Mild joint pain and swelling (nonerosive arthritis) that may persist or recur for weeks to months sometimes occurs in adults.

Diagnosis

• Clinical evaluation

The appearance and pattern of spread of the rash are the only diagnostic features; however, some enteroviruses may cause similar rashes. Rubella can be ruled out by serologic testing; an exposure history is also helpful. Serologic testing is not required in otherwise healthy children; however, in children...
with transient aplastic crisis or adults with arthropathy, the presence of IgM-specific antibody to parvovirus B19 in the late acute or early convalescent phase strongly supports the diagnosis. Parvovirus B19 viremia also can be detected by quantitative PCR techniques, which are generally used for patients with transient aplastic crisis, immunocompromised patients with pure RBC aplasia, and infants with hydrops fetalis or congenital infection.

**Treatment**

Only symptomatic treatment is needed. IV immune globulin has been used to curtail viremia and increase erythropoiesis in immunocompromised children with pure RBC aplasia.

**Occult Bacteremia**

Occult bacteremia is the presence of bacteria in the bloodstream of febrile young children who have no apparent foci of infection and look well. Diagnosis is by blood culture and exclusion of focal infection. Treatment is with antibiotics, either in the hospital or as outpatients; select children are treated pending blood culture results.

About 3% (range 2 to 10%) of children aged 1 to 36 mo with a febrile illness (temperature ≥ 39° C) and no localizing abnormalities have bacteremia, which is hence considered occult. Of these, about 5 to 10% develop focal bacterial infections (eg, septic arthritis, osteomyelitis, meningitis) or sepsis (see pp. 2299 and 2832), which could be minimized by early identification and treatment of the bacteremia. The likelihood of progression to serious focal illness depends on the cause: 7 to 25% for *Haemophilus influenzae* type b (Hib) bacteremia but 4 to 6% for *Streptococcus pneumoniae* bacteremia. For further discussion of fever in infants and children, see p. 2741.

**Organisms:** In the 1980s, 80% of occult bacteremia cases were caused by *S. pneumoniae*. The remainder was caused by Hib (10%), *Neisseria meningitidis* (5%), and others (predominantly *Staphylococcus aureus* and *Salmonella* sp). In the US, since the 1990s, routine Hib conjugate vaccination in infancy essentially eliminated Hib bacteremia. More recent routine use of the *S. pneumoniae* conjugate vaccine in infancy has reduced invasive pneumococcal disease in young children by > 66%, and increased use is expected to essentially eliminate the problem. Some meningococcal conjugate vaccines also have proved effective in this age group, so that in the future occult bacteremia may be largely preventable.

**Symptoms and Signs**

The major symptom is fever (temperature ≥ 38° C). By definition, children with apparent focal disease (eg, cough, dyspnea, and pulmonary crackles suggesting pneumonia; skin erythema suggesting cellulitis or septic arthritis) are excluded. A toxic appearance (eg, limpness and listlessness, lethargy, signs of poor perfusion, cyanosis, marked hypoventilation or hyperventilation) suggests sepsis or septic shock; bacteremia in such children is not classified as occult. However, early sepsis can be difficult to distinguish from occult bacteremia.

**Diagnosis**

- Blood culture

Diagnosis requires blood culture. Ideally, two samples are taken (from separate sites, which helps minimize the problem of false positives due to skin contaminants), with results available within 24 h. CBC, urinalysis, and examination of the stool for leukocytes (if diarrhea is present) are done in select patients to identify specific infections and help stratify risk. Lumbar puncture for CSF analysis is done in toxic-appearing infants < 3 mo; some experts do lumbar puncture in all febrile infants < 28 days regardless of their appearance.

Recommendations regarding selection of febrile children for testing and choice of tests vary with age, temperature, and clinical appearance (see Figs. 280-1 and...
the goal is to minimize testing without missing bacteremia. These algorithms are sensitive but relatively nonspecific. Thus, given the relatively low incidence of occult bacteremia in the population of febrile children, the algorithms have high negative predictive value but low positive predictive value (see p. 3391), making them much more effective in identifying children at low risk of infection who can be treated expectantly (bacteremia ruled-out) rather than in identifying children with true bacteremia.

CBC usually shows an elevated WBC count; however, only about 10% of children with WBC counts of > 15,000/μL are bacteremic, so specificity is low. Acute-phase reactants (eg, ESR, C-reactive protein) are used by some clinicians but add little information; however, in combination with elevated procalcitonin levels, acute-phase reactants may be more specific for serious illness. In children < 3 mo, band counts > 1500/μL and either low (< 5000/μL) or high (> 15,000/μL) WBC counts may indicate bacteremia.

Treatment

• Antibiotics (for those with positive cultures and for select patients pending culture results)

Children who receive antibiotics before bacteremia is confirmed by blood culture seem less likely to develop focal infections, although data are inconsistent. However, because of the low overall incidence of bacteremia, many children would receive unnecessary treatment if all who were tested were empirically treated. One common system for management before culture results (see Figs. 280-1 and 280-2) minimizes antibiotic use in most febrile infants and children who do not have serious bacterial infection and provides antibiotics promptly to the few who need them. Nevertheless, some authorities prefer to hospitalize all febrile infants < 1 to 2 mo of age and give parenteral antibiotics (eg, ceftriaxone) pending results of blood, urine, and CSF cultures.

All children are reexamined in 24 to 48 h. Those with persistent fever or positive blood or urine cultures have more cultures done and are hospitalized for evaluation of possible sepsis and parenteral antibiotic therapy. Children who are afebrile and well but have S. pneumoniae in their initial blood culture or an initial positive urine culture receive appropriate oral antibiotics (see elsewhere in THE MANUAL).

Urinary Tract Infection

Urinary tract infection (UTI) is defined by ≥ 5 × 10^4 colonies/mL in a catheterized urine specimen or, in older children, by repeated voided specimens with ≥ 10^5 colonies/mL. In younger children, UTIs are frequently caused by anatomic abnormalities. UTI may cause fever, failure to thrive, flank pain, and signs of sepsis, especially in young children. Treatment is with antibiotics. Follow-up imaging studies of the urinary tract are done.

UTI may involve the kidneys, bladder, or both. Sexually transmitted infections of the urethra (eg, gonococcal or chlamydial urethritis), although involving the urinary tract, are not typically termed UTI.

Mechanisms that maintain the normal sterility of the urinary tract include urine acidity and free flow, a normal emptying mechanism, intact ureterovesical and urethral sphincters, and immunologic and mucosal barriers. Abnormality of any of these mechanisms predisposes to UTI.

Etiology

By age 6 yr, 3 to 7% of girls and 1 to 2% of boys have had a UTI. The peak age of UTI is bimodal, with one peak in infancy and the other peak between ages 2 to 4 yr (at the time of toilet training for many children). The female: male ratio ranges from 1:1 to 1:4 in the first 2 mo of life (estimates vary, likely because of different proportions of uncircumcised males in study groups and the exclusion of infants with
urologic anomalies now more commonly diagnosed in utero by prenatal ultrasonography). The female:male ratio quickly rises with age, being about 2:1 between 2 mo to 1 yr, 4:1 during the 2nd yr, and > 5:1 after 4 yr. In girls, infections usually are ascending and less often cause bacteremia. The marked female preponderance beyond infancy is attributed both to the shorter female urethra and male circumcision.

Predisposing factors include malformations and obstructions of the urinary tract, prematurity, indwelling catheters, and lack of circumcision. Other predisposing factors in younger children include constipation and Hirschsprung’s disease. Risk factors in older children include diabetes, trauma, and, in adolescent females, sexual intercourse.

Urinary tract abnormalities: UTIs in children are a marker of possible urinary tract abnormalities (eg, obstruction, neurogenic bladder, ureteral duplication); these abnormalities are particularly likely to result in infection if vesicoureteral reflux (VUR—see also p. 2984) is present. The likelihood of VUR varies inversely with age at the first UTI. About 30 to 40% of infants and toddlers with UTI have VUR. Severity of reflux may determine the probability of subsequent hypertension and renal failure (caused by repeated infection and chronic pyelonephritis), but proof is lacking (see p. 2847). VUR is classified by grade (see Table 280-1).

Organisms: Many organisms cause infection in anatomically abnormal urinary tracts.

In relatively normal urinary tracts, the most common pathogens are strains of *Escherichia coli* with specific attachment factors for transitional epithelium of the bladder and ureters. *E. coli* causes > 75% of UTIs in all pediatric age groups. The remaining causes are other gram-negative enterobacteria, especially *Klebsiella*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Enterococci (group D streptococci) and coagulase-negative staphylococci (eg, *Staphylococcus saprophyticus*) are the most frequently implicated gram-positive organisms. Fungi and mycobacteria are rare causes, mainly in immunocompromised hosts. Adenoviruses rarely cause UTIs, and when they do, the disorder is predominantly hemorrhagic cystitis.

Symptoms and Signs

In neonates, symptoms and signs are non-specific and include poor feeding, diarrhea, failure to thrive, vomiting, mild jaundice, lethargy, fever, and hypothermia. Neonatal sepsis (see p. 2832) may develop.

Infants and toddlers may also present with poorly localizing signs, such as fever, GI symptoms (eg, vomiting, diarrhea, abdominal pain), or foul-smelling urine.

In children > 2 yr, the more classic picture of cystitis or pyelonephritis can occur. Symptoms of cystitis include dysuria, frequency, hematuria, urinary retention, suprapubic pain, urgency, pruritus, incontinence, foul-smelling urine, and enuresis. Symptoms of pyelonephritis include high fever, chills, and costovertebral pain and tenderness.

Physical findings suggesting associated urinary tract abnormalities include abdominal masses, enlarged kidneys, abnormality of the urethral orifice, and signs of lower spinal malformations. Diminished force of the urinary stream may be the only clue to obstruction or neurogenic bladder.

Diagnosis

- Urine analysis and culture
- Often urinary tract imaging

Urine tests: Diagnosis requires culture showing significant bacteriuria in properly collected urine. Most clinicians obtain urine by transurethral catheterization in infants and young children, reserving suprapubic
aspiration of the bladder for boys with moderate to severe phimosis. Both procedures require technical expertise, but catheterization is less invasive, slightly safer, and has sensitivity of 95% and specificity of 99% compared with suprapubic aspiration. Bagged specimens are unreliable and should not be used for diagnosis.

If urine is obtained by suprapubic aspiration, the presence of any bacteria is significant. In a catheterized specimen, \( \geq 5 \times 10^4 \) colonies/mL commonly defines UTI. Clean-catch, midstream-voided specimens are significant when colony counts of a single pathogen (ie, not the total count of mixed flora) are \( \geq 10^5 \) colonies/mL. However, at times symptomatic children may have UTI despite lower colony counts on urine cultures. Urine should be examined and cultured as soon as possible or stored at 4° C if a delay of > 10 min is expected. Occasionally, UTI may be present despite colony counts lower than the described guidelines, possibly because of prior antibiotic therapy, very dilute urine (sp gr < 1.003), or obstruction to the flow of grossly infected urine. Sterile cultures generally rule out UTI unless the child is receiving antibiotics or the urine is contaminated with antibacterial skin-cleaning agents.

**Microscopic examination** of urine is useful but not definitive. Pyuria (> 5 to 10 WBCs/high-power field in spun urine sediment) is about 70% sensitive for UTI. A WBC count (using a hemocytometer) > 10/\( \mu \)L in unspun urine has greater sensitivity (90%) but is not used by many laboratories. Presence of bacteria on Gram stain of spun or unspun urine is about 80% sensitive. Specificity of microscopy also is about 80%.

**Dipstick tests** on urine to detect bacteria (nitrite test) or leukocytes (leukocyte esterase test) are typically done; if either is positive, the diagnostic sensitivity for UTI is about 93%. The specificity of the nitrite test is quite high; a positive result on a freshly voided specimen is highly predictive of UTI. Specificity of leukocyte esterase is much lower.

Differentiating an upper UTI from a lower UTI can be difficult. High fever, costovertebral angle tenderness, and gross pyuria with casts indicate pyelonephritis. However, many children without these symptoms and signs have an upper UTI. Tests to distinguish upper infection from lower infection are not indicated in most clinical settings, because treatment is not altered.

**Blood tests:** A CBC and tests for inflammation (eg, ESR, C-reactive protein) may help diagnose infection in children with borderline urine findings. Some authorities measure serum BUN and creatinine during a first UTI. Blood cultures are appropriate for infants with UTIs and for children > 1 to 2 yr who appear toxic.

**Urinary tract imaging:** Many major renal or urologic anomalies now are diagnosed in utero by routine prenatal ultrasonography. However, the high incidence of anatomic anomalies still warrants imaging the urinary tracts of all children 2 mo to 2 yr of age after a first UTI. If a first UTI occurs at \( \geq 2 \) yr, most authorities recommend imaging; however, some physicians postpone imaging until after a second UTI in girls > 2 yr. Options include voiding cystourethrogram (VCUG), radionuclide cystogram (RNC) with technetium-99m pertechnetate, and ultrasonography.

VCUG and RNC are better than ultrasonography for detecting VUR and anatomic abnormalities. RNC delivers about 1% of the gonadal radiation of VCUG; it is sensitive in detecting VUR, and some recommend it as the initial test. However, most authorities prefer the better anatomic definition of contrast VCUG as the initial test, using RNC in follow up to determine when VUR has resolved. Low-dose x-ray equipment has narrowed the gap in radiation between the contrast VCUG and RNC. These tests are recommended at the earliest convenient time after clinical response, typically toward the end of therapy, when bladder reactivity has resolved and urine sterility has been regained. If imaging is not scheduled until after therapy is due to be completed, the child should continue antibiotics at prophylactic doses until VUR is excluded.

Ultrasonography helps exclude obstruction and hydronephrosis and is typically done within a week of diagnosing UTI in infants, especially if they do not respond quickly to antimicrobials. Otherwise, ultrasonography can be delayed until VCUG is done.

**Prognosis**
Properly managed children rarely progress to renal failure unless they have uncorrectable urinary tract abnormalities. However, repeated infection, particularly in the presence of VUR, is thought (but not proved) to cause renal scarring, which may lead to hypertension and end-stage renal disease. In children with high-grade VUR, long-term scarring is detected at a 4- to 6-fold greater rate than in children with low-grade VUR and at an 8- to 10-fold greater rate than in children without VUR.

**Treatment**

- **Antibiotics**

- **For severe VUR, sometimes antibiotic prophylaxis and surgical repair**

Treatment aims to eliminate the acute infection, prevent urosepsis, and preserve renal parenchymal function. Antibiotics are begun presumptively in all toxic-appearing children and in nontoxic children with likely UTI (positive leukocyte esterase or nitrite test, or microscopy showing pyuria or bacteriuria). Others can await culture results.

In infants 2 mo to 2 yr with toxicity, dehydration, or inability to retain oral intake, parenteral antibiotics are used, typically a 3rd-generation cephalosporin (eg, ceftriaxone 75 mg/kg IV/IM q 24 h, cefotaxime 50 mg/kg IV q 6 h). A 1st-generation cephalosporin (eg, cefazolin) may be used if typical local pathogens are known to be sensitive. Aminoglycosides (eg, gentamicin), although potentially nephrotoxic, are useful in complex UTIs (eg, urinary tract abnormalities, presence of indwelling catheters, recurrent UTIs) to treat potentially resistant gram-negative bacilli such as *Pseudomonas*. If blood cultures are negative and clinical response is good, an appropriate oral antibiotic (eg, a cephalosporin, trimethoprim/sulfamethoxazole [TMP/SMX], amoxicillin, or, for selected children such as those > 1 yr with complicated UTI caused by multidrug-resistant *E. coli*, *P. aeruginosa*, or other gram-negative bacteria, a fluoroquinolone) selected on the basis of antimicrobial sensitivities can be used to complete a 10- to 14-day course. A poor clinical response suggests a resistant organism or an obstructive lesion and warrants urgent evaluation with ultrasonography and repeat urine culture.

In nontoxic, nondehydrated infants and children who are able to retain oral intake, oral antibiotics may be given initially. The drug of choice is TMP/SMX 5 to 6 mg/kg (of TMP component) bid. Alternatives include cephalosporins such as cefixime 4 mg/kg bid or cephelexin 25 mg/kg qid. Therapy is changed based on the results of cultures and antimicrobial sensitivities. Treatment is generally for > 10 days, although many older children with uncomplicated UTI can be treated for 7 days. Urine culture is repeated 2 to 3 days after therapy starts if efficacy is not clinically apparent.

**Vesicoureteral reflux:** It is generally thought that antibiotic prophylaxis reduces UTI recurrences and prevents kidney damage. However, few long-term data are available on the actual risks of renal scarring and the effectiveness of antimicrobial prophylaxis or operative repair in preventing end-stage renal disease. An ongoing clinical trial is attempting to address these questions, but until results are available, most clinicians provide long-term antimicrobial prophylaxis to children with VUR, especially those with grades II through V. For those with grade IV or grade V VUR, open repair or endoscopic injection of polymeric bulking agents is usually recommended.

Drugs for prophylaxis include nitrofurantoin 2 mg/kg po once/day or TMP/SMX 3 mg/kg po (of TMP component) once/day, usually given at bedtime.
Chapter 281. Human Immunodeficiency Virus Infection in Infants and Children

Introduction

(See also Ch. 154.)

Human immunodeficiency virus (HIV) infection is caused by the retrovirus HIV-1 (and less commonly by the related retrovirus HIV-2). Infection leads to progressive immunologic deterioration and opportunistic infections and cancers. The end stage is acquired immunodeficiency syndrome (AIDS). Diagnosis is by viral antibodies in children > 18 mo and viral PCR assay in children < 18 mo. Treatment is with combinations of antiretroviral drugs.

The general natural history and pathophysiology of pediatric HIV infection is similar to that in adults; however, the method of infection, clinical presentations, and treatments often differ. HIV-infected children also have unique social integration issues (see Sidebar 281-1).

Epidemiology

In the US, HIV probably occurred in children almost as early as in adults but was not clinically recognized for several years. Thus far, > 9300 cases have been reported in children and adolescents, representing only 1% of total cases.

More than 90% of US children acquired the infection from their mother, either before or around the time of birth (vertical transmission). Most of the remainder (including children with hemophilia or other coagulation disorders) received contaminated blood or blood products. A few cases are the result of sexual abuse. Fewer than 5% of cases have no clear source. Vertical transmission now accounts for almost all new cases in US preadolescents. Cases in adolescents represent survivors of vertically transmitted infection and newly acquired infection (typically from sexual contact, particularly by young men who have sex with men).

Worldwide, about 2 million children have HIV infection (6% of the total caseload worldwide), and about 370,000 more children are infected each year (14% of all new infections). In sub-Saharan Africa, where the epidemic has been present longest, some prenatal clinics report that 25 to 40% of all women of childbearing age are seropositive for HIV. HIV infection is rapidly increasing in India, China, Southeast Asia, and some areas of Eastern Europe and Russia. About 270,000 children die of HIV infection worldwide each year.

Transmission: Infection risk for an infant born to an HIV-positive mother who did not receive antiretroviral (ARV) therapy during pregnancy is estimated at 13 to 39%. Risk is greatest for infants born to mothers who seroconvert during pregnancy and for those with advanced disease, low peripheral CD4+ T-cell counts, prolonged rupture of membranes, and high plasma viral RNA concentrations. In vaginal deliveries, a 1st-born twin is at greater risk than a 2nd-born twin, although this relationship may not hold true in developing countries.

Sidebar 281-1 Integration of HIV-Infected Children

Infection in a child affects the entire family. Serologic testing of siblings and parents is recommended. The physician must provide education and ongoing counseling.

The infected child should be taught good hygiene and behavior to reduce risk to others. How much and when the child is told about the illness depends on age and maturity. Older children and adolescents should be made aware of their diagnosis and the possibility of sexual transmission and should be counseled appropriately. Families may be unwilling to share the diagnosis with people outside the immediate family because it can create social isolation. Feelings of guilt are common. Family members, including children, can become clinically depressed and require counseling.

Because HIV infection is not acquired through the typical types of contact that occur among children (eg,
through saliva or tears), most HIV-infected children should be allowed to attend school without restrictions. Similarly, there are no inherent reasons to restrict foster care, adoptive placement, or child care of HIV-infected children. Conditions that may pose an increased risk to others (eg, aggressive biting or the presence of exudative, weeping skin lesions that cannot be covered) may require special precautions.

The number of school personnel aware of the child's condition should be kept to the minimum needed to ensure proper care. The family has the right to inform the school, but people involved in the care and education of an infected child must respect the child's right to privacy. Disclosures of information should be made only with the informed consent of the parents or legal guardians and age-appropriate assent of the child.

Cesarean delivery before onset of active labor reduces the risk of mother-to-child transmission (MTCT). However, it is clear that MTCT is reduced most significantly by giving ARV therapy (including zidovudine [ZDV, AZT]) to the mother and neonate (see p. 2858). ZDV monotherapy reduces MTCT from 25% to about 8%, and current highly active anti-retroviral therapy (HAART) reduces it to < 2%.

HIV has been detected in both the cellular and cell-free fractions of human breast milk. The incidence of transmission by breastfeeding is about 6/100 breastfed children/yr. Estimates of the overall risk of transmission through breastfeeding are 12 to 14%, reflecting varying durations of breastfeeding. Transmission by breastfeeding is greatest in mothers with high plasma viral concentrations (eg, women who become infected during pregnancy or during the period of breastfeeding).

The total number of HIV-infected US adolescents continues to increase despite the marked success in decreasing perinatal HIV infection through comprehensive diagnosis and treatment of infected pregnant women. This paradoxical increase is a result of both greater survival among perinatally infected children and the additional acquisition of new cases of HIV infection by sexual transmission among other adolescents.

**Classification:** HIV infection causes a broad spectrum of disease, of which AIDS is the most severe. Classification schemes established by the Centers for Disease Control and Prevention (CDC) define the progression of clinical and immunologic decline.

**Clinical categories** in children < 13 yr (see Table 281-1) are defined by presence or absence of certain common opportunistic infections or cancers. These categories are

- N = Not symptomatic
- A = Mildly symptomatic
- B = Moderately symptomatic
- C = Severely symptomatic

**Immunologic categories** in children < 13 yr (see Table 281-2) reflect the degree of immune suppression based on the CD4+ T-cell count (absolute count and as percentage of total lymphocyte count):

1 = No evidence of immune suppression
2 = Moderate suppression
3 = Severe suppression

Thus, a child classified in stage B3 would have moderately advanced clinical symptoms and severe immunocompromise. Clinical and immunologic categories form a unidirectional hierarchy; once classified at a certain level, children cannot be reclassified at a less severe level, regardless of clinical or immunologic improvement.

[Table 281-1, Clinical Categories for Children Aged < 13 yr with HIV Infection]
These clinical and immunologic categories are becoming less clinically relevant in the era of HAART, which (when taken as prescribed) almost invariably leads to a decrease in symptoms and an increase in CD4+ T-cell counts. The categories are most useful for clinical research and for describing the severity of illness at the time of diagnosis.

Symptoms and Signs

Natural history in untreated children: Infants infected perinatally usually are asymptomatic during the first few months of life. Although the median age at symptom onset is about 3 yr, some children remain asymptomatic for > 5 yr and, with appropriate ARV therapy, are expected to survive to adulthood. In the pre-ARV therapy era, about 10 to 15% of children had rapid disease progression, with symptoms occurring in the first year of life and death occurring by 18 to 36 mo; these children were thought to have acquired HIV infection earlier in utero. However, most children probably acquire infection at or near birth and have slower disease progression (surviving beyond 5 yr even before ARV therapy was used routinely).

The most common manifestations of HIV infection in children include generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, oral candidiasis, CNS disease (including developmental delay, which can be progressive), lymphoid interstitial pneumonitis, recurrent bacteremia, opportunistic infections, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy, and cancers.

Complications: Pneumocystis jirovecii pneumonia is the most common, serious, opportunistic infection among HIV-infected children and has high mortality. Pneumocystis pneumonia can occur as early as age 4 to 6 wk but occurs mostly in infants aged 3 to 6 mo who acquired infection before or at birth. Infants and children with Pneumocystis pneumonia characteristically develop a subacute, diffuse pneumonitis with dyspnea at rest, tachypnea, O₂ desaturation, nonproductive cough, and fever (in contrast to non-HIV-infected immunocompromised children and adults, in whom onset is often more acute and fulminant).

Other common opportunistic infections include Candida esophagitis, disseminated cytomegalovirus infection, and chronic or disseminated herpes simplex and varicella-zoster virus infections, and, less commonly, Mycobacterium tuberculosis and M. avium complex infections, chronic enteritis caused by Cryptosporidium or other organisms, and disseminated or CNS cryptococcal or Toxoplasma gondii infection.

Cancers in immunocompromised children with HIV infection are relatively uncommon, but leiomyosarcomas and certain lymphomas, including CNS lymphomas and non-Hodgkin B-cell lymphomas (Burkitt's type), occur much more often than in immunocompetent children. Kaposi's sarcoma is very rare in HIV-infected children.

Children receiving combination antiretroviral therapy: Combination ARV therapy has significantly changed the clinical manifestations of pediatric HIV infection. Although bacterial pneumonia and other bacterial infections (eg, bacteremia, recurrent otitis media) still occur more often in HIV-infected children, opportunistic infections and growth failure are much less frequent than in the pretreatment era. New problems, such as alterations in serum lipids, hyperglycemia, fat maldistribution (lipodystrophy and lipoatrophy), nephropathy, and osteonecrosis, are reported, although with lower incidence than in HIV-infected adults. Although combination therapy clearly improves neurodevelopmental outcome, there seems to be an increased rate of behavioral, developmental, and cognitive problems in treated HIV-infected children. It is unclear whether these problems are caused by HIV infection itself, therapeutic drugs, or other bio-psychosocial factors among HIV-infected children.

Diagnosis
• Serum antibody tests

• Virologic assay (HIV DNA PCR or HIV RNA assays)

**HIV-specific tests:** In children > 18 mo, diagnosis is made using serum antibody tests (enzyme immunoassay [EIA] and confirmatory Western blot) as in adults. Only very rarely does an older HIV-infected child lack HIV antibody because of significant hypogammaglobulinemia.

Children < 18 mo retain maternal antibody, causing false-positive results on EIA, so diagnosis is made by HIV virologic assays such as DNA PCR, which can diagnose about 30% of cases at birth and nearly 100% by 4 to 6 mo of age. HIV viral culture has acceptable sensitivity and specificity but is technically more demanding and hazardous and has been replaced by DNA PCR in most laboratories.

HIV RNA assays (the viral load assays used for monitoring efficacy of treatment) are becoming more widely used for diagnostic testing of infants. RNA assays are probably as sensitive as DNA PCR in infants not given ARV therapy, are less expensive, and are more widely available than is DNA PCR. However, care must be taken when using RNA assays for infant diagnosis because test specificity is uncertain at very low RNA concentrations (< 10,000 copies/mL) and sensitivity is unknown in infants of mothers with complete treatment-mediated viral suppression at the time of delivery. The modified p24 antigen assay is less sensitive than either HIV DNA PCR or RNA assays and should be used only if the latter are unavailable.

An initial virologic test should be done within the first 2 wk of life, at about 1 mo of age, and between 4 mo and 6 mo. A positive test should be confirmed immediately by using the same or another virologic test. If the serial HIV virologic tests are all negative, the infant is considered uninfected with > 95% accuracy (in the absence of any AIDS-defining illness). Follow-up antibody tests (1 EIA at > 18 mo or, alternatively, 2 EIAs done between 6 mo and 18 mo) are done to exclude HIV infection and confirm seroreversion (loss of passively acquired HIV antibodies). If an infant < 18 mo with a positive antibody test but negative virologic tests develops an AIDS-defining illness (category C—see Table 281-1), HIV infection is diagnosed.

**Rapid tests** for HIV antibody are derivatives of EIAs that provide results within minutes to hours. They can be done as point-of-care tests on oral secretions, whole blood, or serum. In the US, these tests are perhaps most useful in labor and delivery suites to test women of unknown HIV serostatus, thus allowing counseling, commencement of ARV therapy to prevent MTCT, and testing of the infant to be arranged during the birth visit. Similar advantages accrue in other episodic care settings (eg, emergency departments, adolescent medicine clinics, sexually transmitted disease clinics) and in the developing world. In the US, rapid assays require confirmatory tests, such as Western blot testing. These confirmatory tests are especially important because in areas where the expected HIV prevalence is low, even a specific rapid assay yields mostly false positives (low positive predictive value by Bayes' theorem—see p. 3394). However, if the expected probability of HIV (or seroprevalence) is high, the positive predictive value increases.

Before HIV testing of a child is done, the mother or primary caregiver (and the child, if old enough) should be counseled about the possible psychosocial risks and benefits of testing. Written or oral consent should be obtained and recorded in the patient’s chart, consistent with state, local, and hospital laws and regulations. Counseling and consent requirements should not deter testing if it is medically indicated; refusal of a patient or guardian to give consent does not relieve physicians of their professional and legal responsibilities, and sometimes authorization for testing must be obtained by other means (eg, court order). Test results should be discussed in person with the family, the primary caregiver, and, if old enough, the child. If the child is HIV-positive, appropriate counseling and subsequent follow-up care must be provided. In all cases, maintaining confidentiality is essential.

Children and adolescents meeting the criteria for AIDS must be reported to the appropriate public health department. In many states, HIV infection (before the development of AIDS) also must be reported.

**Other tests:** Once infection is diagnosed, other tests are done:

• CD4+ T-cell count
Infected children require measurement of CD4+ and CD8+ T-cell counts and plasma viral RNA concentration (viral load) to help determine their degree of illness, prognosis, and the effects of therapy. CD4+ counts may be normal (eg, above the age-specific cutoffs of category 1 in Table 281-2) initially but fall eventually. CD8+ counts usually increase initially and do not fall until late in the infection. These changes in cell populations result in a decrease in the CD4+:CD8+ cell ratio, a characteristic of HIV infection (although sometimes occurring in other infections). Plasma viral RNA concentrations in untreated children < 12 mo are typically very high (mean of about 200,000 RNA copies/mL). By 24 mo, viral concentrations in untreated children decrease (to a mean of about 40,000 RNA copies/mL). Although the wide range of HIV RNA concentrations in children make the data less predictive of morbidity and mortality than in adults, determining plasma viral concentrations in conjunction with CD4+ counts still yields more accurate prognostic information than does determining either marker alone. Less expensive alternative surrogate markers such as total lymphocyte counts and serum albumin levels may also predict AIDS mortality in children, which may be useful in developing nations.

Although not routinely measured, serum immunoglobulin concentrations, particularly IgG and IgA, often are markedly elevated, but occasionally some children develop panhypogammaglobulinemia. Patients may be anergic to skin test antigens.

Prognosis

In the pretherapy era, 10 to 15% of children from industrialized countries and perhaps 50 to 80% of children from developing countries died before age 4 yr; however, with appropriate HAART regimens, most perinatally infected children survive well beyond 5 yr. Many children are surviving into young adulthood; increasing numbers have given birth to or fathered their own children.

Nevertheless, opportunistic infections, particularly Pneumocystis pneumonia, progressive neurologic disease, and severe wasting, are associated with a poor prognosis. Mortality due to Pneumocystis pneumonia ranges from 5 to 40% if treated and is almost 100% if untreated. Prognosis is also poor for children in whom virus is detected early (ie, by 7 days of life) or who develop symptoms in the first year of life.

Treatment

• ARV drugs: 2 nucleoside analog reverse transcriptase inhibitors plus either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor

• Supportive care

Because of the success of ARV therapy, much of the current focus is on the management of HIV infection as a chronic disease, addressing both medical and social issues. Important long-term medical issues include the need to manage HIV-related and drug-related metabolic complications and to account for age-related changes in drug pharmacokinetics and pharmacodynamics. Social issues include the need to cope with peer pressure from non-infected adolescents, ensure school success and appropriate career choice, and educate children about transmission risk. Adolescents often have difficulty seeking and following health care advice and need particular help with treatment adherence. Children and adolescents should be managed in collaboration with specialists who have experience in the management of pediatric HIV infection.

ARV drugs: There are > 2 dozen ARV drugs (see Table 281-3), including multidrug combination products, available in the US, each of which may have adverse effects and drug interactions with other ARV drugs or commonly used antibiotics, anticonvulsants, and sedatives. New ARV drugs, immunomodulators, and vaccines are under evaluation.
Standard treatment is with combination ARV therapy to maximize viral suppression and minimize selection of drug-resistant strains. Most commonly, ARV therapy consists of a backbone of 2 nucleoside analog reverse transcriptase inhibitors (ZDV plus lamivudine or emtricitabine, abacavir plus lamivudine or emtricitabine, didanosine plus lamivudine or emtricitabine, or, for postpubertal adolescents, tenofovir plus emtricitabine) given in combination with either a ritonavir-boosted protease inhibitor (lopinavir/ritonavir, ritonavir-boosted atazanavir, ritonavir-boosted fosamprenavir, or ritonavir-boosted darunavir) or a nonnucleoside reverse transcriptase inhibitor (efavirenz or, in some situations, nevirapine). Other combinations sometimes are used, but fewer data are available to support their use as first-line regimens. Monotherapy or dual nucleoside reverse transcriptase inhibitor therapy alone (except for ZDV chemoprophylaxis in HIV-exposed infants) is strongly discouraged. Because expert opinions on therapeutic strategies change rapidly, consultation with specialists is strongly advised.

**Indications:** Initiation of ARV therapy depends on virologic, immunologic, and clinical criteria; authorities differ on these criteria. The goal is to suppress HIV replication (as measured by plasma HIV RNA PCR viral load) and maintain or achieve age-normal CD4+ counts and percentages with the least amount of drug toxicity.

For **children ≥ 12 mo,** ARV therapy is recommended for all children with significant clinical or immunologic disease (clinical category B or C [Table 281-1] or CD4+ percentage < 25% for children < 5 yr or CD4+ cell count < 350/μL for children ≥ 5 yr), regardless of the plasma HIV RNA viral load. Therapy is considered for other children who have plasma HIV RNA concentrations ≥ 100,000 copies/mL. Children who do not meet these criteria may be monitored closely without ARV therapy, but their clinical and laboratory data should be reevaluated every 3 to 4 mo.

For **children < 12 mo,** ARV therapy should be given to all regardless of clinical symptoms, CD4+ T-cell percentages or counts, or plasma HIV RNA viral load; clinical trials have shown that early therapy of infected infants decreases mortality.

**Adherence:** Therapy will be successful only if the family and child are able to adhere to a possibly complex medical regimen. Nonadherence not only leads to failure to control HIV but also selects drug-resistant HIV strains, which reduces future therapeutic choices. Barriers to adherence should be addressed before starting treatment. Barriers include availability and palatability of pills or suspensions, adverse effects (including those due to drug interactions with current therapy), pharmacokinetic factors such as need to take some drugs with food or in the fasted state, a child's dependence on others to give drugs (and HIV-infected parents may have problems with remembering to take their own drugs), and adolescents' denial or fear of their infection, distrust of the medical establishment, and lack of family support.

[Table 281-3. Dosage and Administration of Antiretroviral Drugs for Children^a^]

**Monitoring:** Clinical and laboratory monitoring are important for identifying drug toxicity and therapeutic failure.

- Every 3 to 4 mo: Physical examination, CBC, serum chemistry values, including liver and kidney function tests, amylase and lipase (if taking drugs with pancreatic toxicity, eg, didanosine), HIV RNA viral load, and lymphocyte subsets

- Every 6 to 12 mo: Lipid profiles, and amylase and lipase (if not taking drugs with pancreatic toxicity)

**Vaccination:** Routine pediatric vaccination protocols (see p. 2718) are recommended for children with HIV infection, with several exceptions. The main exception is that live-virus vaccines and live-bacteria vaccines (eg, BCG) should be avoided or used only in certain circumstances (see Table 281-4). In addition, 1 to 2 mo after the last dose of the hepatitis B vaccine series, HIV-infected children should be tested to determine whether the level of antibodies to hepatitis B surface antigen (anti-HBs) is protective (≥ 10 mIU/mL), and children aged ≥ 2 yr should be given pneumococcal polysaccharide vaccine (PPSV) ≥ 2 mo after their last pneumococcal conjugate vaccine (PCV) dose, and a single
revaccination should be given after 5 yr. Certain postexposure treatment recommendations also differ.

Live oral poliovirus vaccine and live-attenuated influenza vaccine are not recommended.

The live measles-mumps-rubella (MMR) and varicella vaccines should not be given to children with AIDS or other manifestations of severe immunosuppression. However, the MMR and varicella vaccines (separately; not combined as MMRV vaccine, which has a higher titer of attenuated varicella virus, the safety of which has not been shown in this population) can be given to asymptomatic patients following the routine schedule and to symptomatic patients who are not severely immunocompromised (ie, not in category 3 [see Table 281-1], including having a CD4+ T-cell percentage of ≥ 15%); if possible, these vaccines should be given starting at age 12 mo in symptomatic patients to enhance the likelihood of an immune response, i.e., before the immune system deteriorates. The 2nd dose of each may be given as soon as 4 wk later in an attempt to induce seroconversion as early as possible, although generally a 3-mo interval between varicella vaccine doses is preferred in noninfected children < 13 yr. If the risk of exposure to measles is increased, as during an outbreak, the measles vaccine should be given at an earlier age, such as 6 to 9 mo.

The live oral rotavirus vaccine may be given to HIV-exposed or HIV-infected infants according to the routine schedule. Safety and efficacy data are limited in symptomatic infants but experts feel that there is overall benefit to immunization, particularly in areas where rotavirus causes significant mortality.

The BCG vaccine is not recommended in the US, an area of low TB prevalence. However, elsewhere in the world, especially in developing countries where TB prevalence is high, the WHO recommends that BCG be given to all infants shortly after birth, unless they have symptoms of HIV infection or already have been confirmed to have HIV infection (eg, positive virologic assay). Some cases of disseminated BCG infection in severely immunocompromised AIDS patients have been reported.

Because children with symptomatic HIV infection generally have poor immunologic responses to vaccines, they should be considered susceptible when they are exposed to a vaccine-preventable disease (eg, measles, tetanus, varicella) regardless of their vaccination history. Such children should receive passive immunization with immune globulin. Immune globulin also should be given to any nonimmunized household member who is exposed to measles.

**Seronegative children living with a person with symptomatic HIV infection** should receive inactivated poliovirus vaccine rather than oral polio vaccine. Influenza (inactivated or live), MMR, varicella, and rotavirus vaccines may be given normally because these vaccine viruses are not commonly transmitted by the vaccinee. Adult household contacts should receive annual influenza vaccination (inactivated or live) to reduce the risk of transmitting influenza to the HIV-infected person.

**Prevention**

For postexposure prevention, see p. 1455.

**Prevention of perinatal transmission:** Appropriate prenatal ARV therapy attempts to optimize maternal health, interrupt MTCT, and minimize in utero drug toxicity. In the US and other countries where ARV drugs and HIV testing are readily available, treatment with ARV drugs is standard for all HIV-infected pregnant women (see p. 1450). Rapid HIV testing of pregnant women who present in labor without documentation of their HIV serostatus may allow immediate institution of such measures.

HIV-infected pregnant women who have not received ARV drugs previously and who do not meet adult criteria (see p. 1450) for HAART are nevertheless recommended to initiate HAART, preferably including ZDV 300 mg po bid, beginning at 14 to 34 wk gestation. Pregnancy is not a contraindication to HAART regimens, although the use of efavirenz is generally contraindicated during the 1st trimester. This regimen is continued throughout the pregnancy. ZDV is given during labor 2 mg/kg IV for the first hour and then 1 mg/kg/h IV until delivery. ZDV 2 mg/kg po qid is given to the neonate for the first 6 wk of life. In the immediate postpartum period, a decision can be made whether to continue maternal therapy.

Most experts believe that HIV-infected women already receiving combination ARV therapy who become
pregnant should continue that therapy, even during the 1st trimester. An alternative is to stop all therapy until the beginning of the 2nd trimester and resume at that time.

**Table 281-4. Considerations for Use of Live Vaccines in Children with HIV Infection**

For HIV-infected pregnant women who present in labor and have had no prior therapy, clinicians have used ARV combinations, cesarean delivery, or both; the woman and her infant are given ZDV as described previously (ie, the woman receives drugs IV during labor and delivery; the infant receives drugs by mouth). Some authorities give additional antiretrovirals in this situation; an expert in pediatric or maternal HIV infection should be immediately consulted (see information at www.aidsinfo.nih.gov or www.nccc.ucsf.edu).

Although the final decision to accept ARV therapy remains with the pregnant woman, it should be stressed that the proven benefits of therapy far outweigh the theoretical risks of fetal toxicity.

**Breastfeeding** (or donating to milk banks) is contraindicated for HIV-infected women in the US and other countries where safe and affordable alternative sources of feeding are readily available. However, in countries where infectious diseases and undernutrition are major causes of early childhood mortality and safe, affordable infant formula is not available, the protection breastfeeding offers against the mortality risks of respiratory and GI infections may counterbalance the risk of HIV transmission. In these developing countries, the WHO recommends that mothers continue to breastfeed.

**Prevention of adolescent transmission:** Because adolescents are at special risk of HIV infection, they should receive education, have access to HIV testing, and know their serostatus. Education should include information about transmission, implications of infection, and strategies for prevention, including abstaining from high-risk behaviors and engaging in safe sex practices (eg, correct and consistent use of condoms [see p. 2587]) for those who are sexually active. Efforts should especially target adolescents at high risk of HIV infection, although all adolescents should receive risk-reduction education.

In most US states, informed consent is necessary for testing and the release of information regarding HIV serostatus. Decisions regarding disclosure of HIV status to a sex partner without the patient's consent should be based on the possibility of domestic violence to the patient after disclosure to the partner, likelihood that the partner is at risk, whether the partner has reasonable cause to suspect the risk and to take precautions, and presence of a legal requirement to withhold or disclose such information.

**Prevention of opportunistic infections:** Prophylactic drug treatment is recommended in certain HIV-infected children for prevention of *Pneumocystis* pneumonia and *M. avium* complex infections. Data are limited on the use of prophylaxis for opportunistic infection by other organisms, such as cytomegalovirus, fungi, and toxoplasma. Guidance on prophylaxis of these and other opportunistic infections is also available at www.aidsinfo.nih.gov.

**Prophylaxis against *Pneumocystis* pneumonia** is indicated for

- HIV-infected children > 6 yr of age with CD4+ count < 200 cells/μL or CD4+ percentage < 15%
- HIV-infected children 1 to 5 yr of age with CD4+ count < 500 cells/μL or CD4+ percentage < 15%
- HIV-infected infants < 12 mo of age regardless of CD4+ count or percentage (at 1 yr of age, need for prophylaxis is reassessed using CD4+ counts and percentages)
- Infants born to HIV-infected women (beginning at 4 to 6 wk of age), until HIV infection is either presumptively excluded (by documentation of 2 negative virologic test results, 1 at ≥ 2 wk of age and 1 at ≥ 4 wk of age) or definitively excluded (by documentation of 2 negative virologic test results, 1 at ≥ 1 mo of age and 1 at ≥ 4 mo of age). For these definitions of HIV exclusion to be valid, the infant must not be breastfeeding.

Once immune reconstitution with HAART occurs, discontinuation of *Pneumocystis* pneumonia prophylaxis may be considered for HIV-infected children who have received HAART for > 6 mo and whose CD4+
percentage and CD4+ count have remained higher than the previously described treatment thresholds for > 3 consecutive mo. Subsequently, the CD4+ percentage and count should be reevaluated at least every 3 mo, and prophylaxis should be reinstituted if the original criteria are reached.

The drug of choice for Pneumocystis prophylaxis at any age is trimethoprim/sulfamethoxazole (TMP/SMX) TMP 75 mg/SMX 375 mg/m$^2$ po bid on 3 consecutive days/wk (eg, Monday-Tuesday-Wednesday); alternative schedules include the same dose bid every day, the same dose bid on alternate days, or twice the dose (TMP 150 mg/SMX 750 mg/m$^2$) po once/day for 3 consecutive days/wk.

For patients ≥ 5 yr who cannot tolerate TMP/SMX, dapsone 2 mg/kg (not to exceed 100 mg) po once/day is an alternative, especially for those < 5 yr of age. Oral atovaquone given daily or aerosolized pentamidine (300 mg via specially designed inhaler) given once/mo is an additional alternative. IV pentamidine has also been used but is less effective and potentially more toxic.

**Prophylaxis against Mycobacterium avium complex** infection is indicated in

- Children ≥ 6 yr with CD4+ count < 50/μL
- Children 2 to 6 yr with CD4+ count < 75/μL
- Children 1 to 2 yr with CD4+ count < 500/μL
- Children < 1 yr with CD4+ count < 750/μL

Weekly azithromycin or daily clarithromycin is the drug of choice, and daily rifabutin is an alternative.
Chapter 282. Rheumatic Fever

Introduction

Rheumatic fever is a nonsuppurative, acute inflammatory complication of group A streptococcal infection, causing combinations of arthritis, carditis, subcutaneous nodules, erythema marginatum, and chorea. Diagnosis is based on applying the Jones criteria to information gleaned from history, examination, and laboratory testing. Treatment includes aspirin or other NSAIDs, corticosteroids during severe carditis, and antimicrobials to eradicate residual streptococcal infection and prevent reinfection.

A first episode of acute rheumatic fever (ARF) can occur at any age but occurs most often between 5 yr and 15 yr and is uncommon before 3 yr and after 21 yr. Therefore, testing for group A streptococcal (GAS) infection for primary prevention of rheumatic fever is usually not necessary in patients < 3 yr with pharyngitis.

Worldwide, incidence is 19/100,000 (range, 5 to 51/100,000), with lowest rates (< 10/100,000) in North America and Western Europe and highest rates (> 10/100,000) in Eastern Europe, the Middle East, Asia, Australia, and New Zealand. The attack rate (percentage of patients with untreated GAS pharyngitis who develop ARF) varies from 0.4 to 3.0%. Higher attack rates occur with certain streptococcal M protein serotypes and a stronger host immune response. In patients with a prior episode of ARF, the attack rate in untreated GAS pharyngitis approaches 50%, underscoring the importance of long-term antistreptococcal prophylaxis. Incidence has declined in most developed countries but remains high in less developed parts of the world. However, recurrent local outbreaks of ARF suggest that more rheumatogenic strains of streptococci are still present in the US. The prevalence of chronic rheumatic heart disease is uncertain because criteria are not standardized and autopsy is not done routinely.

Pathophysiology

GAS infection is the etiologic precursor of ARF, but host and environmental factors are important. GAS M proteins share epitopes (antigenic-determinant sites that are recognized by antibodies) with proteins found in synovium, heart muscle, and heart valve, suggesting that molecular mimicry contributes to the arthritis, carditis, and valvular damage. Genetic host risk factors include the D8/17 B-cell antigen and certain class II histocompatibility antigens. Undernutrition, overcrowding, and lower socioeconomic status predispose to streptococcal infections and subsequent episodes of rheumatic fever.

The joints, heart, skin, and CNS are most often affected. Pathology varies by site.

**Joints:** Joint involvement manifests as non-specific inflammation in a synovial biopsy specimen, sometimes with small foci resembling Aschoff bodies (granulomatous collections of leukocytes, myocytes, and interstitial collagen).

**Heart:** Cardiac involvement manifests as carditis, typically affecting the heart from the inside out, ie, valves and endocardium, then myocardium, and finally pericardium. It is sometimes followed years later by chronic rheumatic heart disease, primarily manifested by valvular stenosis, but also sometimes by regurgitation, arrhythmias, and ventricular dysfunction. Aschoff bodies often develop in the myocardium and other parts of the heart. Fibrinous nonspecific pericarditis, sometimes with effusion, occurs only in patients with endocardial inflammation and usually subsides without permanent damage. Characteristic and potentially dangerous valve changes may occur. Acute interstitial valvulitis may cause valvular edema. Left untreated, valve thickening, fusion, and retraction or other destruction of leaflets and cusps may result, leading to stenosis or insufficiency. Similarly, chordae tendineae can shorten, thicken, or fuse, adding to regurgitation of damaged valves or causing regurgitation of an otherwise unaffected valve. Dilation of valve rings may also cause regurgitation. The mitral, aortic, tricuspid, and pulmonic valves are affected, in order of decreasing frequency. Regurgitation and stenosis are the usual effects on the mitral and tricuspid valves; the aortic valve generally becomes regurgitant initially and stenotic much later.

**Skin:** Subcutaneous nodules appear indistinguishable from those of RA, but biopsy shows features resembling Aschoff bodies. Erythema marginatum differs histologically from other skin lesions with similar
macroscopic appearance, eg, the rash of systemic juvenile idiopathic arthritis (JIA), Henoch-Schonlein purpura, erythema chronicum migrans, and erythema multiforme. Perivascular neutrophilic and mononuclear infiltrates of the dermis occur.

**CNS:** Sydenham's chorea, the form of chorea that occurs with ARF, manifests in the CNS as hyperperfusion and increased metabolism in the basal ganglia. Increased levels of antineuronal antibodies have also been shown.

**Symptoms and Signs**

An initial episode of symptoms occurs typically about 2 to 4 wk after the streptococcal infection. Manifestations typically involve some combination of the joints, heart, skin, and CNS.

**Joints:** Migratory polyarthritis is the most common manifestation, occurring in about 70% of children; it is often accompanied by fever. Occasionally monarthritis occurs. Joints become extremely painful and tender and may be red, hot, and swollen. Ankles, knees, elbows, and wrists are usually involved. Shoulders, hips, and small joints of the hands and feet also may be involved, but almost never alone. If vertebral joints are affected, another disorder should be suspected.

Arthralgia-like symptoms may be due to nonspecific myalgia or tenodynia in the periarticular zone; tenosynovitis may develop at the site of muscle insertions. Joint pain and fever usually subside within 2 wk and seldom last > 1 mo.

**Heart:** Carditis can occur alone or in combination with pericardial rub, murmurs, cardiac enlargement, or heart failure. In the first episode of ARF, carditis occurs in about 50%. Patients may have high fever, chest pain, or both. In about 50% of cases, cardiac damage (ie, valve dysfunction) occurs much later.

Murmurs are common and, although usually evident early, may not be heard at initial examination; in such cases, repeated examinations are recommended to determine the presence of carditis. The soft diastolic blow of aortic regurgitation and the presystolic murmur of mitral stenosis may be difficult to detect. Murmurs often persist indefinitely. If no worsening occurs during the next 2 to 3 wk, new manifestations of carditis seldom follow. ARF typically does not cause chronic, smoldering carditis. Scars left by acute valvular damage may contract and change, and secondary hemodynamic difficulties may develop in the myocardium without persistence of acute inflammation.

Heart failure caused by the combination of carditis and valvular dysfunction may cause dyspnea without rales, nausea and vomiting, a right upper quadrant or epigastric ache, and a hacking, nonproductive cough. Marked lethargy and fatigue may be early manifestations of heart failure.

**Skin:** Cutaneous and subcutaneous features are uncommon and almost never occur alone, usually developing in a patient who already has carditis, arthritis, or chorea.

Subcutaneous nodules, which occur most frequently on the extensor surfaces of large joints, usually coexist with arthritis and carditis. About 2% of children with ARF have nodules. Ordinarily, the nodules are painless and transitory and respond to treatment of joint or heart inflammation.

Erythema marginatum is a serpiginous, flat or slightly raised, nonscarring, and painless rash. About 2% of children have this rash. It sometimes lasts < 1 day. Its appearance is often delayed after the inciting streptococcal infection; it may appear with or after the other manifestations of rheumatic inflammation.

**CNS:** Sydenham's chorea occurs in about 10% of children. It may develop along with other manifestations but frequently arises after the other manifestations have subsided (often months after the acute streptococcal infection). Onset of chorea is typically insidious and may be preceded by inappropriate laughing or crying. Chorea consists of rapid and irregular jerking movements that may begin in the hands but often becomes generalized, involving the feet and face. Characteristic findings include fluctuating grip strength (milkmaid's grip), tongue darting (the tongue cannot protrude without darting in and out), facial grimacing, and explosive speech with or without tongue clucking. Associated motor symptoms include loss of fine motor control, and weakness and hypotonia (that can be severe enough to
be mistaken for paralysis).

Obsessive-compulsive behavior develops in many patients.

**Other:** Fever and other systemic manifestations such as anorexia and malaise can be prominent but are not specific. ARF can occasionally manifest as FUO until a more identifiable sign develops. Abdominal pain and anorexia can occur because of the hepatic involvement in heart failure or because of concomitant mesenteric adenitis. Because of the fever, elevated WBC count, and abdominal guarding, the situation may resemble acute appendicitis, particularly when other rheumatic manifestations are absent. Epistaxis occurs in about 4% of children with an initial episode and in 9% of those with a recurrence. Both abdominal pain and epistaxis were minor manifestations in earlier versions of the Jones criteria.

Prolonged episodes of ARF (> 8 mo) occur in about 5% of patients, with spontaneous recurrences of inflammation (clinical and laboratory manifestations) unrelated to intervening streptococcal infection or to cessation of anti-inflammatory therapy. Recurrences usually mimic the initial episode.

**Diagnosis**

- Jones criteria (for initial diagnosis)
- Testing for GAS (culture, rapid strep test, or antistreptolysin O and anti-DNase B titers)
- ECG
- ESR and C-reactive protein (CRP) level

Diagnosis of a first episode of ARF is based on the modified Jones criteria (see Table 282-1); 2 major criteria or 1 major and 2 minor criteria are required, along with evidence of preceding GAS infection. Sydenham's chorea alone (ie, without minor criteria) fulfills diagnostic criteria if other causes of movement disorder are ruled out. The Jones criteria should not be used to establish a recurrence.

A preceding streptococcal infection is suggested by a recent history of pharyngitis and is confirmed by a positive throat culture, an increase in the antistreptolysin O titer, or a positive rapid GAS antigen test. Recent scarlet fever is highly suggestive. Throat cultures and rapid antigen tests are often negative by the time ARF manifests, whereas titers of anti-streptolysin O and other antibodies typically are peaking. Only 80% of children with a prior infection have a significantly elevated antistreptolysin O titer; therefore, anti-DNase B antibody level should also be obtained.

Joint aspiration may be needed to exclude other causes of arthritis (eg, infection). The joint fluid is usually cloudy and yellow, with an elevated WBC count composed primarily of neutrophils; culture is negative. Complement levels are usually normal or slightly decreased, compared with decreased levels in other inflammatory arthritides.

ECG is done during the initial evaluation. An echocardiogram and a repeat ECG are done at the time of diagnosis. Serum cardiac marker levels are obtained; normal cardiac troponin I levels exclude prominent myocardial damage. ECG abnormalities such as PR prolongation do not correlate with other evidence of carditis. Only 35% of children with ARF have a prolonged PR interval. Other ECG abnormalities may be due to pericarditis, enlargement of ventricles or atria, or arrhythmias. Echocardiography can detect evidence of carditis in many patients. Chest x-rays are not routinely done but can detect cardiomegaly, a common manifestation of carditis in ARF. Biopsy of a subcutaneous nodule can aid in early diagnosis, especially when other major clinical manifestations are absent. Rheumatic carditis must be distinguished from congenital heart disease and endocardial fibroelastosis; echocardiography or coronary angiography can be used to verify difficult diagnoses.

[Table 282-1, Modified Jones Criteria for a First Episode of Acute Rheumatic Fever*]
ESR and serum CRP are sensitive but not specific. The ESR is often > 120 mm/h. CRP is often > 2 mg/dL; because it rises and falls faster than ESR, a normal CRP may confirm that inflammation is resolving in a patient with prolonged ESR elevation after acute symptoms have subsided. In the absence of carditis, ESR usually returns to normal within 3 mo. Evidence of acute inflammation, including ESR, usually subsides within 5 mo in uncomplicated carditis. The WBC count reaches 12,000 to 20,000/µL and may go higher with corticosteroid therapy.

The differential diagnosis includes JIA (especially systemic JIA and, less so, polyarticular JIA), Lyme disease, reactive arthritis, arthropathy of sickle cell disease, leukemia or other cancer, SLE, embolic bacterial endocarditis, serum sickness, Kawasaki disease, drug reactions, and gonococcal arthritis. These are frequently distinguished by history or specific laboratory tests. The absence of an antecedent GAS infection, the diurnal variation of the fever, evanescent skin rash, and prolonged symptomatic joint inflammation usually distinguish systemic JIA from ARF.

**Prognosis**

Prognosis depends mostly on the severity of the initial carditis. Patients with severe carditis during the first episode may have residual heart disease that is often worsened by the rheumatic fever recurrences to which they are particularly susceptible. Murmurs eventually disappear in about half of patients whose acute episodes were manifested by mild carditis without major cardiac enlargement or decompensation. Risk of recurrent inflammation is intermediate, between the low risk of those without carditis and the high risk of those with a history of severe carditis, but recurrences may cause or worsen permanent cardiac damage. Patients who did not have carditis are less likely to have recurrences and are unlikely to develop carditis if ARF recurs. Sydenham's chorea usually lasts several months and resolves completely in most patients, but about one third of patients have recurrences. All other manifestations subside without residual effects.

**Treatment**

- Aspirin or another NSAID
- Sometimes corticosteroids
- Antibiotics

The primary goals are suppression of inflammation and relief of acute symptoms, eradication of GAS infection, and prophylaxis against future infection to prevent recurrent heart disease.

Patients should generally limit their activities if symptomatic with arthritis, chorea, or heart failure. In the absence of carditis, no physical restrictions are needed after the initial episode subsides. In asymptomatic patients with carditis, strict bed rest has no proven value.

**Aspirin** controls fever and pain caused by arthritis and carditis. The dose is titrated upward until clinical effectiveness is attained or toxicity supervenes. The starting dose for children and adolescents is 15 mg/kg po qid. If not effective overnight, the dosage is increased to 22.5 mg/kg qid the next day and 30 mg/kg qid on the next. Salicylate toxicity is manifested by tinnitus, headache, or hyperpnea and may not appear until after 1 wk. Salicylate levels are measured only to manage toxicity and should not be done until the patient has been receiving aspirin for 5 days. Enteric-coated, buffered, or complex salicylate molecules provide no advantage. Other NSAIDs can be used. For example, naproxen 7.5 to 10 mg/kg po bid is as effective as aspirin.

If a therapeutic effect has not occurred after the 4th day, which is sometimes the case if carditis or arthritis is severe, NSAIDs should be abandoned in favor of a corticosteroid.

**Prednisone** 0.25 to 1 mg/kg po bid (or 0.125 to 0.5 mg/kg po qid) up to 60 mg/day is recommended. If inflammation is not suppressed after 2 days, an IV corticosteroid pulse of methylprednisolone succinate (30 mg/kg IV once/day, maximum 1 g/day, for 3 successive days) may be given. Oral corticosteroids are given until ESR has remained normal for 1 wk and then are tapered at the rate of 5 mg every 2 days. To
prevent worsening of inflammation during the corticosteroid taper, NSAIDs are begun simultaneously and continued until 2 wk after the corticosteroid has been stopped. Inflammatory markers such as ESR and CRP are used to monitor disease activity and response to treatment.

Recurrences of cardiac inflammation (indicated by fever or chest pain) may subside spontaneously, but NSAIDs or corticosteroids should be resumed if recurrent symptoms last longer than a few days or if heart failure is uncontrolled by standard management (eg, diuretics, ACE inhibitors, β-blockers, inotropic agents). In patients with prolonged, recurrent episodes of carditis, immunosuppressants may be effective. Although useful in the acute episode, NSAIDs and corticosteroids do not prevent or reduce long-term valve damage.

Although poststreptococcal inflammation is well developed by the time ARF is detected, antibiotics are used to eradicate any lingering organisms and to prevent reinfection. Appropriate regimens for the treatment of acute infection are described under Streptococcal and Enterococcal Infections on p. 1230.

**Antibiotic prophylaxis:** Antistreptococcal prophylaxis should be maintained continuously after the initial episode of ARF to prevent recurrences (see Table 282-2). Antibiotics taken orally are just as effective as those given by injection. With the oral route, painful injections are avoided, and clinic visits and observation for postinjection reactions are not needed. With the IM route, adherence difficulties of taking a pill once or twice daily are avoided. The IM regimen has been the standard against which other regimens are measured.

The optimal duration of antistreptococcal prophylaxis is uncertain. Children without carditis should receive prophylaxis for 5 yr or up to age 21 (if the patient turns 21 before 5 yr of prophylaxis is completed). The American Academy of Pediatrics recommends that those with carditis without evidence of residual heart damage receive prophylaxis for 10 yr. Children with carditis and evidence of residual heart damage should receive prophylaxis for > 10 yr; many experts recommend that such patients continue prophylaxis indefinitely. Some experts believe prophylaxis should be life long in all patients with chorea and should continue in all patients who have close contact with young children because of their high rate of GAS carriage.

The American Heart Association no longer recommends that patients with known or suspected rheumatic valvular disease (who are not currently taking prophylactic antibiotics) take short-term antibiotic prophylaxis against bacterial endocarditis for dental or oral surgical procedures (see p. 2199).

**Poststreptococcal Reactive Arthritis**

Poststreptococcal reactive arthritis is development of arthritis after group A streptococcal infection in patients who do not meet the criteria for ARF.

Poststreptococcal reactive arthritis may represent an attenuated variant of ARF. Compared with the arthritis of ARF, poststreptococcal reactive arthritis typically involves fewer joints, is less migratory but more protracted, and responds less to aspirin. It can be treated with other NSAIDs (eg, ibuprofen, naproxen, tolmetin). Although clinical practice for secondary prevention of cardiac involvement varies greatly, it is reasonable to give antistreptococcal prophylaxis for 1 yr and then to repeat the echocardiogram. If cardiac lesions are detected by echocardiogram, long-term prophylaxis is indicated.
Chapter 283. Respiratory Disorders in Neonates, Infants, and Young Children

Introduction

Symptoms and signs of respiratory distress vary and include nasal flaring; intercostal, subcostal, and suprasternal retractions; weak breathing, irregular breathing, or a combination; tachypnea and apneic spells; cyanosis, pallor, mottling, delayed capillary refill, or a combination; and hypotension. In neonates, symptoms and signs may be apparent immediately on delivery or develop minutes or hours afterward.

Etiology

Respiratory distress in neonates and infants has multiple causes (see Table 283-1).

Physiology

There are several significant differences in the physiology of the respiratory system in neonates and infants compared with that of older children and adults. These differences include

[Table 283-1. Causes of Respiratory Distress in Neonates and Infants]

- A more compliant collapsible chest wall
- More reliance on diaphragmatic excursions over intercostal muscles
- Collapsible extrathoracic airways

Also, infants' smaller airway caliber gives increased airway resistance, and absence of collateral ventilation increases tendency toward atelectasis. Yet, other principles of respiration are similar in adults and children.

Evaluation

Evaluation starts with a thorough history and physical examination.

History in the neonate focuses on maternal and prenatal history, particularly gestational age, maternal infection or bleeding, meconium staining of amniotic fluid, and oligohydramnios or polyhydramnios.

Physical examination focuses on the heart and lungs. Chest wall asymmetry or sunken abdomen suggests diaphragmatic hernia. Asymmetric breath sounds suggest pneumothorax, pneumonia, or asthma. A displaced left apical impulse, heart murmur, or both suggest a congenital heart defect. Assessment of BP and femoral pulses may identify circulatory collapse with or without congenital defects. Poor capillary refill reflects circulatory compromise.

In both neonates and infants, it is important to assess oxygenation and response to O₂ therapy by pulse oximetry or blood gases. Chest x-ray also is recommended.

Respiratory Support in Neonates and Infants

Initial stabilization maneuvers include mild tactile stimulation, head positioning, and suctioning of the mouth and nose followed as needed by

- Supplemental O₂
- Continuous positive airway pressure (CPAP)
- Bag and mask ventilation or mechanical ventilation
Neonates who cannot be oxygenated by any of these means may require a full cardiac evaluation to exclude congenital heart disease and treatment with high-frequency oscillatory ventilation, nitric oxide, extracorporeal membrane oxygenation, or a combination.

**Oxygen:** $O_2$ may be given using a nasal cannula, face mask, or $O_2$ hood, with $O_2$ concentration set to achieve a $PaO_2$ of 50 to 70 mm Hg in preterm infants and 50 to 80 mm Hg in term infants or an $O_2$ saturation of 84 to 90% in preterm infants and 92 to 96% in term infants. Lower $PaO_2$ in preterm infants provides almost full saturation of Hb, because fetal Hb has a higher affinity for $O_2$; maintaining higher $PaO_2$ increases the risk of retinopathy of prematurity. No matter how $O_2$ is delivered, it should be warmed (36 to 37° C) and humidified to prevent secretions from cooling and drying and to prevent bronchospasm. An umbilical artery catheter (UAC) is usually placed for sampling ABGs in neonates who require fraction of inspired $O_2$ ($FiO_2$) ≥ 40%. If a UAC cannot be placed, a percutaneous radial artery catheter can be used for continuous BP monitoring and blood sampling.

Neonates who are unresponsive to these maneuvers may require fluids to improve cardiac output and are candidates for CPAP ventilation or bag and mask ventilation (40 to 60 breaths/min). If the infant does not oxygenate with or requires prolonged bag-and-mask ventilation, endotracheal intubation with mechanical ventilation is indicated, although very immature neonates (eg, < 28 wk gestation or < 1000 g) are typically begun on ventilatory support immediately after delivery so that they can receive preventive surfactant therapy. Because bacterial sepsis is a common cause of respiratory distress in neonates, it is common practice to draw blood cultures and give antibiotics to neonates with high $O_2$ requirements pending culture results.

**Continuous positive airway pressure:** CPAP delivers $O_2$ at a positive pressure, usually 5 to 7 cm H$_2$O, which keeps alveoli open and improves oxygenation by reducing the amount of blood shunted through atelectatic areas while the infant breathes spontaneously. CPAP can be provided using nasal prongs and various apparatuses to provide the positive pressure; it also can be given using an endotracheal tube connected to a conventional ventilator with the rate set to zero. CPAP is indicated when $FiO_2$ ≥ 40% is required to maintain acceptable $PaO_2$ (50 to 70 mm Hg) in infants with respiratory disorders that are of limited duration (eg, diffuse atelectasis, mild respiratory distress syndrome, lung edema). In these infants, CPAP may preempt the need for positive pressure ventilation.

**Mechanical ventilation:** Endotracheal tubes are required for mechanical ventilation (see also p. 2273):

- Endotracheal tubes 2.5 mm in diameter (the smallest) typically used for infants < 1250 g
- 3 mm for infants 1250 to 2500 g
- 3.5 mm for infants > 2500 g

Intubation is safer if $O_2$ is insufflated into the infant's airway during the procedure. Orotracheal intubation is preferred. The tube should be inserted such that the

- 7-cm mark is at the lip for infants who weigh 1 kg
- 8-cm mark for 2 kg
- 9-cm mark for 3 kg

The endotracheal tube is properly placed when its tip can be palpated through the anterior tracheal wall at the suprasternal notch. It should be positioned about halfway between the clavicles and the carina on chest x-ray, coinciding roughly with vertebral level T2. If position or patency is in doubt, the tube should be removed and the infant should be supported by bag-and-mask ventilation until a new tube is inserted. **Acute deterioration of the infant's condition** (sudden changes in oxygenation, ABGs, BP, or perfusion)
should trigger suspicion of changes in the position of the tube, patency of the tube, or both.

**Ventilators** can be set to deliver fixed pressures or volumes; can provide assist control (AC, in which the ventilator is triggered to deliver a full breath with each patient inspiration) or intermittent mandatory ventilation (IMV, in which the ventilator delivers a set number of breaths within a time period, and patients can take spontaneous breaths in between without triggering the ventilator); and can be normal or high frequency (delivering 400 to 900 breaths/min). Optimal mode or type of ventilation depends on the infant's response. Volume ventilators are considered useful for larger infants with varying pulmonary compliance or resistance (eg, in bronchopulmonary dysplasia), because delivering a set volume of gas with each breath ensures adequate ventilation. AC mode is often used for treating less severe pulmonary disease and for decreasing ventilator dependence while providing a small increase in airway pressure or a small volume of gas with each spontaneous breath. High-frequency jet, oscillatory, and flow-interrupter ventilators are used in extremely premature infants (< 28 wk) and in some infants with air leaks, widespread atelectasis, or pulmonary edema.

**Initial ventilator settings** are estimated by judging the severity of respiratory impairment. Typical settings for an infant in moderate respiratory distress are FIO₂ = 40%; inspiratory time (IT) = 0.4 sec; expiratory time = 1.1 sec; IMV or AC rate = 40 breaths/min; peak inspiratory pressure (PIP) = 15 cm H₂O for very low-birth-weight infants and up to 25 cm H₂O for near-term infants; and positive end-expiratory pressure (PEEP) = 5 cm H₂O. These settings are adjusted based on the infant's oxygenation, chest wall movement, breath sounds, and respiratory efforts along with arterial or capillary blood gases.

- **PaCO₂** is lowered by increasing the minute ventilation through an increase in tidal volume (increasing PIP or decreasing PEEP) or an increase in rate.

- **PaO₂** is increased by increasing the FIO₂ or increasing the mean airway pressure (increasing PIP, PEEP, or rate or prolonging IT).

Patient-triggered ventilation often is used to synchronize the positive pressure ventilator breaths with the onset of the patient's own spontaneous respirations. This seems to shorten the time on a ventilator and may reduce barotrauma. A pressure-sensitive air-filled balloon attached to a pressure transducer (Graseby capsule) taped to the infant's abdomen just below the xiphoid process can detect the onset of diaphragmatic contraction, or a flow or temperature sensor placed at the endotracheal tube adapter can detect the onset of a spontaneous inhalation.

Ventilator pressures or volumes should be as low as possible to prevent barotrauma and bronchopulmonary dysplasia; an elevated PaCO₂ is acceptable as long as pH remains ≥ 7.25 (permissive hypercapnia). Likewise, a PaO₂ as low as 40 mm Hg is acceptable if BP is normal and metabolic acidosis is not present.

**Adjunctive treatments** used with mechanical ventilation in some patients include

- **Paralytics**

- **Sedation**

- **Nitric oxide**

Paralytics (eg, vecuronium or pancuronium bromide 0.03 to 0.1 mg/kg IV q 1 to 2 h prn [with pancuronium, a test dose of 0.02 mg/kg is recommended in neonates]) and sedatives (eg, fentanyl 1 to 4 μg/kg IV push q 2 to 4 h or midazolam 0.05 to 0.15 mg/kg IV over 5 min q 2 to 4 h) may facilitate endotracheal intubation and can help stabilize infants whose movements and spontaneous breathing prevent optimal ventilation. These drugs should be used selectively, however, because paralyzed infants may need greater ventilator support, which can increase barotrauma. Inhaled nitric oxide 5 to 20 ppm may be used for refractory hypoxemia when pulmonary vasoconstriction is a contributor to hypoxia (eg, in idiopathic pulmonary hypertension, pneumonia, or congenital diaphragmatic hernia) and may prevent the need for extracorporeal membrane oxygenation (see below).
**Weaning** from the ventilator can occur as respiratory status improves. The infant can be weaned by lowering

- FIO\(_2\)
- Inspiratory pressure
- Rate

Continuous-flow positive pressure ventilators permit the infant to breathe spontaneously against PEEP while the ventilator rate is progressively slowed. After the rate has been reduced to 10 breaths/min, the infant usually tolerates extubation. The final steps in ventilator weaning involve extubation, possibly support with nasal (or nasopharyngeal) CPAP, and, finally, use of a hood or nasal cannula to provide humidified O\(_2\) or air.

Very-low-birth-weight infants may benefit from the addition of a methylxanthine (eg, aminophylline, theophylline, caffeine) during the weaning process. Methylxanthines are CNS-mediated respiratory stimulants that increase ventilatory effort and may reduce apneic and bradycardic episodes that may interfere with successful weaning. Caffeine is the preferred agent because it is better tolerated, easier to give, safer, and requires less monitoring. Corticosteroids, once used routinely for weaning and treatment of chronic lung disease, are no longer recommended in premature infants because risks (eg, impaired growth and neurodevelopmental delay) outweigh benefits. A possible exception is as a last resort in near-terminal illness, in which case parents should be fully informed of risks.

**Complications:** Mechanical ventilation complications more common among neonates include

- Pneumothorax
- Asphyxia from endotracheal tube obstruction
- Ulceration, erosion, or narrowing of airway structures due to adjacent pressure
- Bronchopulmonary dysplasia

**Extracorporeal membrane oxygenation (ECMO):** ECMO is a form of cardiopulmonary bypass used for infants who cannot be oxygenated adequately or ventilated with conventional ventilators. Eligibility criteria vary by center, but in general, infants should have reversible disease (eg, persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, overwhelming pneumonia) and should have been on mechanical ventilation < 7 days. After systemic heparinization, blood is circulated through large-diameter catheters from the internal jugular vein into a membrane oxygenator, which serves as an artificial lung to remove CO\(_2\) and add O\(_2\). Oxygenated blood is then circulated back to the internal jugular vein (venovenous ECMO) or to the carotid artery (venoarterial ECMO). Venoarterial ECMO is used when both circulatory support and ventilatory support are needed (eg, in overwhelming sepsis). Flow rates can be adjusted to obtain desired O\(_2\) saturation and BP. ECMO is contraindicated in infants < 34 wk, < 2 kg, or both because of the risk of intraventricular hemorrhage with systemic heparinization. Complications include thromboembolism, air embolization, neurologic (eg, stroke, seizures) and hematologic (eg, hemolysis, neutropenia, thrombocytopenia) problems, and cholestatic jaundice.

**Apnea of Prematurity**

Apnea of prematurity is defined as respiratory pauses > 20 sec or airflow interruption and respiratory pauses > 20 sec associated with bradycardia (< 80 beats/min), central cyanosis, or O\(_2\) saturation < 85% in neonates born at < 37 wk gestation and with no underlying disorders causing apnea. Cause may be CNS immaturity (central) or airway obstruction. Diagnosis is by multichannel respiratory monitoring. Treatment is with respiratory stimulants for central apnea and head positioning for obstructive apnea. Prognosis is excellent; apnea resolves in most
neonates by 37 wk.

About 25% of preterm infants have apnea of prematurity, which usually begins 2 to 3 days after birth and only rarely on the first day. Apnea that develops > 14 days after birth in an otherwise healthy infant signifies a serious illness other than apnea of prematurity (eg, sepsis). Risk increases with earlier gestational age.

Pathophysiology

Apnea of prematurity may be

- Central
- Obstructive
- A mixed pattern (most common)

**Central apnea** is caused by immaturity of medullary respiratory control centers; insufficient neural impulses from the respiratory centers in the medulla reach the respiratory muscles, and the infant stops breathing. Hypoxemia and hypercarbia stimulate respiratory efforts.

**Obstructive apnea** is caused by obstructed airflow, neck flexion causing opposition of hypopharyngeal soft tissues, nasal occlusion, or reflex laryngospasm.

Both types of apnea can cause hypoxemia, cyanosis, and bradycardia if the apnea is prolonged. Among infants dying of SIDS, 18% have a history of prematurity, but apnea of prematurity does not seem to be a precursor to SIDS.

Diagnosis

- Clinical evaluation
- Cardiorespiratory monitoring, physiologic parameter recordings
- Other causes (eg, hypoglycemia, sepsis, intracranial hemorrhage, gastroesophageal reflux disease [GERD]) ruled out

Although frequently attributable to immature respiratory control mechanisms, apnea of prematurity can be sign of major infectious, metabolic, thermoregulatory, respiratory, cardiac, GI, or CNS dysfunction. Careful history, physical assessment, and, when necessary, testing should be done before accepting prematurity as the cause of apnea.

Diagnosis of apnea usually is made by visual observation or by use of impedance-type cardiorespiratory monitors used continuously during assessment and ongoing care of preterm infants. Multichannel recordings of multiple physiologic parameters (eg, chest wall movement, airflow, O$_2$ saturation, heart rate, brain electric activity) taken for up to 24 h can be used as adjuncts for diagnosis and planning and monitoring treatment.

Prognosis

Most preterm infants stop having apneic spells by the time they reach about 37 wk gestation. Apnea may continue for weeks in infants born at extremely early gestational ages (eg, 23 to 27 wk). Death is rare.

Treatment

- Stimulation
- Treatment of underlying disorder
Respiratory stimulants (eg, caffeine)

When apnea is noted, either by observation or monitor alarm, infants are stimulated, which may be all that is required; if breathing does not resume, bag-valve-mask or mouth-to-mouth-and-nose ventilation is provided (see p. 2272). For infants at home, the physician is contacted if apnea occurs but ceases after stimulation; if intervention beyond stimulation is required, the infant should be rehospitalized and evaluated.

Frequent or severe episodes should be quickly and thoroughly evaluated, and identifiable causes should be treated. If no infectious or other treatable underlying disorder is found, respiratory stimulants are indicated for treatment of frequent or severe episodes, characterized by hypoxemia, cyanosis, bradycardia, or a combination. Caffeine is the safest and most commonly used respiratory stimulant drug. It can be given as caffeine base (loading dose 10 mg/kg followed by a maintenance dose of 2.5 mg/kg po q 24 h) or caffeine citrate, a caffeine salt that is 50% caffeine (loading dose 20 mg/kg followed by a maintenance dose of 5 to 10 mg/kg q 24 h). Caffeine is preferred because of ease of administration, fewer adverse effects, larger therapeutic window and less need to monitor drug levels. Treatment continues until the infant is 34 to 35 wk gestation and free from apnea requiring physical intervention for at least 5 to 7 days. Monitoring continues until the infant is free of apnea requiring intervention for 5 to 10 days.

If apnea continues despite respiratory stimulants, the infant may be given continuous positive airway pressure starting at 5 to 8 cm H\(_2\)O pressure. Intractable apneic spells require ventilator support.

Discharge practices vary; some practitioners observe infants for 7 days after treatment has ended to ensure that apnea or bradycardia does not recur, whereas others discharge with caffeine if treatment seems effective.

Prevention

Hospitalized high-risk infants who have not had clinically significant cardiopulmonary events (eg, apnea > 20 sec, apnea accompanied by central cyanosis, apnea associated with heart rate < 80 for > 5 sec) during continuous cardiorespiratory monitoring can be discharged home safely without a monitor. A home cardiorespiratory monitor may be prescribed to shorten the hospital stay for infants that are otherwise ready for discharge but are still having clinically significant cardiopulmonary events that reverse without intervention. Caffeine can be used as an adjunct to a home monitor to achieve this status. Parents should be taught how to properly use equipment, assess alarm situations, intervene (eg, CPR), and keep a log of events. Round-the-clock telephone support and triage as well as outpatient follow-up regarding the decision to stop using the monitor should be provided. Monitors that store event information are preferred.

Infants should sleep on their back. The infant's head should be kept in the midline, and the neck should be kept in the neutral position or slightly extended to prevent upper airway obstruction. All premature infants, especially those with apnea of prematurity, are at risk of apnea, bradycardia, and O\(_2\) desaturation while in a car seat and should undergo a car seat challenge test before discharge.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is chronic lung disease of the neonate that typically is caused by prolonged ventilation and is further defined by age of prematurity and extent of O\(_2\) requirement.

BPD is considered present when there is need for supplemental O\(_2\) in premature infants who do not have other conditions requiring O\(_2\) (eg, pneumonia, congenital heart disease).

Etiology

BPD has a multifactorial etiology. Significant risk factors include
• Prolonged mechanical ventilation
• High concentrations of inspired O₂
• Infection
• Degree of prematurity

Additional risk factors include
• Pulmonary interstitial emphysema
• High peak inspiratory pressures
• Large end-tidal volumes
• Increased airway resistance
• Increased pulmonary artery pressures
• Male sex

The lungs of premature infants are more vulnerable to the inflammatory changes that result from mechanical ventilation. The development of normal lung architecture is interrupted; fewer and larger alveoli develop, and the interstitium is thickened.

**Diagnosis**

• National Institute of Child Health and Human Development (NICHD) criteria
• Characteristic x-ray findings

BPD typically is suspected when a ventilated infant is unable to wean from O₂ therapy, mechanical ventilation, or both. Infants typically develop worsening hypoxemia, hypercapnia, and increasing O₂ requirements. Additionally, when an infant cannot be weaned within the expected time, possible underlying disorders, including patent ductus arteriosus and nursery-acquired pneumonia, should be sought.

For diagnosis, the patient has to have required at least 28 days of > 21% O₂. Specific additional diagnostic criteria (see Table 283-2) have been developed by the NICHD.

Chest x-ray initially shows diffuse haziness due to accumulation of exudative fluid; appearance then becomes multicystic or sponge-like, with alternating areas of emphysema, pulmonary scarring, and atelectasis. Alveolar epithelium may slough, and macrophages, neutrophils, and inflammatory mediators may be found in the tracheal aspirate.

**Prognosis**

Prognosis varies with severity. Infants who still depend on mechanical ventilation at 36 wk gestation have a 20 to 30% mortality rate.

[Table 283-2, National Institute of Child Health and Human Development Criteria for Diagnosis of Bronchopulmonary Dysplasia*]

in infancy. Infants with BPD have a 3- to 4-fold increased rate of growth failure and neurodevelopmental problems. For several years, infants are at increased risk of lower respiratory tract infections (particularly
viral pneumonia or bronchiolitis) and may quickly develop respiratory decompensation if pulmonary infection occurs. The threshold for hospitalization should be low if signs of a respiratory infection or respiratory distress develop.

Treatment

• Nutrition supplementation

• Fluid restriction

• Diuretics

• Inhaled bronchodilators

• O₂ supplementation as needed

• Respiratory syncytial virus (RSV) monoclonal antibody

Treatment is supportive and includes nutritional supplementation, fluid restriction, diuretics, and perhaps inhaled bronchodilators. Respiratory infections must be diagnosed early and treated aggressively. Weaning from mechanical ventilation and supplemental O₂ should be accomplished as early as possible.

Feedings should achieve an intake of 150 calories/kg/day; caloric requirements are increased because of the increased work of breathing and to aid lung healing and growth.

Because pulmonary congestion and edema may develop, daily fluid intake is often restricted to about 120 to 140 mL/kg/day. Diuretic therapy is sometimes used: chlorothiazide 10 to 20 mg/kg po bid plus spironolactone 1 to 3 mg/kg po once/day or split into twice-daily doses. Furosemide (1 to 2 mg/kg IV or IM or 1 to 4 mg/kg po q 12 to 24 h for neonates and q 8 h for older infants) may be used for short periods, but prolonged use causes hypercalcemia with resultant osteoporosis, fractures, and renal calculi. If long-term diuretic use is required, chlorothiazide is preferred because it has fewer adverse effects. Hydration and serum electrolytes should be monitored closely during diuretic therapy.

Weeks or months of additional ventilator support, supplemental O₂, or both may be required for advanced BPD. Ventilator pressures and fraction of inspired O₂ (FIO₂) should be reduced as rapidly as tolerated, but the infant should not be allowed to become hypoxemic. Arterial oxygenation should be continuously monitored with a pulse oximeter and maintained at ≥ 88% saturation. Respiratory acidosis may occur during ventilator weaning and treatment and is acceptable as long as the pH remains > 7.25 and the infant does not develop severe respiratory distress.

Passive immunoprophylaxis with palivizumab, a monoclonal antibody to RSV, decreases RSV-related hospitalizations and ICU stays but is costly and is indicated primarily in high-risk infants (see p. 1411 for indications). During RSV season (November through April), children are given 15 mg/kg IM q 30 days until 6 mo after treatment of the acute illness. Infants > 6 mo also should be vaccinated against influenza.

Systemic or inhaled corticosteroids are discouraged except as a last-resort therapy for established BPD with rapidly worsening pulmonary status and impending death. Informed parental consent is required.

Prevention

Practices for prevention of BPD include

• Use of antenatal corticosteroids

• Prophylactic use of exogenous surfactant in selected high-risk infants (eg, < 30 wk gestation)

• Early therapeutic continuous positive airway pressure
• Early use of surfactant for treatment of respiratory distress syndrome
• Prophylactic use of methylxanthines to assist successful early ventilator therapy withdrawal
• Permissive hypercarbia and hypoxemia to achieve low ventilator pressures, volumes, or both
• Prophylactic use of vitamin A (5000 units IM 3 times/wk for a total of 12 doses) for infants with birth weight < 1000 g
• Avoidance of large volumes of fluid
• Early aggressive management of patent ductus arteriosus

Inhaled nitric oxide seems to be promising and is under investigation.

**Meconium Aspiration Syndrome**

Intrapartum meconium aspiration can cause inflammatory pneumonitis and mechanical bronchial obstruction, causing a syndrome of respiratory distress. Findings include tachypnea, rales and rhonchi, and cyanosis or desaturation. Diagnosis is suspected when there is respiratory distress after delivery through meconium-tinged amniotic fluid and is confirmed by chest x-ray. Treatment is vigorous suction immediately on delivery before neonates take their first breath, followed by respiratory support as needed. Prognosis depends on the underlying physiologic stressors.

**Etiology**

Physiologic stress at the time of labor and delivery (eg, due to hypoxia caused by umbilical cord compression or placental insufficiency or caused by infection) may cause the fetus to pass meconium into the amniotic fluid before delivery; meconium passage is noted in about 10 to 15% of births. During delivery, perhaps 5% of neonates with meconium passage aspirate the meconium, triggering lung injury and respiratory distress, termed meconium aspiration syndrome. Postterm infants delivered through reduced amniotic fluid volume are at risk of more severe disease because the less dilute meconium is more likely to cause airway obstruction.

**Pathophysiology**

The mechanisms by which aspiration induces the clinical syndrome probably include

• Nonspecific cytokine release
• Airway obstruction
• Surfactant inactivation
• Chemical pneumonitis

Underlying physiologic stressors also may contribute. If complete bronchial obstruction occurs, atelectasis results; partial blockage leads to air trapping on expiration, resulting in hyperexpansion of the lungs and possibly pulmonary air leak (see p. 2874) with pneumomediastinum or pneumothorax. Persistent pulmonary hypertension can be associated with meconium aspiration as a comorbid condition or because of continuing hypoxia (see p. 2873).

Neonates also may aspirate vernix caseosa, amniotic fluid, or blood of maternal or fetal origin during delivery, which can cause respiratory distress and signs of aspiration pneumonia on chest x-ray.

**Symptoms and Signs**
Signs include tachypnea, nasal flaring, retractions, cyanosis or desaturation, rales, rhonchi, and greenish yellow staining of the umbilical cord, nail beds, or skin. Meconium staining may be visible in the oropharynx and (on intubation) in the larynx and trachea. Neonates with air trapping may have a barrel-shaped chest and also symptoms and signs of pneumothorax, pulmonary interstitial emphysema, and pneumomediastinum (see p. 2875).

Diagnosis

• Meconium passage
• Respiratory distress
• Characteristic x-ray findings

Diagnosis is suspected when a neonate shows respiratory distress in the setting of meconium-tinged amniotic fluid. Diagnosis is confirmed by chest x-ray showing hyperinflation with variable areas of atelectasis and flattening of the diaphragm. Initial x-ray findings can be confused with the findings of transient tachypnea of the newborn (see p. 2877). Fluid may be seen in the lung fissures or pleural spaces, and air may be seen in the soft tissues or mediastinum. Because meconium may enhance bacterial growth and meconium aspiration syndrome is difficult to distinguish from bacterial pneumonia, cultures of blood and tracheal aspirate also should be taken.

Prognosis

Prognosis is generally good, although it varies with the underlying physiologic stressors; overall mortality is slightly increased. Infants with meconium aspiration syndrome may be at greater risk of asthma in later life.

Treatment

• Suctioning at birth before the first breath
• Endotracheal intubation as needed
• Mechanical ventilation as needed
• Supplemental O₂ as needed
• IV antibiotics

Immediate treatment, indicated for all neonates delivered through meconium, is vigorous suctioning of the mouth and nasopharynx using a DeLee suction apparatus as soon as the head is delivered and before the neonate breathes and cries. If suction returns no meconium and the neonate appears vigorous, observation without further intervention is appropriate. If the neonate has labored or depressed respirations, poor muscle tone, or is bradycardic (< 100 beats/min), the trachea should be intubated with a 3.5- or 4.0-mm endotracheal tube. A meconium aspirator connected to a suction apparatus is attached directly to the endotracheal tube, which then serves as the suction catheter. Suction is maintained while the endotracheal tube is removed. Reintubation and continuous positive airway pressure are indicated for continued respiratory distress, followed by mechanical ventilation and admission to the neonatal ICU as needed. Because positive pressure ventilation enhances risk of pulmonary air-leak syndrome, regular evaluation (including physical examination and chest x-ray) is important to detect this complication, which should be sought immediately in any intubated neonate whose BP, perfusion, or O₂ saturation suddenly worsens. See p. 2874 for treatment of air-leak syndromes.

Additional treatments may include surfactant for mechanically ventilated neonates with high O₂ requirements, which can decrease the need for extracorporeal membrane oxygenation, and antibiotics.
(usually ampicillin and an aminoglycoside). Inhaled nitric oxide in the range of 5 to 20 ppm and high-frequency ventilation are other therapies that are used if refractory hypoxemia develops; they also may decrease need for extracorporeal membrane oxygenation.

**Persistent Pulmonary Hypertension of the Newborn**

Persistent pulmonary hypertension of the newborn is the persistence of or reversion to pulmonary arteriolar constriction, causing a severe reduction in pulmonary blood flow and right-to-left shunting. Symptoms and signs include tachypnea, retractions, and severe cyanosis or desaturation unresponsive to O$_2$. Diagnosis is by history, examination, chest x-ray, and response to O$_2$. Treatment is with O$_2$; alkalinization; high-frequency ventilation; nitric oxide; pressors, inotropes, or both; and extracorporeal membrane oxygenation if other therapies fail.

Persistent pulmonary hypertension of the newborn is a disorder of pulmonary vasculature that affects term or postterm infants.

**Etiology**

The most common causes involve

- Perinatal asphyxia or hypoxia

A history of meconium staining of amniotic fluid or meconium in the trachea is common. Hypoxia triggers reversion to or persistence of intense pulmonary arteriolar constriction, a normal state in the fetus.

Additional causes include

- Premature ductus arteriosus or foramen ovale closure, which increases fetal pulmonary blood flow and may be triggered by maternal NSAID use

- Polycythemia, which obstructs blood flow

- Congenital diaphragmatic hernia, in which one lung is severely hypoplastic, forcing most of the pulmonary blood flow through the other lung

- Neonatal sepsis presumably because vasoconstrictive prostaglandins are produced by activation of the cyclooxygenase pathway by bacterial phospholipids

**Pathophysiology**

Whatever the cause, elevated pressure in the pulmonary arteries causes abnormal smooth muscle development and hypertrophy in the walls of the small pulmonary arteries and arterioles and right-to-left shunting via the ductus arteriosus or a foramen ovale, resulting in intractable systemic hypoxemia. Both pulmonary and systemic resistances are high, which leads to an increased load on the heart. This load increase may result in right heart dilation, tricuspid insufficiency, and right heart failure.

**Symptoms and Signs**

Symptoms and signs include tachypnea, retractions, and severe cyanosis or desaturation unresponsive to supplemental O$_2$. In infants with a right-to-left shunt via a patent ductus arteriosus, oxygenation is higher in the right brachial artery than in the descending aorta; thus cyanosis may be differential (ie, O$_2$ saturation in the lower extremities is $\geq$ 5% lower than in the right upper extremity).

**Diagnosis**

- Cyanosis unresponsive to O$_2$ therapy
Echocardiogram

X-ray to identify underlying disorders

Diagnosis should be suspected in any near-term infant with arterial hypoxemia, cyanosis, or both, especially one with a suggestive history whose O\textsubscript{2} saturation does not improve with administration of 100\% O\textsubscript{2}. Diagnosis is confirmed by echocardiogram, which can confirm the presence of elevated pressures in the pulmonary artery and simultaneously can exclude congenital heart disease. On x-ray, lung fields may be normal or may show changes due to the underlying disorder (eg, meconium aspiration syndrome, neonatal pneumonia, congenital diaphragmatic hernia).

Prognosis

An oxygenation index (mean airway pressure [cm H\textsubscript{2}O] × fraction of inspired O\textsubscript{2} [FIO\textsubscript{2}] × 100/PaO\textsubscript{2}) > 40 predicts mortality of > 50\%. Overall mortality ranges from 10 to 80\% and is directly related to the oxygenation index but also varies with the underlying disorder. However, many survivors (perhaps one third) exhibit developmental delay, hearing deficits, functional disabilities, or a combination. This rate of disability may be no different from that of other infants with severe illness.

Treatment

O\textsubscript{2} to dilate pulmonary vasculature and improve oxygenation

Mechanical ventilation support

Use of nitric oxide considered

Extracorporeal membrane oxygenation as needed

Circulatory support

Treatment with O\textsubscript{2}, which is a potent pulmonary vasodilator, is begun immediately to prevent disease progression. O\textsubscript{2} is delivered via bag and mask or mechanical ventilation; mechanical distention of alveoli aids vasodilation. FIO\textsubscript{2} should initially be 1 but can be titrated downward to maintain PaO\textsubscript{2} between 50 and 90 mm Hg to minimize lung injury. Once PaO\textsubscript{2} is stabilized, weaning can be attempted by reducing FIO\textsubscript{2} in decrements of 2 to 3\%, then reducing ventilator pressures; changes should be gradual, because a large drop in PaO\textsubscript{2} can cause recurrent pulmonary artery vasoconstriction. High-frequency oscillatory ventilation expands and ventilates the lungs while minimizing barotrauma and should be considered for infants with underlying lung disease in whom atelectasis and ventilation/perfusion (V/Q) mismatch may exacerbate the hypoxemia of persistent pulmonary hypertension of the newborn.

Inhaled nitric oxide relaxes endothelial smooth muscle, dilating pulmonary arterioles, which increases pulmonary blood flow and rapidly improves oxygenation in as many as half of patients. Initial dose is 20 ppm, titrated downward by effect.

Extracorporeal membrane oxygenation (see p. 2868) may be used in newborns with severe hypoxic respiratory failure defined by an oxygenation index > 35 to 40 despite maximum respiratory support.

Normal fluid, electrolyte, glucose, and Ca levels must be maintained. Infants should be kept in a neutral thermal environment and treated with antibiotics for possible sepsis until culture results are known. Inotropes and pressors may be required as part of circulatory support.

Pulmonary Air-Leak Syndromes

Pulmonary air-leak syndromes involve dissection of air out of the normal pulmonary airspaces.
Air-leak syndromes include pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, pneumopericardium, pneumoperitoneum, and subcutaneous emphysema. Pneumothorax and pneumomediastinum occur in 1 to 2% of normal neonates, probably because large negative intrathoracic forces created when the neonate starts breathing occasionally disrupt alveolar epithelium, which allows air to move from the alveoli into extra-alveolar soft tissues or spaces.

Air leak is more common and severe among neonates with lung disease, who are at risk because of poor lung compliance and the need for high airway pressures (eg, in respiratory distress) or because of air trapping (eg, meconium aspiration syndrome), which leads to alveolar overdistention.

Many affected neonates are asymptomatic; diagnosis is suspected clinically or because of deterioration in O₂ status and is confirmed by x-ray. Treatment varies by type of air leak but in ventilated infants always involves lowering inspiratory pressures to lowest tolerated settings. High-frequency ventilators may be helpful but are of unproven benefit.

**Pulmonary interstitial emphysema:** Pulmonary interstitial emphysema is leakage of air from alveoli into the pulmonary interstitium, lymphatics, or subpleural space. It usually occurs in infants with poor lung compliance, such as those with respiratory distress syndrome who are being treated with mechanical ventilation, but it may occur spontaneously. One or both lungs may be involved, and pathology may be focal or generalized within each lung. If dissection of air is widespread, respiratory status may acutely worsen because lung compliance suddenly is reduced.

Chest x-ray shows a variable number of cystic or linear lucencies in the lung fields. Some lucencies are elongated; others appear as enlarged subpleural cysts ranging from a few millimeters to several centimeters in diameter.

Pulmonary interstitial emphysema may resolve dramatically over 1 or 2 days or persist on x-ray for weeks. Some infants with severe respiratory disease and pulmonary interstitial emphysema develop bronchopulmonary dysplasia (BPD—see p. 2870), and the cystic changes of long-standing pulmonary interstitial emphysema then merge into the x-ray picture of BPD.

Treatment is mainly supportive. If one lung is significantly more involved than the other, the infant may be laid down on the side of the lung with the more severe pulmonary interstitial emphysema; this will help to compress the lung with pulmonary interstitial emphysema, thereby decreasing air leakage and perhaps improving ventilation of the normal (elevated) lung. If one lung is very severely affected and the other is mildly affected or uninvolved, differential bronchial intubation and ventilation of the less-involved lung also may be attempted; total atelectasis of the non-intubated lung soon results. Because only one lung is now being ventilated, ventilator settings and fraction of inspired O₂ may need to be altered. After 24 to 48 h, the endotracheal tube is pulled back into the trachea, at which time the air leak may have stopped.

**Pneumomediastinum:** Pneumomediastinum is dissection of air into connective tissue of the mediastinum (see also p. 2001); the air may further dissect into the subcutaneous tissues of the neck and scalp. Pneumomediastinum usually causes no symptoms or signs, though subcutaneous air causes crepitus. Diagnosis is by x-ray; in an anteroposterior view, air may form a lucency around the heart, whereas on a lateral view, air lifts the lobes of the thymus away from the cardiac silhouette (spinnaker sail sign). No treatment is usually needed, and the condition resolves spontaneously.

**Pneumopericardium:** Pneumopericardium is dissection of air into the pericardial sac. It affects mechanically ventilated infants almost exclusively. Most cases are asymptomatic, but if sufficient air accumulates, it can cause cardiac tamponade (see p. 2201). Diagnosis is suspected if infants experience acute circulatory collapse and is confirmed by lucency around the heart on x-ray or by return of air on pericardiocentesis using an angiocatheter and syringe. Treatment is pericardiocentesis followed by surgical insertion of a pericardial tube.

**Pneumoperitoneum:** Pneumoperitoneum is dissection of air into the peritoneum. It is generally not clinically significant but must be distinguished from pneumoperitoneum due to a ruptured abdominal viscus, which is a surgical emergency. Diagnosis is made by abdominal x-ray and physical examination. Clinical symptoms that include abdominal rigidity, absent bowel sounds, and signs of sepsis suggest
abdominal viscus injury.

**Pneumothorax:** Pneumothorax is dissection of air into the pleural space; sufficient accumulation of air causes tension pneumothorax (see p. 2002). Although sometimes asymptomatic, pneumothorax typically causes worsening of tachypnea, grunting, and cyanosis. Breath sounds decrease, and the chest enlarges on the affected side. Tension pneumothorax causes cardiovascular collapse.

Diagnosis is suspected by deterioration of respiratory status, by transillumination of the chest with a fiberoptic probe, or both. Diagnosis is confirmed by chest x-ray or, in the case of tension pneumothorax, return of air during thoracentesis.

Most small pneumothoraces resolve spontaneously, but larger and tension pneumothoraces require evacuation of the air in the pleural cavity. In tension pneumothorax, a scalp vein needle or an angiocatheter and syringe can be used to temporarily evacuate free air from the pleural space. Definitive treatment is insertion of an 8 or 10 French chest tube attached to continuous suction. Follow-up auscultation, transillumination, and x-ray confirm that the tube is functioning properly.

**Respiratory Distress Syndrome**

(Hyaline Membrane Disease)

**Respiratory distress syndrome (RDS) is caused by pulmonary surfactant deficiency in the lungs of neonates, most commonly in those born at < 37 wk gestation. Risk increases with degree of prematurity. Symptoms and signs include grunting respirations, use of accessory muscles, and nasal flaring appearing soon after birth. Diagnosis is clinical; prenatal risk can be assessed with tests of fetal lung maturity. Treatment is surfactant therapy and supportive care.**

**Etiology**

Surfactant is not produced in adequate amounts until relatively late in gestation; thus, risk of RDS increases with greater prematurity. Other risk factors include multifetal pregnancies, maternal diabetes, and being male and white.

Risk decreases with fetal growth restriction, preeclampsia or eclampsia, maternal hypertension, prolonged rupture of membranes, and maternal corticosteroid use.

Rare cases are hereditary, caused by mutations in surfactant protein (SP-B and SP-C) and ATP-binding cassette transporter A3 (ABCA3) genes.

**Pathophysiology**

Pulmonary surfactant is a mixture of phospholipids and lipoproteins secreted by type II pneumocytes (see p. 2766). It diminishes the surface tension of the water film that lines alveoli, thereby decreasing the tendency of alveoli to collapse and the work required to inflate them.

With surfactant deficiency, the lungs become diffusely atelectatic, triggering inflammation and pulmonary edema. Because blood passing through the atelectatic portions of lung is not oxygenated (forming a right-to-left intrapulmonary shunt), the infant becomes hypoxemic. Lung compliance is decreased, thereby increasing the work of breathing. In severe cases, the diaphragm and intercostal muscles fatigue, and CO2 retention and respiratory acidosis develop.

**Complications:** Complications of RDS include intraventricular hemorrhage, periventricular white matter injury, tension pneumothorax, bronchopulmonary dysplasia, sepsis, and neonatal death. Intracranial complications have been linked to hypoxemia, hypercarbia, hypotension, swings in arterial BP, and low cerebral perfusion (see also Intracranial Hemorrhage on p. 2773 and Hemorrhagic Shock and Encephalopathy Syndrome on p. 2934).

**Symptoms and Signs**
Symptoms and signs include rapid, labored, grunting respirations appearing immediately or within a few hours after delivery, with suprasternal and substernal retractions and flaring of the nasal alae. As atelectasis and respiratory failure progress, symptoms worsen, with cyanosis, lethargy, irregular breathing, and apnea.

Neonates weighing < 1000 g may have lungs so stiff that they are unable to initiate or sustain respirations in the delivery room.

On examination, breath sounds are decreased. Peripheral pulses may be decreased with peripheral extremity edema and decreased urine output.

**Diagnosis**

- Clinical presentation
- ABG (hypoxemia and hypercapnia)
- Chest x-ray
- Blood, CSF, and tracheal aspirate cultures

Diagnosis is by clinical presentation, including recognition of risk factors; ABGs showing hypoxemia and hypercapnia; and chest x-ray. Chest x-ray shows diffuse atelectasis classically described as having a ground-glass appearance with visible air bronchograms; appearance correlates loosely with clinical severity.

Differential diagnosis includes group B streptococcal pneumonia and sepsis, transient tachypnea of the newborn, persistent pulmonary hypertension, aspiration, pulmonary edema, and congenital cardiopulmonary anomalies. Neonates typically require cultures of blood, CSF, and possibly tracheal aspirate. Clinical diagnosis of group B streptococcal pneumonia is extremely difficult; thus, antibiotics usually are started pending culture results.

RDS can be anticipated prenataally using tests of fetal lung maturity, which measure surfactant obtained by amniocentesis or collected from the vagina (if membranes have ruptured) and which can help determine the optimal timing of delivery. These are indicated for elective deliveries before 39 wk when fetal heart tones, human chorionic gonadotropin levels, and ultrasound measurements cannot confirm gestational age and for nonelective deliveries between 34 wk and 36 wk. Risk of RDS is low when lecithin/sphingomyelin ratio is > 2, phosphatidyl glycerol is present, foam stability index = 47, surfactant/albumin ratio (measured by fluorescence polarization) is > 55 mg/g, or a combination.

**Treatment**

- Surfactant
- Supplementary O₂ as needed
- Mechanical ventilation as needed

Prognosis with treatment is excellent; mortality is < 10%. With adequate ventilatory support alone, surfactant production eventually begins, and once production begins, RDS resolves within 4 or 5 days. However, in the meantime, severe hypoxemia can result in multiple organ failure and death.

Specific treatment is intratracheal surfactant therapy. This therapy requires endotracheal intubation, which also may be necessary to achieve adequate ventilation and oxygenation. Less premature infants (those > 1 kg) and those with lower O₂ requirements (fraction of inspired O₂ [FIO₂] < 40 to 50%) may respond well to supplemental O₂ alone or to treatment with nasal continuous positive airway pressure. A
treatment strategy of early (within 20 to 30 min after birth) surfactant therapy is associated with significant
decrease in duration of mechanical ventilation, lesser incidence of air leak syndromes, and lower
incidence of bronchopulmonary dysplasia.

Surfactant hastens recovery and decreases risk of pneumothorax, interstitial emphysema, intraventricular
hemorrhage, bronchopulmonary dysplasia, and neonatal mortality in the hospital and at 1 yr. However,
neonates who receive surfactant for established RDS have an increased risk of apnea of prematurity.
Options for surfactant replacement include beractant (a lipid bovine lung extract supplemented with
proteins B and C, colfosceril palmitate, palmitic acid, and tripalmitin) 100 mg/kg q 6 h prn up to 4 doses;
poractant alfa (a modified porcine-derived minced lung extract containing phospholipids, neutral lipids,
fatty acids, and surfactant-associated proteins B and C) 200 mg/kg followed by up to 2 doses of 100
mg/kg 12 h apart prn; and calfactant (a calf lung extract containing phospholipids, neutral lipids, fatty
acids, and surfactant-associated proteins B and C) 105 mg/kg q 12 h up to 3 doses prn. Lung compliance
can improve rapidly after therapy. The ventilator peak inspiratory pressure may need to be lowered
rapidly to reduce risk of a pulmonary air leak. Other ventilator parameters (eg, FIO\textsubscript{2}, rate) also may need
to be reduced.

Prevention

When a fetus must be delivered between 24 wk and 34 wk, giving the mother 2 doses of betamethasone
12 mg IM 24 h apart or 4 doses of dexamethasone 6 mg IV or IM q 12 h at least 48 h before delivery
induces fetal surfactant production and reduces the risk of RDS or decreases its severity. (See also
Preterm Labor on p. 2683.)

Prophylactic intratracheal surfactant therapy given to neonates that are at high risk of developing RDS
(infants < 30 wk completed gestation especially in absence of antenatal corticosteroid exposure) has
been shown to decrease risk of neonatal death and certain forms of pulmonary morbidity (eg,
pneumothorax).

Transient Tachypnea of the Newborn

(Neonatal Wet Lung Syndrome)

Transient tachypnea of the newborn is respiratory distress caused by delayed resorption of
fetal lung fluid.

Transient tachypnea of the newborn affects premature infants, term infants delivered by cesarean
section, and infants born with respiratory depression, all of whom have delayed clearance of fetal lung
fluid. (Mechanisms for normal resorption of fetal lung fluid are discussed on p. 2766.) For unknown
reasons, maternal diabetes and asthma are also risk factors. The disorder can occur in preterm infants
with respiratory distress syndrome and in term infants born through meconium-stained amniotic fluid.

Transient tachypnea of the newborn is suspected when the infant develops respiratory distress shortly
after birth. Symptoms include tachypnea, intracostal and subcostal retractions, grunting, nasal flaring, and
possible cyanosis.

Pneumonia and sepsis may have similar manifestations, so chest x-ray, CBC, and blood cultures usually
are done. Chest x-ray shows hyperinflated lungs with streaky perihilar markings, giving the appearance of
a shaggy heart border while the periphery of the lungs is clear. Fluid is often seen in the lung fissures. If
initial findings are indeterminate or suggest infection, antibiotics (eg, ampicillin, gentamicin) are given
while awaiting culture results.

Recovery usually occurs within 2 to 3 days. Treatment is supportive and involves giving O\textsubscript{2} by hood and
monitoring ABGs or pulse oximetry. Rarely, extremely premature infants, those with neurologic depression
at birth, or both require continuous positive airway pressure and occasionally even mechanical
ventilation.

**Bacterial Tracheitis**
Bacterial tracheitis is bacterial infection of the trachea.

Bacterial tracheitis is uncommon and can affect children of any age. *Staphylococcus aureus* and group A β-hemolytic streptococci are involved most frequently. Onset is acute and is characterized by respiratory stridor, high fever, and often copious purulent secretions. Rarely, bacterial tracheitis may develop as a complication of viral croup or endotracheal intubation. As in patients with epiglottitis, the child may have marked toxicity and respiratory distress that may progress rapidly and may require intubation.

Diagnosis is suspected clinically and can be confirmed by direct laryngoscopy, which reveals purulent secretions and inflammation in the subglottic area with a shaggy, purulent membrane or by lateral neck x-ray, which reveals subglottic narrowing that may be irregular as opposed to the symmetric tapering typical of croup.

Treatment in severe cases is the same as that of epiglottitis (see p. 476); whenever possible, endotracheal intubation should be done in controlled circumstances by a clinician skilled in managing a pediatric airway (see p. 2273). Initial antibiotics should cover *S. aureus* and streptococcal species; cefuroxime or an equivalent IV preparation may be appropriate empirically unless methicillin-resistant staphylococcus is prevalent in the community, in which case vancomycin should be used. Therapy for critically ill children should be guided by a consultant knowledgeable in local susceptibility patterns. Once definitive microbial diagnosis is made, coverage is narrowed and continued for ≥ 10 days.

Complications include bronchopneumonia, sepsis, and retropharyngeal cellulitis or abscess. Subglottic stenosis secondary to prolonged intubation is uncommon. Most children treated appropriately recover without sequelae.

**Bronchiolitis**

Bronchiolitis is an acute viral infection of the lower respiratory tract affecting infants < 24 mo and is characterized by respiratory distress, wheezing, and crackles. Diagnosis is suspected by history, including presentation during a known epidemic; the primary cause, respiratory syncytial virus, can be identified with a rapid assay. Treatment is supportive with O₂ and hydration. Prognosis is generally excellent, but some patients develop apnea or respiratory failure.

Bronchiolitis often occurs in epidemics and mostly in children < 24 mo, with a peak incidence in infants < 6 mo. The annual incidence in the first year of life is about 11 cases/100 children. Most cases occur between November and April, with a peak incidence during January and February.

**Etiology**

Most cases are caused by

- Respiratory syncytial virus (RSV)
- Parainfluenza 3 virus

Less frequent causes are influenza A and B, parainfluenza 1 and 2, metapneumovirus, and adenoviruses. Rhinoviruses, enteroviruses, measles virus, and *Mycoplasma pneumoniae* are uncommon causes.

**Pathophysiology**

The virus spreads from the upper respiratory tract to the medium and small bronchi and bronchioles, causing epithelial necrosis and initiating an inflammatory response. The developing edema and exudate result in partial obstruction, which is most pronounced on expiration and leads to alveolar air trapping. Complete obstruction and absorption of the trapped air may lead to multiple areas of atelectasis.
Symptoms and Signs

Typically, an affected infant has URI symptoms with progressively increasing respiratory distress characterized by tachypnea, retractions, and a wheezy or hacking cough. Young infants may present with recurrent apneic spells followed by more typical symptoms and signs over 24 to 48 h. Signs of distress may include circumoral cyanosis, deepening retractions, and audible wheezing. Fever is usually but not always present. Infants initially appear nontoxic and in no distress, despite tachypnea and retractions, but may become increasingly lethargic as the infection progresses. Hypoxemia is the rule in more severely affected infants. Dehydration may develop from vomiting and decreased oral intake. With fatigue, respirations may become more shallow and ineffective, leading to respiratory acidosis. Auscultation reveals wheezing, prolonged expiration, and, often, fine moist crackles. Many children have accompanying acute otitis media.

Diagnosis

• Clinical presentation
• Pulse oximetry
• Chest x-ray as needed
• RSV antigen test from nasal swab or washing for seriously ill children

Diagnosis is suspected by history, examination, and occurrence of the illness as part of an epidemic. Symptoms similar to bronchiolitis can result from asthma, which is more likely in a child > 18 mo of age, especially if previous episodes of wheezing and a family history of asthma have been documented. Gastric reflux with aspiration of gastric contents also may cause the clinical picture of bronchiolitis; multiple episodes in an infant may be clues to this diagnosis. Foreign body aspiration occasionally causes wheezing and should be considered if the onset is sudden and not associated with manifestations of URI. Heart failure associated with a left-to-right shunt manifesting at age 2 to 3 mo also can be confused with bronchiolitis.

Patients suspected of having bronchiolitis should undergo pulse oximetry to evaluate oxygenation. No further testing is required for mild cases with normal \( O_2 \) levels, but in cases of hypoxemia, a chest x-ray supports the diagnosis, typically showing hyperinflated lungs, depressed diaphragm, and prominent hilar markings. Infiltrates may be present from atelectasis as well as RSV pneumonia, which is relatively common among infants with RSV bronchiolitis. RSV rapid antigen testing done on a nasal swab or washing is diagnostic but not generally necessary; it may be reserved for patients with illness severe enough to require hospitalization. Other laboratory testing is nonspecific; about two thirds of the children have WBC counts of 10,000 to 15,000/\( \mu L \). Most have 50 to 75% lymphocytes.

Prognosis

Prognosis is excellent. Most children recover in 3 to 5 days without sequelae, although wheezing and cough may continue for 2 to 4 wk. Mortality is < 1% when medical care is adequate. An increased incidence of asthma is suspected in children who have had bronchiolitis in early childhood, but the association is controversial and the incidence seems to decrease as children age.

Treatment

• Supportive therapy
• \( O_2 \) supplementation as needed
• IV hydration as needed

Treatment is supportive, and most children can be managed at home with hydration and comfort.
Indications for hospitalization include accelerating respiratory distress, ill appearance (eg, cyanosis, lethargy, fatigue), apnea by history, hypoxemia, and inadequate oral intake. Children with underlying disorders such as cardiac disease, immunodeficiency, or bronchopulmonary dysplasia, which put them at high risk of severe or complicated disease, also should be considered candidates for hospitalization.

In hospitalized children, 30 to 40% $O_2$ delivered by tent or face mask is usually sufficient to maintain $O_2$ saturation > 90%. Endotracheal intubation is indicated for severe recurrent apnea, hypoxemia unresponsive to $O_2$ therapy, or $CO_2$ retention or if the child cannot clear bronchial secretions.

Hydration may be maintained with frequent small feedings of clear liquids. For sicker children, fluids should be given IV initially, and the level of hydration should be monitored by urine output and specific gravity and by serum electrolyte determinations.

There is some evidence that systemic corticosteroids are beneficial when given very early in the course of the illness or in children with underlying corticosteroid-responsive conditions (eg, bronchopulmonary dysplasia, asthma), but benefit in most hospitalized infants is unproven.

Antibiotics should be withheld unless a secondary bacterial infection (a rare sequela) occurs. Bronchodilators are not uniformly effective, but a substantial subset of children may respond with short-term improvement. This is particularly true of infants who have wheezed previously. Hospital stays probably are not shortened.

Ribavirin, an antiviral drug active in vitro against RSV, influenza, and measles, is probably not effective clinically and is no longer recommended; it also is potentially toxic to hospital staff. RSV immune globulin has been tried but is probably ineffective.

Prevention of RSV infection by passive immunoprophylaxis with monoclonal antibody to RSV (palivizumab) decreases the frequency of hospitalization but is costly and is indicated primarily in high-risk infants (see p. 1411 for indications and dosage).

Croup (Laryngotraceobronchitis)

Croup is acute inflammation of the upper and lower respiratory tracts most commonly caused by parainfluenza virus type 1 infection. It is characterized by a barking cough and inspiratory stridor. Diagnosis is usually obvious clinically but can be made by anteroposterior neck x-ray. Treatment is antipyretics, hydration, nebulized racemic epinephrine, and corticosteroids. Prognosis is excellent.

Croup affects mainly children aged 6 mo to 3 yr.

Etiology

The parainfluenza viruses, especially type 1, are the most common pathogens. Less common causes are respiratory syncytial virus (RSV) and influenza A and B viruses, followed by adenovirus, enterovirus, rhinovirus, measles virus, and Mycoplasma pneumoniae. Croup caused by influenza may be particularly severe and may occur in a broader age range of children.

Seasonal outbreaks are common. Cases caused by parainfluenza viruses tend to occur in the fall; those caused by RSV and influenza viruses tend to occur in the winter and spring. Spread is usually through the air or by contact with infected secretions.

Pathophysiology

The infection causes inflammation of the larynx, trachea, bronchi, bronchioles, and lung parenchyma.
Obstruction caused by swelling and inflammatory exudates develops and becomes pronounced in the subglottic region. Obstruction increases the work of breathing; rarely, tiring results in hypercapnia. Atelectasis may occur concurrently if the bronchioles become obstructed.

**Symptoms and Signs**

Croup is usually preceded by URI symptoms. A barking, often spasmodic, cough and hoarseness then occur, commonly at night; inspiratory stridor may be present as well. The child may awaken at night with respiratory distress, tachypnea, and retractions. In severe cases, cyanosis with increasingly shallow respirations may develop as the child tires.

The obvious respiratory distress and harsh inspiratory stridor are the most dramatic physical findings. Auscultation reveals prolonged inspiration and stridor. Rales also may be present, indicating lower airway involvement. Breath sounds may be diminished with atelectasis. Fever is present in about half of children. The child's condition may seem to have improved in the morning but worsens again at night.

Recurrent episodes are often called spasmodic croup. Allergy or airway reactivity may play a role in spasmodic croup, but the clinical manifestations cannot be differentiated from those of viral croup. Also, spasmodic croup usually is initiated by a viral infection.

**Diagnosis**

- Clinical presentation (eg, barking cough, inspiratory stridor)
- Anteroposterior (AP) and lateral neck x-rays as needed

Diagnosis is usually obvious by the barking nature of the cough. Similar inspiratory stridor can result from epiglottitis, bacterial tracheitis, foreign body, diphtheria, and retropharyngeal abscess. Epiglottitis (see p. 475), retropharyngeal abscess (see p. 471), and bacterial tracheitis (see p. 2878) have a more rapid onset and cause a more toxic appearance, odynophagia, and fewer upper respiratory tract symptoms. A foreign body may cause respiratory distress and a typical croupy cough, but fever and a preceding URI are absent. Diphtheria is excluded by a history of adequate immunization and is confirmed by identification of the organism in viral cultures of scrapings from typical grayish diphtheritic membrane.

If the diagnosis is unclear, patients should have AP and lateral x-rays of the neck and chest; subepiglottic narrowing (steeple sign) seen on AP neck x-ray supports the diagnosis. Seriously ill patients, in whom epiglottitis is a concern, should be examined in the operating room by appropriate specialists able to establish an airway (see p. 476). Patients should have pulse oximetry, and those with respiratory distress should have ABG measurement.

**Treatment**

- For outpatients, cool humidified air and possibly a single dose of oral corticosteroids

- For inpatients, humidified O₂, racemic epinephrine, and oral corticosteroids

The illness usually lasts 3 to 4 days and resolves spontaneously. A mildly ill child may be cared for at home with hydration and antipyretics. Keeping the child comfortable is important, because fatigue and crying can aggravate the condition. Humidification devices (eg, cold-steam vaporizers or humidifiers) may ameliorate upper airway drying and are frequently used at home by families but have not been shown to alter the course of the illness. The vast majority of children with croup recover completely.

Increasing or persistent respiratory distress, tachycardia, fatigue, cyanosis or hypoxemia, or dehydration indicates need for hospitalization. Pulse oximetry is helpful for assessing and monitoring severe cases. If O₂ saturation falls below 92%, humidified O₂ should be given, and ABGs should be measured to assess CO₂ retention. A 30 to 40% inspired O₂ concentration is usually adequate. CO₂ retention (PaCO₂ > 45 mm Hg) generally indicates fatigue and the need for endotracheal intubation, as does inability to maintain...
Nebulized racemic epinephrine 5 to 10 mg in 3 mL of saline q 2 h offers symptomatic relief and relieves fatigue. However, the effects are transient; the course of the illness, the underlying viral infection, and the PaO₂ are not altered by its use. Tachycardia and other adverse effects may occur.

High-dose dexamethasone 0.6 mg/kg IM or po once (maximum dose 10 mg) may benefit children early in the first 24 h of the disease. It can help prevent hospitalization or help the child who is hospitalized with moderate to severe croup. The viruses that most commonly cause croup do not usually predispose to secondary bacterial infection, and antibiotics are rarely indicated.
Introduction

Cystic fibrosis (CF) is an inherited disease of the exocrine glands affecting primarily the GI and respiratory systems. It leads to chronic lung disease, exocrine pancreatic insufficiency, hepatobiliary disease, and abnormally high sweat electrolytes. Diagnosis is by sweat test or identification of 2 CF-causing mutations in patients with characteristic symptoms or a positive newborn screening test result. Treatment is supportive through aggressive multidisciplinary care.

CF is the most common life-threatening genetic disease in the white population. In the US, it occurs in about 1/3,300 white births, 1/15,300 black births, and 1/32,000 Asian-American births. Because of improved treatment and life expectancy, 45% of patients are adults.

Etiology

CF is carried as an autosomal recessive trait by about 3% of the white population. The responsible gene has been localized on the long arm of chromosome 7. It encodes a membrane-associated protein called the cystic fibrosis transmembrane conductance regulator (CFTR). The most common gene mutation, ΔF508, occurs in about 70% of CF alleles; > 1500 less common CFTR mutations have been identified. CFTR seems to be part of a cAMP-regulated Cl channel, regulating Cl and Na transport across epithelial membranes. A number of additional functions are considered likely. Disease manifests only in homozygotes. Heterozygotes may show subtle abnormalities of epithelial electrolyte transport but are clinically unaffected.

Pathophysiology

Nearly all exocrine glands are affected in varying distribution and degree of severity. Glands may

- Become obstructed by viscid or solid eosinophilic material in the lumen (pancreas, intestinal glands, intrahepatic bile ducts, gallbladder, and submaxillary glands)

- Appear histologically abnormal and produce excessive secretions (tracheobronchial and Brunner's glands)

- Appear histologically normal but secrete excessive Na and Cl (sweat, parotid, and small salivary glands)

Respiratory: Although the lungs are generally histologically normal at birth, most patients develop pulmonary disease beginning in infancy or early childhood. Mucus plugging and chronic bacterial infection, accompanied by a pronounced inflammatory response, damage the airways, ultimately leading to bronchiectasis and respiratory insufficiency. The course is characterized by episodic exacerbations with infection and progressive decline in pulmonary function.

Pulmonary damage is probably initiated by diffuse obstruction in the small airways by abnormally thick mucus secretions. Bronchiolitis and mucopurulent plugging of the airways occur secondary to obstruction and infection. Airway changes are more common than parenchymal changes, and emphysema is not prominent. About 40% of patients have bronchial hyperreactivity that is responsive to bronchodilators; however, benefits of bronchodilator therapy may not persist into adulthood. Chronic hypoxemia results in muscular hypertrophy of the pulmonary arteries, pulmonary hypertension, and right ventricular hypertrophy. Much of the pulmonary damage may be caused by inflammation secondary to the release of proteases by neutrophils in the airways.

The lungs of most patients are colonized by pathogenic bacteria. Early in the course, Staphylococcus aureus is the most common pathogen, but as the disease progresses, Pseudomonas aeruginosa is most frequently isolated. A mucoid variant of P. aeruginosa is uniquely associated with CF. Colonization with Burkholderia cepacia occurs in about 3% of patients and may be associated with rapid pulmonary
deterioration.

**GI:** The pancreas, intestines, and hepatobiliary system are frequently affected. Exocrine pancreatic function is compromised in 85 to 95% of patients. Exceptions are a subset of patients who have certain mild CF mutations, in whom pancreatic function is unaffected. Patients with pancreatic insufficiency have malabsorption of fats (and fat-soluble vitamins) and protein. Duodenal fluid is abnormally viscid and shows absence or diminution of enzyme activity and decreased \( \text{HCO}_3^- \) concentration; stool trypsin and chymotrypsin are absent or diminished. Endocrine pancreatic dysfunction is less common, but about 40% of older patients have abnormal glucose tolerance secondary to reduced and delayed insulin response, and about 17% develop diabetes.

Bile duct involvement with bile stasis and biliary plugging leads to asymptomatic hepatic fibrosis in 30% of patients. About 5 to 6% of patients progress to irreversible multi-nodular biliary cirrhosis with varices and portal hypertension, usually by 12 yr of age. Hepatocellular failure is a rare and late event. There is an increased incidence of cholelithiasis, which is usually asymptomatic.

Abnormally viscid intestinal secretions often cause meconium ileus in neonates (see p. 2801) and sometimes meconium plugging of the colon. Older children and adults also may develop intestinal obstruction.

Other GI problems include intussusception, rectal prolapse, periappendiceal abscess, pancreatitis, an increased risk of cancer of the hepatobiliary and GI tracts, gastroesophageal reflux, and esophagitis.

**Other:** Infertility occurs in 98% of adult men secondary to maldevelopment of the vas deferens or to other forms of obstructive azoospermia. In women, fertility is decreased secondary to viscid cervical secretions, although many women with CF have carried pregnancies to term. However, the incidence of maternal complications and preterm births is increased.

Other complications include osteopenia/osteoporosis, renal stones, iron deficiency anemia, and episodic arthralgias/arthritis.

**Symptoms and Signs**

**Respiratory:** Fifty percent of patients not diagnosed through newborn screening present with pulmonary manifestations, often beginning in infancy. Recurrent or chronic infections manifested by cough and wheezing are common. Cough is the most troublesome complaint, often accompanied by sputum, gagging, vomiting, and disturbed sleep. Intercostal retractions, use of accessory muscles of respiration, a barrel-chest deformity, digital clubbing, and cyanosis occur with disease progression. Upper respiratory tract involvement includes nasal polyposis and chronic or recurrent sinusitis. Adolescents may have retarded growth, delayed onset of puberty, and a declining tolerance for exercise. Pulmonary complications in adolescents and adults include pneumothorax, infection with nontuberculous mycobacteria, hemoptysis, and right heart failure secondary to pulmonary hypertension.

**GI:** Meconium ileus due to obstruction of the ileum by viscid meconium may be the earliest sign and is present in 15 to 20% of affected neonates. It typically manifests with abdominal distention, vomiting, and failure to pass meconium. Some infants have intestinal perforation, with signs of peritonitis and shock. Infants with meconium plug syndrome have a delayed passage of meconium. They can have similar signs of obstruction or very mild and transient symptoms that go unnoticed. Older patients with CF can have partial bowel obstruction similar to what is seen in infancy. Distal intestinal obstruction syndrome (DIOS) can occur in 10 to 20% of adolescents and adults with CF.

In infants without meconium ileus, disease onset may be heralded by a delay in regaining birth weight and inadequate weight gain at 4 to 6 wk of age.

Occasionally, infants who are undernourished, especially if on hypoallergenic formula or soy formula, present with generalized edema secondary to protein malabsorption.
Pancreatic insufficiency is usually clinically apparent early in life and may be progressive. Manifestations include the frequent passage of bulky, foul-smelling, oily stools; abdominal protuberance; and poor growth pattern with decreased subcutaneous tissue and muscle mass despite a normal or voracious appetite. Clinical manifestations may occur secondary to deficiency of fat-soluble vitamins.

Rectal prolapse occurs in 20% of untreated infants and toddlers. Gastroesophageal reflux is relatively common among older children and adults.

Other: Excessive sweating in hot weather or with fever may lead to episodes of hypotonic dehydration and circulatory failure. In arid climates, infants may present with chronic metabolic alkalosis. Salt crystal formation and a salty taste on the skin are highly suggestive of CF.

Diagnosis

• Suggested by a positive prenatal or newborn screening, family history, or symptomatic presentation

• Confirmed by a sweat test showing elevated sweat Cl on ≥ 2 occasions

• Sometimes confirmed by genetic testing or in vivo ion transport abnormalities across nasal epithelium

People are suspected of having CF by prenatal or newborn screening, family history, or symptoms. In all cases, diagnosis needs to be confirmed by a quantitative pilocarpine iontophoresis sweat test.

Sweat testing: In this test, localized sweating is stimulated with pilocarpine, the amount of sweat is measured, and its Cl concentration is determined (see Table 284-1). The results are valid after 48 h of life, but an adequate sweat sample (> 75 mg on filter paper or > 15 μL in microbore tubing) may be difficult to obtain before 2 wk of age. False-negative results are rare but may occur in the presence of edema and hypoproteinemia or an inadequate quantity of sweat. False-positive results are usually due to technical error. Transient elevation of sweat Cl concentration can occur from psychosocial deprivation (eg, child abuse, neglect) and in patients with anorexia nervosa. Although the sweat Cl concentration increases slightly with age, the sweat test is valid at all ages. A positive sweat test result should be confirmed by a 2nd sweat test or by identification of 2 CF-causing mutations.

Intermediate sweat test results: A small subset of patients have a mild or partial CF phenotype and sweat Cl values that are persistently in the intermediate or even normal range. In addition, there are patients who have single organ manifestations such as pancreatitis, chronic sinusitis, or congenital bilateral absence of the vas deferens that may be due to partial CFTR protein dysfunction. In some of these patients, the diagnosis of CF can be confirmed by the identification of 2 CF-causing mutations. If 2 CF-causing mutations are not identified, ancillary evaluations such as pancreatic function testing and pancreatic imaging, high-resolution chest CT, pulmonary function testing, urogenital evaluation in males, and bronchoalveolar lavage including assessment of microbial flora may be useful. Additional potentially helpful tests include expanded CFTR genetic analysis and measurement of nasal transepithelial potential difference (based on the observation of increased Na reabsorption across epithelium that is relatively impermeable to Cl in patients with CF).

[Table 284-1: Sweat Cl Concentration Ranges]

Pancreatic tests: Pancreatic function should be assessed at the time of diagnosis, usually by measuring 72 h fecal fat excretion or the concentration of human pancreatic elastase in stool. This latter test is valid even in the presence of exogenous pancreatic enzymes. Infants who are initially pancreatic sufficient and who carry 2 severe mutations should have serial measurements to detect progression to pancreatic insufficiency.

Respiratory assessment: Chest x-rays are done at times of pulmonary deterioration or exacerbations and routinely every 1 to 2 yr. High-resolution CT may be helpful to more precisely define the extent of lung damage and to detect subtle airway abnormalities. Both may show hyperinflation and bronchial wall thickening as the earliest findings. Subsequent changes include areas of infiltrate, atelectasis, and hilar
adenopathy. With advanced disease, segmental or lobar atelectasis, cyst formation, bronchiectasis, and pulmonary artery and right ventricular enlargement occur. Branching, fingerlike opacifications that represent mucoid impaction of dilated bronchi are characteristic.

Sinus CT studies are indicated in patients with significant sinus symptoms or nasal polyps in whom endoscopic sinus surgery is being considered. These studies almost always show persistent opacification of the paranasal sinuses.

Pulmonary function tests are the best indicators of clinical status and should be done 2 to 4 times/yr. Pulmonary function can now be evaluated in infants by using a raised volume rapid thoracoabdominal compression technique. Pulmonary function tests indicate hypoxemia; reduction in forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV$_1$), forced expiratory flow between 25% and 75% expired volume (FEF$_{25-75}$), and FEV$_1$/FVC ratio; and an increase in residual volume and the ratio of residual volume to total lung capacity. Fifty percent of patients have evidence of reversible airway obstruction as shown by improvement in pulmonary function after aerosol administration of a bronchodilator.

Oropharyngeal or sputum cultures should be done 2 to 4 times/yr, especially in patients not yet colonized with *P. aeruginosa*. Bronchoscopy/bronchoalveolar lavage is indicated when it is important to precisely define the patient's lower airway microbial flora (eg, to direct antibiotic selection).

Newborn screening: Newborn screening for CF is rapidly expanding in the US and should be universal by 2010. Screening is based on detecting an elevated concentration of immunoreactive trypsinogen (IRT) in the blood. There are two methods of confirming an elevated IRT level. In one method, a second IRT test is done, which, if also elevated, is followed by a sweat test. In the other method, an elevated IRT level is followed by CFTR mutation testing and, if 1 or 2 mutations are identified, then a sweat test is done. Both strategies have about 95% sensitivity.

Carrier screening: CF carrier screening is available in the US and is recommended for couples who are planning a pregnancy or seeking prenatal care. If both potential parents carry a CFTR mutation, prenatal screening of the fetus can be done by chorionic villus sampling or amniocentesis. Prenatal counseling in such cases is complicated by the wide phenotypic variability of CF and incomplete information on the clinical consequences of many of the CFTR mutations that are identified through screening.

Prognosis

The course is largely determined by the degree of pulmonary involvement. Deterioration is inevitable, leading to debilitation and eventual death, usually due to a combination of respiratory failure and cor pulmonale. Prognosis has improved steadily over the past 5 decades, mainly because of aggressive treatment before the onset of irreversible pulmonary changes. Median survival in the US is to age 37 yr. Long-term survival is significantly better in patients without pancreatic insufficiency. Outcomes are also affected by CFTR mutation profile, modifier genes, airway microbiology, exposure to air pollutants (including tobacco smoke), and socioeconomic status. The FEV$_1$, adjusted for age and sex, is the best predictor of survival.

Treatment

• Comprehensive, multidisciplinary support

• Antibiotics, aerosol drugs to thin airway secretions, and physical maneuvers to clear airway secretions

• Inhaled bronchodilators and sometimes corticosteroids for responders

• Pancreatic enzyme supplementation

Comprehensive and intensive therapy should be directed by an experienced physician working with a multidisciplinary team that includes other physicians, nurses, dieticians, physical and respiratory therapists, counselors, pharmacists, and social workers. The goals of therapy are maintenance of normal
nutritional status, prevention or aggressive treatment of pulmonary and other complications, encouragement of physical activity, and provision of psychosocial support. With appropriate support, most patients can make an age-appropriate adjustment at home and school. Despite myriad problems, the educational, occupational, and marital successes of patients are impressive.

**Respiratory:** Treatment of pulmonary problems centers on prevention of airway obstruction and prophylaxis against and control of pulmonary infection. Prophylaxis against pulmonary infections includes maintenance of pertussis, *Haemophilus influenzae*, varicella, *Streptococcus pneumoniae*, and measles immunity and annual influenza vaccination. In patients exposed to influenza, a neuraminidase inhibitor can be used prophylactically. Giving palivizumab to infants with CF for prevention of respiratory syncytial virus infection has been shown to be safe, but efficacy has not been documented.

Chest physical therapy consisting of postural drainage, percussion, vibration, and assisted coughing is recommended at the first indication of pulmonary involvement (see p. 1867). In older patients, alternative airway clearance techniques, such as active cycle of breathing, autogenic drainage, positive expiratory pressure devices, and mechanical vest therapy, may be effective.

For those with reversible airway obstruction, bronchodilators may be given by aerosol. Corticosteroids by aerosol usually are not effective. O₂ therapy is indicated for patients with severe pulmonary insufficiency and hypoxemia.

Mechanical ventilation is generally not indicated for chronic respiratory failure. Its use should be restricted to patients with good baseline status in whom acute reversible respiratory complications develop, in association with pulmonary surgery, or to patients in whom lung transplantation is imminent. Noninvasive positive pressure ventilation nasally or by face mask also can be beneficial. Oral expectorants are widely used, but few data support their efficacy. Cough suppressants should be discouraged. Long-term daily aerosol therapy with dornase alfa (recombinant human deoxyribonuclease) as well as 7% hypertonic saline has been shown to slow the rate of decline in pulmonary function and to decrease the frequency of severe respiratory tract exacerbations.

Pneumothorax can be treated with closed chest tube thoracostomy drainage. Open thoracotomy or thoracoscopy with resection of pleural blebs and sponge abrasion of the pleural surfaces is effective in treating recurrent pneumothoraces.

Massive or recurrent hemoptysis is treated by embolizing involved bronchial arteries.

Oral corticosteroids are indicated in infants with prolonged bronchiolitis and in patients with refractory bronchospasm, allergic bronchopulmonary aspergillosis, and inflammatory complications (eg, arthritis, vasculitis). Long-term use of alternate-day corticosteroid therapy can slow the decline in pulmonary function, but because of corticosteroid-related complications, it is not recommended for routine use. Patients receiving corticosteroids must be closely monitored for evidence of diabetes and linear growth retardation.

Ibuprofen, when given over several years at a dose sufficient to achieve a peak plasma concentration between 50 and 100 μg/mL, has been shown to slow the rate of decline in pulmonary function, especially in children 5 to 13 yr. The appropriate dose must be individualized based on pharmacokinetic studies.

**Antibiotics:** Antibiotics should be used in symptomatic patients according to culture and sensitivity testing. A penicillinase-resistant penicillin (eg, cloxacillin or dicloxacillin) or a cephalosporin (eg, cephalaxin) is the drug of choice for staphylococci. Erythromycin, amoxicillin/clavulanate, ampicillin, tetracycline, linezolid, trimethoprim/sulfamethoxazole, or occasionally chloramphenicol may be used individually or in combination for protracted ambulatory therapy of pulmonary infection due to a variety of organisms. Fluoroquinolones are effective against sensitive strains of *P. aeruginosa* and have been used safely in young children.

For severe pulmonary exacerbations, especially in patients colonized with *P. aeruginosa*, parenteral antibiotic therapy is advised. Patients often require hospital admission, but carefully selected patients can safely receive the therapy at home. Combinations of an aminoglycoside (eg, tobramycin, gentamicin) and
an antipseudomonal penicillin are given IV. IV administration of cephalosporins and monobactams with antipseudomonal activity may also be useful. The usual starting dose of tobramycin or gentamicin is 2.5 to 3.5 mg/kg tid, but higher doses (3.5 to 4 mg/kg tid) may be required to achieve acceptable serum concentrations (peak level 8 to 10 μg/mL [11 to 17 μmol/L], trough value of < 2 μg/mL [< 4 μmol/L]). Alternatively, tobramycin can be given safely and effectively in one daily dose (10 to 12 mg/kg). Because of enhanced renal clearance, large doses of some penicillins may be required to achieve adequate serum levels. The goal of treating pulmonary infections should be to improve the patient's clinical status sufficiently so that continuous use of antibiotics is unnecessary. However, in patients who are colonized with *P. aeruginosa*, long-term use of alternate-month aerosol tobramycin therapy and oral azithromycin given 3 times/wk may be effective in improving or stabilizing pulmonary function and decreasing the frequency of pulmonary exacerbations.

In symptomatic patients who are chronically colonized with *P. aeruginosa*, the role of antibiotic therapy is to improve clinical parameters and possibly reduce the bacterial burden in the airways. Eradication of *Pseudomonas* is not usually possible. It has been shown, however, that early antibiotic treatment around the time of initial airway colonization with nonmucoid strains of *P. aeruginosa* may be effective in eradicating the organism for some period of time. Treatment strategies vary but usually consist of inhaled tobramycin or colistin often in association with an oral fluoroquinolone.

GI: Neonatal intestinal obstruction can sometimes be relieved by enemas containing a hyperosmolar or iso-osmolar radiopaque contrast material; otherwise, surgical enterostomy to flush out the viscid meconium in the intestinal lumen may be necessary. After the neonatal period, episodes of partial intestinal obstruction (distal intestinal obstruction syndrome) can be treated with enemas containing a hyperosmolar or iso-osmolar radiopaque contrast material or acetylcysteine, or by oral administration of a balanced intestinal lavage solution. A stool softener such as dioctyl sodium sulfosuccinate or lactulose may help prevent such episodes. Ursodeoxycholic acid, a hydrophilic bile acid, is often used in patients with liver disease caused by CF, but there is little evidence to support its efficacy.

**Pancreatic enzyme replacement** should be given with all meals and snacks. The most effective enzyme preparations contain pancrelipase in pH-sensitive, enteric-coated micro-spheres or microtablets. Infants are usually started at a dose of 2000 to 4000 IU lipase per 120 mL of formula or per breastfeeding session. After infancy, weight-based dosing is used starting at 1000 IU lipase/kg/meal for children < 4 yr and at 500 IU lipase/kg/meal for those > 4 yr. Usually, half the standard dose is given with snacks. Doses > 2500 IU lipase/kg/meal or > 10,000 IU lipase/kg/day should be avoided because high enzyme dosages have been associated with fibrosing colonopathy. In patients with high enzyme requirements, acid suppression with an H₂ blocker or proton pump inhibitor may improve enzyme effectiveness.

**Diet** therapy includes sufficient calories and protein to promote normal growth—30 to 50% more than the usual recommended dietary allowances may be required (see Table 1-4 on p. 5) as well as a normal-to-high total fat in-take to increase the caloric density of the diet; a water-miscible multivitamin supplement in double the recommended daily allowance; and salt supplementation during infancy and periods of thermal stress and increased sweating. Infants receiving broad-spectrum antibiotics and patients with liver disease and hemoptysis should be given supplemental vitamin K. Formulas containing protein hydrolysates and medium-chain triglycerides may be used instead of modified whole-milk formulas for infants with severe malabsorption. Glucose polymers and medium-chain triglyceride supplements can be used to increase caloric intake. In patients who fail to maintain adequate nutritional status, enteral supplementation via NGT, gastrostomy, or jejunostomy may restore normal growth and stabilize pulmonary function (see p. 20). The use of appetite stimulants to enhance growth may be helpful in some patients.

**Other:** Patients with symptomatic right heart failure should be treated with diuretics, salt restriction, and O₂.

**Surgery** may be indicated for localized bronchiectasis or atelectasis that cannot be treated effectively with drugs, nasal polyps, chronic sinusitis, bleeding from esophageal varices secondary to portal hypertension, gall-bladder disease, and intestinal obstruction due to a volvulus or an intussusception that cannot be medically reduced. Liver transplantation has been done successfully in patients with end-stage
liver disease. Bilateral cadaveric lung and live donor lobar transplantation has been done successfully in patients with advanced cardiopulmonary disease, as well as combined liver-lung transplantation for patients with end-stage liver and lung disease. Double lung transplantation for severe lung disease is becoming more routine and more successful with experience and improved techniques. About 60% of people are alive 5 yr after transplantation of both lungs, and their condition is much improved.

Gene therapy, in which normal CF genes are delivered directly to the airways, holds promise for treating CF. However, this therapy is only available in research trials. A number of new drugs to improve chloride channel function, delivered by mouth or aerosol, are under investigation.

**End-of-life care:** The patient and family deserve sensitive discussions of prognosis and preferences for care throughout the course of illness, especially as the patient's pulmonary reserves become increasingly limited. Most people facing the end of life with CF will be older adolescents or adults and will be appropriately responsible for their own choices. Thus, they must know what is in store and what can be done. One mark of respect for patients living with CF is to ensure that they are given the information and opportunity to make life choices, including having a substantial hand in determining how and when to accept dying. Often, discussion of transplantation is needed. In considering transplantation, patients need to weigh the merits of longer survival with a transplant against the uncertainty of getting a transplant and the ongoing (but different) illness of living with an organ transplant.

Deteriorating patients need to discuss the eventuality of dying. Patients and their families need to know that most often dying is actually gentle and not profoundly symptomatic. When appropriate, palliative care, including sufficient sedation, should be offered to ensure peaceful dying. A useful strategy for the patient to consider is to accept a time-limited trial of fully aggressive treatment when needed, but to agree in advance to parameters that indicate when to stop aggressive measures.
Chapter 285. Endocrine Disorders in Children

Introduction

(See also Hypopituitarism in Children Resulting in Short Stature on p. 767 and see p. 866 for diabetes in adults and children.)

Some endocrine disorders occur mostly in children (eg, precocious or delayed puberty); others occur in children and adults (eg, diabetes, thyroid disorders). Those that affect both adults and children may cause different symptoms in children.

Congenital Goiter

Congenital goiter is a diffuse or nodular enlargement of the thyroid gland present at birth. Thyroid hormone secretion may be decreased, increased, or normal. Diagnosis is by confirming thyroid size with ultrasonography. Treatment is thyroid hormone replacement when hypothyroidism is the cause. Surgery is indicated when breathing or swallowing is impaired.

Etiology

Congenital goiters may be caused by dyshormonogenesis (abnormal thyroid hormone production), transplacental passage of maternal antibodies, or transplacental passage of goitrogens. Some causes are hereditary.

Dyshormonogenesis: Genetic defects in thyroid hormone production result in increased levels of thyroid-stimulating hormone (TSH), which in turn can cause congenital goiter. There are 4 main types of dyshormonogenesis.

• Type 1 is caused by a defect in iodide transport secondary to altered synthesis of a cell surface protein necessary for transport.

• Type 2 is caused by one of several defects in thyroid iodination mechanisms. The enzyme peroxidase, necessary for iodine organification, may be absent (resulting in goitrous cretinism) or dysfunctional. Another defect may impair hydrogen peroxide generation. Children with Pendred's syndrome have mild hypothyroidism or euthyroidism, goiter, and sensorineural hearing loss due to an abnormal transport protein (pendrin) involved in iodine transport and cochlear function.

• Type 3 is caused by complete or partial deiodination defects of monoiodotyrosine and diiodotyrosine in thyroglobulin.

• Type 4 is caused by one of several defects in thyroglobulin synthesis, usually via X-linked inheritance and thus commonly occurs in boys. This condition does not cause clinical hypothyroidism. It is, however, characterized by a very low level of total serum thyroxine ($T_4$) but normal levels of free $T_4$ and TSH.

Transplacental passage of maternal antibodies: Women with an autoimmune thyroid disorder produce antibodies that may cross the placenta during the 3rd trimester. Depending on the disorder, the antibodies either block TSH receptors, causing hypothyroidism, or stimulate them, causing hyperthyroidism. Typically, in affected infants, the changes in hormone secretion and the associated goiter resolve spontaneously within 3 to 6 mo.

Transplacental passage of goitrogens: Goitrogens such as amiodarone or antithyroid drugs (eg, propylthiouracil, methimazole) can cross the placenta, sometimes causing hypothyroidism and rarely causing goiter.

Symptoms and Signs
The most common manifestation is firm, nontender enlargement of the thyroid. Enlargement is most often diffuse but can be nodular. It may be noticeable at birth or detected later. In some patients, enlargement is not directly observable, but continued growth can cause deviation or compression of the trachea, compromising breathing and swallowing. Many children with goiters are euthyroid, but some present with hypothyroidism or hyperthyroidism.

**Diagnosis**

If the diagnosis is suspected, thyroid size is typically assessed by ultrasonography. T₄ and TSH are measured.

**Treatment**

Hypothyroidism is treated with thyroid hormone. Goiters that compromise breathing and swallowing can be treated surgically.

**Hypothyroidism**

Hypothyroidism is thyroid hormone deficiency. Symptoms in infants include poor feeding and growth failure; symptoms in older children and adolescents are similar to those of adults but also include growth failure, delayed puberty, or both. Diagnosis is by thyroid function testing (eg, serum thyroxine, thyroid-stimulating hormone). Treatment is thyroid hormone replacement.

**Etiology**

Hypothyroidism in infants and young children may be congenital or acquired.

**Congenital hypothyroidism** occurs in about 1/4000 live births. Most congenital cases are sporadic, but about 10 to 20% are inherited. The most frequent cause of congenital hypothyroidism is dysgenesis, either absence (agenesis) or underdevelopment (hypoplasia) of the thyroid gland. About 10% of congenital hypothyroidism results from dys hormonogenesis (abnormal thyroid hormone production), of which there are 4 types (see p. 2887). Rarely in the US but commonly in certain developing countries, hypothyroidism results from maternal iodine deficiency. Rarely, transplacental transfer of antibodies, goitrogens (eg, amiodarone), or antithyroid drugs (eg, propylthiouracil, methimazole) causes transient hypothyroidism.

**Acquired hypothyroidism** is typically caused by autoimmune thyroiditis (Hashimoto's thyroiditis) and occurs during later childhood and adolescence.

**Symptoms and Signs**

Symptoms and signs in infants and young children differ from those in older children and adults. If iodine deficiency occurs very early during pregnancy, infants may present with endemic cretinism (a syndrome involving deaf-mutism), intellectual disability, and spasticity. Most other hypothyroid infants initially have few if any symptoms or signs. Symptoms that do occur may be subtle or develop slowly because some maternal thyroid hormone crosses the placenta. However, after the maternal thyroid hormone is metabolized, if the underlying cause of hypothyroidism persists and hypothyroidism remains undiagnosed or untreated, it usually slows CNS development moderately to severely and may be accompanied by low muscle tone, prolonged hyperbilirubinemia, umbilical hernia, respiratory distress, macroglossia, large fontanelles, poor feeding, and hoarse crying. Rarely, delayed diagnosis and treatment of severe hypothyroidism lead to intellectual disability and short stature.

Some symptoms and signs in older children and adolescents are similar to those of adults (eg, weight gain; constipation; coarse, dry hair; sallow, cool, or mottled coarse skin—see p. 781). Signs specific to children are growth retardation, delayed skeletal maturation, and usually delayed puberty.

**Diagnosis**
• Routine neonatal screening

• Thyroid function tests

Routine neonatal screening detects hypothyroidism before clinical signs are evident. If screening is positive, confirmation is necessary with thyroid function tests, including measurement of serum thyroxine (T4), free T4, and thyroid-stimulating hormone (TSH). These tests are also done in older children and adolescents in whom hypothyroidism is suspected.

Severe congenital hypothyroidism, even when treated promptly, may still cause subtle developmental problems and sensorineural hearing loss. Hearing loss may be so mild that initial screening misses it, although it may still interfere with language acquisition. Retesting after infancy is advised to detect subtle hearing loss.

**Treatment**

• Thyroid hormone replacement

Most cases of congenital hypothyroidism require lifelong thyroid hormone replacement. Treatment with L-thyroxine 10 to 15 μg/kg po once/day must be started immediately and be closely monitored. This dosage is intended to rapidly normalize serum T4 and should then be adjusted to maintain the serum T4 level between 10 and 15 μg/dL during infancy. After age 1 yr, the usual dosage is 5 to 6 μg/kg po once/day, titrated to maintain serum T4 and TSH levels within the normal range for age. This dosing regimen is also used for acquired hypothyroidism in children and adolescents. In later childhood or adolescence, the starting dosage may be calculated as 100 μg/m2 po once/day. In most treated infants, motor and intellectual development is normal. Thyroxine-binding globulin deficiency, detected by screening that relies primarily on T4 measurement, does not require treatment because affected infants are euthyroid.

**Hyperthyroidism**

Hyperthyroidism is excessive thyroid hormone production. Diagnosis is by thyroid function testing (eg, free serum thyroxine, thyroid-stimulating hormone). Treatment is with propylthiouracil or methimazole.

**Etiology**

Hyperthyroidism is rare in infants but potentially life-threatening. It develops in fetuses of women with current or prior Graves' disease who have elevated titers of thyroid-stimulating immunoglobulins, which overstimulate thyroid hormone production by binding to thyroid-stimulating hormone (TSH) receptors in the thyroid gland. These antibodies cross the placenta and cause thyroid hyperfunction in the fetus (intrauterine Graves' disease), which can result in fetal death or premature birth. Because infants clear the antibodies after birth, neonatal Graves' disease is usually transient. However, because the clearance rate varies, duration of neonatal Graves' disease varies. In children and adolescents, Graves' disease is the usual cause of hyperthyroidism.

**Symptoms and Signs**

Symptoms and signs in infants include irritability, feeding problems, hypertension, tachycardia, exophthalmos, goiter, frontal bossing, and microcephaly. Other early findings are failure to thrive, vomiting, and diarrhea. Affected infants almost always recover within 6 mo; the course is rarely longer. Persistent hyperthyroidism may result in craniosynostosis (premature fusion of the cranial sutures), impaired intellect, growth failure, short stature, and hyperactivity later in childhood. Mortality rate may reach 10 to 15%. In children and adolescents, acquired Graves' disease is characterized by diffuse goiter, thyrotoxicosis, and, rarely, infiltrative ophthalmopathy.

**Diagnosis**
Thyroid function tests

Diagnosis is suspected in infants whose mothers have Graves' disease and high titers of stimulatory antibodies (thyroid-stimulating immunoglobulins) and is confirmed by measuring free serum thyroxine (T₄) and TSH. Diagnosis in adolescents is similar to that in adults and also includes thyroid function tests.

Treatment

• Antithyroid drugs
• Radioactive sodium iodine
• Sometimes surgery

Infants are given an antithyroid drug (eg, propylthiouracil 1.7 to 3.3 mg/kg po tid, methimazole 0.17 to 0.33 mg/kg po tid), sometimes with a β-blocker (eg, propranolol 0.8 mg/kg po tid) to treat symptoms. Treatment must be monitored closely and stopped as soon as the disease has run its course (for treatment of Graves' disease during pregnancy, see p. 2650). For older children and adolescents, treatment is similar to that for adults (see p. 782) and includes antithyroid drugs, radioactive sodium iodine, and sometimes surgery.

Congenital Adrenal Hyperplasia

(Adrenogenital Syndrome; Adrenal Virilism)

Congenital adrenal hyperplasia is a group of genetic disorders, each characterized by inadequate synthesis of cortisol, aldosterone, or both. In the most common forms, accumulated hormone precursors are shunted into androgen production, causing androgen excess; in rarer forms, synthesis of androgens is also inadequate.

In the various forms of congenital adrenal hyperplasia, production of cortisol (a glucocorticoid), aldosterone (a mineralocorticoid), or both is impaired because of an autosomal recessive genetic defect in one of the adrenal enzymes involved in synthesizing adrenal steroid hormones from cholesterol. The enzyme may be absent or deficient, completely or partially disabling synthesis of cortisol, aldosterone, or both. In the forms in which cortisol synthesis is absent or decreased, ACTH (corticotropin) release, normally suppressed by cortisol, is excessive. In the most common forms, 21-hydroxylase deficiency and 11β-hydroxylase deficiency, precursors proximal to the enzyme block accumulate and are shunted into adrenal androgens. The consequent excess androgen secretion causes varying degrees of virilization in external genitals of affected female fetuses; no defects are discernible in external genitals of male fetuses. In some less common forms affecting enzymes other than 21-hydroxylase and 11β-hydroxylase, the enzyme block impairs androgen synthesis (dehydroepiandrosterone [DHEAS] or androstenedione). As a result, virilization of male fetuses is inadequate, but no defect is discernible in female fetuses.

21-Hydroxylase Deficiency

21-Hydroxylase (CYP21A2) deficiency causes defective conversion of adrenal precursors to cortisol and, in some cases, to aldosterone, resulting in virilization and sometimes severe hyponatremia and hyperkalemia. Diagnosis is by measurement of cortisol, its precursors, and adrenal androgens, sometimes after ACTH administration. Treatment is with a glucocorticoid plus, if needed, a mineralocorticoid and, for some female neonates with genital ambiguity, surgical reconstruction.

21-Hydroxylase deficiency causes 90% of all cases of congenital adrenal hyperplasia. Incidence ranges from 1/10,000 to 1/15,000 live births. The deficiency completely or partially blocks conversion of adrenal precursors into cortisol and aldosterone, resulting in increased levels of progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone (DHEA, a weak androgen that masculinizes affected female infants), and androstenedione. Plasma deoxycorticosterone, deoxycortisol, cortisol, and aldosterone levels are low or absent.
Complete 21-hydroxylase deficiency, the salt-wasting form, accounts for 70% of 21-hydroxylase deficiency cases. The salt-wasting form (sometimes called the classic form of congenital adrenal hyperplasia) is the most severe form of 21-hydroxylase deficiency; aldosterone is not secreted and salt is lost, leading to hyponatremia, hyperkalemia, and increased plasma renin activity.

Partial 21-hydroxylase deficiency causes a less severe, non-salt-losing form, in which aldosterone levels are normal or only slightly decreased.

Symptoms and Signs

The salt-wasting form causes hyponatremia (sometimes severe), hyperkalemia, and hypotension as well as virilization. If undiagnosed and untreated, this form can lead to life-threatening adrenal crisis, with vomiting, diarrhea, hypoglycemia, hypovolemia, and shock.

Very young female infants with the salt-wasting form have ambiguous external genitals, with clitoral enlargement, fusion of the labia majora, and a urogenital sinus rather than distinct urethral and vaginal openings. Male infants typically have normal sexual development. When the enzyme deficiency is much milder, neonates have little or no virilization, but androgen excess manifests later with early appearance of pubic hair and increase in growth velocity in both sexes, clitoral enlargement in girls, and penile enlargement and earlier deepening of voice in boys.

In affected females, especially those with the salt-wasting form, reproductive function may be impaired as they reach adulthood; they may have labial fusion and anovulatory cycles or amenorrhea. Some males with the salt-wasting form are fertile as adults, but others have Leydig cell dysfunction, decreased testosterone, and impaired spermatogenesis. Most affected males with the non-salt-losing form, even if untreated, are fertile, but in some, spermatogenesis is impaired. Patients with the non-salt-losing form are normotensive.

Diagnosis

- Blood tests
- Possibly ACTH stimulation test
- Possibly genotyping

Routine neonatal screening typically includes measuring serum levels of 17-hydroxyprogesterone. If levels are elevated, the diagnosis is confirmed by identifying low blood levels of deoxycortisol, cortisol, deoxycorticosterone, corticosterone, progesterone, and 17-hydroxyprogesterone and by identifying high blood levels of DHEA and androstenedione. Rarely, the diagnosis is uncertain, and levels of these hormones must be measured before and 60 min after ACTH is given (ACTH or cosyntropin stimulation test). In patients who develop symptoms later, ACTH stimulation testing may help, but genotyping may be required. In children with the salt-wasting form, deoxycorticosterone, corticosterone, and aldosterone levels are low, and renin levels are high. Levels of urinary metabolites of cortisol precursors (eg, pregnanetriol) and androgen precursors (eg, 17-ketosteroids) are also high but rarely necessary for the diagnosis.

Prenatal screening and diagnosis (and experimental treatment) are possible; CYP21 genes are analyzed if risk is high (eg, the fetus has an affected sibling with the genetic defect). Carrier status (heterozygosity) can be determined in children and adults.

Treatment

- Corticosteroid replacement
- Mineralocorticoid replacement (salt-wasting form)
Possibly reconstructive surgery

For adrenal crisis in infants, urgent therapy with IV fluids is needed. Stress doses of hydrocortisone (100 mg/m²/day) are given by continuous IV infusion; the dose is reduced over several weeks to a more physiologic replacement dose. Stress doses of hydrocortisone are also given to prevent adrenal crisis if the salt-wasting form is suspected.

Maintenance treatment is corticosteroids as replacement for deficient steroids (typically, oral hydrocortisone 5 to 8 mg/m² tid or prednisone 1.5 to 2 mg/m² bid). Dexamethasone is used only in postpubertal adolescents and adults. Cortisone acetate 18 to 36 mg/m² IM q 3 days may be used in infants when oral therapy is unreliable. Response to therapy is monitored in infants every 3 mo and in children aged > 12 mo every 3 to 4 mo. Overtreatment with a corticosteroid results in iatrogenic Cushing’s disease, causing obesity, subnormal growth, and delayed skeletal maturation. Under-treatment results in inability to suppress ACTH with consequent hyperandrogenism, causing virilization and supranormal growth velocity in children and, eventually, premature termination of growth and short stature. Monitoring involves measuring serum 17-hydroxyprogesterone and DHEA or androstenedione, as well as assessing growth velocity and skeletal maturation each year.

Maintenance treatment for the salt-wasting form, in addition to corticosteroids, is mineralocorticoid replacement for restoration of Na and K homeostasis. Oral fludrocortisone (usually 0.1 mg once/day, range 0.05 to 0.3 mg) is given if salt loss occurs. Infants often require supplemental oral salt for about 1 yr. Close monitoring during therapy is critical.

Affected female infants may require surgical reconstruction with reduction clitoroplasty and construction of a vaginal opening. Often, further surgery is required during adulthood. With appropriate care and attention to psychosexual issues, a normal sex life and fertility may be expected.

For prenatal treatment, a corticosteroid (usually dexamethasone) is given to the pregnant mother to suppress fetal pituitary secretion of ACTH and thus reduce or prevent masculinization of affected female fetuses. Treatment, which is experimental, must begin in the first several weeks of gestation.

11β-Hydroxylase Deficiency

11β-Hydroxylase (CYP11B1) deficiency involves defective conversion of adrenal precursors to cortisol, resulting in virilization, hypernatremia, hypokalemia, and hypertension. Diagnosis is by measurement of cortisol, its precursors, and adrenal androgens and sometimes by measuring 11-deoxycortisol and 11-deoxycorticosterone after ACTH administration. Treatment is with a corticosteroid.

11β-Hydroxylase deficiency causes about 5% of all cases of congenital adrenal hyperplasia. Conversion of 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone is partially blocked, leading to increased levels of ACTH and overproduction of 11-deoxycortisol, 11-deoxycorticosterone (which has mineralocorticoid activity), and adrenal androgens.

Symptoms and Signs

Female neonates may present with genital ambiguity, including clitoral enlargement, labial fusion, and a urogenital sinus. Male neonates usually appear normal, but some present with penile enlargement. Some children present later, with sexual precocity or, in females, menstrual irregularities and hirsutism. Salt retention with hypernatremia, hypertension, and hypokalemic alkalosis may result from increased mineralocorticoid activity.

Diagnosis

Prenatal diagnosis is not available. Plasma levels in neonates are determined for 11-deoxycortisol, 11-deoxycorticosterone, adrenal androgens, and renin. Diagnosis is established by increased levels. If the diagnosis is uncertain, levels of 11-deoxycortisol and 11-deoxycorticosterone are measured before and 60
min after ACTH stimulation. In affected adolescents, basal plasma levels may be normal, so ACTH stimulation is recommended.

**Treatment**

- Corticosteroid replacement
- Possibly mineralocorticoid replacement
- Possibly reconstructive surgery

Treatment is cortisol replacement, typically with hydrocortisone 5 to 8 mg/m\(^2\) tid, which reduces ACTH secretion and reduces levels of 11-deoxycorticosterone and adrenal androgens to normal. Mineralocorticoid replacement is usually not necessary for restoration of Na and K homeostasis but may be required in the neonate or during severe stress. Response to treatment should be monitored, typically by measuring serum 11-deoxycortisol, DHEA, and androstenedione and by assessing growth velocity and skeletal maturation. BP should be monitored in patients who presented with hypertension.

Affected female infants may require surgical reconstruction with reduction clitoroplasty and construction of a vaginal opening. Often, further surgery is required in adulthood, but with appropriate care and attention to psychosexual issues, a normal sex life and fertility may be expected.

**Male Hypogonadism**

(See also p. 2340.)

**Male hypogonadism is decreased production of testosterone, sperm, or both or, rarely, decreased response to testosterone, resulting in delayed puberty, reproductive insufficiency, or both.** Diagnosis is by measurement of serum testosterone, luteinizing hormone, and follicle-stimulating hormone and by stimulation tests with human chorionic gonadotropin or gonadotropin-releasing hormone. Treatment depends on the cause.

**Classification**

There are 3 types of hypogonadism: primary, secondary, and a type caused by defective androgen action, primarily due to defective androgen receptor activity.

**Primary:** In primary (hypergonadotropic) hypogonadism, damage to the Leydig cells impairs testosterone production, damages the seminiferous tubules, or does both; oligospermia or azoospermia and elevated gonadotropins result. The most common cause is Klinefelter's syndrome; other causes are gonadal dysgenesis (rare), cryptorchidism, bilateral anorchia, Leydig cell aplasia, Noonan's syndrome, and myotonic dystrophy. Rare causes include orchitis due to mumps (which is becoming even rarer as immunization rates increase), testicular torsion, and trauma.

**Klinefelter's syndrome** is seminiferous tubule dysgenesis associated with the 47,XXY karyotype, in which an extra X chromosome is acquired through maternal or, to a lesser extent, paternal meiotic nondisjunction (see also p. 3005). The syndrome is usually identified at puberty, when inadequate sexual development is noted, or later, when infertility is investigated. Diagnosis is based on elevated gonadotropin levels and low to low-normal testosterone levels.

**Gonadal dysgenesis** occurs in hermaphroditism, which is rare.

In **cryptorchidism**, one or both testes are undescended (see p. 2987). Etiology is usually unknown. Sperm counts may be slightly low if one testis is undescended but are almost always very low if both are undescended.

In **bilateral anorchia (vanishing testes syndrome)**, the testes were presumably present but were
resorbed before or after birth. External genitals and wolffian structures are normal, but mullerian duct structures are lacking. Thus, testicular tissue must have been present during the first 12 wk of embryogenesis because testicular differentiation occurred and testosterone and mullerian-inhibiting factor were produced.

**Leydig cell aplasia** occurs when congenital absence of Leydig cells causes male pseudohermaphroditism with ambiguous external genitals. Although wolffian ducts develop to some extent, testosterone production is insufficient to induce normal male differentiation of the external genitals. Mullerian ducts are absent because of normal production of mullerian-inhibiting hormone by Sertoli cells. Gonadotropin levels are high with low testosterone levels.

**Noonan's syndrome** may occur sporadically or as an autosomal dominant disorder. Phenotypic abnormalities include hyperelasticity of the skin, hypertelorism, ptosis, low-set ears, short stature, shortened 4th metacarpals, high-arched palate, and primarily right-sided cardiovascular abnormalities (eg, pulmonic valve stenosis, atrial septal defect). Testes are often small or cryptorchid. Testosterone levels may be low with high gonadotropin levels.

**Defective androgen synthesis** is caused by enzyme defects that impair androgen synthesis, which may occur in any of the pathways leading from cholesterol to dihydrotestosterone. These congenital problems may occur in congenital adrenal hyperplasia when the same enzyme defect occurs in the adrenal glands and the testes, resulting in defective androgen activity and ambiguous external genitals (ie, male pseudohermaphroditism) of varying degrees.

**Secondary:** Causes of secondary hypogonadism include panhypopituitarism, hypothalamic pituitary tumors, isolated gonadotropin deficiency, Kallmann syndrome, Laurence-Moon syndrome, constitutional delay of puberty, isolated luteinizing hormone deficiency, Prader-Willi syndrome, and functional and acquired disorders of the CNS (eg, trauma, infection). Several acute disorders and chronic systemic disorders (eg, chronic renal insufficiency, anorexia nervosa) may lead to hypogonadotropic hypogonadism, which resolves after recovery from the underlying disorder. Relative hypogonadism is becoming more common among long-term survivors of childhood cancers treated with craniospinal irradiation. Chemotherapy with alkylating drugs may lead to testicular damage and relative hypogonadism.

**Panhypopituitarism** may occur congenitally or anatomically (eg, in septo-optic dysplasia or Dandy-Walker malformation), causing deficiency of hypothalamic-releasing factors or pituitary hormones. Acquired hypopituitarism may result from tumors, neoplasia, their treatment, vascular disorders, infiltrative disorders (eg, sarcoidosis, Langerhans' cell histiocytosis), infections (eg, encephalitis, meningitis), or trauma. Hypopituitarism in childhood may cause delayed growth, hypothyroidism, diabetes insipidus, hypoadrenalism, and lack of sexual development when puberty is expected. Hormone deficiencies, whether originating in the anterior or posterior pituitary, may be varied and multiple.

**Kallmann syndrome** is characterized by anosmia due to aplasia or hypoplasia of the olfactory lobes and by hypogonadism due to deficiency of hypothalamic-gonadotropin-releasing hormone (GnRH). It occurs when fetal GnRH neurosecretory neurons do not migrate from the olfactory placode to the hypothalamus. The genetic defect is known; inheritance is usually X-linked. Other manifestations include microphallus, cryptorchidism, midline defects, and unilateral kidney agenesis.

**Laurence-Moon syndrome** is characterized by obesity, intellectual disability, retinitis pigmentosa, and polydactyly.

**Constitutional delay of puberty** is absence of pubertal development in boys ≥ 14 yr. Many have a family history of delayed sexual development in a parent or sibling. Most affected boys have some evidence of sexual maturation by age 18 yr or have a skeletal age of at least 12 yr (the average age at which testicular enlargement is first noted). Typically, stature is usually short during childhood, adolescence, or both but ultimately reaches normal range. Growth velocity is nearly normal, and growth pattern parallels the lower percentile curves of the growth chart; the pubertal growth spurt is delayed. When skeletal age is plotted on the growth curve, it essentially equals the percentile curve of the genetic target. Diagnosis is by exclusion of growth hormone deficiency, hypothyroidism, and hypogonadism.
Isolated luteinizing hormone (LH) deficiency (fertile eunuch syndrome) is monotropic loss of LH secretion in boys; follicle-stimulating hormone (FSH) levels are normal. At puberty, growth of the testes is normal because most testicular volume consists of seminiferous tubules, which respond to FSH. Spermatogenesis may occur as tubular development proceeds. However, absence of LH results in Leydig cell atrophy and testosterone deficiency. Therefore, patients do not develop normal secondary sexual characteristics, but they continue to grow, reaching eunuchoidal proportions because the epiphyses do not close.

Prader-Willi syndrome is characterized by diminished fetal activity, muscular hypotonia, and failure to thrive during early childhood, obesity from early childhood, intellectual disability, and hypogonadotropic hypogonadism. The syndrome is caused by deletion or disruption of a gene or genes on the proximal long arm of paternal chromosome 15 or by uniparental disomy of maternal chromosome 15. Failure to thrive due to hypotonia and feeding difficulties during infancy usually resolves after age 6 to 12 mo. From 12 to 18 mo onward, uncontrollable hyperphagia causes excessive weight gain and psychologic problems; plethoric obesity becomes the most striking feature. Rapid weight gain continues into adulthood; stature remains short. Features include emotional lability, poor gross motor skills, facial abnormalities (eg, a narrow bitemporal dimension, almond-shaped eyes, a mouth with thin upper lips and down-turned corners), and skeletal abnormalities (eg, scoliosis, kyphosis, osteopenia). Hands and feet are small. Other features include cryptorchidism and a hypoplastic penis and scrotum.

Symptoms and Signs

Clinical presentation depends on whether, when, and how testosterone and sperm production are affected. (For presentation in adulthood, see p. 2341.)

If androgen deficiency or defects in androgen activity occur during the 1st trimester (< 12 wk gestation), differentiation of internal wolffian ducts and external genitals is inadequate. Presentation may range from ambiguous external genitals (ie, male pseudohermaphroditism) to normal-appearing female external genitals. Androgen deficiency during the 2nd and 3rd trimesters may cause a microphallus and partially or completely undescended testes.

Androgen deficiency that develops early in childhood has few consequences, but if it occurs when puberty is expected, secondary sexual development is impaired. Such patients have poor muscle development, a high-pitched voice, inadequate phallic and testicular growth, a small scrotum, sparse pubic and axillary hair, and absent body hair. They may develop gynecomastia and grow to eunuchoidal body proportions (arm span exceeds height by 5 cm; pubic to floor length exceeds crown to pubic length by > 5 cm) because fusion of the epiphyses is delayed and long bone growth continues.

Diagnosis

• Measurement of testosterone, LH, FSH

• Karyotyping (for primary hypogonadism)

Diagnosis is often suspected based on developmental abnormalities or delayed puberty but requires confirmation by testing, including measurement of testosterone, LH, and FSH. LH and FSH levels are more sensitive than testosterone levels, especially for detecting primary hypogonadism.

LH and FSH levels also help determine whether hypogonadism is primary or secondary:

• High levels, even with low-normal testosterone levels, indicate primary hypogonadism.

• Levels that are low or lower than expected for the testosterone level indicate secondary hypogonadism.

In boys with short stature, delayed pubertal development, low testosterone, and low FSH and LH levels may indicate constitutional delay. Elevated serum FSH levels with normal serum testosterone and LH
levels typically indicate impaired spermatogenesis but not impaired testosterone production. In primary hypogonadism, it is important to determine the karyotype to investigate for Klinefelter's syndrome.

Measurement of testosterone, FSH, and LH for diagnosis of hypogonadism requires an understanding of how the levels vary. Before puberty, serum testosterone levels are < 20 ng/dL (< 0.7 nmol/L) and in adulthood, levels are > 300 to 1200 mg/dL. Serum testosterone secretion is primarily circadian. In the 2nd half of puberty, levels are higher at night than during the latter part of the day. A single sample obtained in the morning can establish that circulating testosterone levels are normal. Because 98% of testosterone is bound to carrier proteins in serum (testosterone-binding globulin), alterations in these protein levels alter total testosterone levels. Measurement of total serum testosterone (protein bound and free) is usually the most accurate indicator of testosterone secretion.

For LH and FSH levels, 3 blood samples should be taken at 20-min intervals. This approach maximizes the likelihood of detecting LH pulsations, which occur at 90- to 120-min intervals. Serum LH and FSH levels are usually < 5 mIU/mL before puberty and fluctuate between 5 and 20 mIU/mL during the 2nd half of puberty and into adulthood.

The human chorionic gonadotropin (hCG) stimulation test is done to assess the presence and secretory ability of testicular tissue; hCG 100 IU/kg is given to children. hCG stimulates Leydig cells, as does LH, with which it shares a structural subunit, and stimulates testicular production of testosterone. Testosterone levels should double after 3 to 4 days.

The GnRH stimulation test is done in boys to distinguish between hypothalamic dysfunction and pituitary dysfunction as the cause of hypogonadotropic hypogonadism. GnRH 2.5 μg/kg or leuprolide acetate 500 μg is rapidly injected IV. The injection directly stimulates the pituitary to secrete LH and FSH, which are measured every 20 to 30 min for 2 h. Throughout childhood and into early puberty, response to GnRH is predominantly an increase in FSH with little or no increase in LH. During puberty, LH and FSH respond more or less equally (by doubling or tripling). An inadequate to absent increase in FSH and LH may indicate hypopituitarism.

Treatment

• Surgery as needed

• Hormone replacement

Cryptorchidism is corrected early to obviate concerns about cancer developing in later adulthood and to prevent testicular torsion (see p. 2987).

For secondary hypogonadism, any underlying pituitary or hypothalamic disorder is treated. Overall, the goal is to provide androgen replacement starting with a low dose and progressively increasing the dose over 18 to 24 mo.

Adolescents with androgen deficiency should be given long-acting injectable testosterone enanthate or cypionate 50 mg q 2 to 4 wk; the dose is increased up to 200 mg over 18 to 24 mo. A transdermal patch or gel may be used instead.

Treatment of Kallmann syndrome with hCG can correct cryptorchidism and establish fertility. Pulsatile GnRH therapy given subcutaneously by a portable pump leads to endogenous sex hormone secretion, progressive virilization, and even fertility.

In isolated LH deficiency, testosterone, via conversion to estrogen by aromatase, induces normal epiphyseal closure.

Delayed Puberty

Delayed puberty is absence of sexual maturation at the expected time.
Delayed puberty may result from constitutional delay (see p. 2893), which often occurs in adolescents with a family history of delayed growth. Prepubertal growth velocity is normal, but skeletal maturation and adolescent growth spurt are delayed; sexual maturation is delayed but normal. Other causes include Turner's syndrome in girls, Klinefelter's syndrome in boys, CNS disorders (eg, pituitary tumors that reduce gonadotropin secretion), certain chronic disorders (eg, diabetes mellitus, inflammatory bowel disorders, renal disorders, cystic fibrosis), and excess physical activity, especially in girls.

In girls, delayed puberty is diagnosed if no breast development occurs by age 13, if no pubic hair appears by age 14, if > 5 yr elapse between the beginning of breast growth and menarche, or if menstruation does not occur by age 16. In boys, delayed puberty is diagnosed if no testicular enlargement occurs by age 14, if no pubic hair appears by age 15, or if > 5 yr elapse between initial and complete growth of the genitals. Short stature may indicate delayed puberty in either sex. Although many children seem to be starting puberty earlier than in past years, there are no indications that the criteria for delayed puberty should change.

Constitutional delay of puberty is more prevalent in boys. Girls with severe pubertal delay should be investigated for primary amenorrhea (see p. 2501). If boys show no sign of pubertal development or of skeletal maturation beyond 11 to 12 yr by age 15, they may be given a 4- to 8-mo course of IM testosterone enanthate 50 mg once/mo. These low doses induce puberty with some degree of virilization and do not jeopardize adult height potential.

Precocious Puberty

Precocious puberty is onset of sexual maturation before age 8 in girls or age 9 in boys. Diagnosis is by comparison with population standards, x-rays of the left hand and wrist to assess skeletal maturation and check for accelerated bone growth, and measurement of serum levels of gonadotropins and gonadal and adrenal steroids. Treatment depends on the cause.

The definition of precocious puberty depends on reliable population standards for onset of puberty (ie, when pubertal milestones occur); because onset seems to be occurring earlier in the US, these standards are being reevaluated. Almost 8 to 10% of white girls, almost 30% of black girls, and an intermediate percentage of Hispanic girls reach early puberty at age 8. The lower limit of normal puberty may be 7 yr for white girls and 6 yr for black girls. The mean age for early breast development is about 10 yr for white girls and 9 yr for black girls (range 8 to 13 yr). The mean age for pubic hair growth is 9 to 10.5 yr for both groups. These findings imply that guidelines for evaluating disorders that cause precocious puberty can be interpreted more leniently if children are otherwise healthy and are not at risk of not reaching their full adult height potential.

In girls, the first pubertal milestone is typically breast development (thelarche), followed soon after by appearance of pubic hair (pubarche) and axillary hair and later by the first menstrual period (menarche). In boys, the first pubertal milestone is typically testicular growth, followed by penile growth and appearance of pubic and axillary hair. In both sexes, appearance of pubic and axillary hair is called adrenarche.

Precocious puberty can be divided into 2 types:

• Gnadotropin-releasing hormone (GnRH)-dependent

• GnRH-independent

GnRH-dependent precocious puberty is 5 to 10 times more frequent in girls; in boys, GnRH-dependent and GnRH-independent precocious puberty occur with similar frequency. In GnRH-dependent precocious puberty, the hypothalamic-pituitary axis is activated, resulting in enlargement and maturation of the gonads, development of secondary sexual characteristics, and oogenesis or spermatogenesis. In GnRH-independent precocious puberty, secondary sexual characteristics result from high circulating levels of estrogens or androgens, without activation of the hypothalamic-pituitary axis.

Precocious puberty may also be classified by whether gonadarche or adrenarche occurs. In girls,
gonadarche includes breast development, change in body habitus, growth of the uterus, and eventually menarche. In boys, gonadarche includes testicular enlargement; phallic growth; the initial appearance of pubic, facial, and axillary hair; adult body odor; and facial skin oiliness or acne. Adrenarche for both girls and boys involves the development of body hair, body odor, and acne.

Premature appearance of only one specific pubertal milestone is generally considered a benign variant of development. Examples are precocious appearance of pubic and axillary hair before age 8 in girls and age 9 in boys, and precocious onset of breast development before age 8 in girls.

**Etiology**

**GnRH-dependent precocious puberty:** In most affected girls ≥ 4 yr, a specific cause cannot be identified. However, many girls < 4 yr have a CNS lesion. Most (60%) affected boys have an identifiable underlying lesion. Such lesions include intracranial tumors, especially of the hypothalamus (hamartoma, rarely craniopharyngioma) or pineal gland region (teratoma, pinealoma). Neurofibromatosis and a few other rare disorders have also been linked to precocious puberty.

**GnRH-independent precocious puberty:** Follicular ovarian cysts cause most cases; other causes include granulosa-theca cell tumors, adrenal enzyme defects, and McCune-Albright syndrome (a triad of follicular cysts, polyostotic fibrous dysplasia, and cafe-au-lait spots). Causes of GnRH-independent precocious puberty in boys include certain enzyme defects, familial male gonadotropin-independent precocity (due to an activating mutation of the gene for luteinizing hormone [LH] receptors), testosterone-producing testicular tumors, and occasionally McCune-Albright syndrome.

Rarely in girls and boys, puberty results from pituitary adenomas (hamartomas) that secrete gonadotropins.

**Symptoms and Signs**

In girls, breasts develop, and pubic hair, axillary hair, or both appear. Girls may begin to menstruate. In boys, facial, axillary, and pubic hair appears and the penis grows, with or without enlargement of testes. Body odor, acne, and behavior changes may develop in either sex. Height gain is initially rapid in both sexes, but premature closure of the epiphyses results in short adult stature. Ovarian or testicular enlargement occurs in precocious puberty but is usually absent in isolated precocious adrenarche.

**Diagnosis**

- Bone age x-rays
- Serum hormone measurement
- Possibly pelvic ultrasonography and brain MRI or CT

Diagnosis is clinical. X-rays of the left hand and wrist are done to check for accelerated skeletal maturation as a result of sex hormone effect. Unless history and examination suggest an abnormality, no further evaluation is required for children with pubertal milestones that are within 1 yr of population standards. Girls and boys with precocious adrenarche and girls with precocious thelarche also do not require further evaluation as long as x-rays confirm that skeletal maturation is not accelerated.

When further evaluation is necessary, the following serum hormones may be measured: β-human chorionic gonadotropin, estradiol, testosterone, dehydroepiandrosterone, 17-hydroxyprogesterone, LH, follicle-stimulating hormone (FSH), and prolactin. Pelvic and adrenal ultrasonography and MRI or CT of the brain may be done.

A GnRH stimulation test (see p. 2894) confirms a diagnosis of GnRH-independent precocious puberty when gonadotropin responses to exogenous GnRH are prepubertal in boys or girls with no tumor or other obvious cause of early sexual development. If the response is pubertal, CNS lesions must be excluded.
**Treatment**

- GnRH agonist therapy (GnRH-dependant precocious puberty)

- Androgen or estrogen antagonist therapy (GnRH-independent precocious puberty)

- Tumor excision as needed

If pubertal milestones are within 1 yr of population standards, reassurance and regular reexamination are sufficient. Treatment is not needed for premature adrenarche or thelarche, but regular reexamination is warranted to check for later development of precocious puberty. For GnRH-dependent precocious puberty, pituitary LH and FSH secretion can be suppressed until normal puberty begins with the GnRH agonist leuprolide acetate 0.2 to 0.3 mg/kg (minimum, 7.5 mg) IM q 4 wk. Responses to treatment must be monitored, and drug dosages modified accordingly.

In girls with McCune-Albright syndrome, testolactone, an aromatase inhibitor, reduces serum estradiol and effectively treats affected girls; alternatively, tamoxifen, an estrogen antagonist, may be beneficial.

If GnRH-independent precocious puberty in boys is due to familial male gonadotropin-independent precocity or McCune-Albright syndrome, androgen antagonists (eg, spironolactone) ameliorate the effects of excess androgen. The antifungal drug ketoconazole reduces testosterone in boys with familial male gonadotropin-independent precocity.

If GnRH-independent precocious puberty is due to a hormone-producing tumor (eg, granulosatheca cell tumors in girls, testicular tumors in boys), the tumor should be excised. However, girls require extended follow-up to check for recurrence in the contralateral ovary.
Chapter 286. Neurologic Disorders in Children

Introduction

Related topics are discussed elsewhere in THE MANUAL: see Chs. 176, 180, and 298 and p. 2830.

Cerebral Palsy Syndromes

Cerebral palsy (CP) refers to nonprogressive syndromes characterized by impaired voluntary movement or posture and resulting from prenatal developmental malformations or perinatal or postnatal CNS damage. Syndromes manifest before age 5 yr. Diagnosis is clinical. Treatment may include physical and occupational therapy, braces, drug therapy or botulinum toxin injections, orthopedic surgery, intrathecal baclofen, or, in certain cases, dorsal rhizotomy.

CP is a group of syndromes that causes non-progressive spasticity, ataxia, or involuntary movements; it is not a specific disorder or single syndrome. CP syndromes occur in 0.1 to 0.2% of children and affect up to 15% of premature infants.

Etiology

Etiology is multifactorial, and a specific cause is often hard to establish. Prematurity, in utero disorders, neonatal encephalopathy, and kernicterus often contribute. Perinatal factors (eg, perinatal asphyxia, stroke, CNS infections) probably cause 15 to 20% of cases. Spastic diplegia after premature birth, spastic quadriplegia after perinatal asphyxia, and athetoid and dystonic forms after perinatal asphyxia or kernicterus are examples of types of CP. CNS trauma or a severe systemic disorder (eg, stroke, meningitis, sepsis, dehydration) during early childhood may also cause a CP syndrome.

Symptoms and Signs

Before a specific syndrome develops, symptoms include lagging motor development and often persistent infantile reflex patterns, hyperreflexia, and altered muscle tone.

Categories: Syndromes are categorized mainly as one of the following, depending on which parts of the CNS are malformed or damaged:

- **Spastic syndromes** occur in > 70% of cases. Spasticity is a state of resistance to passive range of motion; resistance increases with increasing speed of that motion. It is due to upper motor neuron involvement and may mildly or severely affect motor function. These syndromes may cause hemiplegia, quadriplegia, diplegia, or paraplegia. Usually, deep tendon reflexes in affected limbs are increased, muscles are hypertonic, and voluntary movements are weak and poorly coordinated. Joint contractures develop, and joints may become misaligned. A scissors gait and toe walking are typical. In mild cases, impairment may occur only during certain activities (eg, running). Corticobulbar impairment of oral, lingual, and palatal movement, with consequent dysarthria or dysphagia, commonly occurs with quadriplegia.

- **Athetoid or dyskinetic syndromes** occur in about 20% of cases and result from basal ganglia involvement. The syndromes are defined by slow, writhing, involuntary movements of the proximal extremities and trunk (athetoid movements), often activated by attempts at voluntary movement or by excitement. Abrupt, jerky, distal (choreic) movements may also occur. Movements increase with emotional tension and disappear during sleep. Dysarthria occurs and is often severe.

- **Ataxic syndromes** occur in < 5% of cases and result from involvement of the cerebellum or its pathways. Weakness, incoordination, and intention tremor cause unsteadiness, a wide-based gait, and difficulty with rapid or fine movements.

- **Mixed syndromes** are common—most often with spasticity and athetosis.

Associated findings: About 25% of patients, most often those with spasticity, have other manifestations.
Strabismus and other visual defects may occur. Children with athetosis due to kernicterus commonly have nerve deafness and upward gaze paralysis. Many children with spastic hemiplegia or paraplegia have normal intelligence; children with spastic quadriplegia and mixed syndromes may have severe intellectual disability.

Diagnosis

- Cranial MRI

If CP is suspected, cranial MRI is done; it can detect abnormalities in most cases.

CP can rarely be confirmed during early infancy, and the specific syndrome often cannot be characterized until age 2 yr. High-risk children (eg, those with evidence of asphyxia, stroke, periventricular abnormalities seen on cranial ultrasonography in premature infants, jaundice, meningitis, neonatal seizures, hypertonia, hypotonia, or reflex suppression) should be followed closely.

CP should be differentiated from progressive hereditary neurologic disorders and disorders requiring surgical or other specific neurologic treatments. Ataxic forms are particularly hard to distinguish, and in many children with ataxia, a progressive cerebellar degenerative disorder is ultimately identified as the cause. Athetosis, self-mutilation, and hyperuricemia in boys indicate Lesch-Nyhan syndrome (see p. 3024). Cutaneous or ocular abnormalities may indicate tuberous sclerosis, neurofibromatosis, ataxia-telangiectasia, von Hippel-Lindau disease, or Sturge-Weber syndrome. Infantile spinal muscular atrophy and muscular dystrophies associated with hypotonia and hyporeflexia usually lack signs of cerebral disease. Adrenoleukodystrophy begins later in childhood, but other leukodystrophies begin earlier and may be mistaken for CP at first.

Laboratory tests can exclude certain progressive storage disorders that involve the motor system (eg, Tay-Sachs disease, metachromatic leukodystrophy, mucopolysaccharidoses). Other progressive disorders (eg, infantile neuroaxonal dystrophy) may be suggested by nerve conduction studies and electromyography but must be diagnosed clinically or pathologically. Children with pronounced intellectual disability and symmetric motor abnormalities should be evaluated for amino acid and other metabolic abnormalities (see p. 3009).

Prognosis

Most children survive to adulthood. Severe limitations in sucking and swallowing, which may require feeding by gastrostomy tube, decrease likelihood of survival. The goal is for children to develop maximal independence within the limits of their motor and associated deficits. With appropriate management, many children, especially those with spastic paraplegia or hemiplegia, can lead near-normal lives.

Treatment

- Physical and occupational therapy
- Braces, drugs, or surgery to treat spasticity
- Assistive devices

Physical therapy and occupational therapy for stretching, strengthening, and facilitating good movement patterns are usually used first. Bracing, drug therapy, and surgery are used to treat spasticity. Botulinum toxin may be injected into muscles to decrease their uneven pull at joints and to prevent fixed contractures. Drugs such as baclofen, benzodiazepines (eg, diazepam), tizanidine, and sometimes dantrolene may diminish spasticity. Intrathecal baclofen (via subcutaneous pump and catheter) is the most effective treatment for severe spasticity. Orthopedic surgery (eg, muscle-tendon release) may help reduce restricted joint motion or misalignment. Selective dorsal rhizotomy may help a few children if spasticity affects primarily the legs and if cognitive abilities are good.

When intellectual and physical limitations are not severe, children should attend mainstream schools.
However, some children require varying degrees of lifelong supervision and assistance. Speech training or other forms of facilitated communication may be required. Even severely affected children can benefit from training in activities of daily living (eg, washing, dressing, feeding), which increases their independence and self-esteem and greatly reduces the burden for family members or other caregivers. Assistive devices may increase mobility and communication, help maintain range of motion, and help children and their caregivers with activities of daily living.

Parents of a child with chronic limitations need assistance and guidance in understanding the child's status and potential and in dealing with their own feelings of guilt, anger, denial, and sadness (see p. 2755). Such children reach their maximal potential only with stable, sensible parental care and the assistance of public and private agencies (eg, community health agencies, vocational rehabilitation organizations, lay health organizations such as the United Cerebral Palsy Association).

**Febrile Seizures**

Febrile seizures are diagnosed in children < 6 yr with body temperature > 38°C and no previous afebrile seizures when no cause can be identified. Diagnosis is clinical after exclusion of other causes. Treatment of seizures lasting < 15 min is supportive. Seizures lasting ≥ 15 min are treated with IV lorazepam and, if persistent, IV fosphenytoin, phenobarbital, valproate, or levetiracetam. Maintenance drug therapy is usually not indicated.

Febrile seizures occur in about 2 to 5% of children < 6 yr; most occur at age 6 to 36 mo. Febrile seizures may be simple or complex:

- Simple febrile seizures last < 15 min and have no focal features, and if they occur in a series, total duration is < 30 min.

- Complex febrile seizures last 15 min and have focal features or postictal paresis, or occur in a series with a total duration of > 30 min.

Most (> 90%) febrile seizures are simple.

Febrile seizures occur during bacterial or viral infections. They sometimes occur after certain vaccinations such as measles, mumps, and rubella. Genetic and familial factors may increase susceptibility to febrile seizures. Monozygotic twins have a much higher concordance rate than dizygotic twins. Several genes associated with febrile seizures have been identified.

**Symptoms and Signs**

Often, febrile seizures occur during the initial rapid rise in body temperature, and most develop within 24 h of fever onset. Typically, seizures are generalized; most are clonic, but some manifest as periods of atonic or tonic posturing.

**Diagnosis**

- Exclusion of other causes

Seizures are diagnosed as febrile after exclusion of other causes. A fever may trigger seizures in children with previous afebrile seizures; such events are not termed "febrile seizures" because such children have already shown a tendency to have seizures.

Tests to exclude other disorders are determined clinically:

- CSF analysis to rule out meningitis and encephalitis if children are < 6 mo, have meningeal signs or signs of CNS depression, or have seizures after several days of febrile illness

- Serum glucose, Na, Ca, Mg, and P and liver and kidney function tests to rule out metabolic disorders if the history includes recent vomiting, diarrhea, or impaired fluid intake; if there are signs of dehydration
or edema; or if a complex febrile seizure occurs

- Cranial CT or MRI if examination detects focal features or if there are signs of increased intracranial pressure

- Consideration of EEG if febrile seizures are complex or recurrent

EEG typically does not identify specific abnormalities or help predict recurrent seizures; it is not recommended after an initial simple febrile seizure in children with a normal neurologic examination.

**Prognosis**

Overall recurrence rate is about 35%. Risk of recurrence is higher if children are < 1 yr when the initial seizure occurs or have 1st-degree relatives who have had febrile seizures. Risk of developing an afebrile seizure disorder after experiencing febrile seizures is about 2 to 5%, unless children have additional risk factors (eg, complex febrile seizures, family history of seizures, developmental delay), which increase risk up to 10%.

**Treatment**

- Supportive therapy if seizures last < 15 min
- Drugs and sometimes intubation if seizures last ≥ 15 min

Treatment is supportive if seizures last < 15 min.

Seizures lasting ≥ 15 min require drugs to end them, with careful monitoring of circulatory and respiratory status. Intubation may be necessary if response is not immediate and the seizure persists.

Drug therapy is usually IV, with a short-acting benzodiazepine (eg, lorazepam 0.05 to 0.1 mg/kg IV over 2 to 5 min repeated q 5 to 10 min for up to 3 doses). Fosphenytoin 15 to 20 mg PE (phenytoin equivalents)/kg may be given over 15 min if the seizure persists. In children 2 to 5 yr, diazepam rectal gel 0.5 mg/kg may be given once and repeated in 4 to 12 h if lorazepam cannot be given IV. Phenobarbital, valproate, or levetiracetam can also be used to treat a persistent seizure.

Maintenance drug therapy to prevent recurrent febrile seizures or development of afebrile seizures is usually not indicated unless multiple or prolonged episodes have occurred.

**Infantile Spasms**

Infantile spasms (salaam seizures) are seizures characterized by sudden flexion of the arms, forward flexion of the trunk, extension of the legs, and hypsarrhythmia on EEG.

Infantile spasms last a few seconds and can recur many times a day. They usually manifest in children < 1 yr; peak incidence is 2 to 3 yr. Seizures may resolve spontaneously by about age 5 yr but can be replaced by other types of seizures.

Pathophysiology is unknown; however, infantile spasms may reflect abnormal interactions between the cortex and brain stem and within the hypothalamic-pituitary-adrenal axis. An immature CNS may also be a factor.

Malformations of the brain and disorders that damage the brain before a few months of age can cause infantile spasms; tuberous sclerosis is a common cause (see p. 2905). The cause may be idiopathic.

**Symptoms and Signs**

Spasms begin with a sudden, rapid, tonic contraction of the trunk and limbs, sometimes for several seconds. Spasms range from subtle head nodding to contraction of the whole body. They involve flexion,
extension, or, more often, both (mixed). The spasms usually occur in clusters, often several dozens, in close succession; they occur typically after children wake up and occasionally during sleep.

Developmental defects (eg, in intellect) are usually present. In the first stages of the disorder, developmental regression can occur (eg, children may lose the ability to sit up or roll over).

Rate of premature death rate ranges from 5 to 31%; death often occurs before age 10 yr and is related to the etiology of the infantile spasms.

**Diagnosis**

- Neuroimaging
- Waking and sleep EEG
- Laboratory testing as clinically indicated

Symptoms suggest the diagnosis. Physical and neurologic examinations are done, but often no pathognomonic findings are identified except in tuberous sclerosis.

Waking and sleep EEG is done to check for specific abnormalities. Typically, the interictal pattern is hypsarrhythmic (chaotic, high-voltage polymorphic delta and theta waves with superimposed multifocal spike discharges). Multiple variations (eg, focal or asymmetric hypsarrhythmia) are possible. The ictal pattern varies. Usually, electrical activity is markedly attenuated diffusely.

Tests to determine the cause may include

- Laboratory tests (eg, CBC with differential, serum glucose, electrolytes, BUN, creatinine, Na, Ca, Mg, and P, liver function tests) if a metabolic disorder is suspected
- CSF analysis
- Neuroimaging (MRI)

**Treatment**

Infantile spasms are difficult to treat, and the optimal regimen is controversial. ACTH 20 to 60 units IM once/day may be used but has become very hard to obtain. Corticosteroids for 8 to 10 wk can also be effective. Many anticonvulsants are ineffective; valproate is preferred, followed by clonazepam. Nitrazepam, topiramate, zonisamide, or vigabatrin may help.

A ketogenic diet may help but is difficult to maintain.

In some patients, focal cortical resection can eliminate seizures.

**Neonatal Seizure Disorders**

(See also Ch. 176.)

Neonatal seizures are abnormal electrical discharges in the CNS of neonates and usually manifest as stereotyped muscular activity or autonomic changes. Diagnosis is confirmed by EEG; testing for causes is indicated. Treatment depends on the cause.

Seizures occur in up to 1.4% of term infants and 20% of premature infants. Seizures may be related to a serious neonatal problem and require immediate evaluation. Most neonatal seizures are focal, probably because generalization of electrical activity is impeded in neonates by lack of myelination and incomplete formation of dendrites and synapses in the brain.
Some neonates undergoing EEG to assess seizures or other symptoms of encephalopathy (eg, hypoactivity, decreased responsiveness) are found to have clinically silent seizures (epileptiform electrical activity during an EEG but without any visible seizure activity). Occasionally, clinically silent electrical activity is continuous and persists for > 20 min; at that point, it is defined as electrical status epilepticus.

Etiology

The abnormal CNS electrical discharge may be caused by a

• Primary intracranial process (eg, meningitis, ischemic stroke, encephalitis, intracranial hemorrhage, tumor, malformation)

• Systemic problem (eg, hypoxia-ischemia, hypoglycemia, hypocalcemia, hyponatremia, other disorders of metabolism)

Seizures resulting from an intracranial process usually cannot be differentiated from seizures resulting from a systemic problem by their clinical features (eg, focal vs generalized).

Hypoxia-ischemia, the most common cause of neonatal seizures, may occur before, during, or after delivery. Such seizures may be severe and difficult to treat, but they tend to abate after about 3 to 4 days.

Ischemic stroke is more likely to occur in neonates with polycythemia, with thrombophilia due to a genetic disorder, or with severe hypotension but may occur in neonates without any risk factors. Stroke occurs typically in the middle cerebral artery distribution or, if associated with hypotension, in watershed zones. Seizures resulting from stroke tend to be focal and may cause apnea.

Infections such as meningitis and sepsis may cause seizures; in such cases, seizures are usually accompanied by other symptoms and signs. Group B streptococci and gram-negative bacteria are common causes of such infections in neonates. Encephalitis due to cytomegalovirus, herpes simplex virus, rubella virus, Treponema pallidum, or Toxoplasma gondii can also cause seizures.

Hypoglycemia is common among neonates whose mothers have diabetes, who are small for gestational age, or who have hypoxiaischemia or other stresses. Seizures due to hypoglycemia tend to be focal and variable. Prolonged or recurrent hypoglycemia may permanently affect the CNS.

Intracranial hemorrhage, including subarachnoid, intracerebral, and intraventricular hemorrhage, may cause seizures. Intraventricular hemorrhage, which occurs in premature infants, results from bleeding in the germinal matrix (an area that is adjacent to the ventricles and that gives rise to neurons and glial cells during development).

Hyponatremia may cause seizures. Hyponatremia can result from accidental oral or IV NaCl overload. Hyponatremia can result from dilution (when too much water is given po or IV) or may follow Na loss in stool or urine.

Hypocalcemia (serum Ca level < 7.5 mg/dL [< 1.87 mmol/L]) is usually accompanied by a serum P level of > 3 mg/dL (> 0.95 mmol/L) and can be asymptomatic. Risk factors for hypocalcemia include prematurity and a difficult birth.

Hypomagnesemia is a rare cause of seizures, which may occur when the serum Mg level is < 1.4 mEq/L (< 0.7 mmol/L). Hypomagnesemia often occurs with hypocalcemia and should be considered in neonates with hypocalcemia if seizures continue after adequate Ca therapy.

Inborn errors of metabolism (eg, amino or organic aciduria) can cause neonatal seizures. Rarely, pyridoxine deficiency or dependency causes seizures; it is readily treated. Other causes include CNS malformations. Maternal substance abuse (eg, cocaine, heroin, diazepam) is an increasingly common problem; seizures can accompany acute withdrawal after birth. Neonatal seizures may be familial; some have genetic causes.
Symptoms and Signs

Neonatal seizures are usually focal and may be difficult to recognize. Common manifestations include migratory clonic jerks of extremities, alternating hemiseizures, and primitive subcortical seizures (which cause respiratory arrest, chewing movements, persistent eye deviations or nystagmoid movements, and episodic changes in muscle tone). Generalized tonic-clonic seizures are uncommon.

Clinically silent electrical seizure activity is often present after a hypoxic-ischemic insult (including perinatal asphyxia or stroke) and in neonates with CNS infections, especially after initial seizure treatment, which is more likely to stop clinical manifestations than electrical seizure activity.

Diagnosis

- EEG
- Laboratory testing (eg, CSF analysis, electrolytes) as clinically indicated
- Usually cranial imaging

Evaluation begins with a detailed family history and a physical examination. EEG (waking and sleep) is essential, especially when it is difficult to determine whether the neonate is having seizures; EEG is also helpful for monitoring response to treatment. EEG should capture periods of active and quiet sleep and thus may require ≥ 2 h of recording. A normal EEG with expected variation during sleep stages is a good prognostic sign; an EEG with diffuse severe abnormalities (eg, suppressed voltage or burst suppression pattern) is a poor one.

Other tests should include pulse oximetry; measurement of serum glucose, Na, K, Cl, HCO₃, Ca, and Mg; and lumbar puncture for CSF analysis (cell count and differential, glucose, protein) and culture. Urine and blood cultures are obtained. The need for other metabolic tests (eg, arterial pH, blood gases, serum bilirubin, urine amino or organic acids) or tests for commonly abused drugs (passed to the neonate transplacentally or by breast-feeding) depends on the clinical situation.

Most infants should have cranial CT because it can detect intracranial bleeding and some brain malformations. Cranial ultrasonography may detect intraventricular bleeding but not subarachnoid bleeding; it may be preferred as a bedside test for very sick infants who cannot be moved to radiology. Diffusion-weighted MRI and magnetic resonance spectroscopy may detect ischemic tissue within a few hours but cannot be done until infants are stable.

Jitteriness (alternating contraction and relaxation of opposing muscles in the extremities) must be distinguished from true seizure activity. Jitteriness is usually stimulus-induced and can be stopped by holding the extremity still. Seizures occur spontaneously, and motor activity is felt even when the extremity is held still.

Prognosis

Prognosis depends on the etiology. About 50% of neonates with seizures due to hypoxiaischemia develop normally. Most neonates with seizures due to subarachnoid hemorrhage, hypocalcemia, or hyponatremia do well. Those with severe intraventricular hemorrhage have a high morbidity rate. For idiopathic seizures or seizures due to malformations, earlier onset is associated with higher morbidity and mortality rates.

Whether neonatal seizures cause damage beyond that caused by the underlying disorder is unknown, although there is concern that the metabolic stress of prolonged nerve cell firing during lengthy seizures may cause additional brain damage. When caused by hypoxia-ischemia, stroke, or infection, neonates may have a series of seizures, but seizures typically abate after about 3 to 4 days; they may recur months to years later if brain damage has occurred. Seizures due to other conditions may be more persistent during the neonatal period.
Treatment

• Treatment of cause

• Anticonvulsants

Treatment focuses primarily on the underlying disorder and secondarily on seizures.

For low serum glucose, 10% dextrose 2 mL/kg IV is given, and the serum glucose level is monitored; additional infusions are given as needed.

For hypocalcemia, 10% Ca gluconate 1 mL/kg IV (9 mg/kg of elemental Ca) is given; this dosage can be repeated for persistent hypocalcemic seizures. Rate of Ca gluconate infusion should not exceed 0.5 mL/min (50 mg/min); continuous cardiac monitoring is necessary during the infusion. Extravasation should be avoided because skin may slough.

For hypomagnesemia, 0.2 mL/kg of a 50% Mg sulfate solution is given IM.

Bacterial infections are treated with antibiotics; herpes encephalitis is treated with acyclovir.

Anticonvulsants are used unless seizures stop quickly after correction of reversible disorders such as hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, or hypernatremia. Phenobarbital is the drug of choice; a loading dose of 15 to 20 mg/kg IV is given. If seizures continue, 5 to 10 mg/kg can be given q 15 to 30 min until seizures cease or until a maximum of 30 mg/kg is given. Maintenance therapy may be started about 12 h later at 1.5 to 2 mg/kg bid and increased to 2.5 mg/kg bid based on clinical or EEG response or serum drug levels. Phenobarbital is continued IV, especially if seizures are frequent or prolonged. When seizures are controlled, phenobarbital can be given orally. Therapeutic serum levels of phenobarbital are 15 to 40 μg/mL (65 to 170 μmol/L).

If a 2nd drug is needed, fosphenytoin or phenytoin is used. The loading dose is 20 mg PE (phenytoin equivalents)/kg IV. It is given over 40 min to avoid hypotension or arrhythmias. A maintenance dose is then started at 2 to 3 mg/kg q 12 h and adjusted based on clinical response or serum levels. Therapeutic serum levels for phenytoin are 10 to 20 μg/mL (40 to 80 μmol/L). Appropriate duration of therapy with any drug is not known.

Lorazepam 0.1 mg/kg IV may be used for resistant seizures and repeated at 5- to 10-min intervals, up to 3 doses in any 8-h period.

Some of the newer anticonvulsants are being investigated for treatment of neonatal seizures.

Neonates given IV anticonvulsants are closely observed; overmedication may result in respiratory depression.

Tourette's Syndrome

(Gilles de la Tourette's Syndrome)

Tourette's syndrome is a hereditary tic disorder that begins during childhood. Symptoms include simple, complex, and vocal tics. Diagnosis is clinical. Treatment may include clonidine and antipsychotics.

Tourette's syndrome is probably autosomal dominant with variable penetrance; the specific genetic abnormality is unknown. Male:female ratio is 3:1. Simple transient tics, chronic tic disorder, and Tourette's syndrome form a continuum or spectrum.

Symptoms and Signs

The movement disorder may begin with simple tics (eg, facial grimacing, head jerking, blinking, sniffing)
that progress to multiple complex tics, including respiratory and vocal ones (eg, loud, irritating vocalizations; snorting). Vocal tics may begin as grunting or barking noises and evolve into compulsive utterances that are often loud or shrill. Patients may voluntarily suppress tics for seconds or minutes. Coprolalia (involuntary scatologic or obscene utterances) occurs in a few patients. Severe tics and coprolalia are physically and socially disabling. Echolalia (immediate repetition of one's own or another person's words or phrases) is common. In most children, tics tend to wane during the teenage years.

Comorbid disorders (eg, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, learning disabilities, anxiety) and poor socialization are common and may be more problematic and more likely to need intervention than the tics.

**Diagnosis**

- Clinical evaluation

Diagnosis is clinical. To differentiate Tourette's syndrome from transient tics, physicians may have to monitor patients over time.

**Treatment**

- Clonidine

- Sometimes antipsychotics

Treatment to suppress tics is recommended only if they are significantly interfering with the children's activities or self-image; treatment does not alter the natural history of the disorder. Clonidine 0.05 to 0.1 mg po tid or qid is effective in some patients. Adverse effects of fatigue may limit dosage; hypotension is uncommon.

Antipsychotics (eg, risperidone 0.25 to 1.5 mg po bid, haloperidol 0.5 to 2 mg po bid or tid, pimozide 1 to 2 mg po bid, olanzapine 2.5 to 5 mg once/day) may be required. The lowest dose required to make tics tolerable is used; doses are tapered as tics wane. Adverse effects of dysphoria, parkinsonism, akathisia, and tardive dyskinesia may limit use of anti-psychotics; using lower daytime doses and higher bedtime doses may decrease adverse effects.
Chapter 287. Neurocutaneous Syndromes

Introduction

Neurocutaneous syndromes (eg, neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis, von Hippel-Lindau disease) are neurologic syndromes with cutaneous manifestations. These disorders frequently also cause eye lesions, brain malformations, seizures, and intellectual disability.

Neurofibromatosis

Neurofibromatosis is an autosomal dominant disorder that causes tumors to develop along the course of peripheral nerves and that occasionally results in marked soft-tissue or bone deformities. Diagnosis is clinical. There is no specific treatment, but tumors can be removed surgically.

Neurofibromatosis has 2 types. Type 1 (von Recklinghausen's disease) is most prevalent, causing neurologic, cutaneous, and sometimes soft-tissue or bone manifestations. Type 2 accounts for 10% of cases, manifesting primarily as congenital bilateral acoustic neuromas. The gene for type 1 is located on band 17q11.2, and that for type 2 is located on band 22q11.

Neurofibromas (benign tumors consisting of Schwann cells and neural fibroblasts) may be peripheral or central.

Peripheral neurofibromas can develop anywhere along the course of peripheral nerves. Most appear during adolescence. There are 4 forms:

• Cutaneous neurofibromas are soft and fleshy.

• Subcutaneous neurofibromas are firm and nodular.

• Nodular plexiform neurofibromas may involve spinal nerve roots, typically growing through an intervertebral foramen to cause intraspinal and extraspinal masses (dumb-bell tumor). The intraspinal part may compress the spinal cord.

• Diffuse plexiform neurofibromas (subcutaneous nodules or amorphous overgrowth of underlying bone or Schwann cells) can be disfiguring and may cause deficits distal to the neurofibroma. These neurofibromas can become malignant.

Central (cranial nerve) neurofibromas have 2 forms:

• Optic gliomas: These may cause progressive blindness. They may occur in both types 1 and 2.

• Acoustic neuromas (vestibular schwannomas): These may cause dizziness, ataxia, deafness, and tinnitus. They occur in type 2.

Symptoms and Signs

Type 1: Most patients are asymptomatic. Some present with neurologic symptoms or bone deformities. In > 90%, characteristic skin lesions (see Plate 72) are apparent at birth or develop during infancy. Lesions are medium-brown (cafe-au-lait), freckle-like macules, distributed most commonly over the trunk, pelvis, and flexor creases of elbows and knees. During late childhood, flesh-colored cutaneous tumors of various sizes and shapes appear, ranging in number from several to thousands. Rarely, plexiform neurofibromas develop, causing an irregularly thickened, distorted structure with grotesque deformities.

Neurologic symptoms vary, depending on location and number of neurofibromas. Bone abnormalities include
• Fibrous dysplasia

• Subperiosteal bone cysts

• Vertebral scalloping

• Scoliosis

• Thinning of the long-bone cortex

• Pseudarthrosis

• Absence of the greater wing of the sphenoid bone (posterior orbital wall), with consequent pulsating exophthalmos

An optic glioma and Lisch nodules (iris hamartomas) occur in some patients. Changes in arterial walls may lead to Moyamoya disease or intracranial artery aneurysms. Some children have learning problems and slightly larger heads.

Type 2: Bilateral acoustic neuromas develop and become symptomatic during childhood or early adulthood. They cause hearing loss, unsteadiness, and sometimes headache or facial weakness. Bilateral 8th cranial (vestibulocochlear) nerve masses may be present. Family members may have gliomas, meningiomas, or schwannomas.

Diagnosis

• Clinical evaluation

• CT or MRI

Most patients with type 1 are identified during routine examination, examination for cosmetic complaints, or evaluation of a positive family history. Diagnosis is clinical (see Table 287-1). CT or MRI is done in patients with neurologic symptoms or signs on presentation and in those with other examination findings that suggest neurofibromatosis. Neuroimaging may detect 8th cranial nerve masses in type 2; MRI may show focal density changes in type 1.

Genetic testing exists but is not routinely available.

Treatment

• Possibly surgery or irradiation

No general treatment is available. Neurofibromas that cause severe symptoms may require surgical removal or irradiation, although surgery may obliterate function of the involved nerve.

Genetic counseling is advisable. If either parent has neurofibromatosis, risk to subsequent offspring is 50%; if neither has it, risk for subsequent children is unclear because new mutations are common.

Sturge-Weber Syndrome

Sturge-Weber syndrome is a rare congenital vascular disorder characterized by a facial port-wine stain, a leptomeningeal angioma, and neurologic complications (eg, seizures, focal neurologic deficits, intellectual disability).

Sturge-Weber syndrome causes a port-wine stain typically on the forehead and upper eyelid in the distribution of the 1st or 2nd division of the trigeminal nerve. A leptomeningeal angioma occurs in 90% of patients when the port-wine stain involves upper and lower eyelids on one side but only in 10 to 20% when only one eyelid is affected. Neurologic complications include seizures, focal neurologic deficits (eg,
hemiparesis), and intellectual disability. The disorder can also cause glaucoma and vascular
malformations, which may increase risk of vascular events (eg, stroke, thrombosis, venous occlusion, infarction). It is not inherited; etiology is unclear.

**Types:** There are 3 types:

- Type I: Port-wine stain and brain angiomas
- Type II: Port-wine stain but no brain angiomas
- Type III: Brain angioma but no port-wine stain

**Symptoms and Signs**

The port-wine stain can vary in size and color, ranging from light pink to deep purple.

Seizures occur in about 75 to 90% of patients and typically start by age 1 yr. Seizures are usually focal but can become generalized. Hemiparesis of the side opposite the port-wine stain occurs in 25 to 50% of patients. About 50% of patients have intellectual disability, and more have some kind of learning difficulty. Development may be delayed.

Glaucoma may be present at birth or develop later. The eyeball may enlarge and bulge out of its socket (buphthalmos).

**Diagnosis**

Diagnosis is suggested by a characteristic port-wine stain. CT and MRI are used to check for a leptomeningeal angioma. Neurologic examination is done to check for neurologic complications.

**Treatment**

Treatment focuses on symptoms. Anticonvulsants and drugs to treat glaucoma are used. Low-dose aspirin is often given to help prevent strokes. Selective photothermolysis can lighten the port-wine stain.

**Tuberous Sclerosis**

Tuberous sclerosis (TS) is a dominantly inherited genetic disorder in which tumors (usually hamartomas) develop in multiple organs.

Children with TS or TS complex have tumors in multiple organs, including the heart, eyes, kidneys, lungs, and skin. Many children have kidney tumors, usually angiomylipomas, which can cause hypertension and cystic kidney disease. Renal carcinoma can also occur. Some children also have cardiac rhabdomyomas. Brain tubers (gyral enlargements) and tumors, usually astrocytomas, can occur.

In families with several affected members, up to 4 separate gene sites have been identified. If either parent has the disorder, children have a 50% risk of having it. However, new mutations account for most new cases.

**Symptoms and Signs**

Affected children may have seizures, intellectual disability, autism, learning disorders, or behavioral problems. Infants may present with a type of seizure called infantile spasms (see p. 2899). Retinal patches are common and may be visible with funduscopy.
• Initially pale, ash leaf-shaped macules, which develop during infancy or early childhood
• Angiofibromas of the face (adenoma sebaceum), which develop during later childhood
• Congenital shagreen patches (raised lesions resembling an orange peel), usually on the back
• Subcutaneous nodules
• Cafe-au-lait spots
• Subungual fibromas, which can develop any time during childhood or early adulthood

Diagnosis

• Imaging of affected organs
• Genetic testing

Cardiac or cranial manifestations may be visible on prenatal ultrasonography. MRI or ultrasonography of the affected organs is necessary for confirmation.

Specific genetic testing is available.

Prognosis

Prognosis depends on symptom severity. Infants with mild symptoms generally do well and live long, productive lives; infants with severe symptoms may have serious disabilities. Regardless of severity, most children show continued developmental progress. Occasionally, neurologic degeneration may occur and requires investigation.

Treatment

Treatment is symptomatic:

• For seizures: Anticonvulsants or even brain surgery
• For skin lesions: Dermabrasion or laser techniques
• For neurobehavioral problems: Behavior management techniques or drugs
• For hypertension caused by renal problems: Antihypertensives or surgery to remove growing tumors
• For developmental delays: Special schooling or occupational therapy

Genetic counseling is indicated for adolescents and adults of childbearing age.

Von Hippel-Lindau Disease

Von Hippel-Lindau disease (VHL) is a rare hereditary neurocutaneous disorder characterized by tumors in multiple organs.

VHL most commonly causes cerebellar hemangioblastomas and retinal angiomas. Tumors, including pheochromocytomas and cysts (renal, hepatic, or pancreatic), can occur in other organs; risk of developing renal cell carcinoma increases with age and by age 60 may be as high as 70%. Manifestations typically appear between ages 10 and 30 but can appear earlier.
The disorder is inherited as an autosomal dominant trait with variable penetrance. The VHL gene is located on the short arm of chromosome 3.

**Symptoms and Signs**

Symptoms depend on the size and location of the tumors. Symptoms may include headaches, dizziness, weakness, impaired vision, and high BP.

Retinal angiomas, detected by direct ophthalmoscopy, appear as a dilated artery leading from the disk to a peripheral tumor with an engorged vein. These angiomas are usually asymptomatic, but if they are centrally located and enlarge, they can result in substantial loss of vision. These tumors increase risk of retinal detachment, macular edema, and glaucoma.

Untreated, VHL can result in blindness, brain damage, or death. Death usually results from complications of cerebellar hemangioblastomas or renal cell carcinoma.

**Diagnosis**

The disorder is diagnosed when typical tumors are detected and one of the following criteria is met:

- More than one tumor in the brain or eye
- Single tumor in the brain or eye and one elsewhere in the body
- Family history of VHL and presence of a tumor

If one cerebellar hemangioblastoma, retinal angioma, or pheochromocytoma is detected, clinicians should look for other tumors.

Genetic testing is done to check for an abnormal VHL gene in at-risk family members. If an abnormal gene is detected, family members are monitored for tumors for the rest of their life.

**Treatment**

- Surgery or sometimes radiation therapy
- For retinal angiomas, laser coagulation or cryotherapy
- Regular monitoring

Treatment often involves surgical removal of the tumor before it becomes harmful. Some tumors can be treated with focused high-dose radiation. Typically, retinal angiomas are treated with laser coagulation or cryotherapy to preserve vision.

Patients should be monitored regularly for progression of the disorder. Appropriate monitoring and treatment can improve prognosis.
Chapter 288. Bone and Connective Tissue Disorders in Children

Introduction

Many bone disorders, particularly those affecting the lower extremities (eg, Osgood-Schlatter disease), result from the dramatic changes that occur in a growing child's musculoskeletal system. These disorders may resolve or worsen with continued growth. Other bone disorders may be inherited (eg, achondroplasia) or acquired (eg, Legg-Calve-Perthes disease).

There are over 200 disorders that involve connective tissue. Certain disorders are characterized by overactivity of the immune system with resulting inflammation and systemic damage to the tissues (eg, SLE [see p. 305] and juvenile idiopathic arthritis [formerly known as juvenile RA—see p. 339]). Other disorders involve biochemical abnormalities or structural defects of the connective tissue. Some of these disorders are inherited, and some are of unknown etiology.

Cutis Laxa

Cutis laxa (CL) is characterized by lax skin hanging in loose folds. Diagnosis is clinical. There is no specific treatment, but plastic surgery is sometimes done.

CL may be inherited or acquired. There are 4 hereditary forms: autosomal dominant, X-linked recessive, and 2 autosomal recessive. The autosomal recessive forms tend to be more common. One of the recessive forms causes potentially lethal cardiovascular, respiratory, and GI complications. The other inherited forms are relatively benign.

Rarely, infants can acquire CL after a febrile illness or after exposure to a specific drug (eg, hypersensitivity reaction to penicillin, fetal exposure to penicillamine). In children or adolescents, CL usually develops after a severe illness involving fever, polyserositis, or erythema multiforme. In adults, it may develop insidiously. The underlying defect is unknown, but fragmented elastin is present in all forms.

Pathophysiology

CL is caused by abnormal elastin metabolism that results in reduced elasticity of the skin. The precise cause is unknown. Several factors, such as copper deficiency, elastin quantity and morphology, and elastases and elastase inhibitors, are implicated in the abnormal elastin degradation.

Symptoms and Signs

In hereditary forms, dermal laxity may be present at birth or develop later; it occurs wherever the skin is normally loose and hanging in folds, most obviously on the face. Affected children have mournful or Churchillian facies and a hooked nose. The benign autosomal recessive form also causes developmental retardation and joint laxity. GI tract hernias and diverticula are common. If the disorder is severe, progressive pulmonary emphysema may precipitate cor pulmonale. Bronchiectasis, heart failure, and aortic aneurysms can also occur.

Diagnosis

Diagnosis is clinical. There are no specific laboratory findings; however, a skin biopsy may be done. Certain tests (eg, echocardiography, chest x-ray) may be done to check for associated conditions (eg, emphysema, cardiomegaly, heart failure). Typical CL can be distinguished from Ehlers-Danlos syndrome because dermal fragility and articular hypermobility are absent. Other disorders sometimes cause localized areas of loose skin. In Turner's syndrome, lax skinfolds at the base of an affected girl's neck tighten and resemble webbing as she ages. In neurofibromatosis, unilateral pendular plexiform neuromas occasionally develop, but their configuration and texture distinguish them from CL.

Treatment

There is no specific treatment. Plastic surgery considerably improves appearance in patients with
hereditary CL but is less successful in those with acquired CL. Healing is usually uncomplicated, but dermal laxity may recur. Extracutaneous complications are treated appropriately.

**Ehlers-Danlos Syndrome**

Ehlers-Danlos syndrome is a hereditary collagen disorder characterized by articular hypermobility, dermal hyperelasticity, and widespread tissue fragility. Diagnosis is clinical. Treatment is supportive.

Inheritance is usually autosomal dominant, but Ehlers-Danlos syndrome is heterogeneous. Different gene mutations affect the amount, structure, or assembly of different collagens. Mutations can exist in the genes that encode collagens (eg, type I, III, or V) or collagen-modifying enzymes (eg, lysyl hydroxylase, a collagen cleaving protease). The 6 major types are classic, hypermobility, vascular, kyphoscoliosis, arthrochalasis, and dermatosparaxis. There are also several rare or hard-to-classify types.

**Symptoms and Signs**

Symptoms and signs vary widely. Predominant symptoms include hypermobile joints, abnormal scar formation and wound healing, fragile vessels, and velvety, hyperextensible skin. Skin can be stretched several centimeters but returns to normal when released. Wide papyraceous scars often overlie bony prominences, particularly elbows, knees, and shins; scarring is less severe in the hypermobility type. Molluscoid pseudotumors (fleshy outgrowths) frequently form on top of scars or at pressure points. Extent of joint hypermobility varies but may be marked in the arthrochalasis, classic, and hypermobility types. Bleeding tendency is rare, although the vascular type is characterized by vascular rupture and bruising. Subcutaneous calcified spherules may be palpated or seen on x-ray studies.

**Complications:** Minor trauma may cause wide gaping wounds but little bleeding; surgical wound closure may be difficult because sutures tend to tear out of the fragile tissue. Surgical complications occur because of deep tissue fragility. Sclera may be fragile, leading to perforation of the globe in the kyphoscoliosis type.

Bland synovial effusions, sprains, and dislocations occur frequently. Spinal kyphoscoliosis occurs in 25% of patients (especially those with the kyphoscoliosis type), thoracic deformity in 20%, and talipes equinovarum in 5%. About 90% of affected adults have pes planus (flat feet). Congenital hip dislocation occurs in 1% (the arthrochalasis type is characterized by bilateral congenital hip dislocation).

GI hernias and diverticula are common. Rarely, portions of the GI tract spontaneously hemorrhage and perforate, and dissecting aortic aneurysm and large arteries spontaneously rupture. Valvular prolapse is a common complication in the most severe type (vascular type). In pregnant women, tissue extensibility may cause premature birth, cervical incompetence, and possibly uterine rupture; if the fetus is affected, fetal membrane is fragile, sometimes resulting in early rupture. Maternal tissue fragility may complicate episiotomy or cesarean delivery. Antenatal, perinatal, and postnatal bleeding may occur. Other potentially serious complications include arteriovenous fistula, ruptured visscus, and pneumothorax or pneumohemothorax.

**Diagnosis**

Diagnosis is largely clinical, and specialized genetic and biochemical tests are available at some research centers for some types. Ultra-structural examination of skin biopsy can help in diagnosing the classic, hypermobility, and vascular types. Echocardiography is done to check for heart disorders (eg, valvular prolapse, arterial aneurysm) that are associated with some of the types.

**Prognosis**

Life span is usually normal with most types. Potentially lethal complications occur in certain types (eg, arterial rupture in the vascular type).

**Treatment**
There is no specific treatment. Trauma should be minimized. Protective clothing and padding may help. If surgery is done, hemostasis must be meticulous. Wounds are carefully sutured, and tissue tension is avoided. Obstetric supervision during pregnancy and delivery is mandatory. Genetic counseling should be provided.

**Marfan Syndrome**

Marfan syndrome consists of connective tissue anomalies resulting in ocular, skeletal, and cardiovascular abnormalities (eg, dilation of ascending aorta, which can lead to aortic dissection). Diagnosis is clinical. Treatment may include prophylactic β-blockers to slow dilation of the ascending aorta and prophylactic aortic surgery.

Inheritance is autosomal dominant. The basic molecular defect results from mutations in the gene encoding the glycoprotein fibrillin-1 (FBN1), which is the main component of microfibrils and helps anchor cells to the extracellular matrix. The principal structural defect involves the cardiovascular, musculoskeletal, and ocular systems. The pulmonary system and CNS are also affected. There are many different manifestations of the genetic mutation that causes Marfan syndrome; however, it is typically recognized by the constellation of long limbs, aortic root dilation, and dislocated lenses.

**Symptoms and Signs**

**Cardiovascular system:** Findings include valvular prolapse and aortic aneurysm. A diastolic murmur may be heard over the aortic valve. Those with mitral valve prolapse may have a systolic click and a late systolic murmur or, in severe cases, a holosystolic murmur. Most severe complications result from pathologic changes in the aortic root and ascending aorta. The aortic media is affected preferentially in areas subject to the greatest hemodynamic stress. The aorta progressively dilates or acutely dissects, beginning in the coronary sinuses, sometimes before age 10 yr. The aortic root dilates in 50% of children and in 60 to 80% of adults and can cause aortic regurgitation. Bacterial endocarditis may develop. Redundant cusps and chordae tendineae may lead to mitral valve prolapse or regurgitation.

**Musculoskeletal system:** Severity varies greatly. Patients are taller than average for age and family; arm span exceeds height. Arachnodactyly (disproportionately long, thin digits) is noticeable, often by the thumb sign (the distal phalanx of the thumb protrudes beyond the edge of the clenched fist). Sternum deformity—pectus carinatum (outward displacement) or pectus excavatum (inward displacement)—is common, as are joint hyperextensibility, genu recurvatum (backward curvature of the legs at the knees), pes planus (flat feet), kyphoscoliosis, and diaphragmatic and inguinal hernias. Subcutaneous fat usually is sparse. The palate is often high-arched.

[Table 288-1. Diagnostic Criteria for Marfan Syndrome (Ghent Nosology)]

**Ocular system:** Findings include ectopia lentis (subluxation or upward dislocation of the lens) and iridodonesis (tremulousness of the iris). The margin of the dislocated lens can often be seen through the undilated pupil. High-grade myopia may be present, and spontaneous retinal detachment sometimes occurs.

**Pulmonary system:** Cystic lung disease and recurrent spontaneous pneumothorax may occur. These disorders can cause pain and shortness of breath.

**CNS:** Dural ectasia is a common finding and most frequently occurs in the lumbosacral spine. It is widening of the dural sac surrounding the spinal cord and may cause headache, lower back pain, or neurologic deficits manifested by bowel or bladder weakness.

**Diagnosis**

• Clinical criteria
• Echocardiography/MRI (measurement of the aortic root, detection of valve prolapse)

• Slit-lamp examination (lens abnormalities)

• X-rays of skeletal system (hand, spine, pelvis, chest, foot, and skull for characteristic abnormalities)

• MRI (dural ectasia)

Diagnosis can be difficult because many patients have few typical symptoms and signs and no specific histologic or biochemical changes. Considering this variability, diagnostic criteria are based on constellations of clinical findings and family and genetic history (see Table 288-1). Nonetheless, diagnosis is uncertain in many partial cases of Marfan syndrome. Homocystinuria can partially mimic Marfan syndrome but can be differentiated by detecting homocystine in the urine. Prenatal diagnosis by linkage analysis of the \textit{FBN1} gene mutation is hampered by poor genotype/phenotype correlation. Standard imaging of the skeletal, cardiovascular, and ocular systems is done to detect any clinically relevant structural abnormalities and to provide information contributing to the diagnostic criteria (eg, echocardiography to identify aortic root enlargement). In addition to the criteria established within organ systems, family history (1st-degree relative with Marfan syndrome) and genetic history (presence of the \textit{FBN1} mutation known to cause Marfan syndrome) are considered major criteria.

**Prognosis**

Advancements in therapy and regular monitoring have improved quality of life and reduced mortality. Median life expectancy increased from 48 yr in 1972 to 72 yr as of 1992. However, life expectancy is still reduced for the average patient, primarily because of the cardiac and vascular complications. This decreased life expectancy can take an emotional toll on an adolescent and the family.

**Treatment**

• Induction of precocious puberty in tall girls

• β-Blockers

• Elective aortic repair and valve repair

• Bacterial endocarditis prophylaxis

• Bracing and surgery for scoliosis

Treatment focuses on prevention and treatment of complications. For very tall girls, inducing precocious puberty by age 10 with estrogens and progesterone may reduce potential adult height. All patients should routinely be given β-blockers (eg, atenolol, propranolol) to help prevent cardiovascular complications. These drugs lower myocardial contractility and pulse pressure and reduce progression of aortic root dilation and risk of dissection. Prophylactic surgery is offered if aortic diameter is > 5 cm (less in children). Pregnant women are at especially high risk of aortic complications; elective aortic repair before conception should be discussed. Severe valve regurgitation is also surgically repaired. Bacterial endocarditis prophylaxis before certain invasive procedures (see p. 2199) is not indicated except in patients who have prosthetic valves or who previously had infective endocarditis (see Tables 215-3 and 215-4). Scoliosis is managed with bracing as long as possible, but surgical intervention is encouraged in patients with curves of 40 to 50°.

Cardiovascular, skeletal, and ocular findings should be reevaluated annually. Appropriate genetic counseling is indicated.

**Nail-Patella Syndrome**

(Osteo-Onychodysplasia; Arthro-Onychodysplasia; Onycho-Osteodysplasia)
Nail-patella syndrome is a rare inherited disorder of mesenchymal tissue characterized by abnormalities of bones, joints, fingernails and toenails, and kidneys.

Nail-patella syndrome is an autosomal dominant disorder caused by a mutation in the gene for the transcription factor \textit{LMX1B}, which plays an important role in vertebrate limb and kidney development.

There is bilateral hypoplasia or absence of the patella, subluxation of the radial head at the elbows, and bilateral accessory iliac horns. Fingernails and toenails are absent or hypoplastic, with pitting and ridges.

Renal dysfunction occurs in up to 50% of patients due to focal segmental glomerular deposits of IgM and C3. Proteinuria is the most common manifestation, but about 30% of people with renal involvement slowly progress to renal failure.

Diagnosis is suggested clinically; sometimes renal biopsy is indicated, which is diagnostic. \textit{LMX1B} mutation analysis is possible, including for prenatal diagnosis, but the type of mutation does not usually predict clinical severity.

There is no specific treatment, but when indicated, kidney transplantation has been successful without evidence of recurrent disease in the graft.

**Osteogenesis Imperfecta**

Osteogenesis imperfecta (OI) is a hereditary collagen disorder causing diffuse abnormal fragility of bone and is sometimes accompanied by sensorineural hearing loss, blue sclerae, dentinogenesis imperfecta, and joint hypermobility.

There are 4 main types of OI; types I and IV are autosomal dominant, whereas types II and III are autosomal recessive. Other types are rare.

**Symptoms and Signs**

Hearing loss is present in 50 to 65% of all patients with OI and may occur in any of the 4 types.

**Type I** is the mildest. Symptoms and signs in some patients are limited to blue sclerae (due to a deficiency in connective tissue, allowing the underlying vessels to show through) and musculoskeletal pain due to joint hypermobility. Recurrent fractures in childhood are possible.

**Type II** (neonatal lethal type or OI congenita) is the most severe and is lethal. Multiple congenital fractures result in shortened extremities. Sclerae are blue. The skull is soft and, when palpated, feels like a bag of bones. Because the skull is soft, trauma during delivery may cause intracranial hemorrhage and stillbirth, or neonates may die suddenly during the first few days or weeks of life.

**Type III** is the most severe nonlethal form of OI. Patients with type III have short stature, spinal curvature, and multiple, recurrent fractures. Macrocephaly with triangular facies and pectal deformities are common. Scleral hue varies.

**Type IV** is intermediate in severity. Survival rate is high. Bones fracture easily in childhood before adolescence. Sclera are typically normal in color. Height is moderate-short stature. Accurate diagnosis is important because these patients may benefit from treatment.

**Diagnosis**

Diagnosis is usually clinical, but there are no standardized criteria. Analysis of type I pro-collagen (a structural component of bones, ligaments, and tendons) from cultured fibro-blasts (from a skin biopsy) or sequence analysis of the \textit{COL1A1} and \textit{COL1A2} genes can be used when clinical diagnosis is unclear. Severe OI can be detected in utero by level II ultrasonography.
Treatment

• Growth hormone

• Bisphosphonates

Growth hormone helps growth-responsive children (types I and IV). There is limited experience with the use of IV bisphosphonates (eg, pamidronate 0.5 to 3 mg/kg once/day for 3 days, repeated as needed q 4 to 6 mo) with children, but they can increase bone density and decrease bone pain and fracture frequency. Preliminary studies suggest that oral alendronate (1 mg/kg, 20 mg maximum) is also effective. Orthopedic surgery, physical therapy, and occupational therapy help prevent fractures and improve function. Cochlear implantation is indicated in selected cases of hearing loss.

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is a rare genetic disorder characterized by calcification of the elastic fibers of the skin, retina, and cardiovascular system.

Pseudoxanthoma elasticum is caused by mutations in the ABCC6 gene that are inherited in both autosomal dominant and recessive forms. The ABCC6 gene product is a trans-membrane transporter protein that probably plays roles in cellular detoxification. Characteristic cutaneous papular lesions begin in childhood and are primarily of cosmetic concern. They appear as small yellowish papules that typically occur on the neck and axillae and flexural surfaces. Elastic tissues become calcified and fragmented, leading to disruption of the involved organ systems. Ocular involvement includes angioid streaks of the retina, retinal hemorrhages, and gradual vision loss. Cardiovascular manifestations can include intermittent claudication, premature atherosclerosis with subsequent hypertension, angina, and MI. Fragility of vessels can lead to GI hemorrhage and small vessel bleeding with subsequent anemia.

Diagnosis is based on clinical and histologic findings. Laboratory and imaging studies are done for associated conditions (eg, CBC, echocardiography, head CT).

Treatment of retinal angioid streaks with intravitreal injections of the angiogenesis-blocking antibody bevacizumab shows promise. Otherwise, there is no specific treatment, and the aim is to prevent complications. People should avoid drugs that may cause stomach or intestinal bleeding, such as aspirin, other NSAIDs, and anticoagulants. People with pseudoxanthoma elasticum should avoid contact sports because of the risk of injury to the eye. Complications may limit life span.

Congenital Hypophosphatasia

Congenital hypophosphatasia is absence or low levels of serum alkaline phosphatase due to mutations in the gene encoding tissue nonspecific alkaline phosphatase.

Because serum alkaline phosphatase is absent or decreased, Ca++ is not diffusely deposited in bones, causing low bone density and hypercalcemia. Vomiting, inability to gain weight, and enlargement of the epiphyses (similar to that in rickets) usually occur. Patients who survive infancy have bony deformities and short stature, but mental development is normal. No treatment is effective, but infusions of alkaline phosphatase and bone marrow transplantation have limited roles. NSAIDs reduce bone pain.

Idiopathic Scoliosis

Idiopathic scoliosis is lateral curvature of the spine.

Idiopathic scoliosis is the most common form of scoliosis and is present in 2 to 4% of children aged 10 to 16 yr. Boys and girls are equally affected; however, it is 10 times more likely to progress and require treatment in girls.
Scoliosis may first be suspected when one shoulder seems higher than the other or when clothes do not hang straight, but it is often detected during routine physical examination. Other findings include asymmetry in shoulder height, apparent leg-length discrepancy, and asymmetry of the chest wall. Patients may initially report fatigue in the lumbar region after prolonged sitting or standing. Muscular backaches in areas of strain (e.g., in the lumbosacral angle) may follow.

**Diagnosis**

- X-ray of the spine

The curve is most pronounced when patients bend forward. Most curves are convex to the right in the thoracic area and to the left in the lumbar area, so that the right shoulder is higher than the left. X-ray examination should include standing anteroposterior and lateral views of the spine.

The greater the curve, the greater the likelihood that it will progress after the skeleton matures. Curves > 10° are considered significant. Prognosis depends on site and severity of the curve and age at symptom onset. Significant intervention is required in < 10% of patients.

**Treatment**

- Physical therapy and bracing
- Sometimes surgery

Prompt referral to an orthopedist is indicated when progression is of concern or the curve is significant. Likelihood of progression is greatest around puberty for boys and girls. Moderate curves (20 to 40°) are treated conservatively (e.g., physical therapy and bracing) to prevent further deformity. Severe curves (> 40°) can often be ameliorated surgically (e.g., spinal fusion with rod placement). Scoliosis and its treatment often interfere with an adolescent's self-image and self-esteem. Counseling or psychotherapy may be needed.

**Chondromalacia Patellae**

(Patellofemoral Syndrome)

Chondromalacia patellae is softening of the cartilage underneath the patella.

Chondromalacia patellae often causes generalized knee pain, without swelling, especially when climbing or descending stairs, playing sports that exert an axial load on the knees, or sitting for a long time. This disorder probably results from angular or rotational changes in the leg that unbalance elements of the quadriceps and cause patellar misalignment during movement.

Acute pain due to chondromalacia patellae is treated by applying ice and taking analgesics. Children with chondromalacia patellae should avoid pain-causing activities (typically, those that involve bending the knee) for several days. Persistent or recurrent pain due to chondromalacia patellae may be relieved by arthroscopic smoothing of the patella's undersurface.

**Osteochondrodysplasias**

(Genetic Skeletal Dysplasias)

Osteochondrodysplasias involve abnormal bone or cartilage growth, leading to skeletal maldevelopment, often short-limbed dwarfism. Diagnosis is by physical examination, x-rays, and, in some cases, genetic testing. Treatment is surgical.

The basic genetic defects have been identified in most of the osteochondrodysplasias. The mutations typically cause perturbation of function in proteins involved in growth and development of connective tissue, bone, or cartilage (see...
Dwarfism is markedly short stature (adult height < 4 ft 10 in) frequently associated with disproportionate growth of the trunk and extremities. Achondroplasia is the most common and best-known type of short-limbed dwarfism, but there are many other distinct types, which differ widely in genetic background, course, and prognosis (see Table 288-2). Lethal short-limbed dwarfism (thanatophoric dysplasia, caused by mutations in the same gene as achondroplasia) causes severe chest wall deformities and respiratory failure in neonates, resulting in death.

**Diagnosis**

Characteristic x-ray changes may be diagnostic. A whole-body x-ray of every affected neonate, even if stillborn, should be taken because diagnostic precision is essential for predicting prognosis. Prenatal diagnosis by fetoscopy or ultrasonography is possible in some cases (eg, when fetal limb shortening is severe). Standard laboratory tests do not help, but molecular diagnosis is feasible for chondrodysplasias with known molecular defects.

**Treatment**

In achondroplasia, treatment with human growth hormone is generally not effective. An increase in adult height may be achieved by surgical limb lengthening. In this and other nonlethal osteochondrodysplasias, surgery (eg, hip replacement) can help improve joint function. Hypoplasia of the odontoid process can predispose to subluxation of the 1st and 2nd cervical vertebrae and compression of the spinal cord. Therefore, the odontoid process should be evaluated preoperatively, and if it is abnormal, the patient's head should be carefully supported when hyperextended for endotracheal intubation during anesthesia.

Because the inheritance pattern in most types is known, genetic counseling can be effective. Organizations such as Little People of America (www.lpaonline.org) provide resources for affected people and act as advocates on their behalf. Similar societies are active in other countries.

**Osteochondroses**

Osteochondroses are noninflammatory, noninfectious derangements of bony growth at various ossification centers. These derangements occur during the period of greatest developmental activity and affect the epiphyses.

Etiology is unknown, and inheritance is complex. Osteochondroses differ in their anatomic distribution, course, and prognosis; they typically cause pain and have important orthopedic implications. Rare osteochondroses and the involved bones include Freiberg's disease (head of 2nd metatarsal), Panner's disease (capitulum), and Blount disease (proximal tibia). Sever's disease is a more common osteochondrosis.

**Infrapatellar Tendinitis**  
*(Jumper's Knee; Sinding-Larsen-Johansson Syndrome)*

Infrapatellar tendinitis is an osteochondrosis that is an overuse injury to the patellar tendon at the attachment to the lower pole of the patella.

Knee pain with infrapatellar tendon tenderness in physically active children is caused by an overuse syndrome that usually occurs in figure skaters and basketball or volleyball players. It typically affects children 10 to 13 yr. Pain is the most exaggerated when straightening the knee against force (eg, climbing stairs, jumping, doing knee bends). Etiology is thought to be trauma due to excessive traction by the patellar tendon at its site of origin, leading to microavulsion fractures. History and physical examination are usually sufficient for diagnosis; however, MRI can show the extent of the injury.

Pain is treated with modification of activities, NSAIDs, and physical therapy. Persistent pain may be treated with surgical repair; however, this is usually not necessary.
Kohler's Bone Disease

Kohler's bone disease is osteochondrosis of the tarsal navicular bone.

Kohler's bone disease usually affects children aged 3 to 5 yr (more commonly boys) and is unilateral. The foot becomes swollen and painful; tenderness is maximal over the medial longitudinal arch. Weight bearing and walking increase discomfort, and gait is disturbed. On x-ray, the navicular bone is initially flattened and sclerotic and later becomes fragmented, before reossification. X-rays comparing the affected side with the unaffected side help assess progression.

The course is chronic, but the disease rarely persists ≥ 2 yr. Rest, pain relief, and avoiding excessive weight bearing are required. The condition usually resolves spontaneously with no long-term sequelae. In acute cases, a few weeks of wearing a below-knee walking plaster cast, well molded under the longitudinal arch, may help.

Legg-Calve-Perthes Disease

Legg-Calve-Perthes disease is idiopathic aseptic necrosis of the femoral capital epiphysis.

Legg-Calve-Perthes disease has a maximum incidence at age 5 to 10 yr, is more common among boys, and is usually unilateral. About 10% of cases are familial. Characteristic symptoms are pain in the hip joint and gait disturbance; onset is gradual, and progression is slow. Joint movements are limited, and thigh muscles may become wasted.

Diagnosis

Diagnosis is suspected based on symptoms. Bone scan or MRI should be done to confirm the diagnosis. X-rays initially may not be useful, because they can be normal or show minimal flattening. Later x-rays can show fragmentation of the femoral head, which contains areas of lucency and sclerosis.

In bilateral or familial cases, a skeletal survey to exclude hereditary skeletal disorders, particularly multiple epiphyseal dysplasia, is mandatory because prognosis and optimal management differ. Hypothyroidism, sickle cell anemia, and trauma must also be excluded.

Treatment

Orthopedic treatment includes prolonged bed rest, mobile traction, slings, and abduction plaster casts and splints to contain the femoral head. Some experts advocate subtrochanteric osteotomy with internal fixation and early ambulation. The bisphosphonate alendronate is effective in treating avascular necrosis of the femur in adults. Therefore, bisphosphonates may prove useful in the nonsurgical treatment of Legg-Calve-Perthes disease.

Without treatment, the course is usually prolonged but self-limited (usually 2 to 3 yr). When the disease eventually becomes quiescent, residual distortion of the femoral head and acetabulum predisposes to secondary degenerative osteoarthritis. With treatment, sequelae are less severe.

Osgood-Schlatter Disease

Osgood-Schlatter disease is osteochondrosis of the tibial tubercle.

Osgood-Schlatter disease occurs between ages 10 yr and 15 yr and is usually unilateral. Although the disease is more common among boys, this status is changing as girls become more active in sports programs. Etiology is thought to be trauma due to excessive traction by the patellar tendon on its immature epiphyseal insertion, leading to microavulsion fractures. Characteristic symptoms are pain,
swelling, and tenderness over the tibial tubercle at the patellar tendon insertion. There is no systemic disturbance.

**Diagnosis**

Diagnosis is by examination. Lateral knee x-rays show fragmentation of the tibial tubercle. However, x-rays are not needed unless pain and swelling extend beyond the area over the tibial tubercle or unless pain is accompanied by redness and warmth. In such cases, x-rays are useful to rule out injuries or acute inflammatory conditions.

**Treatment**

Resolution is usually spontaneous within weeks or months. Usually, taking analgesics and avoiding excessive exercise, especially deep knee bending, are the only necessary measures. Complete avoidance of sports is unnecessary. Rarely, immobilization in plaster, intralesional injection of hydrocortisone, surgical removal of loose bodies (eg, ossicles, avulsed fragments of bone), drilling, and grafting are required.

**Scheuermann's Disease**

*Scheuermann's disease causes localized changes in vertebral bodies, leading to backache and kyphosis.*

Scheuermann's disease manifests in adolescence and is slightly more common among boys. It probably represents a group of diseases with similar symptoms, but etiology and pathogenesis are uncertain. It may result from osteochondritis of the upper and lower cartilaginous vertebral end plates or trauma. Some cases are familial.

Most patients present with a round-shouldered posture and they may have persistent low-grade backache. Some have an appearance similar to people with Marfan syndrome; trunk and limb length are disproportionate. Normal thoracic kyphosis is increased diffusely or locally.

**Diagnosis**

Some cases are recognized during routine screening for spinal deformity at school. Lateral spinal x-rays confirm the diagnosis by showing anterior wedging of the vertebral bodies, usually in the lower thoracic and upper lumbar regions. Later, the end plates become irregular and sclerotic. Spinal misalignment is predominantly kyphotic but is sometimes partly scoliotic. In atypical cases, generalized skeletal dysplasia must be excluded by x-ray skeletal survey, and spinal TB must be excluded by CT or MRI.

**Treatment**

The course is mild but long, often lasting several years (although duration varies greatly). Trivial spinal misalignment often persists after the disorder has become quiescent.

Mild, nonprogressive disease can be treated by reducing weight-bearing stress and by avoiding strenuous activity. Occasionally, when kyphosis is more severe, a spinal brace or rest with recumbency on a rigid bed is indicated. Rarely, progressive cases require surgical stabilization and correction of misalignment.

**Osteopetroses**

*(Marble Bones)*

**Osteopetroses are characterized by increased bone density and skeletal modeling abnormalities.*

Osteopetroses can be categorized based on whether sclerosis or defective skeletal modeling
predominates. Some types are comparatively benign; others are progressive and fatal. Bony overgrowth sometimes severely distorts the face. Malocclusion of the teeth may require specialized orthodontic measures. Surgical decompression may be required to relieve elevated intracranial pressure or to release a trapped facial or auditory nerve.

**Craniotubular Dysplasias**

Craniotubular dysplasias involve minor osteosclerosis with normal skeletal modeling.

**Metaphyseal dysplasia (Pyle’s disease):** This rare, autosomal recessive disorder is often confused semantically with craniometaphyseal dysplasia. Affected people are clinically normal, apart from genu valgum, although scoliosis and bone fragility occasionally occur. The diagnosis is usually made when x-rays are done for an unrelated reason. X-ray changes are striking. Long bones are undermodeled, and bony cortices are generally thin. Tubular leg bones have gross Erlenmeyer flask flaring, particularly in the distal femur. Pelvic bones and thoracic cage are expanded. However, the skull is essentially spared.

**Craniometaphyseal dysplasia:** In this autosomal dominant disorder, paranasal bossing develops during infancy, and progressive expansion and thickening of the skull and mandible distort the jaw and face. The encroaching bone entraps cranial nerves, causing dysfunction. Malocclusion of the teeth may be troublesome; partial sinus obliteration predisposes to recurrent nasorespiratory infection. Height and general health are normal, but progressive elevation of intracranial pressure is a rare, serious complication.

X-ray changes are age-related and usually evident by age 5 yr. Sclerosis is the main feature in the skull. Long bones have widened metaphyses, appearing club-shaped, particularly at the distal femur. However, these changes are much less severe than those in Pyle's disease. The spine and pelvis are unaffected.

**Frontometaphyseal dysplasia:** This disorder has distinct autosomal dominant and X-linked forms; it becomes evident during early childhood. The supraorbital ridge is prominent, resembling a knight's visor. The mandible is hypoplastic with anterior constriction; dental anomalies are common. Deafness develops during adulthood because sclerosis narrows the internal acoustic foramina and middle ear. Long leg bones are moderately bowed. Progressive contractures in the digits may simulate RA. Height and general health are normal.

On x-ray examination, bony overgrowth of the frontal region is obvious; patchy sclerosis is seen in the cranial vault. Vertebral bodies are dysplastic but not sclerotic. Iliac crests are abruptly flared, with expansion of the femoral heads and coxa valga (hip deformity). Finger bones are undermodeled, with erosion and loss of joint space. Corrective surgery is indicated for severely disfiguring deformities or those causing orthopedic problems.

**Craniotubular Hyperostoses**

Craniotubular hyperostoses are bony overgrowths that alter contour and increase skeletal density.

**Endosteal hyperostosis (van Buchem’s syndrome):** This disorder is usually autosomal recessive. Overgrowth and distortion of the mandible and brow become evident during mid-childhood. Subsequently, cranial nerves become entrapped, leading to facial palsy and deafness. Life span is not compromised, stature is normal, and bones are not fragile. X-rays show widening and sclerosis of the calvaria, cranial base, and mandible. Diaphyseal endosteum in the tubular bones is thickened. Surgical decompression of entrapped nerves may be helpful.

**Sclerosteosis:** This autosomal recessive disorder is most common among Afrikaners of South Africa. Overgrowth and sclerosis of the skeleton, particularly of the skull, develop during early childhood. Height and weight are often excessive. Initial symptoms and signs may include deafness and facial palsy due to cranial nerve entrapment. Distortion of facies, apparent by age 10 yr, eventually becomes severe. Cutaneous or bony syndactyly of the 2nd and 3rd fingers distinguishes sclerosteosis from other forms of craniotubular hyperostoses. Predominant x-ray features are gross widening and sclerosis of the calvaria.
and mandible. Vertebral bodies are spared, although their pedicles are dense. Pelvic bones are sclerotic but have normal contours. Long bones have sclerosed, hyperostotic cortices and undermodeled shafts. Surgery to relieve intracranial pressure may help.

**Diaphyseal dysplasia (Camurati-Engelmann disease):** This autosomal dominant disorder manifests during mid-childhood with muscular pain, weakness, and wasting, typically in the legs. These symptoms usually resolve by age 30. Cranial nerve compression and elevated intracranial pressure occur occasionally. Some patients are severely handicapped; others are virtually asymptomatic. The predominant x-ray feature is marked thickening of the periosteal and medullary surfaces of the diaphyseal cortices of the long bones, but findings vary. Medullary canals and external bone contours are irregular. The extremities and axial skeleton usually are spared. Rarely, the skull is involved, with calvarial widening and basal sclerosis. Corticosteroids may help relieve bone pain and improve muscle strength.

**Osteosclerosis**

**Osteosclerosis is abnormal hardening of bone that involves increased skeletal density with little disturbance of modeling.**

**Osteopetrosis with delayed manifestations (Albers-Schonberg disease):** This type of osteopetrosis is autosomal dominant, benign, and delayed (tarda), manifesting during childhood, adolescence, or young adulthood. The defective *CLCN7* gene encodes a chloride channel that is apparently important in osteoclast function. This type is relatively common and has a wide geographic and ethnic distribution. Affected people may be asymptomatic; general health is usually unimpaired. However, facial palsy, deafness, and anemia (due to bone marrow compromise or hypersplenism) may occur.

The skeleton usually is radiologically normal at birth. However, bone sclerosis becomes increasingly apparent as children age, and diagnosis is typically based on x-rays done for unrelated reasons. Bony involvement is widespread but patchy. The calvaria is dense, and sinuses may be obliterated. Sclerosis of the vertebral end plate causes the characteristic rugby-shirt appearance (horizontal banding). Bone marrow can be compromised by bony overgrowth, leading to pancytopenia. Extramedullary hematopoiesis may occur, resulting in hepatosplenomegaly. Some patients require transfusion or splenectomy to treat anemia.

**Osteopetrosis with precocious manifestations:** This type of osteopetrosis is autosomal recessive, malignant, and congenital, manifesting during infancy. It is uncommon, frequently lethal, and often due to a mutation in the osteoclast-associated gene *TCIRG1*. Bony overgrowth causes marrow dysfunction. Initial symptoms include failure to thrive, spontaneous bruising, abnormal bleeding, and anemia. Palsies of the 2nd, 3rd, and 7th cranial nerves and hepatosplenomegaly occur later. Death due to bone marrow failure (anemia, overwhelming infection, or hemorrhage) usually occurs in the first year of life.

General increased bone density is the predominant feature on x-rays. Penetrated x-rays of long bones show transverse bands in the metaphyseal regions and longitudinal striations in the shafts. As the disorder progresses, the ends of the long bones, particularly the proximal humerus and distal femur, become flask-shaped. Characteristic endobones (bone within a bone) form in the vertebrae, pelvis, and tubular bones. The skull becomes thickened, and the spine has a rugby-shirt appearance.

Bone marrow transplantation with HLA-identical sibling grafts has had excellent results. However, prognosis is poor with HLA-mismatched grafts. Prednisone, calcitriol, and interferon-γ are effective in some cases.

**Osteopetrosis with renal tubular acidosis:** This type of osteopetrosis is autosomal recessive. It causes weakness, stunted stature, and failure to thrive. Bones appear dense on x-rays, and cerebral calcifications are seen; renal tubular acidosis (RTA) is present, and RBC carbonic anhydrase activity is decreased. The genetic defect involves mutations of the gene encoding carbonic anhydrase II. Bone marrow transplantation cures the osteopetrosis but has no effect on the RTA. Maintenance therapy consists of bicarbonate and electrolyte supplementation to correct renal losses.
**Pyknody sostosis**: This autosomal recessive disorder is caused by loss of function mutations in the gene encoding cathepsin K, an osteoclast-derived protease important in degradation of extracellular matrix. Short stature becomes evident in early childhood; adult height is ≤ 150 cm (5 ft). Other manifestations include an enlarged skull, short and broad hands and feet, and dystrophic nails. Blue sclerae (due to a deficiency in connective tissue, allowing the underlying vessels to show through) are usually recognized during infancy. Affected people resemble each other closely; they have a small face, a receding chin, and carious, misplaced teeth. The cranium bulges, and the anterior fontanelle remains patent. Terminal phalanges are short, and fingernails are dysplastic. Pathologic fractures are a complication.

Bone sclerosis appears on x-rays during childhood, but neither bone striations nor endobones are seen. Facial bones and paranasal sinuses are hypoplastic, and the mandibular angle is obtuse. Clavicles may be gracile, and their lateral portions may be underdeveloped; distal phalanges are rudimentary. Plastic surgery has been used to correct severe deformities of the face and jaw.

**Slipped Capital Femoral Epiphysis**

**Slipped capital femoral epiphysis (SCFE)** is movement of the femoral neck upward and forward on the femoral epiphysis.

SCFE usually occurs in early adolescence and preferentially affects boys. Obesity is a significant risk factor. Genetic factors also contribute. SCFE is bilateral in one fifth of patients, and unilateral SCFE becomes bilateral in up to two thirds of patients. The exact cause is unknown but probably relates to weakening of the physis (growth plate), which can result from trauma, hormonal changes, inflammation, or increased shearing forces due to obesity.

**Symptoms and Signs**

Onset is usually insidious, and symptoms are associated with stage of slippage. The first symptom may be hip stiffness that abates with rest; it is followed by a limp, then hip pain that radiates down the anteromedial thigh to the knee. Up to 15% of patients present with knee or thigh pain, and the true problem (hip) may be missed until slippage worsens. Early hip examination may detect neither pain nor limitation of movement. In more advanced stages, findings may include pain during movement of the affected hip, with limited flexion, abduction, and medial rotation; knee pain without specific knee abnormalities; and a limp. The affected leg is externally rotated. If blood supply to the area is compromised, avascular necrosis and collapse of the epiphysis may occur.

**Diagnosis**

Because treatment of advanced slippage is difficult, early diagnosis is vital. Anteroposterior and frog-leg lateral x-rays of both hips are taken. X-rays show widening of the epiphyseal line or apparent posterior and inferior displacement of the femoral head. Ultrasonography and MRI are also useful, especially if x-rays are normal.

**Treatment**

SCFE usually progresses; it requires surgery as soon as it is diagnosed. Patients should not bear weight on the affected leg until SCFE has been ruled out or treated. Surgical treatment consists of screw fixation through the physis.
Chapter 289. Eye Defects and Conditions in Children

Introduction

Defects and conditions can affect any part of the eye. They often affect vision, and some can result in blindness if not adequately treated. Other defects and conditions that affect vision during childhood are discussed elsewhere in THE MANUAL (see Chs. 63, 64, and 181).

Amblyopia

Amblyopia is functional reduction in visual acuity of an eye caused by disuse during visual development. Blindness can occur in the affected eye if amblyopia is not detected and treated before age 8 yr. Diagnosis is based on detecting a difference in visual acuity between the two eyes. Treatment depends on the cause.

Amblyopia affects about 2 to 3% of children and almost always develops before age 2.

The brain must simultaneously receive a clear, focused, properly aligned, overlapping image from each eye for the visual system to develop properly. This development takes place mainly in the first 3 yr of life but is not complete until about 8 yr of age. Amblyopia results when there is persistent interference with the image from one eye but not the other. The visual cortex suppresses the image from the affected eye. If suppression persists long enough, vision loss can be permanent.

Etiology

There are 3 causes. Strabismus (see p. 2920) can cause amblyopia because misalignment of the eyes results in different retinal images being sent to the visual cortex. Because the visual pathways are developed in adults, presentation of 2 different images results in diplopia rather than suppression of one image.

Similarly, anisometropia (inequality of refraction in the 2 eyes, most often resulting from astigmatism, myopia, or hyperopia) results in different focus of the retinal images, with the image from the eye with the greater refractive error being less well focused.

Obstruction of the visual axis at some point between the surface of the eye and the retina (eg, by a cataract) interferes with or completely prevents formation of a retinal image in the affected eye.

Symptoms and Signs

Children rarely complain of unilateral vision loss, although they may squint or cover one eye. Very young children either do not notice or are unable to express awareness that their vision differs in one eye compared with the other. Some older children may report impaired vision in the affected eye or exhibit poor depth perception. When strabismus is the cause, deviation of gaze may be noticeable to others. A cataract causing occlusion of the visual axis may go unnoticed.

Diagnosis

• Early screening

• Photoscreening

• Additional testing (eg, cover test, cover-uncover test, refraction, ophthalmoscopy, slit lamp)

Screening for amblyopia (and strabismus) is recommended for all children before starting school, optimally around age 3 yr. Photoscreening is one approach for screening very young children and children with learning and developmental disorders who are unable to undergo subjective testing. Photoscreening involves use of a camera to record images of pupillary reflexes during fixation on a visual target and red reflexes in response to light; the images are then compared for symmetry. Screening in
Identifying the underlying cause requires additional testing. Strabismus can be confirmed with the cover test or the cover-uncover test (see p. 2922). Ophthalmologists can confirm anisometropia by doing a refraction on each eye. Obstruction of the visual axis can be confirmed by ophthalmoscopy or slit lamp examination.

**Prognosis and Treatment**

- **Eyeglasses or contact lenses**
- **Cataract removal**
- **Patching**

Amblyopia may become irreversible if not diagnosed and treated before age 8, at which time the visual system has matured. Most children identified and treated before age 5 have some vision improvement. Earlier treatment increases the likelihood of complete vision recovery. Recurrence (recidivism) is possible in certain cases until the visual system matures. Some patients have a small decrease in visual acuity of a line or two even after visual maturity has occurred.

Treatment should be directed by an ophthalmologist. Any underlying causes must be treated (eg, eyeglasses or contact lenses to correct refractive error, removal of a cataract). Use of the amblyopic eye is then encouraged by patching the better eye or by administering atropine drops into the better eye to provide a visual advantage to the amblyopic eye. Adherence to treatment is better with drop therapy. Maintenance treatment for prevention of recurrences may be recommended after improvement has stabilized, until a child is about 8 to 10.

**Congenital Cataract**

*(Infantile Cataract)*

**Congenital cataract is a lens opacity that is present at birth or shortly after birth.**

Congenital cataracts may be sporadic, or they may be caused by chromosomal anomalies, metabolic disease (eg, galactosemia), or intrauterine infection (eg, rubella) or other maternal disease during pregnancy. Cataracts may be located in the center of the lens (nuclear), or they may involve the lens material underneath the anterior or posterior lens capsule (subcapsular or cortical). They may be unilateral or bilateral. They may not be noticed unless the red reflex is checked or unless ophthalmoscopy is done at birth. As with other cataracts, the lens opacity obscures vision. Cataracts may obscure the view of the optic disk and vessels and should always be evaluated by an ophthalmologist.

Removal of a cataract within 17 wk after birth permits the development of vision and cortical visual pathways. Cataracts are removed by aspirating them through a small incision. In many children, an intraocular lens may be implanted. Postoperative visual correction with eyeglasses, contact lenses, or both is usually required to achieve the best outcome.

After a unilateral cataract is removed, the quality of the image in the treated eye is inferior to that of the other eye (assuming the other eye is normal). Because the better eye is preferred, the brain suppresses the poorer-quality image, and amblyopia (see p. 2919) develops. Thus, effective amblyopia therapy is necessary for the treated eye to develop normal sight. Some children are unable to attain good visual acuity because of accompanying structural defects. In contrast, children with bilateral cataract removal in which image quality is similar in both eyes more frequently develop equal vision in both eyes.

Some cataracts are partial (posterior lenticonus) and opacify during the 1st decade of life. Eyes with partial cataracts have a better visual outcome.
Primary Infantile Glaucoma

(Infantile Glaucoma; Congenital Glaucoma; Buphthalmos)

Primary infantile glaucoma is a rare developmental defect in the iridocorneal filtration angle of the anterior chamber that prevents aqueous fluid from properly draining from the eye. This obstruction can cause increases in the intraocular pressure, which if untreated can damage the optic nerve.

The disorder occurs in infants and young children and may be unilateral (40%) or bilateral (60%). Intraocular pressure increases above the normal range (10 to 22 mm Hg). Glaucoma can also occur in infants after trauma or intraocular surgery (eg, cataract extraction). Glaucoma associated with aniridia or Lowe syndrome or Sturge-Weber syndrome is called secondary glaucoma.

The eye becomes enlarged because the collagen of the sclera and cornea can stretch from the increased intraocular pressure. The large-diameter (> 12 mm) cornea is thinned and sometimes cloudy. The infant may have tearing and photophobia. If untreated, corneal clouding progresses, the optic nerve is damaged (as evidenced clinically by optic nerve cupping), and blindness may occur. Early surgical intervention (eg, goniotomy, trabeculotomy, trabeculectomy) is the mainstay of treatment.

Strabismus

Strabismus is misalignment of the eyes, which causes deviation from the parallelism of normal gaze. Diagnosis is clinical, including observation of the corneal light reflex and use of a cover test. Treatment may include correction of visual impairment with patching and corrective lenses, alignment by corrective lenses, and surgical repair.

Strabismus occurs in about 3% of children. Although most strabismus is caused by refractive errors or muscle imbalance, rare causes include retinoblastoma or other serious ocular defects and neurologic disease. Left untreated, about 50% of children with strabismus have some visual loss due to amblyopia (see p. 2919).

Several varieties of strabismus have been described, based on direction of deviation, specific conditions under which deviation occurs, and whether deviation is constant or intermittent. Description of these varieties requires the definition of several terms.

The prefix "eso" refers to nasal deviations, and the prefix "exo" refers to temporal deviations. The prefix "hyper" refers to upward deviations, and the prefix "hypo" refers to downward deviations (see Fig. 289-1). Manifest deviations, detectable with both eyes open so that vision is binocular, are designated as tropia. Tropia can be constant or intermittent and may involve one eye or both eyes. Latent deviation, detectable only when one eye is covered so that vision is monocular, is designated as phoria. The deviation in phoria is latent because the brain, using the extraocular muscles, corrects the minor misalignment. Deviations that are the same (amplitude or degree of misalignment remains the same) in all gaze directions are designated as comitant, whereas deviations that vary (amplitude or degree of misalignment changes) depending on gaze direction are referred to as incomitant.

Etiology

Strabismus may be congenital (the term infantile is preferred because detection of strabismus at birth is uncommon, and infantile permits inclusion of varieties that develop within the first 6 mo of life) or acquired (includes those that develop after 6 mo).

Risk factors for infantile strabismus include family history (1st- or 2nd-degree relative), genetic disorders (Down syndrome and Crouzon syndrome), prenatal drug exposure (including alcohol), prematurity or low birth weight, congenital eye defects, and cerebral palsy.

Acquired strabismus can develop acutely or gradually. Causes of acquired strabismus include tumors (eg, retinoblastoma), head trauma, neurologic conditions (eg, cerebral palsy; spina bifida; palsy of the 3rd,
Esotropia is commonly infantile. Infantile esotropia is considered idiopathic, although an anomaly of fusion is the suspected cause. Accommodative esotropia, a common variety of acquired esotropia, develops between 2 yr and 4 yr of age and is associated with hyperopia. Sensory esotropia occurs when severe visual loss (due to conditions such as cataracts, optic nerve anomalies, or tumors) interferes with the brain’s effort to maintain ocular alignment.

Esotropia can be paralytic, so designated because the cause is a 6th (abducens) cranial nerve palsy, but it is an uncommon cause. Esotropia can also be a component of a syndrome. Duane’s syndrome (congenital absence of the abducens nucleus with anomalous innervation of the lateral rectus extraocular muscle by the 3rd [oculomotor] cranial nerve) and Mobius’ syndrome (anomalies of multiple cranial nerves) are specific examples.

[Fig. 289-1. Ocular deviations in strabismus.]

Exotropia may be intermittent and idiopathic. Less often, exotropia is constant and paralytic, as with 3rd (oculomotor) cranial nerve palsy.

Hypertropia can be paralytic, caused by 4th (trochlear) cranial nerve palsy that occurs congenitally or after head trauma or, less commonly, as a result of 3rd cranial nerve palsy.

Hypotropia can be restrictive, caused by mechanical restriction of full movement of the globe rather than neurologic interference with eye movement. For example, restrictive hypotropia can result from a blowout fracture of the orbit floor or walls. Less commonly, restrictive hypotropia can be caused by Graves’ ophthalmopathy (thyroid eye disease). Third cranial nerve palsy and Brown syndrome (congenital or acquired tightness and restriction of the superior oblique muscle tendon) are other uncommon causes.

**Symptoms and Signs**

Unless severe, phorias rarely cause symptoms.

Tropias sometimes result in symptoms. For example, torticollis may develop to compensate for the brain’s difficulty in fusing images from misaligned eyes and to reduce diplopia. Some children with tropias have normal and equal visual acuity. However, amblyopia frequently develops with tropias; it is due to cortical suppression of the image in the deviating eye to avoid confusion and diplopia.

**Diagnosis**

- Physical and neurologic examinations at well-child checkups
- Tests (eg, corneal light reflex, alternate cover, cover-uncover)
- Prisms

Strabismus can be detected during well-child checkups. History should include questions about family history of amblyopia or strabismus and, if family or caregivers have noticed deviation of gaze, questions about when the deviation began, when or how often it is present, and whether there is a preference for using one eye for fixation. Physical examination should include an assessment of visual acuity, pupil reactivity, and the extent of extraocular movements. Neurologic examination, particularly of the cranial nerves, is important.

The corneal light reflex test is a good screening test, but it is not very sensitive for detecting small deviations. The child looks at a light and the light reflection (reflex) from the pupil is observed; normally, the reflex appears symmetric (ie, in the same location on each pupil). The light reflex for an exotropic eye is nasal to the pupillary center, whereas the reflex for an esotropic eye is temporal to the pupillary center. Vision screening machines operated by trained personnel are being introduced to identify children at risk.
When performing the alternate cover test, the child is asked to fixate on an object. One eye is then covered while the other is observed for movement. No movement should be detected if the eyes are properly aligned, but strabismus is present if the unoccluded eye shifts to establish fixation once the other eye, which had fixed on the object, is occluded. The test is then repeated on the other eye.

In a variation of the cover test, called the cover-uncover test, the child is asked to fix on an object while the examiner alternately covers and uncovers one eye and then the other, back and forth. An eye with a latent strabismus shifts position when it is uncovered. In exotropia, the eye that was covered turns in to fixate; in esotropia, it turns out to fixate. Tropia can be quantified by using prisms positioned such that the deviating eye need not move to fixate. The power of the prism used to prevent deviation quantifies the tropia and provides a measurement of the magnitude of misalignment of the visual axes. The unit of measurement used by ophthalmologists is the prism diopter. One prism diopter is a deviation of the visual axes of 1 cm at 1 m.

Strabismus should be distinguished from pseudostrabismus, which is the appearance of esotropia in a child with good visual acuity in both eyes but a wide nasal bridge or broad epicanthal folds that obscure much of the white sclera nasally when looking laterally. The light reflex and cover tests are normal in a child with pseudostrabismus.

**Prognosis and Treatment**

- Patching
- Contact lenses or eyeglasses
- Topical agents
- Eye exercises
- Surgical repair to align eyes

Strabismus should not be ignored on the assumption that it will be outgrown. Permanent vision loss can occur if strabismus and its attendant amblyopia are not treated before age 4 to 6 yr. As a result, all children should have formal vision screening in the preschool years.

Treatment aims to equalize vision and then align the eyes. Children with amblyopia require patching or penalization of the normal eye; improved vision offers a better prognosis for development of binocular vision and for stability if surgery is done. Patching is not, however, a treatment for strabismus. Eyeglasses or contact lenses are sometimes used if the amount of refractive error is significant enough to interfere with fusion, especially in children with accommodative esotropia. Topical miotic agents, such as echothiophate iodide 0.125%, may facilitate accommodation in children with accommodative esotropia. Orthoptic eye exercises can help correct intermittent exotropia with convergence insufficiency.

Surgical repair is generally done when non-surgical methods are unsuccessful in aligning the eyes satisfactorily. Surgical repair consists of loosening (recession) and tightening (resection) procedures, most often involving the rectus muscles. Surgical repair is typically done in an outpatient setting. Rates for successful realignment can exceed 80%. The most common complications are overcorrection or undercorrection and recurrence of the strabismus later in life. Rare complications include infection, excessive bleeding, and vision loss.
Chapter 290. Incontinence in Children

Urinary Incontinence

(Enuresis)

Urinary incontinence is defined as involuntary voiding of urine ≥ 2 times/mo during the day or night. Daytime incontinence (diurnal enuresis) is usually not diagnosed until age 5 or 6. Nighttime incontinence (nocturnal enuresis, or bed-wetting) is usually not diagnosed until age 7. Before this time, nocturnal enuresis is typically referred to as nighttime wetting. These age limits are based on children who are developing typically and so may not be applicable to children with developmental delay. Both nocturnal and diurnal enuresis are symptoms—not diagnoses—and necessitate consideration of an underlying cause.

The age at which children attain urinary continence varies, but > 90% are continent during the day by age 5. Nighttime continence takes longer to achieve. Nocturnal enuresis affects about 30% of children at age 4, 10% at age 7, 3% at age 12, and 1% at age 18. About 0.5% of adults continue to have nocturnal wetting episodes. Nocturnal enuresis is more common among boys and when there is a family history.

In primary enuresis, children have never achieved urinary continence for ≥ 6 mo. In secondary enuresis, children have developed incontinence after a period of at least 6 mo of urinary control. An organic cause is more likely in secondary enuresis. Even when there is no organic cause, appropriate treatment and parental education are essential because of the physical and psychologic impact of urine accidents.

Pathophysiology

Bladder function has a storage phase and a voiding phase. Abnormalities in either phase can cause primary or secondary enuresis.

In the storage phase, the bladder acts as a reservoir for urine. Storage capacity is affected by bladder size and compliance. Storage capacity increases as children grow. Compliance can be decreased by repeated infections or by outlet obstruction, with resulting bladder muscle hypertrophy.

In the voiding phase, bladder contraction synchronizes with the opening of the bladder neck and the external urinary sphincter. If there is dysfunction in the coordination or sequence of voiding, enuresis can occur. There are multiple reasons for dysfunction. One example is bladder irritation, which can lead to irregular contractions of the bladder and asynchrony of the voiding sequence, resulting in enuresis. Bladder irritation can result from a UTI or from anything that presses on the bladder (eg, a dilated rectum caused by constipation).

Etiology

Urinary incontinence in children has different causes and treatments than urinary incontinence in adults. Although some abnormalities cause both nocturnal and diurnal enuresis, etiology can vary depending on whether enuresis is nocturnal (see Table 290-1) or diurnal (see Table 290-2), as well as primary or secondary. Most primary enuresis is nocturnal and not due to an organic disorder. Nocturnal enuresis can be divided into monosymptomatic (occurring only during sleep) and complex (other abnormalities are present, such as urgency or diurnal enuresis).

Nocturnal enuresis: Organic disorders account for about 30% of cases and are more common in complex compared to monosymptomatic enuresis. The remaining majority are of unclear etiology but are thought to be due to a combination of factors, including

• Maturational delay

• Functionally small bladder capacity (the bladder is not actually small but contracts before it is completely full)
• Increased nighttime urine volume

• Difficulties in arousal from sleep

• Family history (if one parent had nocturnal enuresis, there is a 30% chance offspring will have it, increasing to 70% if both parents were affected)

The factors contributing to organic causes of nocturnal enuresis include

• Conditions that increase urine volume (eg, diabetes mellitus, diabetes insipidus, renal failure, excessive water intake, sickle cell disease and sometimes sickle trait [hyposthenuria])

• Conditions that increase bladder irritability (eg, UTI, pressure on the bladder by the rectum and sigmoid colon [caused by constipation])

• Structural abnormalities (eg, ectopic ureter, which can cause both nocturnal and diurnal enuresis)

[Table 290-1. Some Factors Contributing to Nocturnal Enuresis]

• Abnormal sphincter weakness (eg, spinal cord abnormalities, which can cause both nocturnal and diurnal enuresis)

Diurnal enuresis: Common causes include

• Bladder irritability

• Relative weakness of the detrusor muscle (making it difficult to inhibit incontinence)

• Constipation, urethrovaginal reflux, or vaginal voiding: girls who use an incorrect position during voiding or have redundant skin folds may have reflux of urine into the vagina, which subsequently leaks out on standing

• Structural abnormalities (eg, ectopic ureter)

• Abnormal sphincter weakness (eg, spinal cord abnormality, tethered cord)

Evaluation

Evaluation should always include assessment for constipation (which can be a contributing factor to both nocturnal and diurnal enuresis).

History: History of present illness inquires about onset of symptoms (ie, primary vs secondary), timing of symptoms (eg, at night, during the day, only after voiding), and whether symptoms are continuous (ie, constant dribbling) or intermittent. Recording a voiding schedule, including timing, frequency, and volume of voids, can be helpful. Important associated symptoms include polydipsia, dysuria, urgency, frequency, dribbling, and straining. Position during voiding and strength of urine stream should be noted. To prevent leakage,

[Table 290-2. Some Organic Causes of Diurnal Enuresis]

children with enuresis may cross their legs or use other postures, which increase their risk of UTIs.

Review of systems should seek symptoms suggesting a cause, including frequency and consistency of stools (constipation); fever, abdominal pain, dysuria, and hematuria (UTI); perianal itching and vaginitis (pinworm infection); polyuria and polydipsia (diabetes insipidus or diabetes mellitus); and snoring or breathing pauses during sleep (sleep apnea). Children should be screened for the possibility of sexual abuse, which, although an uncommon cause, is too important to miss.
Past medical history should identify known possible causes, including perinatal insults or birth defects (eg, spina bifida), neurologic disorders, renal disorders, and history of UTIs. Any current or previous treatments for enuresis and how they were actually instituted should be noted, as well as a list of current drugs.

Developmental history should note developmental delay or other developmental disorders related to voiding dysfunction (eg, attention-deficit/hyperactivity disorder, which increases the likelihood of enuresis).

Family history should note the presence of nocturnal enuresis and any urologic disorders.

Social history should note any stressors occurring near the onset of symptoms, including difficulties at school, with friends, or at home; although enuresis is not a psychologic disorder, a brief period of wetting may occur during stress.

Clinicians also should ask about the impact of enuresis on the child because it also affects treatment decisions.

Physical examination: Examination begins with review of vital signs for fever (UTI), signs of weight loss (diabetes), and hypertension (renal disorder). Examination of the head and neck should note enlarged tonsils, mouth breathing, or poor growth (sleep apnea). Abdominal examination should note any masses consistent with stool or a full bladder.

In girls, genital examination should note any labial adhesions, scarring, or lesions suspicious of sexual abuse. An ectopic ureteral orifice is often difficult to see but should be sought. In boys, examination should check for meatal irritation or any lesions on the glans or around the rectum. In either sex, perianal excoriations can suggest pinworms.

The spine should be examined for any midline defects (eg, deep sacral dimple, sacral hair patch). A complete neurologic evaluation is essential and should specifically target lower-extremity strength, sensation and deep tendon reflexes, sacral reflexes (eg, anal wink), and, in boys, cremasteric reflex to identify possible spinal dysraphism. A rectal examination may be useful to detect constipation or decreased rectal tone.

Red flags: Findings of particular concern are

- Signs or concerns of sexual abuse
- Excessive thirst, polyuria, and weight loss
- Prolonged primary diurnal enuresis (beyond age 6 yr)
- Any neurologic signs, especially in the lower extremities
- Physical signs of spinal disruption

Interpretation of findings: Usually, primary nocturnal enuresis occurs in children with an otherwise unremarkable history and examination and probably represents maturational delay. A small percentage of children have a treatable medical disorder; sometimes findings suggest possible causes (see Table 290-1).

In diurnal enuresis, dysfunctional voiding is suggested by intermittent enuresis preceded by a sense of urgency, a history of being distracted by play, or a combination. Enuresis after urination (due to lack of total bladder emptying) can also be part of the history.

Enuresis caused by a UTI is likely a discrete episode rather than a chronic, intermittent problem and may be accompanied by typical symptoms (eg, urgency, frequency, pain on urination); however, other causes
of enuresis can result in secondary UTI.

Constipation should be considered in the absence of other findings in children who have hard stools and difficulty with elimination (and sometimes palpable stool on examination).

Sleep apnea should be considered with a history of excessive daytime sleepiness and disrupted sleep. Rectal itching (especially at night), vaginitis, urethritis, or a combination can be an indication of pinworms. Excessive thirst, diurnal and nocturnal enuresis, and weight loss suggest a possible organic cause (eg, diabetes mellitus). Stress or sexual abuse can be difficult to ascertain but should be considered.

**Testing:** Diagnosis is often apparent after history and physical examination. Urinalysis is appropriate for both sexes, often with addition of urine culture for girls. Further testing is useful mainly when history, physical examination, or both suggest an organic cause (see Tables 290-1 and 290-2).

**Treatment**

The most important part of treatment is family education about the cause and clinical course of enuresis. Education helps decrease the negative psychologic impact of urine accidents and results in increased adherence with treatment.

Treatment should be targeted toward any cause that is identified; however, frequently no cause is found. In such cases, the following treatments may be useful.

**Nocturnal enuresis:** The most effective long-term strategy is a bed-wetting alarm. Although labor intensive, the success rate can be as high as 70% when children are motivated to end the enuresis, and the family is able to adhere. It can take up to 4 mo of nightly use for complete resolution of symptoms. It is essential to avoid punitive approaches because these undermine treatment and lead only to poor self-esteem.

Drugs such as desmopressin (DDAVP) and imipramine (see Table 290-3) can decrease nighttime wetting episodes; however, results are not sustained in most patients when the treatment is stopped. DDAVP is preferable to imipramine because of the rare potential of sudden death with imipramine use.

**Diurnal enuresis:** It is important to treat any underlying constipation. Information from the voiding diary can help identify opportunities for intervention. General measures may include:

- Urgency containment exercises: Children are directed to go to the bathroom as soon as they feel the urge to urinate. They then hold the urine as long as they can and, when they can hold it no longer, start to urinate and then stop and start the urine stream. This exercise strengthens the sphincter and gives children confidence that they can make it to the bathroom before they have an accident.

- Gradual lengthening of voiding intervals (if detrusor instability or dysfunctional voiding is suspected)

- Changes in behaviors (eg, delayed urination) through positive reinforcement and scheduled urination: Children are reminded to urinate by a clock that vibrates or sounds an alarm (preferable to having a parent in the reminder role).

- Use of correct voiding methods to discourage retention of urine in the vagina (eg, sitting facing backward on the toilet or with the knees wide apart)

For labial adhesions, a conjugated estrogen cream may also be used.

Drug treatment (see Table 290-3) is sometimes helpful but is not typically first-line therapy. Anticholinergic drugs may benefit patients with diurnal enuresis due to voiding dysfunction when behavioral therapy or physiotherapy is unsuccessful. Drugs for nocturnal enuresis may be useful in decreasing nighttime wetting episodes and are sometimes useful to encourage dryness during overnight events such as sleepovers.
Key Points

• Primary urinary incontinence most frequently manifests as nocturnal enuresis.

• Constipation should be considered as a contributing source.

• Most nocturnal enuresis abates with maturation (15%/yr resolve with no intervention), but at least 0.5% of adults have nighttime wetting episodes.

• Organic causes of enuresis are infrequent but should be considered.

[Table 290-3, Drugs Used for Enuresis in Children*]

• Alarms are the most effective treatment for nocturnal enuresis.

• Other treatments include behavioral interventions and sometimes drugs.

• Parental education is essential to the child's outcome and well-being.

Stool Incontinence (Encopresis)

Stool incontinence is the voluntary or involuntary passage of stool in inappropriate places in children > 4 yr (or developmental equivalent) who do not have an organic defect or illness with the exception of constipation.

Encopresis is a common childhood problem; it occurs in about 3 to 4% of 4-yr-old children and decreases in frequency with age.

Etiology

Encopresis is most commonly caused by constipation in children with behavioral and physical predisposing factors. It rarely occurs without retention or constipation, but when it does, other organic processes (eg, Hirschsprung's disease, celiac disease) or psychologic problems should be considered.

Pathophysiology

Stool retention and constipation result in dilation of the rectum and sigmoid colon, which leads to changes in the reactivity of muscles and nerves of the bowel wall. These changes decrease the efficacy of bowel excretory function and lead to further retention. As stool remains in the bowel, water is absorbed, which hardens the stool, making passage more difficult and painful. Softer, looser stool may then leak around the hardened stool bolus, resulting in overflow. Both leakage and ineffective bowel control result in stool accidents.

Diagnosis

Any organic process that results in constipation (see p. 2726) can result in encopresis and so should be considered. For most routine cases of encopresis, a thorough history and physical examination can help identify any physical cause. However, if further concerns arise, additional diagnostic tests (eg, abdominal x-rays, rarely rectal wall biopsy, and even more rarely bowel motility studies—see p. 2980) can be considered.

Treatment

• Education and demystification (for parents and child)
• Relief of stool impaction

• Maintenance (eg, behavioral and dietary interventions, laxative therapy)

• Slow withdrawal of laxatives with continued behavioral and dietary intervention (see Table 268-14)

Any underlying disorders are treated. If there is no specific underlying pathology, symptoms are addressed. Initial treatment involves educating the parents and child about the physiology of encopresis, removing blame from the child, and diffusing the emotional reactions of those involved. Next the goal is to relieve any stool impaction.

Stool impaction can be relieved by a variety of regimens and drugs (see p. 2731); choice depends on the age of the child and other factors. A combination of polyethylene glycol (PEG) with electrolytes plus a stimulant laxative (eg, bisacodyl or senna), or a sequence of Na phosphate enemas plus a 2-wk regimen of oral drugs (eg, bisacodyl tablets) and suppositories are often used.

After evacuation, a follow-up visit should be held to assess whether the evacuation has been successful, make sure soiling has resolved, and establish a maintenance plan. This plan includes encouragement of maintenance of regular bowel movements (usually via ongoing laxative management) and behavioral interventions to encourage stool evacuation. There are many options for maintenance laxative therapy (see Table 268-14), but PEG without electrolytes is used most often, typically 1 to 2 doses of 17 g/day titrated to effect. At times a stimulant laxative may also be continued on the weekends to encourage extra evacuation of stool.

Behavioral strategies include structured toilet sitting times (eg, having children sit on the toilet for 5 to 10 min after each meal to take advantage of the gastrocolic reflex). If children have accidents during certain times of the day, they also should sit immediately prior to those times. Small rewards are often useful incentives. For example, giving children stickers to place on a chart each time they sit (even if there is no stool production) can increase adherence to a plan. Often a stepwise program is used in which children receive small tokens (eg, stickers) for sitting and larger rewards for consistent adherence. Rewards may need to be changed over time to maintain children's interest in the plan. In the maintenance phase, regular toilet sitting sessions still are needed to encourage evacuation of stool before the sensation is felt. This strategy decreases the likelihood of stool retention and allows the rectum to return to its normal size. During the maintenance phase, parent and child education about toilet sitting is instrumental to the success of the regimen.

Regular follow-up visits are necessary for ongoing guidance and support. Bowel retraining is a long process that may take months to years and includes slow withdrawal of laxatives once symptoms resolve and continued encouragement of toilet sitting.

Encopresis can recur in times of stress or transition, so family members must be prepared for this possibility. Success rates are affected by physical and psychosocial factors, but 1-yr cure rates are about 30 to 50% and 5-yr cure rates are about 48 to 75%. The mainstay of treatment is family education, bowel cleanout and maintenance, and ongoing support.
Chapter 291. Miscellaneous Disorders in Infants and Children

Apparent Life-Threatening Event

An apparent life-threatening event (ALTE) is the sudden appearance of certain alarming symptoms (eg, apnea, change in color or muscle tone, coughing, gagging), typically in children < 1 yr. Causes may be digestive, neurologic, respiratory, cardiac, or metabolic. Treatment is aimed at specific causes when identified.

An ALTE is not a diagnosis but a group of symptoms that occur acutely in young children.

Etiology

The most common causes include

• Gastroesophageal reflux disease

• Neurologic disorders (eg, seizures, meningitis, brain tumors, abnormal brainstem neuro-regulation of cardiorespiratory control)

• Infection

Less common causes include

• Cardiac disorders

• Metabolic disorders

• Upper airway obstruction

Causes may be genetic or acquired. About 50% of cases are considered idiopathic. If an infant is under the care of one person and has repeated episodes with no clear etiology, child abuse should be considered.

Table 291-1. Diagnostic Tests for Causes of Apparent Life-Threatening Event (ALTE)

Symptoms and Signs

An ALTE usually is characterized by an unexpected, acute change in an infant's breathing that alarms the parent or caretaker. Features of an event include some or all of the following:

• Apneic episode

• Color change

• Change in muscle tone

• Choking or gagging

Diagnosis

Evaluation initially involves a thorough history, including

• Observations by the caregiver who witnessed the event (including description of changes in breathing, color, muscle tone, and eyes; noises made; and length of episode)
Interventions taken (eg, gentle stimulation, mouth-to-mouth breathing, CPR)

Prenatal (maternal) and current family use of drugs, tobacco, and alcohol

Information about the infant’s birth (eg, gestational age, perinatal complications)

Feeding habits (whether gagging, coughing, vomiting, or poor weight gain has occurred)

Developmental history (eg, milestones)

Prior history of ALTE or recent trauma

Family history of ALTE, early deaths, or possible causative disorders

Physical examination is done to check for obvious malformations, neurologic abnormalities (eg, posturing, inappropriate head lag), and signs of infection or trauma (particularly including retinal hemorrhage on funduscopic examination).

Laboratory and imaging tests (see Table 291-1) are done to check for possible causes. Some are routinely done, and others are done based only on history and physical examination findings.

Prognosis

Prognosis depends on the cause of ALTE. That is, risk of death is higher if the cause is a serious neurologic disorder. The relationship of ALTE to SIDS is unclear. About 4 to 10% of infants who die of SIDS have a history of ALTE, and the risk of SIDS is higher if an infant has had 2 or more ALTEs. Also, infants who have had an ALTE share many of the same characteristics with infants who die of SIDS. However, incidence of ALTE, unlike that of SIDS, has not decreased in response to the Back to Sleep campaign.

There seem to be no long-term effects on development.

Treatment

The cause, if identified, is treated. If infants have required resuscitation or if evaluation has detected any abnormalities, they are hospitalized for evaluation and monitoring that includes respiratory and cardiac monitoring and some of the tests listed in Table 291-1 as indicated.

Parents and caregivers should be trained in CPR for infants and in safe infant care. Home monitoring devices may be considered depending on risk of recurrent episodes. Monitors should be equipped with event recorders and used for a predetermined period of time. Parents should be taught how to use the monitor and be advised that home monitoring has not been shown to reduce the mortality rate. Also, exposure to tobacco smoke must be eliminated.

Failure to Thrive

Failure to thrive (FTT) is weight consistently below the 3rd to 5th percentile for age, progressive decrease in weight to below the 3rd to 5th percentile, or a decrease in the percentile rank of 2 major growth parameters in a short period. The cause may be an identified medical condition or may be related to environmental factors. Both types relate to inadequate nutrition. Treatment aims to restore proper nutrition.

Etiology

The physiologic basis for FTT of any etiology is inadequate nutrition and is divided into

- Organic FTT
Nonorganic FTT

**Organic FTT:** Growth failure is due to an acute or chronic disorder that interferes with nutrient intake, absorption, metabolism, or excretion or that increases energy requirements (see Table 291-2). Illness of any organ system can be a cause.

**Nonorganic FTT:** Up to 80% of children with growth failure do not have an apparent growth-inhibiting (organic) disorder; growth failure occurs because of environmental neglect (eg, lack of food), stimulus deprivation, or both.

Lack of food may be due to

- Impoverishment
- Poor understanding of feeding techniques
- Improperly prepared formula (eg, overdiluting formula to stretch it because of financial difficulties)
- Inadequate supply of breast milk (eg, because the mother is under stress, exhausted, or poorly nourished)

Nonorganic FTT is often a complex of disordered interaction between a child and caregiver. In some cases, the psychologic basis of nonorganic FTT seems similar to that of hospitalism, a syndrome observed in infants who have depression secondary to stimulus deprivation. The unstimulated child becomes depressed, apathetic, and ultimately anorexic. Stimulation may be lacking because the caregiver

- Is depressed or apathetic
- Has poor parenting skills
- Is anxious about or unfulfilled by the caregiving role
- Feels hostile toward the child
- Is responding to real or perceived external stresses (eg, demands of other children in large or chaotic families, marital dysfunction, a significant loss, financial difficulties)

Poor caregiving does not fully account for all cases of nonorganic FTT. The child's temperament, capacities, and responses help shape caregiver nurturance patterns. Common scenarios involve parent-child mismatches, in which the child's demands, although not pathologic, cannot be adequately met by the

[Table 291-2, Some Causes of Organic Failure to Thrive]

parents, who might, however, do well with a child who has different needs or even with the same child under different circumstances.

**Mixed FTT:** In mixed FTT, organic and nonorganic causes can overlap; children with organic disorders also have disturbed environments or dysfunctional parental interactions. Likewise, those with severe undernutrition caused by nonorganic FTT can develop organic medical problems.

**Diagnosis**

- Frequent weight monitoring
- Thorough medical, family, and social history
- Diet history
Laboratory testing

Children with organic FTT may present at any age depending on the underlying disorder. Most children with nonorganic FTT manifest growth failure before age 1 yr and many by age 6 mo. Age should be plotted against weight, height, and head size. Until premature infants reach 2 yr, age should be corrected for gestation.

Weight is the most sensitive indicator of nutritional status. Reduced linear growth usually indicates more severe, prolonged undernutrition. Because the brain is preferentially spared in protein-energy undernutrition (see p. 14), reduced growth in head circumference occurs late and indicates very severe or longstanding undernutrition.

Usually, when growth failure is noted, a history (including diet history—see Table 291-3) is obtained, diet counseling is provided, and the child's weight is monitored frequently. A child who does not gain weight satisfactorily in spite of outpatient assessment and intervention usually is admitted to the hospital so that all necessary observations can be made and diagnostic tests can be done quickly. Without historic or physical evidence of a specific underlying etiology for growth failure, no single clinical feature or test can reliably distinguish organic from nonorganic FTT. Because nonorganic FTT is not a diagnosis of exclusion, the physician should search simultaneously for an underlying physical problem and for personal, family, and child-family characteristics that support a psychosocial etiology. Optimally, evaluation is multidisciplinary, involving a physician, a nurse, a social worker, a nutritionist, an expert in child development, and often a psychiatrist or psychologist. The child's feeding behaviors with health care practitioners and with the parents must be observed, whether the setting is inpatient or outpatient.

Engaging the parents as co-investigators is essential. It helps foster their self-esteem and avoids blaming those who may already feel frustrated or guilty because of a perceived inability to nurture their child. The family should be encouraged to visit as often and as long as possible. Staff members should make them feel welcome, support their attempts to feed the child, and provide toys and ideas that promote parent-child play and other interactions. Staff members should avoid any comments implying parental inadequacy, irresponsibility, or other fault as the cause of FTT. However, parental adequacy and sense of responsibility should be evaluated. Suspected neglect or abuse must be reported to social services, but in many instances, referral for preventive services that are targeted to meet the family's needs for support and education (e.g., additional food stamps, more accessible child care, parenting classes) is more appropriate.

During hospitalization, the child's interaction with people in the environment is closely observed, and evidence of self-stimulatory behaviors (e.g., rocking, head banging) is noted. Some children with nonorganic FTT have been described as hypervigilant and wary of close contact with people, preferring interactions with inanimate objects if they interact at all. Although nonorganic FTT is more consistent with neglectful than abusive parenting, the child should be examined closely for evidence of abuse (see p. 3062). A screening test of developmental level should be done and, if indicated, followed with more sophisticated assessment.

Testing: Extensive laboratory testing is usually nonproductive. If a thorough history or physical examination does not indicate a particular cause, most experts recommend limiting screening tests to

- CBC with differential
- ESR
- BUN or serum creatinine level
• Urinalysis (including ability to concentrate and acidify) and culture

• Stool for pH, reducing substances, odor, color, consistency, and fat content

Depending on prevalence of specific disorders in the community, blood lead level, HIV, or TB testing may be warranted.

Other tests that are sometimes appropriate include electrolyte concentrations if the child has a history of significant vomiting or diarrhea; a thyroxine level if growth in height is more severely affected than growth in weight; and a sweat test if the child has a history of recurrent upper or lower respiratory tract disease, a salty taste when kissed, a ravenous appetite, foul-smelling bulky stools, hepatomegaly, or a family history of cystic fibrosis. Investigation for infectious diseases should be reserved for children with evidence of infection (eg, fever, vomiting, cough, diarrhea). Radiologic investigation should be reserved for children with evidence of anatomic or functional pathology (eg, pyloric stenosis, gastroesophageal reflux).

Prognosis

Prognosis with organic FTT depends on the cause. With nonorganic FTT, the majority of children age > 1 yr achieve a stable weight above the 3rd percentile. Children who develop FTT before age 1 yr are at high risk of cognitive delay, especially verbal and math skills. Children diagnosed at age < 6 mo, when the rate of postnatal brain growth is maximal, are at highest risk. General behavioral problems, identified by teachers or mental health practitioners, occur in about 50% of children. Problems specifically related to eating (eg, pickiness, slowness) or elimination tend to occur in a similar proportion of children, usually those with other behavioral or personality disturbances.

Treatment

• Sufficient nutrition

• Treatment of underlying disorder

• Long-term social support

Treatment aims to provide sufficient health and environmental resources to promote satisfactory growth. A nutritious diet containing adequate calories for catch-up growth (about 150% of normal caloric requirement) and individualized medical and social supports are usually necessary. Ability to gain weight in the hospital does not always differentiate infants with nonorganic FTT from those with organic FTT; all children grow when given sufficient nutrition. However, some children with nonorganic FTT lose weight in the hospital, highlighting the complexity of this condition.

For children with organic or mixed FTT, the underlying disorder should be treated quickly. For children with apparent nonorganic FTT or mixed FTT, management includes provision of education and emotional support to correct problems interfering with the parent-child relationship. Because long-term social support or psychiatric treatment is often required, the evaluation team may be able only to define the family's needs, provide initial instruction and support, and institute appropriate referrals to community agencies. The parents should understand why the referrals are being made and, if options exist, should participate in decisions concerning which agencies will be involved. If the child is hospitalized in a tertiary care center, the referring physician should be consulted regarding local agencies and the level of expertise available in the community.

A predischarge planning conference involving hospital-based personnel, representatives from the community agencies that will provide follow-up services, and the child's primary physician is ideal. Areas of responsibility and lines of accountability must be clearly defined, preferably in writing, and distributed to everyone involved. The parents should be invited to a summary session after the conference so that they can meet the community workers, ask questions, and arrange follow-up appointments.

In some cases, the child must be placed in foster care. If the child is expected to eventually return to the
biologic parents, parenting skill training and psychologic counseling must be provided for them. Their child's progress must be monitored scrupulously. Return to the biologic parents should be based on the parents' demonstrated ability to care for the child adequately, not only on the passage of time.

Hemorrhagic Shock and Encephalopathy Syndrome

Hemorrhagic shock and encephalopathy syndrome (HSES) is an extremely rare disease characterized by acute onset of severe shock, coagulopathy, encephalopathy, and hepatic and renal dysfunction in previously healthy children, resulting in death or catastrophic neurologic outcome.

HSES occurs predominantly in infants aged 3 to 8 mo (median age, 5 mo) but has been reported in a 15 yr old. HSES resembles heatstroke, with extremely high temperature and multiple organ dysfunction, but the cause is unknown. Overwrapping of infants who have febrile illness has been suggested, but evidence is slim. Other theories include a reaction to intestinal or environmental toxins, pancreatic release of trypsin, or an unidentified virus or bacterium. Diffuse cerebral edema with herniation and focal hemorrhages and infarcts in the cerebral cortex and other organs are common. The lungs and myocardium are not primarily involved.

Symptoms and Signs

A prodrome of fever, upper respiratory tract symptoms, or vomiting and diarrhea occurs in most patients. The major features are an acute onset of encephalopathy, cerebral edema (manifested as seizures, coma, and hypotonia), and severe shock (ie, hypotension and poor perfusion). Other common features include hyperpyrexia (up to 43.9° C rectally), bloody or watery diarrhea, disseminated intravascular coagulation (DIC), myoglobinuria, and rhabdomyolysis.

Diagnosis

• Laboratory testing

Similar symptoms can result from sepsis, Reye's syndrome, and hemolytic-uremic syndrome. Patients require laboratory evaluation, including blood and urine culture, ABG, CBC, electrolytes, BUN, creatinine, PT/PTT, and liver function tests. Multiple abnormalities include metabolic acidosis, elevated liver transaminases, acute renal failure, thrombocytopenia, falling Hct, leukocytosis, hypoglycemia, and hyperkalemia. Bacteriologic and viral cultures are negative. Diagnosis is by exclusion.

Prognosis

In all cases, > 60% of patients died, and ≥ 70% of survivors had severe neurologic sequelae.

Treatment

• Supportive measures

Treatment is entirely supportive. Infusions of large volumes of isotonic solutions and blood products (fresh frozen plasma, albumin, whole blood, packed RBCs) along with inotropic support (eg, dopamine, epinephrine) are necessary to maintain circulation. Marked temperature elevation (eg, > 39° C) requires external cooling (see p. 3266). Increased intracranial pressure caused by cerebral edema requires intubation and hyperventilation. DIC often progresses despite use of fresh frozen plasma.

Kawasaki Disease

Kawasaki disease (KD) is a vasculitis, sometimes involving the coronary arteries, that tends to occur in infants and children between ages 1 yr and 8 yr. It is characterized by prolonged fever, exantheme, conjunctivitis, mucous membrane inflammation, and lymphadenopathy. Coronary artery aneurysms may develop and rupture or cause MI. Diagnosis is by clinical criteria; once the disease is diagnosed, echocardiography is done. Treatment is aspirin and IV immune
globulin. Coronary thrombosis may require fibrinolysis or percutaneous interventions.

KD is a vasculitis of medium-sized arteries, most significantly the coronary arteries, which are involved in about 20% of untreated patients. Early manifestations include acute myocarditis with heart failure, arrhythmias, endocarditis, and pericarditis. Coronary artery aneurysms may subsequently form. Giant coronary artery aneurysms (> 8 mm internal diameter on echocardiography), though rare, have the greatest risk of causing cardiac tamponade, thrombosis, or infarction. KD is the leading cause of acquired heart disease in children. Extravascular tissue also may become inflamed, including the upper respiratory tract, pancreas, biliary tract, and kidneys.

**Etiology**

The etiology is unknown, but the epidemiology and clinical presentation suggest an infection or an abnormal immunologic response to an infection in genetically predisposed children. Children of Japanese descent have a particularly high incidence, but KD occurs worldwide. In the US, 3000 to 5000 cases occur annually. The male:female ratio is about 1.5:1. Eighty percent of patients are < 5 yr (peak, 18 to 24 mo). Cases in adolescents, adults, and infants < 4 mo are rare. Cases occur year-round, but most often in spring or winter. Clusters have been reported in communities without clear evidence of person-to-person spread. About 2% of patients have recurrences, typically months to years later.

**Symptoms and Signs**

The illness tends to progress in stages, beginning with fever lasting at least 5 days, usually remittent and > 39°C, associated with irritability, occasional lethargy, or intermittent colicky abdominal pain. Usually within a day or two of fever onset, bilateral bulbar conjunctival injection appears without exudate. Within 5 days, a polymorphous, erythematous macular rash appears, primarily over the trunk, often with accentuation in the perineal region. The rash may be urticarial, morbilliform, erythema multiforme, or scarlatiform. It is accompanied by injected pharynx; reddened, dry, fissured lips; and a red strawberry tongue (see Plate 74). During the first week, pallor of the proximal portion of the fingernails or toenails (leukonychia partialis) may occur. Erythema or a purple-red discoloration and variable edema of the palms and soles usually appear on about the 3rd to 5th day. Although edema may be slight, it is often tense, hard, and nonpitting. Periungual, palmar, and plantar and perineal desquamation begins on about the 10th day. The superficial layer of the skin sometimes comes off in large casts, revealing new normal skin. Tender, nonsuppurative cervical lymphadenopathy (≥ 1 node ≥ 1.5 cm in diameter) is present throughout the course in about 50% of patients. The illness may last from 2 to 12 wk or longer. Incomplete or atypical cases can occur, especially in younger infants, who have higher risk of developing coronary artery disease. These findings manifest in about 90% of patients.

Other less specific findings indicate involvement of many systems. Arthritis or arthralgias (mainly involving large joints) occur in about 33% of patients. Other clinical features include urethritis, aseptic meningitis, hepatitis, otitis, vomiting, diarrhea, hydrops of the gallbladder, and anterior uveitis.

Cardiac manifestations usually begin in the subacute phase of the syndrome about 1 to 4 wk after onset as the rash, fever, and other early acute clinical symptoms begin to subside.

**Diagnosis**

- **Clinical criteria**
- **Laboratory testing** (CBC, ESR, antinuclear antibody [ANA], rheumatoid factor [RF], throat and blood cultures)
- **Serial ECG and echocardiography**

Diagnosis is by clinical criteria (see Table 291-4). Similar symptoms can result from scarlet fever, staphylococcal exfoliative syndromes, measles, drug reactions, and juvenile idiopathic arthritis; less common mimics are leptospirosis and
Rocky Mountain spotted fever.

Laboratory tests are not diagnostic but may be done to exclude other disorders. Patients generally undergo CBC, ANA, RF, ESR, and throat and blood cultures. Leukocytosis, often with a marked increase in immature cells, is common acutely. Other hematologic findings include a mild normocytic anemia, thrombocytosis ($\geq 450,000/\mu L$) in the 2nd or 3rd wk of illness, and elevated ESR or C-reactive protein. ANA, RF, and cultures are negative. Other abnormalities, depending on the organ systems involved, include sterile pyuria, elevated liver enzymes, proteinuria, and CSF pleocytosis.

Consultation with a pediatric cardiologist is important. At diagnosis, ECG and echocardiography are done; because abnormalities may not appear until later, these tests are repeated 2 to 3 wk, 6 to 8 wk, and perhaps 6 to 12 mo after onset. ECG may show arrhythmias, decreased voltage, or left ventricular hypertrophy. Echocardiography should detect coronary artery aneurysms, valvular regurgitation, pericarditis, or myocarditis. Coronary arteriography occasionally is useful in patients with aneurysms and abnormal stress test results.

[Table 291-4. Criteria for Diagnosis of Kawasaki Disease]

Prognosis

Without therapy, mortality may approach 1%, usually occurring within 6 wk of onset. With adequate therapy, the mortality rate in the US is 0.17%. Long duration of fever increases cardiac risk. Deaths most commonly result from cardiac complications and can be sudden and unpredictable: > 50% occur within 1 mo of onset, 75% within 2 mo, and 95% within 6 mo but may occur as long as 10 yr later. Effective therapy reduces acute symptoms and, more importantly, the incidence of coronary artery aneurysms from 20% to < 5%. In the absence of coronary artery disease, the prognosis for complete recovery is excellent. About two thirds of coronary aneurysms regress within 1 yr, although it is unknown whether residual coronary stenosis remains. Giant coronary aneurysms are less likely to regress and require more intensive follow-up and therapy.

Treatment

- High-dose immune globulin IV (IGIV)
- High-dose aspirin

Children should be treated by or in close consultation with an experienced pediatric cardiologist, pediatric infectious disease specialist, or both. Therapy is started as soon as possible, optimally within the first 10 days of illness, with a combination of high-dose IGIV (single dose of 2 g/kg given over 10 to 12 h) and oral high-dose aspirin 20 to 25 mg/kg po qid. The aspirin dose is reduced to 3 to 5 mg/kg once/day after the child has been afebrile for 4 to 5 days; some authorities prefer to continue high-dose aspirin until the 14th day of illness. Aspirin metabolism is erratic during acute KD, which partially explains the high dose requirements. Some authorities monitor serum aspirin levels during high-dose therapy, especially if therapy is given for 14 days.

Most patients have a brisk response over the first 24 h of therapy. A small fraction continues to be ill with fever for several days and requires repeated dosing with IGIV. An alternative regimen, which may lead to slightly slower resolution of symptoms but may benefit those with cardiac dysfunction who could not tolerate the volume of a 2 g/kg IGIV infusion, is IGIV 400 mg/kg once/day for 4 days (again in combination with high-dose aspirin). The efficacy of IGIV/aspirin therapy when begun > 10 days after onset of illness is unknown, but therapy should still be considered.

After the child's symptoms have abated for 4 to 5 days, aspirin 3 to 5 mg/kg/day is continued for at least 8 wk after onset until repeated echocardiographic testing is completed. If there are no coronary artery aneurysms and signs of inflammation are absent (shown by normalization of ESR and platelets), aspirin may be stopped. Because of its antithrombotic effect, aspirin is continued indefinitely for children with coronary artery abnormalities. Children with giant coronary aneurysms may require additional anticoagulant therapy (eg, warfarin, dipyridamole).
Children who receive IGIV therapy may have a lower response rate to live viral vaccines. Thus, measles-mumps-rubella vaccine should generally be delayed for 11 mo after IGIV therapy, and varicella vaccine should be delayed for ≥ 11 mo. If the risk of measles exposure is high, vaccination should proceed, but revaccination (or serologic testing) should be done 11 mo later.

A small risk of Reye's syndrome exists in children receiving long-term aspirin therapy during outbreaks of influenza or varicella; thus, annual influenza vaccination is indicated for children (≥ 6 mo of age) receiving long-term aspirin therapy. Further, parents of children receiving aspirin should be instructed to contact their child's physician promptly if the child is exposed to or develops symptoms of influenza or varicella. Temporary interruption of aspirin may be considered (with substitution of dipyridamole for children with documented aneurysms).

Progeria

(Hutchinson-Gilford syndrome)

Progeria is a rare syndrome of accelerated aging that manifests early in childhood and causes premature death.

Progeria is caused by a sporadic mutation in the *LMNA* gene that codes for a protein (lamin A) that provides the molecular scaffolding of cell nuclei. The defective protein leads to nuclear instability from cell division and early death of every body cell.

Symptoms and signs develop within 2 yr and include

- Growth failure
- Craniofacial abnormalities (eg, craniofacial disproportion, micrognathia, beaked nose)
- Physical changes of aging (eg, wrinkled skin, balding)

Diagnosis is usually obvious by appearance but must be distinguished from segmental progerias (eg, acrogeria, metageria) and other causes of growth failure. Median age at death is 12 yr; cause is coronary artery and cerebrovascular disease. Of note is that other problems associated with normal aging (eg, increased cancer risk, degenerative arthritis) are not present. There is no known treatment.

Other progeroid syndromes: Premature aging is a feature of other rare progeroid syndromes, including Werner's syndrome (premature aging after puberty with hair thinning and development of conditions of old age [eg, cataracts, diabetes, osteoporosis, atherosclerosis]) and Rothmund-Thomson syndrome (premature aging with increased susceptibility to cancer). Both are caused by gene mutations leading to defective RecQ DNA helicases, which normally repair DNA. Cockayne's syndrome is an autosomal recessive disease caused by mutation in the *ERCC8* gene, which is important in DNA excision repair. Clinical features include severe growth failure, cachectic appearance, retinopathy, hypertension, renal failure, skin photosensitivity, and intellectual disability. Neonatal progeroid (Wiedemann-Rautenstrauch) syndrome is a recessively inherited syndrome of aging causing death by 2 yr. Other syndromes (eg, Down, Ehlers-Danlos) occasionally have progeroid features.

Reye's Syndrome

Reye's syndrome is a rare form of acute encephalopathy and fatty infiltration of the liver that tends to follow some acute viral infections, particularly when salicylates are used. Diagnosis is clinical. Treatment is supportive.

The cause of Reye's syndrome is unknown, but many cases seem to follow infection with influenza A or B or varicella. Using salicylates during such illness increases the risk by as much as 35-fold. This finding has led to a marked decrease in salicylate use in the US since the mid-1980s (except when specifically indicated, such as in juvenile idiopathic arthritis and Kawasaki disease) and a corresponding decrease in
the incidence of Reye's syndrome from several hundred annual cases to < 20. The syndrome occurs almost exclusively in children < 18 yr. In the US, most cases occur in late fall and winter.

The disease affects mitochondrial function, causing disturbance in fatty acid and carnitine metabolism. Pathophysiology is similar to a number of inherited metabolic disorders.

**Symptoms and Signs**

The disease varies greatly in severity but is characteristically biphasic. Initial viral symptoms (URI or sometimes chickenpox) are followed in 5 to 7 days by pernicious nausea and vomiting and a sudden change in mental status. The changes in mental status may vary from a mild amnesia and lethargy to intermittent episodes of disorientation and agitation, which can progress rapidly to deepening stages of coma manifested by

- Progressive unresponsiveness
- Decorticate and decerebrate posturing
- Seizures
- Flaccidity
- Fixed dilated pupils
- Respiratory arrest

Focal neurologic findings usually are not present. Hepatomegaly occurs in about 40% of cases, but jaundice is absent.

**Complications:** Complications include

- Electrolyte and fluid disturbances
- Increased intracranial pressure (ICP)
- Diabetes insipidus
- Syndrome of inappropriate ADH secretion
- Hypotension
- Arrhythmias
- Bleeding diatheses (especially GI)
- Pancreatitis
- Respiratory insufficiency
- Hyperammonemia
- Aspiration pneumonia
- Poor temperature regulation

**Diagnosis**

- Clinical findings in association with laboratory testing
• Liver biopsy

Reye's syndrome should be suspected in any child exhibiting the acute onset of an encephalopathy (without known heavy metal or toxin exposure) and pernicious vomiting associated with hepatic dysfunction. Liver biopsy provides the definitive diagnosis, showing microvesicular, fatty changes, and is especially useful in sporadic cases and in children < 2 yr. The diagnosis may also be made when the typical clinical findings and history are associated with the following laboratory findings: increased liver transaminases (AST, ALT > 3 times normal), normal bilirubin, increased blood ammonia level, and prolonged PT. CSF examination usually shows increased pressure, < 8 to 10 WBCs/μL, and normal protein levels; the CSF glutamine level may be elevated. Hypoglycemia and hypoglycorrhachia occur in 15% of cases, especially in children < 4 yr; they should be screened for metabolic disease. The condition is staged from I to V according to severity.

Signs of metabolic derangement include elevated serum amino acid levels, acid-base disturbances (usually with hyperventilation, mixed respiratory alkalosis-metabolic acidosis), osmolar changes, hypernatremia, hypokalemia, and hypophosphatemia.

Differential diagnosis: The differential diagnosis of coma and liver dysfunction includes sepsis or hyperthermia (especially in infants); potentially treatable inborn abnormalities of urea synthesis (eg, ornithine transcarbamylase deficiency) or fatty acid oxidation (eg, systemic carnitine deficiency, medium chain acyl-CoA dehydrogenase deficiency); phosphorus or carbon tetrachloride intoxication; acute encephalopathy caused by salicylism, other drugs (eg, valproate), or poisons; viral encephalitis or meningoencephalitis; and acute hepatitis. Illnesses such as idiopathic steatosis of pregnancy and tetracycline liver toxicity may show similar light microscopic findings.

Prognosis

Outcome is related to the duration of cerebral dysfunction, severity and rate of progression of coma, severity of increased ICP, and degree of blood ammonia elevation. Progression from stage I to higher stages is likely when the initial blood ammonia level is > 100 μg/dL (> 60 μmol/L) and the PT is ≥ 3 sec longer than that of the control. In fatal cases, the mean time from hospitalization to death is 4 days. Fatality rates average 21% but range from < 2% among patients in stage I to > 80% among patients in stage IV or V. Prognosis for survivors usually is good, and recurrences are rare. However, the incidence of neurologic sequelae (eg, intellectual disability, seizure disorders, cranial nerve palsies, motor dysfunction) is as high as 30% among survivors who developed seizures or decerebrate posturing during illness.

Treatment

• Support measures

Treatment is supportive, with particular attention paid to control of ICP and blood glucose, because glycogen depletion is common. Treatment of elevated ICP includes intubation, hyperventilation, fluid restriction of 1500 mL/m²/day, elevating the head of the bed, and osmotic diuretics. Infusion of 10 or 15% dextrose is common to maintain euglycemia. Coagulopathy may require fresh frozen plasma or vitamin K. Other treatments (eg, exchange transfusion, hemodialysis, barbiturate-induced deep coma) have not been proved effective but are sometimes used.

Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is the sudden and unexpected death of an infant or young child between 2 wk and 1 yr of age in which an examination of the death scene, thorough postmortem examination, and clinical history fail to show cause.

SIDS is the most common cause of death of infants between 2 wk and 1 yr of age, accounting for 35 to 55% of all deaths in this age group. The rate of SIDS occurrence is 0.5/1000 births in the US; there are racial and ethnic disparities (African American and Native American children have twice the average risk.
of SIDS). Peak incidence is between the 2nd and 4th mo of life. Almost all SIDS deaths occur when the infant is thought to be sleeping.

**Etiology**

The cause is unknown, although it is most likely due to dysfunction of neural cardiorespiratory control mechanisms. The dysfunction may be intermittent or transient, and multiple mechanisms are probably involved. Fewer than 5% of infants with SIDS have episodes of prolonged apnea before their death, so the overlap between the SIDS population and infants with recurrent prolonged apnea is very small.

**Risk factors:** The association between a prone (on stomach) sleeping position and an increased risk of SIDS has been documented strongly. Other risk factors (see Table 291-5) include old or unsafe cribs, soft bedding (eg, lamb's wool), waterbed mattresses, smoking in the home, and an overheated environment. Siblings of infants who die of SIDS are 5 times more likely to die of SIDS; it is not clear whether this is related to genetics or environment.

Many risk factors for SIDS apply to non-SIDS infant deaths as well.

**Diagnosis**

The diagnosis, while largely one of exclusion, cannot be made without an adequate autopsy to rule out other causes of sudden, unexpected death (eg, intracranial hemorrhage, meningitis, myocarditis).

[Table 291-5. Risk Factors for Sudden Infant Death Syndrome]

**Management**

Parents who have lost a child to SIDS are grief-stricken and unprepared for the tragedy. Because no definitive cause can be found for their child's death, they usually have excessive guilt feelings, which may be aggravated by investigations conducted by police, social workers, or others. Family members require support not only during the days immediately after the infant's death but for at least several months to help them with their grief and dispel guilt feelings. Such support includes, whenever possible, an immediate home visit to observe the circumstances in which SIDS occurred and to inform and counsel the parents concerning the cause of death.

Autopsy should be done quickly. As soon as the preliminary results are known (usually within 12 h) they should be communicated to the parents. Some clinicians advise a series of home or office visits over the first month to continue the earlier discussions, answer questions, and give the family the final (microscopic) autopsy results. At the last meeting, it is appropriate to discuss the parents' adjustment to their loss, especially their attitude toward having other children. Much of the counseling and support can be complemented by specially trained nurses or by lay people who have themselves experienced the tragedy of and adjustment to SIDS (visit www.sids.org for more information and resources).

**Prevention**

The American Academy of Pediatrics recommends that infants be placed supine (on their back) for sleep unless other medical conditions prevent this. The incidence of SIDS increases with overheating (eg, clothing, blankets, hot room) and in cold weather. Thus, every effort should be made to avoid an overly hot or an overly cold environment, to avoid over-wrapping the infant, and to remove soft bedding, such as sheepskin, pillows, stuffed toys/animals, and comforters, from the crib. Mothers should avoid smoking during pregnancy, and infants should not be exposed to smoke. Parents should not have the infant sleep in their bed. There is no evidence that home apnea monitors reduce the incidence of SIDS and therefore are not suggested for prevention.
Chapter 292. Pediatric Cancers

Introduction

Overall, childhood cancer is relatively rare, with fewer than 11,000 cases and about 1,500 deaths annually among children aged 0 to 14 yr. In comparison, there are 1.4 million cases and 565,000 deaths annually among adults. However, cancer is the 2nd leading cause of death among children, following only injuries.

Childhood cancers include many that also occur in adults. Leukemia (see p. 1004) is by far the most common, representing about 33% of childhood cancers, brain tumors represent about 21%, lymphomas (see p. 1016) about 8%, and certain bone cancers (osteosarcoma and Ewing sarcoma—see p. 407) about 4%. Cancers that are exclusive to children include neuroblastoma (7% of cases), Wilms' tumor (5%), rhabdomyosarcoma (3 to 4%), and retinoblastoma (3%).

Children who survive cancer have more years than adults to develop long-term consequences of chemotherapy and radiation therapy, which include

- Infertility
- Poor growth
- Cardiac damage
- Development of second cancers (in 3 to 12% of survivors)

Consensus guidelines on screening for and management of long-term consequences are available from the Children's Oncology Group at www.survivorshipguidelines.org/.

Because of the severe consequences and complexity of treatment, children with cancer are best treated in centers with expertise in childhood cancers.

The impact of being diagnosed with cancer and the intensity of the treatment are overwhelming to the child and family. Maintaining a sense of normalcy for the child is difficult, especially given the need for frequent hospitalizations and outpatient visits and potentially painful procedures. Overwhelming stress is typical, as parents struggle to continue to work, be attentive to siblings, and still attend to the many needs of the child with cancer. The situation is even more difficult when the child is being treated at a specialty center far from home.

Brain Tumors

Brain tumors are the most common solid cancer in children < 15 yr and are the 2nd leading cause of death due to cancer. Diagnosis is typically by imaging (usually MRI) and biopsy. Treatment may include surgical resection, chemotherapy, and radiation therapy.

Entry into a clinical trial should be considered for all children with a brain tumor. Optimal treatment requires a multidisciplinary team of oncologists who have experience treating brain tumors in children. Because radiation therapy for brain tumors is technically demanding, children should be sent to centers that have experience in this area if possible.

Astrocytomas

Astrocytomas range from low-grade indolent tumors (the most prevalent) to malignant high-grade tumors. As a group, astrocytomas are the most common brain tumor in children, representing about 40% of tumors. Most cases occur between ages 5 yr and 9 yr. These tumors can occur anywhere in the brain or spinal cord, but are most common in the cerebellum.

Symptoms and Signs
Most patients have symptoms consistent with increased intracranial pressure (eg, morning headaches, vomiting, lethargy). Location of the tumor determines other symptoms and signs; for example:

- **Cerebellum**: Weakness, tremor, and ataxia
- **Visual pathway**: Visual loss, proptosis, or nystagmus
- **Spinal cord**: Pain, weakness, and gait disturbance

### Diagnosis

Contrast-enhanced MRI is the imaging test of choice for diagnosing the tumor, determining extent of disease, and detecting recurrence. Contrast-enhanced CT can also be used, although it is less specific and less sensitive. Biopsy is needed for determining tumor type and grade. These tumors are typically classified as low-grade (eg, juvenile pilocytic astrocytoma), intermediate-grade, or high-grade (eg, glioblastoma).

### Treatment

Treatment depends on location and grade of tumor. As a general rule, the lower the grade, the less intensive the therapy and the better the outcome.

- **Low-grade**: Surgical resection is the primary treatment. Radiation therapy is reserved for children who are > 10 yr and whose tumors cannot be completely excised. For children < 10 yr with incompletely excised tumors, chemotherapy is used instead because radiation therapy may cause long-term cognitive impairment. Most children with low-grade astrocytomas are cured.

- **Intermediate-grade**: These tumors are somewhere between low-grade and high-grade lesions. If they are closer to high-grade tumors, they are treated more aggressively (radiation and chemotherapy); if they appear more like low-grade tumors, they are treated with surgery alone or surgery followed by radiation (older children) or chemotherapy (younger children).

- **High-grade**: These tumors are treated with a combination of surgery (unless location precludes it), radiation therapy, and chemotherapy. Prognosis is poor; overall survival is only 20-30%.

### Ependymomas

Ependymomas are the 3rd most common CNS tumor in children (after astrocytomas and medulloblastomas), representing 10% of pediatric brain tumors. Mean age at diagnosis is 6 yr; however, about 30% of ependymomas occur in children < 3 yr.

Ependymomas are derived from the ependymal lining of the ventricular system. Up to 70% of ependymomas occur in the posterior fossa; both high-grade and low-grade tumors in the posterior fossae tend to spread locally to the brain stem.

Initial symptoms are typically related to increased intracranial pressure. Infants may present with developmental delay and irritability. Changes in mood, personality, or concentration may occur. Seizures, balance and gait disturbances, or symptoms of spinal cord compression (eg, back pain, loss of bladder and bowel control) may occur.

Diagnosis is based on MRI and biopsy.

The tumor is surgically removed, followed by MRI to check for residual tumor. Radiation therapy, chemotherapy, or both are then required.

Overall 5-yr survival rate is about 50% but depends partly on age:
• < 1 yr: 25%

• 1 to 4 yr: 46%

• ≥ 5 yr: 70%

Survival rate also depends on how much of the tumor can be removed (51 to 80% with total or near-total removal vs 0 to 26% with < 90% removal). Children who survive are at risk of neurologic deficits.

**Medulloblastoma**

Medulloblastoma is the most common malignant posterior fossa tumor in children and represents about 20% of all pediatric CNS cancers. It most commonly occurs in children aged 5 to 7 yr but can occur throughout adolescence. It is more common among boys. Medulloblastoma is a type of primitive neuroectodermal tumor (PNET).

Etiology is unclear, but medulloblastoma may occur with certain syndromes (eg, Gorlin syndrome, Turcot syndrome).

Patients present most commonly with vomiting, headache, nausea, visual changes (eg, double vision), and unsteady walking or clumsiness.

MRI with gadolinium contrast is the imaging test of choice for initial detection. Biopsy confirms diagnosis. Once the diagnosis is established, MRI of the entire spine along with lumbar puncture and sampling of the CSF are done to assess for spread of tumor into the spinal canal.

Treatment includes surgery, radiation, and chemotherapy. Children under the age of 3 may be effectively treated with chemotherapy alone. Combination therapy typically provides the best long-term survival.

Prognosis depends on the extent, histology, and biologic (eg, histologic, cytogenetic, molecular) parameters of the tumor and patient age:

• > 3 yr: Likelihood of 5-yr disease-free survival is 50 to 60% if the tumor is high-risk (disseminated) and 80% if the tumor is average-risk (no dissemination).

• ≤ 3 yr: Prognosis is more problematic, in part because up to 40% have disseminated disease at diagnosis. Children who survive are at risk of severe long-term neurocognitive deficits (eg, in memory, verbal learning, and executive function).

**Neuroblastoma**

Neuroblastoma is a cancer arising in the adrenal gland or less often from the extra-adrenal sympathetic chain, including the retroperitoneum, chest, and neck. Diagnosis is based on biopsy. Treatment may include surgical resection, chemotherapy, radiation therapy, and high-dose chemotherapy with stem cell transplantation.

Neuroblastoma is the most common cancer among infants. Almost 90% of neuroblastomas occur in children < 5 yr. Neuroblastoma can result from numerous different cytogenetic abnormalities on several chromosomes; in 1 to 2%, abnormalities appear to be inherited. Some markers (eg, N-myc oncogene, hyperdiploidy, histopathology) correlate with progression and prognosis.

Neuroblastomas may begin in the abdomen (about 65%), thorax (15 to 20%), neck, pelvis, or other sites. Neuroblastoma occurs very rarely as a primary CNS cancer.

Most neuroblastomas produce catecholamines, which can be detected as elevated levels of urinary catecholamine breakdown products. Ganglioneuroma is a fully differentiated, benign variant of neuroblastoma.
About 40 to 50% of children have localized or regional disease at diagnosis; 50 to 60% have metastases at diagnosis. Neuroblastoma may metastasize to bone marrow, bone, liver, lymph nodes, or, less commonly, skin or brain.

**Symptoms and Signs**

Symptoms and signs depend on the site of the primary cancer and pattern of disease spread. The most common symptoms are abdominal pain, discomfort, and a sense of fullness due to an abdominal mass.

Certain symptoms may result from metastases. These include bone pain due to widespread bone metastases, periorbital ecchymosis and proptosis due to retrobulbar metastasis, and abdominal distention and respiratory problems due to liver metastases, especially in infants. Occasionally, pallor due to anemia and petechiae due to thrombocytopenia occur in children with bone marrow metastases.

Children occasionally present with focal neurologic deficits or paralysis due to direct extension of the cancer into the spinal canal. They may also present with paraneoplastic syndromes (see p. 1054), such as cerebellar ataxia, opsoclonus-myoclonus, watery diarrhea, or hypertension.

**Diagnosis**

- **CT**
- **Biopsy**
- Sometimes bone marrow aspirate or core biopsy plus measurement of urinary catecholamine intermediates

Routine prenatal ultrasonography occasionally detects neuroblastoma. Patients presenting with abdominal symptoms or a mass require CT. Diagnosis is then confirmed by biopsy of any identified mass. Alternatively, diagnosis can be confirmed by finding characteristic cancer cells in a bone marrow aspirate or core biopsy plus elevated urinary catecholamine intermediates. Urinary vanillylmandelic acid (VMA), homovanillic acid (HVA), or both are elevated in ≥ 90% of patients. A 24-h urine collection can be used, although a spot urine test is usually sufficient. Neuroblastomas must be differentiated from Wilms' tumor, other renal masses, rhabdomyosarcoma, hepatoblastoma, lymphoma, and tumors of genital origin.

The following should be done to evaluate for metastases:

- Bone marrow aspirates and core biopsies from multiple sites (typically, both iliac crests)
- Skeletal survey
- Bone scan or 131I-metaiodobenzylguanidine (MBIG) scan
- Abdominal, pelvis, and chest CT or MRI

Cranial imaging with CT or MRI is indicated if symptoms or signs suggest brain metastases.

When the cancer is resected, a portion should be analyzed for DNA index (a quantitative measure of chromosome content) and amplification of the N-myc oncogene to determine prognosis and intensity of therapy. Risk categorization is complex, but generally classified as

- **Low**: Age < 1 yr, no amplification of the N-myc oncogene, and lower-stage (localized) disease
- **Intermediate**: Regional spread but no amplification of the N-myc oncogene
- **High**: Age ≥ 1 yr plus metastatic disease, amplification of the N-myc oncogene, or both
Prognosis

Prognosis is better for children with low-risk disease.

Treatment

• Surgical resection
• Chemotherapy
• Sometimes stem cell transplantation
• Sometimes radiation therapy

Surgical resection is important for low-risk and intermediate-risk disease. Chemotherapy (typical drugs include vincristine, cyclophosphamide, doxorubicin, cisplatin, carboplatin, ifosfamide, and etoposide) is usually necessary for children with intermediate-risk disease. High-dose chemotherapy with stem cell transplantation and cis-retinoic acid are frequently used for children with high-risk disease. Radiation therapy is sometimes needed for children with intermediate-risk or high-risk disease or for inoperable tumors.

Retinoblastoma

Retinoblastoma is a cancer arising from the immature retina. Symptoms and signs commonly include leukocoria (a white reflex in the pupil), strabismus, and, less often, inflammation and impaired vision. Diagnosis is based on ophthalmoscopic examination and ultrasonography, CT, or MRI. Treatment of small cancers and bilateral disease may include photocoagulation, cryotherapy, and radiation therapy. Treatment of larger cancers is enucleation. Chemotherapy is sometimes used to reduce cancer volume and to treat cancers that have spread beyond the eye.

Retinoblastoma occurs in 1/15,000 to 1/30,000 live births and represents about 3% of childhood cancers. It is usually diagnosed in children < 2 yr; < 5% of cases are diagnosed in those > 5 yr. The cancer may be hereditary. About 25% of patients have bilateral disease, which is always heritable. Another 15% of patients have heritable unilateral disease, and the remaining 60% have nonhereditary unilateral disease.

The pathogenesis of inheritance appears to involve mutational deactivation of both alleles of a retinoblastoma suppressor gene located on chromosome 13q14. In the hereditary form, a germline mutation alters one allele in all cells, and a later somatic mutation alters the other allele in the retinal cells (the 2nd hit in this 2-hit model), resulting in the cancer. The nonhereditary form probably involves somatic mutation of both alleles in a retinal cell.

Symptoms and Signs

Patients typically present with leukocoria (a white reflex in the pupil, sometimes referred to as cat's-eye pupil—see Plate 73) or strabismus. Much less often, patients present with inflammation of the eye or impaired vision. Rarely, the cancer has already spread, via the optic nerve or the choroid or hematogenously, resulting in an orbital or soft-tissue mass, headache, anorexia, or vomiting.

When the diagnosis is suspected, both fundi must be closely examined by indirect ophthalmoscopy with the pupils widely dilated and the child under general anesthesia. The cancers appear as single or multiple gray-white elevations in the retina; cancer seeds may be visible in the vitreous.

Diagnosis

• Orbital ultrasonography, CT, or MRI
Sometimes bone scan, bone marrow aspirate and biopsy, and lumbar puncture

Diagnosis is usually confirmed by orbital ultrasonography or CT. In almost all cancers, calcification can be detected by CT. However, if the optic nerve appears abnormal during ophthalmoscopy, MRI is better for finding cancer extension into the optic nerve or choroid. Whenever extraocular spread is suspected, testing should include a bone scan, a bone marrow aspirate and biopsy, and lumbar puncture.

Children who have a parent or sibling with a history of retinoblastoma should be evaluated by an ophthalmologist shortly after birth and then every 4 mo until age 4 yr. Patients with retinoblastoma require molecular genetic testing, and if a germline mutation is identified, parents should also be tested for the same mutation. If subsequent offspring of parents have the germline mutation, the same genetic testing and regular ophthalmologic examination are required. Recombinant DNA probes may be useful for detecting asymptomatic carriers.

**Prognosis**

If the cancer is treated when it is intraocular, > 90% of patients can be cured. Prognosis for patients with metastatic disease is poor.

In patients with hereditary retinoblastoma, incidence of 2nd cancers is increased; about 50% arise within the irradiated area. These cancers can include sarcomas and malignant melanoma. Within 30 yr of diagnosis, 70% develop a 2nd cancer.

**Treatment**

Unilateral retinoblastoma is managed by enucleation with removal of as much of the optic nerve as possible.

For patients with bilateral cancer, vision can usually be preserved. Options include bilateral photocoagulation or unilateral enucleation and photocoagulation, cryotherapy, and irradiation of the other eye. Radiation therapy is by external beam or, for very small cancers, brachytherapy (attachment of a radioactive plaque to the eye wall near the cancer).

Systemic chemotherapy, such as carboplatin plus etoposide, or cyclophosphamide plus vincristine, may be helpful to reduce the size of large cancers or to treat cancer that has disseminated beyond the eye. However, chemotherapy alone can seldom cure this cancer.

Ophthalmologic reexamination of both eyes and retreatment, if necessary, are required at 2-mo to 4-mo intervals.

**Rhabdomyosarcoma**

Rhabdomyosarcoma is a cancer arising from embryonal mesenchymal cells that have potential to differentiate into skeletal muscle cells. It can arise from almost any type of muscle tissue in any location, resulting in highly variable clinical manifestations. Cancers are typically detected by CT or MRI, and diagnosis is confirmed by biopsy. Treatment involves surgery, radiation therapy, and chemotherpay.

Rhabdomyosarcoma is the 3rd most common extra-CNS solid cancer in children (after Wilms' tumor and neuroblastoma). Nonetheless, it accounts for only 3 to 4% of all childhood cancers. Incidence of rhabdomyosarcoma in children is 4.3/million/yr. Two thirds of cancers are diagnosed in children < 7 yr. The disease is more common among whites than blacks (largely because frequency is lower in black girls) and is slightly more common among boys than girls.

**Histology:** There are 2 major histologic subtypes:

- Embryonal: Characterized by loss of heterozygosity on chromosome 11p15.5
• Alveolar: Associated with a translocation involving PAX3 or PAX7, regulators of transcription during neuromuscular development (chromosome 2;13 or 1;13 translocation)

Location: Although rhabdomyosarcoma can occur almost anywhere in the body, the cancer has predilection for several sites:

• Head and neck region, usually in the orbit or nasopharyngeal passages: 35 to 40%, most common among school-aged children

• GU system, usually in the bladder, prostate, or vagina: 25%, usually occurring in infants and toddlers

• Extremities: 20%, most common among adolescents

Fewer than 25% of children present with metastatic disease.

Symptoms and Signs

Children do not typically have systemic symptoms such as fever, night sweats, or weight loss. Usually, children present with a firm, palpable mass or with organ dysfunction due to impingement on the organ by the cancer.

Orbital and nasopharyngeal cancers may cause tearing, eye pain, or proptosis. Nasopharyngeal cavity cancers may cause nasal congestion, a change in voice, or mucopurulent discharge.

GU cancers cause abdominal pain, a palpable abdominal mass, difficulty urinating, and hematuria.

Extremity cancers appear as firm, indiscrete masses anywhere on the arms or legs. Metastases occur frequently, especially in the lungs, bone marrow, and lymph nodes, and usually do not cause symptoms.

Diagnosis

• CT or MRI

• Biopsy or excision

Masses are evaluated by CT, although head and neck lesions are often better defined by MRI. Diagnosis is confirmed by biopsy or excision of the mass. The standard metastatic evaluation includes chest CT, a bone scan, and bone marrow aspiration and biopsy.

Prognosis

Prognosis is based on

• Cancer location (eg, prognosis is better with head and GU cancers)

• Extent of resection

• Presence of metastasis

• Age (more favorable in younger children)

• Histology (embryonal histology is associated with a better outcome than alveolar histology)

Combinations of these prognostic factors place children at low, intermediate, or high risk. Treatment intensifies with each risk category, and overall survival ranges from > 90% in children with low-risk disease to < 50% in children with high-risk disease.

Treatment
• Surgery and chemotherapy

• Sometimes radiation therapy

Treatment consists of surgery, chemotherapy, and sometimes radiation therapy. Complete excision of the primary cancer is recommended when it can be done safely. Because the cancer is so sensitive to chemotherapy and radiation therapy, aggressive resection is discouraged if it may result in organ damage or dysfunction.

Children in all risk categories are treated with chemotherapy; the most commonly used drugs are vincristine, actinomycin D, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Topotecan and irinotecan are newer drugs that have activity against this cancer; they are being investigated in some frontline treatment regimens.

Radiation therapy is generally reserved for children with residual cancer after surgery and for children with intermediate-risk or high-risk disease.

**Wilms' Tumor**

(Nephroblastoma)

Wilms' tumor is an embryonal cancer of the kidney composed of blastemal, stromal, and epithelial elements. Genetic abnormalities have been implicated in the pathogenesis, but familial inheritance accounts for only 1 to 2% of cases. Diagnosis is by ultrasonography and abdominal CT and is confirmed by biopsy. Treatment may include surgical resection, chemotherapy, and radiation therapy.

Wilms' tumor usually manifests in children < 5 yr but occasionally in older children and rarely in adults. Wilms' tumor accounts for about 6% of cancers in children < 15 yr. Bilateral synchronous tumors occur in about 5% of patients; bilateral disease is more common among very young children, especially girls.

A chromosomal deletion of *WT1*, the Wilms' tumor suppressor gene, has been identified in some cases. Other associated genetic abnormalities include deletion of *WT2* (a 2nd Wilms' tumor suppressor gene), deletion of chromosome 16, and duplication of chromosome 12.

About 10% of cases manifest with other congenital abnormalities, especially GU abnormalities, but also commonly hemihypertrophy (asymmetry of the body). WAGR syndrome is the combination of Wilms' tumor (with *WT1* deletion), aniridia, GU malformations (eg, renal hypoplasia, cystic disease, hypospadias, cryptorchidism), and mental retardation (intellectual disability).

**Symptoms and Signs**

The most frequent finding is a painless, palpable abdominal mass. Less frequent findings include abdominal pain, hematuria, fever, anorexia, nausea, and vomiting. Hematuria (occurring in 15 to 20%) indicates invasion of the collecting system. Hypertension may occur if compression of the renal pedicle or renal parenchyma causes ischemia.

**Diagnosis**

• Abdominal ultrasonography and CT

• Biopsy

Abdominal ultrasonography determines whether the mass is cystic or solid and whether the renal vein or vena cava is involved. Abdominal CT is needed to determine the extent of the tumor and check for spread to regional lymph nodes, the contralateral kidney, or liver. The diagnosis is confirmed by biopsy of the mass. Renal arteriography, vena cavography, retrograde urography, or excretory urography is seldom
required. Chest CT is recommended to detect metastatic pulmonary involvement at initial diagnosis.

Prognosis

Prognosis depends on

• Histology (favorable or unfavorable)

• Stage at diagnosis

• Patient's age (younger is better)

The outcome for children with Wilms' tumor is excellent. Cure rates for lower-stage disease (localized to the kidney) range from 85% to 95%. Even children with more advanced disease fare well; cure rates range from 60% (unfavorable histology) to 90% (favorable histology).

The cancer may recur, typically within 2 yr of diagnosis. Cure is possible in children with recurrent cancer. Outcome after recurrence is better for children who present initially with lower-stage disease, whose tumors recur at a site that has not been irradiated, who relapse > 1 yr after presentation, and who receive less intensive treatment initially.

Treatment

• Surgery and chemotherapy

• Sometimes radiation therapy

The National Wilms' Tumor Study Group has established staging criteria and guidelines for treatment. Prompt surgical exploration of potentially resectable lesions is indicated, with examination of the contralateral kidney. If the cancer is unilateral and limited to the kidney or if extension is minimal, complete resection by nephrectomy is done, followed by treatment with vincristine and actinomycin D. If a unilateral cancer has spread extensively or if the disease is bilateral, chemotherapy with actinomycin D and vincristine, with or without radiation therapy, is used. Children with more advanced disease also receive doxorubicin. Other frequently used drugs include cyclophosphamide, ifosfamide, and etoposide.

Children with very large nonresectable tumors or bilateral tumors are candidates for chemotherapy followed by reevaluation and possibly resection.
Introduction

Congenital anomalies of the heart and blood vessels arise during the first 10 wk of embryonic development and are present at birth. The incidence is 1/120 live births; estimated risk is 2 to 3% in children with an affected 1st-degree relative.

Etiology

About 5% of patients have a chromosomal abnormality (eg, trisomy 13, 18, or 21; Turner's syndrome); other anomalies may be part of a genetic syndrome (eg, Holt-Oram, Noonan's, Williams, 22q11 deletion). Other possible causes are maternal illnesses (eg, diabetes mellitus, SLE, rubella), environmental exposure (eg, to thalidomide, isotretinoin, lithium [Ebstein's anomaly], or alcohol [fetal alcohol syndrome]), or a combination. Usually, no specific cause is identified.

Pathophysiology

Congenital heart anomalies are classified (see Table 293-1) as

- Cyanotic
- Acyanotic (left-to-right shunts or obstructive lesions)

The physiologic consequences of congenital heart anomalies vary greatly, ranging from an asymptomatic heart murmur or abnormal pulses to severe cyanosis and heart failure (HF).

**Left-to-right shunts:** Oxygenated blood from the left heart (left atrium or left ventricle) or the aorta shunts to the right heart (right atrium or right ventricle) or the pulmonary artery through an abnormal opening between

[Table 293-1, Classification of Congenital Heart Anomalies*]

High-pressure shunts (those at the ventricular or great artery level) become apparent several days to a few weeks after birth; low-pressure shunts (atrial septal defects) become apparent considerably later. If untreated, elevated pulmonary artery pressure may lead to Eisenmenger's syndrome (see p. 2966). Large left-to-right shunts (eg, large ventricular septal defect [VSD], patent ductus arteriosus [PDA]) cause volume overload, which may lead to HF and during infancy often results in failure to thrive. A large left-to-right shunt also decreases lung compliance, leading to frequent lower respiratory tract infections.

**Obstructive lesions:** Blood flow is obstructed without shunting, causing a pressure gradient across the obstruction. The resulting pressure overload proximal to the obstruction may cause ventricular hypertrophy and HF. The principal manifestation is a heart murmur, which results from turbulent flow through the obstructed (stenotic) point. Examples are congenital aortic stenosis, which accounts for 3 to 6% of congenital heart anomalies, and congenital pulmonary stenosis, which accounts for 8 to 12% (for both, see Ch. 214).

**Cyanotic heart anomalies:** Varying amounts of deoxygenated venous blood are shunted to the left heart (right-to-left shunt), reducing systemic arterial O₂ saturation. If there is > 5 g/dL of deoxygenated
Hb, cyanosis results. Detection of cyanosis may be delayed in infants with dark pigmentation. Complications of persistent cyanosis include polycythemia, clubbing, thromboembolism (including stroke), bleeding disorders, brain abscess, and hyperuricemia. Hypercyanotic spells frequently occur in infants with tetralogy of Fallot (see p. 2958).

Depending on the anomaly, pulmonary blood flow may be increased (often resulting in HF in addition to cyanosis), normal, or reduced, resulting in cyanosis of variable severity. Heart murmurs are variably audible and are not specific.

Heart failure: Some congenital heart anomalies (eg, bicuspid aortic valve, mild aortic stenosis) do not significantly alter hemodynamics. Others cause pressure or volume overload, sometimes causing HF. HF occurs when cardiac output is insufficient to meet the body's metabolic needs or when the heart cannot adequately handle venous return, causing pulmonary congestion (in left ventricular failure), edema primarily in dependent tissues and abdominal viscera (in right ventricular failure), or both (see p. 2118). HF in infants and children has many causes other than congenital heart anomalies (see Table 293-2).

Symptoms and Signs

Manifestations of the various heart anomalies are limited to several common ones:

- Murmurs
- Cyanosis
- HF

Less commonly, chest pain, diminished or nonpalpable pulses, circulatory shock, and arrhythmias are present.

Murmurs: Most left-to-right shunts and obstructive lesions cause systolic murmurs. Systolic murmurs and thrills are most prominent at the surface closest to their point of origin, making location diagnostically helpful. Increased flow across the pulmonary or aortic valve causes a midsystolic (ejection systolic) murmur. Regurgitant flow through an atrioventricular valve or flow across a VSD causes a holosystolic (pansystolic) murmur, possibly obscuring heart sounds as its intensity increases.

PDA causes a continuous murmur that is uninterrupted by the 2nd heart sound (S2) because blood flows through the ductus during systole and diastole. This murmur is 2-toned, having a different sound during systole (when driven by higher pressure) than during diastole.

Cyanosis: This manifestation is characterized by bluish discoloration of mucous membranes or nail beds, clubbing of nail beds, or pulse oximetry < 93 to 95%.

Heart failure: In infants, symptoms or signs of HF include

- Tachycardia
- Tachypnea
- Dyspnea with feeding
- Diaphoresis
- Restlessness
- Irritability

Dyspnea with feeding causes inadequate intake and poor growth, which may be worsened by increased
metabolic demands in HF and frequent respiratory tract infections. Hepatomegaly is common. However, in contrast to adults and older children, most infants do not have distended neck veins and dependent edema, although they occasionally have edema.

Table 293-2. Common Causes of Heart Failure in Children

in the periorbital area. Findings in older children with HF are similar to those in adults (see p. 2123).

Other manifestations: In neonates, circulatory shock may be the first manifestation of certain anomalies (eg, hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, coarctation of the aorta). Neonates appear extremely ill and have cold extremities, diminished pulses, low BP, and reduced response to stimuli.

Chest pain may be manifested by unexplained irritability in infants with a coronary artery anomaly. In older children and adolescents, chest pain due to a cardiac etiology is usually associated with exertion and may be caused by severe aortic stenosis, pulmonic stenosis, or Eisenmenger's syndrome.

Diagnosis

- Pulse oximetry, ECG, and chest x-ray
- Echocardiography
- Sometimes cardiac MRI or CT angiography, cardiac catheterization with angiography

Diagnosis is suggested by the presence of heart murmurs, abnormal pulses, cyanosis, or HF. Cyanosis is usually noticed during the first few months of life. Cyanosis due to heart defects should be distinguished from that due to other disorders (eg, various respiratory disorders, CNS depression, hypothermia, hypoglycemia, hypocalcemia, sepsis, methemoglobinemia). Pulse oximetry, ECG, and chest x-ray are required. Echocardiography usually confirms the diagnosis.

Cardiac MRI or CT angiography may clarify important anatomic details. Cardiac catheterization with angiography is occasionally needed to confirm the diagnosis or to assess severity of the anomaly; it is done more often for therapeutic purposes.

Treatment

- Medical treatment of HF (eg, with O₂, diuretics, ACE inhibitors, digoxin, and salt restriction)
- Surgical repair of anomalies amenable to correction

After medical stabilization of acute HF symptoms or cyanosis, most children require surgical or transcatheter repair; the exceptions are certain VSDs that are likely to become smaller or close with time. Transcatheter procedures include balloon atrial septostomy for palliation of severely cyanotic neonates with transposition of the great arteries, balloon dilation of severe aortic or pulmonary valve stenosis, and transcatheter closure of cardiac shunts (most often atrial septal defect and PDA).

Heart failure in neonates: Acute, severe HF or cyanosis in the first week of life is a medical emergency. Secure vascular access should be established, preferably via an umbilical venous catheter. For HF, diuretics, inotropic drugs, and drugs to reduce afterload are given. The diuretic furosemide or ethacrynic acid is given as an initial bolus of 1 mg/kg IV and titrated based on urine output. The inotropic drug dopamine or dobutamine is given as an IV infusion of 5 to 15 μg/kg/min. Milrinone or, less frequently, nitroprusside is given to reduce afterload. Milrinone is given as a loading dose of 50 to 75 μg/kg IV over 10 to 60 min followed by an infusion of 0.5 μg/kg/min. Nitroprusside is started at 0.3 to 0.5 μg/kg/min and titrated to desired effect (usual maintenance dose is about 3 μg/kg/min).

Once a congenital cardiac lesion is suspected as the cause of the HF or cyanosis, an IV infusion of prostaglandins should be started (eg, prostaglandin E₁ 0.05 to 0.1 μg/kg/min) and titrated to the lowest
dose that maintains patency of the ductus arteriosus. Keeping the ductus open is important because most cardiac lesions manifesting at this age are ductal-dependent either for systemic blood flow (eg, hypoplastic left heart syndrome, critical aortic stenosis, coarctation of the aorta) or for pulmonary blood flow (cyanotic lesions such as pulmonary atresia or severe tetralogy of Fallot).

Mechanical ventilation is often necessary; O₂ should be given judiciously or even withheld because O₂ can decrease pulmonary vascular resistance, which is harmful to infants with certain defects (eg, hypoplastic left heart syndrome).

Heart failure in older infants and children: Standard approaches to acute and chronic heart failure, similar to those in adults, are used. These approaches may include a diuretic (eg, furosemide 0.5 to 1.0 mg/kg IV or 1 to 3 mg/kg po q 8 to 24 h, titrated upward as needed), an ACE inhibitor (eg, captopril 0.1 to 0.3 mg/kg po tid), digoxin (dose varies by age; see Table 293-3), and salt restriction. A potassium-sparing diuretic (spironolactone 1 mg/kg po once/day or bid, titrated up to 2 mg/kg/dose if needed) may be useful, particularly if high-dose furosemide is required.

A croupette, mask, or nasal prongs with adequate fractional inspired O₂ (FIO₂) should be given to prevent cyanosis and alleviate respiratory distress; when possible, FIO₂ should be kept < 40% to prevent pulmonary epithelial damage. A cardiac chair position may benefit small infants and children; this position reduces upward pressure into the thorax exerted by abdominal organs and thus reduces work required for breathing.

Because HF increases metabolic demands and makes feeding more difficult, enhanced caloric content feedings are recommended; these feedings increase calories supplied and do so with less risk of volume overload. Some children require nasogastric or gastrostomy feedings to maintain growth. If these measures do not result in weight gain, surgical repair of the anomaly is indicated.

[Table 293-3. Oral Digoxin Dosage in Children*]

Endocarditis prophylaxis: Current guidelines of the American Heart Association for prevention of endocarditis (see p. 2199) state that antibiotic prophylaxis is required for children with congenital heart disease (CHD) who have the following:

• Unrepaired cyanotic CHD (including children with palliative shunts and conduits)

• Completely repaired CHD during the first 6 mo after surgery if prosthetic material or a device was used

• Repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device

Atrial Septal Defect

(Ostium Secundum Defect)

An atrial septal defect (ASD) is an opening in the interatrial septum, causing a left-to-right shunt and volume overload of the right atrium and right ventricle. Children are rarely symptomatic, but long-term complications after age 20 yr include pulmonary hypertension, heart failure, and atrial arrhythmias. Adults and, rarely, adolescents may present with exercise intolerance, dyspnea, fatigue, and atrial arrhythmias. A soft midsystolic murmur at the upper left sternal border with a prominently split 2nd heart sound (S₂) is common. Diagnosis is by echocardiography. Treatment is transcatheter or surgical repair.

ASDs account for about 6 to 10% of cases of congenital heart disease. Most cases are isolated and sporadic, but some are part of a genetic syndrome (eg, mutations of chromosome 5, Holt-Oram syndrome).

Classification: ASDs can be classified by location:
• Ostium secundum (defect in the fossa ovalis—in the center [or middle] part of the atrial septum)

• Sinus venosus (defect in the posterior aspect of the septum, near the superior vena cava or inferior vena cava and frequently associated with anomalous return of the right upper or lower pulmonary veins to the right atrium or vena cava)

• Ostium primum (defect in the anteroinferior aspect of the septum, a form of atrioventricular septal [endocardial cushion] defect—see p. 2953).

Pathophysiology

To understand hemodynamic changes seen in ASD (and other anomalies), see Fig. 293-1 for normal hemodynamic data.

In ASD, shunting is left to right initially (see Fig. 293-2). Some small ASDs, often just a stretched patent foramen ovale, close spontaneously during the first few years of life. Persistent moderate-to-large ASDs result in large shunts, leading to right atrial and right ventricular volume overload and, over a number of years, pulmonary artery hypertension, elevated pulmonary vascular resistance, and right ventricular hypertrophy. Atrial fibrillation may also occur later. Ultimately, the increase in the pulmonary artery pressure and vascular resistance may result in a bidirectional atrial shunt with cyanosis during adulthood (Eisenmenger's reaction).

Symptoms and Signs

Most small ASDs are asymptomatic. Larger shunts may cause exercise intolerance, dyspnea during exertion, fatigue, and atrial arrhythmias with palpitations. Passage of microemboli from the venous circulation across the ASD (paradoxical embolization), often associated with arrhythmias, may lead to cerebral or systemic thromboembolic disorders. Rarely, when an ASD is undiagnosed or untreated, Eisenmenger's syndrome develops.

[Fig. 293-1. Normal circulation with representative right and left cardiac pressures (in mm Hg).]

Auscultation typically reveals a grade 2 to 3/6 midsystolic (ejection systolic) murmur and a widely split, fixed S2 at the upper left sternal border in children. A large left-to-right atrial shunt may produce a low-pitched diastolic murmur (due to increased tricuspid flow) at the left lower sternal border. These findings may be absent in infants, even those who have a large defect. A prominent right ventricular cardiac impulse, manifested as a parasternal heave or lift, may be present.

Diagnosis

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suggested by cardiac examination, chest x-ray, and ECG and is confirmed by 2-dimensional echocardiography with color flow and Doppler studies.

With a significant shunt, ECG may show right axis deviation, right ventricular hypertrophy, or right bundle branch block (with rSR’ pattern in V1). Chest x-ray shows cardiomegaly with dilation of the right atrium and right ventricle, a prominent main pulmonary artery segment, and increased pulmonary vascular markings.

Cardiac catheterization is not usually necessary unless a transcatheter intervention is planned.

Treatment

• Observation, transcatheter closure, or surgical repair
Most small ostium secundum ASDs (< 3 mm) close spontaneously; many defects between 3 mm and 8 mm close spontaneously by age 18 mo. However, ostium primum and sinus venosus ASDs do not close spontaneously.

Asymptomatic children with a small shunt require only observation and periodic echocardiography. Although these children are theoretically at risk of paradoxical systemic embolization, it is not standard practice to close a small, hemodynamically insignificant defect.

Children with moderate to large defects (eg, pulmonary flow:systemic flow ratio > 1.5:1, or definite evidence of right ventricular volume overload on echocardiography) should have the ASD closed, typically between ages 2 to 6 yr. Transcatheter closure with various devices (eg, Amplatzer® or Gore HELEX® septal occluder) is preferred when appropriate anatomic characteristics, such as adequate rims of septal tissue and distance from vital structures (eg, aortic root, pulmonary veins, tricuspid annulus), are present. Otherwise, surgical repair is indicated. Sinus venosus and ostium primum (atrioventricular septal type) defects are not amenable to device closure. If ASDs are repaired during childhood, perioperative mortality rate approaches 0, and long-term survival rates approach those of the general population. Before repair, children with large shunts and heart failure should be treated with diuretics, digoxin, and ACE inhibitors.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

**Ventricular Septal Defect**

A ventricular septal defect (VSD) is an opening in the interventricular septum, causing a shunt between ventricles. Large defects result in a significant left-to-right shunt and cause dyspnea with feeding and poor growth during infancy. A loud, harsh, holosystolic murmur at the lower left sternal border is common. Recurrent respiratory infections and heart failure may develop. Diagnosis is by echocardiography. Defects may close spontaneously during infancy or require surgical repair.

VSD (see Fig. 293-3) is the 2nd most common congenital heart anomaly after bicuspid aortic valve, accounting for 20% of all defects. It can occur alone or with other congenital anomalies (eg, tetralogy of Fallot, complete atrioventricular septal defects, transposition of the great arteries).

**Classification:** VSDs are classified by location:

- Perimembranous
- Trabecular muscular
- Subpulmonary outlet (supracristal or doubly committed subarterial)
- Inlet

Perimembranous defects (70 to 80%) are defects in the membranous septum adjacent to the tricuspid valve and they extend into a variable amount of surrounding muscular tissue; the most common type of this defect occurs immediately below the aortic valve.

[Fig. 293-3, Ventricular septal defect.]

Trabecular muscular defects (5 to 20%) are completely surrounded by muscular tissue and may occur anywhere in the septum.
Subpulmonary outlet defects (5 to 7% in the US; about 30% in Far Eastern countries) occur in the ventricular septum immediately under the pulmonary valve. These defects are often referred to as supracristal or doubly committed subarterial defects and are frequently associated with aortic leaflet prolapse into the defect, causing aortic regurgitation.

Inlet defects (5 to 8%) are bordered superiorly by the tricuspid annulus and are located posterior to the membranous septum. These defects are sometimes referred to as atrioventricular septal-type defects.

Pathophysiology

The magnitude of the shunt depends on defect size and downstream resistance (ie, pulmonary outflow tract obstruction and pulmonary vascular resistance); larger defects result in a large left-to-right shunt. Assuming there is no pulmonic stenosis, over time, a large shunt causes pulmonary artery hypertension, elevated pulmonary artery vascular resistance, right ventricular pressure overload, and right ventricular hypertrophy. Ultimately, the increased pulmonary vascular resistance causes shunt direction to reverse (from the right to the left ventricle), leading to Eisenmenger's syndrome (see p. 2966).

Small defects cause a relatively small left-to-right shunt, and pulmonary artery pressure is normal. Heart failure (HF), pulmonary hypertension, and Eisenmenger's syndrome do not develop.

Symptoms and Signs

Symptoms depend on defect size and magnitude of the left-to-right shunt. Children with a small VSD are typically asymptomatic and grow and develop normally. In those with a larger defect, symptoms of HF (eg, respiratory distress, poor weight gain, fatigue after feeding) appear at age 4 to 6 wk when pulmonary vascular resistance falls. Frequent lower respiratory tract infections may occur. Eventually, untreated patients may develop symptoms of Eisenmenger's syndrome.

Auscultatory findings vary with the size of the defect. Small VSDs typically produce murmurs ranging from a grade 1 to 2/6 high-pitched, short systolic murmur (due to tiny defects that actually close during late systole) to a grade 3 to 4/6 holosystolic murmur (with or without thrill) at the lower left sternal border; this murmur is audible shortly after birth. The precordium is not hyperactive, and the 2nd heart sound ($S_2$) is normally split and has normal intensity.

Moderate to large VSDs produce a loud holosystolic murmur that is present by age 2 to 3 wk; $S_2$ is usually narrowly split with an accentuated pulmonary component. An apical diastolic rumble (due to increased flow through the mitral valve) and findings of HF (eg, tachypnea, dyspnea with feeding, failure to thrive, gallop, crackles, hepatomegaly) may be present. With large defects allowing equalization of left ventricular and right ventricular pressures, the systolic murmur is often attenuated.

Diagnosis

- Chest x-ray and ECG
- Echocardiography

Diagnosis is suggested by clinical examination, supported by chest x-ray and ECG, and established by echocardiography.

If the VSD is large, chest x-ray shows cardiomegaly and increased pulmonary vascular markings. ECG shows right ventricular hypertrophy or combined ventricular hypertrophy and, occasionally, left atrial enlargement. ECG and chest x-ray are typically normal if the VSD is small.

Two-dimensional echocardiography with color flow and Doppler studies establishes the diagnosis and can provide important anatomic and hemodynamic information, including the defect's location and size and right ventricular pressure. Cardiac catheterization is rarely necessary.

Treatment
For HF, medical therapy (eg, diuretics, digoxin, ACE inhibitors)

Sometimes surgical repair

Small VSDs, particularly muscular septal defects, often close spontaneously during the first few years of life. A small defect that remains open does not require medical or surgical therapy.

Larger defects are less likely to close spontaneously. Diuretics, digoxin, and ACE inhibitors are indicated before surgery if HF develops. If infants do not respond to medical treatment or have poor growth, surgical repair may be done during the first few months of life. Even in asymptomatic children, a large shunt (pulmonary flow:systemic flow ratio ≥ 2:1) that persists after 2 to 4 yr requires surgical repair. Current surgical mortality rate is < 2%. Surgical complications may include residual ventricular shunt, right bundle branch block, and complete heart block.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

**Atrioventricular Septal Defect**

(Atrioventricular Canal Defect; Endocardial Cushion Defect; Persistent Ostium Primum)

Atrioventricular (AV) septal defect consists of primum type atrial septal defect with AV valve malformation, with or without a ventricular septal defect. These defects result from maldevelopment of the endocardial cushions. Defects may be asymptomatic if small. If large, they may cause heart failure with dyspnea with feeding, poor growth, tachypnea, diaphoresis, or arrhythmias. Heart murmurs are common. Diagnosis is by echocardiography. Treatment is surgical repair for all but the smallest defects.

AV septal defect accounts for about 5% of congenital heart anomalies. The defect may be complete or partial; 30% of patients with the complete form have Down syndrome. AV septal defect is also common among patients with asplenia or polysplenia (heterotaxy) syndromes.

**Complete AV septal defect:** Complete AV septal defect (see Fig. 293-4) consists of a large ostium primum atrial septal defect (ASD) in the anteroinferior aspect of the septum, an inlet ventricular septal defect (VSD), and a common AV valve orifice. A left-to-right shunt occurs at the atrial and ventricular levels; AV valve regurgitation may be significant, sometimes causing a direct left ventricle-to-right atrial shunt. These abnormalities result in enlargement of all 4 cardiac chambers. Hemodynamic findings are similar to those of a large VSD. Over time, the increase in pulmonary blood flow, pulmonary artery pressure, and pulmonary vascular resistance may lead to reversal of shunt direction with cyanosis and Eisenmenger's syndrome (see p. 2966).

**Partial AV septal defect:** A partial defect consists of an ostium primum ASD, partitioning of the common AV valve into 2 separate AV orifices, and a cleft in the mitral valve (left AV orifice). The ventricular septum is intact, or there may be a small VSD. Hemodynamic abnormalities are similar to those of ostium secundum ASD with the additional finding of variable degrees of mitral regurgitation.

[Fig. 293-4. Atrioventricular septal defect (complete form).]

**Symptoms and Signs**

Complete AV septal defect with a large left-to-right shunt causes signs of heart failure (HF—eg, tachypnea, dyspnea with feeding, poor weight gain, diaphoresis) by age 4 to 6 wk. Pulmonary vascular obstructive disease (Eisenmenger's syndrome) is usually a late complication but may occur earlier, especially in children with Down syndrome.

Partial AV septal defects are asymptomatic during childhood if mitral regurgitation is mild or absent. However, symptoms (eg, exercise intolerance, fatigue, palpitations) may develop during adolescence or
early adulthood. Infants with moderate or severe mitral regurgitation often have signs of HF.

Physical examination in children with complete AV septal defects shows an active precordium due to volume and pressure overload of the right ventricle; a single, loud 2nd heart sound (S$_2$) due to pulmonary hypertension; a grade 3 to 4/6 systolic murmur; and sometimes a diastolic murmur at the apex and low left sternal border. Most children with a partial defect have wide splitting of the S$_2$ and a midsystolic (eg, ejection systolic) murmur audible at the upper left sternal border. A mid-diastolic rumble may be present at the lower left sternal border when the atrial shunt is large. A cleft in the left AV valve results in a blowing apical systolic murmur of mitral regurgitation. Thus, cardiac findings in children with the partial form are the same as those described for secundum ASD (see p. 2950); if mitral regurgitation coexists, there will also be a high-pitched holosystolic murmur at the apex.

**Diagnosis**

- Chest x-ray and ECG
- Echocardiography

Diagnosis is suggested by clinical examination, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

Chest x-ray shows cardiomegaly with right atrial enlargement, biventricular enlargement, a prominent main pulmonary artery segment, and increased pulmonary vascular markings.

ECG shows a superiorly directed QRS axis (eg, left axis deviation or northwest axis), frequent 1st-degree AV block, left or right ventricular hypertrophy or both, and occasional right atrial enlargement and right bundle branch block.

Two-dimensional echocardiography with color flow and Doppler studies establishes the diagnosis and can provide important anatomic and hemodynamic information. Cardiac catheterization is not usually necessary unless hemodynamics must be further characterized before surgical repair.

**Treatment**

- Surgical repair
- For HF, medical therapy (eg, diuretics, digoxin, ACE inhibitors) before surgery

Complete AV septal defect should be repaired by age 2 to 4 mo, because most infants have HF and failure to thrive. However, even if infants are growing well without significant symptoms, repair should be done before 6 mo to prevent development of pulmonary vascular disease, especially in infants with Down syndrome. In patients with 2 adequately sized ventricles and no additional defects, the large central defect (combination of the primum ASD and inlet VSD) is closed and the common AV valve is reconstructed into 2 separate valves. For a single-stage complete repair, mortality rate was 5 to 10% in older series but more recently was as low as 3 to 4%. Surgical complications include complete heart block (3%) and mitral regurgitation. Pulmonary artery banding is no longer recommended unless associated abnormalities make complete repair in a small infant high risk. For asymptomatic patients with a partial defect, elective surgery is done at age 1 to 3 yr. Surgical mortality rate should be very low.

For patients with large shunts and HF, diuretics, digoxin, and ACE inhibitors are indicated before surgery.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

**Patent Ductus Arteriosus**

Patent ductus arteriosus (PDA) is a persistence of the fetal connection (ductus arteriosus) between the aorta and pulmonary artery after birth, resulting in a left-to-right shunt. Symptoms
may include failure to thrive, poor feeding, tachycardia, and tachypnea. A continuous murmur at
the upper left sternal border is common. Diagnosis is by echocardiography. Administration of
indomethacin with or without fluid restriction may be tried in premature infants with a significant
shunt, but this therapy is not effective in term infants or older children with PDA. If the
connection persists, surgical or catheter-based correction is indicated.

PDA accounts for 5 to 10% of congenital heart anomalies; the male:female ratio is 1:3. PDA is very
common among premature infants (in 45% with birth weight < 1750 g; in about 80% with birth weight <
dia 1200 g). A significant PDA causes heart failure (HF) in 15% of premature infants with birth weight < 1750
g and in 40 to 50% of infants with birth weight < 1500 g.

Pathophysiology

The ductus arteriosus is a normal connection between the pulmonary artery and aorta; it is necessary for
proper fetal circulation. At birth, the rise in PaO$_2$ and decline in prostaglandin concentration cause closure
of the ductus arteriosus, typically beginning within the first 10 to 15 h of life. If this normal process does
not occur, PDA results (see
Fig. 293-5).

Physiologic consequences depend on ductal size. A small ductus rarely causes symptoms. A large ductus
causes a large left-to-right shunt. Over time, a large shunt results in pulmonary artery hypertension and
elevated pulmonary vascular resistance, ultimately leading to Eisenmenger's syndrome (see p. 2966).

Symptoms and Signs

Clinical presentation depends on PDA size and gestational age at delivery. Infants and children with a
small PDA are generally asymptomatic; infants with a large PDA present with signs

[Fig. 293-5. Patent ductus arteriosus.]

of HF (eg, failure to thrive, poor feeding, tachypnea, dyspnea with feeding, tachycardia). Premature
infants may present with respiratory distress, apnea, worsening mechanical ventilation requirements, or
other serious complications (eg, necrotizing enterocolitis). Signs of HF occur earlier in premature infants
than in full-term infants and may be more severe. A large ductal shunt in a premature infant often is a
major contributor to the severity of the lung disease of prematurity.

Most children with a small PDA have normal heart sounds and peripheral pulses. A grade 1 to 3/6
continuous murmur is heard best in the upper left sternal border. The murmur extends from systole to
beyond the 2nd heart sound (S$_2$) into diastole and typically has a different pitch in systole and diastole.

Full-term infants with a significant PDA shunt have full or bounding peripheral pulses with a wide pulse
pressure. A grade 1 to 4/6 continuous murmur is characteristic. If the murmur is loud, it has a "machinery-
sounding" quality. An apical diastolic rumble (due to high flow across the mitral valve) or gallop rhythm
may be audible if there is a large left-to-right shunt or HF develops.

Premature infants with a significant shunt have bounding pulses and a hyperdynamic precordium. A heart
murmur occurs in the pulmonary area; the murmur may be continuous, systolic with a short diastolic
component, or only systolic, depending on the pulmonary artery pressure. Some infants have no audible
heart murmur.

Diagnosis

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suggested by clinical examination, supported by chest x-ray and ECG, and established by 2-
dimensional echocardiography with color flow and Doppler studies.
Chest x-ray and ECG are typically normal if the PDA is small. If the shunt is significant, chest x-ray shows prominence of the left atrium, left ventricle, and ascending aorta and increased pulmonary vascular markings; ECG may show left ventricular hypertrophy. Cardiac catheterization is not necessary unless used for therapy.

**Treatment**

- Prostaglandin synthesis inhibitor therapy (eg, indomethacin, ibuprofen)
- Sometimes transcatheter occlusion devices or surgical repair

[Table 293-4. Indomethacin Dosing Guidelines (mg/kg)]

In premature infants with compromised respiratory status, the PDA can sometimes be closed by using a prostaglandin synthesis inhibitor (eg, indomethacin [see Table 293-4 for doses] IV q 12 h for 3 doses or ibuprofen 10 mg/kg po followed by 2 doses of 5 mg/kg at 24-h intervals) with or without fluid restriction. If this treatment is ineffective, surgical ligation is indicated.

In full-term infants, indomethacin is usually ineffective. Transcatheter closure has become the treatment of choice in children > 1 yr; a variety of catheter-delivered occlusion devices are available (eg, coils, Amplatzer® duct occluder). In infants < 1 yr or who have certain anatomic varieties of the ductus, surgical division and ligation may be preferred over the transcatheter approach. For a PDA with a shunt large enough to cause symptoms of HF or pulmonary hypertension, closure should be done after medical stabilization. For a persistent PDA without HF or pulmonary hypertension, closure can be done electively any time after 1 yr. Outcomes after PDA closure are excellent.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after closure or if there is a residual defect adjacent to a transcatheter-placed device or surgical material.

**Coarctation of the Aorta**

Coarctation of the aorta is a localized narrowing of the aortic lumen that results in upper-extremity hypertension, left ventricular hypertrophy, and malperfusion of the abdominal organs and lower extremities. Symptoms vary with the anomaly's severity and range from headache, chest pain, cold extremities, fatigue, and leg claudication to fulminant heart failure and shock. A soft bruit may be heard over the coarctation site. Diagnosis is by echocardiography or by CT or MR angiography. Treatment is balloon angioplasty with stent placement, or surgical correction.

Coarctation of the aorta accounts for 6 to 8% of congenital heart anomalies. It occurs in 10 to 20% of patients with Turner's syndrome. The male:female ratio is 2:1.

**Pathophysiology**

Coarctation of the aorta usually occurs at the proximal thoracic aorta just beyond the left subclavian artery. It rarely involves the abdominal aorta. Coarctation may occur alone or with various other congenital anomalies (eg, bicuspid aortic valve, ventricular septal defect, aortic stenosis, patent ductus arteriosus, mitral valve disorders, intracerebral aneurysms).

Physiologic consequences include left ventricular pressure overload, left ventricular hypertrophy, hypertension in the upper part of the body including the brain, and malperfusion of the abdominal organs and lower extremities. Malperfusion of the intestines increases the risk of sepsis due to enteric organisms.

Untreated coarctation may result in left ventricular failure, rupture of the aorta, intracranial hemorrhage, hypertensive encephalopathy, and hypertensive cardiovascular disease during adulthood.
Symptoms and Signs

If coarctation is significant, circulatory shock with renal insufficiency (oliguria or anuria) and metabolic acidosis may develop in the first 7 to 10 days of life and may mimic findings of other systemic disorders such as sepsis.

Less severe coarctation may be asymptomatic during infancy. Subtle symptoms (eg, headache; chest pain, fatigue, and leg claudication during physical activities) may be present as children age. Hypertension is often present, but heart failure (HF) rarely develops after the neonatal period. Rarely, intracerebral aneurysms rupture, resulting in subarachnoid or intracerebral hemorrhage.

Typical physical examination findings include hypertension in the upper extremities, diminished or delayed femoral pulses, and low or unobtainable arterial BP in the lower extremities. A grade 2 to 3/6 ejection systolic murmur is often present at the upper left sternal border, left axilla, and sometimes most prominently in the left interscapular area. An apical ejection click is present if a bicuspid aortic valve is also present. Dilated intercostal collateral arteries may cause a continuous murmur in the intercostal spaces. Affected females may have Turner’s syndrome, a congenital disorder causing lymphedema of the feet, webbed neck, squarely shaped chest, cubitus valgus, and widely spaced nipples.

Diagnosis

- Chest x-ray and ECG
- Echocardiography or CT or MR angiography

Diagnosis is suggested by clinical examination (including BP measurement in all 4 extremities), supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies or with CT or MR angiography.

Chest x-ray shows coarctation as a “3” sign in the upper left mediastinal shadow. Heart size is normal unless HF supervenes. Dilated intercostal collateral arteries may erode the 3rd to 8th ribs, causing rib notching, but this is seldom seen before age 5 yr.

ECG usually shows left ventricular hypertrophy but may be normal. In neonates and small infants, ECG usually shows right ventricular hypertrophy rather than left ventricular hypertrophy.

Treatment

- For symptomatic neonates, prostaglandin E₁ infusion
- For hypertension, β-blockers
- Surgical correction or balloon angioplasty (sometimes with stent placement)

Symptomatic neonates require cardio-pulmonary stabilization with infusion of prostaglandin E₁ (0.05 to 0.10 μg/kg/min—may titrate up to 0.4 μg/kg/min then back down to lowest effective dose) to reopen the constricted ductus arteriosus. Opening the ductus and its aortic ampulla provides some relief of the aortic obstruction and allows pulmonary artery blood to increase perfusion of the descending aorta through the ductus, improving systemic perfusion and reversing metabolic acidosis. IV cardioactive drugs (eg, milrinone, dopamine, dobutamine), diuretics, and O₂ are used to treat HF.

In nonemergent situations, patients with hypertension may be treated with β-blockers; ACE inhibitors may adversely affect renal function. After repair of the coarctation, hypertension may persist or develop years after repair and can be treated with β-blockers, ACE inhibitors, angiotensin II receptor blockers, or Ca channel blockers.

The preferred definitive treatment is controversial. Some centers prefer balloon angioplasty with or
without stent placement, but most prefer surgical correction and reserve the balloon procedure for recoarctation after surgical correction or for primary treatment of discrete coarctation in older children or adolescents. Initial success rate after balloon angioplasty is 80 to 90%; subsequent catheterization can dilate the stent as children grow.

Surgical options include resection and end-to-end anastomosis, patch aortoplasty, and left subclavian flap aortoplasty. In severe coarctation manifesting early in life, the transverse aorta and isthmus are often hypoplastic, and this region of the aorta may need to be surgically enlarged. Choice of surgical technique depends on anatomy and center preference. Surgical mortality rate is < 5% for symptomatic infants and < 1% for older children. Residual coarctation is common (6 to 33%). Rarely, paraplegia results from cross-clamping of the aorta during surgery.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

**Tetralogy of Fallot**

**Tetralogy of Fallot** consists of 4 features: a large ventricular septal defect, right ventricular outflow tract and pulmonary valve obstruction, right ventricular hypertrophy, and over-riding of the aorta. Symptoms include cyanosis, dyspnea with feeding, poor growth, and tet spells (sudden, potentially lethal episodes of severe cyanosis). A harsh systolic murmur at the left upper sternal border with a single 2nd heart sound (S₂) is common. Diagnosis is by echocardiography or cardiac catheterization. Definitive treatment is surgical repair.

Tetralogy of Fallot (see [Fig. 293-6](#)) accounts for 7 to 10% of congenital heart anomalies. Associated anomalies include right aortic arch (25%), abnormal coronary artery anatomy (5%), stenosis of the pulmonary artery branches, presence of aortico pulmonary collateral vessels, patent ductus arteriosus, complete atrioventricular septal defect, atrial septal defect, additional muscular ventricular septal defects (VSDs), and aortic valve regurgitation.

**Pathophysiology**

The VSD is typically large; thus, systolic pressures in the right and left ventricles (and in the aorta) are the same. Pathophysiology depends on the degree of right ventricular outflow obstruction. A mild obstruction may result in a left-to-right shunt through the VSD; a severe obstruction causes a right-to-left shunt, resulting in low systemic arterial saturation (cyanosis) that is unresponsive to supplemental O₂.

In some children with tetralogy of Fallot, most often those several months up to 2 yr of age, sudden episodes of profound cyanosis and hypoxia (tet spell) may occur, which may be lethal. A spell may be triggered by any event that slightly decreases O₂ saturation (eg, crying, defecating) or that suddenly decreases systemic vascular resistance (eg, playing, kicking legs when awakening) or by sudden onset of tachycardia or hypovolemia. The mechanism of a tet spell remains uncertain, but several factors are probably important in causing an increase in right to left shunting and a fall in arterial saturation. Factors include an increase in right ventricular outflow tract obstruction and a decrease in systemic resistance—a vicious circle caused by the initial fall in arterial PO₂, which stimulates the respiratory center and causes hyperpnea and increased adrenergic tone. The increased circulating catecholamines then stimulate increased contractility, which increases outflow tract obstruction.

![Fig. 293-6. Tetralogy of Fallot.]

**Symptoms and Signs**

Neonates with severe right ventricular outflow obstruction (or atresia) have severe cyanosis and dyspnea with feeding with poor weight gain. But those with mild obstruction may not have cyanosis at rest.

**Tet spells** may be precipitated by activity and are characterized by paroxysms of hyperpnea (rapid and
deep respirations), irritability and prolonged crying, increasing cyanosis, and decreasing intensity of the heart murmur. The spells occur most often in young infants; peak incidence is age 2 to 4 mo. A severe spell may lead to limpnness, seizures, and occasionally death. During play, some toddlers may intermittently squat, a position that increases systemic vascular resistance and aortic pressure, which decreases right to left ventricular shunting and thus raises arterial O\textsubscript{2} saturation.

Auscultation detects a harsh grade 3 to 5/6 systolic ejection murmur at the left mid and upper sternal border. The murmur in tetralogy is always due to the pulmonary stenosis; the VSD is silent because it is large and has no pressure gradient. The 2nd heart sound (S\textsubscript{2}) is often single because the pulmonary component is markedly reduced. A prominent right ventricular impulse and a systolic thrill may be present.

Diagnosis

• Chest x-ray and ECG
• Echocardiography

Diagnosis is suggested by history and clinical examination, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies. Chest x-ray shows a boot-shaped heart with a concave main pulmonary artery segment and diminished pulmonary vascular markings. A right aortic arch is present in 25%. ECG shows right ventricular hypertrophy and may also show right atrial hypertrophy. Cardiac catheterization is rarely needed, unless there is suspicion of a coronary anomaly that might affect the surgical approach (eg, anterior descending arising from the right coronary artery) that cannot be clarified with echocardiography.

Treatment

• For symptomatic neonates, prostaglandin E\textsubscript{1} infusion
• For tet spells, positioning, calming, O\textsubscript{2}, and sometimes drugs
• Surgical repair

Neonates with severe cyanosis may be palliated with an infusion of prostaglandin E\textsubscript{1} (0.05 to 0.1 \textmu g/kg/min IV) to open the ductus arteriosus.

Tet spells: Tet spells are treated by placing infants in a knee-chest position (older children usually squat spontaneously and do not develop tet spells), establishing a calm environment, and giving O\textsubscript{2}. If the spell persists, options (roughly in order of preference) include morphine 0.1 to 0.2 mg/kg IV or IM, IV fluids for volume expansion, NaHCO\textsubscript{3} 1 mEq/kg IV, and propranolol starting at 0.02 to 0.05 mg/kg, titrated up to 0.1 to 0.2 mg/kg IV if needed for effect. If these measures do not control the spell, systemic BP can be increased with ketamine 0.5 to 3 mg/kg IV or 2 to 3 mg/kg IM (ketamine also has a beneficial sedating effect) or phenylephrine starting at 5 \textmu g/kg and titrating up to 20 \textmu g/kg IV for effect. Ultimately, if the preceding steps do not relieve the spell or if the infant is rapidly deteriorating, intubation with muscle paralysis and general anesthesia may be necessary. Propranolol 0.25 to 1 mg/kg po q 6 h may prevent recurrences, but most experts feel that even one significant spell indicates the need for expeditious surgical repair.

Definitive management: Complete repair consists of patch closure of the VSD, widening of the right ventricular outflow tract with muscle resection and pulmonary valvuloplasty, and a limited patch across the pulmonic annulus or main pulmonary artery if necessary. Surgery is usually done electively at age 3 to 6 mo but can be done at any time if symptoms are present.

In neonates and very small infants with complex anatomy, initial palliation may be preferred to complete repair; the usual procedure is a modified Blalock-Taussig shunt, in which the subclavian artery is connected to the ipsilateral pulmonary artery with a synthetic graft.
Perioperative mortality rate for complete repair is < 5% for uncomplicated tetralogy of Fallot. For untreated patients, survival rates are 55% at 5 yr and 30% at 10 yr.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

**Transposition of the Great Arteries**

Transposition of the great arteries (TGA) occurs when the aorta arises directly from the right ventricle and the pulmonary artery arises from the left ventricle, resulting in independent, parallel pulmonary and systemic circulations; oxygenated blood cannot reach the body except through openings connecting the right and left sides (eg, patent foramen ovale, ventricular septal defect [VSD]). Symptoms are primarily severe neonatal cyanosis and occasionally heart failure, if there is an associated VSD. Heart sounds and murmurs vary depending on the presence of associated congenital anomalies. Diagnosis is by echocardiography. Definitive treatment is surgical repair.

TGA (see Fig. 293-7) accounts for 5 to 7% of congenital heart anomalies. About 30 to 40% of patients have a VSD; 5% have subpulmonary stenosis.

**Pathophysiology**

Systemic and pulmonary circulations are completely separated. After returning to the right heart, desaturated systemic venous blood is pumped into the systemic circulation without being oxygenated in the lungs; oxygenated blood entering the left heart goes back to the lungs rather than to the rest of the body. This anomaly is not compatible with life unless desaturated and oxygenated blood can mix through openings at one or more levels (eg, atrial, ventricular, or great artery level).

[Fig. 293-7. Transposition of the great arteries.]

**Symptoms and Signs**

Severe cyanosis occurs within hours of birth, progressing rapidly to metabolic acidosis secondary to poor tissue oxygenation. Patients with a large VSD, a patent ductus arteriosus, or both are less cyanotic, but symptoms and signs of heart failure (eg, tachypnea, dyspnea, tachycardia, diaphoresis, inability to gain weight) may develop during the first 3 to 6 wk of life.

Except for generalized cyanosis, physical examination is usually unremarkable. Heart murmurs may be absent unless associated anomalies are present. The 2nd heart sound (S2) is single and loud.

**Diagnosis**

- Chest x-ray and ECG

- Echocardiography

Diagnosis is suspected clinically, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

On chest x-ray, the cardiac shadow may have the classic egg-on-a-string appearance with a narrow upper mediastinum. ECG shows right ventricular hypertrophy but may be normal for a neonate.

Cardiac catheterization is not usually necessary for diagnosis but may be done to enlarge the atrial communication.

**Treatment**
• Prostaglandin E₁ (PGE₁) infusion
• Sometimes balloon atrial septostomy
• Surgical repair

Unless arterial O₂ saturation is only mildly decreased and the atrial communication is adequate, a PGE₁ infusion (0.05 to 0.1 μg/kg/min IV) is used to open and maintain patency of the ductus arteriosus; this infusion increases pulmonary blood flow, which promotes left to right atrial shunting, leading to improved systemic oxygenation. Metabolic acidosis is corrected via infusion of NaHCO₃. Pulmonary edema and respiratory failure may require intubation and mechanical ventilation.

For severely hypoxemic neonates who do not immediately respond to PGE₁ or who have a very restrictive foramen ovale, cardiac catheterization and balloon atrial septostomy (Rashkind's procedure) can immediately improve systemic arterial O₂ saturation. A balloon-tipped catheter is advanced into the left atrium through the patent foramen ovale. The balloon is inflated with diluted radiopaque dye and abruptly withdrawn to the right atrium to enlarge the opening in the atrial septum. As an alternative to taking the neonate to the catheterization laboratory, the septostomy procedure can be done at the bedside under echocardiographic guidance.

Definitive repair is the arterial switch (Jatene) operation, typically done during the first week of life. The proximal portions of the great arteries are transected, the coronary arteries are transplanted to the native pulmonary root (which will become the neoaortic root), and the aorta is connected to the left ventricle and the pulmonary artery is connected to the right ventricle. Survival rate after surgery is > 95%. An associated VSD should be closed at the time of primary repair unless it is small and hemodynamically insignificant. Pulmonic stenosis is problematic unless it can be addressed surgically at the time of the arterial switch procedure.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

Tricuspid Atresia

Tricuspid atresia is absence of the tricuspid valve accompanied by a hypoplastic right ventricle. Associated anomalies are common and include atrial septal defect, ventricular septal defect, patent ductus arteriosus, and transposition of the great arteries. Symptoms include cyanosis and those of heart failure. The 2nd heart sound (S₂) is single, and murmurs depend on the presence of associated anomalies. Diagnosis is by echocardiography or cardiac catheterization. Definitive treatment is surgical repair.

Tricuspid atresia accounts for 1 to 3% of congenital heart anomalies. The most common type (sometimes referred to as classic tricuspid atresia) includes a ventricular septal defect (VSD) and pulmonary stenosis, which results in decreased pulmonary blood flow, elevated right atrial pressure, and an obligatory right-to-left shunt at the atrial level through a stretched patent foramen ovale or an atrial septal defect (ASD), causing cyanosis (see Fig. 293-8). In 12 to 25% of cases, the great arteries are transposed with a VSD and a normal pulmonary valve, with unrestricted pulmonary blood flow coming directly from the left ventricle, typically resulting in heart failure (HF) and pulmonary hypertension.

Symptoms and Signs

Infants with decreased pulmonary blood flow usually have mild to moderate cyanosis at birth, which increases, sometimes dramatically, over the first several months of life. Infants with increased pulmonary blood flow usually show signs of HF (eg, tachypnea, dyspnea with feeding, poor weight gain, diaphoresis) by age 4 to 6 wk.

[Fig. 293-8. Tricuspid atresia.]
Physical examination usually detects a single 2nd heart sound (S₂) and a grade 2 to 3/6 holosystolic or early systolic murmur of a VSD at the lower left sternal border. A systolic ejection murmur of pulmonary stenosis or a continuous murmur of patent ductus arteriosus may be present in the upper left sternal border. A systolic thrill is rarely palpable. An apical diastolic rumble may be audible if pulmonary blood flow is markedly increased. Cyanosis, when present for > 6 mo, may result in clubbing.

**Diagnosis**

- Chest x-ray and ECG
- Echocardiography
- Usually cardiac catheterization

Diagnosis is suspected clinically, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

In the most common form, chest x-ray shows normal or slightly increased heart size, right atrial enlargement, and decreased pulmonary vascular markings. Occasionally, the cardiac silhouette resembles that of tetralogy of Fallot (with a boot-shaped heart and concave pulmonary artery segment). Pulmonary vascular markings may be increased and cardiomegaly may be present in infants with associated transposition of the great arteries. ECG characteristically shows left axis deviation (between 0° and -90°) and left ventricular hypertrophy. Left axis deviation is not usually present if there is associated transposition of the great arteries. Right atrial or combined atrial enlargement is also common.

Cardiac catheterization may be necessary before the first palliative procedure to define hemodynamics and pulmonary artery anatomy unless echocardiography or other modalities clearly show the pulmonary vascular anatomy and confidently predict normal pulmonary artery pressures.

**Treatment**

- For severely cyanotic neonates, prostaglandin E₁ infusion
- Sometimes balloon atrial septostomy
- Staged surgical repair

Most neonates with tricuspid atresia, although cyanotic, are well compensated in the first several weeks of life. In severely cyanotic neonates, prostaglandin E₁ (beginning at 0.05 to 0.1 μg/kg/min IV) is infused to prevent closure of the ductus arteriosus or to reopen the constricted ductus before cardiac catheterization or surgical repair.

Although not usually required, balloon atrial septostomy (Rashkind’s procedure) may be done as part of the initial catheterization to decompress the right atrium and facilitate unrestricted right-to-left atrial shunting when the interatrial communication is inadequate. Some infants with transposition of the great arteries and signs of HF require medical treatment (eg, diuretics, digoxin, ACE inhibitors—see p. 2949).

Definitive repair requires staged operations. If intervention is needed within the first 4 to 8 wk of life, a modified Blalock-Taussig shunt (connection of a systemic and a pulmonary artery by a Gore-Tex tube) is done. Otherwise, if the infant remains stable with good growth, the first procedure would be a bidirectional Glenn shunt (anastomosis between the superior vena cava and right pulmonary artery) at 3 to 6 mo, then a modified Fontan procedure is done by 2 yr. The Fontan procedure involves diverting the inferior vena cava flow directly to the pulmonary artery, usually by an extracardiac conduit, completely bypassing the right atrium. The proximal pulmonary root is ligated, which prevents anterograde flow across the pulmonary outflow tract, and an adequate interatrial opening is created, if not already present, to allow equalization of right and left atrial pressures and free communication between these chambers.
Because the systemic venous and conduit pressure must be at least 3 to 5 mm Hg greater than the left atrial pressure to provide an adequate transpulmonary pressure gradient for pulmonary blood flow, a fenestration (small opening) is frequently made between the conduit and the right atrium. Right-to-left shunting from the conduit to the atria and left ventricle allows decompression of the systemic venous pressure and improvement in cardiac output, albeit at the expense of mild arterial desaturation. This approach has increased early survival rates to > 90%, 5-yr survival rates to > 80%, and 10-yr survival rates to > 70%.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

**Hypoplastic Left Heart Syndrome**

Hypoplastic left heart syndrome consists of hypoplasia of the left ventricle and ascending aorta, maldevelopment and hypoplasia of the aortic and mitral valves (frequently aortic atresia is present), an atrial septal defect, and a large patent ductus arteriosus. Unless normal closure of the patent ductus arteriosus is prevented with prostaglandin infusion, cardiogenic shock and death ensue. A loud, single 2nd heart sound (S₂) and nonspecific systolic murmur are common. Diagnosis is by emergency echocardiography. Definitive treatment is staged surgical correction or heart transplantation.

Hypoplastic left heart syndrome accounts for 2% of congenital heart anomalies. Because the mitral valve, left ventricle, and aortic valve are hypoplastic (often with aortic atresia), oxygenated blood coming into the left atrium from the lungs is diverted across the atrial communication into the right heart, where it mixes with desaturated systemic venous return (see Fig. 293-9). This relatively desaturated blood exits the right ventricle through the pulmonary artery to the lungs and through the ductus arteriosus to the systemic circulation. Systemic blood flow is maintained only through the right-to-left ductal shunt; thus immediate survival depends on patency of the ductus arteriosus.

**Symptoms and Signs**

Symptoms appear when the ductus arteriosus begins to close during the first 24 to 48 h of life. Subsequently, the clinical picture of cardiogenic shock (eg, tachypnea, dyspnea, weak pulse, pallor, cyanosis, hypothermia, metabolic acidosis, lethargy, oliguria or anuria) rapidly develops. When systemic circulation is compromised, coronary and cerebral perfusion may be reduced, leading to symptoms of myocardial or cerebral ischemia. If the ductus arteriosus is not reopened, death rapidly ensues.

Physical examination shows a very active precordium with a marked parasternal lift associated with very poor peripheral perfusion, cool extremities, bluish gray skin color, and absent or barely palpable pulses. The 2nd heart sound (S₂) is loud and single. Occasionally, a soft, nonspecific systolic murmur is present. Severe metabolic acidosis out of proportion to the PO₂ and PCO₂ is characteristic.

**Diagnosis**

- Chest x-ray and ECG
- Echocardiography

Diagnosis is suspected clinically and confirmed by emergency echocardiography with color flow and Doppler studies. Cardiac catheterization is rarely required.

Chest x-ray shows cardiomegaly and pulmonary venous congestion or pulmonary edema. ECG shows right ventricular hypertrophy.
Treatment

• Prostaglandin E$_1$ (PGE$_1$) infusion

• Staged surgical repair

• Sometimes heart transplantation

All affected infants should be stabilized immediately in a neonatal ICU. Vascular access should be established, usually via an umbilical venous catheter; then PGE$_1$ (beginning at 0.05 to 0.1 μg/kg/min IV) is infused to prevent closure of the ductus arteriosus or to reopen a constricted ductus. Neonates usually require intubation and mechanical ventilation. Metabolic acidosis is corrected via infusion of NaHCO$_3$.

Severely ill neonates with cardiogenic shock may require inotropic drugs (eg, milrinone) and diuretics to improve cardiac function and control volume status. It is critical to keep pulmonary vascular resistance relatively high and systemic vascular resistance low in order to prevent marked pulmonary overcirculation at the expense of systemic perfusion. These resistance ranges are maintained by avoiding hyperoxia, alkalosis, and hypocarbia, all of which may lead to pulmonary vasodilation. Because O$_2$ is one of the most potent pulmonary vasodilators, infants are ventilated with room air or even hypoxic mixtures to aim for systemic saturations of 70 to 80%. If the infant requires mechanical ventilation, PCO$_2$ can be controlled in the high normal or mildly elevated range. Systemic vascular resistance is managed by avoiding, or minimizing, the use of vasoconstricting drugs (eg, epinephrine or high-dose dopamine). Milrinone may be beneficial because it can cause systemic vasodilation.

Survival ultimately requires staged procedures that enable the right ventricle to function as the systemic ventricle. Stage 1, done during the first week of life, is the Norwood procedure. The main pulmonary artery is divided, the distal stump is closed with a patch, and the ductus arteriosus is ligated. Then, a right-sided modified Blalock-Taussig shunt (see p. 2959) or right ventricular-pulmonary artery conduit (Sano modification) is done; the atrial septum is enlarged, and the proximal pulmonary artery and hypoplastic aorta are connected with an aortic or pulmonary artery allograft to create a neoaorta. Stage 2, done at 3 to 6 mo of age, consists of a bidirectional Glenn operation (end-to-side connection of the superior vena cava to the right pulmonary artery). The 3rd stage, done at 18 to 36 mo, is a modified Fontan procedure (see p. 2962). Survival rate is 75% for stage 1, 95% for stage 2, and 90% for stage 3. Overall survival rate is 70% at 5 yr after surgical correction. Many survivors have neurodevelopmental disabilities, which may be due to preexisting developmental abnormalities of the CNS or to overt or occult CNS hypoperfusion or thromboemboli occurring during the multistage procedures.

In some centers, heart transplantation is the procedure of choice; however, PGE$_1$ infusion must be continued along with careful management of pulmonary and systemic vascular resistance until a donor heart is available. Because availability of donor hearts is very limited, about 20% of infants die while waiting for one. The 5-yr survival rates after transplantation and after multistage surgery are similar. After heart transplantation, immunosuppressants are required. These drugs make patients more susceptible to infections and cause pathologic changes in the coronary arteries of the transplanted heart in >50% of patients over a 5-yr period. The only known treatment for allograft coronary artery disease is retransplantation.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

Total Anomalous Pulmonary Venous Return

In total anomalous pulmonary venous return, the pulmonary veins do not connect to the left atrium. Instead, the entire pulmonary venous return enters the systemic venous circulation through a variety of connections. If there is no obstruction to pulmonary venous return, cyanosis is mild and heart failure develops within the first 2 to 4 wk of life. Severe obstruction of the pulmonary venous return may occur, resulting in severe neonatal cyanosis, pulmonary edema, and pulmonary hypertension. Diagnosis is by echocardiography. Surgical repair is
Total anomalous pulmonary venous return (see Fig. 293-10) accounts for 1 to 2% of congenital heart anomalies. The clinical manifestation depends on the connection between the pulmonary venous confluence and the right side of the circulation. The most common types include:

- Return via an ascending left vertical vein that drains to the innominate vein
- A descending vein that drains infradiaphragmatically to the portal circulation
- Connection of the confluence to the coronary sinus

The infradiaphragmatic drainage type is invariably severely obstructed, leading to dramatic pulmonary edema and cyanosis unresponsive to \( \text{O}_2 \). The other 2 types do not typically involve obstruction and lead to heart failure (HF) and mild cyanosis in the first month of life.

**Symptoms and Signs**

Neonates with obstructed pulmonary venous return present with severe pulmonary hypertension, pulmonary edema, and cyanosis. Physical examination usually shows a parasternal lift and a single, loud 2nd heart sound (S\(_2\)), with no significant murmur.

If pulmonary venous return is not obstructed, symptoms of HF are prominent and physical examination detects a hyperdynamic precordium, a loud and split S\(_2\), and a grade 2 to 3/6 systolic ejection murmur audible along the left sternal border. A mid-diastolic tricuspid flow murmur may be audible at the lower left sternal border.

**Diagnosis**

- Chest x-ray and ECG
- Echocardiography

Diagnosis is suspected by chest x-ray and established by 2-dimensional echocardiography with color flow and Doppler studies. Cardiac catheterization is rarely necessary; occasionally, cardiac MRI or CT angiography may need to be done to better delineate the anatomy of pulmonary venous return.

Chest x-ray shows a small heart and severe diffuse pulmonary edema when there is pulmonary venous obstruction; otherwise, there is cardiomegaly with increased pulmonary vascular markings. ECG shows right axis deviation, right ventricular hypertrophy, and occasionally right atrial enlargement.

**Treatment**

- Surgical repair
- Medical treatment of HF (eg, diuretics, digoxin, ACE inhibitors) before surgery

Neonates with infradiaphragmatic return with obstruction require emergent surgical repair. In older infants, HF should be treated, followed by surgical repair as soon as the infant is stabilized.

Surgical repair consists of creating a wide anastomosis between the pulmonary venous confluence and the posterior wall of the left atrium, along with ligation of the vein decompressing the confluence into the systemic venous circulation. The repair is different for return to the coronary sinus, in which case the
coronary sinus is unroofed into the left atrium and its opening to the right atrium is closed.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

**Persistent Truncus Arteriosus**

Persistent truncus arteriosus occurs when, during fetal development, the primitive truncus does not divide into the pulmonary artery and aorta, resulting in a single, large, arterial trunk that overlies a large, malaligned, perimembranous ventricular septal defect. Consequently, a mixture of oxygenated and deoxygenated blood enters systemic, pulmonary, and coronary circulations. Symptoms include cyanosis and heart failure, with poor feeding, diaphoresis, and tachypnea. A normal 1st heart sound (S₁) and a loud, single 2nd heart sound (S₂) are common; murmurs may vary. Diagnosis is by echocardiography or cardiac catheterization. Medical treatment for heart failure is typically followed by early surgical repair.

Persistent truncus arteriosus (see [Fig. 293-11](#)) accounts for 1 to 2% of congenital heart anomalies. About 35% of patients have 22q11 deletion syndrome, which includes DiGeorge syndrome and velocardiofacial syndromes.

**Classification:** There are 3 types.

- **Type I:** The main pulmonary artery arises from the truncus and then divides into the right and left pulmonary arteries.
- **Type II:** The right and left pulmonary arteries arise separately (but adjacent to each other) from the posterior aspect of the truncus.
- **Type III:** The right and left pulmonary arteries arise from the lateral aspects of the truncal root reasonably distant from each other.

[Fig. 293-11. Truncus arteriosus.]

Previously, a type IV was defined, in which arteries supplying blood to the lungs arose from the descending aorta. However, this anomaly is now placed in the category of tetralogy of Fallot with pulmonary atresia.

Other anomalies (eg, truncal valve insufficiency, right aortic arch, interrupted aortic arch, coronary artery anomalies, atrioventricular septal defect) may be present and may contribute to the high surgical mortality rate.

Physiologic consequences of truncus arteriosus include mild cyanosis, significant pulmonary overcirculation, and heart failure (HF).

**Symptoms and Signs**

Infants usually present with mild cyanosis and symptoms and signs of HF (eg, tachypnea, poor feeding, diaphoresis) in the first few weeks of life. Physical examination may detect a hyperdynamic precordium, increased pulse pressure with bounding pulses, a loud and single 2nd heart sound (S₂), and an ejection click. A grade 2 to 4/6 systolic murmur is audible along the left sternal border. A mid-diastolic mitral flow murmur may be audible at the apex when pulmonary blood flow is increased. With truncal valve insufficiency, a high-pitched diastolic decrescendo murmur is audible over the mid left sternal border.

**Diagnosis**

- Chest x-ray and ECG
- Echocardiography
Occasionally cardiac catheterization, cardiac MRI, or CT angiography

Diagnosis is suspected clinically, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies. Cardiac catheterization is occasionally necessary to delineate associated anomalies before surgery, but cardiac MRI or CT angiography may supplant the need for catheterization.

Chest x-ray shows varying degrees of cardiomegaly with increased pulmonary vascular markings, right aortic arch (in about 30%), and relatively high position of pulmonary arteries. ECG commonly shows combined ventricular hypertrophy. Substantial pulmonary overcirculation may produce evidence of left atrial enlargement.

Treatment

- Surgical repair
- Medical treatment of HF (eg, diuretics, digoxin, ACE inhibitors) before surgery

HF is treated vigorously with diuretics, digoxin, and ACE inhibitors, followed by early surgical repair. Prostaglandin infusion is not beneficial.

Surgical management consists of complete repair. The ventricular septal defect is closed so that the left ventricle ejects into the truncal root. A conduit with or without a valve is placed between the right ventricle and the confluence of the pulmonary arteries. Surgical mortality rates have decreased to as low as 10% in recent years. Because the conduit is placed during early infancy, its size becomes inadequate as children grow, and the conduit must be revised during childhood.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

Eisenmenger's Syndrome

(Pulmonary Vascular Obstructive Disease)

Eisenmenger's syndrome is a complication of uncorrected congenital heart anomalies that cause left-to-right shunting. Increased pulmonary resistance may develop over time, reversing left-to-right shunting to right-to-left shunting. Deoxygenated blood enters the systemic circulation, causing symptoms of hypoxia. Murmurs and heart sounds depend on the underlying anomaly. Diagnosis is by echocardiography or cardiac catheterization. Treatment is generally supportive, but heart and lung transplantation may be an option when symptoms are severe. Endocarditis prophylaxis is recommended.

Congenital heart anomalies that, if untreated, result in Eisenmenger's syndrome include

- Ventricular septal defect
- Atrioventricular canal defect
- Atrial septal defect
- Patent ductus arteriosus
- Persistent truncus arteriosus
- Transposition of the great arteries

In the US, the incidence has markedly decreased because of early diagnosis and definitive repair of the
Right-to-left shunting due to Eisenmenger's syndrome results in cyanosis and its complications. Systemic desaturation leads to clubbing of fingers and toes, secondary polycythemia, hyperviscosity, hemoptysis, CNS events (eg, brain abscess or cerebrovascular accident), and sequelae of increased RBC turnover (eg, hyperuricemia causing gout, hyperbilirubinemia causing cholelithiasis, iron deficiency with or without anemia).

Symptoms and Signs

Symptoms usually do not occur until age 20 to 40 yr; they include cyanosis, syncope, dyspnea during exertion, fatigue, chest pain, palpitations, atrial and ventricular arrhythmias, and rarely right heart failure (eg, hepatomegaly, peripheral edema, jugular venous distention).

Hemoptysis is a late symptom. Signs of cerebral embolic phenomena, brain abscess, or endocarditis may develop.

Secondary polycythemia commonly causes symptoms (eg, transient ischemic attacks with slurred speech or other neurologic symptoms, visual problems, headaches, increased fatigue, signs of thromboembolism). Abdominal pain may result from cholelithiasis.

Physical examination detects central cyanosis and digital clubbing. Rarely, signs of right ventricular failure (see p. 2947) may be present. A holosystolic murmur of tricuspid regurgitation may be present at the lower left sternal border. An early diastolic, decrescendo, high-pitched murmur of pulmonary insufficiency may be audible along the left sternal border. A loud, single 2nd heart sound (S2) is a constant finding; an ejection click is common. Scoliosis is present in about one third of patients.

Diagnosis

• Chest x-ray and ECG

• Echocardiography or cardiac catheterization

Diagnosis is suspected by history of uncorrected cardiac anomalies, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies or cardiac catheterization.

Laboratory testing shows polycythemia with Hct > 55%. Increased RBC turnover may be reflected as an iron deficiency state (eg, microcythemia), hyperuricemia, and hyperbilirubinemia.

Chest x-ray usually shows prominent central pulmonary arteries, peripheral pulmonary vessel pruning, and right heart enlargement. ECG shows right ventricular hypertrophy, right axis deviation, and, occasionally, right atrial enlargement.

Treatment

• Drugs to lower pulmonary artery pressure (eg, prostacyclin antagonists, endothelin antagonists, nitric oxide enhancers)

• Supportive therapy

• Heart and lung transplantation

Ideally, corrective operations should have been done earlier to prevent Eisenmenger's syndrome. There is no specific treatment once the syndrome develops, other than heart and lung transplantation, but drugs that may lower pulmonary artery pressure are being studied. They include prostacyclin antagonists (eg, treprostinil, epoprostenol), endothelin antagonists (eg, bosentan), and nitric oxide enhancers (eg, sildenafil).
Supportive treatment includes avoidance of conditions that may exacerbate the syndrome (eg, pregnancy, volume depletion, isometric exercise, high altitudes) and use of supplemental O\textsubscript{2}. Symptomatic polycythemia can be treated by cautious phlebotomy to lower Hct to 55 to 65% plus simultaneous volume replacement with normal saline. However, compensated and asymptomatic polycythemia does not require phlebotomy, regardless of Hct; phlebotomy eventually leads to iron deficiency and does not change the natural history. Hyperuricemia can be treated with allopurinol 300 mg po once/day. Anticoagulation therapy with warfarin is potentially harmful and its use should be individualized, but aspirin 81 mg po once/day is indicated to prevent thrombotic complications.

Life expectancy depends on type and severity of the underlying congenital anomaly and ranges from 20 to 50 yr; median age at death is 37 yr. However, low exercise tolerance and secondary complications severely limit quality of life.

Heart and lung transplantation may be an option but is reserved for patients with severe symptoms and unacceptable quality of life. Long-term survival after transplantation is not promising.

All patients should be given endocarditis prophylaxis (see Table 215-4 on p. 2200) before dental or surgical procedures that are likely to cause bacteremia.

**Other Less Common Congenital Cardiac Anomalies**

Less frequent structural congenital cardiac anomalies include the following:

- Single ventricle with or without pulmonary stenosis
- Pulmonary atresia with an intact ventricular septum
- Double outlet right ventricle
- Ebstein’s anomaly
- Congenitally corrected transposition

**Single ventricle spectrum:** These anomalies include any complex lesion with only one functional ventricle and include hypoplastic right ventricle (RV) and left ventricle (LV) and, less commonly, a true undifferentiated single ventricular chamber. Surgical management involves ensuring adequate pulmonary blood flow via a systemic-to-pulmonary artery anastomosis (eg, modified Blalock-Taussig shunt [see p. 2959]) for patients with decreased pulmonary blood flow or protecting the pulmonary vascular bed via pulmonary artery banding if pulmonary overcirculation exists. Later, the Fontan procedure (see p. 2962) can be used as definitive treatment to make the functioning single ventricle solely a systemic ventricle.

**Pulmonary atresia with intact septum:** This anomaly is most frequently associated with a hypoplastic RV and follows the same treatment algorithm as tricuspid atresia (see p. 2961).

**Double outlet right ventricle:** This anomaly is associated with a very wide spectrum of anatomy and physiology depending on the size and location of the ventricular septal defect (VSD), as well as the presence and degree of pulmonic stenosis. In the most common variety with a subaortic VSD, a complete repair is possible with closure of the VSD in such a way as to direct LV outflow to the aorta.

**Ebstein’s anomaly:** This anomaly consists of variable apical displacement and dysplasia of the septal and inferior leaflets of the tricuspid valve with dysplasia, but normal origin, of the anterior leaflet as well. These abnormalities displace the effective valve orifice downward, resulting in compromise of the function of the RV with an atrialized portion that is proximal to the valve opening. This anomaly has been associated with maternal use of lithium during pregnancy. Associated abnormalities include atrial septal defect, pulmonic stenosis, and Wolff-Parkinson-White syndrome.

There is a remarkably wide spectrum of presentation, ranging from severely cyanotic newborns to
cardiomegaly with mild cyanosis in childhood to a previously asymptomatic adult presenting with atrial arrhythmias or reentry supraventricular tachycardia. The onset of symptoms depends on the degree of tricuspid valve anatomic and functional derangement and presence of accessory pathways (eg, Wolff-Parkinson-White syndrome). When symptoms result from a severely dysfunctional tricuspid valve, surgical repair or replacement should be considered.

**Congenitally corrected transposition:** This anomaly is relatively rare and accounts for about 0.5% of congenital cardiac anomalies. The normal embryologic looping of the fetal heart tube is reversed, resulting in atrioventricular and ventriculoarterial discordance. The result is the right atrium connects to a right-sided morphologic LV and the left atrium connects to a left-sided morphologic RV. In almost all cases, the morphologic LV connects to the pulmonary artery and the morphologic RV connects to the aorta. The circulation is thus physiologically “corrected,” but associated anomalies are invariably present, including VSD, pulmonic stenosis, Ebstein’s anomaly of the tricuspid valve, congenital atrioventricular block, mesocardia or dextrocardia, and heterotaxy syndromes. These anomalies result in a wide range of clinical manifestations. As patients reach adulthood, a common concern is development of dysfunction of the morphologic RV, which serves as the systemic ventricle. This dysfunction may be subclinical or manifest as severe cardiomyopathy and heart failure, leading to consideration of heart transplantation.

Rare nonstructural cardiac anomalies include

- Congenital complete heart block
- Congenital metabolic errors leading to cardiomyopathy

See p. 2176 for prolonged QT syndrome and other genetic arrhythmia syndromes with risks of severe and possibly fatal ventricular arrhythmias.
Chapter 294. Congenital Craniofacial and Musculoskeletal Abnormalities

Introduction

Many craniofacial and musculoskeletal abnormalities occur only at a single, specific site. They may be a deformity (alteration in shape due to unusual pressure and malpositioning [eg, clubfoot]) or a malformation (an error in normal organ or tissue development [eg, anencephaly]). Both deformities and malformations affect function. Some abnormalities (eg, arthrogryposis multiplex congenita) affect multiple sites.

Arthrogryposis Multiplex Congenita

(Multiple Congenital Contractures)

Arthrogryposis multiplex congenita (AMC) refers to a variety of conditions that involve congenital limitation of joint movement. Intelligence is relatively normal except when the arthrogryposis is caused by a disorder or syndrome that also affects intelligence.

There are two major types of AMC:

- **Amyoplasia (classic arthrogryposis):** Multiple symmetric contractures occur in the limbs.

- **Distal arthrogryposis:** The hands and feet are involved, but the large joints are spared.

Etiology

Any condition that impairs in utero movement for > 3 wk can result in AMC. Causes may involve

- Physical limitation of movement (eg, due to uterine malformations, multiple gestations, or oligohydramnios)

- Maternal disorders (eg, multiple sclerosis, impaired uterine vascularity)

- Fetal disorders (eg, neuropathies; myopathies, including muscular dystrophies; connective tissue abnormalities; impaired fetal vascularity; anterior horn cell disease)

More than 35 specific genetic disorders (eg, spinal muscular atrophy type I, trisomy 18) have been linked to AMC.

Symptoms and Signs

Deformities are prominent at birth. AMC is not progressive; however, the condition that causes it (eg, muscular dystrophy) may be. Affected joints are contracted in flexion or extension. In classic AMC, shoulders are sloped, adducted, and internally rotated; the elbows are extended; and the wrists and digits are flexed. Hips may be dislocated and are usually slightly flexed. Knees are extended; feet are often in the equinovarus position. Leg muscles are usually hypoplastic, and limbs tend to be tubular and featureless. Soft-tissue webbing sometimes occurs over ventral aspects of the flexed joints. The spine may be scoliotic. Except for slenderness of the long bones, the skeleton appears normal on x-rays. Physical disabilities may be severe. As noted, some children may have primary CNS dysfunction, but intelligence is usually unimpaired.

Endotracheal intubation during surgery may be difficult because children have small immobile jaws. Other abnormalities that rarely accompany arthrogryposis include microcephaly, cleft palate, cryptorchidism, and cardiac and urinary tract abnormalities.

Diagnosis

- **Clinical evaluation**
Testing for cause

Evaluation should include a thorough assessment for associated abnormalities. Electromyography and muscle biopsy are useful to diagnose neuropathic and myopathic disorders. In classic AMC, muscle biopsy typically shows amyoplasia, with fatty and fibrous replacement of tissues.

Treatment

- Joint manipulation and casting
- Sometimes surgical procedures

Early orthopedic and physical therapy evaluations are indicated. Joint manipulation and casting during the first few months of life may produce considerable improvement. Orthotics may help. Surgery may be needed later to align the angle of ankylosis, but mobility is rarely enhanced. Muscle transfers (eg, surgically moving the triceps so that it can flex the elbow) may improve function. Many children do remarkably well; two thirds are ambulatory after treatment.

Congenital Amputations

Congenital amputations are missing or incomplete limbs at birth. Mechanism can involve primary intrauterine growth inhibition or secondary intrauterine destruction of normal embryonic tissues. Etiology is often unclear, but teratogenic agents (eg, thalidomide) and amniotic bands, which are loose strands of amnion that entangle or fuse with fetal tissue, are known causes.

Limb deficiencies can be

- Transverse
- Longitudinal

In transverse deficiencies, all elements beyond a certain level are absent, and the limb resembles an amputation stump. Amniotic bands are the most common cause; the degree of deficiency varies based on the location of the band.

Longitudinal deficiencies involve specific maldevelopments (eg, complete or partial absence of the radius, fibula, or tibia). They may result from syndromes or associations such as VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies and radial aplasia, and limb anomalies).

Infants with transverse or longitudinal limb deficiencies may also have hypoplastic or bifid bones, synostoses, duplications, dislocations, or other bony defects; eg, in proximal femoral focal deficiency, the proximal femur and acetabulum do not develop. One or more limbs may be affected, and the type of defect may be different in each limb. CNS abnormalities are rare. X-rays are essential to determine which bones are involved.

Treatment

- Prosthetic devices

Treatment consists mainly of prosthetic devices, which are most valuable for lower-limb deficiencies and for completely or almost completely absent upper limbs. If any activity in an arm or hand exists, no matter how great the malformation, functioning capacity must be thoroughly assessed before a prosthesis or surgical procedure is recommended. Therapeutic amputation of any limb or portion of a limb should be considered only after evaluating the functional and psychologic implications of the loss and when essential for fitting a prosthesis.
An upper-limb prosthesis should be designed to serve as many needs as possible so that the number of
devices is kept to a minimum. Children use a prosthesis most successfully when it is fitted early and
becomes an integral part of their body and body image during the developmental years. Devices used
during infancy should be as simple and durable as possible; eg, a hook rather than a bioelectric arm. With
effective orthopedic and ancillary support, most children with congenital amputations lead normal lives.

**Craniofacial Abnormalities**

Various craniofacial abnormalities result from maldevelopment of the 1st and 2nd visceral arches, which
form facial bones and ears during the 2nd mo of gestation. Causes include over 500 genetic syndromes
as well as prenatal factors (eg, inadequate folate [folic acid]).

These deformities include cleft lip and cleft palate, various named syndromes (see
Table 294-1), hypertelorism (widely spaced eyes), and many other rarer deformities. Most infants with
craniofacial abnormalities have normal intelligence.

**Cleft palate and cleft lip:** The most common 1st arch deformities are cleft palate and cleft lip, which
occur in 1/700 to 800 births. Both environmental and genetic factors are thought to contribute. Prenatal
maternal use of tobacco and alcohol may increase risk. Having one affected child increases risk of having
a second one. Folate, taken just before becoming pregnant and through the 1st trimester, decreases the
risk.

The cleft may vary from involvement of only the soft palate to a complete fissure of the soft and hard
palates, the alveolar process of the maxilla, and the lip. The mildest form is a bifid uvula. An isolated cleft
lip can occur.

A cleft palate interferes with feeding and speech development and increases the risk of ear infections.
Goals of treatment are to ensure normal feeding, speech, and maxillofacial growth and to avoid formation
of fistulas.

Early treatment, pending surgical repair, depends on the specific abnormality but may include specially
designed bottle nipples (to facilitate flow), dental appliances (to occlude the cleft so suckling can occur), a
feeder that can be squeezed to deliver formula, taping, and an artificial palate molded to the child's own
 palate. The frequent episodes of acute otitis media must be recognized and treated.

Ultimate treatment is surgical closure; however, timing of surgery, which may interfere with growth centers
around the premaxilla, is somewhat controversial. For a cleft palate, a 2-stage procedure is often done. The

[Table 294-1, Common Craniofacial Syndromes]

cleft lip, nose, and soft palate are repaired during infancy (at age 3 to 6 mo). Then, the residual hard
palate cleft is repaired at age 15 to 18 mo. Surgery can result in significant improvement, but if deformities
are severe or treatment is inadequate, patients may be left with a nasal voice, compromised appearance,
and a tendency to regurgitate. Dental and orthodontic treatment, speech therapy, and counseling may be
required.

**Deformities characterized by a small mandible:** These deformities include

- Pierre Robin sequence
- Treacher Collins syndrome

**Pierre Robin sequence** is characterized by glossoptosis (a tongue that falls to the back of the throat)
and respiratory problems. A cleft palate as well as conductive hearing loss may also be present. Feeding
can be difficult, and sometimes cyanosis develops because the tongue is posterior and may obstruct the
pharynx. Prone positioning during feeding may help, but uncoordinated swallowing may require
nasogastric gavage feedings or a gastrostomy tube. If cyanosis or respiratory problems persist,
tracheostomy or surgery to affix the tongue in a forward position (eg, sewing it to the inner lower lip) may be required. Otologic evaluation is indicated.

In Treacher Collins syndrome, which is associated with Pierre Robin sequence, patients have downward slant of the eyes, coloboma of the eyelid, malformed pinna (microtia), and hearing loss.

Surgical extension of the mandible can improve appearance and function. In the typical procedure, called distraction osteogenesis, an osteotomy is done, and a distraction (separator) device is attached to both pieces. Over time, the distance between the 2 pieces is widened, and new bone grows in between to enlarge the mandible.

Agenesis of the jaw: Congenital absence of the condyloid process (and sometimes the coronoid process, the ramus, and parts of the mandibular body) is a severe malformation. The mandible deviates to the affected side, resulting in severe malocclusion; the unaffected side is elongated and flattened. Abnormalities of the external, middle, and inner ears, temporal bone, parotid gland, masticatory muscles, and facial nerve often coexist.

X-rays of the mandible and temporomandibular joint show the degree of underdevelopment and distinguish agenesis from other conditions that result in similar facial deformities but do not involve severe structural loss.

Treatment consists of prompt reconstruction with autogenous bone grafting (costochondral graft) to limit progression of facial deformity. Often, mentoplasty, onlay grafts of bone and cartilage, and soft-tissue flaps and grafts further improve facial symmetry. Distraction osteogenesis is being increasingly used. Orthodontic treatment in early adolescence helps correct malocclusion.

Congenital ear malformations: Microtia and external auditory canal atresia (which causes conductive hearing loss) involve the external ear. These malformations, which frequently coexist, are often identified at or soon after birth. Occasionally, school-based screening tests identify a partially occluded external auditory canal in children with a normal pinna.

Hearing tests (see p. 431) and CT of the temporal bone are necessary to evaluate possible additional bony malformations.

Treatment can include surgery and a bone-conduction hearing aid, depending on whether the malformation is unilateral or bilateral; whether it affects hearing, learning, and social development; and whether complications (eg, facial nerve involvement, cholesteatoma, otitis media) are present. Surgery may include pinna reconstruction and the creation of an external auditory canal, tympanic membrane, and ossicles.

Hip, Leg, and Foot Abnormalities

Orthopedic abnormalities of the hip, leg, and foot are sometimes not apparent at birth. Causes include in utero positioning, ligamentous laxity, and skeletal deformities. Some abnormalities resolve without intervention; however, others require treatment.

Developmental dysplasia of the hip (DDH—formerly congenital dislocation of the hip): DDH is abnormal development of the hip joint, leading to subluxation or dislocation; it can be unilateral or bilateral. It is more common among infants with a breech presentation, especially females, particularly those with a positive family history. It seems to result from laxity of the ligaments around the joint or from in utero positioning. Asymmetric skin creases in the thigh and groin are common, but such creases also occur in infants without DDH. If DDH remains undetected and untreated, the affected leg eventually becomes shorter, and the hip may become painful. Abduction of the hip is often impaired due to adductor spasm.

All infants are screened by physical examination. Because physical examination has limited sensitivity, high-risk infants (and those with abnormalities found during physical examination) typically should have an imaging study.
Two screening maneuvers commonly are used. The Ortolani maneuver detects the hip sliding back into the acetabulum, and the Barlow maneuver detects the hip sliding out of the acetabulum. Each hip is examined separately. Both maneuvers begin with the infant supine and the hips and knees flexed to 90° (the feet will be off the bed). To do the Ortolani maneuver, the thigh of the hip being tested is abducted (ie, the knee is moved away from the midline into a frog-leg position) and gently pulled anteriorly. Instability is indicated by the palpable, sometimes audible, clunk of the femoral head moving over the posterior rim of the acetabulum and relocating in the cavity. Next, in the Barlow maneuver, the hip is returned to the starting position and then slightly adducted (ie, the knee is drawn across the body) and the thigh is pushed posteriorly. A clunk indicates that the head of the femur is moving out of the acetabulum. Also, a difference in knee height when the child is supine with hips flexed, knees bent, and feet on the examining table (Galeazzi sign—see Fig. 294-1) suggests dysplasia, especially unilateral. Somewhat later (eg, by 3 or 4 mo of age), subluxation or dislocation is indicated by inability to completely abduct the thigh when the hip and knee are flexed; abduction is impeded by adductor spasm, which is often present even if the hip is not actually dislocated at the time of examination. Minor benign clicks are commonly detected. Although clicks usually disappear within 1 or 2 mo, they should be checked regularly. Because bilateral dysplasia may be difficult to detect at birth, periodic testing for limited hip abduction during the first year of life is advised.

Ultrasonography of the hips is recommended at 6 wk of age for infants at high risk, including those with a breech presentation, those born with other deformities (eg, torticollis, congenital foot deformity), and girls with a positive family history of DDH.

Imaging is also required when any abnormality is suspected during examination. Hip ultrasonography can accurately establish the diagnosis earlier in life. Hip x-rays are helpful after the bones have started to ossify, typically after age 4 mo.

Early treatment is critical. With any delay, the potential for correction without surgery decreases steadily. The hip usually can be reduced immediately after birth, and with growth, the acetabulum can form a nearly normal joint. Treatment is with devices, most commonly the Pavlik harness, which hold the affected hips abducted and externally rotated. The Frejka pillow and other splints may help. Padded diapers and double or triple diapering are not effective and should not be done to correct DDH.

**Femoral torsion (twisting):** The femoral head may be twisted. Torsion may be either internal (femoral anteversion—knees pointing toward each other with toes in) or external (femoral retroversion—knees pointing in opposite directions) and is common among neonates. At birth, internal torsion can be as much as 40° and still be normal. External torsion can also be prominent at birth and still be normal. Torsion is recognized by laying the child prone on the examining table. The hips are rotated externally and internally. Limitation of internal rotation indicates femoral anteversion, whereas limitation of external rotation indicates femoral retroversion.

Children with internal torsion may regularly sit in the W position (ie, knees are together and feet are spread apart) or sleep prone with legs extended or flexed and internally rotated. These children probably assume this position because it is more comfortable. The W sitting position was thought to worsen torsion, but there is little evidence that the position should be discouraged or avoided. By adolescence, internal torsion tends to gradually decrease to about 15° without intervention. Orthopedic referral and treatment, which includes derotational osteotomy (in which the bone is broken, rotated into normal alignment, and casted), is reserved for children who have a neurologic deficit such as spina bifida or those in whom torsion interferes with ambulation.

External torsion may occur if in utero forces result in an abduction or external rotation of the lower extremity. If external torsion is prominent at birth, a thorough evaluation (including x-rays or ultrasonography) for hip dislocation is indicated. External torsion typically corrects spontaneously, especially after children begin to stand and walk, but orthopedic referral is needed when excessive
torsion persists after 8 yr. Treatment includes derotational osteotomy.

**Genu varum and genu valgum:** The 2 major types of knee or femoral-tibial angular deformities are genu varum (bowlegs) and genu valgum (knock-knees). Untreated, both can cause osteoarthritis of the knee in adulthood.

**Genu varum** is common among toddlers and usually resolves spontaneously by age 18 mo. If it persists or becomes more severe, Blount disease (tibia vara) should be suspected, and rickets and other metabolic bone diseases should also be ruled out (see p. 2991). Blount disease is due to a growth disturbance of the medial aspect of the proximal tibial growth plate; genu varum and tibial torsion may occur. Blount disease may occur in early childhood or in adolescence (when it is associated with overweight). Early diagnosis of Blount disease is difficult, because x-rays may be normal; the classic x-ray finding is angulation (beaking) of the medial metaphysis. Early use of splints or braces can be effective, but surgery with or without an external fixator is often needed.

**Genu valgum** is less common and, even if severe, usually resolves spontaneously by age 9 yr. Skeletal dysplasia or hypophosphatasia should be excluded. If marked deformity persists after age 10 yr, surgical stapling of the medial distal femoral epiphysis is indicated.

**Knee dislocation:** Anterior knee dislocation with hyperextension is rare at birth but requires emergency treatment. It may occur with Larsen's syndrome, which consists of multiple congenital dislocations (eg, elbows, hips, knees), clubfoot, and characteristic facies (eg, prominent forehead, depressed nasal bridge, wide-spaced eyes), or with arthrogryposis (see p. 2969). The dislocation may be related to muscle imbalance (if myelodysplasia or arthrogryposis is present) or intrauterine positioning. Ipsilateral hip dislocation often coexists.

On examination the leg is extended and cannot be flexed more than a few degrees.

If the infant is otherwise normal, immediate treatment with daily passive flexion movements and splinting in flexion usually results in a functional knee.

**Tibial torsion:** Tibial torsion can be external (lateral) or internal (medial) twisting. External torsion occurs normally with growth: from 0° at birth to 20° by adulthood. External torsion is rarely a problem.

Internal torsion is common at birth, but it typically resolves with growth. However, an excessive degree of torsion may indicate a neuromuscular problem. Torsion also occurs with Blount disease (see p. 2973). Persistent, excessive torsion can lead to toeing-in and bowlegs.

To evaluate for tibial torsion, the angle between the axis of the foot and the axis of the thigh is measured with the child prone and the knees flexed to 90°. Typically the foot axis is 10° lateral relative to the thigh axis. This angle can also be measured by seating the child and drawing an imaginary line connecting the lateral and medial malleoli.

**Talipes equinovarus:** Sometimes called clubfoot, talipes equinovarus is characterized by plantar flexion, inward tilting of the heel (from the midline of the leg), and adduction of the forefoot (medial deviation away from the leg's vertical axis). It results from an abnormality of the talus. It occurs in about 2/1000 births, is bilateral in up to 50% of affected children, and may occur alone or as part of a syndrome. Developmental dysplasia of the hip is more common among these children. Similar deformities that result from in utero positioning can be distinguished from talipes equinovarus because they can be easily corrected passively.

Treatment requires orthopedic care, which consists initially of repeated cast applications, taping, or use of malleable splints to normalize the foot's position. If casting is not successful and the abnormality is severe, surgery may be required. Optimally, surgery is done before 12 mo, while the tarsal bones are still cartilaginous. Talipes equinovarus may recur as children grow.

**Talipes calcaneovalgus:** The foot is flat or convex and dorsiflexed with the heel turned outward. The foot can easily be approximated against the lower tibia. Developmental dysplasia of the hip is more
common among these children. Early treatment with a cast (to place the foot in the equinovarus position) or with corrective braces is usually successful.

**Metatarsus adductus:** The forefoot turns toward the midline. The foot may be supinated at rest. Usually, the foot can be passively abducted and everted beyond the neutral position when the sole is stimulated. Occasionally, an affected foot is rigid, not correcting to neutral. Developmental dysplasia of the hip is more common among these children.

The deformity usually resolves without treatment during the first year of life. If it does not, casting or surgery (abductory midfoot osteotomy) is required.

**Metatarsus varus:** The plantar surface of the foot is turned inward, so that the arch is raised. This deformity usually results from in utero positioning. It typically does not resolve after birth and may require corrective casting.

**Muscle Abnormalities**

Individual muscles or groups of muscles may be absent at birth. Muscle abnormalities can occur alone or as part of a syndrome.

Partial or complete agenesis of the pectoralis major is common and occurs alone or with ipsilateral hand abnormalities and various degrees of breast and nipple aplasia, as in Poland's syndrome. Poland's syndrome may be associated with Mobius' syndrome (paralysis of the lower cranial nerves, especially the 6th, 7th, and 12th), which has been linked to autism.

In prune-belly syndrome (see p. 2988), ≥ 1 layers of the abdominal musculature are absent at birth; this often occurs with severe GU abnormalities, particularly hydronephrosis. Incidence is higher in males who often also have bilateral undescended testes. Malformations involving the feet and rectum also often coexist. Prognosis is guarded, even with early relief of urinary tract obstruction.

Treatment depends on severity of the condition and can range from minimal intervention to reconstructive surgery.

**Neck and Back Abnormalities**

Neck and back abnormalities can be caused by soft-tissue or bony injuries or by vertebral anomalies. Vertebral anomalies can be singular or part of a syndrome.

**Congenital torticollis:** The head becomes tilted at or soon after birth. The most common cause is neck injury during delivery. Torticollis that develops within the first few days or weeks of life may result from hematoma, fibrosis, and contracture of the sternocleidomastoid (SCM) muscle. A nontender mass may be noted in the SCM, usually in the midsegment.

Other causes include spinal abnormalities, such as Klippel-Feil syndrome (fusion of the cervical vertebrae, short neck, and low hairline, often with urinary tract abnormalities) or atlanto-occipital fusion. CNS tumors, bulbar palsies, and ocular dysfunction are common neurologic causes but are rarely present at birth (see also Spasmodic Torticollis on p. 382). Fractures, dislocations, or subluxations of the cervical spine (especially C1 and C2) or odontoid abnormalities are rare but serious causes; permanent neurologic damage may result from spinal cord injury.

Cervical imaging should be done to exclude bony causes, which may require stabilization.

When torticollis is due to birth trauma, frequent passive SCM stretching (rotating the head and stretching the neck laterally to the opposite side) is indicated. Injections of botulinum toxin into the SCM may help in refractory cases. Untreated torticollis may lead to plagiocephaly (flattening of one side of the head) and asymmetrical facies.

**Vertebral defects:** Examples are idiopathic scoliosis (see p. 2912), which is rarely apparent at birth, and
isolated vertebral defects (eg, hemivertebrae, wedge or butterfly vertebrae), which are more likely to be diagnosed at birth. Vertebral defects should be suspected when posterior midline cutaneous, renal, or congenital lower-limb abnormalities exist. Some syndromes or associations such as VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies and radial aplasia, and limb anomalies) include vertebral defects.

As children grow, the spinal curve caused by a vertebral defect or defects can progress rapidly; therefore, the spine should be monitored closely. Braces or body jackets, which may have to be worn 18 h/day, are often necessary initially. Surgery may be needed if the curvature progresses. Because renal abnormalities commonly coexist, renal ultrasonography is indicated for initial screening.
Chapter 295. Congenital Gastrointestinal Anomalies

Introduction

Most congenital GI anomalies result in some type of intestinal obstruction, frequently manifesting with feeding difficulties, distention, and emesis at birth or within 1 or 2 days. Infants with GI malformations have a high mortality rate, ranging from 10 to 40%; the highest rate occurs in those with congenital diaphragmatic hernia.

A common type of anomaly is atresia, in which a segment of the GI tract fails to form or develop normally. The most common type is esophageal atresia, followed by atresia in the jejunoileal region and in the duodenum.

Immediate management includes bowel decompression (by continuous nasogastric suction to prevent emesis, which can lead to aspiration pneumonia or further abdominal distention with respiratory embarrassment) and referral to a center for neonatal surgery. Also vital are maintenance of body temperature, prevention of hypoglycemia with IV 10% dextrose and electrolytes, and prevention or treatment of acidosis and infections so that the infant is in optimal condition for surgery.

Because about one third of infants with a GI malformation have another congenital anomaly (up to 50% in those with congenital diaphragmatic hernia and 70% in those with omphalocele), they should be evaluated for malformations of other organ systems, especially of the CNS, heart, and kidneys.

High Alimentary Tract Obstruction

Esophageal, gastric, duodenal, and sometimes jejunal obstruction should be considered when excess amniotic fluid (polyhydramnios) is diagnosed, because such obstructions prevent the fetus from swallowing and absorbing amniotic fluid (jejunal obstruction—see p. 2978). An NGT should be passed into the neonate's stomach immediately after delivery. Finding large amounts of fluid in the stomach, especially if bile-stained, supports the diagnosis of upper GI obstruction, whereas inability to pass the NGT into the stomach suggests esophageal atresia (or nasal obstruction [eg, choanal atresia]).

Diaphragmatic hernia sometimes causes high alimentary tract obstruction.

Esophageal Atresia

Esophageal atresia is incomplete formation of the esophagus, frequently associated with tracheoesophageal fistula. Diagnosis is suspected by failure to pass an NGT. Treatment is surgical repair.

Esophageal atresia is the most common GI atresia. The estimated incidence is 1 in 3000 live births. Other congenital malformations are present in up to 50% of cases.

There are 5 major types of esophageal atresia (see Fig. 295-1). Most also involve a fistula between the trachea and esophagus.

Characteristic signs are excessive secretions, coughing and cyanosis after attempts at feeding, and aspiration pneumonia. Esophageal atresia with a distal fistula leads to abdominal distention because, as the infant cries, air from the trachea is forced through the fistula into the lower esophagus and stomach.

Diagnosis

• Prenatal: Ultrasonography

• Postnatal: NGT placement and x-ray

Routine prenatal ultrasonography may suggest esophageal atresia. Polyhydramnios may be present but is not diagnostic because it can occur with many other disorders. The fetal stomach bubble may be absent but only in < 50% of cases. Less commonly, there is a dilated upper esophageal pouch, but this is
typically looked for only in fetuses with polyhydramnios and no stomach bubble.

After delivery, an NGT is inserted if esophageal atresia is suspected by prenatal ultra-sonography or clinical findings; diagnosis is suggested by inability to pass the tube into the stomach. A radiopaque catheter determines the location of the atresia on x-ray. In atypical cases, a small amount of water-soluble contrast material may be needed to define the anatomy.

[Fig. 295-1. Types and relative frequencies of esophageal atresia and tracheoesophageal fistula.]

under fluoroscopy. The contrast material should be quickly aspirated back because it can cause a chemical pneumonitis if it enters the lungs. This procedure should be done only by an experienced radiologist at the center where neonatal surgery will be done.

Treatment

• Surgical repair

Preoperative management aims to get the infant into optimal condition for surgery and prevent aspiration pneumonia, which makes surgical correction more hazardous. Oral feedings are withheld. Continuous suction with a double-lumen catheter in the upper esophageal pouch prevents aspiration of swallowed saliva. The infant should be positioned prone with the head elevated 30 to 40° and with the right side down to facilitate gastric emptying and minimize the risk of aspirating gastric acid through the fistula. If definitive repair must be deferred because of extreme prematurity, aspiration pneumonia, or other congenital malformations, gastrostomy is done to decompress the stomach. Suction through the gastrostomy tube then reduces the risk that gastric contents will reflux through the fistula into the tracheobronchial tree.

When the infant's condition is stable, extrapleural surgical repair of the esophageal atresia and closure of the tracheoesophageal fistula can be done. Occasionally, interposing a segment of colon between the esophageal segments may be required.

The most common acute complications are leakage at the anastomosis site and stricture formation. Feeding difficulties are common after successful surgical repair because of poor motility of the distal esophageal segment, which occurs in up to 85% of cases. This poor motility predisposes the infant to gastroesophageal re-flux. If medical management for reflux fails, a Nissen fundoplication may be required.

Diaphragmatic Hernia

Diaphragmatic hernia is protrusion of abdominal contents into the thorax through a defect in the diaphragm. Lung compression may cause persistent pulmonary hypertension. Diagnosis is by chest x-ray. Treatment is surgical repair.

Diaphragmatic hernia usually occurs in the posterolateral portion of the diaphragm (Bochdalek's hernia) and is on the left side in 90% of cases. The estimated incidence is 1 in 2200 live births. Anterior hernias (Morgagni's hernia) are far less common. Other congenital anomalies are present in about 50% of cases.

Loops of small and large bowel, stomach, liver, and spleen may protrude into the hemithorax on the involved side. If the hernia is large, the lung on the affected side is hypoplastic. Other pulmonary consequences include underdevelopment of the pulmonary vasculature, resulting in an elevation of pulmonary vascular resistance and hence pulmonary hypertension. Persistent pulmonary hypertension (see p. 2873) leads to right-to-left shunting at the level of the foramen ovale or through a patent ductus arteriosus, which prevents adequate oxygenation even with O₂ supplementation or mechanical ventilation. Persistent pulmonary hypertension is the major cause of death among infants with congenital diaphragmatic hernia.

Symptoms and Signs

After delivery, as the neonate cries and swallows air, the loops of intestine quickly fill with air and rapidly
enlarge, causing further acute respiratory embarrassment as the heart and mediastinal structures are pushed to the right, compressing the more normal right lung. Respiratory distress is immediate in severe cases. A scaphoid abdomen (due to displacement of abdominal viscera into the chest) is likely. Bowel sounds (and an absence of breath sounds) may be heard over the involved hemithorax. In less severe cases, mild respiratory difficulty develops a few hours or days later as abdominal contents progressively herniate through a smaller diaphragmatic defect.

Diagnosis

- Sometimes prenatal ultrasonography
- Chest x-ray

Sometimes diagnosis is by prenatal ultrasoundography. After delivery, diagnosis is by chest x-ray showing intestine protruding into the chest. In a large defect, there are numerous air-filled loops of intestine filling the hemithorax and contralateral displacement of the heart and mediastinal structures. If the x-ray is taken immediately after delivery before the neonate has swallowed air, the abdominal contents appear as an opaque airless mass in the hemithorax.

Treatment

- Surgical repair

The neonate should be immediately endotracheally intubated and ventilated in the delivery room; bag-and-mask ventilation may fill the intrathoracic viscera with air and worsen respiratory compromise. Continuous nasogastric suction with a double-lumen tube prevents swallowed air from progressing through the GI tract and causing further lung compression. Sometimes paralytic drugs are needed to prevent swallowing of air. Surgery is required to replace the intestine in the abdomen and to close the diaphragmatic defect after the neonate has had optimal management of pulmonary hypertension.

Severe persistent pulmonary hypertension requires stabilization before surgery with IV NaHCO₃ and inhaled nitric oxide, which may help dilate the pulmonary arteries and improve systemic oxygenation. Recent studies show improved outcome with use of extracorporeal membrane oxygenation (ECMO); however, neonates with extreme pulmonary hypoplasia still do not survive. Successful transport of a critically ill neonate with congenital diaphragmatic hernia and persistent pulmonary hypertension is very difficult. Therefore, if diaphragmatic hernia is diagnosed by prenatal ultrasonography, delivery at a pediatric center with ECMO facilities is prudent.

Duodenal Obstruction

The duodenum can be obstructed by atresia, stenosis, and pressure due to an extrinsic mass.

Duodenal atresia: This anomaly is the 3rd most common atresia of the GI tract. The estimated incidence is 1 in 20,000 live births. Duodenal atresia is due to the failure of canalization of the embryonic duodenum. About 30% of infants with duodenal atresia have Down syndrome. Other congenital anomalies, particularly malrotation of the intestine, occur in 50 to 70% of cases.

Diagnosis can be suspected prenatally if there is polyhydramnios, dilated bowel, ascites, or a combination. Infants with duodenal atresia present with polyhydramnios, feeding difficulties, and emesis that may be bilious. The diagnosis is suspected by symptoms and classic double-bubble x-ray findings—one bubble is in the stomach and the other is in the proximal duodenum; little to no air is in the distal gut. An upper GI series provides definitive diagnosis but must be done carefully by a radiologist experienced with doing this procedure on children to avoid aspiration. Once the disorder is suspected, infants should receive nothing by mouth, and an NGT should be placed to decompress the stomach. Surgery is the definitive therapy.

Duodenal stenosis: This anomaly occurs less commonly than duodenal atresia but manifests in a similar fashion and requires surgery. It too is frequently associated with Down syndrome.
Choledochal cyst or annular pancreas: These anomalies may obstruct the duodenum by extrinsic pressure. Infants with choledochal cyst classically present with a triad of abdominal pain (a very difficult finding to infer in the neonate), right upper quadrant mass, and jaundice. If the cyst is large, it may also manifest with variable degrees of duodenal obstruction. Choledochal cyst is most commonly diagnosed by ultrasonography. Treatment is surgical and requires complete excision of the cyst because of the risk of developing cancer in the cyst remnants.

Annular pancreas is a rare congenital anomaly in which pancreatic tissue encircles the 2nd portion of the duodenum, causing duodenal obstruction; manifestation is usually during the neonatal period but may be delayed until adulthood. The diagnosis can be suggested by an upper GI series and is more definitively made with CT. Treatment is surgical.

Jejunoileal and Large-Bowel Obstruction

(See also Meconium ileus on p. 2801 and Meconium Plug Syndrome on p. 2802.)

Obstruction of the jejunum and ileum can occur as the result of jejunoileal atresia, mal-rotation, intestinal duplication, or meconium ileus. Large-bowel obstruction is typically caused by Hirschsprung's disease, meconium plug syndrome, and colonic or anal atresia.

In 75% of cases, no history of maternal polyhydramnios exists because much of the swallowed amniotic fluid can be absorbed from the intestine proximal to the obstruction. These disorders, other than malrotation, intestinal duplication, and Hirschsprung's disease, typically manifest in the first few days of life with feeding problems, abdominal distention, and emesis that may be bilious or fecal. The neonate may pass a small amount of meconium initially but thereafter does not pass stools. Malrotation, intestinal duplication, and Hirschsprung's disease can manifest in the first several days of life or years later.

General diagnostic approach and preoperative management include giving nothing by mouth, placing an NGT to prevent further bowel distention or possible aspiration of vomitus, correcting fluid and electrolyte disturbances, taking a plain abdominal x-ray, and then doing a contrast enema to delineate the anatomy (the enema may also relieve obstruction in meconium plug syndrome or meconium ileus). For Hirschsprung's disease, a rectal biopsy is needed.

Jejunoileal Atresia

Jejunoileal atresia is incomplete formation of the jejunum, usually caused by an ischemic insult.

There are 5 major types of jejunoileal atresia:

• Type I consists of a membrane completely occluding the lumen with the intestine intact.

• Type II is a gap in the intestine with a fibrous cord between the proximal and distal segments of intestine.

• Type IIIA is a mesenteric gap without any connection between the segments.

• Type IIIB is jejunal atresia with absence of the distal superior mesenteric artery; the distal small bowel is coiled like an apple peel, and the gut is short.

• Type IV consists of multiple atretic segments.

Neonates with jejunoileal atresia usually present late during day 1 or on day 2 with increasing abdominal distention, failure to pass stools, and, finally, regurgitated feedings.

Plain abdominal x-rays are done; they may reveal dilated loops of small bowel with air-fluid levels and a paucity of air in the colon and rectum. Because about 10% of patients also have cystic fibrosis (nearly 100% if meconium ileus is also present), testing for that disease (see p. 2883) should be done.
Treatment

- Surgical repair

Preoperative management consists of placing an NGT, giving nothing by mouth, and providing IV fluids. Surgical repair is the definitive therapy. During surgery, the entire intestine should be inspected for multiple areas of atresia. The atretic portion is resected, usually with a primary anastomosis. If the proximal portion of the ileum is extremely dilated and difficult to anastomose to the distal, unused part of the intestine, it is sometimes safer to do a double-barreled ileostomy and defer anastomosis until the caliber of the distended proximal intestine has diminished.

Prognosis is based on the length of remaining small bowel and the presence of the ileocecal valve. Infants who subsequently develop short bowel syndrome require TPN for extended periods. They should be provided continuous enteral feedings to promote gut adaptation, maximize absorption, and minimize the use of TPN. Infants should also be provided small amounts of nutrition by mouth to maintain sucking and swallowing.

Malrotation of the Bowel

Malrotation of the bowel is failure of the bowel to assume its normal place in the abdomen during intrauterine development.

During embryonic development, the primitive bowel protrudes from the abdominal cavity. As it returns to the abdomen, the large bowel normally rotates counterclockwise, with the cecum coming to rest in the right lower quadrant. Incomplete rotation, in which the cecum ends up elsewhere (usually in the right upper quadrant or midepigastrium), may cause bowel obstruction due to retroperitoneal bands (Ladd's bands) that stretch across the duodenum or due to a volvulus of the small bowel, which, lacking its normal peritoneal attachment, twists on its narrow, stalk-like mesentery. Other malformations occur in 30 to 60% of patients, most commonly other GI malformations (eg, gastroschisis, omphalocele, diaphragmatic hernia, intestinal atresia).

Patients with malrotation can present in infancy or in adulthood with acute abdominal pain and bilious emesis, with an acute volvulus, with typical reflux symptoms, or with chronic abdominal pain. Bilious emesis in an infant is an emergency and should be evaluated immediately to make sure the infant does not have malrotation and a midgut volvulus; untreated, the risk of bowel infarction and subsequent short bowel syndrome or death is high.

Plain films of the abdomen should be done immediately. If they show dilated small bowel, a paucity of bowel gas distal to the duodenum, or both (suggesting a midgut volvulus), further diagnosis and treatment must be done emergently. Barium enema typically identifies malrotation by showing the cecum outside the right lower quadrant. If the diagnosis remains uncertain, an upper GI series can be done cautiously.

The presence of malrotation and midgut volvulus is an emergency requiring immediate surgery, which consists of Ladd's procedure with lysis of the retroperitoneal bands and relief of the midgut volvulus.

Intestinal Duplication

Intestinal duplications are tubular structures attached to the intestines that share a common blood supply; their lining resembles that of the GI tract.

Intestinal duplications are uncommon. The most common site of duplication is the jejunum and ileum followed by the esophagus, stomach, colon, and duodenum. Colonic duplication is often associated with anomalies of the urogenital system. Intestinal duplications usually manifest in the 1st or 2nd yr of life. Duplications can be asymptomatic or cause obstructive symptoms, chronic pain, or abdominal mass. If they are detected, treatment is surgical with complete resection of the duplicated portion.

Hirschsprung's Disease

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Hirschsprung's disease is a congenital anomaly of innervation of the lower intestine, usually limited to the colon, resulting in partial or total functional obstruction. Symptoms are obstipation and distention. Diagnosis is by barium enema and biopsy. Treatment is surgical.

Hirschsprung's disease is caused by congenital absence of Meissner's and Auerbach's autonomic plexus in the intestinal wall. The estimated incidence is 1 in 5000 live births. Disease is usually limited to the distal colon but can involve the entire colon or even the entire large and small bowel. Males are more commonly affected unless the entire colon is involved, in which case there is no gender difference. Peristalsis in the involved segment is absent or abnormal, resulting in continuous smooth muscle spasm and partial or complete obstruction with accumulation of intestinal contents and massive dilation of the more proximal, normally innervated intestine. Skip lesions almost never occur.

Symptoms and Signs

Patients most commonly present early in life; 15% in the first month, 60% by age 1 yr, and 85% by age 4 yr. Infants present with failure to pass meconium in the first 24 h of life, obstipation, abdominal distention, and, finally, vomiting as in other forms of distal bowel obstruction. Occasionally, infants with ultra-short segment aganglionosis have only mild or intermittent constipation, often with intervening bouts of mild diarrhea, resulting in delay in diagnosis. In older infants, symptoms and signs may include anorexia, lack of a physiologic urge to defecate, and, on digital rectal examination, an empty rectum with stool palpable higher up in the colon and an explosive passage of stool upon withdrawal of the examining finger (blast sign). The infant may also fail to thrive.

Diagnosis

- Barium enema
- Rectal biopsy

Diagnosis should be made as soon as possible. The longer the disease goes untreated, the greater the chance of developing Hirschsprung's enterocolitis (toxic megacolon), which may be fulminant and fatal (see below). Most cases can be diagnosed in early infancy.

Initial approach is typically with barium enema or sometimes rectal suction biopsy. Barium enema may show a transition in diameter between the dilated, normally innervated colon proximal to the narrowed distal segment (which lacks normal innervation). Barium enema should be done without prior preparation, which can dilate the abnormal segment, rendering the test nondiagnostic. Because characteristic findings may not be present in the neonatal period, a 24-h post-evacuation x-ray should be taken; if the colon is still filled with barium, Hirschsprung's disease is likely. A rectal suction biopsy can disclose the absence of ganglion cells. Acetylcholinesterase staining can be done to highlight the enlarged nerve trunks. Some centers also can do rectal manometrics, which can reveal the dysmotility characteristic of the abnormal innervation. Definitive diagnosis requires a full-thickness biopsy of the rectum.

Treatment

- Surgical repair

Treatment in the neonate typically involved a colostomy proximal to the aganglionic segment to decompress the colon and allow the neonate to grow before the 2nd stage of the procedure. Later resection of the entire aganglionic portion of the colon and a pull-through procedure was done. However, a number of centers now do a 1-stage procedure in the neonatal period. Results using laparoscopic technique are similar to those of the open method and are associated with shorter hospitalizations, earlier initiation of feeding, and less pain.

After definitive repair, the prognosis is good, although a number of infants have chronic dysmotility with
constipation, obstructive problems, or both.

**Hirschsprung's Enterocolitis**

(Toxic Megacolon)

Hirschsprung's enterocolitis is a life-threatening complication of Hirschsprung's disease resulting in a grossly enlarged colon, often followed by sepsis and shock.

The etiology of Hirschsprung's enterocolitis seems to be marked proximal dilatation secondary to obstruction, with thinning of the colonic wall, bacterial overgrowth, and trans-location of gut bacteria. Shock can develop, and death can follow rapidly; mortality rate is 10%. Close monitoring of infants with Hirschsprung's disease is therefore essential.

Hirschsprung's enterocolitis occurs most commonly in the first several months of life before surgical correction but can occur postoperatively, typically in the first year after surgery. Infants present with fever, abdominal distention, diarrhea (which may be bloody), and, subsequently, obstipation.

Initial treatment is supportive with fluid resuscitation, decompression with an NGT and rectal tube, and broad-spectrum antibiotics to include anaerobic coverage (eg, a combination of ampicillin, gentamicin, and clindamycin). Some experts advocate saline enemas to clean out the colon, but this must be done carefully so as not to increase colonic pressure and cause perforation. Surgery is the definitive treatment for infants who have not yet undergone surgical repair, as well as for infants with perforation or necrotic gut.

**Anal Atresia**

Anal atresia is an imperforate anus.

A fistula often extends from the anal pouch to the perineum or the urethra in males and to the vagina, the fourchette, or, rarely, the bladder in females. The blind anus and the skin of the perineum may be several centimeters apart or separated by just a thin membrane of skin covering the anal opening.

Anal atresia is obvious on routine physical examination of the neonate because the anus is not patent. If the diagnosis is missed and the neonate is fed, signs of distal bowel obstruction soon develop.

The urine should be filtered and examined for meconium, indicating the presence of a fistula to the urinary tract. Plain x-rays and fistulograms with the neonate in a lateral prone position can define the level of the lesion. A cutaneous fistula generally indicates low atresia. In such cases, definitive repair using a perineal approach is possible. If no perineal fistula exists, a high lesion is likely.

Definitive repair is usually deferred until the infant is older and the structures to be repaired are larger. Until then, a colostomy is done to relieve the obstruction.

**Defects in Abdominal Wall Closure**

Several congenital defects involve the abdominal wall, allowing protrusion of the viscera.

**Omphalocele**

An omphalocele is a protrusion of abdominal viscera from a midline defect at the base of the umbilicus.

In omphalocele, the herniated viscera are covered by a thin membrane and may be small (only a few loops of intestine) or may contain most of the abdominal viscera (intestine, stomach, liver). Immediate dangers are drying of the viscera, hypothermia and dehydration due to evaporation of water from the exposed viscera, and infection of the peritoneal surfaces. Infants with omphalocele have a very high incidence of other congenital anomalies (up to 70%), including
• Bowel atresia
• Chromosomal abnormalities (eg, Down syndrome)
• Cardiac and renal anomalies

Omphalocele can be detected by routine prenatal ultrasonography; if the disorder is present, delivery should be at a tertiary care center by personnel experienced in dealing with this disorder and the other associated congenital anomalies.

At delivery, the exposed viscera should be immediately covered with a sterile, moist, nonadherent dressing (eg, medicated petrolatum gauze) to maintain sterility and prevent evaporation.

The infant is evaluated for associated anomalies before surgical repair of the omphalocele. Primary closure is done when feasible. With a large omphalocele, the abdominal cavity may be too small to accommodate the viscera. In this case, the viscera are covered by a pouch or silo of polymeric silicone sheeting, which is progressively reduced in size over several days as the abdominal capacity slowly increases, until all of the viscera are enclosed within the abdominal cavity.

Gastrochisis

Gastrochisis is protrusion of the abdominal viscera through an abdominal wall defect, usually to the right of the umbilical cord insertion.

The estimated incidence is 1 in 2000 live births (more common than omphalocele). In gastrochisis, unlike omphalocele, there is no membranous covering over the intestine, which is markedly edematous and erythematous and is often enclosed in a fibrin mat. These findings indicate long-standing inflammation due to the intestine being directly exposed to amniotic fluid (ie, chemical peritonitis). Infants with gastrochisis have low incidence of associated congenital anomalies other than malrotation. As in omphalocele, gastrochisis can be detected by prenatal ultrasonography, and delivery should take place at a tertiary care center. Surgery is similar to that for omphalocele. It often takes several weeks before GI function recovers and oral feedings can be given; occasionally, infants have long-term problems caused by abnormal intestinal motility.
Chapter 296. Congenital Renal and Genitourinary Anomalies

Introduction

Congenital anatomic anomalies of the GU tract are more common than those of any other organ system. Urinary tract anomalies predispose to many complications, including infection, obstruction, stasis, calculus formation, and impaired renal function. Genital anomalies may cause sexual dysfunction or impaired fertility. Treatment of GU anomalies is often surgical.

Some congenital renal anomalies (eg, autosomal dominant polycystic kidney disease and medullary cystic disease [see Ch. 234], hereditary nephritis [see p. 2387]) typically do not manifest until adulthood.

Renal Anomalies

Renal agenesis: Bilateral renal agenesis as part of a syndrome of oligohydramnios, pulmonary hypoplasia, and extremity and facial anomalies (classic Potter syndrome) is fatal within minutes to hours. Many are stillborn.

Unilateral renal agenesis is not uncommon and accounts for about 5% of renal anomalies. It usually is accompanied by ureteral agenesis with absence of the ipsilateral trigone and ureteral orifice. No treatment is necessary; compensatory hypertrophy of the solitary kidney maintains normal renal function.

Autosomal recessive polycystic kidney disease: Incidence of autosomal recessive polycystic kidney disease is about 1/10,000 to 1/20,000 births. Autosomal dominant polycystic kidney disease is much more common, occurring in about 1/500 to 1/1000 live births (see p. 2385).

Autosomal recessive disease affects

• Kidneys
• Liver

Kidneys are usually greatly enlarged and contain small cysts; renal failure is common in childhood.

The liver is enlarged and has periportal fibrosis, bile duct proliferation, and scattered cysts; the remainder of the hepatic parenchyma is normal. Fibrosis causes portal hypertension by age 5 to 10 yr, but hepatic function is normal or minimally impaired.

Disease severity and progression vary. Severe disease may manifest prenatally or soon after birth or in early childhood with renal-related symptoms; less severely affected patients present in late childhood or adolescence with hepatic-related symptoms.

Affected neonates have a protuberant abdomen with huge, firm, smooth, symmetric kidneys. Severely affected neonates commonly have pulmonary hypoplasia secondary to the in utero effects of renal dysfunction and oligohydramnios.

In patients aged 5 to 10 yr, signs of portal hypertension, such as esophageal and gastric varices and hypersplenism, occur. If the patient presents in adolescence, nephromegaly is less marked, renal insufficiency may be mild to moderate, and the major symptoms are those related to portal hypertension.

Diagnosis may be difficult, especially without a family history. Ultrasonography may show renal or hepatic cysts; definitive diagnosis may require biopsy. Ultrasonography in late pregnancy usually allows presumptive in utero diagnosis.

Many neonates die in the first few days or weeks of life from pulmonary insufficiency. Most who survive develop progressive renal failure often requiring renal replacement therapy. Experience with renal transplantation with or without hepatic transplantation is limited. When transplantation is done, hypersplenism must be controlled (see p. 985) to obviate difficulty with hypersplenism-induced
leukopenia, which increases the risk of systemic infection. Portal hypertension may be treated by portacaval or splenorenal shunts, which reduce morbidity but not mortality.

**Duplication anomalies:** Supernumerary collecting systems may be unilateral or bilateral and may involve the renal pelvis and ureters (accessory renal pelvis, double or triple pelvis and ureter), calyx, or ureteral orifice. Duplex kidney, a single renal mass with > 1 collecting system, differs from a fused kidney, which involves fusion of 2 renal parenchymal masses. Some duplication anomalies have ureteral ectopy with or without ureterocele. Management depends on the anatomy and function of each separately drained segment. Surgery may be needed to correct obstruction or vesicoureteral reflux.

**Fusion anomalies:** With fusion anomalies, the kidneys are joined, but the ureters enter the bladder on each side. These anomalies increase the risk of ureteropelvic junction obstruction, vesicoureteral reflux, congenital renal cystic dysplasia (see p. 2381), and injury caused by anterior abdominal trauma.

Horseshoe kidney, the most common fusion anomaly, occurs when renal parenchyma on each side of the vertebral column is joined at the corresponding (usually lower) poles; an isthmus of renal parenchyma or fibrous tissue joins at the midline. The ureters course medially and anteriorly over this isthmus and generally drain well. Obstruction, if present, is usually secondary to insertion of the ureters high in the renal pelvis. Pyeloplasty relieves the obstruction and can be done without resecting the isthmus.

Crossed fused renal ectopia is the 2nd most common fusion anomaly. The renal parenchyma (representing both kidneys) is on one side of the vertebral column. One of the ureters crosses the midline and enters the bladder on the side opposite the kidneys. When ureteropelvic junction obstruction is present, pyeloplasty is the treatment of choice.

Fused pelvic kidney (pancake kidney) is much less common. A single pelvic kidney is served by 2 collecting systems and ureters. If obstruction is present, reconstruction is needed.

**Malrotation:** Malrotation is usually of little clinical significance. Ultrasonography often shows hydronephrosis, but diagnosis is best made with IVU, which identifies an axis shift and defines the collecting system anatomy.

**Multicystic dysplastic kidney:** In this condition, a nonfunctioning renal unit consists of noncommunicating cysts with intervening solid tissue composed of fibrosis, primitive tubules, and foci of cartilage. Usually, ureteral atresia is also present. Uncommonly, the kidney develops tumors or infection, and hypertension may develop. Most experts recommend observation unless solid tissue is extensive or unusual-appearing on ultrasonography, in which case the kidney may be removed.

**Renal dysplasia:** In renal dysplasia (a histologic diagnosis), the renal vasculature, tubules, collecting ducts, or drainage apparatus develops abnormally. Diagnosis is by biopsy. If dysplasia is segmental, treatment is often unnecessary. If dysplasia is extensive, renal dysfunction may necessitate nephrologic care, including renal replacement therapy.

**Renal ectopia:** Renal ectopia (abnormal renal location) usually results when a kidney fails to ascend from its origin in the true pelvis; a rare exception occurs with a superiorly ascended (thoracic) kidney. Pelvic ectopia increases the incidence of ureteropelvic junction obstruction, vesicoureteral reflux, and multicystic renal dysplasia. Obstruction is corrected surgically. Severe reflux can be corrected surgically when indicated (if causing hypertension, recurrent infections, or renal growth retardation).

**Renal hypoplasia:** Hypoplasia usually occurs because inadequate ureteral bud branching causes an underdeveloped, small kidney with histologically normal nephrons. If hypoplasia is segmental, hypertension can occur, and ablative surgery may be needed.

**Ureteral Anomalies**

Ureteral anomalies frequently occur with renal anomalies but may occur independently. Complications include...
• Obstruction, infection, and calculus formation (due to urinary stasis)

• Urinary incontinence (due to abnormal termination of the ureter in the urethra, perineum, or vagina)

Diagnosis may be suggested by abnormalities on routine prenatal ultrasonography (eg, hydronephrosis) and occasionally by physical examination (eg, finding an external ectopic ureteral orifice). However, many anomalies are first suspected when children develop UTIs. Ureteral anomalies should be suspected in children with an episode of pyelonephritis or children with recurrent UTIs. Testing typically involves ultrasonography of the kidneys, ureters, and bladder before and after voiding, and then voiding cystourethrography.

Treatments are surgical.

**Duplication anomalies:** Partial or complete duplication of one or both ureters may occur with duplication of the ipsilateral renal pelvis. The ureter from the upper pole of the kidney opens at a more caudal location than the orifice of the lower pole ureter. Ectopia or stenosis of one or both orifices, vesicoureteral reflux into the lower ureter or both ureters, and ureterocele may occur. Surgery may be necessary if there is obstruction, vesicoureteral reflux, or urinary incontinence.

**Ectopic orifices:** Openings of single or duplicated ureters may be malpositioned on the lateral bladder wall, distally along the trigone, in the bladder neck, in the female urethra distal to the sphincter (leading to continuous incontinence despite a normal voiding pattern), in the genital system (prostate and seminal vesicle in the male, uterus or vagina in the female), or externally. Lateral ectopic orifices frequently lead to vesicoureteral reflux, whereas distal ectopic orifices more often cause obstruction and incontinence. Surgery is needed for obstruction and incontinence and sometimes for vesicoureteral reflux.

**Retrocaval ureter:** Anomalous development of the vena cava (pre-ureteric vena cava) allows the infrarenal vena cava to form anterior to the ureter (usually the right); a retrocaval ureter on the left occurs only with persistence of the left cardinal vein system or with complete situs inversus. Retrocaval ureter can cause ureteral obstruction. For significant ureteral obstruction, the ureter is surgically divided with uretero-ureteral anastomosis anterior to the vena cava or iliac vessel.

**Stenosis:** Narrowing may occur at any location in the ureter, most frequently at the ureteropelvic junction and less commonly at the ureterovesical junction (primary megaureter). Consequences include infection, hematuria, and obstruction. Stenoses often diminish as the child grows.

In primary megaureter, ureteral tapering and reimplantation may be needed when dilation increases or infection or obstruction occurs. In ureteropelvic junction obstruction, pyeloplasty (excision of the obstructed segment and reanastomosis) may be done by open, laparoscopic, or robotic techniques.

**Ureterocele:** Prolapse of the lower end of the ureter into the bladder with pinpoint obstruction may cause progressive ureterectasis, hydronephrosis, infection, occasional calculus formation, and impaired renal function. Treatment options include endoscopic transurethral incision and open repair.

When a ureterocele involves the upper pole of duplex ureters, treatment depends on function in that renal segment, because of the significant incidence of renal dysplasia. Removal of the affected renal segment and ureter may be preferable to obstruction repair if no segmental renal function is found or if significant renal dysplasia is suspected.

**Vesicoureteral Reflux**

**Vesicoureteral reflux (VUR)** is retrograde passage of urine from the bladder back into the ureter and collecting system.

**Etiology**

VUR is most often due to congenital anomalous development of the ureterovesical junction. Incomplete development of the intramural ureteral tunnel causes failure of the normal flap valve mechanism at the
ureterovesical junction that permits reflux of bladder urine into the ureter and renal pelvis. Reflux can occur even when the tunnel is ordinarily sufficient if bladder outlet obstruction increases intravesical pressures.

Pathophysiology

Reflux of urine from the bladder into the ureter may damage the upper urinary tract by bacterial infection and occasionally by increased hydrostatic pressure. Bacteria in the lower urinary tract can easily be transmitted by reflux to the upper tract, leading to recurrent parenchymal infection with potential scarring and renal dysfunction. VUR is a common cause of UTI in children; about 30 to 40% of infants and toddlers with UTI have VUR.

Chronically elevated emptying pressures (> 40 cm H$_2$O) and increased bladder volume and pressure often cause progressive kidney damage, even without infection or reflux.

Symptoms and Signs

Symptoms and signs are typically those of UTI; these may include fever, abdominal or flank pain, dysuria or flank pain with voiding, frequency, and urgency.

Diagnosis

- Ultrasonography
- Voiding cystourethrography
- Sometimes radioisotope scan

Urinalysis and culture are done to detect infection; pyuria, hematuria, proteinuria, and bacteriuria may be present.

Children typically should have ultrasonography of the kidneys, ureters, and bladder before and after voiding, and then voiding cystourethrography. Renal ultrasonography evaluates kidneys for size, hydrenephrosis, and scarring, and voiding cystourethrography is best to diagnose bladder outlet obstruction. A radioisotope cystogram may be used to monitor reflux. Renal cortical involvement with acute infection or scarring is precisely delineated with succimer (dimercaptosuccinic acid) nuclear scans when indicated. Urodynamic studies may show elevated filling and voiding pressures in the bladder.

Reflux findings on voiding cystourethrogram are graded on a scale from I to V (see Table 280-1 on p. 2845). Clinical severity can be classified based on reflux severity. However, the grades of reflux can be affected by bladder capacity.

- Mild: Grades I and II
- Moderate: Grade III
- Severe: Grades IV and V

Treatment

- Antibiotic prophylaxis
- Sometimes injection of a bulking agent or ureteral reimplantation

Mild to moderate VUR often resolves spontaneously over months to several years while daily antibacterial prophylaxis (eg, with trimethoprim/sulfamethoxazole, amoxicillin, nitrofurantoin, a cephalosporin, or sulfisoxazole) is maintained; it is very important to keep children free of infection.
Severe reflux accompanied by high-pressure storage of urine in the bladder or high intravesical pressures with voiding is treated by lowering bladder pressures with drugs (eg, oxybutynin), behavioral modification using perineal electromyography, or both.

Reflux with complications (eg, infection, impaired renal growth, renal scarring) is treated with endoscopic subtrigonal injection of a bulking agent (eg, dextranomer/hyaluronic acid) or ureteral reimplantation. Obstruction is also surgically repaired.

**Monitoring:** Reflux is monitored by voiding cystourethrography or radioisotope cystography every 1 or 2 yr depending on severity of the reflux.

Renal growth is monitored by annual ultra-sonography until age 5, then every other year until spontaneous resolution or for 3 yr after surgical correction.

**Bladder Anomalies**

Congenital urinary bladder anomalies often occur without other GU abnormalities. They may cause infection, retention, incontinence, and reflux. Symptomatic anomalies may require surgery.

**Bladder diverticula:** Bladder diverticula predispose to UTIs and may coexist with vesicoureteral reflux. They are usually discovered during evaluation of recurrent UTIs in young children. Diagnosis is by voiding cystourethrography. Surgical removal of diverticula and reconstruction of the bladder wall may be needed.

**Exstrophy:** The bladder is open suprapubically, and urine drips from the opening rather than through the urethra. The bladder mucosa is continuous with the abdominal skin, and the pubic bones are separated. Despite the seriousness of the deformity, normal renal function usually is maintained. The bladder can usually be reconstructed and returned to the pelvis, although vesicoureteral reflux invariably occurs and is managed as needed. Continent urinary diversion may be used to treat a bladder reservoir that fails to expand sufficiently or has sphincter insufficiency. Reconstruction of the genitals is required.

**Megacystis syndrome:** In this syndrome, a large, thin-walled, smooth bladder without evident outlet obstruction develops, usually in girls. Megacystis syndrome is poorly understood. The syndrome may be a manifestation of a primary myoneural defect, especially when intestinal obstruction (megacystis-microcolon, intestinal hypoperistalsis syndrome) is also present. Symptoms are related to UTIs, and vesicoureteral reflux is common. Ultrasonography with the bladder empty may disclose normal-appearing upper tracts, but voiding cystourethrography may show reflux with massive upper tract dilation. Ureteral reimplantation may be effective, although some patients benefit from antibacterial prophylaxis, timed voiding with behavioral modification, intermittent catheterization, or a combination.

**Penile and Urethral Anomalies**

Congenital anomalies of the urethra in boys usually involve anatomic abnormalities of the penis and vice versa. In girls, urethral anomalies may exist without other external genital abnormalities. Surgical repair is needed when function is impaired or cosmetic correction is desired.

**Chordee:** This anomaly is ventral or rotational curvature of the penis, which is most apparent with erection and is caused by fibrous tissue along the usual course of the corpus spongiosum. It is often associated with hypospadias.

**Epispadias:** The urethra opens on the dorsum of the glans or penile shaft, or at the penopubic junction. In girls, the urethra opens between the clitoris and labia or in the abdomen. Epispadias can be partial (in 15%) or complete; the most severe form occurs with bladder exstrophy (see above). Symptoms and signs are incontinence, reflux, and UTIs. Treatment is surgical. In partial epispadias, prognosis for continence with treatment is good. In the complete form, surgical reconstruction of the penis alone may lead to persistent incontinence; bladder outlet reconstruction is required to achieve complete urinary control.

**Hypospadias:** This anomaly is caused by failure of tubularization and fusion of the urethral groove. It
almost always occurs in boys, in whom the urethra opens onto the underside of the penile shaft, at the penoscrotal junction, between the scrotal folds, or in the perineum. The foreskin fails to become circumferential and appears as a dorsal hood. Hypospadias is frequently associated with chordee.

Prognosis for functional and cosmetic correction is good. Outpatient surgery at about 6 mo of age involves construction of a neourethra using penile shaft skin or foreskin and repair of the chordee.

Hypospadias is extremely rare in girls; the urethra opens into the vaginal introitus.

**Phimosis and paraphimosis:** Phimosis, the most common penile abnormality, is constriction of the foreskin with inability to retract over the glans; it may be congenital or acquired. Paraphimosis is inability of the retracted constricting foreskin to be reduced distally over the glans. (See full discussion on p. 2457.)

Phimosis may respond to topical corticosteroids and gentle stretching; some patients require circumcision.

Paraphimosis should be reduced immediately because the constricting foreskin functions as a tourniquet, causing edema and pain. Firm circumferential compression of the edematous foreskin with the fingers may reduce edema sufficiently to allow the foreskin to be restored to its normal position by pushing the glans back through the tight foreskin using both thumbs. If this technique is ineffective, a dorsal slit done using a local anesthetic relieves the condition temporarily. Circumcision is then done when edema has resolved.

**Other penile anomalies:** Less common anomalies include penile agenesis, duplication, and lymphedema. Many anomalies also involve urethral abnormality, or other anomalies, such as exstrophy. Treatment of most anomalies is surgical and may include complete removal of the genitals with sex reassignment.

Microphallus results from androgen deficiency or insensitivity; in boys with deficiency, treatment is testosterone supplementation.

**Urethral meatal stenosis:** Most commonly acquired after newborn circumcision in boys, urethral meatal stenosis is occasionally congenital and associated with hypospadias. Meatotomy is needed for a significantly deflected stream or for a pinpoint stream.

**Urethral stricture:** Urethral stricture causes obstruction along some part of the length of the urethra. It almost always occurs in boys, is usually acquired, and typically results from a crush injury after straddle trauma. Congenital urethral stricture may manifest similarly to urethral valves and may be diagnosed by prenatal ultrasonography, or postnatally by symptoms and signs of outlet obstruction or patent urachus and is confirmed by retrograde urethrography. Initial management is often with endoscopic urethrotomy, although open urethroplasty may be necessary.

**Urethral valves:** In boys, folds in the posterior urethra may act as valves impairing urine flow. Urethral valves can cause urinary hesitancy and a weak urinary stream, UTI, overflow incontinence, myogenic bladder malfunction, vesicoureteral reflux, upper urinary tract damage, and renal insufficiency. They occasionally occur with a patent urachus. Diagnosis is often made by routine prenatal ultrasonography; cases suspected postnatally are confirmed by voiding cystourethrography. Surgery (usually via endoscopy) is done at time of diagnosis to prevent progressive renal deterioration.

A much less common anomaly, diverticulum of the anterior urethra, may act as a valve (anterior urethral valve) and is also treated endoscopically.

**Vaginal Anomalies**

Most congenital anomalies of the vagina are rare. Vaginal anomalies include vaginal agenesis, obstruction, duplication, and fusion. Duplication and fusion anomalies have numerous manifestations (eg, as 2 uteri, 2 cervices, and 2 vaginas, or 2 uteri with 1 cervix and 1 vagina). Girls may also have urogenital
sinus anomalies, in which urinary and genital tracts open into a common channel, and cloacal anomalies, in which urinary, genital, and anorectal tracts open into a common channel.

Imperforate hymen manifests as a bulge at the location of the vaginal opening due to collection of uterine and vaginal secretions caused by maternal estrogens. Treatment is surgical drainage.

Diagnosis of most is by physical examination, ultrasonography, and retrograde contrast studies. Duplication and fusion anomalies may not require treatment, but others require surgical correction.

**Testicular and Scrotal Anomalies**

The most common anomalies are

- Congenital hydrocele
- Undescended testes (cryptorchidism)
- Testicular torsion (see p. 2457)

Rare anomalies include scrotal agenesis, hypoplasia, ectopia, or hemangioma; penoscrotal transposition; and bifid scrotum.

**Congenital hydrocele:** A congenital hydrocele is a collection of fluid in the scrotum between layers of the tunica vaginalis. It may be isolated or may communicate with the abdominal cavity through a patent processus vaginalis (a potential hernia space). Hydrocele manifests as a painless, enlarged scrotum. The condition may resolve spontaneously but usually requires repair if it persists after 6 to 9 mo or if it enlarges.

**Cryptorchidism**

(Undescended Testes)

Cryptorchidism is failure of one or both testes to descend into the scrotum; it is typically accompanied by inguinal hernia. Diagnosis is by examination, sometimes followed by laparoscopy or a human chorionic gonadotropin stimulation test. Treatment is surgical orchiopexy.

Cryptorchidism affects about 3% of term infants and up to 30% of preterm infants; two thirds of undescended testes spontaneously descend within the first 4 mo of life. Thus, about 0.8% of male infants require treatment.

**Pathophysiology**

Normally, the testes develop at 7 to 8 wk gestation and remain cephalad to the internal inguinal ring until about 28 wk, when they begin their descent into the scrotum guided by condensed mesenchyme (the gubernaculum). Onset of descent is mediated by hormonal (eg, androgens, mullerian-inhibiting factor), physical (eg, gubernacular regression, intra-abdominal pressure), and environmental (eg, maternal exposure to estrogenic or antiandrogenic substances) factors.

A true undescended testis remains in the inguinal canal along the path of descent or is less commonly present in the abdominal cavity or retroperitoneum. An ectopic testis is one that descends normally through the external ring but diverts to an abnormal location and lies outside the normal course of descent (eg, suprapubically, in the superficial inguinal pouch, within the perineum, or along the inner aspect of the thigh).

**Complications:** Undescended testes may cause subfertility and are associated with testicular carcinoma, mainly in the undescended testis and particularly with intra-abdominal malposition. However, in patients with one undescended testis, 10% of cancers develop on the normal side. In untreated cases
of intra-abdominal testes, testicular torsion may occur, manifesting as an acute abdomen. Almost all neonates who present with an undescended testis at birth also have an inguinal hernia (patent processus).

**Etiology**

Undescended testes are almost always idiopathic. About 10% of cases are bilateral; suspicion should be high for female virilization caused by congenital adrenal hyperplasia in phenotypic boys with bilateral, nonpalpable, undescended testes at birth (especially if associated with hypospadias).

**Symptoms and Signs**

In about 80% of cases, the scrotum is empty at birth; in the remainder of cases, a testis is palpable in the scrotum at birth but appears to ascend with linear growth because of an ectopic gubernacular attachment that restrains it from following the normal "descent" of the scrotum. Inguinal hernia rarely causes a palpable mass lesion, but the patent process is often detectable, especially in infants (but less commonly in those with ectopic undescended testes).

**Diagnosis**

- Clinical evaluation
- Sometimes laparoscopy or a human chorionic gonadotropin (hCG) stimulation test

Undescended and ectopic testes must be distinguished from hypermobile (retractile) testes, which are present in the scrotum but easily retract into the inguinal canal. Diagnosis is by physical examination; a warm environment, warm examiner's hands, and a relaxed patient are important to avoid stimulating testicular retraction.

In patients with a unilateral nonpalpable testis, a descended testis that is larger than expected suggests an atrophic undescended testis; confirmation requires abdominal laparoscopy.

For bilateral nonpalpable testes, an hCG stimulation test is done. Patients receive injections of hCG 2000 IU IM once/day for 3 to 4 days; blood levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are obtained before and testosterone levels within 24 h of the final injection. Patients with bilateral cryptorchidism should respond by producing testosterone, whereas those without testes (including genotypic females) produce none. In addition, basal levels of FSH and possibly LH are elevated.

**Treatment**

- Surgical repair

For a palpable undescended testis, treatment is surgical orchiopexy, in which the testis is brought into the scrotum and sutured into place; the associated inguinal hernia also is repaired. For nonpalpable undescended testis, abdominal laparoscopy is done; if the testis is located, it is surgically fixed in place, or if it is atrophic, the tissue is removed. Surgery should be done at about 6 mo of age because early intervention improves fertility potential and may reduce cancer risk. Also, the shorter the child, the shorter the distance necessary to place the testis into the scrotum. Atrophic undescended testes are likely the result of prenatal testicular torsion.

hCG 250 to 1000 IU IM 2 or 3 times/wk for up to 6 wk may stimulate local testosterone production and precipitate testicular descent, either complete or enough to make the testis palpable, increase its blood supply, or both, making surgery easier.

No intervention is needed for a retractile testis as long as the spermatic cord length is sufficient to allow the testis to rest in a dependent scrotal position without traction when the cremasteric reflex is not stimulated. Hypermobility usually resolves without treatment by puberty when increased testicular size
Prune-Belly Syndrome

(Triad Syndrome)

Prune-belly syndrome consists of abdominal muscle deficiency, urinary tract abnormalities, and intra-abdominal undescended testes.

The name "prune-belly syndrome" derives from the characteristic wrinkled appearance of the abdominal wall in neonates. The cause of this congenital syndrome, which occurs primarily but not exclusively in males, is unclear. Urinary abnormalities may include hydro-nephrosis, megaureters, vesicoureteral reflux, and urethral abnormalities. Severe cases may involve renal failure, bronchopulmonary dysplasia, and stillbirth.

Diagnosis is often made during routine prenatal ultrasonography. Further evaluation includes voiding cystourethrography, ultra-sonography, and isotope renography.

Urinary tract abnormalities may require open surgical reconstruction; orchidopexy can be done at the same time. If no urinary intervention is necessary, laparoscopic orchidopexy is done in childhood.
Chapter 297. Congenital Renal Transport Abnormalities

Introduction

Defects in renal tubular transport can lead to a number of metabolic disorders, some of which are serious.

For a discussion of renal transport abnormalities that are not congenital, see Ch. 237.

Bartter Syndrome and Gitelman's Syndrome

Bartter syndrome and Gitelman's syndrome are characterized by fluid, electrolyte, and hormonal abnormalities, including renal K, Na, Cl, and H wasting; hypokalemia; hyperaldosteronism; hyperreninemia; and normal BP. Findings include electrolyte, growth, and sometimes neuromuscular abnormalities. Diagnosis is assisted by urine electrolyte measurements and hormone assays but is typically a diagnosis of exclusion. Treatment consists of NSAIDs, K-sparing diuretics, low-dose ACE inhibitors, and electrolyte replacement.

Pathophysiology

Bartter syndrome and the more common Gitelman's syndrome result from deranged NaCl transport and reabsorption. In Bartter syndrome, the defect is in the ascending thick limb of the loop of Henle. In Gitelman's syndrome, the defect is in the distal tubule. Subsequent K, Na, Cl, and H wasting leads to increased renin and aldosterone release, metabolic alkalosis, hyperuricemia, and, particularly in Bartter syndrome, increased prostaglandin secretion. Hypomagnesemia is common, particularly in Gitelman's syndrome. Urinary Ca excretion is decreased in Gitelman's syndrome and is normal or increased in Bartter syndrome. In both disorders, Na wasting results in a chronically low plasma volume reflected by a normal BP despite high renin and angiotensin levels.

The features at clinical presentation vary (see Table 297-1).

[Table 297-1. Some Differences Between Bartter Syndrome and Gitelman's Syndrome]

Etiology

Both syndromes are usually autosomal recessive, although sporadic cases and other types of familial patterns can occur; there are several genotypes of both syndromes.

Symptoms and Signs

Bartter syndrome tends to manifest prenatally or during infancy or early childhood. Gitelman's syndrome tends to manifest during late childhood or adulthood. Bartter syndrome can manifest prenatally with intrauterine growth restriction and polyhydramnios. After birth, affected children with Bartter syndrome and sometimes those with Gitelman's syndrome have poor growth rates and appear undernourished. Most patients have low or low-normal BP and may have signs of volume depletion. Inability to retain K, Ca, or Mg can lead to muscle weakness, spasms, tetany, or palpitations, particularly in Gitelman's syndrome. Polydipsia, polyuria, and vomiting may also be present. Intellectual disability and nephrocalcinosis sometimes result, particularly in Bartter syndrome.

Bartter syndrome may result in premature birth and severe electrolyte disorders and symptoms, but neither Bartter syndrome nor Gitelman's syndrome typically leads to chronic renal insufficiency.

Diagnosis

• Serum and urine electrolyte levels

• Exclusion of similar disorders
Bartter syndrome and Gitelman's syndrome should be suspected in children with characteristic symptoms or incidentally noted laboratory abnormalities, such as metabolic alkalosis and hypokalemia. Measurement of urine electrolytes shows high levels of Na, K, and Cl that are inappropriate for the euvoletic or hypovolemic state of the patient. Diagnosis is by exclusion of other disorders:

- Primary and secondary aldosteronism can often be distinguished by the presence of hypertension and normal or low plasma levels of renin (see Table 94-3 on p. 800).

- Bulimia nervosa and surreptitious vomiting or laxative abuse can often be distinguished by low levels of urinary Cl (usually < 20 mmol/L).

- Surreptitious diuretic abuse can often be distinguished by low levels of urinary Cl and by a urine assay for diuretics.

Definitive diagnosis is through genetic testing, which is not commercially available and thus is rarely done.

Gitelman's syndrome can usually be differentiated from Bartter syndrome by the presence of hypomagnesemia and hypocalciuria.

**Treatment**

- NSAIDs
- Spironolactone or amiloride
- Low-dose ACE inhibitors
- K, Mg, and Ca supplements

The combination of NSAIDs (eg, indomethacin 1 to 2 mg/kg po once/day) and a K-sparing diuretic (eg, spironolactone 150 mg po bid or amiloride 10 to 20 mg po bid) helps correct most features. Plasma electrolyte levels can be further improved by using ACE inhibitors (at low doses to minimize further hypovolemia and hypotension). However, no therapy can completely eliminate K wasting, and K supplementation (KCl 20 to 40 mEq po once/day or bid) is often necessary. Mg and Ca supplements may also be needed.

Exogenous growth hormone is sometimes considered to treat short stature in affected children, but this treatment is not widely used.

**Cystinuria**

Cystinuria is an inherited defect of the renal tubules in which resorption of the amino acid cystine is impaired, urinary excretion is increased, and cystine stones form in the urinary tract. Symptoms are colic caused by stones and perhaps urinary infection or the sequela of renal failure. Diagnosis is by measurement of cystine excretion in the urine. Treatment is with increased fluid intake and alkalinization of the urine.

Cystinuria is inherited as an autosomal recessive trait. Heterozygotes may excrete increased quantities of cystine in the urine but seldom enough to form stones. Cystinuria should not be confused with cystinosis (see p. 2423).

**Pathophysiology**

The primary defect is in one of several genes responsible for cystine transport in the kidneys and intestine. Diminished renal tubular resorption of cystine increases cystine concentration in the urine. Cystine is poorly soluble in acidic urine, so that when its urinary concentration exceeds its solubility,
crystals precipitate and stones form.

Resorption of dibasic amino acids (lysine, ornithine, arginine) is also impaired but causes no problems because these amino acids have an alternative transport system separate from that shared with cystine. Furthermore, they are more soluble than cystine in urine, and their increased excretion does not result in crystal or stone formation. Their absorption (and that of cystine) is also decreased in the small bowel.

Symptoms and Signs

Symptoms, most commonly renal colic, may occur in infants but usually appear between ages 10 and 30. UTI and renal failure due to obstruction may develop.

Diagnosis

• Measurement of urinary cystine excretion

Radiopaque cystine stones form in the renal pelvis or bladder. Staghorn stones are common. Cystine may appear in the urine as yellow-brown hexagonal crystals. Excessive cystine in the urine may be detected with the nitroprus-side cyanide test. Diagnosis is confirmed by observing a cystine excretion of > 400 mg/day (normal is < 30 mg/day).

Treatment

• High fluid intake
• Alkalinization of the urine

Eventually, end-stage renal disease usually develops. Decreasing the urinary concentration of cystine decreases renal toxicity. This decrease is accomplished by increasing urine volume. Fluid intake must be sufficient to provide a urine flow rate of 3 to 4 L/day. Hydration is particularly important at night when urinary pH drops. Alkalinization of the urine to pH > 7.0 with K citrate or KHCO₃ 1 mEq/kg po tid to qid and perhaps acetazolamide 5 mg/kg (up to 250 mg) po at bedtime increases the solubility of cystine significantly. Mild restrictions of dietary Na (100 mEq/day) and protein (0.8 to 1.0 g/kg/day) may help reduce cystine excretion.

When high fluid intake and alkalinization do not reduce stone formation, other drugs may be tried. Penicillamine (7.5 mg/kg po qid in young children and 125 mg to 0.5 g po qid in older children) is effective, but toxicity limits its usefulness. About half of all patients develop some toxic manifestation, such as fever, rash, arthralgias, or, less commonly, nephrotic syndrome, pancytopenia, or SLE-like reaction. Pyridoxine supplements (50 mg po once/day) should be given with penicillamine. Tiopronin (100 mg to 300 mg po qid) is being used instead of penicillamine to treat some children. Captopril (0.3 mg/kg po tid) is not as effective as penicillamine but is much less toxic. Close monitoring of response to therapy is very important.

Hartnup Disease

Hartnup disease is a rare disease due to abnormal absorption and excretion of tryptophan and other amino acids. Symptoms are rash, CNS abnormalities, short stature, headache, and collapsing or fainting. Diagnosis is by high urinary content of tryptophan and other amino acids. Prevention is with niacinamide or niacin, and attacks are treated with nicotinamide.

Hartnup disease is caused by a mutation in the Na-dependent neutral amino acid transporter gene that is expressed in kidney and intestinal epithelia. It is inherited as an autosomal recessive trait. Small-bowel malabsorption of tryptophan, phenylalanine, methionine, and other monoaminomonocarboxylic amino acids occurs. Accumulation of unabsorbed amino acids in the GI tract increases their metabolism by bacterial flora. Some tryptophan degradation products, including indoles, kynurenine, and serotonin, are absorbed by the intestine and appear in the urine. Renal amino acid resorption is also defective, causing a generalized aminoaciduria involving all neutral amino acids except proline and hydroxyproline.
Conversion of tryptophan to niacinamide is also defective.

**Symptoms and Signs**

Although the disorder is present from birth, symptoms may manifest in infancy, childhood, or early adulthood. Symptoms may be precipitated by sunlight, fever, drugs, or other stresses.

Poor nutritional intake nearly always precedes appearance of symptoms. Symptoms and signs are due to niacinamide deficiency and resemble those of pellagra (see p. 31), particularly the rash on parts of the body exposed to the sun; mucous membrane and neurologic symptoms also occur. Neurologic manifestations include cerebellar ataxia and mental abnormalities. Intellectual disability, short stature, headache, and collapsing or fainting are common.

**Diagnosis**

- Urine testing for amino acids

Diagnosis is made by showing the characteristic amino acid excretion pattern in the urine. Indoles and other tryptophan degradation products in the urine provide supplementary evidence of the disease.

**Treatment**

- Niacin or niacinamide supplements
- Nicotinamide for attacks

Prognosis is good, and frequency of attacks usually diminishes with aging. The number and severity of attacks can be reduced by maintaining good nutrition and supplementing the diet with niacin or niacinamide 50 to 100 mg po tid. Attacks may be treated with nicotinamide 20 mg po once/day.

**Hypophosphatemic Rickets**

(Vitamin D-Resistant Rickets)

Hypophosphatemic rickets is a disorder characterized by hypophosphatemia, defective intestinal absorption of Ca, and rickets or osteomalacia unresponsive to vitamin D. It is usually hereditary. Symptoms are bone pain, fractures, and growth abnormalities. Diagnosis is by serum phosphate, alkaline phosphatase, and 1,25-dihydroxyvitamin D₃ levels. Treatment is oral phosphate plus calcitriol.

Familial hypophosphatemic rickets is usually inherited as an X-linked dominant trait; other familial patterns occur but are rarer.

Sporadic acquired cases sometimes are associated with benign small-cell mesenchymal tumors that produce a humoral factor that decreases proximal renal tubular resorption of phosphate (oncogenic rickets).

**Pathophysiology**

The observed abnormality is decreased proximal renal tubular resorption of phosphate, resulting in hypophosphatemia. This defect is due to a circulating factor or factors and is associated with a primary abnormality in osteoblast function. Decreased intestinal Ca and phosphate absorption also occurs. Deficient bone mineralization is due to low phosphate levels and osteoblast dysfunction rather than to the low Ca and elevated parathyroid hormone (PTH) levels in Ca-deficient rickets (see p. 41). Because 1,25-dihydroxyvitamin D₃ levels are normal to slightly low, a defect in conversion is presumed; hypophosphatemia would normally cause elevated 1,25-dihydroxyvitamin D₃ levels.
**Symptoms and Signs**

The disease manifests as a spectrum of abnormalities, from hypophosphatemia alone to growth retardation and short stature to severe rickets or osteomalacia. Children usually present after they begin walking, with bowing of the legs and other bone deformities, pseudofractures, bone pain, and short stature. Bony outgrowth at muscle attachments may limit motion. Rickets of the spine or pelvis, dental enamel defects, and tetany that occur in dietary vitamin D deficiency are rarely present in hypophosphatemic rickets.

**Diagnosis**

- Serum levels of Ca, phosphate, alkaline phosphatase, 1,25-dihydroxyvitamin D₃, and PTH
- Urinary phosphate levels

Serum phosphate levels are depressed, but urinary phosphate excretion is large. Serum Ca and PTH are normal, and alkaline phosphatase often is elevated. In Ca-deficient rickets, hypocalcemia is present, hypophosphatemia is mild or absent, and urinary phosphate is not elevated.

**Treatment**

- Oral phosphate and calcitriol

Treatment consists of neutral phosphate solution or tablets. Starting dose in children is 10 mg/kg (based on elemental phosphorus) po qid. Because this phosphate may cause hyperparathyroidism, vitamin D is given as calcitriol, initially 5 to 10 ng/kg po bid. Phosphate dose may need to be increased to achieve bone growth or relieve bone pain. Diarrhea may limit oral phosphate dosage. Increase in plasma phosphate and decrease in alkaline phosphatase concentrations, healing of rickets, and improvement of growth rate occur. Hypercalcemia, hypercalciuria, and nephrocalcinosis with reduced renal function may complicate treatment. Patients undergoing treatment need frequent follow-up evaluations.

Adults with oncogenic rickets may dramatically improve once the mesenchymal tumor that causes the disorder is removed. Otherwise, oncogenic rickets is treated with calcitriol 5 to 10 ng/kg po bid and elemental phosphorus 250 mg to 1 g po tid or qid.
Chapter 298. Congenital Neurologic Anomalies

Introduction

Some of the most serious neurologic anomalies (eg, anencephaly, encephalocele, spina bifida) develop in the first 2 mo of gestation and represent defects in neural tube formation (dysraphism). Others, such as lissencephaly, result from problems with neuronal migration, which occurs between 9 wk and 24 wk of gestation. Hydranencephaly and porencephaly are secondary to destructive processes that occur after the brain has formed. Some anomalies (eg, meningocele) are relatively benign.

Amniocentesis (see p. 2602) and ultra-sonography (see p. 2600) permit accurate in utero detection of many malformations. Parents need psychologic support when a malformation is detected and also genetic counseling, because the risk of having a subsequent child with such a malformation is high.

Women who have had a fetus or infant with a neural tube defect should take folate (folic acid) supplementation 4 mg po once/day beginning 3 mo before conception and continuing through the 1st trimester. Folate supplementation reduces the risk of neural tube defects in future pregnancies by 75%.

All women of childbearing age who have not had a fetus or infant with a neural tube defect should consume at least 400 µg/day of folate through diet or by taking a supplement (some experts recommend 800 µg/day to further reduce risk) and continue doing so through the 1st trimester. Although folate supplementation reduces the risk of having a child with a neural tube defect, risk reduction is less than in women who previously had a fetus or infant with a neural tube defect (ie, risk reduction is < 75%).

Brain Anomalies

Congenital brain anomalies usually cause severe neurologic deficits; some may be fatal.

Hydrocephalus

Hydrocephalus is ventricular enlargement with excessive CSF. Manifestations include an enlarged head and brain atrophy. Increased cranial pressure causes irritability and a bulging fontanelle in infants. Diagnosis is by ultrasonography in neonates and young infants with an open fontanelle and by CT or MRI in older infants and children. Treatment usually is with a ventricular shunt procedure.

Hydrocephalus is the most common cause of abnormally large heads in neonates. Hydrocephalus that develops only after the fontanelles have closed does not increase head circumference but can markedly increase intracranial pressure.

Etiology

Hydrocephalus can result from

• Obstruction of CSF flow (obstructive hydrocephalus)

• Impaired resorption of CSF (communicating hydrocephalus)

Obstruction most often occurs in the aqueduct of Sylvius but sometimes at the outlets of the 4th ventricle (Luschka and Magendie foramina). Obstructive hydrocephalus can be caused by Dandy-Walker malformation or Chiari II type (formerly Arnold-Chiari) malformation. Dandy-Walker malformation is progressive cystic enlargement of the 4th ventricle. In Chiari II type malformation, which frequently occurs with spina bifida (see p. 2995) and syringomyelia (see p. 1812), severe elongation of the cerebellar tonsils causes them to protrude through the foramen magnum, with beaking of the colliculi and thickening of the upper cervical spinal cord.
Impaired resorption in the subarachnoid spaces usually results from meningeal inflammation, secondary either to infection or to blood in the subarachnoid space (eg, in the premature infant who has intraventricular hemorrhage).

Symptoms and Signs

Neurologic findings depend on whether intracranial pressure is increased, symptoms of which in infants include irritability, high-pitched cry, vomiting, lethargy, strabismus, and bulging fontanelle. Older, verbal children may complain of headache, decreased vision, or both. Papilledema is a late sign of increased intracranial pressure; initial absence is not reassuring.

Consequences of chronic hydrocephalus may include precocious puberty in girls, learning disorders (eg, difficulties with attention, information processing, and memory), and impaired executive function (eg, problems with conceptualizing, abstracting, generalizing, reasoning, and organizing and planning information for problem-solving).

Diagnosis

• Prenatal ultrasonography
• Neonates: Cranial ultrasonography
• Older infants and children: CT or MRI

Diagnosis is often made by routine prenatal ultrasonography. After birth, diagnosis is suspected if routine examination reveals an increased head circumference; infants may have a bulging fontanelle or widely separated cranial sutures. Similar findings can result from intracranial, space-occupying lesions (eg, subdural hematomas, porencephalic cysts, tumors). Macrocephaly may result from an underlying brain problem (eg, Alexander disease or Canavan disease) or it may be benign, such as when excessive CSF surrounds a normal brain. Children suspected of having hydrocephalus require cranial imaging by CT, MRI, or ultrasonography (if the anterior fontanelle is open). Cranial CT or ultrasonography is used to monitor progression of hydrocephalus once an anatomic diagnosis has been made. If seizures occur, an EEG may be helpful.

Treatment

• Usually a ventricular shunt procedure

Treatment depends on etiology, severity, and whether hydrocephalus is progressive (ie, size of the ventricles increases over time relative to the size of the brain). To temporarily reduce CSF pressure in infants, ventricular taps or serial lumbar punctures (if the hydro-cephalus is communicating) may be used. Progressive hydrocephalus usually requires a ventricular shunt. Shunts typically connect the right lateral ventricle to the peritoneal cavity or, rarely, to the right atrium via a plastic tube with a one-way, pressure-relief valve. When a shunt is first placed in an infant or older child whose fontanelle is closed, rapid withdrawal of fluid can cause subdural bleeding as the brain shrinks away from the skull. When the fontanelles are open, the skull can decrease in circumference to match the decrease in brain size; thus, some clinicians recommend an early decision regarding shunt placement so that it can be done before fontanelle closure.

In a third ventriculostomy, an opening is created endoscopically between the 3rd ventricle and the subarachnoid space, allowing CSF to drain. This procedure is often combined with ablation of the choroid plexus and is becoming more common, particularly in less developed countries where access to emergency neurosurgical care is often limited. In certain cases (eg, hydrocephalus caused by primary aqueductal stenosis), third ventriculostomy may be adequate primary treatment.

A ventricular shunt that goes to the subgaleal space may be used in infants as a temporary measure for patients who may not require a more permanent shunt.
Although some children do not need the shunt as they age, shunts are rarely removed because of the risk of bleeding and trauma. Fetal surgery to treat congenital hydrocephalus has not been successful.

**Shunt complications:** The type of ventricular shunt used depends on the neurosurgeon's experience, although ventriculoperitoneal shunts cause fewer complications than ventriculoatrial shunts. Shunt complications include

- Infection
- Malfunction

Any shunt has a risk of infection. Manifestations include chronic fever, lethargy, irritability, headache, or a combination and other symptoms and signs of increased intracranial pressure; sometimes redness becomes apparent over the shunt tubing. Antibiotics effective against the organism infecting the shunt, which may include skin flora, are given, and typically the shunt must be removed and replaced.

Shunts can malfunction due to mechanical obstruction (typically blockage at the ventricular end) or to fracture of the tubing. In either case, intracranial pressure can increase, which, if sudden, can be a medical emergency. Children present with headache, vomiting, lethargy, irritability, esotropia, or paralysis of upward gaze. Seizures may occur. If the obstruction is gradual, more subtle symptoms and signs can occur, such as irritability, poor school performance, and lethargy, which may be mistaken for depression. To assess shunt function, a shunt series (x-rays of the shunt tubing) and neuroimaging studies are done. The ability to compress the bulb that is present on many shunt systems is not a reliable sign of shunt function.

After the shunt is placed, head circumference and development are assessed, and imaging is done periodically.

**Other Brain Anomalies**

**Anencephaly:** This anomaly is absence of the cerebral hemispheres. The absent brain is sometimes replaced by malformed cystic neural tissue, which may be exposed or covered with skin. Parts of the brain stem and spinal cord may be missing or malformed. Infants are stillborn or die within days or weeks. Treatment is supportive.

**Encephalocele:** This anomaly is a protrusion of nervous tissue and meninges through a skull defect. The defect is caused by incomplete closure of the cranial vault (cranium bifidum). Encephaloceles usually occur in the midline and protrude anywhere along a line from the occiput to the nasal passages but can be present asymmetrically in the frontal or parietal regions. Small encephaloceles may resemble cephalhematomas, but x-rays show a bony skull defect at their base. Hydrocephalus (see p. 2992) often occurs with encephalocele. About 50% of affected infants have other congenital anomalies. Symptoms and signs include the visible defect, seizures, and impaired cognition, including intellectual and developmental disability.

Prognosis, which depends on the location and size of the lesion, is often good. Most encephaloceles can be repaired. Even large ones often contain mostly heterotopic nervous tissue, which can be removed without worsening functional ability. When other serious malformations coexist, the decision to repair may be more difficult.

**Malformed cerebral hemispheres:** Cerebral hemispheres may be large, small, or asymmetric; the gyri may be absent, unusually large, or multiple and small; and microscopic sections of normal-appearing brain may show disorganization of the normal laminar neuronal arrangement. Microcephaly, moderate to severe motor and intellectual disability, and epilepsy often occur with these defects. Treatment is supportive, including anticonvulsants, if needed.

**Holoprosencephaly** occurs when the embryonic prosencephalon does not undergo segmentation and cleavage. The anterior midline brain, cranium, and face are abnormal. This malformation may be caused by defects of the *sonic hedgehog* gene. Severely affected fetuses may die before birth. Treatment is
Lissencephaly consists of an abnormally thick cortex, reduced or abnormal lamination, and diffuse neuronal heterotopia. It is caused by abnormal neuronal migration, the process by which immature neurons attach to radial glia and move from their points of origin near the ventricle to the cerebral surface. Several single-gene defects may cause this anomaly (eg, \textit{LIS1}). Affected infants may have intellectual disability, muscle spasms, and seizures. Treatment is supportive, but many children die before age 2 yr.

Polymicrogyria, in which the gyri are small and overabundant, is believed to result from injuries occurring between 17 wk and 26 wk gestation. It can cause intellectual disability and seizures. Treatment is supportive.

Porencephaly: This anomaly is a cyst or cavity in a cerebral hemisphere that communicates with a ventricle. It may develop prenatally or postnatally. Porencephaly may be caused by a developmental anomaly, inflammatory disease, or a vascular accident such as intraventricular hemorrhage with parenchymal extension. Neurologic examination is usually abnormal. Diagnosis is confirmed by cranial CT, MRI, or ultrasonography. Progressive hydrocephalus occurs rarely with porencephaly. Prognosis is variable; a few children develop only minor neurologic signs and have normal intelligence. Treatment is supportive.

Hydranencephaly is an extreme form of porencephaly in which the cerebral hemispheres are almost totally absent. Usually, the cerebellum and brain stem are formed normally, and the basal ganglia are intact. The meninges, bones, and skin over the cranial vault are normal. Often hydranencephaly is diagnosed by prenatal ultrasonography. Neurologic examination is usually abnormal, and the infant does not develop normally. Externally, the head may appear normal, but when transilluminated, light shines completely through. CT or ultrasonography confirms the diagnosis. Children with this condition often have seizures and intellectual disability. Treatment is supportive, with shunting if head growth is excessive.

Schizencephaly, which many classify as a form of porencephaly, results from formation of abnormal slits, or clefts, in the cerebral hemispheres. Unlike porencephalies, however, which are thought to result from brain injury, schizencephaly is thought to represent a defect in neuronal migration and is thus a true malformation. Affected infants often have seizures and developmental delay and, depending on the location of the defect, may have focal neurologic findings such as weakness. Treatment is supportive.

Septo-optic dysplasia: This anomaly (also called de Morsier’s syndrome) is a malformation of the front of the brain that occurs toward the end of the first month of gestation and includes optic nerve hypoplasia, absence of the septum pellucidum (the membranes that separate the front of the 2 lateral ventricles), and pituitary deficiencies. Although the cause may be multiple, abnormalities of one particular gene (\textit{HESX1}) have been found in some children with septo-optic dysplasia. Symptoms may include decreased visual acuity in one or both eyes, nystagmus, strabismus, and endocrine dysfunction (including growth hormone deficiency, hypothyroidism, adrenal insufficiency, diabetes insipidus, and hypogonadism). Seizures may occur. Although some children have normal intelligence, others have learning disabilities, intellectual disability, cerebral palsy, or other developmental delay. Diagnosis is by MRI. All children diagnosed with this anomaly should be screened for endocrine and developmental dysfunction. Treatment is supportive.

Spina Bifida

Spina bifida is defective closure of the vertebral column. Although the cause is not known, low folate levels during pregnancy increase risk. Some children are asymptomatic, and others have severe neurologic dysfunction below the lesion. Open spina bifida can be diagnosed prenatally by ultra-sonography or suggested by elevated α-fetoprotein levels in maternal serum and amniotic fluid. After birth, a lesion is typically visible on the back. Treatment is usually surgical.

Spina bifida is one of the most serious neural tube defects compatible with prolonged life. This defect is one of the more common congenital anomalies overall, with an incidence in the US of about 1/1500. It is most common in the lower thoracic, lumbar, or sacral region and usually extends for 3 to 6 vertebral
segments. Severity ranges from occult, in which there are no apparent anomalies, to protruding sacs (spina bifida cystica), to a completely open spine (rachischisis) with severe neurologic disability and death.

In occult spinal dysraphism (OSD), anomalies of the skin overlying the lower back (typically in the lumbosacral area) occur; these include sinus tracts that have no visible bottom, are above the lower sacral area, or are not in the midline; hyperpigmented areas; and tufts of hair (see Fig. 298-1). These children often have anomalies in the underlying portion of the spinal cord, such as lipomas and tethering (in which the cord has an abnormal attachment).

In spina bifida cystica, the protruding sac can contain meninges (meningocele), spinal cord (myelocele), or both (myelomeningocele). In a myelomeningocele, the sac usually consists of meninges with a central neural plaque. If not well covered with skin, the sac can easily rupture, increasing the risk of meningitis.

Hydrocephalus is common because many children have a Chiari II type malformation (see p. 2992).

Other congenital anomalies, such as syringomyelia and soft-tissue masses around the spinal cord, may be present.

Etiology

Causes seem multifactorial. Folate deficiency is a significant factor, and there seems to be a genetic component. Other risk factors include maternal use of certain drugs (eg, valproate) and maternal diabetes.

Symptoms and Signs

Many children with minor defects are asymptomatic.

Neurologic: When the spinal cord or lumbosacral nerve roots are involved, as is usual, varying degrees of paralysis and sensory deficits are present below the lesion. Rectal tone is usually decreased.

Hydrocephalus (see p. 2992) may cause minimal symptoms or signs of increased intracranial pressure. Brainstem involvement may cause manifestations such as stridor, swallowing difficulties, and intermittent apnea.

Orthopedic: Lack of muscle innervation leads to atrophy of the legs. Because paralysis occurs in the fetus, orthopedic problems may be present at birth (eg, clubfoot, arthrogryposis of the legs, dislocated hip). Kyphosis is sometimes present and can hinder surgical closure and prevent the child from lying supine.

[U] [Fig. 298-1. Forms of spina bifida.]

Scoliosis may develop later and is more common among children with higher lesions (ie, above L3).

Urologic: Paralysis also impairs bladder function, occasionally leading to a neurogenic bladder and, consequently, urinary reflux, which can cause hydronephrosis, frequent UTIs, and, ultimately, kidney damage.

Diagnosis

• Ultrasonography or MRI

Spinal cord imaging, with ultrasonography or MRI, is essential in children with OSD; even children with minimal cutaneous findings may have underlying spinal abnormalities (those with overt defects do not require spinal cord imaging because the anatomy is known). Plain x-rays of the spine, hips, and, if they are malformed, lower extremities are done. Cranial imaging using ultrasonography, CT, or MRI is done to look for hydrocephalus.
Once the diagnosis of spina bifida is made, urinary tract evaluation is essential and includes urinalysis, urine culture, BUN and creatinine determination, and ultrasonography. Measurement of bladder capacity and pressure at which urine exits into the urethra can determine prognosis and intervention. Need for further testing, such as urodynamics and voiding cystourethrogram, depends on previous findings and associated anomalies.

**Screening:** Prenatal screening can be done by doing fetal ultrasonography and by measuring maternal serum levels of α-fetoprotein (see p. 2603), ideally between 16 and 18 wk gestation; levels can also be done on amniotic fluid samples if previous testing suggests an increased risk. Elevated levels suggest increased risk of spina bifida cystica (OSD rarely causes elevated levels).

**Prognosis**

Prognosis varies by the level of cord involvement and the number and severity of associated anomalies. Prognosis is worse for children with higher cord level (eg, thoracic) lesions or who have kyphosis, hydrocephalus, early hydronephrosis, and associated congenital anomalies. With proper care, however, most children do well. Loss of renal function and ventricular shunt complications are the usual causes of death in older children.

**Treatment**

• Surgical repair of the spinal lesion

• Sometimes a ventricular shunt

• Various measures for orthopedic and urologic complications

Without early surgical treatment, neurologic damage can progress in OSD. Treatment for all spina bifida requires a united effort by specialists from several disciplines; neurosurgical, urologic, orthopedic, pediatric, and social service evaluations are important. It is important to assess the type, vertebral segment, and extent of the lesion; the infant's health status; and associated anomalies. Discussion with the family should ascertain the family's strengths, desires, and resources, and community resources, including availability of ongoing care.

A meningomyelocele identified at birth is covered immediately with a sterile dressing. If the meningomyelocele is leaking CSF, antibiotics are started to prevent meningitis. Neurosurgical repair of a meningomyelocele or an open spine typically is done within the first 72 h after birth to reduce the risk of meningeal or ventricular infection. If the lesion is large or is in a difficult location, plastic surgeons may be consulted to ensure adequate closure.

Hydrocephalus may require a shunt procedure in the neonatal period; sometimes a ventricular shunt is inserted when the back is repaired.

Kidney function must be monitored closely, and UTI should be treated promptly. Obstructive uropathy at either the bladder outlet or ureteral level must be treated vigorously to prevent infection. When children are between 2 and 3 yr of age, or at any time if they have elevated pressure in the bladder with vesicoureteral reflux, clean intermittent catheterization is done to empty the bladder on a regular basis. Catheterization increases continence and maintains bladder and kidney health.

At around the same time, children are placed on the commode or toilet after meals to encourage fecal continence. Well-balanced diets are encouraged; stool softeners, laxatives, or a combination may be helpful to ensure regular bowel movements and to increase continence. In older children, an antegrade colonic enema procedure, in which a hole is placed through the abdominal wall into the colon to allow infusion of liquids, can improve continence. The hole is kept open by a tube (eg, a gastrostomy feeding tube).

Orthopedic care should begin early. If a club-foot is present, a cast is applied; surgery is often necessary.
after casting. Hip joints are checked for dislocation. Affected children should be monitored for development of scoliosis, pathologic fractures, pressure sores, and muscle weakness and spasm.

**Prevention**

Folate supplementation (400 to 800 μg po once/day) in women beginning 3 mo before conception and continuing through the 1st trimester reduces the risk of neural tube defects (see p. 2992).
Chapter 299. Chromosomal Anomalies

Introduction

Chromosomal anomalies cause various disorders. Anomalies that affect autosomes (the 22 paired chromosomes that are alike in males and females) are more common than those that affect sex chromosomes (X and Y). Chromosomal abnormalities fit into several major categories:

- Trisomies (extra chromosomes)
- Translocations (anomalies in which segments of chromosomes inappropriately join with other chromosomes)
- Deletions and duplications of various chromosomes or parts of chromosomes
- Mosaicism (anomalies in which a person starting from a single fertilized egg develops ≥ 2 cell lines differing in genotype [genetic constitution])

Some specific terms from the field of genetics are important for describing chromosomal anomalies:

- Karyotype: The full set of chromosomes in a person's cells.
- Genotype: The genetic constitution determined by the karyotype.
- Phenotype: The person's outward appearance—the biochemical, physiologic, and physical makeup as determined by the genotype and environmental factors (see p. 3374).

Diagnosis

Lymphocytes are used for chromosomal analysis, except prenatally, when amniocytes or cells from placental chorionic villi are used (see p. 2602). A karyotype analysis involves blocking cells in mitosis during metaphase and staining the condensed chromosomes. Chromosomes from single cells are photographed, and their images are arranged, forming a karyotype.

Several techniques are used to better delineate the chromosomes:

- In classical banding (eg, G [Giemsa]-, Q [fluorescent]-, and C-banding), a dye is used to stain bands on the chromosomes.
- High-resolution chromosome analysis uses special culture methods to obtain a high percentage of prophase and prometaphase spreads. The chromosomes are less condensed than in routine metaphase analysis, and the number of identifiable bands is expanded, allowing a more sensitive karyotype analysis.
- Spectral karyotyping analysis (also called chromosome painting) uses chromosome-specific multicolor fluorescent in situ hybridization (FISH) techniques that improve the visibility of certain defects, including translocations and inversions.
- Comparative genomic hybridization is a single-step technique that allows the entire genome to be scanned for mutations, including increases (duplications) or decreases (deletions) in DNA and unbalanced translocations.

Fragile X Syndrome

Fragile X syndrome is a genetic abnormality in an X chromosome that leads to intellectual disability and behavioral disorders.

Fragile X syndrome is the most common inherited cause of intellectual disability. The symptoms of fragile...
X syndrome are caused by abnormalities in DNA on the X chromosome. It affects about 1/4000 males and 1/8000 females. Females with the disorder are typically less impaired than males. Fragile X is inherited in an X-linked pattern and does not always cause clinical symptoms.

Examination of the karyotype reveals a constriction at the end of the long arm of the X chromosome, followed by a thin strand of genetic material. The constriction and thin strand give the appearance of a fragile portion of the X chromosome. Sequencing of the genetic material reveals a repeating base pair triplet that is responsible for the syndrome.

**Symptoms and Signs**

People with fragile X syndrome have physical, cognitive and behavioral abnormalities. They have large, protuberant ears; a prominent chin and forehead; a high arched palate; and, in postpubertal males, macroorchidism. The joints may be hyperextensible, and heart disease (mitral valve prolapse) may occur. Cognitive abnormalities may include mild to moderate intellectual disability. Features of autism may develop, including perseverative speech and behavior, poor eye contact, and social anxiety. Women may experience menopause in their mid-30s.

**Diagnosis**

Fragile X syndrome is frequently not suspected until school age or adolescence, depending on the severity of the symptoms. Boys with autism and intellectual disability should be tested for fragile X syndrome. DNA testing can detect abnormal DNA on the fragile X chromosome. The greater the number of abnormal repetitions of DNA found, the more likely the child will have symptoms.

**Treatment**

Early intervention, including speech and language therapy and occupational therapy, can help children with fragile X syndrome to maximize their abilities. Stimulants, antidepressants, and antianxiety drugs may be beneficial for some children.

**Down Syndrome**

(Trisomy 21; Trisomy G)

Down syndrome is an anomaly of chromosome 21 that causes intellectual disability, microcephaly, short stature, and characteristic facies. Diagnosis is suggested by physical anomalies and abnormal development and confirmed by karyotype analysis. Treatment depends on specific manifestations and anomalies.

Overall incidence among live births is about 1/800 but increases as maternal age increases. At 20 yr of maternal age, the risk is 1/2000 births; at 35, it is 1/365; and at 40, it is 1/100. However, because most births occur among younger women, just 20% of infants with Down syndrome are born to mothers > 35 yr.

**Etiology**

In about 95% of cases, there is an extra whole chromosome 21 (trisomy 21), which is almost always maternally derived. Some people with Down syndrome have the normal 46 chromosomes, but a piece of an additional chromosome 21 has been translocated to another chromosome. The most common translocation is t(14;21), in which a piece of an additional chromosome 21 is attached to chromosome 14. In about half of the cases, both parents have normal karyotypes, indicating a de novo translocation. In the other half, one parent (almost always the mother), although phenotypically normal, has only 45 chromosomes, one of which is t(14;21). Theoretically, the chance that a carrier mother will have a child with Down syndrome is 1:3, but the actual risk is lower (about 1:10). If the father is the carrier, the risk is only 1:20. The next most common translocation is t(21;22). In these cases, carrier mothers have about a 1:10 risk of having a child with Down syndrome; the risk is smaller for carrier fathers.

Down syndrome mosaicism presumably results from nondisjunction (when chromosomes fail to pass to
Pathophysiology

As with most conditions that result from chromosome imbalance, Down syndrome affects multiple systems and causes both structural and functional defects (see Table 299-1). Not all defects are present in each person.

Most people have some degree of cognitive impairment, ranging from severe (IQ 20 to 35) to mild (IQ 50 to 75). Gross motor and language delays also are evident early in life. Height is significantly reduced, and the person has an increased risk of obesity. About 40 to 50% of affected neonates have congenital heart disease; ventricular septal defect and atrioventricular canal (endocardial cushion) defect are most common. About 5% of people have GI anomalies, particularly duodenal atresia, sometimes along with annular pancreas. Hirschsprung's disease and celiac disease also are more common. Many people develop endocrinopathies, including thyroid disease (most often hypothyroidism) and diabetes. Atlanto-occipital and atlantoaxial hypermobility, as well as bony anomalies of the cervical spine, can cause atlanto-occipital and cervical instability; weakness and paralysis may result. About 60% of people have eye problems, including congenital cataracts, glaucoma, strabismus, and refractive errors. Most people have hearing loss, and ear infections are very common.

Table 299-1. Some Complications of Down Syndrome*

The aging process seems to be accelerated. The median age at death is 49; however, many reach their 50s or 60s. Life expectancy is decreased primarily by heart disease and, to a lesser degree, by increased susceptibility to infections and acute myelocytic leukemia. Many people develop clinical signs of Alzheimer's disease at an early age, and at autopsy, brains of adults with Down syndrome show typical microscopic findings. The results of recent research indicate that blacks with Down syndrome have a substantially shorter life span than whites. This finding may be the result of poor access to medical, educational, and other support services.

Affected women have a 50% chance of having a fetus that also has Down syndrome. However, many affected fetuses abort spontaneously. Men with Down syndrome are infertile, except for those with mosaicism.

Symptoms and Signs

Affected neonates tend to be placid, rarely cry, and have hypotonia. Most have a flat facial profile (particularly flattening of the bridge of the nose), although some appear normal at birth and then develop characteristic facial features during infancy. A flattened occiput, microcephaly, and extra skin around the back of the neck are common. The outer sides of the eyes are slanted upward, and epicanthal folds at the inner corners usually are present. Brushfield's spots (gray to white spots resembling grains of salt around the periphery of the iris) may be visible. The mouth is often held open because of a large, protruding, furrowed tongue that lacks the central fissure. The ears are often small and rounded. The hands are short and broad and often have a simian crease (a single, palmar crease). The fingers are short, with clinodactyly (incurving) of the 5th digit, which often has only 2 phalanges. The feet may have a wide gap between the 1st and 2nd toes, and a plantar furrow often extends backward on the foot. Hands and feet show characteristic dermatoglyphics.

As affected children grow, retardation of physical and mental development quickly becomes apparent. Stature is short, and the mean IQ is about 50. Behavior suggestive of attention-deficit/hyperactivity disorder is often present in childhood, and the incidence of autistic behavior is increased (particularly in those with profound intellectual disability). Depression is common among children and adults.

Symptoms of heart disease are determined by the type and extent of the cardiac anomaly. Infants with
ventricular septal defects can either be asymptomatic or show signs of heart failure (eg, labored breathing, fast respiratory rate, difficulty with feeding, sweating, poor weight gain). A high-frequency, 2/6 or louder systolic murmur may be present depending on the size of the defect. Infants with atrioventricular canal defects can show signs of heart failure or be asymptomatic. Characteristic heart sounds include a wide fixed splitting of the second sound. Murmurs may not be appreciated; however, a number of different murmurs are possible.

Infants with Hirschsprung's disease usually have delay in passage of meconium for 48 h after birth. Severely affected infants may have signs of intestinal obstruction (eg, bilious vomiting, failure to pass stool, abdominal distention). Duodenal atresia or stenosis can manifest with bilious vomiting or with no symptoms, depending on the extent of the stenosis.

**Diagnosis**

- Prenatal amniocentesis with karyotype analysis

Sometimes neonatal karyotype analysis (if prenatal diagnosis not done)

Diagnosis may be suspected prenatally based on physical anomalies detected by fetal ultra-sonography (eg, nuchal translucency) or based on abnormal levels of plasma protein A in late 1st trimester and α-fetoprotein, β-hCG (human chorionic gonadotropin), unconjugated estriol, and inhibin in early 2nd trimester (15 to 16 wk gestation) on maternal serum screening. The diagnosis is confirmed by amniocentesis with karyotyping. Screening and diagnostic testing for Down syndrome are recommended for all women who present for prenatal care before 20 wk gestation regardless of maternal age. If diagnosis is not made prenatally, then neonatal diagnosis is based on physical anomalies and confirmed by karyotype analysis.

**Concomitant medical conditions:** Certain routine testing helps identify conditions associated with Down syndrome:

- Echocardiogram—at prenatal visit or at birth

- Thyroid screening (thyroid-stimulating hormone [TSH], or thyroxine [T₄] with TSH follow-up)—newborn, 6 mo, 12 mo, and annually thereafter

- Hearing evaluations—at birth, every 6 mo thereafter until 3 yr, then annually

- Ophthalmology evaluation—by 6 mo, then annually or more frequently as indicated

- X-ray screening for atlantoaxial instability—once between 3 and 5 yr, then as needed for sports (eg, Special Olympics) participation

- Celiac sprue screening—at 2 to 3 yr using anti-tissue transglutaminase antibodies and IgA anti-endomysial antibodies

- Growth—height and weight plotted at each health supervision visit using a Down syndrome growth chart

**Treatment**

The underlying disorder cannot be treated. Treatment depends on specific manifestations. Some congenital cardiac anomalies are repaired surgically. Hypothyroidism is treated with thyroid hormone replacement. Treatment should also include genetic counseling for the family, social support, and educational programming appropriate for the level of intellectual functioning (see **Intellectual Disability** on p. 3044).

**Trisomy 18**

(Edwards' Syndrome; Trisomy E)
Trisomy 18 is caused by an extra chromosome 18 and usually causes intellectual disability, small birth size, and many developmental anomalies, including severe microcephaly, heart defects, prominent occiput, low-set malformed ears, and a characteristic pinched facial appearance.

Trisomy 18 occurs in 1/6000 live births, but spontaneous abortions are common. More than 95% of affected children have complete trisomy 18. The extra chromosome is almost always maternally derived, and advanced maternal age increases risk. The female: male ratio is 3:1.

**Symptoms and Signs**

A history of feeble fetal activity, polyhydramnios, a small placenta, and a single umbilical artery often exist. Size at birth is markedly small for gestational age, with hypotonia and marked hypoplasia of skeletal muscle and subcutaneous fat. The cry is weak, and response to sound is decreased. The orbital ridges are hypoplastic, the palpebral fissures are short, and the mouth and jaw are small; all of these characteristics give the face a pinched appearance. Microcephaly, prominent occiput, low-set malformed ears, narrow pelvis, and a short sternum are common. A clenched fist with the index finger overlapping the 3rd and 4th fingers usually occurs. The distal crease on the 5th finger is often absent, and there is a low-arch dermal ridge pattern on the fingertips. Redundant skinfolds, especially over the back of the neck, are common. The fingernails are hypoplastic, and the big toe is shortened and frequently dorsiflexed. Club-feet and rocker-bottom feet are common. Severe congenital heart disease is common, especially patent ductus arteriosus and ventricular septal defects. Anomalies of lungs, diaphragm, GI tract, abdominal wall, kidneys, and ureters are frequent. Boys may have un-descended testes. Common muscular manifestations include hernias, separation of the rectus muscles of the abdominal wall, or both.

**Diagnosis**

Diagnosis may be suspected prenatally on ultrasound (eg, with abnormalities of extremities and fetal growth restriction) or by amniocentesis or chorionic villi sampling or postnatally by appearance. Confirmation in all cases is by karyotyping.

**Treatment**

No specific treatment is available. More than 50% die within the first week; < 10% are still alive at 1 yr. Those who survive have marked developmental delay and disability. Support for the family is critical.

**Trisomy 13**

(Patau's Syndrome; Trisomy D)

Trisomy 13 is caused by an extra chromosome 13 and causes abnormal forebrain, midface, and eye development; severe intellectual disability; heart defects; and small birth size.

Trisomy 13 occurs in about 1/10,000 live births; about 80% of cases are complete trisomy 13. Advanced maternal age increases the likelihood, and the extra chromosome is usually maternally derived.

Infants tend to be small for gestational age. Midline anomalies (eg, scalp defects, dermal sinuses) are characteristic. Holoprosencephaly (failure of the forebrain to divide properly) is common. Concurrent facial anomalies can include cleft lip and cleft palate. Microphthalmia, colobomas (fissures) of the iris, and retinal dysplasia are also common. Supraorbital ridges are shallow, and palpebral fissures usually are slanted. The ears are abnormally shaped and usually low-set. Deafness is common. Loose folds of skin often are present over the back of the neck. Simian crease (a single, palmar crease), polydactyly, and hyperconvex narrow fingernails are also common. About 80% of cases have severe congenital cardiovascular anomalies; dextrocardia is common. Genitals are frequently abnormal in both sexes; cryptorchidism and an abnormal scrotum occur in boys, and a bicornuate uterus occurs in girls. Apneic spells in early infancy are frequent. Intellectual disability is severe.
Diagnosis

Diagnosis may be suspected prenatally by abnormalities on ultrasound (eg, intrauterine growth restriction) or by amniocentesis or chorionic villi sampling and may be suspected postnatally by appearance. Confirmation in all cases is by karyotyping.

Treatment

Most patients (80%) are so severely affected that they die before age 1 mo; < 10% survive longer than 1 yr. Support for the family is critical.

Chromosomal Deletion Syndromes

Chromosomal deletion syndromes result from loss of parts of chromosomes. They tend to cause severe congenital anomalies and markedly retarded mental and physical development. Chromosomal deletion syndromes are rarely suspected prenatally but may be incidentally discovered at that time if karyotyping is done for other reasons. Post-natal diagnosis is suspected by clinical appearance and is confirmed by karyotyping and other genetic analysis.

5p-Deletion (cri du chat syndrome): Deletion of the end of the short arm of chromosome 5 (5p—usually paternal) is characterized by a high-pitched, mewing cry, closely resembling the cry of a kitten, which is heard in the immediate neonatal period, lasts several weeks, and then disappears. Affected neonates are hypotonic and have low birth weight, micro-cephaly, a round face with wide-set eyes, downward slanting of the palpebral fissures (with or without epicanthal folds), strabismus, and a broad-based nose. The ears are low-set, abnormally shaped, and frequently have narrow external auditory canals and preauricular tags. Syndactyly, hypertelorism, and heart anomalies occur often. Mental and physical development is markedly retarded. Many affected children survive into adulthood but have significant disability.

4p-Deletion (Wolf-Hirschhorn syndrome): Deletion of the short arm of chromosome 4 (4p) results in profound intellectual disability. Manifestations also may include epilepsy, a broad or beaked nose, midline scalp defects, ptosis and colobomas, cleft palate, delayed bone development, and, in boys, hypospadias and cryptorchidism. Many affected children die during infancy; those who survive into their 20s have severe disability.

Contiguous gene syndromes: These include microscopic and submicroscopic deletions of contiguous genes on particular parts of many chromosomes; small duplications of chromosomes also occur. The effects of duplications, however, are usually milder than those of deletions. Almost all cases are sporadic; however, mildly affected parents, as in some 22q11.21 deletions, can pass on the syndrome. Numerous syndromes have been identified, with widely varying manifestations (see Table 299-2). Deletions and duplications are often detectable with fluorescent probes and other techniques. Sometimes deletions and duplications cannot be shown cytogenetically, but their presence can be confirmed by DNA probes specific to the deleted or duplicated area.

Telomeric deletions: These deletions are small and often submicroscopic and may occur at either telomere (the end of a chromosome). Phenotypic changes may be minimal. Telomeric deletions may account for many cases of nonspecific intellectual disability in which the affected person has mildly dysmorphic features.

Sex Chromosome Anomalies

Sex chromosome anomalies may involve aneuploidy, partial deletions or duplications of sex chromosomes, or mosaicsisms.

Sex chromosome anomalies are common and cause syndromes that include a range of congenital and developmental anomalies. They are rarely suspected prenatally but may be incidentally discovered if karyotyping is done for other reasons. They are often hard to recognize at birth and may not be diagnosed until puberty.
The effects of X chromosome anomalies are not as severe as those from analogous autosomal anomalies. Females with 3 X chromosomes often appear normal physically and mentally and are fertile. In contrast, all known autosomal trisomies have devastating effects. Similarly, whereas the absence of 1 X chromosome leads to a specific syndrome (Turner's syndrome), the absence of an autosome is invariably lethal.

**Lyon hypothesis (X-inactivation):** By virtue of having 2 X chromosomes, females have 2 loci for every X-linked gene, as compared with a single locus in males. This imbalance would seem to cause a genetic "dosage" problem. However, according to the Lyon hypothesis, 1 of the 2 X chromosomes in each female somatic cell is inactivated genetically early in embryonic life (on or about day 16). In fact, no matter how many X chromosomes are present, all but 1 are inactivated. However, recent molecular genetic studies have shown that some genes on the inactivated X chromosome (or chromosomes) remain functional, and these few are essential to normal female development. *XIST* is the gene responsible for inactivating the genes of the X chromosome, producing RNA that triggers inactivation.

Whether the maternal or paternal X is inactivated usually is a random event within each cell at the time of inactivation; that same X then remains inactive in all descendant cells. Thus, all females are mosaics, with some cells having an active maternal X and others having an active paternal X.

Sometimes, random statistical distribution of inactivation in the relatively small number of cells present at the time of inactivation results in a particular descendant tissue having a preponderance of active maternal or paternal X (skewed inactivation). Skewed inactivation may account for the occasional manifestation of minor symptoms in females who are heterozygous for X-linked disorders such as hemophilia and muscular dystrophy (all would presumably be asymptomatic if they had a 50:50 distribution of active X chromosomes). Skewed inactivation also may occur by post-inactivation selection.

**Turner's Syndrome**

In Turner's syndrome (gonadal dysgenesis), girls are born with 1 of their 2 X chromosomes partly or completely missing. Diagnosis is based on clinical findings and is confirmed by karyotype analysis. Treatment depends on manifestations and may include surgery for cardiac anomalies and often growth hormone therapy for short stature and estrogen replacement for pubertal failure.

Turner's syndrome occurs in about 1/4000 live female births and is the most common sex chromosome anomaly in females. However, 99% of 45,X conceptions abort spontaneously.

About 50% of affected girls have a 45,X karyotype; about 80% have lost the paternal X. Most of the other 50% are mosaics (eg, 45,X/46,XX or 45,X/47,XXX). Among mosaic girls, phenotype may vary from that of typical Turner's syndrome to normal. Occasionally, affected girls have 1 normal X and 1 X that has formed a ring chromosome. Some affected girls have 1 normal X and 1 long-arm isochromosome formed by the loss of short arms and development of a chromosome consisting of 2 long arms of the X chromosome. These girls tend to have many of the phenotypic features of Turner's syndrome; thus, deletion of the X chromosome's short arm seems to play an important role in producing the phenotype.

**Pathophysiology**

Common cardiac anomalies include coarctation of the aorta and bicuspid aortic valve. Hypertension frequently occurs with aging, even without coarctation. Renal anomalies and hemangiomas are frequent. Occasionally, telangiectasia occurs in the GI tract, with resultant GI bleeding or protein loss. Hearing loss occurs; strabismus and hyperopia (farsightedness) are common and increase the risk of amblyopia. Thyroiditis and celiac disease are more common than among the general population.

Infants are at a higher risk of developmental dysplasia of the hip. Of adolescents, 10% have scoliosis.
Osteoporosis and fractures are fairly common among women with Turner's syndrome. Gonadal dysgenesis (ovaries replaced by bilateral streaks of fibrous stroma and devoid of developing ova) occurs in 90% of females.

Intellectual disability is rare, but many have nonverbal learning disability, attention-deficit/hyperactivity disorder, or both and thus score poorly on performance tests and in mathematics, even though they score average or above in the verbal components of intelligence tests.

**Symptoms and Signs**

Many neonates are very mildly affected; however, some present with marked dorsal lymphedema of the hands and feet and with lymphedema or loose folds of skin over the back of the neck. Other frequent anomalies include a webbed neck and a broad chest with widely spaced and inverted nipples. Affected girls have short stature compared with family members. Less common findings include a low hairline on the back of the neck, ptosis, multiple pigmented nevi, short 4th metacarpals and metatarsals, prominent finger pads with whorls in the dermatoglyphics on the ends of the fingers, and hypoplasia of the nails. Increased carrying angle at the elbow occurs.

Symptoms of cardiac anomalies depend on severity. Coarctation of the aorta can cause high BP in the upper extremities, diminished femoral pulses, and low or absent BP in the lower extremities. Gonadal dysgenesis results in the inability to undergo puberty, develop breast tissue, or begin menses. Other medical problems that are associated with Turner's syndrome develop with aging and may not be evident without screening.

**Diagnosis**

- Clinical appearance
- Karyotype analysis
- Testing for associated conditions

In neonates, diagnosis may be suspected based on the presence of lymphedema or a webbed neck. In the absence of these findings, some children are diagnosed later, based on short stature, lack of pubertal development, and amenorrhea. Diagnosis is confirmed by karyotype analysis. Echocardiography or MRI is indicated to detect cardiac anomalies.

Cytogenetic analysis and Y-specific probe studies are done for all people with gonadal dysgenesis to rule out mosaicism with a Y-bearing cell line (eg, 45,X/46,XY). These people are usually phenotypic females who have variable features of Turner's syndrome. They are at high risk of gonadal cancer, especially gonadoblastoma, and should have the gonads removed prophylactically as soon as the diagnosis is made.

**Concomitant medical conditions:** Certain routine evaluations help identify conditions associated with Turner's syndrome:

- Cardiovascular evaluation by a specialist; MRI and echocardiography at time of diagnosis to rule out coarctation and bicuspid aortic valve and every 3 to 5 yr thereafter to evaluate aortic root diameter
- Renal ultrasonography at time of diagnosis, annual urinalysis, BUN, and creatinine for patients with renal system anomalies
- Hearing evaluation by an audiologist and audiogram every 3 to 5 yr
- Evaluation for scoliosis/kyphosis at yearly examination
- Evaluation for hip dislocation
• Eye examination by pediatric ophthalmologist

• Thyroid function tests at diagnosis and every 1 to 2 yr thereafter

• Celiac screen (eg, endomysial antibody levels)

• Glucose tolerance test at diagnosis and fasting blood sugar, lipid profile annually thereafter

Treatment

There is no specific treatment for the underlying genetic condition. Coarctation of the aorta is usually repaired surgically. Other cardiac anomalies are monitored and repaired as needed. Lymphedema can usually be controlled with support hosiery.

Treatment with growth hormone can stimulate growth. Estrogen replacement is usually needed to initiate puberty and is typically given at age 12 to 13. Thereafter, birth control pills with a progestin are given to maintain secondary sexual characteristics. Growth hormone can be given with estrogen replacement until epiphyses are fused, at which time growth hormone is stopped. Continuation of estrogen replacement helps establish optimal bone density and skeletal development.

Klinefelter's Syndrome (47,XXY)

Klinefelter's syndrome is ≥ 2 X chromosomes plus 1 Y, resulting in a phenotypic male.

Klinefelter's syndrome is the most common sex chromosome disorder, occurring in about 1/700 live male births. The extra X chromosome is maternally derived in 60% of cases. Germ cells do not survive in the testes, leading to decreased sperm and androgens.

Affected boys tend to be tall with disproportionately long arms and legs. They often have small, firm testes, and about 30% develop gynecomastia. Puberty usually occurs at the normal age, but often facial hair growth is light. There is a predisposition for verbal learning disorders. Clinical variation is great, and many 47,XXY males have normal appearance and intellect. Many are diagnosed during an infertility evaluation (probably all 47,XXY males are sterile). Testicular development varies from hyalinized nonfunctional tubules to some production of spermatozoa; urinary excretion of follicle-stimulating hormone is frequently increased.

Mosaicism occurs in 15% of cases. These men may be fertile. Some affected men have 3, 4, and even 5 X chromosomes along with the Y. As the number of X chromosomes increases, the severity of intellectual disability and of malformations also increases. Each extra X is associated with a 15- to 16-point reduction in IQ, with language most affected, particularly expressive language skills. Males with Klinefelter's syndrome should have lifelong testosterone supplementation beginning at puberty to ensure the development of male sexual characteristics, muscle bulk, bone structure, and better psychosocial functioning.

47,XYY Syndrome

47,XYY syndrome is 2 Y chromosomes and 1 X, resulting in a phenotypic male.

The 47,XYY syndrome occurs in about 1/1000 live male births. Affected boys tend to be taller than average and have a 10- to 15-point IQ reduction compared with family members. There are few physical problems. Minor behavior disorders, hyperactivity, attention-deficit disorder, and learning disorders are more common.

Other X Chromosome Anomalies

About 1/1000 apparently normal females have 47,XXX (trisomy X) karyotype. Physical anomalies are rare. Menstrual irregularity and infertility sometimes occur. Affected girls may have mildly impaired intellect and may have more school problems than siblings. Advanced maternal age increases risk of the triple X
anomaly, and the extra X chromosome is usually maternally derived.

Although rare, 48,XXXX and 49,XXXXX females exist. There is no consistent phenotype. The risk of intellectual disability and congenital anomalies increases markedly when there are > 3 X chromosomes. The genetic imbalance in early embryonic life may cause anomalous development.
Chapter 300. Inherited Muscular Disorders

Introduction

Inherited metabolic disorders affecting the muscles, such as disorders of mitochondrial oxidative phosphorylation and glycogen storage diseases, are discussed in Ch. 301. Only those disorders that have all or most of their effects on muscle are discussed in this chapter.

Muscular Dystrophies

Muscular dystrophies are inherited, progressive muscle disorders resulting from defects in one or more genes needed for normal muscle function. They are distinguished by the selective distribution of weakness and the specific nature of the genetic abnormality involved.

Duchenne dystrophy is the most common and severe form of muscular dystrophy. Becker dystrophy, although closely related, has a later onset and causes milder symptoms. Other forms include Emery-Dreifuss dystrophy, myotonic dystrophy, limb-girdle dystrophy, facioscapulohumeral dystrophy, and congenital dystrophies.

Duchenne Muscular Dystrophy and Becker Muscular Dystrophy

Duchenne muscular dystrophy and Becker muscular dystrophy are X-linked recessive disorders characterized by progressive proximal muscle weakness caused by muscle fiber degeneration. Becker dystrophy has later onset and causes milder symptoms. Diagnosis is suggested clinically and is confirmed by analysis of the protein product (dystrophin) of the mutated gene. Treatment focuses on maintaining function through physical therapy and the use of braces and orthotics; prednisone is given to some patients with severe functional decline.

Duchenne dystrophy and Becker dystrophy are caused by mutations at the Xp21 locus. In Duchenne dystrophy, this mutation results in the severe absence (< 5%) of dystrophin, a protein in the muscle cell membrane. In Becker dystrophy, the mutation results in production of abnormal dystrophin or less dystrophin. Duchenne dystrophy affects 1/3000 live male births. Becker dystrophy affects 1/30,000 live male births. Female carriers may have asymptomatic elevated CK levels and possibly calf hypertrophy.

Symptoms and Signs

Duchenne dystrophy: This disorder manifests typically between ages 2 yr and 3 yr. Weakness affects proximal muscles, typically in the lower limbs initially. Children frequently toe walk and have a waddling gait and lordosis. They fall frequently and have difficulty running, jumping, climbing stairs, and rising from the floor. Progression of weakness is steady, and limb flexion contractures and scoliosis develop. Firm pseudohypertrophy (fatty and fibrous replacement of certain enlarged muscle groups, notably the calves) develops. Most children are confined to a wheelchair by age 12 and die of respiratory complications by age 20. Cardiac involvement is usually asymptomatic, although 90% of patients have ECG abnormalities. One third have mild, nonprogressive intellectual impairment that affects verbal ability more than performance.

Becker dystrophy: This disorder typically becomes symptomatic much later and is milder. Ambulation is usually preserved until at least age 15, and many children remain ambulatory into adulthood. Most affected children survive into their 30s and 40s.

Diagnosis

• Immunostaining analysis of dystrophin
• DNA mutation analysis

Diagnosis is suspected by characteristic clinical findings, age at onset, and family history suggestive of X-linked recessive inheritance. Myopathic changes are noted on electromyography (rapidly recruited, short
duration, low-amplitude motor unit potentials) and muscle biopsy (necrosis and marked variation in muscle fiber size not segregated by motor unit). CK levels are elevated to up to 100 times normal.

Diagnosis is confirmed by analysis of dystrophin with immunostaining of biopsy samples. Dystrophin is undetectable in patients with Duchenne dystrophy. In patients with Becker dystrophy, dystrophin is typically abnormal (lower molecular weight) or present in low concentration. Mutation analysis of DNA from peripheral blood leukocytes can also confirm the diagnosis by identifying abnormalities in the dystrophin gene (deletions or duplications in about 65% and point mutations in about 25% of patients).

Carrier detection and prenatal diagnosis are possible by using conventional studies (eg, pedigree analysis, CK determinations, fetal sex determination) combined with recombinant DNA analysis and dystrophin immunostaining of muscle tissue.

**Treatment**

- Supportive measures
- Sometimes prednisone
- Sometimes corrective surgery

No specific treatment exists. Moderate exercise is encouraged for as long as possible. Passive exercises may extend the period of ambulation. Ankle-foot orthoses help prevent flexion during sleep. Leg braces may temporarily help preserve ambulation or standing. Obesity should be avoided; caloric requirements are likely to be less than normal. Genetic counseling is indicated (see p. 2598).

Daily prednisone does not cause significant long-term clinical improvement, but it possibly slows the course of the disease. No consensus on long-term effectiveness exists. Gene therapy is not yet available. Corrective surgery is sometimes needed. Respiratory insufficiency may be treated with noninvasive ventilatory support (eg, nasal mask—see p. 2290). Elective tracheotomy is gaining acceptance, allowing children with Duchenne dystrophy to live into their 20s.

**Other Forms of Muscular Dystrophy**

**Emery-Dreifuss dystrophy:** This disorder can be inherited as an autosomal dominant, autosomal recessive (the rarest), or X-linked recessive disorder. The overall incidence is unknown. Females can be carriers, but only males are affected clinically by X-linked inheritance. Genes associated with Emery-Dreifuss dystrophy encode for the nuclear membrane proteins lamin A/C (autosomal) and emerin (X-linked).

Muscle weakness and wasting can begin any time before age 20 and commonly affect the biceps and triceps and, less often, distal leg muscles. The heart is frequently involved, with atrial paralysis, conduction abnormalities (atrioventricular block), cardiomyopathy, and a high likelihood of sudden death.

Diagnosis is indicated by clinical findings, age at onset, and family history. The diagnosis is supported by mildly increased serum CK levels and myopathic features on electromyography and muscle biopsy and is confirmed by DNA testing.

Treatment involves therapy to prevent contractures. Cardiac pacemakers are sometimes lifesaving in patients with abnormal conduction.

**Myotonic dystrophy:** Myotonic dystrophy, the most common form of muscular dystrophy among whites, affects about 30/100,000 live male and female births. Inheritance is autosomal dominant with variable penetrance. Two genetic loci—DM 1 and DM 2—cause the abnormality. Symptoms and signs begin during adolescence or young adulthood and include myotonia (delayed relaxation after muscle contraction), weakness and wasting of distal limb muscles (especially in the hand) and facial muscles (ptosis is especially common), and cardiomyopathy. Intellectual disability, cataracts, and endocrine disorders can also occur.
Diagnosis is indicated by characteristic clinical findings, age at onset, and family history and is confirmed by DNA testing. Treatment includes braces for foot drop and drug therapy for myotonia (eg, mexiletine 75 to 150 mg po bid or tid).

**Limb-girdle dystrophy:** Limb-girdle dystrophy currently has 21 known subtypes, 15 autosomal recessive and 6 autosomal dominant. The overall incidence is unknown. Males and females are affected equally. Several chromosomal loci have been identified for autosomal dominant (5q [no known gene product]) and recessive (2q, 4q [beta-sarcoglycan], 13q [gamma-sarcoglycan], 15q [calpain, a Ca-activated protease], and 17q [alpha-sarcoglycan or adhalin]) forms. Structural (eg, dystrophin-associated glycoproteins) or nonstructural (eg, proteases) proteins can be affected.

Symptoms involve weakness in a limb girdle and proximal limb distribution. Onset of symptoms ranges from early childhood to adulthood; onset for autosomal recessive types tends to be during childhood, and these types primarily have a pelvic girdle distribution.

Diagnosis is indicated by characteristic clinical findings, age at onset, and family history and requires muscle histology, immunocytochemistry, Western blot analysis, and genetic testing for specific proteins.

Treatment focuses on prevention of contractures.

**Facioscapulohumeral dystrophy:** Facioscapulohumeral dystrophy is an autosomal dominant disorder characterized by weakness of the facial muscles and shoulder girdle, usually beginning at age 7 to 20. Onset is during adolescence or young adulthood and is characterized by slow progression and difficulty whistling, closing the eyes, and raising the arms (due to weakness of the scapular stabilizer muscles). Life expectancy is normal. An infantile variety, characterized by facial, shoulder, and hip girdle weakness, is rapidly progressive.

Diagnosis is indicated by characteristic clinical findings, age at onset, and family history and is confirmed by DNA testing.

Treatment consists of physical therapy.

**Congenital muscular dystrophy:** Congenital muscular dystrophy is not a single disorder but instead refers to muscular dystrophy evident at birth, occurring from any of several rare forms of muscular dystrophy. The diagnosis is suspected in any floppy neonate but must be distinguished from congenital myopathy by muscle biopsy.

Treatment consists of physical therapy, which may help preserve function.

**Congenital Myopathies**

Congenital myopathy is a term sometimes applied to hundreds of distinct neuromuscular disorders that may be present at birth, but it is usually reserved for a group of rare, inherited, primary muscle disorders that cause hypotonia and weakness at birth or during the neonatal period and, in some cases, delayed motor development later in childhood.

The 4 most common types of congenital myopathy are

- Nemaline myopathy
- Myotubular myopathy
- Core myopathies
- Congenital fiber type disproportion

The 4 types are distinguished primarily by their histologic features, symptoms, and prognosis. Diagnosis
is indicated by characteristic clinical findings and is confirmed by muscle biopsy. Treatment consists of physical therapy, which may help preserve function.

**Nemaline myopathy:** This myopathy, the most common congenital myopathy, can be autosomal dominant or recessive; causative mutations have been identified in 6 genes, and all are related to the production of thin-filament proteins. Nemaline myopathy may be severe, moderate, or mild. Severely affected patients may experience weakness of respiratory muscles and respiratory failure. Moderate disease causes progressive weakness in muscles of the face, neck, trunk, and feet, but life expectancy may be nearly normal. Mild disease is nonprogressive, and life expectancy is normal.

**Myotubular myopathy:** This myopathy is X-linked and rare, occurring in about 1/50,000 births. It affects males primarily and results in severe skeletal muscle weakness and hypotonia, facial weakness, impaired swallowing, and respiratory muscle weakness and respiratory failure. Children with milder forms survive to adulthood.

**Core myopathies:** Inheritance is usually autosomal dominant, but recessive and sporadic forms exist. Core myopathies are characterized by regions (cores) on muscle biopsy specimens in which oxidative enzyme staining is absent; regions may be peripheral or central, focal, multiple, or extensive. Central core myopathy was the first congenital myopathy to be identified.

Most affected patients develop hypotonia and mild proximal muscle weakness as neonates, but sometimes symptoms do not manifest until adulthood. Many also have facial weakness. Weakness is nonprogressive, and life expectancy is normal, but some patients are severely affected and wheelchair bound. The gene mutation associated with central core myopathy is also associated with increased susceptibility to malignant hyperthermia.

**Congenital fiber type disproportion myopathy:** This myopathy is inherited, but the pattern is poorly understood. Hypotonia and weakness of the face, neck, trunk, and limbs are often accompanied by skeletal abnormalities and dysmorphic features. Most affected children improve with age, but a small percentage develops respiratory failure.

**Familial Periodic Paralysis**

Familial periodic paralysis is a rare autosomal condition characterized by episodes of flaccid paralysis with loss of deep tendon reflexes and failure of muscle to respond to electrical stimulation. There are 3 forms: hypokalemic, hyperkalemic, and normokalemic. Diagnosis is indicated by history and is confirmed by provoking an episode (eg, by giving dextrose and insulin to cause hypokalemia or KCl to cause hyperkalemia). Treatment depends on the form.

The hypokalemic form of familial periodic paralysis is due to genetic mutation in the dihydropyridine receptor-associated Ca channel gene. The hyperkalemic form is due to mutations in the gene that encodes the α-subunit of the skeletal muscle Na channel (SCN4A). The cause of the normokalemic form is unclear; in some instances it may result from a mutation in a gene that encodes Na channels.

**Symptoms and Signs**

**Hypokalemic:** Episodes usually begin before age 16. The day after vigorous exercise, the patient often awakens with weakness, which may be mild and limited to certain muscle groups or may affect all four limbs. Episodes are also precipitated by carbohydrate-rich meals. Ocular, bulbar, and respiratory muscles are spared. Consciousness is not altered. Serum and urine K are decreased. Weakness lasts up to 24 h.

**Hyperkalemic:** Episodes often begin at an earlier age and usually are shorter, more frequent, and less severe. Episodes are precipitated by exercise after meals or by fasting. Myotonia (delayed relaxation after muscle contraction) is common. Eyelid myotonia may be the only symptom.

**Normokalemic:** Affected patients are sensitive to K ingestion and have episodes of mild weakness that occur without any change in serum K.
Diagnosis

- Clinical evaluation
- Serum K level during symptoms
- Sometimes provocative testing

The best diagnostic indicator is a history of typical episodes. If measured during an episode, serum K may be abnormal. Episodes can sometimes be provoked by giving dextrose and insulin (to cause the hypokalemic form) or KCl (to cause the hyperkalemic form), but only experienced physicians should attempt provocative testing, because respiratory paralysis or cardiac conduction abnormalities may occur with provoked episodes.

Treatment

- Varies with type and severity

**Hypokalemic:** Episodes of paralysis are managed by giving KCl 2 to 10 g in an unsweetened oral solution or giving K IV. Following a low-carbohydrate, low-Na diet, avoiding strenuous activity or alcohol after periods of rest, and taking acetazolamide 250 to 2000 mg po once/day may help prevent hypokalemic episodes.

**Hyperkalemic:** Episodes of paralysis, if mild, can be aborted at onset by light exercise and a 2 g/kg oral carbohydrate load. Established episodes require thiazides, acetazolamide, or inhaled β-agonists. Severe attacks require Ca gluconate or insulin and dextrose IV. Regularly ingesting carbohydrate-rich, low-K meals and avoiding fasting, strenuous activity after meals, and cold exposure help prevent hyperkalemic episodes.

**Normokalemic:** Large doses of Na alleviate the weakness. Dextrose has no effect. Attacks may be prevented by avoiding excess alcohol and cold exposure. People should cool down slowly after strenuous exercise and not immediately rest. Eating some form of carbohydrate (eg, candy bar) may help as well.
Chapter 301. Inherited Disorders of Metabolism

Introduction

Most inherited disorders (also called inborn errors) of metabolism are caused by mutations in genes that code for enzymes; enzyme deficiency or inactivity leads to accumulation of substrate precursors or metabolites or to deficiencies of the enzyme's products. Hundreds of disorders exist, and although most inherited disorders of metabolism are extremely rare individually, collectively they are not rare. The disorders are typically grouped by the affected substrate (eg, carbohydrates, amino acids, fatty acids).

Most states routinely test all neonates for specific inherited disorders of metabolism and other conditions (see p. 2702), including phenylketonuria, tyrosinemia, biotinidase deficiency, homocystinuria, maple syrup urine disease, and galactosemia. Many states have an expanded screening program that covers many more inherited disorders of metabolism, including disorders of fatty acid oxidation and other organic acidemias.

Metabolic defects that primarily cause disease in adults (eg, gout, porphyria), are organ-specific (eg, Wilson's disease, congenital adrenal hypoplasia), or are common (eg, cystic fibrosis, hemochromatosis) are discussed elsewhere in THE MANUAL. For inherited disorders of lipoprotein metabolism, see Table 100-3 on p. 892.

Approach to the Patient with a Suspected Inherited Disorder of Metabolism

Most inherited disorders (inborn errors) of metabolism are rare, and therefore their diagnosis requires a high index of suspicion. Timely diagnosis leads to early treatment and may help avoid acute and chronic complications, developmental compromise, and even death.

Evaluation

Symptoms and signs tend to be nonspecific and are more often caused by something other than an inherited disorder of metabolism (eg, infection); these more likely causes should also be investigated.

History and physical examination: Disorders manifesting in the neonatal period tend to be more serious; manifestations of many of the disorders typically include lethargy, poor feeding, vomiting, and seizures. Disorders that manifest later tend to affect growth and development, but vomiting, seizures, and weakness may also appear.

Growth delay suggests decreased anabolism or increased catabolism and may be due to decreased availability of energy-generating substrates (eg, in glycogen storage disease [GSD]) or inefficient energy or protein use (eg, in organic acidemias or urea cycle defects).

Developmental delay may reflect chronic energy deficit in the brain (eg, oxidative phosphorylation defects), decreased supply of needed carbohydrates that are non-energy substrates for the brain (eg, lack of uridine-5’-diphosphate-galactose [UDP-galactose] in untreated galactosemia), or chronic amino acid deficit in the brain (eg, tyrosine deficiency in phenylketonuria).

Neuromuscular symptoms, such as seizures, muscle weakness, hypotonia, myoclonus, and muscle pain, and strokes or coma may suggest acute energy deficit in the brain (eg, hypoglycemic seizures in GSD type I, strokes in mitochondrial oxidative phosphorylation defects) or muscle (eg, muscle weakness in muscle forms of GSD). Neuromuscular symptoms may also reflect accumulation of toxic compounds in the brain (eg, hyperammonemic coma in urea cycle defects) or tissue breakdown (eg, rhabdomyolysis and myoglobinuria in patients with long-chain hydroxyacyl dehydrogenase deficiency or muscle forms of GSD).

Congenital brain malformation may reflect decreased availability of energy (eg, decreased ATP output in pyruvate dehydrogenase deficiency) or critical precursors (eg, decreased cholesterol in 7-dehydrocholesterol reductase deficiency or Smith-Lemli-Opitz syndrome) during fetal development.
Autonomic symptoms can result from hypoglycemia caused by increased glucose consumption or decreased glucose production (eg, vomiting, diaphoresis, pallor, and tachycardia in GSD or hereditary fructose intolerance) or from metabolic acidosis (eg, vomiting and Kussmaul respirations in organic acidemias). Some conditions cause both (ie, in propionic acidemia, accumulation of acyl-CoAs causes metabolic acidosis and inhibits gluconeogenesis, thus causing hypoglycemia).

Nonphysiologic jaundice after the neonatal period usually reflects intrinsic hepatic disease, especially when accompanied by elevation of liver enzymes, but may be due to inherited disorders of metabolism (eg, untreated galactosemia, hereditary fructose intolerance, tyrosinemia type I).

Unusual odors in body fluids reflect accumulation of specific compounds (eg, sweaty feet odor in isovaleric acidemia, smoky-sweet odor in maple syrup urine disease, mousy or musty odor in phenylketonuria, boiled cabbage odor in tyrosinemia).

Change in urine color on exposure to air occurs in some disorders (eg, darkish brown in alkaptonuria, purplish brown in porphyria).

Organomegaly may reflect a failure in substrate degradation resulting in substrate accumulation within the organ cells (eg, hepatomegaly in hepatic forms of GSD and many lysosomal storage diseases, cardiomegaly in GSD type II).

Eye changes include cataracts in galactokinase deficiency or classic galactosemia, and ophthalmoplegia and retinal degeneration in oxidative phosphorylation defects.

Testing: When an inherited disorder of metabolism is suspected, evaluation begins with simple metabolic screening tests, which typically include the following:

- Glucose
- Electrolytes
- CBC and peripheral smear
- Liver function tests
- Ammonia levels
- Urinalysis

Glucose measurement detects hypoglycemia or hyperglycemia; measurement may have to be timed relative to meals (eg, fasting hypoglycemia in GSD).

Electrolyte measurement detects metabolic acidosis and presence or absence of an anion gap; metabolic acidosis may need to be corroborated by ABG measurement. Non-anion gap acidosis occurs in inherited disorders of metabolism that cause renal tubular damage (eg, galactosemia, tyrosinemia type I). Anion gap acidosis occurs in inherited disorders of metabolism in which accumulation of titratable acids is typical, such as methylmalonic and propionic acidemias; it can also be caused by lactic acidosis (eg, in pyruvate decarboxylase deficiency or mitochondrial oxidative phosphorylation defects). When the anion gap is elevated, lactate and pyruvate levels should be obtained. An increase in the lactate:pyruvate ratio distinguishes oxidative phosphorylation defects from disorders of pyruvate metabolism, in which the lactate:pyruvate ratio remains normal.

CBC and peripheral smear detect hemolysis caused by RBC energy deficits or WBC defects (eg, in some pentose phosphate pathway disorders and GSD type Ib) and cytopenia caused by metabolite accumulation (eg, neutropenia in propionic acidemia due to propionyl CoA accumulation).

Liver function tests detect hepatocellular damage, dysfunction, or both (eg, in untreated galactosemia, hereditary fructose intolerance, or tyrosinemia type I).
Ammonia levels are elevated in urea cycle defects, organic acidemias, and fatty acid oxidation defects.

Urinalysis detects ketonuria (present in some GSDs and many organic acidemias); absence of ketones in the presence of acidosis suggests a fatty acid oxidation defect.

**More specific tests** may be indicated when ≥ 1 of the previously described simple screening tests support an inherited disorder of metabolism. Carbohydrate metabolites, mucopolysaccharides, and amino and organic acids can be measured directly by chromatography and mass spectrometry. Common tests include quantitative plasma amino acids, urine organic acids, plasma acylcarnitine profile, and urine acylglycine profile; these have replaced earlier nonspecific screening tests.

**Confirmatory tests** may also include biopsy (e.g., liver biopsy to distinguish hepatic forms of GSDs from other disorders associated with hepatomegaly, muscle biopsy to detect ragged red fibers in mitochondrial myopathy; enzyme studies (e.g., using blood and skin cells to diagnose lysosomal storage diseases); and DNA studies, which identify gene mutations that cause disease. DNA testing can be done on almost all cells (except RBCs and platelets), thus avoiding the need for tissue biopsies; however, sensitivity for any given disease is often suboptimal because not all mutations that cause disease have been characterized.

**Challenge testing** is used judiciously to detect symptoms, signs, or measurable biochemical abnormalities not detectable in the normal state. The need for challenge testing has diminished with the availability of highly sensitive metabolite detection methods, but it is still occasionally used. Examples include fasting tests (e.g., to provoke hypoglycemia in hepatic forms of GSD); provocative tests (e.g., fructose challenge to trigger symptoms in hereditary fructose intolerance, glucagon challenge in hepatic forms of GSD [failure to observe hyperglycemia suggests disease]); and physiologic challenge (e.g., exercise stress testing to elicit lactic acid production and other deformities in muscle forms of GSD). Challenge tests are often associated with an element of risk so they must be done under well-controlled conditions with a clear plan for reversing symptoms and signs.

**Amino Acid and Organic Acid Metabolism Disorders**

Defects of amino acid transport in the renal tubule are discussed in Ch. 297.

**Phenylketonuria**

Phenylketonuria (PKU) is a clinical syndrome of intellectual disability with cognitive and behavioral abnormalities caused by elevated serum phenylalanine. The primary cause is deficient phenylalanine hydroxylase activity. Diagnosis is by detecting high phenylalanine levels and normal or low tyrosine levels. Treatment is lifelong dietary phenylalanine restriction. Prognosis is excellent with treatment.

PKU is most common among all white populations and relatively less common among Ashkenazi Jews, Chinese, and blacks. Inheritance is autosomal recessive; incidence is about 1/10,000 births among whites.

**Pathophysiology**

Excess dietary phenylalanine (i.e., that not used for protein synthesis) is normally converted to tyrosine by phenylalanine hydroxylase; tetrahydrobiopterin (BH4) is an essential cofactor for this reaction. When one of several gene mutations results in deficiency or absence of phenylalanine hydroxylase, dietary phenylalanine accumulates; the brain is the main organ affected, possibly due to disturbance of myelination. Some of the excess phenylalanine is metabolized to phenylketones, which are excreted in the urine, giving rise to the term phenylketonuria. The degree of enzyme deficiency, and hence severity of hyperphenylalaninemia, varies among patients depending on the specific mutation.

**Variant forms:** Although nearly all cases (98 to 99%) of PKU result from phenylalanine hydroxylase deficiency, phenylalanine can also accumulate if BH4 is not synthesized because of deficiencies of dihydrobiopterin synthase or not regenerated because of deficiencies of dihydropteridine reductase.
Additionally, because BH4 is also a cofactor for tyrosine hydroxylase, which is involved in the synthesis of dopamine and serotonin, BH4 deficiency alters synthesis of neurotransmitters, causing neurologic symptoms independently of phenylalanine accumulation.

**Symptoms and Signs**

Most children are normal at birth but develop symptoms and signs slowly over several months as phenylalanine accumulates. The hallmark of untreated PKU is severe intellectual disability. Children also manifest extreme hyperactivity, gait disturbance, and psychoses and often exhibit an unpleasant, mousy body odor caused by phenylacetic acid (a breakdown product of phenylalanine) in urine and sweat. Children also tend to have a lighter skin, hair, and eye color than unaffected family members, and some may develop a rash similar to infantile eczema.

**Diagnosis**

- Routine neonatal screening
- Phenylalanine levels

In the US and many developed countries, all neonates are screened for PKU 24 to 48 h after birth with one of several blood tests; abnormal results are confirmed by directly measuring phenylalanine levels. In classic PKU, neonates often have phenylalanine levels > 20 mg/dL (1.2 mM/L). Those with partial deficiencies typically have levels < 8 to 10 mg/dL while on a normal diet (levels > 6 mg/dL require treatment); distinction from classic PKU requires a liver phenylalanine hydroxylase activity assay showing activity between 5% and 15% of normal or a mutation analysis identifying mild mutations in the gene.

BH4 deficiency is distinguished from other forms of PKU by elevated concentrations of biopterin or neopterin in urine, blood, CSF, or all 3; recognition is important, and the urine biopterin profile should be determined routinely at initial diagnosis because standard PKU treatment does not prevent neurologic damage.

Children in families with a positive family history can be diagnosed prenatally by using direct mutation studies after chorionic villus sampling or amniocentesis.

**Prognosis**

Adequate treatment begun in the first days of life prevents all manifestations of disease. Treatment begun after 2 to 3 yr may be effective only in controlling the extreme hyperactivity and intractable seizures. Children born to mothers with poorly controlled PKU (ie, they have high phenylalanine levels) during pregnancy are at high risk of microcephaly and developmental deficit.

**Treatment**

- Dietary phenylalanine restriction

Treatment is lifelong dietary phenylalanine restriction. All natural protein contains about 4% phenylalanine. Therefore dietary staples include low-protein natural foods (eg, fruits, vegetables, certain cereals), protein hydrolysates treated to remove phenylalanine, and phenylalanine-free elemental amino acid mixtures. Examples of commercially available phenylalanine-free products include XPhe products (XP Analog for infants, XP Maxamaid for children 1 to 8 yr, XP Maxamum for children > 8 yr); Phenex I and II; Phenyl-Free I and II; PKU-1, -2, and -3; PhenylAde (varieties); Loflex; and Plexy10. Some phenylalanine is required for growth and metabolism; this requirement is met by measured quantities of natural protein from milk or low-protein foods.

Frequent monitoring of plasma phenylalanine levels is required; recommended targets are between 2 mg/dL and 4 mg/dL (120 to 240 μmol/L) for children < 12 yr and between 2 mg/dL and 10 mg/dL (120 to 600 μmol/L) for children > 12 yr. Dietary planning and management need to be initiated in women of childbearing age before pregnancy to ensure a good outcome for the child. Tyrosine supplementation is
increasingly used because it is an essential amino acid in patients with PKU. In addition, sapropterin supplementation is increasingly being used.

For those with BH4 deficiency, treatment also includes tetrahydrobiopterin 1 to 5 mg/kg po tid; levodopa, carbidopa, and 5-OH tryptophan; and folinic acid 10 to 20 mg po once/day in cases of dihydropteridine reductase deficiency. However, treatment goals and approach are the same as those for PKU.

**Disorders of Tyrosine Metabolism**

**Tyrosine is a precursor of several neurotransmitters (eg, dopamine, norepinephrine, epinephrine), hormones (eg, thyroxine), and melanin; deficiencies of enzymes involved in its metabolism lead to a variety of syndromes.**

**Transient tyrosinemia of the newborn:** Transient immaturity of metabolic enzymes, particularly 4-hydroxyphenylpyruvic acid dioxygenase, sometimes leads to elevated plasma tyrosine levels (usually in premature infants, particularly those receiving high-protein diets); metabolites may show up on routine neonatal screening for PKU.

Most infants are asymptomatic, but some have lethargy and poor feeding.

Tyrosinemia is distinguished from PKU by elevated plasma tyrosine levels.

Most cases resolve spontaneously. Symptomatic patients should have dietary tyrosine restriction (2 g/kg/day) and be given vitamin C 200 to 400 mg po once/day.

**Tyrosinemia type I:** This disorder is an autosomal recessive trait caused by deficiency of fumarylacetoacetate hydroxylase, an enzyme important for tyrosine metabolism.

Disease may manifest as fulminant liver failure in the neonatal period or as indolent sub-clinical hepatitis, painful peripheral neuropathy, and renal tubular disorders (eg, normal anion gap metabolic acidosis, hypophosphatemia, vitamin D-resistant rickets) in older infants and children. Children who do not die from associated liver failure in infancy have a significant risk of developing liver cancer.

Diagnosis is suggested by elevated plasma levels of tyrosine; it is confirmed by a high level of succinylacetone in plasma or urine and by low fumarylacetoacetate hydroxylase activity in blood cells or liver biopsy specimens. Treatment with 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclo-hexanedione (NTBC) is effective in acute episodes and slows progression.

A diet low in phenylalanine and tyrosine is recommended. Liver transplantation is effective.

**Tyrosinemia type II:** This rare autosomal recessive disorder is caused by tyrosine transaminase deficiency.

Accumulation of tyrosine causes cutaneous and corneal ulcers. Secondary elevation of phenylalanine, though mild, may cause neuropsychiatric abnormalities if not treated.

Diagnosis is by elevation of tyrosine in plasma, absence of succinylacetone in plasma or urine, and measurement of decreased enzyme activity in liver biopsy.

This disorder is easily treated with mild to moderate restriction of dietary phenylalanine and tyrosine.

**Alkaptonuria:** This rare autosomal recessive disorder is caused by homogentisic acid oxidase deficiency; homogentisic acid oxidation products accumulate in and darken skin, and crystals precipitate in joints.

The condition is usually diagnosed in adults and causes dark skin pigmentation (ochronosis) and arthritis. Urine turns dark when exposed to air because of oxidation products of homogentisic acid. Diagnosis is by finding elevated urinary levels of homogentisic acid (> 4 to 8 g/24 h).
There is no effective treatment, but ascorbic acid 1 g po once/day may diminish pigment deposition by increasing renal excretion of homogentisic acid.

**Oculocutaneous albinism:** Tyrosinase deficiency results in absence of skin and retinal pigmentation, causing a much increased risk of skin cancer and considerable vision loss. Nystagmus is often present, and photophobia is common (see also [Albinism](#) on p. 719).

**Disorders of Branched-Chain Amino Acid Metabolism**

Valine, leucine, and isoleucine are branched-chain amino acids; deficiency of enzymes involved in their metabolism leads to accumulation of organic acids with severe metabolic acidosis.

**Maple syrup urine disease:** This is a group of autosomal recessive disorders caused by deficiency of one or more subunits of a dehydrogenase active in the 2nd step of branched-chain amino acid catabolism. Although quite rare, incidence is significant (perhaps 1/200 births) in Amish and Mennonite populations.

Clinical manifestations include body fluid odor that resembles maple syrup (particularly strong in cerumen) and overwhelming illness in the first days of life, beginning with vomiting and lethargy, and progressing to seizures, coma, and death if untreated. Patients with milder forms of the disease may manifest symptoms only during stress (eg, infection, surgery).

Biochemical findings are profound ketonemia and acidemia. Diagnosis is by finding elevated plasma levels of branched-chain amino acids (particularly leucine).

Acutely, treatment with peritoneal dialysis or hemodialysis may be required, along with IV hydration and nutrition (including high-dose dextrose). Long-term management is restriction of dietary branched-chain amino acids; however, small amounts are required for normal metabolic function. Thiamin is a cofactor for the decarboxylation, and some patients respond favorably to high-dose thiamin (up to 200 mg po once/day). Liver transplantation is curative.

**Isovaleric acidemia:** The 3rd step of leucine metabolism is the conversion of isovaleryl CoA to 3-methylcrotonyl CoA, a dehydrogenation step. Deficiency of this dehydrogenase results in isovaleric acidemia, also known as "sweaty feet" syndrome, because accumulated isovaleric acid emits an odor that smells like sweat.

Clinical manifestations of the acute form occur in the first few days of life with poor feeding, vomiting, and respiratory distress as infants develop profound anion gap metabolic acidosis, hypoglycemia, and hyperammonemia. Bone marrow suppression often occurs. A chronic intermittent form may not manifest for several months or years.

Diagnosis is made by detecting elevated levels of isovaleric acid and its metabolites in blood or urine.

Acute treatment is with IV hydration and nutrition (including high-dose dextrose) and measures to increase renal isovaleric acid excretion by conjugation with glycine. If these measures are insufficient, exchange transfusion and peritoneal dialysis may be needed. Long-term treatment is with dietary leucine restriction and continuation of glycine and carnitine supplements. Prognosis is excellent with treatment.

**Propionic acidemia:** Deficiency of propionyl CoA carboxylase, the enzyme responsible for metabolizing propionic acid to methylmalonate, causes propionic acid accumulation.

Illness begins in the first days or weeks of life with poor feeding, vomiting, and respiratory distress due to profound anion gap metabolic acidosis, hypoglycemia, and hyperammonemia. Seizures may occur, and bone marrow suppression is common. Physiologic stresses may trigger recurrent attacks. Survivors may have tubular nephropathies, intellectual disability, and neurologic abnormalities. Propionic acidemia can also be seen as part of multiple carboxylase deficiency, biotin deficiency, or biotinidase deficiency.
Diagnosis is suggested by elevated levels of propionic acid metabolites, including methylcitrate and tiglate and their glycine conjugates in blood and urine, and confirmed by measuring propionyl CoA carboxylase activity in WBCs or cultured fibroblasts.

Acute treatment is with IV hydration (including high-dose dextrose) and nutrition; carnitine may be helpful. If these measures are insufficient, peritoneal dialysis or hemodialysis may be needed. Long-term treatment is dietary restriction of precursor amino acids and odd-chain fatty acids and possibly continuation of carnitine supplementation. A few patients respond to high-dose biotin because it is a cofactor for propionyl CoA and other carboxylases.

Methylmalonic acidemia: This disorder is caused by deficiency of methylmalonyl CoA mutase, which converts methylmalonyl CoA (a product of the propionyl CoA carboxylation) into succinyl CoA. Adenosylcobalamin, a metabolite of vitamin B₁₂, is a cofactor; its deficiency also may cause methylmalonic acidemia (and also homocystinuria and megaloblastic anemia). Methylmalonic acid accumulates. Age of onset, clinical manifestations, and treatment are similar to those of propionic acidemia except that cobalamin, instead of biotin, may be helpful for some patients.

Disorders of Methionine Metabolism

A number of defects in methionine metabolism lead to accumulation of homocysteine (and its dimer, homocystine) with adverse effects including thrombotic tendency, lens dislocation, and CNS and skeletal abnormalities.

Homocysteine is an intermediate in methionine metabolism; it is either remethylated to regenerate methionine or combined with serine in a series of transsulfuration reactions to form cystathionine and then cysteine. Cysteine is then metabolized to sulfite, taurine, and glutathione. Various defects in remethylation or transsulfuration can cause homocysteine to accumulate, resulting in disease.

The first step in methionine metabolism is its conversion to adenosylmethionine; this conversion requires the enzyme methionine adenosyltransferase. Deficiency of this enzyme results in methionine elevation, which is not clinically significant except that it causes false-positive neonatal screening results for homocystinuria.

Classic homocystinuria: This disorder is caused by an autosomal recessive deficiency of cystathionine β-synthase, which catalyzes cystathionine formation from homocysteine and serine. Homocysteine accumulates and dimerizes to form the disulfide homocystine, which is excreted in the urine. Because remethylation is intact, some of the additional homocysteine is converted to methionine, which accumulates in the blood. Excess homocysteine predisposes to thrombosis and has adverse effects on connective tissue (perhaps involving fibrillin), particularly the eyes and skeleton; adverse neurologic effects may be due to thrombosis or a direct effect.

Arterial and venous thromboembolic phenomena can occur at any age. Many patients develop ectopia lentis (lens subluxation), intellectual disability, and osteoporosis. Patients can have a marfanoid habitus even though they are not usually tall.

Diagnosis is by neonatal screening for elevated serum methionine; elevated total plasma homocysteine levels are confirmatory. Enzymatic assay in skin fibroblasts can also be done.

Treatment is a low-methionine diet, combined with high-dose pyridoxine (a cystathionine synthetase cofactor) 100 to 500 mg po once/day. Because about half of patients respond to high-dose pyridoxine alone, some clinicians do not restrict methionine intake in these patients. Betaine (trimethylglycine), which enhances remethylation, can also help lower homocysteine; dosage is 100 to 125 mg/kg po bid. Folate 500 to 1000 μg once/day is also given. With early treatment, intellectual outcome is normal or near normal.

Other forms of homocystinuria: Various defects in the remethylation process can result in homocystinuria. Defects include deficiencies of methionine synthase (MS) and MS reductase (MSR),
delivery of methylcobalamin and adenosylcobalamin, and deficiency of methylenetetrahydrofolate reductase (MTHFR, which is required to generate the 5-methyltetrahydrofolate needed for the MS reaction). Because there is no methionine elevation in these forms of homocystinuria, they are not detected by neonatal screening.

Clinical manifestations are similar to other forms of homocystinuria. In addition, MS and MSR deficiencies are accompanied by neurologic deficits and megaloblastic anemia. Clinical manifestation of MTHFR deficiency is variable, including intellectual disability, psychosis, weakness, ataxia, and spasticity.

Diagnosis of MS and MSR deficiencies is suggested by homocystinuria and megaloblastic anemia and confirmed by DNA testing. Patients with cobalamin defects have megaloblastic anemia and methylmalonic acidemia. MTHFR deficiency is diagnosed by DNA testing.

Treatment is by replacement of hydroxycobalamin 1 mg IM once/day (for patients with MS, MSR, and cobalamin defects) and folate in supplementation similar to characteristic homocystinuria.

Cystathioninuria: This disorder is caused by deficiency of cystathionase, which converts cystathionine to cysteine. Cystathionine accumulation results in increased urinary excretion but no clinical symptoms.

Sulfite oxidase deficiency: Sulfite oxidase converts sulfite to sulfate in the last step of cysteine and methionine degradation; it requires a molybdenum cofactor. Deficiency of either the enzyme or the cofactor causes similar disease; inheritance for both is autosomal recessive.

In its most severe form, clinical manifestations appear in neonates and include seizures, hypotonia, and myoclonus, progressing to early death. Patients with milder forms may present similarly to cerebral palsy (see p. 2896) and may have choreiform movements.

Diagnosis is suggested by elevated urinary sulfite and confirmed by measuring enzyme levels in fibroblasts and cofactor levels in liver biopsy specimens. Treatment is supportive.

Urea Cycle Disorders

Urea cycle disorders (UCDs) are characterized by hyperammonemia under catabolic or protein-loading conditions.

Primary UCDs include carbamoyl phosphate synthase (CPS) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinate synthetase deficiency (citrullinemia), argininosuccinate lyase deficiency (argininosuccinic aciduria), and arginase deficiency (argininemia). In addition, N-acetylglutamate synthetase (NAGS) deficiency has been reported. The more "proximal" the enzyme deficiency is, the more severe the hyperammonemia; thus, disease severity in descending order is NAGS deficiency, CPS deficiency, OTC deficiency, citrullinemia, argininosuccinic aciduria, and argininemia.

Inheritance for all UCDs is autosomal recessive, except for OTC deficiency, which is X-linked.

Symptoms and Signs

Clinical manifestations range from mild (eg, failure to thrive, intellectual disability, episodic hyperammonemia) to severe (eg, altered mental status, coma, death). Manifestations in females with OTC deficiency range from growth failure, developmental delay, psychiatric abnormalities, and episodic (especially postpartum) hyperammonemia to a phenotype similar to that of affected males.

Diagnosis

• Serum amino acid profiles

Diagnosis is based on amino acid profiles. For example, elevated ornithine indicates CPS deficiency or OTC deficiency, whereas elevated citrulline indicates citrullinemia. To distinguish between CPS deficiency and OTC deficiency, orotic acid measurement is helpful because accumulation of carbamoyl phosphate in
OTC deficiency results in its alternative metabolism to orotic acid.

**Treatment**

- Dietary protein restriction
- Arginine or citrulline supplementation
- Sometimes liver transplantation

Treatment is dietary protein restriction that still provides adequate amino acids for growth, development, and normal protein turnover. Arginine has become a staple of treatment. It supplies adequate urea cycle intermediates to encourage the incorporation of more nitrogen moieties into urea cycle intermediates, each of which is readily excretable. Arginine is also a positive regulator of acetylglutamate synthesis. Recent studies suggest that oral citrulline is more effective than arginine in patients with OTC deficiency. Additional treatment is with Na benzoate, phenylbutyrate, or phenylacetate, which by conjugating glycine (Na benzoate) and glutamine (phenylbutyrate and phenylacetate) provides a "nitrogen sink."

Despite these therapeutic advances, many UCDs remain difficult to treat, and liver transplantation is eventually required for many patients. Timing of liver transplantation is critical. Optimally, the infant should grow to an age when transplantation is less risky (> 1 yr), but it is important to not wait so long as to allow an intercurrent episode of hyperammonemia (often associated with illness) to cause irreparable harm to the CNS.

**Carbohydrate Metabolism Disorders**

**Glycogen Storage Diseases**

Glycogen storage diseases (GSDs) are caused by deficiencies of enzymes involved in glycogen synthesis or breakdown; the deficiencies may occur in the liver or muscles and cause hypoglycemia or deposition of abnormal amounts or types of glycogen (or its intermediate metabolites) in tissues.

Inheritance for GSDs is autosomal recessive except for GSD type VIII/IX, which is X-linked. Incidence is estimated at about 1/25,000 births, which may be an underestimate because milder subclinical forms may be undiagnosed.

Age of onset, clinical manifestations, and severity vary by type, but symptoms and signs are most commonly those of hypoglycemia and myopathy. Diagnosis is suspected by history, examination, and detection of glycogen and intermediate metabolites in tissues by MRI or biopsy.

Diagnosis is confirmed by significant decrease of enzyme activity in liver (types I, III, VI, and VIII/IX), muscle (types IIb, III, VII, and VIII/IX), skin fibroblasts (types IIa and IV), or RBCs (type VII) or by lack of an increase in venous lactate with forearm activity/ischemia (types V and VII). Prognosis and treatment vary by type, but treatment typically includes dietary supplementation with cornstarch to provide a sustained source of glucose for the hepatic forms of GSD and exercise avoidance for the muscle forms.

**Defects in glycolysis** (rare) may cause syndromes similar to GSDs. Deficiencies of phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase mimic the myopathies of GSD types V and VII; deficiencies of glucose transport protein 2 (Fanconi-Bickel syndrome) mimic the hepatopathy of other GSD types (eg, I, III, IV, VI).

**Galactosemia**

Galactosemia is caused by inherited deficiencies in enzymes that convert galactose to glucose. Symptoms and signs include hepatic and renal dysfunction, cognitive deficits, cataracts, and premature ovarian failure. Diagnosis is by enzyme analysis of RBCs. Treatment is dietary elimination of galactose. Physical prognosis is good with treatment, but cognitive and
performance parameters are often subnormal.

Galactose is found in dairy products, fruits, and vegetables. Autosomal recessive enzyme deficiencies cause 3 clinical syndromes.

**Galactose-1-phosphate uridyl transferase deficiency**: This deficiency causes classic galactosemia. Incidence is 1/62,000 births; carrier frequency is 1/125. Infants become anorectic and jaundiced within a few days or weeks of consuming breast milk or lactose-containing formula. Vomiting, hepatomegaly, poor growth, lethargy, diarrhea, and septicemia (usually *Escherichia coli*) develop, as does renal dysfunction (eg, proteinuria, aminoaciduria, Fanconi syndrome), leading to metabolic acidosis and edema. Hemolytic anemia may also occur. Without treatment, children remain short and develop cognitive, speech, gait, and balance deficits in their teenage years; many also have cataracts, osteomalacia (caused by hypercalciuria), and premature ovarian failure. Patients with the Duarte variant have a much milder phenotype.

**Galactokinase deficiency**: Patients develop cataracts from production of galactitol, which osmotically damages lens fibers; idiopathic intracranial hypertension (pseudotumor cerebri) is rare. Incidence is 1/40,000 births.

**Uridine diphosphate galactose 4-epimerase deficiency**: There are benign and severe phenotypes. Incidence of the benign form is 1/23,000 births in Japan; no incidence data are available for the more severe form. The benign form is restricted to RBCs and WBCs and causes no clinical abnormalities. The severe form causes a syndrome indistinguishable from classic galactosemia, although sometimes with hearing loss.

**Diagnosis**

- Galactose levels
- Enzyme analysis

Diagnosis is suggested clinically and supported by elevated galactose levels and the presence of reducing substances other than glucose (eg, galactose, galactose 1-phosphate) in the urine; it is confirmed by enzyme analysis of RBCs, hepatic tissue, or both. Most states require that neonates be screened for galactose-1-phosphate uridyl transferase deficiency.

**Treatment**

- Dietary galactose restriction

Treatment is elimination of all sources of galactose in the diet, most notably lactose, which is a source of galactose present in all dairy products, including milk-based infant formulas and a sweetener used in many foods. A lactose-free diet prevents acute toxicity and reverses some manifestations (eg, cataracts) but may not prevent neurocognitive deficits. Many patients require supplemental Ca and vitamins. For patients with epimerase deficiency, some galactose intake is critical to ensure a supply of uridine-5’-diphosphate-galactose (UDP-galactose) for various metabolic processes.

**Disorders of Fructose Metabolism**

**Deficiency of enzymes that metabolize fructose may be asymptomatic or cause hypoglycemia.**

Fructose is a monosaccharide that is present in high concentrations in fruit and honey and is a constituent of sucrose and sorbitol.

**Fructose 1-phosphate aldolase (aldolase B) deficiency**: This deficiency causes the clinical syndrome of hereditary fructose intolerance. Inheritance is autosomal recessive; incidence is estimated at 1/20,000 births. Infants are healthy until they ingest fructose; fructose 1-phosphate then accumulates, causing hypoglycemia, nausea and vomiting, abdominal pain, sweating, tremors, confusion, lethargy, seizures,
and coma. Prolonged ingestion may cause cirrhosis, mental deterioration, and proximal renal tubular
calicis with urinary loss of phosphate and glucose.

Diagnosis is suggested by symptoms in relation to recent fructose intake and is confirmed by enzyme
analysis of liver biopsy tissue or by induction of hypoglycemia by fructose infusion 200 mg/kg IV.
Diagnosis and identification of heterozygous carriers of the mutated gene can also be made by direct
DNA analysis.

Short-term treatment is glucose for hypoglycemia; long-term treatment is exclusion of dietary fructose,
sucrose, and sorbitol. Many patients develop a natural aversion to fructose-containing food. Prognosis is
excellent with treatment.

**Fructokinase deficiency:** This deficiency causes benign elevation of blood and urine fructose levels
(benign fructosuria). Inheritance is autosomal recessive; incidence is about 1/130,000 births.

The condition is asymptomatic and diagnosed accidentally when a non-glucose reducing substance is
detected in urine.

**Deficiency of fructose-1,6-bisphosphatase:** This deficiency compromises gluconeogenesis and
results in fasting hypoglycemia, ketosis, and acidosis. This deficiency can be fatal in neonates.
Inheritance is autosomal recessive; incidence is unknown. Febrile illness can trigger episodes.

Acute treatment is oral or IV glucose. Tolerance to fasting generally increases with age.

**Disorders of Pyruvate Metabolism**

**Inability to metabolize pyruvate causes lactic acidosis and a variety of CNS abnormalities.**

Pyruvate is an important substrate in carbohydrate metabolism.

**Pyruvate dehydrogenase deficiency:** Pyruvate dehydrogenase is a multi-enzyme complex responsible
for the generation of acetyl CoA from pyruvate for the Krebs cycle. Deficiency results in elevation of
pyruvate and thus elevation of lactic acid levels. Inheritance is X-linked or autosomal recessive.

Clinical manifestations vary in severity but include lactic acidosis and CNS malformations and other
postnatal changes, including cystic lesions of the cerebral cortex, brain stem, and basal ganglia; ataxia;
and psychomotor retardation.

Diagnosis is confirmed by enzyme analysis of skin fibroblasts, DNA testing, or both.

There is no clearly effective treatment, although a low-carbohydrate or ketogenic diet and dietary thiamin
supplementation have been beneficial for some patients.

**Pyruvate carboxylase deficiency:** Pyruvate carboxylase is an enzyme important for gluconeogenesis
from pyruvate and alanine generated in muscle. Deficiency may be primary, or secondary to deficiency of
holocarboxylase synthetase, biotin, or biotinidase; inheritance for both is autosomal recessive, and both
result in lactic acidosis.

Primary deficiency incidence is < 1/250,000 births but may be higher in certain American Indian
populations. Psychomotor retardation with seizures and spasticity are the major clinical manifestations.
Laboratory abnormalities include hyperammonemia; lactic acidosis; ketoacidosis; elevated levels of
plasma lysine, citrulline, alanine, and proline; and increased excretion of α-ketoglutarate. Diagnosis is
confirmed by enzyme analysis of cultured skin fibroblasts.

Secondary deficiency is clinically similar, with failure to thrive, seizures, and other organic aciduria.

There is no effective treatment, but some patients with primary deficiency and all those with secondary
deficiencies should be given biotin supplementation 5 to 20 mg po once/day.
Other Disorders of Carbohydrate Metabolism

Phosphoenolpyruvate carboxykinase deficiency impairs gluconeogenesis and results in symptoms and signs similar to the hepatic forms of glycogen storage disease but without hepatic glycogen accumulation.

Other deficiencies include those of glycolytic enzymes or enzymes in the pentose phosphate pathway. Common examples are pyruvate kinase deficiency (see p. 941) and glucose-6-phosphate dehydrogenase (G6PD) deficiency (see p. 941), both of which may result in hemolytic anemia. Wernicke-Korsakoff syndrome (see p. 33) is caused by a partial deficiency of transketolase, which is an enzyme for the pentose phosphate pathway that requires thiamin as a cofactor.

Fatty Acid and Glycerol Metabolism Disorders

Fatty acids are the preferred energy source for the heart and an important energy source for skeletal muscle during prolonged exertion. Also, during fasting, the bulk of the body's energy needs must be supplied by fat metabolism. Using fat as an energy source requires catabolizing adipose tissue into free fatty acid and glycerol. The free fatty acid is metabolized in the liver and peripheral tissue via β-oxidation into acetyl CoA; the glycerol is used by the liver for triglyceride synthesis or for gluconeogenesis. Primary disorders of carnitine are discussed on p. 18, but secondary carnitine deficiency is a secondary biochemical feature of many organic acidemias and fatty acid oxidation defects.

Disorders of the β-Oxidation Cycle

In these processes, there are numerous inherited defects, which typically manifest during fasting with hypoglycemia and acidosis; some cause cardiomyopathy and muscle weakness.

Acetyl CoA is generated from fatty acids through repeated β-oxidation cycles. Sets of 4 enzymes (an acyl dehydrogenase, a hydratase, a hydroxyacyl dehydrogenase, and a lyase) specific for different chain lengths (very long chain, long chain, medium chain, and short chain) are required to catabolize a long-chain fatty acid completely. Inheritance for all fatty acid oxidation defects is autosomal recessive.

Medium-chain acyl dehydrogenase deficiency (MCADD): This deficiency is the most common defect in the β-oxidation cycle and has been incorporated into expanded neonatal screening in many states.

Clinical manifestations typically begin after 2 to 3 mo of age and usually follow fasting (as little as 12 h). Patients have vomiting and lethargy that may progress rapidly to seizures, coma, and sometimes death (which can also appear as SIDS). During attacks, patients have hypoglycemia, hyperammonemia, and unexpectedly low urinary and serum ketones. Metabolic acidosis is often present but may be a late manifestation.

Diagnosis is by detecting medium-chain fatty acid conjugates of carnitine in plasma or glycine in urine or by detecting enzyme deficiency in cultured fibroblasts; however, DNA testing can confirm most cases.

Treatment of acute attacks is with 10% dextrose IV at 1.5 times the fluid maintenance rate (see p. 2808); some clinicians also advocate carnitine supplementation during acute episodes. Prevention is a low-fat, high-carbohydrate diet and avoidance of prolonged fasting. Cornstarch therapy is often used to provide a margin of safety during overnight fasting.

Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD): This deficiency is the 2nd most common fatty acid oxidation defect. It shares many features of MCADD, but patients may also have cardiomyopathy; rhabdomyolysis, massive creatine kinase elevations, and myoglobinuria with muscle exertion; peripheral neuropathy; and abnormal liver function. Mothers with an LCHADD fetus often have HELLP syndrome (hemolysis, elevated liver enzymes, low platelets—see p. 2670) during pregnancy.

Diagnosis is based on the presence of excess long-chain hydroxy acids on organic acid analysis and on the presence of their carnitine conjugates in an acylcarnitine profile or glycine conjugates in an
acylglycine profile. LCHADD can be confirmed by enzyme study in skin fibroblasts.

Treatment during acute exacerbations includes hydration, high-dose glucose, bed rest, urine alkalization, and carnitine supplementation. Long-term treatment includes a high-carbohydrate diet, medium-chain triglyceride supplementation, and avoidance of fasting and strenuous exercise.

**Very long-chain acyl-coA dehydrogenase deficiency (VLCADD):** This deficiency is similar to LCHADD but is commonly associated with significant cardiomyopathy.

**Glutaric acidemia type II:** A defect in the transfer of electrons from the coenzyme of fatty acyl dehydrogenases to the electronic transport chain affects reactions involving fatty acids of all chain lengths (multiple acylcoA dehydrogenase deficiency); oxidation of several amino acids is also affected.

Clinical manifestations thus include fasting hypoglycemia, severe metabolic acidosis, and hyperammonemia.

Diagnosis is by increased ethylmalonic, glutaric, 2- and 3-hydroxyglutaric, and other dicarboxylic acids in organic acid analysis, and glutaryl and isovaleryl and other acylcarnitines in tandem mass spectrometry studies. Enzyme deficiencies in skin fibroblasts can be confirmatory.

Treatment is similar to that for MCADD, except that riboflavin may be effective in some patients.

**Disorders of Glycerol Metabolism**

**Glycerol is converted to glycerol-3-phosphate by the hepatic enzyme glycerol kinase; deficiency results in episodic vomiting, lethargy, and hypotonia.**

Glycerol kinase deficiency is X-linked; many patients with this deficiency also have a chromosomal deletion that extends beyond the glycerol kinase gene into the contiguous gene region, which contains the genes for congenital adrenal hypoplasia and Duchenne muscular dystrophy. Thus, patients with glycerol kinase deficiency may have one or more of these disease entities.

Symptoms begin at any age and are usually accompanied by acidosis, hypoglycemia, and elevated blood and urine levels of glycerol.

Diagnosis is by detecting an elevated level of glycerol in serum and urine and is confirmed by DNA analysis.

Treatment is with a low-fat diet, but glucocorticoid replacement is critical for those with adrenal hypoplasia.

**Lysosomal Storage Disorders**

Lysosomal enzymes break down macromolecules, either those from the cell itself (eg, when cellular structural components are being recycled) or those acquired outside the cell. Inherited defects or deficiencies of lysosomal enzymes (or other lysosomal components) can result in accumulation of undegraded metabolites. Because there are numerous specific deficiencies, storage diseases are usually grouped biochemically by the accumulated metabolite. Subgroups include

- Mucopolysaccharidoses
- Sphingolipidoses (lipidoses)
- Mucolipidoses

The most important are the mucopolysaccharidoses and sphingolipidoses. Type 2 glycogenosis is a lysosomal storage disorder, but most glycogenoses are not.
Because reticuloendothelial cells (eg, in the spleen) are rich in lysosomes, reticuloendothelial tissues are involved in a number of lysosomal storage disorders, but generally, tissues richest in the substrate are most affected. Thus the brain, which is rich in gangliosides, is particularly affected by gangliosidoses, whereas mucopolysaccharidoses affect many tissues because mucopolysaccharides are present throughout the body.

**Mucopolysaccharidoses (MPS):** MPS are inherited deficiencies of enzymes involved in glycosaminoglycan breakdown. Glycosaminoglycans (previously termed mucopolysaccharides) are polysaccharides abundant on cell surfaces and in extracellular matrix and structures. Enzyme deficiencies that prevent glycosaminoglycan breakdown cause accumulation of glycosaminoglycan fragments in lysosomes and cause extensive bone, soft tissue, and CNS changes. Inheritance is usually autosomal recessive (except for MPS type II).

Age at presentation, clinical manifestations, and severity vary by type. Common manifestations include coarse facial features, neurodevelopmental delays and regression, joint contractures, organomegaly, stiff hair, progressive respiratory insufficiency (caused by airway obstruction and sleep apnea), cardiac valvular disease, skeletal changes, and cervical vertebral subluxation.

Diagnosis is suggested by history, physical examination, bone abnormalities (eg, dysostosis multiplex) found during skeletal survey, and elevated total and fractionated urinary glycosaminoglycans. Diagnosis is confirmed by enzyme analysis of cultured fibroblasts (prenatal) or peripheral WBCs (postnatal). Additional testing is required to monitor organ-specific changes (eg, echocardiography for valvular disease, audiometry for hearing changes).

Treatment of MPS type I (Hurler's disease) is enzyme replacement with α-l-iduronidase, which effectively halts progression and reverses all non-CNS complications of the disease. Hematopoietic stem cell (HSC) transplantation has also shown promise in early studies but is ineffective for CNS disease. The combination of enzyme replacement and HSC transplantation is under study.

**Sphingolipidoses:** Sphingolipids are normal lipid components of cell membranes; they accumulate in lysosomes and cause extensive neuronal, bone, and other changes when enzyme deficiencies prevent their breakdown. Although incidence is low, carrier rate of some forms is high. Gaucher's disease is the most common sphingolipidosis. Others include Niemann-Pick, Tay-Sachs, Sandhoff's, Fabry's, Krabbe's, and cholesteryl ester storage diseases and metachromatic leukodystrophy.

**Gaucher's Disease**

Gaucher's disease is a sphingolipidosis resulting from glucocerebrosidase deficiency, causing deposition of glucocerebroside and related compounds. Symptoms and signs vary by type but are most commonly hepatosplenomegaly or CNS changes. Diagnosis is by enzyme analysis of WBCs.

Glucocerebrosidase normally hydrolyzes glucocerebroside to glucose and ceramide. Genetic defects of the enzyme cause glucocerebroside accumulation in tissue macrophages through phagocytosis, forming Gaucher's cells. Accumulation of Gaucher's cells in the perivascular spaces in the brain causes gliosis in the neuronopathic forms. There are 3 types, which vary in epidemiology, enzyme activity, and manifestations.

**Type I** (nonneuronopathic) is most common (90% of all patients). Residual enzyme activity is highest. Ashkenazi Jews are at greatest risk; 1/12 is a carrier. Onset ranges from age 2 yr to late adulthood. Symptoms and signs include splenomegaly, bone disease (eg, osteopenia, pain crises, osteolytic lesions with fractures), growth failure, delayed puberty, ecchymoses, and pinguiculae. Epistaxis and ecchymoses resulting from thrombocytopenia are common. X-rays show flaring of the ends of the long bones (Erlenmeyer flask deformity) and cortical thinning.

**Type II** (acute neuronopathic) is rarest, and residual enzyme activity in this type is lowest. Onset occurs during infancy. Symptoms and signs are progressive neurologic deterioration (eg, rigidity, seizures) and death by age 2 yr.
Type III (subacute neuronopathic) falls between types I and II in incidence, enzyme activity, and clinical severity. Onset occurs at any time during childhood. Clinical manifestations vary by subtype and include progressive dementia and ataxia (IIIa), bone and visceral involvement (IIlb), and supranuclear palsy with corneal opacities (IIlc). Patients who survive to adolescence may live for many years.

Diagnosis

- Enzyme analysis

Diagnosis is by enzyme analysis of WBCs. Carriers are detected, and types are distinguished by mutation analysis. Although biopsy is unnecessary, Gaucher's cells—lipid-laden tissue macrophages in the liver, spleen, lymph nodes, or bone marrow that have a wrinkled tissue-paper appearance—are diagnostic.

Treatment

- Types I and III: Enzyme replacement with placental or recombinant glucocerebrosidase

- Sometimes miglustat, splenectomy, or stem cell transplantation

Enzyme replacement with placental or recombinant glucocerebrosidase is effective in types I and III; there is no treatment for type II. The enzyme is modified for efficient delivery to lysosomes. Patients receiving enzyme replacement require routine Hb and platelet monitoring, routine assessment of spleen and liver volume by CT or MRI, and routine assessment of bone disease by skeletal survey, dual-energy x-ray absorptiometry scanning, or MRI.

Miglustat (100 mg po tid), a glucosylceramide synthase inhibitor, reduces glucocerebroside concentration (the substrate for glucocerebrosidase) and is an alternative for patients unable to receive enzyme replacement.

Splenectomy may be helpful for patients with anemia, leukopenia, or thrombocytopenia or when spleen size causes discomfort. Patients with anemia may also need blood transfusions.

Bone marrow or stem cell transplantation provides a definitive cure but is considered a last resort because of substantial morbidity and mortality.

Niemann-Pick Disease

Niemann-Pick disease is a sphingolipidosis caused by deficient sphingomyelinase activity, resulting in accumulation of sphingomyelin (ceramide phosphocholine) in reticuloendothelial cells.

Niemann-Pick disease inheritance is autosomal recessive and appears most often in Ashkenazi Jews; 2 types, A and B, exist. Type C Niemann-Pick disease is an unrelated enzymatic defect involving abnormal cholesterol storage.

Type A patients have < 5% of normal sphingomyelinase activity. The disease is characterized by hepatosplenomegaly, failure to thrive, and rapidly progressive neurodegeneration. Death occurs by age 2 or 3 yr.

Type B patients have sphingomyelinase activity within 5 to 10% of normal. Type B is more variable clinically than type A. Hepatosplenomegaly and lymphadenopathy may occur. Pancytopenia is common. Most patients with type B have little or no neurologic involvement and survive into adulthood; they may be clinically indistinguishable from those with type I Gaucher's disease. In severe cases of type B, progressive pulmonary infiltrates cause major complications.

Diagnosis
• Prenatal screening

• WBC sphingomyelinase assay

Both types are usually suspected by history and examination, most notably hepatosplenomegaly. Diagnosis can be confirmed by sphingomyelinase assay on WBCs and can be made prenatally by using amniocentesis or chorionic villus sampling.

Treatment

Bone marrow or stem cell transplantation is under investigation as a potential treatment option.

Tay-Sachs Disease and Sandhoff's Disease

Tay-Sachs disease and Sandhoff's disease are sphingolipidoses caused by hexosaminidase deficiency that causes severe neurologic symptoms and early death.

Gangliosides are complex sphingolipids present in the brain. There are 2 major forms, GM₁ and GM₂, both of which may be involved in lysosomal storage disorders; there are 2 main types of GM₂ gangliosidosis, each of which can be caused by numerous different mutations.

Tay-Sachs disease: Deficiency of hexosaminidase A results in accumulation of GM₂ in the brain. Inheritance is autosomal recessive; the most common mutations are carried by 1/27 normal adults of Eastern European (Ashkenazi) Jewish origin, although other mutations cluster in some French-Canadian and Cajun populations.

Children with Tay-Sachs disease start missing developmental milestones after age 6 mo and develop progressive cognitive and motor deterioration resulting in seizures, intellectual disability, paralysis, and death by age 5 yr. A cherry-red macular spot is common.

Diagnosis is clinical and can be confirmed by enzyme assay.

In the absence of effective treatment, management is focused on screening adults of childbearing age in high-risk populations to identify carriers (by way of enzyme activity and mutation testing) combined with genetic counseling.

Sandhoff's disease: There is a combined hexosaminidase A and B deficiency. Clinical manifestations include progressive cerebral degeneration beginning at 6 mo, accompanied by blindness, cherry-red macular spot, and hyperacusis. It is almost indistinguishable from Tay-Sachs disease in course, diagnosis, and management, except that there is visceral involvement (hepatomegaly and bone change) and no ethnic association.

Krabbe’s Disease

Krabbe’s disease is a sphingolipidosis that causes intellectual disability, paralysis, blindness, deafness, and pseudobulbar palsy, progressing to death.

Krabbe's disease (galactosylceramide lipidosis, globoid cell leukodystrophy) is caused by an autosomal recessive galactocerebroside β-galactosidase deficiency.

It affects infants and is characterized by intellectual disability, paralysis, blindness, deafness, and pseudobulbar palsy, progressing to death.

Diagnosis is by detecting enzyme deficiency in WBCs or cultured skin fibroblasts.

Because bone marrow transplantation effectively delays onset of symptoms, prenatal testing or neonatal screening (routine in New York) is sometimes done.
Metachromatic Leukodystrophy

Metachromatic leukodystrophy is a sphingolipidosis caused by arylsulfatase A deficiency, which causes progressive paralysis and dementia resulting in death by age 10 yr.

In metachromatic leukodystrophy (sulfatide lipidosis), arylsulfatase A deficiency causes metachromatic lipids to accumulate in the white matter of the CNS, peripheral nerves, kidney, spleen, and other visceral organs; accumulation in the nervous system causes central and peripheral demyelination. Numerous mutations exist; patients vary in age at onset and speed of progression.

The infantile form is characterized by progressive paralysis and dementia usually beginning before age 4 yr and resulting in death about 5 yr after onset of symptoms. The juvenile form manifests between 4 yr and 16 yr of age with gait disturbance, intellectual impairment, and findings of peripheral neuropathy. Contrary to the infantile form, deep tendon reflexes are usually brisk. There is also a milder adult form.

Diagnosis is suggested clinically and by findings of decreased nerve conduction velocity; it is confirmed by detecting enzyme deficiency in WBCs or cultured skin fibroblasts.

There is no effective treatment.

Fabry's Disease

Fabry's disease is a sphingolipidosis caused by deficiency of α-galactosidase A, which causes angiokeratomas, acroparesthesias, corneal opacities, recurrent febrile episodes, and renal or heart failure.

Fabry's disease (angiokeratoma corporis diffusum) is an X-linked deficiency of the lysosomal enzyme α-galactosidase A, which is needed for normal trihexosylceramide catabolism. Glycolipid (globotriaosylceramide) accumulates in many tissues (eg, vascular endothelium, lymph vessels, heart, kidney).

Diagnosis in males is clinical, based on appearance of typical skin lesions (angiokeratomas) over the lower trunk and by characteristic features of peripheral neuropathy (causing recurrent burning pain in the extremities), corneal opacities, and recurrent febrile episodes. Death results from renal failure or cardiac or cerebral complications of hypertension or other vascular disease. Heterozygous females are usually asymptomatic but may have an attenuated form of disease often characterized by corneal opacities.

Diagnosis is by assay of galactosidase activity—prenatally in amniocytes or chorionic villi and postnatally in serum or WBCs.

Treatment is enzyme replacement with recombinant α-galactosidase A (agalsidase beta) combined with supportive measures for fever and pain. Kidney transplantation is effective for treating renal failure.

Cholesteryl Ester Storage Disease and Wolman's Disease

Cholesteryl ester storage disease and Wolman's disease are sphingolipidoses caused by lysosomal acid lipase deficiency resulting in hyperlipidemia and hepatomegaly.

These diseases are rare, autosomal recessive disorders that result in accumulation of cholesteryl esters and triglycerides, mainly in lysosomes of histiocytes, resulting in foam cells in the liver, spleen, lymph nodes, and other tissues. Serum low-density lipoprotein (LDL) is usually elevated.

Wolman's disease is the more severe form, manifesting in the first weeks of life with poor feeding, vomiting, and abdominal distention secondary to hepatosplenomegaly; infants usually die within 6 mo.

Cholesteryl ester storage disease is less severe and may not manifest until later in life, even adulthood, at which time hepatomegaly may be detected; premature atherosclerosis, often severe, may develop.
Diagnosis is based on clinical features and detection of acid lipase deficiency in liver biopsy specimens or cultured skin fibroblasts, lymphocytes, or other tissues. Prenatal diagnosis is based on the absence of acid lipase activity in cultured chorionic villi.

There is no proven treatment, but statins reduce plasma LDL levels, and cholestyramine combined with a low-cholesterol diet has reportedly alleviated other signs.

**Mitochondrial Oxidative Phosphorylation Disorders**

Impairment of oxidative phosphorylation often, but not always, causes lactic acidosis, particularly affecting the CNS, retina, and muscle.

Cellular respiration (oxidative phosphorylation) occurs in the mitochondria, where a series of enzymes catalyze the transfer of electrons to molecular oxygen and the generation of energy-storing ATP. Mitochondrial or nuclear genetic defects involving enzymes used in this process impair cellular respiration, decreasing the ATP:ADP ratio. Tissues with a high energy demand (eg, brain, nerves, retina, skeletal and cardiac muscle) are particularly vulnerable. The most common clinical manifestations are seizures, hypotonia, ophthalmoplegia, stroke-like episodes, muscle weakness, and cardiomyopathy.

Biochemically, there is profound lactic acidosis because the NADH:NAD ratio increases, shifting the equilibrium of the lactate dehydrogenase reaction toward lactate. The increase in the lactate:pyruvate ratio distinguishes oxidative phosphorylation defects from other genetic causes of lactic acidosis such as pyruvate carboxylase or pyruvate dehydrogenase deficiency, in which the lactate:pyruvate ratio remains normal. A large number of oxidative phosphorylation defects have been described; only the most common ones are outlined here, along with their distinguishing features.

Mitochondrial mutations and variants have also been implicated in a number of diseases of aging (eg, Parkinson's disease, Alzheimer's disease, diabetes, deafness, cancer).

**Leber's hereditary optic neuropathy (LHON):** This disease is characterized by acute or sub-acute bilateral central vision loss caused by retinal degeneration. Onset usually occurs in the patient's 20s or 30s but can occur from childhood to adulthood. Male:female ratio is 4:1. Many mutations have been defined, but 3 common ones account for 90% of those in European patients. LHON pedigrees usually show a pattern of maternal inheritance typical of mitochondrial disorders.

**Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS):** Mutations in the mitochondrial tRNA\(^{leu}\) gene cause this progressive neurodegenerative disease characterized by repeated episodes of "chemical strokes," myopathy, and lactic acidosis. In many cases, cells contain both wild-type and mutant mitochondrial DNA (heteroplasmy); thus, expression is variable.

**Myoclonic epilepsy with ragged-red fibers (MERRF):** This progressive disorder is characterized by uncontrolled muscle contractions (myoclonic seizures), dementia, ataxia, and myopathy, which shows ragged-red fibers (indicating mitochondrial proliferation) with specialized stains when biopsied. Mutations are in the mitochondrial tRNA\(^{lys}\) gene. Heteroplasmy is common; thus, expression is variable.

**Kearns-Sayre syndrome and chronic progressive external ophthalmoplegia (CPEO):** These disorders are characterized by ophthalmoplegia, ptosis, atypical retinitis pigmentosa, ragged-red fiber myopathy, ataxia, deafness, and cardiomyopathy typically occurring before age 20 yr. Most mutations involve contiguous deletion/duplication of part of the mitochondrial transfer RNA and other protein-coding genes.

**Neurogenic muscle atrophy and retinitis pigmentosa (NARP) and Leigh disease:** Pigmentary retinopathy in the presence of neuromuscular degeneration and Leigh disease (subacute necrotizing encephalopathy characterized by ataxias and basal ganglia degeneration) is a genetically heterogeneous syndrome. Mutations can be seen in the ATP6 gene of the mitochondrial genomes.
Peroxisomal Disorders

Peroxisomes are intracellular organelles that contain enzymes for β-oxidation. These enzymes overlap in function with those in mitochondria, with the exception that mitochondria lack enzymes to metabolize very long-chain fatty acids (VLCFA), those 20 to 26 carbons in length. Therefore, peroxisomal disorders generally manifest with elevated VLCFA levels (except rhizomelic chondrodysplasia). Although VLCFA levels may help screen for these disorders, other assays are also required (eg, plasma levels of phytanic, pristanic, and pipecolic acids; RBC plasmalogen levels).

There are 2 types of peroxisomal disorders: those with defective peroxisome formation and those with defects in single peroxisomal enzymes. X-linked adrenoleukodystrophy is the most common peroxisomal disorder (incidence 1/17,000 births); all others are autosomal recessive, with a combined incidence of about 1/50,000 births.

Zellweger syndrome (ZS), neonatal adrenoleukodystrophy, and infantile Refsum's disease (IRD):
These disorders are 3 expressions of a disease continuum, from most (ZS) to least (IRD) severe. The responsible genetic defect occurs in 1 of at least 11 genes involved in peroxisomal formation or protein import (the PEX gene family).

Manifestations include facial dysmorphism, CNS malformations, demyelination, neonatal seizures, hypotonia, hepato-megaly, cystic kidneys, short limbs with stippled epiphyses (chondrodysplasia punctata), cataracts, retinopathy, hearing deficit, psychomotor delay, and peripheral neuropathy. Diagnosis is by detecting elevated blood levels of VLCFA, phytanic acid, bile acid intermediates, and pipecolic acid. Experimental treatment with docosahexaenoic acid (DHA—levels of which are reduced in patients with disorders of peroxisome formation) has shown some promise.

Rhizomelic chondrodysplasia punctata: This defect of peroxisomal biogenesis is caused by PEX7 gene mutations and characterized by skeletal changes that include midface hypoplasia, strikingly short proximal limbs, frontal bossing, small nares, cataracts, ichthyosis, and profound psychomotor retardation. Vertebral clefts are also common. Diagnosis is by x-ray findings, serum elevation of phytanic acid, and low RBC plasmalogen levels; VLCFA levels are normal. There is no effective treatment.

X-linked adrenoleukodystrophy: This disorder is caused by deficiency of the peroxisomal membrane transporter ALDP, which is coded for by the gene ABCD1.

The cerebral form affects 40% of patients. Onset occurs between age 4 yr and 8 yr, and symptoms of attention deficit progress over time to severe behavioral problems; dementia; and vision, hearing, and motor deficits, causing total disability and death 2 to 3 yr after diagnosis. Milder adolescent and adult forms have also been described.

About 45% of patients have a milder form called adrenomyeloneuropathy (AMN); onset occurs in the 20s or 30s, with progressive paraparesis, and sphincter and sexual disturbance. About one third of these patients also develop cerebral symptoms.

Patients with any form may also develop adrenal insufficiency; about 15% have isolated Addison's disease without neurologic involvement.

Diagnosis is confirmed by isolated elevation of VLCFA. Bone marrow or stem cell transplantation may help stabilize symptoms in some cases. Adrenal steroid replacement is needed for patients with adrenal insufficiency. Dietary supplement with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) can normalize plasma VLCFA levels and may be beneficial in some cases but is under study.

Classic Refsum's disease: Genetic deficiency of a single peroxisomal enzyme, phytanoyl-CoA hydroxylase, which catalyzes metabolism of phytanic acid (a common dietary plant component), causes phytanic acid accumulation.

Clinical manifestations include progressive peripheral neuropathy, impaired vision caused by retinitis pigmentosa, hearing deficit, anosmia, cardiomyopathy and conduction defects, and ichthyosis. Onset is
usually in the 20s. Diagnosis is confirmed by elevation of serum phytanic acid and decreased levels of pristanic acid (phytanic acid elevation is accompanied by pristanic acid elevation in several other peroxisomal disorders).

Treatment is dietary restriction of phytanic acid (< 10 mg/day), which can be effective in preventing or delaying symptoms when started before symptom onset.

**Purine and Pyrimidine Metabolism Disorders**

Purines are key components of cellular energy systems (eg, ATP, NAD), signaling (eg, GTP, cAMP, cGMP), and, along with pyrimidines, RNA and DNA production. Purines and pyrimidines may be synthesized de novo or recycled by a salvage pathway from normal catabolism. The end product of complete catabolism of purines is uric acid; catabolism of pyrimidines produces citric acid cycle intermediates.

**Disorders of Purine Salvage**

**Lesch-Nyhan syndrome:** This is a rare, X-linked, recessive disorder caused by deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT); degree of deficiency (and hence manifestations) vary with the specific mutation. HPRT deficiency results in failure of the salvage pathway for hypoxanthine and guanine. These purines are instead degraded to uric acid. Additionally, a decrease in inositol monophosphate and guanosyl monophosphate leads to an increase in conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) to 5-phosphoribosylamine, which further exacerbates uric acid overproduction. Hyperuricemia predisposes to gout and its complications. Patients also have a number of cognitive and behavioral dysfunctions, etiology of which is unclear; they do not seem related to uric acid.

The disease usually manifests between 3 mo and 12 mo of age with the appearance of orange sandy precipitate (xanthine) in the urine; it progresses to CNS involvement with intellectual disability, spastic cerebral palsy, involuntary movements, and self-mutilating behavior (particularly biting). Later, chronic hyperuricemia causes symptoms of gout (eg, urolithiasis, nephropathy, gouty arthritis, tophi).

Diagnosis is suggested by the combination of dystonia, intellectual disability, and self-mutilation. Serum uric acid levels are usually elevated, but confirmation by HPRT enzyme assay is usually done.

CNS dysfunction has no known treatment; management is supportive. Self-mutilation may require physical restraint, dental extraction, and sometimes drug therapy; a variety of drugs has been used. Hyperuricemia is treated with a low-purine diet (eg, avoiding organ meats, beans, sardines) and allopurinol, a xanthine oxidase inhibitor (the last enzyme in the purine catabolic pathway). Allopurinol prevents conversion of accumulated hypoxanthine to uric acid; because hypoxanthine is highly soluble, it is excreted.

**Adenine phosphoribosyltransferase deficiency:** This is a rare autosomal recessive disorder that results in the inability to salvage adenine for purine synthesis. Accumulated adenine is oxidized to 2,8-dihyroxadenine, which precipitates in the urinary tract, causing problems similar to those of uric acid nephropathy (eg, renal colic, frequent infections, and, if diagnosed late, renal failure). Onset can occur at any age.

Diagnosis is by detecting elevated levels of 2,8-dihyroxadenine, 8-hydroxyadenine, and adenine in urine and confirmed by enzyme assay; serum uric acid is normal.

Treatment is with dietary purine restriction, high fluid intake, and avoidance of urine alkalinization. Allopurinol can prevent oxidation of adenine; renal transplantation may be needed for end-stage renal disease.

**Disorders of Purine Nucleotide Synthesis**

**Phosphoribosylpyrophosphate synthetase superactivity:** This X-linked, recessive disorder causes purine overproduction. Excess purine is degraded, resulting in hyperuricemia and gout and neurologic
and developmental abnormalities.

Diagnosis is by enzyme studies on RBCs and cultured skin fibroblasts.

Treatment is with allopurinol and a low-purine diet.

**Adenylosuccinase deficiency:** This autosomal recessive disorder causes profound intellectual disability, autistic behavior, and seizures.

Diagnosis is by identifying elevated levels of succinylaminoimidazole carboxamide ribo-side and succinyladenosine in CSF and urine.

There is no effective treatment.

**Disorders of Purine Catabolism**

**Myoadenylate deaminase deficiency (or muscle adenosine monophosphate deaminase deficiency):** The enzyme myoadenylate deaminase converts AMP to inosine and ammonia. Deficiency may be asymptomatic or it may cause exercise-induced myalgias or cramping; expression seems to be variable because, despite the high frequency of the mutant allele (10 to 14%), the frequency of the muscle phenotype is quite low in patients homozygous for the mutant allele. When symptomatic patients exercise, they do not accumulate ammonia or inosine monophosphate as do unaffected people; this is how the disorder is diagnosed.

Treatment is exercise modulation as appropriate.

**Adenosine deaminase deficiency:** Adenosine deaminase converts adenosine and deoxyadenosine to inosine and deoxyinosine, which are further broken down and excreted. Enzyme deficiency (from 1 of > 60 known mutations) results in accumulation of adenosine, which is converted to its ribonucleotide and deoxyribonucleotide (dATP) forms by cellular kinases. The dATP increase results in inhibition of ribonucleotide reductase and under-production of other deoxyribonucleotides. DNA replication is compromised as a result. Immune cells are especially sensitive to this defect; adenosine deaminase deficiency causes one form of severe combined immunodeficiency (see p. 1106).

Diagnosis is by low RBC and WBC enzyme activity.

Treatment is by bone marrow or stem cell transplantation and enzyme replacement therapy. Somatic cell gene therapy is being evaluated as well.

**Purine nucleoside phosphorylase deficiency:** This rare, autosomal recessive deficiency is characterized by immunodeficiency with severe T-cell dysfunction and often neurologic symptoms. Manifestations are lymphopenia, thymic deficiency, recurrent infections, and hypouricemia. Many patients have developmental delay, ataxia, or spasticity.

Diagnosis is by low enzyme activity in RBCs.

Treatment is with bone marrow or stem cell transplantation.

**Xanthine oxidase deficiency:** Xanthine oxidase is the enzyme that catalyzes uric acid production from xanthine and hypoxanthine. Deficiency causes buildup of xanthine, which may precipitate in the urine, causing symptomatic stones with hematuria, urinary colic, and UTIs.

Diagnosis is by low serum uric acid and high urine and plasma hypoxanthine and xanthine. Enzyme determination requires liver or intestinal mucosal biopsy and is rarely indicated.

Treatment is high fluid intake to minimize likelihood of stone formation and allopurinol in some patients.

**Disorders of Pyrimidine Metabolism**
Uridine monophosphate synthase deficiency (hereditary orotic aciduria): Uridine monophosphate is the enzyme that catalyzes orotate phosphoribosyltransferase and orotidine-5′-monophosphate decarboxylase reactions. With deficiency, orotic acid accumulates, causing clinical manifestations of megaloblastic anemia, orotic crystalluria and nephropathy, cardiac malformations, strabismus, and recurrent infections.

Diagnosis is by enzyme assay in a variety of tissues.

Treatment is with oral uridine supplementation.
Chapter 302. Hereditary Periodic Fever Syndromes

Introduction

Hereditary periodic fever syndromes are hereditary disorders characterized by recurrent fever and other symptoms that are not explained by other causes.

Most patients develop symptoms during childhood; < 10% develop symptoms after age 18. Disorders best characterized are

• Familial Mediterranean fever
• Hyper-IgD syndrome
• Tumor necrosis factor (TNF) receptor-associated periodic syndrome

Others include

• The hereditary cryopyrinopathies: Familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID)
• PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome
• PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent bouts of fever and peritonitis, sometimes with pleuritis, skin lesions, arthritis, and, very rarely, pericarditis. Renal amyloidosis may develop, sometimes leading to renal failure. People with genetic origins in the Mediterranean basin are most commonly affected. Diagnosis is largely clinical, although genetic testing is available. Treatment with prophylactic colchicine prevents acute attacks as well as renal amyloidosis in most patients. Prognosis is excellent with treatment.

FMF is a disease of people with genetic origins in the Mediterranean basin, predominantly Sephardic Jews, North African Arabs, Armenians, Turks, Greeks, and Italians. However, cases have occurred among enough other groups (eg, Ashkenazi Jews, Cubans, Japanese) to caution against excluding the diagnosis solely on the basis of ancestry. Up to 50% of patients have a family history of the disorder, usually involving siblings.

Etiology

FMF is caused by mutations in the MEFV gene on the short arm of chromosome 16 and is inherited in an autosomal recessive manner. The MEFV gene normally codes a protein (called pyrin or marenostrin) expressed in circulating neutrophils. Its presumed action is to blunt the inflammatory response, possibly by inhibiting neutrophil activation and chemotaxis. Gene mutations result in defective pyrin molecules; it is hypothesized that the altered pyrin cannot suppress minor, unknown triggers to inflammation that are normally checked by intact pyrin. The clinical consequence is spontaneous bouts of neutrophil-predominant inflammation in the abdominal cavity as well as in other sites.

Symptoms and Signs

Onset is usually between the ages of 5 and 15 yr but may be much later or earlier, even during infancy. Attacks have no regular pattern of recurrence and vary in the same patient. They usually last 24 to 72 h, but some last ≥ 1 wk. Frequency ranges from 2 attacks/wk to 1 attack/yr (most commonly, once every 2 to 6 wk). Severity and frequency tend to decrease during pregnancy and in patients with amyloidosis.
Spontaneous remissions may last years. In some patients, the attacks have a prodromal phase.

Fever as high as 40°C, usually accompanied by peritonitis, is the major manifestation. Abdominal pain (usually starting in one quadrant and spreading to the whole abdomen) occurs in about 95% of patients and can vary in severity with each attack. Decreased bowel sounds, distention, guarding, and rebound tenderness are likely to occur at the peak of an attack and cannot be differentiated from a perforated viscus by physical examination. Consequently, many patients undergo urgent laparotomy before the correct diagnosis is made. With diaphragmatic involvement, splinting of the chest and pain in one or both shoulders may occur.

Other manifestations include acute pleurisy (in 30%); arthritis (in 25%), usually involving the knee, ankle, and hip; an erysipelas-like rash of the lower leg; and scrotal swelling and pain caused by inflammation of the tunica vaginalis of the testis. Pericarditis occurs very rarely. The pleural, synovial, and skin manifestations of FMF vary in frequency among different populations and are less frequently encountered in the US than elsewhere.

The most significant long-term complication is chronic renal failure caused by deposition of amyloid protein in the kidneys. Amyloid may also be deposited in the GI tract, liver, spleen, heart, testes, and thyroid.

FMF causes infertility or spontaneous abortion in about one third of women because peritoneal pelvic adhesions form, interfering with conception. In women with FMF, about 20 to 30% of pregnancies end in fetal loss.

Despite the severity of symptoms during acute attacks, most patients recover swiftly and remain free of illness until their next attack.

**Diagnosis**

- Clinical evaluation
- Genetic testing

Diagnosis is mainly clinical, but genetic testing is available and is particularly useful in evaluation of atypical cases. Nonspecific findings include elevations in WBCs with neutrophil predominance, ESR, C-reactive protein, and fibrinogen. Urinary excretion of > 0.5 g protein/24 h suggests renal amyloidosis. Differential diagnosis includes acute intermittent porphyria, hereditary angioedema with abdominal attacks, relapsing pancreatitis, and other hereditary relapsing fevers.

**Treatment**

- Colchicine

Prophylactic colchicine 0.6 mg po bid (some patients require qid dosing; others a single daily dose) provides complete remission or distinct improvement in about 85% of patients. For patients with infrequent attacks that involve a prodromal phase, colchicine can be reserved until initial symptoms occur and then begun at 0.6 mg po q 1 h for 4 h, then q 2 h for 4 h, then q 12 h for 48 h. Initiation of colchicine at the peak of an attack, even if delivered IV, is unlikely to be beneficial. Children often require adult dosages for effective prophylaxis. Widespread use of prophylactic colchicine has led to a dramatic reduction in the incidence of amyloidosis and subsequent renal failure.

Colchicine does not add to the increased risk of infertility and miscarriage among affected women; when taken during pregnancy, it does not increase the risk of teratogenic events. Lack of response to colchicine is often caused by poor adherence to the drug regimen, but a correlation has also been noted between poor response and diminished colchicine concentration in circulating monocytes. Weekly IV colchicine may reduce attack frequency and severity in patients who do not respond to oral colchicine. Untested alternatives in nonresponders include interferon-α 3 to 10 million units sc, prazosin 3 mg po bid, infliximab 5 mg/kg IV q 8 wk, and thalidomide initially 100 mg po once/day.
Opioids are sometimes needed for pain relief but should be used prudently to avoid addiction.

**Hyper-IgD Syndrome**

Hyper-IgD syndrome is a rare autosomal recessive disorder in which recurring attacks of chills and fever begin during the first year of life. Episodes usually last 4 to 6 days and may be triggered by physiologic stress, such as vaccination or minor trauma.

Hyper-IgD syndrome clusters in children of Dutch, French, and other Northern European ancestry and is caused by mutations in the gene coding mevalonate kinase, an enzyme important for cholesterol synthesis. Reduction in the synthesis of anti-inflammatory isoprenylated proteins may account for the clinical syndrome.

In addition to chills and fever, patients may have abdominal pain, vomiting or diarrhea, headache, and arthralgias. Signs include cervical lymphadenopathy, splenomegaly, arthritis, skin lesions (maculopapular rash, petechiae, or purpura), and orogenital aphthous ulcers.

Diagnosis is based on history, examination, and a serum IgD level of > 14 mg/mL. Non-specific abnormalities include leukocytosis and elevated acute-phase reactants during fever; specific but insensitive findings include elevated urinary mevalonic acid.

There are no proven treatments to prevent attacks. Patients can expect to have recurrent bouts of fever throughout their life, although episodes tend to become less frequent after adolescence.

**TNF Receptor-Associated Periodic Syndrome**

(Familial Hibernian Fever)

Tumor necrosis factor (TNF) receptor-associated periodic syndrome is an autosomal dominant disorder causing recurrent fever and painful, migratory myalgias with tender overlying erythema. Levels of type 1 TNF receptors are low. Treatment is with corticosteroids and etanercept.

TNF receptor-associated periodic syndrome was originally described in a family of Irish and Scottish pedigree but has been reported in many different ethnic groups. It results from mutations in the gene coding the TNF receptor. The mutation leads to unchecked TNF signaling, resulting in inflammation, possibly because shedding of the TNF receptor is defective.

Attacks of this rare disorder usually begin before age 20. They may last from 1 or 2 days to > 1 wk. The most distinctive features of an attack are migratory myalgia and swelling in the extremities. The overlying skin is red and tender. Other symptoms may include headache, abdominal pain, diarrhea or constipation, nausea, painful conjunctivitis, joint pain, rash, and testicular pain. Males are prone to develop inguinal hernias. Amyloidosis involving the kidneys has been reported in a minority of families.

With treatment, the prognosis is good, but it is more guarded in patients with renal amyloidosis.

**Diagnosis**

Diagnosis is based on history, examination, and low levels of type 1 TNF receptor (< 1 ng/mL) when measured between attacks. Non-specific findings include neutrophilia, elevated acute-phase reactants, and polyclonal gammopathy during attacks. Patients should be screened regularly for proteinuria.

**Treatment**

Attacks can be effectively treated with prednisone (at least 20 mg po once/day). Dosage may need to be increased over time.
Early therapeutic experience with etanercept, which binds and inactivates TNF, has been promising. Recommended dosage is 0.4 mg/kg sc for children and 25 mg sc for adults twice/wk. Anakinra 1.5 mg/kg sc once/day may be effective in children.

Hereditary Cryopyrinopathies

The hereditary cryopyrinopathies are a group of autoinflammatory conditions triggered by cold ambient temperatures; they include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem autoinflammatory disease.

Hereditary cryopyrinopathies represent a spectrum of progressively severe disease. They are due to mutations in the gene encoding the protein cryopyrin, which mediates inflammation and IL-1β processing. Cryopyrin activity is augmented, triggering increased release of IL-1β from inflammasomes; the result is inflammation and fever.

Typically, familial cold autoinflammatory syndrome causes a cold-induced urticarial rash accompanied by fever.

Muckle-Wells syndrome causes intermittent fevers, urticarial rash, joint pain, and progressive deafness; 25% of patients develop amyloidosis.

Neonatal-onset multisystem autoinflammatory disease tends to cause joint deformities, meningitis, delayed development, and amyloidosis, in addition to fever and rash. As many as 20% of patients die by age 20.

The cryopyrinopathies are inherited as autosomal dominant disorders. They are treated with anakinra or etanercept.

PAPA Syndrome

PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome is an autosomal dominant disorder that affects the skin and joints.

PAPA syndrome is caused by mutations in a gene on chromosome 15q. The mutated gene produces a hyperphosphorylated protein that binds excessively to pyrin, thus restricting pyrin's anti-inflammatory activity.

Arthritis begins in the first decade of life and is progressively destructive. Episodes of mild trauma may trigger the arthritis. Poorly healing ulcers with undermined edges may appear, often at sites of injury (eg, at vaccination sites). Acne is usually nodulocystic and, if untreated, causes scarring.

Diagnosis is based on clinical findings and a family history. The ulcers may be biopsied. Biopsy shows superficial ulceration and neutrophilic inflammation.

Treatment with etanercept or anakinra may be useful. Acne is treated with oral tetracycline or isotretinoin.

PFAPA Syndrome

PFAPA (periodic fevers with aphthous stomatitis, pharyngitis, and adenitis) syndrome is a periodic fever syndrome that typically manifests between ages 2 yr and 5 yr; it is characterized by febrile episodes lasting 3 to 6 days, pharyngitis, aphthous ulcers, and adenopathy. Etiology and pathophysiology are undefined.

PFAPA syndrome is a relatively common periodic fever among children. Although genetic causes have not been determined, this syndrome tends to be grouped with hereditary fever syndromes. It typically starts in early childhood (between ages 2 yr and 5 yr) and tends to be more common among males.

Febrile episodes last 3 to 6 days and recur about every 28 days. The syndrome causes fatigue, chills,
and occasionally abdominal pain and headache, as well as fever, pharyngitis, aphthous ulcers, and lymphadenopathy. Patients are healthy between episodes, and growth is normal.

**Diagnosis**

Diagnosis is based on clinical findings, which include the following:

- ≥ 3 febrile episodes, lasting up to 5 days and occurring at regular intervals
- Pharyngitis plus adenopathy or aphthous ulcers
- Good health between episodes and normal growth

Acute-phase reactants (eg, C-reactive protein, ESR) are elevated during a febrile episode but not between episodes. Neutropenia or other symptoms (eg, diarrhea, rash, cough) are not present; their presence suggests a different disorder.

**Treatment**

Treatment is optional; it can include glucocorticoids, cimetidine, and, rarely, tonsillectomy. Patients tend to outgrow this syndrome without sequelae.
Chapter 303. Behavioral Concerns and Problems in Children

Introduction

Many behaviors exhibited by children or adolescents concern parents or other adults. Behaviors or behavioral patterns become clinically significant if they are frequent or persistent and maladaptive (eg, interfere with emotional maturation or social and cognitive functioning). Severe behavioral problems may be classified as mental disorders (eg, oppositional defiant disorder—see p. 3058—or conduct disorder—see p. 3060). Prevalence rates vary according to how behavioral problems are defined and measured.

Evaluation

Diagnosis consists of a multistep behavioral assessment. Concerns with infants and young children generally involve bodily functions (eg, eating, eliminating, sleeping), whereas in older children and adolescents interpersonal behavioral concerns (eg, activity level, disobedience, aggression) predominate.

Problem identification: A behavioral problem may manifest alarmingly and abruptly as a single incident (eg, setting a fire, fighting at school). More often, problems manifest gradually, and identification involves gathering information over time. Behavior is best assessed in the context of the child's

• Physical and mental development

• General health

• Temperament (eg, difficult, easygoing)

• Relationships with parents and caregivers

Direct observation of parent-child interaction during an office visit provides valuable clues, including parental response to behaviors. These observations are supplemented, whenever possible, by information from others, including relatives, teachers, and school nurses.

Interviewing parents or caregivers provides a chronology of the child's activities during a typical day. Parents are asked to provide examples of events that precede and follow the specific behavior. Parents also are asked for their interpretation of

• Typical age-related behaviors

• Expectations for the child

• Level of parenting interest

• Support (eg, social, emotional, financial) for fulfilling their parenting role

• The child's relationship with the rest of their family

Problem interpretation: The child's history may include factors thought to increase the likelihood of developing behavioral problems, such as exposure to toxins, complications during pregnancy, or occurrence of a serious illness in the family.

Some problems may involve the parent-child relationship and can be interpreted in a number of ways:

• Unrealistic parental expectations: For example, some parents may expect that a 2-yr-old will pick up toys without help. Parents may misinterpret other normal, age-related behaviors, such as oppositional behavior (eg, refusal of a 2-yr old to follow an adult's request or rule) as problematic.

• Poor quality of parent-child interactions: For example, children of disinterested parents may have behavioral problems.
• Over-indulgent parenting: Well-meaning parental reactions to a problem may worsen it (eg, overprotecting a fearful, clinging child or giving in to a manipulative child).

• Circular behavioral pattern: In young children, some problems represent a circular behavioral pattern in which negative parental reaction to a child's behavior causes an adverse response from the child, which in turn leads to continued negative parental reaction. In this pattern, children often respond to stress and emotional discomfort with stubbornness, back talk, aggressiveness, and temper outbursts rather than with crying. Most commonly, a parent reacts to an aggressive and resistant child by scolding, yelling, and spanking; the child then escalates the behaviors that led to the parent's initial response, and the parent reacts more forcibly.

In older children and adolescents, behavioral problems may arise as independence is sought from parental rules and supervision. Such problems must be distinguished from occasional errors in judgment.

Treatment

Once a behavioral problem has been identified and its etiology has been investigated, early intervention is desirable because behaviors are more difficult to change the longer they exist.

The clinician reassures parents that the child is physically well (ie, that the child's misbehavior is not a manifestation of physical illness). By identifying with parental frustrations and pointing out the prevalence of behavioral problems, the clinician often can allay parental guilt and facilitate exploration of possible sources and treatment of problems. For simple problems, parental education, reassurance, and a few specific suggestions often are sufficient. Parents should be reminded of the importance of spending at least 15 to 20 min/day in a pleasurable activity with the child, "catching the child being good." Parents also can be encouraged to regularly spend time away from the child.

For some problems, however, parents benefit from additional strategies for disciplining children and modifying behavior.

• Parents can limit the child's dependency-seeking and manipulative behavior so that mutual respect is reestablished.

• Desired and undesired behavior should be clearly defined.

• Consistent rules and limits should be established.

• Parents need to track compliance on an ongoing basis and provide appropriate rewards for success and consequences for inappropriate behavior.

• Parents should try to minimize anger when enforcing rules and increase positive contact with the child.

(NOTE: Positive reinforcement for appropriate behavior is a powerful tool with no adverse effects.)

Helping parents to understand that "discipline" implies structure and not just punishment allows them to provide the structure and clear expectations that children need. Ineffective discipline may result in inappropriate behavior. Scolding or physical punishment may briefly control a child's behavior but eventually may decrease the child's sense of security and self-esteem. Threats to leave or send the child away are damaging.

A time-out technique (see Sidebar 303-1), in which the child must sit alone in a dull place (a corner or room [other than the child's bedroom] that is not dark or scary and has no television or toys) for a brief period, is a good approach to altering unacceptable behavior. Time-outs are learning processes for the child and are best used for one inappropriate behavior or a few at one time. Physical restraint should be avoided. For children who escalate in the intensity of their reactions when put in time-out, parents may prefer to move more rapidly to redirection once they recognize the children have registered the reprimand for inappropriate behavior.
The circular behavioral pattern may be interrupted if parents ignore behavior that does not disturb others (eg, refusal to eat) and use distraction or temporary isolation to limit behavior that cannot be ignored (public tantrums).

A behavioral problem that does not change in 3 to 4 mo should be reevaluated; mental health consultation may be indicated.

**Breath-Holding Spells**

A breath-holding spell is an episode in which the child stops breathing involuntarily and loses consciousness for a short period immediately after a frightening or emotionally upsetting event or after a painful experience.

Breath-holding spells occur in 5% of otherwise healthy children. They usually begin in the first year of life and peak at age 2. They disappear by age 4 in 50% of children and by age 8 in about 83% of children. The remainder may continue to have spells into adulthood. There are 2 forms of breath-holding spells:

- **Cyanotic form:** This form is the most common and often occurs as part of a temper tantrum or in response to a scolding or other upsetting event.

- **Pallid form:** This form typically follows a painful experience, such as falling and banging the head, but can follow frightening or startling events.

Both forms are involuntary and readily distinguished from uncommon brief periods of voluntary breath-holding by stubborn children, who invariably resume normal breathing after getting what they want or after becoming uncomfortable when they fail to get what they want.

During a cyanotic breath-holding spell, children hold their breath (without necessarily being aware they are doing so) until they lose consciousness. Typically, the child cries out, exhales, and stops breathing. Shortly afterward, the child begins to turn blue and unconsciousness ensues. A brief seizure may occur. After a few seconds, breathing resumes and normal skin color and consciousness return. It may be possible to interrupt a spell by placing a cold rag on the child's face at onset. Despite the spell's frightening nature, parents must try to avoid reinforcing the initiating behavior. As the child recovers, parents should continue to enforce household rules. Distracting the child and avoiding situations that lead to tantrums are good strategies. Cyanotic breath-holding has been found to respond to iron therapy, even in the absence of anemia, and to treatment for obstructive sleep apnea (when present).

**Sidebar 303-1 Time-Out Technique**

This disciplinary technique is best used when children are aware that their actions are incorrect or unacceptable and when they perceive withholding of attention as a punishment; typically this is not the case until age 2 yr. Care should be taken when this technique is used in group settings like daycare, because it can result in harmful humiliation.

The technique can be applied when a child misbehaves in a way that is known to result in a time-out. Usually, verbal reprimands and reminders should precede the time-out.

- The misbehavior is explained to the child, who is told to sit in the time-out chair or is led there if necessary.

- The child should sit in the chair 1 min for each year of age (maximum, 5 min).

- A child who gets up from the chair before the allotted time is returned to the chair, and the time-out is restarted. Talking and eye contact are avoided.

- When it is time for the child to get up, the caregiver asks the reason for the time-out without anger and
nagging. A child who does not recall the correct reason is briefly reminded. The child does not need to express remorse for the inappropriate behavior as long as it is clear that the child understands the reason for the time-out.

As soon as possible after the time-out, the caregiver should praise the child’s good behavior, which may be easier to achieve if the child is redirected to a new activity far from the scene of the inappropriate behavior.

During a pallid breath-holding spell, vagal stimulation severely slows the heart rate. The child stops breathing, rapidly loses consciousness, and becomes pale and limp. If the spell lasts more than a few seconds, muscle tone increases, and a seizure and incontinence may occur. After the spell, the heart speeds up again, breathing restarts, and consciousness returns without any treatment. Because this form is rare, further diagnostic evaluation and treatment may be needed if the spells occur often. Simultaneous ECG and EEG can help to differentiate cardiac and neurologic causes.

**Eating Problems**

Eating problems range from age-appropriate variability in appetite to serious or even life-threatening eating disorders (see p. 1535) such as anorexia nervosa, bulimia nervosa, and binge-eating. Eating problems also can result in overeating and obesity (see p. 56). Parents of young children are often concerned that a child is not eating enough or eating too much, eating the wrong foods, refusing to eat certain foods, or engaging in inappropriate mealtime behavior (eg, sneaking food to a pet, throwing or intentionally dropping food).

Assessment includes problem frequency, duration, and intensity. Height and weight are measured and plotted on appropriate charts. Often, when parents are shown charts that show the child is growing at a normal rate, their concerns about eating diminish. Children should be assessed more thoroughly for serious eating disorders if

- They voice persistent concerns about their appearance or weight
- Their weight decreases
- Their weight begins to increase at a noticeably faster rate than their previous growth rate

However, most eating problems do not persist long enough to interfere with growth and development. If children appear well and growth is within an acceptable range, parents should be reassured and encouraged to minimize conflict and coercion related to eating. Prolonged and excessive parental concern may in fact contribute to subsequent eating disorders. Attempts to force-feed are unlikely to increase intake; children may hold food in their mouth or vomit. Parents should offer meals while sitting at a table with the family, without distractions such as television or pets, and show little emotion when putting the food in front of children. Food should be removed in 20 to 30 min without comment about what is or is not eaten. Children should participate in cleaning up any food that is thrown or intentionally dropped on the floor. These techniques, along with restricting between-meal eating to one morning and one afternoon snack, usually restore the relationship between appetite, the amount eaten, and children's nutritional needs.

**School Avoidance**

Avoiding school occurs in about 5% of all school-aged children and affects girls and boys equally. It usually occurs between ages 5 and 6 and between ages 10 and 11.

The cause is often unclear, but psychologic factors (eg, anxiety, depression) and social factors (eg, having no friends, feeling rejected by peers, being bullied) may contribute. If school avoidance behaviors escalate to the point at which a child is missing a lot of school, the behaviors may be an indication of more serious problems (see p. 3049). A sensitive child may be overreacting with fear to a teacher's strictness or rebukes. Younger children tend to fake illness or make other excuses to avoid school.
Children may complain of a stomachache, nausea, or other symptoms that justify staying home. Some children directly refuse to go to school. Alternatively, children may go to school without difficulty but become anxious or develop various symptoms during the school day, often going regularly to the nurse's office. This behavior is unlike that of adolescents, who may decide not to attend school (truancy).

School avoidance tends to result in

- Poor academic performance
- Family difficulties
- Difficulties with peers

Most children recover from school avoidance, although some develop it again after a real illness or a vacation.

Home tutoring generally is not a solution. Children with school avoidance should return to school immediately, so that they do not fall behind in their schoolwork. If school avoidance is so intense that it interferes with the child's activity and if the child does not respond to simple reassurance by parents or teachers, referral to a mental health practitioner may be warranted.

Treatment should include communication between parents and school personnel, regular attendance at school, and sometimes therapy involving the family and child with a psychologist. Therapy includes treatment of underlying disorders as well as behavioral techniques to cope with the stresses at school.

### Sleep Problems

For most children, sleep problems are intermittent or temporary and often do not require treatment.

**Normal sleep:** Most children sleep for a stretch of at least 5 h by age 3 mo but then experience periods of night waking later in the first years of life, often associated with illness. With maturation, the amount of rapid eye movement (REM) sleep increases, with increasingly complex transitions between sleep stages. For most people, non-REM sleep predominates early in the night, with increasing REM as the night progresses. Thus, non-REM phenomena cluster early in the night, and REM-related phenomena occur later. Differentiating between true sleep (REM or non-REM)-related phenomena and awake behaviors can help to direct treatment.

It is important to determine whether parents view the child sleeping with them as a problem, because there is much cultural variation among sleep habits.

**Nightmares:** Nightmares are frightening dreams that occur during REM sleep. A child having a nightmare can awaken fully and vividly recall the details of the dream. Nightmares are not a cause for alarm, unless they occur very often. They can occur more often during times of stress or even when the child has seen a movie or television program containing frightening content. If nightmares occur often, parents can keep a diary to see whether they can identify the cause.

**Night terrors and sleepwalking:** Night terrors, non-REM episodes of incomplete awakening with extreme anxiety shortly after falling asleep, are most common between the ages of 3 and 8. The child screams and appears frightened, with a rapid heart rate and rapid breathing. The child seems unaware of the parents' presence, may thrash around violently, and does not respond to comforting. The child may talk but is unable to answer questions. Usually, the child returns to sleep after a few minutes. Unlike with nightmares, the child cannot recall these episodes. Night terrors are dramatic because the child screams and is inconsolable during the episode. About one third of children with night terrors also experience sleepwalking (rising from bed and walking around while apparently asleep, also called somnambulism). About 15% of children between the ages of 5 and 12 have at least one episode of sleepwalking.

Night terrors and sleepwalking almost always stop on their own, although occasional episodes may occur for years. Usually, no treatment is needed, but if a disorder persists into adolescence or adulthood and is
severe, treatment may be necessary. In children who need treatment, night terrors may sometimes respond to a sedative or certain antidepressants. There is some evidence that disrupted sleep associated with periodic leg movements often responds to iron supplementation, even in the absence of anemia. If children snore and thrash, evaluation for obstructive sleep apnea also should be considered.

**Resistance to going to bed:** Children, particularly between the ages of 1 and 2, often resist going to bed due to separation anxiety, whereas older children may be attempting to control more aspects of their environment. Young children often cry when left alone in their crib, or they climb out and seek their parents. Another common cause of bedtime resistance is delayed sleep onset time. These situations arise when children are allowed to stay up later and sleep later than usual for enough nights to reset their internal clock to a later sleep onset time. It can be difficult to move bedtime earlier, but brief treatment with an OTC antihistamine or melatonin can help children reset their clock.

Resistance to going to bed is not helped if parents stay in the room at length to provide comfort or let children get out of bed. In fact, these responses reinforce night waking, in which children attempt to reproduce the conditions under which they fell asleep. To avoid these problems, a parent may have to sit quietly in the hallway in sight of the child and make sure the child stays in bed. The child then establishes a sleep-onset routine of falling asleep alone and learns that getting out of bed is discouraged. The child also learns that the parents are available but will not provide more stories or play. Eventually, the child settles down and goes to sleep. Providing the child with an attachment object (like a teddy bear) often is helpful. A small night-light, white noise, or both also can be comforting.

**Awakening during the night:** Everyone awakens multiple times each night. Most, however, usually fall back to sleep with no intervention. Children often experience repeated night awakening after a move, an illness, or another stressful event. Sleeping problems may be worsened when children take long naps late in the afternoon or are over-stimulated by playing before bedtime.

Allowing the child to sleep with the parents because of the night awakening reinforces the behavior. Also counterproductive are playing with or feeding the child during the night, spanking, and scolding. Returning the child to bed with simple reassurance is usually more effective. A bedtime routine that includes reading a brief story, offering a favorite doll or blanket, and using a small night-light (for children > 3) is often helpful. To prevent arousal, it is important that the conditions under which the child awakens during the night are the same as those under which the child falls asleep. Parents and other caregivers should try to keep to a routine each night, so that the child learns what is expected. If children are physically healthy, allowing them to cry for a few minutes often allows them to settle down by themselves, which diminishes the night awakening.

**Temper Tantrums**

A temper tantrum is a violent emotional outburst, usually in response to frustration.

Temper tantrums usually appear toward the end of the first year, are most common at age 2 (terrible twos) to 4, and are infrequent after age 5. If tantrums are frequent after age 5, they may persist throughout childhood.

Causes include frustration, tiredness, and hunger. Children also may have temper tantrums to seek attention, obtain something, or avoid doing something. Parents often blame themselves (because of imagined poor parenting) when the actual cause is often a combination of the child's personality, immediate circumstances, and developmentally normal behavior. An underlying mental, physical, or social problem rarely may be the cause but is likely only if tantrums last > 15 min or occur multiple times each day.

Temper tantrums may involve

- Shouting
- Screaming
Children and adolescents may engage in occasional physical confrontations, but most do not develop a sustained pattern of violent behavior or engage in violent crime. Those who become violent before puberty may be at higher risk of committing crimes.

Violent behavior is increasingly common among children and adolescents. Almost 10% of students in middle or junior high school and high school report being victims of bullying. In 2005, almost 16% of high school students in the US reported carrying a weapon at least once during the month before they were surveyed as part of a study on youth risks.

Despite growing interest in the possibility of a relationship between violent behavior and genetic defects or chromosomal anomalies, there is minimal evidence for such a relationship. However, several risk factors have been associated with violent behavior, including:

- Violent discipline
- Alcohol and drug abuse
- Gang involvement
- Developmental issues
- Poverty
- Access to firearms

There seems to be a relationship between violence and access to firearms, exposure to violence through media, and exposure to child abuse and domestic violence. Children who are bullied may reach a breaking point, at which time they strike back with potentially dangerous or catastrophic results.

**Bullying:** Bullying is intentional infliction of psychologic or physical damage on less powerful children. Bullying can take several forms, including:

- Persistent teasing
- Threats
• Intimidation
• Harassment
• Violent assaults

**Cyber-bullying:** This is a newly described form in which bullies use e-mail and instant messaging to convey threats. Bullies act to inflate their sense of self-worth. Bullies often report that bullying creates feelings of power and control. Both bullies and their victims are at risk of poor outcomes. Victims often tell no one about being bullied due to feelings of helplessness, shame, and fear of retaliation. Victims are at risk of physical injury, poor self-esteem, anxiety, depression, and school absence. Bullies are more likely to be incarcerated; they are less likely to remain in school, be employed, or have stable relationships as adults.

**Gang involvement:** Participation in gangs has been linked with violent behavior. Youth gangs are self-formed associations of ≥ 3 members, typically ages 13 to 24. Gangs usually adopt a name and identifying symbols, such as a particular style of clothing, the use of certain hand signs, or graffiti. Some gangs require prospective members to perform random acts of violence before membership is granted. Increasing youth gang violence has been blamed at least in part on gang involvement in drug distribution and drug use, particularly methamphetamines and heroin. Use of firearms is a frequent feature of gang violence.

**Prevention**

Violence prevention should begin in early childhood. Strategies include

• Violence-free discipline in young children
• Limiting access to weapons and exposure to violence through media and video games
• Creating and maintaining a safe school environment for school-age children
• Encouraging victims to discuss problems with parents, school authorities, and their doctor
• Teaching older children and adolescents strategies for avoiding high-risk situations (eg, places or settings where others have weapons or are using alcohol or drugs) and for reacting to or defusing tense situations
Chapter 304. Learning and Developmental Disorders

Introduction

Developmental disorders (including attention-deficit/hyperactivity disorder, autism spectrum disorders, learning disabilities, and intellectual disability) are neurologically based conditions that can interfere with the acquisition, retention, or application of specific skills or sets of information. They may involve dysfunction in attention, memory, perception, language, problem-solving, or social interaction.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a syndrome of inattention, hyperactivity, and impulsivity. The 3 types of ADHD are predominantly inattentive, predominantly hyperactive-impulsive, and combined. Diagnosis is made by clinical criteria. Treatment usually includes drug therapy with stimulant drugs, behavioral therapy, and educational interventions.

ADHD has been classified as a developmental disorder, although increasingly it is considered a disruptive behavior disorder. ADHD affects an estimated 5 to 15% of school-aged children. However, many experts think ADHD is overdiagnosed, largely because criteria are applied inaccurately. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR), there are 3 types:

• Predominantly inattentive
• Predominantly hyperactive-impulsive
• Combined

The predominantly hyperactive-impulsive type occurs 2 to 9 times more frequently in boys; the predominantly inattentive type occurs with about equal frequency in both sexes. ADHD tends to run in families.

ADHD has no known single, specific cause. Potential causes include genetic, biochemical, sensorimotor, physiologic, and behavioral factors. Some risk factors include birth weight < 1000 g, head trauma, and lead exposure, as well as prenatal exposure to alcohol, tobacco, and cocaine. Fewer than 5% of children with ADHD have other symptoms and signs of neurologic damage. Increasing evidence implicates abnormalities in dopaminergic and noradrenergic systems with decreased activity or stimulation in upper brain stem and frontal-midbrain tracts.

Symptoms and Signs

Onset often occurs before age 4 and invariably before age 7. The peak age for diagnosis is between ages 8 and 10; however, patients with the predominantly inattentive type may not be diagnosed until after adolescence.

Core symptoms and signs of ADHD involve

• Inattention
• Hyperactivity
• Impulsivity

These symptoms (see Table 304-1) must be more pronounced than expected for the child's developmental level; impaired academic or social function is common.

Inattention tends to appear when a child is involved in tasks that require vigilance, rapid reaction time,
Inattention tends to appear when a child is involved in tasks that require vigilance, rapid reaction time, visual and perceptual search, and systematic and sustained listening. Inattention and impulsivity impede development of academic skills and thinking and reasoning strategies, motivation for school, and adjustment to social demands. Children who have predominantly inattentive ADHD tend to be hands-on learners who have difficulty in passive learning situations that require continuous performance and task completion. Overall, about 20 to 60% of children with ADHD have learning disabilities, but some school dysfunction occurs in most children with ADHD.

Behavioral history can reveal low frustration tolerance, opposition, temper tantrums, aggressiveness, poor social skills and peer relationships, sleep disturbances, anxiety, dysphoria, depression, and mood swings.

Although there are no specific physical examination or laboratory findings associated with ADHD, signs can include

- Motor incoordination or clumsiness
- Nonlocalized, "soft" neurologic findings
- Perceptual-motor dysfunctions

**Diagnosis**

- Clinical criteria

Diagnosis is clinical and is based on comprehensive medical, developmental, educational, and psychologic evaluations.

DSM-IV-TR diagnostic criteria include 9 symptoms and signs of inattention, 6 of hyperactivity, and 3 of impulsivity (see Table 304-1); diagnosis using these criteria requires

[Table 304-1, DSM-IV-TR Symptom Criteria for ADHD*]

that symptoms and signs occur in at least 2 situations (eg, home and school) and be present before age 7. Diagnosis of the predominantly inattentive type requires at least 6 of the 9 possible symptoms and signs of inattention. Diagnosis of the hyperactive-impulsive type requires at least 6 of the 9 possible symptoms and signs of hyperactivity and impulsivity. Diagnosis of the combined type requires at least 6 symptoms and signs each of inattention and hyperactivity-impulsivity.

Differentiating between ADHD and other conditions can be challenging. Overdiagnosis must be avoided, and other conditions must be accurately identified. Many ADHD signs expressed during the preschool years could also indicate communication problems that can occur in other developmental disorders (eg, autism spectrum [pervasive developmental] disorders) or in certain learning disorders, anxiety, depression, or behavioral disorders (eg, conduct disorder). Clinicians should consider whether the child is distracted by external factors (ie, environmental input) or by internal factors (ie, thoughts, anxieties, worries). However, during later childhood, ADHD signs become more qualitatively distinct; affected children often exhibit continuous movement of the lower extremities, motor impersistence (eg, purposeless movement, fidgeting of hands), impulsive talking, and a seeming lack of awareness of their environment.

Medical assessment focuses on identifying potentially treatable conditions that may contribute to or worsen symptoms and signs. Developmental assessment focuses on determining the onset and course of symptoms and signs. Educational assessment focuses on documenting core symptoms and signs; it may involve reviewing educational records and using rating scales or checklists. However, rating scales and checklists alone often cannot distinguish ADHD from other developmental disorders or from behavioral disorders.

**Prognosis**
Traditional classrooms and academic activities often exacerbate symptoms and signs in children with untreated or inadequately treated ADHD. Social and emotional adjustment problems may be persistent. Poor acceptance by peers and loneliness tend to increase with age and with the obvious display of symptoms. Substance abuse may result if ADHD is not identified and treated.

Although hyperactivity symptoms and signs tend to diminish with age, adolescents and adults may display residual difficulties. Predictors of poor outcomes in adolescence and adulthood include

• Coexisting low intelligence

• Aggressiveness

• Social and interpersonal problems

• Parental psychopathology

Problems in adolescence and adulthood manifest predominantly as academic failure, low self-esteem, and difficulty learning appropriate social behavior. Adolescents and adults who have predominately impulsive ADHD may have an increased incidence of personality trait disorders and antisocial behavior; many continue to display impulsivity, restlessness, and poor social skills. People with ADHD seem to adjust better to work than to academic and home situations.

Treatment

• Behavioral therapy

• Drug therapy, typically with stimulants such as methylphenidate or dextroamphetamine

Randomized, controlled studies show behavioral therapy alone is less effective than therapy with stimulant drugs alone; combination therapy has mixed results. Although correction of the underlying neurophysiologic differences of patients with ADHD does not occur with drug therapy, drugs are effective in alleviating ADHD symptoms, and they permit participation in activities previously inaccessible because of poor attention and impulsivity. Drugs often interrupt the cycle of inappropriate behavior, enhancing behavioral and academic interventions, motivation, and self-esteem. Treatment of adults follows similar principles, but drug selection and dosing are determined on an individual basis, depending on other medical conditions.

Drugs: Stimulant preparations that include methylphenidate or dextroamphetamine are most widely used. Response varies greatly, and dosage depends on the severity of the behavior and the child's ability to tolerate the drug. Dosing is adjusted in frequency and amount until the optimal response is achieved.

Methylphenidate is usually started at 0.3 mg/kg po once/day (immediate-release form) and increased in frequency weekly, usually to about tid or q 4 h. If response is inadequate but drug is tolerated, dose can be increased. Most children find an optimal balance between benefits and adverse effects at individual doses between 0.3 and 0.6 mg/kg.

Dextroamphetamine is typically started (either alone or in combination with amphetamine) at 0.15 to 0.2 mg/kg po once/day, which can then be increased to bid, tid, or q 4 h. Individual doses in the range of 0.15 to 0.4 mg/kg are usually effective. Dose titration should balance effectiveness against adverse effects. In general, dextroamphetamine doses are about two thirds those of methylphenidate doses.

For methylphenidate or dextroamphetamine, once an optimal dosage is reached, an equivalent dosage of the same drug in a sustained-release form is often substituted to avoid the need for drug administration in school. Long-acting preparations include wax matrix slow-release tablets, biphasic capsules containing the equivalent of 2 doses, and osmotic release pills and transdermal patches that provide up to 12 h of coverage. Learning is often enhanced by low doses, but improvement in behavior often requires higher doses.
Dosing schedules of stimulant drugs can be adjusted to cover specific days and times (eg, during school hours, while doing homework). Drug holidays should be tried on weekends, on holidays, or during summer vacations. Placebo periods (for 5 to 10 school days to ensure reliability of observations) are recommended to determine whether the drugs are still needed.

Common adverse effects of stimulant drugs include

- Sleep disturbances (eg, insomnia)
- Depression
- Headache
- Stomachache
- Appetite suppression
- Elevated heart rate and BP

Some studies have shown slowing of growth over 2 yr of stimulant drug use, but whether slowing persists over longer periods of use remains unclear. Some patients who are sensitive to stimulant drug effects appear over-focused or dulled; decreasing the stimulant drug dosage or trying a different drug may be helpful.

Atomoxetine, a selective norepinephrine reuptake inhibitor, is also used. The drug is effective, but data are mixed regarding its efficacy compared with stimulant drugs. Many children experience nausea, sedation, irritability, and temper tantrums; rarely, liver toxicity and suicidal ideation occur. A typical starting dose is 0.5 mg/kg po once/day, titrated weekly to 1.2 to 1.4 mg/kg once/day. The long half-life allows once/day dosing but requires continuous use to be effective. The maximum recommended daily dosage is 100 mg.

Antidepressants such as bupropion, α-2 agonists such as clonidine and guanfacine, and other psychoactive drugs are sometimes used in cases of stimulant drug ineffectiveness or unacceptable adverse effects, but they are less effective and are not recommended as first-line drugs. Pemoline is no longer recommended. Sometimes these drugs are used in combination with stimulants for synergistic effects; close monitoring for adverse effects is essential.

Behavioral management: Counseling, including cognitive-behavioral therapy (eg, goal-setting, self-monitoring, modeling, role-playing), is often effective and helps children understand ADHD. Structure and routines are essential.

Classroom behavior is often improved by environmental control of noise and visual stimulation, appropriate task length, novelty, coaching, and teacher proximity.

When difficulties persist at home, parents should be encouraged to seek additional professional assistance and training in behavioral management techniques. Adding incentives and token rewards reinforces behavioral management and is often effective. Children with ADHD in whom hyperactivity and poor impulse control predominate are often helped at home when structure, consistent parenting techniques, and well-defined limits are established.

Elimination diets, megavitamin treatments, use of antioxidants or other compounds, and nutritional and biochemical interventions have had the least consistent effects. Biofeedback can be helpful in some cases but is not recommended for routine use because evidence of sustained benefit is lacking.

**Autism Spectrum Disorders**

(Pervasive Developmental Disorders)
Autism spectrum disorders are neurodevelopmental disorders characterized by impaired social interaction and communication, repetitive and stereotyped patterns of behavior, and uneven intellectual development often with intellectual disability. Symptoms begin in early childhood. The cause in most children is unknown, although evidence supports a genetic component; in some patients, the disorders may be caused by a medical condition. Diagnosis is based on developmental history and observation. Treatment consists of behavioral management and sometimes drug therapy.

Autism, a neurodevelopmental disorder, is the most common of the disorders called autism spectrum disorders (ASD) or pervasive developmental disorders (PDD)—see Table 304-2. Current estimates of prevalence of ASD are in the range of 1/150. Autism is 2 to 4 times more common among boys. In recent years, there has been a rapid rise in the diagnosis of ASD, partially because of changes in diagnostic criteria.

Etiology

The specific cause in most cases of ASD remains elusive. However, some cases have occurred with congenital rubella syndrome, cytomegalic inclusion disease, phenylketonuria, or fragile X syndrome.

Strong evidence supports a genetic component. For parents of one child with an ASD, risk of having a subsequent child with an ASD is 50 to 100 times greater. The concordance rate of autism is high in monozygotic twins. Research on families has suggested several potential target gene areas, including those related to neurotransmitter receptors (gamma-aminobutyric acid [GABA]) and CNS structural control (HOX genes). Environmental causes have been suspected but are unproved. There is strong evidence that vaccinations do not cause autism.

Abnormalities of brain structure and function probably underlie much of the pathogenesis of autism. Some children with autism have enlarged ventricles, some have hypoplasia of the cerebellar vermis, and others have abnormalities of brain stem nuclei.

Symptoms and Signs

Classic autistic disorder usually manifests in the first year of life and almost always by age 3. The disorder is characterized by

- Atypical interaction (ie, lack of attachment, inability to cuddle or to form reciprocal relationships, avoidance of eye gaze)
- Insistence on sameness (ie, resistance to change, rituals, intense attachment to familiar objects, repetitive acts)
- Speech and language problems (ranging from total muteness to delayed onset of speech to markedly idiosyncratic use of language)
- Uneven intellectual performance

Some affected children injure themselves. About 25% of affected children experience a documented loss of previously acquired skills.

All children with ASD have similar problems with interaction, behavior, and communication; however, the severity of the problems varies widely. Nevertheless, some characteristic features often point to the specific diagnosis (see Table 304-2). Children with Asperger's syndrome generally have better intellectual performance than children with classic autistic disorder. They also lack the language delays typical of children with classic autistic disorder. Children with childhood disintegrative disorder develop normally until about age 2, and then their skills deteriorate.
Current theory holds that a fundamental problem in ASD is mind blindness, the inability to imagine what another person might be thinking. This difficulty is thought to result in interaction abnormalities that, in turn, lead to abnormal language development. One of the earliest and most sensitive markers for autism is a 1-yr-old child's inability to point communicatively at objects. It is theorized that the child cannot imagine that another person would understand what was being indicated; instead, the child indicates wants only by physically touching the desired object or using the adult's hand as a tool.

Nonfocal neurologic findings include poorly coordinated gait and stereotyped motor movements. Seizures occur in 20 to 40% of these children (particularly those with an intelligence quotient [IQ] < 50).

**Diagnosis**

- Clinical evaluation

Diagnosis is made clinically and usually requires evidence of impairment of social interaction and communication and presence of restricted, repetitive, stereotyped behaviors or interests. Screening tests include the Social Communication Questionnaire and the modified checklist for autism in toddlers (MCHAT). Formal gold standard diagnostic tests such as the Autism Diagnostic Observation Schedule (ADOS), based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (DSM-IV-TR), are usually given by psychologists. Children with ASD are difficult to test; they usually do better on performance items than verbal items in IQ tests and may show instances of age-appropriate performance despite cognitive limitation in most areas. Nonetheless, an IQ test given by an experienced examiner often can provide a useful predictor of outcome.

**Treatment**

- Behavioral therapy
- Speech and language therapy
- Sometimes physical and occupational therapy
- Drug therapy

Treatment is usually multidisciplinary, and recent studies show measurable benefits from intensive, behaviorally based approaches that encourage interaction and meaningful communication. Psychologists and educators typically focus on behavioral analysis and then match behavioral management strategies to specific behavioral problems at home and at school.

Speech and language therapy should begin early and use a range of media, including signing, picture exchange, and speech. Physical and occupational therapists plan and implement strategies to help affected children compensate for specific deficits in motor function and motor planning.

SSRIs may improve control of ritualistic behaviors. Antipsychotics and mood stabilizers such as valproate may help control self-injurious behavior.

Dietary interventions, including some vitamin supplements and a gluten-free and casein-free diet, have not been fully investigated. Other complementary and investigational approaches to therapy (eg, facilitated communication) have not yet shown efficacy and require additional study.

**Learning Disabilities**

Learning disabilities are conditions that cause a discrepancy between potential and actual levels of academic performance as predicted by the person's intellectual abilities. Learning disabilities involve impairments or difficulties in concentration or attention, language development, or visual and aural information processing. Diagnosis includes cognitive, educational, speech and language, medical, and psychologic evaluations. Treatment consists
primarily of educational management and sometimes medical, behavioral, and psychologic therapy.

Specific learning disabilities affect the ability to understand or use spoken or written language, do mathematical calculations, coordinate movements, or focus attention on a task. These disabilities include problems in reading, mathematics, spelling, written expression or handwriting, and understanding or using verbal and nonverbal language (see Table 304-3). Most learning disabilities are complex or mixed, with deficits in more than one system.

Although the number of children with learning disabilities is unknown, about 5% of the school-age population in the US receives special educational services for learning disabilities. Among affected children, boys outnumber girls 5:1.

Learning disabilities may be congenital or acquired. No single cause has been defined, but neurologic deficits are evident or presumed. Genetic influences are often implicated. Other possible causes include

- Maternal illness or use of toxic drugs during pregnancy
- Complications during pregnancy or delivery (eg, spotting, toxemia, prolonged labor, precipitous delivery)
- Neonatal problems (eg, prematurity, low birth weight, severe jaundice, perinatal asphyxia, postmaturity, respiratory distress)

[Table 304-3. Common Learning Disabilities]

Potential postnatal factors include exposure to environmental toxins (eg, lead), CNS infections, cancers and their treatments, trauma, undernutrition, and severe social isolation or deprivation.

Symptoms and Signs

Children with learning disabilities typically have at least average intelligence, although such disabilities can occur in children with lower cognitive function as well. Symptoms and signs of severe disabilities tend to manifest at an early age. Mild to moderate learning disabilities are usually not recognized until school age, when the rigors of academic learning are encountered. Affected children may have trouble learning the alphabet and may be delayed in paired associative learning (eg, color naming, labeling, counting, letter naming). Speech perception may be limited, language may be learned at a slower rate, and vocabulary may be decreased. Affected children may not understand what is read, have very messy handwriting or hold a pencil awkwardly, have trouble organizing or beginning tasks or retelling a story in sequential order, or confuse math symbols and misread numbers.

Disturbances or delays in expressive language or listening comprehension are predictors of academic problems beyond the preschool years. Memory may be defective, including short-term and long-term memory, memory use (eg, rehearsal), and verbal recall or retrieval. Problems may occur in conceptualizing, abstracting, generalizing, reasoning, and organizing and planning information for problem solving. Visual perception and auditory processing problems may occur; they include difficulties in spatial cognition and orientation (eg, object localization, spatial memory, awareness of position and place), visual attention and memory, and sound discrimination and analysis.

Some children with learning disabilities have difficulty following social conventions (eg, taking turns, standing too close to the listener, not understanding jokes); these difficulties are often components of mild autism spectrum disorders as well (see p. 3038). Short attention span, motor restlessness, fine motor problems (eg, poor printing and copying), and variability in performance and behavior over time are other early signs. Difficulties with impulse control, non-goal-directed behavior and overactivity, discipline problems, aggressiveness, withdrawal and avoidance behavior, excessive shyness, and excessive fear may occur. Learning disabilities and attention-deficit/hyperactivity disorder (ADHD) often occur together.

Diagnosis
Children with learning disabilities are typically identified when a discrepancy is recognized between academic potential and academic performance. Speech and language, intellectual, educational, medical, and psychologic evaluations are necessary for determining deficiencies in skills and cognitive processes. Social and emotional-behavioral evaluations are also necessary for planning treatment and monitoring progress.

**Cognitive evaluation** typically includes verbal and nonverbal intelligence testing and is usually done by school personnel. Psychoeducational testing may be helpful in describing the child's preferred manner of processing information (eg, holistically or analytically, visually or aurally). Neuropsychologic assessment is particularly useful in children with known CNS injury or illness to map the areas of the brain that correspond to specific functional strengths and weaknesses. Speech and language evaluations establish integrity of comprehension and language use, phonologic processing, and verbal memory.

**Behavioral assessment** and performance evaluation by teachers' observations of classroom behavior and determination of academic performance are essential. Reading evaluations measure abilities in word decoding and recognition, comprehension, and fluency. Writing samples should be obtained to evaluate spelling, syntax, and fluency of ideas. Mathematical ability should be assessed in terms of computation skills, knowledge of operations, and understanding of concepts.

**Medical evaluation** includes a detailed family history, the child's medical history, a physical examination, and a neurologic or neurodevelopmental examination to look for underlying disorders. Although infrequent, physical abnormalities and neurologic signs may indicate medically treatable causes of learning disabilities. Gross motor coordination problems may indicate neurologic deficits or neurodevelopmental delays. Developmental level is evaluated according to standardized criteria.

**Psychologic evaluation** helps identify ADHD, conduct disorder, anxiety disorders, depression, and poor self-esteem, which frequently accompany and must be differentiated from learning disabilities. Attitude toward school, motivation, peer relationships, and self-confidence are assessed.

**Treatment**

- Educational management
- Medical, behavioral, and psychologic therapy
- Occasionally drug therapy

Treatment centers on educational management but may also involve medical, behavioral, and psychologic therapy. Effective teaching programs may take a remedial, compensatory, or strategic (ie, teaching the child how to learn) approach. A mismatch of instructional method and a child's learning disability and learning preference aggravates the disability.

Some children require specialized instruction in only one area while they continue to attend regular classes. Other children need separate and intense educational programs. Optimally and as required by US law, affected children should participate as much as possible in inclusive classes with peers who do not have learning disabilities.

Drugs minimally affect academic achievement, intelligence, and general learning ability, although certain drugs (eg, stimulants, such as methylphenidate and several amphetamine preparations—see p. 3037) may enhance attention and concentration, allowing children to respond more efficiently to instruction. Many popular remedies and therapies (eg, eliminating food additives, using antioxidants or megadoses of vitamins, patterning by sensory stimulation and passive movement, sensory integrative therapy through postural exercises, auditory nerve training, optometric training to remedy visual-perceptual and sensorimotor coordination processes) are unproved.

**Dyslexia**
Dyslexia is a general term for primary reading disorder. Diagnosis is based on intellectual, educational, speech and language, medical, and psychologic evaluations. Treatment is primarily educational management, consisting of instruction in word recognition and component skills.

No definition of dyslexia is universally accepted; thus, incidence is undetermined. An estimated 15% of public school children receive special instruction for reading problems; about one half of these children may have persistent reading disabilities. Dyslexia is identified more often in boys than girls, but sex is not a proven risk factor for developing dyslexia.

The inability to learn derivational rules of printed language is often considered part of dyslexia. Affected children may have difficulty determining root words or word stems and determining which letters in words follow others.

Reading problems other than dyslexia are usually caused by difficulties in language comprehension or low cognitive ability. Visual-perceptual problems and abnormal eye movements are not dyslexia. However, these problems can interfere further with word learning.

Etiology

Phonologic processing problems cause deficits in discrimination, blending, memory, and analysis of sounds. Dyslexia may affect both production and understanding of written language, which is often restricted further by problems with auditory memory, speech production, and naming or word finding. Underlying weaknesses in verbal language are often present.

Pathophysiology

Dyslexia tends to run in families. Children with a family history of reading or learning difficulties are at higher risk. Because changes have been identified in the brains of people with dyslexia, experts believe dyslexia results predominantly from cortical dysfunction stemming from congenital neurodevelopmental abnormalities. Lesions affecting the integration or interactions of specific brain functions are suspected. Most researchers concur that dyslexia is left hemisphere-related and linked to dysfunctions in brain areas responsible for language association (Wernicke's motor speech area) and sound and speech production (Broca's area) and in the interconnection of these areas via the fasciculus arcuatus. Dysfunctions or defects in the angular gyrus, the medial occipital area, and the right hemisphere cause word recognition problems. Research suggests some malleability of brain systems in response to training.

Symptoms and Signs

Dyslexia may manifest as

- Delayed language production
- Speech articulation difficulties
- Difficulties remembering the names of letters, numbers, and colors

Children with phonologic processing problems often have difficulty blending sounds, rhyming words, identifying the positions of sounds in words, and segmenting words into pronounceable components. They may reverse the order of sounds in words. Delay or hesitation in choosing words, substituting words, or naming letters and pictures is often an early sign. Short-term auditory memory and auditory sequencing difficulties are common.

Fewer than 20% of children with dyslexia have difficulties with the visual demands of reading. However, some children confuse letters and words with similar configurations or have difficulty visually selecting or identifying letter patterns and clusters (sound-symbol association) in words. Reversals or visual confusions can occur, most often because of retention or retrieval difficulties that cause affected children to forget or confuse the names of letters and words that have similar structures; subsequently, d' becomes...
Although dyslexia is a lifelong problem, many children develop functional reading skills. However, other children never reach adequate literacy.

**Diagnosis**

- Reading evaluation
- Speech, language, and auditory evaluations
- Psychologic evaluations

Most children with dyslexia are not identified until kindergarten or 1st grade, when they encounter symbolic learning. Children with a history of delayed language acquisition or use, who are not accelerating in word learning by the end of 1st grade, or who are not reading at the level expected for their verbal or intellectual abilities at any grade level should be evaluated. Often, the best diagnostic indicator is the child's inability to respond to traditional or typical reading approaches during 1st grade, although wide variation in reading skills can still be seen at this level. Demonstration of phonologic processing problems is essential for diagnosis.

Children suspected of having dyslexia should undergo reading, speech and language, auditory, cognitive, and psychologic evaluations to identify their functional strengths and weaknesses and their preferred learning styles. Such evaluations can be requested of school staff by the child's teacher or family based on the Individuals with Disabilities Education Act (IDEA), a US special education law. Evaluation findings then guide the most effective instructional approach.

Comprehensive reading evaluations test word recognition and analysis, fluency, reading or listening comprehension, and level of understanding of vocabulary and the reading process.

Speech, language, and auditory evaluations assess spoken language and deficits in processing phonemes (sound elements) of spoken language. Receptive and expressive language functions are also assessed. Cognitive abilities (eg, attention, memory, reasoning) are tested.

Psychologic evaluations address emotional concerns that can exacerbate a reading disability. A complete family history of mental disorders and emotional problems is obtained.

Physicians should ensure that children have normal vision and hearing, either through office-based screening or referral for formal audiologic or vision testing. Neurologic evaluations may help detect secondary features (eg, neurodevelopmental immaturity or minor neurologic abnormalities) and rule out other disorders (eg, seizures).

**Treatment**

- Educational interventions

Treatment consists of educational interventions, including direct and indirect instruction in word recognition and component skills. Direct instruction includes teaching specific phonics skills separate from other reading instruction. Indirect instruction includes integrating phonics skills into reading programs. Instruction may teach reading from a whole-word or whole-language approach or by following a hierarchy of skills from the sound unit to the word to the sentence. Multisensory approaches that include whole-word learning and the integration of visual, auditory, and tactual procedures to teach sounds, words, and sentences are then recommended.

Component skills instruction consists of teaching children to blend sounds to form words, segment words into word parts, and identify the positions of sounds in words. Component skills for reading comprehension include identifying the main idea, answering questions, isolating facts and details, and
reading inferentially. Many children benefit from using a computer to help isolate words within text samples or for word processing of written work.

Other treatments (eg, optometric training, perceptual training, auditory integration training) and drug therapies are unproved and not recommended.

**Intellectual Disability**

Intellectual disability (ID, previously called mental retardation) is characterized by significantly sub-average intellectual functioning (often expressed as an intelligence quotient < 70 to 75) combined with limitations of > 2 of the following: communication, self-direction, social skills, self-care, use of community resources, and maintenance of personal safety. Management consists of education, family counseling, and social support.

Basing severity on intelligence quotient (IQ) alone (eg, mild, 52 to 70 or 75; moderate, 36 to 51; severe, 20 to 35; and profound, < 20) is inadequate. Classification must also account for the level of support needed, ranging from intermittent to ongoing high-level support for all activities. Such an approach focuses on a person's strengths and weaknesses, relating them to the demands of the person's environment and the expectations and attitudes of the family and community.

About 3% of the population functions at an IQ of < 70, which is at least 2 standard deviations below the mean IQ of the general population (IQ of 100); if the need for support is considered, only about 1% of the population has severe ID. Severe ID occurs in families from all socioeconomic groups and educational levels. Less severe ID (requiring intermittent or limited support) occurs most often in lower socioeconomic groups, paralleling with observations that IQ correlates best with success in school and socioeconomic status rather than specific organic factors. Nevertheless, recent studies suggest that genetic factors play roles even in milder cognitive disabilities.

**Etiology**

Intelligence is both genetically and environmentally determined. Children born to parents with ID are at increased risk of a range of developmental disabilities, but clear genetic transmission of ID is unusual. Although advances in genetics, such as chromosomal microarray analysis, have increased the likelihood of identifying the cause of an ID, a specific cause cannot be identified in 60 to 80% of cases. A cause is most likely to be identified in severe cases. Deficits in language and personal-social skills may be due to emotional problems, environmental deprivation, learning disorders, or deafness rather than ID.

Prenatal: A number of chromosomal anomalies and genetic metabolic and neurologic disorders can cause ID (see Table 304-4).

**Table 304-4. Chromosomal and Genetic Causes of Intellectual Disability**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella</td>
<td>Congenital infections that can cause ID include rubella and those due to cytomegalovirus, Toxoplasma gondii, Treponema pallidum, or HIV.</td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
<td>Prenatal drug and toxin exposure (see p. 2625) can cause ID. Fetal alcohol syndrome (see p. 2799) is the most common of these conditions. Anticonvulsants such as phenytoin or valproate, chemotherapy drugs, radiation exposure, lead, and methylmercury are also causes. Severe undernutrition during pregnancy may affect fetal brain development, resulting in ID.</td>
</tr>
<tr>
<td>Perinatal complications</td>
<td>Complications related to prematurity, CNS bleeding, periventricular leukomalacia, breech or high forceps delivery, multiple births, placenta previa, preeclampsia, and perinatal asphyxia may increase the risk of ID. The risk is increased in small-for-gestational-age infants; intellectual impairment and decreased weight share the same cause. Very low- and extremely low-birth-weight infants have variably increased chances of having ID, depending on gestational age, perinatal events, and quality of care.</td>
</tr>
<tr>
<td>Postnatal undernutrition</td>
<td>Undernutrition and environmental deprivation (lack of physical, emotional, and cognitive</td>
</tr>
</tbody>
</table>
support required for growth, development, and social adaptation) during infancy and early childhood may be the most common causes of ID worldwide. Viral and bacterial encephalitides (including AIDS-associated neuroencephalopathy) and meningitides, poisoning (eg, lead, mercury), and accidents that cause severe head injuries or asphyxia may result in ID.

**Symptoms and Signs**

The primary manifestations are:

- Delayed intellectual development
- Immature behavior
- Limited self-care skills

Some children with mild ID may not develop recognizable symptoms until preschool age. However, early identification is common among children with moderate to severe ID and among children in whom ID is accompanied by physical abnormalities or signs of a condition (eg, cerebral palsy) that may be associated with a particular cause of ID (eg, perinatal asphyxia). Delayed development is usually apparent by preschool age. Among older children, hallmark features are a low IQ combined with limitations in adaptive behavior skills. Although developmental patterns may vary, it is much more common for children with ID to experience slow progress than developmental arrest.

Some children may have cerebral palsy or other motor deficits, language delays, or hearing loss. Such motor or sensory impairments can mimic cognitive impairment but are not in themselves causes of it. As children mature, some develop anxiety or depression if they are socially rejected by other children or if they are disturbed by the realization that others see them as different and deficient. Well-managed, inclusive school programs can help maximize social integration, thereby minimizing such emotional responses.

Behavioral disorders are the reason for most psychiatric referrals and out-of-home placements for people with ID. Behavioral problems are often situational, and precipitating factors can usually be identified. Factors that predispose to unacceptable behavior include:

- Lack of training in socially responsible behavior
- Inconsistent discipline
- Reinforcement of faulty behavior
- Impaired ability to communicate
- Discomfort due to coexisting physical problems and mental health disorders such as depression or anxiety

In institutional settings, overcrowding, understaffing, and lack of activities contribute.

**Diagnosis**

- Developmental and intelligence assessment
- Imaging testing
- Genetic testing

For suspected cases, development and intelligence are assessed, typically by early intervention or school staff. Standardized intelligence tests can measure subaverage intellectual ability but are subject to error, and results should be questioned when they do not match clinical findings; illness, motor or sensory
impairments, language barriers, or cultural differences may hamper a child's test performance. Such tests also have a middle-class bias but are generally reasonable in appraising intellectual ability in children, particularly in older ones. Developmental screening tests such as the Ages and Stages Questionnaire or the Parents' Evaluation of Developmental Status (PEDS) provide gross assessments of development for young children and can be given by a physician or others. Such measures should be used only for screening and not as substitutes for standardized intelligence tests, which should be given by qualified psychologists. A neurodevelopmental assessment should be initiated as soon as developmental delays are suspected. A developmental pediatrician or pediatric neurologist should investigate all cases of

- Moderate to severe developmental delays
- Progressive disability
- Neuromuscular deterioration
- Suspected seizure disorders

Establishing ID is followed by efforts to determine a cause. Accurate determination of the cause may provide a developmental prognosis, suggest plans for educational and training programs, help in genetic counseling, and relieve parental guilt. History (including perinatal, developmental, neurologic, and familial) may identify causes. An algorithm for the diagnostic evaluation of the child with ID (global developmental delay) has been proposed by the Child Neurology Society. Cranial imaging (eg, MRI) can show CNS malformations (as seen in neurodermatoses such as neurofibromatosis or tuberous sclerosis), treatable hydrocephalus, or more severe brain malformations such as schizencephaly. Genetic tests may help identify disorders such as Down syndrome (trisomy 21) via standard karyotyping, 5p-deletion (cri du chat syndrome) or DiGeorge syndrome (chromosome 22q deletion) via fluorescent in situ hybridization (FISH), or fragile X syndrome via direct DNA studies. Recently, chromosomal microarray analysis has become more widely available, affording opportunities for identifying otherwise unrecognized chromosome disruptions.

Genetic metabolic disorders may be suggested by their clinical manifestations (eg, failure to thrive, lethargy, vomiting, seizures, hypotonia, hepatosplenomegaly, coarse facial features, abnormal urinary odor, macroglossia). Isolated delays in sitting or walking (gross motor skills) and in pincer grasp, drawing, or writing (fine motor skills) may indicate a neuromuscular disorder. Specific laboratory tests are done depending on the suspected cause (see Table 304-5). Visual and auditory assessments should be done at an early age, and screening for lead poisoning is often appropriate.

<table>
<thead>
<tr>
<th>Tests for Some Causes of Intellectual Disability</th>
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</table>

**Prognosis**

Many people with mild to moderate ID can support themselves, live independently, and be successful at jobs that require basic intellectual skills. Life expectancy may be shortened, depending on the etiology of the disability, but health care is improving long-term health outcomes for people with all types of developmental disabilities. People with severe ID are likely to require life-long support. The more severe the cognitive disability and the greater the immobility, the higher the mortality risk.

**Treatment**

- Early intervention program
- Multidisciplinary team support

Treatment and support needs depend on social competence and cognitive function. Referral to an early intervention program during infancy may prevent or decrease the severity of disability resulting from a perinatal insult. Realistic methods of caring for affected children must be established.
Family support and counseling are crucial. As soon as ID is confirmed or strongly suspected, the parents should be informed and given ample time to discuss causes, effects, prognosis, education and training of the child, and the importance of balancing known prognostic risks against negative self-fulfilling prophecies in which diminished expectations result in poor functional outcomes later in life. Sensitive ongoing counseling is essential for family adaptation. If the family’s physician cannot provide coordination and counseling, the child and family should be referred to a center with a multidisciplinary team that evaluates and serves children with ID; however, the family’s physician should provide continuing medical care and advice.

A comprehensive, individualized program is developed with the help of appropriate specialists, including educators.

A multidisciplinary team includes

- Neurologists or developmental pediatricians
- Orthopedists
- Physical therapists and occupational therapists (who assist in managing comorbidities in children with motor deficits)
- Speech pathologists and audiologists (who help with language delays or with suspected hearing loss)
- Nutritionists (who help with treatment of undernutrition)
- Social workers (who help reduce environmental deprivation)

Affected children with concomitant mental health disorders such as depression may be given appropriate psychoactive drugs in dosages similar to those used in children without ID. Use of psychoactive drugs without behavioral therapy and environmental changes is rarely helpful.

Every effort should be made to have children live at home or in community-based residences. Although the presence of a child with ID in the home can be disruptive, it can also be extremely rewarding. The family may benefit from psychologic support and help with daily care provided by day care centers, homemakers, and respite services. The living environment must encourage independence and reinforce learning of skills needed to accomplish this goal. Whenever possible, children with ID should attend an appropriately adapted day care center or school with peers without cognitive disability. The Individuals with Disabilities Education Act (IDEA), a US special education law, stipulates that all children with disabilities should receive appropriate educational opportunities and programming in the least restrictive and most inclusive environments. As people with ID reach adulthood, an array of supportive living and work settings is available. Large residential institutions are being replaced by small group or individual residences matched to the affected person’s functional abilities and needs.

Prevention

Genetic counseling (see also p. 2598) may help high-risk couples understand possible risks. If a child has ID, evaluation of the etiology can provide the family with appropriate risk information for future pregnancies.

High-risk couples who choose to have children often undergo prenatal testing, which enables couples to consider pregnancy termination and subsequent family planning. Testing includes

- Amniocentesis
- Ultrasonography
- Maternal serum α-fetoprotein
Amniocentesis or chorionic villus sampling may detect inherited metabolic and chromosomal disorders, carrier states, and CNS malformations (eg, neural tube defects, anencephaly). Amniocentesis is indicated for all pregnant women > 35 yr (because their risk of having an infant with Down syndrome is increased) and for women with family histories of inherited metabolic disorders. Ultrasonography may also identify CNS defects. Maternal serum α-fetoprotein is a helpful screen for neural tube defects, Down syndrome, and other abnormalities.

Rubella vaccine has all but eliminated congenital rubella as a cause. A vaccine for cytomegalovirus infection is being sought. Continuing improvements in and increased availability of obstetric and neonatal care and the use of exchange transfusion and Rh0(D) immune globulin to prevent hemolytic disease of the newborn have reduced the incidence of ID; the increase in survival of very-low-birth-weight infants has kept the prevalence constant.
Chapter 305. Mental Disorders in Children and Adolescents

Introduction

Although it is sometimes assumed that childhood and adolescence are times of carefree bliss, as many as 20% of children and adolescents have one or more diagnosable mental disorders. Most of these disorders may be viewed as exaggerations or distortions of normal behaviors and emotions.

Like adults, children and adolescents vary in temperament. Some are shy and reticent; others are socially exuberant. Some are methodical and cautious; others are impulsive and careless. Whether a child is behaving like a typical child or has a disorder is determined by the presence of impairment and the degree of distress related to the symptoms. For example, a 12-yr-old girl may be frightened by the prospect of delivering a book report in front of her class. This fear would be viewed as social phobia only if her fears were severe enough to cause significant impairments and distress.

There is much overlap between the symptoms of many disorders and the challenging behaviors and emotions of normal children. Thus, many strategies useful for managing behavioral problems in children (see p. 3030) can also be used in children who have mental disorders. Furthermore, appropriate management of childhood behavioral problems may prevent temperamentally vulnerable children from developing a full-blown disorder.

The most common mental disorders of childhood and adolescence fall into 4 broad categories:

• Anxiety disorders
• Schizophrenia
• Mood disorders (primarily depression)
• Disruptive behavioral disorders

However, more often than not, children and adolescents have symptoms and problems that cut across diagnostic boundaries.

Evaluation

Evaluation of mental complaints or symptoms in children and adolescents differs from that in adults in 3 important ways:

• Developmental context is critically important in children. Behaviors that are normal at a young age may indicate a serious mental disorder at an older age.

• Children exist in the context of a family system, and that system has a profound effect on children's symptoms and behaviors; normal children living in a family troubled by domestic violence and substance abuse may superficially appear to have one or more mental disorders.

• Children often do not have the cognitive and linguistic sophistication needed to accurately describe their symptoms. Thus, the clinician must rely very heavily on direct observation, corroborated by observations of other people, such as parents and teachers.

In many cases, developmental and behavioral problems (eg, poor academic progress, delays in language acquisition, deficits in social skills) are difficult to distinguish from those due to a mental disorder. In such cases, formal developmental and neuropsychologic testing should be part of the evaluation process.

Because of these factors, evaluation of children with a mental disorder is typically more complex than that of adults. However, most cases are not severe and can be competently managed by an appropriately trained primary care practitioner. However, uncertain or severe cases are best managed in consultation with a child and adolescent psychiatrist.
Anxiety Disorders in Children and Adolescents

Anxiety disorders are characterized by fear, worry, or dread that greatly impairs the ability to function normally and that is disproportionate to the circumstances at hand. Anxiety may result in physical symptoms. Diagnosis is clinical. Treatment is with behavioral therapy and drugs, usually SSRIs.

Some anxiety is a normal aspect of development, as in the following:

• Most toddlers become fearful when separated from their mother, especially in unfamiliar surroundings.
• Fears of the dark, monsters, bugs, and spiders are common in 3- to 4-yr-olds.
• Shy children may initially react to new situations with fear or withdrawal.
• Fears of injury and death are more common among older children.
• Older children and adolescents often become anxious when giving a book report in front of their classmates.

Such difficulties should not be viewed as evidence of a disorder. However, if manifestations of anxiety become so exaggerated that they greatly impair functioning or cause severe distress, an anxiety disorder should be considered.

At some point during childhood, about 10 to 15% of children experience an anxiety disorder (eg, generalized anxiety disorder, social phobia, separation anxiety disorder, obsessive-compulsive disorder, specific phobia, panic disorder, acute and posttraumatic stress disorders).

Etiology

Etiology seems to have a genetic basis but is heavily modified by psychosocial experience; heritability is polygenetic, and only a small number of the specific genes have been characterized thus far.

Anxious parents tend to have anxious children; having such parents may make children's problems worse than they otherwise might be. Even normal children have difficulty remaining calm and composed in the presence of an anxious parent, and children who are genetically predisposed to anxiety have even greater difficulty. In as many as 30% of cases, treating the parents' anxiety in conjunction with the child's anxiety is helpful (see p. 1493 for treatment of anxiety in adults).

Symptoms and Signs

Perhaps the most common manifestation is school refusal. "School refusal" has largely supplanted the term "school phobia." Actual fear of school is exceedingly rare. Most children who refuse to go to school probably have separation anxiety, social phobia, panic, or a combination. Some have a specific phobia. The possibility that the child is being bullied at school must also be considered.

Some children complain directly about their anxiety, describing it in terms of worries—eg, "I am worried that I will never see you again" (separation anxiety) or "I am worried the kids will laugh at me" (social phobia). However, most children couch their discomfort in terms of somatic complaints: "I cannot go to school because I have a stomachache." These children are often telling the truth because an upset stomach, nausea, and headaches often develop in children with anxiety.

Diagnosis

Diagnosis is clinical. A thorough psychosocial history can usually confirm it.
The physical symptoms that anxiety can cause in children can complicate the evaluation. In many children, considerable testing for physical disorders is done before clinicians consider an anxiety disorder.

**Prognosis**

Prognosis depends on severity, availability of competent treatment, and the child's resiliency. Many children struggle with anxiety symptoms into adulthood. However, with early treatment, many children learn how to control their anxiety.

**Treatment**

- Behavioral therapy
- Drugs, usually SSRIs

Anxiety disorders in children are treated with behavioral therapy (using principles of exposure and response prevention), sometimes in conjunction with drug therapy.

In behavioral therapy, children are systematically exposed to the anxiety-provoking situation in a graded fashion. By helping children remain in the anxiety-provoking situation (response prevention), therapists enable them to gradually become desensitized and feel less anxiety. Behavioral therapy is most effective when an experienced therapist knowledgeable in child development individualizes these principles.

In mild cases, behavioral therapy alone is usually sufficient, but drug therapy may be needed when cases are more severe or when access to an experienced child behavior therapist is limited. SSRIs are usually the first choice (see Table 305-1).

Most children tolerate SSRIs without difficulty. Occasionally, upset stomach, diarrhea, or insomnia may occur. Some children have behavioral side effects (eg, activation, disinhibition—see Depressive Disorders in Children and Adolescents on p. 3055).

**Generalized Anxiety Disorder**

Generalized anxiety disorder (GAD) is a persistent state of heightened anxiety and apprehension characterized by excessive worrying, fear, and dread. Physical symptoms can include tremor, sweating, multiple somatic complaints, and exhaustion. Diagnosis is by history. Treatment is often with relaxation therapy, sometimes combined with drug therapy.

**Symptoms and Signs**

Children have multiple and diffuse worries, which are exacerbated by stress. These children often have difficulty paying attention and may be hyperactive and restless. They may sleep poorly, sweat excessively, feel exhausted, and complain of physical discomfort (eg, stomachache, muscle aches, headache).

**Diagnosis**

GAD is diagnosed in children and adolescents who have prominent and impairing anxiety symptoms that are not focused enough to meet criteria for a specific disorder such as social phobia or panic disorder. GAD is also an appropriate diagnosis for children who have a specific anxiety disorder, such as separation anxiety, but also have other significant anxiety symptoms above and beyond those of the specific anxiety disorder.

Occasionally, GAD can be confused with attention-deficit/hyperactivity disorder

[Table 305-1, SSRIs for Treating Children ≥ 12 yr]

(ADHD—see p. 3035) because GAD can cause difficulty paying attention and can also result in
psychomotor agitation (ie, hyperactivity). A key difference is that children with ADHD tend to be no more prone to worries than children without ADHD, whereas children with GAD have many distressing worries.

**Treatment**

- Relaxation therapy
- Sometimes anxiolytic drugs, usually SSRIs

Because the focus of symptoms is diffuse, GAD is especially challenging to treat with behavioral therapy. Relaxation training is often more appropriate.

Patients who have severe GAD or who do not respond to psychotherapeutic interventions may need anxiolytic drugs. As with other anxiety disorders, SSRIs (see Table 305-1) are typically the drugs of choice. Buspirone is a useful alternative, especially for children who cannot tolerate SSRIs; starting dose is 5 mg po bid and may be gradually increased to 30 mg bid (or 20 mg tid) as tolerated. GI distress or headache may be limiting factors in dosage escalation.

**Social Phobia**

((Social Anxiety Disorder))

Social phobia is a persistent fear of embarrassment, ridicule, or humiliation in social settings. Typically, affected children avoid situations that might provoke social scrutiny (eg, school). Diagnosis is by history. Treatment is with behavioral therapy; in severe cases, SSRIs are used.

School refusal is often the initial presentation of social phobia, particularly in adolescents. Complaints often have a somatic focus (eg, "My stomach hurts," "I have a headache"). Some children have a history of many medical appointments and evaluations in response to these somatic complaints.

Affected children are terrified that they will humiliate themselves in front of their peers by giving the wrong answer, saying something inappropriate, becoming embarrassed, or even vomiting. In some cases, social phobia emerges after an unfortunate and embarrassing incident. In severe cases, children may refuse to talk on the telephone or even refuse to leave the house.

**Treatment**

- Behavioral therapy
- Sometimes an anxiolytic

Behavioral therapy is the cornerstone of treatment. Children should not be allowed to miss school. Absence serves only to make them even more reluctant to attend school.

If children and adolescents are not sufficiently motivated to participate in behavioral therapy or do not respond adequately to it, an anxiolytic such as an SSRI may help (see Table 305-1). Treatment with an SSRI may reduce anxiety enough to facilitate children's participation in behavioral therapy.

**Separation Anxiety Disorder**

Separation anxiety disorder is a persistent, intense, and developmentally inappropriate fear of separation from a major attachment figure (usually the mother). Affected children desperately attempt to avoid such separations. When separation is forced, these children are distressfully preoccupied with reunification. Diagnosis is by history. Treatment is with behavioral therapy for the child and family and, for severe cases, SSRIs.

Separation anxiety is a normal emotion in children between about age 8 mo and 24 mo (see p. 2749); it typically resolves as children develop a sense of object permanence and realize their parents will return.
In some children, separation anxiety persists beyond this time or returns later; it may be severe enough to be considered a disorder. Separation anxiety disorder commonly occurs in younger children and is rare after puberty.

**Symptoms and Signs**

Like social phobia, separation anxiety disorder often manifests as school (or preschool) refusal.

Dramatic scenes typically occur at the time of separation. Separation scenes are typically painful for both the child and attachment figure (usually the mother but can be either parent or a caregiver). Children often wail and plead with such desperation that the parent cannot leave, resulting in protracted scenes that are difficult to interrupt. When separated, children fixate on reunification with the attachment figure and are often worried that this person has been harmed (eg, in a car accident, by a serious illness). Children may refuse to sleep alone and may even insist on always being in the same room as the attachment figure.

Children often develop somatic complaints.

The child's demeanor is often normal when the attachment figure is present. This normal demeanor can sometimes give a false impression that the problem is minor.

Separation anxiety is often compounded by a parent's anxiety, which exacerbates the child's anxiety; the result is a vicious circle that can be interrupted only by sensitive and appropriate treatment of parent and child simultaneously.

**Diagnosis**

Diagnosis is by history and by observation of separation scenes.

**Treatment**

- Behavioral therapy
- Rarely anxiolytics

Treatment is with behavioral therapy that systematically enforces regular separations. The goodbye scenes should be kept as brief as possible, and the attachment figure should be coached to react to protestations matter-of-factly. Assisting children in forming an attachment to one of the adults in the preschool or school may be helpful.

In extreme cases, children may benefit from an anxiolytic such as an SSRI (see Table 305-1). However, separation anxiety disorder often affects children as young as 3 yr, and experience with these drugs in the very young is limited.

Successfully treated children are prone to relapses after holidays and breaks from school. Because of these relapses, parents are often advised to plan regular separations during these periods to help the child remain accustomed to being away from the parents.

**Obsessive-Compulsive Disorder**

Obsessive-compulsive disorder (OCD) is characterized by obsessions, compulsions, or both. Obsessions are irresistible, persistent ideas, images, or impulses to do something. Compulsions are pathologic urges to act on an impulse, which, if resisted, result in excessive anxiety and distress. The obsessions and compulsions cause great distress and interfere with academic or social functioning. Diagnosis is by history. Treatment is with behavioral therapy and SSRIs.

Most cases of OCD have no clear etiology. However, a few cases are thought to be associated with
group Aβ-hemolytic streptococcal infections. This syndrome is called pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS). PANDAS should be considered in all children with a sudden onset of severe OCD-like symptoms because early antibiotic treatment may prevent or attenuate long-lasting impairment. Research in this area is ongoing, and if PANDAS is suspected, consultation with a specialist is strongly recommended.

Symptoms and Signs

Typically, OCD has a gradual, insidious onset. Most children initially hide their symptoms and report struggling with symptoms years before a definitive diagnosis is made.

Obsessions are typically experienced as worries or fears of harm (eg, contracting a deadly disease, sinning and going to hell, injuring themselves or others). Compulsions are deliberate volitional acts, usually done to neutralize or offset obsessional fears; they include checking behaviors, excessive washing, counting, or arranging, and many more. Obsessions and compulsions may have some logical connection (eg, hand washing to avoid disease) or may be illogical and idiosyncratic (eg, counting to 50 over and over to prevent grandpa from having a heart attack). If children are prevented from carrying out their compulsions, they become excessively anxious and concerned.

Most children have some awareness that their obsessions and compulsions are abnormal. Many affected children are embarrassed and secretive. Common symptoms include

• Having raw, chapped hands (the presenting symptom in children who compulsively wash)

• Spending excessively long periods of time in the bathroom

• Doing schoolwork very slowly (because of an obsession about mistakes)

• Making many corrections in schoolwork

• Engaging in repetitive or odd behaviors such as checking door locks, chewing food a certain number of times, or avoiding touching certain things

• Making frequent and tedious requests for reassurance, sometimes dozens or even hundreds of times per day—asking, eg, "Do you think I have a fever? Could we have a tornado? Do you think the car will start? What if we're late? What if the milk is sour? What if a burglar comes?"

Diagnosis

Diagnosis is by history. Once a comfortable relationship with a nonjudgmental therapist is established, the child with OCD usually discloses many obsessions and related compulsions. However, usually several appointments are needed to first establish trust. Children with OCD often have symptoms of other anxiety disorders, including panic attacks, separation problems, and specific phobias. This symptom overlap sometimes confuses the diagnosis.

Prognosis

In about 5% of children, the disorder remits after a few years, and treatment can be stopped. In the others, the disorder tends to be chronic, but normal functioning can usually be maintained with ongoing treatment. About 5% of children do not respond to treatment and remain greatly impaired.

Treatment

If streptococcal infection is not involved, treatment is usually a combination of behavioral therapy and an SSRI. If appropriate services are available and children are highly motivated, behavioral therapy alone may be adequate.

PANDAS is treated with antibiotics.
Panic Disorder and Agoraphobia

Panic disorder is characterized by recurrent, frequent (at least once/wk) panic attacks. Panic attacks are discrete spells lasting about 20 min; during attacks, children experience somatic symptoms, cognitive symptoms, or both. Panic disorder can occur with or without agoraphobia. Agoraphobia is a persistent fear of being trapped in situations or places without a way to escape easily and without help. Diagnosis is by history. Treatment is with benzodiazepines or SSRIs and behavioral therapy.

Panic disorder is much less common among prepubertal children than among adolescents. Panic attacks can occur alone or in other anxiety disorders (eg, OCD, separation anxiety) or certain medical disorders (eg, asthma). Panic attacks can trigger an asthma attack and vice versa.

Symptoms may be cognitive, somatic, or (usually) both (see p. 1497).

Panic attacks usually develop spontaneously, but over time, children begin to attribute them to certain situations and environments. Affected children then attempt to avoid those situations, which can lead to agoraphobia. Avoidance behaviors are considered agoraphobia if they greatly impair normal functioning, such as going to school, visiting the mall, or doing other typical activities.

Diagnosis

• Clinical evaluation

• Evaluation for other causes

Panic disorder is diagnosed based on history, usually after a physical examination is done to rule out physical causes of somatic symptoms. Many children undergo considerable diagnostic testing before panic disorder is suspected. The presence of other disorders, especially asthma, can also complicate the diagnosis. Thorough screening for other anxiety disorders (eg, OCD, social phobia) is needed because any one of these disorders may be the primary problem causing panic attacks as a symptom.

In adults, important diagnostic criteria for panic disorder include concerns about future attacks, the implications of the attacks, and changes in behavior. However, children and younger adolescents usually lack the insight and forethought needed to develop these features, except they may change behavior to avoid situations they believe are related to the panic attack. As compared to those in adults, panic attacks in children and adolescents are often more dramatic in presentation (eg, with screaming, weeping, and hyperventilation). This display can be alarming to parents and others.

Prognosis

Prognosis for children and adolescents who have panic disorder with or without agoraphobia is good with treatment. Without treatment, adolescents may drop out of school, withdraw from society, and become reclusive and suicidal.

Panic disorder often waxes and wanes in severity without any discernible reason. Some patients experience long periods of spontaneous symptom remission, only to experience a relapse years later.

Treatment

• Usually benzodiazepines or SSRIs plus behavioral therapy

Treatment is usually a combination of drug therapy and behavioral therapy. In children, it is difficult to even begin behavioral therapy until after the panic attacks have been controlled by drugs. Benzodiazepines are the most effective drugs, but SSRIs are often preferred because benzodiazepines are sedating and may greatly impair learning and memory. However, SSRIs do not work quickly, and a short course of a benzodiazepine (eg, lorazepam 0.5 to 2.0 mg po tid) may be helpful until the SSRI is
Behavioral therapy is especially useful for agoraphobia symptoms. Drugs are rarely useful for these symptoms because children often continue to fear that they may have a panic attack, even long after attacks have been well controlled by drugs.

**Acute and Posttraumatic Stress Disorders**

**Acute stress disorder (ASD)** is a brief period (about 1 mo) of intrusive recollections (eg, flashbacks and nightmares), dissociation, avoidance, and anxiety occurring within 1 mo of a traumatic incident. Post-traumatic stress disorder (PTSD) causes recurring, intrusive recollections of an overwhelming traumatic incident that persist > 1 mo, as well as emotional numbing and hyperarousal. Diagnosis is by history and examination. Treatment is with behavioral therapy, SSRIs, and antiadrenergic drugs.

Because vulnerability and temperament are different, not all children who are exposed to a severe traumatic event develop a stress disorder. Traumatic events commonly associated with these disorders include assaults, sexual assaults, car accidents, dog attacks, and injuries (especially burns). In young children, domestic violence is the most common cause of PTSD.

**Symptoms and Signs**

ASD and PTSD are closely related and are distinguished primarily by duration of symptoms. ASD is diagnosed within 1 mo of the traumatic event, and PTSD is diagnosed only after 1 mo has passed and symptoms have persisted. In a few cases, onset of PTSD symptoms may be delayed months or even years after the traumatic event.

Emotional numbing and hyperarousal are common. Emotional numbing includes the following:

- General lack of interest
- Social withdrawal
- A subjective sense of feeling numb
- A foreshortened expectation of the future (eg, thinking "I will not live to see 20")

Hyperarousal symptoms include the following:

- Jitteriness
- Exaggerated startle response
- Difficulty relaxing
- Disrupted sleep, sometimes with frequent nightmares

Typically, children with ASD are in a daze and may seem dissociated from everyday surroundings.

Children with PTSD have intrusive recollections that cause them to reexperience the traumatic event. The most dramatic kind of recollection is a flashback. Flashbacks may be spontaneous but are most commonly triggered by something associated with the original trauma. For example, the sight of a dog may trigger a flashback in children who experienced a dog attack. During a flashback, children may be in a terrified state and unaware of their current surroundings while desperately searching for a way to hide or escape; they may temporarily lose touch with reality and believe they are in grave danger. Some children have nightmares. When children reexperience the event in other ways (eg, in thoughts, mental images, or recollections), they remain aware of current surroundings, although they may still be greatly distressed.
Diagnosis

Diagnosis of ASD and PTSD is based on a history of severely frightening and horrifying trauma followed by reexperiencing, emotional numbing, and hyperarousal. These symptoms must be severe enough to cause impairment or distress.

Prognosis

Prognosis for children with ASD is much better than for those with PTSD, but both benefit from early treatment. Severity of the trauma, associated physical injuries, and the underlying resiliency of children and family members affect the final outcome.

Treatment

- SSRIs and sometimes antiadrenergic drugs
- Sometimes psychotherapy
- Behavioral therapy

SSRIs often help reduce emotional numbing and reexperiencing of symptoms but are less effective for hyperarousal. Antiadrenergic drugs (eg, clonidine, guanfacine, prazosin) may help relieve hyperarousal symptoms, but supportive data are preliminary.

Supportive psychotherapy may help children who have adjustment issues associated with trauma, as may result from disfigurement due to burns. Behavioral therapy can be used to systematically desensitize children to situations that cause them to reexperience the event. Behavioral therapy is clearly effective in reducing distress and impairment in children and adolescents with PTSD.

Tic Disorders in Children and Adolescents

Tics are defined as sudden, rapid, and repeating muscle movements often associated with vocalizations.

Tics occur in a wide variety of disorders. Transient tic disorders occur in up to 25% of children—most commonly in boys. Typically, tics do not occur during sleep and can be controlled voluntarily for short periods of time. Stress and fatigue can make these tics worse.

Eventually, most tics disappear spontaneously. However, in fewer than 1% of children, tics persist. Such tics may lead to a diagnosis of Tourette's syndrome (see p. 2902), or they may be associated with obsessive-compulsive disorder, some infections, or certain drugs (eg, stimulants).

Usually, no treatment is required. If tics persist and are bothersome (eg, as in Tourette's syndrome), drugs may be used.

Childhood Schizophrenia

(See also p. 1559.)

Schizophrenia is the presence of hallucinations and delusions causing considerable psychosocial dysfunction and lasting ≥ 6 mo.

Onset of schizophrenia is typically from mid-adolescence to the mid-20s. Features in adolescents and young adults are similar. Schizophrenia in prepubertal children is extremely rare; features are usually similar to those in adolescents and adults, but delusions and visual hallucinations (which may be more...
common among children) may be less elaborate.

Sudden-onset psychosis in young children should always be treated as a medical emergency with a thorough medical assessment to search for a physiologic cause of the mental status change (eg, Wilson's disease, porphyrias, HIV infection, brain trauma).

Treatment is complex, and referral to a child and adolescent psychiatrist should be considered.

**Depressive Disorders in Children and Adolescents**

(See also p. 1538.)

Depressive disorders in children and adolescents are characterized by a pervasive and abnormal mood state that consists of sadness or irritability and that is severe or persistent enough to interfere with functioning or cause considerable distress. Decreased interest or pleasure in activities may be as apparent as or even more apparent than mood abnormalities. Diagnosis is by history and examination. Treatment is with antidepressants, psychotherapy, or both.

Major depression occurs in as many as 2% of children and 5% of adolescents. Rates for other depressive disorders are unknown. The exact cause of depression in children and adolescents is unknown, but in adults, it is believed to result from interactions of genetically determined risk factors and environmental stress (particularly deprivation and loss early in life).

**Symptoms and Signs**

Basic manifestations are similar to those in adults but are related to typical concerns of children, such as schoolwork and play. Children may be unable to explain inner feelings or moods. Depression should be considered when previously well-performing children do poorly in school, withdraw from society, or commit delinquent acts.

Common symptoms include

- A sad appearance
- Excessive irritability
- Apathy and withdrawal
- Reduced capacity for pleasure (often expressed as profound boredom)
- Feeling rejected and unloved
- Somatic complaints (eg, headaches, abdominal pain, insomnia)
- Persistent self-blame

In some children with major depressive disorder, the predominant mood is irritability rather than sadness (an important difference between childhood and adult forms).

Other symptoms include anorexia, weight loss (or failure to achieve expected weight gain), sleep disruption (including nightmares), despondency, and suicidal ideation. The irritability associated with childhood depression may manifest as overactivity and aggressive, antisocial behavior.

In children with intellectual disability, depressive or other mood disorders may manifest as somatic symptoms and behavioral disturbances.

Major depression in adolescents is a risk factor for academic failure, substance abuse, and suicidal
behavior (see p. 3060). While depressed, children and adolescents tend to fall far behind academically and lose important peer relationships. Untreated, major depression may remit in 6 to 12 mo, but recurrences are common.

Diagnosis

• Clinical evaluation

Diagnosis is based on symptoms and signs. A careful review of the history and appropriate laboratory tests are needed to exclude other disorders (eg, infectious mononucleosis, thyroid disorders, drug abuse). History should include causative factors such as domestic violence, sexual abuse and exploitation, and drug adverse effects. Questions about suicidal behavior (eg, ideation, gestures, attempts) should be asked.

Other mental disorders that can cause depressive symptoms (eg, anxiety, bipolar disorders) must be considered. Some children who eventually develop a bipolar disorder or schizophrenia may present initially with major depression.

After depression is diagnosed, the family and social setting must be evaluated to identify stresses that may have precipitated depression.

Treatment

• Concurrent measures directed at the family and school

• For adolescents, usually antidepressants plus psychotherapy

• For preadolescents, psychotherapy followed, if needed, by antidepressants

Appropriate measures directed at the family and school must accompany direct treatment of the child to enhance continued functioning and provide appropriate educational accommodations. Brief hospitalization may be necessary in acute crises, especially when suicidal behavior is identified.

For adolescents (as for adults), a combination of psychotherapy and antidepressants usually greatly outperforms either modality used alone. For preadolescents, the situation is much less clear. Most clinicians opt for psychotherapy in younger children; however, drugs can be used in younger children (fluoxetine can be used in children ≥ 8 yr), especially when depression is severe or has not previously responded to psychotherapy.

Usually, an SSRI (see Table 305-1) is the first choice when an antidepressant is indicated. Children should be closely monitored for the emergence of behavioral side effects (eg, disinhibition, behavioral activation—see footnote in Table 305-1). Adult-based research has suggested that antidepressants that act on both the serotonergic and adrenergic/dopaminergic systems may be modestly more effective; however, such drugs (eg, duloxetine, venlafaxine, mirtazapine; certain tricyclics, particularly clomipramine) also tend to have more adverse effects. Such drugs may be especially useful in treatment-resistant cases. Nonserotonergic antidepressants such as bupropion and desipramine may also be used with an SSRI to enhance efficacy.

There are recent concerns that antidepressants may increase risk of suicidality in a few children and adolescents. These drugs are now labeled with warnings about suicidality. Paradoxically, several studies suggest that, overall, use of antidepressants significantly reduces risk of suicide. How to interpret these contradictory findings is unclear. However, if suicide is a concern, the following should be done to reduce risk:

• Parents and mental health care practitioners should discuss the issues in depth.

• The child or adolescent should be supervised at an appropriate level.
Psychotherapy with regularly scheduled appointments should be included in the treatment plan.

As in adults, relapse and recurrence are common. Children and adolescents should remain in treatment for at least 1 yr after symptoms have remitted. Most experts recommend that children who have experienced ≥ 2 episodes of major depression be treated indefinitely.

**Bipolar Disorder in Children and Adolescents**

Bipolar disorder is characterized by alternating periods of mania, depression, and normal mood, each lasting for weeks to months at a time. The label "bipolar" has also been applied to prepubertal children disabled by intense, unstable moods. However, in these young children, the mood states last from moments to days. In both cases, diagnosis is by history and mental status examination. Treatment is a combination of mood stabilizers (eg, lithium, certain anticonvulsants and antipsychotic drugs), psychotherapy, and antidepressants.

Bipolar disorder typically begins during mid-adolescence through the mid-20s. In many children, the initial manifestation is one or more episodes of depression; about one third of children who have an episode of severe depression before puberty convert to bipolar disorder during their adolescent or early adult years. The term "bipolar" has been applied to prepubertal children with unstable, intense moods, but typically, the moods last only a short time. Thus, whether this condition constitutes bipolar disorder is unclear; research in this area is ongoing.

**Etiology**

Etiology is unknown, but heredity is involved. Dysregulation of serotonin and norepinephrine may be involved, as may a stressful life event. Certain drugs (eg, cocaine, amphetamines, phencyclidines, certain antidepressants) and environmental toxins (eg, lead) can exacerbate or mimic the disorder. Certain disorders (eg, thyroid disorders) can cause similar symptoms.

**Symptoms and Signs**

The hallmark of bipolar disorder is the manic episode. Manic episodes alternate with depressive episodes, which can be more frequent.

During a manic episode in adolescents, mood may be very positive or hyperirritable and often alternates between the 2 moods depending on social circumstances. Speech is rapid and pressured, sleep is decreased, and self-esteem is inflated. Mania may reach psychotic proportions (eg, "I have become one with God"). Judgment may be severely impaired, and adolescents may engage in risky behaviors (eg, promiscuous sex, reckless driving). Prepubertal children may experience dramatic moods, but the duration of these moods is much shorter (often lasting only a few moments) than that in adolescents. Onset is characteristically insidious, and children typically have a history of always being very temperamental and difficult to manage.

**Diagnosis**

- Clinical evaluation
- Testing for toxicologic causes

Diagnosis is based on history and mental status examination. A number of medical disorders (eg, thyroid disorders, brain infections or tumors) and drug intoxication must be ruled out with appropriate medical assessment, including a toxicology screen for drugs of abuse and environmental toxins. The interviewer should also search for precipitating events, such as severe psychologic stress, including sexual abuse or incest.

**Prognosis**

Prognosis for adolescents with bipolar disorder varies. Those who have mild to moderate symptoms, who
have a good response to treatment, and who remain adherent and cooperative with treatment have an excellent prognosis. However, treatment response is often incomplete, and adolescents are notoriously nonadherent to drug regimens. For such adolescents, the long-term prognosis is not as good.

Little is known about the long-term prognosis of prepubertal children diagnosed with bipolar disorder based on highly unstable and intense moods.

**Treatment**

- Mood stabilizers and antidepressants
- Psychotherapy

For adolescents and prepubertal children, mood stabilizers are used to treat manic or agitated episodes, and psychotherapy and anti-depressants treat the depressive episodes.

Mood stabilizers (see [Table 305-2](#)) roughly fall into 3 categories:

- Mood-stabilizing anticonvulsants
- Mood-stabilizing antipsychotics
- Lithium

All mood stabilizers have a potential for troubling and even dangerous adverse effects. Thus, treatment must be individualized. Furthermore, drugs that are highly successful during initial stabilization may be unacceptable for maintenance because of adverse effects, most notably weight gain.

Antidepressants may trigger a switch from depression to mania; therefore, they are usually used with a mood stabilizer.

**Disruptive Behavioral Disorders**

Disruptive behavioral disorders are so-named because affected children tend to disrupt people around them, including family members, school staff, and peers. The most common disruptive behavioral disorder is attention-deficit/hyperactivity disorder (see p. 3035).

**Oppositional Defiant Disorder**

Oppositional defiant disorder (ODD) is a recurrent or persistent pattern of negative, defiant, or even hostile behavior directed at authority figures. Diagnosis is by history. Treatment is with individual psychotherapy combined with family or caretaker therapy. Occasionally, drugs may be used to reduce irritability.

Prevalence estimates of ODD vary widely because the diagnostic criteria are highly subjective; prevalence in children and adolescents may be as high as 15%. Before puberty, affected boys greatly outnumber girls; after puberty, the difference narrows.

Although ODD is sometimes viewed as a mild version of conduct disorder, similarities between the 2 disorders are only superficial. The hallmark of ODD is an interpersonal style characterized by irritability and defiance. However, children with a conduct disorder seemingly lack a conscience and repeatedly violate the rights of others (eg, bullying, threatening or causing harm, being cruel to animals), sometimes without any evidence of irritability.

Etiology of ODD is unknown, but it is probably most common among children from families in which the adults model loud, argumentative, interpersonal conflicts. This diagnosis should not be viewed as a circumscribed disorder but rather as an indication of underlying problems that may require further
investigation and treatment.

**Symptoms and Signs**

Typically, children with ODD tend to frequently do the following:

- Lose their temper easily and repeatedly
- Argue with adults
- Defy adults
- Refuse to obey rules
- Deliberately annoy people
- Blame others for their own mistakes or misbehavior
- Be easily annoyed and angered
- Be spiteful or vindictive

Many affected children also lack social skills.

**Diagnosis**

ODD is diagnosed if children have had ≥ 4 of the above symptoms for at least 6 mo. Symptoms must also be severe and disruptive.

ODD must be distinguished from the following, which may cause similar symptoms:

- **Mild to moderate oppositional behaviors**: Such behaviors occur periodically in nearly all children and adolescents.

- **Untreated attention-deficit/hyperactivity disorder (ADHD)**: The ODD-like symptoms often resolve when ADHD is adequately treated.

- **Major depressive disorder**: In some children with this disorder, the predominant mood is irritability rather than sadness. Major depressive disorder with irritability is distinguished from ODD by the presence of anhedonia and neurovegetative symptoms (eg, sleep and appetite disruption); these symptoms are easily overlooked in children.

[Table 305-2, Selected Drugs for Bipolar Disorder*]

**Treatment**

- Behavior modification therapy
- Sometimes drugs

Underlying problems (eg, family dysfunction) and coexisting disorders (eg, ADHD) should be identified and corrected. However, even without corrective measures or treatment, most children with ODD gradually improve over time.

Initially, the treatment of choice is a rewards-based behavior modification program designed to make the child’s behaviors more socially appropriate. Many children can benefit from group-based therapy that builds social skills.
Sometimes drugs used to treat depressive disorders (see p. 3056) may be beneficial.

**Conduct Disorder**

Conduct disorder (CD) is a recurrent or persistent pattern of behavior that violates the rights of others or violates major age-appropriate societal norms or rules. Diagnosis is by history. Treatment of comorbid disorders and psychotherapy may help; however, many children require considerable supervision.

Prevalence of some level of CD is about 10%. Onset is usually during late childhood or early adolescence, and the disorder is much more common among boys than girls.

Etiology is likely a complex interplay of genetic and environmental factors. Parents of adolescents with CD often have engaged in substance abuse and antisocial behaviors and frequently have been diagnosed with ADHD, mood disorders, schizophrenia, or antisocial personality disorder. However, CD can occur in children from high-functioning, healthy families.

**Symptoms and Signs**

Children or adolescents with CD lack sensitivity to the feelings and well-being of others and sometimes misperceive the behavior of others as threatening. They may act aggressively, by bullying and making threats, brandishing or using a weapon, committing acts of physical cruelty, or forcing someone into sexual activity, and have few or no feelings of remorse. Sometimes their aggression and cruelty is directed at animals. These children or adolescents may destroy property, lie, and steal. They tolerate frustration poorly and are commonly reckless, violating rules and parental prohibitions (eg, by running away from home, being frequently truant from school).

Aberrant behaviors differ between the sexes: Boys tend to fight, steal, and vandalize; girls are likely to lie, run away, and engage in prostitution. Both sexes are likely to use and abuse illicit drugs and have difficulties in school. Suicidal ideation is common, and suicide attempts must be taken seriously.

**Diagnosis**

CD is diagnosed in children or adolescents who have demonstrated ≥ 3 of the following behaviors in the previous 12 mo plus at least 1 in the previous 6 mo:

- Aggression toward people and animals
- Destruction of property
- Deceitfulness, lying, or stealing
- Serious violations of parental rules

Symptoms or behaviors must be significant enough to impair functioning in relationships, at school, or at work.

**Prognosis**

Usually, disruptive behaviors stop during early adulthood, but in about one third of cases, they persist. Many of these cases meet the criteria for antisocial personality disorder. Early onset is associated with a poorer prognosis. Some children and adolescents subsequently develop mood or anxiety disorders, somatoform and substance-related disorders, or early adult-onset psychotic disorders. Children and adolescents with CD tend to have higher rates of physical and other mental disorders.

**Treatment**

- Drugs to treat comorbid disorders
• Psychotherapy

• Sometimes placement in a residential center

Treating comorbid disorders with drugs and psychotherapy may improve self-esteem and self-control and ultimately improve control of CD. Drugs may include stimulants, mood stabilizers, and atypical antipsychotics, especially short-term use of risperidone.

Moralization and dire admonitions are ineffective and should be avoided. Individual psychotherapy, including cognitive therapy and behavior modification, may help. Often, seriously disturbed children and adolescents must be placed in residential centers where their behavior can be managed appropriately, thus separating them from the environment that may contribute to their aberrant behavior.

Suicidal Behavior in Children and Adolescents

(See also p. 1579.)

Suicidal behavior includes completed suicide, attempted suicide, and suicide gestures; suicidal ideation is thoughts and plans about suicide. Psychiatric referral is usually required.

Youth suicide rates have declined in recent years after more than a decade of steady increase, only to have started climbing again. The exact reasons for these fluctuations are unclear. Many experts believe that the changing rates with which antidepressants are prescribed may be a factor. Some experts hypothesize that antidepressants have paradoxical effects, making children and adolescents more vocal about suicidal feelings but less likely to commit suicide. Nonetheless, suicide is the 2nd or 3rd leading cause of death in 15- to 19-yr-olds and remains a considerable public health concern.

Etiology

Risk factors vary by age. Predisposing factors include

• Depression (implicated in more than one half of suicidal behaviors in adolescents)

• History of suicide in family members or close friends

• Recent death in the family

• Substance abuse

• Bipolar disorder

• Psychosis

• Conduct disorder, characterized by poor control of aggressive impulses against others, possibly redirected against self (see p. 3060)

More immediate precipitating factors can include

• Loss of self-esteem (eg, resulting from family arguments, a humiliating disciplinary episode, pregnancy, or school failure)

• Loss of a boyfriend or girlfriend

• Loss of familiar surroundings (eg, school, neighborhood, friends) due to a geographic move

Other contributing factors may include a lack of structure and boundaries, leading to an overwhelming feeling of lack of direction, and intense parental pressure to succeed accompanied by the feeling of
falling short of expectations. A frequent motive for a suicide attempt is an effort to manipulate or punish others with the fantasy "You will be sorry after I am dead."

A rise in suicides is seen after a well-publicized suicide (eg, of a rock star) and among groups (eg, a high school, a college dormitory) in which a suicide occurred, indicating the power of suggestion. Early intervention to support youths in such circumstances may be helpful.

Treatment

- Possibly hospitalization
- Possibly drugs to treat underlying disorders
- Psychiatric referral

Every suicide attempt is a serious matter that requires thoughtful and appropriate intervention. Once the immediate threat to life is removed, a decision regarding the need for hospitalization must be made. The decision involves balancing the degree of risk with the family's capacity to provide support. Hospitalization (even in an open medical or pediatric ward with special-duty nursing) is the surest form of short-term protection and is usually indicated if depression, psychosis, or both are suspected.

Lethality of suicidal intent can be assessed based on the following:

- Degree of forethought evidenced (eg, by writing a suicide note)
- Steps taken to prevent discovery
- Method used (eg, firearms are more lethal than pills)
- Degree of self-injury sustained
- Circumstances or immediate precipitating factors surrounding the attempt

Drugs may be indicated for any underlying disorder (eg, depression, bipolar or conduct disorder, psychosis) but cannot prevent suicide. Antidepressant use may increase risk of suicide in some adolescents. Use of drugs should be carefully monitored, and only sub-lethal amounts should be supplied.

Psychiatric referral is usually needed to provide appropriate drug treatment and psychotherapy; treatment is most successful if the primary care practitioner continues to be involved.

Rebuilding morale and restoring emotional equilibrium within the family are essential. A negative or unsupportive parental response is a serious concern and may suggest a need for a more intensive intervention such as out-of-home placement. A positive outcome is most likely if the family shows love and concern.

Prevention

Suicidal incidents are often preceded by behavioral changes (eg, despondent mood, low self-esteem, sleep and appetite disturbances, inability to concentrate, truancy from school, somatic complaints, and suicidal preoccupation), which often bring the child or adolescent to the physician's office. Statements such as "I wish I had never been born" or "I would like to go to sleep and never wake up" should be taken seriously as possible indications of suicidal intent. A suicidal threat or attempt represents an important communication about the intensity of experienced despair.

Early recognition of the risk factors mentioned above may help prevent a suicide attempt. In response to these early cues, to threatened or attempted suicide, or to severe risk-taking behavior, vigorous intervention is appropriate. Adolescents should be directly questioned about their unhappy or self-
destructive feelings; such direct questioning may diminish suicide risk. A physician should not provide unfounded reassurance, which can undermine the physician's credibility and further lower the adolescent's self-esteem.

The effectiveness of suicide prevention programs is being evaluated. The most effective programs are those that strive to ensure that the child has a supportive nurturing environment, ready access to mental health services, and a social setting that is characterized by respect for individual, racial, and cultural differences.

**Self-Injurious Behavior**

Self-injurious behaviors that are sometimes confused with suicidal intentions include superficial scratching and cutting, burning the skin with cigarettes or curling irons, and crude ballpoint pen tattoos.

In some communities, self-injurious behaviors suddenly sweep through a high school in fad-like fashion and then gradually diminish over time.

In many adolescents, these behaviors do not indicate suicidality but instead are an effort to establish autonomy, identify with a peer group, or provocatively gain parental attention. However, even when these behaviors are not an expression of suicidality, they are serious and warrant intervention. Such behaviors are often associated with illicit substance abuse and suggest that an adolescent is in great distress.

All self-injurious behaviors should be evaluated by a clinician experienced in working with troubled adolescents to assess whether suicidality is an issue and to identify the underlying distress leading to the self-injurious behaviors.
Chapter 306. Child Maltreatment

Introduction

Child maltreatment is behavior toward a child that is outside the norms of conduct and entails substantial risk of causing physical or emotional harm. Four types of maltreatment are generally recognized: physical abuse, sexual abuse, emotional abuse (psychologic abuse), and neglect. The causes of child maltreatment are varied and not well understood. Abuse and neglect are often associated with physical injuries, delayed growth and development, and mental problems. Diagnosis is based on history and physical examination. Management includes documentation and treatment of any injuries and urgent physical and mental conditions, mandatory reporting to appropriate state agencies, and sometimes hospitalization or other steps such as foster care to keep the child safe.

In 2007, 3.2 million cases of child abuse and neglect were reported in the US, and about 750,000 of these were substantiated. Both sexes are affected equally; the younger the child, the higher the rate of victimization.

More than half of all reports to Child Protective Services were made by professionals who are mandated to report maltreatment (eg, educators, law enforcement personnel, social services personnel, legal professionals, day care providers, medical or mental health personnel, foster care providers).

Of substantiated cases in the US in 2007, 59.9% involved neglect (including medical neglect); 10.8% involved physical abuse; 7.6% involved sexual abuse; and 4.2% involved psychologic maltreatment. In addition, 4.2% experienced other types of maltreatment, such as abandonment and congenital drug addictions. Many children were victims of multiple types of maltreatment.

About 1760 children died in the US from maltreatment in 2007, about three quarters of whom were < 4 yr. One third of the deaths were attributed to neglect. In substantiated cases of abuse or neglect in 2007, > 80% of perpetrators were parents; 56.5% of perpetrators were women.

Classification

Different forms of abuse often coexist, and overlap is considerable.

Physical abuse: Physical abuse is inflicting physical harm or engaging in actions that create a high risk of harm. Specific forms include shaking, dropping, striking, biting, and burning (eg, by scalding or touching with cigarettes). Abuse is the most common cause of serious head injury in infants. In toddlers, abdominal injury is common.

Infants and toddlers are the most vulnerable (perhaps because perpetrators know they cannot complain), with risk declining in the early school years and increasing again in adolescence.

Medical child abuse (previously called Munchausen syndrome by proxy) is discussed on p. 1576.

Sexual abuse: Any action with a child that is done for the sexual gratification of an adult or significantly older child constitutes sexual abuse (see also Pedophilia on p. 1572). Forms of sexual abuse include intercourse, which is oral, anal, or vaginal penetration; molestation, which is genital contact without intercourse; and nonspecific forms, which do not involve physical contact, including exposure, showing sexual material to a child, and forcing a child to participate in a sex act with another child or to participate in the making of sexual material.

Sexual abuse does not include sexual play, in which children close in age (typically considered < 4 yr apart) view or touch each other's genital area without force or coercion.

Emotional abuse: Emotional abuse is inflicting emotional harm through the use of words or actions. Specific forms include berating a child by yelling or screaming, spurning by belittling the child's abilities and achievements, intimidating and terrorizing with threats, and exploiting or corrupting by encouraging
deviant or criminal behavior. Emotional abuse can also occur when words or actions are omitted or withheld, in essence becoming emotional neglect (e.g., ignoring or rejecting children or isolating them from interaction with other children or adults).

**Neglect:** Neglect is the failure to provide for or meet a child's basic physical, emotional, educational, and medical needs. Neglect differs from abuse in that it usually occurs without intent to harm. Physical neglect includes failure to provide adequate food, clothing, shelter, supervision, and protection from potential harm. Emotional neglect is failure to provide affection or love or other kinds of emotional support. Educational neglect is failure to enroll a child in school, ensure attendance at school, or provide home schooling. Medical neglect is failure to ensure that a child receives appropriate preventive care (e.g., vaccinations, routine dental examinations) or needed treatment for injuries or physical or mental disorders.

**Cultural factors:** Severe corporal punishment (e.g., whipping, burning, scalding) clearly constitutes physical abuse, but for lesser degrees of physical and emotional chastisement, the boundary between socially accepted behavior and abuse varies among different cultures. Likewise, certain cultural practices (e.g., female genital mutilation [see p. 3067]) are so extreme as to constitute abuse. However, certain folk remedies (e.g., coining, cupping, irritant poultices) often create lesions (e.g., bruises, minor burns) that can mimic those caused by abuse; in such cases, the line between acceptable cultural practices and abuse may be blurred.

Similarly, failing to obtain life-saving treatment (e.g., for diabetic ketoacidosis or meningitis) or failing to take children for any routine medical care is considered neglect whatever the parents' or caregivers' intent. However, in the US, certain people and cultural groups have increasingly been declining vaccination of their children, citing safety concerns. It is not clear whether this refusal of vaccination is true medical neglect; it may be considered similar to refusal of non life-saving treatments for religious reasons. In such cases, as long as the children are healthy, there is usually no need to ascertain whether the refusal constitutes medical neglect. However, in the face of illness, refusal of scientifically and medically accepted treatment often requires further investigation and sometimes legal intervention.

**Etiology**

**Abuse:** Generally, abuse can be attributed to a breakdown of impulse control in the parent or caregiver. Several factors contribute.

Parental characteristics and personality features can play a role. The parent's own childhood may have lacked affection and warmth, may not have been conducive to the development of adequate self-esteem or emotional maturity, and, in most cases, also included other forms of abuse. Abusive parents may see their children as a source of unlimited and unconditional affection and look to them for the support that they never received. As a result, they may have unrealistic expectations of what their children can supply for them; they are frustrated easily and lose control; and they may be unable to give what they never experienced. Drug or alcohol use may provoke impulsive and uncontrolled behaviors toward their children. Parental mental disorders may also increase the risk of abuse.

Irritable, demanding, or hyperactive children may provoke parents' tempers, as may developmentally or physically disabled children, who often are more dependent. Sometimes strong emotional ties do not develop between parents and premature or sick infants separated from parents early in infancy or with biologically unrelated children (e.g., stepchildren), increasing the risk of abuse.

Situational stress may precipitate abuse, particularly when emotional support of relatives, friends, neighbors, or peers is unavailable.

Physical abuse, emotional abuse, and neglect are associated with poverty and lower socioeconomic status. However, all types of abuse, including sexual abuse, occur across the spectrum of socioeconomic groups. The risk of sexual abuse is increased in children who have several caregivers or a caregiver with several sex partners.

**Neglect:** Neglect usually results from a combination of factors such as poor parenting, poor stress-
coping skills, unsupportive family systems, and stressful life circumstances. Neglect often occurs in impoverished families experiencing financial and environmental stresses, particularly those in which parents also have mental disorders (typically depression or schizophrenia), abuse drugs or alcohol, or have limited intellectual capacity. Children in single-parent families may be at risk of neglect due to a lower income and fewer available resources.

Symptoms and Signs

Symptoms and signs depend on the nature and duration of the abuse or neglect.

**Physical abuse:** Skin lesions are common and may include handprints or oval fingertip marks caused by slapping or grabbing and shaking; long, bandlike ecchymoses caused by belt whipping or narrow arcuate bruises caused by extension cord whipping; multiple small round burns caused by cigarettes; symmetric scald burns of upper or lower extremities or buttocks caused by intentional immersion; bite marks; and thickened skin or scarring at the corners of the mouth caused by being gagged. Patchy alopecia, with varying hair lengths, can result from hair pulling.

Fractures frequently associated with physical abuse include rib fractures, vertebral fractures, long bone and digit fractures in nonambulatory children, and metaphyseal fractures; in children < 1 yr, about 75% of fractures are inflicted by others. Confusion and localizing neurologic abnormalities can occur with CNS injuries. Lack of visible head lesions does not exclude traumatic brain injury, particularly in infants subjected to violent shaking. These infants may be comatose or stuporous from brain injury yet lack visible signs of injury (with the common exception of retinal hemorrhage). Traumatic injury to organs within the chest or abdominal region may also occur without visible signs.

Children who are frequently abused are often fearful and irritable and sleep poorly. They may have symptoms of depression, post-traumatic stress reactions (see p. 1500), or anxiety. Violent or suicidal behavior may occur.

**Sexual abuse:** In most cases, children do not freely disclose sexual abuse and rarely exhibit behavioral or physical signs of sexual abuse. If a disclosure is made, it is generally delayed, sometimes days to years. In some cases, abrupt or extreme changes in behavior may occur. Aggressiveness or withdrawal may develop, as may phobias or sleep disturbances. Some sexually abused children act in ways that are sexually inappropriate for their age. Physical signs of sexual abuse that involves penetration may include difficulty in walking or sitting; bruises or tears around the genitals, rectum, or mouth; vaginal discharge, bleeding, or pruritus; or a sexually transmitted disease. Within a few days of the abuse, examination of the genitals, rectum, or mouth may be normal or may show healed lesions or subtle hymen changes.

**Emotional abuse:** In early infancy, emotional abuse may blunt emotional expressiveness and decrease interest in the environment. Emotional abuse commonly results in failure to thrive and is often misdiagnosed as intellectual disability or physical illness. Delayed development of social and language skills often results from inadequate parental stimulation and interaction. Emotionally abused children may be insecure, anxious, distrustful, superficial in interpersonal relationships, passive, and overly concerned with pleasing adults. Children who are spurned may have very low self-esteem. Children who are terrorized or threatened may seem fearful and withdrawn. The emotional effect on children usually becomes obvious at school age, when difficulties develop in forming relationships with teachers and peers. Often, emotional effects are appreciated only after the child has been placed in another environment or after aberrant behaviors abate and are replaced by more acceptable behaviors. Children who are exploited may commit crimes or abuse alcohol or drugs.

**Neglect:** Undernutrition, fatigue, lack of hygiene or appropriate clothing, and failure to thrive are common signs of inadequate provision of food, clothing, or shelter. Stunted growth and death resulting from starvation or exposure may occur. Neglect that involves inadequate supervision may result in preventable illness or injury.

**Diagnosis**

• High index of suspicion (eg, for history that does not match physical findings or for atypical injury
• Supportive, open-ended questioning

• Sometimes imaging and laboratory tests

• Reporting to authorities for further investigation

Evaluation of injuries and nutritional deficiencies is discussed elsewhere in THE MANUAL. Recognizing maltreatment as the cause can be difficult, and a high index of suspicion must be maintained. Because of social biases, abuse is considered less often in children living in a 2-parent household with a median-level income; child abuse can occur regardless of family composition or socioeconomic status.

Sometimes direct questions provide answers. Children who have been maltreated may describe the events and the perpetrator, but some children, particularly those who have been sexually abused, may be sworn to secrecy, threatened, or so traumatized that they are reluctant to speak (and may even deny abuse when specifically questioned). Children should be interviewed alone and in a relaxed manner, with open-ended questions (eg, "Tell me what happened"); yes-or-no questions (eg, "Did daddy do this?", "Did he touch you here?") can easily sculpt an untrue history in young children.

Examination includes observation of interactions between the child and possible perpetrators whenever possible. Documentation of the history and physical examination should be as comprehensive and accurate as possible, including recording of exact quotes from the history and photographs of injuries.

Sometimes it is unclear after the initial evaluation whether abuse occurred. In such cases, the mandatory reporting requirement of suspected abuse allows appropriate authorities and social agencies to investigate in depth; if their evaluation confirms abuse, appropriate legal and social interventions can be done.

**Physical abuse:** Both history and physical examination provide clues suggestive of maltreatment.

Features suggestive of abuse in the history are

• Parental reluctance or inability to give a history of injury

• History that is inconsistent with the injury (eg, bruises on the backs of the legs attributed to a fall) or apparent stage of resolution (eg, old injuries described as recent)

• History that varies depending on the information source

• History of injury that is incompatible with the child's stage of development (eg, injuries ascribed to a fall down stairs in an infant too young to crawl)

• Inappropriate response by the parents to the severity of the injury—either overly concerned or unconcerned

• Delay in reporting the injury

Major indicators of abuse on examination are

• Atypical injuries

• Injuries incompatible with stated history

Childhood injuries resulting from falls are typically solitary and occur on the forehead, chin, or mouth or extensor surfaces of the extremities, particularly elbows, knees, forearms, and shins. Bruises on the back, buttocks, and the back of the legs are extremely rare from falls. Fractures, apart from clavicular fracture, tibial (toddler's) fractures, and distal radius (Colles') fracture, are less common in typical falls during play.
or down stairs. No fractures are pathognomonic of abuse, but classic metaphyseal lesions, rib fractures (especially posterior and 1st rib), and depressed or multiple skull fractures (caused by apparently minor trauma), scapular fractures, sternal fractures, and spinous processes fractures should raise concern.

Physical abuse should be considered when an infant who is not walking has a serious injury. Young infants with minor injuries to the face should be further evaluated. The younger infant may appear to be perfectly normal or sleeping despite significant brain trauma, and inflicted acute head trauma in infants should be part of the differential diagnosis of every lethargic infant. Other hints are multiple injuries at different stages of resolution or development; cutaneous lesions specific for particular sources of injury; and repeated injury, which is suggestive of abuse or inadequate supervision.

A dilated eye examination may be useful in children < 1 yr with suspected abuse. Retinal hemorrhage occurs in 65 to 95% of cases of abusive head trauma vs < 10% of cases of accidental head trauma. It also may result from childbirth and persist for up to 4 wk. When retinal hemorrhages result from accidental trauma, the mechanism is usually obvious and life-threatening (eg, major motor vehicle crash), and the hemorrhages are typically few in number and confined to the posterior pole.

Children < 2 yr with possible physical abuse should undergo a skeletal survey for evidence of previous bony injuries (fractures in various stages of healing or subperiosteal elevations in long bones). Surveys are sometimes done on children aged 2 to 5 yr but are generally not helpful for those > 5 yr. The standard survey includes anteroposterior (AP) views of the skull and chest, lateral views of the spine and long bones, AP views of the pelvis, and AP and oblique views of the hands. Physical disorders causing multiple fractures include osteogenesis imperfecta and congenital syphilis.

Sexual abuse: Sexually transmitted disease of any sort in a child < 12 yr must be considered the result of sexual abuse until proved otherwise. When a child has been sexually abused, behavioral changes (eg, irritability, fearfulness, insomnia) may be the only clues initially. If sexual abuse is suspected, the perioral and rectal areas and the external genitals must be examined for evidence of injury. If the suspected abuse is thought to have occurred recently, hair samples and swabs of body fluids are obtained for legal evidence (see p. 2549). An examination involving use of a magnifying light source with a camera, such as with a specially equipped colposcope, may be helpful for documentation for legal purposes.

Emotional abuse and neglect: Evaluation focuses on general appearance and behavior to determine whether the child is failing to develop normally. Teachers and social workers are often the first to recognize neglect. The physician may notice a pattern of missed appointments and vaccinations that are not up-to-date. Medical neglect of life-threatening, chronic diseases, such as asthma or diabetes, can lead to a subsequent increase in office or emergency department visits and poor adherence with recommended drug regimens.

Treatment

• Treatment of injuries

• Assurance of safety

• Family counseling and support

• Sometimes removal from the home

Treatment first addresses urgent medical needs (including possible sexually transmitted diseases) and the child’s immediate safety. Referral to a pediatrician specializing in child abuse should be considered. Ultimately, treatment is directed at long-standing disturbed patterns of personal interaction. In both abuse and neglect situations, families should be approached in a helping rather than a punitive manner.

Immediate safety: Physicians and other professionals in contact with children (eg, nurses, teachers, day care workers, police) are required by law in all states to report incidents of suspected abuse or neglect. Every state has its own laws. Members of the general public are encouraged, but not mandated, to report suspected abuse. Any person who makes a report of abuse based on reasonable cause and in
good faith is immune from criminal and civil liability. A mandated reporter who fails to make a report can be subject to criminal and civil penalties. The reports are made to Child Protective Services or another appropriate child protection agency. In most situations, it is appropriate for professionals to tell parents that a report is being made pursuant to the law and that they will be contacted, interviewed, and possibly visited at their home. In some cases, the professional may determine that informing the parent before police or other agency assistance is available creates greater risk of injury to the child. Under those circumstances, the professional may choose to delay informing the parent or caregiver.

Representatives of child protective agencies and social workers can help the physician determine likelihood of subsequent harm and thus identify the best immediate disposition for the child. Options include

- Protective hospitalization
- Placement with relatives or in temporary housing (sometimes a whole family is moved out of an abusive partner’s home)
- Temporary foster care
- Going home with prompt social service follow-up

The physician plays an important role in working with community agencies to advocate for the best and safest disposition for the child.

**Follow-up:** A source of primary medical care is fundamental. However, the families of abused and neglected children frequently relocate, making continuity of care difficult. Broken appointments are common; outreach and home visits by social workers or a public health nurse may be needed to relay the child’s progress to all concerned. A local child advocacy center can help community agencies, health care practitioners, and the legal system work together as a multidisciplinary team in a more coordinated, child-friendly, and effective manner.

A close review of the family setting, prior contacts with various community service agencies, and the parents’ needs is essential. A social worker can conduct such reviews and help with interviews and family counseling. Social workers also provide tangible assistance to the parents by helping them obtain public assistance and day care and homemaker services (which can relieve a parent under stress, allowing a few hours each day for relaxation) and coordinating mental health services for parents. Periodic or ongoing social work contact usually is needed.

Parent-aide programs, which employ trained nonprofessionals to relate closely to abusive and negligent parents, are available in some communities. Other parent support groups also have been successful.

Sexual abuse may have lasting effects on the child's development and sexual adaptation, particularly among older children and adolescents. Counseling or psychotherapy for the child and the adults concerned may lessen these effects.

**Removal from the home:** Although emergency temporary removal from the home until evaluation is complete and safety is ensured is not uncommon, the ultimate goal of Child Protective Services is to keep children with their family in a safe, healthy environment. If the previously described interventions do not ensure safety, consideration must be made for long-term removal and possibly termination of parental rights. This significant step requires a court petition, presented by the legal counsel of the appropriate welfare department. The specific procedure varies from state to state but usually entails family court testimony by a physician. When the court decides in favor of removing the child from the home, a disposition is arranged. The family's physician should participate in this disposition planning; if not, the physician's agreement and consent to the disposition should be sought. While the child is in temporary placement, the physician should, if possible, maintain contact with the parents and ensure that adequate efforts are being made to help them. Occasionally, children are re-abused while in foster care. The physician should be alert to this possibility. The physician's input is integral to the decision for reuniting the child and parents. As the dynamics of the family setting improve, the child may be able to return to the
parents’ care. However, recurrences of abuse are common.

Prevention

Prevention of maltreatment should be a part of every well-child office visit through education of parents or caregivers and referrals for appropriate community services of identified at-risk families. Parents who have been victims of abuse or neglect may be at risk of abusing their own children. Such parents often verbalize anxiety about their abusive background and are amenable to assistance. First-time parents and teenage parents as well as parents with several children < 5 yr are also at risk. Often, maternal risk factors for abuse are identified prenatally, eg, a mother who does not seek prenatal care, smokes, abuses drugs, or has a history of domestic violence. Medical problems during pregnancy, delivery, or early infancy that may affect the infant's health can weaken parent-infant bonding (see also p. 2754). During such times it is important to elicit the parents' feelings about their own inadequacies and the infant's well-being. How well can they tolerate an infant with many needs or health demands? Do the parents give moral and physical support to each other? Are there relatives or friends to help in times of need? The health care practitioner who is alert to clues and able to provide support in such settings goes a long way toward preventing tragic events.

Female Genital Mutilation

Female genital mutilation is practiced routinely in parts of Africa (usually northern or central Africa), where it is deeply ingrained as part of some cultures. Women who experience sexual pleasure are considered impossible to control, are shunned, and cannot be married.

The average age of girls who undergo mutilation is 7 yr, and mutilation is done without anesthesia. Mutilation may be limited to partial clitoral excision. Infibulation, the most extreme form, is removal of the clitoris and labia, usually followed by suturing the remaining tissue closed except for a 1- to 2-cm opening for menses and urine. The legs are often bound together for weeks afterward. Traditionally, infibulated females are cut open on their wedding night.

Sequelae of genital mutilation may include operative or postoperative bleeding and infection (including tetanus). For infibulated females, recurrent urinary or gynecologic infection and scarring are possible; they have increased susceptibility to AIDS, and childbirth may result in fatal hemorrhage. Psychologic sequelae may be severe.

Female genital mutilation may be decreasing due to the influence of religious leaders who have spoken out against the practice and growing opposition in some communities.
Introduction

Geriatrics refers to medical care for the elderly, an age group that is not easy to define precisely. "Older people" is sometimes preferred but is equally imprecise; > 65 is the age often used. Gerontology is the study of aging, including biologic, sociologic, and psychologic changes.

Around 1900 in the US, people > 65 accounted for 4% of the population; now, they account for > 13% (38 million, with a net gain of > 1000/day). In 2026, when post-World War II baby boomers begin to reach age 80, estimates suggest that > 20% (almost 80 million) will be > 65. Mean age of those > 65 is now a little more than 75, and the proportion of those > 85 is predicted to increase.

Life expectancy is an additional 16 yr at age 65 and 9 yr at age 75 for men and an additional 19 yr at age 65 and 12 yr at age 75 for women. Overall, women live about 5 yr longer than men, probably because of genetic, biologic, and environmental factors. These differences in survival have not changed, despite changes in women's lifestyle (eg, increased smoking, increased stress).

Changes with Aging

Most age-related biologic functions peak before age 30 and gradually decline linearly thereafter (see Table 307-1); the decline may be critical during stress, but it usually has little or no effect on daily activities. Therefore, disorders, rather than normal aging, are the primary cause of functional loss during old age. Also, in many cases, the declines that occur with aging may be due at least partly to lifestyle, behavior, diet, and environment and thus can be modified. For example, aerobic exercise can prevent or partially reverse a decline in maximal exercise capacity (O\textsubscript{2} consumption per unit time, or Vo\textsubscript{2}\text{max}), muscle strength, and glucose tolerance in healthy but sedentary older people (see Sidebar 307-1).

The unmodifiable effects of aging may be less dramatic than thought, and healthier, more vigorous aging may be possible for many people. Today, people > 65 are in better health than their predecessors and remain healthier longer. Because health has improved, decline tends to be most dramatic in the oldest old.

Evaluation of the Elderly Patient

Evaluation of the elderly usually differs from a standard medical evaluation. For elderly patients, especially those who are very old or frail, history-taking and physical examination may have to be done at different times, and physical examination may require 2 sessions because patients become fatigued.

The elderly also have different, often more complicated health care problems, such as multiple disorders, which may require use of many drugs (polypharmacy). Diagnosis may be complicated, resulting in delays or missed diagnoses, and sometimes drugs are used inappropriately. Early detection of problems results in early intervention, which can prevent deterioration and improve quality of life often through relatively minor, inexpensive interventions (eg, lifestyle changes). Thus, some elderly patients, particularly the frail or chronically ill, are best evaluated using a comprehensive geriatric assessment (see p. 3086), which includes evaluation of function and quality of life, often by an interdisciplinary team.

Sidebar 307-1 Exercise

Only about 20 to 25% of the elderly participate in regular exercise for > 30 min 5 times/wk (a common
recommendation). About 35 to 45% participate in minimal exercise. The elderly tend to exercise less than other age groups for many reasons, most commonly because disorders limit their physical activity.

The benefits of exercise for the elderly are many and far exceed its risks (eg, falls, torn ligaments, pulled muscles). Benefits include

- Reduced mortality rates, even for smokers and the obese
- Preservation of skeletal muscle strength, aerobic capacity, and bone density, contributing to mobility and independence
- Reduced risk of obesity
- Prevention and treatment of cardiovascular disorders (including rehabilitation after MI), diabetes, osteoporosis, colon cancer, and psychiatric disorders (especially mood disorders)
- Prevention of falls and fall-related injuries by improving muscle strength, balance, coordination, joint function, and endurance
- Improved functional ability
- Opportunities for social interaction
- Enhanced sense of well-being
- Possibly improved sleep quality

Exercise is one of the few interventions that can restore physiologic capacity after it has been lost.

All elderly patients starting an exercise program should be screened (by interview or questionnaire) to identify those with chronic disorders and to determine an appropriate exercise program (see p. 3295). Exercise is inappropriate for only a few elderly people (eg, those with unstable medical conditions). Whether those with chronic disorders need a complete preexercise medical examination depends on tests that have already been done and on clinical judgment. Some experts recommend such an examination, possibly with an exercise stress test, for patients who have ≥ 2 cardiac risk factors (eg, hypertension, obesity).

Exercise programs may include any combination of 4 types of exercise: endurance, muscle strengthening, balance training (eg, tai chi), and flexibility (see p. 3292). The combination of exercises recommended depends on the patient's medical condition and fitness level. For example, a seated exercise program that uses cuff weights for strength training and repeated movements for endurance training may be useful for patients who have difficulty standing and walking. An aquatics exercise program may be suggested for patients with arthritis. Patients should be able to select activities they enjoy but should be encouraged to include all 4 types of exercise. Of all types of exercise, endurance exercises (eg, walking, cycling, dancing, swimming, low-impact aerobics) have the most well-documented health benefits for the elderly.

Some patients, particularly those with a heart disorder (eg, angina, ≥ 2 MIs), require medical supervision during exercise.

High-intensity muscle-strengthening programs are particularly appropriate for frail or near-frail elderly patients with sarcopenia. For these patients, machines that use air pressure rather than weights are useful because the resistance can be set lower and changed in smaller increments. High-intensity programs are safe even for nursing home residents > 80; in them, strength and mobility can be substantially improved. However, these programs are time-consuming because participants usually require close supervision.

**Drugs and exercise:** Doses of insulin and oral hypoglycemics in diabetics may need to be adjusted (according to the amount of anticipated exercise) to prevent hypoglycemia during exercise. Doses of
drugs that can cause orthostatic hypotension (eg, antidepressants, antihypertensives, hypnotics, anxiolytics, diuretics) may need to be lowered to avoid exacerbation of orthostasis by fluid loss during exercise. For patients taking such drugs, adequate fluid intake is essential during exercise.

Some sedative-hypnotics may reduce physical performance by reducing activity levels or by inhibiting effects on muscles and nerves. These and other psychoactive drugs increase the risk of falls. Stopping such drugs or reducing their dose may be necessary to make exercise safe and to help patients adhere to their exercise regimen.

**Multiple disorders:** On average, elderly patients have 6 diagnosable disorders, and the primary care physician is often unaware of some of them. A disorder in one organ system can weaken another system, exacerbating the deterioration of both and leading to disability, dependence, and, without intervention, death. Multiple disorders complicate diagnosis and treatment, and effects of the disorders are magnified by social disadvantage (eg, isolation) and poverty (as patients outlive their resources and supportive peers) and by functional and financial problems.

Clinicians should also pay particular attention to certain common geriatric symptoms (eg, acute confusion, dizziness, syncope, falling, mobility problems, weight or appetite loss, urinary incontinence) because they may result from disorders of multiple organ systems.

If patients have multiple disorders, treatments (eg, bed rest, surgery, drugs) must be well integrated; treating one disorder without treating associated disorders may accelerate decline. Also, careful monitoring is needed to avoid iatrogenic consequences. With complete bed rest, elderly patients can lose 5 to 6% of muscle mass and strength each day (causing sarcopenia), and effects of bed rest alone can ultimately result in death.

**Missed or delayed diagnosis:** Disorders that are common among the elderly are frequently missed, or the diagnosis is delayed. Clinicians should use the history, physical examination, and simple laboratory tests to actively screen elderly patients for disorders that occur only or commonly in the elderly (see Table 307-2); when diagnosed early, these disorders can often be more easily treated. Early diagnosis frequently depends on the clinician's familiarity with the patient's behavior and history, including mental status. Commonly, the first signs of a physical disorder are mental or emotional. If clinicians are unaware of this possibility and attribute these signs to dementia, diagnosis and treatment can be delayed.

**Polypharmacy:** Prescription and OTC drug use should be reviewed frequently, particularly for drug interactions and use of drugs considered inappropriate for the elderly (see p. 3098). When multiple drugs are used, computer-based management is more efficient.

**Caregiver problems:** Occasionally, problems of elderly patients are related to neglect or abuse by their caregiver (see p. 3146). Clinicians should consider the possibility of patient abuse and drug abuse by the caregiver if circumstances and findings suggest it. Certain injury patterns are particularly suggestive, including

- Frequent bruising, especially in difficult-to-reach areas (eg, middle of the back)
- Grip bruises of the upper arms
- Bruises of the genitals
- Peculiar burns
- Unexplained fearfulness of a caregiver

**History**
Often, more time is needed to interview and evaluate elderly patients, partly because they may have characteristics that interfere with the evaluation:

- **Sensory deficits:** Dentures, eyeglasses, or hearing aids, if normally worn, should be worn to facilitate communication during the interview. Adequate lighting also helps.

- **Underreporting of symptoms:** Elderly patients may not report symptoms that they consider part of normal aging (eg, dyspnea, hearing or vision deficits, memory problems, incontinence, gait disturbance, constipation, dizziness, falls). However, no symptom should be attributed to normal aging unless a thorough evaluation is done and other causes have been eliminated.

- **Unusual manifestations of a disorder:** In the elderly, typical manifestations of a disorder may be absent (see p. 3088). Instead, the elderly may present with general symptoms (eg, fatigue, confusion, weight loss).

- **Functional decline as the only manifestation:** Disorders may manifest solely as functional decline. In such cases, standard questions may not apply. For example, when asked about joint symptoms, patients with severe arthritis may not report pain, swelling, or stiffness, but if asked about changes in activities, they may report that they no longer take walks or no longer volunteer at the hospital. Questions about duration of functional decline (eg, "How long have you been unable to do your own shopping?") can elicit useful information. Identifying people when they have just started to have difficulty doing basic activities of daily living (ADLs) or instrumental ADLs (IADLs) may provide more opportunities for interventions to restore function or to prevent further decline and thus maintain independence.

- **Difficulty recalling:** Patients may not accurately remember past illnesses, hospitalizations, operations, and drug use; clinicians may have to obtain these data elsewhere (eg, from family members, a home health aide, or medical records).

- **Fear:** The elderly may be reluctant to report symptoms because they fear hospitalization, which they may associate with dying.

- **Age-related disorders and problems:** Depression (common among the elderly), the cumulative losses of old age, and discomfort due to a disorder may make the elderly less apt to provide health-related information to clinicians. Patients with impaired cognition may have difficulty describing problems, impeding the physician's evaluation.

Information acquired during the interview and history should be recorded in the patient's medical record.

**Interview:** A clinician's knowledge of an elderly patient's everyday concerns, social circumstances, mental function, emotional state, and sense of well-being helps orient and guide the interview. Asking patients to describe a typical day elicits information about their quality of life and mental and physical function. This approach is especially useful during the first meeting. Patients should be given time to speak about things of personal importance. Clinicians should also ask whether patients have specific concerns, such as fear of falling. The resulting rapport can help the clinician communicate better with patients and their family members.

A mental status examination may be necessary early in the interview to determine the patient's reliability; this examination should be conducted tactfully so that the patient does not become embarrassed, offended, or defensive.

Often, verbal and nonverbal clues (eg, the way the story is told, tempo of speech, tone of voice, eye contact) can provide information, as for the following:

- **Depression:** Elderly patients may omit or deny symptoms of anxiety or depression but betray them by a lowered voice, subdued enthusiasm, or even tears.

- **Physical and mental health:** What patients say about sleep and appetite may be revealing.
• **Weight gain or loss:** Clinicians should note any change in the fit of clothing or dentures.

Unless mental status is impaired, a patient should be interviewed alone to encourage the discussion of personal matters. Clinicians often also need to speak with a relative or caregiver—with the patient absent, present, or both. Such people often give a different perspective on function, mental status, and emotional state.

The clinician should ask the patient's permission before inviting a relative or caregiver to be present and should explain that such interviews are routine. When the caregiver is interviewed alone, the patient should be kept usefully occupied (eg, filling out a standardized assessment questionnaire, being interviewed by another member of the interdisciplinary team).

If indicated, clinicians should consider the possibility of drug abuse and patient abuse by the caregiver.

**Medical history:** When asking patients about their past medical history, a clinician should ask about disorders that used to be more common (eg, rheumatic fever, poliomyelitis) and about outdated treatments (eg, pneumothorax therapy for TB, mercury for syphilis). A history of immunizations (eg, tetanus, influenza, pneumococcus), adverse reactions to immunizations, and skin test results for TB is needed. If patients recall having surgery but do not remember the procedure or its purpose, surgical records should be obtained if possible.

Clinicians should ask questions designed to systematically review each body area or system and thus check for other disorders and common problems that patients may have forgotten to mention (see [Table 307-3](#)).

**Drug history:** The drug history should be recorded, and a copy should be given to patients or their caregiver. It should contain

- Drugs used
- Dose
- Dosing schedule
- Prescriber
- Reason for prescribing the drugs
- Precise nature of any drug allergies

All drugs used should be recorded: topical drugs (which may be absorbed systemically), OTC drugs (which can have serious consequences if overused and may interact with prescription drugs), dietary supplements, and medicinal herb preparations (because many can interact adversely with prescription and OTC drugs). Patients or a family member should be asked to bring in all of the above drugs and supplements at the initial visit and periodically thereafter. Clinicians can make sure patients have the prescribed drugs, but possession of these drugs does not guarantee adherence. Counting the number of tablets in each vial during the first and subsequent visits may be necessary. If someone other than a patient administers the drugs, that person is interviewed.

Patients should be asked to demonstrate their ability to read labels (often printed in small type), open containers (especially the child-resistant type), and recognize drugs. Patients should be advised not to put their drugs into one container.
Alcohol, tobacco, and recreational drug use history: Patients who smoke should be counseled to stop and, if they continue, not to smoke in bed because the elderly are more likely to fall asleep while doing so.

Patients should be checked for signs of alcohol use disorders, which are underdiagnosed in the elderly. Such signs include confusion, anger, hostility, alcohol odor on the breath, impaired balance and gait, tremors, peripheral neuropathy, and nutritional deficiencies. Screening questionnaires (eg, CAGE questionnaire—see Table 309-1 on p. 3105) and questions about quantity and frequency of alcohol consumption can help.

Questions about use of other recreational drugs or substances of abuse are appropriate.

Nutrition history: Type, quantity, and frequency of food eaten are determined. Patients who eat ≤ 2 meals a day are at risk of undernutrition. Clinicians should ask about the following:

- Any special diets (eg, low-salt, low-carbohydrate) or self-prescribed fad diets
- Intake of dietary fiber and prescribed or OTC vitamins
- Weight loss and change of fit in clothing
- Amount of money patients have to spend on food
- Accessibility of food stores and suitable kitchen facilities
- Variety and freshness of foods

The ability to eat (eg, to chew and swallow) is evaluated. It may be impaired by xerostomia, which is common among the elderly. Decreased taste or smell may reduce the pleasure of eating, so patients may eat less. Patients with decreased vision, arthritis, immobility, or tremors may have difficulty preparing meals and may injure or burn themselves when cooking. Patients who are worried about urinary incontinence may reduce their fluid intake; as a result, they may eat less food.

Mental health history: Mental health problems may not be detected easily in elderly patients. Symptoms that may indicate a mental health disorder in younger patients (eg, insomnia, changes in sleep patterns, constipation, cognitive dysfunction, anorexia, weight loss, fatigue, preoccupation with bodily functions, increased alcohol consumption) may have another cause in the elderly. Sadness, hopelessness, and crying episodes may indicate depression. Irritability may be the primary affective symptom of depression, or patients may present with cognitive dysfunction. Generalized anxiety is the most common mental disorder encountered in elderly patients and often accompanies depression.

Patients should be asked about delusions and hallucinations, past mental health care (including psychotherapy, institutionalization, and electroconvulsive therapy), use of psychoactive drugs, and recent changes in circumstances. Many circumstances (eg, recent loss of a loved one, hearing loss, a change in residence or living situation, loss of independence) may contribute to depression.

Patients' spiritual and religious preferences, including their personal interpretation of aging, declining health, and death, should be clarified.

Functional status: Whether patients can function independently, need some help with basic activities of daily living (ADLs) or instrumental ADLs (IADLs), or need total assistance is determined, often as part of comprehensive geriatric assessment. Patients may be asked open-ended questions about their ability to do activities, or they may be asked to fill out a standardized assessment instrument with questions about specific ADLs and IADLs (eg, Katz ADL Scale [see Table 350-3 on p. 3457], Lawton IADL Scale [see Table 307-4]).

Social history: Clinicians should identify patients' living arrangements, particularly where and with whom
they live (eg, alone in an isolated house, in a busy apartment building), accessibility of their residence (eg, up stairs or a hill), and what modes of transportation are available to them. Such factors affect the ability of the elderly to obtain food, health care, and other important resources. A home visit, although difficult to arrange, can provide critical information. For example, clinicians can gain insight about nutrition from the refrigerator's contents and about multiple ADLs from the bathroom's condition. The number of rooms, number and type of phones, presence of smoke and carbon monoxide detectors, and condition of plumbing and heating system are determined, as is the availability of elevators, stairs, and air conditioning. Home safety evaluations can identify home features that can lead to falls (eg, poor lighting, slippery bathtubs, unanchored rugs), and solutions can be suggested.

Having patients describe a typical day, including activities such as reading, television viewing, work, exercise, hobbies, and interactions with other people, provides valuable information.

Clinicians should ask about the following:

- Frequency and nature of social contacts (eg, friends, senior citizens’ groups), family visits, and religious or spiritual participation
- Driving and availability of other forms of transportation
- Caregivers and support systems (eg, church, senior citizens' groups, friends, neighbors) that are available to the patient
- The ability of family members to help the patient (eg, their employment status, their health, traveling time to the patient's home)
- The patient's attitude toward family members and their attitude toward the patient (including their level of interest in helping and willingness to help)

Marital status of patients is noted. Questions about sexual practices and satisfaction must be sensitive and tactful but thorough. The number and sex of sex partners are determined, and risk of sexually transmitted diseases is evaluated. Many sexually active elderly people do not know about safe sex practices.

Patients should be asked about educational level, jobs held, known exposures to radioactivity or asbestos, and current and past hobbies.

[Table 307-4. Lawton Instrumental Activities of Daily Living Scale*]

Economic difficulties due to retirement, a fixed income, or death of a spouse or partner are discussed. Financial or health problems may result in loss of a home, social status, or independence. Patients should be asked about past relationships with physicians; a longtime relationship with a physician may have been lost because the physician retired or died or because the patient relocated.

Patient wishes regarding measures for prolonging life must be documented. Patients are asked what provisions for surrogate decision making (advance directives—see p. 3471) have been made in case they become incapacitated, and if none have been made, patients are encouraged to make them.

**Key Points**

- Unless corrected, sensory deficits, especially hearing deficits, may interfere with history-taking.
- Many disorders in the elderly manifest only as functional decline.
- As part of the drug history, the patient or a family member should be asked to bring in all the patient's drugs, including OTC drugs, at the initial visit and periodically thereafter.
- Health care practitioners must often interview caregivers to obtain the history of functionally dependent
elderly patients.

Physical Examination

Observing patients and their movements (eg, walking into the examination room, sitting in or rising from a chair, getting on and off an examination table, taking off or putting on socks and shoes) can provide valuable information about their function. Their personal hygiene (eg, state of dress, cleanliness, smell) may provide information about mental status and the ability to care for themselves.

If patients become fatigued, the physical examination may need to be stopped and continued at another visit. Elderly patients may require additional time to undress and transfer to the examining table; they should not be rushed. The examining table should be adjusted to a height that patients can easily access; a footstool facilitates mounting. Frail patients must not be left alone on the table. Portions of the examination may be more comfortable if patients sit in a chair.

Clinicians should describe the general appearance of patients (eg, comfortable, restless, undernourished, inattentive, pale, dyspneic, cyanotic). If they are examined at bedside, use of protective padding or a protective mattress, bedside rails (partial or full), restraints, a urinary catheter, or an adult diaper should be noted.

Vital Signs

Weight should be recorded at each visit. During measurement, patients with balance problems may need to grasp grab bars placed near or on the scale. Height is recorded annually to check for height loss due to osteoporosis.

Temperature is recorded. Hypothermia can be missed if the thermometer cannot measure temperatures more than a few degrees lower than normal. Absence of fever does not exclude infection.

Pulses and BP are checked in both arms. Pulse is taken for 30 sec, and any irregularity is noted. Because many factors can alter BP, BP is measured several times after patients have rested > 5 min.

BP may be overestimated in elderly patients because their arteries are stiff. This condition, called pseudohypertension, should be suspected if dizziness develops after antihypertensives are begun or doses are increased to treat elevated systolic BP.

All elderly patients are checked for orthostatic hypotension because it is common. BP is measured with patients in the supine position, then after they have been standing for 3 to 5 min. If systolic BP falls ≥ 20 mm Hg after patients stand, orthostatic hypotension is diagnosed. Caution is required when testing hypovolemic patients.

A normal respiratory rate in elderly patients may be as high as 25 breaths/min. A rate of > 25 breaths/min may be the first sign of a lower respiratory tract infection, heart failure, or another disorder.

Skin

Initial observation includes color (normal rubor, pale, cyanotic). Examination includes a search for premalignant and malignant lesions, tissue ischemia, and pressure ulcers. In the elderly, the following should be considered:

• Ecchymoses may occur readily when skin is traumatized, often on the forearm, because the dermis thins with aging.

• Uneven tanning may be normal because melanocytes are progressively lost with aging.

• Longitudinal ridges on the nails and absence of the crescent-shaped lunula are normal age-related findings.
Nail plate fractures may occur because with aging, the nail plate thins.

Black splinter hemorrhages in the middle or distal third of the fingernail are more likely to be due to trauma than to bacteremia.

A thickened, yellow toenail indicates onychomycosis, a fungal infection.

Toenail borders that curve in and down indicate ingrown toenail (onychocryptosis).

Whitish nails that scale easily, sometimes with a pitted surface, indicate psoriasis.

Unexplained bruises may indicate abuse.

**Head and Neck**

**Face:** Normal age-related findings may include the following:

- Eyebrows that drop below the superior orbital rim
- Descent of the chin
- Loss of the angle between the submandibular line and neck
- Wrinkles
- Dry skin
- Thick terminal hairs on the ears, nose, upper lip, and chin

The temporal arteries should be palpated for tenderness and thickening, which may indicate giant cell arteritis.

**Nose:** Progressive descent of the nasal tip is a normal age-related finding. It may cause the upper and lower lateral cartilage to separate, enlarging and lengthening the nose.

**Eyes:** Normal age-related findings include the following:

- Loss of orbital fat: It may cause gradual sinking of the eye backward into the orbit (enophthalmos). Thus, enophthalmos is not necessarily a sign of dehydration in the elderly. Enophthalmos is accompanied by deepening of the upper eyelid fold and slight obstruction of peripheral vision.

- Pseudoptosis (decreased size of the palpebral aperture)

- Entropion (inversion of lower eyelid margins)

- Ectropion (eversion of lower eyelid margins)

- Arcus senilis (a white ring at the limbus)

With aging, presbyopia develops; the lens becomes less elastic and less able to change shape when focusing on close objects.

The eye examination should focus on testing visual acuity (eg, using a Snellen chart). Visual fields can be tested at the bedside by confrontation—ie, patients are asked to stare at the examiner so that the examiner can determine differences between their and the examiner's visual field. However, such testing has low sensitivity for most visual disorders. Tonometry is occasionally done in primary care; however, it is usually done by ophthalmologists or optometrists as part of routine eye examinations or by ophthalmologists when a patient is referred to them because glaucoma is clinically suspected.
Ophthalmoscopy is done to check for cataracts, optic nerve or macular degeneration, and evidence of glaucoma, hypertension, or diabetes. Findings may be unremarkable unless a disorder is present because the retina's appearance may not change much with aging. In elderly patients, mild to moderate elevated intracranial pressure may not result in papilledema because cortical atrophy occurs with aging; papilledema is more likely when pressure is markedly increased. Areas of black pigment or hemorrhages in and around the macula indicate macular degeneration.

For all elderly patients, an eye examination by an ophthalmologist or optometrist is recommended every 1 to 2 yr because such an examination may be much more sensitive for certain common eye disorders (eg, glaucoma, cataracts, retinal disorders).

**Ears:** Tophi, a normal age-related finding, may be noted during inspection of the pinna. The external auditory canal is examined for cerumen, especially if a hearing problem is noted during the interview. If a patient wears a hearing aid, it is removed and examined. The ear mold and plastic tubing can become plugged with wax, or the battery may be dead, indicated by absence of a whistle (feedback) when the volume of the hearing aid is turned up.

To evaluate hearing, examiners, with their face out of the patient's view, whisper 3 to 6 random words or letters into each of the patient's ears. If a patient correctly repeats at least half of these words for each ear, hearing is considered functional for one-on-one conversations. Patients with presbycusis (age-related, gradual, bilateral, symmetric, and predominantly high-frequency hearing deficits) are more likely to report difficulty in understanding speech than in hearing sounds. Evaluation with a portable audioscope, if available, is also recommended.

**Mouth:** The mouth is examined for bleeding or swollen gums, loose or broken teeth, fungal infections, and signs of cancer (eg, leukoplakia, erythroplakia, ulceration, mass). Findings may include

- Darkened teeth: Due to extrinsic stains and less translucent enamel, which occur with aging
- Fissures in the mouth and tongue and a tongue that sticks to the buccal mucosa: Due to xerostomia
- Erythematous, edematous gingiva that bleeds easily: Usually indicating a gingival or periodontal disorder
- Bad breath: Possibly indicating caries, periodontitis, another oral disorder, or sometimes a pulmonary disorder

The dorsal and ventral surfaces of the tongue are examined. Common age-related changes include varicose veins on the ventral surface, erythema migrans (geographic tongue), and atrophied papillae on the sides of the tongue. In edentulous patients, the tongue may enlarge to facilitate chewing; however, enlargement may also indicate amyloidosis or hypothyroidism. A smooth, painful tongue may indicate vitamin B₁₂ deficiency.

Dentures should be removed before the mouth is examined. Dentures increase risk of oral candidiasis and resorption of the alveolar ridges. Inflammation of the palatal mucosa and ulcers of the alveolar ridges may result from poorly fitting dentures.

The interior of the mouth is palpated. A swollen, firm, and tender parotid gland may indicate parotitis, particularly in dehydrated patients; pus may be expressed from Stensen's duct when bacterial parotitis is present. The infecting organisms are often staphylococci.

Painful, inflamed, fissured lesions at the lip commissures (angular cheilitis) may be noted in edentulous patients who do not wear dentures; these lesions are usually accompanied by a fungal infection.

**Temporomandibular joint:** This joint should be evaluated for degeneration (osteoarthritis), a common age-related change. The joint can degenerate as teeth are lost and compressive forces in the joint become excessive. Degeneration may be indicated by joint crepitus felt at the head of the condyle as
patients lower and raise their jaw, by painful jaw movements, or by both.

**Neck:** The thyroid gland, which is located low in the neck of elderly people, often beneath the sternum, is examined for enlargement and nodules.

Carotid bruits due to transmitted heart murmurs can be differentiated from those due to carotid artery stenosis by moving the stethoscope up the neck: A transmitted heart murmur becomes softer; the bruit of carotid artery stenosis becomes louder. Bruits due to carotid artery stenosis suggest systemic atherosclerosis. Whether asymptomatic patients with carotid bruits require evaluation or treatment for cerebrovascular disease is unclear.

The neck is checked for flexibility. Resistance to passive flexion, extension, and lateral rotation may indicate a cervical spine disorder. Resistance to flexion and extension can also occur in patients with meningitis, but unless meningitis is accompanied by a cervical spine disorder, the neck can be rotated passively from side to side without resistance.

**Chest and Back**

All areas of the lungs are examined by percussion and auscultation. Basilar rales may be heard in the lungs of healthy patients but should disappear after patients take a few deep breaths. The extent of respiratory excursions (movement of the diaphragm and ability to expand the chest) should be noted.

The back is examined for scoliosis and tenderness. Severe low back, hip, and leg pain with marked sacral tenderness may indicate spontaneous osteoporotic fractures of the sacrum, which can occur in elderly patients.

**Breasts:** In men and women, the breasts should be examined annually for irregularities and nodules. For women, monthly self-examinations are also recommended, as is annual screening mammography, especially for women who have a family history of breast cancer. If nipples are retracted, pressure should be applied around the nipples; pressure everts the nipples when retraction is due to aging but not when it is due to an underlying lesion.

**Heart:** Heart size can usually be assessed by palpating the apex. However, displacement caused by kyphoscoliosis may make assessment difficult.

Auscultation should be done systematically. In elderly patients, a systolic murmur most commonly indicates

- **Aortic valve sclerosis:** Typically, this murmur is not hemodynamically significant. It peaks early during systole and is rarely heard in the carotid arteries.

However, systolic murmurs may be due to other disorders, which should be identified:

- **Aortic valve stenosis:** This murmur, in contrast to that of aortic valve sclerosis, typically peaks later during systole, is transmitted to the carotid arteries, and is loud (greater than grade 2); the 2nd heart sound is dampened, pulse pressure is narrow, and the carotid up-stroke is slowed. However, in elderly patients, the murmur of aortic valve stenosis may be difficult to identify because it may be softer, a 2nd heart sound is rarely audible, and narrow pulse pressures are uncommon. Also, in many elderly patients with aortic valve stenosis, the carotid upstroke does not slow because vascular compliance is diminished.

- **Mitral regurgitation:** This murmur is usually loudest at the apex and radiates to the axilla.

- **Hypertrophic obstructive cardiomyopathy:** This murmur intensifies when patients do a Valsalva maneuver.

Fourth heart sounds are common among elderly people without evidence of a cardiovascular disorder and are commonly absent among elderly people with evidence of a cardiovascular disorder. Diastolic
murmurs are abnormal in people of any age. Unexplained and asymptomatic sinus bradycardia in apparently healthy elderly people may not be clinically important.

If new neurologic or cardiovascular symptoms develop in patients with a pacemaker, evaluation for variable heart sounds, murmurs, and pulses and for hypotension and heart failure is required. These symptoms and signs may be due to loss of atrioventricular synchrony.

**GI System**

The abdomen is palpated to check for weak abdominal muscles, which are common among elderly people and which may result in hernias. Most abdominal aortic aneurysms are palpable as a pulsatile mass; however, only their lateral width can be assessed during physical examination. In some patients (particularly thin ones), a normal aorta is palpable, but the vessel and pulsations do not extend laterally. The liver and spleen are palpated for enlargement. Frequency and quality of bowel sounds are checked, and the suprapubic area is percussed for tenderness, discomfort, and evidence of urinary retention.

The anorectal area is examined externally for fissures, hemorrhoids, and other lesions. Sensation and the anal wink reflex are tested. A digital rectal examination (DRE) to detect a mass, stricture, tenderness, or fecal impaction is done in men and women. Fecal occult blood testing is also done.

**Male GU System**

The prostate gland is palpated for nodules, tenderness, and consistency. Estimating prostate size by DRE is inaccurate, and size does not correlate with urethral obstruction; however, DRE provides a qualitative evaluation.

**Female Reproductive System**

Regular pelvic examinations, with a Pap-nicolaou (Pap) test every 2 to 3 yr until age 70, are recommended. At age 70, testing can be stopped if results of the previous 2 consecutive tests were normal. If women ≥ 70 have not had regular Pap tests, they should have at least 2 negative tests, 1 yr apart, before testing is stopped. Once Pap testing has been stopped, it is restarted only if new symptoms or signs of a possible disorder develop. If women have had a hysterectomy, Pap tests are required only if cervical tissue remains.

For pelvic examination, patients who lack hip mobility may lie on their left side. Postmenopausal reduction of estrogen leads to atrophy of the vaginal and urethral mucosa; the vaginal mucosa appears dry and lacks rugal folds. The ovaries should not be palpable; palpable ovaries suggest cancer. Patients should be examined for evidence of prolapse of the urethra, vagina, cervix, and uterus. They are asked to cough to check for urine leakage and intermittent prolapse.

**Musculoskeletal System**

Joints are examined for tenderness, swelling, subluxation, crepitus, warmth, redness, and other abnormalities, which may suggest a disorder:

- Heberden's nodes (bony overgrowths at the distal interphalangeal joints) or Bouchard's nodes (bony overgrowths at the proximal interphalangeal joints): Osteoarthritis
- Subluxation of the metacarpophalangeal joints with ulnar deviation of the fingers: Chronic RA
- Swan-neck deformity (hyperextension of the proximal interphalangeal joint with flexion of the distal interphalangeal joint) and boutonniere deformity (hyperextension of the distal interphalangeal joint with flexion of the proximal interphalangeal joint): RA

These deformities may interfere with functioning or usual activities.

Active and passive range of joint motion should be determined. The presence of contractures should be
noted. Variable resistance to passive manipulation of the extremities (gegenhalten) sometimes occurs with aging.

Feet

Diagnosis and treatment of foot problems, which become common with aging, help elderly people maintain their independence. Common age-related findings include hallux valgus, medial prominence of the 1st metatarsal head with lateral deviation and rotation of the big toe, and lateral deviation of the 5th metatarsal head. Hammer toe (hyperflexion of the proximal interphalangeal joint) and claw toe (hyperflexion of the proximal and distal interphalangeal toe joints) may interfere with functioning and daily activities. Toe deformities may result from years of wearing poorly fitting shoes or from RA, diabetes, or neurologic disorders (eg, Charcot-Marie-Tooth disease). Occasionally, foot problems indicate other systemic disorders (see Table 44-1 on p. 395).

Patients with foot problems should be referred to a podiatrist for regular evaluation and treatment.

Neurologic System

Neurologic examination for elderly patients is similar to that for any adult. However, nonneurologic disorders that are common among elderly people may complicate this examination. For example, visual and hearing deficits may impede evaluation of cranial nerves, and periarthritis (inflammation of tissues around a joint) in certain joints, especially shoulders and hips, may interfere with evaluation of motor function.

Signs detected during the examination must be considered in light of the patient's age, history, and other findings. Symmetric findings unaccompanied by functional loss and other neurologic symptoms and signs may be noted in elderly patients. Clinicians must decide whether these findings justify a detailed evaluation to check for a neurologic lesion. Patients should be reevaluated periodically for functional changes, asymmetry, and new symptoms.

Cranial nerves: Evaluation may be complex. Elderly people often have small pupils; their pupillary light reflex may be sluggish, and their pupillary mitotic response to near vision may be diminished. Upward gaze and, to a lesser extent, downward gaze are slightly limited. Eye movements, when tracking an examiner's finger during evaluation of visual fields, may appear jerky and irregular. Bell's phenomenon (reflex upward movement of the eyes during closure) is sometimes absent. These changes occur normally with aging.

In many elderly people, sense of smell is diminished because they have fewer olfactory neurons, have had numerous upper respiratory infections, or have chronic rhinitis. However, asymmetric loss (loss of smell in one nostril) is abnormal. Taste may be altered because the sense of smell is diminished or because patients take drugs that decrease salivation.

Visual and hearing deficits may result from abnormalities in the eyes and ears rather than in nerve pathways.

Motor function: Patients can be evaluated for tremor during handshaking and other simple activities. If tremor is detected, amplitude, rhythm, distribution, frequency, and time of occurrence (at rest, with action, or with intention) are noted.

Muscle strength: Elderly people, particularly those who do not do resistance training regularly, may appear weak during routine testing. For example, during the physical examination, the clinician may easily straighten a patient's elbow despite the patient's effort to sustain a contraction. If weakness is symmetric, does not bother the patient, and has not changed the patient's function or activity level, it is likely to be clinically insignificant. Increased muscle tone, measured by flexing and extending the elbow or knee, is a normal finding in elderly people; however, jerky movements during examination and cogwheel rigidity are abnormal.
Sarcopenia (a decrease in muscle mass) is a common age-related finding. It is insignificant unless accompanied by a decline or change in function (eg, patients can no longer rise from a chair without using chair arms). Sarcopenia affects the hand muscles (eg, interosseous and thenar muscles) in particular. Weak extensor muscles of the wrist, fingers, and thumb are common among patients who use wheelchairs because compression of the upper arm against the armrest injures the radial nerve. Arm function can be tested by having patients pick up an eating utensil or touch the back of their head with both hands.

**Coordination:** Motor reaction time and motor coordination are tested. Reaction time often increases with aging, partly because conduction of signals along peripheral nerves slows. Coordination decreases because of changes in central mechanisms, but this decrease is usually subtle and does not impair function.

**Gait and posture:** All components of gait should be assessed; they include initiation of walking; step length, height, symmetry, continuity, and cadence (rhythm); velocity (speed of walking); stride width; and walking posture (see Table 307-5). Sensation, musculoskeletal and motor control, and attention, which are necessary for independent, coordinated walking, must also be considered.

Normal age-related findings may include the following:

- Shorter steps, possibly because calf muscles are weak or because balance is poor
- Reduced gait velocity in patients > 70 because steps are shorter
- Increased time in double stance (when both feet are on the ground), which may be due to impaired balance or fear of falling
- Reduced motion in some joints (eg, ankle plantar flexion just before the back foot lifts off, pelvic motion in the frontal and transverse planes)
- Slight changes in walking posture (eg, greater downward pelvic rotation, possibly due to a combination of increased abdominal fat, abdominal muscle weakness, and tight hip flexor muscles; a slightly greater turn-out of the toes, possibly due to loss of hip internal rotation or to an attempt to increase lateral stability)

Aging has little effect on walking cadence or posture; typically, the elderly walk upright unless a disorder is present.

Overall postural control is evaluated using Romberg's test (patients stand with feet together and eyes closed). With aging, postural control is often impaired, and postural sway (movement in the anteroposterior plane when patients remain stationary and upright) may increase.

**Reflexes:** The deep tendon reflexes are checked. Aging usually has little effect on them. However, eliciting the Achilles tendon

[Table 307-5. Some Causes of Gait Dysfunction]

reflex may require special techniques (eg, testing while patients kneel with their feet over the edge of a bed and with their hands clasped). A diminished or absent reflex, present in nearly half of elderly patients, may be normal. It occurs because tendon elasticity decreases and nerve conduction in the tendon's long reflex arc slows. Asymmetric Achilles tendon reflexes may indicate sciatica.

Cortical release reflexes (known as pathologic reflexes), which include snout, sucking, and palmomental reflexes, occasionally occur in elderly patients who have no detectable brain disorders (eg, dementia). Babinski's reflex (extensor plantar response) in elderly patients is abnormal; it indicates an upper motor neuron lesion, often cervical spondylosis with partial cord compression.
**Sensation:** Evaluation of sensation includes touch (using a skin prick test), cortical sensory function, temperature sense, proprioception (joint position sense), and vibration sense testing. Aging has limited effects on sensation. Many elderly patients report numbness, especially in the feet. It may result from a decrease in size of fibers in the peripheral nerves, particularly the large fibers. Nonetheless, patients with numbness should be checked for peripheral neuropathies. In many patients, no cause of numbness can be identified.

Many elderly people lose vibratory sensation below the knees. It is lost because small vessels in the posterior column of the spinal cord change. However, proprioception, which is thought to use a similar pathway, is unaffected.

**Mental status:** A mental status examination is important (see also Sidebar 168-1 on p. 1588). Patients who are disturbed by such a test should be reassured that it is routine. The examiner must make sure that patients can hear; hearing deficits that prevent patients from hearing and understanding questions may be mistaken for cognitive dysfunction. Evaluating the mental status of patients who have a speech or language disorder (eg, mutism, dysarthria, speech apraxia, aphasia) can be difficult.

Orientation may be normal in many patients with dementia or other cognitive disorders. Thus, evaluation may require questions that identify abnormalities in consciousness, judgment, calculations, speech, language, praxis, executive function, or memory, as well as orientation. Abnormalities in these areas cannot be attributed solely to age, and if abnormalities are noted, further evaluation, including a formal test of mental status, is needed.

With aging, information processing and memory retrieval slow but are essentially un-impaired. With extra time and encouragement, patients do such tasks satisfactorily (unless a neurologic abnormality is present).

**Nutritional Status**

Aging changes the interpretation of many measurements that reflect nutritional status in younger people. For example, aging can alter height. Weight changes can reflect alterations in nutrition, fluid balance, or both. The proportion of lean body mass and body fat content changes. Despite these age-related changes, body mass index (BMI) is still useful in elderly patients. If abnormalities in the nutrition history (eg, weight loss, suspected deficiencies in essential nutrients) or BMI are identified, thorough nutritional evaluation, including laboratory measurements, is indicated.

**Key Points**

- Valuable information about a patient's function can be gained by observing the patient.
- Physical examination should include all systems, particularly mental status, and may require 2 sessions.

**Comprehensive Geriatric Assessment**

Comprehensive geriatric assessment is a multidimensional process designed to assess the functional ability, health (physical, cognitive, and mental), and socioenvironmental situation of elderly people.

The comprehensive geriatric assessment specifically and thoroughly evaluates functional and cognitive abilities, social support, financial status, and environmental factors as well as physical and mental health (see Table 307-6). Ideally, a regular examination of elderly patients incorporates many aspects of the comprehensive geriatric assessment, making the 2 approaches very similar. Assessment results are coupled with sustained individually tailored interventions (eg, rehabilitation, education, counseling, supportive services).

The cost of geriatric assessment limits its use. Thus, this assessment may be used mainly in high-risk elderly patients, such as the frail or chronically ill (eg, identified via mailed health questionnaires or
interviews in the home or meeting places). Family members may also request a referral for geriatric assessment.

Assessment can have the following benefits:

- Improved care and clinical outcomes

[Table 307-6, A Geriatric Assessment Instrument]

- Greater diagnostic accuracy

- Improved functional and mental status

- Reduced mortality

- Decreased use of nursing homes and acute care hospitals

- Greater satisfaction with care

If elderly patients are relatively healthy, a standard medical evaluation may be appropriate.

Comprehensive geriatric assessment is most successful when done by a geriatric interdisciplinary team (typically, a geriatrician, nurse, social worker, and pharmacist). Usually, assessments are done in an outpatient setting. However, patients with physical or mental impairments and chronically ill patients may require inpatient assessment.

Assessment Domains

The principal domains assessed are

- **Functional ability**: Ability to do activities of daily living (ADLs) and instrumental ADLs (IADLs) are assessed. ADLs include eating, dressing, bathing, transferring between the bed and a chair, using the toilet, and controlling bladder and bowel. IADLs enable people to live independently and include preparing meals, doing housework, taking drugs, going on errands, managing finances, and using a telephone.

- **Physical health**: History and physical examination should include problems common among the elderly (eg, problems with vision, hearing, continence, gait, and balance).

- **Cognition and mental health**: Several validated screening tests for cognitive dysfunction (eg, mental status examination—see Sidebar 168-1 on p. 1588) and for depression (eg, Geriatric Depression Scale [see Table 307-7], Hamilton Depression Scale) can be used.

- **Socioenvironmental situation**: The patient's social interaction network, available social support resources, and special needs and the safety and convenience of the patient's environment are determined, often by a nurse or social worker. Such factors influence the treatment approach used. A checklist can be used to assess home safety.

Standardized instruments make evaluation of these domains more reliable and efficient (see Table 307-6). They also facilitate communication of clinical information among health care practitioners and monitoring of changes in the patient’s condition over time.

Unusual Presentations of Illness in the Elderly

In the elderly, many common conditions can exist without their characteristic features. Instead, the elderly may have ≥ 1 nonspecific geriatric syndromes (eg, acute confusion, dizziness, syncope, falling, weight loss, incontinence). These syndromes result from multiple disorders and impairments; nonetheless,
patients may improve when only some of the precipitating factors are corrected. An even better strategy is to identify risk factors for these syndromes and correct as many as possible, thus reducing the likelihood of the syndrome's developing at all.

Although virtually any illness or drug intoxication can cause geriatric syndromes, the following disorders are especially likely to trigger one or more of them, sometimes instead of causing the typical symptoms and signs.

**Acute bowel infarction** may be indicated by acute confusion. Abdominal pain and tenderness may be absent.

**Appendicitis** pain tends to begin in the right lower quadrant rather than periumbilically. Eventually, pain may be diffuse in the abdomen rather than localized to the right lower quadrant. However, tenderness in this quadrant is a significant early sign.

**Bacteremia** causes a low-grade (at least) fever in most elderly patients, although fever may be absent. The source of bacteremia may be difficult to identify. Elderly patients may have nonspecific manifestations (eg, general malaise, anorexia, night sweats, unexplained change in mental status).

**Biliary disorders** may result in nonspecific mental and physical deterioration (eg, malaise, confusion, loss of mobility) without jaundice, fever, or abdominal pain. Abnormal liver function test results may be the only indication.

**Heart failure** may cause confusion, agitation, anorexia, weakness, insomnia, fatigue, weight loss, or lethargy; patients may not report dyspnea. Orthopnea may cause nocturnal agitation in patients who also have dementia. Peripheral edema is less specific as a sign of heart failure in elderly than in younger patients. In bedbound patients, edema may occur in the sacral area rather than in the lower extremities.

**Hyperparathyroidism** may cause nonspecific symptoms: fatigue, cognitive dysfunction, emotional instability, anorexia, constipation, and hypertension. Characteristic symptoms are often absent.

**Hyperthyroidism** may not cause the characteristic signs (eg, eye signs, enlarged thyroid gland). Instead, symptoms and signs may be subtle and may include tachycardia, weight loss, fatigue, weakness, palpitations, tremor, atrial fibrillation, and heart failure. Patients may appear apathetic rather than hyperkinetic.

**Hypothyroidism** may manifest subtly in elderly patients. The most common symptoms are nonspecific (eg, fatigue, weakness, falling). Anorexia, weight loss, and arthralgias may occur. Cold intolerance, weight gain, depression, paresthesias, hair loss, and muscle cramps are less common than among younger patients; cognitive dysfunction is more common. The most specific sign—delayed tendon reflex relaxation—may not be detectable in elderly patients because of decreased amplitude or absent reflexes.

**Meningitis** may cause fever and a change in mental status without symptoms of meningeal irritation (eg, headache, nuchal rigidity).

**MI** may manifest as diaphoresis, dyspnea, epigastric distress, syncope, weakness, vomiting, or confusion rather than as chest pain. After the onset of chest pain or other presenting symptoms of MI, elderly patients tend to delay longer than younger patients in seeking medical assistance.

**Peptic ulcer disease** may not cause characteristic ulcer symptoms; pain may be absent, nonspecific, or masked by NSAIDs. Dyspepsia (usually epigastric discomfort with bloating, nausea, or early satiety) is more common among elderly than among younger patients. Elderly patients have more frequent, more severe GI bleeding, which may be painless. Slow, unrecognized blood loss may occur, resulting in severe anemia.

**Pneumonia** may be indicated by malaise, anorexia, or confusion. Tachycardia and tachypnea are

[Table 307-7: Geriatric Depression Scale (Short Form)]

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**Table 307-7: Geriatric Depression Scale (Short Form)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel restless or fidgety</td>
<td>0-3</td>
</tr>
<tr>
<td>2. I feel empty inside</td>
<td>0-3</td>
</tr>
<tr>
<td>3. I have trouble sleeping</td>
<td>0-3</td>
</tr>
<tr>
<td>4. I have trouble concentratino</td>
<td>0-3</td>
</tr>
<tr>
<td>5. I have difficulty concentrating</td>
<td>0-3</td>
</tr>
<tr>
<td>6. I can't make decisions</td>
<td>0-3</td>
</tr>
<tr>
<td>7. I am dependent on others</td>
<td>0-3</td>
</tr>
<tr>
<td>8. I am irritable</td>
<td>0-3</td>
</tr>
<tr>
<td>9. I am sad</td>
<td>0-3</td>
</tr>
<tr>
<td>10. I have no interest in things</td>
<td>0-3</td>
</tr>
<tr>
<td>11. I feel worthless</td>
<td>0-3</td>
</tr>
<tr>
<td>12. I have a hard time getting going</td>
<td>0-3</td>
</tr>
<tr>
<td>13. I feel I lack energy</td>
<td>0-3</td>
</tr>
<tr>
<td>14. I often feel that things are not going my way</td>
<td>0-3</td>
</tr>
<tr>
<td>15. I have a hard time finding things</td>
<td>0-3</td>
</tr>
<tr>
<td>16. I feel I am urinating more often</td>
<td>0-3</td>
</tr>
<tr>
<td>17. I feel I have food on my mind too much</td>
<td>0-3</td>
</tr>
<tr>
<td>18. I feel I have trouble breathing</td>
<td>0-3</td>
</tr>
<tr>
<td>19. I feel I am quite or eccentric</td>
<td>0-3</td>
</tr>
<tr>
<td>20. I feel I am going to make a mess</td>
<td>0-3</td>
</tr>
</tbody>
</table>

**Total Score:** 0-20
common, but fever may be absent. Coughing may be mild and without copious, purulent sputum, especially in dehydrated patients.

**TB** may manifest differently in elderly patients with coexisting disorders. Symptoms may be nonspecific (e.g., fever, weakness, confusion, anorexia). Pulmonary TB may manifest with fewer respiratory symptoms (e.g., cough, excessive sputum production, hemoptysis) than in younger patients.

**UTIs** may be present in afebrile elderly patients. These patients may not report dysuria, frequency, or urgency but may experience dizziness, confusion, anorexia, fatigue, or weakness.

**Other problems** that manifest differently in the elderly include alcohol abuse, adverse drug effects, alcohol abuse, depression, pulmonary embolism, systemic infections, and unstable angina.
Chapter 308. Drug Therapy in the Elderly

Introduction

Prevalence of prescription drug use among ambulatory adults increases substantially with age. Among people ≥ 65, 90% use at least 1 drug per week, > 40% use at least 5 different drugs per week, and 12% use ≥ 10 different drugs per week. Women take more drugs, particularly psychoactive and arthritis drugs. Drug use is greatest among the frail elderly, hospitalized patients, and nursing home residents; typically, a nursing home resident is given 7 to 8 different drugs on a regular basis.

Providing safe, effective drug therapy for the elderly is challenging for many reasons:

• They use more drugs than any other age group, increasing risk of adverse effects and making adherence difficult.

• They are more likely to have chronic disorders that affect drug response.

• Their physiologic reserves are reduced and can be further reduced by acute and chronic disorders.

• Aging alters pharmacodynamics and pharmacokinetics.

• They may be less able to obtain or afford drugs.

There are 2 main approaches to optimizing drug therapy in the elderly:

• Using appropriate drugs as indicated to maximize effectiveness

• Avoiding adverse drug effects

Because the risk of adverse drug effects is high, overprescribing has been targeted as a major problem in the treatment of the elderly. However, underprescribing appropriate drugs must also be avoided.

Pharmacokinetics

Pharmacokinetics (see p. 3172) is best defined as what the body does to the drug; it includes absorption, distribution across body compartments, metabolism, and excretion.

With aging, the metabolism and excretion of many drugs decrease, requiring that doses of some drugs be adjusted. Toxicity may develop slowly because levels of chronically used drugs tend to increase for about 5 to 6 half-lives. For example, certain benzodiazepines (diazepam, flurazepam, chlordiazepoxide) have half-lives of up to 96 h in many elderly patients; signs of toxicity may not appear until days or weeks after therapy is started.

Absorption: Despite an age-related decrease in small-bowel surface area, slowed gastric emptying, and an increase in gastric pH, changes in drug absorption tend to be clinically inconsequential for most drugs.

Distribution: With aging, body fat generally increases, and total body water decreases. Increased fat increases the volume of distribution for highly lipophilic drugs (eg, diazepam) and may increase their elimination half-lives.

Serum albumin decreases and α1-acid glycoprotein increases with age, but the clinical effect of these changes on serum drug binding is unclear. In patients with an acute disorder or undernutrition, rapid reductions in serum albumin may enhance drug effects because serum levels of unbound drug may increase (eg, with phenytoin or warfarin).

Hepatic metabolism: Overall hepatic metabolism of many drugs through the cytochrome P-450 enzyme system decreases with age. For drugs with decreased hepatic metabolism (see Table 308-1), clearance typically decreases 30 to 40%. Theoretically, maintenance drug doses should be
Hepatic clearance of drugs with multistage metabolism (nonsynthetic and synthetic reactions) is more likely to be prolonged in the elderly (see also Metabolism on p. 3177). Usually, age does not greatly affect clearance of drugs that are metabolized by conjugation, typically with glucuronic acid.

Renal elimination: After age 30, creatinine clearance decreases an average of 8 mL/min/1.73 m²/decade; however, the age-related decrease varies substantially from person to person. Serum creatinine levels often remain within normal limits despite a decrease in GFR because the elderly generally have less muscle mass and thus produce less creatinine. Decreases in tubular function parallel those in glomerular function.

These changes decrease renal elimination of some drugs (see Table 308-1). Clinical implications depend on the extent that renal elimination contributes to total systemic elimination and on the drug's therapeutic index.

Table 308-1. Effect of Aging on Drug Metabolism* and Elimination

(ratio of maximum tolerated dose to minimum effective dose). Creatinine clearance (measured or estimated using computer programs or a formula, such as Cockcroft-Gault—see p. 2313) is used to guide drug dosing. Because renal function is dynamic, maintenance doses of drugs should be adjusted when patients become ill or dehydrated or have recently recovered from dehydration.

Pharmacodynamics

Pharmacodynamics is defined as what the drug does to the body or the response of the body to the drug; it is affected by receptor binding, postreceptor effects, and chemical interactions (see p. 3181). In the elderly, the effects of similar drug concentrations at the site of action (sensitivity) may be greater or smaller than those in younger people (see Table 308-2). Differences may be due to changes in drug-receptor interaction, in post-receptor events, or in adaptive homeostatic responses and, among frail patients, are often due to pathologic changes in organs.

Elderly patients are particularly sensitive to anticholinergic drug effects. Many drugs (eg, tricyclic antidepressants, most nonselective antihistamines, some antipsychotic drugs, antiparkinsonian drugs with atropine-like activity, many OTC hypnotics and cold preparations) are anticholinergic. The elderly, most notably those with dementia, are particularly prone to CNS adverse effects of such drugs and may become more confused and drowsy. Anticholinergic drugs also commonly cause constipation, urinary retention (especially in elderly men with benign prostatic hyperplasia), blurred vision, orthostatic hypotension, and dry mouth. Even in low doses, these drugs can increase risk of heat-stroke by inhibiting diaphoresis.

Drug-Related Problems

Drug-related problems include

• Adverse effects

• Ineffectiveness

Adverse drug effects are effects that are unwanted, uncomfortable, or dangerous. Common examples are oversedation, confusion, hallucinations, falls, and bleeding. Among ambulatory people ≥ 65, adverse drug effects occur at a rate of about 50 events per 1000 person-years. Hospitalization rates due to adverse drug effects are 4 times higher in elderly patients (≈ 17%) than in younger patients (4%).

Reasons for Drug-Related Problems
Adverse drug effects can occur in any patient, but certain characteristics of the elderly make them more susceptible. For example, the elderly often take many drugs (polypharmacy) and have age-related changes in pharmacodynamics and pharmacokinetics; both increase the risk of adverse effects.

At any age, adverse drug effects may occur when drugs are prescribed and taken appropriately; eg, new-onset allergic reactions are not predictable or preventable. However, adverse effects are thought to be preventable in almost 90% of cases in the elderly (compared with only 24% in younger patients). Certain drug classes are commonly involved. In nursing home patients, preventable adverse drug effects commonly result from use of atypical antipsychotics, warfarin, antidepressants, and sedative-hypnotics. In community-dwelling elderly, the most common causes are hypoglycemic drugs, NSAIDs, and benzodiazepines.

In the elderly, a number of common reasons for adverse drug effects, ineffectiveness, or both are preventable (see Table 308-3). Several of these reasons involve inadequate communication with patients or among health care practitioners (particularly during health care transitions).

**Inappropriate drugs:** A drug is inappropriate if its potential for harm is greater than its potential for benefit. Inappropriate use of a drug may involve

- Choice of an unsuitable drug, dose, frequency of dosing, or duration of therapy
- Duplication of therapy
- Failure to consider drug interactions and correct indications for a drug
- Appropriate drugs that are mistakenly continued once an acute condition resolves (as may happen when patients move from one health care setting to another)

Adverse effects of inappropriate drugs account for about 3% of emergency department visits for patients ≥ 65; anticoagulants, anti-platelet drugs, drugs used to treat diabetes, and drugs with a narrow therapeutic index account for about half, and 3 drugs—warfarin, digoxin, and insulin—account for about one third. Thus, some classes of drugs are of special concern in the elderly (see p. 3098). Some are so problematic that they should be avoided in the elderly; others can be used with increased caution. The Beers Criteria (see Table 308-5) lists inappropriate drugs for the elderly by drug class; other similar lists are available. However, there is no similar list of drugs that should be used in the elderly; clinicians must weigh benefits and risks of therapy in each patient.

Despite the Beers and other criteria, inappropriate drugs are still being prescribed for the elderly; typically, about 20% of community-dwelling elderly use at least one inappropriate drug. In such patients, risk of hospitalization is increased. In nursing home patients, inappropriate use increases risk of hospitalization and death. In one study of hospitalized patients, 27.5% were given an inappropriate drug.

Some inappropriate drugs are available OTC; thus, clinicians should specifically question patients about use of OTC drugs and tell patients about the potential problems such drugs can cause.

The elderly are often given drugs (typically, analgesics, H₂ blockers, hypnotics, or laxatives) for minor symptoms (including adverse

Table 308-2, Effect of Aging on Drug Response]

Table 308-3, Preventable Causes of Drug-Related Problems]

effects of other drugs) that may be better treated nonpharmacologically. Using such drugs is often inappropriate; benefit is low, and use increases cost and may lead to toxicity.

Solving the problem of inappropriate use in the elderly requires more than avoiding a short list of drugs.
and noting drug categories of concern. A patient’s entire drug regimen should also be assessed to
determine its potential benefit vs harm.

**Overdosage:** An excessive dose of an appropriate drug may be prescribed for elderly patients if the
prescriber does not consider age-related changes that affect pharmacokinetics (see p. 3090) and
pharmacodynamics (see p. 3091). Doses of renally cleared drugs should be adjusted in patients with
renal impairment, which is common among the elderly.

Generally, doses should be lower in the elderly, although dose requirements vary considerably from
person to person. Typically, starting doses of about one third to one half the usual adult dose are
indicated when a drug has a low therapeutic index or when another condition may be exacerbated by a
drug. The dose is then titrated upward as tolerated to the desired effect. When the dose is increased,
patients should be evaluated for adverse effects, and drug levels should be monitored when possible.

Overdosage can also occur when drug interactions (see p. 3095) increase the amount of drug available
or when different practitioners prescribe a drug and are unaware that another practitioner prescribed the
same or a similar drug.

**Underprescribing:** Appropriate drugs may be underprescribed—not used for maximum effectiveness.
Underprescribing may increase morbidity and mortality and reduce quality of life. Clinicians should use
adequate drug doses and, when indicated, multidrug regimens.

Drugs that are often underprescribed in the elderly include those used to treat depression, Alzheimer’s
disease, pain (eg, opioids), heart failure, post-MI (β-blockers), atrial fibrillation (warfarin), hypertension,
and incontinence and drugs to prevent glaucoma, influenza, and pneumococcal infection.

• **Opioids:** Clinicians are often reluctant to prescribe opioids for elderly patients with cancer or other
types of chronic pain, typically because of concerns about adverse drug effects (eg, sedation,
constipation, delirium) and development of dependence. When opioids are prescribed, the doses are
often inadequate. Underprescribing opioids may mean that some elderly patients have needless pain
and discomfort; elderly patients are more likely to report inadequate pain management than younger
adults.

• **β-Blockers:** In patients with a history of MI, even in elderly patients at high risk of complications (eg,
those with heart failure, pulmonary disorders, or diabetes mellitus), these drugs reduce mortality rates.

• **Antihypertensives:** Guidelines for treating hypertension (including isolated systolic hypertension) in
the elderly are available, and treatment appears to be beneficial (reducing risk of stroke and major
cardiovascular events). Nonetheless, studies indicate that hypertension is often not controlled in elderly
patients.

• **Drugs for Alzheimer’s disease:** Acetylcholinesterase inhibitors and NMDA (N-methyl-D-aspartate)
antagonists have been shown to benefit patients with Alzheimer’s disease. The amount of benefit is
unclear, but patients and family members should be given the opportunity to make an informed decision
about their use.

In elderly patients with a chronic disorder, acute or unrelated disorders may be under-treated (eg,
hypercholesterolemia may be untreated in patients with emphysema). Clinicians may withhold these
treatments because of concern about increasing the risk of adverse effects. Clinicians may think that
treatment of the primary problem is all patients can or want to handle or that patients cannot afford the
additional drugs.

**Drug-disease interactions:** A drug given to treat one disease can exacerbate another disease
regardless of patient age, but such interactions are of special concern in the elderly, who are more likely
to have multiple disorders. Distinguishing often subtle adverse drug effects from the effects of disease is
difficult (see
Table 308-4) and may lead to a prescribing cascade.
A **prescribing cascade** occurs when the adverse effect of a drug is misinterpreted as a symptom or sign of a new disorder and a new drug is prescribed to treat it. The new, unnecessary drug may cause additional adverse effects, which may then be misinterpreted as yet another disorder and treated unnecessarily, and so on.

Many drugs have adverse effects that resemble symptoms of disorders common among the elderly or changes due to aging. The following are examples:

- **Antipsychotics** may cause symptoms that resemble Parkinson's disease. In elderly patients, these symptoms may be diagnosed as Parkinson's disease and treated, possibly leading to adverse effects from the antiparkinson drugs (eg, orthostatic hypotension, delirium).

- **Cholinesterase inhibitors** (eg, donepezil) may be prescribed for patients with dementia. These drugs may cause diarrhea or urinary incontinence. Patients may then be prescribed an anticholinergic drug (eg, oxybutynin). Thus, an unnecessary drug is added, increasing the risk of adverse drug effects and drug-drug interactions. A better strategy is to reduce the dose of the cholinesterase inhibitor or consider a different treatment for dementia (eg, memantine) with a different mechanism of action.

In elderly patients, prescribers should always consider the possibility that a new symptom or sign is due to drug therapy.

**Drug-drug interactions:** Because the elderly often take many drugs, they are particularly vulnerable to drug-drug interactions. The elderly also frequently use medicinal herbs and other dietary supplements (see p. 3421) and may not tell their physician. Medicinal herbs can interact with prescribed drugs and lead to adverse effects. For example, ginkgo bilob extract taken with warfarin can increase risk of bleeding, and St. John's wort taken with an SSRI can increase risk of serotonin syndrome. Therefore, physicians should ask patients specifically about dietary supplements, including medicinal herbs and vitamin supplements.

Drug-drug interactions in the elderly differ little from those in the general population. However, induction of cytochrome P-450 drug metabolism by certain drugs (eg, dichloralphenazone, glutethimide, rifampin) may be decreased in the elderly; therefore, the change (increase) in drug metabolism may be less pronounced in the elderly. Concurrent use of ≥ 1 drug with similar toxicity can increase risk or severity of adverse effects.

**Inadequate monitoring:** Monitoring drug use involves

- Documenting the indication for a new drug
- Keeping a current list of drugs used by the patient in medical records
- Monitoring for achievement of therapeutic goals and other responses to new drugs
- Monitoring necessary laboratory tests for efficacy or adverse effects
- Periodically reviewing drugs for continued need

Such measures are especially important for elderly patients. Lack of close monitoring, especially after new drugs are prescribed, increases risk of adverse effects and ineffectiveness. Criteria to facilitate monitoring have been developed by the Health Care Financing Administration expert consensus panel as part of drug utilization review criteria. The criteria focus on inappropriate dosage or duration of therapy, duplication of therapy, and possible drug-drug interactions.

**Poor communication:** Poor communication of medical information at transition points (from one health care setting to another) causes up to 50% of all drug errors and

[Table 308-4, Drug-Disease Interactions in the Elderly]
up to 20% of adverse drug effects in the hospital. When patients are discharged from the hospital, drug
regimens that were started and needed only in the hospital (eg, benzodiazepines, stool softeners,
antacids) may be unnecessarily continued by another prescriber, who is reluctant to communicate with
the previous prescriber. Conversely, at admission to a health care facility, lack of communication may
result in unintentional omission of a necessary maintenance drug.

**Lack of patient adherence:** Drug effectiveness is often compromised by lack of patient adherence
among the ambulatory elderly. Adherence is affected by many factors but not by age per se. Up to half of
elderly patients do not take drugs as directed, usually taking less than prescribed (underadherence).
Causes are similar to those for younger adults (see p. 3166). In addition, the following contribute:

- Financial and physical constraints, which may make purchasing drugs difficult
- Dementia, which may make taking drugs as instructed difficult
- Use of multiple drugs
- Use of drugs that must be taken several times a day
- Lack of understanding about what a drug is intended to do

A regimen using too frequent dosing, multiple drugs, or both may be too complicated for patients to follow.
Clinicians should assess patients’ ability to adhere to a drug regimen (eg, dexterity, hand strength,
cognition, vision) and try to accommodate their limitations—eg, by arranging for or recommending easy-
access containers, drug labels and instructions in large type, containers equipped with reminder alarms,
containers filled based on daily drug needs, or reminder telephone calls. Pharmacists and nurses may
help by providing education and reviewing prescription instructions with elderly patients. Pharmacists may
be able to identify a problem by noting whether patients obtain refills on schedule or whether a
prescription seems illogical or incorrect.

**Prevention**

**Before starting a new drug:** To reduce the risk of adverse drug effects in the elderly, clinicians should
do the following before starting a new drug:

- Consider nondrug treatment
- Document the indication for each new drug (to avoid using unnecessary drugs)
- Consider age-related changes in pharmacokinetics and pharmacodynamics and their effect on dosing
  requirements
- Choose the safest possible alternative (eg, for noninflammatory arthritis, acetaminophen instead of an
  NSAID)
- Check for potential drug-disease and drug-drug interactions
- Start with a low dose
- Use the fewest drugs necessary
- Note coexisting disorders and their likelihood of contributing to adverse drug effects
- Explain the uses and adverse effects of each drug
- Provide clear instructions to patients about how to take their drugs (including generic and brand names,
  spelling of each drug name, indication for each drug, and explanation of formulations that contain more
  than one drug)
• Anticipate confusion due to sound-alike drug names and pointing out any names that could be confused (eg, Glucophage and Glucovance)

**After starting a drug:** The following should be done after starting a drug:

• Assume a new symptom may be drug-related until proved otherwise (to prevent a prescribing cascade)

• Monitor patients for signs of adverse drug effects, including measuring drug levels and doing other laboratory tests as necessary

• Document the response to therapy and increase doses as necessary to achieve the desired effect

**Ongoing:** The following should be ongoing:

• Keep a current list of drugs (including OTC and dietary supplements) and periodically review it

• Evaluate the adverse effect profile for each drug

• Encourage patients to be responsible for and involved in adherence to their drug regimen

• At each move to another health care setting, review the drug list with the patient or a family member

• Use multidisciplinary interventions, including a pharmacist, as patients move from one health care setting to another

• Ensure clear, correct, and complete transfer of information when patients move from one health care setting to another

**Medication reconciliation** is a process that helps ensure transfer of information about drug regimens at any transition point in the health care system. The process includes identifying and listing all drugs patients are taking (name, dose, frequency, route) and comparing the resulting list with the physician's orders at a transition point. Medication reconciliation should occur at each move (admission, transfer, and discharge).

**Computerized physician ordering programs** can alert clinicians to potential problems (eg, allergy, need for reduced dosage in patients with impaired renal function, drug-drug interactions). These programs can also cue clinicians to monitor certain patients closely for adverse drug effects.

**Drug Categories of Concern**

Some drug categories (eg, analgesics, anticoagulants, antihypertensives, antiparkinsonian drugs, diuretics, hypoglycemic drugs, psychoactive drugs) pose special risks for elderly patients. Some, although reasonable for use in younger adults, are so risky as to be considered inappropriate for the elderly. The Beers Criteria are most commonly used to identify such inappropriate drugs (see **Table 308-5**). The Zhan expert panel further categorized some inappropriate drugs from the Beers Criteria into 3 groups:

• Always to be avoided

• Rarely appropriate

• Sometimes indicated but often misused

**Analgesics:** NSAIDs are used by > 30% of people aged 65 to 89, and half of all NSAID prescriptions are for people > 60. Several NSAIDs are available without prescription.

The elderly may be prone to adverse effects of these drugs, and adverse effects may be more severe because of the following:
• NSAIDs are highly soluble in lipids, and because adipose tissue increases with age, distribution of the drugs is extensive.

• Plasma protein is often decreased, resulting in higher levels of unbound drug and exaggerated pharmacologic effects.

• Renal function is reduced in many of the elderly, resulting in decreased renal clearance and higher drug levels.

Serious adverse effects include peptic ulceration and upper GI bleeding; risk is increased when an NSAID is begun and when dose is increased. Risk of upper GI bleeding increases when NSAIDs are given with warfarin, aspirin, or other antiplatelet drugs (eg, clopidogrel). NSAIDs may increase risk of cardiovascular events and can cause fluid retention and, rarely, nephropathy. NSAIDs can also increase BP; this effect may be unrecognized and lead to intensification of antihypertensive treatment (a prescribing cascade). Thus, clinicians should keep this effect in mind when BP increases in elderly patients and ask them about their use of NSAIDs, particularly OTC NSAIDs.

Selective COX-2 (cyclooxygenase-2) inhibitors (coxibs) cause less GI irritation and platelet inhibition than other NSAIDs. Nonetheless, coxibs have a risk of GI bleeding, especially for patients taking warfarin or aspirin (even at a low dose) and for those who have had GI events. Coxibs, as a class, appear to increase risk of cardiovascular events, but risk may vary by drug; they should be used cautiously. Coxibs have renal effects comparable to those of other NSAIDs.

Lower-risk alternatives (eg, acetaminophen) should be used when possible. If NSAIDs are used in the elderly, the lowest effective dose should be used, and continued need should be reviewed frequently. If NSAIDs are used long-term, serum creatinine and BP should be monitored closely, especially in patients with other risk factors (eg, heart failure, renal impairment, cirrhosis with ascites, volume depletion, diuretic use).

Anticoagulants: Aging may increase sensitivity to the anticoagulant effect of warfarin. Careful dosing and scrupulous monitoring can largely overcome the increased risk of bleeding in elderly patients taking warfarin. Also, because drug interactions with warfarin are common, closer monitoring is necessary when new drugs are added or old ones are stopped; computer drug interaction programs should be consulted if patients take multiple drugs.

Antidepressants: Tricyclic antidepressants are effective but should rarely be used in the elderly. SSRIs and mixed serotonin/dopamine reuptake inhibitors are as effective as tricyclic antidepressants and cause less toxicity; however, there are some concerns about some of these drugs:

• Fluoxetine: A possible disadvantage is the long elimination half-life, especially of its active metabolite.

• Paroxetine: This drug is more sedating than other SSRIs, has anticholinergic effects, and, like some other SSRIs, can inhibit hepatic cytochrome P-450 2D6 enzyme activity, possibly impairing the metabolism of several drugs, including some antipsychotics, antiarrhythmics, and tricyclic anti-depressants.

• Sertraline: This drug is more activating; diarrhea is a common adverse effect.

Doses of these drugs should be reduced by up to 50%. Many SSRIs are available, but data on their use in the elderly are sparse.

Antihyperglycemics: Doses of antihyperglycemics should be titrated carefully in patients with diabetes mellitus. Risk of hypoglycemia due to sulfonylureas may increase with age. Chlorpropamide is not recommended because elderly patients are at increased risk of hyponatremia due to the syndrome of inappropriate antiuretic hormone secretion (SIADH) and because the drug's long duration of action is dangerous if adverse effects or hypoglycemia occurs. Risk of hypoglycemia is greater with glyburide than...
with other oral anti-hyperglycemics because like chlorpropamide, it is eliminated by the kidneys, and clearance can be reduced when renal function is impaired.

Metformin, a biguanide excreted by the kidneys, increases peripheral tissue sensitivity to insulin and can be effective given alone or with sulfonylureas. Risk of lactic acidosis, a rare but serious complication, increases with degree of renal impairment and with patient age. Heart failure is a contraindication.

**Antihypertensives:** In many elderly patients, lower starting doses of antihypertensives may be necessary to reduce risk of adverse effects; however, for most elderly patients with hypertension, achieving BP goals requires standard doses and multidrug therapy. Initially, a thiazide-type diuretic is usually given alone or with one of the other classes shown to be beneficial (ACE inhibitors, angiotensin II receptor blockers, β-blockers, Ca channel blockers). Short-acting dihydropyridines (e.g., nifedipine) may increase mortality risk and should not be used. Sitting and standing BP can be monitored, particularly when multiple antihypertensives are used, to check for orthostatic hypotension, which may increase risk of falls and fractures.

**Antiparkinsonian drugs:** Levodopa clearance is reduced in elderly patients, who are also more susceptible to the drug's adverse effects, particularly orthostatic hypotension and confusion. Therefore, elderly patients should be given a lower starting dose of levodopa and carefully monitored for adverse effects (see also p. 1767). Patients who become confused while taking levodopa may also not tolerate newer dopamine agonists (e.g., pramipexole, ropinirole). Because elderly patients with parkinsonism may be cognitively impaired, anticholinergic drugs should be avoided.

**Antipsychotics:** In nonpsychotic, agitated patients, antipsychotics control symptoms only marginally better than placebos and can have severe adverse effects. Antipsychotics should be reserved for psychosis.

When an antipsychotic is used, the starting dose should be about one quarter the usual starting adult dose and should be increased gradually. Clinical trial data relating to dosing, efficacy, and safety of these drugs in the elderly are limited.

Antipsychotics can reduce paranoia but may worsen confusion (see also p. 1562). Elderly patients, especially women, are at increased risk of tardive dyskinesia, which is often irreversible. Sedation, orthostatic hypotension, anticholinergic effects, and akathisia (subjective motor restlessness) can occur in up to 20% of elderly patients taking an antipsychotic, and drug-induced parkinsonism can persist for up to 6 to 9 mo after the drug is stopped.

The FDA has issued a warning regarding the use of 2nd-generation (atypical) antipsychotics, once thought to be safer, in the treatment of behavioral disorders in elderly patients with dementia; a review of placebo-controlled studies has shown a higher mortality rate associated with their use. Extrapyramidal dysfunction can develop when 2nd-generation antipsychotics (e.g., olanzapine, quetiapine, risperidone) are used, especially at higher doses. Risks and benefits of using an antipsychotic should be discussed with the patient or the person responsible for the patient's care.

**Anxiolytics and hypnotics:** Treatable causes of insomnia should be sought and managed before using hypnotics (see also p. 1707). Nonpharmacologic measures and sleep hygiene (e.g., avoiding caffeinated beverages, limiting daytime napping, modifying bedtime) should be tried first. If they are ineffective, nonbenzodiazepine hypnotics (e.g., the imidazopyridines, alpidem and zolpidem) are options. These drugs bind mainly to a benzodiazepine receptor subtype. Imidazopyridines disturb the sleep pattern less than benzodiazepines and have a more rapid onset, fewer rebound effects, fewer next-day effects, and less potential for dependence. Short- or intermediate-acting benzodiazepines with half-lives of < 24 h (e.g., alprazolam, lorazepam, oxazepam, temazepam) are preferable to long-acting benzodiazepines but may have adverse effects, including those that lead to falls and fractures.

Longer-acting benzodiazepines (e.g., clonazepam, diazepam, flurazepam) should be avoided because they
have active metabolites, are likely to accumulate, and have adverse effects (eg, drowsiness, impaired memory, impaired balance leading to falls and fractures).

Duration of anxiolytic or hypnotic therapy should be limited if possible because tolerance and dependence may develop; withdrawal may lead to rebound anxiety or insomnia.

Antihistamines (eg, diphenhydramine, hydroxyzine) are not recommended as anxiolytics or hypnotics because they have anticholinergic effects.

Buspirone, a partial serotonin agonist, can be effective for general anxiety disorder; elderly patients tolerate doses up to 30 mg/day well. The slow onset of anxiolytic action (up to 2 to 3 wk) can be a disadvantage in urgent cases.

**Digoxin**: Digoxin, a cardiac glycoside, is used to increase the force of myocardial contractions and to treat supraventricular arrhythmias. However, it must be used with caution in patients with heart failure. In men with heart failure and a left ventricular ejection fraction of ≤ 45%, serum digoxin levels > 0.8 ng/mL are associated with increased mortality risk. Adverse effects are typically related to its narrow therapeutic index. One study found digoxin to be beneficial in women when serum levels were 0.5 to 0.9 ng/mL but possibly harmful when levels were ≥ 1.2 ng/mL. A number of factors increase the likelihood of digoxin toxicity in the elderly. Renal impairment, temporary dehydration, and NSAID use (all common among the elderly) can reduce renal clearance of digoxin. Furthermore, digoxin clearance decreases an average of 50% in elderly patients with normal serum creatinine levels. Also, if lean body mass is reduced, as may occur with aging, volume of distribution for digoxin is reduced. Therefore, starting doses should be low (0.125 mg/day) and adjusted according to response and serum digoxin levels (normal range 0.8 to 2.0 ng/mL). However, serum digoxin level does not always correlate with likelihood of toxicity.

**Diuretics**: Lower doses of thiazide diuretics (eg, hydrochlorothiazide or chlorthalidone 12.5 to 25 mg) can effectively control hypertension in many elderly patients and have less risk of hypokalemia and hyperglycemia than other diuretics (see also p. 2070). Thus, K supplements may be required less often.

K-sparing diuretics should be used with caution in the elderly; the K level must be carefully monitored, particularly when these diuretics are given with ACE inhibitors.
Chapter 309. Prevention of Disease and Disability in the Elderly

Introduction

For the elderly, prevention focuses mainly on disease, frailty, accidents (i.e., unintentional injury), iatrogenic complications, and psychosocial problems. Not all elderly patients benefit from every preventive measure. Choice of preventive measures is guided by the patient's general condition:

- Healthy: These elderly people have minimal or no chronic disease and are functionally independent. Primary and secondary prevention of disease and prevention of frailty are the most beneficial measures for this group.

- Chronically ill: These people typically have several noncurable but treatable diseases, are usually functionally independent or minimally dependent, often take several prescription drugs, and occasionally are hospitalized for exacerbations of their chronic diseases. Secondary and tertiary prevention of disease and prevention of frailty are priorities, as are primary prevention of disease and prevention of iatrogenic complications and accidents.

- Frail: These people typically have many severe chronic diseases, are functionally dependent, and have lost their physiologic reserve. They are frequently hospitalized and institutionalized. For them, prevention of accidents and iatrogenic complications is most important.

Some preventive measures apply to all elderly people. For example, exercise can help prevent frailty in healthy or chronically ill elderly people. In frail elderly people, exercise can help preserve functional ability and reduce the incidence of accidents. Influenza vaccination (yearly) and pneumococcal vaccination (needed only once, except for patients at high risk) are effective, inexpensive, and associated with minimal morbidity.

Patient and caregiver issues: Healthy elderly people should visit their primary care physician at least annually to ensure timely completion of primary and secondary disease prevention measures, including screening (see Tables 309-1 and 309-2) and chemoprevention (e.g., vaccination, aspirin—see Table 309-3). For more information, see recommendations for clinical preventive services from the U.S. Preventive Services Task Force (USPSTF).

Medicare covers a comprehensive "Welcome to Medicare" preventive physical examination, which must occur within 6 mo of Part B enrollment.

Regular exercise (see p. 3294) and a healthy diet (see Table 309-4) help prevent or postpone frailty and many diseases, as can other disease prevention measures (see Table 309-5). Chronically ill patients should learn about their diseases and treatment plans, as should their caregivers. Regular physician visits and prompt reporting of a change in symptoms can help reduce severe disease exacerbations, which can lead to hospitalization and functional decline.

Caregivers of the frail elderly must work assiduously to prevent accidents by completing a home safety checklist and correcting any potential problems that are identified. Caregivers should watch for even subtle functional changes in elderly patients and promptly report any changes to a health care practitioner. If a patient has multiple unmet needs, especially when coupled with functional decline, a caregiver should consider seeking the care of a geriatric interdisciplinary team.

Prevention of Disease

Primary and Secondary Prevention

Primary prevention aims to stop disease before it starts, often by reducing or eliminating risk factors. Primary prevention may include immunoprophylaxis (vaccinations), chemoprophylaxis, and behavioral
change (eg, via counseling). In secondary prevention, disease is detected and treated at an early stage, before symptoms or functional losses occur, thereby minimizing morbidity and mortality.

Screening can be a primary or secondary preventive measure; it can be used to detect risk factors, which may be altered to prevent disease, or to detect disease in asymptomatic people, who can then be treated early.

[Table 309-1. Screening Recommendations for Elderly Patients]

**Tertiary Prevention**

In tertiary prevention, an existing symptomatic, usually chronic disease is appropriately managed to prevent further functional loss. Disease management is enhanced by using disease-specific practice guidelines and protocols. Several disease management programs have been developed:

- **Disease-specific care management:** A specially trained nurse, working with a primary care physician or geriatrician, coordinates protocol-driven care, arranges support services, and teaches patients.

- **Chronic care clinics:** Patients with the same chronic disease are taught in groups and are visited by a health care practitioner; this approach can help patients with diabetes achieve better glucose control.

- **Specialists:** Patients with a chronic disease that is difficult to stabilize can be referred to a specialist. This approach works best when the specialist and primary care physician work collaboratively.

Patients with the following chronic disorders, which are common among the elderly, can potentially benefit from tertiary prevention.

**Arthritis:** Arthritis (primarily osteoarthritis; much less commonly, RA) affects about half of people ≥ 65. It leads to impaired mobility and increases risk of osteoporosis, aerobic and muscular deconditioning, falls, and pressure ulcers.

**Osteoporosis:** Tests to measure bone density can detect osteoporosis before it leads to a fracture. Ca and vitamin D supplementation, exercise, and, if needed, cessation of cigarette smoking can help prevent osteoporosis from progressing, and treatment can prevent new fractures.

**Diabetes:** Hyperglycemia, especially when the glycosylated hemoglobin (Hb A1C) concentration is > 7.9%, increases the risk of retinopathy, neuropathy, nephropathy, and coronary artery disease. The goal of treatment is an Hb A1C concentration of < 8% for frail diabetic patients and an even lower concentration (< 7%) for patients who are not frail or who have a remaining life expectancy > 7 yr.

[Table 309-2. Cancer Screening Recommendations for Elderly Patients]

[Table 309-3. Chemoprevention and Immunization for Elderly Patients]

[Table 309-4. Nutritional Recommendations for Prevention of Frailty]

Patient education and foot examinations at each visit can help prevent foot ulcers.

**Vascular disorders:** Elderly patients with a history of coronary artery disease, cerebrovascular disease, or peripheral vascular disease are at high risk of disabling events. Risk can be reduced by aggressive management of vascular risk factors (eg, hypertension, smoking, diabetes, obesity, atrial fibrillation, dyslipidemia).

**Heart failure:** Morbidity due to heart failure is significant among the elderly, and the mortality rate is higher than that of many cancers. Appropriate, aggressive treatment, especially of systolic dysfunction, reduces functional decline, hospitalization, and mortality rate.
**Chronic obstructive pulmonary disease (COPD):** Smoking cessation, appropriate use of inhalers and other drugs, and patient education regarding energy-conserving behavioral techniques can decrease the number and severity of exacerbations of COPD leading to hospitalization.

**Prevention of Frailty**

Frailty is loss of physiologic reserve, which makes people susceptible to disability due to minor stresses. Common features of frailty include weakness, weight loss, muscle wasting (sarcopenia), exercise intolerance, frequent falls, immobility, incontinence, and frequent exacerbations of chronic diseases.

Exercise (see p. 3294) and a healthy diet (see Table 309-4) are recommended for preventing or reducing frailty. Elderly people who engage in regular aerobic exercise (eg, walking, swimming, running) increase their life expectancy and have less functional decline than those who are sedentary. Mood and possibly cognitive function may also be improved. Weight training can help increase bone mass and reduce risk of falls and fractures. A healthy diet may prevent or reduce risk of many diseases that contribute to frailty, including breast and colon cancers.

**Table 309-5.** Lifestyle Measures that Help Prevent Common Chronic Diseases

osteoporosis, obesity, and undernutrition; morbidity and mortality may also be reduced.

**Prevention of Injuries**

**Falls:** The elderly are vulnerable to injury due to falls (see p. 3134). A falls prevention program should be implemented for people who are at high risk of falls or who have already fallen.

**Driving hazards:** All elderly people should be reminded to use lap and shoulder belts and to refrain from driving when they are under the influence of alcohol or psychoactive drugs.

For the elderly, risk of injuring themselves and others while driving is higher than that for younger adults because of age-associated changes and conditions common among the elderly. Driving ability should be investigated with further questions and, if indicated, with formal assessment for any of the following:

- Poor visual acuity
- Dementia
- Functionally significant impairment of neck or trunk movement
- Poor motor coordination
- Bradykinesia

Also, a family member's or friend's concern about the patient's driving ability should prompt further inquiry and assessment.

Formal assessment of driving ability can be done by an occupational therapist (see p. 3152). Many states have laws that mandate physician reporting of suspected impaired drivers. Sensitivity is required when a health care practitioner must recommend cessation of driving because such a recommendation threatens autonomy.

**Home hazards:** The home may have many hazards. For example, people with peripheral neuropathy are at increased risk of burns from excessively hot water; burns can be prevented by setting the hot water heater temperature at < 49° C. For people with dementia, using electrical and gas appliances is particularly dangerous; use of alarms and automatic shutoff features on appliances can help. Smoke and carbon monoxide detectors should be installed and maintained. Firearms should be safely stored or removed from the home.
All patients or their caregivers can complete a home safety checklist to identify hazards. Physical and occupational therapists may visit a patient's home to assess its safety.

**Prevention of Iatrogenic Complications**

Iatrogenic complications are more common and may be more severe among the elderly than among younger patients. These complications include adverse drug effects (eg, interactions), falls, nosocomial infections, pressure ulcers, delirium, and complications related to surgery. Prevention is often possible.

**Risk Factors**

The first step in prevention is to identify patients at high risk. Risk factors include the following.

**Multiple chronic diseases:** The greater the number of chronic diseases, the greater the risk that treatment of one disease will exacerbate others. For example, treatment of arthritis with an NSAID may exacerbate heart failure, coronary artery disease, or chronic gastritis.

**Multiple physicians:** Having multiple physicians can result in uncoordinated care and polypharmacy. Consultation among multiple physicians every time one of them sees a common patient is difficult. As a result, a patient's therapeutic regimen is frequently changed without the input of the patient's other physicians, thereby increasing risk of iatrogenic complications.

**Multiple drugs (polypharmacy) and inappropriate drugs:** Taking multiple drugs concurrently and having multiple chronic diseases markedly increase risk of adverse drug-drug or drug-disease interactions (see p. 3092). Risk of such interactions is particularly high among patients who are undernourished or who have renal failure. Also, certain drugs have an especially high risk of adverse effects in the elderly (see p. 3098).

**Hospitalization:** Risks due to hospitalization include hospital-acquired infection, polypharmacy, and transfusion reactions. Hospitalized patients who have dementia or who are immobilized (eg, after surgery) are at high risk of iatrogenic complications.

Medical technology may contribute to iatrogenic complications, including sudden death or MI after valvular replacement surgery, stroke after carotid endarterectomy, fluid overload after transfusions and infusions, unwanted prolongation of life via artificial life support, and hypoxic encephalopathy after potentially life-prolonging CPR.

**Prevention**

Interventions that can prevent iatrogenic complications include the following.

**Care management:** Care managers facilitate communication among health care practitioners, ensure that needed services are provided, and prevent duplication of services. Care managers may be employed by physician groups, health plans, or community or governmental organizations. The frail elderly benefit the most from case management.

**Geriatric interdisciplinary team:** A geriatric interdisciplinary team (see p. 3115) evaluates all of the patient's needs, develops a coordinated care plan, and manages (or, along with the primary care physician, co-manages) care. Because this intervention is resource-intensive, it is best reserved for very complex cases.

**Pharmacist consultation:** A pharmacist can help prevent potential complications caused by polypharmacy and inappropriate drug use.

**Acute Care for the Elderly (ACE) units:** These units are hospital wards with protocols to ensure that elderly patients are thoroughly evaluated for potential iatrogenic problems before problems occur and that such problems are identified and appropriately managed.
Advance directives: Patients are encouraged to prepare advance directives, including designation of a proxy to make medical decisions (see p. 3471). These documents can help prevent unwanted treatment for critically ill patients who cannot speak for themselves.

Prevention of Psychosocial Problems

Depression screening is recommended because depression is common among the elderly. Screening is relatively easy; several instruments do not require a physician for administration. For patients who feel lonely or isolated, social worker assistance to increase social contacts may prevent morbidity and postpone death. For those who are depressed, appropriate intervention with counseling or drugs is warranted.

A sense of self-worth may contribute to better health. Patients should be encouraged to remain productive, engage in leisure activities, and remain or become involved with other people. These actions can enhance self-worth. Suggesting activities that confirm a sense of social connectedness, such as obtaining a pet, contributing to household chores, or doing volunteer work, may help prevent psychosocial problems (and physical disability).
Chapter 310. Quality of Life and Therapeutic Objectives

Quality of life often depends on health and health care. However, health care practitioners, especially when establishing therapeutic objectives, may underemphasize its importance to patients.

Health-Related Quality of Life

How health affects quality of life is variable and subjective. Health-related quality of life has multiple dimensions, including the following:

- Absence of distressing physical symptoms (eg, pain, dyspnea, nausea, constipation)
- Emotional well-being (eg, happiness, absence of anxiety)
- Functional status (eg, capacity to do activities of daily living and higher-order functions, such as pleasurable activities)
- Quality of close interpersonal relationships (eg, with family members)
- Participation in and enjoyment of social activities
- Satisfaction with medical and financial aspects of treatments
- Sexuality, body image, and intimacy

Influences: Some of the factors that influence health-related quality of life (eg, institutionalization, reduced life expectancy, cognitive impairment, disability, chronic pain, social isolation, functional status) may be obvious to health care practitioners. Practitioners may need to ask about others (eg, nature and quality of close relationships, cultural influences, religion, personal values, previous experiences with health care). However, how factors affect quality of life cannot necessarily be predicted, and some factors that cannot be anticipated may have effects.

Also, perspectives on quality of life can change. For example, after a stroke that caused severe disability, patients may choose treatment (eg, life-saving surgery) to sustain a quality of life that they would have considered poor or even unacceptable before the stroke.

Assessment

Barriers to assessment: Assessing patients' perspectives on quality of life may be difficult for the following reasons:

- Such an assessment is not always taught or emphasized sufficiently in traditional medical education.
- Quality of life is subjective, so decision models cannot be applied to individual patients.
- Assessing the patient's perspectives on quality of life takes time because it requires thoughtful conversation between patient and health care practitioner.

Method: Quality of life is best assessed by a direct interview with patients. During assessment, practitioners should be careful not to reveal their own biases. Determining a patient's preferences is usually possible; even patients with mild dementia or cognitive impairment can make their preferences known when practitioners use simple explanations and questions. Having family members present when discussing preferences of a patient with cognitive impairment is recommended.

Instruments that measure health-related quality of life can be useful in research studies for assessing group trends but tend not to be useful clinically for assessing individual patients.

Therapeutic Objectives
Before a treatment or major diagnostic test is used, potential adverse effects should be weighed against potential benefits in the context of the patient's individual desires and goals.

Potential adverse effects include the following:

• Complications

• Discomfort

• Inconvenience

• Cost

• Need for additional tests or treatments

Potential benefits include the following:

• Cure

• Prolongation of life

• Slowing of disease progression

• Functional improvement

• Symptom relief

• Prevention of complications

When treatments are very likely to achieve benefits and very unlikely to have adverse effects, decisions are relatively easy. However, assessing the relative importance of these quality of life factors to each patient is important when treatments may have discordant effects. For example, aggressive cancer therapy may prolong life but have severe adverse effects (eg, chronic nausea and vomiting, mouth ulcers) that greatly reduce quality of life. In this case, the patient's preference for quality vs duration of life and tolerance for risk and uncertainty help guide the decision whether to attempt cure, prolongation of life, or palliation.

The patient's perspective on quality of life may also affect treatment decisions when different treatments (eg, surgical vs drug treatment of severe angina or osteoarthritis) may have different efficacies, toxicities, or both. Practitioners can help patients understand the expected consequences of various treatments, enabling patients to make more informed decisions.

When predicting toxicities and benefits of various treatments, practitioners should use the patient's individual clinical characteristics, rather than chronologic age alone. In general, the patient's chronologic age is irrelevant when deciding among different treatments or therapeutic goals. However, life expectancy may affect treatment choice. For example, patients with a limited life expectancy may not live long enough to benefit from aggressive treatment of a slowly progressive disorder (eg, radical prostatectomy for a localized, slow-growing prostate cancer). Nevertheless, quality of life is important regardless of life expectancy. Thus, invasive treatments that may improve quality of life (eg, joint replacement, coronary artery bypass surgery) should not be automatically rejected for patients with a limited life expectancy.

Regardless of the overall therapeutic goal, symptom relief should always be offered.
Chapter 311. Provision of Care

Introduction

Because the elderly tend to have multiple disorders and may have social or functional problems, they use a disproportionately large amount of health care resources. In the US, they account for

- > 40% of acute hospital bed days
- > 30% of prescription and 40% of OTC drug purchases
- $329 billion or almost 44% of the national health budget
- > 75% of the federal health budget

The elderly are likely to see several health care practitioners and to move from one health care setting to another. Providing consistent, integrated care across specific care settings, sometimes called continuity of care, is thus particularly important for elderly patients. Communication among primary care physicians, specialists, other health care practitioners, and patients and their family members is critical to ensuring that patients receive appropriate care in all settings.

Health care settings: Care may be delivered in the following settings:

- Physician's office: The most common reasons for visits are routine chronic problems, acute problems, flare-ups of a chronic problem, preventive care, and presurgical or postsurgical evaluation.
- Patient's home: Home care (see p. 3116) is most commonly used after hospital discharge, but hospitalization is not a prerequisite.
- Long-term care facilities: These facilities include assisted-living facilities, board-and-care facilities, nursing homes, and life-care communities (see p. 3122). Whether patients require care in a long-term care facility depends partly on the patient's wishes and needs and on the family's ability to meet the patient's needs.
- Day care facilities: These facilities provide medical, rehabilitative, cognitive, and social services several hours a day for several days a week.
- Hospitals: Only seriously ill elderly patients should be hospitalized (see p. 3118). Hospitalization itself poses risks to elderly patients because of confinement, immobility, diagnostic testing, and treatments.
- Hospice: Hospices provide care for the dying (see p. 3482). The goal is to alleviate symptoms and keep people comfortable rather than to cure a disorder. Hospice care can be provided in the home, a nursing home, or a separate inpatient facility.

In general, the lowest, least restrictive level of care suitable to a patient's needs should be used. This approach conserves financial resources and helps preserve the patient's independence and functioning.

Geriatric Interdisciplinary Teams

Geriatric interdisciplinary teams consist of practitioners from different disciplines who provide coordinated, integrated care with collectively set goals and shared resources and responsibilities.

Not all elderly patients need a geriatric interdisciplinary team. However, if patients have complex medical, psychologic, and social needs, such teams are more effective in assessing patient needs and creating an effective care plan than are practitioners working alone. For these patients, care is often best managed by a geriatrician. Interdisciplinary care is not available everywhere.

Interdisciplinary teams aim to ensure the following:
• That patients move safely and easily from one care setting to another and from one practitioner to another

• That the most qualified practitioner provides care for each problem

• That care is not duplicated

To create, monitor, or revise the care plan, interdisciplinary teams must communicate openly, freely, and regularly. Core team members must collaborate, with trust and respect for the contributions of others, and coordinate the care plan (eg, by delegating, sharing accountability, jointly implementing it). Team members may work together at the same site, making communication informal and expeditious.

A team typically includes physicians, nurses, pharmacists, social workers, and sometimes a dietitian, physical and occupational therapists, an ethicist, or a hospice physician. Team members should have knowledge of geriatric medicine, familiarity with the patient, dedication to the team process, and good communication skills.

To function effectively, teams need a formal structure. Teams should set deadlines for reaching their goals, have regular meetings (to discuss team structure, process, and communication), and continuously monitor their progress (using quality improvement measures). In general, team leadership should rotate, depending on the needs of the patient; the key provider of care reports on the patient's progress. For example, if the main concern is the patient's medical condition, a physician leads the meeting and introduces the team to the patient and family members. The physician determines what medical conditions a patient has, informs the team (including differential diagnoses), and explains how these conditions affect care. The team's input is incorporated into medical orders. The physician must write medical orders agreed on through the team process and discusses team decisions with the patient, family members, and caregivers.

If a formally structured interdisciplinary team is not available or practical, a virtual team can be used. Such teams are usually led by the primary care physician but can be organized and managed by an advanced practice nurse, a care coordinator, or a case manager. The virtual team uses information technologies (eg, handheld devices, email, video conferencing, teleconferencing) to communicate and collaborate with team members in the community or within a health care system.

**Patient and caregiver participation:** Practitioner team members must treat patients and caregivers as active members of the team—eg, in the following ways:

• Patients and caregivers should be included in team meetings when appropriate.

• Patients should be asked to help the team set goals (eg, advance directives, end-of-life care).

• Patients and caregivers should be included in discussions of drug treatment, rehabilitation, dietary plans, and other therapies.

• Patients should be asked what their ideas and preferences are; thus, if patients will not take a particular drug or change certain dietary habits, care can be modified accordingly.

Patients and practitioners must communicate honestly to prevent patients from suppressing an opinion and agreeing to every suggestion.

Caregivers, including family members, can help by identifying realistic and unrealistic expectations based on the patient's habits and lifestyle. Caregivers should also indicate what kind of support they can provide.

**Home Health Care**

Usually, home health care is indicated when patients need monitoring, adjustment of drugs, dressing
changes, and limited physical therapy. Home health care is commonly used

• After hospital discharge (postacute care), although hospitalization is not a prerequisite, particularly for the elderly

Home health care can also be used for

• Patients with conditions that require many days of hospitalization each year (medically complex care)

• Medically stable patients with severe functional impairment (long-term care)

Home health care is being increasingly used to meet the demand for long-term care. Home health care, which can reduce nursing home placement of patients by 23%, is less expensive than institutional care when home health aide and skilled care visits are scheduled appropriately.

Home health care is provided by agencies, which vary in ownership, size, location, and services. Some are certified. To be certified, an agency must meet state licensing requirements and federal conditions for participation in Medicare. Such agencies provide skilled nursing care under the direction of referring physicians. Nurses provide services under the supervision of a physician, who consults with them as changes in care are needed. Caring for patients at home requires communication among health care practitioners to ensure that patients are maintaining function and are progressing as expected. The patients or caregivers need to promptly report changes in the patient's condition to nurses or physicians to ensure that patients are monitored appropriately.

Home health care may provide medical and nonmedical services (see Table 311-1).

Reimbursement: Few patients with a serious, chronic disorder can afford full home care even though most would prefer to remain at home. Medicare covers some home care services for patients who are homebound, but it has certain requirements, which depend on the Medicare option chosen (see p. 3155). Some private insurance companies cover some home health care services (eg, infusion services) for patients who are not homebound.

For patients' care to be reimbursed by a third party, physicians must certify that home care is required and, for Medicare, that patients meet Medicare requirements for home care. Medicare requires that home health care agencies tell patients which services are reimbursable. Home care services that are delivered are based on a detailed assessment (Outcome and Assessment Information Set [OASIS]) that is completed by a registered nurse or therapist when the patient is admitted to Medicare. Third-party payers are increasingly limiting personal services to control costs. Home health care agencies are directly reimbursed by Medicare, Medicaid, or private insurers.

[Table 311-1. Services that May be Provided in Home Health Care]

Day Care

Day care provides medical, rehabilitative, and cognitive support services several hours a day for several days a week. All day care facilities provide certain core services: transportation, nutrition, and recreational and social activity programs. In the US, there are only about 2,900 day care programs compared with > 16,000 nursing homes. Most day care programs are small, averaging 20 clients.

There are several models.

• **Day hospital:** This model emphasizes rehabilitation or intensive skilled care. It is designed for patients recovering from an acute condition (eg, stroke, amputation, fracture). Programs are usually limited in duration (6 wk to 6 mo) and are costly because the ratio of staff members to patients is high.

• **Maintenance:** This model combines limited skilled care (screening for and monitoring of chronic disorders) with physical exercise. Goals are to prevent deterioration, to maintain or improve the patient's
functional level for as long as possible, to improve self-image, to eliminate the monotony of daily life, to prevent exacerbation of chronic disorders, and to prevent loneliness, isolation, and withdrawal. Maintenance programs provide long-term care and are less costly than day hospital programs.

**Social:** This model provides counseling, group therapy, and cognitive retraining. It may resemble a typical senior citizens' center, which provides care to elderly people with various psychosocial needs, or a mental health center, which provides care to elderly people with dementia or psychiatric disorders.

Programs are increasingly accepting patients who are in wheelchairs and those who are incontinent; however, patients cannot be socially disruptive. Care may be long-term or limited in duration.

In addition to providing needed medical care, these facilities also provide respite care. By doing so, they may help delay or avoid placement in a nursing home.

**Reimbursement:** Medicare does not reimburse for day care services. Funds generally come from the Older Americans Act, Medicaid waiver programs, long-term care insurance, and private funds. Some centers use donated funds to subsidize transportation and a sliding-fee scale to match aid with the patient's financial need.

**Respite Care**

Respite care is provision of temporary care by a substitute caregiver to provide relief to the regular caretaker. Over 50% of US states have respite programs. Programs may be provided in different settings:

- In the home by respite care agencies or by home health care agencies
- In the community by adult day care centers, respite care cooperatives, or freestanding respite facilities
- In a long-term care facility (eg, by board-and-care facilities or nursing homes)
- In a hospital

Duration of care may vary (eg, limited to 28 days in a calendar year).

Support comes from Medicaid (almost 50%), grants (25%), and private funds (25%).

**Hospital Care**

A hospital may provide emergency medical care, diagnostic testing, intensive treatment, or surgery, which may or may not require admission. The elderly use hospitals more than younger patients; they have more admissions to the hospital from the emergency department and more and longer hospital stays, and they use more resources while in the hospital.

**Emergency Department Care**

In 2006, about 14.5% of emergency department visits were made by people ≥ 65 yr. Elderly patients tend to be sicker. More than 40% of elderly patients seen in an emergency department are admitted to the hospital; 6% go to intensive care units. More than 50% are prescribed new drugs. The elderly may use the emergency department as a substitute for primary care or may come because they are not receiving adequate care from their primary care physician. However, in most cases, the reasons for coming are true emergencies.

A visit to an emergency department may create more stress for the elderly because there are typically no special accommodations for them (eg, quiet rooms, lower beds, extra pillows, indirect lighting).

Evaluation of the elderly usually takes longer and requires more diagnostic tests because many elderly patients do not present with clear-cut or typical symptoms and signs of a disorder (see p. 3088). For example, MI manifests as chest pain in < 50% of patients > 80 yr. Instead, elderly patients may complain
of feeling generally weak or just not feeling themselves.

Factors that are not apparent (eg, polypharmacy, adverse drug effects) may affect an elderly patient's presentation. For example, a fall may result from elder abuse, an adverse drug effect (eg, oversedation), hazards in the home, physical problems (eg, poor vision), depression, or chronic alcoholism. Adverse drug effects account for at least 5% of hospital admissions for the elderly.

About 30 to 40% of elderly patients who come to the emergency department are cognitively impaired but do not have a diagnosis of dementia; in 10%, cognitive impairment consistent with delirium is unrecognized. When indicated (eg, if an elderly patient is having difficulty with orientation to person, place, or time), a standardized cognitive assessment should be done in the emergency department. However, a standardized cognitive assessment is appropriate for any elderly patient coming to the emergency department. Cognitive impairment affects the reliability of the patient history, as well as diagnosis, and must be considered when planning the patient's disposition. Knowing whether onset of cognitive impairment is recent helps determine whether the impairment should be fully assessed in the emergency department. Cognitive impairment of recent onset may indicate sepsis, occult subdural hemorrhage, or an adverse drug effect.

Suicide risk, incontinence, and nutritional and immunization status should be assessed in the emergency department so that follow-up care can be arranged.

**Communication among practitioners:** Good communication among emergency department physicians and patients, caregivers, primary care physicians, and staff members of long-term care facilities greatly enhances the outcome of elderly patients with complicated problems. Advance directives should be promptly and clearly communicated to emergency medicine practitioners. Baseline information from the patient's personal physician facilitates assessment and management planning in the emergency department. Reports to the patient's primary care physician should describe even simple injuries (eg, ankle sprain, Colles' wrist fracture) because such injuries can dramatically affect functional ability and independence.

**Disposition:** Discharge planning may be complex because acute illness or injury may impair functional ability more in elderly patients (eg, a simple ankle sprain may be incapacitating unless patients have good support at home). Discharge planning may be improved when nurses, social workers, and primary care physicians are involved. It should include the following:

- Functional status assessment (see p. 3079)
- Strategies to manage problems (eg, depression, alcoholism, impaired functional status) identified during the emergency department assessment
- Determination of whether patients can take drugs as directed and can obtain the necessary follow-up care
- Assessment of caregiver capabilities (eg, whether respite services are needed)

Many elderly patients are hospitalized after they are evaluated in the emergency department.

Occasionally, elderly patients are brought to the emergency department by a caregiver who refuses to take them home or who leaves, abandoning them in the hospital.

**Hospitalization**

Almost half of adults who occupy hospital beds are ≥ 65 yr; this proportion is expected to increase as the population ages. Hospital care costs Medicare > $100 billion/yr, representing 30% of health care expenditures for hospital care in the US.

Hospitalization can magnify age-related physiologic changes and increase morbidity.
Only seriously ill elderly patients who cannot be appropriately cared for elsewhere should be hospitalized. Hospitalization itself poses risks to elderly patients because it involves confinement, immobility, diagnostic testing, and treatments (particularly changes in drug regimens). When patients are transferred to or from a hospital, drugs are likely to be added or changed, leading to a higher risk of adverse effects (see p. 3095). Treatment in hospitals can be dehumanizing and impersonal. Acute hospital care should last only long enough to allow successful transition to home care, a skilled nursing facility, or an out-patient rehabilitation program.

The outcome of hospitalization appears to be poorer with increasing age, although physiologic age is a more important predictor of outcome than is chronologic age. Outcome is better for patients hospitalized because of elective procedures (eg, joint replacement) than for those hospitalized because of serious disorders (eg, multisystem organ failure).

About 75% of patients who are ≥ 75 and functionally independent at admission are not functionally independent when they are discharged; 15% of patients ≥ 75 are discharged to skilled nursing facilities. The trend toward abbreviated acute hospital stays followed by subacute care and rehabilitation in a skilled nursing facility may explain why these percentages are high. However, even when a disorder is treatable or appears uncomplicated, patients may not return to prehospital functional status.

Improving outcomes: The following strategies can help reduce functional decline and improve care of elderly patients:

- **Geriatric interdisciplinary team**: To identify and meet the complex needs of elderly patients and to watch for and prevent problems that are common among the elderly and that may develop or worsen during hospitalization (see p. 3115)

- **Primary care nurse** (one nurse with around-the-clock responsibility for a particular patient): To administer the team's care plan, to monitor response to nursing and medical care, and to teach and counsel patients, staff members, and family members

- **Changes in the hospital environment, often made by nurses**: Eg, to move disruptive patients into the hall near the nursing station or to change roommates for a patient

- **Rooming-in programs for a family member**: To provide better one-on-one care, to relieve staff members of some caregiving tasks, to allay patient anxiety (particularly if patients have delirium or dementia), and to enable a family member to participate actively in the patient's recovery

- **Good communication among practitioners**: To prevent errors in and duplication of diagnostic procedures and treatments (particularly drugs)

- **Documentation of drug regimen**: To state the indication for each new drug, to maintain a daily list of drugs prescribed and received, and thus to avoid using unnecessary drugs and help prevent drug interactions

- **Advance directives**: To document the patient's choice of health care proxy and health care decisions (see p. 3471)

- **Consideration of problems common among the elderly**: To anticipate and take steps to prevent such problems and to treat them promptly

- **Discharge planning**: To ensure that appropriate care is continued

Advance directives, if already prepared, should be brought to the hospital as soon as possible. Practitioners should reaffirm these choices during acute hospitalization. If directives were not documented, practitioners should make every effort to determine the patient's wishes.

Problems common among the elderly require specific consideration during hospitalization, particularly after surgery (see p. 3448); many of them can be remembered using the acronym ELDERSS (see
In the hospital, elderly patients frequently experience nighttime confusion (sundowning), fracture a bone with no identifiable trauma, fall, or become unable to walk. Hospitalization may precipitate or worsen undernutrition, pressure ulcers, urinary incontinence, fecal impaction, and urinary retention. Such problems can prolong convalescence.

**Table 311-2.** Elderss: Some Important Issues for the Hospitalized Elderly

### Adverse Drug Effects

Hospitalization rates due to adverse drug effects are 4 times higher for elderly patients (≈ 17%) than for younger patients (4%). Reasons for these effects include polypharmacy, age-related changes in pharmacokinetics and pharmacodynamics, and changes in drugs (intentional and unintentional) during hospitalization and at discharge (see Ch. 308).

**Prevention:** Maintaining a daily list of drugs prescribed and received can help prevent adverse drug effects and drug interactions.

Because drug distribution, metabolism, and elimination vary widely among elderly patients, the following should be done:

- Drug doses should be carefully titrated.
- Creatinine clearance for renally excreted drugs should be calculated when doses are adjusted.
- Serum drug levels should be measured.
- Patient responses should be observed.

Certain drugs or drug categories should be avoided in the elderly (see p. 3098). Use of hypnotic drugs should be minimized because tachyphylaxis may occur and risk of falls and delirium is increased. Short-acting benzodiazepines are usually the best choice. Antihistamines have anticholinergic effects and should not be used for sedation.

### Bed Rest Effects

Prolonged bed rest, as can occur during hospitalization, causes deconditioning and is seldom warranted. The resulting inactivity has the following effects:

- With complete inactivity, muscle strength decreases by 5% per day, increasing risk of falls.
- Muscles shorten and periarticular and cartilaginous joint structure changes (most rapidly in the legs), limiting motion and contributing to development of contractures.
- Aerobic capacity decreases markedly, substantially reducing maximum O\textsubscript{2} uptake.
- Bone loss (demineralization) is accelerated.
- Risk of deep venous thrombosis is increased.

After even a few days of bed rest, elderly patients who have reduced physiologic reserves but can still function independently may lose that ability. Even if the loss is reversible, rehabilitation requires extensive, expensive, and relatively lengthy intervention.

In elderly patients, bed rest can cause vertebral bone loss 50 times faster than in younger patients. The loss incurred from 10 days of bed rest takes 4 mo to restore.

**Prevention:** Unless prohibited for a specific reason, activity (particularly walking) should be encouraged. If assistance with walking is needed, therapists provide it at scheduled times. However, physicians,
nurses, and family members should also assist patients with walking throughout the day. Hospital orders should emphasize the need for activity.

If immobilization is necessary or results from prolonged illness, procedures to prevent deep venous thrombosis are recommended unless contraindicated.

Rehabilitation is often needed. Realistic goals for rehabilitation at home can be based on the patient's prehospitalization activity level and current needs.

**Falls**

Age-related changes (eg, baroreceptor insensitivity, decreased body water and plasma volume) result in a tendency to develop orthostatic hypotension. These changes plus effects of bed rest and use of sedatives and certain antihypertensives increase risk of falls (and syncope).

Among hospitalized elderly patients, > 60% of falls occur in the bathroom; often, patients hit hard objects. Some patients fall while getting out of hospital beds. Patients are in a strange bed and in a strange environment, and they may easily become confused. The use of bed rails may help remind elderly patients to call for assistance before attempting to get up, but bed rails may also act as a physical barrier that contributes to patient falls.

**Prevention:** Usually, bed rails should be removed or kept down. The best alternatives to the use of physical or chemical restraints are to identify, carefully analyze, and modify or correct risk factors for falling (including agitation) and to closely observe patients at risk.

**Incontinence**

Urinary or fecal incontinence develops in > 40% of hospitalized patients ≥ 65, often within a day of admission. Reasons include

- An unfamiliar environment
- A cluttered path to the toilet
- Disorders that impair ambulation
- A bed that is too high
- Bed rails
- Hampering equipment such as IV lines, nasal oxygen lines, cardiac monitors, and catheters
- Psychoactive drugs that may reduce the perception of the need to void, inhibit bladder or bowel function, or impair ambulation
- Drugs that may result in urinary incontinence (eg, anticholinergic drugs and opioids, causing overflow urinary incontinence; diuretics, causing urge incontinence)

Bedpans may be uncomfortable, especially for postsurgical patients or patients with chronic arthritis. Patients with dementia or a neurologic disorder may be unable to use the call bell to request toileting assistance.

Fecal impaction, GI tract infection (eg, *Clostridium difficile*-induced colitis), adverse effects of drugs, and liquid nutritional supplements may cause uncontrollable diarrhea.

With appropriate diagnosis and treatment, continence can be reestablished, and nursing home placement avoided.
Mental Status Changes

Elderly patients may appear confused because they have dementia, delirium, depression, or a combination. However, health care practitioners must always remember that confusion may have other causes, and its presence requires thorough evaluation.

Confusion may be due to a specific disorder (see Table 175-2 on p. 1670). However, it may develop because the hospital setting exacerbates the effects of acute illness and age-related changes in cognition. For example, elderly patients who do not have their eye-glasses and hearing aids may become disoriented in a quiet, dimly lit hospital room. Patients may also become confused by hospital procedures, schedules (eg, frequent awakenings in strange settings and rooms), the effects of psychoactive drugs, and the stress of surgery or illness. In an ICU, the constant light and noise can result in agitation, paranoid ideation, and mental and physical exhaustion.

Prevention: Family members can be asked to bring missing eyeglasses and hearing aids. Placing a wall clock, a calendar, and family photographs in the room can help keep patients oriented. The room should be lit well enough to enable patients to recognize what and who is in their room and where they are. At every opportunity, staff and family members should remind patients of the time and place. Procedures should be explained before and as they are done.

Use of physical restraints is discouraged. For agitated patients, restraints invariably increase the level of agitation. Identifying and modifying risk factors for agitation and closely observing patients can help prevent or minimize it.

Pressure Ulcers

Pressure ulcers often develop in elderly hospitalized patients because of age-related changes in the skin. Direct pressure may cause skin necrosis in as few as 2 h if the pressure is greater than the capillary perfusion pressure of 32 mm Hg. During a typical emergency department visit, pressure ulcers can start developing while elderly patients are lying on a hard stretcher waiting to be examined. After short periods of immobilization, sacral pressures reach 70 mm Hg, and pressure under an unsupported heel averages 45 mm Hg. Shearing forces result when patients sitting in wheelchairs or propped up in beds slide downward. Incontinence, poor nutrition, and chronic disorders may contribute to pressure ulcer development.

Prevention: A protocol to prevent and treat pressure ulcers should be started immediately, at admission (see p. 742). It should be followed daily by the patient's primary care nurse and reviewed at least weekly by an interdisciplinary team. Pressure ulcers may be the only reason patients are discharged to a nursing home rather than to the community.

Undernutrition

In the hospital, elderly patients can become undernourished quickly, or they may be undernourished when admitted. Prolonged hospitalization exacerbates preexisting problems and often results in significant nutritional loss. Undernutrition is particularly serious for hospitalized patients because it makes them less able to fight off infection, maintain skin integrity, and participate in rehabilitation; surgical wounds may not heal as well.

Hospitalization contributes to undernutrition in several ways:

• Rigidly scheduled meals, use of drugs, and changes in environment can affect appetite and nutritional intake.

• Hospital food and therapeutic diets (eg, low-salt diets) are unfamiliar and often unappetizing.

• Eating in a hospital bed with a tray is difficult, particularly when bed rails and restraints limit movement.

• Elderly patients may need help with eating; help may be slow to come, resulting in cold, even less
appetizing food.

• The elderly may not drink enough water because their thirst perception is decreased, water is difficult to reach, or both; severe dehydration may develop (sometimes leading to stupor and confusion).

• Dentures may be left at home or misplaced, making chewing difficult; labeling dentures helps prevent them from being lost or discarded with the food tray.

Prevention: Patients with preexisting nutritional abnormalities should be identified when admitted and be treated appropriately. Physicians and staff members should anticipate nutritional deficiencies in elderly patients.

The following measures can help:

• Rescinding restrictive dietary orders as soon as possible

• Monitoring nutritional intake daily

• Conferring with patients and family members about food preferences and attempting to tailor a reasonable diet specific to each patient

• Encouraging family members to join the patient at mealtimes because people eat more when they eat with others

• Making sure patients are fed adequately at all times (eg, temporary or permanent parenteral nutrition or GI tube feedings for patients too sick to swallow)

• Giving explicit oral fluid orders (eg, providing a fresh and readily accessible bedside water pitcher or other fluids unless fluids are restricted; advising family members, friends, and staff members to regularly offer patients a drink)

Discharge Planning and Transfers

Early, effective discharge planning has many benefits:

• Shortening the hospital stay

• Reducing the likelihood of readmission

• Identifying less expensive care alternatives

• Facilitating placement of equipment (eg, hospital bed, O₂) in the patient's home

• Helping increase patient satisfaction

• Possibly preventing placement in a nursing home

As soon as a patient is admitted, all members of the interdisciplinary team begin discharge planning. A social worker or discharge planning coordinator evaluates the patient's needs within 24 h of admission. Nurses help physicians determine when discharge is safe and which setting is most appropriate.

To home: Patients being discharged to their home need detailed instructions about follow-up care, and family members or other care-givers may need training to provide care. If patients and family members are not taught how to give drugs, implement treatment, and monitor recovery, adverse outcomes and readmission are more likely. Writing down follow-up appointments and drug schedules may help patients and family members. At discharge, a copy of a brief discharge summary plan should be given to patients or family members in case they have questions about care before the primary care physician receives the official summary plan.
To another health care facility: When a patient is discharged to a nursing home or to another facility, a written summary should be sent with the patient, and a copy should be faxed to the receiving institution. The summary must include complete, accurate information about the following:

- The patient's mental and functional status
- Times the patient last received drugs
- List of drugs being currently taken and the dosage
- Known drug allergies
- Advance directives, including resuscitation status
- Family contacts and support status
- Follow-up appointments and tests
- Names and phone numbers of a nurse and physician who can provide additional information

A written copy of the patient's medical and social history should accompany the patient during transfer and may be sent via fax to the receiving facility to ensure that there are no information gaps.

Effective communication between staff members of institutions helps ensure continuity of care. For example, the patient's nurse can call the receiving institution to review the information shortly before the patient is transferred and can call the nurse who will care for the patient after discharge.

Long-Term Care

Determining which setting for long-term care is best depends on

- The patient's wishes and medical, social, emotional, and financial needs
- The family's ability to meet the patient's needs
- The setting's capacity for achieving patient goals established by the referring physician

Placement in a nursing home may be unnecessary if community-based long-term care services (eg, independent housing for the elderly, board-and-care facilities, assisted living, life-care communities) are available, accessible, and affordable.

Nursing Homes

The term nursing home refers specifically to a skilled nursing facility. Nursing homes, or skilled nursing facilities (SNFs), provide daily skilled nursing care, skilled rehabilitation services, and other medical services for people ≥ 65 yr (and for younger disabled people—see Table 311-3). Many nursing homes also provide additional community-based services (eg, day care, respite care). Many provide short-term postacute care (including intensive physical, occupational, respiratory, and speech therapy) after an injury or illness (eg, hip fracture, MI, stroke). Hospitals (including rural hospitals with swing-beds) or freestanding facilities that may or may not be affiliated with a hospital may act as nursing homes.

The percentage of people in nursing homes has declined, partly because assisted-living facilities and home health care, which depend substantially on informal caregiving, are being used more.

About 45% of people ≥ 65 spend some time in a nursing home; of these, ≥ 50% stay ≥ 1 yr, and a minority of these die there. The probability of nursing home placement within a person's lifetime is closely related
to age; for people aged 65 to 74, the probability is 17%, but for those > 85, it is 60%. Projections indicate that 43% of people who turned 65 in 1990 will spend some time in a nursing home before they die, and > 50% of those admitted will spend at least 1 yr.

[Table 311-3, Nursing Homes at a Glance]

However, twice as many functionally dependent elderly live in the community as in nursing homes. About 25% of all community-dwelling elderly have no family members to help with their care. Special attention to health and health care needs of the community-dwelling elderly could add quality and years to their life and limit costs by preventing institutionalization.

Supervision of care: Physicians must see nursing home patients as often as medically necessary but not less than every 30 days for the first 90 days and at least once every 60 days thereafter. During routine visits, patients should be examined, drug status assessed, and laboratory tests ordered as needed. Findings must be documented in the patient's chart to keep other staff members informed. Some physicians limit their practice to nursing homes. They are available to participate in team activities and to consult with other staff members, thus promoting better care than that given in hurried visits every other month. Some nurse practitioners and physicians collaborate to manage patients' disorders. By administering antibiotics and monitoring IV lines, suctioning equipment, and sometimes ventilators, nurse practitioners may help prevent patients from being hospitalized.

Detecting, stopping, and preventing abuse is a primary function of physicians, nurses, and other health care practitioners. All practitioners involved in care of the elderly should be familiar with signs of abuse or neglect and be ready to intervene if elder abuse is suspected. A public advocacy system exists, and nursing homes can be cited by regulatory agencies.

The federal and state governments are legally responsible for ensuring that a facility is providing good care; surveyors attempt to assess a facility's performance and to detect deficiencies by monitoring outcome measures, observing care, interviewing patients and staff members, and reviewing clinical records.

Hospitalization: If hospitalization becomes necessary and if possible, the physician who cares for a patient in the nursing home should treat that patient in the hospital. However, hospitalization is avoided whenever possible because of its risks (see p. 3118).

When patients are transferred to a hospital, their medical records should accompany them. A phone call from a nursing home nurse to a hospital nurse is useful to explain the diagnosis and reason for transfer and to describe the patient's baseline functional and mental status, drugs, and advance directives. Similarly, when patients are returned to the nursing home from the hospital, a hospital nurse should call a nursing home nurse.

Costs: Nursing home care is expensive, averaging $68,280 per year in 2004. In the US, nursing home care cost $21 billion in 1980, $70 billion in 2000, and $121.9 billion in 2005. About 44% of the cost is paid by Medicaid, 26.5% by the patient, 16% by Medicare, 7.5% by private insurance, and about 4% by other private funds.

Problems related to reimbursement: Critics suggest the following:

- The rate of reimbursement may be too low, limiting patient access to rehabilitation and services that enhance quality of life, especially for patients with dementia.

- Financial incentives to provide restorative care and rehabilitation for patients with limited functioning may be insufficient.

- Nursing homes may be motivated to foster dependence or to maintain the need for high-level care so that reimbursement is maximized.

Nursing home placement: A patient's preferences and needs can be determined most effectively
through comprehensive geriatric assessment, including identification and evaluation of all disorders and evaluation of the patient's functional ability (see p. 3086). Disabling or burdensome disorders—most commonly dementia, incontinence, and immobility—may trigger consideration of nursing home placement. However, even modest amelioration of a disorder may forestall the need for a nursing home (see Table 311-4).

**Selection:** Nursing homes vary in the types of medical, nursing, and social services provided. Some states set minimum nurse-to-patient ratios that are more stringent than federal requirements; the ratio of other staff members to patients varies considerably.

Physicians should help families select a nursing home that matches the needs of the patient with the services of a nursing home. Physicians should consider the following:

- Which clinical care practice model the nursing home uses (eg, private single-physician practices, large networks of primary care practitioners who routinely visit a certain set of nursing homes)
- Which hospitals have transfer agreements with the nursing home
- Which special therapeutic services, palliative care, hospice, and other services are available
- Whether staff members are employed full-time or part-time
- What the patient's medical coverage is, particularly if it is a Medicare capitated program, which covers certain aspects of ongoing medical care but does not cover long-term custodial care

**Board-and-Care Facilities**

Board-and-care facilities provide care for elderly people who cannot live independently but who do not need the constant supervision provided in nursing homes. Board-and-care facilities (also called rest homes) typically provide the following:

- A room
- Meals in a communal dining room
- Housekeeping services (eg, laundry, cleaning)
- Minimal assistance with personal care
- Sometimes supervision of drug administration

The number of board-and-care facilities is increasing because they offer an economic, federally funded means of accommodating the increasing number of elderly people who would otherwise require nursing home care paid for with state Medicaid funds.

Minimally regulated and sometimes unlicensed, these facilities principally serve 2 groups, often cared for together—the elderly and the deinstitutionalized mentally ill. Although excellent homes exist, some facilities tend to warehouse the disabled in substandard buildings and to employ few skilled staff members.

Physicians should try to ensure that their patients in board-and-care facilities are safe and are receiving appropriate care. Physicians may need to visit the facility or send a nurse or social worker to evaluate it.

**Assisted-Living Programs**

Assisted-living programs enable residents who have problems doing activities of daily living to maintain their independence in
personalized settings by providing or arranging for the provision of daily meals, personal and other supportive services, health care, and 24-h oversight as needed.

Assisted-living programs typically provide the following:

- Meals
- Personal care
- Housekeeping services
- Transportation
- 24-h oversight if needed

These programs are paid for by private funds, long-term care insurance, community-based charity organizations, or church groups.

**Life-Care Communities**

Life-care communities offer a contract intended to remain in effect for the resident's lifetime and, at a minimum, to guarantee shelter and access to various health care services.

Life-care communities (continuing care retirement communities) offer different levels of care:

- For people who can live independently
- For those who need assistance
- For those who need skilled nursing care

Generally, people pay a substantial entrance fee ($50,000 to $500,000) when moving to the community and monthly fees thereafter. In some communities, residents pay only a monthly fee for rent plus service or health packages. In others, residents can purchase a condominium, cooperative, or membership; service or health packages are purchased separately.

There are 3 main types of communities:

- Those covered by an all-inclusive contract
- Those covered by a modified contract limiting the amount of long-term care provided before the monthly fee is increased
- Those covered by a fee-for-service contract with billing for health services as they are used

If well financed and managed, life-care communities provide a broad range of housing, social, supportive, and health services that enable their residents to live comfortably. However, some communities are not well regulated; in some, residents' assets have been wiped out because of unscrupulous real estate dealers or well-intentioned but inept management.

Communities may occupy a single building or be spread across multiacre campuses with housing options ranging from efficiency apartments to cottages with several rooms. Many have community buildings for organized social events, dining rooms, clubs, sports facilities, planned outings, and vacation options. Access to physicians is usually provided, and most programs are affiliated with local acute care facilities.

**Program of All-Inclusive Care for the Elderly**
Program of All-Inclusive Care for the Elderly (PACE) is designed for elderly people who meet criteria for nursing home admission but wish to live at home as long as possible. The program involves an interdisciplinary team that includes physicians, nurses, physical and occupational therapists, social workers, dieticians, and drivers. The services are typically provided in an adult day health center and are available every day. The program provides transportation to the center. However, some services may be provided in the home.

PACE is available only in certain areas of the country. It combines funds from Medicare and Medicaid. The Department of Health and Human Services web site explains the PACE program and provides an up-to-date list of participating health care practitioners.

Pharmacy

For elderly patients, developing a relationship with a pharmacist and using one pharmacy can help ensure consistency in care. A pharmacist can help prevent drug-related problems, which are a particular risk for the elderly (see Ch. 308).

For elderly patients, pharmacists are often the most accessible health care practitioner. In addition to dispensing drugs, pharmacists provide drug information to patients, monitor drug use (including adherence), and liaise between physicians or other health care practitioners and patients to ensure optimal pharmaceutical care. Pharmacists also provide information about interactions between drugs and other substances, including OTC drugs, dietary supplements (eg, medicinal herbs), and foods.

Patient adherence: Pharmacists can help improve patient adherence by doing the following:

- Assessing the patient's ability to adhere to a drug regimen by noticing certain impairments (eg, poor dexterity, lack of hand strength, cognitive impairment, loss of vision)
- Teaching patients how to take certain drugs (eg, inhalers, transdermal patches, injectable drugs, eye or ear drops) or how to measure doses of liquid drugs
- Supplying drugs in ways that are accessible to patients (eg, easy-open bottles, pills without wrappers)
- Making sure that drug labels and take-home printed materials are in large type and in the patient's native language
- Teaching patients how to use drug calendar reminders, commercially available drug boxes, electronic drug-dispensing devices, and pill splitters or crushers
- Eliminating unnecessary complexity and duplication from the overall drug regimen

Settings: Many pharmacists work in a community pharmacy. But they may also work in any health care setting, including hospitals, long-term care facilities, the home (with a home health care agency), mail service and online pharmacies, organized health care systems, and hospice settings (see Table 311-5).

[Table 311-5, Various Duties of Pharmacists]
Chapter 312. Gait Disorders in the Elderly

Introduction

Gait disorders encompass a number of issues, including slowing of gait speed and loss of smoothness, symmetry, or synchrony of body movement.

For the elderly, walking, standing up from a chair, turning, and leaning are necessary for independent mobility. Gait speed, chair rise time, and the ability to do tandem stance (standing with one foot in front of the other—a measure of balance) are independent predictors of the ability to do instrumental activities of daily living (eg, shopping, traveling, cooking) and of the risk of nursing home admission and death.

Walking without assistance requires adequate attention and muscle strength plus effective motor control to coordinate sensory input and muscle contraction.

Normal Age-Related Changes in Gait

Some elements of gait normally change with aging; others do not.

Gait velocity (speed of walking) remains stable until about age 70; it then declines about 15%/decade for usual gait and 20%/decade for fast walking. Velocity is lower because elderly people take shorter steps at the same rate (cadence). The most likely reason for shortened step length (the distance from one heel strike to the next) is weakness of the calf muscles, which propel the body forward; calf muscle strength is substantially decreased in elderly people. However, elderly people seem to compensate for lower calf power by using their hip flexor and extensor muscles more than young adults.

Cadence (reported as steps/min) does not change with aging. Each person has a preferred cadence, which is related to leg length and usually represents the most energy-efficient rhythm. Tall people take longer steps at a slower cadence; short people take shorter steps at a faster cadence.

Double stance time (ie, time with both feet on the ground—a more stable position for moving the center of mass forward) increases with age. The percentage of time in double stance goes from 18% in young adults to ≥ 26% in healthy elderly people. Increased time in double stance reduces the time the swing leg has to advance and shortens step length. Elderly people may increase their double stance time when they walk on uneven or slippery surfaces, when they have impaired balance, or when they are afraid of falling. They may appear as if they are walking on slippery ice.

Walking posture changes only slightly with aging. Elderly people walk upright, with no forward lean. However, elderly people walk with greater anterior (downward) pelvic rotation and increased lumbar lordosis. This posture change is usually due to a combination of weak abdominal muscles, tight hip flexor muscles, and increased abdominal fat. Elderly people also walk with their legs rotated laterally (toes out) about 5°, possibly due to a loss of hip internal rotation or in order to increase lateral stability. Foot clearance in swing is unchanged with advancing age.

Joint motion changes slightly with aging. Ankle plantar flexion is reduced during the late stage of stance (just before the back foot lifts off). The overall motion of the knee is unchanged. Hip flexion and extension are unchanged, but the hips have increased adduction. Pelvic motion is reduced in all planes.

Abnormal Changes in Gait

Causes: A number of disorders can contribute to dysfunctional or unsafe gait. They particularly include

- Neurologic disorders

- Musculoskeletal disorders (eg, spinal stenosis [see p. 384], significant joint disease)

Causative neurologic disorders include dementias (see p. 1673), movement and cerebellar disorders (see p. 1759), and sensory or motor neuropathies (see p. 1790).
**Manifestations:** There are many manifestations of gait abnormality. Some help suggest certain causes.

**Loss of symmetry of motion and timing between left and right sides** usually indicates a disorder. When healthy, the body moves symmetrically; step length, cadence, torso movement, and ankle, knee, hip, and pelvis motion are equal on the right and left sides. A regular asymmetry occurs with unilateral neurologic or musculoskeletal disorders (eg, a limp caused by a painful ankle). Unpredictable or highly variable gait cadence, step length, or stride width indicates breakdown of motor control of gait due to a cerebellar or frontal lobe syndrome.

**Difficulty initiating or maintaining gait** may occur. When patients start walking, their feet may appear stuck to the floor, typically because patients do not shift their weight to one foot to allow the other foot to move forward. This problem may represent isolated gait initiation failure, Parkinson's disease, or frontal or subcortical disease. Once gait is initiated, steps should be continuous, with little variability in the timing of the steps. Freezing, stopping, or almost stopping usually suggests a cautious gait, a fear of falling, or a frontal gait disorder. Scuffing the feet is not normal (and is a risk factor for tripping).

**Retropulsion** is walking backwards when initiating gait or falling backwards while walking. It may occur with frontal gait disorders, parkinsonism, CNS syphilis, and progressive supranuclear palsy.

**Footdrop** causes toe dragging or a stepping gait (ie, exaggerated lift of the leg to avoid catching the toe). It may be secondary to anterior tibialis weakness (eg, caused by trauma to the peroneal nerve at the lateral aspect of the knee or a peroneal mononeuropathy usually associated with diabetes), spasticity of calf muscles (gastrocnemius and soleus), or lowering of the pelvis due to muscle weakness of the proximal muscles on the stance side (particularly the gluteus medius). Low foot swing (eg, due to reduced knee flexion) may resemble footdrop.

**Short step length** is nonspecific and may represent a fear of falling or a neurologic or musculoskeletal problem. The side with short step length is usually the healthy side, and the short step is usually due to a problem during the stance phase of the opposite (problem) leg. For example, a patient with a weak or painful left leg spends less time in single stance on the left leg and develops less power to move the body forward, resulting in shorter swing time for the right leg and a shorter right step. The normal right leg has a normal single stance duration, resulting in a normal swing time for the abnormal left leg and a longer step length for the left leg than for the right leg.

**Wide-based gait** (increased step width) is determined by observing the patient's gait on a floor with 12-in (30-cm) tiles. The gait is considered wide based if the outside of the patient's feet do not stay within the width of the tile. As gait speed decreases, step width increases slightly. Wide-based gait can be caused by cerebellar disease or bilateral knee or hip disease. Variable step width (lurching to one side or the other) suggests poor motor control, which may be due to frontal or sub-cortical gait disorders.

**Circumduction** (moving the foot in an arc rather than a straight line when stepping forward) occurs in patients with pelvic muscle weakness or difficulty bending the knee.

**Forward lean** can occur with kyphosis and with Parkinson's disease or disorders with parkinsonian features associated with dementia (particularly vascular dementia and Lewy body dementia).

**Festination** is a progressive quickening of steps (usually with forward lean), whereby patients may break into a run to prevent falling forward. Festination can occur with Parkinson's disease and rarely as an adverse effect of dopamine-blocking drugs (typical and atypical antipsychotics).

**Sideward trunk lean** that is consistent or predictable to the side of the stance leg may be a strategy to reduce joint pain due to hip arthritis or, less commonly, knee arthritis (antalgic gait). In a hemiparetic gait, the trunk may lean to the strong side. In this pattern, the patient leans to lift the pelvis on the opposite side to permit the limb with spasticity (inability to flex the knee) to clear the floor during the swing phase.

**Irregular and unpredictable trunk instability** can be caused by cerebellar, subcortical, or basal ganglia dysfunction.
Deviations from path are strong indicators of motor control deficits.

Arm swing may be reduced or absent in Parkinson's disease and vascular dementias. Arm swing disorders may also be adverse effects of dopamine-blocking drugs (typical and atypical antipsychotics).

Evaluation

The goal is to determine as many potential contributing factors to gait disorders as possible. A performance-oriented mobility assessment tool may be helpful (see Table 312-1), as may other clinical tests (eg, a screening cognitive examination for patients with gait problems possibly due to frontal lobe syndromes).

Evaluation is best approached in 4 parts:

• Discussing the patient's complaints, fears, and goals related to mobility

• Observing gait with and without an assistive device (if safe)

• Assessing all components of gait (see Table 312-1)

• Observing gait again with a knowledge of the patient's gait components

History: In addition to the standard medical history, elderly patients should be asked about gait-related issues. First, they are asked open-ended questions regarding any difficulty with walking, balance, or both, including whether they have fallen (or fear they might fall). Then specific capabilities are assessed; they include whether patients can go up and down stairs; get in and out of a chair, shower, or tub; and walk as needed to buy and prepare food and do household chores. If they report any difficulties, details of the onset, duration, and progression are sought. History of neurologic and musculoskeletal symptoms and known disorders is important.

Physical examination: A thorough physical examination is done with emphasis on the musculoskeletal examination (see p. 284) and the neurologic examination (see p. 1587).

Lower-extremity strength is assessed. Proximal muscle strength is tested by having patients get out of a chair without using their arms. Calf strength is measured by having patients face a wall, put their palms on the wall, and rise onto their toes first using both feet and then using one foot at a time. Strength of hip internal rotation is assessed.

Gait assessment: Routine gait assessment can be done by a primary care practitioner; an expert may be needed for complex gait disorders. Assessment requires a straight hallway without distractions or obstructions and a stopwatch. A measuring tape and a T square or ruler with a right angle may be needed to accurately measure stride length.

Patients should be prepared for the examination. They should be asked to wear pants or shorts that reveal the knees and be informed that several observations may be needed but that they will be allowed to rest if fatigued.

Assistive devices provide stability but also affect gait. Use of walkers often results in a flexed posture and discontinuous gait, particularly if the walker has no wheels. If safe to do so, the practitioner should have the patient walk without an assistive device, while remaining close to or walking with the patient with a gait belt for safety. If patients use a cane, the practitioner can walk with them on the cane side or take their arm and walk with them. Patients with a suspected peripheral neuropathy should walk touching the practitioner's forearm. If gait improves with this intervention, proprioception from the arm is being used to
supplement the missing proprioception from the leg; such patients usually benefit from using a cane, which transmits information about the type of surface or floor to the cane-holding hand.

Balance is assessed by measuring the time patients can stand on one foot or on both feet in tandem stance (heel to toe); normal is ≥ 5 sec.

Gait velocity is measured using a stopwatch. Patients are timed while walking a fixed distance (preferably 6 or 8 m) at their preferred speed. The test may need to be repeated with patients walking as quickly as possible. Normal gait speed in healthy elderly people ranges from 1.1 to 1.5 m/sec.

Cadence is measured as steps/min. Cadence varies with leg length—about 90 steps/min for tall adults (1.83 m [72 in]) to about 125 steps/min for short adults (1.5 m [60 in]).

Step length can be determined by measuring the distance covered in 10 steps and dividing that number by 10. Because shorter people take shorter steps and foot size is directly related to height, normal step length is 3 foot lengths, and abnormal step length is < 2 foot lengths. A rule of thumb is that if at least 1 foot length is visible between the patient’s steps, step length is normal.

Step height can be assessed by observing the swing foot; if it touches the floor, particularly in the middle of the swing phase, patients may trip. Some patients with fear of falling or a cautious gait syndrome purposefully slide their feet over the floor surface. This gait pattern may be safe on a smooth surface but is a risky strategy when walking on rugs, because patients may trip.

Asymmetry or variability of gait rhythm can be detected when practitioners whisper "dum...dum...dum" to themselves with each of the patient’s steps. Some practitioners have a better ear than an eye for gait rhythm.

Testing: Testing is sometimes required.

CT or MRI of the brain is often done, particularly when there is poor gait initiation, chaotic cadence, or the appearance of a very stiff gait. These tests help identify lacunar infarcts, white matter disease, and focal atrophy and can help determine whether normal-pressure hydrocephalus should be considered.

Treatment

• Strength training

• Balance training

• Assistive devices

Although determining why gait is abnormal is important, interventions to alter gait are not always indicated. A slowed, aesthetically abnormal gait may enable the elderly person to walk safely and without assistance. However, some treatment interventions can lead to improvement; they include exercise, balance training, and assistive devices (see Table 312-2).

Strength training: Frail elderly people with mobility problems achieve modest improvements with exercise programs. In elderly people with arthritis, walking or resistance training reduces knee pain, and gait may improve.

Resistance exercises can improve strength and gait velocity, especially in frail patients with slowed gait. Two or three training sessions a week are usually needed; resistance exercises consist of 3 sets of 8 to 14 repetitions during each session. The load is increased every week or two until a plateau of strength is reached.
Leg press machines train all the large muscle groups of the leg and provide back and pelvic support during lifting. However, these machines are not always accessible to elderly patients. Chair rises with weight vests or weights attached to the waist (waist belts) are an alternative. Instructions are required to reduce the risk of back injury due to excess lumbar lordosis. Step-ups and stair climbing with the same weights are also useful. Ankle plantar flexion can be done with the same weights.

Using knee extension machines or attaching weights to the ankle strengthens the quadriceps. The usual starting weight for frail people is 3 kg (7 lb). Resistance for all exercises should be increased every week until the patient reaches a plateau of strength.

**Balance training:** Many patients with balance deficits benefit from balance training. Good standing posture and static balance are taught first. Patients are then taught to be aware of the location of pressure on their feet and how the location of pressure moves with slow leaning or turning the torso to look to the left or right. Leaning forward (using a wall or counter for support), backward (with a wall directly behind), and to each side is then practiced. The goal is for the patient to be able stand on one leg for 10 sec.

Dynamic balance training can involve slow movements in single stance, simple tai chi movements, tandem walking, turns while walking, walking backwards, walking over a virtual object (eg, a 15-cm stripe on the floor), slow forward lunges, and slow dance movements. Multicomponent balance training is probably most effective in improving balance.

**Assistive devices:** Assistive devices can help maintain mobility and quality of life (see p. 3457). New motor strategies must be learned. Physical therapists should be involved in choice of and training with assistive devices.

**Canes** are particularly helpful for patients with pain caused by knee or hip arthritis or with peripheral neuropathy of the feet because a cane transmits information about the type of surface or floor to the cane-holding hand. Quad canes can stabilize the patient but usually slow gait. Canes are usually used on the side opposite the painful or weak leg. Many store-bought canes are too long but can be adjusted to the correct height (see Fig. 350-2 on p. 3459) by cutting (a wooden cane) or moving the pin settings (an adjustable cane). For maximal support, cane length should be such that patients have their elbow flexed 20 to 30° when holding the cane.

**Walkers** can reduce the force and pain at arthritic joints more than a cane, assuming adequate arm and shoulder strength. Walkers provide good lateral stability and moderate protection from forward falls but do little or nothing to help prevent backward falls for patients with balance problems. When prescribing a walker, the physical therapist should consider the sometimes competing needs of providing stability and maximizing efficiency (energy efficiency) of walking. Four-wheeled walkers with larger wheels and brakes maximize gait efficiency but provide less lateral stability. These walkers have the added advantage of a small seat to sit on if patients become fatigued.

**Prevention**

Although no large-scale prospective studies have confirmed the effect of increasing physical activity on gait and independence, prospective cohort studies provide convincing evidence that high levels of physical activity help maintain mobility, even in patients with disease.

Regular walking or a physically active lifestyle is the most important recommendation. The effects of deconditioning and of inactivity cannot be overstated. A regular walking program of 30 min/day is the best single activity for maintaining mobility; however, an active lifestyle that includes multiple shorter walking episodes is probably equivalent to a single 30-min walk. A safe walking course should be recommended. The patient should be instructed to increase gait speed and duration over several months.

Prevention also includes resistance and balance training. The effects of an active lifestyle on mood and confidence are probably as important as their effect on physiology.
Chapter 313. Falls in the Elderly

Introduction

A fall results in a person coming to rest on the ground or another lower level; sometimes a body part strikes against an object that breaks the fall. Typically, events caused by acute disorders (eg, stroke, seizure) or overwhelming environmental hazards (eg, being struck by a moving object) are not considered falls.

Annually, 30 to 40% of elderly people living in the community fall; 50% of nursing home residents fall. In the US, falls are the leading cause of accidental death and the 7th leading cause of death in people ≥ 65; 75% of deaths caused by falls occur in the 12.5% of the population who are ≥ 65. In 2000, direct medical costs totaled $0.2 billion ($179 million) for fatal falls and $19 billion for nonfatal fall injuries. By 2020, the costs are projected to reach $44 billion.

Falls threaten the independence of elderly people and cause a cascade of individual and socioeconomic consequences. However, physicians are often unaware of falls in patients who do not present with an injury because a routine history and physical examination typically do not include a specific evaluation for falls. Many elderly people are reluctant to report a fall because they attribute falling to the aging process or because they fear being subsequently restricted in their activities or institutionalized.

Etiology

The best predictor of falling is a previous fall. However, falls in elderly people rarely have a single cause or risk factor. A fall is usually caused by a complex interaction among the following:

- Intrinsic factors (age-related decline in function, disorders, and adverse drug effects)
- Extrinsic factors (environmental hazards)
- Situational factors (related to the activity being done—eg, rushing to the bathroom)

**Intrinsic factors:** Age-related changes can impair systems involved in maintaining balance and stability (eg, while standing, walking, or sitting). Visual acuity, contrast sensitivity, depth perception, and dark adaptation decline. Changes in muscle activation patterns and ability to generate sufficient muscle power and velocity may impair the ability to maintain or recover balance in response to perturbations (eg, stepping onto an uneven surface, being bumped).

Chronic and acute disorders (see Table 313-1) and use of drugs (see Table 313-2) are major risk factors for falls. The risk of falls increases with the number of drugs taken. Psychoactive drugs are the drugs most commonly reported as increasing the risk of falls and fall-related injuries.

**Extrinsic factors:** Environmental factors can increase the risk of falls independently or, more importantly, by interacting with intrinsic factors. Risk is highest when the environment requires greater postural control and mobility (eg, when walking on a slippery surface) and when the environment is unfamiliar (eg, when relocated to a new home).

**Situational factors:** Certain activities or decisions may increase the risk of falls and

[Table 313-1, Some Disorders that Contribute to Risk of Falls]

[Table 313-2, Some Drugs that Contribute to Risk of Falls]

fall-related injuries. Examples are walking while talking or being distracted by dual-tasking or multitasking and then failing to attend to an environmental hazard (eg, a curb or step), rushing to the bathroom (especially at night when not fully awake or when lighting may be inadequate), and rushing to answer the
Complications: Falling, particularly falling repeatedly, increases risk of injury, hospitalization, and death, particularly in elderly people who are frail and have preexisting disease comorbidities and deficits in activities of daily living. Longer-term complications can include decreased physical function, fear of falling, and institutionalization; falls reportedly contribute to 40% of nursing home admissions.

Over 50% of falls among elderly people result in an injury. Although most injuries are not serious (eg, contusions, abrasions), fall-related injuries account for about 5% of hospitalizations in patients ≥ 65. About 5% of falls result in fractures of the humerus, wrist, or pelvis. About 2% of falls result in a hip fracture. Other serious injuries (eg, head and internal injuries, lacerations) occur in about 10% of falls. Some fall-related injuries are fatal. About 5% of elderly people with hip fractures die while hospitalized; overall mortality in the 12 mo after a hip fracture ranges from 18 to 33%.

About half of elderly people who fall cannot get up without help. Remaining on the floor for > 2 h after a fall increases risk of dehydration, pressure ulcers, rhabdomyolysis, hypothermia, and pneumonia.

Function and quality of life may deteriorate drastically after a fall; at least 50% of elderly people who were ambulatory before fracturing a hip do not recover their previous level of mobility. After falling, elderly people may fear falling again, so mobility is sometimes reduced because confidence is lost. Some people may even avoid certain activities (eg, shopping, cleaning) because of this fear. Decreased activity can increase joint stiffness and weakness, further reducing mobility.

Evaluation

• Clinical evaluation
• Performance testing
• Sometimes laboratory testing

After treatment of acute injuries, assessment aims to identify risk factors and appropriate interventions, thus decreasing the risk of future falls and fall-related injuries.

Some falls are promptly recognized because of an obvious fall-related injury or concern about a possible injury. However, because elderly people often do not report falls, they should be asked about falls at least once per year.

Patients who report a single fall should be evaluated for a balance or gait problem using the Get-Up-and-Go Test. For the test, patients are observed as they rise from a standard armchair, walk 3 m (about 10 ft) in a straight line, turn, walk back to the chair, and sit back down. Observation may detect lower-extremity weakness, imbalance while standing or sitting, or an unsteady gait.

Patients who require a more complete assessment of risk factors for falls include

• Those who have difficulty during the Get-Up-and-Go Test
• Those who report multiple falls during screening
• Those who are being evaluated after a recent fall (after acute injuries are identified and treated)

History and physical examination: When a more complete assessment of risk factors is needed, the focus is on identifying intrinsic, extrinsic, and situational factors that can be reduced by interventions targeted at them.

Patients are asked open-ended questions about the most recent fall or falls, followed by more specific questions about when and where a fall occurred and what they were doing. Witnesses are asked the same questions. Patients should be asked whether they had premonitory or associated symptoms (eg,
palpitations, shortness of breath, chest pain, vertigo, light-headedness) and whether consciousness was lost. Patients should also be asked whether any obvious extrinsic or situational factors may have been involved. The history should include questions about past and present medical problems, use of prescription and OTC drugs, and use of alcohol. Because eliminating all risk of future falls may be impossible, patients should be asked whether they were able to get back up without help after falling and whether any injuries occurred; the goal is reducing the risk of complications due to future falls.

The physical examination should be comprehensive enough to exclude obvious intrinsic causes of falls. If the fall occurred recently, temperature should be measured to determine whether fever was a factor. Heart rate and rhythm should be assessed to identify obvious bradycardia, resting tachycardia, or irregular rhythms. BP should be measured with patients supine and after patients stand for 1 and 5 min to rule out orthostatic hypotension. Auscultation can detect many types of valvular heart disorders. Visual acuity should be evaluated with patients wearing their usual corrective lenses if needed. Abnormalities in visual acuity should trigger a more detailed visual examination by an optometrist or ophthalmologist. The neck, spine, and extremities (especially the legs and feet) should be evaluated for weakness, deformities, pain, and limitation in range of motion.

A neurologic examination should be done (see p. 1587); it includes testing muscle strength and tone, sensation (including proprioception), coordination (including cerebellar function), stationary balance, and gait. Basic postural control and the proprioceptive and vestibular systems are evaluated using the Romberg test (in which patients stand with feet together and eyes closed). Tests to establish high-level balance function include the one-legged stance and tandem gait. If patients can stand on one leg for 10 sec with their eyes open and have an accurate 3-m (10-ft) tandem gait, any intrinsic postural control deficit is likely to be minimal. Clinicians should evaluate positional vestibular function (eg, with the Dix-Hallpike maneuver—see Sidebar 46-1 on p. 414) and mental status (see p. 1587).

Performance tests: The Performance-Oriented Assessment of Mobility or Get-Up-and-Go Test can identify problems with balance and stability during walking and other movements that may indicate increased risk of falls.

Laboratory tests: There is no standard diagnostic evaluation. Testing should be based on the history and examination and helps rule out various causes: a CBC for anemia, blood glucose measurement for hypoglycemia or hyperglycemia, and electrolyte measurement for dehydration. Tests such as ECG, ambulatory cardiac monitoring, and echocardiography are recommended only when a cardiac cause is suspected. Carotid massage under controlled conditions (IV access and cardiac monitoring) has been proposed to determine carotid hypersensitivity and ultimately who might respond to pacemaker treatment. Spinal x-rays and cranial CT or MRI are indicated only when the history and physical examination detect new neurologic abnormalities.

Prevention

The focus is on preventing or reducing the number of future falls and fall-related injuries and complications, while maintaining as much of the patient's function and independence as possible.

Patients who report a single fall and who do not have problems with balance or gait on the Get-Up-and-Go Test or a similar test should be given general information about reducing risk of falls. It should include how to use drugs safely and reduce environmental hazards (see Table 313-3).

Exercise: Patients who have fallen more than once or who have problems during initial balance and gait testing should be referred to physical therapy or an exercise program. Physical therapy and exercise programs can be done in the home if patients have limited mobility. Physical therapists customize exercise programs to improve balance and gait and to correct specific problems contributing to fall risk. More general exercise programs in health care or community settings can also improve balance and gait. For example, tai chi may be effective and can be done alone or in [Table 313-3, Home Assessment Checklist for Hazards that Increase Risk of Falling]
groups. The most effective exercise programs to reduce fall risk are those that are tailored to the patient's
deficit, are provided by a trained professional, have a sufficient balance challenge component, and are
provided over the long term (eg, ≥ 4 mo).

**Assistive devices:** Some patients benefit from use of an assistive device (eg, cane, walker). Canes may
be adequate for those with minimal unilateral muscle or joint impairment, but walkers, especially wheeled
walkers, are more appropriate for patients with increased risk of falls attributable to bilateral leg weakness
or impaired coordination (wheeled walkers can be dangerous for patients who cannot control them
properly). Physical therapists can help fit or size the devices and teach patients how to use them (see p.
3457).

**Medical management:** Drugs that can increase the risk of falls should be stopped, or the dosage
should be adjusted to the lowest effective dose. Patients should be evaluated for osteoporosis and, if
osteonprosisis is diagnosed, treated to reduce risk of fractures from any future falls. If any other specific
disorder is identified as a risk factor, targeted interventions are required. For example, drugs and physical
therapy may reduce risk for patients with Parkinson's disease. Vitamin D, particularly taken with Ca, can
reduce fall risk, especially in those with reduced blood vitamin D levels. Pain management, physical
therapy, and sometimes joint replacement surgery may reduce risk for patients with arthritis. A change to
appropriate lenses (single lenses rather than bifocals or trifocals) or surgery, particularly for removal of
cataracts, may help patients with visual impairment.

**Environmental management:** Correcting environmental hazards in the home may reduce the risk of
falls (see Table 313-3). Patients should also be advised on how to reduce risk due to situational factors.
For example, footwear should have flat heels, some ankle support, and firm, nonskid midsoles. Many
patients with chronic limited mobility (eg, severe arthritis, paresis) benefit from combined medical,
rehabilitative, and environmental strategies. Wheelchair adaptations (eg, removable foot plates to reduce
Tripping during transfers, antitip bars to prevent backward tipping), removable belts, and wedge seating
may prevent falls in people with poor sitting balance or severe weakness when they are sitting or
transferring.

Restraints may lead to more falls and other complications and thus should not be used. Surveillance by a
caregiver is more effective and safer. Motion detectors may be used, but a caregiver must be present to
respond to the triggered alarm.

Hip protectors (padding sewn into special undergarments) may help protect patients who have fallen and
are at risk of a hip injury, but many patients are reluctant to wear protectors indefinitely. Compliant flooring
(eg, firm rubber) can help dissipate the impact force, but a floor that is too compliant (eg, soft foam) may
destabilize patients.

Patients should also be taught what to do if they fall and cannot get up. Useful techniques include turning
from the supine position to the prone position, getting on all fours, crawling to a strong support surface,
and pulling up. Having frequent contact with family members or friends, a phone that can be reached from
the floor, a remote alarm, or a wearable emergency response system device can decrease the likelihood
of lying on the floor for a long time after a fall.
Chapter 314. Social Issues in the Elderly

Introduction

Social issues influence an elderly person's risk and experience of illness as well as a health care practitioner's ability to deliver timely and appropriate care.

A social history helps members of the interdisciplinary team evaluate care needs and social supports. It should include questions about the following:

- Marital or companion status
- Living arrangements
- Financial status
- Work history
- Education
- Typical daily activities (eg, how meals are prepared, what activities add meaning to life, where problems may be occurring)
- Need for and availability of caregivers (to help plan care)
- Patients' own caregiving responsibilities (which may make patients reluctant to report their own symptoms lest their symptoms or any resulting interventions interfere with care-giving)

Family Caregiving

Family caregivers play a key role in delaying and possibly preventing institutionalization of chronically ill elderly patients. Although neighbors and friends may help, about 80% of home health care services (physical, emotional, social, economic) are provided by family caregivers. When the patient is mildly or moderately impaired, a spouse or adult children often provide care, but when the patient is severely disabled, a spouse (usually a wife) is more likely to be the caregiver.

The amount and type of care provided by family members depend on economic resources, family structure, quality of relationships, and other demands on the family members' time and energy. Family caregiving ranges from minimal assistance (eg, periodically checking in) to elaborate full-time care. On average, family caregiving consumes about 4 hours a day.

Although society tends to view family members as having a responsibility to care for one another, the limits of filial and spousal obligations vary among families and among individual family members. The willingness of family members to provide care may be bolstered by supportive services (eg, technical assistance in learning new skills, counseling services, family mental health services) and supplemental services (eg, personal care [assistance with grooming, feeding, and dressing], home health care, adult day care, meals programs). Supplemental services may be provided on a regular schedule or as respite care for a few hours or days.

Changes in demographics and social values have reduced the number of family members available to care for impaired elderly relatives because of the following:

- Increased life span: As a result, the population of the very old has been increasing. Thus, their children, who are potential care-givers, are likely to be old also.
- Delayed procreation: Combined with increased longevity, this delay has created a sandwich generation of caregivers who care simultaneously for their children and their parents.
• Increasing mobility of US society and the increased divorce rate: As a result, families are more likely to be geographically separated, and family ties are more likely to be weakened. Nonetheless, 80% of people ≥ 65 live within 20 min of one child.

• An increasing number of women entering the workforce: This increase reflects the increased number of single-parent households, most headed by women, and 2-income households. Previously, such women may have provided care for elderly parents, but the demands of a job may diminish or eliminate their ability to do so.

• The number of dependent and very sick elderly people is increasing.

These factors predict an increasing demand for home health care services provided by someone other than family members, friends, and neighbors.

**Effects:** Although caregiving can be very rewarding, it can also have negative effects. Family caregivers may experience considerable stress (called caregiver burden) and subsequent health problems, isolation, fatigue, and frustration, sometimes leading to a sense of helplessness and exhaustion (caregiver burnout) or elder abuse (see p. 3146).

Caregiving may also become a financial burden. Couples in which one partner cares for the other tend to be disproportionately poor.

Caregivers can often obtain reassurance or learn helpful information or strategies for caregiving from physicians, nurses, social workers, or case managers. Caregivers can also take the following measures to prepare themselves for caregiving and to avoid caregiver burnout:

• Not taking the patient's anger, frustration, or difficult behavior personally

• Attending to their own physical, emotional, recreational, and financial needs

• When appropriate, asking for help with care-giving or psychologic support from other family members and friends

• Investigating outside groups that can offer psychologic support (eg, support groups) or help with caregiving (eg, counseling, home health care, adult day care, meals programs, respite care)

**Living Alone**

In the US, about one third of the nearly 30 million community-dwelling elderly live alone. About half of the community-dwelling oldest old (≥ 85 yr) live alone. About four fifths of elderly people living alone are women. Men are more likely to die before their wives, and widowed or divorced men are more likely to remarry than are widowed or divorced women.

The elderly who live alone are more likely to be poor, especially with advancing age. Many report feelings of loneliness (in 60% of those > 75) and social isolation. In those with health problems or sensory deficits, new or worsening symptoms may be unnoticed. Many have difficulty complying with prescribed treatment regimens. Because they have physical limitations and because eating is a social activity, some elderly people who live alone do not prepare full, balanced meals, making undernutrition a concern.

Despite these problems, almost 90% of elderly people living alone express a keen desire to maintain their independence. Many fear being too dependent on others and, despite the loneliness, want to continue to live alone. To help them maintain their independence, physicians should encourage them to engage in regular physical activity and social interactions, and social workers should help them do so.

Coordination and delivery of services during convalescence are difficult for patients living alone. Physicians should ensure that home care is available and recommend additional services as appropriate. A passive or individually activated emergency response device may reassure patients that help can be obtained if needed.
**Self-Neglect**

Self-neglect implies not caring for self. It can include ignoring personal hygiene, not paying bills, not obtaining or preparing food (leading to undernutrition), not seeking medical care for potentially serious symptoms, not filling prescriptions or taking drugs, and skipping follow-up visits.

Risk factors for self-neglect include social isolation, disorders that impair memory or judgment (eg, dementia), the presence of several chronic disorders, and severe depression. Differentiating between self-neglect and simply choosing to live in a way that others find undesirable can be difficult. Social workers are often in the best position to make this determination.

Adult Protective Services or the state unit on aging (whose numbers are available through the Eldercare Locator at 800-677-1116) can help by coordinating in-home safety assessments and helping the elderly obtain counseling services, emergency response systems, referrals to additional support services, and, if necessary, hospitalization.

**Alternative Living Arrangements**

Living arrangements and relationships that do not involve living with a spouse, with an adult child, or alone are fairly common among the elderly. For example, a substantial proportion of elderly people who never married, are divorced, or are widowed have longstanding and close relationships with siblings, friends, and partners. Understanding the nature of these relationships helps practitioners plan care that is in keeping with a patient's wishes.

About 6 to 10% of the US population are estimated to be homosexual adults, including as many as 3 million of the elderly. Elderly people in a homosexual relationship face special challenges. The health care system may not be aware of their sexual preference, may not recognize their partner as having a role in caregiving decisions or as being part of the patient's family, and may not provide services that are appropriate for their circumstances. For example, a partner may not have legal standing in decision making for a cognitively impaired patient and may not be able to share a room in a nursing home or other congregate living setting. Health care practitioners should ask questions about partners and living arrangements and try to accommodate patient preferences.

**Effects of Life Transitions**

Late life is commonly a period of transitions (eg, retirement, relocation) and adjustment to losses.

**Retirement** is often the first major transition faced by the elderly. Its effects on physical and mental health differ from person to person, depending on attitude toward and reason for retiring. About one third of retirees have difficulty adjusting to certain aspects of retirement, such as reduced income and altered social role and entitlements. Some people choose to retire, having looked forward to quitting unpleasant work; others are forced to retire (eg, because of health problems or job loss). Appropriate preparation for retirement and counseling for retirees and families who experience difficulties may help.

**Relocation** may occur several times during old age—eg, to smaller quarters after selling the family home, to retirement housing to reduce the burden of upkeep, or to a nursing home. Some experts contend that such moves cause relocation trauma; however, recent studies find little or no evidence of increased mortality or other indications of trauma, especially among people prepared for the move. Physical and mental status are significant predictors of relocation adjustment, as is thoughtful and adequate preparation. People who respond poorly to relocation are more likely to be living alone, socially isolated, poor, and depressed. Men respond less well than women.

The less control people perceive they have over the move and the less predictable the new environment seems, the greater the stress of relocation. People should become acquainted with the new setting well in advance. For the cognitively impaired, a move away from familiar surroundings may exacerbate functional dependence and disruptive behavior.
Bereavement affects many aspects of an elderly person's life. For example, social interaction and companionship decrease, and social status may change. The death of a spouse affects men and women differently. In the 2 yr after death of a wife, the mortality rate in men tends to increase, especially if the wife's death was unexpected. For women who lose a husband, data are less clear but generally do not indicate an increased mortality rate.

With bereavement, some sleep disturbance and anxiety are normal; these effects usually resolve in months without drug treatment. In contrast, prolonged, pathologic grief is characterized by the following:

• Symptoms that are typical of a major depressive episode and that last > 2 mo
• Feelings of guilt about things not directly related to the loss
• Thoughts of death unrelated to survivorship
• Morbid preoccupation with worthlessness
• Hallucinations other than hearing and seeing the decedent

Caregivers and health care practitioners should look for such symptoms and be aware that bereaved patients are at high risk of suicide and declining health status.

Counseling and supportive services (eg, support groups for widows) may facilitate difficult transitions. Short-term use of anxiolytic drugs can help patients with excessive anxiety. However, excessive or prolonged use should be avoided because it may interfere with the process of grieving and adjustment. Prolonged, pathologic grief usually requires psychiatric evaluation and treatment.

Intimacy

Intimacy refers to a close feeling shared between 2 people, based on knowledge of and familiarity with the other person. It includes emotional, social (based on shared experiences), and physical intimacy (eg, touching, cuddling, sexual intercourse).

The desire for intimacy does not decrease with age, and there is no age at which intimacy, including physical intimacy, is inappropriate. However, the disorders and emotional changes that often occur with aging can interfere with developing and maintaining an intimate relationship. Aging can also change the way intimacy is expressed.

Intimacy, particularly physical intimacy, may be lost because of the following:

• Loss of a partner: Loss or absence of a partner is probably the most common age-related barrier to intimacy.

• Disorders: Various disorders that become more common with aging can interfere with physical intimacy. Vascular disorders and diabetes can cause erectile dysfunction; arthritis can limit movements and make them painful. The pain, discomfort, drugs, and worry associated with a disorder can dampen the desire for intimacy. For the partner, the stress and demands of care-giving may interfere with intimacy.

• Use of drugs: The elderly are more likely to take drugs (eg, antihypertensives, psychoactive drugs) that can cause problems affecting intimacy (eg, erectile dysfunction, reduced libido).

• Age-related changes: Levels of sex hormones decrease, causing changes (eg, vaginal atrophy, reduced vaginal lubrication) that make sexual intercourse uncomfortable or difficult. Libido may decrease.

• Reluctance to discuss effects of aging: If elderly people develop problems that interfere with physical intimacy or if they feel embarrassed about changes in their body (eg, wrinkles, sagging flesh), they may not want to discuss these changes with their partner or with a health care practitioner, who
may be able to suggest solutions.

- **Negative stereotypes about sexuality in the elderly**: Even healthy elderly people may have internalized negative stereotypes and think sexuality is inappropriate or abnormal after a certain age.

- **Discrepancy in expectations of partners**: One partner may want certain physical expressions of intimacy, but the other does not.

- **Lack of privacy**: Elderly people who live with family members or in a long-term care facility have fewer opportunities for privacy, which are necessary for physical intimacy.

- **Shift to other forms of intimacy**: Passions may mellow after years of living together. Sexual intercourse may become less frequent or stop. Many couples—most without paying much attention to it—grow comfortable with other forms of intimacy (eg, touching, massaging, kissing, verbal expressions of affection) that express familiarity, caring, or engagement with their partner.

Nonetheless, many elderly people continue to have a healthy sexual relationship. Intimacy, particularly physical intimacy, can help prevent depression and improve self-esteem and physical health. If elderly people have a new sex partner, they should practice safe sex. Acquiring sexually transmitted diseases, including AIDS, is a risk, regardless of age.

Many elderly people, especially those that live alone, find satisfaction and a sense of companionship in interactions with a pet. Caring for a pet can give people a sense of purpose and connectedness.

**Religion and Spirituality**

Religion and spirituality are similar but not identical concepts. Religion is often viewed as more institutionally based, more structured, and more traditional and may be associated with organized, well-established beliefs. Spirituality refers to the intangible and immaterial and thus may be considered a more general term, not associated with a particular group or organization. It can refer to feelings, thoughts, experiences, and behaviors related to the soul or to a search for the sacred (eg, a Divine Being, Ultimate Reality, Ultimate Truth).

Traditional religion involves accountability and responsibility; spirituality has fewer requirements. People may reject traditional religion but consider themselves spiritual. In the US, > 90% of elderly people consider themselves religious and spiritual; about 5% consider themselves spiritual but not religious. Most research assesses religion, not spirituality, using measures such as attendance at religious services, frequency of private religious practices, use of religious coping mechanisms (eg, praying, trusting in God, turning problems over to God, receiving support from the clergy), and intrinsic religiosity (internalized religious commitment).

For most of the elderly in the US, religion has a major role in their life:

- 96% believe in God or a universal spirit
- > 90% pray
- > 50% attend religious services weekly or more often

The elderly’s level of religious participation is greater than that in any other age group. For the elderly, the religious community is the largest source of social support outside of the family, and involvement in religious organizations is the most common type of voluntary social activity—more common than all other forms of voluntary social activity combined.

**Benefits**

Religion correlates with improved physical and mental health. However, experts cannot determine whether religion contributes to health or whether psychologically or physically healthier people are
attracted to religious groups. If religion is helpful, the reason—whether it is the religious beliefs themselves or other factors—is not clear. Many such factors (eg, psychologic benefits, encouragement of healthful practices, social support) have been proposed.

**Psychologic benefits:** Religion may provide the following psychologic benefits:

- A positive and hopeful attitude about life and illness, which predicts improved health outcomes and lower mortality rates
- A sense of meaning and purpose in life, which affects health behaviors and social and family relationships
- A greater ability to cope with illness and disability

Many elderly people report that religion is the most important factor enabling them to cope with physical health problems and life stresses (eg, declining financial resources, loss of a spouse or partner). In one study, > 90% of elderly patients relied on religion, at least to a moderate degree, when coping with health problems and difficult social circumstances. For example, having a hopeful, positive attitude about the future helps people with physical problems remain motivated to recover.

People who use religious coping mechanisms are less likely to develop depression and anxiety than those who do not; this inverse association is strongest among people with greater physical disability. Even the perception of disability appears to be altered by the degree of religiousness. Of elderly women with hip fractures, the most religious had the lowest rates of depression and were able to walk significantly further when discharged from the hospital than those who were less religious. Religious people also tend to recover from depression more quickly.

In the elderly, active involvement in a religious community correlates with better maintained physical functioning and health. Elderly people who attend religious services are more likely to stop smoking, exercise more, increase social contacts, stay married, and live longer. In one study, the mortality rate of patients with low levels of comfort from religion and of social support was 14 times that of patients with higher levels of both. Also, better mental health may improve physical health because depression and anxiety may aggravate coronary artery disease, hypertension, stroke, and psychosomatic disorders. Levels of IL-6 are significantly lower among people who attend religious services regularly than among those who do not.

**Health-promoting practices:** Some religious groups (eg, Mormons, Seventh-Day Adventists) advocate behaviors that enhance health, such as avoidance of tobacco and heavy alcohol use. Members of these groups are less likely to develop substance-related disorders, and they live longer than the general population.

**Social benefits:** Religious beliefs and practices often foster the development of community and broad social support networks. Increased social contact for the elderly increases the likelihood that disease will be detected early and that elderly people will comply with treatment regimens because members of their community interact with them and ask them questions about their health and medical care. Elderly people who have such community networks are less likely to neglect themselves.

**Caregivers:** Religious faith also benefits caregivers. In a study of caregivers of patients with Alzheimer's disease or terminal cancer, caregivers with a strong personal religious faith and many social contacts were better able to cope with the stresses of caregiving during a 2-yr period.

**Harmful Effects**

Religion is not always beneficial to the elderly. Religious devotion may promote excessive guilt, narrow-mindedness, inflexibility, and anxiety. Religious preoccupations and delusions may develop in patients with obsessive-compulsive disorder, bipolar disorder, schizophrenia, or psychoses.

Certain religious groups discourage necessary mental and physical health care, including lifesaving
therapies (eg, blood transfusions, treatment of life-threatening infections, insulin therapy), and may substitute religious rituals (eg, praying, chanting, lighting candles). Religious cults may isolate and alienate elderly people from family members and the broader social community; some cults sometimes encourage self-destruction.

**Role of the Health Care Practitioner**

Talking to elderly patients about their religious beliefs and practices helps health care practitioners provide care because these beliefs can affect the patients' mental and physical health. Inquiring about religious issues during a medical visit is appropriate under certain circumstances, including the following:

- When patients are severely ill, under substantial stress, or near death and ask or suggest that a practitioner talk about religious issues
- When patients tell a practitioner that they are religious and that religion helps them cope with illness
- When religious needs are evident and may be affecting patients' health or health behaviors

The elderly often have distinct spiritual needs that may overlap with but are not the same as psychologic needs. Ascertaining a patient's spiritual needs can help mobilize the necessary resources (eg, spiritual counseling or support groups, participation in religious activities, social contacts from members of a religious community).

**Spiritual history:** Taking a spiritual history shows elderly patients that the health care practitioner is willing to discuss spiritual topics. Practitioners may ask patients whether their spiritual beliefs are an important part of their life, how these beliefs influence the way they take care of themselves, whether they are a part of a religious or spiritual community, and how they would like the health care practitioner to handle their spiritual needs.

Alternatively, a practitioner may ask patients to describe their most important coping mechanism. If the response is not a religious one, patients may be asked whether religious or spiritual resources are of any help. If the response is no, patients may be sensitively asked about barriers to those activities (eg, transportation problems, hearing difficulties, lack of financial resources, depression, lack of motivation, unresolved conflicts) to determine whether the reason is circumstances or their choice. However, practitioners should not force religious beliefs or opinions on patients or intrude if patients do not want help.

**Referral to clergy:** Many clergy members provide counseling services to the elderly at home and in the hospital, often free of charge. Many elderly patients prefer such counseling to that from a mental health care practitioner because they are more satisfied with the results and because they believe such counseling does not have the stigma that mental health care does. However, many clergy members do not have extensive training in mental health counseling and may not recognize when elderly patients need professional mental health care. In contrast, many hospital clergy have extensive training in the mental, social, and spiritual needs of the elderly. Thus, including hospital clergy as part of the health care team can be helpful. They can often bridge the gap between hospital care and care in the community by communicating with clergy in the community. For example, when a patient is discharged from the hospital, the hospital clergy may call the patient's clergy, so that support teams in the patient's religious community can be mobilized to help during the patient's convalescence (eg, by providing housekeeping services, meals, or transportation, by visiting the patient or caregiver).

**Support of patients' religious beliefs and practices:** Health care practitioners should support the patient's religious involvement as long as it does not interfere with necessary medical care because such involvement may contribute to good health. People who are actively involved in religious groups, particularly those in major religious traditions, tend to be healthier.

**Religious interventions:** Some practitioners pray with patients, read religious scriptures to them, or make sure patients have the religious materials (eg, large-print scriptures, religious audiotapes) they want. However, practitioners should not feel obligated to do anything that violates their own beliefs.
Recommendation of religious activities: Health care practitioners may suggest that patients consider religious activities if patients seem receptive and may benefit from such activities, which can provide social contact, reduce alienation and isolation, and increase a sense of belonging, of meaning, and of life purpose. These activities may also help the elderly focus on positive activities rather than on their own problems. However, some activities are appropriate only for more religious patients. If patients are not already involved in religious activities, suggesting such activities requires sensitivity. Patients seek medical care for health-related reasons, not religious ones.

Patient and family information: Health care practitioners can provide information about the health benefits of religious beliefs and practices for the elderly and about local religious resources (eg, support groups at local churches, health promotion programs, volunteer activity programs).

Elder Abuse

Elder abuse is physical or psychologic mistreatment, neglect, or financial exploitation of the elderly.

Common types of elder abuse include physical abuse, psychologic abuse, neglect, and financial abuse. Each type may be intentional or unintentional. The perpetrators are usually a spouse or adult children but may be other family members or paid or informal caregivers. Abuse usually becomes more frequent and severe over time.

Physical abuse is use of force resulting in physical or psychologic injury or discomfort. It includes striking, shoving, shaking, beating, restraining, and forceful or improper feeding. It may include sexual assault (any form of sexual intimacy without consent or by force or threat of force).

Psychologic abuse is use of words, acts, or other means to cause emotional stress or anguish. It includes issuing threats (eg, of institutionalization), insults, and harsh commands, as well as remaining silent and ignoring the person. It also includes infantilization (a patronizing form of ageism in which the perpetrator treats the elderly person as a child), which encourages the elderly person to become dependent on the perpetrator.

Neglect is the failure to provide food, medicine, personal care, or other necessities. Neglect that results in physical or psychologic harm is considered abuse.

Financial abuse is exploitation of or inattention to a person's possessions or funds. It includes swindling, pressuring a person to distribute assets, and managing a person's money irresponsibly.

Although the true incidence is unclear, elder abuse appears to be a growing public health problem in the US. In a large US urban study of people ≥ 65, 3.2% were victims of physical abuse, psychologic abuse, or neglect. Because certain forms of abuse (eg, financial exploitation) were not included, the actual incidence of mistreatment was probably higher. In Canadian and western European studies, incidence of abuse was comparable to that in the US.

Risk Factors

For the victim, risk factors for abuse include impairment (chronic disorders, functional impairment, cognitive impairment) and social isolation. For the perpetrator, risk factors include substance abuse, psychiatric disorders, a history of violence, stress, and dependence on the victim (including shared living arrangements—see Table 314-1).

Diagnosis

Abuse is difficult to detect because many of the signs are subtle and the victim is often unwilling or unable to discuss the abuse. Victims may hide abuse because of shame, fear of retaliation, or a desire to protect the perpetrator. Sometimes when abuse victims seek help, they encounter ageist responses from health
care practitioners, who may, for example, dismiss complaints of abuse as confusion, paranoia, or dementia.

Social isolation of the elderly victim often makes detection difficult. Abuse tends to increase the isolation because the perpetrator often limits the victim's access to the outside world (e.g., denies the victim visitors and telephone calls).

[Table 314-1. Risk Factors for Elder Abuse]

Symptoms and signs of abuse may erroneously be attributed to a chronic disorder (e.g., a hip fracture attributed to osteoporosis). However, certain clinical situations are particularly suggestive of abuse (see Table 314-2).

History: If abuse is suspected, the patient should be interviewed alone, at least for part of the time. Other involved people may also be interviewed separately. The patient interview may start with general questions about feelings of safety but should also include direct questions about possible mistreatment (e.g., physical violence, restraints, neglect). If abuse is confirmed, the nature, frequency, and severity of events should be elicited. The circumstances precipitating the abuse (e.g., alcohol intoxication) should also be sought.

Social and financial resources of the patient should be assessed because they affect management decisions (e.g., living arrangements, hiring of a professional caregiver). The examiner should inquire whether the patient has family members or friends able and willing to nurture, listen, and assist. If financial resources are adequate but basic needs are not being met, the examiner should determine why. Assessing these resources can also help identify risk factors for abuse (e.g., financial stress, financial exploitation of the patient).

In the interview with the family caregiver, confrontation should be avoided. The interviewer should explore whether caregiving responsibilities are burdensome for the family member and, if appropriate, acknowledge the caregiver’s difficult role. The caregiver is asked about recent stressful events (e.g., bereavement, financial stresses), the patient's illness (e.g., care needs, prognosis), and the reported cause of any recent injuries.

Physical examination: The patient should be thoroughly examined, preferably at the first visit, for signs of abuse (see Table 314-3). The physician may need help from a trusted family member or friend of the patient, state adult protective services, or, occasionally, law enforcement agencies to persuade the caregiver or patient to permit the evaluation. If abuse is identified, a referral to Adult Protective Services is mandatory in most states.

Cognitive status should be assessed, e.g., using the Mini-Mental State Examination. Cognitive impairment is a risk factor for elder abuse and may affect the reliability of the history and the patient's ability to make management decisions.

Mood and emotional status should be assessed. If the patient feels depressed, ashamed, guilty, anxious, fearful, or angry, the beliefs underlying the emotion should be explored. If the patient minimizes or rationalizes family tension or conflict or is reluctant to discuss abuse, the examiner should determine whether these attitudes are interfering with recognition or admission of abuse.

[Table 314-2. Clinical Situations Suggesting Elder Abuse]

Functional status, including the ability to do activities of daily living (ADLs), should be assessed and any physical limitations that impair self-protection noted. If help with ADLs is needed, the examiner should determine whether the current caregiver has sufficient emotional, financial, and intellectual ability for the task. Otherwise, a new caregiver needs to be identified.

Coexisting disorders caused or exacerbated by the abuse should be sought.
**Laboratory tests:** Imaging and laboratory tests (eg, electrolytes to determine hydration, albumin to determine nutritional status, drug levels to document compliance with prescribed regimens) are done as necessary to identify and document the abuse.

**Documentation:** The medical record should contain a complete report of the actual or suspected abuse, preferably in the patient's own words. A detailed description of any injuries should be included, supported by photographs, drawings, x-rays, and other objective documentation (eg, laboratory test results) when possible. Specific examples of how needs are not being met, despite an agreed-on care plan and adequate resources, should be documented.

**Prognosis**

Abused elderly people are at high risk of death. In a large 13-yr longitudinal study, the

[Table 314-3. Signs of Elder Abuse]

...survival rate was 9% for abuse victims compared with 40% for nonabused controls. Multivariate analysis to determine the independent effect of abuse indicated that risk of mortality for abused patients over a 3-yr period after abuse was 3 times higher than that for controls over a similar period.

**Treatment**

An interdisciplinary team approach (involving physicians, nurses, social workers, lawyers, law enforcement officials, psychiatrists, and other practitioners) is essential. Any previous intervention (eg, court orders of protection) and the reason for its failure should be investigated to avoid repeating any mistakes.

**Intervention:** If the patient is in immediate danger, the physician, in consultation with the patient, should consider hospital admission, law enforcement intervention, or relocation to a safe home. The patient should be informed of the risks and consequences of each option.

If the patient is not in immediate danger, steps to reduce risk should be taken but are less urgent. The choice of intervention depends on the perpetrator's intent to harm. For example, if a family member administers too much of a drug because the physician's directions are misunderstood, the only intervention needed may be to give clearer instructions. A deliberate overdose requires more intensive intervention.

In general, interventions need to be tailored to each situation. Interventions may include

• Medical assistance

• Education (eg, teaching victims about abuse and available options, helping them devise safety plans)

• Psychologic support (eg, psychotherapy, support groups)

• Law enforcement and legal intervention (eg, arrest of the perpetrator, orders of protection, legal advocacy including asset protection)

• Alternative housing (eg, sheltered senior housing, nursing home placement)

• Counseling the victim, which usually requires many sessions (progress may be slow)

If victims have decision-making capacity, they should help determine their own intervention. If they do not, the interdisciplinary team, ideally with a guardian or objective conservator, should make most decisions. Decisions are based on the severity of the violence, the victim's previous lifestyle choices, and legal ramifications. Often, there is no single correct decision; each case must be carefully monitored.

**Nursing and social work issues:** As members of the interdisciplinary team, nurses and social workers...
can help prevent elder abuse and monitor the results of interventions. A nurse, social worker, or both can be appointed as coordinator to ensure that pertinent information is accurately recorded, that relevant parties are contacted and kept informed, and that necessary care is available 24 h/day.

In-service education about elder abuse should be offered to all nurses and social workers annually. In some states (eg, New York), education about child abuse (but not yet about elder abuse) is mandatory for physician, nursing, and social work licensure.

**Reporting:** All states require that suspected or confirmed abuse in an institution be reported, and most states require that abuse in the home also be reported. All US states have laws protecting and providing services for vulnerable, incapacitated, or disabled adults.

In > 75% of US states, the agency designated to receive abuse reports is the state social service department (Adult Protective Services). In the remaining states, the designated agency is the state unit on aging. For abuse within an institution, the local long-term care ombudsman office should be contacted. Telephone numbers for these agencies and offices in any part of the US can be found by calling the Eldercare Locator (800-677-1116) or the National Center on Elder Abuse (202-682-2470) and giving the patient’s county and city of residence or zip code. Health care practitioners should know reporting laws and procedures for their own states.

**Caregiver issues:** Caregivers of a physically or cognitively impaired elderly person may not be able to provide adequate care or may not realize that their behavior sometimes borders on abuse. These caregivers may be so immersed in their caregiving roles that they become socially isolated and lack an objective frame of reference for what constitutes normal caregiving. The deleterious effects of caregiver burden, including depression, an increase in stress-related disorders, and a shrinking social network, are well documented (see p. 3141). Physicians need to point out these effects to caregivers. Services to help caregivers include adult day care, respite programs, and home health care.

**Prevention**

A physician or other health care practitioner may be the only person an abuse victim has contact with other than the perpetrator and should therefore be vigilant for risk factors and signs of abuse. Recognizing high-risk situations can prevent elder abuse—eg, when a frail or cognitively impaired elderly person is being cared for by someone with a history of substance abuse, violence, a psychiatric disorder, or caregiver burden. Physicians should pay particular attention when a frail elderly person (eg, a person with a recent history of stroke or a newly diagnosed condition) is discharged into a precarious home environment. Physicians should also remember that perpetrators and victims may not fit stereotypes.

Elderly people often agree to share their homes with family members who have drug or alcohol problems or serious psychiatric disorders. A family member may have been discharged from a mental or other institution to an elderly person’s home without having been screened for risk of causing abuse. Physicians should therefore counsel elderly patients considering such living arrangements, especially if the relationship was fraught with tension in the past.

Patients can also actively decrease their risk of abuse (eg, by maintaining social relationships, by increasing social and community contacts). They should seek legal advice before signing any documents related to where they live or who makes financial decisions for them.
Chapter 315. The Older Driver

Introduction

Driving is essential for most older adults to maintain their autonomy. In the US, about 20 million drivers are ≥ 65. This number is expected to more than double by 2020.

Safe driving requires the integration of complex visual, physical, and cognitive tasks, and older drivers may have mild to moderate deficits in these domains. Many older drivers successfully self-regulate their behavior and compensate for deficits by avoiding rush hour, driving fewer miles per year, limiting trips to shorter distances, and avoiding driving during twilight, nighttime, or bad weather. Also, older drivers tend to be more cautious, drive more slowly, and take fewer risks. However, some older adults, whether because of denial, dementia, or a strong desire to maintain independence, continue to drive despite significant impairments in driving ability.

Older drivers on average have a lower annual incidence of crashes with injury (rates per 1000 licensed drivers—see Fig. 315-1) than drivers of all other ages. However, because the number of miles driven per year also declines with aging (see Fig. 315-2), the crash rate per mile for drivers ≥ 70 is higher than that for drivers of all other ages except those < 20.

Most crashes involving older drivers occur during the daytime and on weekdays.

[Fig. 315-1. Number of crashes per licensed driver by age (2003).]

[Fig. 315-2. Annual mileage by age and sex (2001).]

These crashes often result from failure to yield the right-of-way or heed a stop sign or red light and tend to occur while going through intersections, making left turns, or merging into traffic. Crashes are more likely to involve multiple vehicles and to result in serious injuries and fatalities. Unlike in younger drivers, alcohol and speeding rarely play a role.

When crashes do occur, older adults seem to be more vulnerable to injury because

• They have less capacity to withstand trauma.

• They often have more comorbidities.

• Many crashes are driver-side impact (eg, occur while making left turns), making the driver more likely to be injured.

• They are more likely than younger drivers to drive very old cars without air bags or other improvements in crash protection.

However, as cars have become more crash-worthy and other efforts have improved traffic safety, the crash fatality rate of older adults has decreased over the past decade.

Assessment: Health care practitioners become involved in driving decisions when deficits are identified during routine examination, when family members express concern, when law enforcement cites unsafe driving behaviors, or when patients solicit advice. The role of practitioners is to do detailed functional and medical assessments related to driving safety.

Driving history should be reviewed; details of driving habits and past violations, accidents, close calls, or getting lost may point to general or specific impairments. Some impairments may obligate practitioners to refer a patient to the state Department of Motor Vehicles for additional testing or driving restrictions. (See the National Highway Traffic Safety Administration's [NHTSA] Physician's Guide to Assessing and Counseling Older Drivers for state licensing requirements and reporting regulations at

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Key Points

• The number of older adults is growing rapidly.

• Driving cessation is inevitable for many and can have negative outcomes (eg, social isolation, depression, fewer driving destinations).

• Age-related and disease-related changes in physical and cognitive function can impair driving ability and account for some of the increased crash rate per miles driven.

• Many older drivers successfully self-regulate their behavior.

• Older adults are more vulnerable to injury in a crash than younger adults.

• The role of practitioners is to do functional and medical assessments, which determine overall driving safety, and to communicate recommendations effectively to older drivers and their family members.

• State licensing requirements and reporting regulations that pertain to older drivers are available from the NHTSA.

Functional Assessment

Functional assessment involves assessment of a patient's visual, physical, and cognitive abilities. (See the National Highway Traffic Safety Administration web site for an Assessment of Driving-Related Skills [ADReS].) Adequate function in these areas is required to drive safely. Much of the assessment can be done by primary health care practitioners, but specialists (eg, ophthalmologists, occupational and physical therapists, driving rehabilitation specialists) may need to be consulted. Identified deficits may require interventions (see p. 3154), including driving rehabilitation, assistive devices, driving cessation, and reporting to the state Department of Motor Vehicles. Some complicated cases may be referred to state medical advisory boards.

Visual function: Visual function is vital to safe driving. Age-related and pathologic changes in vision are common and can contribute to driving impairment. Changes with aging include

• Decreased retinal illuminance (amount of light reaching the retina), visual acuity, and peripheral vision

• Presbyopia (decreased ability to accommodate), which impairs depth perception

• Decreased ability to adapt to changes in light and heightened sensitivity to glare, which impair night driving

In many states, central visual acuity and peripheral vision are routinely tested by the Department of Motor Vehicles when a license is renewed. Most states require 20/40 visual acuity in at least one eye for unrestricted licensing (glasses or contacts are allowed). However, in some states, practitioners can extend the requirement pending medical justification. Additionally, some states have approved use of bioptics (a lens system with a telescope attached to a pair of glasses) for people with severely reduced vision. For horizontal peripheral vision, safe driving thresholds vary widely among states from no requirement to about 140°.

Tests of useful field of view (spatial area from which visual stimuli can be acquired during a single fixed glance) provide integrated measures of visual performance (eg, visual-processing speeds, visual-spatial attention, visual memory) and can be used to predict a higher risk of crash. For example, the incidence of crashes is 6 times higher when useful field of view is reduced by > 40%. However, field-of-view tests are not yet widely available.

Older drivers often require referral to an ophthalmologist for comprehensive testing.
Physical function: Various parameters of physical function can be assessed in the office.

- Motor speed, balance, and coordination can be assessed with the rapid-pace walk test. The patient is asked to walk a 3-m (10-ft) path, turn around, and walk back to the starting point as quickly as possible. If the patient normally walks with a walker or cane, it should be used during the test. A time of > 9 sec may indicate an increased risk of a motor vehicle crash.

- Range of motion should be tested in the cervical region and in all joints of the upper and lower extremities. Decreased cervical range of motion impairs ability to turn the head and scan for traffic (particularly in the blind spot). Decreased range of motion in the extremities impairs ability to operate car controls.

- Strength in upper and lower extremities should be assessed qualitatively (in terms of meeting the needs of driving a vehicle). Grip strength should be measured with a dynamometer. A grip strength of < 16 kg for men or < 14 kg for women may reflect decreased ability to manipulate the steering wheel.

- Proprioception and peripheral sensory function should be tested. Decreased peripheral sensation can impair ability to modulate pressure on foot controls.

Physical and occupational therapists who specialize in driving rehabilitation can provide comprehensive testing of physical function related to driving ability. A rehabilitation driving assessment sometimes also involves the specialist going out in a car with the patient to evaluate actual driving skills. The car used during the evaluation should be equipped with features that allow the specialist to maintain safe control (eg, passenger-side brake). Driving rehabilitation specialists can be located by contacting local rehabilitation facilities or going to www.driver-ed.org. However, in most states, the cost of a rehabilitation driving assessment is not covered by insurance (Medicare or private).

Cognitive function: Cognition is moderately impaired in about 3% of community-dwelling people aged 65 to 74, 14% of those aged 75 to 84, and > 20% of those > 85. People with cognitive impairment often do not recognize their limitations and are at higher risk of crashes; risk increases with severity of impairment. Tests that may predict driving performance include the following:

- The Clock Drawing Test: This test assesses long-term memory, short-term memory, visual perception, visuospatial skills, selective attention, and executive skills.

- The Trail Making Test (Part B): This easily given test assesses divided attention and visual scanning and can be found at the National Highway Traffic Safety Administration web site. Drivers with an abnormal score on this test (eg, > 180 sec) may be candidates for more specialized testing by a driving rehabilitation specialist.

- The Mini-Mental State Examination: Examination of mental status (see Sidebar 168-1 on p. 1588) screens for cognitive impairments.

Drivers with mild cognitive impairment should be considered for referral for more precise neuropsychologic testing.

Medical Assessment

Medical assessment involves a review of medical conditions and drugs that could impair driving ability. In general, any condition or drug that can impair consciousness should raise concern about driving safety.

Falls: Falls and motor vehicle crashes share common causative factors (eg, impaired vision, muscle strength, cognition). A history of falls in the past 1 to 2 yr indicates increased risk of crashes and should prompt further evaluation of physical functioning (see above).

Cardiac disorders: Cardiac disorders may increase driving risk. General guidelines include refraining from driving for...
• 1 mo after MI, coronary artery bypass surgery, or stabilization of unstable angina symptoms

• 3 mo after arrhythmia with syncope

• 6 mo after internal cardioverter defibrillator placement or after resuscitation required because of sustained ventricular tachycardia or ventricular fibrillation

Patients with severe heart failure (eg, class IV heart failure, dyspnea at rest or while driving) should refrain from driving until they can be evaluated with on-road testing.

**Neurologic disorders:** Neurologic disorders also increase driving risk. Specific disorders include

• Stroke or transient ischemic attack (TIA): Drivers with a single TIA should wait 1 mo before resuming driving; those with recurrent TIAs or stroke should be event-free for at least 3 mo before resuming driving. Physical examination should be done to assess how residual disability due to stroke may affect driving ability.

• Seizures: Regulations for drivers who have seizures are state-specific, but most states require a seizure-free interval (often 6 mo) before they reinstate driving privileges. Anticonvulsants can adequately control seizures in about 70% of patients, although relapses may occur when these drugs are withdrawn.

Many other neurologic disorders (eg, Parkinson's disease) cause disability and should be monitored by functional assessment and possibly an on-road test.

**Diabetes mellitus:** Diabetes mellitus poses a risk because patients may become hypoglycemic while driving. Patients who have had a recent hypoglycemic episode affecting awareness should not drive for 3 mo or until factors contributing to the episode (eg, diet, activity, timing and dose of insulin or antihyperglycemic drug) have been assessed and managed. Sensory changes in the extremities due to diabetes can also impair driving ability.

**Sleep disorders:** Sleep disorders, most notably obstructive sleep apnea syndrome, can cause drowsiness leading to crashes, and patients should refrain from driving until they are adequately treated.

**Drugs:** When starting a new drug that could affect visual, physical, or cognitive function, patients should refrain from driving for 1 to 2 days to be sure no adverse effects occur. Drugs that increase driving risk include

• Antihistamines, benzodiazepines, opioids, anticholinergics, hypnotics, antihypertensives, or tricyclic antidepressants: These drugs increase driving risk because they can cause drowsiness; some can also cause hypotension or arrhythmias.

• Antiparkinsonian dopamine agonists (eg, pergolide, pramipexole, ropinirole): These drugs occasionally cause acute sleep attacks, which pose an especially high risk of crashes.

• Antiemetics (eg, prochlorperazine) and muscle relaxants (eg, cyclobenzaprine): These drugs are cause for concern because of their potential for altering sensory perception.

Instructing patients to bring all drug containers to the office can help identify drugs that increase risk.

Older adults are involved in fewer alcohol-related fatal crashes. Fewer older adults consume alcohol, but limiting alcohol consumption is still important because blood alcohol level per amount of alcohol consumed is higher in older adults. Also, concurrent use of alcohol and other drugs, particularly multiple drugs, further impairs cognition, increasing the risk of crashes.

**Interventions**

If older drivers with significant functional deficits decide to limit or stop driving, the role of health care
practitioners is largely supportive. If the medical evaluation identifies potentially correctable deficits and older drivers acknowledge these deficits but still wish to continue driving, practitioners can offer treatment to help correct the deficits or impairments. However, aside from treating medical conditions that impair driving ability, most practitioners are ill-equipped to formulate or execute a driving rehabilitation plan; referral to specialists is often helpful.

Driving rehabilitation programs: Although some older drivers can benefit from driving refresher courses (e.g., American Association of Retired Persons Driver Safety Program available at www.aarp.org), most should be referred to occupational therapists that specialize in driving rehabilitation. Driving rehabilitation specialists can help by

• Clinically assessing skills related to driving and accompanying drivers on a road test for direct evaluation of driving skills and deficits

• Instituting a tailored rehabilitation plan to increase motor skills or cognition and perception in the driver’s daily life

• Providing adaptive equipment, such as a spinner knob to help with one-handed steering or more complicated devices such as hand controls

• Evaluating the response to the rehabilitation plan and providing feedback to the drivers as well as their relatives and physician as to whether the driver’s abilities are adequate to continue driving

However, in most states, the costs of a rehabilitation driving assessment and the adaptive equipment are not covered by insurance (Medicare or private).

Driving cessation: If older drivers deny or are unaware of their limitations or if deficits do not respond to treatment, practitioners may need to be more proactive. In these situations, practitioners should discuss issues relevant to driving safety, potential driving cessation, patient transportation needs, and alternative transportation resources with the patient and family members.

The practitioner should balance the benefits of safety to the patient, pedestrians, and other drivers against the costs of social isolation, worsening functional status, impaired quality of life, and clinical depression. For some patients (e.g., those with severe dementia), the benefits of driving restriction clearly outweigh the costs.

Alternative transportation options should be discussed; they vary from community to community, and contact with local resources such as the Alzheimer’s Association (www.alz.org) or American Automobile Association Foundation for Traffic Safety (www.seniordrivers.org) may prove beneficial. Family members can find information about having conversations with older drivers at www.thehartford.com/talkwitholderdrivers/.

The loss of driving privileges can be relatively devastating in terms of maintaining independence. If alternative transportation cannot be arranged and the ability to maintain activities of daily living is adversely affected, loss of driving privileges sometimes prompts the need to move in with a family member or transition to an assisted-living facility.

Reporting: If the driver’s functional limitations or medical status seems to warrant driving cessation, practitioners should follow the reporting requirements of their state Department of Motor Vehicles. States vary in their reporting laws. All states have voluntary reporting laws, but some states have mandatory reporting laws. In most states, statutes protect the practitioner’s anonymity or provide immunity to the practitioner. Legal consultation may be beneficial when an office or institution is developing a reporting policy and procedure.

Before making a report, practitioners should discuss recommendations for driving cessation directly with the patient and family rather than simply filing a report. Practitioners should make every attempt to persuade the patient to cooperate with driving restrictions. Such discussion should include why the patient’s limitations make driving unsafe and why the practitioner is obligated to report.
In some situations, practitioners must report functional limitations or medical status to state agencies against the wishes of their patients; this action often has a negative impact on the practitioner-patient relationship. Regardless, medical information can be legally disclosed if a patient's driving impairment might jeopardize public safety; practitioners who do not notify appropriate authorities may be legally liable for subsequent injuries.
Chapter 316. Funding Health Care for the Elderly

Introduction

In the US, health care services for the elderly are funded mainly by Medicare, Medicaid, the Veterans Health Administration, private insurance, and out-of-pocket payments. In addition, many states offer health-related benefits and programs, such as subsidies for transportation, housing, utilities, telephone, and food expenses, as well as help at home and nutrition services. Health care workers should help elderly patients learn about health benefits and programs they are entitled to.

Medicare

Medicare, administered by the Center for Medicare and Medicaid Services (CMS), is primarily a health insurance program for the elderly. (Medicare funds are also used to support certain components of postgraduate medical training and programs that regulate and monitor quality of care.) The following groups are eligible for Medicare:

• US citizens who are ≥ 65 and are eligible for benefits under Social Security, Civil Service Retirement, or Railroad Retirement

• People of all ages with end-stage renal disease requiring dialysis or transplantation

• Some people who are < 65 and have certain disabilities

The type and range of services that Medicare covers change regularly with new statutory and regulatory amendments (current information is available at www.medicare.gov). Each state has a State Health Insurance Assistance Program, which patients can call for assistance in understanding and choosing Medicare plans, understanding bills, and dealing with payment denials or appeals.

Physicians should understand basic Medicare rules, supply documentation used to determine whether patients are eligible for benefits, and make referrals to legal and social services for counseling and support.

If a patient's claim is denied, a Medicare Summary Notice is issued to the patient to provide information about services or supplies that Medicare does not cover. The denial of coverage may be reversed by a challenge made within 120 days of the notice. The challenge must be supported by an appeal in a fair hearing administrative forum, in which the insurance company handling Medicare claims reviews the case. If unsatisfied with the outcome of that review, the patient has the right to a hearing before a judge.

The original Medicare Plan (sometimes referred to as the fee-for-service plan) has 2 parts:

• Part A (hospital insurance)

• Part B (medical insurance)

The original Medicare Plan is available nationwide. A complete description of Part A and B services and other provisions (called Medicare & You 2010) is available at www.medicare.gov or by calling 800-633-4227.

In 2003, the Medicare Modernization Act was enacted to provide reimbursement for health care in models other than traditional fee-for-service and to provide reimbursement for prescription drugs. The results were

• Part C (Medicare Advantage Plans), which includes managed care plans, preferred provider organization plans, and private fee-for-service plans

• Part D (for prescription drugs)
Each part covers specific health care services (see Table 316-1). Medicare does not cover intermediate or long-term nursing care (except for the Part A services noted below), nor does it cover routine eye, foot, or dental examinations.

**Part A**

More than 95% of people ≥ 65 are enrolled in Part A. Part A is supported by a payroll tax collected from people who are working; it represents prepaid hospital insurance for Medicare-qualified retirees. Generally, only people who receive monthly Social Security payments are eligible, and most of those who are eligible do not pay premiums. However, people may be required to pay premiums if they or their spouses have worked < 40 quarters at a job that is considered Medicare eligible (ie, if they or their employer paid the payroll tax required by the Federal Insurance Contributions Act [FICA]). Premiums in 2010 were $254/mo for people with 7.5 to 10 yr of eligible employment and $461/mo for those with < 7.5 yr of eligible employment. People whose income and assets are below certain thresholds are eligible for financial assistance from the Medicare Savings Programs (see p. 3162).

Part A covers the following under the circumstances outlined below:

- Inpatient hospital care
- Posthospital care in a skilled nursing facility or a rehabilitation facility
- Hospice care
- Limited custodial care
- Limited home health care

Care in a hospital or a skilled nursing facility is paid for based on benefit periods. A benefit period begins when a person is admitted to a facility and ends when the person has been out of the facility for 60 consecutive days. If a person is readmitted after the 60 days, a new benefit period begins, and another deductible must be paid. If a person is readmitted in < 60 days, an additional deductible is not paid, but the hospital or facility may not receive full payment for the 2nd admission. There is no limit to the number of benefit periods.

Medicare Prospective Payment Systems determine what Medicare will pay for each aspect of care it covers (eg, for hospital inpatient care, skilled nursing facility care, or home health care).

**Inpatient hospital care:** Under Part A, the beneficiary pays only a deductible for the first 60 full coverage days of the benefit period; the deductible is established annually ($1100 in 2010). If the hospital stay exceeds 60 days, the beneficiary pays a daily co-payment equal to one fourth of the deductible (in 2010, $275 per day for days 61 to 90). If the hospital stay exceeds 90 days, the beneficiary pays a daily co-payment equal to half of the deductible (in 2010, $550 per day for days 91 to 150). Days 91 to 150 during a hospital stay are designated as reserve days. Part A benefits include 60 lifetime reserve days for use after a 90-day benefit period has exhausted.

[Table 316-1, Funding Sources by Type of Care]

The 60 days are not renewable and can be used only once during a beneficiary's lifetime. Payment is automatically made for such additional days of hospital care after the 90 days of benefits have been exhausted unless the beneficiary chooses not to have such payment made (thus saving the reserve days for a later time). Beyond 150 days, the beneficiary is responsible for all charges.

Part A covers virtually all medically necessary hospital services, except it provides only limited coverage for inpatient mental health care services. Part A pays for a semiprivate room or, if medically necessary, a private room, but not for amenities. Other covered services include discharge planning and medical social services, such as identification of eligibility for public programs and referrals to community agencies.
The prospective payment system determines payment for inpatient hospital care based on the diagnosis-related group (DRG). The DRG is determined by the beneficiary's principal diagnosis with some adjustment for age, severity, sex, comorbidities, and complications. Hospitals are reimbursed a set amount for a given DRG regardless of their actual expenses in providing care. Thus, a hospital's financial profit or loss depends partly on length of stay and costs of diagnosis and therapy for each patient. Under the prospective payment system, the financial pressure for early discharge and limited intervention may conflict with medical judgment. When a patient cannot be discharged home safely or to a nursing home because no bed is available, Medicare typically pays a relatively low per diem cost for an alternative level of care.

**Inpatient care in a skilled nursing facility**: Coverage of skilled nursing care and skilled rehabilitation services is complex and can change every year. These services are covered only if initiated immediately or shortly after discharge from a hospital. The period of coverage is usually < 1 mo (specific duration of coverage depends on documented improvement in the patient's condition or level of function). In 2010, the first 20 days were covered completely; the next 80 days were covered but required a co-payment of $137.50/day. Benefits are limited to 100 days per benefit period.

Medicare’s prospective payment system assigns patients in skilled nursing facilities to a resource utilization group system (RUGS III) based on 7 categories:

- Special care
- Rehabilitation
- Clinically complex problems
- Severe behavioral problems
- Impaired cognition
- Reduced physical functioning
- Need for extensive services

These categories reflect the types and amounts of resources a patient's care is expected to cost. They are subdivided based primarily on the patient's functional dependence. This system is updated annually. The goal is to increase efficiency and avoid excessive payment for patients who require little care. Prospective per diem rates cover routine, ancillary, and capital costs of care for a patient in a skilled nursing facility.

RUGS III uses data from the Minimum Data Set (MDS), the mandated uniform assessment instrument for patients in skilled nursing facilities. The MDS requires ongoing review of patients, making it possible to link patient outcomes with RUGS categories.

**Home health care**: Generally, part A covers certain medical services provided in the home (eg, part-time or intermittent skilled nursing care; home health aide services incidental to skilled care; physical, speech, and occupational therapy) if they are part of a physician-approved care plan for a home-bound patient. However, amount and duration of coverage is limited. The recent implementation of a prospective payment system now limits the amount of coverage. Medical supplies are covered when billed by a home health agency.

**Hospice services**: Medical and support services for a terminal illness are generally covered if a physician certifies that the patient is terminally ill (estimated life expectancy of 6 mo). However, the patient must choose to receive hospice care instead of standard Medicare benefits.

**Custodial care**: Assistance with activities of daily living (ADLs), such as eating, dressing, toileting, and bathing, is covered in the home only when skilled care (services of a professional nurse or therapist under a physician-authorized plan of home care) is also required. Such custodial care in a skilled nursing facility is covered under part A.
facility is covered when it is part of posthospital acute or rehabilitation care.

Part B

The federal government pays an average of about 75% of Part B costs, and beneficiaries pay 25%. Part B is optional; although Social Security beneficiaries are automatically enrolled in Part B at age 65, they may decline coverage (95% elect to keep Part B coverage). All beneficiaries pay a monthly premium, which varies by income—$110.50 in 2010 for new beneficiaries whose income in 2008 was <$85,000 ($170,000 if they were married and filing a joint return); premiums are higher for people with a higher income. Premiums are automatically deducted from monthly Social Security checks. People who decline coverage but later change their minds must pay a surcharge based on how long they delayed enrollment. Premiums generally increase by 10% for each year's delay in enrollment, except for people who delay because they are covered by group insurance through their, their spouse's, or a family member's employer; such people do not pay the surcharge if they enroll when employment or health care coverage ends (whichever comes first). Most states have Medicare Savings Programs (see p. 3162) that pay Part B premiums for people who meet certain financial qualifications.

Participants may stop coverage at any time but must pay a surcharge on the premium if they reenroll.

Covered services: Part B covers a percentage of the following: cost of physician services; outpatient hospital care (eg, emergency department care, outpatient surgery, dialysis), with certain restrictions; outpatient physical, speech, and occupational therapy; diagnostic tests, including portable x-ray services in the home; prosthetics and orthotics; and durable medical equipment for home use. If surgery is recommended, Part B covers part of the cost of an optional 2nd opinion and, if these opinions differ, a 3rd opinion.

Part B also covers medically necessary ambulance services, certain services and supplies not covered by Part A (eg, colostomy bags, prostheses), spinal manipulation by a licensed chiropractor for subluxation shown on x-ray, drugs and dental services if deemed necessary for medical treatment, optometry services related to lenses for cataracts, smoking cessation counseling, and the services of physician assistants, nurse practitioners, clinical psychologists, and clinical social workers. Outpatient mental health care, with certain limitations, is covered.

Drugs and biologicals that cannot be administered by the patient (eg, drugs given IV), some oral anticancer drugs, and certain drugs for hospice patients are covered by Part B. However, unless the patient is enrolled in a managed care program, Part B generally does not cover outpatient drugs.

Part B covers several preventive services, including bone mass measurement, serum cholesterol screening, abdominal aortic aneurysm screening, diabetes services (screening, supplies, self-care training, and eye and foot examinations), colorectal cancer screening, prostate cancer screening and prostate-specific antigen tests, an initial physical examination (the "Welcome to Medicare" examination), glaucoma screening, vaccinations (influenza, pneumococcal, hepatitis B), mammograms, and Papanicolaou (Pap) tests. Part B does not cover routine eye, foot, or dental examinations.

Physician reimbursement: Under Part B, physicians may elect to be paid directly by Medicare (assignment), receiving 80% of the allowable charge directly from the program, once the deductible has been met. If physicians accept assignment, their patients are responsible for paying only the deductible. Physicians who do not accept assignment of Medicare payments (or do so selectively) may bill patients up to 115% of the allowable charge; the patient receives reimbursement (80% of the allowable charge) from Medicare. Physicians are subject to fines if their charges exceed the maximum allowable Medicare fees. Physicians who do not accept assignment from Medicare must give patients a written estimate for elective surgery if it is > $500. Otherwise, patients can later claim a refund from physicians for any amount paid over the allowable charge.

Medicare payments to physicians have been criticized as inadequate for the time involved in giving physical and mental status examinations and obtaining the patient history from family members. A Medicare fee schedule based on a resource-based relative value scale for physician services became effective in January 1992 in an attempt to correct this problem. The effects of the fee schedule on patient...
care and on medical practice remain to be determined, but few physicians are satisfied. The paperwork and time involved in documentation have increased.

Part C (Medicare Advantage Plans)

This program (formerly called Medicare + Choice) offers several alternatives to the traditional fee-for-service programs. The alternatives are provided by private insurance companies; Medicare pays these companies a fixed amount for each beneficiary. Several different types of plans are available; they include managed care, preferred provider organizations, private fee-for-service, medical savings accounts, and special needs plans.

Medicare Advantage plans must cover at least the same level and types of benefits covered by Medicare A and B. However, Medicare Advantage plans may include additional benefits (eg, coverage for dentures, prescription drugs, or routine eyeglasses), although participants may pay an additional monthly premium for the additional benefits. Plans differ on whether participants are free to choose any physician and hospital they want, whether they can keep coverage from an employer or union, and what costs are paid out-of-pocket, including how much (if at all) they charge for a premium, whether they pay any of the Part B premium, and how much their deductible and co-payments are. Medicare Advantage plans are available in many but not all areas of the country.

Part D

Medicare Part D helps cover costs of prescription drugs. It is optional. Plans are provided by insurance or other private companies working with Medicare. There are over 1600 plans available nationwide. Premiums generally increase by an additional 1% for each month that people delay enrolling after they first become eligible for Medicare.

Covered drugs: Plans vary in the drugs they cover (formulary) as well as in pharmacies that can be used. However, formularies must include ≥ 2 effective drugs in the categories and classes of drugs most commonly prescribed for people who use Medicare. Formularies must also cover all available drugs for the following 6 classes: anticonvulsants, antidepressants, antiretroviral drugs, antineoplastics, antipsychotics, and immunosuppressants. Formularies may change over time (often annually). Formularies must also have an appeals process by which nonformulary drugs can be approved if necessary.

Benefits and costs: Costs are expected to increase annually until at least 2013. Costs in 2010 are as follows for the basic benefits (see Fig. 316-1):

- **Premiums**: Premiums vary by plan but average about $31 yearly.
- **Annual deductible**: Patients pay the first $310 of drug costs.
- **Co-payments**: For the next $2520 of drug costs (after the $310 deductible), patients pay 25% of drug costs (co-payment). Thus, the co-payment for the first $2830 of drug costs is $630 in addition to the $310 deductible.
- **Coverage gap (doughnut hole)**: After the first $2830 of drug costs, people must pay 100% of the next $3610 of drug costs—that is, until total drug costs equal $6440 (total cost, including deductible and co-payments, is $4550 out-of-pocket).
- **Reduced co-payments**: Once total annual drugs costs are > $6440, Medicare pays about 95% of additional drug costs until the end of the year.

Many companies also offer enhanced plans that provide more coverage (eg, lower deductibles or co-payments), although these plans have higher monthly premiums.

[Fig. 316-1, Medicare Part D drug costs in 2010.]
People with low income and minimal assets (eg, those who have full Medicaid coverage, who belong to a Medicare Savings Program, or who get Supplemental Security Income) may be eligible for financial assistance with premiums, deductibles, and co-payments. In addition to providing insurance assistance, many states have state pharmacy assistance programs that help pay for prescription drugs, based on some combination of the person's need, age, and medical disorders; information about these programs is available from the State Health Insurance Assistance Program.

**Medicaid**

Funded by a federal-state partnership, Medicaid pays for health services for certain categories of the poor (including the aged poor, the blind or disabled, and low-income families with dependent children). The federal government contributes between 50% and about 76% of the payments made under each state's program; the state pays the remainder. Federal reimbursement is higher for states where incomes are lower. About 10% of the elderly receive services under Medicaid, accounting for about 40% of all Medicaid expenditures. Medicaid is the major public payer for long-term care; it contributed about 40% of the $177.6 billion spent for long-term care services in 2006.

**Covered services:** Services covered under federal guidelines include inpatient and out-patient hospital care, laboratory and x-ray services, physician services, skilled nursing care, nursing home care not covered by Medicare, and many home health services for people > 21 yr.

States may cover certain other services and items, including prescription drugs (or the premiums for Medicare Part D if patients are eligible for Part D), dental services, physical therapy, rehabilitation services, and eyeglasses. Each state determines eligibility requirements, which therefore vary, but people receiving funds from cash-assistance programs (eg, the Supplemental Security Income program) must be included. Several states offer enriched packages of Medicaid services under waiver programs, which are intended to delay or prevent nursing home admission by providing additional home and community-based services (eg, day care, personal care, respite care).

**Eligibility:** Eligibility depends on income, assets, and personal characteristics. In 2009, people who are eligible include the following:

- All pregnant women and women with children if income is < 133% of the poverty level
- Children aged 6 to 19 yr if family income is < 100% of the poverty level
- Elderly and disabled people whose income makes them eligible for Supplemental Security Income (SSI)
- Institutionalized patients whose income is < 300% of the SSI income threshold

Most states have other criteria that allow people to qualify for Medicaid.

Assets, excluding equity in a home and certain other assets, are also considered. If the remaining assets exceed the limit, people are not eligible for Medicaid, even if their income is low. Thus, the elderly may have to spend down (ie, pay for care from personal savings and sale of assets until stringent state eligibility requirements are met) to qualify for Medicaid. How much of monthly income and of the couple's assets that the spouse of a nursing home resident may keep varies by state. Divestment of assets at below fair-market value during the 3 yr before entrance into a nursing home may delay eligibility for Medicaid benefits. Medicaid denies coverage for a period of time that is determined by the amount of inappropriately divested funds divided by the average monthly cost of nursing home care in the state. For example, if a person gives away $10,000 in a state where the average monthly cost of care is $3,500, Medicaid coverage is delayed by about 3 mo.

**Medicaid estate recovery:** Under certain circumstances, Medicaid is entitled (and sometimes required) to recover expenditures from the estates of deceased Medicaid recipients. Typically, recovery may be made only from estates of recipients who were ≥ 55 yr when they received Medicaid benefits or were permanently institutionalized regardless of age. The definition of estate varies by state. Some states
include only property that passes through probate; others include assets that pass directly (eg, through joint tenancy with right of survivorship, living trusts, or life insurance payouts). Some states protect the family home from Medicaid claims. The vigor with which claims are pursued varies by state and by case.

**Medicare Savings Programs:** People who are currently eligible for Medicare and whose income and assets are below certain thresholds are eligible for Medicare Savings Programs. These programs are run by individual state Medicaid programs and cover certain out-of-pocket expenses not covered by Medicare. There are several programs. The Qualified Medicare Beneficiary program covers Part A and Part B premiums, deductibles, and co-insurance; the Specified Low-income Medicare Beneficiary program and the Qualified Disabled Working Individual program pay part B premiums.

The federal government has set eligibility requirements based on income and asset value. States are free to adopt less restrictive requirements (eg, permitting enrollment at a higher income level). People enroll through state Medicaid offices.

**Other Federal Programs**

**Veterans Health Administration:** This Department of Veterans Affairs (VA) program provides health care to eligible veterans. Determining eligibility for VA benefits can be complex, and care is not always free. The VA operates > 160 hospitals, 43 domiciliary facilities, and > 130 nursing homes. It also contracts to provide care in community hospitals and nursing homes. Several innovative geriatric programs (including geriatric assessment units; Geriatric Research, Education, and Clinical Centers; and hospital-based home care programs) have been developed within the VA system.

**Tricare:** This healthcare program is for active-duty service members, retired service members, and their families.

**Older Americans Act (OAA):** Enacted in 1965, the OAA has evolved from a program of small grants and research projects into a network of 57 state, territorial, and Indian tribal units on aging; 670 area agencies on aging; and thousands of community agencies. The primary purpose of the OAA is to develop, coordinate, and deliver a comprehensive system of services for elderly people at the community level; services include information and referral, outreach, transportation, senior centers, nutritional programs, advocacy, protective services, senior employment, ombudsman programs, and supportive services. The OAA also funds research and training. People > 60 are eligible regardless of income level.

**Social Security:** Although not usually considered a health program, Social Security provides basic pension payments that the elderly use for health care services. The elderly receive 2 types of payments:

- **Old Age and Survivors Insurance,** which is financed by Social Security trust funds and provides payments to retirees, surviving spouses, or qualified dependents

- **Supplementary Security Income,** which is financed from general revenues and provides a guaranteed minimum income to aged, blind, and disabled people

**Title XX of the Social Security Act:** This program authorizes reimbursements to states for social services, including various home health services and homemaker services (eg, meal preparation, laundry, light housekeeping, grocery shopping) for the frail elderly. These funds have shifted to the Social Services Block Grant program, which was designed to prevent or reduce inappropriate institutional care by providing for community-based care and other assistance that enables the elderly to maintain autonomy in the community. The program is defined, administered, and implemented by states; it does not support institutional care or any service covered by Medicare or Medicaid. The program covers health services only when they are an "integral but subordinate" component of an overall social service program.

**Private Insurance**

**Medigap:** About 87% of beneficiaries enrolled in fee-for-service Medicare programs have Medicare supplemental insurance policies (most are a form of Medigap insurance), which pay for some or all of Medicare deductibles and co-payments, typically in Parts A and B. People must be enrolled in Parts A and
B to be eligible to purchase Medigap insurance. People enrolled in Part C (Medicare Advantage Plan—see p. 3160) cannot purchase a Medigap policy unless they leave the Part C plan and return to original Medicare. Most Medigap insurance is purchased individually from private insurers, although employers may provide it to retirees.

There are 12 different types of Medigap insurance available, labeled A through L. Benefits are the same for all plans with the same letter, regardless of insurance carrier. No plan may duplicate Medicare benefits. The basic plan (Plan A) covers:

- Hospital co-payments
- 100% of expenses eligible for coverage by Medicare Part A after Medicare hospital benefits are exhausted
- Part B co-payments

The other plans, which have higher premiums than Plan A, may provide additional coverage in a skilled nursing facility and may cover Part A and Part B deductibles, preventive medical services, and short-term home-based help with activities of daily living (ADLs) during recovery from an illness, injury, or surgery. Some of these plans, if purchased before Medicare Part D took effect, covered a percentage of the cost of outpatient prescribed drugs.

The Medigap open enrollment period begins the month people turn 65 and lasts 6 mo. During this period, people who have preexisting conditions cannot be denied coverage or charged more; however, they may be made to wait up to 6 mo before preexisting conditions are covered.

**Long-term care insurance**: Very few private medical insurance policies cover services such as long-term home health care or long-term nursing home care. However, some private insurers offer long-term care insurance. Such plans are useful for people who want to preserve their assets and who can afford to pay the premiums until care is needed, possibly for an extended period of time. This insurance is not recommended for people with few assets and may not be worthwhile for people who can easily pay for long-term care.

Benefits usually begin when a person can no longer do a certain number of ADLs.

Some plans, called tax-qualified plans, offer tax advantages (eg, deduction of premiums from taxable income as medical expenses).

For all long-term care services, private insurance pays for only 9%, and people pay for 22% out-of-pocket. A large proportion of out-of-pocket spending occurs as the elderly spend down to qualify for Medicaid.

**Models for Comprehensive Coverage**

Individually, Medicare, Medicaid, Medigap, and private long-term care insurance have shortcomings in providing comprehensive geriatric care:

- Medicare excludes long-term custodial care, some preventive services, and large amounts of prescription drug costs.
- Medicaid belatedly intervenes after the patient is impoverished.
- Medigap, like Medicare, excludes long-term care.
- Private insurance is too expensive for most of the elderly, leaves them vulnerable to financial catastrophe, and supports only fragments of long-term care.

Collectively, these programs rarely promote integration of acute and long-term care or coordination of
health and social services. However, several model projects have demonstrated that with organized
delivery of services using combinations of public funding and private insurance, comprehensive geriatric
care, including some long-term care, can be adequately financed.

Social health maintenance organizations (SHMOs): SHMOs are demonstration programs financed by
Medicare. They use Medicare, Medicaid, and private patient payments to cover a wide range of care
benefits managed by nurses, social workers, and physicians. Patients not eligible for Medicaid benefits
use private payments to cover a limited amount of long-term care, principally in the home. Like an HMO,
an SHMO is at financial risk for the cost of services and therefore has an incentive to manage resources
carefully.

Program of All-Inclusive Care for the Elderly (PACE): PACE is designed to keep patients in the
community as long as medically, socially, and financially possible. A PACE interdisciplinary team assesses
patient needs and develops and implements a care plan.

PACE includes medical and dental care, adult day care (including transportation to and from the facility),
health and personal care at home, prescription drugs, social services, rehabilitation, meals, nutritional
counseling, and hospital and long-term care when needed. PACE programs provide social and medical
services primarily in an adult day health center, supplemented by in-home and referral services. The
PACE service package must include all Medicare and Medicaid covered services, and other services
determined necessary by the interdisciplinary team for the care of the PACE participant. PACE may
require a monthly fee.

As of 2010, 30 states have approved PACE providers.

Extended care communities: A life-care community or continuing care retirement community provides
housing, health care, and other services under packaged financing and management. These communities
may have a clinic, an infirmary, or even a nursing home on the site, and housing is designed to
accommodate disabled people. Many of these communities serve wealthy retirees willing to sign long-
term contracts for their housing and care.

Some life-care communities fail because inflation and an aging population cause costs for services to
exceed income. Some communities keep costs down by providing housing and minimal services with
options to purchase additional services.
Chapter 317. Concepts in Pharmacotherapy

Introduction

Drugs are selected based on characteristics of the drug (eg, efficacy, safety profile, route of administration, route of elimination, dosing frequency, cost) and of the patient (eg, age, sex, likelihood of pregnancy, ethnicity, other genetic determinants). Risks and benefits of the drug are also assessed; every drug poses some risk.

Response to a drug depends partly on the patient's characteristics and behaviors (eg, consumption of foods or supplements; adherence to a dosing regimen; differences in metabolism due to age, sex, race, genetic polymorphisms, or hepatic or renal insufficiency), coexistence of other disorders, and use of other drugs. Drug errors (eg, prescribing an inappropriate drug, misreading a prescription, administering a drug incorrectly) can also affect response.

Adherence to a Drug Regimen

Adherence (compliance) is the degree to which a patient follows a treatment regimen. For drugs, adherence requires that the prescription is obtained promptly and the drug is taken as prescribed in terms of dose, dosing interval, and duration of treatment. Patients should be told to alert their physician if they stop or alter the way they take a drug, but they rarely do so.

Only about half of patients who leave a physician's office with a prescription take the drug as directed. The most common reasons for nonadherence are

- Frequent dosing
- Denial of illness
- Poor comprehension of the benefits of taking the drug
- Cost

Many other reasons contribute to nonadherence (see Table 317-1).

Children are less likely than adults to adhere to a treatment regimen. Adherence is worst with chronic disorders requiring complex, long-term treatment (eg, juvenile diabetes, asthma). Parents may not clearly understand prescription instructions and, within 15 min, forget about half the information given by the physician.

[Table 317-1, Causes of Nonadherence]

The elderly adhere to treatment regimens as well as other adults. However, factors that decrease adherence (eg, inadequate finances, use of multiple drugs or drugs that must be taken several times a day) are more common among the elderly (see p. 3097). Cognitive impairment may further decrease adherence. Sometimes a prescriber must be creative by picking a drug that is easier to use even though it may not be the first choice. For example, a clonidine patch applied weekly by a visiting nurse or family member may be tried for hypertension in patients who cannot adhere to a more preferable daily regimen of oral drugs.

The most obvious result of nonadherence is that the disorder may not be relieved or cured. Nonadherence is estimated to result in 125,000 deaths due to cardiovascular disorders each year in the US. If patients took their drugs as directed, up to 23% of nursing home admissions, 10% of hospital admissions, many physician visits, many diagnostic tests, and many unnecessary treatments could be avoided. In some cases, nonadherence can actually lead to worsening of disease. For example, missed
doses or early cessation of antibiotic or antiviral therapy may lead to resistant organisms.

Pharmacists and nurses may detect and help solve adherence problems. For example, a pharmacist may note that a patient does not obtain refills or that a prescription is being refilled too soon. In reviewing prescription directions with the patient, a pharmacist or nurse may uncover a patient's misunderstandings or fears and alleviate them. Physicians can alter complicated or frequent dosing or substitute safe, effective, but less expensive drugs. Communication among all health care practitioners that provide care for a patient is important.

**Drug Errors**

Drug errors contribute to morbidity. They are estimated to cost the US health care system up to $177 billion (depending on definitions) annually. Drug errors may involve

- The wrong choice of a drug or a prescription for the wrong dose, frequency, or duration
- An error in reading the prescription by the pharmacist so that the wrong drug or dose is dispensed
- An error in reading the label of the drug container by the caregiver so that the wrong drug or dose is given
- Incorrect instructions to the patient
- Incorrect administration by a clinician, caregiver, or patient
- Incorrect storage of a drug by the pharmacist or patient, altering the drug's potency
- Use of outdated drug, altering the drug's potency
- Confusion of the patient so that the drug is taken incorrectly

Errors in prescribing are common, especially for certain populations. The elderly (see Ch. 308, especially Table 308-3 on p. 3094), women of childbearing age, and children are particularly at risk. Drug interactions particularly affect those taking many drugs. To minimize risk, clinicians should know all drugs being taken—including those prescribed by others and OTC drugs—and keep a complete problem list. Patients should be encouraged to write and update a list of their current drugs and dosages and bring the list to every health care appointment or emergency department visit. If there is any doubt as to which drugs are being used, patients should be instructed to bring all their drugs to their health care appointments for review.

Prescriptions must be written as clearly as possible. The names of some drugs are similar and, if not written clearly, cause confusion. Changing some traditional but easily confused notations may also help reduce errors. For example, "qd" (once/day) may be confused with "qid" (4 times/day). Writing "once/day" or "once a day" is preferred. Electronically transmitted or computer-printed prescriptions can avoid problems with illegible handwriting or inappropriate abbreviations.

Drugs may be given incorrectly, especially in institutions. A drug may be given to the wrong patient, at the wrong time, or by the wrong route. Certain drugs must be given slowly when given IV, and some drugs cannot be given simultaneously. When an error is recognized, it should be reported immediately to a clinician, and a pharmacist should be consulted. Bar codes and computerized pharmacy systems may help decrease the incidence of drug errors.

A pharmacist should store drugs in a manner that ensures their potency. Mail-order pharmacies should follow procedures to ensure proper transportation. Storage by patients is often suboptimal. If stored incorrectly, drugs are likely to decrease in potency long before the stated expiration date. Labeling should clearly state whether a drug needs to be stored in the refrigerator or kept cool, needs to be kept out of excessive heat or sun, or otherwise requires special storage. On the other hand, unnecessary precautions decrease adherence and waste the patient's time. For example, unopened insulin should be
refrigerated, but a bottle in use can be stored safely outside the refrigerator for a relatively long time if not exposed to excessive heat and sun.

Use of outdated drugs is common. Outdated drugs are likely to be ineffective and some (eg, aspirin, tetracycline) can be harmful if used when outdated.

Most commonly, drug error results from a patient's confusion about how to take drugs. Patients may take the wrong drug or dose. Dosing instructions for each drug, including why the drug has been prescribed, should be completely explained to patients and given in writing when possible. They should be advised to ask their pharmacist for additional advice about taking their drugs. Packaging should be convenient but safe. If children will not have access to the drug and patients may have difficulty opening the container, drugs do not need to be provided in childproof containers.

**Drug Interactions**

Drug interactions are changes in a drug's effects due to recent or concurrent use of another drug or drugs (drug-drug interactions) or due to ingestion of food (drug-nutrient interactions—see p. 7).

A drug interaction may increase or decrease the effects of one or both drugs. Clinically significant interactions are often predictable and usually undesired (see Table 317-2). Adverse effects or therapeutic failure may result. Rarely, clinicians can use predictable drug-drug interactions to produce a desired therapeutic effect. For example, coadministration of lopinavir and ritonavir to patients with HIV infection results in altered metabolism of lopinavir and increases serum lopinavir concentrations and effectiveness.

In therapeutic duplication, 2 drugs with similar properties are taken at the same time and have additive effects. For example, taking a benzodiazepine for anxiety and another benzodiazepine at bedtime for insomnia may have a cumulative effect, leading to toxicity.

Drug interactions involve

- Pharmacodynamics
- Pharmacokinetics

In **pharmacodynamic interactions**, one drug alters the sensitivity or responsiveness of tissues to another drug by having the same (agonistic) or a blocking (antagonistic) effect. These effects usually occur at the receptor level but may occur intracellularly.

In **pharmacokinetic interactions**, a drug usually alters absorption, distribution, protein binding, metabolism, or excretion of another drug. Thus, the amount and persistence of available drug at receptor sites change. Pharmacokinetic interactions alter magnitude and duration, not type, of effect. They are often predicted based on knowledge of the individual drugs or detected by monitoring drug concentrations or clinical signs.

**Minimizing drug interactions:** Clinicians should know all of their patients' current drugs, including drugs prescribed by other clinicians and all OTC drugs, herbal products, and nutritional supplements. Asking patients relevant questions about diet and alcohol consumption is recommended. The fewest drugs in the lowest doses for the shortest possible time should be prescribed. The effects, desired and undesired, of all drugs taken should be determined because these effects usually include the spectrum of drug interactions. If possible, drugs with a wide safety margin should be used so that any unforeseen interactions do not cause toxicity.
Patients should be observed and monitored for adverse effects, particularly after a change in treatment; some interactions (eg, effects that are influenced by enzyme induction) may take ≥ 1 wk to appear. Drug interactions should be considered as a possible cause of any unexpected problems. When unexpected clinical responses occur, prescribers should determine serum concentrations of selected drugs being taken, consult the literature or an expert in drug interactions, and adjust the dosage until the desired effect is produced. If dosage adjustment is ineffective, the drug should be replaced by one that does not interact with other drugs being taken.

**Pharmacogenetics**

**Pharmacogenetics involves variations in drug response due to genetic makeup.**

The activity of drug-metabolizing enzymes often varies widely among healthy people, making metabolism highly variable. Drug elimination rates vary up to 40-fold. Genetic factors and aging seem to account for most of these variations.

Pharmacogenetic variation (eg, in acetylation, hydrolysis, oxidation, or drug-metabolizing enzymes) can have clinical consequences (see Table 317-3). For example, if patients metabolize certain drugs rapidly, they may require higher, more frequent doses to achieve therapeutic concentrations; if patients metabolize certain drugs slowly, they may need lower, less frequent doses to avoid toxicity, particularly of drugs with a narrow margin of safety. For example, patients with inflammatory bowel disease who require azathioprine therapy are now routinely tested for thiopurine methyltransferase (TPMT) genotype to determine the most appropriate starting dose for drug therapy. Most genetic differences cannot be predicted before drug therapy, but for an increasing number of drugs (eg, carbamazepine, clopidogrel, warfarin), changes in effectiveness and risk of toxicity have been specifically associated with certain genetic variations. Also, many environmental and developmental factors can interact with each other and with genetic factors to affect drug response (see Fig. 317-1).

**Placebos**

**Placebos are inactive substances or interventions, most often used in controlled studies for comparison with potentially active drugs.**

The term placebo (Latin for "I will please") initially referred to an inactive, harmless substance given to patients to make them feel better by the power of suggestion. More recently, sham interventions (eg, mock electrical stimulation or simulated surgical procedures in clinical trials) have also been considered placebos. The term is sometimes used for an active drug that is given solely for its placebo effect on a disorder in which the drug is inactive (eg, an antibiotic for patients with viral illness).

**Effects:** Placebos, although physiologically inactive, may have substantial effects—good and bad. These effects seem to be related to anticipation that the drug will work; anticipation of adverse effects is sometimes called the nocebo effect. The placebo effect typically occurs with subjective responses (eg, pain, nausea) rather than objective ones (eg, rate of healing of leg ulcers, infection rate of burn wounds).

The magnitude of the response varies with many factors, including the

- Expressed confidence of the clinician ("this is going to make you feel a lot better" vs "there is a chance this might help")

- Certainty of the patient's beliefs (effect is larger when patients are sure they are receiving an active drug than when they know there is a chance they are getting a placebo)

- Type of placebo (eg, injectable drugs have a larger effect than oral ones)

[Fig. 317-1. Genetic, environmental, and developmental factors that can interact, causing variations in drug response among patients.]
Table 317-3. Examples of Pharmacogenetic Variations

Not everyone responds to placebos, and it is not possible to predict who will respond; correlations between personality characteristics and response to placebos have been theorized but not well established. However, people who have dependent personalities and who want to please their clinicians may be more likely to report beneficial effects; those with histrionic personalities may be more likely to report any effect, good or bad.

**Use in clinical trials:** Many clinical trials compare an active treatment with a placebo. The apparent effects of the placebo are then subtracted from the apparent effects of the active treatment to identify the true treatment effect; to be meaningful, a clinically and statistically significant difference is required. In some studies, the placebo relieves the disorder in a high percentage of patients, making it more difficult to show the active treatment's efficacy.

**Use in clinical practice:** Rarely today, when a clinician determines that patients have a mild, self-limited disorder for which an active drug does not exist or is not indicated (eg, for nonspecific malaise or tiredness), a placebo may be prescribed. The reasoning is that the placebo satisfies patients' demands for treatment without exposing them to potential adverse effects and often makes them feel better—due to the placebo effect or spontaneous improvement.

**Ethical considerations:** In clinical studies, the ethical consideration is whether a placebo should be given at all. When effective treatment exists (eg, opioid analgesics for severe pain), it is typically considered unethical to deprive study participants of treatment by giving a placebo; in such cases, control groups are given an active treatment. Because participants acknowledge in advance that they may be given a placebo, there is no concern about deception.

However, when a placebo is given in medical practice, patients are not told they are receiving an inactive treatment. This deception is controversial. Some clinicians argue that it is prima facie (Latin for "at first view") unethical and, if discovered, may damage the clinician-patient relationship. Others suggest that it is more unethical to not give something that may make patients feel better. Giving an active treatment solely for placebo effect may be further considered unethical because it exposes patients to actual adverse effects (as opposed to nocebo adverse effects).

**Drug Development**

Promising compounds can be identified by mass screening of hundreds or thousands of molecules for biologic activity. In other cases, knowledge of the specific molecular pathophysiology of various diseases allows for rational drug design via computer modeling or modification of existing pharmaceutical agents.

During **early development**, potentially useful compounds are studied in animals to evaluate desired effects and toxicity. Compounds that seem effective and safe are candidates for human studies. A protocol describing the clinical study must be approved by an appropriate institutional research board (IRB) and the FDA, which then issues an investigational new drug (IND) exemption permit. At this point, the patent time period for the compound begins, which usually provides the owner with exclusive rights for the next 20 yr; however, the drug cannot be sold until it is approved by the FDA.

**Phase 1** evaluates safety and toxicity in humans. Different amounts of the compound are given to a small number (often 20 to 80) of healthy, young, usually male volunteers to determine the dose at which toxicity first appears.

**Phase 2** determines whether the compound is active against the target disorder. The compound is given to up to about 100 patients for treatment or prevention of the target disorder. An additional goal is to determine an optimal dose-response range.

**Phase 3** evaluates the drug's effect in larger (often hundreds to thousands of people), more heterogeneous populations in an attempt to duplicate the drug's proposed clinical use. This phase also compares the drug with existing treatments, a placebo, or both. Studies may involve many practicing
physicians and multiple research sites. The purpose is to verify efficacy and detect effects—good and bad—that may not have been observed during phases 1 and 2.

When sufficient data have been collected to justify and request approval of the drug, a new drug application (NDA) is submitted to the FDA. The process from early development to approval of a drug may sometimes take up to 10 yr.

**Phase 4** studies occur after the drug is approved and marketed. They are ongoing and involve large populations. Often, special subpopulations (eg, pregnant women, children, the elderly) are studied. Phase 4 also includes ongoing reporting of adverse effects. Some drugs approved by the FDA after phase 3 have been withdrawn from the market after newly recognized and serious adverse effects have occurred in phase 4.
Chapter 318. Pharmacokinetics

Introduction

Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion. Pharmacodynamics (see p. 3181), described as what a drug does to the body, involves receptor binding, postreceptor effects, and chemical interactions. Drug pharmacokinetics determines the onset, duration, and intensity of a drug's effect. Formulas relating these processes summarize the pharmacokinetic behavior of most drugs (see Table 318-1).

Pharmacokinetics of a drug depends on patient-related factors as well as on the drug's chemical properties. Some patient-related factors (eg, genetic makeup, sex, age) can be used to predict pharmacologic response of populations. For example, the half-life of some drugs, especially those that require both metabolism and excretion, may be remarkably long in the elderly (see Fig. 318-1). In fact, physiologic changes that occur with aging affect many aspects of pharmacokinetics (see p. 3090). Other factors are related to individual physiology. The effects of some individual factors (eg, renal failure, obesity, hepatic failure, dehydration) can be reasonably predicted, but other factors are idiosyncratic and thus have unpredictable effects. Because of individual differences, drug administration must be based on each patient's needs—traditionally, by empirically adjusting dosage until the therapeutic objective is met. This approach is frequently inadequate because it can delay optimal response or result in adverse effects. Knowledge of pharmacokinetic principles helps prescribers adjust dosage more accurately and rapidly.

Absorption

Drug absorption is determined by the drug's physicochemical properties, formulation, and route of administration. Dosage forms (eg, tablets, capsules, solutions), consisting of the drug plus other ingredients, are formulated to be given by various routes (eg, oral, buccal, sublingual, rectal, parenteral, topical, inhalational).

[Table 318-1. Formulas Defining Basic Pharmacokinetic Parameters]

[Fig. 318-1. Comparison of pharmacokinetic outcomes for diazepam in a younger man (A) and an older man (B).]

Regardless of the route of administration, drugs must be in solution to be absorbed. Thus, solid forms (eg, tablets) must be able to disintegrate and deaggregate.

Unless given IV, a drug must cross several semipermeable cell membranes before it reaches the systemic circulation. Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Drugs may cross cell membranes by passive diffusion, facilitated passive diffusion, active transport, or pinocytosis. Sometimes various globular proteins embedded in the matrix function as receptors and help transport molecules across the membrane.

Passive diffusion: Drugs diffuse across a cell membrane from a region of high concentration (eg, GI fluids) to one of low concentration (eg, blood). Diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, size, degree of ionization, and the area of absorptive surface. Because the cell membrane is lipid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across cell membranes. The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily. The proportion of the unionized form present (and thus the drug's ability to cross a membrane) is determined by the pH and the drug's
\( pK_a \) (acid dissociation constant). The \( pK_a \) is the pH at which concentrations of ionized and un-ionized forms are equal. When the pH is lower than the \( pK_a \), the un-ionized form of a weak acid predominates, but the ionized form of a weak base predominates. Thus, in plasma (pH 7.4), the ratio of un-ionized to ionized forms for a weak acid (eg, with a \( pK_a \) of 4.4) is 1:1000; in gastric fluid (pH 1.4), the ratio is reversed (1000:1). Therefore, when a weak acid is given orally, most of the drug in the stomach is un-ionized, favoring diffusion through the gastric mucosa. For a weak base with a \( pK_a \) of 4.4, the outcome is reversed; most of the drug in the stomach is ionized. Theoretically, weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (eg, quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable (see Oral Administration on p. 3174).

**Facilitated passive diffusion:** Certain molecules with low lipid solubility (eg, glucose) penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.

**Active transport:** Active transport is selective, requires energy expenditure, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids). These drugs are usually absorbed from specific sites in the small intestine.

**Pinocytosis:** In pinocytosis, fluid or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pinocytosis probably plays a small role in drug transport, except for protein drugs.

**Oral Administration**

To be absorbed, a drug given orally must survive encounters with low pH and numerous GI secretions, including potentially degrading enzymes. Peptide drugs (eg, insulin) are particularly susceptible to degradation and are not given orally. Absorption of oral drugs involves transport across membranes of the epithelial cells in the GI tract. Absorption is affected by

- Differences in luminal pH along the GI tract
- Surface area per luminal volume
- Blood perfusion
- Presence of bile and mucus
- The nature of epithelial membranes

The oral mucosa has a thin epithelium and rich vascularity, which favor absorption; however, contact is usually too brief for substantial absorption. A drug placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) is retained longer, enhancing absorption.

The stomach has a relatively large epithelial surface, but its thick mucous layer and short transit time limit absorption. Because most absorption occurs in the small intestine, gastric emptying is often the rate-limiting step. Food, especially fatty food, slows gastric emptying (and rate of drug absorption), explaining why taking some drugs on an empty stomach speeds absorption. Drugs that affect gastric emptying (eg, parasympatholytic drugs) affect the absorption rate of other drugs. Food may enhance the extent of absorption for poorly soluble drugs (eg, griseofulvin), reduce it for drugs degraded in the stomach (eg, penicillin G), or have little or no effect.
The small intestine has the largest surface area for drug absorption in the GI tract, and its membranes are more permeable than those in the stomach. For these reasons, most drugs are absorbed primarily in the small intestine, and acids, despite their ability as un-ionized drugs to readily cross membranes, are absorbed faster in the intestine than in the stomach. The intraluminal pH is 4 to 5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum. GI microflora may reduce absorption. Decreased blood flow (eg, in shock) may lower the concentration gradient across the intestinal mucosa and reduce absorption by passive diffusion.

Intestinal transit time can influence drug absorption, particularly for drugs that are absorbed by active transport (eg, B vitamins), that dissolve slowly (eg, griseofulvin), or that are polar (ie, with low lipid solubility; eg, many antibiotics).

Most drugs are given orally as tablets or capsules primarily for convenience, economy, stability, and patient acceptance. Because solid drug forms must dissolve before absorption can occur, dissolution rate determines availability of the drug for absorption. Dissolution, if slower than absorption, becomes the rate-limiting step. Manipulating the formulation (ie, the drug's form as salt, crystal, or hydrate) can change the dissolution rate and thus control overall absorption.

Parenteral Administration

Drugs given IV enter the systemic circulation directly. However, drugs injected IM or sc must cross one or more biologic membranes to reach the systemic circulation. If protein drugs with a molecular mass > 20,000 g/mole are injected IM or sc, movement across capillary membranes is so slow that most absorption occurs via the lymphatic system. In such cases, drug delivery to systemic circulation is slow and often incomplete because of 1st-pass metabolism (metabolism of a drug before it reaches systemic circulation) by proteolytic enzymes in the lymphatics.

Perfusion (blood flow/gram of tissue) greatly affects capillary absorption of small molecules injected IM or sc. Thus, injection site can affect absorption rate. Absorption after IM or sc injection may be delayed or erratic for salts of poorly soluble bases and acids (eg, parenteral form of phenytoin) and in patients with poor peripheral perfusion (eg, during hypotension or shock).

Controlled-Release Forms

Controlled-release forms are designed to reduce dosing frequency for drugs with a short elimination half-life and duration of effect. These forms also limit fluctuation in plasma drug concentration, providing a more uniform therapeutic effect. Absorption rate is slowed by coating drug particles with wax or other water-insoluble material, by embedding the drug in a matrix that releases it slowly during transit through the GI tract, or by complexing the drug with ion-exchange resins. Most absorption of these forms occurs in the large intestine. Crushing or otherwise disturbing a controlled-release tablet or capsule can often be dangerous.

Transdermal controlled-release forms are designed to release the drug for extended periods, sometimes for several days. Drugs for transdermal delivery must have suitable skin penetration characteristics and high potency because the penetration rate and area of application are limited.

Many non-IV parenteral forms are designed to sustain plasma drug concentrations. Absorption of antimicrobials can be extended by using their relatively insoluble salt form (eg, penicillin G benzathine) injected IM. For other drugs, suspensions or solutions in non-aqueous vehicles (eg, crystalline suspensions for insulin) are designed to delay absorption.

Bioavailability

Bioavailability refers to the extent to and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.

Bioavailability of a drug is largely determined by the properties of the dosage form (which depend partly
on its design and manufacture), rather than by the drug’s physicochemical properties, which determine absorption potential. Differences in bioavailability among formulations of a given drug can have clinical significance; thus, knowing whether drug formulations are equivalent is essential.

**Chemical equivalence** indicates that drug products contain the same compound in the same amount and meet current official standards; however, inactive ingredients in drug products may differ.

**Bioequivalence** indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues.

**Therapeutic equivalence** indicates that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic and adverse effects.

Bioequivalent products are expected to be therapeutically equivalent. Therapeutic non-equivalence (eg, more adverse effects, less efficacy) is usually discovered during long-term treatment when patients who are stabilized on one formulation are given a nonequivalent substitute.

Sometimes therapeutic equivalence is possible despite differences in bioavailability. For example, the therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) of penicillin is so wide that efficacy and safety are usually not affected by the moderate differences in plasma concentration due to bioavailability differences in penicillin products. In contrast, for drugs with a relatively narrow therapeutic index, bioavailability differences may cause substantial therapeutic nonequivalence.

**Causes of low bioavailability:** Orally administered drugs must pass through the intestinal wall and then through the portal circulation to the liver; both are common sites of 1st-pass metabolism (metabolism of a drug before it reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bio-availability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs.

Insufficient time for absorption in the GI tract is a common cause of low bioavailability. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low.

Age, sex, physical activity, genetic pheno-type, stress, disorders (eg, achlorhydria, mal-absorption syndromes), or previous GI surgery (eg, bariatric surgery) can also affect drug bioavailability.

Chemical reactions that reduce absorption can reduce bioavailability. They include formation of a complex (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (eg, sulfonoconjugation of isoproterenol), adsorption to other drugs (eg, digoxin to cholestyramine), and metabolism by luminal microflora.

**Assessing bioavailability:** Bioavailability is usually assessed by determining the

- Maximum (peak) plasma drug concentration
- Peak time (when maximum plasma drug concentration occurs)
- Area under the plasma concentration-time curve (AUC—see Fig. 318-2)

![Fig. 318-2.](Representative plasma concentration-time relationship after a single oral dose of a hypothetical drug.)

Plasma drug concentration increases with extent of absorption; the peak is reached when drug elimination rate equals absorption rate. Bioavailability determinations based on the peak plasma
Concentration can be misleading because drug elimination begins as soon as the drug enters the bloodstream. Peak time is the most widely used general index of absorption rate; the slower the absorption, the later the peak time. The most reliable measure of a drug's bioavailability is AUC. AUC is directly proportional to the total amount of unchanged drug that reaches systemic circulation. Drug products may be considered bio-equivalent in extent and rate of absorption if their plasma concentration curves are essentially superimposable.

For drugs excreted primarily unchanged in urine, bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally, urine is collected over a period of 7 to 10 elimination half-lives for complete urinary recovery of the absorbed drug. After multiple dosing, bioavailability may be estimated by measuring unchanged drug recovered from urine over a 24-h period under steady-state conditions.

Distribution

After a drug enters the systemic circulation, it is distributed to the body's tissues. Distribution is generally uneven because of differences in blood perfusion, tissue binding (eg, because of lipid content), regional pH, and permeability of cell membranes.

The entry rate of a drug into a tissue depends on the rate of blood flow to the tissue, tissue mass, and partition characteristics between blood and tissue. Distribution equilibrium (when entry and exit rates are the same) between blood and tissue is reached more rapidly in richly vascularized areas, unless diffusion across cell membranes is the rate-limiting step. After equilibrium, drug concentrations in tissues and in extracellular fluids are reflected by the plasma concentration. Metabolism and excretion occur simultaneously with distribution, making the process dynamic and complex.

For interstitial fluids of most tissues, drug distribution rate is determined primarily by perfusion. For poorly perfused tissues (eg, muscle, fat), distribution is very slow, especially if the tissue has a high affinity for the drug.

Volume of distribution: The apparent volume of distribution is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the concentration in plasma. For example, if 1000 mg of a drug is given and the subsequent plasma concentration is 10 mg/L, that 1000 mg seems to be distributed in 100 L (dose/volume = concentration; 1000 mg/L = 10 mg/L; therefore, x = 1000 mg/10 mg/L = 100 L). Volume of distribution has nothing to do with the actual volume of the body or its fluid compartments but rather involves the distribution of the drug within the body. For drugs that are highly tissue-bound, comparatively little of a dose remains in the circulation to be measured; thus, plasma concentration is low and volume of distribution is high. Drugs that remain in the circulation tend to have a low volume of distribution. Volume of distribution provides a reference for the plasma concentration expected for a given dose but provides little information about the specific pattern of distribution. Each drug is uniquely distributed in the body. Some drugs distribute mostly into fat, others remain in ECF, and others are bound extensively to specific tissues.

Many acidic drugs (eg, warfarin, aspirin) are highly protein-bound and thus have a small apparent volume of distribution. Many basic drugs (eg, amphetamine, meperidine) are extensively taken up by tissues and thus have an apparent volume of distribution larger than the volume of the entire body.

Binding: The extent of drug distribution into tissues depends on the extent of plasma protein and tissue binding. In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly as reversibly bound to blood components (eg, plasma proteins, blood cells). Of the many plasma proteins that can interact with drugs, the most important are albumin, α1-acid glycoprotein, and lipoproteins. Acidic drugs are usually bound more extensively to albumin; basic drugs are usually bound more extensively to α1-acid glyco-protein, lipoproteins, or both.

Only unbound drug is available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug occur. Therefore, the unbound drug concentration in systemic circulation typically determines drug concentration at the active site and thus efficacy.
At high drug concentrations, the amount of bound drug approaches an upper limit determined by the number of available binding sites. Saturation of binding sites is the basis of displacement interactions among drugs (see Drug-Receptor Interactions on p. 3181).

Drugs bind to many substances other than proteins. Binding usually occurs when a drug associates with a macromolecule in an aqueous environment but may occur when a drug is partitioned into body fat. Because fat is poorly perfused, equilibration time is long, especially if the drug is highly lipophilic.

Accumulation of drugs in tissues or body compartments can prolong drug action because the tissues release the accumulated drug as plasma drug concentration decreases. For example, thiopental is highly lipid soluble, rapidly enters the brain after a single IV injection, and has a marked and rapid anesthetic effect; the effect ends within a few minutes as the drug is redistributed to more slowly perfused fatty tissues. Thiopental is then slowly released from fat storage, maintaining subanesthetic plasma levels; these levels may become significant if doses of thiopental are repeated, causing large amounts to be stored in fat. Thus, storage in fat initially shortens the drug's effect but then prolongs it.

Some drugs accumulate within cells because they bind with proteins, phospholipids, or nucleic acids. For example, chloroquine concentrations in WBCs and liver cells can be thousands of times higher than those in plasma. Drug in cells is in equilibrium with drug in plasma and moves into plasma as the drug is eliminated from the body.

**Blood-brain barrier:** Drugs reach the CNS via brain capillaries and CSF. Although the brain receives about one sixth of cardiac output, distribution of drugs to brain tissue is restricted because the brain's permeability characteristics differ from those of other tissues. Although some lipid-soluble drugs (eg, thiopental) enter the brain readily, polar compounds do not. The reason is the blood-brain barrier, which consists of the endothelium of brain capillaries and the astrocytic sheath. The endothelial cells of brain capillaries, which appear to be more tightly joined to one another than those of most capillaries, slow the diffusion of water-soluble drugs. The astrocytic sheath consists of a layer of glial connective tissue cells (astrocytes) close to the basement membrane of the capillary endothelium. With aging, the blood-brain barrier may become less effective, allowing increased passage of compounds into the brain.

Drugs may enter ventricular CSF directly via the choroid plexus, then passively diffuse into brain tissue from CSF. Also in the choroid plexus, organic acids (eg, penicillin) are actively transported from CSF to blood.

The drug penetration rate into CSF, as for other tissue cells, is determined mainly by the extent of protein binding, degree of ionization, and lipid-water partition coefficient of the drug. The penetration rate into the brain is slow for highly protein-bound drugs and nearly nonexistent for the ionized form of weak acids and bases. Because the CNS is so well perfused, the drug distribution rate is determined primarily by permeability.

**Metabolism**

The liver is the principal site of drug metabolism. Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active—sometimes even more so than the parent compound. An inactive or weakly active substance that has an active metabolite is called a prodrug, especially if designed to deliver the active moiety more effectively.

Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization; whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver. Drug metabolism rates vary among patients. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not reached; in others, metabolism may be so slow that usual doses have toxic effects. Individual drug metabolism rates are influenced by genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions (especially those involving induction or inhibition of metabolism).

For many drugs, metabolism occurs in 2 phases. Phase I reactions involve formation of a new or modified
functional group or cleavage (oxidation, reduction, hydrolysis); these reactions are nonsynthetic. Phase II reactions involve conjugation with an endogenous substance (eg, glucuronic acid, sulfate, glycine); these reactions are synthetic. Metabolites formed in synthetic reactions are more polar and more readily excreted by the kidneys (in urine) and the liver (in bile) than those formed in nonsynthetic reactions. Some drugs undergo only phase I or phase II reactions; thus, phase numbers reflect functional rather than sequential classification.

**Rate:** For almost all drugs, the metabolism rate in any given pathway has an upper limit (capacity limitation). However, at therapeutic concentrations of most drugs, usually only a small fraction of the metabolizing enzyme's sites are occupied, and the metabolism rate increases with drug concentration. In such cases, called first-order elimination (or kinetics), the metabolism rate of the drug is a constant fraction of the drug remaining in the body (rather than a constant amount of drug per hour); ie, the drug has a specific half-life. For example, if 500 mg is present in the body at time zero, after metabolism, 250 mg may be present at 1 h and 125 mg at 2 h (illustrating a half-life of 1 h). However, when most of the enzyme sites are occupied, metabolism occurs at its maximal rate and does not change in proportion to drug concentration; ie, a fixed amount of drug is metabolized per unit time (zero-order kinetics). In this case, if 500 mg is present in the body at time zero, after metabolism, 450 mg may be present at 1 h and 400 mg at 2 h (illustrating a maximal clearance of 50 mg/h and no specific half-life). As drug concentration increases, metabolism shifts from first-order to zero-order kinetics.

**Cytochrome P-450:** The most important enzyme system of phase I metabolism is cytochrome P-450 (CYP450), a microsomal superfamily of isoenzymes that catalyze the oxidation of many drugs. The electrons are supplied by NADPH-CYP450 reductase, a flavo-protein that transfers electrons from NADPH (the reduced form of nicotinamide adenosine dinucleotide phosphate) to CYP450. CYP450 enzymes can be induced or inhibited by any drugs and substances, helping explain many drug interactions in which one drug enhances the toxicity or reduces the therapeutic effect of another drug. For examples of drugs that interact with specific enzymes, see Table 318-2 (see also Drug Interactions on p. 3167).

With aging, the liver's capacity for metabolism through the CYP450 enzyme system is reduced by ≥ 30% because liver volume and hepatic blood flow are decreased. Thus, drugs that are metabolized through this system reach higher levels and have prolonged half-lives in the elderly (see Fig. 318-1). Because neonates have partially developed liver microsomal enzyme systems, they also have difficulty metabolizing many drugs.

**Conjugation:** Glucuronidation, the most common phase II reaction, is the only one that occurs in the liver microsomal enzyme system. Glucuronides are secreted in bile and eliminated in urine. Thus, conjugation makes most drugs more soluble and easily excreted by the kidneys. Amino acid conjugation with glutamine or glycine produces conjugates that are readily excreted in urine but not extensively secreted in bile. Aging does not affect glucuronidation. However, in neonates, conversion to glucuronide is slower, sometimes with serious effects.

Conjugation may also occur through acetylation or sulfoconjugation. Sulfate esters are polar and readily excreted in urine. Aging does not affect these processes.

**Excretion**

The kidneys, which excrete water-soluble substances, are the principal organs of excretion. The biliary system contributes to excretion to the degree that drug is not reabsorbed from the GI tract. Generally, the contribution of intestine, saliva, sweat, breast milk, and lungs to excretion is small, except for exhalation of volatile anesthetics. Excretion via breast milk, although not important to the mother, may affect the breastfeeding infant (see Table 268-4 on p. 2706).

Hepatic metabolism often makes drugs more polar and thus more water soluble. The resulting metabolites are then more readily excreted.

**Renal excretion:** Renal filtration accounts for most drug excretion. About one fifth of the plasma
reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. However, polar compounds, which include most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption (eg, as for glucose, ascorbic acid, and B vitamins). With aging, renal drug excretion decreases (see Ch. 308, especially Table 308-1 on p. 3091); at age 80, clearance is typically reduced to half of what it was at age 30.

The principles of transmembrane passage govern renal handling of drugs. Drugs bound to plasma proteins remain in the circulation;

only unbound drug is contained in the glomerular filtrate. Un-ionized forms of drugs and their metabolites tend to be reabsorbed readily from tubular fluids.

Urine pH, which varies from 4.5 to 8.0, may markedly affect drug reabsorption and excretion by determining whether a weak acid or base is in an un-ionized or ionized form (see p. 3173). Acidification of urine increases reabsorption and decreases excretion of weak acids and decreases reabsorption of weak bases. Alkalization of urine has the opposite effect. In some cases of overdose, these principles are used to enhance the excretion of weak bases or acids; eg, urine is alkalized to enhance excretion of acetylsalicylic acid. The extent to which changes in urinary pH alter the rate of drug elimination depends on the contribution of the renal route to total elimination, the polarity of the unionized form, and the molecule’s degree of ionization.

Active tubular secretion in the proximal tubule is important in the elimination of many drugs. This energy-dependent process may be blocked by metabolic inhibitors. When drug concentration is high, secretory transport can reach an upper limit (transport maximum); each substance has a characteristic transport maximum.

Anions and cations are handled by separate transport mechanisms. Normally, the anion secretory system eliminates metabolites conjugated with glycine, sulfate, or glucuronic acid. Anions compete with each other for secretion. This competition can be used therapeutically; eg, probenecid blocks the normally rapid tubular secretion of penicillin, resulting in higher plasma penicillin concentrations for a longer time. In the cation transport system, cations or organic bases (eg, pramipexole, dofetilide) are secreted by the renal tubules; this process can be inhibited by cimetidine, trimethoprim, prochlorperazine, megestrol, or ketoconazole.

**Biliary excretion:** Some drugs and their metabolites are extensively excreted in bile. Because they are transported across the biliary epithelium against a concentration gradient, active secretory transport is required. When plasma drug concentrations are high, secretory transport may approach an upper limit (transport maximum). Substances with similar physicochemical properties may compete for excretion.

Drugs with a molecular weight of > 300 g/mole and with both polar and lipophilic groups are more likely to be excreted in bile; smaller molecules are generally excreted only in negligible amounts. Conjugation, particularly with glucuronic acid, facilitates biliary excretion.

In the enterohepatic cycle, a drug secreted in bile is reabsorbed into the circulation from the intestine. Biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete—when some of the secreted drug is not reabsorbed from the intestine.
Chapter 319. Pharmacodynamics

Introduction

Pharmacodynamics, sometimes described as what a drug does to the body, involves receptor binding (including receptor sensitivity), postreceptor effects, and chemical interactions. Pharmacodynamics, with pharmacokinetics (what the body does to a drug—see p. 3172), helps explain the relationship between the dose and response, ie, the drug's effects. The pharmacologic response depends on the drug's binding to its target. The concentration of the drug at the receptor site influences the drug's effect.

A drug's pharmacodynamics can be affected by physiologic changes due to disorders, aging, or other drugs. Disorders that affect pharmacodynamic responses include genetic mutations, thyrotoxicosis, malnutrition, myasthenia gravis, Parkinson's disease, and some forms of insulin-resistant diabetes mellitus. These disorders can change receptor binding, alter the level of binding proteins, or decrease receptor sensitivity. Aging tends to affect pharmacodynamic responses through alterations in receptor binding or in postreceptor response (see Table 308-2 on p. 3093). Pharmacodynamic drug-drug interactions result in competition for receptor binding sites or alter postreceptor response.

Drug-Receptor Interactions

Receptors are macromolecules involved in chemical signaling between and within cells; they may be located on the cell surface membrane or within the cytoplasm (see Table 319-1). Activated receptors directly or indirectly regulate cellular biochemical processes (eg, ion conductance, protein phosphorylation, DNA transcription, enzymatic activity). Molecules (eg, drugs, hormones, neurotransmitters) that bind to a receptor are called ligands. A ligand may activate or inactivate a receptor; activation may increase or decrease a particular cell function. Each ligand may interact with multiple receptor subtypes. Few if any drugs are absolutely specific for one receptor or subtype, but most have relative selectivity. Selectivity is the degree to which a drug acts on a given site relative to other sites; selectivity relates largely to physicochemical binding of the drug to cellular receptors.

A drug's ability to affect a given receptor is related to the drug's affinity (probability of the drug occupying a receptor at any given instant) and intrinsic efficacy (intrinsic activity—degree to which a ligand activates receptors and leads to cellular response). A drug's affinity and activity are determined by its chemical structure.

Physiologic functions (eg, contraction, secretion) are usually regulated by multiple receptor-mediated mechanisms, and several steps (eg, receptor-coupling, multiple intracellular 2nd messenger substances) may be interposed between the initial molecular drug-receptor interaction and ultimate tissue or organ response. Thus, several dissimilar drug molecules can often be used to produce a desired response.

Ability to bind to a receptor is influenced by external factors as well as by intracellular regulatory mechanisms. Baseline receptor [Table 319-1, Some Types of Physiologic and Drug-Receptor Proteins] density and the efficiency of stimulus-response mechanisms vary from tissue to tissue. Drugs, aging, genetic mutations, and disorders can increase (up-regulate) or decrease (down-regulate) the number and binding affinity of receptors. For example, clonidine down-regulates α2-receptors; thus, rapid withdrawal of clonidine can cause hypertensive crisis. Chronic therapy with β-blockers up-regulates β-receptor density; thus, severe hypertension or tachycardia can result from abrupt withdrawal. Receptor up-regulation and down-regulation affect adaptation to drugs (eg, desensitization, tachyphylaxis, tolerance, acquired resistance, postwithdrawal supersensitivity).

Ligands bind to precise molecular regions, called recognition sites, on receptor macromolecules. The binding site for a drug may be the same as or different from that of an endogenous agonist (hormone or neurotransmitter). Agonists that bind to an adjacent site or a different site on a receptor are sometimes
called allosteric agonists. Nonspecific drug binding also occurs—ie, at molecular sites not designated as receptors (eg, plasma proteins). Drug binding to such nonspecific sites prohibits the drug from binding to the receptor and thus inactivates the drug. Unbound drug is available to bind to receptors and thus have an effect.

**Agonists and antagonists:** Agonist drugs activate receptors to produce the desired response. Conventional agonists increase the proportion of activated receptors. Inverse agonists stabilize the receptor in its inactive conformation and act similarly to competitive antagonists (see p. 3183). Many hormones, neurotransmitters (eg, acetylcholine, histamine, norepinephrine), and drugs (eg, morphine, phenylephrine, isoproterenol) act as agonists.

Antagonists prevent receptor activation. Preventing activation has many effects. Antagonist drugs increase cellular function if they block the action of a substance that normally decreases cellular function. Antagonist drugs decrease cellular function if they block the action of a substance that normally increases cellular function.

Receptor antagonists can be classified as reversible or irreversible. Reversible antagonists readily dissociate from their receptor; irreversible antagonists form a stable, permanent or nearly permanent chemical bond with their receptor (eg, by alkylation). Pseudo-irreversible antagonists slowly dissociate from their receptor.

In competitive antagonism, binding of the antagonist to the receptor prevents binding of the agonist to the receptor. In noncompetitive antagonism, agonist and antagonist can be bound simultaneously, but antagonist binding reduces or prevents the action of the agonist. In reversible competitive antagonism, agonist and antagonist form short-lasting bonds with the receptor, and a steady state among agonist, antagonist, and receptor is reached. Such antagonism can be overcome by increasing the concentration of the agonist. For example, naloxone (an opioid receptor antagonist that is structurally similar to morphine), when given shortly before or after morphine, blocks morphine's effects. However, competitive antagonism by naloxone can be overcome by giving more morphine.

Structural analogs of agonist molecules frequently have agonist and antagonist properties; such drugs are called partial (low-efficacy) agonists, or agonist-antagonists. For example, pentazocine activates opioid receptors but blocks their activation by other opioids. Thus, pentazocine provides opioid effects but blunts the effects of another opioid if the opioid is given while pentazocine is still bound. A drug that acts as a partial agonist in one tissue may act as a full agonist in another.

**Chemical Interactions**

Some drugs produce effects without altering cellular function and without binding to a receptor. For example, most antacids decrease gastric acidity through simple chemical reactions; antacids are bases that chemically interact with acids to produce neutral salts. The primary action of cholestyramine, a bile acid sequestrant, is to bind bile acids in the GI tract.

**Dose-Response Relationships**

Regardless of how a drug effect occurs—through binding or chemical interaction—the concentration of the drug at the site of action controls the effect. However, response to concentration may be complex and is often nonlinear. The relationship between the drug dose, regardless of route used, and the drug concentration at the cellular level is even more complex (see Ch. 318).

Dose-response data are typically graphed with the dose or dose function (eg, log₁₀ dose) on the x-axis and the measured effect (response) on the y-axis. Because a drug effect is a function of dose and time, such a graph depicts the dose-response relationship independent of time. Measured effects are frequently recorded as maxima at time of peak effect or under steady-state conditions (eg, during continuous IV infusion). Drug effects may be quantified at the level of molecule, cell, tissue, organ, organ system, or organism.
A hypothetical dose-response curve has features that vary (see Fig. 319-1): potency (location of curve along the dose axis), maximal efficacy or ceiling effect (greatest attainable response), and slope (change in response per unit dose). Biologic variation (variation in magnitude of response among test subjects in the same population given the same dose of drug) also occurs. Graphing dose-response curves of drugs studied under identical conditions can help compare the pharmacologic profiles of the drugs (see Fig. 319-2). This information helps determine the dose necessary to achieve the desired effect.

Dose-response, which involves the principles of pharmacokinetics and pharmacodynamics, determines the required dose and frequency as well as the therapeutic index for a drug in a population. The therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) helps determine the efficacy and safety of a drug. Increasing the dose of a drug with a small therapeutic index increases the probability of toxicity or ineffectiveness of the drug. However, these features differ by population and are affected by patient-related factors (eg, pregnancy [see p. 2625], age [see p. 3091]).
Chapter 320. Adverse Drug Reactions

Introduction

Adverse drug reaction (ADR, or adverse drug effect) is a broad term referring to unwanted, uncomfortable, or dangerous effects that a drug may have. ADRs can be considered a form of toxicity; however, toxicity is most commonly applied to effects of overingestion (accidental or intentional—see p. 3333) or to elevated blood levels or enhanced drug effects that occur during appropriate use (eg, when drug metabolism is temporarily inhibited by a disorder or another drug). Side effect is an imprecise term often used to refer to a drug's unintended effects that occur within the therapeutic range. Because all drugs have the potential for ADRs, risk-benefit analysis (analyzing the likelihood of benefit vs risk of ADRs) is necessary whenever a drug is prescribed.

In the US, 3 to 7% of all hospitalizations are due to ADRs. ADRs occur during 10 to 20% of hospitalizations; about 10 to 20% of these ADRs are severe. Incidence of death due to ADRs is unknown; suggested rates of 0.5 to 0.9% may be falsely high because many of the patients included had serious and complex disorders.

Incidence and severity of ADRs vary by patient characteristics (eg, age, sex, ethnicity, coexisting disorders, genetic or geographic factors) and by drug factors (eg, type of drug, administration route, treatment duration, dosage, bioavailability). Incidence is probably higher and ADRs are more severe among the elderly (see p. 3092), although age per se may not be the primary cause. The contribution of prescribing and adherence errors to the incidence of ADRs is unclear (see p. 3166).

Etiology

Most ADRs are dose-related; others are allergic or idiosyncratic. Dose-related ADRs are usually predictable; ADRs unrelated to dose are usually unpredictable.

Dose-related ADRs are particularly a concern when drugs have a narrow therapeutic index (eg, hemorrhage with oral anticoagulants). ADRs may result from decreased drug clearance in patients with impaired renal or hepatic function or from drug-drug interactions.

Allergic ADRs are not dose-related and require prior exposure. Allergies develop when a drug acts as an antigen or allergen. After a patient is sensitized, subsequent exposure to the drug produces one of several different types of allergic reaction (see p. 1122). Clinical history and appropriate skin tests can sometimes help predict allergic ADRs.

Idiosyncrasy is an imprecise term used to classify unexpected ADRs that are not dose-related or allergic. They occur in a small percentage of patients given a drug. Idiosyncrasy has been defined as a genetically determined abnormal response to a drug, but not all idiosyncratic reactions have a pharmacogenetic cause. The term may become obsolete as specific mechanisms of ADRs become known.

Symptoms and Signs

ADRs are usually classified as mild, moderate, severe, or lethal (see Table 320-1). Symptoms and signs may manifest soon after the first dose or only after chronic use. They may obviously result from drug use or be too subtle to identify as drug-related. In the elderly, subtle ADRs can cause functional deterioration, changes in mental status, failure to thrive, loss of appetite, confusion, and depression.

Table 320-1, Classification of Adverse Drug Reactions

Allergic ADRs typically occur soon after a drug is taken but generally do not occur after the first dose; typically, they occur when the drug is given after an initial exposure. Symptoms include itching, rash, fixed-drug eruption, upper or lower airway edema with difficulty breathing, and hypotension.

Idiosyncratic ADRs can produce almost any symptom or sign and usually cannot be predicted.
Diagnosis

• Consideration of rechallenge

• Reporting of suspected ADRs to MedWatch

Symptoms that occur soon after a drug is taken are often easily connected with use of a drug. However, diagnosing symptoms due to chronic drug use requires a significant level of suspicion and is often complicated. Stopping a drug is sometimes necessary but is difficult if the drug is essential and does not have an acceptable substitute. When proof of the relationship between drug and symptoms is important, rechallenge should be considered, except in the case of serious allergic reactions.

Physicians should report most suspected ADRs to MedWatch (the FDA's ADR monitoring program), which is an early alert system. Only through such reporting can unexpected ADRs be identified and investigated. Med-Watch also monitors changes in the nature and frequency of ADRs. Forms for and information about reporting ADRs are available in the Physicians' Desk Reference, AMA Drug Evaluations, and FDA Drug Bulletin (mailed to all physicians at least yearly) and at www.fda.gov/medwatch; forms may also be obtained by calling 800-FDA-1088. Nurses, pharmacists, and other health care practitioners should also report ADRs.

Treatment

• Modification of dosage

• Discontinuation of drug if necessary

• Switching to a different drug

For dose-related ADRs, modifying the dose or eliminating or reducing precipitating factors may suffice. Increasing the rate of drug elimination is rarely necessary. For allergic and idiosyncratic ADRs, the drug usually should be withdrawn and not tried again. Switching to a different drug class is often required for allergic ADRs and sometimes required for dose-related ADRs.

Prevention

Prevention of ADRs requires familiarity with the drug and potential reactions to it. Computer-based analysis should be used to check for potential drug interactions; analysis should be repeated whenever drugs are changed or added. Drugs and initial dosage must be carefully selected for the elderly (see Ch. 308). If patients develop nonspecific symptoms, ADRs should always be considered before beginning symptomatic treatment.
Chapter 321. Approach to the Trauma Patient

Injury is the number one cause of death for people aged 1 to 44. In the US, there were 175,000 trauma deaths in 2006, about two thirds being accidental. Of intentional injury deaths, about 60% were due to self-harm. In addition to deaths, injury results in about 40 million emergency department visits annually.

Patients whose injuries are serious but not immediately fatal benefit the most from treatment in designated trauma centers, hospitals that have special staffing and protocols to provide immediate care to critically injured patients. Criteria for such designation (and for the necessity of transport to them) vary by state but usually follow guidelines of the American College of Surgeons' Committee on Trauma.

Many traumatic injuries are discussed elsewhere in THE MANUAL; for bone and joint injuries, see p. 3201; for spinal cord injury, see p. 3227; for head injury, see p. 3218; for facial injury, see p. 3231; for eye injury, see p. 3235; for genitourinary injury, see p. 3238; for lacerations, see p. 3193.

Etiology

Of the myriad ways people are injured, most can be categorized as blunt or penetrating. Blunt injury involves a forceful impact (eg, blow, kick, strike with object, fall, motor vehicle crash, blast). Penetrating injury involves breach of the skin by an object (eg, knife, broken glass) or projectile (eg, bullet, shrapnel from an explosion).

Other injury types include thermal and chemical burns, toxic inhalations or ingestions, and radiation injury.

Pathophysiology

All injuries, by definition, cause direct tissue damage, the nature and extent depending on the anatomic site, mechanism, and intensity of trauma. Severe direct tissue damage to critical organs (eg, to the heart, brain, spinal cord) is responsible for most immediate trauma deaths.

Additionally, patients surviving the initial insult may develop indirect injury effects. Disruption of blood vessels causes hemorrhage, which may be external (and hence visible) or internal, either confined within an organ as a contusion or hematoma, or as free hemorrhage into a body compartment (eg, peritoneal cavity, thorax). Small amounts of hemorrhage (ie, < 10% of blood volume) are tolerated well by most patients. Larger amounts cause progressive declines in BP and organ perfusion (shock—see p. 2292), leading to cellular dysfunction, organ failure, and eventually death. Hemorrhagic shock causes most short-term (ie, within hours) deaths, and multiple organ failure from prolonged shock causes many of the near-term (ie, first 14 days) deaths. Additional near-term deaths result from infection because of disruption of normal anatomic barriers and immune system dysfunction.

Evaluation and Treatment

• A, B, C, D, E evaluation and stabilization of Airway, Breathing, Circulation, Disability (neurologic status), and Exposure/environmental control

• After stabilization, head-to-toe examination

• Liberal use of CT and other imaging studies

Care in the emergency department rather than emergency care delivered at the accident site is discussed here. Evaluation and treatment are done simultaneously, beginning with systems that pose the most immediate threat to life if damaged. Attending to dramatic but not deadly injuries (eg, open lower-extremity fracture, finger amputations) before evaluating immediate life threats can be a fatal mistake. A helpful mnemonic is A, B, C, D, E. Systems are rapidly examined for serious abnormalities (primary survey); a more detailed examination (secondary survey) is done after the patient is stable.
Airway: Airway patency is threatened by blood clots, teeth, or foreign bodies in the oropharynx; soft-tissue laxity and posterior retraction of the tongue caused by obtundation (eg, from head injury, shock, intoxication); and edema or hematoma due to direct neck trauma. These obstructions are readily visible on direct inspection of the mouth or neck; having the patient speak can rapidly confirm that the airway is not likely in immediate danger.

Blood and foreign material are removed by suction or manually. Obtunded patients whose airway patency is in doubt and patients with significant oropharyngeal injury require endotracheal intubation; usually drugs are given for paralysis and sedation before intubation is done (see p. 2273). If patients require an artificial airway and endotracheal intubation is not possible (eg, due to edema of the airway caused by a thermal burn) or contraindicated (eg, due to severe maxillofacial injury), surgical cricothyrotomy is indicated (see p. 2277). NOTE: When evaluating or manipulating a patient's airway, cervical spine immobilization should be maintained (eg, by rigid collar, inline immobilization techniques) until cervical spine injury has been excluded by examination, imaging, or both.

Breathing: Adequate ventilation is threatened by decreased central respiratory drive (usually from head injury, intoxication, or nearly fatal shock) or by chest injury (eg, hemothorax or pneumothorax, multiple rib fractures, pulmonary contusion).

Adequacy of air exchange is usually apparent on auscultation. Tension pneumothorax (see p. 2002) may cause the trachea to deviate to the side opposite the injury, as well as decreased breath sounds and sometimes distended neck veins. The chest wall is fully exposed to look for ample chest wall expansion and is palpated for obvious rib fractures and presence of subcutaneous air (sometimes the only finding in pneumothorax).

Pneumothorax is decompressed by chest tube (see p. 2003) and must be excluded before initiating positive-pressure ventilation (which may markedly enlarge a pneumothorax and convert it to a tension pneumothorax). Suspected tension pneumothorax can be decompressed with needle thoracostomy (eg, a 14-gauge needle inserted in the midclavicular line, 2nd intercostal space) to stabilize the patient if a chest tube cannot be inserted immediately. Inadequate ventilation is treated with endotracheal intubation and mechanical ventilation.

Circulation: Significant external hemorrhage can occur from any major vessel but is always apparent. Life-threatening internal hemorrhage is often less obvious. However, this volume of hemorrhage can occur in only a few body compartments: the chest, abdomen, and soft tissues of the pelvis or thigh (eg, from a pelvic or femoral fracture).

Pulse and BP are assessed, and signs of shock are noted (eg, tachypnea, dusky color, diaphoresis, altered mental status). Abdominal distention and tenderness, pelvis instability, and thigh deformity and instability are often present when internal hemorrhage in those areas is large enough to be life threatening.

External hemorrhage is controlled by direct pressure. Two large-bore (eg, 14- or 16-gauge) IVs are started with 0.9% saline or Ringer's lactate; rapid infusion of 1 to 2 L (20 mL/kg for children) is given for signs of shock and hypovolemia. Subsequently, additional fluids and, if necessary, blood component therapy is given as indicated (see p. 2296). Patients in whom there is strong clinical suspicion of serious intra-abdominal hemorrhage may require immediate laparotomy. Patients with massive intrathoracic hemorrhage may require immediate thoracotomy and possibly autotransfusion of blood recovered via tube thoracostomy.

Disability: Neurologic function is evaluated for serious deficits involving the brain and spinal cord. The Glasgow Coma Scale (GCS—see Table 324-2 on p. 3221 and, for infants and children, see Table 324-3 on p. 3222) and pupillary response to light are used to screen for serious intracranial injury. Gross motor movement and sensation in each extremity are evaluated to screen for serious spinal cord injury. The cervical spine is palpated for tenderness and deformity and stabilized in a rigid collar until cervical spine injury is excluded. With careful manual stabilization of the head and neck, the patient is
logrolled onto a side to allow palpation of the thoracic and lumbar spine, inspection of the back, and rectal examination to check tone (decreased tone indicates possible spinal cord injury), the prostate (a high-riding prostate suggests urethral injury), and presence of blood. In the US, most patients arriving by ambulance are immobilized on a long, rigid board for ease of transport and to stabilize possible spinal fractures. If examination reveals no sign of spinal injury, patients are taken off the board because it is quite uncomfortable and pressure ulcers may occur within a few hours.

Patients with severe traumatic brain injury (GCS < 9) require endotracheal intubation, neurosurgical evaluation, and therapy to prevent secondary brain injury (eg, osmotic diuresis, sometimes hyperventilation for patients with signs of impending brain herniation—see Fig. 174-1 on p. 1657).

Exposure/environmental control: To ensure injuries are not missed, patients are completely undressed (by cutting off garments) and the entire body surface is examined for signs of occult trauma. The patient is kept warm (eg, with heated blankets and by using only warmed IV fluids) to prevent hypothermia.

Secondary survey: After immediate life threats are assessed and the patient is stable, a more thorough evaluation is done, and a focused history is obtained. If only limited conversation is possible, an "AMPLE" history covers essential information:

- Allergies
- Medications
- Past medical history
- Last meal
- Events of the injury

After the patient is completely undressed, the examination generally proceeds from head to toe; it includes all orifices and a more detailed look at areas examined in the initial survey. All soft tissues are inspected for lesions and swelling, all bones are palpated for tenderness, and range of motion is assessed in joints (unless there is obvious fracture or deformity).

A urinary catheter is usually placed in seriously injured and obtunded patients provided there is no evidence of urethral injury (eg, blood at the meatus, ecchymosis of the perineum, high-riding prostate). Seriously injured patients often also have a nasogastric tube placed, provided there is no serious midface trauma (rare reports exist of intracranial tube insertion through a cribriform plate fracture).

Open wounds are covered with sterile dressings, but cleansing and repair are deferred until completion of evaluation and treatment of more serious injuries. Serious clinically apparent dislocations with marked deformity or neurovascular compromise are imaged and reduced as soon as immediate life threats have been addressed. Obvious or suspected fractures are splinted pending full assessment of serious injuries and appropriate imaging studies.

Testing: Imaging tests are the cornerstone; laboratory tests are generally ancillary. Patients with penetrating trauma typically have focal injuries that can limit necessary imaging to the obviously involved region or regions. Blunt trauma, particularly when significant deceleration is involved (eg, serious fall, motor vehicle crash), can affect any part of the body, and imaging is used more liberally. Such patients traditionally have x-rays of the chest, cervical spine, and pelvis unless they are awake and alert, completely lacking in symptoms or findings suggesting injury to those areas, and have no distracting injuries (eg, femur fracture) that might keep them from complaining about injuries elsewhere. These imaging tests are directed at life threats that may not be clinically obvious.

Chest x-ray can identify airway disruption, lung injury, and pneumothorax and can suggest thoracic aorta tears (eg, by mediastinal widening).
CT of the chest, abdomen and pelvis, spine, head, or, particularly, combinations of these is increasingly being used instead of plain x-rays for patients who require imaging after severe multiple blunt trauma.

Identification of intra-abdominal injury is essential. Bedside ultrasonography (FAST examination: focused assessment with sonography in trauma) is being used increasingly, particularly for unstable patients; it is sensitive for significant volumes of intraperitoneal blood and thus the need for immediate laparotomy. If patients are stable, CT has the advantages of high accuracy, imaging of the retroperitoneal structures and bones, and showing the volume and sometimes the origin of hemorrhage. For unstable patients in whom bedside ultrasonography is not feasible, diagnostic peritoneal aspiration can be used, in which a peritoneal dialysis catheter is inserted through the abdominal wall into the peritoneal cavity. If > 10 mL of blood is aspirated, immediate laparotomy is indicated.

Head CT is typically done in patients with altered mental status or focal neurologic abnormalities and in patients who sustained loss of consciousness (some clinicians feel that patients with a brief loss of consciousness who are completely alert and neurologically intact do not require CT). Imaging is obtained more liberally in children < 2 yr with scalp hematoma, the elderly, patients taking anticoagulants, and patients who are alcoholics.

Aortic injury should be considered in patients with severe deceleration chest injury or suggestive signs (eg, pulse deficits or asymmetric BP measurements, end-organ ischemia, suggestive findings on chest x-ray); these patients may require CT angiography or other aortic imaging. All patients suspected of having significant blunt chest injury have an ECG to diagnose myocardial injury and cardiac monitoring for subsequent arrhythmias. Patients with abnormalities on ECG usually have blood levels of cardiac markers measured and sometimes echocardiography (see p. 2053).

Plain x-rays are obtained of any suspected fractures and dislocations. Other imaging tests are obtained for specific indications (eg, angiography to diagnose and sometimes embolize vascular injury; CT to better delineate spinal, pelvic, or complex joint fractures).

Laboratory tests that may be useful include ABGs for PO$_2$, PCO$_2$, and base deficit; urine examination for blood; CBC to establish a baseline to monitor ongoing hemorrhage; glucose to evaluate for hypoglycemia; and type and cross-match for possible blood transfusion. Measures of perfusion (serum lactate, base deficit on ABG measurement, and, in patients with a catheterized central vein, central venous O$_2$ saturation) may help identify early or partially treated shock. Other reflexively obtained tests (eg, electrolytes and other chemistries, coagulation studies) are unlikely to be helpful unless suggested by relevant medical history (eg, renal insufficiency, diuretic use). Toxicology screening (eg, blood alcohol, urine drug screen) is often done; results of this testing rarely change immediate management but can help identify substance abuse causative of injury, allowing intervention to prevent subsequent trauma.
Chapter 322. Lacerations

Introduction

Care of lacerations enables prompt healing, minimizes risk of infection, and optimizes cosmetic result.

Physiology

Healing begins immediately after injury with coagulation and introduction of WBCs; neutrophils and macrophages remove debris (including devitalized tissue) and bacteria. Macrophages also encourage fibroblast replication and neovascularization. Fibroblasts deposit collagen, typically beginning within 48 h and reaching a maximum in about 7 days. Collagen deposition is essentially complete in 1 mo, but collagen fiber strength builds more slowly as fibers undergo crosslinking. Wound tensile strength is only about 20% of ultimate by 3 wk, 60% by 4 mo, and maximum at 1 yr; strength never becomes equivalent to the undamaged state.

Epithelial cells from the wound edge migrate across the wound shortly after injury. In a surgically repaired wound (healing by primary intention), they form an effective protective barrier to water and bacteria in 12 to 24 h and resemble normal epidermis within 5 days. In a wound that is not repaired (ie, heals by secondary intention), epithelialization is prolonged proportionally to the defect size.

There are static forces on the skin because of its natural elasticity and the underlying muscles (see Fig. 322-1). Because scar tissue is not as strong as adjacent undamaged skin, these forces tend to widen scars, sometimes resulting in a cosmetically unacceptable appearance after apparently adequate wound closure. Scar widening is particularly likely when the forces are perpendicular to the wound edge. This tendency (and resultant wound stress) is readily observed in the fresh wound; gaping edges indicate perpendicular tension, and relatively well approximated edges indicate parallel forces.

Scars tend to be red and prominent for about 8 wk. As collagen remodeling occurs, the scar becomes thinner and loses its erythema. In some patients, however, the scar hypertrophies, becoming unsightly and raised. Keloids are exuberant scars that extend beyond the limits of the original wound (see p. 743).

The most common factors that interfere with wound healing involve tissue ischemia, infection, or both (see Table 322-1); tissue ischemia predisposes to infection.

[Fig. 322-1. Representative minimal skin tension lines.]

Lower extremities are usually at greatest risk of poor healing due to impaired circulation. The scalp and face are at lowest risk. Certain drugs and disorders can also interfere with wound healing.

Bite wounds (see p. 3306) are usually heavily contaminated.

Evaluation

Sequential steps in evaluation include the following:

• Finding and treating serious injuries

• Obtaining hemostasis

• Looking for damage to underlying structures

Clinicians must find and treat serious injuries (see p. 3190) before focusing on skin lacerations, however dramatic. Actively bleeding wounds require hemostasis before evaluation. Hemostasis is best obtained by direct pressure and, when possible, elevation; clamping bleeding vessels with instruments is generally avoided because of the possibility of damaging adjacent nerves. Use of topical anesthetics containing epinephrine may also help reduce bleeding. Wound evaluation also requires good lighting. Magnification
(eg, with magnifying glasses) can help, particularly for examiners with imperfect near-vision.

**Table 322-1. Factors that Interfere with Wound Healing**

Full wound evaluation may require probing or manipulation, and thus local anesthesia, but sensory examination should precede administration of a local anesthetic.

The wound is evaluated for damage to underlying structures, including nerves, tendons, vessels, joints, and bones, as well as the presence of foreign bodies or body cavity penetration (eg, peritoneum, thorax). Failure to recognize these complications is one of the most significant errors in wound management.

**Nerve injury** is suggested by sensory abnormality distal to the wound; suspicion is increased for lacerations near the course of significant nerves. Examination should test light touch and motor function. Two-point discrimination is useful for hand and finger injuries; the clinician touches the skin with 2 ends of a bent paper clip simultaneously to determine the minimum separation that allows perception of 2 points (usually 2 to 3 mm). Normal varies among patients and by location on the hand; the identical site on the uninjured side is the best control.

**Tendon injury** is suspected in any laceration over the course of a tendon. Complete tendon laceration usually causes a resting deformity (eg, foot drop from Achilles tendon laceration, loss of normal resting finger flexion with digital flexor laceration) because forces from antagonist muscles are unopposed. Resting deformity does not occur with partial tendon laceration, which may manifest with only pain or relative weakness on strength testing or be discovered only on exploration of the wound. The injured area should be examined through the full range of motion; the injured tendon may sometimes retract and not be visible on inspection or wound exploration when the injured area is in the resting position.

**Vascular injury** is suggested by signs of ischemia, such as pallor, decreased pulses, or perhaps delayed capillary refill distal to the laceration (all compared with the uninjured side). Vascular injury is occasionally suspected in the absence of ischemia when a laceration traverses the territory of a major artery and is deep or complex or results from penetrating trauma. Other signs of vascular injury can include a rapidly expanding or pulsatile mass or a bruit.

**Bone injury** is possible, particularly after penetrating trauma or when injury occurs over a bony prominence. If the mechanism or location of injury is concerning, plain x-rays are taken to rule out fracture.

**Foreign bodies** are sometimes present in wounds, depending on the mechanism. Wounds involving glass are likely to have foreign bodies, lacerations from sharp metal rarely do, and wounds involving other substances are of intermediate risk. Although not very sensitive, a patient's complaint of feeling a foreign body is fairly specific and should not be ignored. Localized pain or tenderness in a high-risk wound also is suggestive, particularly if pain worsens with active or passive motion. Wound examination and exploration are not sensitive for small foreign bodies unless the wound is superficial and its full depth is visible. Imaging studies are recommended for all wounds involving glass and for other wounds if a foreign body is suspected because of the mechanism, the symptoms, or an inability to examine the wound's full depth. If glass or inorganic material (eg, stones, metal fragments) is involved, plain x-rays are taken; glass bits as small as 1 mm are usually visible. Organic materials (eg, wood splinters, plastic) are rarely detected with plain x-rays (although the outline of larger objects may be visible because of their displacement of normal tissue); various other modalities have been used, including xerography, ultrasonography, CT, and MRI. None of these is 100% sensitive, but CT may offer the best balance between accuracy and practicality. A high index of suspicion and careful exploration of all wounds are always appropriate.

**Joint penetration** should be suspected when wounds near a joint are deep or involve penetrating trauma.

**Penetration of the abdominal or thoracic cavity** should be considered in any wound over those locations in which the bottom of the laceration is not clearly visible. Wounds should not be blindly probed; blind probing is unreliable and may cause further injury. Patients with suspected thoracic lacerations require a chest x-ray initially, with a repeat film after 4 to 6 h of observation; any slowly developing
pneumothorax should be visible by that time. In patients with abdominal lacerations, local anesthesia facilitates exploration (lacerations can be extended horizontally if necessary). Patients with wounds penetrating the fascia should be observed in the hospital; sometimes abdominal CT is used to identify hemoperitoneum.

Treatment

Treatment involves

• Cleansing and local anesthesia (sequence can vary)
• Exploration
• Debridement
• Closure

Tissue should be handled as gently as possible.

Cleansing: Both the wound and the surrounding skin are cleaned. Subepidermal tissue in the wound is relatively delicate and should not be exposed to harsh substances (eg, full-strength povidone iodine, chlorhexidine, hydrogen peroxide) and vigorous scrubbing.

Removing hair from laceration edges is not necessary for wound hygiene but can make markedly hairy areas (eg, scalp) easier to work on. If necessary, hair is removed by clipping with scissors, not shaving; razors create microtrauma, allowing skin pathogens to enter and increasing risk of infection. Hair is clipped before wound irrigation so that any clipped hair entering the wound is removed. Eyebrows are never trimmed because the hair-skin border is needed for proper alignment of wound edges. Furthermore, eyebrows may grow back abnormally or not at all.

Although wound cleansing is not particularly painful, local anesthesia is usually administered first, except for heavily contaminated wounds; these wounds are best initially cleansed with running tap water and mild soap before a local anesthetic is administered. Tap water is clean and free of typical wound pathogens, and, used in this manner, does not seem to increase risk of infection. Wounds are then cleansed by a high-velocity stream of liquid and sometimes scrubbed with a fine-pore sponge; brushes and rough materials are avoided. An appropriate irrigation stream can be created using a 20-, 35-, or 50-mL syringe with a 20-gauge needle or IV catheter; commercially available devices incorporating a splash guard help limit splatter. Sterile 0.9% saline is an effective irrigant; specialized surfactant irrigants are costly and of doubtful additional benefit. If bacterial contamination is of particular concern (eg, bites, old wounds, organic debris), povidone iodine solution diluted 1:10 in 0.9% saline may be beneficial and is not harmful to tissues at this concentration. The volume necessary varies. Irrigation continues until visible contamination is removed and at least 100 to 300 mL has been applied (more for large wounds).

Painting the skin with povidone iodine before suturing may reduce skin flora, but the substance should not be introduced into the wound.

Local anesthesia: Generally, injectable local anesthetics are used. Topical anesthetics are beneficial in certain cases, especially for wounds of the face and scalp and when topical skin adhesives are used to close wounds.

Common injectable agents are lidocaine 0.5%, 1%, and 2%, and bupivacaine 0.25% and 0.5%, both from the amide group of local anesthetics; the ester group includes procaine, tetracaine, and benzocaine. Lidocaine is most commonly used. Bupivacaine has a slightly slower onset (several minutes vs almost immediate) and a significantly longer duration (2 to 4 h vs 30 to 60 min). Duration of action of both can be prolonged by adding epinephrine 1:100,000, a vasoconstrictor. Because vasoconstriction may impair wound vascularity (and thus defenses), epinephrine is mostly used for wounds in highly vascular areas (eg, face, scalp). Although traditional teaching has been to avoid using epinephrine in distal parts (eg, nose, ears, fingers, penis) to prevent tissue ischemia, complications from use on distal parts are rare, and
such use is now considered safe. Epinephrine can be particularly helpful in achieving hemostasis in wounds that are bleeding heavily.

The maximum dose of lidocaine is 3 to 5 mg/kg (1% solution = 1 g/100 mL = 10 mg/mL), and that of bupivacaine is 2.5 mg/kg. Addition of epinephrine increases the allowable dose of lidocaine to 7 mg/kg, and of bupivacaine to 3.5 mg/kg.

Adverse reactions to local anesthetics include allergic reactions (hives and, occasionally, anaphylaxis see p. 1120) and sympathomimetic effects from epinephrine (eg, palpitations, tachycardia). True allergic reaction is rare, particularly to amide anesthetics; many patient-reported events represent anxiety or vagal reactions. Furthermore, allergic reactions are often due to methylparaben, the preservative used in multidose vials of anesthetic. If the offending agent can be identified, a drug from another class (eg, ester instead of amide) can be used. Otherwise, a test dose of 0.1 mL preservative-free (single-dose vial) lidocaine can be given intradermally; if there is no reaction within 30 min, that anesthetic can be used.

Techniques recommended to minimize the pain of injection include the following:

- Using a small needle (a 27-gauge needle is best, and a 25-gauge is acceptable; a 30-gauge may be too flimsy)
- Giving the injection slowly
- Giving the injection into the subcutaneous plane instead of intradermally
- Buffering lidocaine with 1 mL of NaHCO₃ (concentration from 4.2 to 7.4%) for every 9 to 10 mL of lidocaine solution (NOTE: Buffering decreases the shelf life of multidose lidocaine vials, and buffering is ineffective for bupivacaine.)
- Warming the anesthetic solution to body temperature

Local or occasionally regional nerve blocks are sometimes preferred to wound injection. Nerve blocks cause less distortion of wound edges by injected anesthetic; this decreased distortion is important when alignment of wound edges must be particularly precise (eg, infraorbital nerve block for lacerations through the vermilion border of the lip) or when wound injection would be difficult because the space for injection is small (eg, digital nerve block for finger lacerations). Also, large areas can be anesthetized without using toxic doses of anesthetic. Slight disadvantages of nerve blocks are slower onset of anesthesia and sometimes < 100% effectiveness with the first injection.

Use of topical anesthesia makes injection unnecessary and is completely painless—factors particularly desirable in children and fearful adults. The most common solution is LET, which consists of lidocaine 2 to 4%, epinephrine 1:2000, and tetracaine 0.5 to 2%. A cotton dental pledget (or cotton ball) the length of the wound soaked in several milliliters of the solution and placed within the wound for 30 min usually provides adequate anesthesia; sometimes supplemental injectable anesthetic is required. If anesthesia is incomplete after application of a topical anesthetic, supplementary local anesthetic can be injected, usually with minimal pain.

Exploration: The full extent of the wound is explored to look for foreign material and possible tendon injury. Foreign material may also often be discerned by palpating gently with the tip of a blunt forceps, feeling for a discrete object and listening for a click characteristic of glass or metal foreign bodies. Occasionally, contaminated puncture wounds (eg, human bite wounds near the metacarpophalangeal joint) must be extended so that they can be adequately explored and cleansed. Deep wounds near a major artery should be explored in the operating room by a surgeon.

Debridement: Debridement uses a scalpel, scissors, or both to remove dead tissue, devitalized tissue (eg, tissue with a narrow base and no viable blood supply), and sometimes firmly adherent wound contaminants (eg, grease, paint). Macerated or ragged wound edges are excised; usually 1 to 2 mm is sufficient. Otherwise, debridement is not used to convert irregular wounds into straight lines. Sharply
beveled wound edges are sometimes trimmed so that they are perpendicular.

**Closure:** Decision to close a wound depends on the wound’s location, age, cause, and degree of contamination and on patient risk factors.

Most wounds can be closed immediately (primary closure). Primary closure is usually appropriate for uninfected and relatively un-contaminated wounds < 6 to 8 h old (< 12 to 24 h for face and scalp wounds).

Many other wounds can be closed after several days (delayed primary closure). Delayed primary closure is appropriate for wounds too old for primary closure, particularly if signs of infection have begun to appear, and for wounds of any age with significant contamination, particularly if organic debris is involved. The threshold for using delayed primary closure is lowered for patients with risk factors for poor healing. At initial presentation, anesthesia, exploration, and debridement are done at least as thoroughly as for other wounds, but the wound is loosely packed with moist gauze. The dressing is changed at least daily and evaluated for closure after 3 to 5 days. If there are no signs of infection, the laceration is closed by standard techniques. Loosely closing such wounds initially is ineffective and inappropriate because the wound edges nonetheless seal shut within 12 to 24 h.

Some wounds should not be closed. These wounds include the following:

- Cat bites
- Small bites to hands or feet (see also p. 3307)
- Puncture wounds
- High-velocity missile wounds

**Materials and methods:** Traditionally, sutures have been used for laceration repair, but metal staples, adhesive strips, and liquid topical skin adhesives are now used for certain wounds, mainly linear lacerations subject to only small amounts of tension. Whatever the material used, preliminary wound care is the same; a common error is to do cursory exploration and no debridement because a noninvasive closure not requiring local anesthesia is planned.

**Staples** are quick and easy to apply and, because there is minimal foreign material in the skin, are less likely to cause infection than sutures. However, they are suited mainly for straight, smooth cuts with perpendicular edges in areas of low skin tension. Improper wound edge apposition (sometimes causing wound edges to overlap) is the most common error.

**Topical skin adhesives** usually contain octylcyanoacrylate, butylcyanoacrylate, or both. They harden within a minute; are strong, nontoxic, and waterproof; form a microbial barrier; and have some antibacterial properties. However, adhesive should not be allowed into the wound. Infections are very unlikely, and cosmetic results are generally good. Adhesive is best for simple, regular lacerations; it should not be used for wounds under tension unless tension is relieved with deep dermal sutures, immobilization, or both. In wounds requiring debridement, deep dermal suturing, or exploration under local anesthesia, the advantages of decreased pain and time are minimized. However, patients do not require follow up for suture or staple removal. With long lacerations, skin edges can be held together by a 2nd person or with skin tapes while the adhesive is applied. One or 2 layers are applied as recommended by the manufacturer. The adhesive sloughs spontaneously in about a week. Excess or inadvertently applied adhesive can be removed with any petrolatum-based ointment or, in areas away from the eyes or open wounds, acetone.

**Adhesive strips** are probably the quickest repair method and have a very low infection rate. They are useful for wounds not subject to tension. Use on lax tissue (eg, dorsum of hand) is difficult because edges tend to invert. Adhesive strips cannot be used on hairy areas. Adhesive strips are particularly advantageous for lacerations in an extremity that is to be casted (thus blocking appropriate suture removal). Adhesive strips can also be used to reinforce wounds after suture or staple removal. Skin must
be dry before application. Many clinicians apply tincture of benzoin to boost adhesion. Improper application may result in blister formation. Adhesive strips may be removed by the patient.

**Sutures** are the best choice for irregular or complex lacerations, areas of loose skin, areas under tension, and other wounds requiring deep dermal closure. Because sutures can serve as an entry site for bacteria and there is a significant amount of foreign material under the skin, they have the highest rate of infection. Suture materials can be monofilament or braided and absorbable or nonabsorbable. Characteristics and uses vary (see Table 322-2); generally, absorbable material is used for deep dermal sutures, and nonabsorbable material is used for cutaneous ones. Braided material generally has higher tissue reactivity and thus poses a slightly higher risk of infection than does monofilament but is soft and easy to handle and has good knot security.

**Suture technique:** General goals include the following:

- Closely approximating skin margins
- Evertting wound edges
- Eliminating dead space
- Minimizing tension in the wound and of individual sutures
- Minimizing the amount of subcutaneous material

The relative importance of minimizing wound tension and minimizing the amount of material buried under the skin (eg, deep dermal sutures) vary by wound location. For example, in facial wounds, cosmetic result is very important and, because of the excellent vascular supply, infection risk is low. Thus, for gaping wounds, deep dermal sutures, which decrease wound tension and improve cosmetic result, are desired; infection risk is low even if they are used. In areas where vascular supply or cosmetic result is less important, deep dermal sutures are less desirable.

Sutures may be placed and tied individually (interrupted sutures) or be continuous (running suture). They may be completely buried under the skin (subcuticular or deep dermal sutures) or enter and exit the skin to be tied externally (percutaneous sutures).

If the wound is gaping, deep dermal suturing tends to be used initially (see Fig. 322-2); the resultant narrow epidermal gap is then closed by percutaneous sutures. For wounds on the face, any gaping > 5 to 10 mm may benefit from deep dermal suturing (not used on nose and eyelids); in other body areas, a wider gap is acceptable. Interrupted sutures using size 4-0 or 5-0 (smaller numbers indicate thicker material) braided absorbable material (eg, polyglactic acid) are most common. They are placed with the knot at the bottom of the wound to avoid a palpable lump and must not be too tight. A running subcuticular suture is sometimes used, especially for cosmetic repairs.

Epidermal closure is typically with simple, interrupted sutures (see Fig. 322-3) of nonabsorbable monofilament (eg, nylon, polypropylene). In areas over large joints and the scalp, size 3-0 or 4-0 sutures are used; size 6-0 sutures are used for repairing face wounds; in most other areas, size 4-0 or 5-0 sutures are used. Suture size can vary slightly depending on how much static and dynamic tension is predicted (eg, for facial lacerations subject to frequent movement or high tension, size 5-0 sutures may be used). Sutures are placed about as deep as they are wide and are spaced as far apart as the distance from the needle entry point to wound edge (see Fig. 322-4). Small bites (suture typically inserted 1 to 3 mm from the wound edge) are used for repairs in areas where cosmetic results are of particular concern and when tissues are thin. For other repairs, wider...
bites are used, varying with the tissue thickness. Wound edges can be everted by making the width of the bite greater at the deepest part of the wound than at the surface. Eversion is more easily obtained when the skin is entered with the needle at a 90° angle and angled slightly away from the skin edge.

A vertical mattress suture (see Fig. 322-5) is sometimes used instead of a layered closure, provided skin tension is not marked; it also helps ensure proper edge eversion in loose tissue. A running suture (see Fig. 322-6) is quicker to place than interrupted sutures and can be used when wound edges are well aligned.

In all cases, epidermal closure must precisely realign edges horizontally using natural skin landmarks (eg, folds, creases, lip margins) when available. Vertical alignment is equally important to avoid a step-off deformity. Excess tension after closure is evidenced by indenting of the skin or a sausage link appearance. Such a repair should be redone, adding deep dermal sutures, additional percutaneous sutures, or both as needed. Adjustments to suture technique are needed to achieve optimal alignment when wound edges are beveled. For example, edges may be debrided or suture bite size may differ from one side of the wound to the other.

Aftercare: Tetanus immunization is given if necessary (see Table 140-1 on p. 1299).

Topical antibiotic ointment is applied daily; it can reduce risk of infection and help maintain a moist wound environment that optimizes healing. However, ointment is not used over tissue adhesives or adhesive strips.

Prophylactic systemic antibiotics are not indicated except for the following cases:

- Bite wounds on the extremities (see p. 3307)
- Human bites
- Wounds involving tendons, bones, or joints
- Possibly intraoral lacerations
- Some heavily contaminated wounds

If deemed necessary, antibiotics are given as early as possible; the first dose may be given parenterally.

Wounds are immobilized because excess movement of the affected area may interfere with healing. Wounds near joints should be immobilized with splints. Bulky dressings are used to immobilize fingers and hands. Wounds should be elevated, above heart level when feasible, for the first 48 h after suturing. A sling may help maintain some degree of elevation of an upper extremity wound. Patients with distal lower extremity lacerations (other than minor) should probably stay off their feet for several days (eg, by using crutches); restrictions on walking probably result in better healing.

Wound care is meticulous. The wound is kept clean and dry; dressings that are nonadherent and impermeable to bacteria are usually applied. Antibiotic ointment is applied daily until the wound closure device is removed. A reliable patient may inspect minor, clean lacerations, but early physician examination is preferable for higher risk wounds and wounds in unreliable patients. After 12 h, well-healing wounds
can be cleansed gently of residual secretions with water, half-strength hydrogen peroxide, or soap and water. Brief wetting in the shower is safe, but prolonged soaking should be avoided.

**Wound infection** occurs in 2 to 5% of lacerations; steadily increasing pain ≥ 12 h after closure is often the earliest manifestation, and initial signs are redness more than about 0.5 cm from the wound edge, swelling, tenderness, and warmth. Later signs may include fever, purulent drainage, and ascending lymphangitis. Systemic antibiotics effective against skin flora are begun; a 1st-generation cephalosporin (eg, cephalexin 500 mg po qid) or, for intraoral infection, penicillin 500 mg po qid, is typically used. Infection beginning > 5 to 7 days after injury suggests retained foreign body.

**Closure material** (except for tissue adhesive) is removed after various intervals depending on location. For facial lacerations, sutures are removed in 3 to 5 days to prevent cross-hatching and visible needle entrance marks; some clinicians apply adhesive strips to bolster the wound for a few more days. Sutures and staples on the torso and upper extremities are removed in 7 to 10 days. Sutures and staples on the extensor surface of the elbow, knee, and anywhere below the knee should remain for 10 to 12 days.

**Abrasions**

**Abrasions are skin scrapes that may involve epidermis or part or all of the dermis.**

Abrasions are evaluated, cleansed, and debrided similarly to lacerations. They are harder to anesthetize, however, which is particularly problematic when large amounts of dirt, stones, or glass are embedded as is frequently the case, particularly with deep, scraping wounds; a regional nerve block or IV sedation may be needed. After thoroughly removing all debris (vigorous scrubbing may be needed), antibiotic ointment (eg, bacitracin) and a nonadherent gauze dressing that is impermeable to bacteria can be applied. Other commercial wound dressings may be used; the goals are to keep the wound from drying out, because drying interferes with re-epithelialization, and to keep the dressing from adhering.
Chapter 323. Fractures, Dislocations, and Sprains

Introduction

Fractures, joint dislocations, ligament sprains, muscle strains, and tendon injuries are common injuries that vary greatly in severity and treatment. Limbs are most often affected, although any part of the body can be. Injuries may be open (in communication with a skin wound) or closed.

Complications may be serious. Some are potentially life threatening:

- **Rapid blood loss**: Bleeding can be external or internal. Sometimes transfusion is required.

- **Fat embolism** (see Sidebar 194-1 on p. 1910): This rare, possibly preventable, complication may occur when a long bone is fractured.

Complications may also threaten limb viability or cause permanent limb dysfunction. Such complications occur in only a small percentage of limb injuries. The greatest threats come from open injuries that predispose to infection and injuries that disrupt the vascular supply (causing ischemia), primarily by directly injuring arteries or occasionally veins. However, some closed injuries (eg, posterior knee dislocations, hip dislocations, displaced supracondylar humeral fractures) can also disrupt the vascular supply, causing ischemia. The following can threaten a limb:

- **Compartment syndrome**: Tissue pressure increases in a closed fascial space, disrupting the vascular supply and reducing tissue perfusion. Crush injuries or markedly comminuted fractures are a common cause. Compartment syndrome can lead to rhabdomyolysis and thus infection, which threatens limb viability and, if untreated, survival.

- **Nerve or spinal cord injuries**: A penetrating injury may sever a peripheral nerve (see p. 3227). A blunt, closed injury may result in neuropraxia (bruised peripheral nerve) or axonotmesis (crushed nerve), which is more severe.

- **Dislocations**: The bones in a joint are completely separated, sometimes disrupting the vascular supply and injuring nerves. Vascular and nerve injuries are more likely when reduction (realignment of fracture fragments or dislocated joints) is delayed. Partial dislocation, termed subluxation, can also result in significant sequelae.

- **Infection**: Open injuries can become infected, potentially leading to osteomyelitis, which can be difficult to cure.

Closed injuries that do not involve blood vessels or nerves, including fractures, sprains, strains, and tendon tears, are least likely to result in serious complications.

Evaluation

In the emergency department, if the mechanism suggests potentially severe or multiple injuries (as in a high-speed motor vehicle crash or fall from a height), patients are first evaluated from head to toe for serious injuries to all organ systems and are resuscitated (see p. 3190). Patients, especially those with pelvic or femoral fractures, are evaluated for hemorrhagic shock due to occult blood loss. If the limb is injured, patients are immediately evaluated for symptoms or signs of ischemia (eg, absent pulses, marked pallor, coolness distal to the injury, severe pain).

**History**: The mechanism (eg, the direction of force, or torque, applied to a bone or joint) often suggests the type of injury. However, many patients do not remember, or cannot describe, the exact mechanism. Fractures and serious ligamentous injuries usually cause immediate pain; pain that begins hours to days after the injury suggests minor injury. Pain out of proportion to the apparent severity of the injury or pain that steadily worsens in the first hours to days immediately after injury suggests compartment syndrome or ischemia; compartmental pressure is then measured (see p. 3213). If a patient reports a deformity that has resolved before the patient is medically evaluated, the deformity should be assumed to be a true...
deformity that spontaneously reduced. A perceived snap or pop at the time of injury may signal a fracture or a ligament or tendon injury.

**Physical examination:** Examination includes vascular and neurologic assessment, inspection for deformity, swelling, ecchymoses, and decreased or abnormal motion and palpation for tenderness, crepitation, and gross instability. Motor or sensory deficits suggest neurologic injury. Paresthesias or sensory deficits alone suggest neuropraxia; motor plus sensory deficits suggest axonotmesis. Deformity suggests dislocation, subluxation (partial separation of bones in a joint), or fracture. Swelling commonly indicates a significant musculoskeletal injury but may require several hours to develop. If no swelling occurs within this time, fracture or severe ligament disruption is unlikely. With some fractures (eg, buckle fractures, small fractures without displacement), swelling may be subtle but is rarely absent.

Nearly all injuries are tender, and for many patients, palpation anywhere around the injured area causes discomfort. However, a noticeable increase in tenderness in one localized area (point tenderness) suggests a fracture or sprain. Localized ligamentous tenderness and pain with stressing the joint are consistent with sprain.

Crepitation (a characteristic cracking or popping sound) may be a sign of fracture. Gross joint instability suggests dislocation or severe ligamentous disruption. Stability of an injured joint is evaluated by stress testing (see p. 3215); however, if fracture is suspected, stress testing is deferred until x-rays exclude fracture.

Some partial tendon injuries escape initial clinical detection since function appears intact. Tendon tenderness, dysfunction, weakness, or palpable defects suggest partial tendon tears. Partial tendon tears may be impossible to detect initially; they may progress to complete tears with continued use. If the mechanism or examination suggests partial tendon injury, or if the examination is inconclusive, a splint that limits further injury is applied. Subsequent examination, occasionally supplemented with MRI, may further delineate the extent of injury. A partial tendon tear generally heals well if the joint is immobilized for 3 wk to prevent progression.

Attention to certain areas during examination can help detect commonly missed injuries (see Table 323-1).

If muscle spasm and pain limit physical examination (particularly stress testing), examination is sometimes easier after the patient is given a systemic or local anesthetic with or without sedation. Alternatively, the injury can be immobilized for a few days, and then the patient can be reexamined.

**Imaging:** Evaluation of suspected vascular injury, typically by arteriography, takes precedence over bone imaging.

Not all limb injuries require imaging. Some fractures are minor and are treated similarly to soft-tissue injuries. For example, most injuries of toes 2 through 5 are treated symptomatically whether a fracture is present or not. Many ankle sprains do not require x-rays during the initial evaluation because the probability of finding a fracture that would require a change in treatment is low. There are explicit, generally accepted criteria for obtaining certain kinds of x-rays; eg, if ankle sprain is suspected, x-rays are unnecessary unless specific criteria suggest fracture.

Plain x-rays show primarily bone (also joint effusion secondary to bleeding or occult fracture) and thus are useful for diagnosing most fractures as well as dislocations and subluxations that have not spontaneously reduced. X-rays are usually indicated for a suspected fracture or dislocation that requires treatment. Plain x-rays and other imaging studies should include at least 2 views taken in different planes (usually 1 anteroposterior and 1 lateral view). Additional views (such as oblique) may be obtained when the evaluation suggests fracture and 2 projections are negative.

CT or MRI can be used to better delineate fractures (eg, complex pelvic fractures) identified on plain x-rays and to check for fractures that require treatment and that are suspected even though plain x-rays do not show them (common with scaphoid fractures and impacted subcapital hip fractures). MRI can also be done to diagnose complex sprains (including complete rupture of a ligament) and other soft-tissue injuries.
Treatment

- Treatment of life- or limb-threatening injuries
- Splinting
- Definitive treatment (eg, reduction) for certain injuries
- Rest, ice, compression, and elevation (RICE)
- Usually immobilization

In the emergency department, hemorrhagic shock is treated. Injuries to arteries are repaired surgically unless they affect only small arteries with good collateral circulation. Severed nerves are surgically repaired; for neuropraxia and axonotmesis, initial treatment is usually observation, supportive measures, and sometimes physical therapy.

Most injuries, particularly grossly unstable ones, are immobilized immediately by splinting (immobilization with a nonrigid or noncircumferential device) to prevent further injury to soft tissues by unstable injuries and to decrease pain. In patients with long-bone fractures, splinting may prevent fat embolism. Pain is treated, typically with opioids (see p. 1623). Definitive treatment often involves reduction, which usually requires analgesia or sedation. Closed reduction (without skin incision) is done when possible; if not, open reduction (with skin incision) is done. Closed reduction

[Table 323-1. Examination for Some Commonly Missed Injuries]

of fractures is usually maintained by casting; some dislocations require only a splint or sling. Open reduction is usually maintained by various surgical hardware (eg, pins, screws, plates, external fixators).

**RICE:** Patients who have soft-tissue injuries, with or without musculoskeletal injuries, benefit from RICE (rest, ice, compression, elevation). Rest prevents further injury and may speed healing. Ice and compression minimize swelling and pain. Ice is enclosed in a plastic bag or towel and applied intermittently during the first 24 to 48 h (for 15 to 20 min, as often as possible). Injuries can be compressed by a splint, an elastic bandage, or, for certain injuries likely to cause severe swelling, a Jones compression dressing. The Jones dressing is 4 layers; layers 1 (the innermost) and 3 are cotton batting, and layers 2 and 4 are elastic bandages. The injured limb is elevated above the heart for the first 2 days in a position that allows gravity to help drain edema fluid and thus minimize swelling. After 48 h, periodic application of warmth (eg, a heating pad) for 15 to 20 min may relieve pain and speed healing.

**Immobilization:** Immobilization decreases pain and facilitates healing by preventing further injury and is helpful except for very rapidly healing injuries. Joints proximal and distal to the injury should be immobilized.

A cast is usually used for fractures or other injuries that require weeks of immobilization. Rarely, swelling under a cast is severe enough to contribute to compartment syndrome (see p. 3213). Sometimes, if severe swelling is likely, a cast (and all padding) is cut open from end to end medially and laterally (bivalved). Patients with casts should be given written instructions:

- To keep the cast dry
- Never to put an object inside the cast
- To inspect the cast's edges and skin around the cast every day and apply lotion to any red or sore areas
- To pad any rough edges with soft adhesive tape, cloth, or other soft material to prevent the cast's edges
from injuring the skin

• To seek medical care at once if an odor emanates from within the cast or if a fever, which may indicate infection, develops

Good hygiene is important.

A splint (see \textit{Fig. 323-1}) can be used to immobilize some stable injuries, including some suspected but unproven fractures, sprains, and other injuries that require immobilization for several days or less. A splint allows patients to apply ice and to move more and does not contribute to compartment syndrome.

Immobilization with bed rest, which is occasionally required for fractures (eg, some vertebral or pelvic fractures), can cause problems (eg, deep venous thrombosis, UTI).

Prolonged immobilization (more than 3 to 4 wk) of a joint can cause stiffness, contractures, and muscle atrophy. These complications may develop rapidly and may be permanent, particularly in the elderly. Some rapidly healing injuries are best treated with resumption of active motion within the first few days or weeks (early mobilization); this approach may minimize contractures and muscle atrophy, thus accelerating functional recovery.

\textbf{Fractures}

(For vertebral compression fractures, see p. 356; for dental fractures, see p. 524; for spinal fractures, see p. 3227; for fractures of the temporal bone, jaw and contiguous structures, and nose, see pp. 3232-3334; for metatarsal stress fractures, see p. 3304; for orbital fractures, see p. 3238, and for fractures that occur during birth, see p. 2774.)

Fractures are cracks in bones. Symptoms include pain, swelling, ecchymosis, crepitation, deformity, and abnormal motion. Occasional complications include fat embolism, arterial injury, compartment syndrome, nerve injuries, and infection. Diagnosis is by clinical criteria and usually plain x-rays. Treatment involves analgesics, immobilization, and sometimes surgery.

Most fractures result from a single application of significant force to otherwise normal bone. Pathologic fractures result from application of mild or minimal force to a bone weakened by a disorder such as cancer, cysts, or osteoporosis. Stress fractures (eg, metatarsal stress fracture—see p. 3304) result from repetitive application of force.

\textbf{Pathophysiology}

If Ca and vitamin D levels are adequate and bone tissue is healthy and the fracture edges are kept reasonably close to each other and with little or no relative motion, most fractures heal within weeks or months via remodeling. New tissue (callus) is produced within weeks, and bone reshapes at variable rates during the first weeks or months. Ultimately, optimal remodeling requires gradual resumption of normal motion and load-bearing stress. However, remodeling can be disrupted and refracture can occur if force is applied or the joint moves prematurely; thus, immobilization is usually needed.

Serious complications are unusual. Arteries are injured occasionally in closed supracondylar fractures of the humerus and femur but rarely in other closed fractures. Compartment syndrome or nerve injury may occur. Open fractures predispose to bone infection (see p. 370), which can be intractable. Fractures of long bones may release fat (and other marrow contents) that embolizes to the lungs and causes respiratory complications (see \textit{Sidebar 194-1} on p. 1910). Fractures that extend into joints usually disrupt articular cartilage; misaligned articular cartilage tends to scar, causing osteoarthritis and impairing joint motion. Occasionally, fractures do not heal (called nonunion); rarely, nonunion occurs even when treatment is expeditious and correct. If the vascular supply is injured by the initial injury (such as a
scaphoid fracture), aseptic necrosis may ensue even if the fracture was properly immobilized.

**Symptoms and Signs**

Pain is usually immediate. Swelling increases for several hours. Children may not exhibit significant soft-tissue swelling in the presence of a fracture (buckle [torus] fracture or greenstick fracture). Pain and swelling usually begin to resolve after 12 to 24 h; worsening pain after this period suggests compartment syndrome. Other symptoms and signs may include bone tenderness, ecchymosis, decreased or abnormal motion, deformity, and crepitation. With some fractures (eg, rib fractures), motion can be sensed by the patient and is described as a popping or cracking sensation.

**Diagnosis**

- Clinical assessment for complicating injuries
- Plain x-rays
- Sometimes CT or MRI

Patients with findings that suggest fracture are examined for ischemia, compartment syndrome, and nerve injury. If a wound is close to a fracture, open fracture is assumed. Fractures are diagnosed by imaging, beginning with plain x-rays. If no fracture line is obvious, bone density, trabecular pattern, and cortical margins are examined for subtle clues to fracture. If a fracture is not visible on plain x-rays but is strongly suspected or if more detail is needed to guide treatment, MRI or CT is done. Some experts recommend imaging the joints proximal and distal to the fracture.

A fracture's appearance on x-rays can be described precisely using 5 terms:

- Type of fracture line (see **Fig. 323-2**)
- Location of fracture line
- Angulation
- Displacement (see **Fig. 323-3**)
- Open or closed

Location may be the bone's head (sometimes involving the articular surface), neck, or shaft (proximal, middle, or distal third).

**Treatment**

- Analgesia, splinting, and reduction as indicated
- Treatment of complicating injuries
- Immobilization
- Sometimes surgery

Immediate treatment includes analgesics and, for suspected unstable fractures or fractures of long bones, splinting. Suspected open fractures require sterile wound dressings, tetanus prophylaxis, and broad-spectrum antibiotics (eg, a 2nd-generation cephalosporin plus an aminoglycoside).

[**Fig. 323-2.** Common types of fracture lines.]
Rotational malalignment or significant angulation or displacement is corrected with reduction (realignment of bone fragments by manipulation). Exceptions include some diaphyseal fractures in children. In these fractures, remodeling gradually corrects some types of significant angulation, and end-to-end realignment of fractured bone fragments can stimulate bone growth, which may then be excessive.

Closed reduction (without skin incision) is done when possible; if not, open reduction (with skin incision) is done.

In open reduction and internal fixation (ORIF), fracture fragments are aligned and held in place using hardware. ORIF is usually indicated for the following:

- When an intra-articular fracture is displaced (to precisely align the joint cartilage)
- When ORIF has been shown to have better results for a particular type of fracture
- When closed reduction was ineffective
- When the fracture traverses a cancerous lesion (because normal bone healing does not occur)
- When prolonged immobility (required for callus formation and remodeling) is undesirable (eg, for hip fractures), because ORIF provides early structural stability, which facilitates mobilization

Surgery is required when injury to a major vessel is suspected (for vessel repair) or when the fracture is open (for irrigation and debridement to prevent infection). Open reduction may be done without using hardware when closed reduction is ineffective.

Fractures, whether they require reduction, surgery, or neither, are typically immobilized, as are the proximal and distal joints. Usually, a cast is applied for weeks or months, but a splint may be used instead, particularly for fractures that heal faster when mobilized early. Home care for fractures includes supportive measures such as RICE (rest, ice, compression, elevation—see p. 3203).

Patients are told to seek care immediately if symptoms of compartment syndrome occur (see p. 3213).

Geriatrics Essentials

The elderly are predisposed to fractures because of osteoporosis, a tendency to fall frequently, drug adverse effects, and impaired protective reflexes during falls. Age-related fractures tend to affect the metaphysis (the flared area between the end and shaft). They include fractures of the distal radius, proximal humerus, proximal tibia, proximal femur, pubic ramus, and vertebrae.

The goal of treatment is rapid return to activities of daily living rather than restoration of perfect limb alignment and length. Because immobilization (joint immobilization or bed rest) is more likely to cause adverse effects in the elderly, use of ORIF is increasing. Early mobilization and physical therapy are essential to recovery of function. Coexisting disorders (eg, arthritis) can interfere with recovery.

Specific Fractures

Stress fractures: Stress fractures are small and result from repetitive force (eg, from overuse); they occur most often in the metatarsals (usually in runners—see p. 3304), followed by the fibula and tibia. Symptoms include gradual onset of intermittent pain that worsens with weight bearing and eventually becomes constant. Sometimes swelling occurs.

Examination detects localized bone tenderness. Plain x-rays are done but may not show the fracture at first. Thus, many such fractures are treated presumptively, and plain x-ray is repeated 2 to 3 wk later when callus may be visible. Treatment is rest, elevation, analgesics, and sometimes immobilization. CT or
MRI is rarely needed.

**Growth plate fractures:** Bone grows as tissue is added proximally by the epiphyseal disk (growth plate), which is bordered by the metaphysis proximally and the epiphysis distally (see Fig. 323-4). The age at which the growth plate closes and bone growth stops varies by bone, but the growth plate is closed in all bones by the end of puberty. If there is question about a growth plate injury or if a fracture is suspected, opposite side comparison x-rays may be helpful.

The growth plate is the most fragile part of the bone and thus is usually the first structure disrupted when force is applied. Growth plate fractures are classified by the Salter-Harris system (see Fig. 323-5). Disruption of future bone growth is common with types III, IV, and V but uncommon with types I and II.

Growth plate fractures are suspected in children with tenderness localized over the growth plate. These fractures cause circumferential tenderness and thus can be clinically differentiated from contusions. In fracture types I and V, x-rays may appear normal. If so, these fractures can sometimes be differentiated from each other by injury mechanism—eg, distraction (separation in longitudinal axis) vs compression.

Closed treatment is usually sufficient for types I and II; ORIF is often required for types III and IV. Patients with type V injuries should be referred to a pediatric orthopedist because such injuries almost always lead to growth abnormalities.

**Rib fractures:** Typically, rib fractures result from blunt injury to the chest wall, usually involving a strong force (eg, from high-speed deceleration, a baseball bat, a major fall); however, sometimes in the elderly, only mild or moderate force (eg, in a minor fall) is required. Concomitant injuries may include

- Aortic, subclavian, or cardiac injuries (uncommon but can occur with high-speed deceleration, particularly if rib 1 or 2 is fractured)
- Splenic or abdominal injuries (with fractures of any of ribs 7 through 12)
- Pulmonary laceration or contusion
- Pneumothorax
- Other tracheobronchial injuries (uncommon)

Pain is severe, is aggravated by movement of the trunk (including coughing or deep breathing), and lasts for several weeks. Inspiratory splinting (incomplete inspiration due to pain) can cause atelectasis and pneumonia, especially in the elderly or those with multiple fractures. Young, healthy patients and those with 1 or 2 rib fractures rarely develop these complications.

Palpation of the chest wall may identify some fractures, and sometimes the patient and the examining clinician can feel the broken ribs move when the lungs are expanded. A chest x-ray is taken routinely to check for concomitant injuries (eg, pneumothorax, pulmonary contusion). Many rib fractures are not visible on a chest x-ray; specific rib views may be needed, but identifying all rib fractures by x-rays is not always necessary. Other tests are done to check for concomitant injuries that are clinically suspected.

Treatment requires opioid analgesics, which can depress respiration and worsen atelectasis. To minimize pulmonary complications, patients should consciously and frequently (eg, hourly) breathe deeply or cough while awake. Holding (essentially splinting) the affected area with the flat palm of the hand or a pillow can help minimize the pain during deep breathing or coughing. Patients are hospitalized if they have ≥ 3
fractures or underlying cardiopulmonary insufficiency. Immobilization (eg, by strapping or taping) should usually be avoided; it constricts respiration and may predispose to atelectasis and pneumonia.

**Clavicle fractures:** The usual injury mechanism is a fall on an outstretched arm or a direct blow. About 80% involve the middle one third of the bone and are immobilized with a sling. Previously used figure-of-eight braces are no more helpful (and are more uncomfortable) than a simple sling. Reduction is not necessary even for greatly angulated fractures. Clavicle fractures that significantly tent the skin or that involve areas other than the middle one third of the bone may require additional intervention.

**Proximal humeral fractures:** The usual injury mechanism is direct force or a fall on an outstretched arm. Usually, displacement and angulation are minimal. Contractures may develop after only a few days of immobilization, particularly in the elderly. Minimally displaced or angulated fractures are treated with immobilization in a sling and swathes (see Fig. 323-1) and early range-of-motion exercises. More severe fracture may require ORIF or surgery to insert a prosthetic joint (shoulder replacement).

**Distal humeral fractures:** The usual injury mechanism is direct force or a fall on an outstretched arm. The brachial artery or radial nerve may be damaged. Angulation, if present, must be corrected. Casting with closed reduction may be tried, but ORIF may be necessary.

**Radial head fractures:** The usual injury mechanism is a fall on an outstretched arm. The radial head is palpated on the lateral elbow as a structure that rotates during pronation and supination. Routine anteroposterior and lateral x-rays usually show a joint effusion or a displaced anterior fat pad (sail sign) but often do not show the fracture. Patients with localized radial head tenderness and effusion require oblique views (which are more sensitive for fracture) or presumptive treatment of a fracture. For fractures with minimal angulation and displacement, treatment is a splint with the elbow flexed 90° or a sling. Arthrocentesis to remove blood from the joint often helps relieve pain and facilitate recovery. Starting range-of-motion exercises 10 days after the injury maximizes joint flexibility.

**Distal radial fractures:** The usual injury mechanism is wrist hyperextension, usually during a fall. Dorsally displaced or angulated fractures (sometimes called Colles’ fractures) are common. Treatment is reduction and immobilization at 15 to 30° of wrist extension. ORIF may be necessary if the joint is disrupted or if there is excessive impaction or shortening.

**Metacarpal neck fractures (except thumb):** The usual injury mechanism is an axial load (eg, from punching with a clenched fist). If wounds are near the metacarpophalangeal joint, contamination with human oral flora should be considered, and measures to prevent infection are often required (see p. 3307). Reduction is necessary for fractures of the 2nd and 3rd metacarpals but is unnecessary for dorsal or volar angulation of < 35° for the 4th metacarpal or of 45° for the 5th metacarpal. Treatment is a splint (eg, an ulnar gutter splint for fractures of the 4th or 5th metacarpal—see Fig. 323-1).

**Scaphoid (navicular) fractures:** The usual injury mechanism is wrist hyperextension, usually during a fall on the outstretched hand. Avascular necrosis is a common complication, even when initial care is ideal, and can cause disabling, degenerative arthritis of the wrist. Fracture signs include pain with axial compression of the thumb, pain with wrist supination against resistance, and, particularly, tenderness in the anatomic snuffbox with ulnar wrist deviation. The anatomic snuffbox is palpated just distal to the radius between the extensor pollicis longus, extensor pollicis brevis, and abductor pollicis longus tendons. The initial plain x-ray is often normal. If a fracture is still suspected, MRI, which is more sensitive than x-rays, is done, or fracture is presumed and treated with a thumb spica splint (see Fig. 323-1), with a follow-up plain x-ray taken in 1 to 2 wk. Rarely, this subsequent x-ray is falsely normal.

**Fingertip (tuft of the distal phalanx) fractures:** The usual mechanism is a crush injury. Subungual (beneath the nail) hematoma usually occurs and produces a blue-black, tender bruise, which may elevate the nail; hematoma indicates a nail bed laceration. Most fingertip fractures are treated symptomatically with a protective covering (eg, commercially available aluminum and foam splint material) wrapped around the fingertip. Subungual hematomas can be drained to relieve pain by puncturing the nail (trephination), usually with an 18-gauge needle in a rotatory motion or, if no nail polish is on the nail, with an electrocautery device. If trephination is done gently and rapidly, anesthesia is often unnecessary. Large displaced fractures are rarely repaired surgically. Markedly disrupted nail beds are repaired with sutures.
but are best left alone if the nail is closely adherent to the nail bed. Hyperesthesia frequently persists long after a large fracture has healed and requires desensitization therapy.

**Pelvic fractures:** Pelvic fractures may be stable or unstable. Compression of the pubic symphysis or simultaneous compression of both anterior superior iliac spines is often painful, particularly in severe fractures. For pelvic fractures, CT is more sensitive than plain x-rays.

Stable fractures do not disrupt the pelvic ring. Some (eg, symphyseal or pubic ramus fractures) result from minor injuries (eg, falls at home), especially in patients with osteoporosis. Treatment is often symptomatic, particularly if patients can walk unaided.

Unstable fractures disrupt the pelvic ring in ≥ 2 places; disruptions can be fractures within bones or separations between the fibrous joints (syndesmoses) between bones. Unstable fractures usually result from substantial forces (eg, high-speed motor vehicle crashes). Intestinal injuries may occur. Concomitant GU injuries (eg, urethral or bladder tears) are common, particularly with anterior pelvic fractures. Vascular injuries may occur and cause hemorrhagic shock, especially with posterior pelvic fractures. Mortality rate is high. Initial evaluation and treatment are directed at associated injuries. The fracture often requires surgical repair.

**Hip fractures:** Hip fractures are most common among the elderly, particularly those with osteoporosis (mostly women—see p. 356). Most fractures result from falls, but in the elderly, seemingly minimal force (eg, rolling over in bed, getting up from a chair, walking) can result in hip fracture, usually because osteoporosis has weakened bone. Subcapital femoral neck and intertrochanteric fractures are the most common types. Hip fractures often cause referred pain in the knee and thus may be misinterpreted as a knee abnormality. Pubic ramus fractures can cause hip pain.

**Subcapital fractures** may result from a single injury but often result from repeated stress or minimal force, resulting in a small or large stress fracture. A fall after the initial fracture may worsen or displace the fracture. Patients with small fractures may be ambulatory and have only mild pain. However, such patients may be unable to flex the entire lower limb against resistance with the knee extended. Passive hip rotation with the knee flexed aggravates the pain, helping to differentiate hip fracture from extra-articular disorders such as trochanteric bursitis. Large or displaced fractures tend to limit hip motion more, shorten the leg, and cause the leg to rotate externally. Displacement predisposes to osteonecrosis of the femoral head and fracture nonunion.

Plain x-rays are occasionally normal when fractures are small or impacted or when osteoporosis is severe. If a fracture is still suspected, MRI is done; if MRI is unavailable or contraindicated, CT is done. If patients are expected to resume walking and have no contraindication to surgery, treatment is usually surgical repair (typically ORIF—see Fig. 323-6) and early ambulation.

If patients are elderly, are not active, and have displaced fractures, treatment is often prosthetic replacement of the femoral head, typically with a Moore prosthesis, or total hip replacement. Occasionally, the femoral head must be replaced when the fracture is displaced in younger adults, particularly those who are inactive. Usually, prolonged bed rest should be avoided in elderly patients. Bed rest increases the risk of deep venous thrombosis, a common complication of hip fractures. Prophylactic anticoagulation may reduce the incidence of post-hip fracture venous thrombosis.

![Open reduction with internal fixation (ORIF).](Fig. 323-6)
Ankle fractures: The ankle bones and ligaments form a ring that connects the tibia and fibula to the talus and calcaneus. Within the ring, stability is provided by 2 bones (the medial malleolus of the tibia and lateral malleolus of the fibula) and 2 ligament complexes (medially, the deltoid ligament; laterally, mainly the anterior and posterior talofibular ligaments and calcaneofibular ligament—see Fig. 323-7). Ankle fractures are common and can result from multiple injury mechanisms. Fractures that disrupt the ring in one place often disrupt it in another (eg, if only one bone is fractured, a ligament is often simultaneously and severely torn). If fractures disrupt ≥ 2 of the structures stabilizing the ankle ring, the ankle is unstable. Disruption of the medial deltoid ligament also causes instability. For unstable injuries, surgery may be required, and prognosis is guarded. Most stable ankle fractures without other indications for surgery can be treated with a cast for 6 wk; prognosis is good.

Fractures of the 2nd metatarsal bone base with dislocation (Lisfranc's fracture-dislocation): The usual mechanism is a fall on a foot in plantar flexion. Usually there is significant soft-tissue swelling. These rare fractures are difficult to appreciate on plain x-rays and are often misdiagnosed, leading to sometimes serious complications, such as osteoarthritis and rarely compartment syndrome. A plain x-ray can show a fracture at the base of the 2nd metatarsal or chip fractures of the cuneiform but may not show disruption of the tarsometatarsal joint, which should be suspected even if it is not visible on plain x-rays. Dislocations often spontaneously reduce, but immediate referral, usually for closed reduction, which requires general anesthesia, may be warranted.

Fractures of the 5th metatarsal bone base (dancer's fracture): The usual injury mechanism is a twist (typically, inversion) or crush injury. These fractures usually heal relatively quickly; nonunion is uncommon. Treatment is a protective walking shoe.

Fractures of the 5th metatarsal bone diaphysis (Jones fracture): The usual injury mechanism is a crush injury. These fractures are less common than those of the metatarsal bone base, and delayed union or nonunion occurs more commonly. Treatment is a cast that immobilizes the ankle. Avulsion fractures of the base of the fifth metatarsal can occur with inversion ankle injuries and are less significant than a true Jones fracture, the latter being predisposed to nonunion.

Toe fractures: The usual injury mechanism is a crush injury. Unless rotational deformity or joint involvement is suspected or the proximal phalanx of the great toe is injured, x-rays are usually unnecessary. Treatment is taping the injured toe to an adjacent toe (dynamic splinting or buddy taping). Markedly displaced toe fractures should be reduced to restore alignment.

Compartment Syndrome

Compartment syndrome is increased tissue pressure within a closed fascial space, resulting in tissue ischemia. The earliest symptom is pain out of proportion to the severity of injury. Diagnosis is by measuring compartmental pressure. Treatment is fasciotomy.

Compartment syndrome is a self-perpetuating cascade of events. It begins with the tissue edema that normally occurs after injury (eg, because of soft-tissue swelling or a hematoma). If edema develops within a closed fascial compartment, typically in the anterior or posterior compartments of the leg, there is little room for tissue expansion, so interstitial (compartmental) pressure increases. As compartmental pressure exceeds about 20 mm Hg, cellular perfusion slows and may ultimately stop. (NOTE: Because 20 mm Hg is much lower than arterial pressure, cellular perfusion can stop long before pulses disappear.) Resultant tissue ischemia further worsens edema in a vicious circle. As ischemia progresses, muscles necrose, sometimes leading to rhabdomyolysis and infections; these complications can cause loss of limb and, if untreated, death. If arteries are injured, arterial pressure can drop below even mildly elevated compartmental pressures, causing or worsening compartment syndrome.

Etiology

Common causes include fractures and severe contusions. Rare causes include snakebites, severe...
exertion, drug overdose (heroin, cocaine), casts, tight bandages, and other rigid circumferential devices that limit swelling and thus increase compartmental pressure. Prolonged pressure on a muscle during coma may cause rhabdomyolysis.

**Symptoms and Signs**

Compartment syndrome usually occurs in the anterior lower leg. The earliest symptom is worsening pain. It is typically out of proportion to the severity of the apparent injury and is exacerbated by passive stretching of the muscles within the compartment (eg, for the anterior leg compartment, by passive toe flexion, which stretches the toe extensor muscles). Pain, one of the 5 P's of tissue ischemia, is followed by the other 4: paresthesias, paralysis, pallor, and pulselessness. Compartments may feel tense when palpated.

**Diagnosis**

- Measurement of compartmental pressure

Diagnosis must be made and treatment started before pallor or pulselessness develop, indicating necrosis. Diagnosis is by measuring compartmental pressure (normal ≤ 20 mm Hg), usually with a commercially available wick catheter.

**Treatment**

- Often fasciotomy

Pressures of 20 to 40 mm Hg can sometimes be treated conservatively with analgesics, elevation, and splinting; casts, if present, are removed or bivalved. Pressures > 40 mm Hg usually require immediate fasciotomy to relieve pressure. If necrosis occurs, amputation may be needed.

**Dislocations**

(For spinal dislocations, see p. 384; for atlantoaxial subluxation, see p. 385; and for mandibular dislocation, see p. 524.)

Dislocation is a complete separation of the bone ends that normally articulate to form a joint; subluxation is a partial separation.

The most commonly dislocated limb joint is the glenohumeral (shoulder). Arterial and nerve injuries, although uncommon, are a risk with dislocations (eg, of the knee, elbow, or hip), particularly those that are not rapidly reduced.

Symptoms and signs include pain, swelling, deformity, and inability to move. Diagnosis is by plain x-rays. Treatment is usually closed reduction as soon as possible; it requires sedation and analgesia or, occasionally, general anesthesia. Neurovascular assessment is done before and after reduction. If closed reduction is ineffective, open reduction is necessary.

**Specific Dislocations**

**Glenohumeral (shoulder) dislocations:** Glenohumeral dislocations are anterior in ≥ 95% of patients; the cause is abduction and external rotation of the humerus. Occasionally, the axillary nerve is injured, or the greater tuberosity is fractured, particularly in patients > 45. The acromion is prominent; the humeral head is displaced anteriorly and inferiorly and cannot be palpated in its usual position. Sensation over the lateral deltoid is tested to check for axillary nerve injury. Treatment is usually closed reduction with using conscious sedation. The traction-countertraction technique is one of many commonly used methods of reduction (see Fig. 323-8). After reduction, the joint is immobilized immediately with a sling and swathe (see Fig. 323-1).

Occasionally, dislocation is posterior—a commonly missed injury—or inferior (luxatio erecta). In patients
with luxatio erecta, the brachial artery or brachial plexus is often also injured.

**Elbow dislocations:** Most elbow dislocations result from a fall on an extended, abducted arm. They are common and usually posterior. Associated injuries may include fractures, injuries to the ulnar or median nerve, and possibly injury to the brachial artery. The joint is usually flexed about 45°, and the olecranon is prominent and posterior to the humeral epicondyles; however, these anatomic relationships may be difficult to determine because of swelling. Reduction is usually with sustained, gentle traction after sedation and analgesia.

**Radial head subluxations (nursemaid's elbow):** In adults, the radial head is wider than the radial neck; consequently, the head cannot fit through ligaments that tightly surround the neck. However, in toddlers (about 2 to 3 yr old), the radial head is no wider than the radial neck and can easily slip through these ligaments (radial head subluxation). Subluxation results from traction on the forearm as when a caregiver pulls a reluctant toddler forward or catches the toddler by the wrist during a fall—actions many caregivers do not remember. Symptoms may include pain and tenderness; however, many toddlers cannot describe their symptoms and simply avoid moving the affected elbow (pseudoparalysis).

[Fig. 323-8. Traction-countertraction technique for reducing anterior shoulder dislocations.]

Plain x-rays are normal and considered unnecessary by some experts unless an alternate diagnosis is clinically suspected. Reduction may be diagnostic and therapeutic. The elbow is completely extended and supinated, then flexed, usually without sedation or analgesia. Reduction is often marked by a subtle palpable pop or click as the radial head resumes normal position. Children may start to move the elbow after about 20 min. Immobilization is unnecessary. If pain or dysfunction lasts longer than 24 h, incomplete reduction or an occult fracture should be suspected.

**Proximal interphalangeal (PIP) joint dislocations:** PIP joint dislocations are common. Dorsal dislocations, which are more common than volar, are usually due to hyperextension, sometimes displacing the volar joint structures intra-articularly. Volar dislocations can rupture the central slip of the extensor tendon, causing boutonniere deformity (see p. 387). Dislocations usually cause obvious deformities. A lateral x-ray should be taken with the affected digit visibly separated from the others.

For most dislocations, closed reduction using digital block anesthesia is done. Axial traction and volar force are used for dorsal dislocations, and dorsal force is used for volar dislocations. Dorsal dislocations are splinted at 15° of flexion for 3 wk. Volar dislocations are splinted at extension for 1 to 2 wk. Some dorsal dislocations require open reduction.

**Hip dislocations:** Most hip dislocations are posterior and result from a severe posteriorly directed force to the knee with the knee and hip flexed (eg, against a car dashboard). Complications may include arterial injury (particularly if the dislocation is anterior) with subsequent avascular necrosis of the femoral head and sciatic nerve injury. Treatment is reduction as soon as possible, followed by bed rest or joint immobilization.

**Knee (tibiofemoral) dislocations:** Most anterior dislocations result from hyperextension; most posterior dislocations result from a posteriorly directed force to the proximal tibia with the knee slightly flexed. Most knee dislocations result from severe trauma (eg, high-speed motor vehicle collisions), but seemingly slight trauma, such as stepping in a hole, coupled with a twisting movement, can dislocate the knee. Some dislocations spontaneously reduce before medical evaluation, resulting in a large hemarthrosis and gross instability of the knee. Concomitant arterial injury may be seen with a spontaneously reduced knee dislocation.

Popliteal artery injury is a serious complication, but it is often a subtle injury in the early stages. The popliteal artery may be injured, even if ischemia is not initially evident. When the intima is torn, occlusion of the artery may be delayed. Thus, some experts believe that serial clinical evaluations of the distal pulse can rule out a popliteal artery injury if the pulse is normal over a period of time. However, some experts believe that angiography is indicated for every patient with a knee dislocation or with gross instability.
Treatment is immediate reduction and surgical repair.

**Lateral patellar dislocations:** The usual injury mechanism is quadriceps contraction plus flexion and external tibial rotation. Most patients have an underlying chronic patellofemoral abnormality. Many dislocations spontaneously reduce before medical evaluation. Treatment is reduction; with the hip flexed, the patella is gently moved medially while the knee is extended. Reduction is followed by a cylindrical leg cast or surgical repair.

**Sprains, Strains, and Tendon Tears**

Tears may occur in ligaments (sprains), in muscles (strains), or in tendons. Tears may be graded as minimal (1st degree), moderate to severe (2nd degree), or complete (3rd degree). Third-degree sprains may result in joint instability and are differentiated from 2nd-degree sprains by stress testing. Third-degree tendon tears disrupt muscle function. Treatment of all tears includes analgesics, immobilization, and, for some 3rd-degree sprains and tendon tears, surgical repair.

Sprains commonly involve the acromioclavicular joint, proximal interphalangeal joint, knee (see p. 3217), or ankle. Tendon tears commonly involve the knee extensor mechanism or Achilles tendon. Various muscles are commonly strained. Sprains, strains, and tendon tears cause pain, tenderness, and usually swelling. Second-degree sprains are very painful when stretched. Third-degree sprains often cause joint instability because ligaments that stabilize joints may be disrupted. In 3rd-degree tendon tears, the muscle cannot move the bone normally attached to it by the tendon; a tendon defect may be palpable.

**Diagnosis**

- Bedside stress testing

Bedside stress testing involves passively opening the joint in a direction other than the normal range of motion (stressing) to check for joint instability; this test helps differentiate between 2nd- and 3rd-degree sprains. Because muscle spasm during acutely painful injuries may mask joint instability, the surrounding muscles are relaxed as much as possible, and examinations are begun gently, then repeated, with slightly more force each time. Findings are compared with those for the opposite, normal side. With 2nd-degree sprains, stress is painful, and joint opening is limited. With 3rd-degree sprains, stress is less painful because the ligament is completely torn and is not being stretched, and joint opening is less limited. If muscle spasm is severe, the examination should be repeated after injection of a local anesthetic, after use of systemic analgesia or sedation, or after a few days, when the spasm has subsided.

**Treatment**

- Rest, ice, compression, and elevation (RICE)

- Immobilization and repair as indicated based on injury location and severity

Treatment of all tears includes RICE (see p. 3203) and, if necessary, analgesics. For 1st-degree tears, early mobilization is usually best. Mild 2nd-degree tears are often immobilized with a sling or splint for a few days. Severe 2nd-degree and some 3rd-degree sprains and tendon tears are immobilized for days or weeks, sometimes with a cast. Many 3rd-degree sprains and tendon tears require surgical repair.

**Specific Sprains and Tendon Tears**

**Acromioclavicular joint sprains (separation):** The usual injury mechanism is a fall on the point of a shoulder or on an outstretched arm. Severe sprains tear the coracoclavicular ligament, displacing the clavicle upward from the acromion. Treatment is immobilization (eg, with a sling) and early mobility exercises. Some severe sprains are surgically repaired. This injury is often termed a shoulder separation.

**Ulnar collateral ligament sprains (gamekeeper's thumb):** The ulnar collateral ligament connects the
base of the thumb's proximal phalanx to the thumb's metacarpal bone on the ulnar aspect of the joint. The usual injury mechanism is lateral deviation of the thumb. Falling on the hand while holding a ski pole is a common mechanism. Diagnosis is by stress testing to check for radial deviation of the thumb; digital nerve block anesthesia is required. Treatment is immobilization with a thumb spica splint; if maximum possible radial deviation is > 20° more than that in the opposite thumb, surgical repair is necessary.

**Quadriceps tendon injuries:** The quadriceps tendon can be partially or completely disrupted. The elderly and people who have osteoarthritis or who are taking corticosteroids are especially at risk. The mechanism can seem minor, but includes forceful flexion of the knee, often while descending stairs. Patients with complete tears cannot stand, do a straight leg raise while lying on their back, or extend the knee while seated. An examiner can sometimes feel a rent in the tendon. X-rays may be normal or show a high-riding patella. Swelling in the area is diffuse and may be misinterpreted as a ligamentous knee joint injury with hemarthrosis. MRI confirms the diagnosis. Treatment is surgical repair as soon as possible, but long-term complications (eg, loss of motion and weakness) are common.

**Ankle sprains:** The most important ankle ligaments are the deltoid (the strong, medial ligament) and the anterior and posterior talofibular and calcaneofibular (lateral—see Fig. 323-7). Ankle sprains are very common, typically resulting from turning the foot inward (inversion); inversion tears the lateral ligaments, usually beginning with the anterior talofibular ligament. Severe 2nd- and 3rd-degree sprains often cause chronic joint buckling and instability and predispose to additional sprains. Ankle sprains cause pain and swelling, which are usually maximal at the anterolateral ankle. Third-degree sprains often cause more diffuse pain and swelling (sometimes egg-shaped). Forcefully turning the foot outward (eversion) may tear the syndesmotic ligaments between the tibia and fibula proximal to the ankle (high ankle sprain). Occasionally, the deltoid ligament is sprained during eversion, often with simultaneous fracture of the fibular head.

Diagnosis is primarily clinical. The ankle anterior drawer test assesses stability of the anterior talofibular ligament, helping differentiate between 2nd- and 3rd-degree lateral sprains. For this test, patients sit or lie supine with the knee at least slightly flexed; one of the examiner's hands prevents forward movement of the anterior distal tibia while the other hand cups the heel, pulling it anteriorly. Avulsion fractures of the base of the 5th metatarsal and Achilles tendon injuries may be misdiagnosed as ankle sprains. High ankle sprains are considered when eversion is the mechanism and when eversion reproduces pain. Routine ankle x-rays are done to exclude significant fractures in patients with any of the following:

- Age > 55
- Inability to bear weight immediately after the injury and inability to take 4 steps when first examined
- Bone tenderness at the posterior edge or tip of either malleolus

Complex ligamentous injuries to the ankle may require additional testing, such as MRI.

Most ankle sprains do well with minimal intervention and early immobilization. Splinting alleviates pain but does not appear to affect final outcome. First-degree sprains are treated with RICE and early weight bearing. Second-degree sprains are treated with RICE and immobilization of the ankle in a neutral position with a posterior splint, followed by mobilization; for mids sprains, mobilization can occur within a few days. Third-degree sprains may require casting or surgical repair. If clinical evaluation or determination of the extent of injury is impossible (eg, due to muscle spasm or pain), the injury may be immobilized and reexamined after a few days. Rarely MRI is used. High ankle sprains usually require a cast for several weeks.

**Achilles tendon tears:** The usual injury mechanism is ankle dorsiflexion, particularly if the tendon is taut. The calf is squeezed while the patient is prone (Thompson test); decreased passive ankle plantar flexion indicates a tear. Most tears are complete. Partial tears are often missed. Treatment of incomplete tears and some complete tears is a posterior ankle splint with the ankle in plantar flexion for 4 wk. Treatment of complete tears is usually immediate surgical repair. Spontaneous Achilles tendon rupture has been associated with the use of fluoroquinolone antibiotics.
Knee Sprains and Meniscal Injuries

Sprains of the external (medial and lateral collateral) or internal (anterior and posterior cruciate) ligaments or injuries of the menisci commonly result from knee trauma. Symptoms include pain, effusion, instability (with severe sprains), and locking (with some meniscal injuries). Diagnosis is by physical examination and sometimes MRI or arthroscopy. Treatment is RICE (rest, ice, compression, elevation) and, for severe injuries, casting or surgical repair.

Many structures that help stabilize the knee are located mainly outside the joint: muscles (e.g., quadriceps, semimembranosus), their insertions (e.g., pes anserinus), and extracapsular ligaments. The lateral collateral ligament is extracapsular; the medial (tibial) collateral ligament has a superficial extracapsular portion and a deep portion that is part of the joint capsule.

Inside the knee, the joint capsule and the posterior and highly vascular anterior cruciate ligaments help stabilize the joint. The medial and lateral menisci are intra-articular cartilaginous structures that act mainly as shock absorbers but provide some stabilization (Fig. 323-9).

The most commonly injured knee structures are the medial collateral and anterior cruciate ligaments. The most common mechanism for ligamentous knee injuries is an inward, medial force usually accompanied by some external rotation and flexion (as when being tackled in football). In such cases, the medial collateral ligament is usually injured first, followed by the anterior cruciate ligament, then the medial meniscus. The next most common mechanism is an outward force, often injuring the lateral collateral ligament, anterior cruciate ligament, or both. Anterior or posterior forces and hyperextension typically injure the cruciate ligaments. Weight bearing and rotation at the time of injury tend to cause meniscal injuries.

Symptoms and Signs

Swelling and muscle spasm progress over the first few hours. With 2nd-degree sprains, pain is typically moderate or severe. With 3rd-degree sprains, pain may be mild, and surprisingly, some patients can walk unaided. An audible pop suggests an anterior cruciate tear but is uncommon. An effusion suggests injury to the anterior cruciate and possibly other intra-articular structures. However, with severe 3rd-degree tears of the medial collateral ligament or anterior cruciate, no effusion may be apparent because these tears can result in an open joint capsule, allowing blood to exit the joint. Tenderness is often maximal over the injured structure: Medial meniscal injuries cause tenderness in the joint plane (joint line tenderness) medially, and lateral meniscal injuries cause tenderness in the joint plane laterally. These injuries also cause swelling and sometimes restrict passive motion (called locking).

Diagnosis

- Bedside testing for specific injuries
- Imaging (e.g., MRI) or arthroscopy as indicated

A spontaneously reduced knee dislocation should be suspected in patients with a large hemarthrosis, gross instability, or both; serial evaluation of distal pulses or immediate angiography should be considered. Otherwise, the knee is fully examined first. Knee extension is assessed to check for disruption of the extensor mechanism (e.g., tears of the quadriceps muscle or patellar tendon, which can be missed on x-rays; fracture of the patella or tibial tubercle). Knee pain and effusion may indicate disruption of the extensor mechanism.

Other bedside testing is done to check for specific injuries. For the Apley compression test, the patient is prone, and the examiner stabilizes the patient's thigh. The examiner flexes the patient's knee 90° and rotates the lower leg while pressing the lower leg downward toward the knee (compression), then rotates the lower leg while pulling it away from the knee (distraction). Pain during compression and knee rotation...
suggests a meniscal injury; pain during distraction and knee rotation suggests a ligamentous or joint capsule injury.

For assessment of the medial and lateral collateral ligaments, the patient is examined supine, with the knee flexed about 20° and the hamstring muscles relaxed. The examiner puts one hand over the side of the knee opposite the ligament being tested. With the other hand, the examiner cups the heel and pulls the lower leg outward to test the medial collateral ligament or inward to test the lateral collateral ligament. Moderate instability after acute injury suggests that a meniscus or cruciate ligament is torn as well as the collateral ligament.

Lachman’s test is the most sensitive physical test for acute anterior cruciate ligament tears. With the patient supine, the examiner supports the patient’s thigh and calf, and the patient’s knee is flexed 20°. The lower leg is moved anteriorly. Excessive passive anterior motion of the lower leg from the femur suggests a significant tear.

If patients cannot tolerate stress testing (eg, because of pain or muscle spasm), they should be reexamined after injection of a local anesthetic, after use of systemic analgesia and sedation, or at a follow-up examination 2 to 3 days later (after swelling and spasm have subsided); alternatively, MRI or arthroscopy can be done. MRI or arthroscopy is also done when severe injury cannot be excluded clinically.

**Treatment**

- Rest, ice, compression, and elevation (RICE)
- Immobilization and repair as indicated based on injury location and severity

Draining large effusions (see Fig. 32-3 on p. 288) may decrease pain and spasm. Most 1st-degree and mild or moderate 2nd-degree injuries can be treated initially with RICE and immobilization of the knee at 20° of flexion with a commercially available knee immobilizer or splint. Severe 2nd-degree and most 3rd-degree sprains and most meniscal injuries require casting for ≥ 6 wk. However, some 3rd-degree injuries of the medial collateral ligament, anterior cruciate ligament, and menisci require arthroscopic surgical repair.
Chapter 324. Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is physical injury to brain tissue that temporarily or permanently impairs brain function. Diagnosis is suspected clinically and confirmed by imaging (primarily CT). Initial treatment consists of ensuring a reliable airway and maintaining adequate ventilation, oxygenation, and blood pressure. Surgery is often needed in patients with more severe injury to place monitors to track and treat intracranial pressure, decompress the brain if intracranial pressure is increased, or remove intracranial hematomas. In the first few days after the injury, maintaining adequate brain perfusion and oxygenation and preventing complications of altered sensorium are important. Subsequently, many patients require rehabilitation.

In the US, as in much of the world, TBI is a common cause of death and disability. Causes include motor vehicle crashes and other transportation-related causes (eg, bicycle crashes, collisions with pedestrians), falls (especially in older adults and young children), assaults, and sports activities.

Pathology

Structural changes from head injury may be gross or microscopic, depending on the mechanism and forces involved. Patients with less severe injuries may have no gross structural damage. Clinical manifestations vary markedly in severity and consequences. Injuries are commonly categorized as open or closed.

Open injuries involve penetration of the scalp and skull (and usually the meninges and underlying brain tissue). They typically involve bullets or sharp objects, but a skull fracture with overlying laceration due to severe blunt force is also considered an open injury.

Closed injuries typically occur when the head is struck, strikes an object, or is shaken violently, causing rapid brain acceleration and deceleration. Acceleration or deceleration can injure tissue at the point of impact (coup), at its opposite pole (contrecoup), or diffusely; the frontal and temporal lobes are particularly vulnerable. Axons, blood vessels, or both can be sheared or torn. Disrupted blood vessels leak, causing contusions, intracerebral or subarachnoid hemorrhage, and epidural or subdural hematomas (see Table 324-1).

Concussion: Concussion is defined as a transient and reversible posttraumatic alteration in mental status (eg, loss of consciousness or memory) lasting from seconds to minutes and, by arbitrary definition, < 6 h. Gross structural brain lesions and serious neurologic residua are not part of concussion, although temporary disability can occur due to symptoms, such as nausea, headache, dizziness, and memory disturbance (postconcussion syndrome).

Brain contusions: Contusions (bruises of the brain) can occur with open or closed injuries and can impair a wide range of brain functions, depending on contusion size and location. Larger contusions may cause brain edema and increased intracranial pressure (ICP). Contusions may enlarge in the hours and days following the initial injury and cause neurologic deterioration.

Diffuse axonal injury: Diffuse axonal injury (DAI) occurs when deceleration causes shear-type forces that result in generalized, widespread disruption of axonal fibers and myelin sheaths. A few DAI lesions may also result from minor head injury. Gross structural lesions are not part of DAI, but small petechial hemorrhages in the white matter are often observed on CT and on histopathologic examination. DAI is sometimes defined clinically as a loss of consciousness lasting > 6 h in the absence of a specific focal lesion. Edema from the injury often increases ICP, leading to various manifestations (see below). DAI is typically the underlying injury in shaken baby syndrome.
Hematomas: Hematomas (collections of blood in or around the brain) can occur with open or closed injuries and may be epidural, subdural, or intracerebral. Subarachnoid hemorrhage (SAH—bleeding into the subarachnoid space—see p. 1654) is common in TBI, although the appearance on CT is not usually the same as aneurysmal SAH.

Subdural hematomas are collections of blood between the dura mater and the pia-arachnoid mater. Acute subdural hematomas arise from laceration of cortical veins or avulsion of bridging veins between the cortex and dural sinuses. They often occur with head trauma from falls and motor vehicle crashes. Compression of the brain by the hematoma and swelling of the brain due to edema or hyperemia (increased blood flow due to engorged blood vessels) can increase ICP. When these processes both occur, mortality and morbidity can be high. A chronic subdural hematoma may appear and cause symptoms gradually over several weeks after trauma. These hematomas occur more often in elderly patients (especially in those taking antiplatelet or anticoagulant drugs, or in those with brain atrophy). Elderly patients may consider the head injury relatively trivial or may have even forgotten it. In contrast to acute subdural hematomas, edema and increased ICP are unusual.

Epidural hematomas are collections of blood between the skull and dura mater and are less common than subdural hematomas. Epidural hematomas that are large or rapidly expanding are usually caused by arterial bleeding, classically due to damage to the middle meningeal artery by a temporal bone fracture. Without intervention, patients with arterial epidural hematomas may rapidly deteriorate and die. Small, venous epidural hematomas are rarely lethal.

Intracerebral hematomas are collections of blood within the brain itself. In the traumatic setting, they result from coalescence of contusions. Exactly when one or more contusions become a hematoma is not well defined. Increased ICP, herniation, and brain stem failure can subsequently develop, particularly with contusions in the temporal lobes.

Skull fractures: Penetrating injuries by definition involve fractures. Closed injuries may also cause skull fractures, which may be linear, depressed, or comminuted. The presence of a fracture suggests that significant force was involved in the injury. However, most patients with simple linear fractures and no neurologic impairment are not at high risk of brain injuries. Fractures that involve special risks include

- Fractures in patients with neurologic impairment: Such patients are at increased risk of intracranial hematomas.
- Depressed fractures: These fractures have the highest risk of tearing the dura, damaging the underlying brain, or both.
- Temporal bone fractures that cross the area of the middle meningeal artery: In these fractures, an epidural hematoma is a risk.
- Fractures that cross one of the major dural sinuses: These fractures may cause significant hemorrhage and venous epidural or venous subdural hematoma. Injured venous sinuses can later thrombose and cause cerebral infarction.
- Fractures that involve the carotid canal: These fractures can result in carotid artery dissection.
- Fractures of the occipital bone and base of the skull (basilar bones): These bones are thick and strong, so fractures in these areas indicate a high-intensity impact and meaningfully increase risk of brain injury. Basilar skull fractures that extend into the petrous part of the temporal bone often damage middle and inner ear structures and can impair facial, acoustic, and vestibular nerve function.
- Fractures in infants: The meninges may become trapped in a linear skull fracture with subsequent development of a leptomeningeal cyst and expansion of the original fracture (growing fracture).

Pathophysiology
Brain function may be immediately impaired by direct damage (e.g., crush, laceration) of brain tissue. Further damage may occur shortly thereafter from the cascade of events triggered by the initial injury. TBI of any sort can cause cerebral edema and decrease brain blood flow. The cranial vault is fixed in size (constrained by the skull) and filled by noncompressible CSF and minimally compressible brain tissue; consequently, any swelling from edema or an intracranial hematoma has nowhere to expand and thus increases ICP. Cerebral blood flow is proportional to the cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (MAP) and mean ICP. Thus, as ICP increases (or MAP decreases), CPP decreases. When CPP falls below 50 mm Hg, the brain may become ischemic. Ischemia and edema may trigger various secondary mechanisms of injury (e.g., release of excitatory neurotransmitters, intracellular Ca, free radicals, and cytokines), causing further cell damage, further edema, and further increases in ICP. Systemic complications from trauma (e.g., hypotension, hypoxia) can also contribute to cerebral ischemia and are often called secondary brain insults.

Excessive ICP initially causes global cerebral dysfunction. If excessive ICP is unrelieved, it can push brain tissue across the tentorium or through the foramen magnum, causing herniation (see Fig. 174-1 on p. 1657) and increased morbidity and mortality. If ICP increases to equal MAP, CPP becomes zero, resulting in complete brain ischemia and brain death; absent cranial blood flow is objective evidence of brain death (see p. 1667).

Hyperemia and increased brain blood flow may result from concussive injury in adolescents or children. Second impact syndrome is a rare and debated entity defined by sudden increased ICP and death after a second traumatic insult that follows a minor head injury. It is attributed to loss of autoregulation of cerebral blood flow that leads to vascular engorgement, increased ICP, and herniation.

**Symptoms and Signs**

Initially, most patients with moderate or severe TBI lose consciousness (usually for seconds or minutes), although some patients with minor injuries have only confusion or amnesia (amnesia is usually retrograde and lasts for seconds to a few hours). Young children may simply become irritable. Some patients have seizures, often within the first hour or day. After these initial symptoms, patients may be fully awake and alert, or consciousness and function may be altered to some degree, from mild confusion to stupor to coma. Duration of unconsciousness and severity of obtundation are roughly proportional to injury severity but are not specific.

The [Glasgow Coma Scale](#) (GCS—see Table 324-2) is a quick, reproducible scoring system to be used during the initial examination to estimate severity of TBI. It is based on eye opening, verbal response, and the best motor response. The lowest total score (3) indicates likely fatal damage, especially if both pupils fail to respond to light and oculovestibular responses are absent. Higher initial scores tend to predict better recovery. By convention, the severity of head injury is initially defined by the GCS:

- 14 or 15 is mild TBI
- 9 to 13 is moderate TBI
- 3 to 8 is severe TBI

However, the severity and prognosis are predicted more accurately by also considering CT findings and other factors. Some patients with initially moderate TBI and a few patients with initially mild TBI deteriorate. For infants and young children, the Modified Glasgow Coma Scale for Infants and Children is used (see Table 324-3). Because hypoxia and hypotension can decrease the GCS, GCS values after resuscitation from cardiopulmonary insults are more specific for brain dysfunction than values determined before.
resuscitation. Similarly, sedating drugs can decrease GCS values and should be avoided before full neurologic evaluation.

Symptoms of various types of TBI may overlap considerably. Symptoms of epidural hematoma usually develop within minutes to several hours after the injury (the period without symptoms is the so-called lucid interval) and consist of increasing headache, decreased level of consciousness, and focal neurologic deficits (eg, hemiparesis). Pupillary dilation with loss of light reactivity usually indicates herniation. Some patients lose consciousness, then have a transient lucid interval, and then gradual neurologic deterioration. Most patients with subdural hematomas have immediate loss of consciousness. Intracerebral hematoma and subdural hematoma can cause focal neurologic deficits such as hemiparesis, progressive decrease in consciousness, or both. Progressive decrease in consciousness may result from anything that increases ICP (eg, hematoma, edema, hyperemia).

(Table 324-3. Modified Glasgow Coma Scale for Infants and Children)

Vomiting may indicate increased ICP but is nonspecific. Markedly increased ICP classically manifests as a combination of hypertension (usually with increased pulse pressure), bradycardia, and respiratory depression (Cushing's triad); respirations are usually slow and irregular. Severe diffuse brain injury or markedly increased ICP may cause decorticate or decerebrate posturing. Both are poor prognostic signs.

Transtentorial herniation (see Fig. 174-1 on p. 1657) may result in coma, unilaterally or bilaterally dilated and unreactive pupils, hemiplegia (usually on the side opposite a unilaterally dilated pupil), and Cushing's triad.

Basilar skull fracture may result in leakage of CSF from the nose (CSF rhinorrhea) or ear (CSF otorrhrea), blood behind the tympanic membrane (hemotympanum) or in the external ear canal if the tympanic membrane has ruptured, and ecchymosis behind the ear (Battle's sign) or in the periorbital area (raccoon eyes). Loss of smell and hearing is usually immediate, although these losses may not be noticed until the patient regains consciousness. Facial nerve function may be impaired immediately or after a delay. Other fractures of the cranial vault are sometimes palpable, particularly through a scalp laceration, as a depression or step-off deformity. However, blood under the galea aponeurotica may mimic such a step-off deformity.

Patients with chronic subdural hematomas may present with increasing daily headache, fluctuating drowsiness or confusion (which may mimic early dementia), and mild-to-moderate hemiparesis or other focal neurologic deficits.

Long-term symptoms: Amnesia may persist and be both retrograde and anterograde. Post-concussion syndrome, which commonly follows a moderate or severe concussion, includes headache, dizziness, fatigue, difficulty concentrating, variable amnesia, depression, apathy, and anxiety. Commonly smell (and thus taste), sometimes hearing, or rarely vision is altered or lost. Symptoms usually resolve spontaneously over weeks to months.

A range of cognitive and neuropsychiatric deficits can persist after severe and even moderate TBI, particularly if structural damage was significant. Common problems include amnesia, behavioral changes (eg, agitation, impulsivity, disinhibition, lack of motivation), emotional lability, sleep disturbances, and decreased intellectual function.

Late seizures (> 7 days after the injury) develop in a small percentage of patients, often weeks, months, or even years later. Spastic motor impairment, gait and balance disturbances, ataxia, and sensory losses may occur.

A persistent vegetative state (see p. 1665) can result from a TBI that destroys forebrain cognitive functions but spares the brain stem. The capacity for self-awareness and other mental activity is absent; however, autonomic and motor reflexes are preserved, and sleep-wake cycles are normal. Few patients recover normal neurologic function when a persistent vegetative state lasts for 3 mo after injury, and almost none recover after 6 mo.
Neurologic function may continue to improve for a few years after TBI, most rapidly during the initial 6 mo.

**Diagnosis**

- Initial rapid trauma assessment
- Glasgow coma scale and neurologic examination
- CT

**Initial measures:** An initial overall assessment of injuries should be done (see p. 3190). Diagnosis and treatment occur simultaneously in seriously injured patients.

A rapid, focused neurologic evaluation is part of the initial assessment, including assessment of the components of the GCS, adequacy of the airway and breathing, and pupillary light response. Patients are ideally assessed before paralytics and sedatives are given. Patients are reassessed at frequent intervals (eg, q 15 to 30 min initially, then q 1 h after stabilization). Subsequent improvement or deterioration helps estimate injury severity and prognosis.

**Complete clinical evaluation:** Complete neurologic examination is done as soon as the patient is sufficiently stable. Infants and children should be examined carefully for retinal hemorrhages, which may indicate shaken baby syndrome. Funduscopic examination in adults may disclose traumatic retinal detachment and absence of retinal venous pulsations due to elevated ICP, but examination may be normal despite brain injury. Concussion is diagnosed when loss of consciousness or memory lasts < 6 h and symptoms are not explained by brain injury seen on neuroimaging. DAI is suspected when loss of consciousness exceeds 6 h and microhemorrhages are seen on CT. Diagnosis of other types of TBI is made by CT or MRI.

**Neuroimaging:** Imaging should always be done in patients with more than transiently impaired consciousness, GCS score < 15, focal neurologic findings, persistent vomiting, seizures, a history of loss of consciousness, or clinically suspected fractures. However, a case can be made for obtaining a CT scan of the head in all patients with more than a trivial head injury, because the clinical and medicolegal consequences of missing a hematoma are severe.

Although plain x-rays can detect some skull fractures, they cannot help assess the brain and they delay more definitive brain imaging; thus, plain x-rays are usually not done. CT is the best choice for initial imaging, because it can detect hematomas, contusions, skull fractures (thin cuts are obtained to reveal clinically suspected basilar skull fractures, which may otherwise not be visible), and sometimes DAI. On CT, contusions and acute bleeding appear opaque (dense) compared with brain tissue. Arterial epidural hematomas classically appear as lenticonular-shaped opacities over brain tissue, often in the territory of the middle meningeal artery. Subdural hematomas classically appear as crescent-shaped opacities overlying brain tissue. A chronic subdural hematoma appears hypodense compared with brain tissue, whereas a subacute subdural hematoma may have a similar radiopacity as brain tissue (isodense). Isodense subdural hematoma, particularly if bilateral and symmetric, may appear only subtly abnormal. In patients with severe anemia, an acute subdural hematoma may appear isodense with brain tissue. Among individual patients, findings may differ from these classic appearances. Signs of mass effect include sulcal effacement, ventricular and cisternal compression, and midline shift. Absence of these findings does not exclude increased ICP, and mass effect may be present with normal ICP. A shift of > 5 mm from the midline is generally considered to be an indication for surgical evacuation of the hematoma.

MRI may be useful later in the clinical course to detect more subtle contusions and DAI. It is usually more sensitive than CT for the diagnosis of very small acute or isodense subacute and isodense chronic subdural hematomas. Preliminary, unconfirmed evidence suggests that certain MRI findings predict prognosis. Angiography, CT angiography, and magnetic resonance angiography are all useful for the evaluation of vascular injury. For example, vascular injury is suspected when CT findings are inconsistent with the physical examination findings (eg, hemiparesis with a normal or nondiagnostic CT due to suspected evolving ischemia secondary to vascular thrombosis or embolism from a carotid artery dissection).
Prognosis

In the US, adults with severe TBI who are treated have a mortality rate of about 25 to 33%. Mortality is lower with higher GCS scores. Mortality rates are lower in children ≥ 5 yr (≤ 10% with a GCS score of 5 to 7). Children overall do better than adults with a comparable injury.

The vast majority of patients with mild TBI retain good neurologic function. With moderate or severe TBI, the prognosis is not as good but is much better than is generally believed. The most commonly used scale to assess outcome in TBI patients is the Glasgow Outcome Scale. On this scale the possible outcomes are:

• Good recovery (return to previous level of function)
• Moderate disability (capable of self-care)
• Severe disability (incapable of self-care)
• Vegetative (no cognitive function)
• Death

Over 50% of adults with severe TBI have a good recovery or moderate disability. Occurrence and duration of coma after a TBI are strong predictors of disability. Of patients whose coma exceeds 24 h, 50% have major persistent neurologic sequelae, and 2 to 6% remain in a persistent vegetative state at 6 mo. In adults with severe TBI, recovery occurs most rapidly within the initial 6 mo. Smaller improvements continue for perhaps as long as several years. Children have a better immediate recovery from TBI regardless of severity and continue to improve for a longer period of time.

Cognitive deficits, with impaired concentration, attention, and memory, and various personality changes are a more common cause of disability in social relations and employment than are focal motor or sensory impairments. Posttraumatic anosmia and acute traumatic blindness seldom resolve after 3 to 4 mo. Hemiparesis and aphasia usually resolve at least partially, except in the elderly.

Treatment

• For mild injuries discharge and observation
• For moderate and severe injuries optimization of ventilation, oxygenation, and brain perfusion; treatment of complications (eg, increased ICP, seizures, hematomas); and rehabilitation

Multiple noncranial injuries, which are likely with motor vehicle crashes and falls, often require simultaneous treatment. Initial resuscitation of trauma patients is discussed elsewhere (see p. 3190).

At the injury scene, a clear airway is secured and external bleeding is controlled before the patient is moved. Particular care is taken to avoid displacement of the spine or other bones to protect the spinal cord and blood vessels. Proper immobilization should be maintained with a cervical collar and long spine board until stability of the entire spine has been established by appropriate examination and imaging (see p. 3229). After the initial rapid neurologic assessment, pain should be relieved with a short-acting opioid (eg, fentanyl).

In the hospital, after quick initial evaluation, neurologic findings (GCS and pupillary reaction), BP, pulse, and temperature should be recorded frequently for several hours because any deterioration demands prompt attention. Serial GCS and CT results stratify injury severity, which helps guide treatment (see Table 324-4).

The cornerstone of management for all patients is maintenance of adequate ventilation, oxygenation, and brain perfusion to avoid secondary brain insult. Aggressive early management of hypoxia, hypercapnia,
hypotension, and increased ICP helps avoid secondary complications. Bleeding from injuries (external and internal) is rapidly controlled, and intravascular volume is promptly replaced with crystalloid (eg, 0.9% saline) or sometimes blood transfusion to maintain cerebral perfusion. Hypotonic fluids (especially 5% D/W) are contraindicated because they contain excess free water, which can increase brain edema and ICP.

Other complications to check for and to prevent include hyperthermia, hyponatremia, hyperglycemia, and fluid imbalance.

**Mild injury:** Injury is mild (by GCS score) in 80% of patients who have TBI and present to an emergency department. If there is brief or no loss of consciousness and if patients have stable vital signs, a normal head CT scan, and normal mental and neurologic function, they may be discharged home provided family members or friends can observe them closely for an additional 24 h. These observers are instructed to return patients to the hospital if any of the following develop: decreased level of consciousness, focal neurologic deficits, worsening headache, vomiting, or deterioration of mental function.

**[Table 324-4. Management of Traumatic Brain Injury Based on Severity of Injury]**

Patients who have had loss of consciousness or have any abnormalities in mental or neurologic function and cannot be observed closely after discharge are generally observed in the emergency department or overnight in the hospital, and follow-up CT is done in 4 to 8 h. Patients who have no neurologic changes but minor abnormalities on head CT (eg, small contusions, small subdural hematomas with no mass effect, or punctuate or small traumatic subarachnoid hemorrhage) may need only a follow-up CT within 24 h. With a stable CT and normal neurologic examination results, these patients may be discharged home.

**Moderate and severe injury:** Injury is moderate in 10% of patients who have TBI and present to an emergency department. They often do not require intubation and mechanical ventilation (unless other injuries are present) or ICP monitoring. However, because deterioration is possible, these patients should be admitted and observed even if head CT is normal.

Injury is severe in 10% of patients who have TBI and present to an emergency department. They are admitted to a critical care unit. Because airway protective reflexes are usually impaired and ICP may be increased, patients are intubated endotracheally while measures are taken to avoid increasing ICP. Close monitoring using the GCS and pupillary response should continue, and CT is repeated, particularly if there is an unexplained ICP rise.

**Increased intracranial pressure:** Treatment principles for patients with increased ICP include

- Rapid sequence orotracheal intubation
- Mechanical ventilation
- Monitoring of ICP and CCP
- Ongoing sedation as needed
- Maintaining euvoolemia and serum osmolality of 295 to 320 mOsm/kg
- For intractable increased ICP, possibly CSF drainage, temporary hyperventilation, decompressive craniotomy, or pentobarbital coma

Patients with TBI who require airway support or mechanical ventilation undergo rapid sequence oral intubation (using paralysis) rather than awake nasotracheal intubation (see [Ch. 225](#)), which can cause coughing and gagging and thereby raise the ICP. Drugs are used to minimize the ICP increase when the airway is manipulated—eg, lidocaine 1.5 mg/kg IV 1 to 2 min before giving the paralytic. Etomidate is an excellent induction agent because it has minimal effects on BP; IV dose in adults is 0.3 mg/kg (or 20 mg for an average-sized adult) and in children is 0.2 to 0.3 mg/kg. An alternative, if hypotension is absent and unlikely, is propofol 0.2 to 1.5 mg/kg IV. Succinylcholine 1.5 mg/kg IV is typically used as a paralytic.
Pulse oximetry and ABGs (if possible, end-tidal CO\textsubscript{2}) should be used to assess adequacy of oxygenation and ventilation. The goal is a normal PaCO\textsubscript{2} level (38 to 42 mm Hg). Prophylactic hyperventilation (PaCO\textsubscript{2} 25 to 35 mm Hg) is no longer recommended. The lower PaCO\textsubscript{2} reduces ICP by causing cerebral vasoconstriction, but this vasoconstriction also decreases cerebral perfusion, thus potentiating ischemia. Therefore, hyperventilation (target PaCO\textsubscript{2} of 30 to 35 mm Hg) is used only during the first several hours and if ICP is unresponsive to other measures.

In patients with severe TBI who cannot follow simple commands, especially those with an abnormal head CT scan, ICP and CPP monitoring (see p. 2246) and control are recommended. The goal is to maintain ICP at < 20 mm Hg and CPP as close as possible to 60 mm Hg. Cerebral venous drainage can be enhanced (thus lowering ICP) by elevating the head of the bed to 30\textdegree and by keeping the patient's head in a midline position. If needed, a ventricular catheter can be inserted for CSF drainage to lower the ICP.

Preventing agitation, excessive muscular activity (eg, from delirium), and pain can also help prevent increases in ICP. For sedation, propofol is often used in adults (contraindicated in children) because it has quick onset and very brief duration of action; dose is 0.3 mg/kg/h continuous IV infusion, titrated gradually upward as needed (up to 3 mg/kg/h). An initial bolus is not used. The most common adverse effect is hypotension. Prolonged use at high doses can cause pancreatitis. Benzodiazepines (eg, midazolam, lorazepam) can also be used for sedation, but they are not as rapidly acting as propofol and individual dose-response can be hard to predict. Antipsychotics can delay recovery and should be avoided if possible. Rarely, paralytics may be needed; if so, adequate sedation must be ensured. Opioids are often needed for adequate pain control.

Patients should be kept euvoletic and normosmolar or slightly hyperosmolar (target serum osmolality 295 to 320 mOsm/kg). Osmotic diuretics (eg, mannitol) may be given IV to lower ICP and maintain serum osmolality. However, they should be reserved for patients whose condition is deteriorating or used preoperatively for patients with hematomas. Mannitol 20% solution is given 0.5 to 1 g/kg IV (2.5 to 5 mL/kg) over 15 to 30 min and repeated in a dose ranging from 0.25 to 0.5 g/kg (1.25 to 2.5 mL/kg) given as often as needed (usually q 6 to 8 h); it lowers ICP for a few hours. Mannitol must be used cautiously in patients with severe coronary artery disease, heart failure, renal insufficiency, or pulmonary vascular congestion because mannitol rapidly expands intravascular volume. Because osmotic diuretics increase renal excretion of water relative to Na, prolonged use of mannitol may also result in water depletion and hypernatremia. Furosemide 1 mg/kg IV is also helpful to decrease total body water, particularly when the transient hypervolemia associated with mannitol is to be avoided. Fluid and electrolyte balance should be monitored closely while osmotic diuretics are used. A hypertonic saline solution (usually 2% to 3%) is being studied as another potential osmotic agent to control ICP.

When increased ICP is refractory to other interventions, decompressive craniotomy can be considered. For this procedure, a bone flap is removed (to be replaced later), and duraplasty is done to allow outward brain swelling.

A more involved and currently less popular option for intractable increased ICP is pentobarbital coma. Coma is induced by giving pentobarbital 10 mg/kg over 30 min, 5 mg/kg/h for 3 h, then 1 mg/kg/h maintenance infusion. The dose may be adjusted to suppress bursts of EEG activity, which is continuously monitored. Hypotension is common and managed by giving fluids and, if necessary, vasopressors.

Therapeutic systemic hypothermia has not proved helpful. Corticosteroids are not useful to control ICP and are not recommended; they were associated with a worse outcome in a recent multinational study. A variety of neuroprotective agents are being studied, but thus far, none has demonstrated efficacy in clinical trials.

**Seizures:** Seizures can worsen brain damage and increase ICP and therefore should be treated promptly. In patients with significant structural injury (eg, larger contusions or hematomas, brain laceration, depressed skull fracture) or a GCS score < 10, a prophylactic anticonvulsant should be considered. If phenytoin is used, a loading dose of 20 mg/kg IV is given (at a maximum rate of 50 mg/min.
to prevent cardiovascular adverse effects such as hypotension and bradycardia). The starting maintenance IV dose for adults is 2 to 2.7 mg/kg tid; children require higher doses (up to 5 mg/kg bid for children < 4 yr). Serum levels should be measured to adjust the dose. Duration of treatment depends on the type of injury and EEG results. If no seizures develop within 1 wk, anticonvulsants should be stopped because their value in preventing future seizures is not established. Newer anticonvulsants are under study. Fosphenytoin, a form of phenytoin that has better water solubility, is being used in some patients without central venous access because it decreases the risk of thrombophlebitis when given through a peripheral IV. Dosing is the same as for phenytoin.

**Skull fractures:** Aligned closed fractures require no specific treatment. Depressed fractures sometimes require surgery to elevate fragments, manage lacerated cortical vessels, repair dura mater, and debride injured brain. Open fractures require debridement. Use of antibiotic prophylaxis is controversial because of limited data on its efficacy and the concern that it promotes drug-resistant strains.

**Surgery:** Intracranial hematomas may require urgent surgical evacuation to prevent or treat brain shift, compression, and herniation; hence, early neurosurgical consultation is mandatory. However, not all hematomas require surgical removal. Small intracerebral hematomas rarely require surgery. Patients with small subdural hematomas can often be treated without surgery. Factors that suggest a need for surgery include a midline brain shift of > 5 mm, compression of the basal cisterns, and worsening neurologic examination findings. Chronic subdural hematomas may require surgical drainage but much less urgently than acute subdural hematomas. Large or arterial epidural hematomas are treated surgically, but small epidural hematomas that are thought to be venous in origin can be followed with serial CT.

**Rehabilitation:** When neurologic deficits persist, rehabilitation is needed. Rehabilitation is best provided through a team approach that combines physical, occupational, and speech therapy, skill-building activities, and counseling to meet the patient's social and emotional needs (see also p. 3467). Brain injury support groups may provide assistance to the families of brain-injured patients.

For patients whose coma exceeds 24 h, 50% of whom have major persistent neurologic sequelae, a prolonged period of rehabilitation, particularly in cognitive and emotional areas, is often required. Rehabilitation services should be planned early.
Chapter 325. Spinal Trauma

**Introduction**

Trauma to the spine may cause injuries involving the spinal cord, vertebrae, or both. Occasionally, the spinal nerves are affected (see p. 1791). The anatomy of the spinal column is reviewed in Ch. 186 (see p. 1800).

**Etiology**

**Cord injury:** During a typical year, there are about 11,000 spinal cord injuries in the US. Nearly 48% occur in motor vehicle crashes, and 23% result from falls. The remainder are attributed to violence (14%), sports (9%), and work-related accidents. About 80% of patients are male.

Spinal cord injuries occur when blunt physical force damages the vertebrae, ligaments, or disks of the spinal column, causing bruising, crushing, or tearing of spinal cord tissue, and when the spinal cord is penetrated (eg, by a gunshot or a knife wound). Such injuries can also cause vascular injury with resultant ischemia or hematoma (typically extradural), leading to further damage. All forms of injury can cause spinal cord edema, further decreasing blood flow and oxygenation. Damage may be mediated by excessive release of neurotransmitters from damaged cells, an inflammatory immune response with release of cytokines, accumulation of free radicals, and apoptosis.

**Vertebral injury:** Fractures may involve the vertebral body, lamina, and pedicles as well as the spinous, articular, articular, and transverse processes. Dislocations typically involve the facets. Subluxation involves ligament rupture without bony injury. In the neck, fractures of the posterior elements and dislocations can damage the vertebral arteries, causing a stroke-like syndrome.

Unstable vertebral injuries are those in which bony and ligamentous integrity is disrupted sufficiently that free movement can occur, potentially compressing the spinal cord or its vascular supply and resulting in marked worsening of neurologic function or pain. Such vertebral movement may occur even with a shift in patient position (eg, for ambulance transport, during initial evaluation). Stable fractures are able to resist such movement.

Specific injuries typically vary with mechanism of trauma. Flexion injuries can cause wedge fractures of the vertebral body or spinous process fractures. Greater flexion force may cause bilateral cervical cervical facet dislocation, or if the force occurs at the level of C1 or C2, odontoid fracture, atlantooccipital or atlantoaxial subluxation, or both fracture and subluxation. Rotational injury can cause unilateral facet dislocation. Extension injury most often causes posterior neural arch fracture. Compression injuries can cause burst fractures of vertebral bodies.

**Cauda equina injury:** The lower tip of the spinal cord (conus medullaris) is usually at the level of the L1 vertebra. Spinal nerves below this level comprise the cauda equina. Findings in spinal injuries below this level may mimic those of spinal cord injury, particularly conus medullaris syndrome.

**Symptoms and Signs**

The cardinal sign of cord injury is a discrete injury level in which neurologic function above the injury is intact, and function below the injury is absent or markedly diminished. Specific manifestations depend on the exact level (see Table 325-1) and whether cord injury is complete or partial. Priapism may occur in the acute phase of spinal cord injury.

Vertebral injury, as with other fractures and dislocations, typically is painful, but patients who are distracted by other painful injuries (eg, long bone fractures) or whose level of consciousness is altered by intoxicants or head injury may not complain of pain.

**Complete cord injury:** Transection leads to immediate, complete, flaccid paralysis (including loss of anal sphincter tone), loss of all sensation and reflex activity, and autonomic dysfunction below the level of
the injury.

High cervical injury (at or above C5) affects the muscles controlling respiration, causing respiratory insufficiency; ventilator dependence may occur, especially in patients with injuries at or above C3. Autonomic dysfunction from cervical injury can result in bradycardia and hypotension, termed neurogenic shock; unlike in other forms of shock, the skin remains warm and dry. Arrhythmias and BP instability may develop. Pneumonia is a frequent cause of death in people with a high spinal cord injury, especially in those who are ventilator dependent.

Flaccid paralysis gradually changes over hours or days to spastic paralysis with increased deep tendon reflexes due to loss of descending inhibition. Later, if the lumbosacral cord is intact, flexor muscle spasms appear and autonomic reflexes return.

**Partial cord injury:** Partial motor and sensory loss occurs, and deep tendon reflexes may be exuberant. Motor and sensory loss may be permanent or temporary depending on the etiology; function may be lost briefly due to concussion or more lastingly due to a contusion

[Table 325-1. Effects of Spinal Cord Injury by Location]

or laceration. Sometimes, however, rapid swelling of the cord results in total neurologic dysfunction resembling complete cord injury. Termed spinal shock (not to be confused with neurogenic shock), symptoms resolve over one to several days; residual disability often remains.

Manifestations depend on which portion of the cord is involved; several discrete syndromes are recognized.

**Brown-Sequard syndrome** results from unilateral hemisection of the cord. Patients have ipsilateral spastic paralysis and loss of postural sense below the lesion, and contralateral loss of pain and temperature sensation.

**Anterior cord syndrome** results from direct injury to the anterior spinal cord or to the anterior spinal artery. Patients lose motor and pain sensation bilaterally below the lesion. Posterior cord function (vibration, proprioception) is intact.

**Central cord syndrome** usually occurs in patients with a narrowed spinal canal (congenital or degenerative) after a hyperextension injury. Motor function in the arms is impaired to a greater extent than that in the legs. If the posterior columns are affected, posture, vibration, and light touch are lost. If the spinothalamic tracts are affected, pain, temperature, and, often, light or deep touch are lost. Hemorrhage in the spinal cord from trauma (hematomyelia) is usually confined to the cervical central gray matter, resulting in signs of lower motor neuron damage (muscle weakness and wasting, fasciculations, and diminished tendon reflexes in the arms), which is usually permanent. Motor weakness is often proximal and accompanied by selective impairment of pain and temperature sensation.

**Cauda equina lesions:** Motor or sensory loss, or both, usually partial, occurs in the distal legs. Sensation is usually diminished in the perineal region (saddle anesthesia). Bowel and bladder dysfunction, either incontinence or retention, may occur. Men may have erectile dysfunction, and women diminished sexual response. Anal sphincter tone is lax, and bulbocavernosus and anal wink reflexes are abnormal. These findings may be similar to those of conus medullaris syndrome, a spinal cord injury.

**Complications:** Sequelae depend on the severity and level of the injury. Breathing may be impaired if the injury is at or above the C5 segment. Reduced mobility increases the risk of blood clots, UTIs, contractures, atelectasis and pneumonia, and pressure ulcers. Disabling spasticity may develop. Autonomic dysreflexia may occur in response to triggering events such as pain or pressure on the body. Chronic neurogenic pain may manifest as burning or stinging.

**Diagnosis**

- Consideration of injury in high-risk patients, even those without symptoms
Spinal cord injuries with trauma are not always obvious. Injury to the spine and spinal cord must be considered in patients with injuries that involve the head, pelvic fractures, penetrating injuries in the area of the spine, in most motor vehicle crashes, in any kind of major blunt injury, and in any injuries related to falling from heights or diving into water.

Injury should also be considered in patients with altered sensorium, localized spinal tenderness, painful distracting injuries, or compatible neurologic deficits. Motor function is tested in all extremities. Sensation testing should involve both light touch (posterior column function), pinprick (anterior spinothalamic tract), and position sense. Identification of the sensory level is best done by testing from distal to proximal and by testing thoracic roots on the back to avoid being misled by the cervical cape. Priapism indicates spinal cord damage. Rectal tone may be decreased, and deep tendon reflexes may be exuberant or absent.

When spinal cord injury is suspected, the spine is immediately immobilized. Traditionally, plain x-rays are taken of any possibly injured areas. CT is done of areas that appear abnormal on x-rays and areas at risk of injury based on clinical findings. However, CT is being used increasingly as the primary imaging study for spinal trauma because it has better diagnostic accuracy and, at many trauma centers, can be obtained rapidly. MRI helps identify the type and location of cord injury; it is the most accurate study for imaging the spinal cord and other soft tissues but may not be immediately available. Manifestations of injury may be characterized using the ASIA (American Spinal Injury Association) Impairment Scale or a similar instrument (see Table 325-2).

Prognosis

Transected or degenerated nerves in the cord do not recover, and functional damage is permanent. Compressed nerve tissue can recover its function. Return of a movement or sensation during the first week after injury heralds a favorable recovery. Dysfunction remaining after 6 mo is likely to be permanent.

Table 325-2. Spinal Injury Impairment Scale*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Immobilization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maintenance of oxygenation and perfusion</td>
</tr>
<tr>
<td></td>
<td>Supportive care</td>
</tr>
<tr>
<td></td>
<td>Sometimes surgical stabilization</td>
</tr>
<tr>
<td></td>
<td>Possibly methylprednisolone for blunt injuries</td>
</tr>
<tr>
<td></td>
<td>Long-term symptomatic care and rehabilitation</td>
</tr>
</tbody>
</table>

Immediate care: An important goal is to prevent secondary injury to the spine or spinal cord. In unstable injuries, flexion or extension of the spine can contuse or transect the cord. Thus, when injured people are moved, inappropriate handling can precipitate paraplegia, quadriplegia, or even death from spinal injury. Patients who may have a spinal injury should have the spine immobilized immediately; the neck is held straight manually (in line stabilization) during endotracheal intubation. As soon as possible, the spine is fully immobilized on a firm, flat, padded backboard or similar surface to stabilize the position without excessive pressure. A rigid collar should be used to immobilize the cervical spine. Patients with thoracic or lumbar spine injuries can be carried prone or supine. Those with cervical cord damage that could induce respiratory difficulties should be carried supine, with attention to maintaining a patent airway and avoiding chest constriction. Transfer to a trauma center is desirable.
Medical care should be directed at avoiding hypoxia and hypotension, both of which can further stress the injured cord. In cervical injuries higher than C5, intubation and respiratory support are usually needed.

Large doses of corticosteroids, started within 8 h after spinal cord injury, may improve the outcome in blunt injuries, but this finding has not been firmly established. Methylprednisolone 30 mg/kg IV over 1 h, followed by 5.4 mg/kg/h for the next 23 h is the recommended regimen. Injuries are treated with rest, analgesics, and muscle-relaxing drugs with or without surgery until swelling and local pain have subsided. Additional general treatment for trauma patients is discussed elsewhere (see p. 3190).

Unstable injuries are immobilized until bone and soft tissues have healed to ensure proper alignment; surgery with fusion and internal fixation is sometimes needed. Patients with incomplete cord injuries can have significant neurologic improvement after decompression. In contrast, in complete injury, return of useful neurologic function below the level of the injury is unlikely. Thus, surgery aims to stabilize the spine to allow early mobilization. The timing of surgery in incomplete lesions is debatable. Early surgery (eg, within 24 h) may have a better neurologic outcome and allows for earlier mobilization and rehabilitation. For complete injuries, surgery is sometimes done in the first few days, but it is not clear that this is necessary.

Nursing care includes preventing urinary and pulmonary infections and pressure ulcers—eg, by turning the immobile patient every 2 h (on a Stryker frame when necessary). Deep venous thrombosis prophylaxis is required. An inferior vena cava filter could be considered in immobile patients.

**Long-term care:** Drugs effectively control spasticity in some patients. Oral agents such as baclofen 5 mg po tid (maximum, 80 mg during a 24-h period) and tizanidine 4 mg po tid (maximum, 36 mg during a 24-h period) are typically used for spasticity occurring after spinal cord injury. Intrathecal baclofen 50 to 100 μg once/day may be considered in patients in whom oral drugs are ineffective.

Rehabilitation is needed to help people recover as fully as possible (see p. 3467). Rehabilitation, best provided through a team approach, combines physical therapies, skill-building activities, and counseling to meet social and emotional needs. The rehabilitation team is best directed by a physician with training and expertise in rehabilitation (physiatrist); it usually includes nurses, social workers, nutritionists, psychologists, physical and occupational therapists, recreational therapists, and vocational counselors (see also Ch. 350).

Physical therapy focuses on exercises for muscle strengthening, passive stretch exercises to prevent contractures, and appropriate use of assistive devices such as braces, a walker, or a wheelchair that may be needed to improve mobility. Strategies for controlling spasticity, autonomic dysreflexia, and neurogenic pain are taught. Occupational therapy focuses on redeveloping fine motor skills. Bladder and bowel management programs teach toileting techniques, which may require intermittent catheterization. A bowel regimen, involving timed stimulation with laxatives, is often needed.

Vocational rehabilitation involves assessing both fine and gross motor skills, as well as cognitive capabilities, to determine the likelihood for meaningful employment. The vocational specialist then helps identify possible work sites and determines need for assistive equipment and workplace modifications. Recreation therapists use a similar approach in identifying and facilitating participation in hobbies, athletics, and other activities.

Emotional care aims to combat the depersonalization and the almost unavoidable depression that occur after losing control of the body. Emotional care is fundamental to the success of all other components of rehabilitation and must be accompanied by efforts to educate the patient and encourage active involvement of family and friends.

Treatments to promote nerve regeneration are under study. Such treatments include injections of autologous, incubated macrophages; epidural administration of BA-210, an experimental drug that may be neuroprotective and may stimulate nerve growth; and oral administration of HP-184 for treatment of chronic spinal cord injury. Also, one trial aims to determine optimal timing of surgery. Stem cell research is in its infancy; some early animal studies have shown promising results.
Spinal Cord Injury in Children

Although children < 10 yr have the lowest rate of spinal cord injuries, such injuries are not rare. In children < 8 yr, cervical spine injuries occur most commonly above C4; in those > 8 yr, injuries at C5 to C8 are more common. Of increasing importance has been the recognition of spinal cord injury without evidence of radiologic abnormality (SCIWORA). This type of injury occurs almost exclusively in children and is related to direct spinal cord traction, spinal cord concussion, and vascular injury.

Diagnosis

Spinal cord injury should be suspected in any child that has been in a motor vehicle crash, has fallen from a height ≥ 3 m, or has had a submersion injury. SCIWORA is suspected in children who have even transient symptoms of neurologic dysfunction or lancinating pains down the spine or extremities and a mechanism of injury compatible with spinal cord injury.

Treatment

Treatment is similar to that in adults, with immobilization and attention to the adequacy of oxygenation, ventilation, and circulation. Treatment may also include high-dose corticosteroids (same weight-based dose as for adults). Children with significant spinal cord trauma should be transferred to a pediatric trauma center as soon as possible.
Chapter 326. Facial Trauma

Introduction

Patients with trauma to the face and head require evaluation of all structures; injuries often occur in combination (for dental trauma, see p. 524; for tympanic membrane trauma, see p. 453; and for eye trauma, see p. 3235).

External Ear Trauma

Trauma to the external ear may result in hematoma, laceration, avulsion, or fracture.

Subperichondral hematomas: Blunt trauma to the pinna may cause a subperichondrial hematoma; the accumulation of blood between the perichondrium and cartilage renders all or part of the pinna a shapeless, reddish purple mass. Because the perichondrium supplies blood to the cartilage, infection, abscess formation, or avascular necrosis of the cartilage may follow. The resultant destruction causes the cauliflower ear characteristic of wrestlers and boxers.

Treatment consists of evacuating the clot through an incision and preventing reaccumulation of the hematoma with through-and-through ear sutures over dental gauze rolls or insertion of a Penrose drain plus a pressure dressing. Because these injuries are prone to infection, an oral antibiotic effective against staphylococci (eg, cephalaxin 500 mg tid) is given for 5 days.

Lacerations: If lacerations of the pinna penetrate the cartilage and skin on both sides, the skin margins are sutured; then the cartilage is splinted externally with benzoin-impregnated cotton, and a protective dressing is applied. If there is sufficient skin to fully cover the cartilage, the cartilage should be repaired. Otherwise, external splinting suffices. Oral antibiotics are given as for a hematoma.

Avulsions: Complete or partial avulsions are repaired by an otolaryngologist, facial plastic surgeon, or plastic surgeon.

Trauma secondary to mandibular fractures: Forceful blows to the mandible may be transmitted to the anterior wall of the ear canal (posterior wall of the glenoid fossa). Displaced fragments from a fractured anterior wall may cause stenosis of the canal and must be reduced or removed surgically after a general anesthetic is given.

Fractures of the Jaw and Contiguous Structures

Blunt facial trauma can fracture the jaw and other bones of the midface. Symptoms depend on the location of the fracture. A dental x-ray or CT scan is diagnostic. Treatment may include surgery and/or external fixation.

Fractures of the lower jaw (mandible) are suspected in patients with post-traumatic malocclusion or focal swelling and tenderness over a segment of the mandible. Other clues include defects (stepoff) of the dental occlusal surface, alveolar ridge disruptions, and anesthesia in the distribution of the inferior alveolar or mental nerve. Some fractures result in palpable instability. Fractures of the mandibular condyle usually cause preauricular pain, swelling, and limited opening of the mouth (trismus). With a unilateral condylar fracture, the jaw deviates to the affected side when the mouth is opened.

Fractures of the midface, which includes the area from the superior orbital rim to the maxillary teeth, can cause irregularity in the smooth contour of the cheeks, malar eminences, zygomatic arch, or orbital rims. Infracrural nerve anesthesia, enophthalmos, or diplopia suggests an orbital floor fracture. An injury near the orbit requires an eye examination, including, at least, assessment of visual acuity, pupils, and extraocular movements. Trismus and a defect on palpation of the zygomatic arch suggest zygomatic arch fracture. The Le Fort classification (see Fig. 326-1) can be used to describe midface fractures. Traumatic malocclusion and upper alveolar ridge fractures may suggest a maxillary fracture that involves the occlusal surface. Brain injury and fractured cervical vertebrae are possible when trauma has been severe enough to fracture facial bones. In major
impact injuries, hemorrhage and edema due to a facial fracture may compromise the airway.

A panoramic dental x-ray is preferred for an isolated mandibular fracture. Fine-cut CT (1-mm slices) is done in axial and coronal planes to diagnose facial fractures.

Treatment

An oral endotracheal airway may be required to maintain airway patency in patients with hemorrhage, edema, or significant tissue disruption. Definitive facial fracture management is complex and may include internal fixation.

**Tooth socket fractures:** Fractures through a tooth socket are open fractures. They require antibiotic prophylaxis (typically with a broad-spectrum antibiotic that is particularly effective against anaerobes, such as penicillin) given orally as a liquid or parenterally.

**Mandible fractures:** For a fractured mandible, treatment ranges from soft diet alone to maxillomandibular fixation (wiring the jaw shut), rigid open fixation, or both. If fixation is available within the first few hours after injury, closure of any lip or oral lacerations should be delayed until the fracture has been reduced. For maxillomandibular fixation, metal bars (arch bars) are attached to the buccal surface of the upper and lower teeth and then wired to each other after correct occlusion has been established. Patients with maxillomandibular fixation should always carry wire cutters in case of vomiting. Fixation may need to last several weeks. Eating is restricted to liquids, pureed foods, and supplements. Because only part of the teeth surfaces can be brushed, control of plaque formation, infection, and halitosis is accomplished using a 60-sec rinse with 30 mL of chlorhexidine 0.12% every morning and evening. Jaw-opening exercises usually help restore function after fixation is discontinued.

Condylar fractures may require only 2 to 3 wk of maxillomandibular fixation, followed by a soft diet. However, severely displaced, bilaterally fractured condyles may require open reduction and fixation. Condylar fractures in children should not be rigidly immobilized because ankylosis and abnormal facial development may result. Flexible (elastic) fixation for 5 to 10 days is usually sufficient.

**Midface fractures:** Fractures of the midface are treated surgically if they cause malocclusion, enophthalmos, diplopia, infraorbital nerve anesthesia, or unacceptable cosmetic deformity. Surgical treatment usually consists of internal stabilization using fine screws and plates. Surgery can often be delayed until swelling subsides, particularly if the indication for surgery is not clear.

**Fractures of the Nose**

Fractures of the nasal bones or cartilaginous injury may result in swelling, point tenderness, hypermobility, crepitus, epistaxis, and periorbital bruising. Diagnosis is usually clinical. Treatment may include reduction, stabilization through internal packing, and splinting. A septal hematoma is drained without delay.

The nasal bones are the most frequently fractured facial bones because of their central location and protrusion. Depending on the mechanism of injury, fractures of the maxilla, orbit, or cribiform plate and injury to the nasolacrimal ducts may also occur.

Complications include cosmetic deformity and functional obstruction. Septal hematoma may lead to avascular or septic necrosis of the cartilage with resultant deformity. Cribiform plate fracture may cause a CSF leak, with increased risk of meningitis or brain abscess.

**Symptoms and Signs**

Facial trauma resulting in epistaxis may indicate a nasal fracture. Other symptoms and signs include obvious or subtle nasal deformity, swelling, point tenderness, crepitus, and instability. Lacerations,
ecchymosis (nasal and periorbital), septal deviation, and nasal obstruction may be present. Septal hematoma appears as a purplish bulge on the septum. CSF rhinorrhea appears as clear drainage but may be mixed with blood, making it difficult to identify.

Diagnosis

• Examination

Diagnosis is based on physical examination. Plain x-rays of an uncomplicated nasal fracture are not helpful because their sensitivity and specificity are poor. If other facial fractures or complications are suspected, CT of facial bones is done.

Treatment

• Symptomatic care

• For deformities, delayed reduction

• For septal hematomas, immediate drainage

Immediate treatment includes symptomatic control with ice and analgesics. Reduction is needed only for fractures causing clinically visible deformity or nasal airway obstruction. The end-point of reduction is determined by clinical appearance or improved airway. Reduction is usually deferred for 3 to 5 days after injury to allow swelling to subside but should take place within 2 to 3 wk of the injury, before bony callous formation. Nasal fractures in adults may be reduced after a local anesthetic is given; children require general anesthesia. A blunt elevator is passed through the nares and placed under the depressed nasal bone, which is lifted anteriorly and laterally while pressure is applied to the other side of the nose to bring the nasal dorsum to the midline. The nose may be stabilized with internal packing (consisting of antibiotic-impregnated strip gauze) placed high within the nasal vestibule, as well as with external splinting. Internal packing is left in place for 4 to 7 days; external splinting is left for 7 to 14 days. Antibiotic prophylaxis effective against staphylococci is required for the duration of nasal packing, to decrease the risk of toxic shock syndrome.

Cartilaginous injuries often do not require reduction. In the rare circumstance that a deformity persists after swelling subsides, reduction and splinting after a local anesthetic is given are usually sufficient.

Septal hematomas must be immediately incised and drained to prevent infection and cartilage necrosis. Septal fractures are difficult to hold in position and often require septal surgery later. Patients with cribiform plate fractures and CSF leak require hospital admission with bedrest and placement of a lumbar drain for 5 days. If the CSF leak does not resolve, surgical repair of the skull base may be required.

Temporal Bone Fractures

Temporal bone fractures can occur after severe blunt trauma to the head and sometimes involve structures of the ear, causing hearing loss, vertigo, balance disturbance, or facial paralysis.

Temporal bone fractures are suggested by Battle's sign (postauricular ecchymosis) and bleeding from the ear. Bleeding may come from the middle ear (hemotympanum) through a ruptured tympanic membrane or from a fracture line in the ear canal. A hemotympanum makes the tympanic membrane appear blue-black. CSF otorrhea indicates a communication between the middle ear and the subarachnoid space.

Temporal bone fractures have been classified by orientation with respect to the long axis of the petrous portion of the temporal bone. Longitudinal fractures make up 70 to 90% of temporal bone fractures, and transverse fractures make up 10 to 30%. Some fractures may have characteristics of both patterns. Longitudinal fractures can extend through the middle ear and rupture the tympanic membrane; they cause facial paralysis in 20% of cases and may cause hearing loss (usually conductive). Transverse fractures cross the fallopian canal and otic capsule, causing facial paralysis in about 40% of patients and
sometimes hearing loss (usually sensorineural) and vestibular dysfunction (eg, vertigo, balance disturbance). Rarely, fluctuating sensorineural hearing loss and vestibular dysfunction occur with temporal bone fracture and may be due to a perilymph fistula. Immediate complete facial paralysis may indicate a severed or crushed facial nerve, whereas delayed-onset complete facial paralysis usually indicates edema within an intact nerve.

Diagnosis

• CT
• Assessment of hearing and facial nerve function

If a temporal bone fracture is suspected, immediate CT of the head with special attention to the temporal bone is recommended. The Weber and Rinne tuning fork tests can be done during the initial physical examination in conscious patients to help differentiate between conductive and sensorineural hearing loss. However, formal audiometric examination is required for all patients with temporal bone fractures. If facial paralysis is present, electrical testing of the facial nerve is warranted.

Treatment

• Management of facial nerve injury, hearing loss, vestibular dysfunction, and CSF leakage

If immediate facial nerve paralysis occurs with loss of electrical response, surgical exploration may be warranted. Delayed-onset or incomplete facial paralysis almost always resolves with conservative management, including use of corticosteroids, which are gradually tapered.

Conductive hearing loss requires ossicular chain reconstruction several weeks to months after the injury. Good results can be expected. When sensorineural hearing loss occurs, it is typically permanent, and there are no medical or surgical therapies available to improve hearing. However, in the rare case of fluctuating sensorineural hearing loss, an exploratory tympanotomy to search for a perilymph fistula may be indicated.

When vestibular dysfunction results from perilymph fistula, repair may reduce severity and frequency of vertiginous episodes. When dysfunction results from injury to the vestibular nerve or vestibular labyrinth, few interventions can improve outcome. Symptoms may subside when benzodiazepines are used. More lasting improvement may occur with vestibular rehabilitation.

Patients who have a temporal bone fracture and CSF otorrhea should be hospitalized because meningitis is a risk. The leak usually stops spontaneously within a few days, although a lumbar drain or surgical closure of the defect is occasionally required.
Chapter 327. Eye Injuries

Introduction

(See also Retinal Detachment on p. 617.)

Common causes of eye injury include domestic accidents (eg, during hammering or exposure to household chemicals or cleaners), assault, car battery explosions, sporting injuries (including air- or paint pellet-gun injuries), and motor vehicle crashes (including air-bag injuries). Injury may be to the eyeball (globe), surrounding soft tissues (including muscles, nerves, and tendons), or bones of the orbit.

General evaluation should include the following:

• Tests of visual acuity
• Range of extraocular motion
• Pupillary appearance and responses
• Intraocular pressure determination
• Visual fields to confrontation
• Depth of anterior chamber
• Location and depth of lid and conjunctival lacerations and of foreign bodies
• Presence of anterior chamber or vitreous hemorrhage, cataract, or red reflex
• Retinal examination

Detailed examination of the anterior segment, lens, and anterior vitreous is best done with a slit lamp. Detailed examination of the posterior vitreous and the retina is best done with indirect ophthalmoscopy, usually by an ophthalmologist. Indications include clinical suspicion of traumatic cataracts, vitreous abnormalities (eg, hemorrhage, foreign body), and retinal abnormalities; clinical suspicion may be based on injury mechanism, absence of the red reflex, or retinal abnormalities visible with direct ophthalmoscopy. About 15 to 30 min before this examination, the pupil is usually dilated with 1 drop of cyclopentolate 1% and 1 drop of phenylephrine 2.5%. If an intraocular or orbital foreign body or an orbital fracture is suspected, CT is done.

Use of eye guards, goggles, or special eyeglasses, such as those constructed of polycarbonate lenses in a wrap-around polyamide frame, is a simple precaution that greatly reduces the risk of injury.

When eye drops are prescribed, each dose includes only one drop.

Ocular Burns

Thermal burns: The blink reflex usually causes the eye to close in response to a thermal stimulus. Thus, thermal burns tend to affect the eyelid rather than the conjunctiva or cornea. Eyelid burns should be cleansed thoroughly with sterile isotonic saline solution followed by application of an antimicrobial ointment (eg, bacitracin bid). Most thermal burns affecting the conjunctiva or cornea are mild and heal without significant sequellae. They are treated with topical antibiotics and corticosteroids.

Chemical burns: Burns of the cornea and conjunctiva can be serious, particularly when strong acid or alkali is involved. They are a true emergency; treatment must begin immediately.

Burns should be irrigated with copious amounts of water or with 0.9% saline if available. The eye may be anesthetized with one drop of proparacaine 0.5%, but irrigation should not be delayed and should last for...
at least 30 min. In acid and alkali burns, some experts suggest 1 to 2 h of irrigation; others recommend that the pH of the conjunctiva be measured with expanded pH paper (which measures over a wide range of pH) and irrigation continued until pH is normal.

After irrigation, the conjunctival fornices should be examined for chemical embedded in the tissue and swept with a swab to remove trapped particles. The superior fornices are exposed by using double eyelid eversion (ie, pushing the fornix downward until its mucosal surface is visible using a swab inserted under the everted eyelid).

**Chemical iritis** is suspected in a patient with photophobia (deep eye pain with exposure to light) that develops hours or days after a chemical burn and is diagnosed by finding flare and WBCs in the anterior chamber on slit-lamp examination. Chemical iritis is treated by instilling a long-acting cycloplegic (eg, a single dose of homatropine 2% or 5% or scopolamine 0.25% solution). Corticosteroid drops (eg, prednisolone 1% qid) may be given by an ophthalmologist. Used inappropriately, topical corticosteroids can result in corneal perforation after chemical burns and should be used only by an ophthalmologist. Corneal epithelial defects are treated by applying an antibiotic ointment (eg, erythromycin 0.5%). Topical anesthetics should be avoided after initial irrigation; significant pain may be treated with acetaminophen with or without oxycodone.

**Severe chemical burns** require treatment by an ophthalmologist to save vision and prevent complications such as uveitis, perforation of the globe, and lid deformities. Patients with severe conjunctival hyperemia, ciliary flush (prominent conjunctival injection around the limbus), true photophobia (ie, not just sensitivity to light), avascular areas of conjunctiva, or loss of conjunctival or corneal epithelium as demonstrated by fluorescein staining should be examined by an ophthalmologist within 24 h.

**Corneal Abrasions and Foreign Bodies**

**Corneal abrasions** are self-limited, superficial epithelial defects.

The most common conjunctival and corneal injuries are foreign bodies and abrasions. Improper use of contact lenses can damage the cornea. Superficial foreign bodies often spontaneously exit the cornea in the tear film, occasionally leaving a residual abrasion, but other foreign bodies remain on or within the cornea. Sometimes, a foreign body trapped under the upper lid causes a vertical corneal abrasion that worsens with blinking. Intraocular penetration can occur with seemingly minor trauma, particularly with foreign bodies resulting from high-speed machines (eg, drills, saws, anything with a metal-on-metal mechanism), hammering, or explosions. Infection generally does not develop from a corneal injury. However, if intraocular penetration is not recognized, infection within the eye (endophthalmitis), although somewhat rare, may develop.

**Symptoms and Signs**

Symptoms and signs of abrasion or foreign body include foreign body sensation, tearing, redness, and occasionally discharge. Vision is rarely affected (other than by tearing).

**Diagnosis**

• Slit-lamp examination, usually with fluorescein staining

After an anesthetic (eg, 2 drops of proparacaine 0.5%) is instilled into the conjunctiva, each lid is everted, and the entire conjunctiva and cornea are inspected with a binocular lens (loupe) or a slit lamp. Fluorescein staining (see p. 538) with cobalt light illumination renders abrasions and nonmetallic foreign bodies more apparent. Patients with a high-risk intraocular injury or (more rarely) visible globe perforation undergo CT to rule out intraocular foreign body and complete examination by an ophthalmologist, including slit-lamp examination and indirect ophthalmoscopy with eye dilation.

**Treatment**
• For surface foreign bodies, irrigation or removal with a small needle
• For corneal abrasions, antibiotic ointment and pupillary dilation
• For intraocular foreign bodies, surgical removal

After an anesthetic is instilled into the conjunctiva, clinicians can remove conjunctival foreign bodies by irrigation or lift them out with a moist sterile cotton applicator. A corneal foreign body that cannot be dislodged by irrigation may be lifted out carefully on the point of a sterile spud or of a 25- or 27-gauge hypodermic needle under loupe or, preferably, slit-lamp magnification; the patient must be able to stare without moving the eye during removal. Steel or iron foreign bodies remaining on the cornea for more than a few hours may leave a rust ring on the cornea that also requires removal under slit-lamp magnification by scraping or using a low-speed rotary burr; removal is usually done by an ophthalmologist.

Abrasions: For all abrasions, an antibiotic ointment (eg, bacitracin/polymyxin B or ciprofloxacin 0.3% qid for 3 to 5 days) is used. Contact lens wearers with corneal abrasions require an antibiotic with optimal antipseudomonal coverage (eg, ciprofloxacin 0.3% ointment qid). For symptomatic relief of larger abrasions (eg, area > 10 mm²), the pupil is also dilated with a short-acting cycloplegic (eg, one drop cyclopentolate 1% or homatropine 5%). Eye patches may increase risk of infection and are usually not used, particularly for an abrasion caused by a contact lens or an object that may be contaminated with soil or vegetation. Ophthalmic corticosteroids tend to promote the growth of fungi and reactivation of herpes simplex virus and are contraindicated. Continued use of topical anesthetics can impair healing and is thus contraindicated.

The corneal epithelium regenerates rapidly; even large abrasions heal within 1 to 3 days. A contact lens should not be worn for 5 to 7 days. Follow-up examination by an ophthalmologist 1 or 2 days after injury is wise, especially if a foreign body was removed with a needle or spud.

Intraocular foreign bodies: Intraocular foreign bodies require immediate surgical removal by an ophthalmologist. Systemic and topical antimicrobials (effective against Bacillus cereus if the injury involved contamination with soil or vegetation) are indicated; they include ceftazidime 1 g IV q 12 h, in combination with vancomycin 15 mg/kg IV q 12 h and moxifloxacin 0.5% ophthalmic solution q 1 to 2 h. Ointment should be avoided if the globe is lacerated. A protective shield (such as a Fox shield or the bottom third of a paper cup) is placed and taped over the eye to avoid inadvertent pressure that could extrude ocular contents through the penetration site. Tetanus prophylaxis is indicated after open globe injuries. As with any laceration of the globe, vomiting, which can increase intraocular pressure, should be prevented. If nausea occurs, an antiemetic is given.

Eye Contusions and Lacerations

Consequences of blunt trauma to the eye range from eyelid to orbital injury.

Eyelids: Eyelid contusions (which result in black eyes) are more cosmetically than clinically significant, although more serious injuries may sometimes accompany them and should not be overlooked. Uncomplicated contusions are treated with ice packs to inhibit swelling during the first 24 to 48 h, followed by hot compresses to aid absorption of the hematoma.

Minor lid lacerations not involving the lid margin or tarsal plate may be repaired with nylon (or, in children, plain gut) 6-0 or 7-0 sutures. Lid-margin lacerations are best repaired by an ophthalmic surgeon to ensure accurate apposition and to avoid a notch in the contour. Major lid lacerations, which include those of the medial portion of the lower or upper eyelid (possibly involving the lacrimal canaliculus), through-and-through lacerations, those in which the patient has ptosis, and those that expose orbital fat or involve the tarsal plate, should also be repaired by an ophthalmic surgeon.

Globe: Trauma may cause the following:

• Conjunctival, anterior chamber, and vitreous hemorrhage
• Retinal hemorrhage, edema, or detachment
• Laceration of the iris
• Cataract
• Dislocated lens
• Glaucoma
• Globe rupture (laceration)

Evaluation can be difficult when massive lid edema or laceration is present. Even so, unless the need for immediate eye surgery is obvious (necessitating evaluation by an ophthalmologist as soon as possible), the lid is opened, taking care not to exert inward pressure, and as complete an examination as possible is conducted. At a minimum, the following are noted:

• Visual acuity
• Pupillary responses
• Extraocular movements
• Anterior chamber depth or hemorrhage
• Presence of red reflex

An analgesic or, after obtaining any surgical consent, an anxiolytic may be given to facilitate examination. Gentle and careful use of eyelid retractors or an eyelid speculum makes it possible to open the lids. If a commercial instrument is not available, the eyelids can be separated with makeshift retractors fashioned by bending the ends of paper clips 180°. Globe laceration should be suspected with any of the following:

• A corneal or scleral laceration is visible.
• Aqueous humor is leaking.
• The anterior chamber is very shallow (eg, making the cornea appear to have folds) or very deep (due to rupture posterior to the lens).
• The pupil is irregular.

If globe laceration is suspected, measures that can be taken before an ophthalmologist is available consist of applying a protective shield (see above) and combating possible infection with systemic antimicrobials as for intraocular foreign bodies (see p. 3236). Topical antibiotics are avoided. Vomiting, which can increase intraocular pressure (IOP) and contribute to extravasation of ocular contents, is suppressed using antiemetics as needed. Because fungal contamination of open wounds is dangerous, corticosteroids are contraindicated until after wounds are closed surgically. Tetanus prophylaxis is indicated after open globe injuries. Very rarely, after laceration of the globe, the uninjured, contralateral eye becomes inflamed (sympathetic ophthalmia—see p. 612) and may lose vision to the point of blindness unless treated. The mechanism is an autoimmune reaction; corticosteroid drops can prevent the process.

**Anterior chamber hemorrhage (hyphema):** This injury may be followed by recurrent bleeding, glaucoma, and blood staining of the cornea, any of which may result in permanent vision loss. Symptoms are of associated injuries unless the hyphema is large enough to obstruct vision. Direct inspection typically reveals layering of blood or the presence of clot or both in the anterior chamber. Layering is seen as a meniscus-like blood level in the lower part of the anterior chamber. Microhyphema, a less severe
form, may be detectable by direct inspection as haziness in the anterior chamber or by slit-lamp examination as suspended RBCs.

An ophthalmologist should attend to the patient as soon as possible. The patient is placed on bed rest with the head elevated 30° and is given an eye shield to protect the eye from further trauma (see p. 3237). Patients who are at high risk of recurrent bleeding (eg, those with large hyphemas, bleeding diatheses, anticoagulant use, or sickle cell disease), who have IOP that is difficult to control, or who are not likely to adhere to recommended treatment may be hospitalized. Oral and topical NSAIDs are contraindicated because they may contribute to recurrent bleeding.

IOP can rise acutely (within hours, usually in patients with sickle cell disease or trait) or months to years later. Thus, IOP is monitored daily for several days and then regularly over subsequent weeks and months and if symptoms develop (eg, eye ache, decreased vision, nausea—similar to symptoms of acute angle-closure glaucoma). If pressure rises, timolol 0.5% bid, brimonidine 0.2% or 0.15% bid, or both are given. Response to treatment is determined by pressure, often checked every 1 or 2 h until controlled or until a significant rate of reduction is demonstrated; thereafter, it is usually checked once or twice daily. Mydriatic drops (eg, scopolamine 0.25% tid or atropine 1% tid for 5 days) and topical corticosteroids (eg, prednisolone acetate 1% 4 to 8 times/day for 2 to 3 wk are often given. Administration of aminocaproic acid 50 to 100 mg/kg po q 4 h (not exceeding 30 g/day) for 5 days may reduce recurrent bleeding. In these cases, miotic or mydriatic drugs must be given by an ophthalmologist. Rarely, recurrent bleeding with secondary glaucoma requires surgical evacuation of the blood.

**Blowout fracture:** Blowout fracture occurs when blunt trauma forces the orbital contents through the most fragile portion of the orbital wall, typically the floor. Medial and roof fractures also can occur. Symptoms include diplopia, enophthalmos, inferiorly displaced globe, hypesthesia of the cheek and upper lip (from infraorbital nerve injury), and subcutaneous emphysema. Epistaxis, lid edema, and ecchymosis may occur. Diagnosis is best made using CT. If diplopia or cosmetically unacceptable enophthalmos persists beyond 2 wk, surgical repair is indicated. Patients should be told to avoid blowing the nose. Using a topical vasoconstrictor for 2 to 3 days may alleviate epistaxis.

**Posttraumatic Iridocyclitis**

**(Traumatic Anterior Uveitis; Traumatic Iritis)**

Posttraumatic iridocyclitis is an inflammatory reaction of the uvea and iris, typically developing within 3 days of blunt eye trauma.

Symptoms of posttraumatic iridocyclitis include tearing, throbbing ache and redness of the eye, photophobia, and blurred vision. Diagnosis is by history, symptoms, and slit-lamp examination, which typically reveals flare (due to an increase in protein content of the aqueous humor from the inflammatory exudate) and WBCs in the anterior chamber. Treatment involves a cycloplegic (usually scopolamine 0.25% tid, or homatropine 5% tid). Topical corticosteroids (eg, prednisolone acetate 1% 4 to 8 times/day) are often used to shorten symptom duration.
Chapter 328. Genitourinary Tract Trauma

Introduction

The GU tract can be injured by blunt trauma (eg, motor vehicle crashes, falls) or penetrating trauma (eg, gunshot or stab wounds). Some injuries are caused during surgical procedures. Symptoms and signs are often subtle or nonspecific; therefore, diagnosis requires a high level of suspicion. Whenever urinalysis shows any hematuria in a patient with trauma, GU injury should be presumed until proved otherwise. Depending on the suspected site of injury, imaging studies, most often contrast-enhanced CT, are typically used to make a diagnosis. General evaluation of the trauma patient is discussed elsewhere (see p. 3190).

Bladder Trauma

Bladder injuries are caused by either blunt or penetrating trauma to the lower abdomen, pelvis, or perineum. Blunt trauma is the more common mechanism, usually by a sudden deceleration, such as in a high-speed motor vehicle crash or fall, or from an external blow to the lower abdomen. The most frequently accompanying injury is a pelvic fracture, occurring in > 95% of bladder ruptures caused by blunt trauma. Other concomitant injuries include long bone fractures and CNS and chest injuries. Penetrating injuries, most often gunshot wounds, account for about 25% of bladder injuries.

The bladder is the most frequently injured organ during pelvic surgery. Such injuries can occur during transurethral surgery, colon resection, or gynecologic procedures (most commonly abdominal hysterectomy, cesarean section, pelvic mass excision). Predisposing factors include scarring from prior surgery or radiation therapy, inflammation, and extensive tumor burden.

Bladder injuries are classified as contusions or ruptures based on the extent of injury seen radiographically. Bladder ruptures can be extraperitoneal, intraperitoneal, or both.

Complications of bladder injuries include infection, fistula, incontinence, and bladder instability. Mortality with bladder rupture approaches 20% from the concomitant organ injuries rather than the bladder injury.

Symptoms and Signs

Symptoms may include suprapubic pain and inability to void; signs may include suprapubic tenderness, distention, and, in the case of intraperitoneal rupture, peritoneal signs.

Diagnosis

- Retrograde cystography

Diagnosis is suspected on the basis of history and physical examination findings and hematuria (gross or microscopic). Confirmation is by retrograde cystography using plain film x-rays or CT. Plain film x-rays are accurate, but CT also helps delineate concomitant intra-abdominal injuries. If urethral disruption is suspected in a male, retrograde catheter placement is avoided, pending results of urethrography.

Treatment

- Catheter drainage
- Sometimes surgical repair

All penetrating trauma and intraperitoneal ruptures from blunt trauma require surgical exploration and repair. Contusions require only catheter drainage until gross hematuria resolves. Extraperitoneal ruptures require only catheter drainage if urine is draining freely and the bladder neck is spared. If the bladder neck is involved, surgical exploration and repair are required.

Genital Trauma
Most genital trauma occurs in men and includes injury to the testes, scrotum, and penis. Genital mutilation of women by removing the clitoris, which is done in some cultures, is a form of genital trauma and child abuse (see p. 3067).

Most testicular injuries result from blunt trauma; penetrating testicular injuries are less common. Testicular injuries are classified as contusions or, if the tunica albuginea is disrupted, as ruptures.

Scrotal injury may be caused by penetrating trauma, burns, and avulsions.

Penile injuries have diverse mechanisms. Zipper injuries are common. Penile fractures, which are ruptures of the corpus cavernosum, occur most often when the penis is forcibly bent during sexual activity; urethral injury may also be present. Amputations (usually self-inflicted or from clothing trapped by heavy machinery) and strangulations (usually from constricting penile rings used to enhance erections) are additional mechanisms. Penetrating injuries, including animal bites and gunshot wounds, are less common and may also involve the urethra.

Complications of genital injuries include erectile dysfunction, hypogonadism, infection, tissue loss, and urethral scarring.

Symptoms and Signs

Symptoms after a direct scrotal blow are usually scrotal pain and swelling. Signs may include scrotal discoloration and a tender, firm scrotal mass that fails to transilluminate, suggesting a hematocele. Scrotal penetration suggests the possibility of testicular involvement. Often the examination is limited by patient discomfort. Penile fracture typically results in a cracking sound, immediate pain, marked swelling and ecchymosis, and usually visible deformity.

Diagnosis

- Clinical evaluation
- Sometimes ultrasonography or retrograde urethrography

Diagnosis of external scrotal and penile injury is made clinically. Clinical diagnosis of testicular contusion and rupture can be difficult because the degree of injury may be out of proportion to the physical findings, so patients with blunt testicular injury typically require scrotal ultrasonography. Most penile injuries are evident on physical examination. An x-ray with urethral contrast (retrograde urethrogram) should be done for any patient with penile fracture or penetrating penile injury because of the high incidence of coexisting urethral injury.

Treatment

- Sometimes surgical repair

Patients with penetrating testicular injuries or clinical or sonographic characteristics that suggest testicular rupture require surgical exploration and repair. Similarly, all penile fractures and penetrating injuries should be surgically explored and the defects repaired. Penile amputations should be repaired by microsurgical reimplantation if the amputated segment is viable. Strangulation injuries can usually be managed simply by removing the constricting agent. Zippers should be removed (see Fig. 328-1).

Renal Trauma

The kidney is injured in up to 10% of patients who sustain significant abdominal trauma. About 65% of
GU injuries involve the kidney. Most renal injuries (85 to 90% of cases) occur from blunt trauma, typically due to motor vehicle crashes, falls, or assaults. Most injuries are low grade. The most common accompanying injuries are to the head, CNS, spleen, and liver. Penetrating injuries usually result from gunshot wounds. Such patients usually have multiple intra-abdominal injuries, most commonly to the liver, intestine, and spleen.

Renal injuries are classified according to severity into 5 grades (see Table 328-1).

**Diagnosis**

- Urinalysis and Hct
- If moderate or severe injury is suspected, contrast-enhanced CT

Diagnosis should be suspected in any patient with the following:

- Penetrating injury between the mid chest and lower abdomen
- Significant deceleration injury
- Direct blow to the flank

In such patients, hematuria strongly suggests renal injury; other indicators include the following:

- Seat belt marks
- Diffuse abdominal tenderness
- Flank contusions
- Lower rib fractures

Patients who develop hematuria after relatively minor trauma may have a previously undiagnosed congenital renal anomaly.

Laboratory testing should include Hct and urinalysis. When imaging is indicated, contrast-enhanced CT is usually used to determine the grade of renal injury and identify accompanying intra-abdominal trauma and complications, including retroperitoneal hemorrhage and urinary extravasation. Patients with blunt trauma and microscopic hematuria usually have minor renal injuries that almost never require surgical repair; thus, CT is usually unnecessary. CT is indicated in blunt trauma with any of the following:

- The mechanism involves a fall from a significant height or a high-speed motor vehicle crash
- Gross hematuria
- Microscopic hematuria with hypotension (systolic pressure < 90 mm Hg)
- Clinical signs potentially suggesting severe renal injury (eg, flank contusion, seat belt marks, lower rib or vertebral transverse process fractures)

For **penetrating trauma**, CT is indicated for all patients with microscopic or gross hematuria. Rarely, angiography is indicated to assess persistent or delayed bleeding and may be combined with selective arterial embolization.

**Pediatric renal injuries** are evaluated similarly, except that all children with blunt trauma in whom urinalysis shows > 50 RBCs/high-power field require imaging.
[Table 328-1: Grades of Renal Injury]

**Treatment**

- Strict bed rest

- Surgical repair for moderate or severe injuries and some penetrating injuries

Most blunt renal injuries, including all grade 1 and 2 and most grade 3 and 4 injuries, can be safely treated without surgery. Patients require strict bed rest until gross hematuria has resolved. Surgical repair is required for patients with the following:

- Persistent bleeding (ie, enough to necessitate treatment for hypovolemia)

- Expanding perinephric hematoma

- Renal pedicle avulsion

Penetrating trauma usually requires surgical exploration, although observation may be appropriate for patients in whom the renal injury has been accurately staged by CT, BP is stable, and no associated intra-abdominal injuries require surgery.

**Ureteral Trauma**

Most ureteral injuries are iatrogenic. Procedures that most often injure a ureter include ureterscopy, hysterectomy, low anterior colon resection, and abdominal aneurysm repair. Noniatrogenic ureteral injury accounts for only about 1 to 3% of all GU trauma. It usually results from gunshot wounds and rarely from stab wounds. In children, avulsion injuries are more common. Complications include ureteral stricture, obstruction, or both; peritoneal or retroperitoneal urinary leakage; and fistula (eg, ureterovaginal, ureterocutaneous) formation.

**Diagnosis**

- Imaging, exploratory surgery, or both

Diagnosis is suspected on the basis of history and requires a high index of suspicion, because symptoms are nonspecific and hematuria is absent in > 30% of patients. Diagnosis is confirmed by imaging (eg, CT with contrast, IVU), exploratory surgery, or both. Flank pain and fever are the main symptoms of otherwise occult injuries.

**Treatment**

- For minor, nephrostomy tube or ureteral stent

- For major, surgical repair

All injuries require intervention. A diverting percutaneous nephrostomy tube or cystoscopic placement of a ureteral stent is often sufficient for minor injuries (eg, contusions or partial transections). Complete transection or avulsion injuries typically require reconstructive techniques, including ureteral reimplantation, primary ureteral anastomosis, anterior bladder flap, ileal interposition, and, as a last resort, autotransplantation.

**Urethral Trauma**

Urethral injury usually occurs in men. Most major urethral injury is due to blunt trauma. Penetrating urethral trauma is less common, occurring mainly from gunshot wounds, or, alternatively, from inserting objects into the urethra during sexual activity or because of psychiatric illness.
Urethral injuries are classified as contusions, partial disruptions, or complete disruptions, and they may involve the posterior or anterior urethral segments. Posterior urethral injuries occur almost exclusively with pelvic fractures. Anterior urethral injuries are often consequences of a perineal straddle injury from a fall, perineal blow, or motor vehicle crash.

Complications include stricture formation, infection, erectile dysfunction, and incontinence.

**Symptoms and Signs**

Symptoms include pain with voiding and inability to void. Blood at the urethral meatus is the most important sign of a urethral injury. Additional signs include perineal, scrotal, and penile ecchymosis, edema, or both, and a high-riding prostate on rectal examination.

**Diagnosis**

- Retrograde urethrography

In any patient with suggestive symptoms or signs, the diagnosis is confirmed by retrograde urethrography, which should be done before catheterization. Urethral catheterization in a patient with an undetected significant urethral injury may potentiate urethral disruption (eg, convert a partial disruption to a complete disruption).

**Treatment**

- Usually urethral catheterization or suprapubic cystostomy

Contusions can be safely treated with an indwelling transurethral catheter for 10 days. Partial disruptions are best treated with bladder drainage via suprapubic cystostomy. In selected cases of posterior partial disruptions, primary urethral realignment using catheterization may be attempted; if successful, this approach limits subsequent urethral strictures.

Complete disruptions are treated with bladder drainage via suprapubic cystostomy. This option is simplest and can be used safely in all patients. Definitive surgery is deferred for about 8 to 12 wk until the urethral scar tissue has stabilized and the patient has recovered from any accompanying injuries.

Selected penetrating urethral injuries and blunt urethral injuries that occur with penile fractures may be sutured primarily.
Chapter 329. Burns

Introduction

(See also Ocular Burns on p. 3235 and Caustic Ingestion on p. 3335.)

Burns are injuries of skin or other tissue caused by thermal, radiation, chemical, or electrical contact. Burns are classified by depth (1st-degree, superficial and deep partial-thickness, and full-thickness) and percentage of total body surface area (BSA) involved. Complications and associated problems include hypovolemic shock, inhalation injury, infection, scarring, and contractures. Patients with large burns (> 20% BSA) require fluid resuscitation. Treatment for burn wounds includes topical antibacterials, regular cleaning, elevation, and sometimes skin grafting. Intensive rehabilitation, consisting of range-of-motion exercises and splinting, is often necessary.

Burns cause between 3000 and 4000 deaths/yr in the US and about 2 million physician visits.

Etiology

Thermal burns may result from any external heat source (flame, hot liquids, hot solid objects, or, occasionally, steam). Fires may also result in toxic smoke inhalation (see Sidebar 329-1 and p. 3334).

Radiation burns most commonly result from prolonged exposure to solar ultraviolet radiation (sunburn—see p. 676) but may result from prolonged or intense exposure to other sources of ultraviolet radiation (eg, tanning beds) or from exposure to sources of x-ray or other nonsolar radiation (see also p. 3252).

Chemical burns may result from strong acids, strong alkalis (eg, lye, cement), phenols, cresols, mustard gas, phosphorus, and certain petroleum products (eg, gasoline, paint thinner). Skin and deeper tissue necrosis caused by these agents may progress over several hours.

Electrical burns (see also p. 3248) result from heat generation and electroporation of cell membranes associated with massive current of electrons. Electrical burns may cause extensive deep tissue damage to electrically conductive tissues, such as muscles and nerves, despite minimal apparent cutaneous injury.

Events associated with a burn (eg, jumping from a burning building, being struck by debris, motor vehicle crash) may cause other injuries. Abuse should be considered in young children and elderly patients with burns.

Pathophysiology

Burns cause protein denaturation and thus coagulative necrosis. Around the coagulated tissue, platelets aggregate, vessels constrict, and marginally perfused tissue (known as the zone of stasis) can extend the injury. Around the zone of stasis, tissue is hyperemic and inflamed.

Damage to the normal epidermal barrier allows bacterial invasion and external fluid loss; damaged tissues often become edematous, further enhancing volume loss. Heat loss can be significant because thermoregulation of the damaged dermis is absent, particularly in wounds that are exposed.

Sidebar 329-1 Smoke Inhalation

Burns and smoke inhalation often occur together but may occur separately. When smoke is inhaled, toxic products of combustion injure airway tissues. Hot smoke usually burns only the pharynx because the incoming gas cools quickly. A common exception is steam, which carries much more heat energy than smoke and thus can also burn the lower airways (below the glottis). Many toxic chemicals produced in routine house fires (eg, hydrogen chloride, phosgene, sulfur dioxide, toxic aldehydes, ammonia) injure lower airways chemically. Some toxic products of combustion, such as carbon monoxide (see p. 3334) or
cyanide, impair cellular respiration systemically.

Upper airway injury usually causes symptoms within minutes but occasionally over several hours; upper airway edema may cause stridor. Lower airway injury may also occur with upper airway injury and usually causes symptoms (eg, oxygenation problems highlighted by increasing O$_2$ requirements or decreases in lung compliance) 24 h or later.

Smoke inhalation is suspected in patients with respiratory symptoms, a history of confinement in a burning environment, or carbonaceous sputum. Perioral burns and singed nasal hair may also be clues.

Diagnosis of upper airway injury is by endoscopy (laryngoscopy or bronchoscopy) that is adequate to see the upper airways and trachea fully and that shows edema or soot in the airways; however, injury occasionally develops after an early normal study. Endoscopy is done as soon as possible, usually with a flexible fiberoptic scope typically followed by endotracheal intubation in patients with significant findings. Diagnosis of lower airway injury is by chest x-ray and oximetry or ABGs, but abnormalities may develop only days later. Cyanide and carbon monoxide toxicity should be considered; carboxyhemoglobin levels are measured in patients with significant smoke inhalation.

All patients at risk of smoke inhalation injury are given 100% O$_2$ by face mask initially. Patients with airway obstruction or respiratory distress require endotracheal intubation or another artificial airway and mechanical ventilation (see p. 2279). Patients with edema or significant soot in the upper airways require intubation as soon as possible because intubation becomes more difficult as edema increases. Bronchoscopy is usually done at the same time as intubation. Patients with lower airway injury may require supplemental O$_2$, bronchodilators, and other supportive measures.

**Burn depth:** First-degree burns are limited to the epidermis.

**Partial-thickness** (also called 2nd-degree) burns involve part of the dermis (see Plate 76) and can be superficial or deep.

Superficial partial-thickness burns involve the papillary (more superficial) dermis. These burns heal within 1 to 2 wk and rarely scar. Healing occurs from epidermal cells lining sweat gland ducts and hair follicles; these cells grow to the surface, then migrate across the surface to meet cells from neighboring glands and follicles.

Deep partial-thickness burns involve the deeper dermis and take ≥ 2 wk to heal. Healing occurs only from hair follicles, and scarring is common and may be severe.

**Full-thickness** (3rd-degree) burns extend through the entire dermis and into the underlying fat (see Plate 75). Healing occurs only from the periphery; these burns, unless small, require excision and skin grafting.

**Complications**

Burns cause both systemic and local complications. The major factors contributing to systemic complications are breakdown of skin integrity and fluid loss. Local complications include eschars and contractures and scarring.

**Systemic:** The greater the percentage of BSA involved, the greater the risk of developing systemic complications. Risk factors for severe systemic complications and mortality include all of the following:

- Burns of > 40% of BSA
- Age > 60 yr or < 2 yr
- Presence of simultaneous major trauma or smoke inhalation
The most common systemic complications are hypovolemia and infection.

**Hypovolemia**, causing hypoperfusion of burned tissue and sometimes shock, can result from fluid losses due to burns that are deep or that involve large parts of the body surface; whole-body edema from escape of intravascular volume into the interstitium and cells also develops. Hypoperfusion of burned tissue also may result from direct damage to blood vessels or from vasoconstriction secondary to hypovolemia.

**Infection**, even in small burns, is a common cause of sepsis and mortality, as well as local complications. Impaired host defenses and devitalized tissue enhance bacterial invasion and growth. The most common pathogens are streptococci and staphylococci during the first few days and gram-negative bacteria after 5 to 7 days; however, flora are almost always mixed.

**Metabolic abnormalities** may include hypoalbuminemia that is partly due to hemodilution (secondary to replacement fluids) and partly due to protein loss into the extravascular space through damaged capillaries. Dilutional electrolyte deficiencies can develop; they include hypomagnesemia, hypophosphatemia, and hypokalemia. Metabolic acidosis may result from shock. Rhabdomyolysis or hemolysis can result from deep thermal or electrical burns of muscle or from muscle ischemia due to constricting eschars. Rhabdomyolysis causing myoglobinuria or hemolysis causing hemoglobinuria can lead to acute tubular necrosis and renal failure.

**Hypothermia** may result from large volumes of cool IV fluids and extensive exposure of body surfaces to a cool emergency department environment, particularly in patients with extensive burns.

**Ileus** is common after extensive burns.

**Local:** **Eschar** is stiff, dead tissue caused by deep burns. A circumferential eschar, which completely encircles a limb (or sometimes the torso), is constricting. A constricting eschar limits tissue expansion in response to edema; instead, tissue pressure increases, eventually causing local ischemia. The ischemia threatens viability of limbs and digits, and an eschar around the thorax can compromise respiration.

**Scarring and contractures** result from spontaneous healing of deep burns; if the burn is located near joints or in the hands, feet, or perineum, function can be severely impaired. Infection can increase scarring. Keloids form in some patients with burns, especially in patients with darker skin.

**Symptoms and Signs**

Wound symptoms and signs depend on burn depth:

- **First-degree burns:** These burns are red, blanch markedly and widely with light pressure, and are painful and tender. Vesicles or bullae do not develop.

- **Superficial partial-thickness burns:** These burns blanch with pressure and are painful and tender. Vesicles or bullae develop within 24 h. The bases of vesicles and bullae are pink and subsequently develop a fibrinous exudate.

- **Deep partial-thickness burns:** These burns may be white, red, or mottled red and white. They do not blanch and are less painful and tender than more superficial burns. A pinprick is often interpreted as pressure rather than sharp. Vesicles or bullae may develop; these burns are usually dry.

- **Full-thickness burns:** These burns may be white and pliable, black and charred, brown and leathery, or bright red because of fixed Hb in the subdermal region. Pale full-thickness burns may simulate normal skin except the skin does not blanch to pressure. Full-thickness burns are usually anesthetic or hypoesthetic. Hairs can be pulled easily from their follicles. Vesicles and bullae usually do not develop. Sometimes features that differentiate full-thickness from deep partial-thickness burns take a few days to develop.

**Diagnosis**
• Clinical assessment of burn extent and depth

• Laboratory testing and chest x-ray in admitted patients

Location and depth of burned areas are recorded on a burn diagram. Burns with an appearance compatible with either deep partial-thickness or full-thickness are presumed to be full-thickness until differentiation is possible.

The percentage of BSA involved is calculated; only partial-thickness and full-thickness burns are included in this calculation. For adults, the percentage BSA for parts of the body is estimated by the rule of nines (see Fig. 329-1); for smaller scattered burns, estimates can be based on the size of the patient’s entire hand (not the palm only), which is about 1% of BSA. Children have proportionally larger heads and smaller lower extremities, so the percentage BSA is more accurately estimated using the Lund-Browder chart (see Fig. 329-1).

In patients who require hospitalization, Hb and Hct, serum electrolytes, BUN, creatinine, albumin, protein, phosphate, and ionized Ca should be measured. ECG, urinalysis for myoglobin, and a chest x-ray are also required. Myoglobinuria (suggesting hemolysis or rhabdomyolysis) is suggested by urine that is grossly dark or that tests positive for blood on dipstick in the absence of microscopic RBCs. These tests are repeated as needed. Muscle compartments are evaluated in patients with myoglobinuria.

Infection is suggested by wound exudate, impaired wound healing, or systemic evidence of infection (eg, feeding intolerance, decrease in platelet count, increase in serum glucose level). Fever and WBC count elevation are common in burns without infection, and therefore are unreliable signs of developing sepsis. If the diagnosis is unclear, infection can be confirmed by biopsy; cultures from the wound surface or exudate are unreliable.

Treatment

• IV fluids for burns > 10% BSA

• Wound cleaning, dressing, and serial assessment

• Supportive measures

• Transfer or referral of selected patients to burn centers

• Surgery and physical therapy for deep partial-thickness and full-thickness burns

Initial treatment: Treatment begins in the prehospital setting. The first priorities are the same as for any injured patient: ABC (airway, breathing, and circulation). An airway is provided, ventilation is supported, and possible associated smoke inhalation is treated with 100% O₂ (see Sidebar 329-1). Ongoing burning is extinguished, and smoldering and hot material is removed. All clothing is removed. Chemicals, except powders, are flushed with water; powders should be brushed off before wetting. Burns caused by acids, alkalis, or organic compounds (eg, phenols, cresols, petrochemicals) are flushed with copious amounts of water continuing for at least 20 min after nothing of the original solution seems to remain.

Intravenous fluids: IV fluids are given to patients in shock or with burns > 10% BSA. A 14- to 16-gauge venous cannula is placed in 1 or 2 peripheral veins through unburned skin if possible. Venous cutdown, which has a high risk of infection, is avoided.
Initial fluid volume is guided by treatment of clinically evident shock (see p. 2296). If shock is absent, fluid administration aims to replace the predicted deficit and supply maintenance fluids. The Brooke formula (2 mL/kg/%BSA burned) or Parkland formula (4 mL/kg/%BSA burned) is used to estimate the fluid volume needs in the first 24 h after the burn (not after presentation to the hospital). Both formulas use lactated Ringers’ solution.

For example, in a 100-kg man with a 50% total BSA burn, fluid volume by the Brooke formula would be 2 × 100 × 50 = 10,000 mL. Half of the volume, 5 L, is given in the first 8 h after injury as a constant infusion, and the remaining 5 L is given over the following 16 h. In practice, these formulas are only a starting point, and infusion rates are adjusted based on clinical response. Urine output, typically measured with an indwelling catheter, is the usual indicator of clinical response; the goal is to maintain output at ≥ 30 mL/h in adults and between 0.5 and 1.0 mL/kg/h in children. When giving typical large volumes of fluid, it is also important to avoid fluid overload and consequent heart failure. Clinical parameters, including urine output and signs of shock or heart failure, are recorded at least hourly on a flow chart.

Some clinicians give colloid after 12 h to patients who have larger burns, are very young or very old, or have heart disease and require large fluid volumes.

If urine output is inadequate despite administration of a large volume of crystalloid, consultation with a burn center is necessary. Such patients may respond to an infusion of colloid or other measures. Patients with inadequate urine output despite administration of a large volume of crystalloid are at risk of resuscitation complications including compartment syndromes.

For patients of any age with rhabdomyolysis, fluid should be given to maintain urine output between 0.5 and 1 mL/kg/h. Some authorities recommend alkalinizing the urine by adding 50 mEq NaHCO₃ (one 50-mL ampule of 8.4% solution) to a liter of IV fluid.

**Initial wound care:** After analgesia, the wound is cleaned with soap and water, and all loose debris is removed. Water should be room temperature or warmer to avoid inducing hypothermia. Blisters, except for small ones on palms, fingers, and soles, are debrided. In patients who are to be transferred to a burn center, clean dry dressings can be applied (burn creams interfere with burn wound assessment at the receiving facility), and patients are kept warm and relatively comfortable with IV opioids.

After the wound is cleaned and is assessed by the final treatment provider, burns can be treated topically. For shallow partial-thickness burns, topical treatment alone is usually adequate. All deep partial-thickness burns and full-thickness burns should ultimately be treated with excision and grafting, but in the interim, topical treatments are appropriate.

Topical treatment may be with antimicrobial salves (eg, 1% silver sulfadiazine), commercial dressings incorporating silver (eg, sustained-release nanocrystalline silver dressings), or biosynthetic wound dressings (also called artificial skin products). Topical salves must be changed daily, and silver sulfadiazine may induce transient leukopenia. Silver-impregnated dressings must be kept moist but can be changed only every 3 days. Artificial skin products are not changed routinely but can result in underlying purulence necessitating removal, particularly with deeper wounds. Burned extremities should be elevated.

A tetanus toxoid booster (0.5 mL sc or IM) is given to patients with all but minor burns who have been previously fully vaccinated and who have not received a booster within the past 5 yr. Patients whose booster was more remote or who had not received a full vaccine series are given tetanus immune globulin 250 units IM and concomitant active vaccination (see p. 1299).

Escharotomy (incision of the eschar) of constricting eschars may be necessary to allow adequate expansion of the thorax or perfusion of an extremity. However, constricting eschars rarely threaten extremity viability during the first few hours, so if transfer to a burn center can occur within that time, escharotomy can typically be deferred until then.

**Supportive measures:** Hypothermia is treated (see p. 3274), and pain is relieved. Opioids (eg,
morphine, fentanyl) are always given IV. Treatment of electrolyte deficits may require supplemental Ca, Mg, K, or phosphate (PO₄). Nutritional support (see p. 20) is indicated for patients with burns > 20% BSA or preexisting undernutrition. Support with a feeding tube begins as soon as possible. Parenteral support is rarely necessary.

Hospitalization and referral: After initial treatment and stabilization, the need for hospitalization is assessed. Inpatient treatment, optimally at a burn center, is required for

- Full-thickness burns > 1% BSA
- Partial-thickness burns > 5% BSA
- Burns of the hands, face, feet, or perineum (partial-thickness or deeper)

In addition, hospitalization may be necessary if

- Patients are < 2 yr or > 60 yr.
- Adherence to home care measures is likely to be poor or difficult (eg, if continuous elevation of the hands or feet, usually difficult at home, is required).

Many experts recommend that all burns, except for 1st-degree burns < 1% BSA, be treated by experienced physicians and that brief inpatient care be strongly considered for all burns > 2% BSA. Maintaining adequate analgesia and exercise can be difficult for many patients and caregivers.

Infection: Prophylactic antibiotics are not given. Initial empiric antibiotic treatment for apparent infection during the first 5 days should target staphylococci and streptococci (eg, with vancomycin for inpatients). Infections that develop after 5 days are treated with broad-spectrum antibiotics that are effective against gram-positive and gram-negative bacteria. Antibiotic selection is subsequently adjusted based on culture and sensitivity results.

Surgery: Surgery is indicated for burns that are not expected to heal within 2 wk, which includes most deep partial-thickness burns and all full-thickness burns. Eschars are removed as soon as possible, ideally within 3 days to prevent sepsis and facilitate early wound grafting, which shortens hospitalization and improves the functional result. If burns are extensive and life threatening, the largest eschars are removed first to close as much burn area as early as possible.

After excision, grafting proceeds ideally using partial-thickness autografts (the patient's skin), which are permanent. Autografts can be transplanted as sheets (solid pieces of skin) or meshed grafts (sheets of donor skin that are stretched to cover a larger area by making multiple, regularly spaced, small incisions). Meshed grafts are used in areas where appearance is less of a concern when burns are > 20% BSA and donor skin is scarce. Meshed grafts heal with an uneven gridlike appearance, sometimes with excessive hypertrophic scarring. When burns are > 40% BSA and the supply of autograft material appears insufficient, an artificial dermal regeneration template can be used as temporary coverage. Allografts (viable skin usually from cadaver donors) or xenografts (eg, pig skin) can also be used temporarily; they are rejected, sometimes within 10 to 14 days. Both types of temporary coverage must ultimately be replaced with autografts.

Fasciotomy is done when edema within a muscle compartment elevates compartment pressure > 30 mm Hg.

Physical and occupational therapy: Physical and occupational therapy are begun at admission to help minimize scarring and contractures, particularly for body surfaces with high skin tension and frequent movement (eg, face, hands), and to optimize function. Active and passive range-of-motion exercises...
become easier as the initial edema subsides; they are done once or twice daily. After grafting, exercises are usually suspended for 3 days, then resumed. Extremities affected by deep partial-thickness burns or full-thickness burns are splinted in functional positions as soon as possible and kept splinted continuously (except during exercise) until the graft has been placed, healing has occurred, or both.

**Outpatient treatment:** Outpatient treatment includes keeping burns clean and, to the extent possible, keeping the affected body part elevated. Dressings should be changed daily for burns treated with topical salves. The salve is applied and then covered with a dry nonadherent gauze dressing and compression wraps. Silver dressings should be changed every 3 to 7 days. Dressing change simply involves removing the older dressing and replacing it with new one. Biosynthetic wound dressings should not be changed in the absence of purulence. Biosynthetic dressings should simply be covered with dry gauze, which is changed daily.

Outpatient follow-up visits are scheduled as needed depending on burn severity (eg, for very minor burns, initial visit within 24 h, then subsequent visits every 5 to 7 days). Visits include debridement if indicated, reassessment of burn depth, and evaluation of the need for physical therapy and grafting. Patients should return earlier if they note signs of infection, such as increasing redness extending from the wound edges, increasing purulence and pain, or a change in the appearance of the wound with development of black or red spots. Should these signs occur, medical evaluation should ensue urgently. Outpatient treatment is acceptable for minor burn-wound cellulitis in healthy patients aged 2 to 60 yr; hospitalization is indicated for other infections.
Chapter 330. Electrical and Lightning Injuries

Introduction

Electricity may be from generated sources (e.g., from high- or low-voltage power lines) or atmospheric (lightning).

Electrical Injuries

Electrical injury is damage caused by generated electrical current passing through the body. Symptoms may include skin burns, damage to internal organs and other soft tissues, cardiac arrhythmias, and respiratory arrest. Diagnosis is by history, clinical criteria and selective laboratory testing. Treatment is supportive, with aggressive care for severe injuries.

Although accidental electrical injuries encountered in the home (e.g., touching an electrical outlet or getting shocked by a small appliance) rarely result in significant injury or sequelae, accidental exposure to high voltage causes about 400 deaths annually in the US.

Pathophysiology

Traditional teaching is that the severity of electrical injury depends on Kouwenhoven's factors:

• Type of current (direct [DC] or alternating [AC])
• Voltage and amperage (measures of current strength)
• Duration of exposure (longer exposure increases injury severity)
• Body resistance
• Pathway of current (which determines the specific tissue damaged)

However, electrical field strength, a newer concept, seems to predict injury severity more accurately.

Kouwenhoven's factors: AC changes direction frequently; it is the current usually supplied by household electrical outlets in the US and Europe. DC flows in the same direction constantly; it is the current supplied by batteries. Defibrillators and cardioverters usually deliver DC current. How AC affects the body depends largely on frequency. Low-frequency (50- to 60-Hz) AC is used in US (60 Hz) and European (50 Hz) households; it can be more dangerous than high-frequency AC and is 3 to 5 times more dangerous than DC of the same voltage and amperage. Low-frequency AC causes extended muscle contraction (tetany), which may freeze the hand to the current's source, prolonging exposure. DC is most likely to cause a single convulsive contraction, which often forces the person away from the current's source.

Usually, for both AC and DC, the higher the voltage (V) and amperage, the greater the ensuing electrical injury (for the same duration of exposure). Household current in the US is 110 V (standard electrical outlet) to 220 V (large appliance, such as a dryer). High-voltage (> 500 V) currents tend to cause deep burns, and low-voltage (110 to 220 V) currents tend to cause muscle tetany and freezing to the current's source. The threshold for perceiving DC current entering the hand is about 5 to 10 milliamperes (mA); for AC at 60 Hz, the threshold is about 1 to 10 mA. The maximum amperage that can cause flexors of the arm to contract but that allows release of the hand from the current's source is called the let-go current. Let-go current varies with weight and muscle mass. For an average 70-kg man, let-go current is about 75 mA for DC and about 15 mA for AC.

Low-voltage 60-Hz AC traveling through the chest for a fraction of a second can cause ventricular fibrillation at amperage as low as 60 to 100 mA; for DC, about 300 to 500 mA are required. If current has a direct pathway to the heart (e.g., via a cardiac catheter or pacemaker electrodes), < 1 mA (AC or DC) can cause ventricular fibrillation.
Amount of dissipated heat energy equals amperage\(^2\) × resistance × time; thus, for any given current and duration, tissue with the highest resistance tends to suffer the most damage. Body resistance (measured in ohms/cm\(^2\)) is provided primarily by the skin. Skin thickness and dryness increase resistance; dry, well-keratinized, intact skin averages 20,000 to 30,000 ohms/cm\(^2\). For a thickly calloused palm or sole, resistance may be 2 to 3 million ohms/cm\(^2\); for moist, thin skin, resistance is about 500 ohms/cm\(^2\). Resistance for punctured skin (eg, cut, abrasion, needle puncture) or moist mucous membranes (eg, mouth, rectum, vagina) may be as low as 200 to 300 ohms/cm\(^2\). If skin resistance is high, much electrical energy may be dissipated at the skin, resulting in large skin burns where the energy contacts the skin but less internal damage. If skin resistance is low, skin burns are less extensive or absent, with more electrical energy transmitted to internal structures. Thus, the absence of external burns does not predict the absence of electrical injury, and the severity of external burns does not predict the severity of electrical injury.

Damage to internal tissues depends also on their resistance and additionally on current density (current per unit area; energy is concentrated when the same current flows through a smaller area). For example, as electrical energy flows in an arm (primarily through lower-resistance tissues, eg, muscle, vessels, nerves), current density increases at joints because a significant proportion of the joint's cross-sectional area consists of higher-resistance tissues (eg, bone, tendon), which decreases the area of lower-resistance tissue; thus, damage to the lower-resistance tissues tends to be most severe at joints.

The current's pathway through the body determines which structures are injured. Because AC current continually reverses direction, the commonly used terms "entry" and "exit" are inappropriate; "source" and "ground" are more precise. The hand is the most common source point, followed by the head. The foot is the most common ground point. Current traveling between arm and arm or between arm and foot is likely to traverse the heart, possibly causing arrhythmia. This current tends to be more dangerous than current traveling from one foot to the other. Current to the head may damage the CNS.

**Electrical field strength:** Electrical field strength determines the degree of tissue injury. For instance, 20,000 volts (20 kV) distributed across the body of a man who is about 2 m (6 ft) tall result in a field strength of about 10 kV/m. Similarly, 110 volts, if applied only to 1 cm (eg, across a young child's lip), result in a similar field strength of 11 kV/m; this relationship is why such a low-voltage injury can cause the same severity of tissue injury as some high-voltage injuries applied to a larger area. Conversely, when considering voltage rather than electrical field strength, minor or trivial electrical injuries technically could be classified as high voltage. For example, the shock received from shuffling across a carpet in the winter involves thousands of volts but produces inconsequential injury.

The electrical field effect can cause cell membrane damage (electroporation) even when the energy is insufficient to cause any thermal damage.

**Pathology:** Application of low electrical field strength causes an immediate, unpleasant feeling (being "shocked") but seldom results in serious or permanent injury. Application of high electrical field strength may cause thermal or electrochemical damage to internal tissues. Damage may include hemolysis, protein coagulation, coagulation necrosis of muscle and other tissues, vascular thrombosis, dehydration, and muscle and tendon avulsion. High electrical field strength injuries may result in massive edema, which, as veins coagulate and muscles swell, results in compartment syndromes. Massive edema may also cause hypovolemia and hypotension. Muscle destruction may result in rhabdomyolysis and myoglobinuria. Myoglobinuria, hypovolemia, and hypotension increase risk of acute renal failure. Electrolyte disturbances can also occur. The consequences of organ dysfunction do not always correlate with the amount of tissue destroyed (eg, ventricular fibrillation may occur with relatively little tissue destruction).

**Symptoms and Signs**

Burns may be sharply demarcated on the skin even when current penetrates irregularly into deeper tissues. Severe involuntary muscular contractions, seizures, ventricular fibrillation, or respiratory arrest
due to CNS damage or muscle paralysis may occur. Brain, spinal cord, and peripheral nerve damage may result in various neurologic deficits. Cardiac arrest may occur without burns in bathtub accidents (when a wet [grounded] person contacts a 110-V circuit—eg, from a hair dryer or radio).

Young children who bite or suck on extension cords can burn their mouth and lips. Such burns may cause cosmetic deformities and impair growth of the teeth, mandible, and maxilla. Labial artery hemorrhage, which results when the eschar separates 5 to 10 days after injury, occurs in up to 10% of these young children.

An electrical shock can cause powerful muscle contractions or falls (eg, from a ladder or roof), resulting in dislocations (electrical shock is one of the few causes of posterior shoulder dislocation), vertebral or other fractures, injuries to internal organs, and other blunt force injuries.

**Diagnosis**

- Head to toe examination
- Sometimes ECG, cardiac enzyme measurement, and urinalysis

The person, once away from current, is assessed for cardiac arrest (see p. 2255) and respiratory arrest (see p. 2269). Necessary resuscitation is done. After initial resuscitation, patients are examined from head to toe.

Asymptomatic patients who are not pregnant, have no known heart disorders, and who have had only brief exposure to household current usually have no significant acute internal or external injuries and do not require testing or monitoring. For other patients, ECG, CBC, measurement of cardiac enzymes, and urinalysis (especially to check for myoglobin) should be considered. Patients with impaired consciousness may require CT or MRI.

**Treatment**

- Shutting off current
- Resuscitation
- Analgesia
- Sometimes cardiac monitoring for 6 to 12 h
- Wound care

**Prehospital care:** The first priority is to break contact between the person and the current source by shutting off the current (eg, by throwing a circuit breaker or switch, by disconnecting the device from its electrical outlet). High- and low-voltage power lines are not always easily differentiated, particularly outdoors. **CAUTION:** *If power lines could be high voltage, no attempts to disengage the person should be made until the power is shut off.*

**Resuscitation:** Patients are resuscitated while being assessed. Shock, which may result from trauma or massive burns, is treated (see p. 2295). Standard burn fluid resuscitation formulas, which are based on the extent of skin burns, may underestimate the fluid requirement in electrical burns; thus, such formulas are not used. Instead, fluids are titrated to maintain adequate urine output (about 100 mL/h in adults and 1.5 mL/kg/h in children). For myoglobinuria, alkalinizing the urine and maintaining adequate urine output decrease the risk of renal failure. Surgical debridement of large amounts of muscle tissue may also help to decrease myoglobinuric renal failure.

Severe pain due to an electrical burn is treated by the judicious titration of IV opioids.
Other measures: Asymptomatic patients who are not pregnant, have no known heart disorders, and who have had only brief exposure to household current usually have no significant acute internal or external injuries that can be mitigated by admission and can be discharged. Cardiac monitoring for 6 to 12 h is indicated for patients with the following conditions:

• Arrhythmias

• Chest pain

• Any suggestion of cardiac damage

• Pregnancy (possibly)

• Known heart disorders (possibly)

Appropriate tetanus prophylaxis (see p. 1299) and topical burn wound care (see p. 3246) are required. Pain is treated with NSAIDs or other analgesics.

All patients with significant electrical burns should be referred to a specialized burn unit. Young children with lip burns should be referred to a pediatric orthodontist or oral surgeon familiar with such injuries.

Prevention

Electrical devices that touch or may be touched by the body should be properly insulated, grounded, and incorporated into circuits containing protective circuit-breaking equipment. Ground-fault circuit breakers, which trip when as little as 5 mA of current leaks to ground, are effective and readily available. Outlet guards reduce risk in homes with infants or young children.

Lightning Injuries

Lightning injuries include cardiac arrest, loss of consciousness, and temporary or permanent neurologic deficits; serious burns and internal tissue injury are rare. Diagnosis is clinical; evaluation requires ECG and cardiac monitoring. Treatment is supportive.

Lightning strikes cause about 30 to 50 deaths and several times more injuries annually in the US. Lightning tends to strike tall or isolated objects, including trees, towers, shelters, flagpoles, bleachers, and fences. A person may be the tallest object in an open field. Metal objects and water do not attract lightning but easily transmit electricity once they are hit. Lightning can strike a person directly, or the current can be transferred to the person through the ground or a nearby object. Lightning can also travel from outdoor power or electrical lines to indoor electrical equipment or telephone lines. The force may throw the person several yards.

Because the physics of lightning injury is different from that of generated electrical energy, knowledge of the effects of exposure to household current or high voltage cannot be extrapolated to lightning injuries. For example, damage from lightning injury is not determined by voltage or amperage. Although lightning current contains a large amount of energy, it flows for an extremely brief period (1/10,000 to 1/1000 sec). It rarely, if ever, causes serious skin wounds and seldom causes rhabdomyolysis or serious internal tissue damage, unlike high-voltage and high-current electrical injury from generated sources. Patients may have intracranial hemorrhage resulting from secondary injury or, rarely, from lightning itself.

Lightning can affect the heart but primarily affects the nervous system, damaging the brain, autonomic nervous system, and peripheral nerves.

Symptoms and Signs

The electrical charge can cause asystole or other arrhythmias or cause symptoms of brain dysfunction, such as loss of consciousness, confusion, or amnesia.
Keraunoparalysis is paralysis and mottling, coldness, and pulselessness of the lower and sometimes upper extremities with sensory deficits; the cause is probably sympathetic nervous system injury. Keraunoparalysis is common and usually resolves within several hours, although some degree of permanent paresis occasionally results. Other manifestations of lightning injury may include minor skin burns in a punctate or feathered, branched pattern, tympanic membrane perforation, and, within days, cataracts. Neurologic problems may include confusion, cognitive deficits, and peripheral neuropathy. Neuropsychologic problems (eg, sleep disturbances, attention deficit, memory problems) may occur. Cardiopulmonary arrest at the time of the strike is the most common cause of death. Cognitive deficits, pain syndromes, and sympathetic nervous system damage are the most common long-term sequelae.

**Diagnosis**

- Recognition of cardiac and brain complications

Lightning injuries may be witnessed or unwitnessed. Unwitnessed injuries should be suspected when people found outside during or after storms have amnesia or are unconscious.

ECG may be done if injury is severe. Cardiac enzymes are measured for patients with the following:

- Chest pain
- Abnormal ECG
- Altered mental status

Patients with initially abnormal or deteriorating mental status or focal neurologic deficits compatible with a brain lesion require a head CT or MRI.

**Treatment**

- Supportive care

CPR is initiated for cardiac or respiratory arrest or both. If an automated external defibrillator is available, it should be used.

Supportive care is provided. Fluids are usually restricted to minimize potential brain edema. Most people who have been injured by lightning can be safely discharged unless cardiac effects or brain lesions are suspected.

**Prevention**

Most lightning injuries can be prevented by following lightning safety guidelines. People should know the weather forecast and have backup plans if a storm is predicted. They should have an escape plan involving evacuation to a safer area (ideally a large habitable building) and pay attention to the weather while outdoors so they can implement the escape plan if an unexpected storm comes up. By the time thunder is heard, people are already in danger and should seek shelter (eg, in a building or fully enclosed metal vehicle). Small, open structures, such as gazebos, are not safe. People should not go outdoors until 30 min after the last lightning is seen or thunder is heard. When indoors during an electrical storm, people should avoid plumbing and electrical appliances, stay away from windows and doors, and not use hard-wired telephones, video game consoles, or computers. Cellular phones, personal digital assistants (PDAs), and MP3 players are safe because they do not attract lightning.
Chapter 331. Radiation Exposure and Contamination

Introduction

Ionizing radiation injures tissues variably, depending on factors such as radiation dose, rate of exposure, type of radiation, and part of the body exposed. Symptoms may be local (eg, burns) or systemic (eg, acute radiation sickness). Diagnosis is by history of exposure, symptoms and signs, and sometimes use of radiation detection equipment to localize and identify radionuclide contamination. Management focuses on associated traumatic injuries, decontamination, supportive measures, and minimizing exposure of health care workers. Patients with severe acute radiation sickness receive reverse isolation and bone marrow support. Patients internally contaminated with certain specific radionuclides may receive uptake inhibitors or chelating agents. Prognosis is initially estimated by the time between exposure and symptoms, the severity of those symptoms, and by the lymphocyte count during the initial 24 to 72 h.

Ionizing radiation is emitted by radioactive elements and by equipment such as x-ray and radiation therapy machines.

Types of radiation: Radiation includes

• High-energy electromagnetic waves (x-rays, gamma rays)

• Particles (alpha particles, beta particles, neutrons)

Alpha particles are energetic helium nuclei emitted by some radionuclides with high atomic numbers (eg, plutonium, radium, uranium); they cannot penetrate skin beyond a shallow depth (< 0.1 mm).

Beta particles are high-energy electrons that are emitted from the nuclei of unstable atoms (eg, cesium-137, iodine-131). These particles can penetrate more deeply into skin (1 to 2 cm) and cause both epithelial and subepithelial damage.

Neutrons are electrically neutral particles emitted by a few radionuclides (eg, californium-252) and produced in nuclear fission reactions (eg, in nuclear reactors); they can penetrate deeply into tissues (> 2 cm), where they collide with the nuclei of stable atoms, resulting in emission of energetic protons, alpha and beta particles, and gamma radiation.

Gamma radiation and x-rays are electromagnetic radiation (ie, photons) of very short wavelength that can penetrate deeply into tissue (many centimeters). While some photons deposit all their energy in the body, other photons of the same energy may only deposit a fraction of their energy and others may pass completely through the body without interacting.

Because of these characteristics, alpha and beta particles cause the most damage when the radioactive atoms that emit them are within the body (internal contamination) or, in the case of beta-emitters, directly on the body; only tissue in close proximity to the radionuclide is affected. Gamma rays and x-rays can cause damage distant from their source and are typically responsible for acute radiation syndromes (ARS—see p. 3255).

Measurement of radiation: Conventional units of measurement include the roentgen, rad, and rem. The roentgen (R) is a unit of exposure measuring the ionizing ability of x- or gamma radiation in air. The radiation absorbed dose (rad) is the amount of that radiation energy absorbed per unit of mass. Because biologic damage per rad varies with radiation type (eg, it is higher for neutrons than for x- or gamma radiation), the dose in rad is corrected by a quality factor; the resulting effective dose unit is the roentgen equivalent in man (rem). Outside the US and in the scientific literature, SI units are used, in which the rad is replaced by the gray (Gy) and the rem by the sievert (Sv); 1 Gy = 100 rad and 1 Sv = 100 rem. The rad and rem (and hence Gy and Sv) are essentially equal (ie, the quality factor equals 1) when describing gamma or beta radiation.
Types of exposure: Radiation exposure may involve

- Contamination
- Irradiation

Radioactive contamination is the unintended contact with and retention of radioactive material, usually as a dust or liquid. Contamination may be

- External
- Internal

External contamination is that on skin or clothing, from which some can fall or be rubbed off, contaminating other people and objects. Internal contamination is unintended radioactive material within the body, which it may enter by ingestion, inhalation, or through breaks in the skin. Once in the body, radioactive material may be transported to various sites (eg, bone marrow), where it continues to emit radiation until it is removed or decays. Internal contamination is more difficult to remove. Although internal contamination with any radionuclide is possible, historically, most cases in which contamination posed a significant risk to the patient involved a relatively small number of radionuclides: hydrogen-3, cobalt-60, strontium-90, cesium-137, iodine-131, radium-226, uranium-235, uranium-238, plutonium-238, plutonium-239, polonium-210, and americium-241.

Irradiation is exposure to radiation but not radioactive material (ie, no contamination is involved). Radiation exposure can occur without the source of radiation (eg radioactive material, x-ray machine) being in contact with the person. When the source of the radiation is removed or turned off, exposure ends. Irradiation can involve the whole body, which, if the dose is high enough, can result in systemic symptoms and radiation syndromes (see p. 3255), or a small part of the body (eg, from radiation therapy), which can result in local effects. People do not emit radiation (ie, become radioactive) following irradiation.

Sources of exposure: Sources may be naturally occurring or man-made (see Table 331-1).

People are constantly exposed to low levels of naturally occurring radiation called background radiation. Background radiation comes from cosmic radiation and from radioactive elements in the air, water, and earth. Cosmic radiation is concentrated at the poles by the earth's magnetic field and attenuated by the atmosphere. Thus, exposure is greater for people living at high latitudes, at high altitudes, or both and during airplane flights. Radioactive elements, particularly uranium and its radioactive progeny and potassium-40, are present in many rocks and minerals. These elements end up in various substances, including food, water, and construction materials. Radon, a radioactive gas resulting from the decay of uranium, typically accounts for about two thirds of naturally occurring radiation dose to the US population. In the US, people receive an average effective dose of about 3 millisieverts (mSv)/yr from natural sources. However, in some parts of the world, people receive between 5 and 10 mSv/yr. The doses from natural background radiation are far too low to cause radiation injuries, although they may increase the risk of cancer.

In the US, people receive on the average about 3 mSv/yr from man-made sources, the vast majority of which involve medical imaging. Imaging exposure tends to be highest from CT and nuclear cardiology procedures. However, medical diagnostic procedures rarely impart doses sufficient to cause radiation injury, although they may increase the risk of cancer. Exceptions may include certain prolonged fluoroscopically guided interventional procedures (eg, endovascular reconstruction, vascular embolization, cardiac radiofrequency ablation); these procedures have caused injuries to skin and underlying tissues. Radiation therapy commonly causes injury to some normal tissues near the target tissue.

[Table 331-1, Average Annual Radiation Exposure in the Us]
A small portion of public exposure results from radiation accidents and fallout from nuclear weapons testing. Accidents may involve industrial irradiators, industrial radiography sources, and nuclear reactors. These accidents commonly result from failure to follow safety procedures (eg, interlocks being bypassed). Radiation injuries have also been caused by lost or stolen medical or industrial sources containing radionuclides. People seeking medical care for these injuries may be unaware that they were exposed to radiation.

Radioactive material has escaped from nuclear power plants, including the Three Mile Island plant in Pennsylvania in 1979 and at Chernobyl in Ukraine in 1986. Exposure from Three Mile Island was minimal; people living within 1.6 km of the plant received only about 0.08 mSv. However, people living in 2 villages near the Chernobyl plant received an average dose of about 300 mSv, and people at the Chernobyl plant itself received significantly higher doses. More than 30 workers and emergency responders died, and many more were injured. Low-level contamination from that accident was detected as far away as Europe, Asia, and even the US. The average cumulative exposure for the general population in various affected regions of Belarus, Russia, and Ukraine over a 20-yr period after the accident is estimated to be between 10 and 30 mSv.

Another significant radiation event was the detonation of 2 atomic bombs over Japan in August 1945, which caused about 110,000 deaths from the immediate trauma of the blast and heat. A much smaller number of deaths resulted later from radiation-induced illnesses.

While several criminal cases of intentional contamination of individuals have been reported, radiation exposure to a population through terrorist activities has not occurred but is a concern. A possible scenario involves the use of a device to contaminate an area by dispersing radioactive material (a radiation dispersal device that uses conventional explosives is referred to as a dirty bomb). Other terrorist scenarios include using a hidden radiation source to expose unsuspecting people to large doses of radiation, attacking a nuclear reactor or radioactive material storage facility, and detonating a nuclear weapon.

Pathophysiology

Ionizing radiation can damage DNA, RNA, and proteins directly, but more often the damage to these molecules is indirect, caused by highly reactive free radicals generated by radiation's interaction with intracellular water molecules. Large doses of radiation can cause cell death, and lower doses may interfere with cellular proliferation. Damage to other cellular components can result in progressive tissue hypoplasia, atrophy, and eventually fibrosis.

Factors affecting response: Biologic response to radiation varies with

- Tissue radiosensitivity
- Dose
- Duration of exposure

Cells and tissues differ in their radiosensitivity. In general, cells that are undifferentiated and those that have high mitotic rates (eg, stem cells) are particularly vulnerable to radiation. Because radiation preferentially depletes rapidly dividing stem cells over the more resistant mature cells, there is typically a latent period between radiation exposure and overt radiation injury. Injury does not manifest until a significant fraction of the mature cells die of natural senescence and, due to loss of stem cells, are not replaced.

Cellular sensitivities in approximate descending order from most to least sensitive are

- Lymphoid cells
- Germ cells
• Proliferating bone marrow cells
• Intestinal epithelial cells
• Epidermal stem cells
• Hepatic cells
• Epithelium of lung alveoli and biliary passages
• Kidney epithelial cells
• Endothelial cells (pleura and peritoneum)
• Nerve cells
• Bone cells
• Muscle and connective tissue cells

The severity of radiation injury depends on the dose and the length of time over which it is delivered. A single rapid dose is more damaging than the same dose given over weeks or months. Dose response also depends on the fraction of the body exposed. Significant illness is certain, and death is possible, after a whole-body dose > 4.5 Gy delivered over a short time interval; however, 10s of Gy can be well tolerated when delivered over a long period to a small area of tissue (eg, for cancer therapy).

Other factors can increase the sensitivity to radiation injury. Children are more susceptible to radiation injury because they have a higher rate of cellular proliferation. People who are homozygous for the ataxia-telangiectasia gene exhibit greatly increased sensitivity to radiation injury. Disorders, such as connective tissue disorders and diabetes, may increase the sensitivity to radiation injury. Chemotherapeutic agents also increase the sensitivity to radiation injury.

**Cancer and teratogenicity:** Genetic damage to somatic cells may result in malignant transformation, and damage to germ cells raises the possibility of transmissible genetic defects.

Ionizing radiation can cause cancer; whole-body exposure to 1 Gy increases the average adult's lifetime risk of cancer death from 25% to about 30%, a 20% relative risk increase but only a 5% absolute risk increase. The cancer risk due to commonly encountered doses (ie, from background radiation and typical imaging tests—see [Table 343-1 on p. 3403](#)) is much less. Children are more susceptible because they have a higher number of future cell divisions and a longer life span during which cancer may manifest; CT of the abdomen done in a 1-yr-old child is estimated to increase the estimated lifetime absolute risk of developing cancer by 0.18%. Radionuclides that are incorporated into specific tissues are potentially carcinogenic at those sites (eg, radioactive iodine increases risk of thyroid cancer).

The fetus is exceptionally susceptible to high-dose radiation injury. However, at doses < 100 mGy, teratogenic effects are unlikely; the fetal risk from radiation at doses from imaging tests that pregnant women might typically undergo is small compared with the overall risk of birth defects and the potential diagnostic benefit of the examination.

Damage to reproductive cells has been shown to cause birth defects in progeny of severely irradiated animals. However, hereditary effects have not been found in children of radiation-exposed humans, including survivors of the atomic bomb attacks in Japan.

**Symptoms and Signs**

Clinical manifestations depend on whether radiation exposure involves the whole body (acute radiation syndrome) or is limited to a small portion of the body (focal radiation injury).
**Acute radiation syndromes (ARS):** After the whole body, or a large portion of the body, receives a high dose of radiation, several distinct syndromes may occur:

- Cerebrovascular syndrome
- GI syndrome
- Hematopoietic syndrome

These syndromes have 3 different phases:

- Prodromal phase (0 to 2 days after exposure): Lethargy and GI symptoms (nausea, anorexia, vomiting, diarrhea) are possible.
- Latent asymptomatic phase (0 to 31 days after exposure)
- Overt systemic illness phase: Illness is classified by the main organ system affected.

Which syndrome develops, how severe it is, and how quickly it progresses depend on radiation dose (see Table 331-2). The symptoms and time course are fairly consistent for a given dose of radiation and thus can help estimate radiation exposure.

The **cerebrovascular syndrome**, the dominant manifestation of extremely high whole-body doses of radiation (> 30 Gy), is always fatal. The prodrome develops within minutes to 1 h after exposure. There is little or no latent phase. Patients develop tremors, seizures, ataxia, and cerebral edema and die within hours to 1 or 2 days.

The **GI syndrome** is the dominant manifestation after whole-body doses of about 6 to 30 Gy. Prodromal symptoms, often marked, develop within about 1 h and resolve within 2 days. During the latent period of 4 to 5 days, GI mucosal cells die. Cell death is followed by intractable nausea, vomiting, and diarrhea, which lead to severe dehydration and electrolyte imbalances, diminished plasma volume, and vascular collapse. Necrosis of intestine may also occur, predisposing to bacteremia and sepsis. Death is common. Patients receiving > 10 Gy may have cerebrovascular symptoms (suggesting a lethal dose). Survivors also have the hematopoietic syndrome.

The **hematopoietic syndrome** is the dominant manifestation after whole-body doses of about 1 to 6 Gy and consists of a generalized pancytopenia. A mild prodrome may begin after 1 to 6 h, lasting 24 to 48 h. Bone marrow stem cells are significantly depleted, but mature blood cells in circulation are largely unaffected (circulating lymphocytes are an exception, and lymphopenia may be evident within hours to days after exposure). As the cells in circulation die by senescence, they are not replaced in sufficient numbers, resulting in pancytopenia. Thus, patients remain asymptomatic during a latent period of up to 4 1/2 wk after a 1-Gy dose as marrow production falls. Risk of various infections is increased as a result of the neutropenia (most prominent at 2 to 4 wk) and decreased antibody production. Petechiae and mucosal bleeding result from thrombocytopenia, which develops within 3 to 4 wk and may persist for months. Anemia develops slowly, because preexisting RBCs have a longer life span than WBCs and platelets. Survivors have an increased incidence of radiation-induced cancer, including leukemia.

**Cutaneous radiation injury** (CRI) is injury to the skin and underlying tissues from acute radiation doses as low as 3 Gy (see Table 331-3). CRI can occur with ARS or with focal radiation exposure and ranges from mild transient erythema to necrosis. Delayed effects (> 6 mo after exposure) include hyperpigmentation and hypopigmentation, progressive fibrosis,

[Table 331-2, Effects of Whole-Body Irradiation from External Radiation or Internal Absorption]

[Table 331-3, Focal Radiation Injury*]
and diffuse telangiectasia. Thin atrophic skin can be easily damaged by mild mechanical trauma. Exposed skin is at increased risk of squamous cell carcinoma. In particular, the possibility of radiation exposure should be considered when patients present with a painful nonhealing skin burn without a history of thermal injury.

**Focal injury:** Radiation to almost any organ can have both acute and chronic adverse effects (see Table 331-3). In most patients, these adverse effects result from radiation therapy (see p. 1064). Other common sources of exposure include inadvertent contact with unsecured food irradiators, radiotherapy equipment, x-ray diffraction equipment, and other industrial or medical radiation sources capable of producing high dose rates. Also, overexposure to x-rays during medical fluoroscopy is a source of exposure and of CRI in particular. Radiation-induced sores or ulcers may take months or years to fully develop. Patients with these injuries often have severe pain.

**Diagnosis**

- Symptoms, severity, and symptom latency
- Serial absolute lymphocyte counts

Diagnosis is by history of exposure, symptoms and signs, and laboratory testing. The onset, time course, and severity of symptoms can help determine radiation dose and thus also help triage patients relative to their likely consequences. However, some prodromal symptoms (eg, nausea, vomiting, diarrhea, tremors) are nonspecific, and causes other than radiation should be considered. Many patients without enough exposure to cause acute radiation sickness may present with similar, nonspecific symptoms, particularly after a terrorist attack or reactor accident, when anxiety is high.

After acute radiation exposure, CBC with differential and calculation of absolute lymphocyte count is done and repeated 24, 48, and 72 h after exposure to estimate the initial radiation dose and prognosis (see Table 331-4). The relationship between dose and lymphocyte counts can be altered by physical trauma, which can shift lymphocytes from the interstitial spaces into the vasculature, raising the lymphocyte count. This stress-related increase is transient and typically resolves within 24 to 48 h after the physical insult. CBC is repeated weekly to monitor marrow activity and as needed based on the clinical course.

**Contamination:** When contamination is suspected, the entire body should be surveyed with a thin window Geiger-Muller probe

[Table 331-4. Relationship Between Absolute Lymphocyte Count in Adults at 48 H, Radiation Dose,* and Prognosis]

attached to a survey meter (Geiger counter) to identify the location and extent of external contamination. Additionally, to detect possible internal contamination, the nares, ears, mouth, and wounds are wiped with moistened swabs that are then tested with the counter. Urine, feces, and emesis should also be tested for radioactivity if internal contamination is suspected.

**Prognosis**

**Without medical care**, the LD50/60 (dose expected to be fatal to 50% of patients within 60 days) for whole-body radiation is about 3 Gy; 6 Gy exposure is nearly always fatal. When exposure is < 6 Gy, survival is possible and is inversely related to total dose. Time to death decreases as the dose increases. Death may occur within hours to a few days in patients with the cerebral syndrome and usually within 2 days to several weeks in patients with the GI syndrome. In patients with the hematopoietic syndrome, death may occur within 4 to 8 wk because of a supervening infection or massive hemorrhage. Patients exposed to whole-body doses < 2 Gy should fully recover within 1 mo, although long-term sequelae (eg, cancer) may occur.

**With medical care**, the LD50/60 is 6 Gy and occasional patients have survived exposures of up to 10 Gy. Significant comorbidities, injuries, and burns worsen prognosis.
Treatment

- Treatment of severe traumatic injuries or life-threatening medical conditions first
- Minimization of health care worker radiation exposure and contamination
- Treatment of external and internal contamination
- Sometimes specific measures for particular radionuclides
- Supportive care

Radiation exposure may be accompanied by physical injuries (eg, from burn, blast, fall); associated trauma is more immediately life threatening than radiation exposure and must be treated expeditiously (see p. 3190). Trauma resuscitation of the seriously injured takes priority over decontamination efforts and must not be delayed awaiting special radiation management equipment and personnel. Standard universal precautions, as routinely used in trauma care, adequately protect the critical care team.

Extensive, reliable information about principles of radiation injuries, including management, is available at the US Department of Health and Human Services Radiation Event Medical Management web site (http://remm.nlm.gov). This information can be downloaded to a personal computer or personal digital assistant (PDA) in case Internet connectivity is lost during a radiation incident.

Preparation: The Joint Commission mandates that all hospitals have protocols and that personnel have training to deal with patients contaminated with hazardous material, including radioactive material. Identification of radioactive contamination on patients should prompt their isolation in a designated area (if practical), decontamination, and notification of the hospital radiation safety officer, public health officials, hazardous material teams, and law enforcement agencies as appropriate to investigate the source of radioactivity.

Treatment area surfaces may be covered with plastic sheeting to aid in facility decontamination; this preparation should never take precedence over provision of medical stabilization. Waste receptacles (labeled "Caution, Radioactive Material"), sample containers, and Geiger counters should be readily available. All equipment that has come into contact with the room or with the patient (including ambulance equipment) should remain isolated until lack of contamination has been verified. An exception is a mass casualty situation, during which lightly contaminated critical equipment such as helicopters, ambulances, trauma rooms, and x-ray, CT, and surgical facilities, should be quickly decontaminated to the extent possible and returned to service.

Personnel involved in treating or transporting the patient should follow standard precautions, wearing caps, masks, gowns, gloves, and shoe covers. Used gear should be placed in specially marked bags or containers. Dosimeter badges should be worn to monitor radiation exposure. Personnel may be rotated to minimize exposure, and pregnant personnel should be excluded from the treatment area.

Due to the low exposure rates anticipated from most contaminated patients, medical staff members caring for typical patients are unlikely to receive doses in excess of the occupational limit of 0.05 Gy/yr. Even in the extreme case of radiation casualties from the Chernobyl nuclear reactor accident, medical personnel who treated patients in the hospital received < 0.01 Sv. Several authoritative sources suggest that a dose of up to at least 0.5 Gy may be considered an acceptable risk for lifesaving activity.

External decontamination: Typical sequence and priorities are

- Removing clothing and external debris
- Decontaminating wounds before intact skin
- Cleaning the most contaminated areas first
Using radiation survey meter to monitor progress of decontamination

Continuing decontamination until areas are at < 2 to 3 times background radiation levels or there is no significant reduction between decontamination efforts

Clothes are removed carefully to minimize the spread of contamination and placed in labeled containers. Clothing removal eliminates about 90% of external contamination. Foreign objects should be considered contaminated until cleared by a radiation survey meter.

Contaminated wounds are decontaminated before intact skin; they are irrigated with saline and gently scrubbed with a surgical sponge. Minimal debridement of wound edges may be done if there is residual contamination after multiple attempts at cleaning. Debridement beyond the wound margin is not required, although embedded radioactive shrapnel should be removed and placed in a lead container.

If necessary, consultation is available 24 h/day from the Department of Energy Radiation Emergency Assistance Center/Training Site (REAC/TS) at (865) 576-1005 and www.orau.gov/reacts or the Centers for Disease Control and Prevention (CDC) at (888) 246-2675 and www.bt.cdc.gov/radiation/.

Contaminated skin and hair are washed with lukewarm water and mild detergent until radiation survey meter measurements indicate < 2 to 3 times normal background radiation levels or until successive washings do not significantly reduce contamination levels. All wounds are covered during washing to prevent the introduction of radioactive material. Scrubbing may be firm but should not abrade the skin. Special attention is usually required for fingernails and skinfolds. Hair that remains contaminated is removed with scissors or electric clippers; shaving is avoided. Inducing sweating (eg, placing a rubber glove over a contaminated hand) may help remove residual skin contamination.

Burns are rinsed gently because scrubbing may increase injury severity; subsequent dressing changes help remove residual contamination.

Decontamination is not necessary for patients who have been irradiated by an external source and are not contaminated.

**Internal decontamination:** Ingested radioactive material should be removed promptly by induced vomiting or lavage if exposure is recent. Frequent mouth rinsing with saline or dilute hydrogen peroxide is indicated for oral contamination. Exposed eyes should be decontaminated by directing a stream of water or saline laterally to avoid contaminating the nasolacrimal duct.

The urgency and importance of using more specific treatment measures depend on the type and amount of the radionuclide, its chemical form and metabolic characteristics (eg, solubility, affinity for specific target organs), the route of contamination (eg, inhalation, ingestion, contaminated wounds), and the efficacy of the therapeutic method. The decision to treat internal contamination requires knowledge of the potential risks; consultation with a specialist (eg, CDC or REAC/TS) is recommended.

Current methods to remove radioactive contaminants from the body (decorporation) include

- Saturation of the target organ (eg, potassium iodide [KI] for iodine isotopes)
- Chelation at the site of entry or in body fluids followed by rapid excretion (eg, Ca or zinc diethyleneetriamine penta-acetate [DTPA] for americium, californium, plutonium, and yttrium)
- Acceleration of the metabolic cycle of the radionuclide by isotope dilution, (eg, water for hydrogen-3)
- Precipitation of the radionuclide in the intestinal lumen followed by fecal excretion (eg, oral Ca or aluminum phosphate solutions for strontium-90)
- Ion exchange in the GI tract, (eg, Prussian blue for cesium-137, rubidium-82, thallium-201)
Because a serious nuclear power reactor accident that released fission products into the environment could expose large groups of people to radioiodine, decorporation using oral KI has been studied in great detail. KI is > 95% effective when given at the optimal time (shortly before or immediately after exposure) and dose. However, effectiveness diminishes significantly within several hours after exposure. KI can be given either in tablet form or as a supersaturated solution (dosage: adult, 130 mg; age 3 to 18 yr, 65 mg; age 1 to 36 mo, 32 mg; age < 1 mo, 16 mg). KI is effective only for internal contamination with radioactive iodides and has no benefit in internal contamination with other radioactive elements. Most other drugs used for decorporation are much less effective than KI and reduce the dose to the patient only by 25 to 75%.

Specific management: Symptomatic treatment is given as needed and includes managing shock and hypoxia, relieving pain and anxiety, and giving sedatives (lorazepam 1 to 2 mg IV q 2 to 6 h) to control seizures, antiemetics (metoclopramide 10 to 20 mg IV q 4 to 6 h; prochlorperazine 5 to 10 mg IV q 4 to 6 h; ondansetron 4 to 8 mg IV q 8 to 12 h) to control vomiting, and antidiarrheal agents (kaolin/pectin 30 to 60 mL po with each loose stool; loperamide 4 mg po initially, then 2 mg po with each loose stool) for diarrhea.

There is no specific treatment for the cerebrovascular syndrome. It is universally fatal; care should address patient comfort.

The GI syndrome is treated with aggressive fluid resuscitation and electrolyte replacement. Parenteral nutrition should be initiated to promote bowel rest. In febrile patients, broad-spectrum antibiotics (eg, imipenem 500 mg IV q 6 h) should be initiated immediately. Septic shock from overwhelming infection remains the most likely cause of death.

Management of the hematopoietic syndrome is similar to that of bone marrow hypoplasia and pancytopenia of any cause. Blood products should be transfused to treat anemia and thrombocytopenia, and hematopoietic growth factors (granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor) and broad-spectrum antibiotics should be given to treat neutropenia and neutropenic fever, respectively (see p. 951). Patients with neutropenia should also be placed in reverse isolation. With a whole-body radiation dose > 4 Gy, the probability of bone marrow recovery is poor, and hematopoietic growth factors should be given as soon as possible. Stem cell transplantation has had limited success but should be considered for exposure > 7 to 10 Gy (see p. 1132).

Radiation-induced sores or ulcers that fail to heal satisfactorily may be repaired by skin grafting or other surgical procedures.

Aside from regular monitoring for signs of certain disorders (eg, ophthalmic examination for cataracts, thyroid function studies for thyroid disorders), there is no specific monitoring, screening, or treatment for specific organ injury or cancer.

Prevention

Protection from radiation exposure is accomplished by avoiding contamination with radioactive material and minimizing the duration of exposure, maximizing the distance from the source of radiation, and shielding the source. During imaging procedures that involve ionizing radiation and especially during radiation therapy for cancer, the most susceptible parts of the body (eg, female breasts, gonads, thyroid) that are not being treated or imaged are shielded by lead aprons or blocks.

Although shielding of personnel with lead aprons or commercially available transparent shields effectively reduces exposure to low-energy scattered x-rays from diagnostic imaging studies, these aprons and shields are almost useless in reducing exposure to the high-energy gamma rays produced by radio-nuclides that would likely be used in a terrorist incident or be released in a nuclear power plant accident. In such cases, measures that can minimize exposure include using standard precautions, undergoing decontamination efforts, and maintaining distance from contaminated patients when not actively providing care. All personnel working around radiation sources should wear dosimeter badges if they are at risk for exposures > 10% of the maximum permissible occupational dose (0.05 Sv).

Public response: After widespread high-level environmental contamination from a nuclear power plant...
accident or intentional release of radioactive material, exposure can be reduced either by

• Sheltering in place

• Evacuating the contaminated area

The better approach depends on many event-specific variables, including the elapsed time since initial release, whether release has stopped or is ongoing, weather conditions, availability and type of shelter, and evacuation conditions (e.g., traffic, transportation availability). The public should follow the advice of local public health officials as broadcast on TV or radio as to which response option is best. If sheltering is recommended, a concrete or metal structure, particularly one below grade (e.g., in a basement) is best.

Consistent and concise messages from public health officials can help reduce unnecessary panic and reduce the number of emergency department visits from people at low risk, thus keeping the emergency department from being overwhelmed. Such a communication plan should be developed prior to any event. A plan to counsel distressed people is also recommended.

People living within 16 km (10 miles) of a nuclear power plant should have ready access to KI tablets. These tablets can be obtained from local pharmacies and some public health agencies.

Preventive drugs: Radioprotective drugs, such as thiol compounds with radical scavenging properties, have been shown to reduce mortality when given before or at the time of irradiation. Amifostine is a powerful injectable radioprotective agent in this category; it prevents xerostomia in patients undergoing radiation therapy. Although thiol compounds have good efficacy in radioprotection, these compounds cause adverse effects, such as hypotension, nausea, vomiting, and allergic reactions. Other experimental drugs and chemicals have also been shown to increase survival rates in animals if given before or during irradiation. However, these drugs can be very toxic at doses necessary to provide substantial protection, and none currently are recommended.
Chapter 332. Heat Illness

Introduction

Exposure to warm environments affects many physiologic functions and may cause dehydration. Most people experience mild but uncomfortable symptoms; however, effects may range from cramps and edema to syncope, heat exhaustion, and heatstroke. Core temperature is elevated in some types of heat illness. People with dehydration (see pp. 822 and 2806) may have tachycardia, tachypnea, and orthostatic hypotension. CNS dysfunction suggests heatstroke, the most serious disorder; confusion and lethargy may further impair the ability to escape the heat and rehydrate.

Pathophysiology

Heat input comes from

- The environment
- Metabolism

Heat output occurs through the skin via the following:

- Radiation
- Evaporation (eg, via sweat)
- Convection

The contribution of each of these mechanisms varies with environmental temperature and humidity. Radiation predominates at room temperature, but as environmental temperature approaches body temperature, evaporation becomes more important, providing essentially 100% of cooling at > 35°C. However, high humidity greatly limits evaporative cooling (see Heatstroke on p. 3265).

Heat output is modulated by changes in cutaneous blood flow and sweat production. Cutaneous blood flow is 200 to 250 mL/min at normal temperatures but increases to 7 to 8 L/min with heat stress, requiring a marked increase in cardiac output. Also, heat stress increases sweat production from negligible to > 2 L/h; thus, significant dehydration can occur rapidly. Because sweat contains electrolytes, electrolyte loss may be substantial. However, prolonged exposure triggers physiologic changes to accommodate heat load (acclimatization); eg, sweat Na levels are 40 to 100 mEq/L in people who are not acclimatized but decrease to 10 to 70 mEq/L in acclimatized people.

The body can compensate for large variations in heat load, but significant or prolonged exposure to heat increases core temperature. Modest, transient core temperature elevations are tolerable, but severe elevations (typically > 41°C) lead to protein denaturation and, especially during hard work in the heat, release of inflammatory cytokines (eg, tumor necrosis factor-α, IL-1β). As a result, cellular dysfunction occurs and the inflammatory cascade is activated, leading to dysfunction of most organs and activation of the coagulation cascade. These pathophysiologic processes are similar to those of multiple organ dysfunction syndrome (see p. 2293), which follows prolonged shock.

Compensatory mechanisms include an acute-phase response by other cytokines that moderate the inflammatory response (eg, by stimulating production of proteins that decrease production of free radicals and inhibit release of proteolytic enzymes). Also, increased core temperature triggers expression of heat-shock proteins. These proteins transiently enhance heat tolerance by poorly understood mechanisms (eg, possibly by preventing protein denaturation) and by regulation of cardiovascular responses. With prolonged or extreme temperature elevation, compensatory mechanisms are overwhelmed or malfunction, allowing inflammation and multiple organ dysfunction syndrome to occur.

Etiology
Heat disorders are caused by some combination of increased heat input and decreased output (see Table 332-1).

Excess heat input typically results from strenuous exertion, high environmental temperatures, or both. Medical disorders and use of stimulant drugs can increase heat production.

Impaired cooling can result from obesity, high humidity, wearing heavy clothing, and anything that impairs sweating or evaporation of sweat.

Clinical effects of heat illnesses are exacerbated by the following:

- Inability to tolerate increased cardiovascular demands (eg, due to aging, heart failure, chronic kidney disease, respiratory disorders, or liver failure)
- Dehydration
- Electrolyte disturbance
- Use of certain drugs (see Table 332-1)

The elderly and the very young and people with cardiovascular disorders or electrolyte depletion (eg, due to diuretic use) are at highest risk.

Prevention

Common sense is the best prevention. Physicians should recommend the following measures:

- During excessively hot weather, the elderly and the young should not remain in unventilated residences without air-conditioning.
- Children should not be left in automobiles in the hot sun.

[Table 332-1, Common Factors Contributing to Heat Disorders]

- If possible, strenuous exertion in a very hot environment or an inadequately ventilated space should be avoided, and heavy, insulating clothing should not be worn.

- Weight loss after exercise or work can be used to monitor dehydration; people who lose 2 to 3% of their body weight should be reminded to drink extra fluids and should be within 1 kg of starting weight before the next day's exposure. If people lose > 4%, activity should be limited for 1 day.

- If exertion in the heat is unavoidable, fluid (often lost imperceptibly in very hot, very dry air) should be replaced by drinking water frequently, and evaporation should be facilitated by wearing open-mesh clothing or by using fans.

Thirst is a poor indicator of dehydration during exertion; fluids should be drunk every few hours regardless of thirst. However, over-hydration must be avoided; significant hyponatremia (see p. 823) has occurred in endurance athletes who drink very frequently during exercise. Plain water is adequate for hydration during most activity; cool water is absorbed more readily. Special hydrating solutions (eg, sports drinks) are not required, but their flavoring enhances consumption, and their modest salt content is helpful if fluid requirements are high.

Drinking fluids and consuming generously salted foods should be encouraged. Laborers or others who sweat heavily can lose ≥ 20 g of salt/day, making heat cramps more likely; such people need to replace the Na loss with drink and food. A palatable drink providing about 20 mmol of salt/L may be prepared by adding about 5 g (a rounded teaspoon) of table salt to 20 L (about 5 gallons) of any sweetened beverage prepared from a powdered mix. People on low-salt diets should increase salt intake.
Successively and incrementally increasing the level and amount of work done in the heat eventually results in acclimatization, which enables people to work safely at temperatures that were previously intolerable or life threatening. Progressing from 15 min/day of moderate activity (enough to stimulate sweating) during a hot time of day to 90 min of vigorous activity over 10 to 14 days is typically adequate. Acclimatization markedly increases the amount of sweat (and hence cooling) produced at a given level of exertion and markedly decreases the electrolyte content of sweat. Acclimatization significantly decreases risk of a heat illness.

**Heat Cramps**

Heat cramps are exertion-induced muscle contractions that occur during or after exertion in the heat.

Although exertion may induce cramps during cool weather, such cramps are not heat related and probably reflect lack of fitness. In contrast, heat cramps can occur in physically fit people who sweat profusely and replace lost water but not salt, thereby causing hyponatremia. Heat cramps are common among the following:

- Manual laborers (eg, engine room personnel, steel workers, roofers, miners)
- Military trainees
- Athletes

Cramping is abrupt, usually occurring in muscles of the extremities. Severe pain and carpopedal spasm may incapacitate the hands and feet. Temperature is normal, and other findings are unremarkable. The cramp usually lasts minutes to hours. Diagnosis is by history and clinical evaluation.

**Treatment**

Cramps may be relieved immediately by firm passive stretching of the involved muscle (eg, plantar dorsiflexion for a calf cramp). Fluids and electrolytes should be replenished orally (1 to 2 L water containing 10 g [2 level tsp] salt or sufficient amounts of a commercial sports drink) or IV (1 to 2 L 0.9% saline solution). Adequate conditioning, acclimatization, and appropriate management of salt balance help prevent cramps.

**Heat Exhaustion**

Heat exhaustion is a non-life-threatening clinical syndrome of weakness, malaise, nausea, syncope, and other nonspecific symptoms caused by heat exposure. Thermoregulation is not impaired. IV fluids and electrolyte replacement are needed.

Heat exhaustion is caused by water and electrolyte imbalance due to heat exposure, with or without exertion.

Rarely, severe heat exhaustion after hard work may be complicated by rhabdomyolysis, myoglobinuria, acute renal failure, and disseminated intravascular coagulation.

**Symptoms and Signs**

Symptoms are often vague, and patients may not realize that heat is the cause. Symptoms may include weakness, dizziness, headache, nausea, and sometimes vomiting. Syncope due to standing for long periods in the heat (heat syncope) is common and may mimic cardiovascular disorders. On examination, patients appear tired and are usually sweaty and tachycardic. Mental status is typically normal, unlike in heatstroke. Temperature is usually normal and, when elevated, usually does not exceed 40° C.

**Diagnosis**
Clinical evaluation

Diagnosis is clinical and requires exclusion of other possible causes (e.g., hypoglycemia, acute coronary syndrome, various infections). Laboratory testing is required only if needed to rule out such disorders.

Treatment

• IV fluid and electrolyte replacement

Treatment involves removing patients to a cool environment, having them lie flat, and giving IV fluid and electrolyte replacement therapy, typically using 0.9% saline solution; oral rehydration does not provide sufficient electrolytes. Rate and volume of rehydration are guided by age, underlying disorders, and clinical response. Replacement of 1 to 2 L at 500 mL/h is often adequate. Elderly patients and patients with heart disorders may require only slightly lower rates; patients with suspected hypovolemia may require higher rates initially. External cooling measures (see p. 3266) are usually not required. However, if patients with heat exhaustion have a core temperature of ≥ 40°C, measures may be taken to reduce it.

Heatstroke

Heatstroke is hyperthermia accompanied by a systemic inflammatory response causing multiple organ dysfunction and often death. Symptoms include temperature > 40°C and altered mental status; sweating is often absent. Diagnosis is clinical. Treatment is rapid external cooling, IV fluid resuscitation, and support as needed for organ dysfunction.

Heatstroke occurs when thermoregulatory mechanisms do not function and core temperature increases substantially. Inflammatory cytokines are activated, and multiple organ dysfunction may develop. Endotoxin from GI flora may also play a role. Organ dysfunction may occur in the CNS, skeletal muscle (rhabdomyolysis), liver, kidneys, lungs (acute respiratory distress syndrome), and heart. The coagulation cascade is activated, sometimes causing disseminated intravascular coagulation. Hyperkalemia and hypoglycemia may occur.

There are 2 variants (see Table 332-2):

• Classic

• Exertional

Classic heatstroke takes 2 to 3 days of exposure to develop. It occurs during summer heat waves, typically in elderly, sedentary people with no air-conditioning and often with limited access to fluids.

Exertional heatstroke occurs abruptly in healthy active people (e.g., athletes, military recruits, factory workers). Intense exertion in a hot environment causes a sudden massive heat load that the body cannot modulate. Rhabdomyolysis is common; renal failure and coagulopathy are somewhat more likely and severe.

A syndrome similar to heatstroke may occur after using certain drugs (e.g., cocaine, phencyclidine [PCP], amphetamines, monoamine oxidase inhibitors). Usually, an overdose is required, but exertion and environmental conditions can be additive.

Malignant hyperthermia (see p. 3266) can result from exposure to some anesthetics in genetically predisposed patients. Neuroleptic malignant syndrome (see p. 3268) can develop in patients taking antipsychotics. These disorders are life threatening; malignant hyperthermia has a high mortality rate.

Symptoms and Signs

Global CNS dysfunction, ranging from confusion to delirium, seizures, and coma, is the hallmark. Tachycardia, even when the patient is supine, and tachypnea are common. In classic
Table 332-2: Some Differences Between Classic and Exertional Heatstroke

heatstroke, the skin is hot and dry. In exertional heatstroke, sweating is relatively common. In both,
temperature is > 40° C and may be > 46° C.

Diagnosis

- Clinical evaluation, including core temperature measurement
- Laboratory testing for organ dysfunction

Diagnosis is usually clear from a history of exertion and environmental heat. Heatstroke is differentiated
from heat exhaustion by presence of the following:

- CNS dysfunction
- Temperature > 40° C

When the diagnosis of heatstroke is not obvious, other disorders that can cause CNS dysfunction and
hyperthermia should be considered. These disorders include the following:

- Acute infection (eg, sepsis, malaria, meningitis, toxic shock syndrome)
- Drugs
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Status epilepticus (interictal)
- Stroke
- Thyroid storm

Laboratory testing includes CBC, PT, PTT, electrolytes, BUN, creatinine, Ca, CK, and hepatic profile to
evaluate organ function. A urethral catheter is placed to obtain urine, which is checked for occult blood by
dipstick, and to monitor output. Tests to detect myoglobin are unnecessary. If a urine sample contains no
RBCs but has a positive reaction for blood and if serum CK is elevated, myoglobinuria is likely. A urine
drug screen may be helpful. Continual monitoring of core temperature, usually by rectal or esophageal
probe, is desired.

Prognosis

Mortality rate is significant but varies markedly with age, underlying disorders, maximum temperature,
and, most importantly, duration of hyperthermia and promptness of cooling. About 20% of survivors have
residual brain damage, regardless of intervention. In some patients, renal insufficiency persists.
Temperature may be labile for weeks.

Treatment

- Aggressive cooling
- IV cooled normal saline

The importance of rapid recognition and effective, aggressive cooling cannot be overemphasized. Cooling
methods that do not cause shivering or cutaneous vasoconstriction are preferred, although ice-
soaked towels and ice water immersion are effective.

**Cooling techniques:** Evaporative cooling is comfortable and convenient and considered the most rapid method by some experts. During the process, patients are continually wetted with water, and the skin is fanned and vigorously massaged to promote blood flow. A spray hose and larger fans are best and may be used for large groups of people in the field. Comfortable, tepid (eg, 30° C) water is adequate because evaporation causes cooling; cold or ice water is not needed. Cool water immersion in a pond or stream can also be used in the field.

Ice packs applied to the axillae and groin can be used but not as the sole cooling method. In life-threatening cases, packing a patient in ice, with close monitoring, has been advocated to rapidly reduce core temperature.

**Other measures:** The patient is admitted to an ICU, and IV hydration with 0.9% saline solution is begun as in heat exhaustion (see p. 3265). Theoretically, 1 to 2 L of IV 0.9% saline cooled to 4° C, as used in protocols to induce hypothermia after cardiac arrest, may also help cooling. Organ dysfunction and rhabdomyolysis are treated (see elsewhere in THE MANUAL). An injectable benzodiazepine (eg, lorazepam, diazepam) may be used aggressively to prevent agitation and seizures (which increase heat production); seizures may occur during cooling. Because vomiting and aspiration of gastric contents are possible, measures to protect the airway may be required. Severely agitated patients may require paralysis and mechanical ventilation.

Platelets and fresh frozen plasma may be required for severe disseminated intravascular coagulation. IV NaHCO₃ to alkalinize the urine may help prevent nephrotoxicity if myoglobinuria is present. IV Ca salts may be necessary to treat hyperkalemic cardiotoxicity. Vasoconstrictors used to treat hypotension may reduce cutaneous blood flow and decrease heat loss. Hemodialysis may be required. Antipyretics (eg, acetaminophen) are of no value. Dantrolene is used to treat anesthetic-induced malignant hyperthermia but has no proven benefit for other causes of severe hyperthermia.

**Malignant Hyperthermia**

Malignant hyperthermia is a life-threatening elevation in body temperature usually resulting from a hypermetabolic response to concurrent use of a depolarizing muscle relaxant and a potent, volatile inhalational general anesthetic. Manifestations can include muscle rigidity, hyperthermia, tachycardia, tachypnea, rhabdomyolysis, and respiratory and metabolic acidosis. Diagnosis is clinical; patients at risk can be tested for their susceptibility. The highest priority treatments are rapid cooling and aggressive supportive measures.

The muscle relaxant involved is usually succinylcholine; the inhalational anesthetic is most often halothane, but other anesthetics (eg, isoflurane, sevoflurane, desflurane) may also be involved. This drug combination causes a similar reaction in some patients with muscular dystrophy and myotonia.

**Pathophysiology**

Malignant hyperthermia affects about 1/20,000 people. Susceptibility is inherited, with autosomal dominant inheritance and variable penetrance. Most often, the causative mutation affects the ryanodine receptor of skeletal muscle; however, > 22 other causative mutations have been identified.

The mechanism may involve anesthetic-induced potentiation of Ca exit from the sarcoplasmic reticulum of skeletal muscle in susceptible patients. As a result, Ca-induced biochemical reactions are accelerated, causing severe muscle contractions and elevation of the metabolic rate.

**Complications:** Hyperkalemia, respiratory and metabolic acidosis, hypocalcemia, and rhabdomyolysis with CK elevation and myoglobinemia may occur, as may coagulation abnormalities (particularly disseminated intravascular coagulation [DIC]). In older patients and patients with comorbidities, DIC may increase the risk of death.

**Symptoms and Signs**
Malignant hyperthermia may develop during anesthesia or the early postoperative period. Clinical presentation varies, depending on the drugs used and the patient's susceptibility. Muscular rigidity, especially in the jaw, is often the first sign, followed by tachycardia, other arrhythmias, tachypnea, acidosis, shock, and hyperthermia. Temperature is usually ≥ 40° C and may be extremely high (ie, > 43° C). Urine may appear brown or bloody if rhabdomyolysis and myoglobinuria have occurred.

Diagnosis

- Clinical evaluation
- Testing for complications
- Susceptibility testing for people at risk

The diagnosis is suspected by the appearance of typical symptoms and signs within 10 min to, occasionally, several hours after inhalational anesthesia is begun. Early diagnosis can be facilitated by prompt recognition of jaw rigidity, tachypnea, tachycardia, and increased end-tidal CO₂.

There are no immediately confirmatory tests, but patients should have testing for complications, including ECG, blood tests (CBC with platelets, electrolytes, BUN, creatinine, CK, Ca, PT, PTT, fibrinogen, D-dimer), and urine testing for myoglobinuria.

Other diagnoses must be excluded. Peri-operative sepsis may cause hyperthermia but rarely as soon after induction. Inadequate anesthesia can cause increased muscle tone and tachycardia but not elevated temperature. Thyroid storm and pheochromocytoma rarely manifest immediately after anesthetic induction.

Susceptibility testing: Testing for susceptibility to malignant hyperthermia is recommended for people at risk based on a family history of the disorder or a personal history of a severe or incompletely characterized previous adverse reaction to general anesthesia. The caffeine halothane contracture test (CHCT) is the most accurate. It measures the response of a muscle tissue sample to caffeine and halothane. This test can be done only at certain referral centers and requires excision of about 2 g of muscle tissue. Genetic testing has limited sensitivity (about 30%) but is quite specific; patients in whom a mutation is identified do not require the CHCT.

Treatment

- Rapid cooling and supportive measures
- Dantrolene

It is critical to cool patients as quickly and effectively as possible (see p. 3266) to prevent damage to the CNS and also to give patients supportive treatment to correct metabolic abnormalities. Outcome is best when treatment begins before muscular rigidity becomes generalized and before development of rhabdomyolysis, severe hyperthermia, and DIC. Dantrolene (2.5 mg/kg IV q 5 min as needed, up to a total dose of 10 mg/kg) should be given in addition to the usual physical cooling measures. In some patients, tracheal intubation, paralysis, and induced coma are required to control symptoms and provide support. Benzodiazepines given IV, often in high doses, can be used to control agitation. Malignant hyperthermia has a high mortality and may not respond to even early and aggressive therapy.

Prevention

Local or regional anesthesia is preferred to general anesthesia when possible. Potent inhalational anesthetics and depolarizing muscular relaxants should be avoided in patients who are susceptible. Nondepolarizing muscular blockers are the preferred preanesthetic drugs. Preferred anesthetics include barbiturates (eg, thiopental), etomidate, and propofol. Dantrolene should be available at the bedside.
Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is characterized by altered mental status, muscle rigidity, hyperthermia, and autonomic hyperactivity that occur when certain neuroleptic drugs are used. Clinically, neuroleptic malignant syndrome resembles malignant hyperthermia. Diagnosis is clinical. Treatment is aggressive supportive care.

Among patients taking neuroleptic drugs, about 0.02 to 3% develop neuroleptic malignant syndrome. Patients of all ages can be affected.

Etiology

Many antipsychotics and antiemetics can be causative (see Table 332-3). The factor common to all drug causes is a decrease in dopaminergic transmission; however, the reaction is not allergic but rather idiosyncratic. Etiology and mechanism are unknown. Risk factors appear to include high drug doses, rapid dose increases, parenteral administration, and switching from one potentially causative drug to another.

Neuroleptic malignant syndrome can also occur in patients withdrawing from levodopa or dopamine agonists.

Symptoms and Signs

Symptoms begin most often during the first 2 wk of treatment but may occur earlier or after many years. The 4 characteristic symptoms usually develop over a few days and often in the following order:

• Altered mental status: Usually the earliest manifestation is a change in mental status, often an agitated delirium, and may progress to lethargy or unresponsiveness (reflecting encephalopathy).

• Motor abnormalities: Patients may have generalized, severe muscle rigidity (sometimes with simultaneous tremor, leading to cog-wheel rigidity), or, less often, dystonias, chorea, or other abnormalities. Reflex responses tend to be decreased.

[Table 332-3. Drugs that Can Cause Neuroleptic Malignant Syndrome]

• Hyperthermia: Temperature is usually > 38° C and often > 40° C.

• Autonomic hyperactivity: Autonomic activity is increased, tending to cause tachycardia, arrhythmias, tachypnea, and labile hypertension.

Diagnosis

• Clinical evaluation

• Exclusion of other disorders and complications

The diagnosis should be suspected based on clinical findings. Early manifestations can be missed because mental status changes may be overlooked or dismissed in patients with psychosis.

Other disorders can cause similar findings. For example:

• Serotonin syndrome (see p. 3269) tends to cause rigidity, hyperthermia, and autonomic hyperactivity, but it is usually caused by SSRIs, and patients typically have hyperreflexia. Also, temperature elevations and muscle rigidity are usually less severe than in neuroleptic malignant syndrome, and nausea and diarrhea may precede serotonin syndrome.

• Malignant hyperthermia (see p. 3266) and withdrawal of intrathecal baclofen can cause findings similar
to those of neuroleptic malignant syndrome, but they are usually easily differentiated by history.

- Systemic infections, including sepsis (see p. 2299), pneumonia, and CNS infection, can cause altered mental status, hyperthermia, and tachypnea and tachycardia, but generalized motor abnormalities are not expected. Also, in neuroleptic malignant syndrome, unlike most infections, altered mental status and motor abnormalities tend to precede hyperthermia.

There are no confirmatory tests, but patients should have testing for complications, including serum electrolytes, BUN, creatinine, glucose, Ca, Mg, and CK, urine myoglobin, and usually neuroimaging and CSF analysis. EEG may be done to exclude nonconvulsive status epilepticus.

Treatment

- Rapid cooling, control of agitation, and other aggressive supportive measures

The causative drug is stopped and complications are treated supportively, usually in an ICU. Severe hyperthermia is treated very aggressively, mainly with physical cooling (see p. 3266). Some patients may require tracheal intubation and induced coma. Benzodiazepines, given IV in high doses, can be used to control agitation. Adjunctive drug therapy can be used, although efficacy has not been shown in clinical trials. Dantrolene (0.25 to 2 mg/kg IV q 6 to 12 h; maximum of 10 mg/kg/24 h) can be given for hyperthermia. Bromocriptine (2.5 mg q 6 to 8 h) or, alternatively, amantadine (100 to 200 mg q 12 h) can be given po or via NGT to help restore some dopaminergic activity. This condition may not respond to even rapid and aggressive therapy, and mortality in treated cases is about 10 to 20%.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening condition resulting from increased CNS serotonergic activity that is usually drug related. Symptoms may include mental status changes, hyperthermia, and autonomic and neuromuscular hyperactivity. Diagnosis is clinical. Treatment is supportive.

Serotonin syndrome can occur with therapeutic drug use, self-poisoning, or, most commonly, unintended drug interactions when 2 serotonergic drugs are used (see Table 332-4). It can occur in all age groups.

Complications in severe serotonin syndrome can include metabolic acidosis, rhabdomyolysis, seizures, acute renal failure, and disseminated intravascular coagulation. Causes probably include severe hyperthermia and muscle activity.

Symptoms and Signs

Manifestations can range widely in severity. They can be grouped into the following categories:

- Mental status alterations: Anxiety, agitation and restlessness, easy startling, delirium

- Autonomic hyperactivity: Tachycardia, hypertension, hyperthermia, diaphoresis, shivering, vomiting, diarrhea

- Neuromuscular hyperactivity: Tremor, muscle hypertonia or rigidity, myoclonus, hyperreflexia, clonus (including ocular clonus), extensor plantar responses

Neuromuscular hyperactivity may be more pronounced in the lower than the upper extremities.

Symptoms usually resolve in 24 h, but symptoms may last longer after use of drugs that have a long half-life or active metabolites (eg, monoamine oxidase inhibitors, SSRIs).

Diagnosis
Clinical criteria

Diagnosis is clinical. Various explicit criteria have been proposed.

The Hunter criteria are currently preferred because of ease of use and high accuracy (almost 85% sensitivity and > 95% specificity compared with diagnosis by a toxicologist). These criteria require that patients have taken a serotonergic drug and have one of the following:

- Muscle hypertonia
- Spontaneous clonus
- Tremor plus hyperreflexia
- Ocular or inducible clonus, plus either agitation, diaphoresis, or temperature > 38°C

Systemic infections, drug or alcohol withdrawal syndromes, and toxicity caused by sympathomimetic or anticholinergic drugs should also be considered in the differential diagnosis. Differentiation of serotonin syndrome from neuroleptic malignant syndrome may be difficult because symptoms (eg, muscle rigidity, hyperthermia, autonomic hyperactivity, altered mental status) overlap. Clues to serotonin syndrome include use of serotonergic drugs, rapid onset (eg, within 24 h), and hyperreflexia, in contrast to the often decreased reflex responses in neuroleptic malignant syndrome.

[Table 332-4, Drugs that Can Cause Serotonin Syndrome]

(see p. 3268) may be difficult because symptoms (eg, muscle rigidity, hyperthermia, autonomic hyperactivity, altered mental status) overlap. Clues to serotonin syndrome include use of serotonergic drugs, rapid onset (eg, within 24 h), and hyperreflexia, in contrast to the often decreased reflex responses in neuroleptic malignant syndrome.

There are no confirmatory tests, but patients should have testing to exclude other disorders (eg, CSF analysis for possible CNS infection, urine testing for drugs of abuse). Also, some tests (eg, serum electrolytes, platelet count, renal function tests, CK, PT, testing for urine myoglobin) may be necessary to identify complications in severe serotonin syndrome.

Treatment

- Supportive measures
- Sometimes cyproheptadine

All serotonergic drugs should be stopped. Mild symptoms are often relieved with sedation using a benzodiazepine. If symptoms rapidly resolve, patients should be observed for at least several hours. Most will require hospitalization for further testing, treatment, and monitoring.

In severe cases, admission to an ICU is required. Hyperthermia is treated by cooling (see p. 3266). Neuromuscular blockade with appropriate sedation, muscle paralysis, and other supportive measures may be necessary. Drug treatment of autonomic abnormalities (eg, hypertension, tachycardia) should be with shorter-acting drugs (eg, nitroprusside, esmolol) because autonomic effects can change rapidly.

If symptoms persist despite supportive measures, the serotonin antagonist cyproheptadine can be given orally or, after crushing, via NGT (12 mg, then 2 mg q 2 h until response occurs). Dantrolene is not recommended.

Consultation with a toxicologist is encouraged and can be accomplished by calling the United States Poison Control Network (1-800-222-1222) or accessing the WHO's list of international poison centers (www.who.int/ipcs/poisons/centre/directory/en).
Chapter 333. Cold Injury

Introduction

Exposure to cold may cause decreased body temperature (hypothermia) and focal soft-tissue injury. Tissue injury with freezing is frostbite. Tissue injury without freezing includes frostnip, immersion foot, and chilblains. Treatment is rewarming and selective, usually delayed, surgical treatment for injured tissues.

Susceptibility to all cold injury is increased by exhaustion, undernutrition, dehydration, hypoxia, impaired cardiovascular function, and contact with moisture or metal.

Prevention

Prevention is crucial. Several layers of warm clothing and protection against moisture and wind are important even when the weather does not seem to threaten cold injury. Clothing that remains insulating when wet (eg, made of wool or polypropylene) should be worn. Gloves and socks should be kept as dry as possible; insulated boots that do not impede circulation should be worn in very cold weather. A warm head covering is also important. Consuming ample fluids and food helps sustain metabolic heat production. Paying attention to when body parts become cold or numb and immediately warming them may prevent cold injury.

Nonfreezing Tissue Injuries

Acute or chronic injuries without freezing of tissue may result from cold exposure.

Frostnip: The mildest cold injury is frostnip. Affected areas are numb, swollen, and red. Treatment is rewarming, which causes pain and itching. Rarely, mild hypersensitivity to cold persists for months to years.

Immersion (trench) foot: Prolonged exposure to wet cold can cause immersion foot. Peripheral nerves and the vasculature are usually injured; muscle and skin tissue may be injured in severe cases.

Initially, the foot is pale, edematous, clammy, cold, and numb. Tissue maceration may occur if patients walk extensively. Rewarming causes hyperemia, pain, and often hypersensitivity to light touch, which persist for 6 to 10 wk. Skin may ulcerate, or a black eschar may develop. Autonomic dysfunction is common, with increased or decreased sweating, vasomotor changes, and local hypersensitivity to temperature change. Muscle atrophy and dysesthesia or anesthesia may occur and become chronic.

Immersion foot can be prevented by not wearing tight-fitting boots, keeping feet and boots dry, and changing socks frequently. Immediate treatment is rewarming by immersing the affected area in warm (40 to 42°C) water, followed by sterile dressings. Chronic neuropathic symptoms are difficult to treat; amitriptyline may be tried (see p. 1632).

Chilblains (pernio): Localized areas of erythema, swelling, pain, and pruritus result from repeated exposure to dry cold; the mechanism is unclear. Blistering or ulceration may occur. Chilblains most commonly affects the fingers and pretibial area and is self-limited. Occasionally, symptoms recur.

Pernio is often used to refer to a vasculitic disorder most common among young females with a history of Raynaud's syndrome. Endothelial and neuronal damage results in vasospasm and exaggerated sympathetic response when exposed to cold. Nifedipine 20 mg po tid may be effective for refractory pernio. Sympatholytic drugs may also help.

Frostbite

Frostbite is injury due to freezing of tissue. Initial presentation may be deceptively benign. Skin may appear white or blistered and is numb; rewarming causes substantial pain. Gangrene may develop. Severely damaged tissue may autoamputate. Treatment is rewarming in warm (40 to 42°C) water and local care. Surgical amputation is occasionally necessary, but a decision, often
guided by imaging results, should usually be delayed until after definitive demarcation of necrotic tissue.

Frostbite usually occurs in extreme cold, especially at high altitude, and is aggravated by hypothermia. Distal extremities and exposed skin are affected most often.

Ice crystals form within or between tissue cells, essentially freezing the tissue and causing cell death. Adjacent unfrozen areas are at risk because local vasoconstriction and thrombosis can cause endothelial and ischemic damage. With reperfusion during rewarming, inflammatory cytokines (eg, thromboxanes, prostaglandins) are released, exacerbating tissue injury.

**Symptoms and Signs**

The affected area is cold, hard, white, and numb. When warmed, the area becomes blotchy red, swollen, and painful. Blisters form within 4 to 6 h, but the full extent of injury may not be apparent for several days. Blisters filled with clear serum indicate superficial damage; blood-filled, proximal blisters indicate deep damage and likely tissue loss. Superficial damage heals without residual tissue loss. Freezing of deep tissue causes dry gangrene with a hard black carapace over healthy tissue. Wet gangrene, which is gray, edematous, and soft, is less common. Wet gangrene is characterized by infection, but dry gangrene is less likely to become infected. Depth of tissue loss depends on duration and depth of freezing. Severely damaged tissue may autoamputate. Compartment syndrome may develop. All degrees of frostbite may cause long-term neuropathic symptoms: sensitivity to cold, excessive sweating, faulty nail growth, and numbness (symptoms resembling those of complex regional pain syndrome—see p. 1633—although any relationship is speculative).

**Diagnosis**

- Clinical evaluation

Diagnosis is based on clinical findings. However, because many of the early characteristics of frostbite (eg, coldness, numbness, white or red color, blisters) are also characteristic of nonfreezing cold injuries, differentiation of frostbite may require repeated observation until more specific characteristics (eg, black carapace, gangrene) develop.

**Treatment**

- Rewarming in warm (40 to 42° C) water

- Supportive measures

- Local wound care

- Sometimes delayed surgery

**Prehospital care:** In the field, frostbitten extremities should be rewarmed rapidly by totally immersing the affected area in water that is tolerably warm to the touch (40 to 42° C, ideally about 40.5° C). Because the area is numb, rewarming with an uncontrolled dry heat source (eg, fire, heating pad) risks burns. Rubbing may further damage tissue and is avoided. The longer an area remains frozen, the greater the ultimate damage may be. However, thawing the feet is inadvisable if a patient must walk any distance to receive care because thawed tissue is particularly sensitive to the trauma of walking and, if refrozen, will be more severely damaged than if left frozen. If thawing must be delayed, the frozen area is gently cleaned, dried, and protected in sterile compresses. Patients are given analgesics, if available, and the whole body is kept warm.

**Acute care:** Once the patient is in the hospital, core temperature is stabilized and extremities are rapidly rewarmed in large containers of circulating water kept at about 40.5° C; 15 to 30 min is usually adequate. Thawing is often mistakenly ended prematurely because pain may be severe during rewarming. Parenteral analgesics, including opioids, may be used. Patients are encouraged to move the affected part
gently during thawing. Large, clear blisters are left intact or aspirated using sterile technique. Hemorrhagic blisters are left intact to avoid secondary desiccation of deep dermal layers. Broken vesicles are debrided. If there is no perfusion after thawing, thrombolytic (fibrinolytic) therapy is considered.

Anti-inflammatory measures (eg, topical aloe vera q 6 h, ibuprofen 400 mg po q 8 h, ketorolac 30 to 60 mg IV) probably help. Affected areas are left open to warm air, and extremities are elevated to decrease edema. Anticoagulants, IV low molecular weight dextran, and intra-arterial vasodilators (eg, reserpine, tolazoline) have no proven clinical benefit. Phenoxybenzamine (10 to 60 mg po once/day), a long-acting α-blocker, may theoretically decrease vasospasm and improve blood flow.

Preventing infection is fundamental; streptococcal prophylaxis (eg, with penicillin) is sometimes provided. If wet gangrene is present, broad-spectrum antibiotics are used. Tetanus toxoid is given if vaccination is not up to date. If tissue damage is severe, tissue pressure is monitored.

**Ongoing care:** Adequate nutrition is important to sustain metabolic heat production.

Imaging tests (eg, radionuclide scanning, MRI, microwave thermography, laser-Doppler flowmetry) can help assess circulation, determine tissue viability, and thus guide treatment. MRI and particularly magnetic resonance angiography may establish the line of demarcation before clinical demarcation and thus make earlier surgical debridement or amputation possible. However, whether earlier surgery improves long-term outcome is unclear. Usually, surgery is delayed as long as possible because the black carapace is often shed, leaving viable tissue. Patients with severe frostbite are warned that many weeks of observation may be required before demarcation and the extent of tissue loss become apparent.

Whirlpool baths at 37° C 3 times/day followed by gentle drying, rest, and time are the best long-term management. No totally effective treatment for the long-lasting symptoms of frostbite (eg, numbness, hypersensitivity to cold) is known, although chemical or surgical sympathectomy may be useful for late neuropathic symptoms.

**Hypothermia**

Hypothermia is a core body temperature < 35°C. Symptoms progress from shivering and lethargy to confusion, coma, and death. Mild hypothermia requires a warm environment and insulating blankets (passive rewarming). Severe hypothermia requires active rewarming of the body surface (eg, with forced-air warming systems, radiant sources) or core (eg, inhalation, heated infusion and lavage, extracorporeal blood rewarming).

Primary hypothermia causes about 600 deaths each year in the US. Hypothermia also has a significant and underrecognized effect on mortality risk in cardiovascular and neurologic disorders.

**Etiology**

Hypothermia results when body heat loss exceeds body heat production. Hypothermia is most common during cold weather or immersion in cold water, but it may occur in warm climates when people lie immobile on a cool surface (eg, when they are intoxicated) or after very prolonged immersion in swimming-temperature water (eg, 20 to 24° C). Wet clothing and wind chill increase risk of hypothermia.

Conditions that cause loss of consciousness, immobility, or both (eg, trauma, hypoglycemia, seizure disorders, stroke, drug or alcohol intoxication) are common predisposing factors. The elderly and the very young also are at high risk. The elderly often have diminished temperature sensation and impaired mobility and communication, resulting in a tendency to remain in an overly cool environment. These impairments, combined with diminished subcutaneous fat, contribute to hypothermia in the elderly—sometimes even indoors in cool rooms. The very young have similarly diminished mobility and communication and have an increased surface area/mass ratio, which enhances heat loss. Intoxicated people who lose consciousness in a cold environment are likely to become hypothermic.

**Pathophysiology**
Hypothermia slows all physiologic functions, including cardiovascular and respiratory systems, nerve conduction, mental acuity, neuromuscular reaction time, and metabolic rate. Thermoregulation ceases below about 30° C; the body must then depend on an external heat source for rewarming. Renal cell dysfunction and decreased levels of ADH lead to production of a large volume of dilute urine (cold diuresis). Diuresis plus fluid leakage into the interstitial tissues causes hypovolemia. Vasoconstriction, which occurs with hypothermia, may mask hypovolemia, which then manifests as sudden shock or cardiac arrest during rewarming (rewarming collapse) when peripheral vasculature dilates.

Immersion in cold water can trigger the diving reflex, which involves reflex vasoconstriction in visceral muscles; blood is shunted to essential organs (eg, heart, brain). The reflex is most pronounced in small children and may help protect them. Also, hypothermia due to total immersion in near-freezing water may protect the brain from hypoxia by decreasing metabolic demands. The decreased demand probably accounts for the occasional survival after prolonged cardiac arrest due to extreme hypothermia.

Symptoms and Signs

Intense shivering occurs initially, but it ceases below about 31° C, allowing body temperature to drop more precipitously. CNS dysfunction progresses as body temperature decreases; people do not sense the cold. Lethargy and clumsiness are followed by confusion, irritability, sometimes hallucinations, and eventually coma. Pupils may become unreactive. Respirations and heartbeat slow and ultimately cease. Initially, sinus bradycardia is followed by slow atrial fibrillation; the terminal rhythm is ventricular fibrillation or asystole. However, these rhythms are potentially less ominous than in normothermia.

Diagnosis

- Core temperature measurement
- Consideration of intoxication, myxedema, sepsis, and trauma

Diagnosis is by core temperature, not oral temperature. Electronic thermometers are preferred; many standard mercury thermometers have a lower limit of 34° C. Rectal and esophageal probes are most accurate.

Laboratory tests include CBC, glucose, electrolytes, BUN, creatinine, and ABGs. ABGs are not corrected for low temperature. ECG typically shows J (Osborn) waves (see Fig. 333-1) and interval prolongation (PR, QRS, QT), although these findings are not always present. Causes are sought. If the cause is unclear, alcohol level is measured, and drug screening and thyroid function tests are done. Sepsis and occult head or skeletal trauma must be considered.

Prognosis

Patients who have been immersed in icy water for 1 h or (rarely) longer have sometimes been successfully rewarmed without permanent brain damage (see p. 3281), even when core temperature was 13.7° C or when pupils were unreactive. Outcome is difficult to predict and cannot be based on the Glasgow Coma Scale. Grave prognostic markers include evidence of cell lysis (hyperkalemia > 10 mEq/L), intravascular thrombosis (fibrinogen < 50 mg/dL), and presence of a nonperfusing cardiac rhythm (ventricular fibrillation or asystole). For a given degree and duration of hypothermia, children are more likely to recover than adults.

Treatment

- Drying and insulation
- Fluid resuscitation
- Active rewarming unless hypothermia is mild, accidental, and uncomplicated

The first priority is to prevent further heat loss by removing wet clothing and insulating the patient.
Subsequent measures depend on how severe hypothermia is and whether cardiovascular instability or cardiac arrest is present. Returning patients to a normal temperature is less urgent in hypothermia than in severe hyperthermia. For stable patients, elevation of core temperature by 1° C/h is acceptable.

If hypothermia is mild and thermoregulation is present (indicated by shivering and temperature typically 31 to 35° C), insulation with heated blankets and warm fluids to drink are adequate.

Fluid resuscitation is essential for hypovolemia. Patients are given 1 to 2 L of 0.9% saline solution (20 mL/kg for children) IV; the solution is heated if possible to 45° C. More is given as needed to maintain perfusion.

Active rewarming is required if patients have cardiovascular instability, temperature < 32.2° C, hormone insufficiency (such as hypoadrenalism or hypothyroidism), or hypothermia secondary to trauma, toxins, or predisposing disorders. If body temperature is at the warmer end of the range, external rewarming with forced hot air enclosures may be used. Patients with lower temperatures, particularly those with low BP or cardiac arrest, require core rewarming.

Core rewarming options include

- Inhalation
- IV infusion
- Lavage
- Extracorporeal core rewarming (ECR)

Inhalation of heated (40 to 45° C), humidified O₂ via mask or endotracheal tube eliminates respiratory heat loss and can add 1 to 2° C/h to the rewarming rate.

IV crystalloids or blood should be heated to 40 to 42° C, especially with massive volume resuscitations.

Heated lavage of the bladder or GI tract transfers minimal heat, although closed thoracic lavage through 2 thoracostomy tubes is very efficient in severe cases. Peritoneal lavage with 40 to 45° C dialysate requires 2 catheters with outflow suction and is especially useful with severely hypothermic patients who have rhabdomyolysis, toxin ingestions, or electrolyte abnormalities.

There are 4 types of ECR: hemodialysis, venovenous, arteriovenous, and cardiopulmonary bypass. ECR measures require a prearranged protocol with appropriate specialists. Although they are intuitively attractive and heroic, these measures are not routinely available, and they are not commonly used in most hospitals.

CPR is not done if patients have a perfusing rhythm, even if pulses are not palpable. Fluids are given, and active rewarming is done. Hypotension and bradycardia are expected when core temperature is low and, if due solely to hypothermia, need not be aggressively treated. Patients with a nonperfusing rhythm require cardiopulmonary resuscitation. Chest compressions and endotracheal intubation are done. Defibrillation is difficult if body temperature is low; one attempt may be made, but if ineffective, further attempts are deferred until temperature reaches > 28° C. Advanced life support should be continued until temperature reaches 32° C unless obviously lethal injuries or disorders are present. However, advanced cardiac life-support drugs (eg, antiarrhythmics, vasopressors, inotropes) are usually not given. Low-dose dopamine (1 to 5 μg/kg/min) or other catecholamine infusions are typically reserved for patients who have disproportionately severe hypotension and who do not respond to fluid resuscitation and rewarming. Severe hyperkalemia (> 10 mEq/L) during resuscitation typically indicates a fatal outcome and can guide resuscitation efforts.
Chapter 334. Altitude Sickness

Altitude sickness (AS) includes several related syndromes caused by decreased O$_2$ availability at high altitudes. Acute mountain sickness (AMS), the mildest form, is headache plus one or more systemic manifestations. High-altitude cerebral edema (HACE) is encephalopathy in people with AMS. High-altitude pulmonary edema (HAPE) is a form of noncardiogenic pulmonary edema causing severe dyspnea and hypoxemia. AMS may occur in recreational hikers and skiers in mountains. Diagnosis is clinical. Treatment of mild AMS is with analgesics and acetazolamide. Severe syndromes require descent and supplemental O$_2$ if available. In addition, dexamethasone may be useful for HACE, and nifedipine may be useful for HAPE.

As altitude increases, atmospheric pressure decreases while the percentage of O$_2$ in air remains constant; thus, the partial pressure of O$_2$ decreases with altitude and, at 5800 m (19,000 ft), is about one half that at sea level.

Most people can ascend to 1500 to 2000 m (5000 to 6500 ft) in one day without problems, but about 20% of those who ascend to 2500 m (8000 ft) and 40% of those who ascend to 3000 m (10,000 ft) develop some form of AS. Rate of ascent, maximum altitude reached, and sleeping altitude influence the likelihood of developing the disorder.

**Risk factors:** Effects of high altitude vary greatly among individuals. But generally, risk is increased by

- Going too high too fast
- Exertion

Risk is greater in people who have had previous AS and in those who live at low altitude (< 900 m [< 3000 ft]). Young children and young adults are probably more susceptible. Disorders such as diabetes, coronary artery disease, and mild COPD are not risk factors for AS, but hypoxia may adversely affect these disorders. Physical fitness is not protective.

**Pathophysiology**

Acute hypoxia (eg, as occurs during rapid ascent to high altitude in an unpressurized aircraft) alters CNS function within minutes. However, AS results from the body's neurohumoral and hemodynamic responses to hypoxia and develops over hours to days.

The CNS and lungs are primarily affected. In both, elevated capillary pressure, capillary leakage, and consequent edema formation probably occur.

In the lungs, hypoxia-induced elevation of pulmonary artery pressure causes interstitial and alveolar pulmonary edema, resulting in impaired oxygenation. Small-vessel hypoxic vasoconstriction is patchy, causing overperfusion with elevated pressure, capillary wall damage, and capillary leakage in less constricted areas. Various additional mechanisms have been proposed; they include sympathetic overactivity, endothelial dysfunction, decreased alveolar nitric oxide (perhaps due to decreased nitric oxide synthase), and a defect in the amiloride-sensitive Na channel. Some of these factors may have a genetic component.

Pathophysiology in the CNS is less clear but may involve a combination of hypoxia-induced cerebral vasodilation, alteration of the blood-brain barrier, and Na and water retention causing cerebral edema. One hypothesis is that patients with a low ratio of CSF to brain volume are less able to tolerate swelling (ie, by displacement of CSF) and thus are more likely to develop AS. The roles of atrial natriuretic peptide, aldosterone, renin, and angiotensin are unclear.

**Acclimatization:** Acclimatization is an integrated series of responses that gradually restores tissue oxygenation toward normal in people exposed to altitude. However, in spite of acclimatization, all people at high altitude have tissue hypoxia. Most people acclimatize to altitudes of up to 3000 m (10,000 ft) in a
few days. The higher the altitude, the longer full acclimatization takes. However, no one can fully acclimatize to long-term residence at altitudes > 5100 m (>17,000 ft).

Features of acclimatization include sustained hyperventilation, which increases tissue oxygenation but also causes respiratory alkalosis. Blood pH tends to normalize within days as \( \text{HCO}_3^- \) is excreted in urine; as pH normalizes, ventilation can increase further. Cardiac output increases initially; RBC mass and tolerance for aerobic work also increase. After many generations at altitude, some ethnic groups have adapted in slightly different ways.

**Symptoms and Signs**

The clinical forms of AS are not separate entities but parts of a spectrum in which one or more forms may be present in different degrees.

**Acute mountain sickness (AMS):** This form is by far the most common and may develop at altitudes as low as 2000 m (6500 ft). It may be due to mild cerebral edema and is characterized by headache plus at least one of the following: fatigue, GI symptoms (anorexia, nausea, vomiting), dizziness, and sleep disturbance. Exertion aggravates the symptoms. Symptoms typically develop 6 to 10 h after ascent and subside in 24 to 48 h, but they occasionally evolve into HAPE, HACE, or both. AMS is common at ski resorts, and some people affected by it mistakenly attribute it to excessive alcohol intake (hangover) or a viral illness.

**High-altitude cerebral edema (HACE):** Marked cerebral edema manifests as headache and diffuse encephalopathy with confusion, drowsiness, stupor, and coma. Gait ataxia is a reliable early warning sign. Seizures and focal deficits (eg, cranial nerve palsy, hemiplegia) are less common. Papilledema and retinal hemorrhage may be present but are not necessary for diagnosis. Coma and death may occur within a few hours.

**High-altitude pulmonary edema (HAPE):** HAPE usually develops 24 to 96 h after rapid ascent to >2500 m (>8000 ft) and is responsible for most deaths due to AS. Respiratory infections, even minor ones, appear to increase risk. HAPE is more common among men (unlike other forms of AS). Long-time high-altitude residents can develop HAPE when they return after a brief stay at low altitude.

Initially, patients have dyspnea, decreased exertion tolerance, and dry cough. Pink or bloody sputum and respiratory distress are later findings. On examination, cyanosis, tachycardia, tachypnea, and low-grade fever (<38.5°C) are common. Focal or diffuse rales (sometimes audible without a stethoscope) are usually present. HAPE may worsen rapidly; coma and death may occur within hours.

**Other disorders:** Peripheral and facial edema is common at high altitude.

**Headache,** without other symptoms of AMS, is also common.

**Retinal hemorrhages** may develop at altitudes as low as 2700 m (9000 ft) and are common at > 5000 m (> 16,000 ft). They are usually asymptomatic unless they occur in the macular region; they resolve rapidly without sequelae.

People who have had radial keratotomy may have significant visual disturbances at altitudes > 5000 m (>16,000 ft) or even as low as 3000 m (10,000 ft). These alarming symptoms disappear rapidly after descent.

**Chronic mountain sickness** (Monge's disease) is a disorder that affects long-time high-altitude residents; it is characterized by fatigue, dyspnea, aches and pains, cyanosis, excessive polycythemia, and occasionally thromboembolism. The disorder often involves alveolar hypoventilation. Patients should descend to low altitude; recovery is slow, and return to high altitude may cause recurrence. Repeated phlebotomy can reduce polycythemia, but polycythemia may recur.

**Diagnosis**
Clinical evaluation

Diagnosis of most forms of AS is clinical; laboratory tests are nonspecific and usually unnecessary. HACE can usually be differentiated from other causes of coma (e.g., infection, ketoacidosis) by the history and by absence of fever and nuchal rigidity. If done, blood and CSF studies are normal. In HAPE, hypoxemia is often severe, with pulse oximetry showing 40 to 70% saturation. If obtained, chest x-ray shows a normally sized heart and patchy lung edema (often middle or lower lobes), unlike what is seen in heart failure.

Treatment

- For mild or moderate AMS, halting of ascent and treatment with fluids, analgesics, and sometimes acetazolamide
- For severe symptoms, immediate descent and treatment with O₂, drugs, and pressurization

AMS: Patients should halt ascent and reduce exertion until symptoms resolve. Other treatment includes fluids and analgesics for headache. For severe symptoms, descent of 500 to 1000 m (1650 to 3200 ft) is usually rapidly effective. Acetazolamide 250 mg po bid may relieve symptoms and improve sleep.

HAPE and HACE: Patients should descend to low altitude immediately. If descent is delayed, patients should rest and be given O₂. If descent is impossible, O₂, drugs, and pressurization in a portable hyperbaric bag help buy time but are not substitutes for descent.

For HAPE, nifedipine 10 mg sublingually followed by a 30-mg slow-release tablet lowers pulmonary artery pressure and is beneficial. Diuretics (e.g., furosemide) are contraindicated. The heart is normal in HAPE, and digitalis is of no value. When promptly treated by descent, patients usually recover from HAPE within 24 to 48 h. People who have had one episode of HAPE are likely to have another and should be so warned.

For HACE (and severe AMS), dexamethasone 4 to 8 mg initially, followed by 4 mg q 6 h, may help. It may be given po, sc, IM, or IV. Acetazolamide 250 mg po bid may be added.

Prevention

The most important measure is a slow ascent. Drinking extra water is important because breathing large volumes of dry air at altitude greatly increases water loss, and dehydration with some degree of hypovolemia aggravates symptoms. Alcohol seems to worsen AMS and reduces nocturnal ventilation, thus accentuating sleep disturbance. Although physical fitness enables greater exertion at altitude, it does not protect against any form of AS.

Ascent: Graded ascent is essential for activity at > 2500 m (> 8000 ft). Sleeping on the first night should be at < 2500 to 3000 m (8,000 to 10,000 ft), and climbers should sleep at that altitude for 2 to 3 nights if subsequent higher sleeping altitudes are planned. Each day thereafter, sleeping altitude can be increased by about 300 m (1000 ft), although higher day hikes are acceptable with return to the lower level for sleep. Climbers vary in ability to ascend without developing symptoms; a climbing party should be paced for its slowest member.

Acclimatization reverses quickly. After descent to low levels for more than a few days, acclimatized climbers should once more follow a graded ascent.

Drugs: Acetazolamide 125 to 250 mg po q 12 h reduces the incidence of AMS. Sustained-release capsules (500 mg once/day) are also available. Acetazolamide can be started on the day of the ascent; it acts by inhibiting carbonic anhydrase and thus increasing ventilation. Acetazolamide 125 mg po at bedtime reduces the amount of periodic breathing (almost universal during sleep at high altitude), thus limiting sharp falls in blood O₂. Acetazolamide should not be given to patients allergic to sulfa drugs. Analogs of acetazolamide offer no advantage. Acetazolamide may cause numbness and paresthesias of the fingers; these symptoms are benign but can be annoying. Carbonated drinks taste flat to people.
taking acetazolamide. Dexamethasone 2 mg po q 6 h is an alternative to acetazolamide.

Low-flow O₂ during sleep at altitude is effective but inconvenient and may pose logistic difficulties.

Patients who have had a previous episode of HAPE should consider prophylaxis with sustained-release nifedipine 20 to 30 mg po bid. Inhaled β-agonists may also be effective.

Analgesics may prevent high-altitude headache.
Chapter 335. Motion Sickness

Motion sickness is a symptom complex that usually includes nausea, often accompanied by vague abdominal discomfort, vomiting, dizziness, and related symptoms; it is caused by repetitive angular and linear acceleration and deceleration. Behavioral change and drug therapy can help prevent or control symptoms.

Individual susceptibility to motion sickness varies greatly. However, motion sickness is more common among women, and incidence ranges from < 1% on airplanes to nearly 100% on ships in rough seas and upon becoming weightless during space travel.

Etiology

Excessive stimulation of the vestibular apparatus by motion is the primary cause. Afferent pathways from the labyrinth to the vomiting center in the medulla are undefined, but motion sickness occurs only when the 8th cranial nerve and cerebellar vestibular tracts are intact. Movement via any form of transportation, including ship, motor vehicle, train, plane, spacecraft, and playground or amusement park ride, can cause excessive vestibular stimulation.

The trigger may involve conflicting vestibular, visual, and proprioceptive inputs. For example, visual input that indicates being stationary may conflict with the sensation of movement (eg, looking at an apparently unmoving ship cabin wall while sensing the ship rolling). Alternatively, moving visual input may conflict with lack of perception of movement (eg, viewing a rapidly moving slide with a microscope or watching a virtual reality game while sitting still). Another possible trigger is a pattern of motion that differs from the expected pattern (eg, in a zero gravity environment, floating instead of falling).

Risk factors: Factors that may increase the risk of developing motion sickness or increase the severity of symptoms include the following:

- Poor ventilation (eg, with fumes, smoke, or carbon monoxide)
- Emotional factors (eg, fear, anxiety)
- Migraine headaches
- Labyrinthitis
- Hormonal factors (eg, pregnancy, use of hormonal contraceptives)

In space adaptation syndrome (motion sickness during space travel), weightlessness (zero gravity) is an etiologic factor. This syndrome reduces the efficiency of astronauts during the first few days of space flight, but adaptation occurs over several days.

Symptoms and Signs

Nausea and vague abdominal discomfort are characteristic. Vomiting may also occur. These symptoms may be preceded by yawning, hyperventilation, salivation, pallor, profuse cold sweating, and somnolence. Other symptoms include aerophagia, dizziness, headache, fatigue, weakness, and inability to concentrate. Pain, shortness of breath, and visual and speech disturbances are absent. With prolonged exposure to motion, patients often adapt. However, symptoms may recur if motion increases or if motion resumes after a short respite from the inciting trigger.

Prolonged vomiting due to motion sickness may rarely lead to dehydration with hypotension, inanition, and depression.

Diagnosis

- Clinical evaluation
The diagnosis is suspected in patients with compatible symptoms who have been exposed to typical triggers. Diagnosis is clinical and usually straightforward. However, the possibility of another diagnosis (eg, CNS hemorrhage or infarction) should be considered in some people, particularly the elderly and patients with no prior history of motion sickness or those with risk factors for CNS hemorrhage or infarction, who develop acute dizziness and vomiting during travel. Patients with focal neurologic symptoms or signs, significant headache, or other findings atypical of motion sickness should be further evaluated.

**Treatment**

- Scopolamine, antihistamines, or antidopaminergic drugs
- Positioning
- Avoidance of alcoholic beverages and over-eating

People prone to motion sickness should take prophylactic drugs and use other preventive measures before symptoms start; interventions are less effective after symptoms develop. If vomiting occurs, an antiemetic, given rectally or parenterally, can be effective. If vomiting is prolonged, IV fluids and electrolytes may be required for replacement and maintenance.

**Scopolamine:** Scopolamine, an anticholinergic drug, is effective for prevention, but efficacy in treatment is uncertain. Scopolamine is available as a prescription transdermal patch or in oral form. The patch is a good choice for longer trips because after being applied behind the ear at least 4 h before travel (optimally 8 to 12 h), it is effective for up to 72 h as it releases about 1 mg. The oral form of scopolamine is given as 0.4 mg to 0.8 mg 1 h before travel and then q 8 h as needed.

Adverse effects, which include drowsiness, blurred vision, dry mouth, and bradycardia, occur less commonly with patches. Inadvertent contamination of the eye with patch residue may cause a fixed and widely dilated pupil. Additional adverse effects of scopolamine in the elderly can include confusion, hallucinations, and urinary retention. Scopolamine is contraindicated in people who are at risk of angle-closure glaucoma.

Scopolamine can be used by children > 12 yr in the same dosages as for adults. Use in children ≤ 12 yr may be safe but is not recommended due to the higher risk of adverse effects.

**Antihistamines:** The mechanism of action for antihistamines is probably anticholinergic. These drugs can be effective for prevention and possibly treatment. Beginning 1 h before departure, susceptible people may be given nonprescription dimenhydrinate, diphenhydramine, or meclizine 25 to 50 mg po qid (dimenhydrinate for children 2 to 6 yr, 12.5 to 25 mg po q 6 to 8 h, maximum 75 mg/day; for children 6 to 12 yr, 25 to 50 mg po q 6 to 8 h, maximum 150 mg/day), or cyclizine 50 mg po qid (for children 6 to 12 yr, 25 mg tid) to minimize vagally mediated GI symptoms. However, anticholinergic adverse effects may be troublesome, especially in the elderly. Nonsedating antihistamines do not appear to be effective.

**Antidopaminergic drugs:** Promethazine (25 to 50 mg po 1 h before departure and then bid; for children < 12 yr, 0.5 mg/kg po 1 h before departure and then bid) appears to be effective for prevention and treatment; adding caffeine may increase efficacy. Metoclopramide may also be effective, but evidence suggests it is less so than promethazine.

**Nondrug measures:** Susceptible people should minimize exposure by positioning themselves where motion is the least (eg, in the middle of a ship close to water level, over the wings in an airplane). Also, they should try to minimize the discrepancy between visual and vestibular stimuli. If traveling in a motor vehicle, driving or riding in the front passenger seat, where vehicle motion is most evident, is best. When traveling on a ship, viewing the horizon or land masses is usually better than viewing a cabin wall. Whatever the form of transportation, reading and rear-facing seats should be avoided. A supine or semirecumbent position with the head supported is best.
Adequate ventilation helps prevent symptoms. Consuming alcoholic beverages and overeating before or during travel increase the likelihood of motion sickness. Small amounts of fluids and bland food consumed frequently are preferred to large meals during extended travel; some people find that dry crackers and carbonated beverages, especially ginger ale, are best. If travel time is short, food and fluids should be avoided.

In space adaptation syndrome, movement, which aggravates the symptoms, should be avoided.

**Alternative therapies:** Some alternative therapies are unproved but may be helpful. These alternative therapies include wrist-bands that apply acupressure and wristbands that apply electrical stimulation. Both can be safely used by people of all ages. Ginger (0.5- to 1-g dose, which can be repeated but should be limited to 4 g/day) may help prevent motion sickness.
Drowning is respiratory impairment resulting from submersion in a liquid medium. It can be nonfatal (previously called near drowning) or fatal. Drowning results in hypoxia, which can damage multiple organs, including the lungs and brain. Treatment is supportive, including reversal of respiratory and cardiac arrest, hypoxia, hypoventilation, and hypothermia.

Drowning is one of the leading causes of accidental death in the US. It is the 2nd most common cause of death in children ages 1 to 14 yr. Rates are higher for the following:

- Children < 4 yr
- Children from African American, immigrant, or impoverished families
- Males
- People who have used alcohol or sedatives
- People with conditions that cause temporary incapacitation (eg, seizure, hypoglycemia, stroke, MI, cardiac arrhythmia)
- People with a long QT syndrome (swimming can trigger arrhythmias that cause unexplained drowning in people with a long QT syndrome, particularly LQT1)

Drowning is common in pools, hot tubs, natural water settings, and, among infants and toddlers, in toilets, bathtubs, buckets of water, and cleaning fluids. About 4 times as many people are hospitalized for nonfatal drowning as for fatal drowning.

Pathophysiology

Hypoxia: Hypoxia is the major insult in drowning, affecting the brain, heart, and other tissues; respiratory arrest followed by cardiac arrest may occur. Brain hypoxia may cause cerebral edema and, occasionally, permanent neurologic sequelae. Generalized tissue hypoxia may cause metabolic acidosis. Immediate hypoxia results from aspiration of fluid or gastric contents, acute reflex laryngospasm, or both. Lung injury due to aspiration or hypoxia itself may cause delayed hypoxia. Aspiration, particularly with particulate matter or chemicals, may cause chemical pneumonitis or secondary bacterial pneumonia and may impair alveolar secretion of surfactant, resulting in patchy atelectasis. Extensive atelectasis may make the affected areas of the lungs stiff, noncompliant, and poorly ventilated, potentially causing respiratory failure (see p. 2284) with hypercapnia and respiratory acidosis. Perfusion of poorly ventilated areas of the lungs (V/Q mismatch) worsens hypoxia. Alveolar hypoxia may cause noncardiogenic pulmonary edema.

Hypothermia: Exposure to cold water induces systemic hypothermia (see p. 3273), which can be a significant problem. However, hypothermia can be protective by stimulating the mammalian diving reflex, slowing the heartbeat, and constricting the peripheral arteries, shunting oxygenated blood away from the extremities and the gut to the heart and brain. Also, hypothermia decreases the O₂ needs of tissues, possibly prolonging survival and delaying the onset of hypoxic tissue damage. The diving reflex and overall clinically protective effects of cold water are usually greatest in young children.

Fluid aspiration: Laryngospasm often limits the volume of fluid aspirated; however, large volumes of water are occasionally aspirated, rarely enough to change electrolyte concentrations and blood volume. Seawater may increase Na and Cl slightly. In contrast, large quantities of fresh water can decrease electrolyte concentration significantly, increase blood volume, and cause hemolysis.

Associated injuries: Skeletal, soft-tissue, head, and internal injuries may occur. People who dive into shallow water may sustain cervical and other spine injuries (which may be the cause of drowning).

Rarely, drowning occurs when people develop carbon monoxide poisoning when they are swimming near
an exhaust port of a boat. Only a few breaths may cause unconsciousness.

**Symptoms and Signs**

Panic and air hunger occur. Children who are unable to swim may become submerged in < 1 min, more rapidly than adults. After rescue, anxiety, vomiting, wheezing, and altered consciousness are common. Patients may have respiratory failure with tachypnea, retraction, or cyanosis. Sometimes respiratory symptoms are delayed until several hours after submersion.

**Diagnosis**

- For concomitant injuries, clinical evaluation and sometimes imaging studies
- Pulse oximetry and, if results are abnormal or if respiratory symptoms and signs are present, ABG and chest x-ray
- Core temperature measurement to rule out hypothermia
- Possibly evaluation for causative disorders (eg, hypoglycemia, MI)
- Ongoing monitoring as indicated for delayed respiratory complications

Most people are found in or near water, making the diagnosis obvious clinically. Resuscitation may need to precede completion of the diagnostic assessment. Cervical spine injury is assumed, and the spine is immobilized in patients who have altered consciousness or whose mechanism of injury involves diving. Procedures to remove water from the lungs are generally not helpful. Secondary head injury and conditions that may have contributed to drowning (eg, hypoglycemia, stroke, MI) are considered.

All patients undergo assessment of oxygenation by oximetry or, if results are abnormal or if there are respiratory symptoms or signs, ABG and chest x-ray. Because respiratory symptoms may be delayed, even asymptomatic patients are transported to the hospital and observed for several hours.

In patients with symptoms or a history of prolonged submersion, core body temperature is measured, ECG and serum electrolytes are obtained, and continuous oximetry and cardiac monitoring are done. Patients with possible cervical spine injury undergo cervical spine imaging (see p. 3229).

Patients with altered consciousness undergo head CT. Any other suspected predisposing or secondary conditions are evaluated with appropriate testing (eg, fingerstick glucose for hypoglycemia, ECG for MI). Patients who drown without apparent risk factors are evaluated for long QT syndrome. In patients with pulmonary infiltrates, bacterial pneumonia is differentiated from chemical pneumonitis using blood cultures and sputum Gram stain and culture.

**Prognosis**

Factors that increase the chance of surviving submersion without permanent injury include the following:

- Brief duration of submersion
- Cold water temperature
- Young age
- Absence of underlying medical conditions, secondary trauma, and aspiration of particulate matter or chemicals
- Rapid institution of resuscitation (most important)

Survival may be possible in cold water submersion that lasts > 1 h, especially among children; thus, even
patients with prolonged submersion are vigorously resuscitated.

Treatment

- Resuscitation
- Correction of physiologic abnormalities
- Intensive respiratory support

Treatment aims to correct cardiac arrest, hypoxia, hypoventilation, hypothermia, and other physiologic insults.

Resuscitation: In apneic patients, rescue breathing is started immediately—in the water, if necessary. If spinal immobilization is necessary, it is done in a neutral position, and rescue breathing is done using a jaw thrust without head tilt or chin lift. Emergency medical services are called. If necessary, cardiac compression is started, followed by advanced cardiac life support (see p. 2256). Oxygenation, endotracheal intubation, or both are done as soon as possible. Hypothermic patients are warmed as soon as possible (see p. 3274).

Hospital care: All hypoxic or moderately symptomatic patients are hospitalized. In the hospital, supportive treatment continues, aimed primarily at achieving acceptable arterial O_2 and CO_2 levels. Mechanical ventilation may be necessary. Patients are given 100% O_2; the concentration is titrated lower based on ABG results. Positive end-expiratory pressure (see p. 2283) or intermittent positive pressure ventilation may be necessary to help expand or maintain patency of alveoli to maintain adequate oxygenation; pulmonary support may be necessary for hours or days. Nebulized β_2-agonists may help reduce bronchospasm and wheezing. Patients with bacterial pneumonia are treated with antibiotics directed at organisms identified or suspected based on results of sputum analysis or blood cultures. Corticosteroids are not used.

Fluids or electrolytes are rarely required to correct significant electrolyte imbalances. Fluid restriction is rarely indicated, even if pulmonary or cerebral edema occurs. For prolonged brain hypoxia, treatment is similar to that for brain hypoxia after cardiac arrest (see p. 2266). Concomitant disorders (eg, head or cervical injury, carbon monoxide poisoning) require treatment.

Discharge: Patients with mild symptoms and normal oxygenation can be observed in the emergency department for several hours. If symptoms resolve and oxygenation remains normal, they can be discharged with instructions to return if symptoms recur.

Prevention

Use of alcohol or drugs, a major risk factor, should be avoided before and during swimming and boating and when supervising children around water.

Swimmers should be accompanied by an experienced swimmer or swim only in guarded areas. Swimming should stop if the swimmer looks or feels very cold, because hypothermia may impair judgment. Ocean swimmers should learn to escape rip currents by swimming parallel to the beach rather than toward the beach. Swimmers should avoid swimming near a boat exhaust port, which can cause carbon monoxide poisoning.

Children must wear flotation devices when in or near water. They must be supervised by an adult when around water, including beaches, pools, and ponds. Infants and toddlers should also be supervised, ideally within arm's length, when near toilets and bathtubs. Swimming lessons are not recommended for children < 4 yr. Young children who have taken swim lessons or infant water safety classes still require supervision because these classes have not been proved to reduce drowning. Adults should remove water from containers such as pails and buckets immediately after use. Swimming pools should be surrounded with a locked fence ≥ 1.5 m in height.
Boaters are encouraged to wear flotation devices. Nonswimmers and small children are required to wear these devices.

People who are debilitated or elderly or have seizure disorders or other medical conditions that can alter consciousness require particular care when they are boating or swimming.

People with a personal and family history of unexplained drowning not attributable to alcohol, drug use, or a seizure disorder merit evaluation for long QT syndrome.

Community swimming areas should be supervised by trained lifeguards. Comprehensive community prevention programs should target high-risk groups, teach children to swim as early as possible, and teach CPR to as many adolescents and adults as possible.
Chapter 337. Injury During Diving or Work in Compressed Air

Introduction

More than 1000 diving-related injuries occur annually in the US; > 10% are fatal. Similar injuries can befall workers in tunnels or caissons (watertight retaining structures used for construction), in which pressurized air is used to exclude water from work sites. Many injuries are related to high pressure, which, at depth or in a caisson, results from the water weight above plus the atmospheric pressure at the surface. At a depth of 10 m (33 ft), seawater exerts a pressure equivalent to standard sea level atmospheric pressure, which is 0.1 kg/cm$^2$ (14.7 lb/sq in), 760 mm Hg, or 1 atmosphere absolute (atm abs); thus, the total pressure at that depth is 2 atm abs. Every additional 10 m of descent adds 1 atm.

The volume of gases in body compartments is inversely related to external pressure; an increase or a decrease in gas volume due to pressure change exerts direct physical forces that can disrupt various body tissues (barotrauma). The amount of gas dissolved in the bloodstream increases as ambient pressure increases. Increased gas content can cause injury directly (eg, $N_2$ narcosis, $O_2$ toxicity) or indirectly during ascent when decompression of the super-saturated blood or tissues releases $N_2$ bubbles (decompression sickness). Arterial gas embolism can result from barotrauma or decompression. For other diving-related injuries (eg, drowning, hypothermia, trauma), see elsewhere in THE MANUAL.

Physicians caring for patients with diving or compressed air injuries may contact the Divers Alert Network (919-684-8111; www.diversalertnetwork.org).

Barotrauma

Barotrauma is tissue injury caused by a pressure-related change in body compartment gas volume; it affects air-containing areas, including lungs, ears, sinuses, GI tract, air spaces in tooth fillings, and space contained by the diving face mask. Symptoms may include ear pain, vertigo, hearing loss, sinus pain, epistaxis, and abdominal pain. Dyspnea and loss of consciousness are life threatening and may result from alveolar rupture and pneumothorax. Diagnosis is clinical but sometimes requires imaging tests. Treatment generally is supportive but may include decongestants and analgesics for ear and sinus barotrauma or $O_2$ and chest tube placement for pneumothorax. If arterial gas embolism accompanies lung barotrauma, recompression therapy (in a hyperbaric chamber) is needed. Proper diving safety techniques and prophylactic use of decongestants may reduce incidence of barotrauma.

Risk of barotrauma (often called squeeze by divers) is greatest from the surface to 10 m (33 ft); risk is increased by any condition that can interfere with equilibration of pressure (eg, sinus congestion, eustachian tube blockage, structural anomaly, infection) in the air-containing spaces of the body. Ear barotrauma constitutes about two thirds of all diving injuries. In divers who inspire even a single breath of air or other gas at depth and do not let it escape freely during ascent, or when ascent is rapid, the expanding gas may overinflate the lungs. Lung overinflation occurs mostly in divers breathing compressed air but can occur even in swimming pools when compressed air is inspired at the bottom of the pool (eg, when scuba gear is used there) and, rarely, from an inverted bucket.

Manifestations depend on the affected area; all occur almost immediately when pressure changes. Some nonfatal disorders, if they occur at depth, may be disabling or disorienting and thus lead to drowning. Secondary infection is sometimes a late complication.

Diagnosis is primarily clinical; imaging tests can sometimes confirm barotrauma. Sometimes patients are evaluated for other problems or organ dysfunction.

Treatment

• Symptomatic treatment

• Other treatment depending on specific injury
Most barotrauma injuries resolve spontaneously and require only symptomatic treatment and outpatient follow-up; however, some injuries are life-threatening. Potentially life-threatening barotrauma emergencies are those involving alveolar or GI rupture, particularly in patients who present with any of the following:

- Neurologic symptoms
- Pneumothorax
- Peritoneal signs
- Abnormal vital signs

Initial stabilizing treatment includes high-flow 100% O\textsubscript{2} and, if respiratory failure appears imminent, endotracheal intubation. Positive pressure ventilation may cause or exacerbate pneumothorax.

Patients with suspected pneumothorax who are hemodynamically unstable or have signs of tension pneumothorax require immediate chest decompression (see p. 2004) with a large-bore (eg, 14-gauge) needle placed into the 2nd inter-costal space in the midclavicular line, followed by tube thoracostomy. Patients with neurologic symptoms or other evidence of arterial gas embolism are transported to a recompression chamber (see p. 3289) for treatment as soon as transportation can be arranged.

When stable, patients are treated for the specific type of barotrauma sustained.

Patients treated for severe or recurrent diving-related injuries should not return to diving until they have consulted with a diving medicine specialist.

Prevention of other diving injuries is discussed elsewhere (see p. 3290).

**Pulmonary Barotrauma**

During very deep breath-hold diving, compression of the lungs during descent may rarely lead to a decrease in volume below residual volume, causing mucosal edema, vascular engorgement, and hemorrhage, which manifest clinically as dyspnea and hemoptysis on ascent.

Overexpansion and alveolar rupture can occur when breathing compressed air during ascent, particularly rapid ascent. The result can be pneumothorax (causing dyspnea, chest pain, and unilateral decrease in breath sounds) or pneumomediastinum (causing sensation of fullness in the chest, neck pain, pleuritic chest pain that may radiate to the shoulders, dyspnea, coughing, hoarseness, and dysphagia). Pneumomediastinum may cause crepitation in the neck, due to associated subcutaneous emphysema, and a crackling sound may rarely be heard over the heart during systole (Hamman's sign). Tension pneumothorax, although rare with barotrauma, can cause hypotension, distended neck veins, hyperresonance to percussion, and tracheal deviation. Alveolar rupture often allows air into the pulmonary venous circulation with subsequent arterial gas embolism (see p. 3285).

**Diagnosis**

- Chest x-ray

Patients require a neurologic examination for signs of brain dysfunction due to arterial gas embolism. Chest x-ray is done to look for signs of pneumothorax or pneumomediastinum (radiolucent band along the cardiac border). If chest x-ray is negative but there is strong clinical suspicion, then helical CT, which may be more sensitive than plain film x-rays, may be diagnostic.

**Treatment**

- 100% O\textsubscript{2}
• Sometimes tube thoracostomy

Suspected tension pneumothorax is treated with needle decompression followed by tube thoracostomy (see p. 1866). If a smaller (eg, 10 to 20%) pneumothorax is present and there is no sign of hemodynamic or respiratory instability, the pneumothorax may resolve when high-flow 100% O\textsubscript{2} is given for 24 to 48 h. If this treatment is ineffective or if a larger pneumothorax is present, tube thoracostomy is done.

No specific treatment is required for pneumomediastinum; symptoms usually resolve spontaneously within hours to days. After a few hours of observation, most patients can be treated as outpatients; high-flow 100% O\textsubscript{2} is recommended to hasten resorption of extra-alveolar gas in these patients. Rarely, mediastinotomy is required to relieve tension pneumomediastinum.

Prevention

Prevention of pulmonary barotrauma is usually the top priority. Proper ascent timing and techniques are essential. Patients with pulmonary blebs, Marfan syndrome, or COPD are at very high risk of pneumothorax and should not dive or work in areas of compressed air. Patients with asthma may be at risk of pulmonary barotrauma, although many people with asthma can dive safely after they are evaluated and treated appropriately.

Gastrointestinal Barotrauma

Breathing improperly from a regulator or using ear and sinus pressure-equalization techniques may cause divers to swallow small amounts of air during a dive. This air expands during ascent, causing abdominal fullness, cramps, pain, belching, and flatulence; these symptoms are self-limited. GI rupture rarely occurs, manifesting with severe abdominal pain and tenderness with rebound and guarding.

If signs of GI rupture are present, immediate upright chest x-ray or CT is done to detect free air. Milder symptoms require no testing.

Patients with GI rupture require aggressive fluid resuscitation, broad-spectrum antibiotic therapy (eg, imipenem 500 mg IV q 6 h), and immediate surgical consultation for possible exploratory laparotomy.

Ear and Sinus Barotrauma

Diving can affect the external, middle, and inner ear. Typically, divers experience ear fullness and pain during descent; if pressure is not quickly equilibrated, middle ear hemorrhage or tympanic membrane rupture may occur. Inflow of cold water to the inner ear may result in vertigo, nausea, and disorientation while submerged. On examination of the ear canal, the tympanic membrane may show congestion, hemotympanum, and lack of mobility during air insufflation with a pneumatic otoscope; conduction hearing loss is usually present.

Inner ear barotrauma often involves rupture of the round or oval window, which causes tinnitus, sensorineural hearing loss, vertigo, nausea, and vomiting. The resulting labyrinthine fistula and perilymph leakage can permanently damage the inner ear.

Sinus barotrauma most often affects the frontal sinuses, followed by the ethmoid and maxillary sinuses. Divers experience mild pressure to severe pain, with a feeling of congestion in the involved sinus compartments during ascent or descent and sometimes epistaxis. Pain can be severe, sometimes accompanied by facial tenderness on palpation. Rarely, the sinus may rupture and cause pneumocephalus with facial or oral pain, nausea, vertigo, or headache. Physical examination may detect tenderness in the sinuses or nasal hemorrhage.

Diagnosis

• Audiometry and vestibular testing

Patients with symptoms of inner ear trauma should be examined for signs of vestibular dysfunction and
referred for formal audiometry and vestibular testing (see p. 428).

Imaging (eg, plain x-rays, CT) is not necessary for diagnosis of uncomplicated sinus barotrauma, but CT is useful if sinus rupture is suspected.

**Treatment**

- Decongestants and analgesics
- Sometimes oral corticosteroids, surgical repair, or both

Most ear and sinus barotrauma injuries resolve spontaneously and require only symptomatic treatment and outpatient follow-up.

Drug treatment for sinus and middle ear barotrauma is identical. Decongestants (oxymetazoline 0.05%, 2 sprays each nostril bid for 3 to 5 days; pseudoephedrine 60 to 120 mg po bid to qid up to a maximum of 240 mg/day for 3 to 5 days) can help open occluded chambers. Severe cases can be treated with nasal corticosteroids. Doing the Valsalva maneuver immediately after nasal spray therapy may help distribute the decongestant into the occluded chamber. Pain can be controlled with NSAIDs or opioids. If bleeding or evidence of effusion is present, antibiotics are given (eg, amoxicillin 500 mg po q 12 h for 10 days, trimethoprim/sulfamethoxazole 1 double-strength tablet po bid for 10 days). For middle ear barotrauma, some physicians also advocate a short course of oral corticosteroids (eg, prednisone 60 mg po once/day for 6 days, then tapered over 7 to 10 days).

Referral to an otorhinolaryngologist is indicated for severe or persistent symptoms. Surgery (eg, tympanotomy for direct repair of a ruptured round or oval window, myringotomy to drain fluid from the middle ear, sinus decompression) may be necessary for serious inner or middle ear or sinus injuries.

**Prevention**

Ear barotrauma may be avoided by frequently swallowing or exhaling against pinched nostrils to open the eustachian tubes and equalize pressure between the middle ear and the environment. Pressure behind ear plugs cannot be equalized, so they should not be used for diving. Prophylaxis with pseudoephedrine (60 to 120 mg po bid or qid up to a maximum of 240 mg/day), beginning 12 to 24 h before a dive, can reduce the incidence of ear and sinus barotrauma. Diving should not be done if congestion does not resolve or if a URI or uncontrolled allergic rhinitis is present.

**Other Types of Barotrauma**

- **Dental barotrauma** can occur during descent or ascent, when pressure in the air spaces at the roots of infected teeth or adjacent to fillings changes rapidly and causes pain or tooth damage. The affected tooth may be tender when percussed with a tongue blade.

- **Mask barotrauma** occurs when the pressure in the space behind the face mask is not equalized during descent. The resulting relative vacuum can lead to local pain, conjunctival hemorrhage, and ecchymosis of the skin enclosed by the mask. Retro-orbital hemorrhage is possible but rare. If retro-orbital hemorrhage is suspected, head CT is done. Mask barotrauma may be avoided when pressures are equalized within the face mask by exhaling from the nose into the mask.

- **Eye barotrauma** occurs when small air bubbles are trapped behind hard contact lenses. The air bubbles can damage the eye and cause soreness, decreased visual acuity, and halos around lights. A screening ophthalmic examination should be done to rule out other causes. Pressure behind goggles cannot be equalized, so they should not be used for diving.

**Arterial Gas Embolism**

(Air Embolism)
Arterial gas embolism is a potentially catastrophic event that occurs when gas bubbles enter or form in the arterial vasculature and occlude blood flow, causing organ ischemia. Arterial gas embolism can cause CNS ischemia with rapid loss of consciousness, other CNS manifestations, or both; it may also affect other organs. Diagnosis is clinical and may be corroborated by imaging tests. Treatment is immediate recompression.

Gas emboli may enter the arterial circulation in any of the following ways:

- From ruptured alveoli after lung barotrauma
- From within the arterial circulation itself in severe decompression sickness
- Via migration from the venous circulation (venous gas embolism) either via a right-to-left shunt (patent foramen ovale, atrial septal defect) or by overwhelming the filtering capacity of the lungs

Even asymptomatic venous gas embolism can cause serious manifestations (eg, stroke) in the presence of a right-to-left shunt. Venous gas embolism that does not enter the arterial circulation is less serious.

Although cerebral embolism is considered the most serious manifestation, arterial gas embolism can cause significant ischemia in other organs (eg, spinal cord, heart, skin, kidneys, spleen, GI tract).

Symptoms and Signs

Symptoms occur within a few minutes of surfacing and may include altered mental status, hemiparesis, focal motor or sensory deficits, seizures, loss of consciousness, apnea, and shock; death may follow. Signs of pulmonary barotrauma (see p. 3283) or type II decompression sickness (see p. 3287) may also be present.

Other symptoms may result from arterial gas embolism in any of the following:

- Coronary arteries (eg, arrhythmias, MI, cardiac arrest)
- Skin (eg, cyanotic marbling of the skin, focal pallor of the tongue)
- Kidneys (eg, hematuria, proteinuria, renal failure)

Diagnosis

- Clinical evaluation
- Sometimes confirmation by imaging

Diagnosis is primarily clinical. A high level of suspicion is necessary when divers lose consciousness during or immediately after ascent. Confirming the diagnosis is difficult because air may be reabsorbed from the affected artery before testing. However, imaging techniques that may support the diagnosis (each with limited sensitivity) include the following:

- Echocardiography (showing air in the cardiac chambers)
- Ventilation-perfusion scan (showing results consistent with pulmonary emboli)
- Chest CT (showing local lung injury or hemorrhage)
- Head CT (showing intravascular gas and diffuse edema)

Sometimes decompression sickness can cause similar symptoms and signs (for a comparison of features, see Table 337-1).
Treatment

• Immediate 100% O₂

• Recompression therapy

[Table 337-1: Comparison of Gas Embolism and Decompression Sickness]

Divers thought to have gas embolism should be recompressed promptly (see p. 3289). Transport to a recompression chamber takes precedence over nonessential procedures. Transport by air may be justified if it saves significant time, but exposure to reduced pressure at altitude must be minimized (see p. 3288).

Before transport, high-flow 100% O₂ enhances N₂ washout by widening the N₂ pressure gradient between the lungs and the circulation, thus accelerating reabsorption of embolic bubbles. Patients should remain in a supine position to decrease the risk of brain embolism. Mechanical ventilation, vasopressors, and volume resuscitation are used as needed. Placing patients in the left lateral decubitus position (Durant's maneuver) or Trendelenburg position is no longer recommended.

Immersion Pulmonary Edema

Immersion pulmonary edema is sudden-onset noncardiogenic pulmonary edema that typically occurs early during a dive while at depth.

Immersion pulmonary edema has become more common over the past 2 decades. This disorder is similar to negative pressure pulmonary edema encountered during induction of anesthesia when a patient with laryngo-spasm attempts to take deep breaths against a closed larynx, thereby causing negative intra-alveolar pressure. Immersion pulmonary edema is not related to lung barotrauma or decompression sickness. Cold water and a history of hypertension are risk factors.

Severe dyspnea develops. Divers usually ascend rapidly and have cough, frothy sputum, scattered crackles throughout both lung fields, and sometimes cyanosis. Hypoxia is present. Chest x-ray shows typical pulmonary edema. Cardiac evaluation usually shows normal right and left ventricular function and normal coronary arteries. Diuretic therapy and O₂ by positive pressure mask are usually sufficient therapy. Mechanical ventilation may be necessary. Recompression therapy is not indicated.

Decompression Sickness

(Caisson Disease; The Bends)

Decompression sickness occurs when rapid pressure reduction (eg, during ascent from a dive, exit from a caisson or hyperbaric chamber, or ascent to altitude) causes gas previously dissolved in blood or tissues to form bubbles in blood vessels. Symptoms typically include pain, neurologic symptoms, or both. Severe cases can be fatal. Diagnosis is clinical. Definitive treatment is recompression therapy. Proper diving techniques are essential for prevention.

Henry's law states that the solubility of a gas in a liquid is directly proportional to the pressure exerted on the gas and liquid. Thus, the amount of inert gases (eg, N₂, helium) dissolved in the blood and tissues increases at higher pressure. During ascent, when the surrounding pressure decreases, bubbles may form. The liberated gas bubbles can arise in any tissue and cause local symptoms, or they can travel via the blood to distant organs. Bubbles cause symptoms by blocking vessels, rupturing or compressing tissue, or activating clotting and inflammatory cascades. Because N₂ dissolves readily in fat, tissues with a high lipid content (eg, in the CNS) are particularly susceptible.

Risk factors: Decompression sickness occurs in about 2 to 4/10,000 dives. Risk factors include all of the following:
• Cold-temperature dives
• Dehydration
• Exercise after diving
• Fatigue
• Flying after diving
• Obesity
• Older age
• Prolonged or deep dives
• Rapid ascents
• Right-to-left cardiac shunts

Because excess N₂ remains dissolved in body tissues for at least 12 h after each dive, repeated dives within 1 day are most likely to cause decompression sickness. Decompression sickness can also develop if pressure suddenly decreases after recompression therapy (eg, after exposure to altitude).

**Classification:** Generally, there are 2 types of decompression sickness. Type I, which involves muscles, skin, and lymphatics, is milder and not typically life threatening. Type II is serious, is sometimes life threatening, and affects various organ systems. The spinal cord is especially vulnerable; other vulnerable areas include the brain, respiratory system (eg, pulmonary emboli), and circulatory system (eg, heart failure, cardiogenic shock). "The bends" refers to local joint or muscle pain due to decompression sickness but is often used as a synonym for any component of the disorder.

**Symptoms and Signs**

Severe symptoms may manifest within minutes of surfacing, but in most patients, symptoms begin gradually, sometimes with a prodrome of malaise, fatigue, anorexia, and headache. Symptoms occur within 1 h of surfacing in about 50% of patients and by 6 h in 90%. Rarely, symptoms can manifest 24 to 48 h after surfacing, particularly after exposure to altitude after diving.

**Type I decompression sickness** typically causes progressively worsening pain in the joints (typically elbows and shoulders), back, and muscles; the pain intensifies during movement and is described as "deep" and "boring." Other manifestations include lymphadenopathy, skin mottling, itching, and rash.

**Type II decompression sickness** tends to cause neurologic and sometimes respiratory symptoms. It typically manifests with paresis, numbness and tingling, difficulty urinating, and loss of bowel or bladder control. Headache and fatigue may be present but are non-specific. Dizziness, tinnitus, and hearing loss may result if the inner ear is affected. Severe symptoms include seizures, slurred speech, vision loss, confusion, and coma. Death can occur. The chokes (respiratory decompression sickness) is a rare but grave manifestation; symptoms include shortness of breath, chest pain, and cough. Massive bubble embolization of the pulmonary vascular tree can result in rapid circulatory collapse and death.

**Dysbaric osteonecrosis** is a late manifestation of decompression sickness. It is an insidious form of aseptic bone necrosis caused by prolonged or closely repeated exposures to pressurized areas (typically in people working in compressed air and in deep commercial rather than recreational divers). Deterioration of shoulder and hip articular surfaces can cause chronic pain and severe disability.

**Diagnosis**
Clinical evaluation

Diagnosis is clinical. CT and MRI may be helpful to rule out other disorders that cause similar symptoms (eg, herniated intervertebral disk, ischemic stroke, CNS hemorrhage). Although these studies may show brain or spinal cord abnormalities, they are not sensitive for decompression sickness, and treatment should usually begin based on clinical suspicion. Sometimes arterial gas embolism is similar (for a comparison of features, see Table 337-1).

For dysbaric osteonecrosis, plain x-rays may show joint degeneration, which cannot be distinguished from that caused by other joint disorders; MRI is usually diagnostic.

Treatment

• 100% O₂

• Recompression therapy

About 80% of patients recover completely.

Initially, high-flow 100% O₂ enhances N₂ washout by widening the N₂ pressure gradient between the lungs and the circulation, thus accelerating reabsorption of embolic bubbles.

Recompression therapy (see p. 3289) is indicated for all patients except perhaps those whose symptoms are limited to itching, skin mottling, and fatigue; they should be observed for deterioration. Other patients are transported to a suitable recompression facility. Because time to treatment is a main determinant of outcome, transport should not be delayed even in cases that appear mild or for performance of nonessential procedures. If air evacuation is required, an aircraft capable of 1 atmosphere internal pressure is preferred. In unpressurized aircraft, low altitude (< 609 m [< 2000 ft]) must be maintained. Commercial aircraft, although pressurized, typically have a cabin pressure equivalent to 2438 m (8000 ft) at normal cruise altitude, which may exacerbate symptoms. Flying in commercial aircraft shortly after a dive can precipitate symptoms.

Prevention

Significant bubble formation can usually be avoided by limiting the depth and duration of dives to a range that does not need decompression stops during ascent (called no-stop limits) or by ascending with decompression stops as specified in published guidelines (eg, the decompression table in the US Navy Diving Manual). Many divers wear a portable dive computer that continually tracks depth and time at depth and calculates a decompression schedule. In addition to following published and computer-generated guidelines, many divers make a safety stop for a few minutes at about 4.6 m (15 ft) below the surface. However, a few cases develop after appropriately identified no-stop dives, and the incidence of decompression sickness has not decreased despite widespread use of dive computers. The reason may be that published tables and computer programs do not completely account for the variation in risk factors among divers or that people do not obey the recommendations precisely.

Dives < 24 h apart (repetitive dives) require special techniques to determine proper decompression procedures.

Gas Toxicity

Various physiologic (eg, O₂, N₂, CO₂) and nonphysiologic (eg, carbon monoxide) gases can cause symptoms during diving.

Oxygen toxicity: O₂ toxicity typically occurs when the partial pressure of O₂ exceeds 1.4 atmospheres (atm), equivalent to about 57 m (187 ft) depth when air is breathed. Symptoms include paresthesias, focal seizures, vertigo, nausea, vomiting, and constricted vision. About 10% of patients have generalized seizures or syncope, which typically results in drowning. Risk is increased when divers breathe mixtures
of O₂ and N₂ (nitrox) that have an increased percentage of O₂.

**Nitrogen narcosis:** When compressed air is breathed at depths of > 30 m (> 100 ft), the elevated partial pressure of N₂ can exert an anesthetic-like effect similar to that of nitrous oxide. N₂ narcosis (rapture of the deep) causes symptoms and signs similar to those of alcohol intoxication (eg, impaired intellectual and neuromuscular performance, changes in behavior and personality). Impairment of judgment can lead to drowning. Hallucinations and loss of consciousness can occur at depths of > 91 m (> 300 ft).

Because divers recover rapidly during ascent, diagnosis is clinical. Treatment entails immediate but controlled ascent. N₂ narcosis can be prevented by using helium to dilute O₂ for deep diving because helium lacks the anesthetic properties of N₂. However, using pure helium/O₂ mixtures in very deep dives (> 180 m [> 600 ft]) increases the risk of developing high-pressure neurologic syndrome (see below).

**Carbon dioxide poisoning:** CO₂ poisoning may be caused by any of the following:

- Inadequate respiratory effort (hypoventilation)
- A tight wetsuit
- Overexertion
- Regulator malfunction
- Deep diving
- Air supply contamination by exhaled gases

Hypoventilation can increase blood CO₂ levels and cause shortness of breath and sedation. Severe CO₂ poisoning can cause nausea, vomiting, dizziness, headache, rapid breathing, flushing, confusion, seizures, and loss of consciousness. Mild CO₂ poisoning is suspected if divers frequently have dive-related headaches or low air-use rates.

CO₂ intoxication usually resolves during ascent; thus, ABG testing after a dive typically does not detect any increase in CO₂ levels.

Treatment is gradual ascent and termination of the diving exercise or correction of the precipitating cause.

**Carbon monoxide poisoning:** Carbon monoxide can enter a diver's air if the air compressor intake valve is placed too close to engine exhaust or if the lubricating oil in a malfunctioning compressor becomes hot enough to partially combust (flushing), producing carbon monoxide.

Symptoms include nausea, headache, weakness, clumsiness, and mental changes. Severe carbon monoxide poisoning can cause seizures, syncope, or coma. Diagnosis is by detecting an elevated carboxyhemoglobin (COHb) level in blood; pulse oximetry readings are nondiagnostic and usually normal because pulse oximeters cannot distinguish between oxyhemoglobin and COHb. The diver's air supply can be tested for carbon monoxide.

Treatment is with high-flow 100% O₂, best given via a nonrebreather mask, which decreases the half-life of COHb from 4 to 8 h in room air to 40 to 80 min. For severe cases, hyperbaric O₂ therapy may be considered if readily available. COHb levels will drop quickly in the hyperbaric chamber (half-life 15 to 30 min); however, the benefit of hyperbaric O₂ therapy is controversial. Some studies indicate that hyperbaric O₂ therapy lessens neurologic sequelae, but others do not support this finding.

**High-pressure neurologic syndrome:** A poorly understood syndrome of neuromuscular and cerebral abnormalities can develop at ≥ 180 m (≥ 600 ft), particularly when divers are compressed rapidly while
breathing helium/O\textsubscript{2} mixtures. Symptoms include nausea, vomiting, fine tremors, incoordination, dizziness, fatigue, somnolence, myoclonic jerking, stomach cramps, and decrements in intellectual and psychomotor performance. Diagnosis is clinical. Prevention is usually accomplished by slowing the rate of compression.

**Recompression Therapy**

(Hyperbaric O\textsubscript{2} Therapy)

Recompression therapy is administration of 100% O\textsubscript{2} for several hours in a sealed chamber pressurized to > 1 atmosphere, gradually lowered to atmospheric pressure. In divers, this therapy is used primarily for decompression sickness and arterial gas embolism. A shorter time to start of therapy is associated with a better patient outcome. Untreated pneumothorax requires chest tube placement before or during recompression therapy.

The goals of recompression therapy in diving injuries include all of the following:

- Increasing O\textsubscript{2} solubility and delivery
- Increasing N\textsubscript{2} washout
- Decreasing gas bubble size

For carbon monoxide poisoning, mechanisms include decreasing the half-life of carboxyhemoglobin, reducing ischemia, and possibly improving mitochondrial function.

Hyperbaric O\textsubscript{2} therapy is also used for several disorders unrelated to diving (see Table 337-2).

Because recompression is relatively well tolerated, it should be started if there is any likelihood that it would promote recovery; recompression may help even if started up to 48 h after surfacing.

Recompression chambers are either multi-place, with space for one or more patients on a gurney and for a medical attendant, or mono-place, with space for only one patient. Although monoplace chambers are less expensive, because patients cannot be accessed during recompression, their use for critically ill patients, who may require intervention, can be risky.

[Table 337-2. Hyperbaric O\textsubscript{2} Therapy*]

Information regarding the location of the nearest recompression chamber, the most rapid means of reaching it, and the most appropriate source to consult by telephone should be known by most divers, medical staff members, and rescue and police personnel in popular diving areas. Such information is also available from the Divers Alert Network (919-684-8111; www.diversalertnetwork.org) 24 h/day; the Undersea and Hyperbaric Medical Society (www.uhms.org) is another invaluable source of general information about recompression.

**Recompression protocols:** Pressure and duration of treatment are usually decided by a hyperbaric medicine specialist at the recompression facility. Treatments are given once or twice/day for 45 to 300 min until symptoms abate; 5- to 10-min air breaks are added to reduce risk of O\textsubscript{2} toxicity. Chamber pressure is usually maintained between 2.5 and 3.0 atmospheres (atm), but patients with life-threatening neurologic symptoms due to gas embolism may begin with an excursion to 6 atm to rapidly compress cerebral gas bubbles.

Although recompression therapy is usually done with 100% O\textsubscript{2} or compressed air, special gas mixtures (eg, helium/O\textsubscript{2} or N\textsubscript{2}/O\textsubscript{2} in nonatmospheric proportions) may be indicated if the diver used an unusual gas mixture or if depth or duration of the dive was extraordinary. Specific protocol tables for treatment are
Patients with residual neurologic deficits should be given repetitive, intermittent hyperbaric treatments and may require several days to reach maximum improvement.

Complications and contraindications: Recompression therapy can cause problems similar to those that occur with barotrauma (see p. 3282), including ear and sinus barotrauma. O₂ toxicity can cause reversible myopia. Rarely, pulmonary barotrauma, pulmonary O₂ toxicity, hypoglycemia, or seizures result. Sedatives and opioids may obscure symptoms and cause respiratory insufficiency; they should be avoided or used only in the lowest effective doses.

Relative contraindications include

- Obstructive lung disorders
- Upper respiratory or sinus infections
- Severe heart failure
- Recent ear surgery or injury
- Fever
- Claustrophobia
- Seizure disorder
- Chest surgery
- Pneumothorax

Patients with pneumothorax require tube thoracostomy before recompression therapy.

Diving Precautions and Prevention of Diving Injuries

Diving is a relatively safe recreational activity for healthy people who have been appropriately trained and educated. Diving safety courses offered by national diving organizations are widely available.

Diving safety: Incidence of barotrauma can be decreased through active equalization of various air spaces, including the face mask (by blowing out air from the nose into the mask) and the middle ear (by yawning, swallowing, or performing a Valsalva maneuver). Divers should avoid holding their breath and breathe normally during ascent, which should be no faster than 0.15 to 0.3 m/sec (0.5 to 1 ft/sec), a rate that allows for gradual offloading of N₂ and emptying of air-filled spaces (eg, lungs, sinuses). Divers should ascend with decompression stops as specified in published guidelines (eg, the decompression table in the US Navy Diving Manual). Current recommendations also include a 3- to 5-min safety stop at 4.6 m (15 ft) for further equilibration. Also, divers should not fly for 15 to 18 h after diving.

Divers should be aware of and avoid certain diving conditions (eg, poor visibility, currents requiring excessive effort). Cold temperatures are a particular hazard because hypothermia can develop rapidly and affect judgment and dexterity or induce fatal cardiac arrhythmias in susceptible people. Diving alone is not recommended.
Recreational or sedative drugs and alcohol in any amount may have unpredictable or unanticipated effects at depth and should be strictly avoided. Otherwise, prescription drugs rarely interfere with recreational diving, but if the disorder being treated is a contraindication to diving, the dive should not be pursued.

Contraindications to diving: Because diving can involve heavy exertion, divers should not have a functionally significant cardiovascular or pulmonary disorder and should have above-average aerobic capacity. Disorders that can impair consciousness, alertness, or judgment generally prohibit diving. If there is any doubt as to whether diving is contraindicated by a specific disorder, a recognized expert should be consulted. For specific diving contraindications, see Table 337-3.
Chapter 338. Exercise and Sports Injury

Introduction

Regular exercise enhances health and a sense of well-being. However, injury, particularly over-use injury, is a risk for people who exercise regularly. (For musculoskeletal injuries not particularly associated with sports, see p. 3201.)

Exercise

Exercise stimulates tissue change and adaptation, whereas rest and recovery allow such change and adaptation to occur. Recovery from exercise is as important as the exercise stimulus. Regular physical activity decreases the incidence of the major causes of death, improves functional status for sports and activities of daily living, and protects against injury. Specific exercise programs are also commonly prescribed to rehabilitate patients after MI, major surgery, and musculoskeletal injury. Regardless of indication, recommendations for exercise should be based on 2 principles:

• Goals for activity should be specific to the patient, accounting for motivation, needs, physical ability, and psychology, to maximize the likelihood of patient participation and desired outcome.

• Activity should be prescribed in a proper dose to achieve a desired effect. An exercise stimulus should be sufficient for the body to adapt to a higher state of function but not so great that it causes injury. More activity is not always better; too little or too much activity may prevent achievement of desired outcomes.

A prescription for exercise should specify intensity (level of exertion), volume (amount of activity in a session), frequency (number of exercise sessions), and progressive overload (either the amount of increase in one or more of these elements over time, or the actual load). The balance of these elements depends on individual tolerance and physiologic principles (ie, as intensity increases, volume and frequency may need to decrease, whereas as volume increases, intensity may need to decrease). Intensity, volume, and frequency can be increased concurrently but only to a point because human tolerance to strain is finite. The objective is to discover the appropriate amount of exercise for optimal benefit in the context of the patient's goals. Fixed and traditional recommendations (eg, 3 sets of 10 to 12 repetitions, running 30 min 3 times/wk) may be suboptimal because they do not address a person's specific requirements.

Exercise programs should encompass multiple dimensions of fitness:

• Stretching and flexibility

• Aerobic capacity

• Strength

• Balance

Stretching and flexibility: Flexibility is important for safe, comfortable performance of physical activities. Stretching may be beneficial in strength training to improve range of motion and help relax muscles. Specific flexibility exercises involve slowly and steadily stretching muscle groups without jerking or bouncing. These exercises can be done before or after other forms of training or as a regimen itself, as occurs in yoga and Pilates sessions. Although stretching before exercise enhances mental preparedness, there is no evidence that stretching decreases risk of injury. However, there is no need to discourage preactivity stretching if patients enjoy it. General warming-up (eg, with low-intensity simulation of the exercise to be done, jogging on the spot, calisthenics, or other light activities that increase core temperature) seems to be more effective than stretching for facilitating safe exercise. Stretching after exercise may be preferred because tissues stretch more effectively when warmed.

Aerobic exercise: Aerobic exercise is continuous, rhythmic physical activity. Exertion occurs at a level
that can be supported by aerobic metabolism (although brief periods of more intense exertion triggering anaerobic metabolism may be interspersed) continuously for at least 5 min as a starting point and increased slowly over time. Aerobic conditioning increases maximal O$_2$ uptake and cardiac output (mainly an increase in stroke volume), decreases resting heart rate, and reduces cardiac and all-cause mortality; however, too much activity causes excessive wear on the body and increases cellular oxidation. Examples of aerobic exercise include running, jogging, fast walking, swimming, bicycling, rowing, kayaking, skating, cross-country skiing, and using aerobic exercise machines (eg, tread-mill, stair-climbing, or elliptical machines).

Aerobic metabolism starts within 2 min of beginning activity, but more sustained effort is needed to achieve health benefits. The usual recommendation is to exercise ≥ 30 min/day at least 3 times/wk with a 5-min warm-up and a 5-min cool-down period, but this recommendation is based on convenience as much as evidence. Optimal aerobic conditioning can occur with as little as 10 to 15 min of activity per session 2 to 3 times/wk if interval cycling is used. In interval cycling, short periods of moderate activity are alternated with intense exertion. In one regimen, about 90 sec of moderate activity (60 to 80% maximum heart rate [HR$_{max}$]) is alternated with about 20 to 30 sec of all-out sprint-type work (85 to 95% HR$_{max}$ or as hard as the person can exert for that time). This regimen is more stressful on joints and tissues and so should be done infrequently or alternated with more conventional low- to moderate-intensity training.

Resistance training machines or free weights can be used for aerobic exercise as long as a sufficient number of repetitions are done per set, rest between sets is minimal (20 to 60 sec), and intensity of effort is relatively high. In circuit training, the large muscles (of the legs, hips, back, and chest) are exercised followed by the smaller muscles (of the shoulders, arms, abdomen, and neck). Circuit training for only 15 to 20 min can benefit the cardiovascular system more than jogging or using aerobic exercise machines for the same amount of time because the workout is often more intense and heart rate increases more as a result.

Volume of aerobic exercise is graded simply by duration. Intensity is guided by heart rate. Target heart rate for appropriate intensity is 60 to 85% of a person's HR$_{max}$ (the heart rate at peak O$_2$ consumption [VO$_2$peak], or the rate beyond which aerobic metabolism can no longer be sustained because O$_2$ is lacking and anaerobic metabolism begins). HR$_{max}$ can be directly measured, or calculated as

\[
\text{HR}_{max} = 220 - \text{age}
\]

Alternatively, the Karvonen formula can be used to calculate target heart rate:

\[
\text{Target heart rate} = [(0.50 \text{ to } 0.85) \times (\text{HR}_{max} - \text{HR}_{resting})] + \text{HR}_{resting}
\]

However, the more athletic or deconditioned the person is compared to average, the less accurate these formulas are, thus making metabolic or VO$_2$ testing more valuable.

Chronologic age should be distinguished from biologic age. People of any age who are less accustomed to aerobic exercise (less conditioned) reach the target heart rate much sooner and with less effort, necessitating briefer exercise periods, at least initially. Obese people may be deconditioned and must move a larger body weight, causing heart rate to increase much faster and to a greater extent with less vigorous activity than in thinner people. Disorders and some drugs (eg, β-blockers) also modify the relationship between age and heart rate. For people who have a disorder or take certain drugs, a target of 50 to 60% of HR$_{max}$ is probably sufficient, at least initially.

**Strength training:** Strength (resistance) training involves forceful muscular contraction against a load—typically provided by free or machine weights or sometimes body weight (eg, push-ups, abdominal crunches, chin-ups). Such training increases muscle strength, endurance, and size and improves functional ability and aerobic performance. Cardiovascular endurance and flexibility increase concurrently.

**Volume** typically is categorized in terms of amount of weight lifted and number of sets and number of repetitions per set. However, an equally important parameter is tension time, which is the total duration of
lifting and lowering the weight in one set. Appropriate tension time may be about 60 sec for moderate conditioning (a good balance in developing muscle mass and strength) and 90 to 120 sec for injury rehabilitation and muscular endurance. For increasing strength, tension time is more important than number of repetitions, which can vary within tension time by technique and set duration. When a person can achieve at least a 60-sec tension time with good technique, resistance (weight) can be increased so that a tension time of at least 60 sec is tolerable at the next weight level. Number of sets is determined by intensity of the training.

**Intensity** is generally a subjective measure of perceived effort and how close a person comes to muscular fatigue in a given set (or exhaustion in a workout). Intensity may be characterized objectively by the amount of weight lifted expressed as a percentage of the person's maximum for one repetition (1 RM) of a given exercise; ie, for a person who can deadlift at most 100 kg one time, 75 kg is 75% RM. A general guideline is to exercise with a load at 70 to 85% RM. Heavier loads increase risk of injury and are appropriate mainly for competitive strength athletes. Lifting < 30 to 40% RM provides minimal strength gain, although aerobic conditioning and muscular endurance may occur with sufficient tension time and effort.

Intensity is limited by motivation and tolerance; for many people undergoing rehabilitation, discomfort, pain, and exercise inexperience result in less effort than may be possible or tolerated, so that more sets are required to derive equal benefit. Intensity should vary on a regular basis to provide both a mental and physical hiatus. If exercise is done at the highest intensity level, it should occur no more often than in about half of the sets and workouts should be avoided for 1 to 2 wk every 3 mo. Continual high-intensity training is counterproductive, even for trained athletes. Symptoms such as fatigue or muscle heaviness when not exercising, lack of motivation to exercise, reduced exercise performance, joint and tendon pains, and increased resting heart rate suggest that exercise has been too intense; exercise should be avoided for 1.5 to 2 wk.

**Good technique** is important for safety and involves avoidance of jerking or dropping weights, which can cause minor tissue injury due to sudden force, and controlled breathing, which prevents dizziness (and in extreme cases, fainting) that can occur with the Valsalva maneuver. People should exhale while lifting a weight and inhale while lowering a weight. If a movement is slow, such as lowering a weight for ≥ 5 sec, people may need to breathe in and out more than once, but breathing should still be coordinated so that a final breath is taken in just before the lifting phase and released during lifting. BP increases during resistance training and tends to be highest when gripping excessively (common with the leg press exercise when working the large lower body muscles and clenching the machines hand grips very tightly). However, BP returns to normal quickly after exercise; the increase is minimal when breathing technique is correct, no matter how hard a person exerts.

**Balance training:** Balance training involves challenging the center of gravity by undertaking exercises in unstable environments, such as standing on one leg or using balance or wobble boards. Balance training can help some people with impaired proprioception and is often used in an attempt to prevent falls in the elderly (see p. 3295).

**Hydration:** Proper hydration is important, particularly when exertion is prolonged or occurs in a hot environment. People should be well-hydrated before activity, drink fluids regularly during extended exertion, and replace any deficit remaining after activity. During exertion, about 120 to 240 mL (1/2 to 1 cup) every 15 to 20 min is reasonable depending on heat and exertion level; however, overhydration, which can cause hyponatremia and consequent seizures, is to be avoided.

Fluid deficit after exertion is calculated by comparing preexercise and postexercise body weight and is replaced on a one-for-one basis (ie, 1 L for each kg lost, or 2 cups/lb). In most cases, plain water is acceptable. Electrolyte-containing sports drinks may be preferred. However, fluids with a carbohydrate content of > 8% (8 g/100 mL, or 20 g in a typical 250-mL serving) decrease gastric emptying and slow fluid absorption. Often it is best to mix plain water with sports drinks at a 50:50 ratio to allow faster absorption of the glucose and electrolytes. People with findings suggesting heat illness (see p. 3262) or dehydration may require oral or IV electrolyte replacement immediately.

**Exercise in the Elderly**
At least 75% of people age > 65 yr do not exercise at recommended levels, despite the known health benefits:

• Longer survival

• Improved quality of life (eg, endurance, strength, mood, flexibility, possibly cognitive function)

Exercise has proven benefits when begun as old as 75 yr. Because of the effects of aging and age-related disorders, the relative benefits of exercise may even be greater in the elderly (see also Sidebar 307-1 on p. 3073). In addition, exercise is one of the safest ways to improve health.

The largest health benefits occur, particularly with aerobic exercise, when changing from being sedentary to exercising. Progressively less benefit occurs as the intensity of exercise increases.

Strength decreases with age and can compromise function. For example, almost half of women > 65 and more than half of women > 75 cannot lift 4.5 kg. Strength training can increase muscle mass by 25 to 100% or more, meaningfully improving function. The same degree of muscle work demands less cardiovascular exertion; increasing leg muscle strength improves walking speed and stair climbing. Also, institutionalized elderly with more muscle mass have better nitrogen balance and a better prognosis and less deconditioning during critical illness.

**Contraindications:** Absolute contraindications to exercise include

• Suspected acute coronary syndrome

• 3rd-degree heart block

• Uncontrolled hypertension

• Acute heart failure

• Uncontrolled diabetes mellitus

Relative contraindications include

• Cardiomyopathy

• Valvular heart disease

• Complex ventricular ectopy

Most patients with relative contraindications can exercise, although at lower levels of intensity than other patients (see p. 3461). Other factors mandate modification of the exercise program (eg, arthritic disorders, particularly those involving major weight-bearing joints, such as the knees, ankles, and hips).

Patients should be told to stop exercising and seek medical attention if they develop chest pain, light-headedness, or palpitations.

**Screening:** Before beginning an exercise program, elderly patients should undergo clinical evaluation aimed at detecting cardiac disorders and physical limitations to exercise. Routine ECG is unnecessary. Exercise stress testing is usually unnecessary for elderly patients who plan to begin exercising slowly and increase intensity only gradually. For sedentary patients who plan to begin intense exercise, stress testing is indicated if they have any of the following:

• Known coronary artery disease
Symptoms of coronary artery disease

≥ 2 cardiac risk factors (eg, hypercholesterolemia, hypertension, obesity, sedentary lifestyle, smoking, family history of early coronary artery disease)

Suspected lung disease

Suspected diabetes

**Exercise program:** Exercise should ideally include

- Aerobic activity
- Strength training
- Flexibility and balance

Time spent doing **aerobic activity** is similar to that for younger adults, but exercise should be less intense. Usually during exercise, the person should be able to comfortably converse, and intensity should be ≤ 6/10 on a perceived scale of exertion. Elderly people who have no contraindications can gradually increase their target heart rate to the one calculated by use of age-based formulas. Some deconditioned elderly people need to improve their functional abilities (eg, by strength training) before they are capable of aerobic exercise.

**Strength training** is done according to the same principles and techniques as in younger adults. When beginning, forces may need to be small (eg, using bands or weights as light as 1 kg or arising from a chair).

To help increase **flexibility**, major muscle groups should be stretched once daily, ideally after exercise when muscles are most compliant.

**Balance training** involves challenging the center of gravity by undertaking exercises in unstable environments, such as standing on one leg or using balance or wobble boards. Balance training can help some people with impaired proprioception and is often used in an attempt to prevent falls in the elderly. However, it is often ineffective because any balance activity is skill specific (eg, good balance while standing on a balance board does not improve balance in dissimilar activities). For most elderly people, flexibility and strengthening exercises prevent falls more effectively. Such a program develops strength around the joints and helps people hold body positions more effectively while standing and walking. In people who have difficulty standing and walking because of poor balance, more challenging balance tasks (eg, standing on a wobble board) are simply likely to facilitate injury and are contraindicated.

**Screening for Sports Participation**

(See also Ch. 220.)

**Cardiovascular screening:** Screening for all children and adults should include a thorough cardiovascular history, with questions about

- Known hypertension or heart murmur
- Chest pain
- Exercise-induced syncope, near-syncope, chest pain, or palpitations
- Family history of sudden cardiac death at age < 50 yr, arrhythmias, dilated or hypertrophic cardiomyopathy, long QT syndrome, or Marfan syndrome
- Risk factors for coronary artery disease in adults
Physical examination should routinely include BP, supine and standing cardiac auscultation, and inspection for features of Marfan syndrome. These measures aim to identify adults as well as rare, apparently healthy young people at high risk of life-threatening cardiac events (eg, people with arrhythmias, hypertrophic cardiomyopathy, or other structural heart disorders). Testing is directed at clinically suspected disorders (eg, exercise stress testing for coronary artery disease, echocardiography for structural heart disease, ECG for long QT syndrome).

**Other screening measures:** Noncardiovascular risk factors are more common than cardiovascular risk factors. Adults are asked about arthritic disorders, particularly those involving major weight-bearing joints (eg, knees, ankles, hips).

Two at-risk populations are commonly overlooked:

- Boys who physically mature late or are short are at greater risk of injury in contact sports with larger and stronger children.

- Overweight or obese people who participate in activities that require high agility are at greater risk of injury due to sudden stops and starts because of excess body weight and associated forces on the joints and tissues.

Adolescents and young adults should be asked about use of illicit and performance-enhancing drugs. In girls and young women, screening should detect delayed onset of menarche. Girls and young women should be screened for the presence of the female athlete triad (eating disorders, amenorrhea or other menstrual dysfunction, and diminished bone mineral density), which is becoming more common as more adolescent and young women engage in overly intensive physical activity and overly zealous loss of body fat.

**Contraindications:** There are almost no absolute contraindications to sports participation. Exceptions in children include

- Myocarditis, which increases the risk of sudden cardiac death

- Acute splenic enlargement because splenic rupture is a risk

- Fever, which decreases exercise tolerance, increases risk of heat-related disorders, and may be a sign of serious illness

- Possibly diarrhea and recent vomiting because dehydration is a risk

Exceptions in adults include angina pectoris and recent (within 6 wk) MI. Contraindications are more commonly relative and lead to recommendations for precautions or for participation in some sports rather than others. For example, people with a history of multiple concussions should participate in noncollision sports; males with a single testis should wear a protective cup for most contact sports; people at risk of heat intolerance and dehydration (eg, those with diabetes or cystic fibrosis) should hydrate frequently during activity; and people with suboptimal seizure control should avoid swimming, weight lifting, and sports such as archery and riflery because of risk to others.

**Approach to Sports Injuries**

Sports participation always has a risk of injury.

Generally, sports injury can be divided into

- Overuse injuries

- Blunt trauma
• Fractures and dislocations (see p. 3201)

• Acute soft-tissue sprains and strains

Many injuries (eg, fractures, dislocations, soft-tissue contusions, blunt trauma, sprains and strains) are not unique to sports participation and can result from activities that are not athletic or from accidents (see also p. 3201). However, athletes may need to learn how to modify faulty techniques that predispose to injuries or may resist taking an adequate period of rest to recover from a sports injury (working through the pain).

Overuse: Overuse is one of the most common causes of athletic injury and is the cumulative effect of excessive, repetitive stress on anatomic structures. It results in trauma to muscles, tendons, cartilage, ligaments, bursae, fascia, and bone in any combination. Risk of overuse injury depends on complex interactions between individual and extrinsic factors. Individual factors include muscle weakness and inflexibility, joint laxity, previous injury, bone malalignment, and limb asymmetries. Extrinsic factors include training errors (eg, exercise without sufficient recovery time, excess load, building one group of muscles without training the opposing group, and extensive use of the same movement patterns), environmental conditions (eg, excessive running on banked tracks or crowned roads—which stresses the limbs asymmetrically), and training equipment characteristics (eg, unusual or unaccustomed motions, such as those made while on an elliptical trainer). Runners most often sustain injury after too rapidly increasing their intensity or length of workouts. Swimmers may be least prone to overuse injuries because buoyancy has protective effects, although they still are at risk, particularly in the shoulders, from which most movement occurs.

Blunt trauma: Blunt athletic trauma can result in injuries such as soft-tissue contusions, concussions, and fractures. The mechanism of injury usually involves high-impact collisions with other athletes or objects (eg, being tackled in football or checked into the sideboards in hockey), falls, and direct blows (eg, in boxing or the martial arts).

Sprains and strains: Sprains are injuries to ligaments, and strains are injuries to muscles. They typically occur with sudden, forceful exertion, most commonly during running, particularly with sudden changes of direction (eg, dodging and avoiding competitors in football). Such injuries also are common in strength training, when a person quickly drops or yanks at the load rather than moving slowly and smoothly with constant controlled tension.

Symptoms and Signs

Injury always results in pain, which ranges from mild to severe. Physical signs may be absent or may include any combination of soft-tissue edema, erythema, warmth, point tenderness, ecchymosis, instability, and loss of mobility.

Diagnosis

Diagnosis should include a thorough history and physical examination. History should focus on the mechanism of injury, physical stresses of the activity, past injuries, timing of pain onset, and extent and duration of pain before, during, and after activity. Diagnostic testing (eg, x-rays, ultrasonography, CT, MRI, bone scans, electromyography) and referral to a specialist may be required.

Treatment

• Rest, ice, compression, elevation (RICE)

• Analgesics

• Cross training

• Gradual return to activity
RICE: Immediate treatment of most acute sports injuries is RICE.

Rest prevents further injury and helps to reduce swelling.

Ice (or a commercial cold pack) causes vasoconstriction and reduces soft-tissue swelling, inflammation, and pain. Ice and cold packs should not be applied directly to the skin. They should be enclosed in plastic or a towel. They should be left in place for no more than 20 min at a time. An elastic bandage can be wrapped around a tightly closed plastic bag containing ice to keep it in place.

Wrapping an injured extremity with an elastic bandage for compression reduces edema and pain. The bandage should not be wrapped too firmly because doing so may cause swelling in the distal extremity.

The injured area should be elevated above heart level so that gravity can facilitate drainage of fluid, which reduces swelling and thus pain. Ideally, fluid should drain on an entirely downhill path from the injured area to the heart (eg, for a hand injury, the elbow, as well as the hand, should be elevated). Ice and elevation should be used periodically throughout the initial 24 h after an acute injury.

Pain control: Pain control usually involves use of analgesics, typically acetaminophen or NSAIDs. However, if pain persists for > 72 h after a seemingly minor injury, referral to a specialist is recommended. For persistent pain, evaluation for additional or more severe injuries is indicated. These injuries are treated as appropriate (eg, with immobilization, sometimes with oral or injectable corticosteroids). Corticosteroids should be given only by a specialist and when necessary because corticosteroids can delay soft-tissue healing and sometimes weaken injured tendons and muscles. The frequency of corticosteroid injections should be monitored by a specialist because too-frequent injections may increase the risk of tissue degeneration and ligament or tendon rupture.

Activity: In general, injured athletes should avoid the specific activity that caused the injury until after healing occurs. To minimize deconditioning, athletes can cross-train (ie, do different or related exercises that do not cause reinjury or pain). Injury may also necessitate reducing exercise range-of-motion if there is intolerable pain at certain points of movement. Initially, exercise of previously injured areas should be low in intensity to gradually strengthen weak muscles, tendons, and ligaments without risking reinjury. It is more important to maintain a good range-of-motion, which helps direct blood to the injured area to accelerate healing, than to rapidly resume full intensity training for fear of losing conditioning. Resumption of full activity should be gradual once pain subsides. Competitive athletes should consider consultation with a professional (eg, physical therapist).

Athletes should be placed in a graduated program of exercises and physical therapy to restore flexibility, strength, and endurance. They also need to feel psychologically ready before re-engaging in an activity at full capacity. Competitive athletes may benefit from motivational counseling.

Prevention

Exercise itself helps prevent injuries because tissues become more resilient and tolerant of the forces they experience during vigorous activities.

General warming up raises muscle temperature and makes muscles more pliable, stronger, and more resistant to injury; it also improves workout performance by enhancing mental and physical preparedness. Cooling down is sometimes thought to prevent dizziness and syncope after aerobic exercise and helps remove metabolic byproducts of exercise, such as lactic acid, from muscles and the bloodstream. Removing lactic acid may help decrease muscle soreness. Cooling down also helps decrease heart rate slowly and gradually to near-resting levels—an important effect for patients with heart disorders.

Injury due to excessive pronation (turning in or inversion of the foot during weight bearing) can be prevented with use of shoe inserts or orthotics (flexible or semirigid).

Rotator Cuff Injury

Rotator cuff injury includes tendinitis and partial or complete tears. Symptoms are shoulder
pain and, with severe tears, weakness. Diagnosis is by examination and, sometimes, diagnostic testing. Treatment includes NSAIDs, maintenance of range of motion, and rotator cuff strengthening exercises.

The rotator cuff, consisting of the supraspinatus, infraspinatus, teres minor, and subscapularis (SITS) muscles, helps stabilize the humeral head in the glenoid fossa of the scapula during overhead arm motions (eg, pitching, swimming, weightlifting, serving in racket sports).

Etiology

Rotator cuff injury can be a sports injury, but it commonly occurs for reasons unrelated to sports activities and in people with no history of overuse.

A strain of the rotator cuff is a single acute, traumatic injury to the muscles. Tendinitis typically results from chronic impingement of the supraspinatus tendon between the humeral head and coracoacromial arch (the acromion, acromioclavicular joint, coracoid process, and coracoacromial ligament). Activities that require the arm to be moved over the head repeatedly, such as pitching in baseball, lifting heavy weights over the shoulder, serving the ball in racket sports, and swimming freestyle, butterfly, or backstroke, increase the risk. The supraspinatus tendon is thought to be particularly susceptible because it has an under-vascularized region near its insertion on the greater tuberosity. The resultant inflammatory reaction and edema further narrow the subacromial space, accelerating tendon irritation or damage. If the process is not interrupted, the resulting inflammation can lead to partial or complete tear of the rotator cuff. Degenerative rotator cuff tendinitis is common among older (> 40 yr) people who are not athletes for the same reason. Subacromial bursitis (inflammation, swelling, and fibrosis of the bursal area above the rotator cuff) commonly results from tendinitis of the cuff.

Symptoms and Signs

Subacromial bursitis, rotator cuff tendinitis, and partial rotator cuff tears cause shoulder pain, especially when the arm is moved overhead. The pain usually is worse between 60° and 120° (painful arc of motion) of shoulder abduction or flexion and is usually minimal or absent at < 60° or > 120°. The pain may be described as a dull ache that is poorly localized. Complete rotator cuff tears result in acute pain and weakness of the shoulder. In larger tears of the rotator cuff, weakness of external rotation is particularly apparent.

Diagnosis

- Physical examination
- Sometimes MRI or arthroscopy

Diagnosis is by history and physical examination, including provocative maneuvers. The rotator cuff cannot be palpated directly, but it can be assessed indirectly by provocative maneuvers that test its individual components; significant pain or weakness is considered a positive result.

The supraspinatus is assessed by having the patient resist downward pressure on the arms held in forward flexion with the thumbs pointing downward (empty can, or Jobe's test).

The infraspinatus and teres minor are assessed by having the patient resist external rotation pressure with the arms held at the sides with elbows flexed to 90°; this position isolates rotator cuff muscle function from that of other muscles such as the deltoid. Weakness during this test suggests significant rotator cuff dysfunction (eg, a complete tear).

The subscapularis is assessed by having the patient place the hand behind the back with the back of the hand resting on the lower back. The examiner lifts the hand off the lower back. The patient should be able to keep the hand off the skin of the back (Gerber lift-off test).

The Neer test checks for impingement of the rotator cuff tendons under the coracoacromial arch. It is
done by placing the arm in forced forward flexion (arm lifted overhead) with the arm fully pronated.

The Hawkins test also checks for impingement. It is done by elevating the arm to 90°, flexing the elbow 90°, and then forcibly rotating the shoulder internally.

The Apley scratch test assesses combined shoulder range of motion by having the patient attempt to touch the opposite scapula: Reaching overhead, behind the neck, and to the opposite scapula with the tips of the fingers tests abduction and external rotation; reaching under, behind the back, and across to the opposite scapula with the back of the hand tests adduction and internal rotation.

Other areas that may be the source of shoulder pain include the acromioclavicular and sternoclavicular joints, cervical spine, biceps tendon, and scapula. These areas should be assessed for any tenderness or deformity indicating a problem in those areas.

The neck is examined as part of any shoulder evaluation because pain can be referred to the shoulder from the cervical spine (particularly with C5 radiculopathy).

Suspected rotator cuff injury can be further evaluated with MRI, arthroscopy, or both.

**Treatment**

- NSAIDs
- Exercises
- Sometimes surgery

In most cases of tendinitis and bursitis, rest, NSAIDs, and rotator cuff strengthening exercises (see Sidebar 338-1) are sufficient. Injections of corticosteroids into the subacromial bursa are occasionally indicated (eg, when symptoms are acute and severe or when prior treatment has been ineffective). Surgery may be necessary in chronic bursitis that is resistant to conservative management to remove excess bone and decrease impingement. Surgical repair may be recommended if a rotator cuff injury is severe (eg, a complete tear).

**Glenoid Labral Tear**

The glenoid labrum usually tears as a result of a specific trauma, such as a fall onto an outstretched arm. Tears can also result from chronic overhead movement, as occurs in pitching. A glenoid labral tear causes pain during motion. Treatment is with physical therapy and sometimes surgery.

The shoulder (unlike the hip or elbow) is an inherently unstable joint; it has been likened to a golf ball sitting on a tee. To enhance structural stability, the glenoid (anatomically, a very shallow socket) is deepened by the labrum, which is a rubbery, fibrocartilaginous material attached around the lip of the glenoid. This structure can tear during athletics, especially during throwing sports, or as a result of blunt trauma when falling and landing on an outstretched upper extremity.

**Sidebar 338-1 Exercises to Strengthen the Shoulders**

**Rotator Cuff Exercises**

**External Rotation**

- Lying on the left side, grasp a light dumbbell in the right hand with the elbow bent 90°. Maintain this position throughout the set.

- Using the right elbow as a pivot point against the side of the waist, externally rotate the arm upward until
it is as vertical as possible.

• Do 3 sets of 10 repetitions with 1 min of rest between each set.

• Repeat with the opposite arm.

• As strength improves, increase the weight.

Internal Rotation

• Lying on the right side, grasp a light dumbbell in the right hand with the right elbow bent at 90°. Maintain this position throughout the set.

• Using the right elbow as a pivot point against the side of the waist, internally rotate the arm upward (inward) until it is vertical against the abdomen.

• Do 3 sets of 10 repetitions with 1 min of rest between each set.

• Repeat with the opposite arm.

• As strength improves, increase the weight.

Deltoid Exercises

Anterior Deltoid

• In the standing position, grasp a light dumbbell with the right hand and with the palm facing down, raise the hand and arm away and in front of the body to shoulder level, keeping the elbow straight.

• Do 3 sets of 10 repetitions with 1 min of rest between each set.

• Repeat with the opposite arm.

Middle Deltoid

• In the standing position, grasp a light dumbbell with the right hand and with the palm facing down, raise the hand and arm away and out to the side from the body to shoulder level, keeping the elbow straight.

• Do 3 sets of 10 repetitions with 1 min of rest between each set.

• Repeat with the opposite arm.

Symptoms and Signs

A glenoid labral tear results in deep shoulder pain during motion, especially when pitching a baseball. This discomfort may be accompanied by a painful clicking or clunking sensation and a feeling of catching in the shoulder.

Diagnosis

A thorough shoulder and neck physical examination should be done initially, but referral to a specialist is frequently needed because more sophisticated diagnostic tests (eg, contrast-enhanced MRI) are often the only way to definitively identify the pathology.

Treatment

Physical therapy is the initial treatment. If symptoms do not subside with physical therapy, and the
diagnosis has been confirmed by MRI, surgical debridement or repair is the treatment of choice. Surgery is usually done arthroscopically.

**Lateral Epicondylitis**

(Tennis Elbow)

Lateral epicondylitis results from inflammation and microtearing of fibers in the extensor tendons of the forearm. Symptoms include pain at the lateral epicondyle of the elbow, which can radiate into the forearm. Diagnosis is by examination and provocative testing. Treatment is with rest, NSAIDs, and physical therapy.

Theories about the pathophysiology of lateral epicondylitis include nonathletic and occupational activities that require repetitive and forceful forearm supination and pronation, as well as overuse or weakness (or both) of the extensor carpi radialis brevis and longus muscles of the forearm, which originate from the lateral epicondyle of the elbow. For example, during a backhand return in racket sports such as tennis, the elbow and wrist are extended, and the extensor tendons, particularly the extensor carpi radialis brevis, can be damaged when they roll over the lateral epicondyle and radial head. Contributing factors include weak shoulder and wrist muscles, a racket strung too tightly, an undersized grip, hitting heavy wet balls, and hitting off-center on the racket.

In resistance trainees, injuries often are caused by overuse (too much activity or doing the same movements too often) or by muscle imbalance between the forearm extensors and flexors. Nonathletic activities that can cause or contribute to lateral epicondylitis include those involving grasping and twisting the elbow (eg, turning a screwdriver).

With time, subperiosteal hemorrhage, calcification, spur formation on the lateral epicondyle, and, most importantly, tendon degeneration can occur.

**Symptoms and Signs**

Pain initially occurs in the extensor tendons of the forearm and around the lateral elbow when the wrist is extended against resistance (eg, as in using a manual screwdriver or hitting a backhand shot with a racket). In resistance trainees, lateral epicondylitis is most noticeable during various rowing and chin-up exercises for the back muscles, particularly when the hands are pronated. Pain can extend from the lateral epicondyle to the mid forearm.

**Diagnosis**

- Provocative testing

Pain along the common extensor tendon when the fingers are extended against resistance and the elbow is held straight is diagnostic. Alternatively, the diagnosis is confirmed if the same pain occurs during the following maneuver: The patient sits on a chair with the forearm on the examination table and the elbow held flexed (bent) and the hand held palm downward; the examiner places a hand firmly on top of that of the patient, who tries to raise the hand by extending the wrist.

**Treatment**

- Rest, ice, NSAIDs, extensor muscle stretches
- Modification of activity
- Later, resistive exercises

Treatment involves a 2-phased approach. Initially, rest, ice, NSAIDs, and stretching of the extensor muscles are used. Occasionally a corticosteroid injection into the painful area around the tendon is needed. When the pain subsides, gentle resistive exercises of the extensor (see Sidebar 338-2) and
flexor (see Sidebar 338-3) muscles in the forearm are done followed by eccentric and concentric resistive exercises. Activity that hurts when the wrist is extended or pronated should be avoided. Use of a tennis elbow brace is often advised. Adjusting the fit and type of racket used can also help prevent further injury.

**Sidebar 338-2 Exercises to Strengthen the Wrist Extensors**

These exercises should be done only after the pain has subsided.

- Sit on a chair next to a table.
- Place the forearm on the table, palm facing down and elbow bent, with the wrist and hand hanging over the edge.
- Hold a light weight in the hand.
- Slowly raise and lower the hand by bending and straightening the wrist, keeping the forearm planted firmly on the table.
- Do 3 sets of 10 repetitions with 1 min of rest between repetitions.
- As the exercise becomes easier, increase the weight.

Next,

- While standing and with both arms held out in front of the body palms downward, wind up a 450-g (1-lb) weight that is attached by a rope to a piece of wood with the diameter of a broomstick (the rope will be attached to the center of the device with the hands grasping on either side). The weight should almost touch the ground when the rope is unrolled.
- Roll the weight up and down 5 or 6 times by using the strength of the forearm extensor muscles (ie, the rotation of the stick is upward and toward the body); stop if pain is felt. Repeat the exercise every other day.
- Gradually increase the weight. Do not increase the number of times that the weight is rolled up. As heavier weights are used and as tissues become stronger, frequency should decrease to once every 7 to 10 days.


Although surgery is not usually needed, surgical techniques to treat lateral epicondylitis involve removing scar and degenerative tissue from the involved extensor tendons at the elbow. Surgery is usually considered only after at least 9 to 12 mo of unsuccessful conservative treatment.

**Medial Epicondylitis**

(Golfer's Elbow)

Medial epicondylitis is inflammation of the flexor pronator muscle mass originating at the medial epicondyle of the elbow. Diagnosis is with provocative testing. Treatment is rest and ice and then exercises and gradual return to activity.

Medial epicondylitis is caused by any activity that places a valgus force on the elbow or that involves forcefully flexing the volar forearm muscles, as occurs during pitching, golfing with improper technique, serving a tennis ball (particularly with top spin, with a racket that is too heavy or too tightly strung or has an undersized grip, or with heavy balls), and throwing a javelin. Nonathletic activities that may cause
medial epicondylitis include bricklaying, hammering, and typing.

**Symptoms and Signs**

Pain occurs in the flexor pronator tendons (attached to the medial epicondyle) and in the medial epicondyle when the wrist is flexed or pronated against resistance.

**Diagnosis**

- Provocative testing

To confirm the diagnosis, the examiner has the patient sit in a chair with the forearm resting on a table and the hand supinated. The patient tries to raise the fist by bending the wrist while the examiner holds it down. Pain around the medial epicondyle and in the flexor tendon origin confirms the diagnosis.

**Treatment**

- Rest, ice, and muscle stretches
- Modification of activity
- Later, resistive exercises

Treatment is symptomatic and similar to that of lateral epicondylitis (see p. 3300). Patients should avoid any activity that causes pain. Initially, rest, ice, NSAIDs, and stretching are used, occasionally with a corticosteroid injection into the painful area around the tendon. When pain subsides, gentle resistive exercises of the extensor and flexor muscles of the forearm are done, followed by eccentric and concentric resistive exercises. In general, surgery is considered only after at least 9 to 12 mo of failed conservative management. Surgical techniques to treat medial epicondylitis involve removing scar tissue and reattaching damaged tissues.

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**Sidebar 338-3 Exercises to Strengthen the Wrist Flexors**

- Sit on a chair next to a table.

- Place the forearm on the table, palm facing up, with the wrist and hand hanging over the edge.

- Hold a light weight in the hand.

- Slowly raise and lower the hand by bending and straightening the wrist.

- The set should last about 90 to 120 sec for rehabilitation and about 50 to 70 sec for general strength and conditioning. Rest 1 min, then do additional sets until the forearms feel fatigued and worked. Repeat every 2 days while rehabilitating but only once every 7 to 10 days with normal or strong forearms and when using heavier weights and greater intensity of effort. If pain is felt, stop the exercise immediately, and try it again the next day.

- As the exercise becomes easier, increase the weight. For rehabilitation, frequency should decrease as the muscles become stronger and heavier weights are used.

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**Piriformis Syndrome**

Piriformis syndrome is compression of the sciatic nerve by the piriformis muscle in the posterior pelvis, causing pain in the buttocks and occasionally sciatica. Diagnosis is by examination. Treatment is symptomatic.
The piriformis muscle extends from the pelvic surface of the sacrum to the upper border of the greater trochanter of the femur. During running or sitting, this muscle can compress the sciatic nerve at the site where it emerges from under the piriformis to pass over the hip rotator muscles. Piriformis syndrome is uncommon.

**Symptoms and Signs**

A chronic nagging ache, pain, tingling, or numbness starts in the buttocks and can extend along the course of the sciatic nerve, down the entire back of the thigh and calf, and sometimes into the foot. Pain worsens when the piriformis is pressed against the sciatic nerve (eg, while sitting on a toilet, a car seat, or a narrow bicycle seat or while running).

**Diagnosis**

- Physical examination and provocative testing

Diagnosis is by physical examination. Pain with forceful internal rotation of the flexed thigh (Freiberg’s maneuver), abduction of the affected leg while sitting (Pace’s maneuver), raising of the knee several centimeters off the table while lying on a table on the side of the unaffected leg (Beatty’s maneuver), or pressure into the buttocks where the sciatic nerve crosses the piriformis muscle while the patient slowly bends to the floor (Mirkin test) is diagnostic. Imaging is not useful except to rule out other causes of sciatic compression. Unlike piriformis pain, lumbar disk compression of the sciatic nerve (sciatica—see p. 383) usually causes low back pain in addition to sciatic pain down the lower extremity. However, differentiation from a lumbar disk disorder is sometimes difficult, and referral to a specialist may be needed.

**Treatment**

- Modification of activity
- Stretches

Patients should temporarily stop running, bicycling, or doing any activity that elicits pain. Patients whose pain is aggravated by sitting should stand or, if unable to do so, change positions to remove the source of pressure around the buttock. Specific stretching exercises for the posterior hip and piriformis can be beneficial. Surgery is rarely warranted. A carefully directed corticosteroid injection near the site where the piriformis muscle crosses the sciatic nerve often helps temporarily. NSAIDs can also provide temporary pain relief.

**Knee Pain**

**Etiology**

There are many causes of pain in or around the knee in athletes, particularly runners, including

- Subluxation of the patella when bending the knee
- Chondromalacia of the undersurface of the patella (runner's knee, which is softening of the knee cap cartilage—see p. 2912)
- Intra-articular pathology, such as meniscal tears and plicae (infolding of the normal synovial lining of the knee)
- Fat pad inflammation
- Stress fractures of the tibia
- Malalignment of the lower extremities
• Patellar (or infrapatellar) tendinitis (jumper's knee, which is an overuse injury to the patellar tendon at the attachment to the lower pole of the patella—see p. 2913)

Knee pain may be referred from the lumbar spine or hip or result from foot problems (eg, excessive pronation or rolling inward of the foot during walking or running).

**Evaluation**

Diagnosis requires a thorough review of the injured athlete's training program, including a history of symptom onset and aggravating factors, and a complete lower-extremity examination (for knee examination, see pp. 285 and 3217).

Mechanical symptoms, such as locking or catching, suggest an internal derangement of the knee such as a meniscal tear. Instability symptoms, such as giving way and loss of confidence in the extremity when twisting or turning on the knee, suggest ligamentous injury or subluxation of the patella.

Chondromalacia is suggested by anterior knee pain after running, especially on hills, as well as pain and stiffness after sitting for any length of time (positive movie sign). On examination, pain is typically reproduced by compression of the patella against the femur.

Pain that becomes worse with weight-bearing suggests a stress fracture.

**Treatment**

Treatment is tailored to the specific cause of the pain.

Treatment of chondromalacia includes quad-riceps strengthening exercises with balanced strengthening exercises for the hamstrings, use of arch supports if excessive pronation is a possible contributor, and use of NSAIDs.

For patellar subluxation, use of patella-stabilizing pads or braces may be necessary, especially in sports that require rapid, agile movements in various planes (eg, basketball, tennis).

If there is excessive pronation of the foot, and all other possible causes of knee pain have been excluded, use of an orthotic insert is sometimes useful.

Stress fractures require rest and cessation of weight-bearing activity.

Intra-articular pathology often requires surgery.

**Shin Splints**

The term shin splints refers to nonspecific pain that occurs in the lower legs during running sports.

Repetitive impact forces during jogging, running, or vigorous walking (eg, hiking) can overload the musculotendinous unit and cause shin pain. Such pain sometimes results from a specific injury (eg, tibial stress fracture, exercise-induced compartment syndrome, tibial periostitis, excessive foot pronation), but often an exact cause cannot be identified. In such cases, the term shin splints is used.

**Symptoms and Signs**

Shin pain can occur in the anterior or posterior aspect of the leg and typically begins at the start of activity but then lessens as activity continues. Pain that persists during rest suggests another cause, such as stress fracture of the tibia.

**Diagnosis**
usually clinical

On examination, severe localized tenderness is usually present over the anterior compartment muscles, and sometimes there is palpable bone pain.

X-ray findings are usually unremarkable, regardless of the cause. If a stress fracture is suspected, a bone scan may be necessary.

Exercise-induced compartment syndrome is diagnosed by using a specialized manometer to document increased intra-compartmental pressure during exercise.

**Treatment**

- Modification of activity
- Stretches, NSAIDs

Running must be stopped until it causes no pain. Early treatment is ice, NSAIDs, and stretching of the anterior and posterior calf muscles (see Sidebar 338-4). During the rest phase of treatment, deconditioning can be minimized by encouraging cross-training techniques that do not require repetitive weight-bearing activity, such as swimming.

Once symptoms have resolved, it is advised that a return to running be gradual. Wearing supportive shoes with rigid heel counters and arch supports helps support the foot and ankle during running and can aid recovery and prevent further symptoms. Avoiding running on hard surfaces (eg, cement roads) can also help. Exercising the front of the calves by dorsiflexing the ankle against resistance (eg, rubber bands or a dorsiflexion machine) increases leg muscle strength and can help prevent shin pain.

**Sidebar 338-4 Strengthening the Calf and Shin Muscles**

### Calf

**Toe raises**

- Stand up. Slowly rise up on the toes, then slowly lower the heels to the floor.
- Do 3 sets of 10 repetitions with 1 min of rest between repetitions.
- When this exercise becomes easy, do it while holding progressively heavier weights.

### Shin

**Heel raises**

- Stand on the heels and walk 3 to 4.5 m (10 to 15 ft).
- Do this exercise 3 times.

**Achilles Tendinitis**

Achilles tendon injuries include inflammation of the paratenon and partial or complete tears.

Achilles tendinitis is very common among running athletes. The calf muscles attach to the calcaneus via the Achilles tendon. During running, the calf muscles help with the lift-off phase of gait. Repetitive forces from running combined with insufficient recovery time can initially cause inflammation in the tendon.
paratenon (fatty areolar tissue that surrounds the tendon). A complete tear of the Achilles tendon is a serious injury, usually resulting from sudden, forceful stress (see p. 3217). Tendon tears can occur with minimal exertion in people who have taken fluoroquinolone antibiotics.

**Symptoms and Signs**

The primary symptom of Achilles tendon inflammation is pain in the back of the heel, which initially increases when exercise is begun and often lessens as exercise continues. A complete tear of the Achilles tendon typically occurs with a sudden forceful change in direction when running or playing tennis and is often accompanied by a sensation of having been struck in the back of the ankle and calf with an object such as a baseball bat.

**Diagnosis**

- Clinical evaluation

On examination, an inflamed or partially torn Achilles tendon is tender when squeezed between the fingers. Complete tears are differentiated by

- Sudden, severe pain and inability to walk on the extremity
- A palpable defect along the course of the tendon
- A positive Thompson test (while the patient lies prone on the examination table, the examiner squeezes the calf muscle; this maneuver by the examiner does not cause the normally expected plantar flexion of the foot)

**Treatment**

- Ice, NSAIDs, and stretches
- Modification of activities

Tendon inflammation should initially be treated with ice, gentle calf muscle stretching, and use of NSAIDs. A heel lift can be placed in the shoes to take tension off the tendon. Athletes should be instructed to avoid uphill and downhill running until the tendon is not painful and to engage in cross-training aerobic conditioning. Complete tears of the Achilles tendon usually require surgical repair.

**Stress Fractures**

Stress fractures are small incomplete fractures that often involve the metatarsal shafts. They are caused by repetitive weight-bearing stress.

Stress fractures do not usually result from a discrete injury (eg, fall, blow) but occur instead following repeated stress and overuse that exceeds the ability of the supporting muscles to absorb the stress. Stress fractures can involve the proximal femur, pelvis, or lower extremity. Over 50% involve the lower leg and, in particular, the metatarsal shafts of the foot. Metatarsal stress fractures (march fractures) usually occur in

- Runners who too quickly change intensity of workouts, time of workouts, or both
- Poorly conditioned people who walk long distances carrying a load (eg, newly recruited soldiers)

They most commonly occur in the 2nd metatarsal. Other risk factors include the following:

- Cavus foot (a foot with a high arch)
- Shoes with inadequate shock-absorbing qualities
• Osteoporosis

Stress fractures also may be a sign of the female athlete triad (amenorrhea, eating disorder, and osteoporosis).

Symptoms and Signs

Forefoot pain that occurs after a long or intense workout and then disappears shortly after stopping exercise is the typical initial manifestation of a metatarsal stress fracture. With subsequent exercise, onset of pain is progressively earlier, and pain may become so severe that it prohibits exercise and persists even when patients are not bearing weight.

Patients who have groin pain with weight bearing must be evaluated for a proximal femur stress fracture. Patients with such fractures should be referred to a specialist.

Diagnosis

• X-ray or bone scan

Standard x-rays are recommended but may be normal until a callus forms 2 to 3 wk after the injury. Often, technetium diphosphonate bone scanning is necessary for early diagnosis. Women with stress fractures may have osteoporosis and should undergo dual-energy x-ray absorptiometry (see p. 357).

Treatment

• Restriction of weight-bearing activity

Treatment includes cessation of weight bearing on the involved foot (in case patients have a metatarsal stress fracture) and use of crutches. Although casting is sometimes used, a wooden shoe or other commercially available supportive shoe or boot is preferable to casting to avoid muscle atrophy. Healing can take anywhere from 6 to 12 wk.

Popliteus Tendinitis

Popliteus tendinitis is inflammation in the popliteus tendon, which extends from the outer surface of the bottom of the femur diagonally across the posterior knee to the medial superior tibia.

The popliteus tendon prevents the lower leg from twisting outward during running as well as helping to prevent forward movement of the femur on the tibia. Excessive running downhill tends to put excessive stress on this tendon.

Pain and soreness, particularly when running downhill, develop along the posterolateral knee. Diagnosis is by physical examination. The patient sits with the involved extremity in a cross-legged position (ie, the hip flexed, abducted, and externally rotated and the knee flexed with the leg crossed over the opposite extremity). The examiner then palpates the posterior lateral corner for tenderness.

Treatment includes rest, NSAIDs, ice, and occasionally physical therapy. Patients should not run until the area is free of pain and then should limit their workouts and downhill running for at least 6 wk. Bicycling is a good alternative exercise during healing.

Hamstring Strain

A hamstring strain is a partial tear of the hamstring muscles most commonly at the musculotendinous junction.
Hamstring strains are common among runners. Athletes at risk include those with poor flexibility of the hamstring muscles, inadequate pre-participation stretching and warm up, and previous injury. Older athletes are also at higher risk. As with any muscle strain, the amount of force that caused the muscle to tear determines the degree of injury.

**Symptoms and Signs**

Strains of the hamstring muscles can manifest as an acute painful area in the posterior thigh when sprinting or running or develop more slowly, usually because of inadequate flexibility training.

**Sidebar 338-5 Strengthening the Hamstrings**

**Upper part of the hamstrings**

- Attach a 2-kg (5-lb) weight to the foot on the injured side. Lie face down on a bed with the lower part of the body (from the waist down) off the bed and the toes touching the floor.

- Keeping the knee straight, slowly raise and lower the leg.

- Do 3 sets of 10 repetitions with 1 min of rest between repetitions.

- As strength returns, use increasingly heavier weights.

- Do this exercise every other day.

**Lower part of the hamstrings**

- Attach a 2-kg (5-lb) weight to the foot on the injured side. Stand on the other leg.

- Without bending the hip, slowly raise the weighted foot toward the buttocks by bending the knee, and lower it toward the floor by straightening the knee.

- Do 3 sets of 10 repetitions with 1 min of rest between repetitions.

- As strength returns, use increasingly heavier weights.

- Do this exercise every other day.

**Diagnosis**

- Clinical evaluation

The diagnosis is confirmed by finding ham-string pain with knee flexion against resistance as well as on palpation of the posterior thigh. In mild strains, tenderness and mild swelling are present. In more severe strains, ecchymosis, moderate to severe swelling, and poor muscle function caused by pain and weakness are present.

**Treatment**

- Rest, ice, and compression

- Stretching, then strengthening exercises

Ice and compression with use of a thigh sleeve should begin as soon as possible. NSAIDs and analgesics are prescribed as necessary, and crutches may be required initially if walking is painful.
Once pain begins to resolve, patients should begin gentle hamstring stretching. When the pain has completely resolved, gradual strengthening of the quadriceps and hamstrings is begun (see Sidebar 338-5).

Only when satisfactory strength has been achieved should patients resume running. Athletes must be made aware that recovery from hamstring injury can often take up to several months, depending on the severity.
Chapter 339. Bites and Stings

Introduction

More than 90,000 bites and stings are reported to poison control centers each year; many more occur but are not reported. Bites and stings result in about 100 deaths/yr in the US. All patients with bites and stings should receive appropriate tetanus prophylaxis (see Table 140-1 on p. 1299).

Centipede and Millipede Bites

Some larger centipedes can inflict a painful bite, causing swelling and redness. Symptoms rarely persist for more than 48 h. Millipedes do not bite but may secrete a toxin that is irritating, particularly when accidentally rubbed into the eye.

An ice cube placed on a centipede bite usually relieves the pain. Toxic secretions of millipedes should be washed from the skin with large amounts of soap and water. If a skin reaction develops, a corticosteroid cream should be applied. Eye injuries should be irrigated immediately.

Human and Mammal Bites

(See also Rat-Bite Fever on p. 1272.)

Human and other mammal (mostly dog and cat, but also squirrel, gerbil, rabbit, guinea pig, and monkey) bites are common and occasionally cause significant morbidity and disability. The hands, extremities, and face are most frequently affected, although human bites can occasionally involve breasts and genitals.

Bites by large animals sometimes cause significant tissue trauma; about 10 to 20 people, mostly children, die from dog bites each year. However, most bites involve relatively minor wounds.

Infection: In addition to tissue trauma, infection from the biting organism's oral flora is a major concern. Human bites can theoretically transmit viral hepatitis and HIV. However, HIV transmission is unlikely because the concentration of HIV in saliva is much lower than in blood and salivary inhibitors render the virus ineffective.

Rabies is a risk with certain mammal bites (see p. 1732). Monkey bites, usually restricted in the US to animal laboratory workers, carry a small risk of herpesvirus simiae infection, which causes vesicular skin lesions at the inoculation site and can progress to encephalitis, which is often fatal.

Bites to the hand (see also p. 388) carry a higher risk of infection, specifically cellulitis, tenosynovitis, septic arthritis, and osteomyelitis, than other bite sites; this higher risk is a particular concern in human bites resulting from a clenched-fist strike to the mouth (fight bite), the most common human bite wound. In fight bites, the skin wound moves away from the underlying damaged structures when the hand is opened, trapping bacteria inside, and patients often delay seeking treatment, allowing bacteria to multiply. Human bites to sites other than the hand have not been proved to carry a greater risk of infection than bites from other mammals. Cat bites to the hand also have a high risk of infection because cats' long, slender teeth often penetrate deep structures, such as joints and tendons, and the small punctures are then sealed off.

Diagnosis

• Evaluation in the position in which the bite was inflicted

• Assessment for damage to underlying nerve, tendon, bone, and vasculature and for presence of foreign bodies

Human bites sustained in an altercation are often attributed to other causes to avoid involvement of the authorities or to ensure insurance coverage. Domestic violence is often denied.
Wounds are evaluated for damage to underlying structures (eg, nerves, vasculature, tendons, bone) and for foreign bodies (see p. 3193). Evaluation should focus on careful assessment of function and the extent of the bite. Wounds over or near joints should be examined in the position in which they were inflicted (eg, with fist clenched) and explored under sterile conditions to assess tendon, bone, and joint involvement and to detect retained foreign bodies. Wounds inflicted by chomping may appear to be minor abrasions but should be examined to rule out deep injury.

Culturing fresh wounds is not valuable for targeting antimicrobial therapy, but infected wounds should be cultured. For patients with human bites, screening for hepatitis or HIV is recommended only if the attacker is known or suspected to be seropositive.

**Treatment**

- Meticulous wound care
- Selective wound closure
- Selective use of prophylactic antibiotics

Hospitalization is indicated if complications mandate very close monitoring, particularly when patient characteristics predict a high risk of nonadherence with outpatient follow-up. Hospitalization should be considered in the following circumstances:

- When a human bite is infected (including clenched-fist injuries)
- When a nonhuman bite is moderately or severely infected
- When loss of function is evident
- When the wound threatens or has damaged deep structures
- When a wound is disabling or difficult to care for at home (eg, significant wounds to both hands or both feet, hand wounds that require continuous elevation)

Priorities of treatment include wound cleaning, debridement, closure, and infection prophylaxis.

**Wound care**: Wounds should first be cleaned with a mild antibacterial soap and water (tap water is sufficient), then pressure irrigated with copious volumes of saline solution using a syringe and IV catheter. A dilute povidoneiiodine solution (10:1 with 0.9% saline) may also be used. A local anesthetic should be used as needed. Dead and devitalized tissue should be debrided.

**Wound closure** is done only for select wounds. Many wounds should initially be left open, including the following:

- Puncture wounds
- Wounds to the hands, feet, perineum, or genitals
- Wounds more than several hours old
- Wounds that are heavily contaminated
- Wounds that are markedly edematous
- Wounds that show signs of inflammation
- Wounds that involve deeper structures (eg, tendon, cartilage, bone)
• Wounds due to human bites
• Wounds sustained in a contaminated environment (eg, marine, field, sewers)

In addition, wound resolution in immunocompromised patients may be better with delayed closure. Other wounds (ie, fresh, cutaneous lacerations) can usually be closed after appropriate wound hygiene. Results with delayed primary closure are comparable to those with primary closure, so little is lost by leaving the wound open initially if there is any question.

Hand bites should be wrapped in sterile gauze, splinted in position of function (slight wrist extension, metacarpophalangeal and both interphalangeal joints in flexion). If wounds are moderate or severe, the hand should be continuously elevated (eg, hanging from a pole).

Facial bites may require reconstructive surgery given the cosmetic sensitivity of the area and the potential for scarring.

Infected wounds may require debridement, suture removal, soaking, splinting, elevation, and IV antibiotics, depending on the specific infection and clinical scenario. Joint infections and osteomyelitis may require prolonged IV antibiotic therapy and orthopedic consultation.

Antimicrobials: Thorough wound cleaning is the most effective and essential way to prevent infection and often suffices. There is no consensus on indications for prophylactic antibiotics. Studies have not confirmed a definite benefit, and widespread use of prophylactic antibiotics has the potential to select resistant organisms. Drugs do not prevent infection in heavily contaminated or inadequately cleaned wounds. However, many practitioners prescribe prophylactic antibiotics for bites to the hand and some other bites (eg, cat bites, monkey bites).

Infections are treated with antimicrobials initially chosen based on animal species. Culture results, when available, guide subsequent therapy.

• Human and dog bites: For outpatients, the preferred drug is amoxicillin/clavulanate 500 to 875 mg po bid for 3 days for prophylaxis or 5 to 7 days for treatment. Ampicillin/sulbactam 1.5 to 3.0 g IV q 6 h is a reasonable empiric choice for inpatients; it covers α-hemolytic streptococci, Staphylococcus aureus, and Eikenella corrodens, the organisms most commonly cultured from human bites, as well as Pasteurella species (P. canis and P. multocida) and Capnocytophaga canimorsus, present in dog bites. Penicillin-allergic patients with human bites can be treated with trimethoprim/sulfamethoxazole 160/800 mg IV q 12 h plus clindamycin 150 to 300 mg IV q 6 h. For penicillin-allergic patients with infected dog bites, doxycycline is an acceptable alternative, except for children > 8 yr and pregnant women. Erythromycin can be used, but the risk of treatment failure is higher because of antimicrobial resistance. Other acceptable combinations include clindamycin and a fluoroquinolone for adults or clindamycin and trimethoprim/sulfamethoxazole for children.

• Cat bites: A fluoroquinolone (eg, ciprofloxacin 500 mg po bid for 5 to 7 days) for prophylaxis and treatment is recommended because of the prevalence of P. multocida. (Bartonella henselae—see p. 1244—is also transmitted by cat bites.) Alternatives for penicillin-allergic patients are clarithromycin 500 mg po bid for 7 to 10 days or clindamycin 150 to 300 mg po qid for 7 to 10 days.

• Squirrel, gerbil, rabbit, and guinea pig bites: These bites rarely become infected, but when they do, they can be treated with the same drugs as infected cat bites.

• Monkey bites: Monkey bites should be treated prophylactically with IV acyclovir 800 mg 5 times/day for 14 days.

Patients with human bites should receive postexposure prophylaxis for viral hepatitis (see p. 254) and HIV (see p. 1459) as indicated by patient and attacker serostatus. If status is unknown, prophylaxis is not indicated.
Insect Stings

Stinging insects are members of the order Hymenoptera of the class Insecta. Hymenoptera venoms cause local toxic reactions in all people and allergic reactions only in those previously sensitized. Severity depends on the dose of venom and degree of previous sensitization. Patients exposed to swarm attacks and patients with high venom-specific IgE levels are most at risk of anaphylaxis; many children never outgrow the risk. The average unsensitized person can safely tolerate 22 stings/kg body weight; thus, the average adult can withstand > 1000 stings, whereas 500 stings can kill a child.

Unexpectedly large numbers of people seek medical attention for stings and their complications after hurricanes and possibly other environmental disasters.

Major Hymenoptera subgroups are

- **Apid** (eg, honeybees, bumblebees)
- **Vespids** (eg, wasps, yellow jackets, hornets)
- **Formicids** (eg, nonwinged fire ants)

**Apids** usually do not sting unless provoked; however, Africanized honeybees (killer bees), migrants from South America that reside in some southern and southwestern US states, are especially aggressive when agitated. Apids typically sting once and dislodge their barbed stinger into the wound, introducing venom and killing the insect. Melittin is thought to be the main pain-inducing component of the venom. The venom of Africanized honeybees is no more potent than that of other honeybees but causes more severe consequences because these insects attack in swarms and inflict multiple stings, increasing the dose of venom. In the US, bee stings cause 3 to 4 times more deaths than do venomous snakebites.

**Vespids** stingers have few barbs and do not stay in the skin, so these insects can inflict multiple stings. The venom contains phospholipase, hyaluronidases, and a protein termed antigen 5, which is the most allergenic. Although vespids also avoid stinging unless provoked, they nest close to humans, so provocative encounters are more frequent. Yellow jackets are the major cause of allergic reactions to insect stings in the US.

**Fire ants** are present in the southern US, particularly in the Gulf region, where in urban areas, they may sting as many as 40% of the population, causing at least 30 deaths/yr. There are several species, but *Solenopsis invicta* predominates and is responsible for an increasing number of allergic reactions. The ant bites to anchor itself to the person and stings repeatedly as it rotates its body in an arc around the bite, producing a characteristic central bite partially encircled by a reddened sting line. The venom has hemolytic, cytolytic, antimicrobial, and insecticidal properties; 3 or 4 small aqueous protein fractions are probably responsible for allergic reactions.

**Symptoms and Signs**

Local apid and vespid reactions are immediate burning, transient pain, and itching, with an area of erythema, swelling, and induration up to a few centimeters across. Swelling and erythema usually peak at 48 h, can persist for a week, and can involve an entire extremity. This local chemical cellulitis is often confused with secondary bacterial cellulitis, which is more painful and uncommon after envenomation. Allergic reactions may manifest with urticaria, angioedema, bronchospasm, refractory hypotension, or a combination; swelling alone is not a manifestation of allergic reaction.

Symptoms and signs of a fire ant sting are immediate pain followed by a wheal and flare lesion, which often resolves within 45 min and gives rise to a sterile pustule, which breaks down within 30 to 70 h. The lesion sometimes becomes infected and can lead to sepsis. In some cases, an edematous, erythematous, and pruritic lesion, rather than a pustule, develops. Anaphylaxis due to fire ant stings probably occurs in < 1% of patients. Mononeuritis and seizures have been reported.

**Diagnosis**
Diagnosis is clinical. Apid stings are checked for the stinger. Upper and lower airways are assessed for signs of allergic reaction. Secondary bacterial cellulitis is rare but is considered when erythema and swelling begin a day or two after the sting (rather than immediately) and pain is significant.

**Treatment**

- **Parenteral epinephrine and antihistamines for systemic allergic reactions**
- **Removal of any apid stingers**
- **Analgesics and antihistamines for local reactions**

Stingers, if present, should be removed as quickly as possible. Suggested methods include scraping with a thin dull edge (e.g., edge of a credit card, dull side of a scalpel, thin table knife).

Pain, burning, and itching can be reduced by placing an ice cube over the sting as soon as possible and giving oral H1 blockers, NSAIDs, or both. Other possibly effective local measures include antihistamine lotion (e.g., with diphenhydramine or tripelennamine), lidocaine patches, eutectic mixture of local anesthetic cream, intradermal injection of 1% lidocaine (with or without 1:100,000 epinephrine), and mid-potency corticosteroid creams or ointments (e.g., triamcinolone 0.1%). Most folk remedies (e.g., application of meat tenderizer) are of limited effectiveness.

Allergic reactions are treated with IV antihistamines; anaphylaxis is treated with parenteral epinephrine and IV fluids and vasopressors if necessary (see p. 1121).

People with known hypersensitivity to stings should carry a kit containing a prefilled syringe of epinephrine. They should use it as soon as possible after a sting and seek medical care immediately. People who have a history of anaphylaxis or a known allergy to insect bites should wear identification such as an alert bracelet.

**Prevention**

People who have had anaphylaxis are at risk from subsequent stings. Desensitization immunotherapy can be considered. Venom immunotherapy (see also p. 1116) is highly effective, reducing the chance of recurrent anaphylaxis from 50% to about 10% after 2 yr of therapy and to about 2% after 3 to 5 yr of therapy. Children who receive venom immunotherapy have a significantly lower risk of systemic reaction to stings 10 to 20 yr after treatment. Venom immunotherapy seems to be safe for use during pregnancy. Single-venom therapy is adequate. After initial immunotherapy, maintenance doses may be needed for up to 5 yr.

**Puss Moth Caterpillar (ASP) Stings**

Puss moth caterpillars (*Megalopyge opercularis*), of the order Lepidoptera, are also known as asps. They are one of the most toxic caterpillars in North America. Puss moth caterpillars are endemic to the southern US and live in shade trees and shrubbery around homes and schools and in parks. They are teardrop shaped and, because they have long silky hair, resemble a tuft of cotton or fur. Their color varies from yellow or gray to reddish brown. When a puss moth caterpillar rubs or is pressed against skin, venomous hairs become embedded.

Envenomation causes intense throbbing pain, burning, and a rash with erythematous spots. More susceptible patients can experience swelling, nausea, abdominal pain, headache, lymphadenopathy, lymphadenitis, shock, and respiratory distress. Wound pain usually subsides within an hour, and the erythematous spots disappear in a day.

Treatments for local reactions can include putting tape on the site and pulling it off to remove embedded hairs. Applying a baking soda slurry or calamine lotion can be soothing, and putting an ice pack on the site can ease pain. Treatment of systemic reactions is symptomatic. Treatment of severe reactions is like
that for insect stings.

**Marine Bites and Stings**

(For fish poisonings [eg, scombroid, ciguatera, fugu] and paralytic shellfish poisoning, see p. 3337.)

Some marine bites and stings are toxic; all create wounds at risk of infection with marine organisms, most notably *Vibrio* sp, *Aeromonas* sp, and *Mycobacterium marinum*.

Shark bites result in jagged lacerations with near-total or total amputations and should be treated in the same way as other major traumas (see p. 3190).

**Cnidaria (Coelenterates)**

Cnidaria include the following:

- Corals
- Sea anemones
- Jellyfish (including sea nettles)
- Hydroids (eg, Portuguese man-of-war)

Cnidaria are responsible for more envenomations than any other marine animal. However, of the 9000 species, only about 100 are toxic to humans. The multiple, highly developed stinging units (nematocysts) on cnidaria tentacles can penetrate human skin; one tentacle may fire thousands of nematocysts into the skin on contact.

**Symptoms and Signs**

Lesions vary with the type of cnidaria. Usually, lesions initially appear as small, linear, papular eruptions that develop rapidly in one or several discontinuous lines, at times surrounded by a raised erythematous zone. Pain is immediate and may be severe; itching is common. The papules may vesiculate and proceed to pustulation, hemorrhage, and desquamation. Systemic manifestations include weakness, nausea, headache, muscle pain and spasms, lacrimation and nasal discharge, increased perspiration, changes in pulse rate, and pleuritic chest pain. Uncommonly, fatal injuries have been inflicted by the Portuguese man-of-war in North American waters and by members of the Cubomedusae order, particularly the box jellyfish (sea wasp, *Chironex fleckeri*), in Indo-Pacific waters.

**Treatment**

- Removal of tentacles
- Symptomatic treatment
- Various rinses, depending on the specific animal

Cnidaria sting treatment includes removal of adherent tentacles with a forceps (preferably) or fingers (double-gloved if possible) and liberal rinsing to remove invisible stinging cells. The type of rinse varies by the stinging animal:

- For jellyfish stings sustained in nontropical waters and for coral stings, seawater rinse can be used.
- For jellyfish stings sustained in tropical waters, vinegar rinse followed by seawater rinse can be used. Fresh water should not be used because it can activate undischarged nematocysts.
- For box jellyfish stings, vinegar inhibits nematocyst firing and is used as the initial rinse if available,
followed by seawater rinse. Fresh water should not be used because it can activate undischarged nematocysts.

- For Portuguese man-of-war stings, saltwater rinse can be used. Vinegar should not be used because it can activate undischarged nematocysts.

Any difficulty breathing or alteration in level of consciousness, no matter how mild, is a medical emergency, requiring transport to a medical center and possibly injection of epinephrine.

Symptoms are treated supportively. Pain caused by sea nettle stings, usually short-lived, can be relieved with baking soda in a 50:50 slurry applied to the skin. For other stings, hot water or cold packs, whichever feels better, can help relieve pain, as can an NSAID or other analgesic. For severe pain, opioids are preferred. Painful muscle spasms may be treated with benzodiazepines. IV fluids and epinephrine can be given if shock develops. Antivenom is available for the stings of the box jellyfish *C. fleckeri* but not for the stings of North American species.

**Seabather's eruption:** This stinging, pruritic, maculopapular rash affects swimmers in some Atlantic locales (eg, Florida, Caribbean, Long Island). It is caused by hypersensitivity to stings from the larvae of the sea anemone (eg, *Edwardsiella lineate*) or the thimble jellyfish (*Linuche unguiculata*). The rash appears where the bathing suit contacts the skin. People exposed to these larvae should shower after taking off their bathing suit. Cutaneous manifestations can be treated with hydrocortisone lotion and, if needed, an oral antihistamine. More severe reactions may require the addition of oral or IV prednisone.

**Stingrays**

Stingrays once caused about 750 stings/yr along North American coasts; the present incidence is unknown, and most cases are not reported. Venom is contained in the one or more spines on the dorsum of the animal's tail. Injuries usually occur when an unwary swimmer wading in ocean surf, bay, or backwater steps on a stingray buried in the sand and provokes it to thrust its tail upward and forward, driving the dorsal spine (or spines) into the patient's foot or leg. The integumentary sheath surrounding the spine ruptures, and the venom escapes into the patient's tissues.

**Symptoms and Signs**

The main symptom is immediate severe pain. Although often limited to the injured area, the pain may spread rapidly, reaching its greatest intensity in < 90 min; in most cases, pain gradually diminishes over 6 to 48 h but occasionally lasts days or weeks. Syncope, weakness, nausea, and anxiety are common and may be due, in part, to peripheral vasodilation. Lymphangitis, vomiting, diarrhea, sweating, generalized cramps, inguinal or axillary pain, respiratory distress, and death have been reported.

The wound is usually jagged, bleeds freely, and is often contaminated with parts of the integumentary sheath. The edges of the wound are often discolored, and some localized tissue destruction may occur. Generally, some swelling and edema are present. Open wounds are subject to infection.

**Treatment**

- Irrigation and debridement

Injuries to an extremity should be gently irrigated with salt water in an attempt to remove fragments of spine, glandular tissue, and integument. The spine should be removed in the field only if it is superficially embedded and is not penetrating the neck, thorax, or abdomen or creating a through-and-through injury of a limb. Significant bleeding should be staunched with local pressure. Warm water immersion, although recommended by some experts, has not been verified as an effective early treatment for stingray injuries.

In the emergency department, the wound should be reexamined for remnants of the sheath and debrided; a local anesthetic may be given as needed. Embedded spines are treated similarly to other foreign bodies. Patients stung on the trunk should be evaluated closely for puncture of viscera. Treatment of systemic manifestations is supportive. Tetanus prophylaxis should be given, and an injured extremity
should be elevated for several days. Use of antibiotics and surgical wound closure may be necessary.

Mollusks

Mollusks include cones (including cone snails), cephalopods (including octopi and squids), and bivalves.

**Conus californicus:** This type is the only known dangerous cone in North American waters. Its sting causes localized pain, swelling, redness, and numbness that rarely progresses to paralysis or shock.

Treatment is largely supportive. Local measures seem to be of little value, and reports that local injection of epinephrine and neostigmine are helpful are unproved. Severe *Conus* stings may require mechanical ventilation and measures to reverse shock.

**Cone snails:** These snails are a rare cause of marine envenomation among divers and shell collectors in the Indian and Pacific Oceans. When the snail is aggressively handled (eg, during shell cleaning, when placed in a pocket), it injects its venom through a harpoon-like tooth. Multiple neurotoxins in the venom block ion channels and neurotransmitter receptors, resulting in paralysis, which is usually reversible but has resulted in some deaths.

Treatment is supportive and may include local pressure immobilization (eg, by wrapping wide crepe or other fabric bandages around the limb), immersion in hot water, and tetanus prophylaxis. Severe cases may require respiratory support.

**Octopi:** The bites of North American octopi are rarely serious.

Bites from the blue-ringed octopus, most common in Australian waters, cause tetrodotoxin envenomation, with local anesthesia, neuromuscular paralysis, and respiratory failure; treatment is supportive.

**Squid:** The large (up to 1.5 m), aggressive Humboldt squid is present off the west coast of the Americas; it has reportedly bitten fishermen and divers. Other squid species are of less concern.

**Sea Urchins**

Sea urchins are present worldwide. Most sea urchin injuries result when spines break off in the skin and cause local tissue reactions. Without treatment, the spines can migrate into deeper tissues, causing a granulomatous nodular lesion, or they may wedge against bone or nerve. Joint and muscle pain and dermatitis may also occur. A few sea urchins (eg, *Grobiferous pedicellariae*) have calcareous jaws with venom organs, enabling them to inject venom, but injuries are rare.

Diagnosis is usually obvious by history. A bluish discoloration at the entry site may help locate the spine. X-rays can help when the location is not obvious during examination.

Treatment is immediate removal. Vinegar dissolves most superficial spines; soaking the wound in vinegar several times a day or applying a wet vinegar compress may be sufficient. Hot soaks may help relieve pain. Rarely, a small incision must be made to extract the spine; care must be taken because the spine is very fragile. A spine that has migrated into deeper tissues may require surgical removal. Once spines are removed, pain may continue for days; pain beyond 5 to 7 days should trigger suspicion of infection or a retained foreign body.

*G. pedicellariae* stings are treated by washing the area and applying a mentholated balm.

**Mite Bites**

There are multiple kinds of biting mites. Chiggers are probably the most common. Chiggers are mite larvae that are ubiquitous outdoors except in arid regions; they bite, feed in the skin, then fall off. Outside the US, chiggers may carry *Rickettsia tsutsugamushi* (see p. 1285). They do not burrow into the skin, but because they are small, they are not readily seen on the skin surface.
Common mite species that bite and burrow into the skin include *Sarcoptes scabiei*, which causes scabies (see p. 713), and *Demodex* mites, which cause a scabies-like dermatitis (sometimes referred to as mange) and are a possible etiologic agent in rosacea.

Dermatitis is caused by mites that occasionally bite humans but are ordinarily ectoparasites of birds, rodents, or pets and by mites associated with plant materials or stored food or feed.

- Bird mites may bite people who handle live poultry or pet birds or who have birds’ nests on their homes.
- Rodent mites from cats, dogs (especially puppies), and rabbits may bite people.
- Swine mange mites (*S. scabiei var suis*) from pig farms or pet pigs may also bite humans.
- The straw itch mite (*Pyemotes tritici*) is often associated with seeds, straw, hay, and other plant material; it is a parasite of soft-bodied insects that are or have been present in such materials. These mites often bite people who handle the infested items. Granary workers, people who handle grass seeds or grass hay, and people who make dried plant arrangements are most at risk.

Allergic dermatitis or grocer’s itch is caused by several species of mites associated with stored grain products, cheese, and other foods. These mites do not bite but cause allergic dermatitis because people become sensitized to allergens on the mites or their waste products.

House dust mites do not bite but feed on sloughed skin cells in pillows and mattresses and on floors (especially on carpets). They are significant because many people develop pulmonary hypersensitivity to allergens in the exoskeletons and feces of house dust mites.

**Symptoms and Signs**

Most bites cause some version of pruritic dermatitis; pruritus due to chigger bites is especially intense.

**Diagnosis**

- **Clinical evaluation**

Diagnosis of nonburrowing mite bites is presumptive based on the patient's history (eg, living, working, and recreational environments) and physical examination. The mites themselves are rarely found because they fall off after biting, the skin reaction is usually delayed, and most patients seek a physician's assistance only after several days. Lesions caused by different mites are usually indistinguishable and may superficially resemble other skin conditions (eg, other insect bites, contact dermatitis, folliculitis).

Diagnosis of burrowing mites can often be made presumptively based on history and a scabies-like pattern of skin lesions. If the diagnosis is unclear or if treatment is ineffective, the diagnosis can be confirmed by skin biopsy.

**Treatment**

- **Topical corticosteroids or oral antihistamines**
- **Antimicrobial therapy for burrowing mites**

Treatment of nonburrowing mite bites is symptomatic. Topical corticosteroids or oral antihistamines are used as needed to control pruritus until the hypersensitivity reaction resolves. Through discussion of possible sources, the physician can help patients avoid repeated exposure to mites. For *Demodex* bites, veterinary consultation is needed. For treatment of scabies, see p. 714.

**Scorpion Stings**

Although all scorpions in North America sting, most are relatively harmless. The stings usually cause only...
localized pain with minimal swelling, some lymphangitis with regional lymphadenopathy, increased skin temperature, and tenderness around the wound.

A significant exception in North America is the bark scorpion (*Centruroides sculpturatus*, also known as *C. exilicauda*), present in Arizona, in New Mexico, and on the California side of the Colorado River. This species is venomous and can cause more serious injury and illness. Initial symptoms are immediate pain and sometimes numbness or tingling over the involved part. Swelling is usually absent, and there are few skin changes. Serious symptoms, most common among children, include restlessness; muscle spasms; abnormal and random head, neck, and eye movements; anxiety and agitation; and sialorrhea and diaphoresis. In adults, tachycardia, hypertension, increased respirations, weakness, muscle spasms, and fasciculations may predominate. Respiratory difficulties are rare in both age groups.

*C. sculpturatus* stings have resulted in death in children < 6 yr and in hypersensitive people.

**Diagnosis**

- Clinical evaluation

Diagnosis is obvious from the history. Determining the scorpion species is usually not. Several species of scorpions kept as exotic pets in the US (known by names that falsely suggest toxicity, such as yellow death stalker and black death scorpion) are similar in appearance to foreign species with dangerously toxic venom. However, the actual species of pet scorpion is seldom known by the patient or, if provided, may be unreliable. Stings should be treated as potentially dangerous until signs or lack of signs indicates otherwise.

**Treatment**

- Supportive care

Antivenom for severe cases in North America

Treatment of nonvenomous scorpion stings is based on symptoms. An ice pack over the wound and oral NSAIDs reduce pain. Treatment of venomous *Centruroides* stings consists of bedrest, benzodiazepines for muscle spasms, and IV drugs as needed to control hypertension, agitation, and pain. Patients should be kept npo for 8 to 12 h after the bite. Antivenom, available only in Arizona, should be given in an ICU setting to all patients with severe cases and to patients who are unresponsive to supportive care, particularly children. Information about availability and dosing may be obtained by contacting a regional poison control center.

**Snakebites**

Of about 3000 snake species throughout the world, only about 15% worldwide and 20% in the US are dangerous to humans because of venom or toxic salivary secretions (see Table 339-1). At least one species of venomous snake is native to every state in the US except Alaska, Maine, and Hawaii. Almost all are crotalines (also called pit vipers because of pitlike depressions on either side of the head, which are heat-sensing organs):

- Rattlesnakes
- Copperheads
- Cottonmouths (water moccasins)

About 45,000 snakebites (of which 7000 to 8000 are venomous) occur annually in the US. Rattlesnakes account for the majority of bites and almost all deaths. Copperheads and, to a lesser extent, cottonmouths account for most other venomous bites. Coral snakes (elapids) and imported species (in zoos, schools, snake farms, and amateur and professional collections) account for < 1% of all bites. Most patients are males between 17 and 27 yr; 50% of them are intoxicated and deliberately handled or
molested the snake. Most bites occur on the upper extremities. Five or 6 deaths occur annually in the US. Risk factors for death include age extremes, handling of captive snakes (rather than wild encounters), delay in treatment, and undertreatment.

Outside the US, fatal snakebites are much more common, accounting for > 100,000 deaths yearly.

[Table 339-1. Significant Venomous Snakes by Region]

Pathophysiology

Snake venoms are complex substances, chiefly proteins, with enzymatic activity. Although enzymes play an important role, the lethal properties of venom are caused by certain smaller polypeptides. Most venom components appear to bind to multiple physiologic receptors, and attempts to classify venom as toxic to a specific system (eg, neurotoxin, hemotoxin, cardiotoxin, myotoxin) are misleading and can lead to errors in clinical judgment.

Pit vipers: The complex venom of most North American pit vipers has local effects as well as systemic effects such as coagulopathy. Effects may include

- Local tissue damage
- Vascular defects
- Hemolysis
- A disseminated intravascular coagulation (DIC)-like (defibrination) syndrome
- Pulmonary, cardiac, renal, and neurologic defects

Venom alters capillary membrane permeability, causing extravasation of electrolytes, albumin, and RBCs through vessel walls into the envenomated site. This process may occur in the lungs, myocardium, kidneys, peritoneum, and, rarely, the CNS. Common clinical syndromes secondary to severe pit viper envenomation include the following:

- **Edema:** Initially, edema, hypoalbuminemia, and hemoconcentration occur.
- **Hypovolemia:** Later, blood and fluids pool in the microcirculation, causing hypotension, lactic acidemia, shock, and, in severe cases, multisystem organ failure. Effective circulating blood volume falls and may contribute to cardiac and renal failure.
- **Bleeding:** Clinically significant thrombocytopenia (platelet count < 20,000/μL) is common in severe rattlesnake bites and may occur alone or with other coagulopathies. Venom-induced intravascular clotting may trigger DIC-like syndrome, resulting in bleeding.
- **Renal failure:** Renal failure may result from severe hypotension, hemolysis, rhabdomyolysis, neurotoxic venom effects, or a DIC-like syndrome. Proteinuria, hemoglobinuria, and myoglobinuria may occur in reaction to severe rattlesnake bites.

The venom of most North American pit vipers causes very minor changes in neuromuscular conduction, except for Mojave and eastern diamondback rattlesnake venom, which may cause serious neurologic deficits.

Coral snakes: Venom of these snakes contains primarily neurotoxic components, which cause a presynaptic neuromuscular blockade, potentially causing respiratory paralysis. The lack of significant proteolytic enzyme activity accounts for the paucity of symptoms and signs at the bite site.

Symptoms and Signs
A snakebite, whether from a venomous or nonvenomous snake, usually causes terror, often with autonomic manifestations (eg, nausea, vomiting, tachycardia, diarrhea, diaphoresis), which may be difficult to distinguish from systemic manifestations of envenomation.

Nonvenomous snakebites cause only local injury, usually pain and 2 to 4 rows of scratches from the snake's upper jaw at the bite site.

Symptoms and signs of envenomation may be local, systemic, or a combination, depending on degree of envenomation and species of snake. Anaphylaxis can occur, particularly in snake handlers who have been previously sensitized.

Pit vipers: About 25% of pit viper bites are dry (venom is not deposited), and no systemic symptoms or signs develop.

Local signs include ≥ 1 fang marks and scratches. If envenomation has occurred, edema and erythema at the bite site and in adjacent tissues occur, usually within 30 to 60 min. Edema can progress rapidly and may involve the entire extremity within hours. Lymphangitis and enlarged, tender regional lymph nodes may develop; temperature increases over the bite area. In moderate or severe envenomations (see Diagnosis, below), ecchymosis is common and may appear at and around the bite site within 3 to 6 h. Ecchymosis is most severe after bites by eastern and western diamondbacks, cottonmouths, and prairie, Pacific, and timber rattlesnakes. Ecchymosis is less common after copperhead and Mojave rattlesnake bites. The skin around the bite may appear tense and discolored. Bullae—serous, hemorrhagic, or both—usually appear at the bite site within 8 h. Edema resulting from North American rattlesnake envenomations is usually limited to dermal and subcutaneous tissues, although severe envenomation rarely causes edema in subfascial tissue, causing compartment syndrome (defined as compartment pressures ≥ 30 mm Hg over 1 h). Necrosis around the bite site is common after rattlesnake envenomations. Most venom effects on soft tissues peak within 2 to 4 days.

Systemic manifestations of envenomation can include nausea, vomiting, diaphoresis, anxiety, confusion, spontaneous bleeding, fever, hypotension, and shock. Some patients with rattlesnake bites develop a rubbery, minty, or metallic taste in their mouth. The venom of most North American pit vipers causes minor neuromuscular conduction changes, including generalized weakness and paresthesias and muscle fasciculations. Some patients have alterations in mental status. Venom of Mojave and eastern diamondback rattlesnakes may cause serious neurologic deficits, including respiratory depression. Rattlesnake envenomations may induce various coagulation abnormalities, including thrombocytopenia, prolongation of PT (measured by the INR) or activated PTT, hypofibrinogenemia, elevated fibrin degradation products, or a combination of these disorders, resembling a DIC-like syndrome. Thrombocytopenia is usually the first manifestation and may be asymptomatic or, in the presence of a multicomponent coagulopathy, cause spontaneous bleeding. Patients with coagulopathy typically hemorrhage from the bite site or from venipuncture sites or mucous membranes, with epistaxis, gingival bleeding, hematemesis, hematochezia, hematuria, or a combination. A rise in Hct is an early finding secondary to edema and hemoconcentration. Later, Hct may fall as a result of fluid replacement and blood loss due to DIC-like syndrome. In severe cases, hemolysis may cause a rapid fall in Hct. Anaphylaxis can cause systemic symptoms immediately.

Coral snakes: Pain and swelling may be minimal or absent and are often transitory. The absence of local symptoms and signs may erroneously suggest a dry bite, producing a false sense of security for both patient and clinician. Weakness of the bitten extremity may become evident within several hours. Systemic neuromuscular manifestations may be delayed for 12 h and include weakness and lethargy; altered sensorium (eg, euphoria, drowsiness); cranial nerve palsies causing ptosis, diplopia, blurred vision, dysarthria, and dysphagia; increased salivation; muscle flaccidity; and respiratory distress or failure. Once the neurotoxic venom effects manifest, they are difficult to reverse and may last 3 to 6 days. Untreated, respiratory muscle paralysis may be fatal.

Diagnosis

• Identification of the snake
Grading severity of envenomation

Definitive diagnosis requires positive identification of the snake and clinical manifestations of envenomation. History should include the time of bite, description of the snake, type of field therapy, underlying medical conditions, allergy to horse or sheep products, and history of previous venomous snakebites and therapy. A complete physical examination, including baseline measurements of limb circumference proximal and distal to the bite site, should be done.

Snakebites should be assumed to be venomous until proved otherwise by clear identification of the species or by a period of observation.

Snake identification: Patients often cannot recall details of the snake's appearance; however, pit vipers differ from nonvenomous snakes (see Fig. 339-1). Consultation with a zoo, an aquarium, or a poison control center can help in the identification of snake species.

Coral snakes in the US have round pupils and black snouts but lack facial pits. They have blunt or cigar-shaped heads and alternating bands of red, yellow (cream), and black, often causing them to be mistaken for the common nonvenomous scarlet king snake, which has alternating bands of red, black, and yellow. The distinguishing feature in the coral snake is that the red bands are adjacent to only yellow bands, not black bands. ("red on yellow, kill a fellow; red on black, venom lack"). Coral snakes have short, fixed fangs and inject venom through successive chewing movements.

Fang marks are suggestive but not conclusive; rattlesnakes may leave single or double fang marks or other teeth marks, whereas bites by nonvenomous snakes usually leave multiple superficial teeth marks. However, the number of teeth marks and bite sites may vary because snakes may strike and bite multiple times.

A dry pit viper bite is diagnosed when no symptoms or signs of envenomation appear over 8 h.

Severity of envenomation: Severity of envenomation depends on the following:

- Size and species of the snake (rattlesnakes > cottonmouths > copperheads)
- Amount of venom injected per bite (cannot be determined by history)

[Fig. 339-1, Identifying pit vipers.]

- Number of bites
- Location and depth of the bite (eg, envenomation in bites to the head and trunk tends to be more severe than in bites to the extremities)
- Age, size, and health of the patient
- Time elapsed before treatment
- Patient's susceptibility (response) to the venom

Severity of envenomation can be graded as minimal, moderate, or severe based on local findings, systemic symptoms and signs, coagulation parameters, and laboratory results (see Table 339-2). Grading should be determined by the most severe symptom, sign, or laboratory finding.

Envenomation may progress rapidly from minimal to severe and must be continually reassessed.

If systemic symptoms begin immediately, anaphylaxis should be assumed.

Treatment
• First aid
• Supportive care
• Antivenom
• Wound care

General approach: Treatment begins immediately, before patients are moved to a medical facility.

In the field, patients should move or be moved beyond the snake’s striking distance. They should avoid exertion and be reassured, kept warm, and rapidly transported to the nearest medical facility. A bitten extremity should be loosely immobilized in a functional position just below heart level, and all rings, watches, and constrictive clothing should be removed. Pressure immobilization to delay systemic absorption of venom (eg, by wrapping wide crepe or other fabric bandages around the limb) may be appropriate for coral snake bites but is not recommended in the US, where most bites are from pit vipers; pressure immobilization may cause arterial insufficiency and necrosis. First responders should support airway and breathing, administer O\textsubscript{2}, and establish IV access in an unaffected extremity while transporting patients. All other out-of-hospital interventions (eg, tourniquets, topical preparations, wound suction by mouth or with a device with or without incision, cryotherapy, electrical shock) are of no proven benefit, may be harmful, and may delay appropriate treatment. However, tourniquets that are already placed, unless causing limb-threatening ischemia, should remain in place until patients are transported to the hospital and envenomation is excluded or definitive treatment is initiated.

Serial assessment and testing begin in the emergency department. Extremity circumference should be measured on arrival and every 15 to 20 min until local progression subsides; outlining the margins of local edema with an indelible marker can help clinicians assess progression of local envenomation. All but trivial pit viper bites require a baseline CBC (including platelets), coagulation profile (eg, PT, PTT, fibrinogen), measurement of fibrin degradation products, and urinalysis, as well as measurement of serum electrolytes, BUN, and creatinine. For moderate and severe envenomations, patients require blood typing and cross-matching, ECG, chest x-ray, and CK tests, as governed by the patient’s status, often as frequently as every 4 h for the first 12 h and then daily. In coral snake bites, neurotoxic venom effects require monitoring of O\textsubscript{2} saturation and baseline and serial pulmonary function tests (eg, peak flow, vital capacity).

[Table 339-2, Severity of Pit Viper Envenomation]

Duration of close observation for all patients with pit viper bites should be > 8 h in the emergency department or ICU. Patients without evidence of envenomation after 8 h may be sent home after adequate wound care (see p. 3319). Coral snake bite patients should be monitored for at least 12 h in an intensive care setting in case respiratory paralysis develops. Envenomation initially assessed as mild may progress to severe within several hours.

Supportive care may include respiratory support, benzodiazepines for anxiety and sedation, opioids for pain, and fluid replacement and vasopressor support for shock. Transfusions (eg, packed RBCs, fresh frozen plasma, cryoprecipitate, platelets) may be required but should not be given before patients have received adequate quantities of neutralizing antivenom because most coagulopathies respond to sufficient quantities of neutralizing antivenom. Suspected anaphylaxis (eg, with immediate onset of systemic symptoms) is treated with standard measures, including epinephrine. Tracheostomy may be needed if trismus, laryngeal spasm, or excessive salivation is present.

Antivenom: Along with aggressive supportive care, antivenom is the mainstay of treatment for patients with moderate to severe envenomation.

For pit viper envenomation, equine-derived antivenom has been largely replaced by ovine-derived Crotalidae polyvalent immune FAb antivenom (purified FAb fragments of IgG harvested from pit viper venom-immunized sheep). The effectiveness of the equine-derived antivenom is time and dose related; it
is most effective within 4 h after the envenomation and less effective after 12 h, although it may reverse coagulopathies after 24 h. Case reports suggest that Crotalidae polyvalent immune FAb may not be affected by time and dose and may be effective even when started 24 h after envenomation. Crotalidae polyvalent immune FAb is also safer than equine-derived antivenom, although it can still cause acute (cutaneous or anaphylactic) reactions and delayed hypersensitivity reactions (serum sickness). Serum sickness develops in up to 16% of patients 1 to 3 wk after administration of the FAb product. A loading dose of 4 to 6 vials of reconstituted Crotalidae polyvalent immune FAb diluted in 250 mL of normal saline should be infused slowly at 20 to 50 mL/h for the first 10 min; then if no adverse reactions occur, the remainder is infused over the next hour. The same dose can be repeated 2 times as needed to control symptoms, reverse coagulopathies, and correct physiologic parameters. In children, the dose is not decreased (eg, based on weight or size). Measuring the circumference of the involved extremity at 3 points proximal to the bite and measuring the advancing border of edema every 15 to 30 min can guide decisions about the need for additional doses. Once control is achieved, a 2-vial dose in 250 mL saline is given at 6, 12, and 18 h to prevent recurrence of limb swelling and other venom effects.

Pit viper species can affect dose. Cottonmouth envenomation may require smaller doses. Antivenom is usually unnecessary for copperhead and pygmy rattlesnake bites, except in children, the elderly, and patients with other medical conditions (eg, diabetes mellitus, coronary artery disease).

For coral snake envenomation, equine-derived polyvalent coral snake antivenom is given at a dose of 5 vials for suspected envenomation and an additional 10 to 15 vials if symptoms develop. Dose is similar for adults and children.

Equine-derived antivenom can cause hypersensitivity reactions and serum sickness. When equine-derived antivenom is required, skin testing for sensitivity to horse serum is controversial. Skin testing has no predictive value for development of acute hypersensitivity reactions, and a negative result does not completely preclude an immediate hypersensitivity reaction. However, if the skin test result is positive and the envenomation is considered life or limb threatening, H₁ and H₂ blockers should be given before antivenom administration in a critical care setting equipped to treat anaphylaxis. Early anaphylactoid reactions to antivenom are common and usually result from too-rapid infusion; treatment is temporary discontinuation of the infusion and treatment with epinephrine, H₁ and H₂ blockers, and IV fluid depending on severity. Usually, antivenom can be resumed after diluting the antivenom further and infusing it at a slower rate. Serum sickness is common and manifests 7 to 21 days after treatment as fever, rash, malaise, urticaria, arthralgia, and lymphadenopathy (see p. 1122). Treatment is H₁ blockers and a tapering course of oral corticosteroids.

Adjunctive measures: Patients should receive tetanus prophylaxis (toxoid and sometimes Ig) as suggested by history (see Table 140-1 on p. 1299). Snakebites rarely become infected, and antibiotics are indicated only for clinical evidence of infection. If necessary, options include a 1st-generation cephalosporin (eg, oral cephalaxin, IV cefazolin) or a broad-spectrum penicillin (eg, oral amoxicillin/clavulanate, IVampicillin/sulbactam). Subsequent antibiotic choices should be based on culture and sensitivity results from wound cultures.

Wound care for bites is similar to that for other puncture wounds. The area is cleaned and dressed. For limb bites, the extremity is splinted in a functional position and elevated. Wounds should be examined and cleaned daily and covered with a sterile dressing. Blebs, bloody vesicles, or superficial necrosis should be surgically debrided between days 3 and 10, in stages if needed. Sterile whirlpool may be indicated for wound debridement and physical therapy. Fasciotomy for compartment syndrome is rarely necessary but is an option when compartment pressure rises ≥ 30 mm Hg over 1 h, causes severe vascular compromise, and is unresponsive to limb elevation, mannitol 1 to 2 g/kg IV, and antivenom. Joint motion, muscle strength, sensation, and limb girth should be evaluated within 2 days after the bite. Contractures can be prevented by interrupting immobilization with frequent periods of gentle exercise, progressing from passive to active.

Regional poison control centers and zoos are excellent resources when dealing with snakebites, including those by nonnative snakes. These facilities maintain a list of physicians trained in snake identification and snakebite care as well as the Antivenin Index, published and periodically updated by the
Other Reptile Bites

Other reptile bites of significance include those of venomous lizards, alligators and crocodiles, and iguanas.

Venomous lizards: These lizards include the following:

- Gila monster (*Heloderma suspectum*), present in the southwestern US and Mexico
- Beaded lizard (*H. horridum*) of Mexico

The complex venom of these lizards contains serotonin, arginine esterase, hyaluronidase, phospholipase A$_2$, and $\geq$ 1 salivary kallikreins but lacks neurotoxic components or coagulopathic enzymes. Bites are rarely fatal. When venomous lizards bite, they clamp on firmly and chew the venom into the person.

Symptoms and signs include intense pain, swelling, ecchymosis, lymphangitis, and lymphadenopathy. Systemic manifestations, including weakness, sweating, thirst, headache, and tinnitus, may develop in moderate or severe cases. Cardiovascular collapse occurs rarely. The clinical course is similar to that of a minimal to moderate envenomation by a larger species of rattlesnake.

Treatment in the field involves removing the lizard's jaws by using pliers, by applying a flame to the lizard's chin, or by immersing the animal entirely underwater. In a hospital, treatment is supportive and similar to that for pit viper envenomation; no antivenom is available. The wound should be probed with a small needle for broken or shed teeth and then cleaned. If the wound is deep, an x-ray can be taken to rule out a retained foreign body or bone fracture. Prophylactic antibiotics are usually not recommended.

Alligators and crocodiles: Bites usually result from handling; however, rarely, native encounters occur. Bites are not venomous, are notable for a high frequency of soft-tissue infections by *Aeromonas* sp, and are generally treated as major trauma.

Wounds are irrigated and debrided; then delayed primary closure is done or the wounds are allowed to heal by secondary intention. Patients are treated preventively with clindamycin and trimethoprim/sulfamethoxazole (first choice) or tetracycline.

Iguanas: Bites and claw injuries are becoming more frequent as more are kept as pets. Wounds are superficial, and treatment is local. Soft-tissue infection is uncommon, but when infection occurs, *Salmonella* is a common cause; infection can be treated with a fluoroquinolone.

Spider Bites

Almost all of the 30,000 species of spiders are venomous. However, the fangs of most species are too short or too fragile to penetrate the skin. Serious systemic reactions most frequently occur with bites from brown spiders (eg, violin, fiddleback, brown recluse—*Loxosceles* sp) and widow spiders (black widow—*Latrodectus* sp). Brown spiders are present in the Midwest and south central US, not in the coastal and Canadian border states, except when imported through clothing or luggage. Widow spiders are present throughout the US. Several venomous species (eg, *Pamphobeteus*, *Cupiennius*, *Phoneutria*) are not native to the US but may be imported on produce or other materials or through commercial trade in spiders as novelty pets. Spider bites cause < 3 deaths/yr in the US, usually in children.

Only a few spider venoms have been studied in detail. Of greatest significance are those having necrotizing venom components (in brown and some house spiders) and neurotoxic venom components (in widow spiders). The most toxic component of widow spider venom seems to be a peptide that affects neuromuscular transmission. The specific fraction of brown spider venom that causes the characteristic
necrotic lesion has not been isolated.

**Symptoms and Signs**

**Brown spider** bites are most common in the US. Some bites are painless initially, but pain, which can be severe and involve the entire extremity, develops within 30 to 60 min in all cases. The bite area becomes erythematous and ecchymotic and may be pruritic. Generalized pruritus may also be present. A central bleb forms at the bite site, often surrounded by an irregular ecchymotic area (bull’s eye lesion). The lesion may mimic pyoderma gangrenosum. The central bleb becomes larger, fills with blood, ruptures, and leaves an ulcer; a black eschar forms over the ulcer and eventually sloughs.

Most bites leave minimal residual scarring but some can leave a large tissue defect, which may involve muscle. Loxoscelism, a venom-induced systemic syndrome, may not be detected until 24 to 72 h after the bite and is uncommon. Systemic effects (eg, fever, chills, nausea and vomiting, arthralgias, myalgias, generalized rash, seizures, hypotension, disseminated intravascular coagulation, thrombocytopenia, hemolysis, renal failure) are responsible for all reported fatalities.

**Widow spider** bites usually cause an immediate, sharp, stinging sensation. Within 1 h after envenomation, there may be progression to persistent local pain, diaphoresis, erythema, and piloerection at the bite site. The pain may be described as dull and numbing and may be disproportionate to the clinical signs. Latrodectism, a systemic syndrome caused by neurotoxic venom components, manifests as restlessness, anxiety, sweating, headache, dizziness, nausea and vomiting, hypertension, salivation, weakness, diffuse erythematous rash, pruritus, ptosis, eyelid and extremity edema, respiratory distress, increased skin temperature over the affected area, and cramping pain and muscular rigidity in the abdomen, shoulders, chest, and back. Abdominal pain may be severe and mimic acute surgical abdomen, rabies, or tetanus. Latrodectism is very uncommon and most commonly develops in patients at age extremes and those with other medical conditions. Death is extremely rare. Symptoms lessen over 1 to 3 days, but residual spasms, paresthesias, agitation, and weakness may persist for weeks to months.

**Tarantula** bites are extremely rare and nonvenomous, but agitation of the spider may cause it to throw needle-like hairs. The hairs act as foreign bodies in skin or eyes and can trigger mast cell degranulation and an anaphylactoid reaction (eg, urticaria, angioedema, bronchospasm, hypotension) in sensitized people, usually pet owners who handle the spider daily.

**Diagnosis**

- Clinical evaluation

- Careful consideration of alternative diagnoses

Spider bites are often falsely suspected by patients. Diagnosis is typically suspected based on history and physical signs, but confirmation is rare because it requires witnessed biting, identification of the spider (the spider is rarely recovered intact), and exclusion of other causes. In nonendemic areas, a brown spider bite should not be diagnosed without identifying the spider. Many patients incorrectly attribute much more common methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections to brown recluse spiders bites. Such infections should be excluded, as should other conditions that mimic spider bites (see [Table 339-3](#)). Severe cases of latrodectism should be distinguished from acute abdomen, rabies, or tetanus.

Spiders are identified by location and markings. Widow spiders live outdoors in protected spaces (eg, rock piles, firewood cords, hay bales, outhouses) and have a red or orange hourglass marking on the ventral abdomen. Brown spiders live indoors in protected spaces (eg, in clothing, behind furniture, under baseboards) and have a fiddle- or violin-like marking on the dorsal cephalothorax, ranging from the eyes to the abdomen. This marking may be difficult to recognize even in the intact spider.

**Treatment**
• Routine wound care

• Delayed excision for necrotic brown spider bites

• Ca gluconate and possibly antivenom for latrodectism

Treatment common to all spider bites includes wound cleaning, ice to reduce pain, extremity elevation, tetanus prophylaxis, and observation. Most local reactions respond to these measures alone.

For **brown spider bites**, limiting intervention to standard wound care and measures that minimize infection risk is usually most prudent:

• Ulcerating lesions should be cleaned daily and debrided as needed; topical antibiotic ointment (eg, polymyxin/bacitracin/neomycin) may be used.

• Urticarial lesions can be treated with antihistamines, topical corticosteroids, or both.

• Necrotic lesions caused by brown recluse spider bites should be cleaned and bandaged. Surgical excision, if necessary, should be delayed until the area of necrosis is fully demarcated, a process that may take weeks.

No intervention has been proved to reduce morbidity or improve outcome after a brown spider bite. Commonly touted or poorly studied treatment options are controversial or potentially harmful. Dapsone (eg, 100 mg po once/day until inflammation subsides) is often considered for ulcers > 2 cm, but its benefit is unproved. Benefit is variable, and dose-related hemolysis almost always develops; agranulocytosis, aplastic anemia, and methemoglobinemia have been documented. Local injection of corticosteroids into necrotic lesions has no value.

**Latrodectism** is initially treated supportively. Myalgias and muscle spasms due to widow spider bites respond poorly to muscle relaxants and opioid analgesics. A 10% Ca gluconate bolus given slowly IV in increments of 2 to 3 mL as needed may relieve pain briefly but requires continuous cardiac monitoring. Patients < 16 yr or > 60 yr, those with hypertension, and those with symptoms of severe envenomation should be hospitalized. Equine-derived antivenom is available for patients with severe latrodectism. It may be considered early in the course if symptoms are severe but can be effective up to 36 h after the bite. Clinical response can be dramatic. The dose for children and adults is 1 vial (6000 units) IV in 10 to 50 mL of normal saline usually over 3 to 15 min. The manufacturer recommends skin testing before administering the antivenom; however, skin testing does not always predict adverse reactions such as acute anaphylaxis.

**Tick Bites**

(See also Lyme Disease on p. 1268, Ch. 139 on p. 1279, and Babesiosis on p. 1375.)

Most tick bites in the US are from various species of Ixodidae, which attach and feed for several days if not removed. Disease transmission becomes more likely if ticks are attached for a longer duration.

Tick bites most often occur in spring and summer and are painless. The vast majority are uncomplicated and do not transmit disease; they often cause a red papule at the bite site and may induce hypersensitivity or granulomatous foreign body reactions. The bites of *Ornithodoros coriaceus* ticks (pajaroello) cause local vesiculation, pustulation with rupture, ulceration, and eschar, with varying degrees of local swelling and pain. Similar reactions have resulted from bites of other ticks.

**Diagnosis**
Diagnosis is by clinical evaluation and identification of the attached tick.

Treatment

- Tick removal with blunt, curved forceps

Ticks should be removed as soon as possible to reduce the cutaneous immune response and the likelihood of disease transmission. If the patient presents with the tick still attached, the best method of extracting the tick and all of its mouth parts from the skin is by using a blunt forceps with medium-sized, curved tips. The forceps should be placed parallel to the skin to grasp the tick's mouth parts firmly as close to the skin as possible. Care should be taken to avoid puncturing the patient's skin and the tick's body. The forceps should be pulled slowly and steadily, directly away from the skin without twisting. Curved-tip forceps are best because the outer curve can be laid against the skin while the handle remains far enough from the skin to grasp easily. Tick mouth parts that remain in the skin and are readily visible should be carefully removed. However, if the presence of mouth parts is questionable, attempts at surgical removal may cause more tissue trauma than would occur if the parts are left in the skin; leaving mouth parts in the skin does not affect disease transmission and, at most, prolongs irritation. Other methods of tick removal, such as burning it with a match (which can damage the patient's tissues) or covering it with petroleum jelly (which is ineffective), are not recommended.

After tick removal, an antiseptic should be applied. If local swelling and discoloration are present, an oral antihistamine may be helpful. Although rarely practical, the tick may be saved for laboratory analysis to check for etiologic agents of tick-borne disease in the geographic area where the patient acquired the tick.

A single dose of doxycycline (200 mg for adults and 4 mg/kg to a maximum of 200 mg for children ≥ 8 yr) should be considered when all of the following criteria are met:

- The tick is an adult or nymphal *Ixodes scapularis*.
- The tick is estimated to have been attached for ≥ 36 h based on degree of engorgement or certainty about time of exposure.
- Prophylaxis can be started within 72 h after the tick was removed.
- The local rate of infection of ticks with *Borrelia burgdorferi* is ≥ 20%.
- Doxycycline is not contraindicated.

Pajaroello tick lesions should be cleaned, soaked in 1:20 Burow's solution, and debrided when necessary. Corticosteroids are helpful in severe cases. Infections are common during the ulcer stage but rarely require more than local antiseptic measures.

**Tick Paralysis**

Tick paralysis is a rare, ascending, flaccid paralysis that occurs when toxin-secreting Ixodidae ticks bite and remain attached for several days.

In North America, some species of *Dermacentor* and *Amblyomma* cause tick paralysis due to a neurotoxin secreted in tick saliva. The toxin is not present in tick saliva during early stages of feeding, so paralysis occurs only when a tick has fed for several days or more. A single tick can cause paralysis, especially if it is attached to the back of the skull or near the spine, but multiple ticks should be sought over the entire body surface.

Symptoms and signs include anorexia, lethargy, muscle weakness, impaired coordination, nystagmus, and ascending flaccid paralysis. Bulbar or respiratory paralysis may develop.

Tick paralysis should be considered in North American patients with acute ascending flaccid paralysis or
bulbar paralysis. Differential diagnosis includes Guillain-Barre syndrome, botulism, myasthenia gravis, hypokalemia, and spinal cord tumor.

The paralysis is rapidly reversible with removal of the tick or ticks. If breathing is impaired, O₂ therapy or respiratory assistance may be needed.

**Other Arthropod Bites**

The more common biting non-tick arthropods in the US include sand flies, horseflies, deerflies, blackflies, stable flies, mosquitoes, fleas, kissing bugs, lice (see p. 711), bedbugs, wheel bugs, and certain water bugs. All of these arthropods, except wheel bugs and water bugs, also suck blood, but none are venomous.

Arthropod saliva composition varies considerably, and the lesions caused by bites vary from small papules to large ulcers with swelling and acute pain. Dermatitis may also occur. Most serious consequences result from hypersensitivity reactions or infection; in sensitized people, they can be fatal. Flea allergens may trigger respiratory allergy even without a bite in some people.

The location and pattern of wheals and lesions is sometimes diagnostic of the bite source. For example, blackfly bites are usually on the neck, ears, and face; flea bites may be numerous, mostly on the feet and legs; and bedbug bites often occur in linear patterns, most commonly on the torso.

The bite should be cleaned, and an antihistamine or corticosteroid cream or ointment should be applied for itching. Severe hypersensitivity reactions should be treated (see p. 1120).
Chapter 340. Poisoning

Introduction

Accidental poisoning and intentional self-poisoning result in many emergency department visits and a few deaths. (For effects of alcohol and illicit drug use, see Ch. 160.)

General Principles of Poisoning

Poisoning is contact with a substance that results in toxicity. Symptoms vary, but certain common syndromes may suggest particular classes of poisons. Diagnosis is primarily clinical, but for some poisonings, blood and urine tests can help. Treatment is supportive for most poisonings; specific antidotes are necessary for a few. Prevention includes labeling drug containers clearly and keeping poisons out of the reach of children.

Most poisonings are dose-related. Toxicity may result from exposure to excess amounts of normally nontoxic substances. Some poisonings result from exposure to substances that are poisonous at all doses. Poisoning is distinguished from hypersensitivity and idiosyncratic reactions, which are unpredictable and not dose-related, and from intolerance, which is a toxic reaction to a usually nontoxic dose of a substance.

Poisoning is commonly due to ingestion but can result from injection, inhalation, or exposure of body surfaces (eg, skin, eye, mucous membranes). Many commonly ingested non-food substances are generally nontoxic (see Table 340-1); however, almost any substance can be toxic if ingested in excessive amounts.

Accidental poisoning is common among young children, who are curious and ingest items indiscriminately despite noxious tastes and odors; usually, only a single substance is involved. Poisoning is also common among older children, adolescents, and adults attempting suicide; multiple drugs, including alcohol, acetaminophen, and other OTC drugs, may be involved. Accidental poisoning may occur in the elderly because of confusion, poor eyesight, mental impairment, or multiple prescriptions of the same drug by different physicians.

Occasionally, people are poisoned by someone who intends to kill or disable them (eg, to rape or rob them). Drugs used to disable (eg, scopolamine, benzodiazepines, y-hydroxy-butyrate) tend to have sedative or amnestic properties or both. Rarely, parents, who may have some medical knowledge, poison their children because of unclear psychiatric reasons or a desire to cause illness and thus gain medical attention (a disorder called Munchausen syndrome by proxy—see p. 1576).

Most poisons are metabolized, pass through the GI tract, or are excreted. Occasionally, tablets (eg, aspirin, iron, enteric-coated drugs) form large concretions (bezoars) in the GI tract, where they tend to remain, continuing to be absorbed and causing toxicity.

Symptoms and Signs

Symptoms and signs vary depending on the substance (see Table 340-8 on p. 3345). Also, different patients poisoned with the same substance may present with very different symptoms. However, 6 clusters of symptoms (toxic syndromes, or toxidromes) occur commonly and may suggest particular classes of substances (see Table 340-2). Patients who ingest multiple substances are less likely to have symptoms characteristic of a single substance.

Symptoms typically begin soon after contact but, with certain poisons, are delayed. The delay may occur because only a metabolite is toxic rather than the parent substance (eg, methanol, ethylene glycol, hepatotoxins). Ingestion of hepatotoxins (eg, acetaminophen, iron, Amanita phalloides mushrooms) may
cause acute liver failure that occurs one to a few days later. With metals or hydrocarbon solvents, symptoms typically occur only after chronic exposure to the toxin.

Ingested toxins generally cause systemic symptoms. Caustics and corrosive liquids damage mainly the mucous membranes of the GI tract, causing stomatitis, enteritis, or perforation. Some toxins (eg, alcohol, hydrocarbons) cause characteristic breath odors. Skin contact with toxins can cause various acute cutaneous symptoms (eg, rashes, pain, blistering); chronic exposure may cause dermatitis. Inhaled toxins are likely to cause symptoms of upper airway injury if they are water-soluble and symptoms of lower airway (lung parenchyma) injury and noncardiogenic pulmonary edema if they are less water-soluble. Inhalation of carbon monoxide, cyanide, or hydrogen sulfide gas can cause organ ischemia or cardiac or respiratory arrest. Eye contact with toxins (solid, liquid, or vapor) may damage the cornea and lens, causing eye pain, redness, and loss of vision.

Some substances (eg, cocaine, phencyclidine, amphetamine) can cause severe agitation, which can result in hyperthermia, acidosis, and rhabdomyolysis.

**Diagnosis**

- Consideration of poisoning in patients with altered consciousness or unexplained symptoms
- History from all available sources
- Selective, directed testing

The first step of diagnosis is to assess the overall status of the patient. Severe poisoning may require rapid intervention to treat cardiopulmonary collapse.

Poisoning may be known at presentation. It should be suspected if patients have unexplained symptoms, especially altered consciousness. If purposeful self-poisoning occurs in adults, multiple substances should be suspected.

History is often the most valuable tool. Because many patients (eg, preverbal children, suicidal or psychotic adults, patients with altered consciousness) cannot provide reliable information, friends, relatives, and rescue personnel should be questioned. Even seemingly reliable patients may incorrectly report the amount or time of ingestion. When possible, the patient's living quarters should be inspected for clues (eg, partially empty pill containers, evidence of recreational drug use). Pharmacy and medical records may provide useful information. In potential workplace poisonings, coworkers and supervisors should be questioned. All industrial chemicals must have a material safety data sheet (MSDS) readily available at the workplace; the MSDS provides detailed information about toxicity and any specific treatment.

In the US, Europe, and parts of Asia and South America, information about household and industrial chemicals can be obtained from poison control centers. Consultation with the centers is encouraged because ingredients, first-aid measures, and antidotes printed on product containers are occasionally inaccurate or outdated. Also, the container may have been replaced, or the package may have been tampered with. Poison control centers may be able to help identify unknown pills based on their appearance. The centers have ready access to toxicologists. The telephone number of the nearest center is often listed with other emergency numbers in the front of the local telephone book; the number is also available from the telephone operator or, in the US, by dialing 1-800-222-1222. More information is available at the American Association of Poison Control Centers web site (www.aapcc.org).

Physical examination sometimes detects signs suggesting particular types of substances (eg, toxidromes, breath odor, needle tracks suggesting IV drug use, stigmas of chronic alcohol use).
Even if a patient is known to be poisoned, altered consciousness may have other causes (eg, CNS infection, head trauma, hypoglycemia, stroke, hepatic encephalopathy, Wernicke's encephalopathy), which should also be considered. Attempted suicide must always be considered in older children, adolescents, and adults who have ingested a drug. After such patients are stabilized, psychiatric intervention should be considered.

Testing: In most cases, laboratory testing provides limited help. Standard, readily available tests to identify common drugs of abuse (often called toxic screens) are qualitative, not quantitative. These tests may provide false results and they check for only a limited number of substances. Also, the presence of a drug of abuse does not necessarily indicate that the drug caused the patient's symptoms or signs. Urine drug screening is used most often but has limited value and usually detects classes of drugs or metabolites rather than specific drugs. For example, an opioid urine immunoassay test does not detect fentanyl or methadone but does react with very small amounts of morphine or codeine analogues. The test used to identify cocaine detects a metabolite rather than cocaine itself.

For most substances, blood levels cannot be easily determined or do not help guide treatment. For a few substances (eg, acetaminophen, aspirin, carbon monoxide, digoxin, ethylene glycol, iron, lithium, methanol, phenobarbital, phenytoin, theophylline), blood levels may help guide treatment. Many authorities recommend measuring acetaminophen levels in all patients with mixed ingestions because acetaminophen ingestion is common, is often asymptomatic during the early stages, and can cause serious delayed toxicity that can be prevented by an antidote. For some substances, other blood tests (eg, PT for warfarin overdose, methemoglobin levels for certain substances) may help guide treatment. For patients who have altered consciousness or abnormal vital signs or who have ingested certain substances, tests should include serum electrolytes, BUN, creatinine, osmolality, glucose, and ABGs. Other tests may be indicated for specific substances.

For certain poisonings (eg, due to iron, lead, arsenic, other metals, or to packets of cocaine or other illicit drugs ingested by so-called body packers), plain abdominal x-rays may show the presence and location of ingested substances.

For poisonings with drugs that have cardiovascular effects or with an unknown substance, ECG and cardiac monitoring are indicated.

If blood levels of a substance or symptoms of toxicity increase after initially decreasing or persist for an unusually long time, a bezoar, a sustained-release preparation, or reexposure (ie, repeated covert exposure to a recreationally used drug) should be suspected.

Treatment

• Supportive care

• Activated charcoal for serious oral poisonings

• Occasional use of specific antidotes or dialysis

• Only rare use of gastric emptying

Seriously poisoned patients may require assisted ventilation or treatment of cardiovascular collapse. Those with impaired consciousness may require continuous monitoring or restraints. The discussion of treatment for specific poisonings, below and in Tables 340-3, 340-4, and 340-8, is general and does not include specific complexities and details. Consultation with a poison control center is recommended for any poisonings except the mildest and most routine.

Initial stabilization: Treatment of any systemic poisoning begins with airway, breathing, and circulatory stabilization (see p. 2256).

If patients have apnea or compromised airways (eg, foreign material in the oropharynx, decreased gag
reflex), an endotracheal tube should be inserted. If patients have respiratory depression or hypoxia, supplemental O\textsubscript{2} or mechanical ventilation should be provided as needed.

In patients with apnea, IV naloxone (2 mg in adults; 0.1 mg/kg in children) should be tried while airway support is maintained. In opioid addicts, naloxone may precipitate withdrawal, but withdrawal is preferable to apnea. If respiratory depression persists despite use of naloxone, endotracheal intubation and continuous mechanical ventilation are required. If naloxone relieves respiratory depression, patients are monitored; if respiratory depression recurs, patients can be treated with another bolus of IV naloxone or mechanical ventilation. Using a low-dose continuous naloxone infusion to maintain respiratory drive without precipitating withdrawal has been suggested but in reality is very difficult to accomplish.

If patients have altered consciousness, blood glucose should be measured immediately at bedside, or IV dextrose (50 mL of a 50% solution for adults; 2 to 4 mL/kg of a 25% solution for children) should be given empirically. For adults with suspected thiamin deficiency (eg, alcoholics, undernourished patients), thiamin 100 mg IV is given with or before glucose.

Hypotension is treated with IV fluids. If fluids are ineffective, invasive hemodynamic monitoring may be necessary to guide fluid and vasopressor therapy. The first-choice vasopressor for most poison-induced hypotension is norepinephrine 0.5 to 1 mg/min IV infusion, but treatment should not be delayed if another vasopressor is more immediately available.

**Topical decontamination:** Any body surface (including the eyes) exposed to a toxin is flushed with large amounts of water or saline. Contaminated clothing, including shoes and socks, and jewelry should be removed.

**Activated charcoal:** Charcoal is usually given, particularly when multiple or unknown substances have been ingested. Use of charcoal adds little risk, unless patients are at risk of vomiting and aspiration, but has not been proved to reduce overall morbidity or mortality. When used, charcoal is given as soon as possible. Activated charcoal adsorbs most toxins because of its molecular configuration and large surface area. Multiple doses of activated charcoal may be effective for substances that undergo enterohepatic recirculation (eg, phenobarbital, theophylline) and for sustained-release preparations. Charcoal may be given at 4- to 6-h intervals for serious poisoning with such substances unless bowel sounds are hypoactive. Charcoal is ineffective for caustics, alcohols, and simple ions (eg, cyanide, iron, other metals, lithium). The recommended dose is 5 to 10 times that of the suspected toxin ingested. However, because the amount of toxin ingested is usually unknown, the usual dose is 1 to 2 g/kg, which is about 10 to 25 g for children < 5 yr and 50 to 100 g for older children and adults. Charcoal is given as a slurry in water or soft drinks. It may be unpalatable and results in vomiting in 30% of patients. Administration via a gastric tube may be considered, but caution should be used to prevent trauma caused by tube insertion or aspiration of charcoal. Activated charcoal should probably be used without sorbitol or other cathartics, which have no clear benefit and can cause dehydration and electrolyte abnormalities.

**Gastric emptying:** Gastric emptying, which used to be well-accepted and seems intuitively beneficial, is not routinely done. It does not clearly reduce overall morbidity or mortality and has risks. Gastric emptying is considered if it can be done within 1 h of a life-threatening ingestion. However, many poisonings manifest too late, and whether a poisoning is life threatening is not always clear. Thus, gastric emptying is seldom indicated and, if a caustic substance has been ingested, is contraindicated (see p. 3335).

If gastric emptying is used, gastric lavage is the preferred method. Gastric lavage may cause complications such as epistaxis, aspiration, or, rarely, opharyngeal or esophageal injury. Syrup of ipecac has unpredictable effects, often causes prolonged vomiting, and may not remove substantial amounts of poison from the stomach. Syrup of ipecac may be warranted if the ingested agent is highly toxic and transport time to the emergency department is unusually long, but this is uncommon in the US.

For gastric lavage, tap water is instilled and withdrawn from the stomach with a tube. The largest tube possible (usually > 36 French for adults or 24 French for children) is used so that tablet fragments can be
retrieved. If patients have altered consciousness or a weak gag reflex, endotracheal intubation should be done before lavage to prevent aspiration. Patients are placed in the left lateral decubitus position to prevent aspiration, and the tube is inserted orally. Because lavage sometimes forces substances farther into the GI tract, a 25-g dose of charcoal is instilled through the tube first. Then aliquots (about 3 mL/kg) of tap water are instilled, and the gastric contents are withdrawn by gravity or syringe. Lavage continues until the withdrawn fluids appear free of the substance; usually, 500 to 3000 mL of fluid must be instilled. After lavage, a 2nd 25-g dose of charcoal is instilled.

**Whole-bowel irrigation:** This procedure flushes the GI tract and theoretically decreases GI transit time for pills and tablets. Irrigation has not been proved to reduce morbidity or mortality. Irrigation is indicated for any of the following:

- Some serious poisonings due to sustained-release preparations or substances that are not adsorbed by charcoal (eg, heavy metals)
- Drug packets (eg, latex-coated packets of heroin or cocaine ingested by body packers)
- A suspected bezoar

A commercially prepared solution of polyethylene glycol (which is nonabsorbable) and electrolytes is given at a rate of 1 to 2 L/h for adults or at 25 to 40 mL/kg/h for children until the rectal effluent is clear; this process may require many hours or even days. The solution is usually given via a gastric tube, although some motivated patients can drink these large volumes.

**Alkaline diuresis:** Alkaline diuresis enhances elimination of weak acids (eg, salicylates, phenobarbital). A solution made by combining 1 L of 5% D/W with 3 50-mEq ampules of NaHCO₃ and 20 to 40 mEq of K can be given at a rate of 250 mL/h in adults and 2 to 3 mL/kg/h in children. Urine pH is kept at > 8. Hypernatremia, alkalemia, and fluid overload may occur but are usually not serious. However, alkaline diuresis is contraindicated in patients with renal insufficiency.

**Dialysis:** Common toxins that may require dialysis or hemoperfusion include

- Ethylene glycol
- Lithium
- Methanol
- Salicylates
- Theophylline

These therapies are less useful if the poison is a large or charged (polar) molecule, has a large volume of distribution (ie, if it is stored in fatty tissue), or is extensively bound to tissue protein (as with digoxin, phencyclidine, phenothiazines, or tricyclic antidepressants). The need for dialysis is usually determined by both laboratory values and clinical status. Methods of dialysis include hemodialysis, peritoneal dialysis, and lipid dialysis (which removes lipid-soluble substances from the blood), as well as hemoperfusion (which more rapidly and efficiently clears specific poisons—see Ch. 240).

**Specific antidotes:** For the most commonly used antidotes, see Table 340-3. Chelating drugs are used for poisoning with heavy metals and occasionally with other drugs (see Table 340-4). IV fat emulsions have been used in 10% and 20% concentrations to successfully treat several different cardiac toxins (eg, bupivacaine, verapamil).
**Ongoing supportive measures:** Most symptoms (eg, agitation, sedation, coma, cerebral edema, hypertension, arrhythmias, renal failure, hypoglycemia) are treated with the usual supportive measures (see elsewhere in THE MANUAL).

Drug-induced hypotension and arrhythmias may not respond to the usual drug treatments. For refractory hypotension, dopamine, epinephrine, other vasopressors, an intra-aortic balloon pump, or even extracorporeal circulatory support may be considered.

For refractory arrhythmias, cardiac pacing may be necessary. Often, torsades de pointes can be treated with Mg sulfate 2 to 4 g IV, overdrive pacing, or a titrated isoproterenol infusion.

Seizures are first treated with benzodiazepines. Phenobarbital or phenytoin can also be used. Severe agitation must be controlled; benzodiazepines in large doses, other potent sedatives (eg, propofol), or, in extreme cases, induction of paralysis and mechanical ventilation may be required.

Hyperthermia is treated with aggressive sedation and physical cooling measures rather than with antipyretics. Organ failure may ultimately require kidney or liver transplantation.

**Hospital admission:** General indications for hospital admission include altered consciousness, persistently abnormal vital signs, and predicted delayed toxicity. For example, admission is considered if patients have ingested sustained-release preparations, particularly of drugs with potentially serious effects (eg, cardiovascular drugs). If there are no other reasons for admission and if symptoms are gone after patients have been observed for 4 to 6 h, most patients can be discharged. However, if ingestion was intentional, patients require a psychiatric evaluation.

**Prevention**

In the US, widespread use of child-resistant containers with safety caps has greatly reduced the number of poisoning deaths in children < 5 yr. Limiting the amount of OTC analgesics in a single container reduces the severity of poisonings, particularly with acetaminophen, aspirin, or ibuprofen. Preventive measures also include clearly labeling household products and prescription drugs, storing drugs and toxic substances in cabinets that are locked and inaccessible to children, promptly disposing of expired drugs by mixing them in cat litter or some other nontempting substance and putting them in a trash container that is inaccessible to children, and using carbon monoxide detectors. Public education measures to encourage storage of substances in their original containers (eg, not placing insecticide in drink bottles) are important. Use of imprint identifications on solid drugs helps prevent confusion and errors by patients, pharmacists, and health care practitioners.

**Acetaminophen Poisoning**

Acetaminophen poisoning can cause gastroenteritis within hours and hepatotoxicity 1 to 3 days after ingestion. Severity of hepatotoxicity after a single acute overdose is predicted by serum acetaminophen levels. Treatment is with N-acetylcysteine to prevent or minimize hepatotoxicity.

Acetaminophen is contained in > 100 products sold OTC. Products include many children's preparations in liquid, tablet, and capsule form and many cough and cold preparations. Many prescription drugs also contain acetaminophen. Consequently, acetaminophen overdose is common.

**Pathophysiology**

The principal toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI), is produced by the hepatic cytochrome P-450 enzyme system; glutathione stores in the liver detoxify this metabolite. An acute overdose depletes glutathione stores in the liver. As a result, NAPQI accumulates, causing hepatocellular necrosis and possibly damage to other organs (eg, kidneys, pancreas). Theoretically, alcoholic liver disease or undernutrition could increase risk of toxicity because hepatic enzyme preconditioning may increase formation of NAPQI and because undernutrition (also common among alcoholics) reduces hepatic glutathione stores. However, whether the risk is actually increased is unclear.
Acute alcohol ingestion may be protective because hepatic P-450 enzymes preferentially metabolize ethanol and thus cannot produce toxic NAPQI.

**Acute Acetaminophen Poisoning**

To cause toxicity, an acute overdose must total ≥ 150 mg/kg (about 7.5 g in adults) within 24 h.

**Symptoms and Signs**

Mild poisoning may not cause symptoms, and when present, symptoms are usually minor until ≥ 48 h after ingestion. Symptoms, which occur in 4 stages (see Table 340-5), include anorexia, nausea, vomiting, and right upper quadrant abdominal pain. Renal failure and pancreatitis may occur, occasionally without liver failure. After > 5 days, hepatotoxicity resolves or progresses to multiple organ failure, which can be fatal.

**Diagnosis**

- Diagnosis considered in all patients with nonaccidental ingestions
- Serum acetaminophen levels
- Rumack-Matthew nomogram

Acetaminophen overdose should be considered in all patients with nonaccidental ingestions that may be suicide attempts because formulations containing acetaminophen are frequently ingested in such overdoses and are not reported. Also, acetaminophen often causes minimal symptoms during the early stages and is potentially lethal but treatable.

Likelihood and severity of hepatotoxicity caused by an acute ingestion can be predicted by the amount ingested or, more accurately, by the serum acetaminophen level. If the time of ingestion is known, the Rumack-Matthew nomogram (see Fig. 340-1) is used to estimate likelihood of hepatotoxicity; if the time of ingestion is unknown, the nomogram cannot be used. For a single acute overdose of traditional acetaminophen or rapid-relief acetaminophen (which is absorbed 7 to 8 min faster), levels are measured ≥ 4 h after ingestion and plotted on the nomogram. A level ≤ 150 μg/mL (≤ 990 μmol/L) and absence of toxic symptoms indicate that hepatotoxicity is very unlikely. Higher levels indicate possible hepatotoxicity. For a single acute overdose with extended-relief acetaminophen (which has 2 peak serum levels about 4 h apart), acetaminophen levels are measured ≥ 4 h after ingestion and 4 h later; if either level is above the Rumack-Matthew line of toxicity, treatment is required.

If poisoning is confirmed or strongly suspected, other tests are done. Liver function tests are done and, in suspected severe poisoning, PT is measured. AST and ALT results correlate with the stage of poisoning (see Table 340-5). AST levels > 1000 IU/L are more likely to result from acetaminophen poisoning than from chronic hepatitis or alcoholic liver disease. If poisoning is severe, bilirubin and INR may be elevated.

**Prognosis**

With appropriate treatment, mortality is uncommon.

**Poor prognostic indicators** at 24 to 48 h postingestion include all of the following:

- pH < 7.3 after adequate resuscitation
• INR > 3
• Serum creatinine > 2.6
• Hepatic encephalopathy grade III (confusion and somnolence) or grade IV (stupor and coma)
• Hypoglycemia
• Thrombocytopenia

Acute acetaminophen toxicity does not predispose patients to cirrhosis.

Treatment

• Oral or IV N-acetylcysteine
• Possibly activated charcoal

Activated charcoal may be given if acetaminophen is likely to still remain in the GI tract.

N-Acetylcysteine is an antidote for acetaminophen poisoning. This drug is a glutathione precursor that decreases acetaminophen toxicity by increasing hepatic glutathione stores and possibly via other mechanisms. It helps prevent hepatic toxicity by inactivating the toxic acetaminophen metabolite NAPQI before it can injure liver cells. However, it does not reverse damage to liver cells that has already occurred.

For acute poisoning, N-acetylcysteine is given if hepatotoxicity is likely based on acetaminophen dose or serum level. The drug is most effective if given within 8 h of acetaminophen ingestion. After 24 h, the benefit of the antidote is questionable.

N-Acetylcysteine is equally effective given IV or orally. IV therapy is given as a continuous infusion. A loading dose of 150 mg/kg in 200 mL of 5% D/W given over 15 min is followed by maintenance doses of 50 mg/kg in 500 mL of 5% D/W given over 4 h, then 100 mg/kg in 1000 mL of 5% D/W given over 16 h. For children, dosing may need to be adjusted to decrease the total volume of fluid delivered; consultation with a poison control center is recommended.

The oral loading dose of N-acetylcysteine is 140 mg/kg. This dose is followed by 17 additional doses of 70 mg/kg q 4 h. Oral acetylcysteine is unpalatable; it is given diluted 1:4 in a carbonated beverage or fruit juice and may still cause vomiting. If vomiting occurs, an antiemetic can be used; if vomiting occurs within 1 h of a dose, the dose is repeated. However, vomiting may be protracted and may limit oral use. Allergic reactions are unusual but have occurred with oral and IV use.

Liver failure is treated supportively. Patients with fulminant liver failure may require liver transplantation.

Chronic Acetaminophen Poisoning

Chronic excessive use or repeated overdoses cause hepatotoxicity in a few patients. Usually, chronic overdose is not an attempt at self-injury but instead results from taking inappropriately high doses to treat pain. Symptoms may be absent or may include any of those that occur with acute overdose.

Diagnosis

• AST, ALT, and serum acetaminophen levels

The Rumack-Matthew nomogram cannot be used, but likelihood of clinically significant hepatotoxicity can be estimated based on AST, ALT, and serum acetaminophen levels.
If AST and ALT levels are normal (< 50 IU/L) and the acetaminophen level is < 10 μg/mL, significant hepatotoxicity is very unlikely.

If AST and ALT levels are normal but the acetaminophen level is ≥ 10 μg/mL, significant hepatotoxicity is possible; AST and ALT levels are remeasured after 24 h. If repeat AST and ALT levels are normal, significant hepatotoxicity is unlikely; if the levels are high, significant hepatotoxicity is assumed.

If initial AST and ALT levels are high, regardless of the acetaminophen level, significant hepatotoxicity is assumed.

**Treatment**

Sometimes *N*-acetylcysteine

The role of *N*-acetylcysteine in treatment of chronic acetaminophen toxicity or in the presence of established acute hepatotoxicity is unclear. Theoretically, the antidote may have some benefit if given > 24 h after an ingestion if residual (unmetabolized) acetaminophen is present. The following approach has not been proved effective but may be used:

If hepatotoxicity is possible (if AST and ALT levels are normal and acetaminophen level is initially elevated), *N*-acetylcysteine is given 140 mg/kg po loading dose and 70 mg/kg po q 4 h for the first 24 h. If repeat AST and ALT levels (after 24 h) are normal, *N*-acetylcysteine is stopped; if repeat levels are high, they are remeasured daily, and *N*-acetylcysteine is continued until levels are normal.

If hepatotoxicity is likely (especially if initial AST and ALT levels are high), a full course of *N*-acetylcysteine is given.

Prognostic factors are similar to those in acute acetaminophen poisoning.

**Aspirin and Other Salicylate Poisoning**

*(Salicylism)*

Salicylate poisoning can cause vomiting, tinnitus, confusion, hyperthermia, respiratory alkalosis, metabolic acidosis, and multiple organ failure. Diagnosis is clinical, supplemented by measurement of the anion gap, ABGs, and serum salicylate levels. Treatment is with activated charcoal and alkaline diuresis or hemodialysis.

Acute ingestion of > 150 mg/kg can cause severe toxicity. Salicylate tablets may form bezoars, prolonging absorption and toxicity. Chronic toxicity can occur after several days of high therapeutic doses; it is common, often undiagnosed, and often more serious than acute toxicity. Chronic toxicity tends to occur in elderly patients.

The most concentrated and toxic form of salicylate is oil of wintergreen (methyl salicylate, a component of some liniments and solutions used in hot vaporizers); ingestion of < 5 mL can kill a young child. Any exposure should be considered serious. Bismuth subsalicylate (8.7 mg salicylate/mL) is another potentially unexpected source of large amounts of salicylate.

**Pathophysiology**

Salicylates impair cellular respiration by uncoupling oxidative phosphorylation. They stimulate respiratory centers in the medulla, causing primary respiratory alkalosis, which is often unrecognized in young children. Salicylates simultaneously and independently cause primary metabolic acidosis. Eventually, as salicylates disappear from the blood, enter the cells, and poison mitochondria, metabolic acidosis becomes the primary acid-base abnormality.

Salicylate poisoning also causes ketosis, fever, and, even when systemic hypoglycemia is absent, low brain glucose levels. Renal Na, K, and water loss and increased but imperceptible respiratory water loss
due to hyperventilation lead to dehydration.

Salicylates are weak acids that cross cell membranes relatively easily; thus, they are more toxic when blood pH is low. Dehydration, hyperthermia, and chronic ingestion increase salicylate toxicity because they result in greater distribution of salicylate to tissues. Excretion of salicylates increases when urine pH increases.

**Symptoms and Signs**

With acute overdose, early symptoms include nausea, vomiting, tinnitus, and hyperventilation. Later symptoms include hyperactivity, fever, confusion, and seizures. Rhabdomyolysis, acute renal failure, and respiratory failure may eventually develop. Hyperactivity may quickly turn to lethargy; hyperventilation (with respiratory alkalosis) progresses to hypoventilation (with mixed respiratory and metabolic acidosis) and respiratory failure.

With chronic overdose, symptoms and signs tend to be nonspecific and vary greatly. They include subtle confusion, changes in mental status, fever, hypoxia, noncardiogenic pulmonary edema, dehydration, lactic acidosis, and hypotension.

**Diagnosis**

- Serum salicylate level
- ABGs

Salicylate poisoning is suspected in patients with any of the following:

- History of a single acute overdose
- Repeated ingestions of therapeutic doses (particularly in patients with fever and dehydration)
- Unexplained metabolic acidosis
- Unexplained confusion and fever (in elderly patients)

If poisoning is suspected, serum salicylate (drawn at least a few hours after ingestion), urine pH, ABGs, serum electrolytes, serum creatinine, plasma glucose, and BUN are measured. If rhabdomyolysis is suspected, serum CK and urine myoglobin are measured.

Significant salicylate toxicity is suggested by serum levels much higher than therapeutic (therapeutic range, 10 to 20 mg/dL), particularly 6 h after ingestion (when absorption is usually almost complete), and by acidemia plus ABG results compatible with salicylate poisoning. Serum levels are helpful in confirming the diagnosis and may help guide therapy, but levels may be misleading and should be clinically correlated.

Usually, ABGs suggest primary respiratory alkalosis during the first few hours after ingestion; later, they suggest compensated metabolic acidosis or mixed metabolic acidosis/respiratory alkalosis. Eventually, usually as salicylate levels decrease, poorly compensated or uncompensated metabolic acidosis is the primary finding. If respiratory failure occurs, ABGs suggest combined metabolic and respiratory acidosis, and chest x-ray shows diffuse pulmonary infiltrates. Plasma glucose levels may be normal, low, or high. Serial salicylate levels help determine whether absorption is continuing; ABGs or serum electrolytes should always be determined simultaneously. Increased serum CK and urine myoglobin levels suggest rhabdomyolysis.

**Treatment**

- Activated charcoal
• Alkaline diuresis with extra KCl

Activated charcoal is given as soon as possible and, if bowel sounds are present, may be repeated every 4 h until charcoal appears in the stool.

After volume and electrolyte abnormalities are corrected, alkaline diuresis can be used to increase urine pH, ideally to ≥ 8. Alkaline diuresis is indicated for patients with any symptoms of poisoning and should not be delayed until salicylate levels are determined. This intervention is safe and exponentially increases salicylate excretion. Because hypokalemia may interfere with alkaline diuresis, patients are given a solution consisting of 1 L of 5% D/W, 3 50-mEq ampules of NaHCO₃, and 40 mEq of KCl at 1.5 to 2 times the maintenance IV fluid rate. Serum K is monitored.

Drugs that increase urinary HCO₃ (eg, acetazolamide) should be avoided because they worsen metabolic acidosis and decrease blood pH. Drugs that decrease respiratory drive should be avoided if possible because they may impair hyperventilation and respiratory alkalosis, decreasing blood pH.

Fever can be treated with physical measures such as external cooling (see p. 3266). Seizures are treated with benzodiazepines. In patients with rhabdomyolysis, alkaline diuresis may help prevent renal failure.

Hemodialysis may be required to enhance salicylate elimination in patients with severe neurologic impairment, renal or respiratory insufficiency, acidemia despite other measures, or very high serum salicylate levels (> 100 mg/dL [> 7.25 mmol/L] with acute overdose or > 60 mg/dL [> 4.35 mmol/L] with chronic overdose).

**Carbon Monoxide Poisoning**

Carbon monoxide (CO) poisoning causes acute symptoms such as headache, nausea, weakness, angina, dyspnea, loss of consciousness, and coma. Neuropsychiatric symptoms may develop weeks later. Diagnosis is by carboxyhemoglobin levels and ABGs, including measured O₂ saturation. Treatment is with supplemental O₂. Prevention is often possible with household carbon monoxide detectors.

CO poisoning, one of the most common fatal poisonings, occurs by inhalation. CO is a colorless, odorless gas that results from incomplete combustion of hydrocarbons. Common sources of CO in poisonings include house fires and improperly vented automobiles, gas heaters, furnaces, hot water heaters, wood-or charcoal-burning stoves, and kerosene heaters. CO is produced when natural gas (methane or propane) burns. Inhaling tobacco smoke results in CO in the blood but not enough to cause poisoning.

Pathophysiology

The elimination half-life of CO is about 4.5 h with inhalation of room air, 1.5 h with 100% O₂, and 20 min with 3 atmospheres (pressure) of O₂ (as in a hyperbaric chamber—see p. 3289).

Mechanisms of CO toxicity are not completely understood. They appear to involve

• Displacement of O₂ from Hb (because CO has greater affinity for Hb than does O₂)

• Shifting of the O₂-Hb dissociation curve to the left (decreasing release of O₂ from Hb to tissues—see Fig. 189-4 on p. 1857)

• Inhibition of mitochondrial respiration

• Possibly direct toxic effects on brain tissue

**Symptoms and Signs**

Symptoms tend to correlate well with the patient’s peak blood carboxyhemoglobin levels. Many symptoms
are nonspecific.

- Headache and nausea can begin when levels are 10 to 20%.

- Levels > 20% commonly cause vague dizziness, generalized weakness, difficulty concentrating, and impaired judgment.

- Levels > 30% commonly cause dyspnea during exertion, chest pain (in patients with coronary artery disease), and confusion.

- Higher levels can cause syncope, seizures, and obtundation.

Hypotension, coma, respiratory failure, and death may occur, usually when levels are > 60%.

Patients may also have many other symptoms, including visual deficits, abdominal pain, and focal neurologic deficits. If poisoning is severe, neuropsychiatric symptoms and signs (eg, dementia, psychosis, parkinsonism, chorea, amnestic syndromes) can develop days to weeks after exposure and become permanent. Because CO poisoning often results from house fires, patients may have concomitant airway injuries (see Sidebar 329-1 on p. 3243), which may increase risk of respiratory failure.

**Diagnosis**

- Diagnosis considered when patients at risk have nonspecific symptoms or metabolic acidosis

- Venous carboxyhemoglobin level

Because symptoms can be vague, nonspecific, and variable, the diagnosis is easily missed. Many cases of mild poisoning with nonspecific symptoms are mistaken for viral syndromes. Physicians must maintain a high level of suspicion. If people from the same dwelling, particularly a heated dwelling, experience nonspecific symptoms, CO exposure should be considered.

If CO poisoning is suspected, the carboxy-hemoglobin level is measured with a COoximeter; venous samples can be used because arteriovenous differences are trivial. ABGs are not measured routinely. ABGs and pulse oximetry, alone or combined, are inadequate for diagnosis of CO poisoning because O₂ saturation reported in ABGs represents dissolved O₂ and is thus unaffected by carboxy-hemoglobin concentration; furthermore, the pulse oximeter cannot differentiate normal Hb from carboxyhemoglobin and thus provides a falsely elevated oxyhemoglobin reading. Although elevated carboxyhemoglobin levels are clear evidence of poisoning, levels may be falsely low because they decrease rapidly after CO exposure ends, particularly in patients treated with supplemental O₂ (eg, in an ambulance). Metabolic acidosis can be a clue to the diagnosis. Other tests may help evaluate specific symptoms (eg, ECG for chest pain, CT for neurologic symptoms).

**Treatment**

- 100% O₂

- Possibly hyperbaric O₂

Patients should be removed from the source of CO and stabilized as necessary. They are given 100% O₂ (by nonrebreather mask) and treated supportively. Hyperbaric O₂ therapy typically should be considered for patients who have any of the following:

- Life-threatening cardiopulmonary complications

- Ongoing chest pain

- Altered consciousness
• Loss of consciousness (no matter how brief)

• A carboxyhemoglobin level > 25%

Hyperbaric O\textsubscript{2} therapy should also be considered for pregnant patients.

Patients are placed in a chamber at 2 to 3 atmospheres of O\textsubscript{2}. Hyperbaric O\textsubscript{2} therapy may decrease the incidence of delayed neuropsychiatric symptoms. However, this therapy may cause barotrauma and, because therapy is not available at most hospitals, may require transfer of patients, who may not be stable; also, a chamber may not be available locally, and evidence for the efficacy of hyperbaric O\textsubscript{2} therapy is somewhat inconclusive.

**Prevention**

Prevention involves checking sources of indoor combustion to make sure they are correctly installed and vented to the outdoors. Exhaust pipes should be inspected periodically for leaks. CO detectors should be installed because they provide early warning that CO is free in a dwelling's atmosphere. If CO is suspected in a dwelling, windows should be opened, and the dwelling should be evacuated and evaluated for the source of CO.

**Caustic Ingestion**

Caustics (strong acids and alkalis), when ingested, burn upper GI tract tissues, sometimes resulting in esophageal or gastric perforation. Symptoms may include drooling, dysphagia, and pain in the mouth, chest, or stomach; strictures may develop later. Diagnostic endoscopy may be required. Treatment is supportive. Gastric emptying and activated charcoal are contraindicated. Perforation is treated surgically.

Common sources of caustics include solid and liquid drain and toilet bowl cleaners. Industrial products are usually more concentrated than household products and thus tend to be more damaging.

**Pathophysiology**

Acids cause coagulation necrosis; an eschar forms, limiting further damage. Acids tend to affect the stomach more than the esophagus. Alkalis cause rapid liquefaction necrosis; no eschar forms, and damage continues until the alkali is neutralized or diluted. Alkalis tend to affect the esophagus more than the stomach, but ingestion of large quantities severely affects both.

Solid products tend to leave particles that stick to and burn tissues, discouraging further ingestion and causing localized damage. Because liquid preparations do not stick, larger quantities are easily ingested, and damage may be widespread. Liquids may also be aspirated, leading to upper airway injury.

**Symptoms and Signs**

Initial symptoms include drooling and dysphagia. In severe cases, pain, vomiting, and sometimes bleeding develop immediately in the mouth, throat, chest, or abdomen. Airway burns may cause coughing, tachypnea, or stridor.

Swollen, erythematous tissue may be visible intraorally; however, caustic liquids may cause no intraoral burns despite serious injury farther down the GI tract. Esophageal perforation may result in mediastinitis, with severe chest pain, tachycardia, fever, tachypnea, and shock. Gastric perforation may result in peritonitis. Esophageal or gastric perforation may occur within hours, after weeks, or any time in between.

Esophageal strictures can develop over weeks, even if initial symptoms had been mild and treatment had been adequate.
Diagnosis

- Endoscopy

Because the presence or absence of intraoral burns does not reliably indicate whether the esophagus and stomach are burned, meticulous endoscopy is indicated to check for the presence and severity of esophageal and gastric burns when symptoms or history suggests more than trivial ingestion.

Treatment

- Avoidance of gastric emptying
- Oral fluids

Treatment is supportive. (CAUTION: Gastric emptying by emesis or lavage is contraindicated because it can reexpose the upper GI tract to the caustic. Attempts to neutralize a caustic acid by correcting pH with an alkaline substance [and vice versa] are contraindicated because severe exothermic reactions may result. Activated charcoal is contraindicated because it may infiltrate burned tissue and interfere with endoscopic evaluation.)

Oral fluids are started when they can be tolerated. Esophageal or gastric perforation is treated with antibiotics and surgery (see p. 111). IV corticosteroids and prophylactic antibiotics are not recommended. Strictures are treated with bougienage or, if they are severe or unresponsive, with esophageal bypass by colonic interposition.

Mushroom Poisoning

Numerous mushroom species cause toxicity when ingested. Symptoms vary by species. Identification of specific species is difficult, so treatment usually is guided by symptoms.

Differentiating toxic and nontoxic species in the wild is difficult, even for highly knowledgeable people. Folklore rules are unreliable, and the same species may have varying degrees of toxicity depending on where they are harvested. If patients have eaten an unidentified mushroom, identifying the species can help determine specific treatment. However, because an experienced mycologist is seldom available for immediate consultation, treatment of patients who become ill after mushroom ingestion is usually guided by symptoms. If a sample of the mushroom, uningested or from the patient's emesis, is available, it can be sent to a mycologist for analysis.

All toxic mushrooms cause vomiting and abdominal pain; other manifestations vary significantly by mushroom type. Generally, mushrooms that cause symptoms early (within 2 h) are less dangerous than those that cause symptoms later (usually after 6 h). Activated charcoal may be useful.

Early GI symptoms: Mushrooms that cause early GI symptoms (e.g., *Chlorophyllum molybdites*, the little brown mushrooms that often grow in lawns) cause gastroenteritis, sometimes with headaches or myalgias. Diarrhea is occasionally bloody. Symptoms usually resolve within 24 h. Treatment is supportive.

Early neurologic symptoms: Mushrooms that cause early neurologic symptoms include hallucinogenic mushrooms, which are usually ingested recreationally because they contain psilocybin, a hallucinogen. The most common are members of the *Psilocybe* genus, but some other genera contain psilocybin.

Symptoms begin within 15 to 30 min and include euphoria, enhanced imagination, and hallucinations. Tachycardia and hypertension are common, and hyperpyrexia occurs in some children; however, serious consequences are rare.

Treatment occasionally involves sedation (e.g., with benzodiazepines).

Early muscarinic symptoms: Mushrooms that cause early muscarinic symptoms include members of the *Inocybe* and *Clitocybe* genera.
Symptoms may include SLUDGE syndrome (see Table 340-2 on p. 3325), including miosis, bronchorrhea, bradycardia, diaphoresis, wheezing, and fasciculations. Symptoms are usually mild, begin within 30 min, and resolve within 12 h.

Atropine may be given to treat severe muscarinic symptoms (eg, wheezing, bradycardia).

**Delayed GI symptoms:** Mushrooms that cause delayed GI symptoms include members of the *Amanita*, *Gyromitra*, and *Cortinarius* genera.

The most toxic *Amanita* mushroom is *Amanita phalloides*, which causes 95% of mushroom poisoning deaths. Initial gastroenteritis, which may occur 6 to 12 h after ingestion, can be severe; hypoglycemia can occur. Initial symptoms abate for a few days; then liver failure and sometimes renal failure develop. Initial care involves close monitoring for hypoglycemia and possibly repeated doses of activated charcoal. Treatment of liver failure may require liver transplantation; other specific treatments (eg, *N*-acetylcysteine, highdose penicillin, silibinin, IV fat emulsion) are unproved.

*Gyromitra* mushrooms can cause hypoglycemia simultaneously with or shortly after gastroenteritis. Other manifestations may include CNS toxicity (eg, seizures) and, after a few days, hepatorenal syndrome. Initial care involves close monitoring for hypoglycemia and possibly repeated doses of activated charcoal. Neurologic symptoms are treated with pyridoxine 70 mg/kg slow IV infusion over 4 to 6 h (maximum daily dose of 5 g); liver failure is treated supportively.

Most *Cortinarius* mushrooms are endogenous to Europe. Gastroenteritis may last for 3 days. Renal failure, with symptoms of flank pain and decreased urine output, may occur 3 to 20 days after ingestion. Renal failure often resolves spontaneously.

**Plant Poisoning**

A few commonly grown plants are highly poisonous, and many are moderately poisonous (see Table 340-6). Few plant poisonings have specific antidotes. Most plant ingestions, including the plants listed in Table 340-6, result in minimal symptoms unless the leaves and other components are concentrated into a paste or brewed into a tea.

**Highly toxic** and potentially fatal plants include the following:

- Castor beans and jequirity beans
- Oleander and foxglove
- Hemlock

**Castor beans and jequirity beans:** Castor beans contain ricin, an extremely concentrated cellular poison. Jequirity beans contain abrin, a related and even more potent toxin. In both, the beans have a relatively impervious shell; thus, the bean must be chewed to release the toxin. However, the seed coating of the jequirity bean is often not intact, and simple bacterial digestion can release the abrin toxin.

Symptoms of either poisoning may include delayed gastroenteritis, sometimes severe and hemorrhagic, followed by delirium, seizures, coma, and death. Whole-bowel irrigation should be considered because it aims to remove all beans ingested.

**Oleander and foxglove:** These plants and lily of the valley (which is similar but less toxic) contain digitalis glycosides. Toxicity includes gastroenteritis, confusion, hyperkalemia, and arrhythmias. The serum digoxin level can confirm ingestion but is not useful as quantitative information.

K levels are closely monitored. Hyperkalemia may respond only to hemodialysis. Ca is not recommended for arrhythmias. Digoxin-specific fractionated antibody (Fab) fragments have been used to treat ventricular arrhythmias.
**Hemlock:** Hemlock poisoning (poison hemlock and water hemlock) can cause symptoms within 15 min.

Poison hemlock has nicotinic effects, beginning with dry mouth and progressing to tachycardia, tremors, diaphoresis, mydriasis, seizures, and muscle paresis. Rhabdomyolysis and bradycardia may occur.

Water hemlock seems to enhance γ-aminobutyric acid (GABA) activity. Symptoms may include gastroenteritis, delirium, refractory seizures, and coma.

**Fish and Shellfish Poisoning**

Fish and shellfish poisoning commonly causes GI, neurologic, or histamine-mediated manifestations.

**Ciguatera poisoning:** Ciguatera poisoning may result from eating any of > 400 species of fish from the tropical reefs of Florida, the West Indies, or the Pacific, where a dinoflagellate produces a toxin that accumulates in the flesh of the fish. Older fish and large fish (eg, grouper, snapper, kingfish) contain more toxin. No known processing procedures, including cooking, are protective, and flavor is unaffected. A commercial product is available to test for ciguatoxin in fish.

Symptoms may begin 2 to 8 h after eating. Abdominal cramps, nausea, vomiting, and diarrhea last 6 to 17 h; then, pruritus, paresthesias, headache, myalgia, reversal of hot and cold sensation, and face pain may occur. For months afterward, unusual sensory phenomena and nervousness may cause debilitation.

IV mannitol has been suggested as a treatment, but no clear benefit has been shown.

**Scombroid poisoning:** Scombroid poisoning is caused by high histamine levels in fish flesh due to bacterial decomposition after the fish is caught. Commonly affected species include

- Tuna
- Mackerel
- Bonito
- Skipjack
- Mahi mahi

The fish may taste peppery or bitter. Facial flushing and possibly nausea, vomiting, epigastric pain, and urticaria occur within a few minutes of eating and resolve within 24 h. Symptoms are often mistaken for those of a seafood allergy. Unlike other fish poisonings, this poisoning can be prevented by properly storing the fish after it is caught.

Treatment may include H₁ and H₂ blockers.

**Tetrodotoxin poisoning:** Tetrodotoxin poisoning is most commonly due to eating the puffer fish (fugu), a sushi delicacy, but > 100 fresh and salt water species contain tetrodotoxin. Symptoms are similar to those of ciguatera poisoning; potentially fatal respiratory paralysis can also occur. Treatment is supportive care with attention to ventilatory assistance until the toxin is metabolized, which may take days.

The toxin cannot be destroyed by cooking or freezing.

**Shellfish poisoning:** Paralytic shellfish poisoning can occur from June to October, especially on the Pacific and New England coasts, when mussels, clams, oysters, and scallops are contaminated by the
poisonous dinoflagellate responsible for red tide. This dinoflagellate produces the neurotoxin saxitoxin, which is resistant to cooking. Circumoral paresthesias occur 5 to 30 min after eating. Nausea, vomiting, and abdominal cramps then develop, followed by muscle weakness. Untreated respiratory paralysis may be fatal; for survivors, recovery is usually complete.

Hydrocarbon Poisoning

Hydrocarbon poisoning may result from ingestion or inhalation. Ingestion, most common among children < 5 yr, can result in aspiration pneumonitis. Inhalation, most common among adolescents, can result in ventricular fibrillation, usually without warning symptoms. Diagnosis of pneumonitis is by clinical evaluation, chest x-ray, and oximetry. Gastric emptying is contraindicated because aspiration is a risk. Treatment is supportive.

Ingestion of hydrocarbons, such as petroleum distillates (eg, gasoline, kerosene, mineral oil, lamp oil, paint thinners), results in minimal systemic effects but can cause severe aspiration pneumonitis. Toxic potential mainly depends on viscosity, measured in Saybolt seconds universal (SSU). Hydrocarbon liquids with low viscosity (SSU < 60), such as gasoline and mineral oil, can spread rapidly over large surface areas and are more likely to cause aspiration pneumonitis than are hydro-carbons with SSU > 60, such as tar. Hydro-carbons, if ingested in large amounts, may be absorbed systemically and cause CNS or hepatic toxicity, which is more likely with halogenated hydrocarbons (eg, carbon tetrachloride, trichloroethylene).

Recreational inhalation of halogenated hydrocarbons (eg, glues, paint, solvents, cleaning sprays, gasoline, fluorocarbons used as refrigerants or propellants in aerosols—see p. 1531), called huffing or bagging, is common among adolescents. It can cause euphoria and mental status changes and can sensitize the heart to endogenous catecholamines. Fatal ventricular arrhythmias may result; they usually occur without premonitory palpitations or other warning, often when patients are startled or chased.

Symptoms and Signs

After ingestion of even a very small amount of liquid hydrocarbon, patients initially cough, choke, and may vomit. Young children may have cyanosis, hold their breath, and cough persistently. Older children and adults may report burning in the stomach. Aspiration pneumonitis causes hypoxia and respiratory distress. Symptoms and signs of pneumonitis may develop a few hours before infiltrates are visible on x-ray. Substantial systemic absorption, particularly of a halogenated hydrocarbon, may cause lethargy, coma, and seizures. Nonfatal pneumonitis usually resolves in about 1 wk; mineral or lamp oil ingestion usually resolves in 5 to 6 wk. Arrhythmias usually occur before presentation and are unlikely to recur after presentation unless patients have excessive agitation.

Diagnosis

• Chest x-ray and oximetry done about 6 h after ingestion

If patients are too obtunded to provide a history, hydrocarbon exposure may be suspected if their breath or clothing has an odor or if a container is found near them. Paint residue on the hands or around the mouth may suggest recent paint sniffing.

Diagnosis of aspiration pneumonitis is by symptoms and signs as well as by chest x-ray and oximetry, which are done about 6 h after ingestion or sooner if symptoms are severe. If respiratory failure is suspected, ABGs are measured.

Treatment

• Supportive care

• Avoidance of gastric emptying

Any contaminated clothing is removed, and the skin is washed. (CAUTION: Gastric emptying, which
Organophosphate and Carbamate Poisoning

Organophosphates and carbamates are common insecticides that inhibit cholinesterase activity, causing acute muscarinic manifestations (eg, salivation, lacrimation, urination, diarrhea, emesis, bronchorrhea, bronchospasm, bradycardia, miosis) and some nicotinic symptoms, including muscle fasciculations and weakness. Neuropathy can develop days to weeks after exposure. Diagnosis is clinical and sometimes with a trial of atropine, measurement of RBC acetylcholinesterase level, or both. Bronchorrhea and bronchospasm are treated with titrated highdose atropine. Neuro-muscular toxicity is treated with IV pralidoxime.

Organophosphates and carbamates, although different structurally, both inhibit cholinesterase activity. Some are used medically to reverse neuromuscular blockade (eg, neostigmine, pyridostigmine, edrophonium) or to treat glaucoma, myasthenia gravis, and Alzheimer's disease (eg, echothiophate, pyridostigmine, tacrine, donepezil).

Some organophosphates were developed as nerve gases. One, sarin, has been used by terrorists. Organophosphates and carbamates are commonly used as insecticides (see Table 340-8). Those most often implicated in human poisoning include

• Carbamates: Aldicarb and methomyl

• Organophosphates: Chlorpyrifos, diazinon, dursban, fenthion, malathion, and parathion

Organophosphates and carbamates are common causes of poisoning and poison-related deaths worldwide.

Pathophysiology

Organophosphates and carbamates are absorbed through the GI tract, lungs, and skin. They inhibit plasma and RBC cholinesterase, preventing breakdown of acetylcholine, which then accumulates in synapses. Carbamates are cleared spontaneously within about 48 h after exposure. Organophosphates, however, can irreversibly bind to cholinesterase.

Symptoms and Signs

Acute: Organophosphates and carbamates cause acute muscarinic and nicotinic cholinergic toxidromes (see Table 340-2). Muscle fasciculations and weakness are typical. Most patients have bradycardia and, if poisoning is severe, hypotension. CNS toxicity is common, sometimes with seizures and excitability and often with lethargy and coma. Pancreatitis is possible, and organophosphates may cause arrhythmias such as heart block and QTc interval prolongation.

Delayed: Weakness, particularly of proximal, cranial, and respiratory muscles, may develop 1 to 3 days after exposure to organo-phosphates or rarely carbamates despite treatment (the intermediate syndrome); these symptoms resolve in 2 to 3 wk. A few organ-o phosphates (eg, chlorpyrifos, triorthocresyl phosphate) may cause an axonal neuropathy that begins 1 to 3 wk after exposure. The mechanism may be independent of RBC cholinesterase, and the risk is independent of the severity of poisoning. Long-term, persistent sequelae of organophosphate poisoning may include cognitive deficits or parkinsonism.

Diagnosis

• Muscarinic toxidrome with muscle fasciculations and weakness

• Sometimes RBC cholinesterase levels
The diagnosis is usually based on the characteristic muscarinic toxidrome in patients with neuromuscular findings, particularly in patients at risk. If findings are equivocal, reversal or abatement of muscarinic symptoms after 1 mg of atropine (0.01 to 0.02 mg/kg in children) supports the diagnosis. The specific toxin should be identified if possible. Many organophosphates have characteristic garlic-like or petroleum odors.

RBC cholinesterase activity, which can be measured by some laboratories, indicates the severity of poisoning. If it can be measured rapidly, values can be used to monitor the effectiveness of treatment.

**Treatment**

- Supportive therapy
- Atropine for respiratory manifestations
- Decontamination
- Pralidoxime for neuromuscular manifestations

**In-hospital treatment**: Supportive therapy is key. Patients should be closely monitored for respiratory failure due to weakness of respiratory muscles. Atropine is given in amounts sufficient to relieve bronchospasm and bronchorrhea rather than to normalize pupil size or heart rate. Initial dosage is 2 to 5 mg IV (0.05 mg/kg in children); the dose can be doubled every 3 to 5 min prn. Grams of atropine may be necessary for severely poisoned patients.

**Decontamination** is pursued as soon as possible after stabilization. Caregivers should avoid self-contamination while providing care. For topical exposure, clothes are removed, and the body surface is flushed thoroughly. For ingestion within 1 h of presentation, activated charcoal can be used. Gastric emptying is usually avoided. If done, the trachea is intubated beforehand to prevent aspiration.

**Pralidoxime** (2-PAM) is given after atropine to relieve neuromuscular symptoms. Pralidoxime (1 to 2 g in adults; 20 to 40 mg/kg in children) is given over 15 to 30 min IV after exposure to an organophosphate or carbamate because, frequently, whether the poison is an organophosphate or carbamate is unknown at the time of treatment. An infusion can be used after the bolus (8 mg/kg/h in adults; 10 to 20 mg/kg/h in children).

**Benzodiazepines** are used for seizures. Prophylactic diazepam may help prevent neurocognitive sequelae after moderate to severe organophosphate poisoning.

**Out-of-hospital exposure**: People exposed to these toxins away from a hospital can give themselves low doses of atropine using commercially prepared autoinjectors (2 mg for adults and for children > 41 kg; 1 mg for children 19 to 41 kg; 0.5 mg for children < 19 kg). Autoinjection of 10 mg diazepam has been recommended for people exposed to a chemical attack.

**Iron Poisoning**

Iron poisoning is the leading cause of poisoning deaths in children. Symptoms begin with acute gastroenteritis, followed by a quiescent period, then shock and liver failure. Diagnosis is by measuring serum iron, detecting radiopaque iron tablets in the GI tract, or detecting unexplained metabolic acidosis in patients with other findings suggesting iron poisoning. Treatment of a substantial ingestion is usually whole-bowel irrigation and chelation therapy with IV deferoxamine.

Many commonly used OTC preparations contain iron. Of the many iron compounds used in OTC and prescription preparations, the most common are

- Ferrous sulfate (20% elemental iron)
• Ferrous gluconate (12% elemental iron)

• Ferrous fumarate (33% elemental iron)

To children, iron tablets may look like candy. Prenatal multivitamins are the source of iron in most lethal ingestions among children. Children's chewable multivitamins with iron usually have such small amounts that toxicity rarely occurs.

**Pathophysiology**

Iron is toxic to the GI system, cardiovascular system, and CNS. Specific mechanisms are unclear, but excess free iron is inserted into enzymatic processes and interferes with oxidative phosphorylation, causing metabolic acidosis. Iron also catalyzes free radical formation, acts as an oxidizer, and, when plasma protein binding is saturated, combines with water to form iron hydroxide and free H\(^+\) ions, compounding the metabolic acidosis. Coagulopathy may appear early because of interference with the coagulation cascade and later because of liver injury.

Toxicity depends on the amount of elemental iron that has been ingested. Up to 20 mg/kg of elemental iron is not toxic, 20 to 60 mg/kg is mildly to moderately toxic, and > 60 mg/kg can cause severe symptoms and morbidity.

**Symptoms and Signs**

Symptoms occur in 5 stages (see Table 340-7); however, symptoms and their progression vary significantly. The severity of stage 1 symptoms usually reflects the overall severity of poisoning; late-stage symptoms develop only if stage 1 symptoms are moderate or severe. If no symptoms develop within the first 6 h after ingestion, risk of serious toxicity is minimal. If shock and coma develop within the first 6 h, the mortality rate is about 10%.

**Diagnosis**

• Abdominal x-ray

• Determination of serum iron, electrolytes, and pH 3 to 4 h after ingestion

Iron poisoning should be considered in mixed ingestions (because iron is ubiquitous) and in small children with access to iron and unexplained metabolic acidosis or severe or hemorrhagic gastroenteritis. Because children often share, siblings and playmates of small children who have ingested iron should be evaluated.

Abdominal x-ray is usually recommended to confirm ingestion; it detects intact iron tablets or iron concretions but misses chewed and dissolved tablets, liquid iron preparations, and iron in multivitamin preparations. Serum iron, electrolytes, and pH are determined 3 to 4 h after ingestion. Toxicity is assumed if suspected ingestion is accompanied by any of the following:

• Vomiting and abdominal pain

• Serum iron levels > 350 μg/dL (63 μmol/L)

• Iron visible on x-ray

• Unexplained metabolic acidosis
These iron levels may indicate toxicity; however, iron levels alone do not predict toxicity accurately. Total iron binding capacity (TIBC) is often inaccurate and not helpful in diagnosing serious poisoning and is not recommended. The most accurate approach is to serially measure levels of serum iron, HCO$_3^-$, and pH (with calculation of the anion gap); these findings are then evaluated together, and results are correlated with the patient's clinical status. For example, toxicity is suggested by increasing iron levels, metabolic acidosis, worsening symptoms, or, more typically, some combination of these findings.

**Treatment**

- Whole-bowel irrigation

- For severe toxicity, IV deferoxamine

If radiopaque tablets are visible on abdominal x-ray, whole-bowel irrigation with polyethylene glycol 1 to 2 L/h for adults or 25 to 40 mL/kg/h for children is done until no iron is visible on repeat abdominal x-ray. Gastric lavage is usually not helpful because vomiting tends to empty the stomach more efficiently. Activated charcoal does not adsorb iron and should be used only if other toxins also were ingested.

All patients with more than mild gastroenteritis are hospitalized. Patients with severe toxicity (metabolic acidosis, shock, severe gastroenteritis, or serum iron level > 500 µg/dL) are treated with IV deferoxamine to chelate free serum iron. Deferoxamine is infused at rates up to 15 mg/kg/h IV, titrated until hypotension occurs. Because both deferoxamine and iron poisoning can decrease BP, patients receiving deferoxamine require IV hydration.

**Lead Poisoning**

(Plumbism)

Lead poisoning often causes minimal symptoms at first but can cause acute encephalopathy or irreversible organ damage, commonly resulting in cognitive deficits in children. Diagnosis is by whole blood lead level. Treatment involves stopping lead exposure and sometimes using chelation therapy with succimer or edetate Ca disodium, with or without dimercaprol.

Leaded paint was commonly used until 1960, used to some degree until the early 1970s, and mostly eliminated in 1978. Thus, for a significant number of older housing units, leaded paint still poses some hazard. Lead poisoning is usually caused by direct ingestion of leaded paint chips (from cracked, peeling paint). During home remodeling, patients may be exposed to significant amounts of aerosolized lead in the form of particles scraped or sanded off during surface preparation for repainting.

Some ceramic glazes contain lead; ceramic ware (eg, pitchers, cups, plates) that is made with these glazes (common outside the US) can leach lead, particularly when in contact with acidic substances (eg, fruits, cola drinks, tomatoes, wine, cider). Lead-contaminated moonshine whiskey and folk remedies are possible sources, as are occasional lead foreign objects in the stomach or tissues (eg, bullets, curtain or fishing weights). Bullets lodged in soft tissues near synovial fluid or CSF may increase blood lead levels, but that process takes years.

Occupational exposure can occur during battery manufacture and recycling, bronzing, brass making, glass making, pipe cutting, soldering and welding, smelting, or working with pottery or pigments. Certain ethnic cosmetic products and imported herbal products and medicinal herbs contain lead and have caused cluster outbreaks of lead poisoning in immigrant communities. Fumes of leaded gasoline (in countries other than the US) recreationally inhaled for CNS effects may cause lead poisoning.

**Symptoms and Signs**

Lead poisoning is most often a chronic disorder and may not cause acute symptoms. With or without acute symptoms, poisoning eventually has irreversible effects (eg, cognitive deficits, peripheral neuropathy, progressive renal dysfunction).
Risk of cognitive deficits increases when the whole blood lead level (PbB) is ≥ 10 mg/dL (≥ 0.48 mmol/L) for an extended period, although the cutoff may be even lower. Other symptoms (eg, abdominal cramping, constipation, tremors, mood changes) may occur if PbB is > 50 mg/dL (> 2.4 mmol/L). Encephalopathy is likely if PbB is > 100 mg/dL (> 4.8 mmol/L).

In children: Acute lead poisoning may cause irritability, decreased attentiveness, and acute encephalopathy. Cerebral edema develops over 1 to 5 days, causing persistent and forceful vomiting, ataxic gait, seizures, altered consciousness, and, finally, intractable seizures and coma. Encephalopathy may be preceded by several weeks of irritability and decreased play activity.

Chronic lead poisoning in children may cause intellectual disability, seizure disorders, aggressive behavior disorders, developmental regression, chronic abdominal pain, and anemia.

In adults: Adults with occupational exposure characteristically develop symptoms (eg, personality changes, headache, abdominal pain, neuropathy) over several weeks or longer. Encephalopathy is unusual. Adults may develop loss of sex drive, infertility, and, in men, erectile dysfunction.

In children and adults: Anemia may develop because lead interferes with the normal formation of Hb. Children and adults who inhale tetra-ethyl or tetra-methyl lead (in leaded gasoline) may develop toxic psychosis in addition to more characteristic symptoms of lead poisoning.

Diagnosis

- Lead levels in capillary or whole blood

Lead poisoning is suspected in patients with characteristic symptoms. However, because symptoms are often nonspecific, diagnosis is often delayed. Evaluation includes CBC and measurement of serum electrolytes, BUN, serum creatinine, plasma glucose, and PbB levels. An abdominal x-ray should be taken to look for lead particles, which are radiopaque. X-rays of long bones are taken in children. Horizontal, metaphyseal lead bands representing lack of RBC remodeling and increased Ca deposition in the zones of provisional calcification in children's long bones are somewhat specific for poisoning with lead or other heavy metals but are insensitive. Normocytic or microcytic anemia suggests lead toxicity, particularly when the reticulocyte count is elevated or RBC basophilic stippling occurs; however, sensitivity and specificity are limited. Diagnosis is definitive if the PbB level is ≥ 10 μg/dL.

Because measuring PbB is not always possible and can be expensive, other preliminary or screening tests for lead poisoning can be used. Capillary blood testing for lead is accurate, inexpensive, and quick. All positive tests should be confirmed with PbB. The erythrocyte protoporphyrin (also called zinc protoporphyrin or free erythrocyte protoporphyrin) test is often inaccurate and now is seldom used.

The edetate Ca disodium (CaNa₂ EDTA) mobilization test, previously used for diagnosis and treatment, is considered obsolete by most toxicologists and is usually not done.

Treatment

- Source of lead eliminated (eg, whole-bowel irrigation if lead in GI tract)

- Chelation for adults with symptoms of poisoning plus PbB > 70 mg/dL

- Chelation for children with encephalopathy or PbB > 45 mg/dL (> 2.15 mmol/L)

For all patients, the source of lead is eliminated. If lead chips are visible on abdominal x-ray, whole-bowel irrigation with a polyethylene glycol electrolyte solution at 1 to 2 L/h for adults or 25 to 40 mL/kg/h for children is done until repeat x-ray shows no lead. If the cause is bullets, surgical removal should be considered. Children with PbB > 70 μg/dL (> 3.40 μmol/L) and all patients with neurologic symptoms should be hospitalized. Patients with acute encephalopathy are admitted to an ICU.

Chelating drugs (eg, succimer [meso-2,3-dimercaptosuccinic acid], CaNa₂ EDTA, dimercaprol [British
antilewisite, or BAL]) can be given to bind lead into forms that can be excreted (see also Table 340-4). Chelation should be supervised by an experienced toxicologist. Chelation is indicated for adults with symptoms of poisoning plus PbB > 70 mg/dL and for children with encephalopathy or PbB > 45 mg/dL (> 2.15 mmol/L). Liver and kidney disorders are relative contraindications for chelating drugs. Chelating drugs should not be given to any patient with ongoing exposure to lead because chelation can increase GI absorption of lead. Chelation removes only relatively small amounts of metal. If total body burden of lead is very large, multiple chelations over many years may be required.

**Regimens:** Patients with encephalopathy are treated with dimercaprol 75 mg/m\(^2\) (or 4 mg/kg) IM q 4 h and CaNa\(_2\)EDTA 1000 to 1500 mg/m\(^2\) IV (infusion) once/day. The first dose of dimercaprol should precede the first dose of CaNa\(_2\)EDTA by at least 4 h to prevent redistribution of lead into the brain. Dimercaprol may be stopped after the first few doses depending on lead levels and symptom severity. Dimercaprol-CaNa\(_2\)EDTA combination therapy is given for 5 days, followed by a 3-day washout period; then the need for continued chelation is reassessed.

Patients without encephalopathy are usually treated with succimer 10 mg/kg po q 8 h for 5 days, followed by 10 mg/kg po q 12 h for 14 days. If these patients have symptoms, they can alternatively be treated for 5 days with dimercaprol 50 mg/m\(^2\) needed deep IM injection q 4 h plus CaNa\(_2\)EDTA 1000 mg/m\(^2\) IV once/day.

**Drugs:** Dimercaprol, which can cause vomiting, is given with parenteral or oral fluids. Dimercaprol can also cause pain at the injection site, numerous systemic symptoms, and, in patients with G6PD deficiency, moderate to severe acute intravascular hemolysis. This drug should not be given concurrently with iron supplements. Dimercaprol is formulated with peanut derivatives and thus is contraindicated in patients with known or suspected peanut allergy.

CaNa\(_2\)EDTA can cause thrombophlebitis, which can be prevented by giving the drug IM, not IV, and by using an IV concentration of < 0.5%. Before beginning treatment with CaNa\(_2\)EDTA, adequate urine flow must be confirmed. Serious reactions to CaNa\(_2\)EDTA include renal insufficiency, proteinuria, microscopic hematuria, fever, and diarrhea. Renal toxicity, which is dose-related, is usually reversible. Adverse effects of CaNa\(_2\)EDTA are probably due to zinc depletion.

Succimer may cause rash, GI symptoms (eg, anorexia, nausea, vomiting, diarrhea, metallic taste), and transient elevations of liver enzymes.

**Lower lead levels:** Patients with PbB > 10 \(\mu g/dL\) should be monitored closely, and they or their parents should be taught how to reduce their exposure to lead.

**Prevention**

Patients at risk should be screened by measuring PbB. Measures that reduce risk of household poisoning include regular hand washing, regular washing of children's toys and pacifiers, and regular cleaning of household surfaces; drinking water, household paint (except in houses built after 1978), and ceramic ware made outside the US should be tested for lead. Adults exposed to lead dust at work should use appropriate personal protective equipment, change their clothing and shoes before going home, and shower before going to bed.

**Specific Poisons**

Symptoms and treatment of specific poisons vary (see Table 340-8); including all the specific complexities and details is impossible. Consultation with a poison control center is recommended for any poisonings except the mildest and most routine.

[Table 340-8, Symptoms and Treatment of Specific Poisons]
Chapter 341. General Principles of Medical Genetics

Introduction

A gene, the basic unit of heredity, is a segment of DNA containing all the information necessary to synthesize a polypeptide (protein). Protein synthesis determines much of the body's structure and function.

Structure

Humans have about 20,000 genes. Genes are contained in chromosomes in the cell nucleus and mitochondria. In humans, somatic (nongerm) cell nuclei, with certain exceptions (e.g., RBCs), normally have 46 chromosomes in 23 pairs. Each pair consists of one chromosome from the mother and one from the father. Twenty-two of the pairs, the autosomes, are usually homologous (identical in size, shape, and position and number of genes). The 23rd pair, the sex chromosomes (X and Y), determines a person's sex. Women have 2 X chromosomes (which are homologous) in somatic cell nuclei; men have one X and one Y chromosome (which are heterologous). The X chromosome carries genes responsible for many hereditary traits; the small, differently shaped Y chromosome carries genes that initiate male sex differentiation, as well as a few other genes. Because the X chromosome has many more genes than the Y chromosome, many X chromosome genes in males are not paired. A karyotype is the full set of chromosomes in a person's cells.

Germ cells (egg and sperm) undergo meiosis, which reduces the number of chromosomes to 23—half the number in somatic cells. In meiosis, the genetic information inherited from a person's mother and father is recombined through crossing over (exchange between homologous chromosomes). When an egg is fertilized by a sperm at conception, the normal number of 46 chromosomes is reconstituted.

Genes are arranged linearly along the DNA of chromosomes. Each gene has a specific location (locus), which is typically the same on each of the 2 homologous chromosomes. The genes that occupy the same locus on each chromosome of a pair (one inherited from the mother and one from the father) are called alleles. Each gene consists of a specific DNA sequence; 2 alleles may have slightly different or the same DNA sequences. Having a pair of identical alleles for a particular gene is homozygosity; having a pair of nonidentical alleles is heterozygosity.

Gene Function

Genes consist of DNA. The length of the gene depends on the length of the protein the gene codes for. DNA is a double helix in which nucleotides (bases) are paired; adenine (A) is paired with thymine (T) and guanine (G) is paired with cytosine (C). DNA is transcribed during protein synthesis. When DNA replicates itself during cell division, one strand of DNA is used as a template against which messenger RNA (mRNA) is made. RNA has the same base pairs as DNA, except that uracil (U) replaces thymine (T). Parts of mRNA travel from the nucleus to the cytoplasm and then to the ribosome, where protein synthesis occurs. Transfer RNA (tRNA) brings each amino acid back to the ribosome where it is added to the growing polypeptide chain in a sequence determined by the mRNA. As a chain of amino acids is assembled, it folds upon itself to create a complex 3-dimensional structure under the influence of nearby chaperone molecules.

The code in DNA is written in triplets of the 4 possible nucleotides. Specific amino acids are coded by specific triplets. Because there are 4 nucleotides, the number of possible triplets is $4^3 = 64$. Because there are only 20 amino acids, there are extra triplet combinations. Some triplets code for the same amino acids as other triplets. Other triplets may code for things such as instructions to start or stop protein synthesis and the order in which to combine and assemble amino acids.

Genes consist of exons and introns. Exons code for amino acid components of the final protein. Introns contain other information that affects control and speed of protein production. Exons and introns together
are transcribed onto mRNA, but the segments transcribed from introns are later spliced out. Transcription is also controlled by antisense RNA, which is synthesized from the DNA strand that is not transcribed into mRNA. Chromosomes consist of histones and other proteins that affect gene expression (which proteins and how many proteins are synthesized from a given gene).

Genotype refers to genetic composition; it determines which proteins are coded for production. Phenotype refers to the entire physical, biochemical, and physiologic makeup of a person—ie, how the cell (and thus the body) functions. Phenotype is determined by the types and amounts of proteins actually synthesized, ie, how the genes are actually expressed. Gene expression depends on factors such as whether a trait is dominant or recessive, the penetrance and expressivity of the gene (see p. 3377), degree of tissue differentiation (determined by tissue type and age), environmental factors, unknown factors, and whether expression is sex-limited or subject to chromosomal inactivation or genomic imprinting. Factors that affect gene expression without changing the genome are epigenetic factors.

Knowledge of the biochemical mechanisms that mediate gene expression is growing rapidly. One mechanism is variability in intron splicing (also called alternative splicing). Because introns are spliced out, the exons may also be spliced out, and then the exons can be assembled in many combinations, resulting in many different mRNAs capable of coding for similar but different proteins. The number of proteins that can be synthesized by humans is > 100,000 even though the human genome has only about 20,000 genes. Other mechanisms mediating gene expression include DNA methylation and histone reactions such as methylation and acetylation. DNA methylation tends to silence a gene. Histones resemble spools around which DNA winds. Histone modifications such as methylation can increase or decrease the quantity of proteins synthesized from a particular gene. Histone acetylation is associated with decreased gene expression. The strand of DNA that is not transcribed to form mRNA may also be used as a template for synthesis of RNA that controls transcription of the opposite strand.

**Traits and Inheritance Patterns**

A trait may be as simple as the color of the eyes or as complex as susceptibility to diabetes. Expression of a trait may involve one gene or many genes. Some single-gene defects cause abnormalities in multiple tissues, an effect called pleiotropy. For example, osteogenesis imperfecta (a connective tissue disorder that often results from abnormalities in a single collagen gene) may cause fragile bones, deafness, blue-colored sclerae, dys-plastic teeth, hypermobile joints, and heart valve abnormalities (see also p. 2911).

**Construction of a family pedigree:** The family pedigree (family tree) can be used to diagram inheritance patterns. It is also commonly used in genetic counseling. The pedigree uses conventional symbols to represent family members and pertinent health information about them (see Fig. 341-1). Some familial disorders with identical phenotypes have several patterns of inheritance.

**Single-Gene Defects**

Genetic disorders determined by a single gene (Mendelian disorders) are easiest to analyze and the most well understood. If expression of a trait requires only one copy of a gene (one allele), that trait is considered dominant. If expression of a trait requires 2 copies of a gene (2 alleles), that trait is considered recessive. An exception is X-linked disorders. Because males usually have no paired allele to offset the effects of most alleles on the X chromosome, the X chromosome allele is expressed in males even if the trait is recessive.

Many specific disorders have been described (see Table 341-1).

**Autosomal Dominant**

Only one abnormal allele of a gene is needed to express an autosomal dominant trait; ie, heterozygotes and homozygotes for the abnormal gene are affected. A typical pedigree of an autosomal dominant trait is shown in Fig. 341-2.
In general, the following rules apply:

• An affected person has an affected parent.

• A heterozygous affected parent and an unaffected parent have, on average, an equal number of affected and unaffected children; ie, risk of occurrence for each child of an affected parent is 50%.

• Unaffected children of an affected parent do not transmit the trait to their descendents.

• Males and females are equally likely to be affected.

[Fig. 341-1. Symbols for constructing a family pedigree.]

[Table 341-1. Examples of Genetic Disorders with Mendelian Inheritance]

**Autosomal Recessive**

Two copies of an abnormal allele are needed to express an autosomal recessive trait. An example of a pedigree is shown in [Fig. 341-3].

In general, the following rules of inheritance apply:

• If normal parents have an affected child, both parents are heterozygotes. On average, one fourth of their children are affected, half are heterozygotes, and one fourth are normal. Therefore, among the children, the chance of not developing the disorder (that is, of being normal or a carrier) is three fourths, and among the unaffected children, the chance of being a carrier is two thirds.

• All children of an affected parent and a genotypically normal parent are phenotypically normal heterozygotes.

• On average, half the children of an affected parent and a heterozygote are affected, and half are heterozygotes.

• All children of 2 affected parents are affected.

• Males and females are equally likely to be affected.

• Heterozygotes are phenotypically normal but carry the abnormal gene.

Relatives are more likely to carry the same mutant allele, so mating between close relatives (consanguinity) increases the likelihood of having affected children. In parent-child or brother-sister unions (incest), the risk of having abnormal children is increased because so much of their genetic material is the same. In certain populations, the percentage of heterozygotes (carriers) is high because of a founder effect (ie, the group started with few members, one of whom was a carrier) or because carriers have a selective advantage (eg, heterozygosity for sickle cell anemia protects against malaria).

[Fig. 341-2. Autosomal dominant inheritance.]

If the trait results in a defect of a specific protein (eg, an enzyme), heterozygotes usually have a reduced amount of that protein. If the mutation is known, molecular genetic techniques can identify heterozygous pheno-typically normal people (eg, those with cystic fibrosis most of the time).

**X-Linked Dominant**

X-linked dominant traits are carried on the X chromosome. Most are rare. Usually, males are more severely affected; some X-linked dominant disorders are often lethal in males. Females who carry only one abnormal allele are affected, but less severely. A typical pedigree is shown in
In general, the following rules of inheritance apply:

- Affected males transmit the trait to all of their daughters but to none of their sons.
- Affected heterozygous females transmit the trait to half of their children, regardless of sex.
- Affected homozygous females transmit the trait to all of their children.
- Because females can be heterozygous or homozygous, more females have the trait than males. The difference between the sexes is even larger if the disorder is lethal in males.

X-linked dominant inheritance may be difficult to differentiate from autosomal dominant inheritance by studying only inheritance patterns. Large pedigrees are required, with particular attention to children of affected males because male-to-male transmission rules out X-linkage (males pass only their Y chromosomes to their sons).

**X-Linked Recessive**

X-linked recessive traits are carried on the X chromosome. Thus, nearly all affected people are male because most females have one normal copy of the involved gene (i.e., they are heterozygous). A typical pedigree is shown in Fig. 341-5.

In general, the following rules of inheritance apply:

- Nearly all affected people are male.
- Heterozygous females are usually phenotype normally but, as carriers, transmit the abnormal gene to half of their children.
- Half the sons of a carrier female are affected, and half the daughters are carriers.
- An affected male never transmits the trait to his sons.
- All daughters of an affected male are carriers.
- No daughters of a carrier female and a normal father are affected, but half are carriers.

Occasionally, females who are heterozygous for X-linked mutations show some expression, but they are rarely affected as severely as affected males.

**Factors Affecting Gene Expression**

Many factors can affect gene expression. Some cause the expression of traits to deviate from the patterns predicted by Mendelian inheritance.

**Penetrance and expressivity:** Penetrance is how often a gene is expressed. It is defined as the percentage of people who have the gene and who develop the corresponding phenotype (see Fig. 341-6). A gene with incomplete (low) penetrance may not be expressed even when the trait is dominant or when it is recessive and the gene responsible for that trait is present on both chromosomes. Penetrance of the same gene may vary from person to person and may depend on a person's age.
when an abnormal allele is not expressed (nonpenetrance), the unaffected carrier of the abnormal allele can pass it to children, who may have the clinical abnormality. In such cases, the pedigree appears to skip a generation. However, some cases of apparent nonpenetrance are due to the examiner's unfamiliarity with or inability to recognize minor manifestations of the disorder. Patients with minimal expression are sometimes considered to have a forme fruste of the disorder.

[Fig. 341-5, X-linked recessive inheritance.]

Expressivity is the extent to which a gene is expressed in one person. It can be graded as a percentage; eg, when a gene has 50% expressivity, only half the features are present or the severity is only half of what can occur with full expression. Expressivity may be influenced by the environment and by other genes, so people with the same gene may vary in phenotype. Expressivity can vary even among members of the same family.

Sex-limited inheritance: A trait that appears in only one sex is called sex-limited. Sex-limited inheritance is distinct from X-linked inheritance, which refers to traits carried on the X chromosome. Sex-limited inheritance, perhaps more correctly called sex-influenced inheritance, refers to special cases in which sex hormones and other physiologic differences between males and females alter the expressivity and penetrance of a gene. For example, premature baldness (known as male-pattern baldness) is an autosomal dominant trait, but such baldness is rarely expressed in females and then usually only after menopause.

Genomic imprinting: Genomic imprinting is the differential expression of genetic material depending on whether it has been inherited from the father or mother. For most autosomes, both the parental and maternal alleles are expressed. However, in < 1% of alleles, expression is possible only from the paternal or maternal allele. For example, expression of the gene for insulin-like growth factor 2 is normally expressed only from the paternal allele. Genomic imprinting is usually determined by effects that occur normally in the development of gametes. Changes such as methylation of DNA may cause certain maternal or paternal alleles to be expressed to different degrees. A disorder may appear to skip a generation if genomic imprinting prevents the causative allele from being expressed. Defective imprinting, such as abnormal activation or silencing of alleles, can result in disorders (eg, Prader-Willi syndrome, Angelman syndrome).

Codominance: Codominant alleles are both observed. Thus, the phenotype of heterozygotes is distinct from that of either homozygote. For example, if a person has one allele coding for blood type A and one allele coding for blood type B, the person has both blood types (blood type AB).

Chromosomal inactivation: In females, who have more than one X chromosome (except in eggs), all but one of the X chromosomes is inactivated; ie, most of the alleles on that chromosome are not expressed. Inactivation occurs individually in each cell early in fetal life; sometimes it is the X from the mother that is inactivated, and sometimes it is the X from the father. Sometimes most of the X chromosome inactivation comes from one parent—called skewed X inactivation. Either way, once inactivation has taken place in a cell, all descendants of that cell have the same X inactivation.

However, some alleles on the inactive X chromosome do express. Many of these alleles are on chromosomal regions corresponding to regions of the Y chromosomes (and are thus called pseudoautosomal regions, because both males and females receive 2 copies of these regions).

Multifactorial (Complex) Inheritance

Expression of many traits may involve multiple genes. Many such traits (eg, height) are distributed along a bell-shaped curve (normal distribution). Normally, each gene adds to or subtracts from the trait independently of other genes. In this distribution, few people are at the extremes and many are in the middle because people are unlikely to inherit multiple factors acting in the same direction. Environmental factors also add to or subtract from the final result.
Many relatively common congenital anomalies and familial disorders result from multifactorial inheritance. In an affected person, the disorder represents the sum of genetic and environmental influences. Risk of the occurrence of such a trait is much higher in 1st-degree relatives (siblings, parents, or children who share, on average, 50% of the affected person's genes) than in more distant relatives, who are likely to have inherited only a few high-liability genes.

Common disorders with multifactorial inheritance include hypertension, coronary artery disease, diabetes mellitus, cancer, cleft palate, and arthritis. Many specific genes contributing to these traits are being identified. Genetically determined predisposing factors, including a family history and specific biochemical pathways often identified by molecular markers (eg, high cholesterol), can sometimes identify people who are at risk and are likely to benefit from preventive measures.

Multigenic, multifactorial traits seldom produce clear patterns of inheritance; however, these traits tend to occur more often among certain ethnic and geographic groups or among one sex or the other.

**Unusual Aspects of Inheritance**

Certain situations represent aberrant inheritance, often because genes or chromosomes are altered. However, some of these alterations, such as mosaicism, are very common; others, such as polymorphisms, are so common that they may be considered normal variants.

**Mutations and polymorphisms:** Variations in DNA can occur spontaneously or in response to cellular insults (eg, radiation, mutagenic drugs, viruses). Some are repaired by the cell's DNA error correction mechanisms. Others are not and can be passed on to subsequently replicated cells; in such cases, the variation is termed a mutation. However, offspring can inherit the mutation only if germ cells are affected. Mutations may be unique to an individual or family. Most mutations are rare. Polymorphisms begin as mutations. They are variations in DNA that have become common in a population (prevalence of ≥ 1%) through sufficient propagation or other mechanisms. Most are stable and inconsequential. A common example is human blood groups (A, B, AB, and O).

Mutations (and polymorphisms) involve random changes in DNA. Most have little effect on cell function. Some change cell function, usually in a detrimental way, and some are lethal to the cell. Examples of detrimental changes in cell function are mutations that cause cancer by creating oncogenes or altering tumor suppressor genes (see p. 1047). Rarely, a change in cell function confers a survival advantage. These mutations are more likely to be propagated. The mutation causing sickle cell anemia confers resistance to malaria. This resistance conferred a survival advantage in areas where malaria was endemic and often fatal. However, by causing symptoms and complications of sickle cell anemia, the mutation also has harmful effects usually when present in the homozygous state.

When and in what cell type mutations occur can explain certain abnormalities in inheritance patterns. Typically, an autosomal dominant disorder is expected to be present in one or both parents of an affected person. However, some disorders with autosomal dominant inheritance can appear de novo (in people whose parents have a normal phenotype). For example, about 80% of people with achondroplastic dwarfism have no family history of dwarfism and thus represent new (de novo) mutations. In many of these people, the mechanism is a spontaneous mutation occurring early in their embryonic life. Thus, other offspring have no increased risk of the disorder. However, in some of them, the disorder develops because of a germ cell mutation in their parents (eg, an autosomal dominant gene in a phenotypically normal parent). If so, other offspring have an increased risk of inheriting the mutation.

**Mosaicism:** Mosaicism occurs when a person starting from a single fertilized egg develops ≥ 2 cell lines differing in genotype. Mosaicism is a normal consequence of X inactivation in females (see p. 3378); in most females, some cells have an inactive maternal X, and other cells have an inactive paternal X. Mosaicism can also result from mutations. Mutations are likely to occur during cell division in any large multicellular organism; each time a cell divides, 4 or 5 changes are estimated to occur in the DNA. Because these changes can be passed on to subsequently produced cells, large multicellular organisms have subclones of cells that have slightly different genotypes.
Mosaicism may be recognized as the cause of disorders in which patchy changes occur. For example, McCune-Albright syndrome is associated with patchy dysplastic changes in the bone, endocrine gland abnormalities, patchy pigmented changes, and occasionally heart or liver abnormalities. Occurrence of the McCune-Albright mutation in all cells would cause early death; however, people with mosaicism survive because normal tissue supports the abnormal tissue. Occasionally, a parent with a single-gene disorder seems to have a mild form but actually represents a mosaic; the parent's offspring is more severely affected if they receive a germ cell with the mutant allele and thus have the abnormality in every cell.

Chromosomal abnormalities are most often fatal to the fetus. However, chromosomal mosaicism occurs in some embryos, resulting in some chromosomally normal cells, which can allow offspring to be born alive. Chromosomal mosaicism can be detected with prenatal genetic testing, particularly chorionic villus sampling.

**Extra or missing chromosomes:** Abnormal numbers of autosomes usually result in severe abnormalities. For example, extra autosomes typically cause abnormalities such as Down syndrome and other severe syndromes or can be fatal to the fetus. Absence of an autosome is always fatal to the fetus. Chromosomal abnormalities (see p. 2997) can usually be diagnosed before birth.

Because of X chromosomal inactivation, having an abnormal number of X chromosomes is usually much less severe than having an abnormal number of autosomes. For example, the abnormalities resulting from the absence of one X chromosome are usually relatively minor (eg, in Turner's syndrome, see p. 3003). Also, females with 3 X chromosomes (triple X syndrome, see p. 3005) are often physically and mentally normal; only one X chromosome of genetic material is fully active even if a female has > 2 X chromosomes (the extra X chromosomes are also partly inactivated).

**Uniparental disomy:** Uniparental disomy occurs when both chromosomes have been inherited from only one parent. It is very rare and is thought to involve trisomy rescue; ie, the zygote started off as a trisomy (having 3 instead of 2 of a particular chromosome) and one of the 3 was lost, a process that leads to uniparental disomy when the 2 chromosomes that remain are from the same parent (in about one third of cases). Uniparental disomy may cause abnormal inheritance patterns. For example, if duplicates of the same chromosome (isodisomy) are present and carry an abnormal allele for an autosomal recessive disorder, affected people can have an autosomal recessive disorder even though only one parent is a carrier.

**Chromosomal translocation:** Chromosomal translocation is exchange of chromosomal parts between nonpaired (nonhomologous) chromosomes. If chromosomes exchange equal parts of genetic material, the translocation is described as balanced. Unbalanced translocations result in loss of chromosomal material, usually the short arms of 2 fused chromosomes, leaving only 45 chromosomes remaining. Most people with translocations are phenotypically normal. However, translocations may cause or contribute to leukemia (acute myelocytic leukemia [AML] or chronic myelocytic leukemia [CML]) or Down syndrome. Translocations may increase risk of chromosomal abnormalities in offspring, particularly unbalanced translocations. Because chromosomal abnormalities are often fatal to an embryo or a fetus, a parental translocation may result in unexplained recurrent spontaneous abortions or infertility.

**Triplet (trinucleotide) repeat disorders:** A triplet repeat disorder results when a triplet of nucleotides is repeated an abnormal number of times within a gene. The number of triplets may increase when the gene is transmitted from one generation to the next or as cells divide within the body. When triplets increase enough, genes stop functioning normally. Triplet repeat disorders are infrequent but cause several neurologic disorders (eg, myotonic dystrophy, fragile X mental retardation), particularly those involving the CNS (eg, Huntington's disease). Triplet repeat disorders can be detected by techniques that analyze DNA.

**Anticipation:** Anticipation occurs when a disorder has an earlier age of onset and is expressed more severely in each successive generation. Anticipation may occur when a parent is a mosaic and the child has the full mutation in all cells. It may also occur in triplet repeat disorders when the number of repeats and thus the severity of gene dysfunction increase with each generation.
Mitochondrial DNA Abnormalities

Each cell has several hundred mitochondria in its cytoplasm. Mitochondria contain DNA in a single circular chromosome that codes for 13 proteins, various RNAs, and several regulating enzymes. However, > 90% of mitochondrial proteins are coded by nuclear genes. For practical purposes, all mitochondria are inherited from the cytoplasm of the egg; thus, mitochondrial DNA comes only from the mother.

Mitochondrial disorders (see also p. 3023) can be due to mitochondrial or nuclear DNA abnormalities (eg, deletions, duplications, mutations). High-energy tissues (eg, muscle, heart, brain) are particularly at risk of malfunction due to mitochondrial abnormalities. Particular mitochondrial DNA abnormalities result in characteristic manifestations (see Table 341-2). Mitochondrial disorders are equally common among males and females.

Mitochondrial abnormalities may occur in many common disorders such as some types of Parkinson's disease (which may involve large mitochondrial deletions in the cells of the basal ganglia) and many types of muscle disorders.

Maternal inheritance patterns characterize abnormalities of mitochondrial DNA. Thus, all offspring of an affected female are at risk of inheriting the abnormality, but no offspring of an affected male are at risk. Variability in clinical manifestations is the rule and may be due in part to variable mixtures of inherited mutant and normal mitochondrial genomes within cells and tissues.

Genetic Diagnostic Technologies

Genetic diagnostic technology is rapidly improving. DNA or RNA can be amplified, producing many copies of a gene or gene segment, using PCR.

Gene probes can be used to locate specific segments of normal or mutated DNA. A known DNA segment may be cloned and then radioactively or fluorescently tagged; this segment is then combined with a test specimen. The tagged DNA binds to its complementary DNA segment and can be detected by measuring the radioactivity or the amount and type of fluorescence. Gene probes can detect a number of disorders before and after birth. In the future, gene probes will probably be used to test people for many major genetic disorders simultaneously.

[Table 341-2, Mitochondrial Disorders]

Microchips are powerful new tools that can be used to identify DNA mutations, pieces of RNA, or proteins. A single chip can test for 30,000 different DNA changes using only one sample.

Clinical Uses of Genetics

Disease Understanding

Genetics has advanced understanding of many disorders, sometimes allowing them to be reclassified. For example, classification of many spinocerebellar ataxias has been changed from one based on clinical criteria to one based on genetic criteria (see p. 1778). The Online Mendelian Inheritance in Man (OMIM) database is a searchable catalog of human genes and genetic disorders.

Diagnosis

Genetic testing is used to diagnose many disorders (eg, Turner's syndrome, Klinefelter's syndrome, hemochromatosis). Diagnosis of a genetic disorder often indicates that relatives of the affected person should be screened for the genetic defect or for carrier status.

Genetic Screening

Genetic screening may be indicated in populations at risk of a particular genetic disorder. The usual criteria for genetic screening are
Genetic inheritance patterns are known.

Effective therapy is available.

Screening tests are sufficiently valid, reliable, sensitive and specific, noninvasive, and safe.

Prevalence in a defined population must be high enough to justify the cost of screening.

One aim of prenatal genetic screening (see p. 2598) is to identify asymptomatic parental heterozygotes carrying a gene for a recessive disorder. For example, Ashkenazi Jews are screened for Tay-Sachs disease, blacks are screened for sickle cell anemia, and several ethnic groups are screened for thalassemia (see Table 259-1 on p. 2600). If a heterozygote's mate is also a heterozygote, the couple is at risk of having an affected child. If the risk is high enough, prenatal diagnosis can be pursued (eg, with amniocentesis, chorionic villus sampling, umbilical cord blood sampling, maternal blood sampling, or fetal imaging). In some cases, genetic disorders diagnosed prenatally can be treated, preventing complications. For instance, special diet or replacement therapy can minimize or eliminate the effects of phenylketonuria, galactosemia, and hypothyroidism. Corticosteroids given to the mother before birth may decrease the severity of congenital virilizing adrenal hypoplasia.

Screening may be appropriate for people with a family history of a dominantly inherited disorder that manifests later in life, such as Huntington's disease or cancers associated with abnormalities of the \textit{BRCA1} or \textit{BRCA2} genes. Screening clarifies the risk of developing the condition for that person, who can then make appropriate plans, such as for more frequent screening or preventive therapy.

Screening may also be indicated when a family member is diagnosed with a genetic disorder. A person who is identified as a carrier can make informed decisions about reproduction.

\textbf{Treatment}

Understanding the genetic and molecular basis of disorders may help guide therapy. For example, dietary restriction can eliminate compounds toxic to patients with certain genetic defects, such as phenylketonuria or homocystinuria. Vitamins or other agents can modify a biochemical pathway and thus reduce toxic levels of a compound; eg, folate (folic acid) reduces homocysteine levels in people with 5,10-methylene tetrahydrofolate reductase polymorphism. Therapy may involve replacing a deficient compound or blocking an overactive pathway.

\textbf{Pharmacogenomics:} Pharmacogenomics is the science of how genetic characteristics affect the response to drugs. One aspect of pharmacogenomics is how genes affect pharmacokinetics. Genetic characteristics of a person may help predict response to treatments. For example, metabolism of warfarin is determined partly by variants in genes for the CYP2C9 enzyme and for the vitamin K epoxide reductase complex protein 1. Genetic variations (eg, in production of UDP [uridine diphosphate]-glucoronosyltransferase 1A1) also help predict whether the anticancer drug irinotecan will have intolerable adverse effects.

Another aspect of pharmacogenomics is pharmacodynamics (how drugs interact with cell receptors—see p. 3181). Genetic and thus receptor characteristics of disordered tissue can help provide more precise targets when developing drugs (eg, anticancer drugs). For example, trastuzumab can target specific cancer cell receptors in metastatic breast cancers that amplify the \textit{HER2/neu} gene. Presence of the Philadelphia chromosome in patients with chronic myelocytic leukemia (CML) helps guide chemotherapy.

\textbf{Gene therapy:} Gene therapy can broadly be considered any treatment that changes gene function. However, gene therapy is often considered specifically the insertion of normal genes into the cells of a person who lacks such normal genes because of a specific genetic disorder. The normal genes can be manufactured, using PCR, from normal DNA donated by another person. Because most genetic disorders are recessive, usually a dominant normal gene is inserted. Currently, such insertion gene therapy is most likely to be effective in the prevention or cure of single-gene defects, such as cystic fibrosis.
One way to transfer DNA into host cells is by viral transfection. The normal DNA is inserted into a virus, which then transfects the host cells, thereby transmitting the DNA into the cell nucleus. Some important concerns about insertion using a virus include reactions to the virus, rapid loss of (failure to propagate) the new normal DNA, and damage to the virus by antibodies developed against the transfected protein, which the immune system recognizes as foreign. Another way to transfer DNA uses liposomes, which are absorbed by the host cells and thereby deliver their DNA to the cell nucleus. Potential problems with liposome insertion methods include failure to absorb the liposomes into the cells, rapid degradation of the new normal DNA, and rapid loss of integration of the DNA.

With antisense technology, rather than inserting normal genes, gene expression can be altered; eg, drugs can combine with specific parts of the DNA, preventing or decreasing gene expression. Antisense technology is currently being tried for cancer therapy but is still very experimental. However, it seems to hold more promise than gene insertion therapy because the success rates may be higher and complications may be fewer.

Another approach to gene therapy is to modify gene expression chemically (eg, by modifying DNA methylation). Such methods have been tried experimentally in treating cancer. Chemical modification may also affect genomic imprinting, although this effect is not clear.

Gene therapy is also being studied experimentally in transplantation surgery. Altering the genes of the transplanted organs to make them more compatible with the recipient's genes makes rejection (and thus the need for immunosuppressive drugs) less likely. However, this process works only rarely.

**Ethical Controversies**

With new genetic diagnostic and therapeutic capabilities come many controversies about how they should be used. For example, there are concerns that genetic information might be used improperly to discriminate (eg, by denying health insurance coverage or employment) against people with genetic risk factors for particular disorders. Issues include the privacy of a person's own genetic information and the question of whether testing should be compulsory.

Prenatal screening for genetic abnormalities that cause serious disorders is widely supported; however, there is concern that screening could also be used to select for traits that are aesthetically desirable (eg, physical appearance, intelligence).

Cloning is highly controversial. Animal studies suggest cloning is much more likely than natural methods to result in defects that are lethal or cause serious health problems. Creating a human by cloning is widely seen as unethical, is usually illegal, and is technically difficult.
Chapter 342. Clinical Decision Making

Introduction

Clinicians must integrate a huge variety of clinical data while facing conflicting pressures to decrease diagnostic uncertainty, risks to patients, and costs. Deciding what information to gather, which tests to order, how to interpret and integrate this information to draw diagnostic conclusions, and which treatments to give is known as clinical decision making.

When presented with a patient, clinicians usually must answer the following questions:

• What disease does this patient have?
• Should this patient be treated?
• Should testing be done?

In straightforward or common situations, clinicians often make such decisions informally; diagnoses are made by recognizing disease patterns, and testing and treatment are initiated based on customary practice. For example, during a flu epidemic, a healthy adult who has had fever, aches, and harsh cough for 2 days is likely to be recognized as another case of influenza and provided only appropriate symptomatic relief. Such pattern recognition is efficient and easy to use but may be subject to error because other diagnostic and therapeutic possibilities are not seriously or systematically considered. For example, a patient with that flu pattern and decreased O₂ saturation might instead have bacterial pneumonia and require antibiotics. In more complex cases, a structured, quantitative, analytical methodology may be a better approach to decision making. Even when pattern recognition provides the most likely diagnostic possibility, analytic decision making is often used to confirm the diagnosis. Analytic methods may include application of the principles of evidence-based medicine, use of clinical guidelines, and use of various specific quantitative techniques (eg, Bayes' theorem).

Evidence-Based Medicine and Clinical Guidelines

Physicians have always felt that their decisions were based on evidence; thus, the current term "evidence-based medicine" is somewhat of a misnomer. However, for many clinicians, the "evidence" is often a vague combination of recollected strategies effective in previous patients, advice given by mentors and colleagues, and a general impression of "what is being done" based on random journal articles, abstracts, symposia, and advertisements. This kind of practice results in wide variations in strategies for diagnosing and managing similar conditions, even when strong evidence exists for favoring one particular strategy over another. Variations exist among different countries, different regions, different hospitals, and even within individual group practices. These variations have led to a call for a more systematic approach to identifying the most appropriate strategy for an individual patient; this approach is called evidence-based medicine (EBM). EBM is built on reviews of relevant medical literature and follows a discrete series of steps.

Evidence-Based Medicine

EBM is not the blind application of advice gleaned from recently published literature to individual patient problems. Rather, EBM requires the use of a series of steps to gather sufficiently useful information to answer a carefully crafted question for an individual patient. Fully integrating the principles of EBM also incorporates the patient's value system, which includes such things as costs incurred, the patient's religious or moral beliefs, and patient autonomy. Applying the principles of EBM typically involves the following steps:

• Formulating a clinical question
• Gathering evidence to answer the question
• Evaluating the quality and validity of the evidence

• Deciding how to apply the evidence to the care of a given patient

**Formulating a clinical question:** Questions must be specific. Specific questions are most likely to be addressed in the medical literature. A well-designed question specifies the population, intervention (diagnostic test, treatment), comparison (treatment A vs treatment B), and outcome. "What is the best way to evaluate someone with abdominal pain?" is not a good question. A better, more specific question may be "Is CT or ultrasonography preferable for diagnosing acute appendicitis in a 30-yr-old male with acute lower abdominal pain?"

**Gathering evidence to answer the question:** A broad selection of relevant studies is obtained from a review of the literature. Standard resources are consulted (eg, MEDLINE, the Cochrane Collaboration [treatment options], the National Guideline Clearinghouse, ACP Journal Club).

**Evaluating the quality and validity of the evidence:** Not all scientific studies are of equal value. Different types of studies have different scientific strengths and legitimacy, and for any given type of study, individual examples often vary in quality of the methodology, internal validity, and generalizability of results (external validity).

**Levels of evidence** are graded 1 through 5 in decreasing order of quality. Types of studies at each level vary somewhat with the clinical question (eg, of diagnosis, treatment, or economic analysis), but typically level 1 evidence (the highest quality) consists of systematic reviews or meta-analyses of randomized controlled trials and high-quality, single, randomized controlled trials. Level 2 evidence is well-designed cohort studies. Level 3 evidence is case-control studies. Level 4 evidence is case series and poor-quality cohort and case-control studies. Level 5 evidence is expert opinion not based on critical appraisal but is based on reasoning from physiology, bench research, or underlying principles.

For EBM analysis, the highest level of evidence available is selected. Ideally, a significant number of large, well-conducted level 1 studies are available. However, because the number of high-quality, randomized, controlled trials is vanishingly small compared with the number of possible clinical questions, less reliable level 4 or 5 evidence is very often all that is available. Lower-quality evidence does not mean that the EBM process cannot be followed, just that the strength of the conclusion is weaker.

**Deciding how to apply the evidence to the care of a given patient:** Because the best available evidence may have come from patient populations with different characteristics from those of the patient in question, some judgment is required. Additionally, patients' wishes regarding aggressive or invasive tests and treatment must be taken into account as well as their tolerance for discomfort, risk, and uncertainty. For example, even though an EBM review may definitively show a 3-mo survival advantage from an aggressive chemotherapy regimen in a certain form of cancer, patients may differ on whether they prefer to gain the extra time or avoid the extra discomfort.

**Limitations:** Dozens of clinical questions are faced during the course of even one day in a busy practice. Although some of them may be the subject of an existing EBM review available for reference, most are not, and preparing an EBM analysis is too time-consuming to be useful in answering an immediate clinical question. Even when time is not a consideration, many clinical questions do not have any relevant studies in the literature.

**Clinical Guidelines**

Clinical guidelines have become common in the practice of medicine; many specialty societies have published such guidelines. Most well-conceived clinical guidelines are developed using a specified method that incorporates principles of EBM and consensus recommendations made by a panel of experts.

Some clinical guidelines follow "if, then" rules (eg, if a patient is febrile and neutropenic, then institute broad-spectrum antibiotics). More complex, multistep rules may be formalized as algorithms. Guidelines and algorithms are generally straightforward and easy to use but should be applied only to patients.
whose clinical characteristics (eg, demographics, comorbidities, clinical features) are similar to those of the patient group used to create the guideline. Furthermore, guidelines do not take into account the degree of uncertainty inherent in test results, the likelihood of treatment success, and the relative risks and benefits of each course of action. To incorporate uncertainty and the value of outcomes into clinical decision making, clinicians must often apply the principles of quantitative or analytical medical decision making.

Clinical Decision-Making Strategies

One of the most commonly used strategies for medical decision making mirrors the scientific method of hypothesis generation followed by hypothesis testing. Diagnostic hypotheses are accepted or rejected based on testing.

Hypothesis generation: Hypothesis generation involves the identification of the main diagnostic possibilities (differential diagnosis) that might account for the patient's clinical problem. The patient's chief complaint (eg, chest pain) and basic demographic data (age, sex, race) are the starting points for the differential diagnosis, which is usually generated by pattern recognition. Each element on the list of possibilities is ideally assigned an estimated probability (see Sidebar 342-1), or likelihood, of its being the correct diagnosis (pre-test probability—see Table 342-1).

Clinicians often use vague terms such as "highly likely," "improbable," and "cannot rule out" to describe the likelihood of disease. Both clinicians and patients often misinterpret such semiquantitative terms; explicit statistical terminology should be used instead when available. Mathematical computations assist clinical decision making and, even when exact numbers are unavailable, can better define clinical probabilities and narrow the list of hypothetical diseases further.

Hypothesis testing: The initial differential diagnosis based on chief complaint and demographics is usually very large, so the clinician first tests the hypothetical possibilities during the history and physical examination, asking questions or doing specific examinations that support or refute a suspected diagnosis. For instance, in a patient with chest pain, a history of leg pain and a swollen, tender leg detected during examination increases the probability of pulmonary embolism.

**Sidebar 342-1 Probability and Odds**

The probability of a disease (or event) occurring in a patient whose clinical information is unknown is the frequency with which that disease or event occurs in a population. Probabilities range from 0.0 (impossible) to 1.0 (certain) and are often expressed as percentages (from 0 to 100). A disease that occurs in 2 of 10 patients has a probability of 2/10 (0.2 or 20%). Rounding very small probabilities to 0, thus excluding all possibility of disease (sometimes done in implicit clinical reasoning), can lead to erroneous conclusions when quantitative methods are used.

Odds represent the ratio of affected to unaffected patients (ie, the ratio of disease to no disease). Thus, a disease that occurs in 2 of 10 patients (probability of 2/10) has odds of 2/8 (0.25, often expressed as 1 to 4). Odds (Ω) and probabilities (p) can be converted one to the other, as in \( Ω = p/(1 - p) \) or \( p = Ω/(1 + Ω) \).

When the history and physical examination form a clear-cut pattern, a presumptive diagnosis is made. Diagnostic testing is used when uncertainties persist after the history and physical examination, particularly when the diseases remaining under consideration are serious or have dangerous or costly treatment. Test results further modify the probabilities of different diagnoses (post-test probability). For example, Table 342-1 shows how the additional findings that the hypothetical patient had leg pain and swelling and a normal ECG and chest x-ray modify diagnostic probabilities—the probability of acute coronary syndrome, dissecting aneurysm, and pneumothorax decreases, and the probability of pulmonary, embolism increases. These changes in probability may lead to additional testing (in this example, probably chest CT angiography) that further modifies post-test probability (see Table 342-1)
and, in some cases, confirms or refutes a diagnosis.

**Probability Estimations and the Treatment Threshold**

The disease probability at and above which treatment is given and no further testing is warranted is termed the treatment threshold (TT).

The above hypothetical example of a patient with chest pain converged on a near-certain diagnosis (98% probability). When diagnosis of a disease is certain, the decision to treat is a straightforward determination that there is a benefit of treatment (compared with no treatment and taking into account adverse effects of treatment). When the diagnosis has some degree of uncertainty, as is almost always the case, the decision to treat also must balance the benefit of treating a sick person against the risk of erroneously treating a well person or a person with a different disorder; benefit and risk encompass both financial and medical consequences. This balance must take into account both the likelihood of disease and the magnitude of the benefit and risk. This balance determines where the clinician sets the TT.

Conceptually, if the benefit of treatment is very high and the risk is very low (as when giving a safe antibiotic to a patient with diabetes who possibly has a life-threatening infection), clinicians tend to accept high diagnostic uncertainty and might initiate treatment even if probability of infection is fairly low (eg, 30%—see Fig. 342-1). However, when the risk of treatment is very high (as when doing a pneumonectomy for possible lung cancer), clinicians want to be extremely sure of the diagnosis and might recommend treatment only when the probability of cancer is very high, perhaps > 95% (see Fig. 342-1). Note that the TT does not necessarily correspond to the probability at which a disease might be considered confirmed or ruled in. It is simply the point at which the risk of not treating is greater than the risk of treating.

Quantitatively, the TT can be described as the point at which probability of disease (p) times benefit of treating a person with disease (B) equals probability of no disease (1 - p) times risk of treating a person without disease (R). Thus, at the TT

\[ p \times B = (1 - p) \times R \]

Solving for p, this equation reduces to

\[ p = \frac{R}{B + R}. \]

From this equation, it is apparent that if B (benefit) and R (risk) are the same, the TT becomes 1/(1 + 1) = 0.5, which means that when the probability of disease is > 50%, clinicians would treat, and when probability is < 50%, clinicians would not treat.

For a clinical example, a patient with chest pain can be considered. How high should the clinical likelihood of acute MI be before thrombolytic therapy should be given, assuming the only risk considered is short-term mortality? If it is postulated (for illustration) that mortality due to intracranial hemorrhage with thrombolytic therapy is 1%, then 1% is R, the fatality rate of mistakenly treating a patient who does not have an MI. If net mortality in patients with MI is decreased by 3% with thrombolytic therapy, then 3% is B. Then, TT is 1/(3 + 1), or 25%; thus, treatment should be given if the probability of acute MI is > 25%.

Alternatively, the TT equation can be rearranged to show that the TT is the point at which the odds of disease p/(1 - p) equal the risk:benefit ratio (R/B). The same numerical result is obtained as in the previously described example, with the TT occurring at the odds of the risk:benefit ratio (1/3); 1/3 odds
corresponds to the previously obtained probability of 25% (see Sidebar 342-1).

**Limitations:** Quantitative clinical decision making seems precise, but because many elements in the calculations are often imprecisely known (if they are known at all), this methodology is difficult to use in all but the most well-defined and studied clinical situations.

**Cognitive Errors in Clinical Decision Making**

Although quantitative mathematical models can guide clinical decision making, clinicians rarely use formal computations to make patient care decisions in day-to-day practice. Rather, an intuitive understanding of probabilities is combined with cognitive processes called heuristics to guide clinical judgment. Heuristics are often referred to as rules of thumb, educated guesses, or mental shortcuts. Heuristics usually involve pattern recognition and rely on a subconscious integration of somewhat haphazardly gathered patient data with prior experience rather than on a conscious generation of a rigorous differential diagnosis that is formally evaluated using specific data from the literature.

Such informal reasoning is often fallible because heuristics may cause several types of unconscious errors (cognitive errors). Studies suggest that more medical errors involve cognitive error than lack of knowledge or information.

**Types of cognitive error:** There are many types of cognitive errors, and although it is obviously more important to avoid errors than to properly classify them once made, being aware of common types of cognitive errors can help clinicians recognize and avoid them.

Cognitive errors may roughly be classified as those involving

- Faulty assessment of pre-test probability (overestimating or underestimating disease likelihood)
- Failure to seriously consider all relevant possibilities

Both types of error can easily lead to improper testing (too much or too little) and missed diagnoses.

**Availability error** occurs when clinicians misestimate the prior probability of disease because of recent experience. Experience often leads to overestimation of probability when there is memory of a case that was dramatic or that involved a patient who fared poorly or a lawsuit. For example, a clinician who recently missed the diagnosis of pulmonary embolism in a healthy young woman who had vague chest discomfort but no other findings or apparent risk factors might then overestimate the risk in similar patients and become more likely to do chest CT angiography for similar patients despite the very small probability of disease. Experience can also lead to underestimation. For example, a junior resident who has seen only a few patients with chest pain, all of whom turned out to have benign causes, may begin to do cursory evaluations of that complaint even among populations in which disease prevalence is high.

**Representation error** occurs when clinicians judge the probability of disease based on how closely the patient's findings fit classic manifestations of a disease without taking into account disease prevalence. For example, although several hours of vague chest discomfort in a thin, athletic, healthy-appearing 60-yr-old man who has no known medical problems and who now looks and feels well does not match the typical profile of an MI, it would be unwise to dismiss that possibility because MI is common among men of that age and has highly variable manifestations. Conversely, a 20-yr-old healthy man with sudden onset of severe, sharp chest pain and back pain may be suspected of having a dissecting thoracic aortic aneurysm because those clinical features are common in aortic dissection. The cognitive error is not taking into account the fact that aortic dissections are exceptionally rare in a 20-yr-old, otherwise healthy patient; that disorder can be dismissed out of hand and other, more likely causes (eg, pneumothorax, pleuritis) should be considered. Representation error is also involved when clinicians fail to recognize that positive test results in a population where the tested disease is rare are more likely to be false positive than true positive.

**Premature closure** is one of the most common errors; clinicians make a quick diagnosis (often based on pattern recognition), fail to consider other possible diagnoses, and stop collecting data (jump to
conclusions); often, even the suspected diagnosis is not confirmed by appropriate testing. Premature closure errors may occur in any case but are particularly common when patients seem to be having an exacerbation of a known disorder—eg, if a woman with a long history of migraine presents with a severe headache (and actually has a new subarachnoid hemorrhage), the headache may be mistakenly assumed to be another attack of migraine. A variation of premature closure occurs when subsequent clinicians (eg, consultants on a complicated case) unquestioningly accept a previous working diagnosis without independently collecting and reviewing relevant data.

**Anchoring errors** occur when clinicians steadfastly cling to an initial impression even as conflicting and contradictory data accumulate. For example, a working diagnosis of acute pancreatitis is quite reasonable in a 60-yr-old man who has epigastric pain and nausea, who is sitting forward clutching his abdomen, and who has a history of several bouts of alcoholic pancreatitis that he states have felt similar to what he is currently feeling. However, if the patient states that he has had no alcohol in many years and has normal blood levels of pancreatic enzymes, clinicians who simply dismiss or excuse (eg, the patient is lying, his pancreas is burned out, the laboratory made a mistake) these conflicting data are committing an anchoring error. Clinicians should regard conflicting data as evidence of the need to continue to seek the true diagnosis (acute MI) rather than as anomalies to be disregarded. There may be no supporting evidence (ie, for the misdiagnosis) in some cases in which anchoring errors are committed.

**Confirmation bias** occurs when clinicians selectively accept clinical data that support a desired hypothesis and ignore data that do not (cherry-picking). Confirmation bias often compounds an anchoring error when the clinician uses confirmatory data to support the anchored hypothesis even when clearly contradictory evidence is also available. For example, a clinician may steadfastly cling to patient history elements suggesting acute coronary syndrome (ACS) to confirm the original suspicion of ACS even when serial ECGs and cardiac enzymes are normal.

**Attribution errors** involve negative stereotypes that lead clinicians to ignore or minimize the possibility of serious disease. For example, clinicians might assume that an unconscious patient with an odor of alcohol is "just another drunk" and miss hypoglycemia or intracranial injury, or they might assume that a known drug abuser with back pain is simply seeking drugs and miss an epidural abscess caused by use of dirty needles. Psychiatric patients who develop a physical disorder are particularly likely to be subject to attribution errors because not only may they be subject to negative stereotyping but they often describe their symptoms in unclear, inconsistent, or confusing ways, leading unwary clinicians to assume their complaints are of mental origin.

**Affective error** involves avoiding unpleasant but necessary tests or examinations because of fondness or sympathy for the patient (eg, avoiding a pelvic examination on a modest patient or blood cultures on a seriously ill patient who has poor veins).

**Minimizing cognitive errors**: Some specific strategies can help minimize cognitive errors. Typically, after history and physical examination are done, clinicians often form a working diagnosis based on heuristics. At this point, it is relatively easy to insert a formal pause for reflection, asking several questions:

- If it is not the working diagnosis, what else could it be?
- What are the most dangerous things it could be?
- Is there any evidence that is at odds with the working diagnosis?

These questions can help expand the differential diagnosis to include things that may have been left out because of cognitive errors and thus trigger clinicians to obtain further necessary information.

**Testing**

Test results may help make a diagnosis in symptomatic patients (diagnostic testing) or identify occult disease in asymptomatic patients (screening). However, test results may interfere with clinical decision making if the test poorly discriminates between patients with and without disease, if the result is
inconsistent with the clinical picture, or if the test result is improperly integrated into the clinical context.

Laboratory tests are imperfect and may mistakenly identify some healthy people as diseased (a false-positive result) or may mistakenly identify some affected people as disease-free (a false-negative result). A test's ability to correctly include or exclude disease depends on how likely a person is to have a disease (prior probability) and on the test's intrinsic operating characteristics.

Although diagnostic testing is often a critical contributor to clinical decision making, testing can have undesired or unintended consequences. Testing must be done with deliberation and purpose and with the expectation that the test result will reduce ambiguity surrounding patient problems and contribute to their health. In addition to the risk of providing incorrect information (thereby delaying initiation of treatment or inducing unnecessary treatment), laboratory tests consume limited resources and may themselves have adverse effects (eg, pneumothorax caused by lung biopsy) or may prompt additional unnecessary testing.

**Defining a Positive Test Result**

Among the most common tests are those that provide results along a continuous, quantitative scale (eg, blood glucose, WBC count). Such tests may provide useful clinical information throughout their ranges, but clinicians often use them to diagnose a condition by requiring that the result be classified as positive or negative (ie, disease present or absent) based on comparison to some established criterion or cutoff point. Such cutoff points are usually selected based on statistical and conceptual analysis that attempts to balance the rate of false-positive results (prompting unnecessary, expensive, and possibly dangerous tests or treatments) and false-negative results (failing to diagnose a treatable disease). Identifying a cutoff point also depends on having a gold standard to identify the disease in question.

Typically, such quantitative test results (eg, WBC count in cases of suspected appendicitis) follow some type of distribution curve (not necessarily a normal curve, although commonly depicted as such). The distribution of test results for patients with disease is centered on a different point than that for patients without disease. Some patients with disease have a very high or very low result, but most have a result centered on a mean. Conversely, some disease-free patients have a very high or very low result, but most have a result centered on a different mean from that for patients with disease. For most tests, the distributions overlap such that many of the possible test results occur in patients with and without disease; such results are more clearly illustrated when the curves are depicted on the same graph (see **Fig. 342-2**). Some patients above and below the selected cutoff point will be incorrectly characterized. Adjusting a cutoff point to identify more patients with disease (increase test sensitivity) also increases the number of false positives (poor specificity), and moving the cutoff point the other way to avoid falsely diagnosing patients as having disease increases the number of false negatives. Each cutoff point is associated with a specific probability of true-positive and false-positive results.

**Receiver operating characteristic (ROC) curves:** Graphing the fraction of true-positive results (number of true positives/number with disease) against the fraction of false-positive results (number of false positives/number without disease) for a series of cutoff points generates what is known as an ROC curve. The ROC curve graphically depicts the tradeoff between the sensitivity and specificity when the cutoff point is adjusted (see **Fig. 342-3**).

By convention, the true-positive fraction is placed on the y-axis, and the false-positive fraction is placed on the x-axis. The greater the area under the ROC curve, the better the test discriminates between patients with or without disease.

ROC curves allow tests to be compared over a variety of cutoff points. In the example, Test A performs better than Test B over all ranges. ROC curves also assist in the selection of the cutoff point designed to
maximize a test’s utility. If a test is designed to confirm a disease, a cutoff point with greater specificity and lower sensitivity is selected. If a test is designed to screen for occult disease, a cutoff point with greater sensitivity and lower specificity is selected.

**Test Characteristics**

Some clinical variables have only 2 possible results (eg, alive/dead, pregnant/not pregnant); such variables are termed categorical and dichotomous. Other categorical results may have many discrete values (eg, blood type, Glasgow Coma Scale) and are termed nominal or ordinal. Nominal variables such as blood type have no particular order. Ordinal variables such as the Glasgow Coma Scale have discrete values that are arranged in a particular order. Other clinical variables, including many typical diagnostic tests, are continuous and have an infinite number of possible results (eg, WBC count, blood glucose level). Many clinicians select a cutoff point that can cause a continuous variable to be treated as a dichotomous variable (eg, patients with a fasting blood glucose level > 126 mg/dL are considered to have diabetes). Other continuous diagnostic tests have diagnostic utility when they have multiple cutoff points or when ranges of results have different diagnostic value.

When test results can be defined as positive or negative, all possible outcomes can be recorded in a simple 2×2 table (see Table 342-2) from which important discriminatory test characteristics, including sensitivity, specificity, positive and negative predictive value, and likelihood ratio (LR), can be calculated (see Table 342-3).

**Sensitivity, specificity, and predictive values:** Sensitivity, specificity, and predictive values are typically considered characteristics of the test itself, independent of the patient population.

**Sensitivity** is the likelihood of a positive test result in patients with disease (true-positive rate); a test that is positive in 8 of 10 patients with a disease has a sensitivity of 0.8 (also expressed as 80%). Sensitivity represents how well a test detects the disease; a test with low sensitivity does not identify many patients with disease, and a test with high sensitivity is useful to exclude a diagnosis when results are negative. Sensitivity is the complement of the false-negative rate (ie, the false-negative rate plus the sensitivity = 100%).

**Specificity** is the likelihood of a negative test result in patients without disease (true-negative rate); a test that is negative in 9 of 10 patients without disease has a specificity of 0.9 (or 90%). Specificity represents how well a test correctly identifies patients with disease because tests with high specificity have a low false-positive rate. A test with low specificity diagnoses many patients without disease as having disease. It is the complement of the false-positive rate.

**Positive predictive value (PPV)** is the proportion of patients with a positive test that actually have disease; if 9 of 10 positive test results are correct (true positive), the PPV is 90%. Because all positive test results have some number of true positives and some false positives, the PPV describes how likely it is that a positive test result in a given patient population represents a true positive.

**Negative predictive value (NPV)** is the proportion of patients with a negative test result that are actually disease free; if 8 of 10 negative test results are correct (true negative), the NPV is 80%. Because not all negative test results are true negatives, some patients with a negative test result actually have disease. The NPV describes how likely it is that a negative test result in a given patient population represents a true negative.

**Likelihood ratios (LRs):** Unlike sensitivity and specificity, which do not apply to specific patient probabilities, the LR allows clinicians to interpret test results in a specific patient provided there is a known (albeit often estimated) pre-test probability of disease.

The LR describes the change in pre-test probability of disease when the test result is known and answers the question, "How much has the post-test probability changed now that the test result is known?" Many
Table 342-3. Distribution of Test Results of a Hypothetical Leukocyte Esterase Test in a Cohort of 1000 Women with an Assumed 30% Prevalence of UTI

Tests are dichotomous; they are either above the cutoff point (positive) or below the cutoff point (negative) and there are only 2 possible results. Other tests give results that are continuous or occur over a range where multiple cutoff points are selected. The actual post-test probability depends on the magnitude of the LR (which depends on test operating characteristics) and the pre-test probability estimation of disease. When the test being done is dichotomous and the result is either positive or negative, the sensitivity and specificity can be used to calculate positive LR (LR+) or negative LR (LR-).

- **LR+:** The ratio of the likelihood of a positive test result occurring in patients with disease (true positive) to the likelihood of a positive test result in patients without disease (false positive)

- **LR-:** The ratio of the likelihood of a negative test result in patients with disease (false negative) to the likelihood of a negative test result in patients without disease (true negative)

When the result is continuous or has multiple cutoff points, the ROC curve, not sensitivity and specificity, is used to calculate an LR that is no longer described as LR+ or LR-.

Because the LR is a ratio of mutually exclusive events rather than a proportion of a total, it represents odds (see Sidebar 342-1) rather than probability. For a given test, the LR is different for positive and negative results.

For example, given a positive test result, an LR of 2.0 indicates the odds are 2:1 (true positives: false positives) that a positive test result represents a patient with disease. Of 3 positive tests, 2 would occur in patients with disease (true positive) and 1 would occur in a patient without disease (false positive). Because true positives and false positives are components of sensitivity and specificity calculations, the LR+ can also be calculated as sensitivity/(1 - specificity). The greater the LR+, the more information a positive test result provides; a positive result on a test with an LR+ > 10 is considered strong evidence in favor of a diagnosis. In other words, the pre-test probability estimation moves strongly toward 100% when a positive test has a high LR+.

For a negative test result, an LR- of 0.25 indicates that the odds are 1:4 (false negatives: true negatives) that a negative test result represents a patient with disease. Of 5 negative test results, 1 would occur in a patient with disease (false negative) and 4 would occur in patients without disease (true negative). The LR- can also be calculated as (1 - sensitivity)/specificity. The smaller the LR-, the more information a negative test result provides; a negative result on a test with an LR < 0.1 is considered strong evidence against a diagnosis. In other words, the pre-test probability estimation moves strongly toward 0% probability when a negative test has a low LR-.

Test results with LRs of 1.0 carry no information and do not affect the post-test probability of disease.

LRs are convenient for comparing tests and are also used in Bayesian analysis (see p. 3394) to interpret test results. Just as sensitivity and specificity change as cutoff points change, so do LRs. As a hypothetical example, a high cutoff for WBC count (eg, 20,000/μL) in a possible case of acute appendicitis is more specific and would have a high LR+ but also a high (and thus not very informative) LR-; choosing a much lower and very sensitive cutoff (eg, 10,000/μL) would have a low LR- but also a low LR+.

**Dichotomous Tests**

An ideal dichotomous test would have no false positives or false negatives; all patients with a positive test result would have disease (100% PPV), and all patients with a negative test result would not have disease (100% NPV).

In reality, all tests have false positives and false negatives, some tests more than others. To illustrate the
consequences of imperfect sensitivity and specificity on test results, consider hypothetical results (Table 342-3) of urine dipstick leukocyte esterase testing in a group of 1000 women, 300 (30%) of whom have a UTI (as determined by a gold-standard test such as urine culture). This scenario assumes for illustrative purposes that the dipstick test has sensitivity of 71% and specificity of 85%.

Sensitivity of 71% means that only 213 (71% of 300) women with UTI would have a positive test result. The remaining 87 would have a negative test result. Specificity of 85% means that 595 (85% of 700) women without UTI would have a negative test result. The remaining 105 would have a positive test result. Thus, of 318 positive test results, only 213 would be correct (213/318 = 67% PPV); a positive test result makes the diagnosis of UTI more likely than not but not certain. There would also be 682 negative tests, of which 595 are correct (595/682 = 87% NPV), making the diagnosis of UTI much less likely but still possible; 13% of patients with a negative test result would actually have a UTI.

However, the PPVs and NPVs derived in this patient cohort cannot be used to interpret results of the same test when the underlying incidence of disease (pre-test or prior probability) is different. Note the effects of changing disease incidence to 5% (see Table 342-4). Now most positive test results are false, and the PPV is only 20%; a patient with a positive test result is actually more likely to not have a UTI. However, the NPV is now very high (98%); a negative result essentially rules out UTI.

Note that in both patient cohorts, even though the PPV and NPV are very different, the LRs do not change because the LRs are determined only by test sensitivity and specificity.

Clearly, a test result does not provide a definitive diagnosis but only estimates the probability of a disease being present or absent, and this post-test probability (likelihood of disease given a specific test result) varies greatly based on the pre-test probability of disease as well as the test's sensitivity and specificity (and thus its LR).

Pre-test probability is not a precise measurement; it is based on clinical judgment of how strongly the symptoms and signs suggest the disease is present, what factors in the patient's history support the diagnosis, and how common the disease is in a representative population. Many clinical scoring systems are designed to estimate pre-test probability; adding points for various clinical features facilitates the calculation of a score. For example, there are criteria for predicting pre-test probability of pulmonary embolism (see p. 1910). Higher calculated scores yield higher estimated probabilities.

Continuous Tests

Many test results are continuous and may provide useful clinical information over a wide range of results. Clinicians often select a certain cutoff point to maximize the test's utility. For example, a WBC count > 15,000 may be characterized as positive; values < 15,000 as negative. When a test yields continuous results but a certain cutoff point is selected, the test operates like a dichotomous test. Multiple cutoff points can also be selected. Sensitivity, specificity, PPV, NPV, LR+, and LR- can be calculated for single or multiple cutoff points. Table 342-5 illustrates the effect of changing the cutoff point of the WBC count in patients suspected of having appendicitis.

Alternatively, it can be useful to group continuous test results into levels. In this case, results are not characterized as positive or negative because there are multiple possible results, so although an LR can be determined for each level of results, there is no longer a distinct LR+ or LR-. For example, Table 342-6 illustrates the relationship between WBC count and bacteremia in febrile children. Because the LR is the probability of a given result in patients with disease divided by the probability of that result in patients without the disease, the LR for each grouping of WBC count is the probability of bacteremia in that group divided by the probability of no bacteremia.

Grouping continuous variables allows for much greater use of the test result than when a single cutoff
point is established. Using Bayesian analyses, the LRs in Table 342-6 can be used to calculate the post-test probability.

For continuous test results, if an ROC curve is known, calculations as shown in Table 342-6 do not have to be done; LRs can be found for various points over the range of results using the slope of the ROC curve at the desired point.

Bayes' Theorem

The process of using the pre-test probability of disease and the test characteristics to calculate the post-test probability is referred to as Bayes' theorem or Bayesian revision. For routine clinical use, Bayesian methodology typically takes several forms:

• Odds-likelihood formulation (calculation or nomogram)
• Tabular approach

Odds-likelihood calculation: If the pre-test probability of disease is expressed as its odds and because a test's LR represents odds, the product of the 2 represents the post-test odds of disease (analogous to multiplying 2 probabilities together to calculate the probability of simultaneous occurrence of 2 events):

\[ \text{Pre-test odds} \times \text{LR} = \text{post-test odds} \]

Because clinicians typically think in terms of probabilities rather than odds, probability can be converted to odds (and vice versa) with these formulas:

\[ \text{Odds} = \frac{\text{probability}}{1 - \text{probability}} \]
\[ \text{Probability} = \frac{\text{odds}}{\text{odds} + 1} \]

Consider the example of UTI as given in Table 342-3, in which the pre-test probability of UTI is 0.3, and the test being used has an LR+ of 4.73 and an LR- of 0.34. A pre-test probability of 0.3 corresponds to odds of \( \frac{0.3}{1 - 0.3} = 0.43 \). Thus, the post-test odds that a UTI is present in a patient with a positive test result equals the product of the pre-test odds and the LR+; \( 4.73 \times 0.43 = 2.03 \), which represents a post-test probability of \( \frac{2.03}{1 + 2.03} = 0.67 \). Thus, Bayesian calculations show that a positive test result increases the pre-test probability from 30% to 67%, the same result obtained in the PPV calculation in Table 342-3.

A similar calculation is done for a negative test; post-test odds = \( 0.34 \times 0.43 = 0.15 \), corresponding to a probability of \( \frac{0.15}{1 + 0.15} = 0.13 \). Thus, a negative test result decreases the pre-test probability from 30% to 13%, again the same result obtained in the NPV calculation in Table 342-3.

Many medical calculator programs that run on handheld devices are available to calculate post-test probability from pre-test probability and LRs.

Odds-likelihood nomogram: Using a nomogram is particularly convenient because it avoids the need to convert between odds and probabilities or create 2×2 tables.

The Fagan nomogram is depicted in Fig. 342-4. To use the nomogram, a line is drawn from the pre-test probability through the LR. The post-test probability is the point at which this line intersects the post-test probability line. Sample lines in the
figure are drawn using data from the UTI test in Table 342-3. Line A represents a positive test result; it is drawn from pre-test probability of 0.3 through the LR+ of 4.73 and gives a post-test value of slightly < 0.7, similar to the calculated probability of 0.67. Line B represents a negative test result; it is drawn from pre-test probability of 0.3 through the LR- value of 0.34 and gives a post-test value slightly > 0.1, similar to the calculated probability of 13%.

Although the nomogram appears less precise than calculations, typical values for pre-test probability are often estimates, so the apparent precision of calculations is usually misleading.

**Tabular approach:** Often, LRs of a test are not known, but sensitivity and specificity are known, and pre-test probability can be estimated. In this case, Bayesian methodology can be done using a 2×2 table illustrated in Table 342-7 using the example from Table 342-3. Note that this method shows that a positive test result increases the probability of a UTI to 67%, and a negative result decreases it to 13%, the same results obtained by calculation using LRs.

**Sequential Testing**

Clinicians often do tests in sequence during many diagnostic evaluations. If the pre-test odds before sequential testing are known and the LR for each of the tests in sequence is known, post-test odds can be calculated using the following formula:

\[
\text{Pre-test odds} \times \text{LR}_1 \times \text{LR}_2 \times \text{LR}_3 = \text{post-test odds}
\]

This method is limited by the important assumption that each of the tests is conditionally independent of each other.

**Screening Tests**

Patients often must consider whether to be screened for occult disease. The premises of a screening program are that early detection improves outcome in patients with occult disease and that the false-positive results that often occur in screening do not create a burden (eg, costs and adverse effects of confirmatory testing, unwarranted treatment) that exceeds such benefit. To minimize these possible burdens, clinicians must choose the proper screening test. Screening is not appropriate when treatments are ineffective or the disease is very uncommon (unless a subpopulation can be identified in which prevalence is higher).

Theoretically, the best test for both screening and diagnosis is the one with the highest sensitivity and specificity. However, such highly accurate tests are often complex, expensive, and invasive (eg, coronary angiography) and are thus not practical for screening large numbers of asymptomatic people. Typically, some tradeoff in sensitivity, specificity, or both must be made when selecting a screening test.

Whether a clinician chooses a test that optimizes sensitivity or specificity depends on the consequences of a false-positive or false-negative test result as well as the pre-test probability of disease. An ideal screening test is one that is always positive in nearly every patient with disease so that a negative result confidently excludes disease in healthy patients. For example, in testing for a serious disease for which an effective treatment is available (eg, coronary artery disease), clinicians would be willing to tolerate more false positives than false negatives (lower specificity and high sensitivity). Although high sensitivity is a very important attribute for screening tests, specificity also is important in certain screening strategies. Among populations with a higher prevalence of disease, the PPV of a screening test
increases; as prevalence decreases, the post-test or posterior probability of a positive result decreases. Therefore, when screening for disease in high-risk populations, tests with a higher sensitivity are preferred over those with a higher specificity because they are better at ruling out disease (fewer false negatives). On the other hand, in low-risk populations or for uncommon diseases for which therapy has lower benefit or higher risk, tests with a higher specificity are preferred.

Multiple screening tests: With the expanding array of available screening tests, clinicians must consider the implications of a panel of such tests. For example, test panels containing 8, 12, or sometimes 20 blood tests are often done when a patient is admitted to the hospital or is first examined by a new clinician. Although this type of testing may be helpful in screening patients for certain diseases, using the large panel of tests has potentially negative consequences. By definition, a test with a specificity of 95% gives false-positive results in 5% of healthy, normal patients. If 2 different tests with such characteristics are done, each for a different occult disease, in a patient who actually does not have either disease, the chance that both tests will be negative is 95% × 95%, or about 90%; thus, there is a 10% chance of at least one false-positive result. For 3 such tests, the chance that all 3 would be negative is 95% × 95% × 95%, or 86%, corresponding to a 14% chance of at least one false-positive result. If 12 different tests for 12 different diseases are done, the chance of obtaining at least one false-positive result is 46%. This high probability underscores the need for caution when deciding to do a screening test panel and when interpreting its results.

Testing Thresholds

A laboratory test should be done only if its results will affect management; otherwise the expense and risk to the patient are for naught. Clinicians can sometimes make the determination of when to test by comparing pre-test and post-test probability estimations with certain thresholds. Above a certain probability threshold, benefits of treatment outweigh risks (including the risk of mistakenly treating a patient without disease), and treatment is indicated. This point is termed the treatment threshold (TT) and is determined as described previously (see p. 3386). By definition, testing is unnecessary when pre-test probability is already above the TT. But testing is indicated if pre-test probability is below the TT as long as a positive test result could raise the post-test probability above the TT. The lowest pre-test probability at which this can occur depends on test characteristics (eg, LR+) and is termed the testing threshold.

Conceptually, if the best test for a serious disorder has a low LR+, and the TT is high, it is understandable that a positive test result might not move the post-test probability above the TT in a patient with a low but worrisome pre-test probability (eg, perhaps 10% or 20%).

For a numerical illustration, consider the previously described case of a possible acute MI (see p. 3386) in which the balance between risk and benefit determined a TT of 25%. When the probability of MI exceeds 25%, thrombolytic therapy is given. When should a rapid echocardiogram be done before giving thrombolytic therapy? Assume a hypothetical sensitivity of 60% and a specificity of 70% for echocardiography in diagnosing an MI; these percentages correspond to an LR+ of 60/(100 - 70) = 2 and an LR- of (100 - 60)/70 = 0.57.

The issue can be addressed mathematically (pre-test odds × LR = post-test odds) or more intuitively graphically by using the Fagan nomogram (see Fig. 342-5). On the nomogram, a line connecting the TT (25%) on the post-test probability line through the LR+ (2.0) on the middle LR line intersects a pre-test probability of about 0.14. Clearly, a positive test in a patient with any pre-test probability < 14% would still result in a post-test probability less than the TT. In this case, echocardiography would be useless because even a positive result would not lead to a decision to treat; thus, 14% pre-test probability is the testing threshold for this particular test (see Fig. 342-6). Another test with a different LR+ would have a different testing threshold.

Because 14% still represents a significant risk of MI, it is clear that a disease probability below the testing threshold (eg, a 10% pre-test probability) does not necessarily mean disease is ruled out, just that a positive test result on the particular test in question would not change management and thus that test is not indicated. In this situation, the clinician would observe the patient for further findings that might elevate the pre-test probability above the testing threshold. In practice, because multiple tests are often
The example considers a test that of itself poses no risk to the patient. If a test has serious risks (eg, cardiac catheterization), the testing threshold should be higher; quantitative calculations can be done but are complex. Thus, decreasing a test’s sensitivity and specificity or increasing its risk narrows the range of probabilities of disease over which testing is the best strategy. Improving the test’s ability to discriminate or decreasing its risk broadens the range of probabilities over which testing is the best strategy. A possible exception to the proscription against testing when pre-test probability is below the testing threshold (but is still worrisome) might be if a negative test result could reduce post-test probability below the point at which disease could be considered ruled out. This determination requires a subjective judgment of the degree of certainty required to say a disease is ruled out and, because low probabilities are involved, particular attention to any risks of testing.

**Economic Analyses**

Given limited societal and personal resources and restrictions under health insurance, cost considerations have become more relevant in clinical decision making. Limited resources should not be wasted; their allocation depends on an understanding of the various costs and outcomes resulting from strategies of care.

**Cost**

The elements included in cost analysis are determined by the perspective of the analysis. Different perspectives often result in different conclusions based on which costs and outcomes are considered.

- **Providers** (eg, health care practitioners, institutions) typically consider only costs within the organization (eg, personnel, supplies, overhead).

- **Payors** (eg, insurance companies) consider only the reimbursements they have to make.

- **Patients** consider out-of-pocket expenses (eg, cost of insurance, deductibles, transportation, parking) and lost income (for themselves and their family).

  [Fig. 342-5. Fagan nomogram used to determine need to test.]

  [Fig. 342-6. Depiction of testing and treatment thresholds.]

From a societal perspective, all such costs are taken into account along with the costs of lost productivity and costs of treating other diseases (iatrogenic and naturally occurring) that may develop in patients who recover from the disease being treated. For example, a young man cured of lymphoma may develop leukemia or coronary artery disease years later. Cost analysis of a screening program needs to include the costs of pursuing false-positive results, which in a screening test for a disease with a low prevalence often exceed the costs of evaluating and treating patients who actually have the disease.

**Marginal cost:** The marginal cost is the cost of providing (or withholding) an additional unit of service. This cost is often one of the most relevant for an individual clinician’s medical decision making and is typically quite different from the overall cost allocated to that service. For example, a hospital may have determined that $50 is the cost of providing a chest x-ray. However, a clinical protocol to better identify patients requiring x-rays that resulted in one fewer chest x-ray a day (with no change in outcome) would not “save” the hospital $50 because personnel and overhead expenses would be unchanged; only the expense of x-ray film would be eliminated. Hence the marginal cost to the hospital of one chest x-ray is essentially the cost of one piece of x-ray film (even less if digital capture techniques are used). Note that marginal cost varies with volume in a quantum fashion; adding or withholding a larger number of x-rays would at some point dictate a change in personnel and perhaps x-ray equipment, resulting in a different marginal cost. Additionally, the marginal cost is different for the payors; withholding one chest x-ray would save the payors the entire amount they typically reimburse for that x-ray, a figure far higher than the.
hospital's marginal cost.

**Outcome**

The effectiveness of medical care is measured by change in outcome. Outcomes can be

- Patient oriented
- Process oriented
- Disease oriented

**Patient-oriented outcomes** can be reduced to one of the three Ds:

- Death
- Disability
- Discomfort

Patient-oriented outcomes are arguably the most important. Improvements in process (eg, reducing the time to antibiotic administration or to operating room) or disease manifestations (eg, shrinking tumor size, improving $O_2$ saturation) that do not reduce mortality, disability, or discomfort at all can hardly be said to benefit the patient. For example, lidocaine was once routinely given to patients with MI because it was known to reduce the incidence of ventricular fibrillation (improved disease outcome). Lidocaine treatment continued for many years before studies showed it did not decrease mortality (no change in patient outcome), and so the practice was stopped.

Change in raw mortality is the most common way to evaluate effect on death. In more complex analysis, death and disability are often evaluated in combination as the quality-adjusted life year (QALY); treatment that results in an additional year of life at 100% of normal functioning is credited with 1 QALY; treatment that results in an additional year of life at only 75% functioning is credited with 0.75 QALY. QALY is more difficult to apply to discomfort, but some believe it can be estimated by the time tradeoff method: A person estimates how many years of discomfort would be acceptable vs a shorter period of perfect health. For example, if a person would prefer 9 yr of health to 10 yr of chronic pain (but would prefer the 10 yr of pain to only 8 yr of life), then each year of life with pain is credited with $9/10 = 0.9$ QALY. All such QALY estimates are somewhat problematic because people vary widely in risk tolerance and acceptance for various outcomes.

The **number needed to treat** (NNT) or harm is another way to quantify patient outcome; NNT is the reciprocal of the absolute change in a dichotomous outcome (death, disability). Thus, if a drug causes a 3% net decrease in mortality, $1/0.03 = 33.3$ patients need to be treated to prevent 1 death. Similarly, for a drug that causes leukopenia in 8% of patients, $1/0.08$ or 12.5 need to be treated to harm 1 person.

**Cost-Benefit Analysis**

Simple analysis of the economic consequences of outcomes (cost-benefit analysis) depends on assumptions about the perceived dollar value of prolonged life and improved health. Such assumptions are often arguable and rarely straightforward. Furthermore, although such analyses determine whether a given strategy saves costs or requires the net expenditure of resources, they do not indicate whether the expenditures are worthwhile.

**Cost-effectiveness analysis** tracks medical costs and health outcomes separately. Both outcome measures can be strongly affected by the perspective and duration of the analysis and by the underlying assumptions. Comparison of the costs and health outcomes of 2 management strategies results in 1 of 9 pairings (see Table 342-8). When health outcomes are equivalent (center column), the choice should be based on cost; when costs are equivalent (center row), the choice should be based on outcome. When one strategy has
better outcomes and lower costs (upper right and lower left cells), the choice is clear. The decision is difficult only when the strategy that is more expensive also produces better outcomes (upper left and lower right cells); in such cases, the marginal cost-effectiveness ratio should be determined.

**Marginal cost-effectiveness ratio**: The marginal cost-effectiveness ratio is the additional cost of a strategy divided by the additional health outcome it achieves and thus pertains to the situation in which there is a choice between $\geq 2$ effective management strategies. Greater health improvement for a given resource expenditure is derived when the ratio is lower.

For policy analysis, the most common measure of effectiveness is the QALY, making the units of the corresponding marginal cost-effectiveness ratio "additional dollars spent per QALY gained." However, the marginal cost-effectiveness ratio has been criticized because elderly patients or patients with life-limiting comorbidities have a smaller potential gain in survival from a treatment and therefore have a higher (less advantageous) cost-effectiveness ratio.

For example (see Table 342-9), consider no antiarrhythmic therapy vs prophylactic use of an implantable cardioverter-defibrillator (ICD) for patients who have survived several months after an acute anterior MI and who have a mildly depressed ejection fraction (between 0.3 and 0.4). (All figures and costs in this example are hypothetical.) Both strategies assume similar baseline costs for routine care ($78,300), but the ICD has an additional (marginal) cost of $53,100, based on the cost of the device and professional fees, initial hospitalization, and ongoing therapy (including extra physician visits, laboratory tests, drugs, rehospitalizations for ICD-related complications, and replacement of ICD generator or leads). If patients with an ICD have a slightly increased life expectancy (7.87 vs 7.42 QALY), the marginal effectiveness of ICD therapy is 7.87 - 7.42 = 0.45 QALY. Thus, prophylactic ICD enhances survival compared to no antiarrhythmic therapy at a cost of $53,100/0.45 QALY, or $118,000/QALY.

Now assume that a third strategy, prophylactic amiodarone therapy, is available. This therapy is less expensive but also less effective than ICD. The effect of adding this third intermediate strategy is noteworthy because marginal cost-effectiveness ratios are calculated sequentially when there are multiple strategies (Table 342-9, Analysis 2). The marginal cost-effectiveness ratio of amiodarone is lower ($68,519/QALY gained) than that for an ICD calculated in the previous example, and furthermore, because the effectiveness of an ICD is now compared to amiodarone rather than to no therapy, the addition of this intermediate cost strategy with partial effectiveness increases the ICD's marginal cost-effectiveness ratio from $118,000 to $192,222/QALY gained. This analysis suggests that for an expensive therapy such as an ICD, an attempt should be made to identify subpopulations expected to reap the greatest benefit.

[Table 342-8. Cost-Effectiveness Comparison of Management Strategies A and B]

[Table 342-9. Calculating a Marginal Cost-Effectiveness Ratio]

($68,519/QALY gained) than that for an ICD calculated in the previous example, and furthermore, because the effectiveness of an ICD is now compared to amiodarone rather than to no therapy, the addition of this intermediate cost strategy with partial effectiveness increases the ICD's marginal cost-effectiveness ratio from $118,000 to $192,222/QALY gained. This analysis suggests that for an expensive therapy such as an ICD, an attempt should be made to identify subpopulations expected to reap the greatest benefit.
Chapter 343. Principles of Radiologic Imaging

Introduction

Continuing improvements in radiologic imaging make it increasingly useful in diagnostic evaluation. Primary care and referring physicians work with radiologists who specialize in diagnostic imaging to choose the best imaging test for each evaluation. Many imaging tests use ionizing radiation (x-rays and radionuclides) and radiographic contrast agents; the associated risks to patients are usually small but should be considered.

Risks of Ionizing Radiation

Most diagnostic tests that use ionizing radiation (eg, x-rays, CT, radionuclide scanning) expose patients to relatively low doses of radiation that are generally considered safe. However, all ionizing radiation is harmful, and there is no threshold below which no harmful effect occurs, so every effort is made to minimize radiation exposure. Doses vary by type of imaging test (see Table 343-1).

There are various ways to measure radiation exposure:

- The absorbed dose is the amount of radiation absorbed per unit mass. It is expressed in special units of gray (Gy) and mGy. It was previously expressed as rad (1 mGy = 0.1 rad).

- The equivalent dose is the absorbed dose multiplied by a radiation weighting factor that adjusts for tissue effects based on the type of radiation delivered (eg, x-rays, gamma rays, electrons). It is expressed in sieverts (Sv) and mSv. It was previously expressed in rem (1 mSv = 0.1 rem). For x-rays, including CT, the radiation weighting factor is 1.

- The effective dose is a measure of cancer risk; it adjusts the equivalent dose based on the susceptibility of the tissue exposed to radiation (eg, gonads are most susceptible). It is expressed in Sv and mSv. In the US, the average yearly effective dose of environmental background radiation (from cosmic radiation and natural isotopes) is 3 mSv. The effective dose is higher in young people.

Radiation may be harmful if the total accumulated dose for a person is high, as when multiple scans are done, because most scans require a high dose. Radiation dose is also a concern in certain high-risk situations (eg, during early pregnancy, infancy, or early childhood; in young women who require mammography).

In the US, CT accounts for > 15% of all imaging tests but for about 70% of total radiation delivered during diagnostic imaging. Multidetector CT scanners, which are usually used now, deliver about 40 to 70% more radiation per scan than do older single detector CT scanners.

Estimated risk of cancer due to radiation exposure in diagnostic imaging has been extrapolated from studies of people exposed to very high radiation doses (eg, survivors of the atomic bomb explosions at Hiroshima and Nagasaki). This analysis suggests a small but real risk of cancer if radiation doses are in the tens of mGy (as used in CT). A CT pulmonary angiogram, routinely done to detect pulmonary embolism, delivers about as much radiation to the breasts as about 10 to 25 two-view mammograms.

Risk is higher in young patients because they live longer, giving cancers more time to develop, and because more cellular growth (and thus susceptibility to DNA damage) occurs in the young. For a 1-yr-old who has a CT scan of the abdomen, estimated lifetime risk of developing cancer is increased by 0.18%. If an elderly patient has this test, risk is lower.

Risk also depends on the tissue being irradiated; for example, risk is higher for breast and abdominal
tissue than for brain tissue.

**Radiation during pregnancy:** Risks of radiation depend on dose, type of test, and area being examined. The fetus may be exposed to much less radiation than the mother; exposure to the fetus is negligible during head, cervical spine, and extremity x-rays and during mammography when the uterus is shielded. The extent of uterine exposure depends on gestational age and thus uterine size. The effects of radiation depend on the age of the conceptus (the time from conception).

**Recommendations:** Diagnostic imaging using ionizing radiation, especially CT, should be done only when clearly required. Alternatives should be considered. For example, in young children, minor head injury can often be diagnosed and treated based on clinical findings, and appendicitis can often be diagnosed by ultrasonography. However, necessary tests should not be withheld, even if risk is high, as long as the benefit outweighs the potential risk.

Before diagnostic tests are done in women of child-bearing age, pregnancy should be considered, particularly because risks of radiation exposure are highest during early, often unrecognized pregnancy. The uterus should be shielded in such women when possible.

**Radiographic Contrast Agents and Contrast Reactions**

Radiopaque contrast agents are often used in radiography and fluoroscopy to help delineate borders between tissues with similar radiodensity. Most contrast agents are iodine-based. Iodinated contrast agents may be ionic or nonionic. Ionic contrast agents, which are salts, are hyperosmolar to blood. These agents should not be used for myelography or in injections that may enter the spinal canal (because neurotoxicity is a risk) or the bronchial tree (because pulmonary edema is a risk). Nonionic contrast agents may be low-osmolar (which is still hyperosmolar relative to blood) or iso-osmolar (with the same osmolarity as blood). Newer nonionic contrast agents are now routinely used at many institutions because they have fewer adverse effects.

The most serious contrast reactions are allergic-type reactions and contrast nephropathy (renal damage after intravascular injection of a contrast agent).

**Allergic-type contrast reactions:** Reactions vary in severity:

- Mild (eg, cough, itching, nasal congestion)
- Moderate (eg, dyspnea, wheezing, slight changes in pulse or BP)
- Severe (eg, respiratory distress, arrhythmias such as bradycardia, seizures, shock, cardiopulmonary arrest)

The mechanism is anaphylactoid (see p. 1120); risk factors include a previous reaction to injected contrast agents, asthma, and allergies.

Treatment begins by stopping contrast infusion. For mild or moderate reactions, diphenhydramine 25 to 50 mg IV is usually effective. Treatment of severe reactions depends on the type of reaction and may include oxygen, epinephrine, IV fluids, and possibly atropine (for bradycardia).

In patients at high risk of contrast reactions, imaging tests that do not require iodinated contrast should be used. If contrast is necessary, a nonionic agent should be used, and patients should be premedicated with prednisone (50 mg po 13 h, 7 h, and 1 h before injection of contrast) and diphenhydramine (50 mg po or IM 1 h before the injection). If patients require imaging immediately, they can be given diphenhydramine 50 mg po or IM 1 h before injection of contrast and hydrocortisone 200 mg IV q 4 h until imaging is completed.

**Contrast nephropathy:** In some patients, intravascular injection of an iodinated contrast agent causes serum creatinine to increase transiently. Most of these patients have no symptoms, and nearly all recover normal function within 1 wk. However, < 1% of patients require dialysis or develop chronic kidney
disease, indicating contrast nephropathy. Common risk factors include the following:

- Preexisting renal insufficiency (elevated creatinine)
- Diabetes mellitus
- Hypertension
- Heart failure
- Multiple myeloma
- Age > 70
- Use of other nephrotoxic drugs
- Solitary kidney (with elevated creatinine)

In patients at risk of developing acute renal failure after receiving iodinated intravascular contrast, reduced dose of contrast, use of iso-osmolality agent, and hydration should be considered. Many hydration regimens exist; one example is IV administration of 0.9% normal saline at 1 mL/kg for 24 h beginning a few hours before the procedure. Acetylcysteine may be given as premedication for patients at risk of developing nephrotoxicity, but its efficacy is uncertain. Oral antihyperglycemic drugs, such as metformin, should be withheld for 48 h after IV contrast administration to avoid drug accumulation if contrast-induced nephrotoxicity occurs. Because many protocols dealing with contrast agents and reactions are specific and continually updated, it is important to discuss such details with the imaging department.

**Angiography**

Angiography is sometimes called conventional angiography to distinguish it from CT angiography (CTA) and magnetic resonance angiography (MRA). Angiography provides detailed images of blood vessels, commonly those in the heart, lungs, brain, and legs. Angiography can provide still images or motion pictures (called cineangiography).

IV contrast is injected through a catheter inserted into a blood vessel that connects with the vessel to be imaged. A local anesthetic or a sedative may be used. If the catheter is inserted into an artery, the insertion site must be steadily compressed for 10 to 20 min after all instruments are removed. Patients may need to lie flat for several hours or be hospitalized to reduce risk of bleeding at the puncture site. Angiography, although invasive, is relatively safe.

**Uses**

Angiography is the traditional gold standard for evaluating vascular lesions (eg, stenosis, obstruction, arteriovenous or other vascular malformations, aneurysms, dissections, sometimes vasculitis).

- **Coronary angiography** is usually done before percutaneous or surgical interventions involving the coronary arteries or heart valves. It is usually done with cardiac catheterization (see p. 2048).

- **Pulmonary angiography** is the gold standard for diagnosis of pulmonary embolism.

- **Cerebral angiography** may be indicated after stroke or transient ischemic attack (TIA)—eg, if stenting or carotid endarterectomy is being considered.

- **Iliac and femoral angiography** may be indicated before interventions to treat peripheral arterial disease.

- **Aortography** is sometimes done to diagnose and provide anatomic detail about aortic aneurysms,
Aortic dissection, and aortic regurgitation.

- **Angiography of the eye arteries** can be done using fluorescein dye.

Angioplasty, stenting, and sometimes vascular repair can be done during angiography.

**Variations**

**Digital subtraction angiography:** Images of arteries are taken before and after contrast injection; then a computer subtracts one image from the other. Images of structures other than arteries are thus eliminated, enabling the arteries to be seen more clearly.

**Disadvantages**

Contrast reactions occasionally occur (see p. 3403).

The injection site may become infected or bleed, sometimes forming a painful hematoma. Rarely, an artery is injured by the catheter. Very rarely, shock, seizures, renal failure, and cardiac arrest occur. Risk of complications is higher in the elderly, although it is still low. The radiation dose used in angiography can vary and be significant (eg, coronary angiography is associated with an effective radiation dose of 4.6 to 15.8 mSv). Angiography must be done by highly skilled physicians, usually interventional radiologists.

**Computed Tomography**

In CT, an x-ray source and x-ray detector housed in a doughnut-shaped assembly move circularly around a patient who lies on a motorized table that is moved through the machine. Usually, multidetector scanners with 4 to 64 or more rows of detectors are used because more detectors allow quicker scanning and higher-resolution images.

Data from the detectors essentially represent a series of x-ray images taken from multiple angles all around the patient. However, the images are not viewed directly but are sent to a computer, which quickly reconstructs them into 2-dimensional images (tomograms) representing a slice of the body in any plane desired. Data can also be used to construct detailed 3-dimensional images. For some CT scans, the table moves incrementally and stops when each scan (slice) is taken. For other CT scans, the table moves continuously during scanning; because the patient is moving in a straight line and the detectors are moving in a circle, the series of images appear to be taken in a spiral fashion around the patient—hence the term helical (spiral) CT.

These same principles of tomographic imaging can also be applied to radionuclide scanning, in which the sensors for emitted radiation encircle the patient and computer techniques convert the sensor data into tomographic images; examples include single-photon emission CT (SPECT) and positron-emission tomography (PET).

**Uses**

Compared with plain x-rays, the tomographic slices of CT provide more spatial detail and can better differentiate between various soft-tissue densities. Because it provides so much more information, CT is preferred to plain x-rays for imaging most intracranial, head and neck, spinal, intrathoracic, and intra-abdominal structures. Three-dimensional images of lesions can help surgeons plan surgery. CT is the most accurate study for detecting and localizing urinary calculi.

CT may be done with or without IV contrast. Noncontrast CT is used to detect acute hemorrhage in the brain, urinary calculi, and lung nodules, as well as to characterize bone fractures and other skeletal abnormalities. IV contrast is used to improve imaging of tumors, infection, inflammation, and trauma in soft tissues and to assess the vascular system, as when pulmonary embolism, aortic aneurysm, or aortic dissection is suspected.
Oral or occasionally rectal contrast is used for abdominal imaging; sometimes gas is used to distend the lower GI tract and make it visible. Contrast in the GI tract helps distinguish the GI tract from surrounding structures. Standard oral contrast is barium-based, but low-osmolar iodinated contrast should be used when intestinal perforation is suspected or when risk of aspiration is high.

**Variations**

**Virtual colonoscopy:** After gas is introduced into the rectum via a flexible, thin-diameter rubber catheter, CT of the entire colon is done. Virtual colonoscopy produces high-resolution 3-dimensional images of the colon that somewhat simulate the appearance of optical colonoscopy. This technique can show colon polyps and colon mucosal lesions as small as 5 mm. It is an alternative to conventional colonoscopy.

**CT IV pyelography (CT IVP) or urography:** IV contrast is injected. The procedure produces detailed images of the kidneys, ureters, and bladder. It is an alternative to conventional IV urography.

**CT angiography:** After a rapid bolus injection of IV contrast, thin-slice images are rapidly taken as the contrast opacifies arteries and veins. Advanced computer graphics techniques are used to remove images of surrounding soft tissues and to provide highly detailed images of blood vessels similar to those of conventional angiography. CT angiography is a less invasive alternative to conventional angiography.

**Disadvantages**

CT accounts for most diagnostic radiation exposure to patients collectively. If multiple scans are done, the total radiation dose may be high, placing the patient at potential risk (see p. 3402). Patients who have recurrent urinary tract stones or who have had major trauma are most likely to have multiple CT scans. The risk of radiation exposure vs benefit of the examination must always be considered because the effective radiation dose of one abdomen CT is equal to 500 chest x-rays.

Some CT scans use IV contrast, which has certain risks (see p. 3403). If barium extravasates outside the GI tract lumen, it can induce severe inflammation; if aspirated, barium can induce severe pneumonia. Barium can also become hard and inspissated, potentially precipitating intestinal obstruction. Gastrografin is safer, but the contrast and images of the GI tract it provides are not as good.

The CT table may not be able to accommodate very obese patients.

**Magnetic Resonance Imaging**

MRI uses magnetic fields and radio waves to produce images of thin slices of tissues (tomographic images). Normally, protons within tissues spin to produce tiny magnetic fields that are randomly aligned. When surrounded by the strong magnetic field of an MRI device, the magnetic axes align along that field. A radiofrequency pulse is then applied, causing the axes of all protons to momentarily align against the field in a high-energy state. After the pulse, some protons relax and resume their baseline alignment within the magnetic field of the MRI device. The magnitude and rate of energy release that occurs as the protons resume this alignment (T1 relaxation) and as they wobble (precess) during the process (T2 relaxation) are recorded as spatially localized signal intensities by a coil (antenna). Computer algorithms analyze these signals and produce anatomic images.

The relative signal intensity (brightness) of tissues in an MRI image is determined by factors such as the radiofrequency pulse and gradient waveforms used to obtain the image, intrinsic T1 and T2 tissue characteristics, and tissue proton density.

By controlling the radiofrequency pulse and gradient waveforms, computer programs produce specific pulse sequences that determine how an image is obtained (weighted) and how various tissues appear. Images can be T1-weighted, T2-weighted, or proton density-weighted. For example, fat appears bright (high signal intensity) on T1-weighted images and relatively dark (low signal intensity) on T2-weighted images; water and fluids appear relatively dark on T1-weighted images and bright on T2-weighted images. T1-weighted images optimally show normal soft-tissue anatomy and fat (eg, to confirm a fat-containing mass). T2-weighted images optimally show fluid and abnormalities (eg, tumors, inflammation,
trauma). In practice, T1- and T2-weighted images provide complementary information, so both are important for characterizing abnormalities.

Uses

MRI is preferred to CT when soft-tissue contrast resolution must be highly detailed (eg, to evaluate intracranial or spinal cord abnormalities, inflammation, trauma, suspected musculoskeletal tumors, internal joint derangement). MRI is also useful for evaluating the following:

- **Vascular imaging**: Magnetic resonance angiography (MRA) is used to image arteries with good diagnostic accuracy and is less invasive than conventional angiography. Gadolinium contrast is sometimes used. MRA can be used to image the thoracic and abdominal aorta and arteries of the brain, neck, kidneys, and lower extremities. Venous imaging (magnetic resonance venography) can also be done.

- **Hepatic and biliary tract abnormalities**: Magnetic resonance cholangiopancreatography (MRCP) is particularly valuable as a noninvasive, highly accurate method of imaging the biliary and pancreatic duct systems.

- **Masses in the female reproductive organs**: MRI is used to characterize adnexal masses and to stage uterine tumors.

- **Certain fractures**: For example, MRI can provide accurate images of hip fractures in patients with osteopenia.

- **Lytic bone metastases**

MRI can also be substituted for CT with contrast in patients with a high risk of contrast reactions.

Contrast: With MRI, contrast agents may be used to highlight vascular structures (for MRA) and to help characterize inflammation and tumors. The most commonly used agents are gadolinium derivatives, which have magnetic properties that affect proton relaxation times. MRI of intra-articular structures may include injection of a gadolinium derivative into a joint.

Variations

**Diffusion (diffusion-weighted) MRI**: Signal intensities are related to diffusion of water molecules in tissue. This type of MRI can be used to detect early cerebral ischemia and infarction and to differentiate intracranial cysts from solid masses.

**Echo planar imaging**: This ultrafast technique (images obtained in > 1 sec) is used for diffusion, perfusion, and functional imaging of the brain and heart. Its potential advantages include showing brain and heart activity and reducing motion artifacts. However, its use is limited because it requires special technical hardware and it is susceptible to other artifacts.

**Functional MRI**: Functional MRI is used to assess brain activity by location. In the most common type, the brain is scanned at low resolution very frequently (eg, every 2 to 3 sec). The change in oxygenated Hb can be discerned and used to estimate metabolic activity. Mechanisms of various neural mechanisms can be studied in research settings.

**Gradient echo imaging**: Gradient echo is a pulse sequence that can be used for fast imaging of moving blood and CSF (eg, in MRA). Because this technique is fast, it can reduce motion artifacts (eg, blurring) during imaging that requires patients to hold their breath (eg, during imaging of cardiac and abdominal structures).

**Magnetic resonance spectroscopy (MRS)**: MRS combines the information obtained by MRI (mainly based on water and fat content of tissues) with that of nuclear magnetic resonance, or NMR; NMR provides information about tissue metabolites. Such information can help differentiate certain
abnormalities (eg, certain types of tumors).

**Perfusion MRI**: Perfusion MRI is a method of assessing relative cerebral blood flow. It can be used to detect an area of ischemia during imaging for stroke.

**Disadvantages**

MRI is relatively expensive and may not be available or available immediately.

**Magnetic field**: MRI is relatively contraindicated in patients with implanted materials that can be affected by powerful magnetic fields. These materials include ferromagnetic metal (containing iron), magnetically activated or electronically controlled medical devices (eg, pacemakers, implantable cardioverter defibrillators, cochlear implants), and nonferromagnetic metal electronically conductive wires or materials (eg, pacemaker wires, certain pulmonary artery catheters). Ferromagnetic material may be moved by the strong magnetic field and injure a nearby organ; movement is more likely if the material has been in place < 6 wk (before scar tissue forms). Ferromagnetic material can also cause imaging artifacts. Magnetically activated medical devices may malfunction when exposed to magnetic fields. Magnetic fields may induce current in conductive materials; this current may produce enough heat to burn tissues. Whether a specific device is compatible with MRI depends on the type of device, its components, and its manufacturer (see the MRI safety web site). Also, MRI machines with different magnetic field strengths have different effects on materials, so safety in one machine does not ensure safety in another.

The MRI magnetic field is very strong and always on. Thus, a ferromagnetic object (eg, an O2 tank, a metal pole) at the entrance of the scanning room may be pulled into the magnet bore at high velocity and injure anyone in its path. The only way to separate the object from the magnet may be to turn off the magnetic field.

**Claustrophobia**: The imaging tube of an MRI machine is a tight, enclosed space that can trigger claustrophobia even in patients without preexisting phobias or anxiety. Also, some obese patients do not fit on the table or within the machine. Premedication with an anxiolytic (eg, alprazolam or lorazepam 1 to 2 mg po) 15 to 30 min before scanning is effective for most anxious patients. MRI scanners with an open side can be used. Its images may be inferior to those of enclosed scanners depending on the field strength of the magnet, but they are usually sufficient for making a diagnosis. Patients should be warned that the MRI machine makes loud, banging noises.

**Contrast reactions**: Gadolinium derivatives, if used, can cause headache, nausea, and pain, as well as sensation of cold at the injection site. However, serious contrast reactions are rare and much less common than with iodinated contrast agents. However, in patients with impaired renal function, nephrogenic systemic fibrosis is a risk. Nephrogenic systemic fibrosis is a rare but life-threatening disorder that involves the skin and probably internal organs, resulting in severe disability or death. For patients with impaired renal function, the following is recommended:

• Gadolinium should be used only when necessary.

• Before this agent is used, renal function should be checked (eg, based on patient history or laboratory tests such as GFR).

• The dose should be as small as possible, and the number of tests done should be limited if possible. If a second test is required, it should be delayed about 1 wk.

**Radiography**

Radiography involves the use of x-rays; the term "plain x-rays" is sometimes used to distinguish x-rays used alone from x-rays combined with other techniques (eg, CT). For plain x-rays, an x-ray beam is generated and passed through a patient to a piece of film or a radiation detector, producing an image. Different soft tissues attenuate x-ray photons differently, depending on tissue density; the denser the tissue, the whiter (more radiopaque) the image. The range of densities, from most to least dense, is represented by metal (white, or radiopaque), bone cortex (less white), muscle and fluid (gray), fat (darker
Radiography is usually the most readily available imaging method. Typically, it is the first imaging method indicated to evaluate the extremities, chest, and sometimes the spine and abdomen. These areas contain important structures with densities that may differ from those of adjacent tissues. For example, radiography is a first-line test for detecting the following:

- **Fractures**: White bone is well seen because it is adjacent to gray soft tissues.
- **Pneumonia**: Inflammatory exudate that fills the lungs is well seen because it contrasts with adjacent air spaces.
- **Intestinal obstruction**: Dilated, air-filled loops of intestine are well seen amidst the surrounding soft tissue.

**Variations**

**Contrast studies**: When the density of adjacent tissues is similar, a radiopaque contrast agent (see p. 3403) is often added to one tissue or structure to differentiate it from its surroundings. Structures typically requiring a contrast agent include blood vessels (for angiography) and the lumina of the GI, biliary, and GU tracts. Gas may be used to distend the lower GI tract and make it visible. Other imaging tests (eg, CT, MRI) have largely replaced contrast studies because their tomographic images provide better anatomic localization of an abnormality.

**Fluoroscopy**: A continuous x-ray beam is used to produce images of moving structures or objects. Fluoroscopy is most often used with contrast agents (eg, in swallowing studies or coronary artery catheterization) or during medical procedures to guide placement of a lead, catheter, or needle (eg, in electro-physiologic testing or percutaneous coronary interventions).

**Disadvantages**

Diagnostic accuracy is limited in many situations. Other imaging tests may provide better image detail, be safer or faster, or have other advantages.

Contrast agents such as barium and gastrografin, if used, have disadvantages (see p. 3406), and IV contrast agents have risks (see p. 3403). Fluoroscopy may involve high doses of radiation.

**Radionuclide Scanning**

Radionuclide scanning uses the radiation released by radionuclides (called nuclear decay) to produce images. A radionuclide is an unstable isotope that becomes more stable by releasing energy as radiation. This radiation can include gamma-ray photons or particulate emission (such as positrons, used in PET). Radiation produced by radionuclides may be used for imaging or for treatment of certain disorders (eg, thyroid disorders).

A radionuclide, usually technetium-99m, is combined with different stable, metabolically active compounds to form a radiopharmaceutical that localizes to a particular anatomic or diseased structure (target tissue). The radiopharmaceutical is given by mouth or by injection. After the radionuclide has had time to reach the target tissue, images are taken with a gamma camera. Gamma rays emitted by the radionuclide interact with scintillation crystals in the camera, creating light photons that are converted into electrical signals by photomultiplier tubes. A computer summarizes and analyzes the signals and integrates them into 2-dimensional images. However, only signals near the camera’s face can be accurately analyzed; thus, imaging is limited by the range of the camera.

Portable gamma cameras can provide radionuclide imaging at bedside. Generally, radionuclide scanning is considered safe (see Table 343-1).

**Uses**
The compound labeled with the radionuclide depends on the target tissue or indication:

- For imaging the skeleton, technetium-99m is combined with diphosphonate and used to check for bone metastasis or infection.
- For identifying inflammation, WBCs are labeled and used to identify inflammation.
- For localizing GI bleeding, RBCs are labeled.
- For imaging the liver, spleen, or bone marrow, sulfur colloid is labeled.
- For imaging the biliary tract, iminodiacetic acid derivatives are labeled and used to check for biliary obstruction, bile leaks, and gallbladder disorders.

Radionuclide scanning is also used to image the thyroid gland and the cerebrovascular, cardiovascular, respiratory, and GU systems. For example, in myocardial perfusion imaging, heart tissue takes up radionuclides (eg, thallium) in proportion to perfusion. This technique can be combined with stress testing. Radionuclide scanning is also used to evaluate tumors.

Variations

**Single-photon emission CT (SPECT):** SPECT uses a gamma camera that rotates around the patient. The resultant series of images are reconstructed by computer into 2-dimensional tomographic slices in a similar manner to that done in conventional CT. The 2-dimensional images can be used for tomographic reconstruction to yield a 3-dimensional image.

Disadvantages

Radiation exposure depends on the radio-nuclide and dose used. Effective doses tend to range from 1.5 to 17 mSv—eg, about 1.5 mSv for lung scans, about 3.5 to 4.5 mSv for bone and hepatobiliary scans, and about 17 mSv for technetium sestimibi heart scans. Reactions to radionuclides are rare.

The area that can be imaged accurately is limited because only signals near the gamma camera's face can be accurately localized. Image detail may also be limited.

Often, imaging must be delayed for up to several hours to give the radionuclide time to reach the target tissue.

**Positron Emission Tomography**

PET, a type of radionuclide scanning, uses compounds containing radionuclides that decay by releasing a positron (the positively charged antimatter equivalent of an electron). The released positron combines with an electron and produces 2 photons whose paths are 180° apart. Ring detector systems encircling the positron-emitting source simultaneously detect the 2 photons to localize the source. Because PET incorporates positron-emitting radionuclides into metabolically active compounds, it can provide information about tissue function.

Fluorine-18 [\(^{18}\text{F}\)]-labeled deoxyglucose (FDG) is used most commonly in clinical PET. FDG is an analog of glucose, and its uptake is proportional to glucose metabolic rates. A patient's relative glucose metabolic rate (called the standardized uptake value [SUV]) is calculated: The amount of FDG taken up from the injected dose is divided by the patient's body weight.

**Uses**

PET has several clinical indications, such as

- Cancer (eg, staging and evaluating specific types of cancer and evaluating response to treatment).
which accounts for about 80% of PET usage

- Cardiac function (eg, evaluating myocardial viability, detecting hibernating myocardium)
- Neurologic function (eg, evaluation of dementia and seizures)

PET applications continue to be investigated, although it is important to determine which applications are reimbursable.

Variations

PET-CT: Functional information provided by PET is superimposed on anatomic information provided by CT.

Disadvantages

The typical effective radiation dose during PET is about 7 mSv. The effective radiation dose with PET-CT is 5 to 18 mSv.

Production of FDG requires a cyclotron. FDG has a short half-life (110 min); thus, shipment from the manufacturer and completion of the scan must occur very rapidly. The resulting expense, inconvenience, and impracticality greatly limit the availability of PET.

Ultrasonography

In ultrasonography, a signal generator is combined with a transducer. Piezoelectric crystals in the signal generator convert electricity into high-frequency sound waves, which are sent into tissues. The tissues scatter, reflect, and absorb the sound waves to various degrees. The sound waves that are reflected back (echoes) are converted into electric signals. A computer analyzes the signals and displays the information on a screen.

Ultrasonography is portable, widely available, and safe. No radiation is used.

Variations

Ultrasound information can be displayed in several ways.

A-mode: This display mode is the simplest; signals are recorded as spikes on a graph. The vertical (Y) axis of the display shows the echo amplitude, and the horizontal (X) axis shows depth or distance into the patient. This type of ultrasonography is used for ophthalmologic scanning.

B-mode (gray-scale): This mode is most often used in diagnostic imaging; signals are displayed as a 2-dimensional anatomic image. B-mode is commonly used to evaluate the developing fetus and to evaluate organs, including the liver, spleen, kidneys, thyroid gland, testes, breasts, and prostate gland. B-mode ultrasonography is fast enough to show real-time motion, such as the motion of the beating heart or pulsating blood vessels. Real-time imaging provides anatomic and functional information.

M-mode: This mode is used to image moving structures; signals reflected by the moving structures are converted into waves that are displayed continuously across a vertical axis. M-mode is used primarily for assessment of fetal heartbeat and in cardiac imaging, most notably to evaluate valvular disorders.

Doppler: This type of ultrasonography is used to assess blood flow. Doppler ultrasoundography uses the Doppler effect (alteration of sound frequency by reflection off a moving object). The moving objects are RBCs in blood.

Direction and velocity of blood flow can be determined by analyzing changes in the frequency of sound waves:
• If a reflected sound wave is lower in frequency than the transmitted sound wave, blood flow is away from the transducer.

• If a reflected sound wave is higher in frequency than the transmitted sound wave, blood flow is toward the transducer.

• The magnitude of the change in frequency is proportional to blood flow velocity.

Changes in frequency of the reflected sound waves are converted into images showing blood flow direction and velocity.

Duplex Doppler ultrasonography combines the graphic display of spectral ultra-sonography with the images of B-mode. For color Doppler ultrasonography, color is superimposed on a gray-scale anatomic image. The color indicates direction of blood flow. By convention, red indicates flow toward and blue indicates flow away from the transducer.

Doppler ultrasonography is also used to evaluate vascularity of tumors and organs, to evaluate heart function (eg, as for echocardiography), to detect occlusion and stenosis of blood vessels, and to detect blood clots in blood vessels (eg, in deep venous thrombosis).

**Disadvantages**

Quality of images depends on the skills of the operator. Obtaining clear images of the target structures can be technically difficult in overweight patients.

Ultrasonography cannot be used to image through bone or gas, so certain images may be difficult to obtain.
Chapter 344. Complementary and Alternative Medicine

Introduction

(See also Ch. 345.)

Complementary and alternative medicine (CAM) refers to healing approaches and therapies that are not based on principles of mainstream, conventional medicine.

• **Complementary medicine** refers to unconventional practices used with mainstream medicine.

• **Alternative medicine** refers to unconventional practices used instead of mainstream medicine.

• **Integrative medicine** is health care that uses all appropriate therapeutic approaches—conventional and alternative—within a framework that focuses on the therapeutic relationship and the whole person.

CAM has been widely used in the US for decades. Almost 40% of adults use some form of CAM, most often to treat pain or anxiety or to modify cholesterol levels. Use is also common among patients with chronic pain, cancer, hepatitis C, or other intractable conditions. The most frequently used therapies include medicinal herbs and other plant-derived supplements (botanicals), mind-body practices, and massage therapy.

Some CAM therapies are now offered in hospitals and are sometimes reimbursed by insurance companies. Some traditional medical schools, including 45 North American medical schools in the Consortium of Academic Health Centers for Integrative Medicine, provide education about CAM and integrative medicine.

Broad, philosophic differences distinguish conventional and alternative approaches to healing (see Table 344-1).

Because patients worry about being criticized, they do not always volunteer information about their use of CAM to physicians. Therefore, it is very important for physicians to specifically ask their patients about CAM use in an open, nonjudgmental way. Learning about patients’ use of CAM can strengthen rapport, build trust, and provide an opportunity to discuss CAM’s benefits and risks. Physicians may also identify and avoid potentially harmful interactions between drugs and CAM therapies or nutritional supplements, monitor patient progress, guide patients to certified or licensed CAM practitioners, and learn from patients’ experiences with CAM.

Efficacy

In 1992, the Office of Alternative Medicine in the National Institutes of Health (NIH) was formed to study the efficacy and safety of alternative therapies. In 1998, this office became the National Center for Complementary and Alternative Medicine (NCCAM; see www.nccam.nih.gov/). Other NIH offices (eg, National Cancer Institute) also fund some CAM research.

There are 3 types of support for CAM therapies:

• Use over periods of time ranging from decades to centuries

• Evidence of established physiologic mechanisms of action (eg, modification of $\gamma$-aminobutyric acid [GABA] activity in the brain by valerian)

• Efficacy as shown in clinical trials

A substantial amount of information about CAM is available in peer-reviewed publications, evidence-based reviews, expert panel consensus documents, and authoritative textbooks; much of it has been published in languages other than English (eg, German, Chinese). However, most CAM therapies have not been tested in definitive clinical trials and probably will not be for the following reasons:
• Industry has no financial incentive to fund research.

• CAM therapies may be difficult to study using conventional methodology.

• Manufacturers of CAM products do not have to prove disease-specific efficacy.

Thus, the FDA allows marketing of dietary supplements and use of CAM devices but significantly restricts efficacy claims. Generally, manufacturers of dietary supplements can claim benefit to the body's structure or function (eg, improves cardiovascular health) but not benefit for treating disease (eg, treats hypertension).

**Research:** Designing studies of CAM therapies poses challenges beyond those faced by researchers of conventional therapies:

• Therapies may not be standardized. For example, there are different systems of acupuncture, and the contents and biologic activity of extracts made from the same plant species vary widely (chemical identification

[Table 344-1, Differences Between Conventional and Alternative Medicine]

and standardization of active ingredients is not considered part of CAM).

• Diagnoses may not be standardized; use of many CAM therapies (eg, traditional herbal medicine, homeopathy, acupuncture) is based on the patient's unique characteristics rather than on a specific disease or disorder.

• Double- or single-blinding is often difficult or impossible. For example, patients cannot be blinded as to whether they are practicing meditation. Reiki practitioners cannot be blinded as to whether or not they are using energy healing.

• Outcomes are difficult to standardize because they are often specific to the individual rather than objective and uniform (as mean arterial pressure, Hb A₁C level, and mortality are).

• Placebos may be difficult to devise because identifying the effective component of a CAM therapy may be difficult. For example, in massage, the effective component could be touching, the specific area of the body massaged, the particular massage technique used, or time spent with the patient.

From a conventional research perspective, use of a placebo control is particularly important when subjective outcomes (eg, pain, nausea, indigestion) are used and when disorders that are intermittent, self-limited, or both (eg, headaches) are being studied; such end points and disorders are often the targets of CAM therapies. However, CAM systems interpret placebo effects as nonspecific healing effects that arise out of the therapeutic interaction and are inseparable from specific treatments. In practice, alternative therapies are intended to optimize the patient's capacity for self-healing (placebo response) as well as treatment-specific effects. Thus, many CAM practitioners strive to enhance the quality of the healing environment and therapeutic relationship. Studying the effective components of a CAM therapy without undermining the integrity of that therapy in a research setting remains a methodologic challenge.

**Safety**

Although the safety of most CAM therapies has not been studied in clinical trials, many of these therapies have a good safety record. Many CAM therapies (eg, nontoxic botanicals, mind-body techniques such as meditation and yoga, body-based practices such as massage) have been used for thousands of years with no evidence of harm, and many seem to have no potential for harm. However, there are some safety considerations, including the following:

• Use of an alternative approach to treat a life-threatening disorder that can be effectively treated conventionally (eg, meningitis, diabetic ketoacidosis, acute leukemia) — perhaps the greatest risk of
CAM, rather than the risk of direct harm from a CAM therapy

- Toxicity from certain herbal preparations (e.g., hepatotoxicity from pyrrolizidine alkaloids, *Atractylis gummifera*, chaparral, germander, greater celandine, Jin Bu Huan, kava, pennyroyal, or others; nephrotoxicity from *Aristolochia*; adrenergic stimulation from ephedra)

- Contamination (e.g., heavy metal contamination of some Chinese and Ayurvedic herbal preparations; contamination of other products, such as PC-SPES and some Chinese herbs, with other drugs)

- Interactions between CAM therapies (e.g., botanicals, micronutrients, other dietary supplements) and other drugs (e.g., induction of cytochrome P-450 [CYP3A4] enzymes by St. John’s wort, resulting in reduced activity of antiretrovirals, immunosuppressants, and other drugs), particularly when the drug has a narrow therapeutic index

- As with any physical manipulation of the body (including mainstream techniques such as physical therapy), injury (e.g., nerve or cord damage due to spinal manipulation in patients at risk, bruising in patients with bleeding disorders)

Current alerts about harmful dietary supplements are available at the FDA web site. Historically, the FDA did not tightly regulate the production of dietary supplements. However, new FDA regulations now require compliance with manufacturing practices that guarantee quality and safety of supplements.

To help prevent injuries due to physical manipulations, patients should look for CAM practitioners who graduated from accredited schools and are professionally licensed. Rates of complications are very low when chiropractic or acupuncture is provided by practitioners with full credentials.

**Categories**

Five categories of alternative medicine are generally recognized (see Table 344-2):

- Alternative whole medical systems
- Mind-body medicine
- Biologically based practices
- Manipulative and body-based practices
- Energy medicine

The name of many therapies only partially describes their components.

**Alternative Whole Medical Systems**

Alternative medical systems are complete systems with explanation of disease, diagnosis, and therapy.

**Ayurveda**

Ayurveda, the traditional medical system of India, originated > 4000 yr ago. It is based on the theory that disease results from an imbalance of the body’s life force (prana). The balance of prana is determined by equilibrium of the 3 bodily qualities (doshas): vata, pitta, and kapha. Most people have a dominant dosha; the specific balance is unique to each person.

**Evidence:** Few well-designed studies of Ayurvedic practices have been done. Use of Ayurvedic herbal combinations to relieve symptoms in patients with RA and to treat diabetes is being studied.

**Uses:** After determining the balance of doshas, practitioners design a treatment specifically tailored to
Ayurveda uses diet, herbs, massage, meditation, yoga, and therapeutic detoxification (panchakarma)—typically with enemas, oil massages, or nasal lavage—to restore balance within the body and with nature.

Possible adverse effects: In some of the herbal combinations used, heavy metals (mainly lead, mercury, and arsenic) are included because they are thought to have therapeutic effects. Cases of heavy metal toxicity have been reported.

Homeopathy

Developed in Germany in the late 1700s, homeopathy is based on the principle that like cures like. A substance that, when given in large doses, causes a certain set of symptoms is believed to cure the same symptoms when it is given in minute doses. The minute dose is thought to stimulate the body's healing mechanisms. Treatments are based on the patient's unique characteristics, including personality and lifestyle, as well as symptoms and general health.

Remedies used in homeopathy are derived from naturally occurring substances, such as plant extracts and minerals. Extremely low concentrations are prepared in a specific way. The more dilute the homeopathic remedy, the stronger it is considered to be.

Some solutions are so dilute that they contain no molecules of the active ingredient. There is no compelling, scientific explanation for how these dilutions could work.

Evidence: Efficacy of homeopathic remedies for various disorders has been studied. No study has clearly shown efficacy for any specific homeopathic remedy, although some studies have shown positive results (eg, one well-conducted, randomized, placebo-controlled clinical study showed a therapeutic benefit greater than placebo in the treatment of diarrhea in children). Homeopathy is commonly incorporated into health care practices in Europe and India.

Table 344-2. Types of Alternative Medicine

Uses: Homeopathy has been used to treat various disorders, such as allergies, rhinitis, digestive problems, musculoskeletal pain, and vertigo. The effect of homeopathic solutions on joint pain and tenderness and quality of life in fibromyalgia is being studied.

Possible adverse effects: Homeopathy is well-tolerated and has few risks; rarely, an allergic or toxic reaction occurs.

Unlike herbal and nutritional supplements, homeopathic remedies are regulated by the FDA as drugs; they are available over the counter or by prescription. Because so little active ingredient is left after dilution, active ingredients are tested before dilution. Homeopathic remedies have been temporarily exempted from limits on the amount of alcohol (the usual diluent) that they can contain. However, the label is required to list the following:

- Manufacturer
- The label "homeopathic"
- At least one indication
- Instructions for safe use
- Unless specifically exempted, the active ingredient and degree of dilution

Conventional clinicians should not assume that a homeopathic remedy taken by a patient is biologically inactive. Patients often use the term homeopathic erroneously in reference to a dietary supplement they are taking. Also, the FDA allows many medicinal herbs to be registered and labeled as homeopathic if they undergo a particular pharmaceutical process.
Naturopathy

This therapy began as a formal health care system in the US during the early 1900s. Founded on the healing power of nature, naturopathy emphasizes prevention and treatment of disease through a healthy lifestyle, treatment of the whole patient, and use of the body's natural healing abilities. This system also focuses on finding the cause of a disease rather than merely treating symptoms. Some of this system's principles are not that different from those of traditional healing systems such as Ayurveda and traditional Chinese medicine.

Naturopathy uses a combination of therapies, including acupuncture, counseling, exercise therapy, medicinal herbs, homeopathy, hydrotherapy, natural childbirth, nutrition, physical therapies (eg, heat or cold therapy, ultrasound, massage), guided imagery, and stress management.

Traditional Chinese Medicine

Originating > 2000 yr ago, traditional Chinese medicine is based on the theory that disease results from improper flow of the life force (qi). The movement of qi is restored by balancing the opposing forces of yin and yang, which manifest in the body as heat and cold, external and internal, and deficiency and excess. Various practices (eg, acupuncture, diet, massage, medicinal herbs, meditative exercise called qi gong) are used to preserve and restore qi and thus health.

Evidence: Chinese medicine traditionally uses formulas containing mixtures of herbs to treat various disorders. Traditional formulas can be studied; for example, efficacy in the treatment of irritable bowel syndrome has been shown. One herb, used by itself, may not be as effective and may have side effects. Nevertheless, current conventional research favors study of single herbs. For example, Tripterygium wilfordii (thunder god vine) has demonstrated anti-inflammatory properties and clinical efficacy in treating RA, and Astragalus may benefit patients with lung cancer. Various Chinese herbs have been studied as treatments for hepatitis and hepatic fibrosis. Some studies suggest efficacy, but data are limited.

Possible adverse effects: One problem is the standardization and quality control of Chinese herbs. Many are unregulated in Asia; they may be contaminated with heavy metals from polluted ground water or may be adulterated with drugs such as antibiotics or corticosteroids. However, high-quality products are available through certain manufacturers that comply with FDA Good Manufacturing Practices.

Mind-Body Medicine

Mind-body medicine is based on the theory that mental and emotional factors influence physical health through a system of neuronal, hormonal, and immunologic connections throughout the body. Behavioral, psychologic, social, and spiritual techniques are used to preserve health and to prevent or cure disease.

Because scientific evidence supporting the benefits of mind-body medicine is abundant, many of these approaches are now considered mainstream, although they remain underused. Techniques such as biofeedback, guided imagery, hypnotherapy, meditation, and relaxation are used in the treatment of chronic pain, coronary artery disease, headaches, insomnia, and incontinence and as aids during childbirth. These techniques are also used to help patients cope with disease-related and treatment-related symptoms of cancer and to prepare patients for surgery. Efficacy of mind-body medicine in patients with asthma, hypertension, or tinnitus is not as clear.

Biofeedback

For this technique, electronic devices are used to provide information to patients about biologic functions (eg, heart rate, BP, muscle activity, skin temperature, skin resistance, brain surface electrical activity).

Uses: With the help of a therapist or with training, patients can then use information from biofeedback to modify the function or to relax, thereby lessening the effects of conditions such as pain, stress, insomnia, and headaches. Biofeedback is also used in patients with fecal or urinary incontinence, chronic abdominal pain, tinnitus, Raynaud's syndrome, or attention or memory disorders (eg, attention-
biofeedback does not seem to be useful in asthma; a possible exception is heart rate variability biofeedback, which may help reduce asthma symptoms and drug use and improve pulmonary function.

Guided imagery

Mental images, self-directed or guided by a practitioner, are used to help patients relax (eg, before a procedure) and to promote wellness and healing (to try to effect physical changes—eg, by mobilizing the immune system). The images can involve any of the senses.

**Uses:** Imagery used with relaxation techniques (muscle relaxation and deep breathing) may help reduce pain and improve quality of life in patients with cancer. Imagery has also been used in patients with psychologic trauma.

Hypnotherapy

Hypnotherapy is derived from western psychotherapeutic practice. Patients are put into an advanced state of relaxation. They become absorbed in the images presented by the hypnotherapist and are relatively distracted from but not unconscious of their surroundings and the experiences they are undergoing. Some patients learn to hypnotize themselves.

**Uses:** Hypnotherapy is used to treat pain syndromes, phobias, and conversion disorders and has been used with some success to manage smoking cessation and weight loss. It can reduce pain and anxiety during medical procedures in adults and children. It may be useful in irritable bowel syndrome, headaches, asthma, and some skin disorders (eg, warts, psoriasis). It may help lower BP. Hypnotherapy helps control nausea and vomiting (particularly anticipatory) related to chemotherapy and is useful in palliative cancer care. Some evidence suggests that hypnotherapy helps lessen anxiety and improve quality of life in patients with cancer.

Meditation

In meditation, patients regulate their attention or systematically focus on particular aspects of inner or outer experience. The most highly studied forms of meditation are transcendental meditation (TM) and mindfulness meditation. Although research is incomplete, results to date suggest that meditation could work via at least 2 mechanisms:

- Producing a relaxed state that counters excessive activation of neurohormonal pathways resulting from repeated stress
- Developing the capacity for metacognitive awareness (the ability to stand back from and witness the contents of consciousness), thus theoretically helping patients not react to stress automatically (with highly conditioned, learned patterns of behavior) and helping them tolerate and regulate emotional distress better

Most meditation practices were developed in a religious or spiritual context; their ultimate goal was some type of spiritual growth, personal transformation, or transcendental experience. However, studies suggest that as a health care intervention, meditation can often be beneficial regardless of a person's cultural or religious background.

**Uses:** Meditation has been used to relieve anxiety, pain, depression, stress, insomnia, and symptoms of chronic disorders such as cancer or cardiovascular disorders. It is also used to promote wellness.

Relaxation Techniques

Relaxation techniques are practices specifically designed to relieve tension and strain. The specific technique may be aimed at

- Reducing activity of the sympathetic nervous system
• Lowering BP
• Easing muscle tension
• Slowing metabolic processes
• Altering brain wave activity

Relaxation techniques may be used with other techniques, such as meditation, guided imagery, or hypnotherapy.

**Biologically Based Practices**

Biologically based practices use naturally occurring substances and include biologic therapies (eg, shark cartilage to treat cancer, glucosamine to treat osteoarthritis), diet therapies, herbalism (see p. 3421), orthomolecular medicine, and chelation therapy.

**Diet Therapy**

Diet therapy uses specialized dietary regimens (eg, Gerson therapy, macrobiotic diets, Pritikin diet) to treat or prevent a specific disorder (eg, cancer, cardiovascular disorders) or generally promote wellness. Some diets (eg, Mediterranean diet) are widely accepted and encouraged in traditional western medicine. The Ornish diet, a very low-fat vegetarian diet, can help reverse arterial blockages that cause coronary artery disease and may help prevent or slow the progression of prostate and other cancers. Some people following a macrobiotic diet have reported cancer remission, but a well-controlled clinical study has not been conducted. Because it usually takes months or years for benefits to be realized, diet therapy is more likely to be effective if started early.

**Orthomolecular Medicine**

Orthomolecular medicine, also called nutritional medicine, aims to provide the body with optimal amounts of substances that naturally occur in the body. Nutrition is the focus in diagnosis and treatment.

This therapy differs from diet therapy because it uses supradietary doses of individual micronutrients. High doses of vitamins, minerals, enzymes, hormones (eg, melatonin), amino acids, or various combinations may be used. Practitioners believe that people's nutritional needs far exceed the recommended daily allowances and that nutritional therapy must be individualized based on each patient's medical profile. High doses of micro-nutrients are also used as biologic response modifiers in an attempt to modulate inflammation and other disease processes. Doses may be administered orally or, far less often, intravenously.

**Evidence and uses:** Treatment claims include benefit for a wide range of disorders (eg, cancer, cardiovascular disease, chronic fatigue, chronic pain, autism, psychiatric disorders). These treatments are widely used, and many patients report clinical improvement. However, no clinical study data support the usefulness of most of these practices. Exceptions include use of high-dose fish oils to treat hypertriglyceridemia (and possibly inflammatory and mood disorders), use of high-dose antioxidants to prevent macular degeneration, and possibly high-dose melatonin to prevent or treat cancer. If sufficient evidence of usefulness is shown, treatments (eg, high-dose fish oils to treat hypertriglyceridemia, high-dose antioxidants to prevent macular degeneration) become part of conventional medicine.

**Possible adverse effects:** Clinicians should be aware that high-dose micronutrients may cause harm; eg, some micronutrients may increase the risk of developing prostate cancer or blunt the effects of certain cancer treatments.

**Chelation Therapy**

In chelation therapy, a drug is used to bind with and remove hypothesized excess or toxic amounts of a
metal or mineral (e.g., lead, copper, iron, calcium) from the bloodstream. In conventional medicine, chelation therapy is a widely accepted way to treat lead and other heavy metal poisoning (see p. 3344). Chelation therapy with EDTA (ethylene diamine tetraacetic acid) has also been suggested as a way to remove calcium and thus treat atherosclerosis; whether this use is safe and effective has not been proved but is under study.

**Manipulative and Body-Based Practices**

Manipulative and body-based practices include chiropractic, massage therapy, postural reeducation, reflexology, and structural integration.

**Chiropractic**

In chiropractic, the relationship between the structure of the spine and function of the nervous system is thought to be the key to maintaining or restoring health. The main method for restoring this relationship is spinal manipulation. Chiropractors may also provide physical therapies (e.g., heat and cold, electrical stimulation, rehabilitation strategies), massage, or acupressure and may recommend exercises or lifestyle changes.

**Uses:** Chiropractic provides short-term relief of low back pain, but continuing adjustments may not provide additional benefit. Thus, the usefulness of chiropractic for chronic back pain is unclear. Chiropractic is sometimes useful in treating headache disorders (although data are inconsistent) and nerve impingement syndromes; it has also been used to treat neck pain. The usefulness of manipulation for conditions not directly related to the musculoskeletal system has not been established.

**Possible adverse effects:** Serious complications resulting from spinal manipulation (e.g., low back pain, damage to cervical nerves, damage to arteries in the neck) are rare. Spinal manipulation is not recommended for patients with osteoporosis or symptoms of neuropathy (e.g., paresthesias, loss of strength in a limb). Whether it is safe for patients who have had spinal surgery or stroke or who have a vascular disorder is unclear.

**Massage Therapy**

In massage therapy, body tissues are manipulated to promote wellness and reduce pain and stress. The therapeutic value of massage for many musculoskeletal symptoms and stress is widely accepted. Massage has been shown to help relieve the following:

- Muscle soreness
- Pain due to back injuries
- Fibromyalgia
- Anxiety, fatigue, pain, nausea, and vomiting in cancer patients

Massage therapy is reported to be effective in treating low birth weight infants, preventing injury to the mother's genitals during childbirth, relieving chronic constipation, and controlling asthma.

Massage can cause bruising and bleeding in patients with thrombocytopenia or bleeding disorders. Therapists must avoid putting pressure on bones affected by osteoporosis or metastatic cancer.

**Reflexology:** This variant of massage therapy relies on manual pressure applied to specific areas of the foot; these areas are believed to correspond to different organs or body systems via meridians. Stimulation of these areas is believed to eliminate the blockage of energy responsible for pain or disease in the corresponding body part. Reflexology may help relieve anxiety in patients with cancer.

**Structural integration:** Structural integration is based on the theory that good health depends on correct body alignment. It is a form of deep tissue manipulation that is typically done over a series of sessions.
Correct alignment of bone and muscle is achieved by manipulating and stretching muscles and fascia. The efficacy has not been proved.

**Other Therapies**

Several lesser known therapies are used in various cultures. They include cupping, scraping (eg, coining, spooning), and moxibustion. Some of these therapies result in lesions that may be mistaken for signs of child abuse. These therapies are thought to stimulate the body's energy and to enable toxins to leave the body.

**Cupping**: This therapy is used in traditional Chinese medicine and in Middle Eastern, Asian, Latin American, and Eastern European cultures. The air inside a cup is heated, often using a cotton ball soaked in alcohol, then ignited. The heated cup is immediately inverted and placed on the skin. The resulting vacuum sucks the skin partway into the cup, which may be left in place for several minutes. Cupping has been used to treat bronchitis, asthma, digestive disorders, and certain types of pain; however, no research has verified its efficacy. Cupping may redden or burn the skin.

**Scraping**: This therapy involves rubbing an implement across lubricated (oiled or wet) skin, usually on the back, neck, and shoulders. Coining uses a coin; spooning uses a spoon. These therapies are used to treat the common cold, influenza, muscle pain and stiffness, and other disorders. Coining results in linear red marks; spooning results in ecchymosis.

**Moxibustion**: Dried moxa herb (a mugwort) is burned usually just above but sometimes directly on the skin over acupuncture points. The herb may be in the form of incense sticks. This therapy is used to treat fever, digestive problems, and pain due to injury or arthritis. Moxibustion can result in circular burns (which resemble burns from cigarette tips) and vesicobullous lesions.

**Energy Medicine**

Energy medicine intends to manipulate subtle energy fields (also called biofields) thought to exist in and around the body. All energy therapies are based on the belief that a universal life force or subtle energy resides in and around the body. Qi gong, which is used in traditional Chinese medicine, is an energy therapy.

**Acupuncture**

Acupuncture, a therapy within traditional Chinese medicine, is one of the most widely accepted alternative therapies in the western world. Specific points on the body are stimulated, usually by inserting thin needles into the skin and underlying tissues. Stimulating these specific points is believed to unblock the flow of qi along energy pathways (meridians) and thus restore balance; > 350 defined points are located along the meridians. The procedure is generally not painful but may cause a tingling sensation. Sometimes stimulation is increased by twisting or warming the needle. Acupuncture points may also be stimulated by pressure (called acupressure), lasers, ultrasound, or a very low voltage electrical current (called electroacupuncture) applied to the needle.

**Evidence and uses**: Research has shown that acupuncture releases various neurotransmitters (eg, endorphins) that act as natural painkillers. Reasonable evidence supports the efficacy of acupuncture as a pain reliever, an antinauseant, and an antiemetic. However, in many studies, results of sham acupuncture are comparable to those of actual acupuncture; the relative efficacy of sham and actual acupuncture is still not clear.

Acupuncture relieves nausea and vomiting related to surgery and chemotherapy. When used with antiemetic drugs, acupuncture has an additive effect. Acupuncture also helps relieve nausea and vomiting during pregnancy. Acupuncture has been used to relieve pain after surgical or dental procedures. As part of a comprehensive treatment plan (sometimes as adjunctive treatment), acupuncture may be useful in treating addiction, carpal tunnel syndrome, fibromyalgia, headache, low back pain, osteoarthritis, and xerostomia (in patients with advanced cancer) and in stroke rehabilitation.
Preliminary evidence suggests that acupuncture may relieve vasomotor symptoms in men taking gonadotropin analogs for prostate cancer. The evidence for relieving symptoms and improving pulmonary function in patients with asthma and for relieving pain or improving function in patients with RA is mixed. Acupuncture is ineffective for smoking cessation and weight loss.

**Possible adverse effects and contraindications:** Adverse effects are rare if the procedure is done correctly. Worsening of symptoms (usually temporary) and vasovagal symptoms are the most common. Because acupuncture can cause fainting and drowsiness (although rarely), patients should be supine at least for their first treatment and should not drive or do any tasks that require alertness after treatment until they know how it affects them. Infection is extremely rare; most practitioners use disposable needles.

Acupuncture is contraindicated in patients with severe bleeding disorders. Electroacupuncture is contraindicated in patients with a pacemaker or an implanted defibrillator. Acupuncture at certain points may stimulate uterine contractions, and in traditional Chinese medicine, it is used to modulate labor. Only specially trained practitioners should use acupuncture in pregnant women.

**Magnets**

Energy therapy may rely on magnetic (alternating- or direct-current) fields.

**Evidence and uses:** Magnets, in particular, are a popular treatment for various musculoskeletal disorders, although multiple studies have shown no effectiveness, especially for pain relief, one of their most common applications.

Preliminary evidence suggests that static (permanent) magnets may help relieve pain in patients with osteoarthritis. However, the evidence that electromagnets may reduce pain and improve physical function is more consistent than that for static magnets. Using pulsating electromagnetic fields to speed healing of nonunion fractures is well-established.

**Possible contraindications:** Possible contraindications for magnets include pregnancy (effects on the fetus are unknown) and use of implanted cardiac devices, an insulin pump, or a drug given by patch.

**Therapeutic Touch**

Therapeutic touch, sometimes referred to as laying on of hands, uses the therapist's healing energy to identify and repair imbalances in a patient's biofield. Usually, practitioners do not touch the patient; instead, they move their hands back and forth over the patient. Therapeutic touch has been used to lessen anxiety and improve the sense of well-being in patients with cancer, but these effects have not been rigorously studied. In the US, nurses have introduced therapeutic touch into ICUs and other hospital settings.

**Reiki:** Reiki, which originated in Japan, is a similar technique; in Reiki, practitioners channel energy through their hands and transfer it into the patient's body to promote healing. Practitioners are thought to have special healing powers, which are required for these treatments.
Chapter 345. Dietary Supplements

Introduction

(See also Ch. 344.)

Dietary supplements are the most commonly used of all complementary and alternative therapies, primarily because they are widely available and can be bought without consulting a health care practitioner.

The FDA regulates dietary supplements differently from drugs. The FDA regulates only quality control and good manufacturing processes but does not ensure standardization of the active ingredients or efficacy.

Definition: The Dietary Supplement Health Education Act (DSHEA) of 1994 defines a dietary supplement as

• Any product (except tobacco)—in pill, capsule, tablet, or liquid form—containing a vitamin, mineral, herb or other plant product, amino acid, or other known dietary substance that is intended as a supplement to the normal diet

In addition, certain hormones, such as dehydroepiandrosterone (DHEA, a precursor to androgens and estrogens) and melatonin, are regulated as dietary supplements and not as prescription drugs.

Labeling: The DSHEA requires that the product label identify the product as a dietary supplement and notify the consumer that the claims for the supplement have not been evaluated by the FDA. The label must also list each ingredient by name, quantity, and total weight and identify plant parts from which ingredients are derived. Manufacturers are permitted to make claims about the product's structure and function (eg, good for urinary tract health) but cannot make or imply claims for the product as a drug or therapy (eg, treats UTIs).

Safety and efficacy: Most people who use dietary supplements assume that they are good for health generally, are safe and effective for treating specific conditions, or both because dietary supplements are natural (ie, derived from plants or animals) and because some are supported by centuries of use in traditional systems of medicine. However, the FDA does not require manufacturers of dietary supplements to prove safety or efficacy (although supplements must have a history of safety). Most supplements have not been rigorously studied. For most, evidence suggesting safety or efficacy comes from traditional use, in vitro studies, certain case reports, and animal studies. However, manufacturers and distributors of supplements now must report serious adverse events to the FDA through the MedWatch system. There are a few supplements (eg, fish oil, chondroitin/glucosamine, saw palmetto) now proved to be safe and useful complements to standard drugs.

Evidence concerning the safety and efficacy of dietary supplements is increasing rapidly as more and more clinically based studies are being done. Information about such studies is available at the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM) web site (www.nccam.nih.gov/research/clinicaltrials/).

Purity and standardization: Lack of regulation and government monitoring also means that supplements are not monitored to ensure that they contain the ingredients or amount of active ingredient the manufacturer claims they contain. The supplement may have un-listed ingredients, which may be inert or harmful (eg, natural toxins, bacteria, pesticides, lead or other heavy metals), or it may contain variable amounts of active ingredients, especially when whole herbs are ground or made into extracts. Consumers are at risk of getting less, more, or, in some cases, none of the active ingredient, if the active ingredient is even known. Most herbal products are mixtures of several substances, and which ingredient is the most active is not always known. The lack of standardization means not only that products from different manufacturers may vary, but also that different batches produced by the same manufacturer may differ. This product variability is a particular source of difficulty in conducting rigorous scientific trials and comparing the results among different trials. However, some supplements have been standardized and may include a designation of standardization on the label.
New regulations governing supplement production in the US include rules for Good Manufacturing Practices (GMPs). These rules strengthen standards for keeping manufacturing facilities and equipment clean and raw materials pure and uncontaminated. GMPs also ensure proper labeling, packaging, and storage of the finished product.

Other concerns: Additional areas of concern include

- Use of dietary supplements instead of conventional drugs
- Stability of supplements (especially herbal products) once manufactured
- Toxicity
- Interactions between supplements and drugs

Most information about these concerns comes from sporadic individual reports (see Table 345-1) and some references.

Despite these concerns, many patients strongly believe in the benefits of supplements and continue to use them with or without a physician's involvement. Patients may not think to disclose or may wish to conceal their use of dietary supplements. For this reason, the outpatient history should periodically include explicit questions about past

and new use of complementary and alternative therapies, including dietary supplements. Many physicians incorporate some supplement use into their practice; their reasons include proven benefit of the supplement, a desire to ensure that supplements are used safely by patients who will use supplements anyway, and the physician's belief that the supplements are safe and effective. There are few data to guide patient counseling regarding supplement safety. But some experts believe that the overall number of problems due to dietary supplements is rare compared with the overall number of doses taken and that the supplement, if correctly manufactured, is likely to be safe. As a result, these experts advise purchase of supplements from a well-known manufacturer, and many recommend buying supplements made in Germany because there they are regulated as drugs and thus oversight is stricter than in the US.

The following supplements are ones that are most popular, are effective, or have some questions about their safety. More complete information is available through the NCCAM web site (www.nccam.nih.gov/).

**Black Cohosh**

Black cohosh is the underground stem of a plant that can be ingested directly in powdered form or extracted into tablet or liquid form. It should be standardized to contain certain triterpenes. Black cohosh contains no phytoestrogens that can account for its purported estrogen-like effects, but it contains small amounts of anti-inflammatory compounds, including salicylic acid.

Claims: Black cohosh is said to be useful for menopausal symptoms (eg, hot flushes, mood lability, tachycardia, vaginal dryness), for menstrual symptoms, and for arthralgias in RA or osteoarthritis.

Scientific evidence regarding benefit in relieving menstrual symptoms is conflicting. There are few reliable data on its effectiveness for other disorders and symptoms.

**Adverse effects:** Adverse effects are uncommon. The most likely are headache and GI distress. Dizziness, diaphoresis, and hypotension (if high doses are taken) may occur.

There is no evidence that black cohosh interferes with any drugs. Theoretically, black cohosh is contraindicated in patients with aspirin sensitivity, liver disease, hormone-sensitive cancers (eg, certain
kinds of breast cancer), stroke, or high BP. The US Pharmacopeia (USP) has recommended that black cohosh products be labeled with a warning declaring that they may be hepatotoxic.

**Chamomile**

The flower of chamomile is dried and drunk as a tea or used topically as an extract.

**Claims:** Chamomile tea is said to reduce inflammation and fever, to act as a mild sedative, to relieve stomach cramps and indigestion, and to promote healing of gastric ulcers. Chamomile extract applied topically in a compress is said to soothe irritated skin. Mechanism is due to essential oil containing bisabolol constituents.

**Adverse effects:** Chamomile is generally safe. It may interact with alcohol and sedatives (eg, barbiturates). Some people are allergic to pollen in chamomile products.

Chamomile may reduce the absorption of oral drugs. Chamomile may also increase the effects of anticoagulants and sedatives (including alcohol) and decrease the absorption of iron supplements.

**Chondroitin Sulfate**

Chondroitin sulfate is a glycosaminoglycan, a natural component of cartilage. It is extracted from shark or cow cartilage or manufactured synthetically. It is frequently combined with glucosamine.

**Claims:** Chondroitin sulfate is used to treat osteoarthritis. Scientific evidence shows no benefit when chondroitin sulfate is taken by itself. However, evidence suggests that in combination with glucosamine, it may reduce joint pain, improve joint mobility, and allow reduction of the doses of conventional anti-inflammatory drugs when it is taken for 6 to 24 mo. Effects over longer periods are unclear. Mechanism is unknown. Dose is 600 mg po once/day to 400 mg po tid.

**Adverse effects:** No serious adverse effects have been reported. Among the most common adverse effects are stomach pain, nausea, and other GI symptoms.

Chondroitin sulfate may also affect the action of warfarin. Chondroitin sulfate is safe for most people, but people who have asthma, blood-clotting disorders, or prostate cancer should use caution when taking it.

**Chromium**

Chromium, a trace mineral, potentiates the action of insulin. Sources include carrots, potatoes, broccoli, whole grains, and molasses. Picolinate is a by-product of tryptophan that is paired with chromium in supplements because it is said to help the body absorb chromium more efficiently.

**Claims:** Chromium picolinate is said to promote weight loss, build muscle, reduce body fat, lower cholesterol and triglyceride levels, and enhance insulin function. Although chromium deficiency impairs insulin function, there is no evidence that supplementation helps patients with diabetes, nor is there evidence that it benefits body composition or lipid levels.

**Adverse effects:** Some evidence suggests that chromium picolinate damages chromosomes and may cause cancer. Some forms of chromium may contribute to GI irritation and ulcers. Chromium supplements interfere with iron absorption.

**Coenzyme Q10**

Coenzyme Q10 (ubiquinone) is an antioxidant that is also a cofactor for mitochondrial ATP generation. The levels of coenzyme Q10 seem to be lower in older people and in people with chronic diseases, such as cardiac problems, cancer, Parkinson’s disease, diabetes, HIV/AIDS, and muscular dystrophies. However, it is not known whether these low levels contribute to these disorders.

**Claims:** Coenzyme Q10 is said to be useful because of its antioxidant effect and role in energy
metabolism. Specific claims include an anticancer effect mediated by immune stimulation, decreased insulin requirements in patients with diabetes, slowed progression of Parkinson's disease, efficacy in treatment of heart failure, and protection against anthracycline cardiotoxicity. Although some preliminary studies suggest coenzyme Q10 may be useful in treating these disorders, results are unclear and more testing is needed.

**Adverse effects:** Coenzyme Q10 may decrease response to warfarin. There are case reports of GI symptoms (eg, loss of appetite, abdominal pain, nausea, vomiting) and CNS symptoms (eg, dizziness, photophobia, irritability, headache). Other adverse effects include itching, rash, fatigue, and flu-like symptoms. Coenzyme Q10 is not recommended for people who exercise vigorously.

**Cranberry**

Cranberries are fruit that can be consumed whole or made into food products such as jellies and juices.

**Claims:** People most often take cranberries to help prevent and relieve the symptoms of UTIs. The effectiveness of cranberries in preventing UTIs has been documented. Natural unprocessed cranberry juice contains anthocyanidins, which prevent *Escherichia coli* from attaching to the urinary tract wall.

Some people take cranberry juice to reduce fever and treat certain cancers; however, there is no scientific proof that it is effective for these uses.

**Adverse effects:** No adverse effects are known. However, because most cranberry juice is highly sweetened to offset its tart taste, people with diabetes should not consume cranberry juice unless it is artificially sweetened. Because cranberry increases urinary acidity, it may promote stone formation in patients with uric acid kidney stones. Cranberry products may increase the effects of warfarin.

**Creatine**

Phosphocreatine is a compound stored in muscle; it donates phosphate to ADP and thereby rapidly replenishes ATP during anaerobic muscle contraction. It is synthesized endogenously in the liver from arginine, glycine, and methionine. Dietary sources are milk, steak, and some fish.

**Claims:** Creatine is said to improve physical and athletic performance and to reduce muscle fatigue. Some evidence suggests creatine is effective at increasing work done in a short maximal effort (eg, sprinting, weightlifting). It has proven therapeutic use in muscle phosphorylase deficiency (glycogen storage disease type V [McArdle disease]) and gyrate atrophy of the choroid and retina; early data also suggest possible effects in Parkinson's disease and amyotrophic lateral sclerosis.

**Adverse effects:** Creatine may cause weight gain (possibly because of an increase in muscle mass) and spurious increases in serum creatinine levels. Minor GI symptoms, dehydration, electrolyte imbalance, and muscle cramps have been reported anecdotally.

**Dehydroepiandrosterone**

Dehydroepiandrosterone (DHEA) is a steroid produced by the adrenal gland and is a precursor of estrogens and androgens. Effects on the body are similar to those of testosterone. DHEA can also be synthesized from precursors in the Mexican yam; this form is the most commonly available.

**Claims:** DHEA supplements are said to improve mood, energy, sense of well-being, and the ability to function well under stress. They are also said to improve athletic performance, stimulate the immune system, deepen nightly sleep, lower cholesterol levels, decrease body fat, build muscles, reverse aging, improve brain function in patients with Alzheimer's disease, and increase libido. The medicinal claims of DHEA have not been proved.

**Adverse effects:** Adverse effects are unknown. There are theoretical risks of gynecomastia in men, hirsutism in women, and stimulation of prostate and breast cancer. There is a case report of mania and one of seizure.
**Echinacea**

Echinacea, a North American wildflower, contains a variety of biologically active substances.

**Claims:** Echinacea is said to stimulate the immune system. When taken at the start of a cold, it is said to shorten the duration of cold symptoms. Well-designed studies have not supported this effect. Topical preparations are used to promote wound healing.

**Adverse effects:** Most adverse effects are mild and transitory; they include dizziness, fatigue, headache, and GI symptoms. No other adverse effects are known. Theoretically, echinacea is contraindicated in patients with autoimmune disorders, multiple sclerosis, AIDS, TB, and organ transplants because it may stimulate T cells. Echinacea inhibits some cytochrome P-450 enzymes and stimulates others; it can therefore potentially interact with drugs metabolized by the same enzymes (eg, anabolic steroids, azole antifungals, methotrexate). Allergic reactions are possible in patients with pollen allergies.

**Feverfew**

Feverfew is a bushy perennial herb. The dried leaves are used in capsules, tablets, and liquid extracts. Parthenolides and glycosides are thought to be the components responsible for its purported anti-inflammatory effects and relaxant effects on smooth muscle.

**Claims:** Feverfew is said to be effective in the prevention of migraine headaches. Evidence from 3 of 4 relatively small but well-designed studies supports these claims, but the largest and best designed of these studies does not. Differences among study findings may reflect the different formulations of feverfew used.

Feverfew is also said to be useful for relieving menstrual pain, asthma, and arthritis. In vitro, feverfew inhibits platelet aggregation.

**Adverse effects:** Mouth ulcers, contact dermatitis, dysgeusia, and mild GI symptoms may occur. Abrupt discontinuation may worsen migraines and cause nervousness and insomnia. Feverfew is contraindicated in pregnant women; theoretically, it is contraindicated in patients taking other antimigraine drugs, iron supplements, NSAIDs, antiplatelet drugs, or warfarin.

**Fish Oil**

Fish oil may be extracted directly or concentrated and put in capsule form. Active ingredients are ω-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]). Western diets typically are low in ω-3 fatty acids.

**Claims:** Fish oil is used for prevention and treatment of atherosclerotic cardiovascular disease. Strong scientific evidence suggests that EPA/DHA 800 to 1500 mg/day reduces risk of MI and death due to arrhythmia in patients who have preexisting coronary artery disease and are taking conventional drugs. It also reduces triglycerides in a dose-dependent way (25 to 40% with EPA/DHA 4 g/day) and slightly lowers BP (2 to 4 mm Hg with EPA/DHA > 3 g/day). Mechanisms are probably multiple but unknown. Benefits are suspected but not yet proved for primary prevention of atherosclerotic cardiovascular disease, treatment of RA, and prevention of cyclosporine nephrotoxicity.

**Adverse effects:** Fishy eructation, nausea, and diarrhea may occur. Risk of bleeding increases with EPA/DHA > 3 g/day. Concerns about mercury contamination are not substantiated in laboratory testing. Even so, pregnant or breastfeeding women should not take ω-3 fatty acid supplements extracted from fish and should limit consumption of certain types and amounts of fish because of the potential risk of mercury contamination.

**Garlic**
Garlic bulbs are extracted and made into tablet form; the major active ingredient is allicin, an amino acid by-product.

**Claims:** Garlic is said to have favorable effects on several cardiac risk factors, including reduction of BP and serum lipid and glucose levels; garlic inhibits platelets in vitro. Garlic is also said to protect against laryngeal, gastric, colorectal, and endometrial cancer and adenomatous colorectal polyps. Scientific evidence shows limited to no protection against cancer. Garlic consumed in high doses has general antimicrobial effects.

**Adverse effects:** Breath and body smell and nausea may occur; high doses may cause burning in the mouth, esophagus, and stomach. Theoretically, garlic is contraindicated in patients who have bleeding diatheses or who take antihypertensives, antiplatelet drugs, or warfarin. Garlic can reduce serum saquinavir levels.

**Ginger**

Ginger root is extracted and made into tablet form. Active ingredients include gingerols (which give ginger its flavor and odor) and shogaols.

**Claims:** Ginger is said to be an effective antiemetic and antinauseant, especially for nausea caused by motion sickness or pregnancy, and to relieve intestinal cramps. Ginger is also used as an anti-inflammatory and analgesic. It may have antibacterial properties and antiplatelet effects in vitro, but data are inconsistent. Scientific studies are consistent with a beneficial effect in pregnancy-related nausea and vomiting.

**Adverse effects:** Ginger is usually not harmful, although some people have a burning sensation when they eat it. Nausea, dyspepsia, and dysgeusia are possible. Theoretically, ginger is contraindicated in patients who have bleeding diatheses or who take anti-platelet drugs or warfarin.

**Ginkgo**

Ginkgo (*Ginkgo biloba*) is prepared from leaves of the ginkgo tree (commonly planted in the US for ornamental purposes). Active ingredients are believed to be terpene ginkgolides and flavonoids.

The fruit of the ginkgo tree, which is quite malodorous, is not used in ginkgo products. Contact with the fruit pulp, which may be present under female ginkgo trees, can cause severe skin inflammation (dermatitis). The raw seeds of the fruit are toxic and can cause seizures and, in large amounts, death. Cooked ginkgo seeds are eaten in Asia and are available in Asian food shops in the US; because the seeds do not contain ginkgolides and flavonoids, they do not have therapeutic effects.

**Claims:** Strong scientific evidence supports use of ginkgo for symptomatic relief of claudication, although exercise and cilostazol may be more effective. Gingko increases the distance that affected people can walk without pain.

Ginkgo has long been used in people with dementia. Benefit in dementia seems unlikely based on a recent large clinical trial in which ginkgo was not effective in reducing the development of dementia and Alzheimer's disease in older people. However, a previous large US clinical trial indicated that ginkgo temporarily stabilized mental and social function in people with mild to moderate dementia. Although data are conflicting, any real effect is likely to be modest.

Studies show ginkgo does not seem to alleviate memory loss, tinnitus, or altitude sickness. Gingko may prevent damage to the kidneys caused by the immunosuppressant cyclosporine.

**Adverse effects:** Nausea, dyspepsia, headache, dizziness, and heart palpitations may occur. Ginkgo may interact with aspirin, other NSAIDs (see p. [1623](#)), and warfarin and may reduce the efficacy of anticonvulsants.

**Ginseng**
Ginseng is a family of plants. Dietary supplements are derived from American ginseng (\textit{Panax quinquefolius}) or Asian ginseng. Siberian ginseng is a different genus and does not contain the ingredients believed to be active in the 2 forms used in supplements. Ginseng can be taken as fresh or dried roots, extracts, solutions, capsules, tablets, sodas, and teas or used as cosmetics. Active ingredients in American ginseng are panaxosides (saponin glycosides). Active ingredients in Asian ginseng are ginsenosides (triterpenoid glycosides).

Ginseng products vary considerably in quality because many contain little or no detectable active ingredient. In very few cases, some ginseng products from Asia have been purposefully mixed with mandrake root, which has been used to induce vomiting, or with the drugs phenylbutazone or aminopyrine. These drugs have been removed from the US market because of significant adverse effects.

**Claims:** Ginseng is said to enhance physical (including sexual) and mental performance and to have adaptogenic effects (ie, to increase energy and resistance to the harmful effects of stress and aging). Other claims include reduction in plasma glucose levels; increases in high density lipoprotein (HDL), Hb, and protein levels; stimulation of the immune system; and anticancer, cardiotoxic, endocrine, CNS, and estrogenic effects. Some studies have shown that Asian ginseng may lower plasma glucose and have possible beneficial effects on immune function, but there is no evidence for other health claims. Recent Canadian studies show that a polysaccharide extract of \textit{P. quinquefolius} is useful in helping prevent colds.

**Adverse effects:** Nervousness and excitability may occur but decrease after the first few days. Ability to concentrate may decrease, and plasma glucose may become abnormally low (causing hypoglycemia). Because ginseng has an estrogen-like effect, women who are pregnant or breastfeeding should not take it, nor should children. Occasionally, there are reports of more serious effects, such as asthma attacks, increased BP, palpitations, and, in postmenopausal women, uterine bleeding. To many people, ginseng tastes unpleasant.

Ginseng can interact with antihyperglycemic drugs, aspirin, other NSAIDs, corticosteroids, digoxin, estrogens, monoamine oxidase inhibitors, and warfarin.

**Glucosamine**

Glucosamine is a precursor of multiple cartilage constituents. It is extracted from chitin (in shells of crabs, oysters, and shrimp) and is taken in tablet or capsule form, usually as glucosamine sulfate, but sometimes as glucosamine hydrochloride. Glucosamine is often taken with chondroitin sulfate (see p. 3425).

**Claims:** Strong scientific evidence supports use of glucosamine sulfate for treatment of mild to moderate osteoarthritis of the knee. Its role in the treatment of more severe knee osteoarthritis and osteoarthritis in other locations is less well-defined. Some evidence suggests it has both analgesic and disease-modifying effects, whereas evidence from other large and well-designed studies shows it to be of no benefit. One very large study showed that glucosamine hydrochloride is beneficial only when combined with chondroitin sulfate. Mechanism is unknown but may be related to improved glycosaminoglycan synthesis as a result of the sulfate moiety. Dose is 500 mg po tid.

**Adverse effects:** Allergy (in patients who have shellfish allergy and take forms extracted from shellfish), dyspepsia, fatigue, insomnia, headache, photosensitivity, and nail changes may occur.

**Goldenseal**

Goldenseal, an endangered US plant, is related to the buttercup. Its active components are hydrastine and berberine, which have antiseptic activity. Berberine also has antidiarrheal properties.

**Claims:** Goldenseal is used as an antiseptic wash for mouth sores, inflamed and sore eyes, and irritated skin and as a douche for vaginal infections. It has been combined with echinacea as a cold remedy, but the efficacy of goldenseal as a cold remedy has not been proved. Goldenseal is also used as a remedy
for indigestion and diarrhea. In 2 relatively well-designed studies, berberine isolated from goldenseal reduced diarrhea.

**Adverse effects:** Goldenseal can have many adverse effects, including nausea, anxiety, dyspepsia, uterine contractions, jaundice in neonates, and worsening of hypertension. If taken in large amounts, goldenseal can cause seizures and respiratory failure and may affect contraction of the heart. Goldenseal may interact with warfarin. Women who are pregnant or breastfeeding, neonates, and people who have seizure disorders or problems with blood clotting should not take goldenseal. Berberine may reduce the anticoagulant effect of heparin.

**Green Tea**

Green tea is made from the dried leaves of the same plant as traditional tea, an evergreen shrub native to Asia. However, traditional tea leaves are fermented, and green tea leaves are steamed but unfermented. Green tea may be brewed and drunk or ingested in extracted tablet or capsule form. It has multiple components that are thought to have antioxidant and anticancer effects. Green tea contains polyphenols and catechins as well as caffeine, but many extracts have been decaffeinated.

**Claims:** Green tea is said to have multiple health benefits, none of which are supported by strong scientific evidence. It has been used for cancer prevention, weight loss, serum lipid reduction, prevention of coronary artery disease, memory enhancement, relief of osteoarthritis pain, treatment of menopausal symptoms, and longevity.

**Adverse effects:** Adverse effects are related to effects of caffeine. They include insomnia, anxiety, tachycardia, and mild tremor. Pregnant women should avoid excessive caffeine.

**Kava**

Kava comes from the root of a shrub (*Piper methysticum*) that grows in the South Pacific. It is ingested as a tea or in capsule form. Active ingredients are thought to be kavalactones.

**Claims:** Strong scientific evidence supports use of kava as an anxiolytic and sleep aid. Mechanism is unknown. Some people use kava for asthma, menopausal symptoms, and UTIs. Dose is 100 mg of standardized extract tid.

**Adverse effects:** Over 20 people in Europe developed liver toxicity (including liver failure) after taking kava, which prompted the FDA to mandate a warning label on kava products. Safety is under continuing surveillance.

When kava is prepared traditionally (as tea) and used in high doses (> 6 to 12 g/day of dried root) or over long periods (up to 6 wk), there have been reports of scaly skin rash (kava dermopathy), blood changes (eg, macrocytosis, leukopenia), and neurologic changes (eg, torticollis, oculogyric crisis, worsening of Parkinson's disease, movement disorders). Also, kava may prolong the effect of other sedatives (eg, barbiturates) and affect driving or other activities requiring alertness.

**Licorice**

Natural licorice, which has a very sweet taste, is extracted from the root of a shrub and used medicinally as a capsule, tablet, or liquid extract. Most licorice candy made in the US is flavored artificially and does not contain natural licorice. Glycyrrhizin is the active ingredient in natural licorice. For people who are particularly sensitive to the effects of glycyrrhizin, specially treated licorice products that contain a much lower amount of glycyrrhizin (about one tenth) are available. These products are called deglycyrrhizinated licorice.

**Claims:** People most often take licorice to suppress coughs, to soothe a sore throat, and to relieve stomach upset. Applied externally, it is said to soothe skin irritation (eg, eczema). There are not enough data to determine whether licorice is effective for stomach ulcers or complications caused by hepatitis C.
**Adverse effects:** High doses of real licorice (> 1 oz/day) and glycyrrhizin cause renal Na and water retention, possibly leading to high BP, and K excretion, possibly causing low K levels. Increased K excretion can be a particular problem for people who have heart disease and for those who take digoxin or diuretics that also increase K excretion. Such people and those who have high BP should avoid taking licorice.

Licorice may increase the risk of premature delivery; thus, pregnant women should avoid licorice.

**Melatonin**

Melatonin, a hormone produced by the pineal gland, regulates circadian rhythms. It is derived from animals or can be manufactured synthetically. In some countries, melatonin is considered a drug and is regulated as such.

**Claims:** Some scientific evidence supports use of melatonin to minimize the effects of jet lag, especially in people traveling eastward over 2 to 5 time zones. However, in one large well-designed study, melatonin supplements did not relieve symptoms of jet lag, and only a few small studies suggest that these supplements can treat insomnia.

Standard dosage is not established and ranges from 0.5 to 5 mg po taken 1 h before usual bedtime on the day of travel and 2 to 4 nights after arrival. Evidence supporting use of melatonin as a sleep aid in adults and children with neuropsychiatric disorders (eg, pervasive developmental disorders) is less strong.

**Adverse effects:** Hangover drowsiness, headache, and transient depression may occur. Melatonin may worsen depression. Theoretically, prion infection caused by products derived from neurologic tissues of animals is a risk.

**Milk Thistle**

Milk thistle is a purple-flowered plant. Its sap and seeds contain the active ingredient silymarin, a potent antioxidant.

**Claims:** Milk thistle is said to treat cirrhosis and to protect the liver from viral hepatitis, the damaging effects of alcohol, and hepatotoxic drugs. In vitro, silymarin increases levels of intrahepatic glutathione, an antioxidant important for detoxification. Well-designed studies do not show that milk thistle significantly benefits people with liver disease, although individual case reports claim fatality reduction in mushroom poisoning.

**Adverse effects:** No serious adverse effects have been reported. Milk thistle may intensify the effects of antihyperglycemic drugs and may interfere with indinavir therapy. Women who have hormone-sensitive conditions (eg, breast, uterine, and ovarian cancer; endometriosis; and uterine fibroids) should avoid the above-ground parts of milk thistle.

**S-Adenosyl-L-Methionine**

S-adenosyl-L-methionine (SAMe) is a derivative of methionine and a cofactor for multiple synthetic pathways. It is produced naturally in the body and is manufactured synthetically in supplement form.

**Claims:** SAMe is said to be effective for treatment of depression, osteoarthritis, and liver disorders, but scientific studies so far do not confirm this claim. More research is needed to verify its efficacy. It is a platelet inhibitor in vitro.

**Adverse effects:** No serious adverse effects have been reported. SAMe is contraindicated in patients with bipolar disorder because SAMe can precipitate manic episodes.

**Saw Palmetto**
Saw palmetto berries contain the plant's active ingredients. The active ingredients, thought to be fatty acids, are unidentified but seem to inhibit 5α-reductase, thus opposing the conversion of testosterone to dihydrotestosterone. The berries can be used to make a tea, or they can be extracted into tablets, capsules, or a liquid preparation. Most formulations evaluated in clinical studies are hexane extracts of saw palmetto berries, which are 80 to 90% essential fatty acids and phytosterols.

**Claims:** Strong scientific evidence supports use of saw palmetto to treat symptoms of benign prostatic hyperplasia (eg, frequent urination); no evidence suggests it reverses the hyperplasia. Also, one large, well-designed study did not show any benefit.

Claims that it increases sperm production, breast size, or sexual vigor are unproved. Dose is 320 mg once/day or 160 mg bid.

**Adverse effects:** Headache and diarrhea may occur, but no other serious adverse effects have been reported. Saw palmetto may interact with estrogens; thus, women who are pregnant or who may become pregnant should not take it.

### St. John's Wort

The flowers of St. John's wort contain its biologically active ingredients hypericin and hyperforin. St. John's wort may increase CNS serotonin and, in very high doses, acts like a monoamine oxidase inhibitor (MAOI).

**Claims:** Study findings are variable, but St. John's wort may benefit patients with mild to moderate depression who have no suicidal ideation. A large, well-designed study found it ineffective in treating major depression.

Dose is 300 to 600 mg po once/day of a preparation standardized to 0.2 to 0.3% hypericin, to 1 to 4% hyperforin, or to both (usually). St. John's wort is also said to be useful for treating HIV infection but has proven adverse interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs). A small trial showed St. John's wort (standardized to hypericin but not hyperforin) did not relieve symptoms of attention-deficit/hyperactivity disorder in children.

**Adverse effects:** Photosensitivity, dry mouth, constipation, dizziness, confusion, and mania (in patients with bipolar disorder) may occur. St. John's wort is contraindicated in pregnant women. Potential adverse interactions occur with cyclosporine, digoxin, iron supplements, MAOIs, NNRTIs, oral contraceptives, protease inhibitors, SSRIs, tricyclic antidepressants, and warfarin.

### Valerian

Valerian's root and rhizomes (underground stems) contain its active ingredients, including valepotriates and pungent odiferous oils.

**Claims:** Valerian is used as a sedative and sleep aid and is especially popular in Europe. In 2 relatively well-designed studies, valerian improved sleep quality and shortened the time needed to fall asleep. However, there is still insufficient clinical data to confirm whether valerian is effective for insomnia.

Some people take valerian for headaches, depression, irregular heartbeat, and trembling. There is not enough scientific evidence to determine whether valerian works for these conditions. It is usually used for short periods of time (4 to 6 wk), and studies suggest that it is generally safe to do so.

**Adverse effects:** Valerian may prolong the effect of other sedatives (eg, barbiturates) and affect driving or other activities requiring alertness.

### Zinc

Zinc, a mineral, is required in small quantities for multiple metabolic processes. Dietary sources include oysters, beef, and fortified cereals.
**Claims:** Some experts believe that when taken soon after cold symptoms develop, zinc taken as zinc gluconate or acetate lozenges can shorten the course of the common cold. Scientific studies are inconsistent, but if zinc has an effect, it probably is small and occurs only when it is taken very soon after cold symptoms develop.

There is stronger evidence that in developing countries, supplements containing zinc 20 mg and iron taken once/wk reduce mortality in infants who have diarrhea and respiratory infection. There is also strong evidence that supplements containing zinc 80 mg and antioxidants taken once/day slow progression of moderate to severe atrophic (dry form) age-related maculopathy in elderly people.

**Adverse effects:** Zinc is generally safe, but toxicity can develop if high doses are used (see p. 55). Common adverse effects of zinc lozenges include nausea, vomiting, diarrhea, mouth irritation, mouth sores, and bad taste. Because zinc is a trace metal and can remove other necessary metals from the body, zinc lozenges should not be taken for more than 14 days. Zinc sprays may cause nose and throat irritation. The effects of certain antibiotics may be lowered by the consumption of zinc supplements.
Chapter 346. Smoking Cessation

Introduction

Nicotine is a highly addictive drug present in tobacco and is a major component of cigarette smoke. This drug stimulates the brain reward system activated during pleasurable activities in a manner similar to that of most other addictive drugs (see p. 1507). People smoke to feed their nicotine addiction but simultaneously inhale thousands of other components, including carcinogens, noxious gases, and chemical additives that are a part of cigarette smoke. These toxic components, rather than nicotine, are responsible for the multiple health consequences of smoking.

Epidemiology

Smoking: The percentage of people in the US who smoke cigarettes has declined since 1964, when the Surgeon General first publicized the link between smoking and ill health. Nevertheless, about 20% of adults still smoke. Smoking is most prevalent among men, people with less than a high school education, people living below the poverty income level, people with psychiatric disorders (including alcohol and substance use), American Indians, and Alaska natives. Smoking is less common among Hispanics and least common among Asian Americans.

Most smokers start during childhood. Children as young as 10 yr experiment with cigarettes. About 31% become addicted before age 16 and over half before age 18, and age of initiation continues to decrease. The younger the age at which smoking starts, the more likely smoking is to continue. Risk factors for childhood initiation include

- Parental, peer, and role model (eg, celebrity) smoking
- Poor school performance
- A poor relationship with parents or a single-parent home
- High-risk behavior (eg, excessive dieting, particularly among girls; physical fighting and drunk driving, particularly among boys)
- Availability of cigarettes
- Poor problem-solving abilities

Complications: Smoking harms nearly every organ in the body and is the leading cause of preventable mortality in the US, accounting for an estimated 435,000 deaths/yr, or about 20% of all deaths. About half of all current smokers die prematurely of a disease directly caused by smoking, losing 10 to 14 yr of life (7 min/cigarette) on average. Most (65%) smoking-attributable deaths are caused by ischemic heart disease, lung cancer, and chronic lung disease; the rest are caused by noncardiac vascular diseases (eg, stroke, aortic aneurysm), other cancers (eg, bladder, cervical, esophageal, kidney, laryngeal, oropharyngeal, pancreatic, stomach, throat), pneumonia, and perinatal conditions (eg, preterm birth, low birth weight, SIDS). In addition, smoking is a risk factor for other conditions that convey significant morbidity and disability, such as acute myelocytic leukemia, frequent URIs, cataracts, reproductive effects (eg, infertility, spontaneous abortion, ectopic pregnancy, premature menopause), peptic ulcer disease, osteoporosis, and periodontitis.

Quitting: About 70% of US smokers say they want to quit and have already tried to quit at least once. More than 70% of smokers present in a primary care setting every year; yet only a minority receive counseling and drugs to help them quit. Most smokers < 18 yr believe they will not be smoking in 5 yr, and 40 to 50% report having tried to quit in the previous year. However, longitudinal studies show that 73% of daily smokers in high school remain daily smokers 5 to 6 yr later.

Passive smoking: Passive exposure to cigarette smoke (secondhand smoke, environmental tobacco smoke) has grave health implications for children and adults. Risks to neonates, infants, and children
include low birth weight, SIDS, asthma and related respiratory illnesses, and otitis media. Children exposed to cigarette smoke lose more school days because of illness than nonexposed children. Smoking-related fires kill 80 children each year and injure almost 300 more; such fires are the leading cause of deaths resulting from unintentional fires in the US. Treating children for smoking-related illnesses is estimated to cost $4.6 billion/yr. In addition, each year, 43,000 children lose one or more caregivers who die from smoking-related diseases.

For adults, passive exposure is linked to the same neoplastic, respiratory, and cardiovascular diseases that threaten active smokers. Overall, secondhand smoke is estimated to be responsible for 50,000 to 60,000 deaths each year in the US (between 2% and 3% of all deaths). These findings have led states and municipalities across the US to ban smoking within workplaces in an effort to protect the health of workers and others from the substantive risks of environmental tobacco smoke. Currently, > 50% of the US population live in a state that has implemented a comprehensive indoor smoke-free ordinance.

Symptoms and Signs

Smoking cessation often causes intense withdrawal symptoms, primarily a craving for cigarettes but also anxiety, depression (mostly mild, sometimes major), inability to concentrate, irritability, restlessness, insomnia, drowsiness, impatience, hunger, tremor, sweating, dizziness, headaches, and digestive disturbances. These symptoms are worst in the first week (when most smokers trying to quit relapse) and subside within 3 to 4 wk in most patients but may continue for months. An average weight gain of 4 to 5 kg is common and is another reason for recidivism. Coughing and oral ulcers may develop temporarily after quitting. Smokers with ulcerative colitis often experience an exacerbation soon after quitting.

Treatment

• Cessation counseling

• Drug treatment (varenicline, bupropion, or a nicotine replacement product) when not contraindicated

Evidence-based counseling and drug treatment are both effective treatments for tobacco dependence; combining counseling and drug treatment is more effective than either intervention alone.

The addiction and withdrawal symptoms are often powerful enough that even with knowledge of the many health risks, many smokers are unwilling to try quitting, and those attempting to quit are often unsuccessful. Only a minority of smokers achieve long-term remission after their initial attempts to quit; many continue to smoke for many years, cycling through multiple periods of relapse and remission. Overall, counseling, drug treatment, or both can boost success rates up to 4 times that achieved by smokers who try to quit on their own (cold turkey) without these treatments.

Smoking has many characteristics of a chronic disorder. Thus, the optimal evidence-based approach to patients, particularly those unwilling to quit or those who have not yet considered quitting, should be guided by the same principles that guide chronic disease management, namely

• Continually assessing and monitoring smoking status

• Using different evidence-based interventions (or combinations) for different patients and building on their prior experiences and treatment preferences

• Although emphasizing that abstinence is the essential goal, encouraging temporary abstinence and reduction in consumption for patients who fall short of total smoking cessation

Although reduction in consumption can increase motivation to quit (particularly when combined with nicotine replacement therapy), smokers should be reminded that reducing the number of cigarettes smoked may not improve health because smokers often inhale more smoke (and thus more toxins) per cigarette to maintain nicotine intake when they reduce the number of cigarettes smoked per day.

Identifying smokers: Effective interventions require first that smokers be consistently identified (eg, by
expanding the vital signs to include smoking status for all patients at every visit).

**Evidence-based counseling:** Counseling efforts begin with the 5 A's:

- Ask at every visit whether a patient smokes and document the response.

- Advise all smokers to quit in clear, strong, personalized language they will understand.

- Assess a smoker's willingness to try quitting within the next 30 days.

- Assist those willing to make a quit attempt by providing brief counseling and drugs.

- Arrange a follow-up, preferably within the first week of the quit date.

For smokers willing to quit, clinicians should establish a quit date, preferably within 2 wk, and stress that total abstinence is better than reduction. Past quitting experiences can be reviewed to identify what helped and what did not, and smoking triggers or challenges to quitting should be planned for in advance. For example, alcohol use is associated with relapse, so alcohol restriction or abstinence should be discussed. In addition, quitting is more difficult with another smoker in the household; spouses and housemates can be encouraged to quit together. In general, smokers should be instructed to develop social support among family and friends for their quit attempt, and clinicians should reinforce their availability and assistance in support of the attempt.

In addition to the brief counseling provided by the patient's clinician, in-person counseling programs can help. They usually use cognitive-behavioral techniques and are offered by various commercial and voluntary health programs. Success rates are higher than with self-help programs. All states in the US have telephone quit lines that can provide counseling support (and sometimes nicotine replacement therapy) to smokers trying to quit. People can call 1-800-QUIT-NOW (1-800-784-8669) toll-free anywhere in the US.

**Drugs:** Effective and safe drugs for smoking cessation include varenicline, bupropion SR, and 5 types of nicotine replacement therapy (in the form of gum, lozenge, patch, inhaler, and nasal spray—see Table 346-1). Bupropion's mechanism may be to increase the brain's release of norepinephrine and dopamine. Varenicline works at the nicotinic acetylcholine receptor (the \(\alpha_4\beta_2\) subunit), where it acts as a partial agonist, having some nicotinic effects, and as a partial antagonist, blocking the effects of nicotine. Some evidence suggests varenicline is the most effective monotherapy available for smoking cessation.

All 7 recommended drugs for smoking cessation are effective as monotherapies, but new research suggests that combination therapy is even more effective; for example, combining the nicotine patch with a shorter-acting nicotine drug (eg, lozenge, gum, nasal spray, inhaler), bupropion, or both is more effective than monotherapy. When used in combination, the patch helps maintain continuous levels, and use of gum, lozenge, inhaler, or nasal spray enables the patient to rapidly increase nicotine levels in response to immediate cravings. In addition, the combination of bupropion with nicotine products may be more effective than any one therapy alone, particularly the combination of bupropion with a nicotine patch and a short-acting nicotine drug.

Smokers may worry that they may remain dependent on nicotine after using nicotine products for smoking cessation; however, such dependence rarely persists. Drug choice is guided by the clinician's familiarity with the drug, patient preference and previous experience (positive or negative), and contraindications.

Despite their proven efficacy, smoking cessation drugs are used by < 25% of smokers attempting to quit. Reasons include low rates of insurance coverage, clinician concerns about the safety of simultaneous smoking and nicotine replacement, and discouragement because of past unsuccessful quit attempts.

Therapies under investigation for smoking cessation include a vaccine that causes nicotine to be intercepted before the nicotine reaches the brain and the drugs selegiline, bromocriptine, and topiramate.

**Drug safety:** Contraindications to bupropion include a history of seizures, an eating disorder, and
monoamine oxidase inhibitor use within 2 wk.

Whether bupropion and varenicline increase risk of suicide is not clear. Varenicline and bupropion may increase risk of serious neuropsychiatric effects and accidents. In 2009, the FDA released a boxed warning for both drugs regarding these possible adverse effects. However, most experts recommend varenicline for most smokers because risks of smoking substantially exceed any possible risks of taking the drug. But varenicline should be avoided in smokers with suicidal risk, unstable psychiatric disorders, and possibly major depression.

Nicotine replacement should be used cautiously in patients with certain cardiovascular risks (those within 2 wk of an MI, with serious arrhythmias, or with serious angina); however, most data suggest that such use is safe. Nicotine gum is contraindicated in patients with temporomandibular joint syndrome, and nicotine patches are contraindicated in patients with severe topical sensitization.

Because of safety concerns, inadequate efficacy data, or both, drugs are not recommended for the following:

- Pregnant smokers
- Light smokers (< 10 cigarettes/day)

[Table 346-1, Drugs for Smoking Cessation]
- Adolescents (< age 18)
- Users of smokeless tobacco

Cessation in children: The counseling approach for children is similar to that for adults; however, drugs are not recommended for patients under the age of 18.

Children should be screened for smoking and risk factors by age 10. Parents should be advised to maintain smoke-free households and to communicate the expectation to their children that the children will remain nonsmokers.

For children who smoke, cognitive-behavioral therapy that involves establishing awareness of tobacco use, providing motivations to quit, preparing to quit, and providing strategies to maintain abstinence after cessation are effective in treating nicotine-dependent patients. Alternative approaches to smoking cessation, such as hypnosis and acupuncture, have not proved to be effective and cannot be recommended for routine use.

Prognosis

About 20 million smokers in the US try to quit each year (almost half of all smokers), usually by using a cold turkey or other nonevidence-based approach, resulting in relapse within days, weeks, or months and a long-term success rate of about 5%. In contrast, success rates of up to 20 to 30% are achieved among smokers who use evidence-based cessation counseling and recommended drugs.

Other Kinds of Tobacco

Cigarette smoking is the most harmful form of tobacco use. However, all tobacco products contain toxins and possible carcinogens and even smokeless tobacco products are not safe alternatives to smoking.

Exclusive pipe smoking is relatively rare in the US (< 1% of people ≥ 12 yr), although it has increased among middle and high school students since 1999. In 2008, about 5.3% of people > 12 yr smoked cigars; this percentage has declined since 2000, people < 18 yr comprise the largest group of new cigar smokers. Risks of pipe and cigar smoking include cardiovascular disease; COPD; cancers of the oral cavity, lung, larynx, esophagus, colon, and pancreas; and periodontal disease and tooth loss.
About 3.3% of people ≥ 18 yr and about 7.9% of high school students use smokeless tobacco (chewing tobacco and snuff). Toxicity of smokeless tobacco varies by brand. Risks include cardiovascular disease, oral disorders (eg, cancers, gum recession, gingivitis, periodontitis and its consequences), and teratogenicity.

**Cessation:** Cessation counseling for smokeless tobacco users, as for cigarette smokers, has been shown to be effective. However, drugs have not proved effective among smokeless tobacco users.

Effectiveness of cessation treatments for pipe and cigar smokers is not well documented. Also, cessation may be affected by whether cigarettes are smoked concurrently and whether smokers inhale.
Chapter 347. Medical Aspects of Travel

Introduction

Planning and preparation reduce medical risks of travel. Travelers should carry their drugs, extra eyeglasses or other corrective lenses (as well as a current written prescription for either), and hearing-aid batteries in a carry-on bag in case their checked baggage is delayed, lost, or stolen. Drugs should be kept in their original labeled containers. Travelers who need to carry opioids, syringes, or large amounts of drugs should have a prescription or verifying letter from a physician to avoid possible security or customs complications. A medical record summary (including ECG for those with significant cardiac history) is invaluable if a traveler becomes ill. Travelers subject to disabling illness (eg, epilepsy) or those with chronic disease should wear a medical identification bracelet or necklace.

Air Travel

Air travel can cause or worsen certain medical problems; some are considered a contraindication to flight (see Table 347-1), and others may cause discomfort. Serious complications are rare.

During a flight, any health care practitioner among the passengers may be asked to help fellow passengers who become ill. Additionally, most commercial aircrafts carry first-aid equipment, including an automatic external cardioverter defibrillator and limited medical supplies. Airline personnel are receiving more first-aid training now than in the past. Although physicians aiding ill or injured passengers are usually protected from litigation by the Good Samaritan concept, they should avoid practicing beyond their training or expertise.

Further information about air travel may be obtained from the medical department of major airlines, the Federal Aviation Administration (www.faa.gov), online travel information sources, or local travel clinics.

Barometric pressure changes: Commercial airplanes and jet aircraft are pressurized only to the equivalent of an altitude of 6000 to 8000 ft (1830 to 2440 m), not to sea level pressure. Thus, air in body cavities or other closed spaces expands by about 25%; this expansion may aggravate certain medical conditions.

Untreated dental problems or recent dental procedures may become painful when air pressure changes. People with upper respiratory inflammation or allergic rhinitis may develop obstructed eustachian tubes, which may cause barotitis media, or obstructed sinus ostia, which may cause barosinusitis. Frequent yawning or closed-nose swallowing during descent, use of decongestant nasal sprays, or use of antihistamines before or during flight often prevents or relieves these conditions. Some people suck on hard candies during descent.

Air travel is contraindicated for patients who have or are likely to develop pneumothorax (eg, those who have large pulmonary blebs or cavities) and for those in whom air or gas is trapped (eg, those who have an incarcerated bowel, those traveling < 10 days after chest or abdominal surgery, those who have intraocular gas injection) because even modest expansion may cause pain or tissue damage.

Water should be substituted for air in devices secured by air-filled cuffs or balloons (eg, feeding tubes, urinary catheters). Patients with a colostomy should wear a large bag and expect frequent filling due to expansion of intestinal gas.

Children: Children are particularly susceptible to barotitis media and should be given fluids or food during descent to encourage swallowing, which can equalize pressures. Infants can be breastfed or given a bottle or pacifier. Precautions for children with chronic disease (eg, congenital heart disease, chronic lung disease, anemia) are the same as those for adults.
Circadian dysrhythmia (jet lag): Rapid travel across multiple time zones disrupts the normal circadian rhythm (see also p. 1710). Bright sunlight resets the internal clock. Exposure to bright late-afternoon or evening light delays the onset of normal sleep time, and exposure to early-morning light advances the biologic clock, so that sleep time is earlier than usual. Thus, managing exposure to light can help adaptation, particularly on the days after arrival in a new time zone. For example, people traveling westward could maximize exposure to bright afternoon light to help delay sleep time. People traveling eastward could maximize exposure to bright light in the early morning to help awakening and promote earlier sleep.

Short-acting hypnotics (see Table 177-6 on p. 1709) may help people fall asleep at the appropriate local time after eastward travel. However, hypnotics may have adverse effects, such as daytime drowsiness, amnesia, and nighttime insomnia. Long-acting hypnotics increase the likelihood of confusion and falls among the elderly and should be avoided. Melatonin, a hormone secreted by the pineal gland, may provide a time-of-night cue; however, large placebo-controlled trials showing melatonin's safety and efficacy are lacking (see p. 3430). Taking melatonin (0.5 to 5 mg po before the desired sleep time) may help those who need to go to sleep earlier because they have traveled east across several time zones. Some therapeutic regimens must be altered to compensate for circadian dysrhythmia. For example, insulin dosage and timing may require modification depending on the number of time zones traversed, time spent at destination, available food, and activity; glucose must be monitored frequently. Target plasma glucose levels should be increased; because so many changes affect levels, tight control is more difficult, and the risk of hypoglycemia is increased. Regimens may require modification based on elapsed rather than local time.

Decreased \(O_2\) tension: In passenger jets at cruising altitude, with a typical 8000 ft (2440 m) cabin altitude, the partial pressure of \(O_2\) is about 25% less than at sea level, which, because of the \(O_2\)-Hb dissociation curve, represents a drop in arterial \(O_2\) saturation of only about 4.4%. This decrease may be significant for people with severe heart or lung disease (see Table 347-1) but is harmless to most people; however, after 3 to 9 h at that altitude equivalent, some people report discomfort (eg, headache, malaise). In general, anyone who can walk 50 m or climb one flight of stairs and whose disease is stable can tolerate normal passenger jet cabin conditions without additional \(O_2\). However, problems may arise for travelers with moderate or severe pulmonary disease (eg, asthma, COPD, cystic fibrosis), heart failure, anemia with Hb < 8.5 g/dL, severe angina pectoris, sickle cell disease (but not trait), and some congenital heart diseases. When flying is essential, such patients can usually fly safely with specially designed continuous \(O_2\) equipment, which must be provided by the airline. Mild ankle edema due to venous stasis commonly develops during long flights and should not be confused with heart failure.

Smoking can aggravate mild hypoxia and should be avoided before flying. Hypoxia and fatigue may increase the effects of alcohol.

Low cabin humidity: Dehydration may develop because of very low cabin humidity. It can be avoided with adequate fluid intake and alcohol avoidance. Contact lens wearers and people with dry eyes should instill artificial tears frequently to avoid corneal irritation resulting from low cabin humidity.

Motion sickness: Motion sickness is often triggered by turbulence and vibration and is made worse by warmth, anxiety, hunger, or overeating (see also p. 3278). Symptoms may include nausea, vomiting, sweating, and vertigo. Motion sickness can be minimized before and during travel by moderating intake of food, fluids, and alcohol. Fixing the eyes on a stationary object or on the horizon can help, as can lying down and keeping the eyes closed. Other measures include choosing a seat where motion is felt least (eg, in the center of an airplane, over the wing), refraining from reading, and using an air vent. Scopolamine patch or an OTC or prescription antihistamine is often useful, especially if taken before travel. However, these drugs can cause drowsiness, dry mouth, confusion, falls, and other problems in the elderly.

Pregnancy: Uncomplicated pregnancy through 36 wk is not a contraindication to air travel; high-risk pregnancies must be individually evaluated. Flight during the 9th mo usually requires a physician's written
approval dated within 72 h of departure and indicating expected delivery date. However, policies may vary by airline. Seat belts should be worn below the abdomen, across the hips.

To prevent effects on development of the fetal thyroid, pregnant women should avoid prolonged use of water purification tablets that contain iodine. If possible, pregnant women should avoid travel to areas where malaria is endemic because malaria can be more virulent in pregnant women, and the safety of all antimalarial prophylactic drugs during pregnancy has not been fully studied. When traveling, pregnant women should be particularly careful about following safe food guidelines and hand washing.

**Psychologic stress:** Hypnosis and behavior modification benefit some people with fear of flying or claustrophobia. Fearful passengers may also benefit from a short-acting anxiolytic (eg, zolpidem, alprazolam) taken before and, depending on duration, during flight. Hyperventilation commonly simulates heart disease and may cause tetany-like symptoms; anxiety and hyperventilation can cause panic, paranoia, and a sense of impending death. Psychotic tendencies may become more acute and troublesome during flight. Patients with violent or unpredictable tendencies must be accompanied by an attendant and appropriately sedated.

**Restricted mobility:** Deep venous thrombosis may develop in anyone sitting for long periods and may result in a pulmonary embolus. Risk factors include those for non-altitude-related deep venous thrombosis (eg, prior deep venous thrombosis, pregnancy, use of oral contraceptives). Frequent (every 1 to 2 h) ambulation, short-movement exercises while seated, and adequate hydration are recommended; however, studies showing benefit from these measures are lacking.

**Turbulence:** Turbulence may cause motion sickness or injury. While seated, passengers should keep their seat belts fastened at all times.

**Other issues:** Most implanted cardiac devices, including pacemakers and cardioverter defibrillators, are effectively shielded from interference from security devices. However, the metal content of some of these devices, as well as certain orthopedic prostheses and braces, may trigger a security alarm. A physician’s letter should be carried to avoid security difficulties.

People with specific dietary and medical needs should plan carefully and carry their own food and supplies. With several days’ notice, all airlines departing from or arriving in the US (and most others) can make reasonable efforts to accommodate passengers with physical handicaps and special needs, including those who require O₂ therapy. Wheelchairs can be accommodated on all US airlines and most foreign ones, but advance notice is advisable. Some airlines accept passengers requiring more highly specialized equipment (eg, IV fluids, respirators) provided that appropriate personnel accompany the passenger and arrangements have been made in advance. If travelers cannot be accommodated on a commercial aircraft because of severe illness, air ambulance service is necessary.

**Foreign Travel**

About 1 in 30 people traveling abroad requires emergency care. Illness in a foreign country may involve significant difficulties. Many insurance plans, including Medicare, are not valid in foreign countries; overseas hospitals often require a substantial cash deposit for nonresidents, regardless of insurance. Travel insurance plans, including some that arrange for emergency evacuation, are available through commercial insurance agents, travel agencies, and some major credit card companies. Directories listing English-speaking physicians in foreign countries, US consulates who may assist in obtaining emergency medical services, and information about foreign travel risks are available (see Table 347-2). Patients with serious disorders should consider pretravel contact or arrangements with an organization that offers medically supervised evacuation from foreign countries. Certain infections are common when traveling to certain areas.

**Vaccinations:** Some countries require specific vaccinations (see Table 347-3).

[Table 347-2. Useful Contacts for People Traveling Abroad]
travel and up-to-date immunization information and malaria chemoprophylaxis requirements are available from the Centers for Disease Control and Prevention (CDC) malaria hotline and web site (see also the CDC recommendations, Travelers' Health: Vaccinations and Malaria: Malaria and Travelers).

**Injury and death:** Road traffic accidents are the most frequent cause of death of nonelderly international travelers. Travelers should use seat belts in vehicles and a helmet when cycling. Travelers should avoid motorcycles and mopeds and avoid riding on bus roofs or in open truck beds. To prevent drowning (another common cause of death while abroad), travelers should avoid beaches with turbulent surf and avoid swimming after drinking alcoholic beverages.

**Traveler’s diarrhea:** Traveler's diarrhea (TD—see also p. \(150\)) is the most common health problem among international travelers. TD is usually self-limited, typically resolving in 5 days; however, 3 to 10% of travelers with TD may have symptoms lasting > 2 wk, and up to 3% of travelers have TD lasting > 30 days. TD lasting < 1 wk requires no testing. For persistent TD, laboratory testing is done (see p. \(90\)).

Self-initiated treatment is indicated for moderate to severe symptoms (≥ 3 unformed stools over 8 h), especially if vomiting, fever, abdominal cramps, or blood in the stool are present. Treatment is with an appropriate antibiotic (eg, a fluoroquinolone for most destinations, a macrolide such as azithromycin for Southeast Asia). Additional measures include loperamide (except in patients with fever, bloody stools, or abdominal pain and in children < 2 yr); replacement of fluids; and, in the elderly and small children, electrolytes (eg, oral rehydration solution).

Measures that may decrease the risk of TD include

- Drinking and brushing teeth with bottled, filtered, boiled, or chlorinated water
- Avoiding ice
- Eating freshly prepared foods only if they have been heated to steaming temperatures
- Eating only fruits and vegetables that travelers peel or shell themselves
- Avoiding food from street vendors
- Washing hands frequently
- Avoiding all foods likely to have been exposed to flies

Prophylactic antibiotics (eg, fluoroquinolones) are effective in preventing diarrhea, but because of concerns about adverse effects and development of resistance, they should probably be reserved for immunocompromised patients.

**Schistosomiasis:** Schistosomiasis is common and is caused by exposure to still water in Africa, Southeast Asia, China, and eastern South America. Schistosomiasis can be prevented by wearing footwear and socks when walking through water and by avoiding freshwater activities in areas where schistosomiasis is common (see p. \(1358\)).

**Problems after returning home:** Persistent TD is the most common medical problem after

[Table 347-3. Vaccines for International Travel*†]

travel. Malaria (see p. \(1381\)), hepatitis A and B (see p. \(246\)), typhoid fever (see p. \(1259\)), sexually transmitted diseases (see p. \(1466\)), including HIV infection (see p. \(1438\)), amebiasis (see p. \(1367\)), and meningitis (see p. \(1734\)) are the most commonly acquired potentially serious diseases. People can also acquire lice (see p. \(711\)) and scabies (see p. \(713\)) after being in crowded living conditions or places where hygienic measures are poor.
Some diseases become evident months after a traveler has returned home; a travel history with exposure risks is a useful diagnostic clue when patients present with a puzzling illness. The International Society of Travel Medicine (www.istm.org) and the American Society of Tropical Medicine and Hygiene (www.astmh.org) have lists of travel clinics on their web sites. Many of these clinics specialize in assisting travelers who are ill after their return home.
Chapter 348. Syndromes of Uncertain Origin

Introduction

Many patients have syndromes for which no specific cause has been identified. Some physicians think that some of these syndromes have psychologic causes, but many physicians and most patients with one of these syndromes reject that idea. Some data—often incomplete, inconsistent, or contradictory—suggest a physical cause, although the exact cause remains uncertain. The causative or contributory role of psychologic factors is also uncertain.

Some patients have scattered, apparently unrelated symptoms that do not form a recognizable syndrome. With better definitions, case recognition may improve; further study of patients with such symptoms is needed to clarify symptom etiology and the clinical significance of these syndromes, to develop appropriate diagnostic strategies, and to define optimum care.

The evaluating physician's first responsibility is to obtain a thorough history, including history of exposure to potentially noxious substances, and to exclude specific, potentially treatable alternative diagnoses. Early stages of known disorders and atypically manifesting common disorders should be considered first. Often, there is little guidance as to what testing is appropriate, but the physician must avoid tests that are inappropriate or not clearly indicated. If no treatable cause is identified after the evaluation, supportive, empathic follow-up is required. A physician should be aware that many patients with such syndromes turn to complementary and alternative medical practices (see p. 3411) in their search for relief.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is defined as longstanding, severe, disabling fatigue without demonstrable muscle weakness. Underlying disorders that could explain the fatigue are absent. Depression, anxiety, and other psychologic diagnoses are typically absent. Treatment is psychologic support, often including antidepressants, and limited rest.

This definition of CFS has several variants, and heterogeneity among patients who meet the criteria of this definition is considerable. Prevalence is impossible to state precisely; it is usually estimated to be between 7 and 38/100,000 people. However, a recent telephone survey found the prevalence to be many times higher. Prevalence estimates may vary because of differences in diagnostic evaluation, physician-patient attitudes, social acceptability, risk of exposure to an infectious or toxic agent, or definition and case finding. CFS occurs slightly more often in women. In office-based studies, prevalence is highest among whites. However, community surveys indicate a higher prevalence among blacks, Hispanics, and American Indians than among whites.

Etiology

Etiology is controversial, and the precise cause remains unknown. Psychologic factors may be the cause in an unknown percentage of cases; however, CFS seems to be distinct from typical depression, anxiety, or other psychologic disorders. A chronic viral infection has been proposed as a cause because many patients relate onset of CFS to an acute bout of Lyme disease, mononucleosis, influenza, Q fever, Ross River virus, parvovirus, and other infectious diseases. Epstein-Barr virus has also been proposed as a cause, but immunologic markers of exposure do not appear to be sensitive or specific. Other possible but unproven viral causes include rubella, HIV, enteroviruses, human herpesvirus 6, and human T-cell lymphotropic virus. Allergic reactions have also been proposed; about 65% of patients report previous allergies, and the rate of cutaneous reactivity to inhalants or foods is 25 to 50% higher in this group than in the general population.

Various immunologic abnormalities have been reported. They include low levels of IgG, decreased lymphocytic proliferation, low interferon-γ levels in response to mitogens, and poor cytotoxicity of natural killer cells. Some patients have abnormal IgG, with circulating autoantibodies and immune complexes. Many other immunologic abnormalities have been studied; none provides adequate sensitivity and specificity for defining CFS. Additionally, no consistent or readily reproducible pattern of immunologic abnormalities has been identified.
Other proposed mechanisms include neuroendocrine abnormalities, abnormal levels of neurotransmitters, inadequate cerebral circulation, prolonged bed rest, undernutrition, and elevated levels of ACE.

Data indicate that relatives of patients with CFS have an increased risk of developing the syndrome, suggesting a familial or genetic component.

Some researchers believe the syndrome ultimately will prove to have multiple causes, including genetic predisposition and exposure to microbial agents, toxins, and other physical and emotional traumas.

**Symptoms and Signs**

Onset is usually abrupt, and many patients report an initial viral-like illness with swollen lymph nodes, extreme fatigue, fever, and upper respiratory symptoms. The main symptom is severe fatigue (usually for ≥ 6 mo) that interferes with daily activities (see Table 348-1 for usual symptoms and signs).

Usually, no signs of muscle weakness, arthritis, neuropathy, or organomegaly are present. However, some definitions require the presence of low-grade fever, nonexudative pharyngitis, or palpable or tender lymph nodes.

**Diagnosis**

- Clinical criteria

[Table 348-1, Diagnostic Criteria for Chronic Fatigue Syndrome]

Because there is no definitive diagnostic test, diagnosis is by clinical criteria (see Table 348-1). However, because multiple definitions exist, the criteria are not agreed on universally and should not always be strictly applied to individual patients. The criteria are more useful for epidemiologic and clinical studies than for excluding the diagnosis in individual patients. Further evaluation aims to exclude treatable disorders. A reasonable assessment includes CBC and measurement of electrolytes, ESR, and thyroid-stimulating hormone. In some cases, chest x-ray and tests for antinuclear antibody, rheumatoid factor, hepatitis, and HIV should be added. Other viral antibody and other expensive tests are unlikely to shed light on the diagnosis or cause. Obvious depression or severe anxiety excludes the diagnosis of CFS.

**Treatment**

- Sometimes nonsedating antidepressants
- Sometimes psychologic intervention, physical rehabilitation, and/or regular exercise
- Avoidance of prolonged rest

Nonsedating antidepressants are commonly prescribed, although their value is undetermined. Antiviral treatments with acyclovir and amantadine do not seem effective. Valganciclovir is under study. Studies of immunologic treatments, including high-dose immune globulins, dialyzable WBC extract, amphigen, interferons, isoprinosine, and corticosteroids, have been inconclusive and mostly disappointing. Dietary supplements and high-dose vitamins are commonly used, but their usefulness has not been substantiated.

Psychologic intervention (eg, individual or group therapy) may help some patients, as may formal, structured physical rehabilitation programs. Regular aerobic exercise (eg, walking, swimming, cycling, jogging) under close medical supervision may reduce fatigue and improve physical function.

Persistent or prolonged rest should be firmly discouraged because it can worsen deconditioning and promote progressive frailty.
Symptoms tend to lessen over time.

**Multiple Chemical Sensitivity Syndrome**

(Idiopathic Environmental Intolerance)

Multiple chemical sensitivity syndrome is characterized by recurrent, nonspecific symptoms attributed to low-level exposure to chemically unrelated substances commonly occurring in the environment. Symptoms are numerous, often involving multiple organ systems, but physical findings are unremarkable. Diagnosis is by exclusion. Treatment is psychologic support and avoidance of perceived triggers, although triggers rarely can be defined.

No universally accepted definition exists, but multiple chemical sensitivity syndrome is generally defined as the development of multiple symptoms attributed to exposure to any number of identifiable or unidentifiable chemical substances (inhaled, touched, or ingested) in the absence of clinically detectable organ dysfunction or related physical signs.

**Etiology**

**Triggers:** Reported triggers for multiple chemical sensitivity include

- Alcohol and drugs
- Caffeine and food additives
- Carpet and furniture odors
- Fuel odors and engine exhaust
- Painting materials
- Perfume and other scented products
- Pesticides and herbicides

**Mechanism:** Many theories—immunologic and nonimmunologic—have been proposed. These theories are all hampered by lack of a consistent dose response to proposed causative substances; ie, symptoms may not be replicated after exposure to high levels of a substance that previously, at much lower levels, seemed to provoke a reaction. Similarly, consistent objective evidence of systemic inflammation, cytokine excess, or immune system activation in relation to symptoms is lacking. Many physicians consider the etiology to be psychologic, probably a form of somatization disorder (see p. 1577). Others suggest that the syndrome is a type of panic attack (see p. 1496) or agoraphobia. Some facets of the syndrome resemble the no-longer-used psychologic diagnosis of neurasthenia.

Multiple chemical sensitivity syndrome develops in 40% of people with chronic fatigue syndrome and in 16% of people with fibromyalgia.

Although measurable biologic abnormalities (eg, decreased levels of B cells, elevated levels of IgE) are rare, some patients have such abnormalities. However, these abnormalities appear without a consistent pattern, and their significance is uncertain.

**Symptoms and Signs**

Symptoms (eg, palpitations, chest pain, sweating, shortness of breath, fatigue, flushing, dizziness, nausea, choking, trembling, numbness, coughing, hoarseness, difficulty concentrating) are numerous and usually involve more than one organ system. Most patients present with a long list of suspected agents, self-identified or identified by a physician during previous testing. Such patients often go to great lengths...
to avoid these agents by changing residence and employment, avoiding all foods containing "chemicals," sometimes wearing masks in public, or avoiding public settings altogether. Physical examination is characteristically unremarkable.

**Diagnosis**

Diagnosis initially involves exclusion of demonstrable allergies and other known disorders with similar manifestation (eg, atopic disorders such as asthma, allergic rhinitis, food allergies, and angioedema). Atopic disorders are excluded based on a typical clinical history, skin-prick testing, serum assays of specific IgE, or all 3. Consultation with an allergy specialist may be necessary. Building-related illnesses, including sick building syndrome, in which many people who spend time in the same building develop symptoms (see p. 1976), should be considered.

**Treatment**

Despite an uncertain cause-and-effect relationship, treatment is usually aimed at avoiding the suspected precipitating agents, which may be difficult because many are ubiquitous. However, social isolation and costly and highly disruptive avoidance behaviors should be discouraged.

Psychologic evaluation and intervention may help, but characteristically many patients resist this approach. However, the point of this approach is not to show that the cause is psychologic but rather to help patients cope with their symptoms.

**Gulf War Syndrome**

**Gulf War syndrome is a group of symptoms experienced by > 100,000 American, British, and Canadian veterans of the 1991 Persian Gulf War.**

Within a few months of returning from the Persian Gulf, veterans from different military units in the US, Britain, and Canada began reporting various unexplained symptoms, including headache, fatigue, difficulty sleeping, joint pain, chest pain, rashes, and diarrhea. In most cases, however, objective evidence of abnormalities was lacking. Even when symptoms such as a rash, could be confirmed, no specific cause could be identified.

The cause of Gulf War syndrome is unknown. Gulf War veterans often have been exposed to a number of potentially toxic substances, including chemical weapons, depleted uranium weapons, insecticides, and smoke from burning oil wells. Veterans may also have been exposed to irritant petroleum products, decontamination solutions, and a variety of airborne substances that may have caused allergies. Vaccination with the anthrax vaccine, which was given to US military personnel involved in the Gulf War as protection against biological warfare, has also been proposed as a cause, although this vaccine has not caused symptoms in other recipients. The use of pyridostigmine tablets to help prevent the lethal effects of chemical weapons has been suggested as a possible cause as well. However, none of these agents has been linked convincingly to Gulf War syndrome; many exposed people have been asymptomatic, and many symptomatic people have had no identifiable exposure.

Symptoms predominantly involve the nervous system. They include problems with memory, reasoning, concentration, and attention; difficulty falling asleep; depression; fatigue; and headache. Other symptoms may include disorientation, dizziness, erectile dysfunction (impotence), myalgias, fatigue, weakness, paresthesias, diarrhea, rashes, cough, and chest pain.

Diagnosis and treatment have not been established; therefore, the aim is to relieve symptoms.

Veterans who have Gulf War syndrome do not have a higher hospitalization or death rate than anyone else of the same age.
Chapter 349. Care of the Surgical Patient

Introduction

Care of surgical patients often involves nonsurgical consultants (eg, primary care physicians, specialists), who may be asked to provide preoperative risk assessment (sometimes requested as medical clearance), suggest ways to minimize perioperative risks (eg, deep venous thrombosis, endocarditis), and manage complex medical conditions. Psychiatric consultation may be needed to assess capacity or help deal with underlying psychiatric problems that can interfere with recovery. Elderly patients may benefit from involvement of an interdisciplinary geriatric team (see p. 3115), which may need to involve social workers, therapists, ethicists, and other practitioners.

Preoperative Evaluation

If an emergency procedure is required, preoperative evaluation must be rapid and is thus limited. In other cases, the surgical team may consult an internist to obtain a formal preoperative evaluation, which helps minimize risk by identifying correctable abnormalities and by determining whether additional monitoring is needed or whether a procedure should be delayed so that an underlying disorder (eg, hypertension, hyperglycemia, hematologic abnormalities) can be controlled optimally.

Routine preoperative evaluation varies substantially from patient to patient, depending on the patient's age, general health, and risks of the procedure.

History: A relevant preoperative history includes information about all of the following:

• Current symptoms suggesting an active cardiopulmonary disorder (eg, cough, chest pain, dyspnea during exertion, ankle swelling) or infection (eg, fever, dysuria)

• Risk factors for thromboembolism (see p. 2224), excessive bleeding (see p. 968), or infection

• Known disorders that increase risk of complications, particularly hypertension, heart disease, kidney disease, liver disease, diabetes, asthma, COPD, and bleeding disorders

• Previous surgery, anesthesia, or both, particularly their complications

• Allergies

• Tobacco and alcohol use

• Current prescription and nonprescription drug and supplement use

If an indwelling catheter may be needed, patients should be asked about prior urinary retention and prostate surgery.

Physical examination: Physical examination should include not only areas affected by the surgical procedure but also the cardiopulmonary system and a search for any signs of ongoing infection (eg, upper respiratory tract, skin). When spinal anesthesia is likely, patients should be evaluated for scoliosis and other anatomic abnormalities that may complicate lumbar puncture. Any cognitive dysfunction, especially in elderly patients who will be given a general anesthetic, should be noted. Preexisting dysfunction may become more apparent postoperatively and, if undetected beforehand, may be misinterpreted as a surgical complication.

Testing: No preoperative tests are required in healthy patients undergoing operations with very low risk of significant bleeding or other complications; abnormal results are more likely to be false positives than in patients with symptoms or risk factors. In symptomatic patients or in patients undergoing operations with a higher risk of significant bleeding or other complications, laboratory evaluation may include the following tests:
• CBC and urinalysis (glucose, protein, and cells) usually are done.

• Serum electrolytes and creatinine and plasma glucose are measured unless patients are extremely healthy and < 50, the procedure is considered very low risk, and use of nephrotoxic drugs is not expected.

• Liver enzymes are measured if abnormalities are suspected based on the patient's history or examination.

• Coagulation studies and bleeding time are needed only if patients have a history of bleeding diathesis or a disorder associated with bleeding.

• ECG is done for patients at risk of coronary artery disease, including all men > 45 and women > 55.

• If a general anesthetic is to be used, a chest x-ray typically is done (or a recent x-ray is reviewed), although its usefulness is limited, particularly in younger patients and in patients without suspicion of heart or lung disease.

• Pulmonary function testing may be done if patients have a known chronic pulmonary disorder or symptoms or signs of pulmonary disease.

Patients with symptomatic coronary artery disease need additional tests (eg, stress testing, coronary angiography) before surgery.

**Surgical risk factors:** Surgical risk varies with patient risk factors and the procedure.

**Procedural risk** is highest with the following:

• Heart or lung surgery

• Prostatectomy

• Major orthopedic procedures (eg, hip replacement)

Patients undergoing elective surgery that has a significant risk of hemorrhage should consider autologous transfusion (see p. 1037). Autologous transfusion decreases the risks of infection and transfusion reactions. Emergency surgery also has a higher risk of morbidity and mortality.

**Patient risk factors** are stratified by some clinicians using published criteria (see Table 349-1). Older age is associated with decreased physiologic reserve and greater morbidity if a complication occurs. However, chronic disorders are more closely associated with increased postoperative morbidity and mortality than is age alone. Older age is not an absolute contraindication to surgery.

**Cardiac risk factors** dramatically increase surgical risk. Among the most serious are the following:

• Unstable angina

• Recent MI

• Poorly controlled heart failure

When a heart disorder cannot be corrected before surgery, intraoperative and sometimes preoperative monitoring with pulmonary artery catheterization may be advised.

**Incidental infections** (eg, UTIs) should be treated with antibiotics but should not delay surgery unless prosthetic material is being implanted; in such cases, incidental infections should be controlled or eliminated before surgery if possible.
Fluid and electrolyte imbalance should be corrected before surgery if possible. Dehydration should be treated with IV normal saline because BP tends to fall when anesthesia is induced. K deficiencies should be corrected to reduce risk of arrhythmias.

Undernutrition (see p. 9) increases surgical risk. For example, serum albumin < 2.8 g/dL is associated with increased morbidity and mortality. If surgery can be delayed for several weeks, sometimes nutritional deficiencies are correctable. Usually, the patient's calorie and protein intake should be increased during the perioperative period. Obesity is unlikely to be correctable in the time available.

**Perioperative Management**

Usually, an anesthesiologist reviews a patient's drugs and stipulates which ones should be taken on the day of surgery. Such a review

*Table 349-1. Cardiac Risk Index in Noncardiac Surgery*

...is necessary because some drugs interact with general anesthetics.

**Diabetes:** On the day of surgery, patients with insulin-dependent diabetes are typically given one third of their usual insulin dose in the morning. Those who take oral drugs are given half of their usual dose. If possible, surgery is done early in the day. The anesthesiologist monitors plasma glucose during surgery and gives additional insulin or dextrose as needed. Close monitoring with fingerstick testing continues throughout the perioperative period.

**Corticosteroids:** Patients who are taking corticosteroids (mineralocorticoids or glucocorticoids) or have taken them within the previous 3 to 6 mo should be given supplemental doses of these drugs in case perioperative stress (eg, fluid shifts, hypotension) causes adrenal suppression.

**Anticoagulants and antiplatelets:** Anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin) are usually stopped 5 to 7 days before surgery. However, if the procedure has a low risk of bleeding, an anticoagulant may be continued even on the day of the procedure, although the risk of postoperative bleeding slightly increases.

**Other drugs that control chronic disorders:** Most drugs taken to control chronic disorders, especially cardiovascular drugs (including antihypertensives), should be continued throughout the perioperative period. Most oral drugs can be given with a small sip of water on the day of surgery. Others may have to be given parenterally or delayed until after surgery. Anticonvulsant levels should be measured preoperatively in patients with a seizure disorder.

**Drug dependence:** Patients who are dependent on drugs or alcohol may experience withdrawal during the perioperative period. Alcoholics should be given prophylactic benzodiazepines (eg, chlor Diazepoxide, diazepam, lorazepam) starting at admission. Opioid addicts may be given opioid analgesics to prevent withdrawal; for pain relief, they may require larger doses than patients who are not addicted. Rarely, opioid addicts require methadone to prevent withdrawal during the perioperative period.

**Smoking:** Smokers are advised to stop smoking as early as possible before any procedure involving the chest or abdomen. Several weeks of smoking cessation are required for ciliary mechanisms to recover. An incentive inspirometer should be used before and after surgery.

**Upper airway:** Before intubation, dentures must be removed. Ideally, before patients are moved from the preanesthetic holding area, they should give dentures to a family member. Patients with a deviated septum or another airway abnormality should be evaluated by an anesthesiologist before surgery requiring intubation.

**Preprocedural checklist:** In the operating room, before the procedure begins, a time out is held during which the team confirms several important factors:
Outpatient Procedures

Many surgical procedures are done in outpatient settings. Patients are evaluated (eg, with laboratory tests—see p. 3445) one to several days before the procedure.

**Preparation:** The general rule is for patients to have no oral intake after midnight the night before surgery. For certain GI procedures, cleansing enemas or oral solutions must be started 1 to 2 days before surgery. When prophylactic antibiotics are needed before a procedure, the initial dose must be given within 1 h before the surgical incision.

**Discharge precautions:** Before discharge, patients should be free of severe pain and should be able to think clearly, breathe normally, drink, walk, and urinate.

If sedatives (eg, opioids, benzodiazepines) were used during an outpatient procedure, patients should not leave the hospital unaccompanied. Even after anesthetic effects have apparently worn off and patients feel fine, they are likely to be weak and have subtle residual effects that make driving inadvisable; many patients require opioids for pain. Elderly patients may be temporarily disoriented because of the combined effects of anesthesia and surgical stress and may develop urinary retention caused by immobility and anticholinergic drug effects.

Antibiotic Prophylaxis

Most surgical procedures do not require prophylactic or postoperative antibiotics. However, certain patient-related and procedure-related factors alter the risk-benefit ratio in favor of prophylactic use.

Patient-related factors include certain valvular heart disorders and immunosuppression. Procedures with higher risk involve areas where bacterial seeding is likely:

- **Mouth**
- **GI tract**
- **Respiratory tract**
- **GU tract**

In so-called clean (likely to be sterile) procedures, prophylaxis generally is beneficial only when prosthetic material or devices are being inserted or when the consequence of infection is known to be serious (eg, mediastinitis after coronary artery bypass grafting).

Drug choice is based on the bacteria most likely to contaminate the wound during a specific procedure. For commonly recommended regimens by procedure, see Table 349-2. Prophylaxis requires that the appropriate antibiotic is given within 1 h before the procedure. Antibiotics may be given orally or IV, depending on the procedure. The need for additional doses after the procedure is controversial, but for clean operations, no additional doses are needed. Postoperative antibiotics are continued > 24 h only when an active infection is detected during surgery; antibiotics are then considered treatment, not prophylaxis.

Postoperative Care
Postoperative care begins in the recovery room and continues throughout the recovery period. Critical concerns are airway clearance, pain control, mental status, and wound healing. Other important concerns are preventing urinary retention, constipation, deep venous thrombosis, and BP variability (high or low). For patients with diabetes, plasma glucose levels are monitored closely by fingerstick testing every 1 to 4 h until patients are awake and eating because better glycemic control improves outcome.

**Airway:** Most patients are extubated before leaving the operating room and soon become able to clear secretions from their airway. Patients should not leave the recovery room until they can clear and protect their airway (unless they are going to an ICU). After intubation, patients with normal lungs and trachea may have a mild cough for 24 h after extubation; for smokers and patients with a history of bronchitis, postextubation coughing lasts longer. Most patients who have been intubated, especially smokers and patients with a lung disorder, benefit from an incentive inspirometer.

**Table 349-2. Antimicrobial Preoperative Prophylaxis Guidelines**

Postoperative dyspnea may be caused by pain secondary to chest or abdominal incisions (nonhypoxic dyspnea) or by hypoxemia (hypoxic dyspnea—see also p. 2250). Hypoxemia secondary to pulmonary dysfunction is usually accompanied by dyspnea, tachypnea, or both; however, oversedation may cause hypoxemia but blunt dyspnea, tachypnea, or both. Thus, sedated patients should be monitored with pulse oximetry or capnometry. Hypoxic dyspnea may result from atelectasis or, especially in patients with a history of heart failure or chronic kidney disease, fluid overload. Whether dyspnea is hypoxic or nonhypoxic must be determined by pulse oximetry and sometimes ABGs; chest x-ray can help differentiate fluid overload from atelectasis.

Hypoxic dyspnea is treated with oxygen. Nonhypoxic dyspnea may be treated with anxiolytics or analgesics.

**Pain:** Pain control may be necessary as soon as patients are conscious (see p. 1623). Opioids are typically the first-line choice and can be given orally or parenterally. Often, oxycodone/acetaminophen 1 or 2 tablets (each tablet can contain 2.5 to 10 mg oxycodone and 325 to 650 mg acetaminophen) po q 4 to 6 h or morphine 2 to 4 mg IV q 3 h is given as a starting dose, which is subsequently adjusted as needed; individual needs and tolerances can vary several-fold. With less frequent dosing, breakthrough pain, which should be avoided, is possible. For more severe pain, IV patient-controlled, on-demand dosing is best (see p. 1627). If patients do not have a renal disorder or a history of GI bleeding, giving NSAIDs at regular intervals may reduce breakthrough pain, allowing the opioid dosage to be reduced.

**Mental status:** All patients are briefly confused when they come out of anesthesia. The elderly, especially those with dementia, are at risk of postoperative delirium, which can delay discharge and increase risk of death. Risk of delirium is high when anticholinergics are used. These drugs are sometimes used before or during surgery to decrease upper airway secretions, but they should be avoided whenever possible. Opioids, given postoperatively, may also cause delirium, as can high doses of H₂ blockers. The mental status of elderly patients should be assessed frequently during the postoperative period. If delirium occurs, oxygenation should be assessed, and all nonessential drugs should be stopped. Patients should be mobilized as they are able, and any electrolyte or fluid imbalances should be corrected.

**Wound care:** The surgeon must individualize care of each wound, but the sterile dressing placed in the operating room is generally left intact for 24 h unless signs of infection (eg, increasing pain, erythema, drainage) develop. After 24 h, the site should be checked twice/day, if possible, for signs of infection. If they occur, wound exploration and drainage of abscesses, systemic antibiotics, or both may be required. Topical antibiotics are usually not helpful. A drain tube, if present, must be monitored for quantity and quality of the fluid collected. Sutures, skin staples, and other closures are usually left in place 7 days or longer depending on the site and the patient. Face and neck wounds may be superficially healed in 3 days; wounds on the lower extremities may take weeks to heal to a similar degree.

**Deep venous thrombosis (DVT) prophylaxis:** Risk of DVT after surgery is small, but because
consequences can be severe and risk is still higher than that in the general population, prophylaxis is often warranted. Surgery itself increases coagulability and often requires prolonged immobility, another risk factor for DVT (see Chs. 194 and 219). Prophylaxis for DVT usually begins in the operating room (see Table 194-5 on p. 1920). Alternatively, heparin may be started shortly after surgery, when risk of bleeding has decreased. Patients should begin moving their limbs as soon as it is safe for them to do so.

Fever: A common cause of fever is a high metabolic rate that occurs with the stress of an operation. Other causes include pneumonia, UTIs, and wound infections. Incentive spirometry and periodic coughing can help decrease risk of pneumonia.

Other issues: Certain types of surgery require additional precautions. For example, hip surgery requires that patients be moved and positioned so that the hip does not dislocate. Any physician moving such patients for any reason, including auscultating the lungs, must know the positioning protocol to avoid doing harm; often, a nurse is the best instructor.

Urinary retention and constipation are common after surgery. Causes include use of anticholinergics or opioids, immobility, and decreased oral intake. Patients must be monitored for urinary retention. Straight catheterization is typically necessary for patients who have a distended bladder and are uncomfortable or who have not urinated for 6 to 8 h after surgery; Crede's maneuver sometimes helps and may make catheterization unnecessary. Chronic retention is best treated by avoiding causative drugs and by having patients sit up as often as possible. Bethanechol 5 to 10 mg can be tried in patients unlikely to have any bladder obstruction and who have not had a laparotomy; doses can be repeated every hour up to a maximum of 50 mg/day. Sometimes an indwelling bladder catheter is needed, especially if patients have a history of retention or a large initial output after straight catheterization. Constipation is treated by avoiding causative drugs and, if patients have not had GI surgery, by giving stimulant laxatives (eg, bisacodyl, senna, cascara). Stool softeners (eg, docusate) do not alleviate postoperative constipation.

Loss of muscle mass (sarcopenia) and strength occur in all patients who require prolonged bed rest. With complete bed rest, young adults lose about 1% of muscle mass/day, but the elderly lose up to 5%/day because growth hormone levels decrease with aging. Avoiding sarcopenia is essential to recovery. Thus, patients should sit up in bed, transfer to a chair, stand, and exercise as much as and as soon as is safe for their surgical and medical condition. Nutritional deficiencies may also contribute to sarcopenia. Thus, nutritional intake of patients on complete bed rest should be optimized. Tube feeding or, rarely, parenteral feeding may be necessary.
Chapter 350. Rehabilitation

Introduction

Rehabilitation aims to facilitate recovery from loss of function. Loss may be due to fracture, amputation, stroke or another neurologic disorder, arthritis, cardiac impairment, or prolonged deconditioning (eg, after some disorders and surgical procedures). Rehabilitation may involve physical, occupational, and speech therapy; psychologic counseling; and social services. For some patients, the goal is complete recovery with full, unrestricted function; for others, it is recovery of the ability to do as many activities of daily living (ADLs) as possible. Results of rehabilitation depend on the nature of the loss and the patient's motivation. Progress may be slow for elderly patients and for patients who lack muscle strength or motivation.

Rehabilitation may begin in an acute care hospital. Rehabilitation hospitals or units usually provide the most extensive and intensive care; they should be considered for patients who have good potential for recovery and can participate in and tolerate aggressive therapy (generally, ≥ 3 h/day). Many nursing homes have less intensive programs (generally, 1 to 3 h/day, up to 5 days/wk) and thus are better suited to patients less able to tolerate therapy (eg, frail or elderly patients). Less varied and less frequent rehabilitation programs may be offered in outpatient settings or at home and are appropriate for many patients. However, outpatient rehabilitation can be relatively intensive (several hours/day up to 5 days/wk).

An interdisciplinary approach is best because disability can lead to various problems (eg, depression, lack of motivation to regain lost function, financial problems). Thus, patients may require psychologic intervention and help from social workers or mental health practitioners. Also, family members may need help learning how to adjust to the patient's disability and how to help the patient.

Referral: To initiate formal rehabilitation therapy, a physician must write a referral/prescription to a physiatrist, therapist, or rehabilitation center. The referral/prescription should state the diagnosis and goal of therapy. The diagnosis may be specific (eg, after left-sided stroke, residual right-sided deficits in upper and lower extremities) or functional (eg, generalized weakness due to bed rest). Goals should be as specific as possible (eg, training to use a prosthetic limb, maximizing general muscle strength and overall endurance). Although vague instructions (eg, physical therapy to evaluate and treat) are sometimes accepted, they are not in the patients' best interests and may be rejected with a request for more specific instructions. Physicians unfamiliar with writing referrals for rehabilitation can consult a physiatrist.

Goals of therapy: Initial evaluation sets goals for restoring mobility and functions needed to do ADLs, which include caring for self (eg, grooming, bathing, dressing, feeding, toileting), cooking, cleaning, shopping, managing drugs, managing finances, using the telephone, and traveling. The referring physician and rehabilitation team determine which activities are achievable and which are essential for the patient's independence. Once ADL function is maximized, goals that can help improve quality of life are added.

Patients improve at different rates. Some courses of therapy last only a few weeks; others last longer. Some patients who have completed initial therapy need additional therapy.

Patient and caregiver issues: Patient and family education is an important part of the rehabilitation process, particularly when the patient is discharged into the community. Often, the nurse is the team member primarily responsible for this education. Patients are taught how to maintain newly regained functions and how to reduce the risk of accidents (eg, falls, cuts, burns) and secondary disabilities. Family members are taught how to help the patient be as independent as possible, so that they do not overprotect the patient (leading to decreased functional status and increased dependence) or neglect the patient's primary needs (leading to feelings of rejection, which may cause depression or interfere with physical functioning).

Emotional support from family members and friends is essential. It may take many forms. Spiritual support and counseling by peers or by religious advisors can be indispensable for some patients.
Disorders requiring rehabilitation (eg, stroke, MI, hip fracture, limb amputation) are common among the elderly. The elderly are also more likely to have become deconditioned before the acute problem that necessitates rehabilitation.

The elderly, even if cognitively impaired, can benefit from rehabilitation. Age alone is not a reason to postpone or deny rehabilitation. However, the elderly may recover slowly because of a reduced ability to adapt to a changing environment, including

• Physical inactivity
• Lack of endurance
• Depression or dementia
• Decreased muscle strength, joint mobility, coordination, or agility
• Impaired balance

Programs designed specifically for the elderly are preferable because the elderly often have different goals, require less intensive rehabilitation, and need different types of care than do younger patients. In age-segregated programs, elderly patients are less likely to compare their progress with that of younger patients and to become discouraged, and the social work aspects of postdischarge care can be more readily integrated. Some programs are designed for specific clinical situations (eg, recovery from hip fracture surgery); patients with similar conditions can work together toward common goals by encouraging each other and reinforcing the rehabilitation training.

**Physical Therapy**

Physical therapy aims to improve joint and muscle function (eg, range of motion, strength) and thus improve the patient's ability to stand, balance, walk, and climb stairs. For example, physical therapy is usually used to train lower-extremity amputees. On the other hand, occupational therapy (see p. 3456) focuses on self-care activities and improvement of fine motor coordination of muscles and joints, particularly in the upper extremities.

**Range of motion**: Limited range of motion impairs function and tends to cause pain and to predispose patients to pressure ulcers. Range of motion should be evaluated with a goniometer before therapy and regularly thereafter (for normal values, see Table 350-1).

Range-of-motion exercises stretch stiff joints. Stretching is usually most effective and least painful when tissue temperature is raised to about 43°C (see p. 3459). There are several types:

• **Active**: This type is used when patients can exercise without assistance; patients must move their limbs themselves.

• **Active assistive**: This type is used when muscles are weak or when joint movement causes discomfort; patients must move their limbs, but a therapist helps them do so.

• **Passive**: This type is used when patients cannot actively participate in exercise; no effort is required from them.

**Strength and conditioning**: Many exercises aim to improve muscle strength (for grading muscle strength, see Table 350-2). Muscle strength may be increased with progressive resistive exercise. When a muscle is very weak, gravity alone is sufficient resistance. When muscle strength becomes fair, additional manual or mechanical resistance (eg, weights, spring tension) is added.
General conditioning exercises combine various exercises to treat the effects of debilitation, prolonged bed rest, or immobilization. The goals are to reestablish hemodynamic balance, increase cardiorespiratory capacity and endurance, and maintain range of motion and muscle strength.

For the elderly, the purpose of these exercises is both to strengthen muscles enough to function normally and possibly to regain normal strength for age.

**Proprioceptive neuromuscular facilitation:** This technique helps promote neuromuscular activity in patients who have upper motor neuron damage with spasticity; it enables them to feel muscle contraction and helps maintain the affected joint's range of motion. For example, applying strong resistance to the left elbow flexor (biceps) of patients with right hemiplegia causes the hemiplegic biceps to contract, flexing the right elbow.

**Table 350-1. Normal Values for Range of Motion of Joints**

**Table 350-2. Grades of Muscle Strength**

**Coordination exercises:** These task-oriented exercises improve motor skills by repeating a movement that works more than one joint and muscle simultaneously (e.g., picking up an object, touching a body part).

**Ambulation exercises:** Before proceeding to ambulation exercises, patients must be able to balance in a standing position. Balancing exercise is usually done using parallel bars with a therapist standing in front of or directly behind a patient. While holding the bars, patients shift weight from side to side and from forward to backward. Once patients can balance safely, they can proceed to ambulation exercises.

Ambulation is often a major goal of rehabilitation. If individual muscles are weak or spastic, an orthosis (e.g., a brace) may be used (see p. 3457). Ambulation exercises are commonly started using parallel bars; as patients progress, they use a walker, crutches, or cane and then walk without devices. Some patients wear an assistive belt used by the therapist to help prevent falls. Anyone assisting patients with ambulation should know how to correctly support them (see Fig. 350-1).

As soon as patients can walk safely on level surfaces, they can start training to climb stairs or to step over curbs if either skill is needed. Patients who use walkers must learn special techniques for climbing stairs and stepping over curbs. When climbing stairs, ascent starts with the better leg, and descent starts with the affected leg (i.e., good leads up; bad leads down). Before patients are discharged, the social worker or physical therapist should arrange to have secure handrails installed along all stairs in the patients' home.

**Transfer training:** Patients who cannot transfer independently from bed to chair, chair to commode, or chair to a standing position usually require attendants 24 h/day. Adjusting the heights of commodes and chairs may help. Sometimes assistive devices are useful; e.g., people who have difficulty standing from a seated position may benefit from a chair with a raised seat or a self-lifting chair.

**Occupational Therapy**

Occupational therapy (OT) focuses on self-care activities and improvement of fine motor coordination of muscles and joints, particularly in the upper extremities. Unlike physical therapy, which focuses on muscle strength and joint range of motion, OT focuses on activities of daily living (ADLs) because they are the cornerstone of independent living. Basic ADLs (BADLs) include eating, dressing, bathing, grooming, toileting, and transferring (i.e., moving between surfaces such as the bed, chair, and bathtub or shower). Instrumental ADLs (IADLs) require more complex cognitive functioning than BADLs. IADLs include preparing meals; communicating by telephone, writing, or computer; managing finances and daily drug regimens; cleaning; doing laundry, food shopping, and other errands; managing finances; traveling as a pedestrian or by public transportation; and driving. Driving is particularly complex, requiring integration of
visual, physical, and cognitive tasks.

**Evaluation:** OT can be initiated when a physician writes a referral for rehabilitation, which is similar to writing a prescription. The referral should be detailed, including a brief history of the problem (eg, type and duration of the disorder or injury) and establishing the goals of therapy (eg, training in IADLs). Lists of occupational therapists may be obtained from a patient's insurance carrier, a local hospital, the telephone book, state occupational training organizations, or the web site of the American Occupational Therapy Association.

Patients are evaluated for limitations that require intervention and for strengths that can be used to compensate for weaknesses. Limitations may involve motor function, sensation, cognition, or psychosocial function. Examiners determine which activities (eg, work, leisure, social, learning) patients want or need help with. Patients may need help with a general type of activity (eg, social) or a specific activity (eg, attending church), or they may need to be motivated to do an activity. Therapists may use an assessment instrument to help in the evaluation. One of the many functional assessment instruments is described in Table 350-3. Patients are asked about their social and family roles, habits, and social support systems. The availability of resources (eg, community programs and services, private attendants) should be determined.

Occupational therapists may also assess the home for hazards and make recommendations to ensure home safety (eg, removing throw rugs, increasing hallway and kitchen lighting, moving a night table within reach of the bed, placing a family picture on a door to help patients recognize their room).

Determining when driving is a risk and whether driver retraining is indicated is best done by occupational therapists with specialized training. Information that can help elderly drivers and their caregivers in coping with changing driving abilities is available from the American Occupational Therapy Association and the American Association for Retired Persons.

**Interventions:** OT may consist of one consultation or frequent sessions of varying intensity. Sessions may occur in various settings:

- Acute care, rehabilitation, outpatient, adult day care, skilled nursing, or long-term care facilities
- The home (as part of home health care)
- Senior housing developments
- Life-care or assisted-living communities

Occupational therapists develop an individualized program to enhance patients' motor, cognitive, communication, and interaction capabilities. The goal is not only to help patients do ADLs but also to do appropriate preferred leisure activities and to foster and maintain social integration and participation.

Before developing a program, a therapist observes patients doing each activity of the daily routine to learn what is needed to ensure safe, successful completion of the activities. Therapists can then recommend ways to eliminate or reduce maladaptive patterns and to establish routines that promote function and health. Specific performance-oriented exercises are also recommended. Therapists emphasize that exercises must be practiced and motivate patients to do so by focusing on exercise as a means of becoming more active at home and in the community.

Patients are taught creative ways to facilitate social activities (eg, how to get to museums or church without driving, how to use hearing aids or other assistive communication devices in different settings, how to travel safely with or without a cane or walker). Therapists may suggest new activities (eg, volunteering in foster grandparent programs, schools, or hospitals).

Patients are taught strategies to compensate for their limitations (eg, to sit when gardening). The therapist may identify various assistive devices that can help patients do many activities of daily living (see...
Most occupational therapists can select wheelchairs appropriate for patients' needs and provide training for upper-extremity amputees.

Occupational therapists may construct and fit devices to prevent contractures and treat other functional disorders.

Speech Therapy

Speech therapists can identify the most effective methods of communication for patients who have aphasia, dysarthria, or verbal apraxia or who have had a laryngectomy:

- Expressive aphasia: A letter or picture board
- Mild to moderate dysarthria or apraxia: Breathing and muscle control plus repetition exercises
- Severe dysarthria or apraxia: An electronic device with a keyboard and message display (print or screen)
- Postlaryngectomy: A new way to produce a voice (eg, by an electrolarynx—see p. 490)

Therapeutic and Assistive Devices

Orthoses provide support for damaged joints, ligaments, tendons, muscles, and bones. Most are customized to a patient's needs and anatomy. Orthoses designed to fit into shoes may shift the patient's weight to different parts of the foot to compensate for lost function, prevent deformity or injury, help bear weight, or relieve pain, as well as provide support. Orthoses are often very expensive and not covered by insurance.

Walking aids include walkers, crutches, and canes (see Fig. 350-2). They help with weight bearing, balance, or both. Each device has advantages and disadvantages, and each is available in many models. After evaluation, a therapist should choose the one that provides the best combination of stability and freedom for the patient (see Table 350-5). Physicians should know how to fit crutches (see Fig. 350-3). Prescriptions for assistive devices should be as specific as possible.

Wheelchairs provide mobility to patients who cannot walk. Some models are designed to be self-propelled and to provide stability for traveling over uneven ground and up and down curbs. Other models are designed to be pushed by an assistant; they provide less stability and speed. Wheelchairs are available with various features. For athletic patients with impaired lower extremities but good upper body strength, racing wheelchairs are available. A one-arm-drive or hemi-height wheelchair may be suitable for hemiplegic patients with good coordination. If patients have little or no arm function, a motorized wheelchair is prescribed. Wheelchairs for quadriplegics may have chin or mouth (sip and puff) controls and built-in ventilators.

Prostheses are artificial body parts, most commonly limbs designed to replace lower or upper extremities after amputation (see p. 3465). Technical innovations have greatly improved the comfort and functionality of prostheses. Many prostheses can be cosmetically altered to appear natural. A prosthetist should be involved early to help patients understand the many options in prosthetic design, which should meet the patients' needs and safety requirements. Many patients can expect to regain considerable function.

Physical therapy
should be started even before the prosthesis is fitted; therapy should continue until patients can function with the new limb. Some patients seem unable to tolerate a prosthesis or complete the physical rehabilitation required to successfully use it.

**Treatment of Pain and Inflammation**

(See also Ch. 171)

Treatment of pain and inflammation aims to facilitate movement and improve coordination of muscles and joints. Nondrug treatments include therapeutic exercise, heat, cold, electrical stimulation, cervical traction, massage, and acupuncture. These treatments are used for many disorders of muscles, tendons, and ligaments (see Table 350-6). Prescribers should include the following:

- **Diagnosis**
- **Type of treatment** (eg, ultrasound, hot pack)
- **Location of application** (eg, right shoulder, low back)
- **Frequency** (eg, once/day, every other day)
- **Duration** (eg, 10 days, 1 wk)

**Heat:** Heat provides temporary relief in subacute and chronic traumatic and inflammatory disorders (eg, sprains, strains, fibrositis, tenosynovitis, muscle spasm, myositis, back pain, whiplash injuries, various forms of arthritis, arthralgia, neuralgia). Heat increases blood flow and the extensibility of connective tissue; heat also decreases joint stiffness, pain, and muscle spasm and helps relieve inflammation, edema, and exudates. Heat application may be superficial (infrared heat, hot packs, paraffin bath, hydrotherapy) or deep (ultrasound). Intensity and duration of the physiologic effects depend mainly on tissue temperature, rate of temperature elevation, and area treated.

**Infrared heat** is applied with a heat lamp, usually for 20 min/day. Contraindications include any advanced heart disorder, peripheral vascular disease, impaired skin sensation (particularly to temperature and pain), and significant hepatic or renal insufficiency. Precautions must be taken to avoid burns.

**Hot packs** are cotton cloth containers filled with silicate gel; they are boiled in water or warmed in a microwave oven, then applied to the skin. The packs must not be too hot. Wrapping the packs in several layers of towels helps protect the skin from burns. Contraindications are the same as those for infrared heat.

For a **paraffin bath**, the affected area is dipped in, immersed in, or painted with melted wax that has been heated to 49° C. The heat can be retained by wrapping the affected area with towels for 20 min. Paraffin is usually applied to small joints—typically, by dipping or immersion for a hand and by painting for a knee or an elbow. Paraffin should not be applied to open wounds or used on patients allergic to it. A paraffin bath is particularly useful for finger arthritis.

**Hydrotherapy** may be used to enhance wound healing. Agitated warm water stimulates blood flow and debrides burns and wounds. This treatment is often given in a Hubbard tank (a large industrial whirlpool) with water heated to 35.5 to 37.7° C. Total immersion in water heated to 37.7 to 40° C may also help relax muscles and relieve pain. Hydrotherapy is particularly useful with range-of-motion exercises.
**Diathermy** is therapeutic heating of tissues using oscillating high-frequency electromagnetic fields, either short-wave or microwave. These modalities do not seem superior to simpler forms of heating and are now seldom used.

**Ultrasound** uses high-frequency sound waves to penetrate deep (4 to 10 cm) into the tissue; its effects are thermal, mechanical, chemical, and biologic. It is indicated for tendinitis, bursitis, contractures, osteoarthritis, bone injuries, and complex regional pain syndrome. Ultrasound should not be applied to ischemic tissue, anesthetized areas, or areas of acute infection nor be used to treat hemorrhagic diathesis or cancer. Also, it should not be applied over the eyes, brain, spinal cord, ears, heart, reproductive organs, brachial plexus, or bones that are healing.

**Cold:** The choice between heat and cold therapies is often empiric. When heat does not work, cold is applied. However, for acute injury or pain, cold seems to be better than heat. Cold may help relieve muscle spasm, myofascial or traumatic pain, acute low back pain, and acute inflammation; cold may also help induce some local anesthesia. Cold is usually used during the first few hours or the day after an injury; consequently, it is seldom used in physical therapy.

Cold may be applied locally using an ice bag, a cold pack, or volatile fluids (eg, ethyl chloride, vapocoolant spray), which cool by evaporation. Spread of cold on the skin depends on the thickness of the epidermis, underlying fat and muscle, water content of the tissue, and rate of blood flow. Care must be taken to avoid tissue damage and hypothermia. Cold should not be applied over poorly perfused areas.

**Electrical stimulation:** Transcutaneous electrical nerve stimulation (TENS) uses low current at low-frequency oscillation to relieve pain. Patients feel a gentle tingling sensation without increased muscle tension. Depending on the severity of pain, 20 min to a few hours of stimulation may be applied several times daily. Often, patients are taught to use the TENS device and decide when to apply treatment. Because TENS may cause arrhythmia, it is contraindicated in patients with any advanced heart disorder or a pacemaker. It should not be applied over the eyes.

[Table 350-6, Indications for Nondrug Pain Treatments]

**Cervical traction:** Cervical traction is often indicated for chronic neck pain due to cervical spondylosis, disk prolapse, whiplash injuries, or torticollis. Vertical traction (with patients in a sitting position) is more effective than horizontal traction (with patients lying in bed). Motorized intermittent rhythmic traction with 7.5 to 10 kg is most effective. For best results, traction should be applied with the patient's neck flexed 15 to 20°. Generally, hyperextension of the neck should be avoided because it may increase nerve root compression in the intervertebral foramina. Traction is usually combined with other physical therapy, including exercises and manual stretching.

**Massage:** Massage may mobilize contracted tissues, relieve pain, and reduce swelling and induration associated with trauma (eg, fracture, joint injury, sprain, strain, bruise, peripheral nerve injury). Massage should be considered for low back pain, arthritis, periartthritis, bursitis, neuritis, fibromyalgia, fibrositis, hemiplegia, paraplegia, quadriplegia, multiple sclerosis, cerebral palsy, and certain types of cancer. Massage should not be used to treat infections or thrombophlebitis. It is not advised for patients with severe allergies because it causes histamine to be released throughout the body. Only a licensed or certified massage therapist should use massage for treatment of an injury because of variability in therapists' training and skills.

**Acupuncture:** Thin needles are inserted through the skin at specific body sites, frequently far from the site of pain (see p. 3419). Acupuncture is sometimes used with other treatments to manage acute and chronic pain.

**Cardiovascular Rehabilitation**

Rehabilitation may benefit some patients who have coronary artery disease or heart failure or who have had a recent MI or coronary artery bypass surgery, particularly those who could do activities of daily living independently and walk before the event. Cardiac rehabilitation aims to help patients maintain or regain
Typically, rehabilitation begins with light activities and progresses on an individualized basis; ECG monitoring is often used. High-risk patients should exercise only in a well-equipped cardiovascular rehabilitation facility under the supervision of a trained attendant.

When patients are able, they are taken by wheelchair to a physical therapy gym in the hospital. Exercise may involve walking, a treadmill, or a stationary bicycle. When patients tolerate these exercises well, they progress to stair-climbing. If shortness of breath, light-headedness, or chest pain occurs during exercise, the exercise should be stopped immediately, and cardiac status should be reassessed. Before hospital discharge, patients are assessed so that an appropriate postdischarge rehabilitation program or exercise regimen can be recommended.

Physical activity is measured in metabolic equivalents (METs), which are multiples of the resting rate of \( O_2 \) consumption; 1 MET (the resting rate) equals about 3.5 mL/kg/min of \( O_2 \) (see Tables 350-7). Normal working and living activities (excluding recreational activities) rarely exceed 6 METs. Light to moderate housework is about 2 to 4 METs; heavy housework or yard work is about 5 to 6 METs.

For hospitalized patients, physical activity should be controlled so that heart rate remains < 60% of maximum for that age (eg, about 160 beats/min for people aged 60); for patients recovering at home, heart rate should remain < 70% of maximum.

For patients who have had an uncomplicated MI, a 2-MET exercise test may be done to evaluate responses as soon as patients are stable. A 4- to 5-MET exercise test done before discharge helps guide physical activity at home. Patients who can tolerate a 5-MET exercise test for 6 min can safely do low-intensity activities (eg, light housework) after discharge if they rest sufficiently between each activity.

Unnecessary restriction of activity is detrimental to recovery. The physician and other members of the rehabilitation team should explain which activities can be done and which cannot and should provide psychologic support. When discharged, patients can be given a detailed home activity program. Most elderly patients can be encouraged to resume sexual activity, but they need to stop and rest if necessary to avoid overexertion. Young couples expend 5 to 6 METs during intercourse; whether elderly couples expend more or less is unknown.

**Stroke Rehabilitation**

Rehabilitation after stroke aims to preserve or improve range of motion, muscle strength, bowel and bladder function, and functional and cognitive abilities. Specific programs are based on the patient's social situation (eg, prospects of returning to home or work), ability to participate in a rehabilitation program supervised by nurses and therapists, learning ability, motivation, and coping skills. A stroke that impairs comprehension often makes rehabilitation very difficult.

To prevent secondary disabilities (eg, contractures) and help prevent depression, rehabilitation should begin as soon as patients are medically stable. Preventive measures for pressure ulcers must be started even before patients are medically stable. Patients can safely begin sitting up once they are fully conscious and neurologic deficits are no longer progressing, usually ≤ 48 h after the stroke. Early in the rehabilitation period, when the affected extremities are flaccid, each joint is passively exercised through the normal range of motion (see Table 350-1) 3 to 4 times/day.

Regaining the ability to get out of bed and to transfer to a chair or wheelchair safely and independently is important for the patient's psychologic and physical well-being. Ambulation problems, spasticity, visual field defects (eg, hemianopia), incoordination, and aphasia require specific therapy.

**Hemiplegia:** For patients with hemiplegia, placing 1 or 2 pillows under the affected arm can prevent...
dislocation of the shoulder. If the arm is flaccid, a well-constructed sling can prevent the weight of the arm and hand from overstretching the deltoid muscle and subluxating the shoulder. A posterior foot splint applied with the ankle in a 90° position can prevent equinus deformity (talipes equinus) and footdrop.

Resistive exercise for hemiplegic extremities may increase spasticity and thus is controversial. However, reeducation and coordination exercises of the affected extremities are added as soon as tolerated, often within 1 wk. Active and active-assistive range-of-motion exercises are started shortly afterward to maintain range of motion. Active exercise of the unaffected extremities must be encouraged, as long as it does not cause fatigue. Various activities of daily living (eg, moving in bed, turning, changing position, sitting up) should be practiced. For hemiplegic patients, the most important muscle for ambulation is the unaffected quadriceps. If weak, this muscle must be strengthened to assist the hemiplegic side.

A gait abnormality in hemiplegic patients is caused by many factors (eg, muscle weakness, spasticity, distorted body image) and is thus difficult to correct. Also, attempts to correct gait often increase spasticity, may result in muscle fatigue, and may increase the already high risk of falls, which often result in a hip fracture; functional prognosis of hemiplegic patients with a hip fracture is very poor. Consequently, as long as hemiplegic patients can walk safely and comfortably, gait correction should not be tried.

Novel treatments for hemiplegia include the following:

- **Constraint-induced movement therapy**: The functional limb is restrained during waking hours, except during specific activities, and patients are forced to do tasks mainly with the affected extremity.

- **Robotic therapy**: Robotic devices are used to provide intensive repetition of the therapeutic movement, guide an affected extremity in executing the movement, provide feedback (eg, on a computer screen) for patients, and measure patient progress.

- **Partial weight-supported ambulation**: A device (eg, treadmill) that bears part of a patient's weight is used during ambulation. The amount of weight borne and speed of ambulation can be adjusted. This approach is often used with robotics, which allows patients to contribute to ambulation but provides force as needed for ambulation.

- **Total body vibration**: Patients stand on an exercise machine with a platform that vibrates by rapidly shifting weight from one foot to the other. The movement stimulates reflexive muscle contraction.

**Ambulation problems**: Before ambulation exercises can be started, patients must be able to stand. Patients first learn to stand from the sitting position. The height of the seat may need to be adjusted. Patients must stand with the hips and knees fully extended, leaning slightly forward and toward the unaffected side. Using the parallel bars is the safest way to practice standing.

The goal of ambulation exercises is to establish and maintain a safe gait, not to restore a normal gait. Most hemiplegic patients have a gait abnormality, which is caused by many factors (eg, muscle weakness, spasticity, distorted body image) and is thus difficult to correct. Also, attempts to correct gait often increase spasticity, may result in muscle fatigue, and may increase the already high risk of falls.

During ambulation exercises, patients place the feet > 15 cm (6 in) apart and grasp the parallel bars with the unaffected hand. Patients take a shorter step with the hemiplegic leg and a longer step with the unaffected leg. Patients who begin walking without the parallel bars may need physical assistance from and later close supervision by the therapist. Generally, patients use a cane or walker when first walking without the parallel bars. The diameter of the cane handle should be large enough to accommodate an arthritic hand.

For stair-climbing, ascent starts with the better leg, and descent with the affected leg (good leads up; bad leads down). If possible, patients ascend and descend with the railing on the unaffected side, so that they can grasp the railing. Looking up the staircase may cause vertigo and should be avoided. During descent, patients should use a cane. The cane should be moved to the lower step shortly before descending with the bad leg.
Patients must learn to prevent falls, which are the most common accident among stroke patients and which often result in hip fracture. Usually, patients explain the fall by saying that their knees gave way. For hemiplegic patients, who almost always fall on their hemiplegic side, leaning their affected side against a railing (when standing or climbing stairs) can help prevent falls. Doing strengthening exercises for weak muscles, particularly in the trunk and legs, can also help.

For patients with symptomatic orthostatic hypotension, treatment includes support stockings, drugs, and tilt table training. Because hemiplegic patients are prone to vertigo, they should change body position slowly and take a moment after standing to establish equilibrium before walking. Comfortable, supportive shoes with rubber soles and with heels ≤ 2 cm (3/4 in) should be worn.

**Spasticity:** In some stroke patients, spasticity develops. Spasticity may be painful and debilitating. Slightly spastic knee extensors can lock the knee during standing or cause hyperextension (genu recurvatum), which may require a knee brace with an extension stop. Resistance applied to spastic plantar flexors causes ankle clonus; a short leg brace without a spring mechanism minimizes this problem.

Flexor spasticity develops in most hemiplegic hands and wrists. Unless patients with flexor spasticity do range-of-motion exercises several times a day, flexion contracture may develop rapidly, resulting in pain and difficulty maintaining personal hygiene. Patients and family members are taught to do these exercises, which are strongly encouraged. A hand or wrist splint may also be useful, particularly at night. One that is easy to apply and clean is best.

Heat or cold therapy can temporarily decrease spasticity and allow the muscle to be stretched. Hemiplegic patients may be given benzodiazepines to minimize apprehension and anxiety, particularly during the initial stage of rehabilitation, but not to reduce spasticity. The effectiveness of long-term benzodiazepine therapy for reducing spasticity is questionable. Methocarbamol has limited value in relieving spasticity and causes sedation.

**Hemianopia:** Patients with hemianopia (defective vision or blindness in half the visual field of one or both eyes) should be made aware of it and taught to move their heads toward the hemiplegic side when scanning. Family members can help by placing important objects and by approaching the patient on the patient's unaffected side. Repositioning the bed so that patients can see a person entering the room through the doorway may be useful. While walking, patients with hemianopia tend to bump into the door frame or obstacles on the hemiplegic side; they may need special training to avoid this problem.

When reading, patients who have difficulty looking to the left may benefit from drawing a red line on the left side of the newspaper column. When they reach the end of a line of text, they scan to the left of the column until they see the red line, cueing them to begin reading the next line. Using a rule to keep focused on each line of text may also help.

**Occupational therapy:** After a stroke, fine coordination may be absent, causing patients to become frustrated. Occupational therapists may need to modify patients' activities and recommend assistive devices (see Table 350-4).

Occupational therapists should also evaluate the home for safety and determine the extent of social support. They can help obtain any necessary devices and equipment (eg, bathtub bench, grab bars by the bathtub or toilet). Occupational therapists can also recommend modifications that enable patients to do activities of daily living (ADLs) as safely and independently as possible—for example, rearranging the furniture in living areas and removing clutter. Patients and caretakers are taught how to transfer between surfaces (eg, shower, toilet, bed, chair) and, if necessary, how to modify ways of doing ADLs. For example, patients may be taught to dress or shave using only one hand and to eliminate unnecessary motion while preparing food or shopping for groceries. Therapists may suggest using clothing and shoes with touch fasteners (eg, Velcro) or dinner plates with rims and rubber grips (to facilitate handling). Patients with impairments in cognition and perception are taught ways to compensate. For example, they can use drug organizers (eg, containers marked for each day of the week).
Before amputation, the physician describes to the patient the extensive postsurgical rehabilitation program that is needed. Psychologic counseling may be indicated. The rehabilitation team and the patient decide whether a prosthesis or a wheelchair is needed.

Rehabilitation teaches ambulation skills; it includes exercises to improve general conditioning and balance, to stretch the hip and knee, to strengthen all extremities, and to help patients tolerate the prosthesis. Because ambulation requires a 10 to 40% increase in energy expenditure after below-the-knee amputation and a 60 to 100% increase after above-the-knee amputation, endurance exercises may be indicated. As soon as patients are medically stable, rehabilitation should be started to help prevent secondary disabilities. Elderly patients should begin standing and doing balancing exercises with parallel bars as soon as possible.

Flexion contracture of the hip or knee may develop rapidly, making fitting and using the prosthesis difficult; contractures can be prevented with extension braces made by occupational therapists.

Physical therapists teach patients how to care for the stump and how to recognize the earliest signs of skin breakdown.

**Stump Conditioning and Prostheses**

Stump conditioning promotes the natural process of stump shrinking that must occur before a prosthesis can be used. After only a few days of conditioning, the stump may have shrunk greatly. An elastic stump shrinker or elastic bandages worn 24 h/day can help taper the stump and prevent edema. The stump shrinker is easy to apply, but bandages may be preferred because they better control the amount and location of pressure. However, application of elastic bandages requires skill, and bandages must be reapplied whenever they become loose.

Early ambulation with a temporary prosthesis helps in the following ways:

- Enables the amputee to be active
- Accelerates stump shrinkage
- Prevents flexion contracture
- Reduces phantom limb pain

The socket of the pylon (the internal framework or skeleton of a prosthesis) is made of plaster of paris (calcium sulfate hemihydrate); it should fit the stump snugly. Various temporary prostheses with adjustable sockets are available. Patients with a temporary prosthesis can start ambulation exercises on the parallel bars and progress to walking with crutches or canes until a permanent prosthesis is made.

The permanent prosthesis should be lightweight and meet the needs and safety requirements of the patient. If the prosthesis is made before the stump stops shrinking, adjustments may be needed. Therefore, manufacture of a permanent prosthesis is generally delayed a few weeks to allow shrinkage of the stump. For most elderly patients with a below-the-knee amputation, a patellar tendon-bearing prosthesis with a solid-ankle, cushion-heel foot, and suprapatellar cuff suspension is best. Unless patients have special needs, a below-the-knee prosthesis with thigh corset and waist belt is not prescribed because it is heavy and bulky. For above-the-knee amputees, several knee-locking options are available according to the patient's skills and activity level.

**Care of the stump and prosthesis:** Patients must learn to care for their stump. Because a leg prosthesis is intended only for ambulation, patients should remove it before going to sleep. At bedtime, the stump should be inspected thoroughly (with a mirror if inspected by the patient), washed with mild soap and warm water, dried thoroughly, then dusted with talcum powder. Patients should treat the following possible problems:
• Dry skin: Lanolin or petrolatum may be applied to the stump.

• Excessive sweating: An unscented antiperspirant may be applied.

• Inflamed skin: The irritant must be removed immediately, and talcum powder or a low potency corticosteroid cream or ointment should be applied.

• Broken skin: The prosthesis should not be worn until the wound has healed.

The stump sock should be changed daily, and mild soap may be used to clean the inside of the socket. Standard prostheses are neither waterproof nor water-resistant. Therefore, if even part of the prosthesis becomes wet, it must be dried immediately and thoroughly; heat should not be applied. For patients who swim or prefer to shower with a prosthesis, a prosthesis that can tolerate immersion can be made.

Complications

Stump pain is the most common complaint. Common causes include:

• A poorly fitted prosthetic socket: This cause is the most common.

• Neuroma: An amputation neuroma is usually palpable. Daily ultrasound treatment for 5 to 10 sessions may be most effective. Other treatments include injection of corticosteroids or analgesics into the neuroma or the surrounding area, cryotherapy, and continuous tight bandaging of the stump. Surgical resection often has disappointing results.

• Spur formation at the amputated end of the bone: Spurs may be diagnosed by palpation and x-ray. The only effective treatment is surgical resection.

Phantom limb sensation (a painless awareness of the amputated limb possibly accompanied by tingling) is experienced by some new amputees. This sensation may last several months or years but usually disappears without treatment. Frequently, patients sense only part of the missing limb, often the foot, which is the last phantom sensation to disappear. Phantom limb sensation is not harmful; however, patients, without thinking, commonly attempt to stand with both legs and fall, particularly when they wake at night to go to the bathroom.

Phantom limb pain is less common and can be severe and difficult to control. Some experts think it is more likely to occur if patients had a painful condition before amputation or if pain was not adequately controlled intraoperatively and postoperatively. Various treatments, such as simultaneous exercise of amputated and contralateral limbs, massage of the stump, finger percussion of the stump, use of mechanical devices (eg, a vibrator), and ultrasound, are reportedly effective. Drugs (eg, gabapentin) may help.

Skin breakdown tends to occur because the prosthesis presses on and rubs the skin and because moisture collects between the stump and prosthetic socket. Skin breakdown may be the first indication that the prosthesis needs adjustment and needs to be managed immediately. The first sign of skin breakdown is redness; then cuts, blisters, and sores may develop, the prosthesis is often painful or impossible to wear for long periods of time, and infection can develop. Several measures can help prevent or delay skin breakdown:

• Having an interface that fits well

• Maintaining a stable body weight (even small changes in weight can affect fit)

• Eating a healthy diet and drinking lots of water (to control body weight and maintain healthy skin)

• For patients with diabetes, monitoring and controlling their blood sugar level (to help prevent vascular disease and thus maintain blood flow to the skin)
For patients with a lower-limb prosthesis, maintaining body alignment (eg, wearing only shoes with a similar heel height)

However, even with a good fit, problems can occur. The stump changes in shape and size throughout a day, depending on activity level, diet, and the weather. Thus, there are times when the interface fits well and times when it fits less well. In response to such ongoing changes, people can help maintain a good fit by switching to a thicker or thinner liner or sock, by using a liner and a sock, or by adding or removing thin-ply socks. But even so, the stump's size may vary enough to cause skin breakdown. If there are signs of skin breakdown, patients should promptly see a health care practitioner and a prosthetist; when possible they should also avoid wearing the prosthesis until it can be adjusted.

**Hip Surgery Rehabilitation**

Rehabilitation is started as soon as possible after hip fracture surgery. The first goals may be to increase strength and to prevent atrophy on the unaffected side. Initially, only isometric exercise of the affected limb while it is fully extended is permitted. Placement of a pillow under the knee is contraindicated because it may lead to flexion contracture of the hip and knee. Gradual mobilization of the affected limb usually results in full ambulation. Speed of rehabilitation depends partly on the type of surgery done. For example, after prosthetic hip replacement, rehabilitation usually progresses more rapidly, less rehabilitation is needed, and the functional outcome is better than after nail-and-plate or pin-and-plate fixation. Ideally, full weight bearing starts on the 2nd day after surgery. Ambulation exercises are started after 4 to 8 days (assuming that patients can bear their full weight and can balance), and stair-climbing exercises are started after about 11 days.

Patients are taught to do daily exercises to strengthen the trunk muscles and quadriceps of the affected leg. Prolonged lifting or pushing of heavy items, stooping, reaching, or jumping can be harmful. During ambulation, the amount of mechanical stress is about the same whether patients use 1 or 2 canes, but using 2 may interfere with certain activities of daily living (ADLs). Patients should not sit on a chair, particularly a low one, for a long period and should use the chair arm for support when standing up. While sitting, they should keep their legs uncrossed.

Occupational therapists teach patients how to modify ways of doing basic ADLs (BADLs) and instrumental ADLs (IADLs) safely after hip replacement, thus promoting healing and improving mobility. For example, patients may learn the following:

- To keep their hip correctly aligned
- To wash dishes and iron while sitting on a high stool
- To use a pillow to raise the seat of the car while transferring in and out
- To use long-handled devices (eg, reachers, shoe horns) to minimize bending over

This instruction may occur in the hospital, in longer-term rehabilitation settings, in the patient's home immediately after discharge, or in outpatient settings.

**Rehabilitation for Other Disorders**

**Arthritis:** Patients with arthritis can benefit from activities and exercises to increase joint range of motion and strength and from strategies to protect the joints. For example, patients may be advised

- To slide a pot of boiling water containing pasta rather than carry it from the stove to the sink (to avoid undue pain and strain to joints)
- How to get in and out of the bathtub safely
- To get a raised toilet seat, a bathtub bench, or both (to reduce pain and stress on the lower-extremity
joints)

- To wrap foam, cloth, or tape around the handles of objects (eg, knives, cooking pots and pans) to cushion the grip
- To use tools with larger, ergonomically designed handles

Such instruction may occur in outpatient settings, in the home via a home health care agency, or in private practice.

**Blindness:** Patients are taught to rely more on the other senses, to develop specific skills, and to use devices for the blind (eg, Braille, cane, reading machine). Therapy aims to help patients function to their maximum and become independent, to restore psychologic security, and to help patients deal with and influence the attitudes of other people. Therapy varies depending on the way vision was lost (suddenly or slowly and progressively), extent of vision loss, the patient's functional needs, and coexisting deficits. For example, patients with peripheral neuropathy and diminished tactile sensation in the fingers may have difficulty reading Braille. Many blind people need psychologic counseling (usually cognitive-behavioral therapy) to help them better cope with their condition.

For ambulation, therapy may involve learning to use a cane; canes used by the blind are usually white and longer and thinner than ordinary canes. People who use a wheelchair are taught to use one arm to operate the wheelchair and the other to use a cane. People who prefer to use a trained dog instead of a cane are taught to handle and care for the dog. When walking with a sighted person, a blind person can hold onto the bent elbow of the sighted person, rather than use an ambulation aid. The sighted person should not lead the blind person by the hand because some blind people perceive this action as dominant and controlling.

**COPD:** Patients with COPD can benefit from exercises to increase endurance and from strategies to simplify activities and thus conserve energy. Activities and exercises that encourage use of the upper and lower extremities are used to increase muscle aerobic capacity, which decreases overall oxygen requirement and eases breathing. Supervising patients while they engage in activity helps motivate them and makes them feel more secure. Such instruction may occur in medical facilities or in the patient's home.

**Head injury:** The term head injury is often used interchangeably with traumatic brain injury (TBI—see p. 3218). Abnormalities vary and may include muscle weakness, spasticity, incoordination, and ataxia; cognitive dysfunction (eg, memory loss, loss of problem-solving skills, language and visual disturbances) is common.

Early intervention by rehabilitation specialists is indispensable for maximal functional recovery (see also p. 3231). Such intervention includes prevention of secondary disabilities (eg, pressure ulcers, joint contractures), prevention of pneumonia, and family education. As early as possible, rehabilitation specialists should evaluate patients to establish baseline findings. Later, before starting rehabilitation therapy, patients should be reevaluated; these findings are compared with baseline findings to help prioritize treatment. Patients with severe cognitive dysfunction require extensive cognitive therapy, which is often begun immediately after injury and continued for months or years.

**Spinal cord injury:** Specific rehabilitation therapy varies depending on the patient's abnormalities, which depend on the level and extent (partial or complete) of the injury (see Ch. 325, particularly Table 325-1 on p. 3228). Complete transsection causes flaccid paralysis; partial transsection causes spastic paralysis of muscles innervated by the affected segment. A patient's functional capacity depends on the level of injury (see p. 1805) and the development of complications (eg, joint contractures, pressure ulcers, pneumonia).

The affected area must be immobilized surgically or nonsurgically as soon as possible and throughout the acute phase. During the acute phase, daily routine care should include measures to prevent contractures, pressure ulcers, and pneumonia; all measures needed to prevent other complications (eg, orthostatic hypotension, atelectasis, deep venous thrombosis, pulmonary embolism) should also be taken. Placing
patients on a tilt table and increasing the angle gradually toward the upright position may help reestablish hemodynamic balance. Compression stockings, an elastic bandage, or an abdominal binder may prevent orthostatic hypotension.
Chapter 351. Medicolegal Issues

Introduction

Medicine is practiced within an expanding and evolving system of legal rights and obligations, patient protections, health care financing regulation, and standards of care. Thus, health care can involve significant legal issues, including capacity of patients to make health care decisions, confidentiality of medical information, advance directives, and malpractice liability.

Capacity (Competence) and Incapacity

Historically, "incapacity" was considered primarily a clinical finding, and "incompetency" was considered a legal finding. That distinction is no longer firmly recognized; most state laws now use "incapacity" rather than "incompetency," although the terms are frequently used interchangeably. The key distinction now is between clinical incapacity and legal incapacity to make a health care decision.

Patients who have clinical and legal capacity have the right to make health care decisions, including refusal of medically necessary care, even if death may result from refusal. Patients who lack either capacity cannot make health care decisions. However, if a patient deemed by a physician to lack clinical capacity expresses a preference, the physician is not entitled to override that preference unless the patient is also found by a court to lack legal capacity to make that decision.

Clinical capacity: Clinical capacity to make health care decisions is the ability to understand the benefits and risks of the proposed health care, to understand possible alternatives, and to make and communicate a health care decision. Health care practitioners determine this type of capacity clinically and document the determination process. The courts become involved only when the determination itself or another aspect of the process is challenged.

Clinical capacity is specific to a particular health care decision and thus is limited to that decision. The level of clinical capacity needed to make a health care decision depends on the complexity of that decision. Patients with some decrease in capacity, even those with fairly severe cognitive deficits, may still have enough capacity to make simple health care decisions, such as whether to allow a rectal examination or placement of an IV. The same patient may lack the capacity to decide whether to participate in a clinical trial. All feasible attempts should be made to involve the patient in decision making. Ignoring the decision of patients with capacity or accepting the decision of patients without capacity is unethical and risks civil liability. A patient's ability to carry out a decision is also important for physicians to assess. For example, a patient with a broken leg may be able to make decisions but be unable to carry them out. Providing the necessary support to carry out a decision becomes an important goal of care.

Capacity may be intermittent, variable, and affected by the environment. Patients who lack capacity due to intoxication, delirium, coma, severe depression, agitation, or other impairment may regain capacity when their impairment resolves. To obtain consent to treat a patient who lacks clinical capacity, health care practitioners must contact an agent or proxy designated in the patient's durable power of attorney for health care or another legally authorized surrogate (see below). If urgent or emergency care is needed (eg, for an unconscious patient after an acute event) and there is no designated surrogate or the surrogate is unavailable, the doctrine of presumed consent applies: Patients are presumed to consent to any necessary treatment.

Legal capacity: Legal capacity (also called competency) is a legal status; it cannot be determined by health care practitioners. In the US, people aged ≥ 18 yr are automatically considered legally capable of making health care decisions for themselves. Emancipated minors are people below the age of majority (usually 18) who are also considered legally capable. The definition of this group varies by state but generally includes minors who are married, who are in the armed forces, or who have obtained a court decree of emancipation.

People remain legally capable until a judge with appropriate jurisdiction declares them legally incapacitated with respect to some or all areas of functioning. The legal requirements for declaring legal incapacity vary by state. However, substantiation of all of the following is typically required:
A disabling condition (e.g., intellectual disability [mental retardation], a mental disorder, dementia, altered consciousness, chronic use of drugs)

- Inability to receive and evaluate information or to make or communicate decisions

- Inability to meet essential requirements of physical health, safety, or self-care without protective intervention

If physicians question a person's legal capacity, they may seek a court's determination. Physicians may be asked to testify at or provide documentation for a hearing to determine legal capacity.

When the court declares a person legally incapacitated, it appoints a guardian or conservator to make legally binding decisions for the person in a specific range of matters. Courts can also make decisions about disputed issues (e.g., the meaning of a particular instruction in the patient's living will about which parties disagree).

**Informed Consent**

Consent of the patient is a prerequisite for any medical intervention. However, that consent often does not need to be expressed. For emergency care, consent is normally presumed. For interventions considered routine and unlikely to cause harm (e.g., routine phlebotomy, placement of an IV line), circumstances are typically considered to imply consent. For example, by holding out their arm, patients are presumed to indicate consent to receive certain routine interventions. For more invasive or risky interventions, express informed consent is always required.

To give informed consent, patients must have legal and clinical capacity (see p. 3468). Health care practitioners obtaining informed consent must be qualified to explain the risks and benefits of the intervention and to answer appropriate questions. The law requires that health care practitioners take reasonable steps to communicate adequately with patients who do not speak English or who have other communication barriers.

Ethical and legal authorities generally agree that health care practitioners are obligated to ensure, at a minimum, that patients understand

- Their current medical status, including its likely course if no treatment is pursued

- Potentially helpful treatments, including a description and explanation of potential risks and benefits

- Usually, the practitioner's professional opinion as to the best alternative

- Uncertainties associated with each of these elements

Generally, these discussions are noted in the medical record, and a document describing the discussion is signed by the patient.

Although practitioners are ethically bound to provide sufficient information and to encourage decisions judged to be in the patient's best interest, patients still have the right to refuse treatment. A patient's refusal of treatment is not considered to be attempted suicide, nor is the health care practitioner's compliance with the patient's wishes legally considered physician-assisted suicide. Rather, the subsequent death is considered legally to be a natural consequence of the disease process itself.

A refusal of care, if puzzling, should prompt the health care practitioner to initiate further discussion. If refusal of treatment will hurt other people, such as a minor child or other dependent, ethical and legal consultation should be sought.

**Consent and Surrogate Decision Making**
When immediate decisions are medically required, the doctrine of presumed consent applies (see above). In other circumstances, consent must be obtained.

**Children:** For most nonemergency medical decisions affecting minors, medical care cannot proceed without a parent's or guardian's consent. The parent's or guardian's decision can be overridden only if a court determines that the decision constitutes neglect or abuse of the minor. In some states, minors can consent to certain medical treatments (eg, treatment of sexually transmitted diseases, prescriptions for birth control, abortion) without parental permission. Individual state law must be consulted.

**Adults:** When adult patients lack capacity to consent to or refuse medical treatment, health care practitioners must rely on an authorized surrogate for consent and decision making. All surrogates—whether appointed by the individual, by default, or by the court—have an obligation to follow the expressed wishes of the patient and to act in the patient's best interests, taking into account the patient's personal values to the extent known.

If adult patients already have a court-appointed guardian with authority to make health care decisions, the guardian is the authorized surrogate. If patients who lack capacity have a durable power of attorney for health care, the agent or proxy appointed by that document is authorized to make health care decisions within the scope of authority granted by the document. Generally, specific instructions that are given in a living will, health care declaration, or other advance directive executed by patients while capacitated can be relied on.

If the decision of an authorized agent or proxy seems to conflict directly with instructions in a living will, the outcome depends on the scope of discretion given to the agent or proxy. Normally, the durable power of attorney for health care confers broad decision-making discretion on the agent. Nevertheless, the health care practitioner should determine whether the document gives the agent broad discretion beyond the written instructions or limits the agent to the written instructions. Legal advice may be needed.

If patients have no authorized surrogate, health care practitioners usually rely on the next of kin or even a close friend. However, the exact scope of authority and the priority of permissible surrogates vary by state. Typically, the order of priority is a spouse (or domestic partner in jurisdictions that recognize this status), an adult child, a parent, a sibling, then possibly other relatives or a close friend. If more than one person has the same priority (eg, several adult children), consensus is preferred, but some states allow health care practitioners to rely on a majority decision.

If a patient's decision-making capacity, a surrogate's authority, or the ethical or legal appropriateness of a particular treatment decision is disputed, consultation with an institutional ethics committee or similar body is advisable. If agreement on an ethically and legally sound resolution cannot be reached, health care practitioners may need to request court review. Many institutions make the ethics committee available on short notice (eg, in 1 or 2 days); judicial review is typically more time-consuming.

**Scope:** Patient choice is not limitless. For example, health care practitioners are not required to provide treatments that are medically inappropriate, such as those that are against generally accepted health care standards. However, sometimes there are legitimate differences of opinion regarding what is inappropriate. Labeling a treatment as “futile” does not generally help if said treatment may affect outcomes other than mortality or morbidity that are important to the patient. Physicians do not have to act against their conscience, but if they cannot comply with a requested course of action, they may have a responsibility to try to transfer a patient to another physician or institution of the patient's choice.

**Confidentiality and HIPAA**

Traditionally, ethical health care has always included the need to keep patients' medical information confidential. However, the Health Insurance Portability and Accountability Act (HIPAA—see www.hhs.gov/ocr/hipaa) has codified the responsibility of health care providers. In HIPAA, “health care providers” include health plans, health care clearing-houses, and health care practitioners who electronically conduct financial and administrative transactions (eg, enrollment, billing, eligibility verification). Key provisions of HIPAA involve the following areas.
Access to medical records: Generally, patients should be able to see and obtain copies of their medical records and request corrections if they identify errors.

Notice of privacy practices: Health care providers must provide a notice about their possible uses of personal medical information and about patient rights under HIPAA regulations.

Limits on use of personal medical information: HIPAA limits how health care providers may use individually identifiable (protected) health information. The act does not restrict physicians, nurses, and other practitioners from sharing information needed to treat their patients. However, practitioners may use or share only the minimum amount of protected information needed for a particular purpose. In most situations, personal health information may not be used for purposes unrelated to health care. For example, a patient must sign a specific authorization before a health care provider can release medical information to a life insurer, a bank, a marketing firm, or another outside business for purposes unrelated to the patient's current health care needs.

Marketing: Marketing is communication designed to encourage people to purchase a particular product or service. HIPAA requires that the patient's specific authorization must be obtained before disclosing information for marketing. The health care practitioner must disclose any payments that will be received as a result of marketing. However, health care practitioners can freely communicate with patients about treatment options, products, and other health-related services, including disease-management programs.

Confidential communications: A patient can request that health care practitioners take reasonable steps to ensure that their communications with the patient are confidential. For example, patients could ask a physician to call their office rather than home. Nonetheless, unless the patient objects, practitioners can share medical information with a patient's immediate family members or someone known to be a close personal friend if the information relates directly to that person's involvement with the patient's care or payment for care. Practitioners are expected to exercise professional judgment.

For purposes of the privacy rule, an authorized personal representative of the patient (eg, a proxy appointed in a power of attorney for health care or a state-authorized decision-making surrogate) should be treated the same as the patient. Thus, the representative has the same access to information and may exercise the same rights regarding confidentiality of information. Nevertheless, practitioners may restrict information or access if there are reasonable concerns about domestic violence, abuse, or neglect by the representative.

Some communication cannot remain confidential. Health care practitioners are sometimes required by law to disclose certain information, usually because the condition may present a danger to other people. For example, certain infectious diseases (eg, HIV, syphilis, TB) must be reported to state or local public health agencies. Conditions that might seriously impair a patient's ability to drive, such as dementia or recent seizures, must be reported to the Department of Motor Vehicles in some states.

Complaints: Patients may file complaints about compliance with these privacy practices. Complaints can be made directly to the health care practitioner or to the Office for Civil Rights in the US Department of Health and Human Services. Patients do not have a right to file a private lawsuit under HIPAA. There are civil and criminal penalties for misuse of personal health information; however, such penalties should not worry health care practitioners who, in good faith, make reasonable attempts to comply.

Advance Directives

Advance directives are legal documents that extend a person's control over health care decisions in the event that the person becomes incapacitated. They are called advance directives because they direct preferences before incapacitation occurs. There are 2 primary types:

• Living will: Expresses preferences for end-of-life care

• Durable power of attorney for health care: Designates a surrogate decision maker

Every state in the US recognizes and has defined these documents by statute to provide a simple legal
tool by which people can express their wishes and have them honored. However, advance directives are not the only means of expressing such wishes. Any authentic expression of patient's wishes should be honored.

An advance directive cannot be completed after a patient becomes mentally incapacitated, and in most states, it does not become effective until after incapacity has been determined. If no advance directive has been prepared, an authorized surrogate (see p. 3469) must be identified or appointed to make health care decisions.

**Living will:** A living will expresses a patient's preferences for end-of-life health care (it is called a "living" will because it is in effect while the person is still alive). In some states, the document is called a directive to doctors or a declaration. State laws vary greatly regarding scope and applicability of living wills.

A living will allows people to express preferences for the amount and nature of their health care, from no interventions to maximum care. Detailed treatment preferences are desirable because they provide more specific guidance to practitioners. A living will cannot compel health care practitioners to provide health care that is medically or ethically unwarranted.

To be valid, a living will must comply with state law. Some states require that living wills be written in a fairly standardized way. Others are more flexible, permitting any language as long as the document is appropriately signed and witnessed. In most states, a health care practitioner involved in the patient's care cannot be a witness. A document that does not comply with state law requirements for statutory living wills may still serve as a valid communication of a patient's wishes as long as it is an authentic expression of the patient's wishes.

Living wills go into effect upon the loss of ability to make health care decisions or the existence of a medical condition specified in the directive—typically a terminal condition, permanent vegetative state, or the end-stage of a chronic condition. Often, state law provides a process for confirming and documenting the loss of decisional capacity and the medical condition.

**Durable power of attorney for health care:** In this document, one person (the principal) names another person (the agent, proxy, or the attorney-in-fact) to make decisions about health care and only health care. In most states, these documents become legally effective when the principal loses clinical capacity to make health care decisions. Some states recognize immediately effective durable powers of attorney for health care, but as a practical matter, the principal retains decision-making authority until incapacity regardless, so there is little practical difference. Like the living will, the durable power of attorney for health care may be referred to by different terms in different states.

While a living will states a person's specific preferences regarding medical treatment, a durable power of attorney for health care designates an agent to make health care decisions. People who have both a living will and a durable power of attorney for health care should stipulate which should be followed if the documents seem to conflict. Because predicting future circumstances in all of their complexity is virtually impossible and because the durable power of attorney for health care designates a decision maker who can respond to here-and-now circumstances, a durable power of attorney is far more practical and flexible than a living will. The agent is granted the power to discuss medical alternatives with the physicians and make decisions if an accident or illness incapacitates the person. In most states, a health care practitioner involved in the care of the patient cannot serve as agent for health care matters, unless the practitioner is a close relative. The durable power of attorney for health care can include a living will provision or any other specific instructions but, preferably, should do so only as guidance for the agent, rather than as a binding instruction.

The durable power of attorney for health care should name an alternate or successor in case the first-named person is unable or unwilling to serve as agent. Two or more people may be named to serve together (jointly) or alone (severally), although reliance on multiple concurrent agents can be problematic. A jointly held power requires that all agents agree and act together. In this arrangement, all named agents must be contacted and must agree on every decision. However, this arrangement can be unwieldy because agreement may be difficult to achieve and because one of the agents may be unreachable when a critical decision must be made. A severally held power may be more functional because it allows any
named agent to act alone. However, this arrangement can also lead to disagreement, and the courts may
eventually have to become involved. For example, if ≥ 2 people serve jointly in severally held power and
they absolutely cannot agree, the parties are likely to end up in court.

The use of the durable power of attorney for health care is valuable for adults of all ages. It is especially
critical for unmarried couples, same-sex partners, friends, or other individuals who are considered legally
unrelated and who wish to grant each other the legal authority to make health care decisions and to
ensure rights of visitation and access to medical information.

Ideally, physicians should obtain a copy of a patient's living will and durable power of attorney for health
care, review the contents with the patient while the patient is still capable, and make it part of the medical
record. A copy of the durable power of attorney for health care should also be given to the patient's
appointed agent and another copy placed with important papers. The patient's attorney should hold a
copy of all documents. An increasing number of states offer optional electronic registries for recording
advance directives.

Do-Not-Resuscitate Orders

The do-not-resuscitate (DNR) order placed in a patient's medical record by a physician informs the
medical staff that CPR (see p. 2256) should not be done. This order has been useful in preventing
unnecessary and unwanted invasive treatment at the end of life.

Physicians discuss with patients the possibility of cardiopulmonary arrest, describe CPR procedures, and
ask patients about treatment preferences. If the patient is incapable of making a decision about CPR, a
surrogate may make the decision based on the patient's previously expressed preferences or, if such
preferences are unknown, in accordance with the patient's best interests.

Almost all states have specialized DNR protocols for patients who are living at home or in any nonhospital
setting. These protocols typically require the signing of an out-of-hospital DNR order by both the
physician and patient (or the patient's surrogate) and the use of a special identifier (eg, a bracelet or
brightly colored form) that is worn by or kept near the patient. If emergency medical personnel are called
in case of emergency and see an intact identifier, they will provide comfort care only and not attempt
resuscitation. These protocols are important to know because normally, emergency medical technicians
are not expected to read or rely upon a living will or durable power of attorney for health care.

A DNR order does not mean "do not treat." Rather, it means only that CPR will not be done. Other
treatments (eg, antibiotic therapy, transfusions, dialysis, use of a ventilator) that may prolong life can still
be provided. CPR itself usually does not result in long-term, neurologically intact survival, but other
treatments, including aggressive or critical care that prevents cardiac arrest, can. Thus, whether to
pursue other treatments is a more important decision than whether to resuscitate. A person with a DNR
order can still be treated aggressively in an intensive care unit if their condition warrants.

Medical Malpractice

Patients can sue health care practitioners if they feel they have been injured. However, successful
medical malpractice lawsuits require proof of the following:

• The care provided was below the ordinary standard of care that would be provided by similar health
care practitioners under similar circumstances.

• A professional relationship existed between the health care practitioner and the injured party.

• The patient was harmed because of the deviation from the standard of care.

Concern about lawsuits sometimes puts pressure on physicians to act in ways that are not necessarily in
the best interest of their patients. For example, physicians may order tests or treatments that are not
clearly medically necessary just because patients request them or to avoid even a remote possibility of
missing something and thus leaving themselves open to a lawsuit. However, such an approach is not
required by law, may not protect against lawsuits, and is generally considered excessive and inappropriate. Also, explaining why a requested test or treatment is not recommended usually satisfies patients. The best defense against malpractice lawsuits is providing excellent health care and building close, trusting, collaborative relationships with patients.
Introduction

Health care in the US is technologically advanced but expensive, costing about $2.2 trillion dollars in 2007. For decades, health care spending in the US has increased more than the rate of growth for the overall economy; it increased from about 6% of the gross domestic product (GDP) in the 1960s to 16.2% in 2007. The percentage of GDP spent on health care in the US is significantly higher than that in any other nation. The next highest are 11.6% for Switzerland and 11.1% for France; the percentage is 9.8% for Canada and 8.0% for Japan. Also, the amount of money spent per capita on health care in relation to GDP per capita is also higher than that in other countries (see Fig. 352-1). The absolute amount and the rate of increase in the US are widely regarded as unsustainable. Consequently, US health care is currently in flux, as the government attempts to find ways to provide universal health care and reduce its costs.

Consequences of increased US spending on health care include the following:

- Increased government spending (resulting in higher national debt, decreased funding for other programs, or both)
- Slowed growth or a real decline in workers' earnings due to higher payments for health insurance premiums
- Increased costs to employers (resulting in increased product cost and movement of jobs to countries with lower health care costs)
- Increased numbers of people without health insurance (resulting in large increases in un-compensated health care, shifting of cost burden, and poor health outcomes)

Even though US health care spending per capita is the highest in the world, about 46 million people in the US do not have health insurance, whereas other developed countries, despite lower per capita expenditures, ensure universal access to health care. Furthermore, the high spending may not lead to correspondingly superior outcomes; the US ranks comparatively low on many health care outcome measures, such as the following:

- Infant mortality: 30th
- Life expectancy at birth: 23rd for males and 25th for females
- Healthy life expectancy: 24th

Funding

Health care providers in the US are paid by the following:

- Private insurance
- Government insurance programs
- Individual out-of-pocket funds

[Fig. 352-1. 2006 health care spending per capita compared to gross domestic product (GDP) per capita.]

In addition, the government directly provides some health care in government hospitals and clinics staffed by government employees. Examples are the Veteran's Health Administration and the Indian Health Service.

Private insurance: Private insurance is purchased from for-profit and not-for-profit insurance.
companies, which are accredited separately in each state. Thus, although there are many health
insurance companies in the US, a given state tends to have a limited number.

Most private insurance is purchased by corporations as a benefit for employees. Premiums are typically
shared by employers and employees. But because the cost of employer-provided health insurance is not
considered taxable income for the employee, the government in effect provides some subsidization.

People may also purchase private health insurance themselves. However, unlike in employer-provided
policies, applicants for privately purchased policies typically undergo extensive evaluation (underwriting)
to identify and reject applicants likely to require costly care, including those with preexisting conditions or
a high likelihood of developing disorders. Many applicants are denied policies. Some cannot purchase
private insurance at any price. For applicants who do qualify, costs can be much higher for a given policy
than when it is purchased through a company or another large group, partly because of administrative
costs (often > 30% of the total).

**Government insurance programs:** The main government insurance programs include

- Medicare (see p. 3155), which funds the elderly, the disabled, and people receiving long-term dialysis
  therapy
- Medicaid (see p. 3161), which funds certain people living below the poverty level

Other government programs include

- State Children’s Health Insurance Program, which provides matching federal funds to states for health
  insurance for families with children and which was designed to help ensure coverage for uninsured
  children when family income was below average but too high to qualify for Medicaid
- Tricare, which covers about 9 million active duty and retired military personnel and their families (some
  Tricare subscribers use government-provided care)
- Veterans Health Administration (VHA), which is a government-operated health care system that provides
  comprehensive health services to eligible military veterans (about 8 million veterans are enrolled)
- Indian Health Service, which is a system of government hospitals and clinics providing health services to
  almost 2 million American Indians and Alaskan natives living on or near a reservation

Overall about 30% of the population is covered by government insurance or government-provided care.

**Out of pocket:** People pay for care not covered by other sources out of their own funds, often using their
savings for small expenditures and borrowing (including using credit cards) for large expenditures.

**Flexible spending accounts** (FSAs) are offered by some employers. Through these accounts,
employees can choose to have a limited amount of money deducted from their paychecks to pay for out-
of-pocket health care expenses. The money deducted is not subject to federal income taxes. However,
the account does not earn interest, and any unused money is forfeited at the end of the year.

**Health savings accounts** can also be used to pay out-of-pocket expenses; these accounts earn
interest, and unused balances need not be forfeited. Most people who are eligible for these accounts are
eligible because their health insurance plans limit their reimbursements enough to be classified as high-
deductible health plans.

About 17% of health care costs in the US are funded out-of-pocket. Out-of-pocket expenditures for health
care contribute significantly to a large number of bankruptcies in the US.

**Causes of High Health Care Costs**

Health care costs in the US are disproportionately high for many reasons.
Use of costly new technologies and drugs: Such use may be the largest single factor increasing health care costs. Use may be appropriate or inappropriate, but in either case, cost is increased. An example of appropriate but costly treatment is the use of fibrinolysis or angioplasty to treat an MI; before the 1980s, when these treatments began to be used commonly, treating an MI was much less costly (but also less effective). On the other hand, many new and costly treatments, including some in popular use, are ineffective, offer only marginal advantages, or are used inappropriately for patients unlikely to benefit. An example is use of lower lumbar spinal fusion to treat chronic low back pain; many experts think this treatment is ineffective or grossly overused.

Use of many such costly treatments tends to vary considerably among geographic areas and among physician practices within a geographic area (termed practice variation). For some specific disorders (eg, coronary artery disease), health outcomes are no better in areas where adjusted health spending is high than in areas where it is low.

Increased costs of health care goods and services: Drug costs have increased. One reason is the increasing cost of developing a new drug, often in the vicinity of $1 billion. The cost of drug development decreases the economic incentive to develop drugs with lower profit potentials, even those that could substantially benefit particular groups (eg, drugs to treat rare diseases) or public health in general (eg, vaccines, antibiotics).

Marketing of new drugs and devices: Intensive marketing to physicians and consumers (with direct-to-consumer advertising) has been suggested as a cause of overuse of costly new technologies and drugs. Some of these new measures may be no more effective than older, less costly ones.

Overuse of specialty care: Specialists are increasingly providing more care; reasons may include a decreasing number of primary care physicians and an increased desire by patients to see a specialist. Specialty care is often more expensive than primary care; specialists have higher fees and may do more testing (often pursuing less common diagnoses) than primary care physicians. Also, evaluation and treatment of a patient who could have been managed by a single primary care physician may require more than one specialist.

High administrative costs: The percentage of health care dollars spent on administration is estimated to be 20 to > 30%. Most administrative costs are generated by private insurance, and most of those costs are generated by marketing and underwriting, processes that do not improve medical care. Also, the existence of numerous private insurance plans in the same geographic area typically increases health care providers’ costs by making processing (eg, claim submission, coding) complicated and time-consuming.

Physician fees: Physicians in the US are more highly compensated relative to other professionals than physicians in many other countries. This disparity occurs partly because physicians in other countries typically spend far less on their medical education and malpractice insurance than those in the US and have lower office overhead. Because physician fees account for only about 20% of total health care costs, even a significant reduction in physician fees would have only a modest effect on overall costs.

Malpractice costs: The issue of malpractice adds to the cost of medicine directly and indirectly (by triggering defensive medicine).

The direct cost is the malpractice insurance premiums paid by physicians, other providers, health care institutions, and medical drug and device manufacturers. These premiums, which cover claim settlements and malpractice insurance company overhead and profits, must ultimately be paid from health care revenues.

As onerous as premiums and the threat of lawsuits can be for individual physicians (particularly in certain high-risk specialties and geographic areas), the total annual malpractice premium amount paid in 2008 by physicians and institutions was about $12 billion, representing only about 0.6% of total annual health care costs. Actual malpractice settlements paid out in 2008 were $3.6 billion (< 0.2% of health care costs).
Thus, even a major reduction in malpractice settlements would not lower total health care costs significantly, although it could greatly affect certain physicians' practices.

Defensive medicine: Defensive medicine refers to diagnostic or treatment procedures that providers do to guard against the possibility of malpractice litigation, even though such procedures may not be warranted clinically. For example, a physician may hospitalize a patient who is likely to do well with outpatient treatment to avoid a lawsuit in the unlikely event of an adverse outcome.

The actual costs attributable to defensive medicine are difficult to measure. Few rigorous studies have assessed this cost, and estimates from these studies vary greatly, ranging from negligible to substantial (some experts believe that these costs are larger than direct malpractice costs). Some of the uncertainty lies in the fact that defensive medicine is defined subjectively (ie, it is the clinician's reason for doing a test, not how unlikely or uncommon the disorder being tested for is). A clinician's motivation is hard to determine, and different clinicians can reasonably vary in their assessment of the need for testing in a given case (except for a relatively few situations that have clear, sensitive, and specific guidelines for testing). In some survey studies of defensive medicine, physicians were asked whether and when they practice defensive medicine. However, such self-reporting may be unreliable, and such surveys often have a low response rate. Thus, the extent of defensive medicine is unknown.

Furthermore, even when defensive testing can be identified, calculating potential cost savings is not straightforward. Decreasing the amount of defensive testing involves a change in marginal costs (the cost of providing or withholding an additional unit of service), which are different from actual charges or reimbursements. In addition, studies of states that have enacted tort reforms to limit compensation to patients for iatropic injuries have had conflicting results about whether such reforms lower health care expenditures.

Aging of the population: Although often cited as a factor, population aging is probably not responsible for recent increased costs because the generation now in old age has not yet increased disproportionately; also, more effective health care has tended to delay serious illness in this generation. However, the aging of baby boomers may affect costs more as the proportion of the population > 65 increases from about 12% currently to about 20% after 2030.

Containing Health Care Costs

Conceptually, total health care costs can be contained or decreased only by some combination of the following:

- Decreasing use of health care services
- Decreasing reimbursement for services that are used
- Decreasing overhead (payor, provider, or both)

Some strategies adversely affect access to care or outcomes; others may improve care. Evaluating different strategies is difficult, partly because accurately measuring patient-centered health outcomes (eg, morbidity and mortality, quality-adjusted life years [QALY]) tends to be expensive and to require large numbers of patients and long follow-up periods. As a result, most measures used to assess health care quality reflect processes (how care was delivered) rather than outcome. How well these process measures predict ultimate health outcomes is not always clear.

Decreasing Use of Health Care Services

Many strategies can decrease the use of health care services. Many involve limiting access to care (aimed at unnecessary care but sometimes affecting necessary care), but some limit need by improving health.

Limiting access to health care: Traditionally, limiting access has been the strategy used to limit health care costs.
Insurance companies may limit access to care by denying coverage to people likely to need care (eg, those with preexisting conditions) and by dropping coverage of heavy users (rescission).

Government may tighten eligibility criteria for medical assistance programs.

Payors may increase out-of-pocket costs, providing an economic incentive for patients to limit their own health care use. For example, payors may

- Limit the type and number of visits that are reimbursed (eg, mental health care, physical therapy)
- Increase deductibles and co-payments
- Decrease allowable amounts for covered procedures
- Establish or decrease lifetime maximum expenditures

These strategies probably affect outcomes because evidence indicates that many patients avoid necessary as well as unnecessary care. For example, women may avoid screening (eg, Papanicolaou testing, mammography) and subsequently present with late-stage cancer; at-risk patients may avoid influenza vaccination.

By erecting administrative hurdles to care (eg, requiring approval for tests, referrals, and procedures; having complex enrollment procedures and regulations), payors, although not technically denying care, decrease use by a small amount.

State agencies may limit issuance of construction permits for new facilities and laboratories (called certificates of need).

Limiting access to health care can cause problems. For example, when people denied access become seriously ill (which is more likely when routine care is lacking), they are often treated in a hospital on an emergency basis. This care is largely uncompensated (not paid for by patient, insurance, or other source), increasing the burden on people who pay into the health care system, and may be more expensive than if routine care had been provided.

**Eliminating unnecessary care:** Unnecessary care is easy to define (care that does not improve patient outcome) but often difficult to recognize and still more difficult to eliminate. First steps include conducting more and better studies of comparative effectiveness and cost-effectiveness, so that best practices can be identified. Comparative effectiveness studies can evaluate areas other than drugs, such as effects of exercise, of physical therapy, and of different providers, systems, settings of medical care, and reimbursement systems. Education and monitoring of providers may decrease practice variation and increase cost-effectiveness. Eliminating the economic incentive for providing more intensive care (fee-for-service model) by using prospective payment systems (see below) and pay-for-performance models may encourage providers to eliminate cost-ineffective care processes.

Better coordination of services among providers (eg, by closer communication and use of universally readable electronic medical records) may make evaluation and treatment more efficient (eg, by eliminating duplication of tests).

Encouraging palliative hospice care, when appropriate, may help decrease use of costly, often technology-intensive, cure-directed care.

**Improving health:** Increased use of relatively inexpensive preventive services (eg, screening, diagnosis, and treatment of diabetes, hypertension, and hyperlipidemia; screening for breast and colon cancer) may decrease the subsequent need for expensive treatments (eg, for MI, stroke, or late-stage cancer). However, preventive measures may not decrease costs for a given private insurance company because savings are often not realized for many years; by that time, many patients have switched insurance plans. In the US, people stay with a given insurance company for an average of about 6 yr (usually determined
by how often they change jobs)—too short to realize a savings via preventive care.

Strategies to increase preventive care include

- Incentives to increase the number of primary care physicians (who can often provide appropriate screening measures and help prevent complications)
- Pay-for-performance measures that financially reward adherence to preventive care guidelines
- Elimination of co-payments for preventive services
- Free preventive services, particularly for needy people

Whether care management programs that attempt to improve patient adherence to treatment plans and clinician adherence to guidelines can improve outcomes or reduce costs (eg, of potentially avoidable hospitalization or complications) is unclear; some studies do not show a benefit.

Decreasing Reimbursement for Care Used

Even when health care is provided, strategies can be used to limit payments.

**Lower fees:** Payors (government and private) may negotiate lower fees with institutions and providers or simply dictate such fees. In the US, reimbursement rates established by Medicare and Medicaid tend to influence rates paid by other plans, sometimes decreasing reimbursement.

**Increased use of primary care:** Measures may help increase the use of less costly primary care vs specialty care. For example, in the patient-centered medical home model, primary care practitioners coordinate and integrate all aspects of medical care, including specialty and interdisciplinary care, in various settings (eg, home, hospital, long-term care facility). Many authorities think that this model can decrease unnecessary specialty care, duplicative care, and care that may be inappropriate for the individual’s health goals (eg, palliation rather than diagnosis).

Measures to increase the supply of primary care physicians have been proposed. They include increasing reimbursement for primary care, shifting more government funding of residency programs to primary care training, and enhancing the attractiveness of primary care among medical students, although how the last strategy could be implemented is unclear.

**Prospective payment systems:** In these systems, providers are paid a fixed amount regardless of how much care is provided. The amount may be based on a specified episode of care or be a fixed annual reimbursement per patient. For example, some Medicare reimbursement is based on diagnosis-related groups (DRGs); in such cases, Medicare pays a fixed amount based on the diagnosis. In capitated systems, providers are paid a fixed annual amount to provide health care for patients regardless of the services used.

Prospective payment systems reward less expensive care (and thus usually use of fewer services), in contrast to fee-for-service systems, which reward use of more services. However, prospective payment creates an economic disincentive to care for complex patients (eg, those who have multiple disorders or who are seriously ill) and may inhibit provision of necessary care. Because a decrease in the amount of care provided has the potential to decrease quality of care, quality control systems (eg, professional review organizations) are often also established.

**Denial of claims:** In the US, unlike in most of the developed world, insurance carriers routinely deny a significant percentage of claims for services delivered to patients. In one study in California, the denial rate averaged about 30% in 2009; some of the claims were paid after appeal, but appealing a claim is quite costly in time and effort for patients, providers, and payors alike.

**Competition:** Competition among providers for patients and among insurance companies for subscribers is thought to encourage lowering of charges (eg, by those who charge more than their competitors for a
similar service). However, the ultimate consumers (ie, patients) usually do not know providers’ charges in advance, and if they know, they often cannot act on this knowledge (eg, because patients are often limited to certain providers and limited in their ability to judge quality of care). Also, because the cost of medical care is subsidized for most consumers (eg, through employer-paid health insurance, tax deductions, and flexible spending accounts or medical savings accounts), consumers have less incentive to price shop than for most other purchases. Thus, competition is most effective in lowering costs and maintaining quality when it is among large organizations. For example, insurance companies can compete for contracts from employers such as corporations or the government; providers such as practitioner organizations and hospitals can compete for contracts with insurance companies.

Competition has some disadvantages. It results in multiple systems of claim submission and evaluation, which require more time from providers, their clerical staff, or both. Also, processes such as eligibility determination, referrals, co-payments, and coding must be coordinated between a large number of incompatible insurance company systems. Thus, competition increases the clerical (administrative) burden of the overall health care system.

Decreased drug costs: Using generic drugs or, when appropriate, more cost-effective brand-name drugs can help decrease drug costs. Strategies include

- Educating providers about cost-effective drug use
- Restricting drug marketing
- Establishing formularies and using pharmacy benefit managers
- Allowing the government to negotiate drug prices for patients covered by government insurance
- Allowing importation of drugs purchased from other countries to the US

Negative effects on medical research: In many academic medical centers, income from clinical practice has enabled physicians and institutions to participate in medical research. Similarly, income from drug sales supports pharmaceutical research. Thus, decreased reimbursement for care and drug sales may cause a decline in medical research. If other sources (eg, government or private grants) are used to fund research, these funds must be considered as health care costs and thus may offset savings realized from decreasing reimbursement.

Decreasing Overhead

Overhead is health care payments that do not go to health care providers (eg, administrative costs, malpractice insurance, corporate profits in for-profit hospitals and insurance companies).

Decreasing payor overhead: Government health care plans in developed countries (including the US) and private health plans outside the US have overhead costs that usually represent 3 to 5% of total costs (ie, ≥ 95% of all health care funds go to the delivery of health care). However, in the US, private insurers have overhead costs of about 20 to 30%, partly because these insurers need staff to do extensive underwriting (identifying and rejecting applicants likely to require costly care, including those with preexisting conditions or a high likelihood of developing disorders), to evaluate claims for denial, and to adjudicate appeals by providers; they also typically need to show a profit. No evidence indicates that these activities and their higher administrative costs improve clinical care or outcomes.

Strategies that may help minimize overhead costs include

- Increased use of standardized electronic health records
- Increased use of government plans and possibly not-for-profit plans, which have lower overhead than for-profit plans

Competition among payors is thought to encourage increased administrative efficiency, but it also
increases the incentives to deny claims and coverage (which itself requires an extensive bureaucracy).

**Decreasing provider overhead:** Any payor reform that eliminates the need for the many billing and claims personnel who manage the billing of multiple payors and negotiate appeals and justify claims will decrease provider overhead. For example, some countries that have multiple insurance companies vying for business (eg, Germany, Japan) require the following:

- The payment amounts and rules are the same for all insurance companies.
- In many cases, payors are required to pay all provider bills.
- The cost of the same service is the same throughout the country.

Although malpractice costs are a small fraction of overall costs, malpractice costs for certain physicians can consume a considerable part of their annual income. Reforms that significantly decrease the number of suits and settlements should eventually lower premiums and greatly benefit these physicians; such reforms may also decrease the use of unnecessary, defensive medicine.
Chapter 353. The Dying Patient

Introduction

(See also pp. 2755 and 3471.)

The traditional medical approach emphasizes goals such as the following:

• Testing until diagnoses are well-established

• Correcting all physiologic abnormalities, even asymptomatic ones

• Pursuing a cure, even when cure is unlikely and therapy is toxic, invasive, or uncomfortable

However, to many patients facing a fatal illness, these goals may be less important than avoiding suffering and (with their family and friends) finding comfort and meaningfulness during the experience of dying. Thus, care of the dying patient should be guided by a realistic assessment of the situation and the merits of various interventions in light of the patient's values and wishes.

People's priorities differ, especially when facing death. Some prefer life to be prolonged, even at the cost of pain, marked confusion, or severe respiratory distress. They may cherish every moment of life, regardless of its quality. For others, quality of life is the overarching concern. They may fear pain or confusion more than death and prefer comfort measures and shorter survival to prolonged disability and struggle. However, to say that a patient's care has changed from curative to supportive or from treatment to palliation is an oversimplification of a complex decision process. Most patients need a customized mix of treatment to correct, prevent, and mitigate the effects of various illnesses and disabilities.

Some people search for closure: They reach out to friends and family to share time and to express love; they complete projects important to their lives and tie up loose ends. Often, with appropriate support, people die at a time and in a way that allows them to experience a satisfying close. Other people cannot accept their imminent mortality and avoid such closure.

Effective care for dying patients usually involves a clinical team because no one caregiver is available 24 h/day and because comprehensive, reliable care requires the skills and perspectives of several disciplines. Palliative care or hospice teams anticipate potential problems and make appropriate arrangements, such as obtaining supplies or opioids in anticipation of a potential emergency. Certain team members can help dying patients who have spiritual needs; such needs should be recognized, acknowledged, and addressed. When death is imminent, an experienced team member can comfort family members and may prevent an inappropriate call to the emergency medical system.

When Death Is Near

The physician and the clinical team should prepare patients and family members for death whenever patients have a condition likely to worsen and cause death, even if death may be a few years in the future. Preparation includes discussion of the likely course and possible complications. Patients should also be advised when death becomes imminent. A health care practitioner must not assume that patients or family members understand the fatal nature of certain disorders (even metastatic cancer) or that they can recognize from a patient's appearance that death is near. Initial discussions should be honest and sensitive to the language and culture of patients and family members. The physician should not delay full disclosure too long because doing so can provide false hope and distort decision making—for example, by reducing the opportunity to attend to spiritual and family concerns. Many patients and family members benefit from making plans based on their priorities and preferences for end-of-life treatments (see p. 3471).

Many patients ask whether the clinician can predict the time until death. Such estimates are ordinarily incorrect, both for slowly progressive disorders and for disorders in which death tends to come suddenly, without reliable warning signs (eg, heart failure, emphysema). For some cancers, recognizable warning signs may presage death by several weeks or months. In contrast, many people live for months or years...
in an unchanging but very fragile state of health. Clinicians tend to give inaccurately optimistic estimates and often are reluctant to predict life expectancy. Some models, such as the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) used to predict in-hospital mortality for ICU patients, are accurate for groups but not for individuals. If a clinician notes that a patient is sick enough that it would be "no surprise" for the patient to die in the coming year, the patient could die with the next complication, which could develop at any time. In such cases, clinicians, patients, and family members should consider prioritizing comfort and life closure over at least the burdensome elements in conventional medical treatment, as well as many preventive services. Family support, advance care planning, focus on relieving symptoms and maximizing function, and attention to spiritual issues are appropriate for patients who are in such fragile health. Clinicians lose many opportunities to help patients and their families live well and meaningfully by postponing the recognition of fragile health until death is clearly imminent.

At some point, virtually every dying patient should have a do-not-resuscitate (DNR) order or a do-not-attempt-resuscitation (DNAR) order written in the medical record. All clinicians in every setting should abide by that decision. Patients, family members, and the clinical team should also make and record other important decisions about medical care (eg, whether patients are to be hospitalized or use a ventilator). Often, implementing these decisions requires specific actions (eg, to have the needed drugs at home). Family members should know about the changes that may occur in the patient's body shortly before and after death. They should not be surprised by irregular breathing, cool extremities, confusion, a purplish skin color, or somnolence in the last hours.

Some patients close to death develop noisy bronchial congestion or palatal relaxation, commonly known as the death rattle. If this symptom distresses family members, scopolamine or diphenhydramine (see p. 3485) can dry the patient's secretions and reduce the noise. Also, CNS irritability, with agitation and restlessness, may develop. If these symptoms, after review, are judged not to be caused by a drug or untreated disorder, they can be relieved by a sedative.

If a patient is expected to die at home, family members should rehearse whom to call (eg, physician, hospice nurse, clergy) and know whom not to call (eg, ambulance service, 911). They should also have help in obtaining legal advice and arranging burial or cremation services. Religious practices that may affect after-death care of the body should be discussed before death with the patient, family members, or both.

The last moments of a patient's life can have a lasting effect on family members, friends, and caregivers. The patient should be in an area that is peaceful, quiet, and physically comfortable. Any stains or tubes on the bed should be covered, and odors should be masked. Family members should be encouraged to maintain physical contact, such as holding hands, with the patient. If desired by the patient and family members, the presence of friends and clergy should be encouraged. Accommodation should be made for spiritual, cultural, ethnic, or personal rites of passage desired by the patient and family members.

When resuscitation is attempted, family members often appreciate being present during the resuscitation.

After Death Occurs

A physician, nurse, or other authorized person should pronounce the patient dead in a timely way to reduce the family's anxiety and uncertainty. The physician should complete the death certificate as soon as possible because funeral directors need a completed death certificate to make final arrangements. Even when death is expected, physicians may need to report the death to the coroner or police; knowledge of local law is important.

Telling family members about death, particularly unexpected death, requires effort. The physician should use clear language when informing the family that death has occurred (eg, using the word "died"). Euphemisms (eg, "passed on") should not be used because they are easily misinterpreted. If the family was not present during resuscitation, any events near death, including resuscitative efforts, should be described and the patient's absence of pain and distress mentioned (if true). It is usually wise to be sure that the closest kin is not alone. When told about death, particularly unexpected death, family members
Physicians, nurses, and other health care practitioners should respond to the psychologic needs of family members and provide appropriate counseling, a comfortable environment where family members can grieve together, and adequate time for them to be with the body. When feasible, it may help for a clinician to be with the family members as they enter the room with a newly dead body because that situation is so unfamiliar to most people. Sometimes it is best then to leave family members alone for a while, then return and offer explanations of treatments provided and give the family a chance to ask questions. Friends, neighbors, and clergy may be able to help provide support. Health care practitioners should be sensitive to cultural differences in behavior at the time of death.

The patient or family members and the clinical care team should discuss organ and tissue donation, if appropriate, before death or immediately after death; such discussions are ordinarily mandated by law. The attending physician should know how to arrange for organ donation and autopsy, even for patients who die at home or in a nursing home. Autopsy should be readily available regardless of where the death occurred, and decisions about autopsies can be made before death or just after death. A substantial minority of families welcome an autopsy to clear up uncertainties, and clinicians should appreciate the role of autopsy in quality assessment and improvement.

**Hospice Care**

- Emphasis on symptom relief and comfort care
- Decreased emphasis on prolonging life
- Little diagnostic testing

Hospice is a concept and program of care that is specifically designed to minimize suffering for dying patients and their family members. In the US, hospice is the only widely available comprehensive program to support very sick people at home. Philosophically, hospice programs forgo most diagnostic testing and life-prolonging treatments in favor of symptom relief, education of patients and family members about appropriate care, and comfort care.

Hospice is always interdisciplinary, relying on a core team of physicians, nurses, social workers, and attendants (eg, home health aides). Pharmacists, nutritionists, and therapists may also be involved. Hospice program personnel care for patients at home, in nursing homes, or in other care facilities. Although hospice program personnel do not usually care for patients in hospitals and rehabilitation centers, many hospitals are establishing palliative care programs to address the same care issues.

Hospice programs differ substantially in the services they provide and in treatments and devices they use. Whether a particular patient and family should participate in a given program depends on their needs and wishes, on their financial considerations, and on the skills and capacity of the local programs.

Hospice care can provide most necessary medical treatments. Nurses ordinarily oversee and implement the general plan of care, including drug use, O₂ therapy, and IV lines or other special equipment. Nurses are usually the first ones to assess and address patient needs. They can usually adjust drug doses and help obtain any new drugs or treatments. Hospice physicians see patients when needed and share in shaping the plan of care. Social workers, chaplains, and volunteers help with interpersonal, spiritual, and financial issues. Bereavement counselors support survivors through the grieving process. Hospice plans of care help family members prepare for the challenges of facing the death of a loved one and dealing with the situation at the time of death, including their role and how to obtain needed help.

Most patients ill enough to require hospice also require some assistance with daily activities (eg, dressing, bathing, preparing food), and some may be completely dependent. Family members and friends often provide this care, but additional help from home health aides and volunteers may be necessary.

Medicare or insurance mostly pays a per diem rate that is intended to cover all hospice services, including a negotiated amount of help from home health aides, but only after a physician certifies that the patient has a fatal disorder with life expectancy < 6 mo.
Physicians may be reluctant to use hospice because a treatable condition could develop. However, this reluctance is not justified because many treatable conditions are within the scope of hospice care, and patients can leave hospice at any time and re-enroll later.

**Other Concerns**

Patient, family members, and clinicians should consider the following:

- They should plan for increasing disability.
- Obtaining payment for end-of-life care may be difficult.
- Emphasis should be on improving quality of end-of-life, not on hastening death.

**Managing disability:** Progressive disability often accompanies fatal illnesses. Patients may gradually become unable to tend to a house or an apartment, prepare food, handle financial matters, walk, or care for themselves. Most dying patients need help during their last weeks. Disability should be anticipated and appropriate preparations made (eg, choosing housing that is wheelchair-accessible and close to family caregivers). Services such as occupational or physical therapy and hospice care may help a patient remain at home, even when the disability progresses.

**Financial concerns:** Financial coverage for care of dying patients is problematic. Medicare regulations restrict payment for many aspects of supportive care. Not all patients qualify for hospice care, and physicians are often reluctant to certify the 6-mo prognosis required for hospice coverage. Sometimes the need for skilled nursing care can justify Medicare payment to a nursing home for short-term, complex medical and nursing needs for dying patients. One study has shown that one third of families deplete most of their savings when caring for a dying relative. The clinical care team should know the financial effects of choices and discuss these issues with patients or family members. Some attorneys specialize in elder care and can help patients and their family members deal with these issues.

**Legal and ethical concerns:** Health care practitioners should know local laws and institutional policy governing living wills, durable powers of attorney, and procedures for forgoing resuscitation and hospitalization. This knowledge helps them ensure that the patient's wishes guide care, even when the patient can no longer make decisions (see p. 3468).

Many health care practitioners worry that medical treatments intended to relieve pain or other suffering can hasten death, but this effect is actually quite uncommon. With thoughtful and skillful medical care, accusations of assisted suicide or other wrongdoing are almost nonexistent. Even if dyspnea requires doses of opioids that may also hasten death, the resulting death is not considered wrongful.

However, actually assisting with suicide (eg, by directly providing a dying patient with lethal drugs and instructions for using them) could be grounds for prosecution in most states but is authorized under specific conditions in Oregon. Charges of homicide are plausible if the patient's interests are not carefully advocated, if the patient lacks capacity or is severely functionally impaired when decisions are made, if decisions and their rationales are not documented, or if the prosecutor's electoral base is expected to approve of such charges. Physicians who manage symptoms vigorously and forgo life-sustaining treatment need to document decision making carefully, provide care in a reputable setting, and discuss these issues willingly, honestly, and sensitively with patients, other practitioners, and the public. A physician should not provide an intervention that is conventionally considered a means of homicide (eg, lethal injection) even if the intention is to relieve suffering.

**Symptom Control in the Dying**

Patients need reassurance that symptoms will not be overwhelming.

Physical and mental distress is common while living with fatal illness, but much distress can be prevented or relieved. Patients commonly fear protracted and unrelieved suffering. Knowing they can count on living
reasonably comfortably enables patients to focus on living as fully as possible and on confronting the
issues presented by fragile health and the approach of death.

Symptom control should be based on etiology when possible. For example, vomiting due to
hypercalcemia requires different treatment from that due to elevated intracranial pressure. However,
diagnosing the cause of a symptom may be inappropriate if testing is burdensome or risky or if specific
treatment (eg, major surgery) has already been ruled out. For dying patients, comfort measures, including
nonspecific treatment or a short sequential trial of empiric treatments, are often better than an exhaustive
diagnostic evaluation.

Because one symptom can have many causes and may respond differently to treatment as the patient's
condition deteriorates, the clinical team must monitor and reevaluate the situation frequently. Drug
overdosage or under-dosage is harmful, and both become more likely as worsening physiology causes
changes in drug disposition.

When survival is likely to be brief, symptom severity frequently dictates initial treatment. Sometimes the
fear that a symptom will worsen can be more crippling than the symptom itself, and reassurance that
effective treatment is available may be all a patient needs. When a symptom is quite severe or the
diagnostic alternatives do not affect treatment, the physician should quickly relieve suffering by treating
the symptom.

Pain

About half of patients dying of cancer have severe pain. Yet, only half of these patients receive reliable
pain relief. Many patients dying of organ system failure and dementia also have severe pain. Sometimes
pain can be controlled but persists because patients, family members, and physicians have
misconceptions about pain and the drugs (especially opioids) that can control it, resulting in significant
underdosing.

Patients perceive pain differently, depending partly on whether other factors (eg, fatigue, insomnia,
anger, depression, nausea) are present. Analgesic choice depends largely on pain intensity and cause,
which can be determined only by talking with and observing patients. Patients and physicians must
recognize that all pain can be relieved by an appropriately potent drug at sufficient dosage, although
aggressive treatment may also cause sedation or confusion. Commonly used drugs are aspirin,
acetaminophen, or NSAIDs for mild pain; oxycodone for moderate pain; and hydromorphone, morphine, or
fentanyl for severe pain (see p. 1623).

In dying patients, oral opioid therapy is most convenient and cost-effective. Rectal opioid therapy provides
more uneven absorption; however, 1st-pass effect is often minimal. Morphine suppositories or pills may
be given rectally at the same dosage used for oral forms and then titrated as needed. IV or sc opioid
therapy is better than IM injections, which are painful and result in variable absorption. Long-acting
opioids are best for long-lasting pain. When giving opioids, the physician should prescribe them in
adequate dosage and on a continuous basis to prevent pain. Unreasonable concerns by the public and
by health care practitioners about addiction often tragically limit appropriate use of opioids.
Pharmacologic dependence may result from regular use but causes no problems in dying patients except
the need to avoid inadvertent withdrawal. Addictive behaviors are rare and usually easy to control.

Adverse effects of opioids include nausea, sedation, confusion, constipation, and respiratory depression.
Constipation should be treated prophylactically (see p. 3486). Patients usually develop substantial
tolerance to the respiratory depressant and sedative effects of morphine but have much less tolerance for
the analgesic and constipating effects. Opioids may also cause myoclonus, agitation, delirium,
hyperalgesia, and seizures. These effects may result from accumulation of toxic metabolites and usually
resolve when another opioid is substituted. Patients with these adverse effects and serious pain often
warrant consultation with a palliative care specialist or pain specialist.

When a stable opioid dose becomes inadequate, increasing the dose by 1 1/2 to 2 times the previous
dose is reasonable. Usually, serious respiratory depression does not occur unless the new dose is much
more than twice the previously tolerated dose. Clinicians often are unfamiliar and thus uncomfortable with
such large dosage increases. Increasing the dose over 1 to 2 h with constant observation and having opioid antagonists immediately available can overcome that reluctance.

Use of adjunctive drugs for pain control often increases comfort and reduces the opioid dosage and consequent adverse effects. Corticosteroids can reduce the pain of inflammation and swelling. Tricyclic antidepressants (eg, nortriptyline, doxepin) help manage neuropathic pain (see p. 1632); doxepin can provide bedtime sedation as well. Gabapentin 300 to 1200 mg po tid helps relieve neuropathic pain. Methadone is effective for refractory or neuropathic pain; however, its kinetics vary and it requires close monitoring. Benzodiazepines are useful for patients whose pain is worsened by anxiety.

For severe localized pain, regional nerve blocks given by an anesthesiologist experienced in pain management may provide relief with few adverse effects. Various nerve-blocking techniques may be used. Indwelling epidural or intrathecal catheters can provide continuous infusion of analgesics, often mixed with anesthetic drugs.

Pain-modification techniques (eg, guided mental imagery, hypnosis, acupuncture, relaxation, biofeedback) help some patients (see p. 3417). Counseling for stress and anxiety may be very helpful, as may spiritual support from a chaplain.

**Dyspnea**

Dyspnea is one of the most feared symptoms and is extremely frightening to dying patients.

Quickly reversible causes should be treated specifically. For example, placing a chest tube for tension pneumothorax or doing thoracentesis for a pleural effusion provides quick and definitive relief. However, if death is imminent or a definitive treatment for the cause of dyspnea is not available, proper symptomatic treatment assures patients they will be comfortable, regardless of the cause.

As a first intervention, O\(_2\) helps correct hypoxemia. Even when its oxygenating benefit is no longer certain, O\(_2\) may continue to be psychologically comforting to patients and family members. O\(_2\) therapy is most comfortable by nasal cannula, so this route is preferred unless higher concentrations are critically important.

Morphine 2 to 10 mg sublingually or 2 to 4 mg sc q 2 to 4 h prn helps reduce breathlessness in an opioid-naive patient. Such a low dosage of morphine may blunt the medullary response to CO\(_2\) retention or O\(_2\) decline, reducing dyspnea and decreasing anxiety without causing harmful respiratory depression. If patients are already taking opioids for pain, dosages that relieve dyspnea must often be more than double the patient's usual dosages.

Airway congestion is best managed with drugs that dry secretions (eg, topical scopolamine gel 0.25 to 0.5 mg q 8 to 12 h applied to the skin behind the ear or on the chest, hyoscyamine 0.125 mg sublingually q 8 h, diphenhydramine 10 to 50 mg IM q 4 to 6 h prn).

Nebulized saline may help patients with viscous secretions. Nebulized albuterol and oral or injectable corticosteroids may relieve bronchospasm and bronchial inflammation.

Benzodiazepines often help relieve anxiety associated with dyspnea and with the fear of a return of dyspnea. Useful nondrug measures include providing a cool draft from an open window or fan and maintaining a calming presence.

**Anorexia**

Anorexia and marked weight loss are common among dying patients. For family members, accepting the patient's poor oral intake is often difficult because it means accepting that the patient is dying. Patients should be offered their favorite foods whenever possible. Conditions that may cause poor intake and that can be easily treated—gastritis, constipation, toothache, oral candidiasis, pain, and nausea—should be treated. Some patients benefit from appetite stimulants such as oral corticosteroids (dexamethasone 2 to
8 mg bid or prednisone 10 to 30 mg once/day) or megestrol 160 to 480 mg po once/day. However, if a patient is close to death, family members should understand that neither food nor hydration is necessary to maintain the patient's comfort.

IV fluids, TPN, and tube feedings do not prolong the life of dying patients. All of these measures seem to increase discomfort and may hasten death. Pulmonary congestion and pneumonia are more common among dying patients who are fed artificially. Artificial hydration may worsen edema and pain associated with inflammation. Conversely, dehydration and ketosis due to caloric restriction correlate with analgesic effects and absence of discomfort. The only reported discomfort due to dehydration near death is xerostomia, which is easily relieved with oral swabs or ice chips.

Family members should be gently told that the patient is dying and that food does not help the patient's strength nor substantially delay death; they should be reassured that the patient does not suffer from having little or no intake. Having family members and friends take on specific tasks (eg, providing favorite foods, small portions, and foods that are easy to swallow) provides other ways to show caring and love, which can help family members.

Even debilitated and cachectic patients may live for several weeks with no food and minimal hydration. Family members should understand that stopping fluids does not result in the patient's immediate death and ordinarily does not hasten death. Supportive care, including good oral hygiene, is imperative for patient comfort during this time.

**Nausea and Vomiting**

Many seriously ill patients experience nausea, frequently without vomiting. Nausea may arise with GI problems (eg, constipation, gastritis), metabolic abnormalities (eg, hypercalcemia, uremia), drug adverse effects, increased intracranial pressure secondary to cerebral cancer, and psychosocial stress. When possible, treatment should match the likely cause—eg, stopping NSAIDs, treating gastritis with H₂ blockers, and trying corticosteroids for patients with known or suspected brain metastases. If nausea is due to gastric distention and reflux, metoclopramide (eg, 10 to 20 mg po or sc qid prn or given on a scheduled basis) is useful because it increases gastric tone and contractions while relaxing the pyloric sphincter.

Patients with no specific cause of nausea may benefit from treatment with a phenothiazine (eg, promethazine 25 mg po qid; prochlorperazine 10 mg po before meals or, for patients who cannot take oral drugs, 25 mg rectally bid). Anticholinergic drugs such as scopolamine and the antihistamines meclizine and diphenhydramine prevent recurrent nausea in many patients. Combining lower doses of the previously mentioned drugs often improves efficacy. Second-line drugs for intractable nausea include haloperidol (started at 1 mg po or sc q 6 to 8 h, then titrated to as much as 15 mg/day). The 5-HT₃ antagonists ondansetron and granisetron often dramatically relieve chemotherapy-induced nausea. Cost often makes these antagonists 2nd-line drugs for more complex causes of nausea in dying patients.

Nausea and pain due to intestinal obstruction are common among patients with widespread abdominal cancer. Generally, IV fluids and nasogastric suction are more burdensome than useful. Symptoms of nausea, pain, and intestinal spasm respond to hyoscyamine (0.125 to 0.25 mg q 4 h sublingually or sc), scopolamine (1.5 mg topically), morphine (given sc or rectally), or any of the other previously mentioned antiemetics. Octreotide 150 μg sc or IV q 12 h inhibits GI secretions and dramatically reduces nausea and painful distention. Given with antiemetics, octreotide usually eliminates the need for nasogastric suctioning. Corticosteroids (eg, dexamethasone 4 to 6 mg IV, IM, or rectally tid) may decrease obstructive inflammation at the tumor site and temporarily relieve the obstruction. IV fluids may exacerbate obstructive edema.

**Constipation**

Constipation is common among dying patients because of inactivity, use of opioids and drugs with anticholinergic effects, and decreased intake of fluids and dietary fiber. Regular bowel movements are essential to the comfort of dying patients, at least until the last day or two of life. Laxatives help prevent fecal impaction, especially in patients receiving opioids. Monitoring bowel function regularly is essential.
Most patients do well on a twice/day regimen of stool softener (eg, docusate) plus a mild stimulant laxative (eg, casanthranol, senna). If stimulant laxatives cause cramping discomfort, patients may respond to increased doses of docusate alone or an osmotic laxative, such as lactulose or sorbitol started at 15 to 30 mL po bid and titrated to effect.

Soft fecal impaction may be treated with a bisacodyl suppository or saline enema. For a hard fecal impaction, a mineral oil enema may be given, possibly with an oral benzodiazepine (eg, lorazepam) or an analgesic, followed by digital disimpaction. After disimpaction, patients should be placed on a more aggressive bowel regimen to avoid recurrence.

Pressure Ulcers

Many dying patients are immobile, poorly nourished, incontinent, and cachectic and thus are at risk of pressure ulcers (see also p. 736). Prevention requires relieving pressure by rotating the patient or shifting the patient's weight every 2 h; a specialized mattress or continuously inflated air-suspension bed may also help. Incontinent patients should be kept as dry as possible. Generally, use of an indwelling catheter, with its inconvenience and risk of infection, is justified only when bedding changes cause pain or when patients or family members strongly prefer it.

Confusion

Mental changes that can accompany the terminal stage of a disorder may distress patients and family members; however, patients are often unaware of them. Confusion (delirium) is common; causes include drugs, hypoxia, metabolic disturbances, and intrinsic CNS disorders. If the cause can be determined, simple treatment may enable patients to communicate more meaningfully with family members and friends. Patients who are comfortable and less aware of their surroundings may do better with no treatment. When possible, the physician should ascertain the preferences of patients and family members and use them to guide treatment.

Simple causes of confusion and agitation should be sought. Agitation and restlessness often result from urinary retention, which resolves promptly with urinary catheterization. Confusion in debilitated patients is worsened by sleep deprivation. Agitated patients may benefit from benzodiazepines; however, benzodiazepines may also cause confusion. Poorly controlled pain may cause insomnia or agitation. If pain has been appropriately controlled, a nighttime sedative may help.

Family members and visitors may help lessen confusion by frequently holding the patient's hand and repeating where the patient is and what is happening. Patients with severe terminal agitation resistant to other measures may respond best to barbiturates; family members should be made aware that when near death, patients do not usually wake up much after starting these drugs. Pentobarbital, a rapid-onset, short-acting barbiturate, may be given as 100 to 200 mg IM q 4 h prn. Phenobarbital, which is longer-acting, may be given po, sc, or rectally. Midazolam, a short-acting benzodiazepine, also is often effective.

Depression

Most dying patients experience some depressive symptoms. Providing psychologic support and allowing patients to express concerns and feelings are usually the best approach. A skilled social worker, physician, nurse, or chaplain can help with these concerns.

A trial of antidepressants is often appropriate for patients who have persistent, clinically significant depression. SSRIs are useful for patients likely to live beyond the 4 wk usually needed for onset of the antidepressant effect. Depressed patients with anxiety and insomnia may benefit from a sedating tricyclic antidepressant given at bedtime. For patients who are withdrawn or who have vegetative signs (see p. 1666), methylphenidate may be started at 2.5 mg po once/day and increased to 2.5 to 5 mg bid (given at breakfast and lunch) as necessary. Methylphenidate (same dosage) can provide a few days or weeks of increased energy for patients who are fatigued or somnolent because of analgesics. Methylphenidate has a rapid effect but may precipitate agitation. Although its duration of action is short, adverse effects are also short-lived.
Stress

A few people approach death peacefully, but more patients and family members experience stressful periods. Death is particularly stressful when interpersonal conflicts keep patients and family members from sharing their last moments together in peace. Such conflicts can lead to excessive guilt or inability to grieve in survivors and can cause anguish in patients. A family member who is caring for a dying relative at home may experience physical and emotional stress. Usually, stress in patients and family members responds to compassion, information, counseling, and sometimes brief psychotherapy. Community services may be available to help relieve care-giver burden. Sedatives should be used sparingly and briefly.

When a partner dies, the survivor may be overwhelmed by having to make decisions about legal or financial matters or household management. For an elderly couple, the death of one may reveal the survivor’s cognitive impairment, for which the deceased partner had compensated. The clinical team should identify such high-risk situations so that they can mobilize the resources needed to prevent undue suffering and dysfunction.

Grief

Grieving is a normal process that usually begins before an anticipated death. For patients, grief often starts with denial caused by fears about loss of control, separation, suffering, an uncertain future, and loss of self. Traditionally, the stages after grief were thought to occur in the following order: denial, anger, bargaining, depression, and acceptance. However, the stages that patients go through and their order of occurrence vary. Members of the clinical team can help patients accept their prognosis by listening to their concerns, helping them understand that they can control important elements of their life, explaining how the disorder will worsen and how death will come, and assuring them that their physical symptoms will be controlled. If grief is still very severe or causes psychosis or suicidal ideation or if the patient has a previous severe mental disorder, referral for professional evaluation and grief counseling may be needed.

Family members may need support in expressing grief. Any clinical team member who has come to know the patient and family members can help them through this process and direct them to professional services if needed. Physicians and other clinical team members need to develop regular procedures that ensure follow-up of grieving family members.
Appendix I: Ready Reference Guides

In the US, most laboratory test results are reported in what are termed conventional units; the rest of the world reports results in Systeme International d'Unites (SI) or international units (IU). The unit basis for SI is updated periodically by a panel.

Many SI units are the same as those used in the US system; however, those for concentrations are not. SI concentrations are reported as moles (mol) or decimal fractions of a mole (eg, millimole, micromole) per unit volume in liters (L). Conventional units are reported as mass (eg, grams, milligrams) or chemical equivalency (eg, milliequivalents) per unit volume, which may be in liters or decimal fractions of liters (eg, deciliters, milliliters). Results reported in amount per 100 mL (1 dL) are sometimes expressed as percent (eg, 10 mg/dL may be written 10 mg%).

Moles, milligrams, and milliequivalents: A mole is an Avogadro's number \((6.023 \times 10^{23})\) of elementary entities (eg, atoms, ions, molecules); the mass of 1 mole of a substance is its atomic weight in grams (eg, 1 mole of sodium = 23 g, 1 mole of calcium = 40 g). Similarly, the mass of a given quantity of substance divided by its atomic weight gives the number of moles (eg, 20 g sodium = 20/23, or 0.87, mole).

An equivalent is a unit that integrates charge and moles; 1 equivalent represents 1 mole of charges and is calculated by multiplying the number of moles of charged particles in a substance times the valence of that substance. Thus, for ions with a +1 or -1 charge (eg, Na\(^+\), K\(^+\), Cl\(^-\)), 1 mole is 1 equivalent (1 \times 1 = 1); for ions with a +2 or -2 charge (eg, Ca\(^{2+}\)), 1/2 mole is 1 equivalent (1/2 \times 2 = 1), and so forth for other valence values. A milliequivalent (mEq) is 1/1000 of an equivalent.

The following can be used to convert between mEq, mg, and mmol:

\[
\begin{align*}
\text{mEq} &= \frac{\text{mg}}{\text{formula wt}} \times \text{valence} = \frac{\text{mmol}}{\text{valence}} \\
\text{mg} &= \frac{\text{mEq}}{\text{formula wt}} \times \text{valence} = \frac{\text{mmol}}{\text{formula wt}} \\
\text{mmol} &= \frac{\text{mg}}{\text{formula wt}} = \frac{\text{mEq}}{\text{valence}}
\end{align*}
\]

(NOTE: formula wt = atomic or molecular wt.)

Alternatively, conversion tables are available in print and on the Internet.

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250 mL 8+ fluid oz
500 mL 1+ pint
1000 mL (1 liter) 1+ quart

**Weight**

65 milligrams (mg) 1 grain (gr)
28.35 grams (g) 1 oz
1 kilogram (kg) 2.2 pounds (lb)

**Linear**

1 millimeter (mm) 0.04 inch (in)
1 centimeter (cm) 0.4 in
2.54 cm 1 in
1 meter (m) 39.37 in

**Household**

4 mL 1 teaspoon (tsp)
5 mL 1 teaspoon, medical
8 mL 1 dessert spoon
15 mL 1 tablespoon (tbsp — 1/2 fluid oz)
240 mL 1 cup (8 fluid oz)

*Approximate.

**ATOMIC WEIGHT OF SOME ELEMENTS IMPORTANT IN MEDICINE**

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*Approximate.

**CENTIGRADE-FAHRENHEIT EQUIVALENTS***

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*Conversion:

To convert °F to °C, subtract 32, then multiply by 5/9 or 0.555.

To convert °C to °F, multiply by 9/5 or 1.8, then add 32.

Appendix II: Normal Laboratory Values

Introduction

Following are 5 tables with reference values (intervals) for blood, urine, CSF, stool, and other fluids (eg, gastric acid). Table 6 lists commonly used panels. (NOTE: The reference values provided in these tables should be used as guidelines only.) Reference values vary based on several factors, including the demographics of the healthy population from which specimens were obtained and the specific methods and/or instruments used to assay these specimens. Laboratories that are accredited by the College of American Pathologists (CAP) are required to establish and/or validate their own reference values at least annually. Thus, any given result should be interpreted based on the reference value of the laboratory in which the test was done; the laboratory typically provides these values with the test result.
Appendix III: Trade Names of Some Commonly Used Drugs

Throughout THE MANUAL, generic (nonproprietary) names for drugs are used whenever possible. Most prescription drugs have trade names (also called proprietary, brand, or specialty names) to distinguish them as being produced and marketed by a particular manufacturer. In the US, these names are usually registered as trademarks with the Patent Office, which confers certain legal rights with respect to their use. A trade name may be registered for a product containing a single active ingredient (with or without additives) or ≥ 2 active ingredients (combination drugs). A chemical substance marketed by several manufacturers may have several trade names. A drug may be marketed under different trade names in different countries.

Trade names are found in many publications and are used extensively in clinical medicine. For convenience, the following table lists trade names for most drugs mentioned in THE MANUAL, primarily those marketed in the US. The table is not all-inclusive and does not list every trade name for each drug. A few drugs in the table are investigational and may subsequently be approved by the FDA. Inclusion of a drug does not indicate approval of its use for any indication, nor does it imply efficacy or safety of its action. Inclusion of a trade name indicates neither endorsement nor preference by THE MANUAL.

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The Merck Manual of Diagnosis & Therapy, 19th Edition  III: Trade Names of Some Commonly Used Drugs
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The Merck Manual of Diagnosis & Therapy, 19th Edition

III: Trade Names of Some Commonly Used Drugs
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Polymyxin B/bacitracin/neomycin
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Potassium citrate
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Practolol
Pralidoxime
Pramipexole
Pramlintide
Pramoxine/hydrocortisone
Pravastatin
Praziquantel
Prazosin
Prednisolone acetate
Pregabalin
Prilocaine/lidocaine
Primidone
Pristinamycin
Probenecid
Procarbazine
Prochlorperazine
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Propafenone
Propamidine
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Protriptyline
Prussian blue
Pseudoephedrine
MITHRACIN
PODOFIN
AETHOXY-SKLEROL
FIBERCON
TRILYTE
POLY-RX
NEOSPORIN
CUROSURF
PHOTOFRIN
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KLOR-CON
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ERALDIN
PROTOPAM CHLORIDE
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PYOSTACINE
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†Not available in the US.
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